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TEXTBOOK *of*
Veterinary Internal Medicine

SIXTH EDITION

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VOLUME 1

1 CHAPTER • 1 General: The Physical Examination Of The Dog And Cat

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2 The physical examination begins long before the veterinarian ever touches the animal. The traditional teachings of *look, smell,* and *listen* are as important as ever. Excellent veterinarians avoid making diagnostic decisions driven by laboratory-derived data that bypass the physical examination, because correlation of all data is relevant to the determination of an appropriate diagnosis. This chapter is dedicated to the concept that veterinarians must bring together data from the history, physical examination, and diagnostic tests to care for an animal in the context of its life—including the life the owner envisions for the pet.

When possible, the animal's temperature and weight should be recorded before the veterinarian enters the examination room. This provides the nursing staff the chance to communicate with the animal's caretaker, gather pertinent information, note changes in weight, and identify the owner's concerns or requests.

This also is a good time for the staff to record any drugs currently administered, the prophylactic agents used (e.g., for heartworms and fleas), the animal's vaccination status, and its reproductive status (i.e., spayed, neutered, or last heat cycle).

The process should be as expeditious as possible, and every effort should be made to provide the client with an on-time, efficient examination. Reading material (magazines of interest to a wide variety of clients *and* their children) should be available if there is a likelihood of the pet's caretaker having to wait. Pet owners should be given an indication as to the doctor's schedule and the length of any delay. Providing the client with this information can offset frustration, anger, or anxiety. If the hospital has new client brochures about its methods and services, this is a good time to deliver these and to allow the client to browse through the material.

1.1 OBSERVING THE PET AND MEETING THE CARETAKER: THE HISTORY

Every veterinarian approaches a pet in his or her own way. With time, it becomes second nature. It is important to develop proper animal handling skills. Furthermore, clients observe a great deal during this process and may determine long before any recommendations are made just how trusting they will be. *Gentle care, compassion, concern,* and *attention* cannot be emphasized enough.

The process begins as the veterinarian enters the area where the owner and pet are waiting. A friendly greeting and a small but appropriate amount of banter are usually appreciated. An occasional client makes it clear that the veterinarian should get down to business immediately, and in such situations, it is wise to do so. People appreciate being greeted and particularly like being acknowledged. Asking owners about something specific to them assures that the veterinarian knows who they are. If the case is a referral, noting the distance traveled or offering a kind word about the trip acknowledges the client in an important way. It is not a technique easily taught, and it is not difficult to see whether the veterinarian “gets it” quickly and learns to communicate or simply turns away from such contact.

The importance of letting each client know that the veterinarian cares about him or her and the pet cannot be overemphasized. This must be done in a genuine way, reflected in dialog, attention, body language, and actions, and not in a lip service way, such as having “We care” or some other logo stamped on hospital leashes or stationery. Every successful veterinarian can relate tales about brilliant doctors whom clients dislike! The smartest veterinarian will never have the opportunity to demonstrate his or her skills if concern and caring are not expressed. In fact, clients are likely to be antagonistic toward veterinarians who fail to express compassion. Complaints are likely to be made much more frequently about an arrogant veterinarian than about one who is poorly trained or medically

inadequate but friendly and compassionate. In a study comparing orthopedic surgeons, physicians with a disproportionately higher number of malpractice claims could be readily separated from those with fewer claims by evaluation of their examination room attitude. Not surprisingly, those with significant problems could consistently be identified.

A skilled veterinarian or physician understands that no part of the entire examination is as important as carefully listening to the client, therefore adequate time must be allowed for this in an environment that enhances the process. Examination rooms should be comfortable and inviting. Privacy for clients is necessary, because the situation may be a difficult one for them. Decisions that may seem routine and perhaps even minor to the veterinarian may not be perceived this way by the owner.

If there has been a delay, it is paramount that the doctor acknowledge this upon entering the room. The veterinarian should show clients the courtesy of recognizing that they have been waiting. Unnecessary interruptions should be minimized, and every hospital should have a policy in this regard. In a large critical care office, delays and interruptions do occur, but these must be limited. Phone calls should be restricted to those that are professionally relevant or urgent. When such calls interrupt me with new clients, I explain that I need to speak with other owners about their hospitalized pet, yet I still make it clear that I am focusing on their pet's problems.

It is important to get the *owners'* version of the history and not one that has been “dictated” to them. For example, when questioned, the owners may acknowledge that a friend or family member told them about the supposed problem. Further questioning may determine that the owners have not noted any clinical signs that warrant such a concern.

There is no single technique for the examination process. Because this chapter is intended to explain my method of examination, I will delineate the regimen I follow, a process learned over decades of experience. When possible, I try to immediately make eye and physical contact with the pet. Even before beginning the process of taking a history, I try to welcome the pet. First, I make a brief attempt at greeting the animal by extending the back of my hand to its face. For this, cats and smaller dogs can be placed on the examination room table. Usually, with medium to large dogs, I kneel down on the examination room floor to greet the animal (I use a gardener's pad for my old, weakened, debilitated knees). Of course, some dogs and cats (those in cages, particularly) let me know beforehand that they are not ready for such a greeting. Then, I bypass the greeting and make a light comment to the owners about the pet not wishing me well (after all, I say, “Who likes going to the doctor?”). This begins a conversation with the owners that acknowledges the possibility of the pet being fearful and allows the owners to let me know how they feel about the process.

Clients are likely to want to tell the veterinarian what they know, think, or understand about the pet's problems. Regardless of how clearly and confidently clients relate their interpretation of the animal's difficulties, it is essential for the examiner to “go back to square one” and self-interpret the pet's problem. Nevertheless, the client's opinion should not be ignored, because this diminishes the trust being developed during this important part of the examination. I like to give clients a few minutes to express themselves, regardless of the relevance, because what they have to say is likely to be important to the ultimate outcome of the process. For example, clients may refuse to acknowledge how sick the pet is, or they may be worried about “cancer” or may focus on something that may not be pertinent. Clients' comments provide valuable insight into their concern and desire to care for the pet. There are different levels of owner commitment, and pets thus receive varied levels of medical attention.

Clients may offer information obtained from friends, breeders, or sources such as the Internet and may wish to have the veterinarian go over this material. A reasonable technique the veterinarian can use that precludes taking time away from the office call is to acknowledge the request and inform the caretaker that the material will be reviewed once the examination and early decision-making processes have been completed.

An owner's expectations may seem to convey that, “OK, you are the doctor, so you tell me what is wrong.” A different tack then becomes necessary, and the approach changes from “Tell me what you have observed” to “It appears that your dog (or cat) has been losing weight; tell me, has this been a recent occurrence?” This may be all that is necessary to get the owners to begin talking about their pet.

Not every owner-veterinarian experience is informative. Valuable information is noted in the record. If the client refuses to provide a history or begins to attack another veterinarian, these comments should be noted in the record. The record provides not only a future legal defense but also a guide to further owner communication. Clients who have been dissatisfied with the results of prior care reasonably object when the same medications are prescribed for their pet. It suggests that the current veterinarian has not been listening. Inquiring in a unobtrusive manner about the owners' needs and desires helps define their wishes and permits the veterinarian to provide options from which the owners can choose.

Specifics about drugs currently being administered should be reviewed. The drug's name, dosage, and frequency of administration are significant. The veterinarian should also ask about prior drugs that may have been prescribed, including over-the-counter (OTC) products, prescriptions from other veterinarians, and holistic products. This is the time to inquire about the foods the animal is currently fed, prior diets provided, canned or kibbled formulations, supplements added, and treats given. The specifics of oral, topical, and injectable prophylactic products administered at home should be identified.

Information should be gathered regarding out of area travel and areas where the pet (or other pets in the family) previously may have lived. Clients should be questioned about the welfare of other pets currently living in the household. The vaccination history is needed for each pet in the household, particularly when laboratory tests for infectious diseases affected by prior exposure or vaccines are under consideration.

The history and the owner's story are equally important. These convey to the examiner the owner's perceptions, needs, and desires during this initial period of acquaintance or contact. I find that this can be the most useful time of the examination process. I can touch the pet, gently stroke it, feel the quality of the haircoat and skin, determine the hydration status, and generally get a good idea of the animal's physical well-being (e.g., debilitated or well conditioned, obese or thin, and so on) (Figures 1-1 and 1-2). This is also a convenient time to gently examine the pet without the animal being fearful, because a pet often seems more aware of its owner's voice than of the veterinarian going over its body. This also allows me to determine the animal's behavior and gives the client a feeling of assurance that I am getting to know or am reacquainting myself with the pet. Pets generally seem less fearful while I am at their eye level and when I refer to them by name. The physical examination begins while the history is still being taken.

It is not always possible to begin the examination process during this period, and I do not make a distinct effort to perform every examination this way. If the dog or cat is sitting anxiously (i.e., protectively or in a frightened manner) in the client's lap, I avoid this contact and dwell on the pet and the owner's story. Pets relax during this period and are less fearful of me as time goes by. A truly frightened or fractious animal presents a different situation, which may require use of a muzzle or, even better, an examination away from the owner in an environment that no longer requires the pet to feel it is protecting the owner. It is important to remember that owners should not be allowed to hold their pets during any examination process that entails a likelihood of injury to anyone in contact with a frightened or injured pet.

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1.2 INITIATING THE PHYSICAL EXAMINATION

The physical examination commences when the veterinarian enters the examination room. The clinician should look at the general appearance of the pet, note odors, and observe irregularities. A severely sick or crisis presentation requires a different approach from that used for a dog or cat with a mild or chronic problem. Clients must also be observed and evaluated. They are prone to be particularly anxious in severe or acute life-threatening situations, and the veterinarian should assess the owner's state when first approaching the pet. Intense questioning may be inappropriate if the owner feels that the pet needs immediate medical attention.

Figure 1-1 Body condition chart for the dog. (Used by permission from Nestle Purina Petcare.)

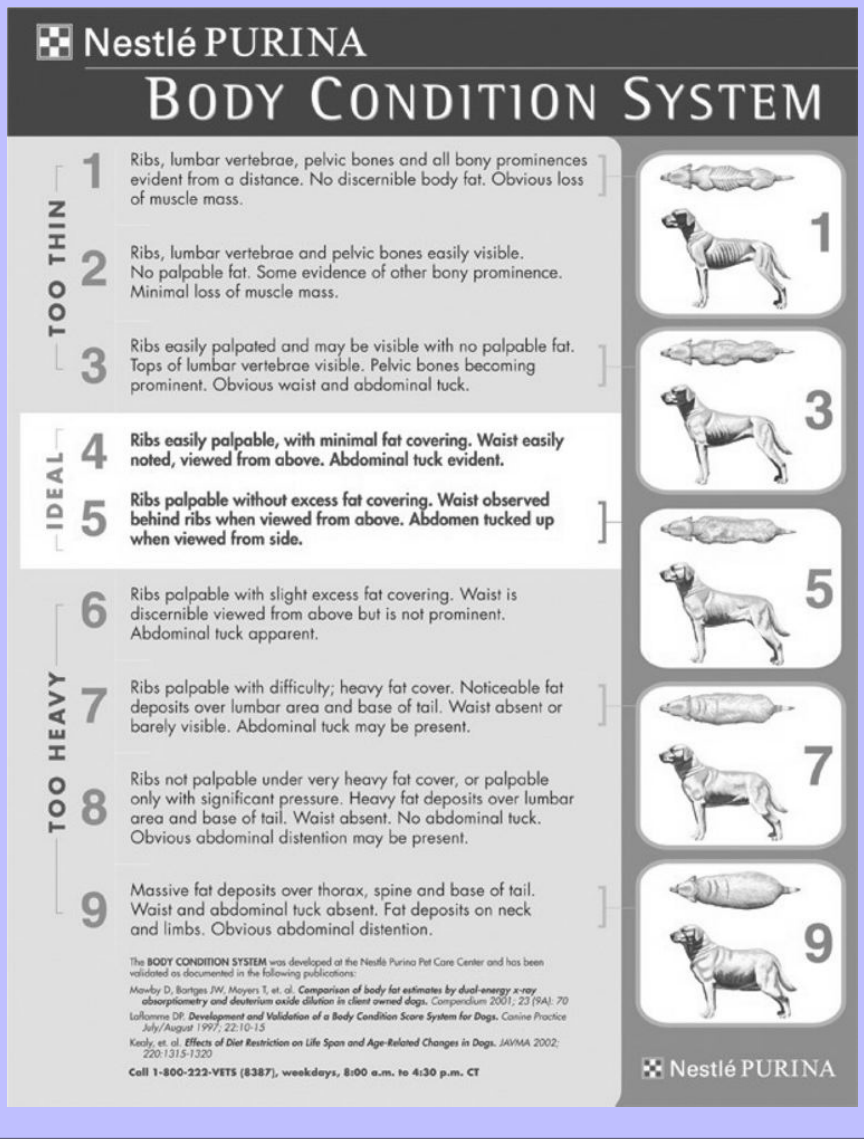

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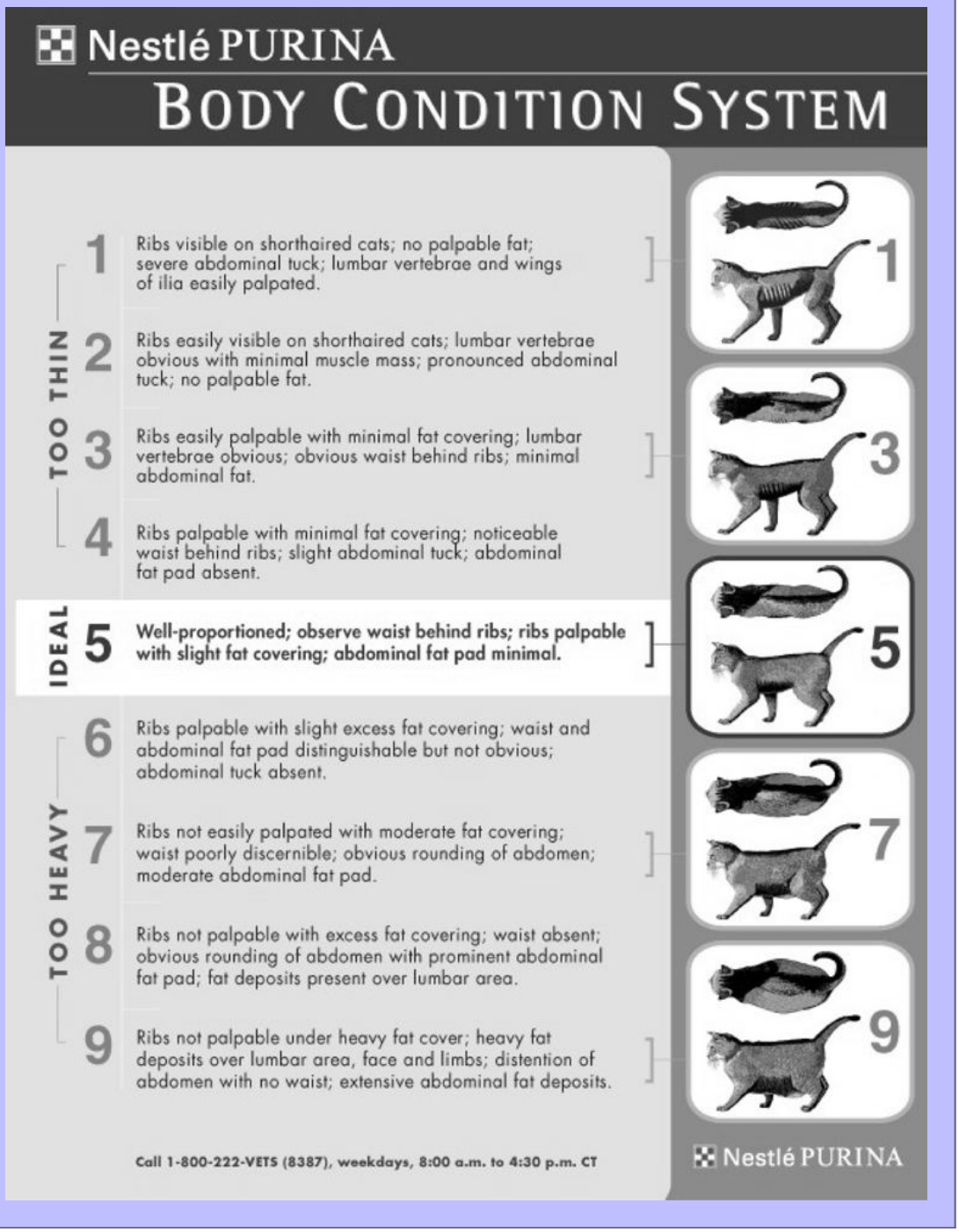
Figure 1-2 Body condition chart for the cat. (Used by permission from Nestle Purina Petcare.)



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The veterinarian should listen for abnormal breathing sounds or grunting. The animal's body size and posture also should be observed: a plantigrade stance could suggest a neuropathy; head hanging in cats may indicate hypokalemia; fat pets may be overfed, hypothyroid, or inactive; thin pets may be hyperthyroid or cachectic. It is true that owners may point out these irregularities, but they may misinterpret such changes or may simply not be cognizant of their significance. In a desire to “wish well” for the pet, the owner also may fail to provide information for fear of its significance. The veterinarian has the responsibility to seek out this information.

Examples of signs and symptoms the veterinarian may observe upon entering the examination area are presented in this textbook under the section “Clinical Manifestations of Disease.” The chapters in this section are not “complete,” because the variety of maladies and the manifestations of disease are infinite. Suffice it to say that the examination process must not be so quick or superficial that an obvious underlying problem is overlooked.

If the animal is ambulatory and has a history of lameness, neurologic deficit, or weakness, it is essential that the veterinarian watch the animal move. This may be done before or after the hands-on physical examination process. At some point during this initial phase of the examination, the veterinarian must observe the pet's gait. This may require having the pet walk on a surface with traction, preferably with the owner as the handler. Lameness, signs of neurologic deficits, or irregularity in gait and appearance is noted. The physical examination is continued, and the clinician attempts to mechanically evaluate any specific lameness or suggestion of a localized abnormality (e.g., patella luxation, stifle cruciate drawer sign, elbow pain or mass).

A review of previous examination notes for prior irregularities can aid the clinical assessment. For example, comparing the size of a mass with previous findings is something clients appreciate, particularly if the records clearly identify prior size, appearance, and location. Measurement of lesions with calipers or a ruler is good for review and trend purposes.

Neurologic changes, such as diminished conscious proprioception, diminished muscle tone, limb dragging, or unusual pain during compression of the muscles or lumbosacral compression, are noted and may require further investigation to point to a diagnosis. Something can be said for performing at this time the “stand back” examination, which allows the veterinarian to observe breathing patterns or abdominal changes.

Every seasoned veterinarian has developed his or her own method of performing the physical examination, derived from a wealth of experience. For example, animals are frightened by a large figure looming overhead and are less anxious when approached at eye level. Therefore, as mentioned before, I prefer to kneel on the examination room floor to perform the physical examination (except for cats and small dogs). I find I am better able to perform auscultation completely and thoroughly in this way, and I also am able to palpate more thoroughly while having a good presence with the pet. Particularly with the neophyte examiner, there is something to be said for having most animals in the same position each time for the examination.

After the initial greeting, I prefer to stroke the pet to gain a more generalized knowledge of the overall body status. The body composition score is assessed (see Figures 1-1 and 1-2), as is hydration status, weight change, physical appearance, and the condition of the haircoat. Masses (size, shape, and appearance) are noted. I then examine the entire torso by touch, attempting to define the patient's status. Findings may include abdominal enlargement (fluid, fat, distention, pain), discomfort, and skin or musculoskeletal abnormalities (masses, changes in the haircoat, open wounds, fleas, dirt, ticks, or other abnormalities). Looking for bumps, lumps, or irregularities, I am able to distinguish lymph node changes, pain or swelling in the joints or limbs, physical deformities, and the nature of the femoral pulse. I evaluate the pulse, including its rate, quality, and character (see Chapter 56), and listen for any irregularities while auscultating the heart.

Swelling in the form of edema or fluid collections are correlated with other changes. Edema is identified as being generalized, localized to one limb or region, or associated with abdominal fluid and is noted to be pitting, cold, warm, or oozing in nature.

Specific lameness associated with trauma is identified and may provide an obvious cause; however, the veterinarian should not make that assumption without giving reasonable consideration to other possible causes (e.g., a pathologic fracture in a dog with osteosarcoma). I like to run both hands down the animal's body to check for asymmetry in body form.

Skin and coat changes must be evaluated in light of the animal's living arrangements, as established in conversation with the caretaker. Indoor pets should not have foreign body material in the coat; fleas, flea dirt, ticks, and other ectoparasites should not be present. Hair loss or thinning is a clue to clinical disease and should be noted. Hair loss should be assessed as unilateral or bilateral, and its full significance should be identified in the records. Coat changes must also be correlated with other body changes that may indicate a systemic illness, such as Cushing's disease. Areas of skin change should be evaluated and comments made with respect to the potential benefit of skin or hair culture, skin scraping, skin biopsy or allergy testing. Pets that live outdoors are more likely to have ectoparasites, weather-related haircoat changes, or bite wounds. As with the indoor pet, these conditions must be correlated with the clinical signs and recommendations made accordingly. Coats with a strong odor of perfume or smoke may indicate to the examiner possible problems with regard to allergic lung disease, highly reactive lungs, or an animal that has been in or around a fire.

My preference is to progress the physical examination from the head toward the tail. First, hydration status and mucous membrane color and moisture should be identified. Pain on dorsiflexion or ventroflexion or lateral movement of the head and neck is significant and may be noted when the head is first moved. The head first should be examined superficially for any changes or problems, such as hair loss or swelling. Areas of discomfort or irregularity are observed. The appearance of the mucous membranes (e.g., pallor gives reason to suspect anemia, hypoperfusion, or hypoxemia), oral cavity, pharynx, and teeth are recorded. Signs of drooling, discharge, or malodor from the oral region should be apparent at this time. It is important for the veterinarian to speak to the owner about the condition of the pet's teeth and gums; it also is important for the owner to see, if possible, any unexpected finding in the oral cavity.

A brief cranial nerve examination can be included during this portion of the examination process. The way the pet holds its jaw closed, the functions both of sensation and of motor ability of the maxillary muscles, and the appearance of the eyes may be relevant. Monitoring for superficial and deep changes within the eyeballs and the periorbital region extends this process. Ophthalmic sensitivity, squinting, or photophobia is recorded. Any discharge is noted and described as to color, composition, and volume and whether the discharge is unilateral or bilateral. Tear production is recorded (Schirmer tear testing), as is nasolacrimal duct patency (e.g., dry, cracked nasal tissue). If nystagmus, strabismus, or other deviations of one or both eyeballs are noted, the veterinarian continues the examination while looking for signs of conjunctival color changes or inflammation. Pupillary size and integrity are noted, as is the pupillary light response, both direct and consensual. Sensation in the eyelids and the surrounding tissue is observed.

The appearance of the skull, the muscles of mastication, and the muscles around the head are noted. Clients frequently suggest that a mass has developed in the occipital region associated with weight loss as the temporal muscles atrophy (occipital bone). Sinking of the eyes into the skull is a sign of periorbital fat loss and may relate to myositis, weight loss, cachexia, or another ophthalmic process. Pain, swelling, or heat in any region is observed. More detailed examination of the eyeballs, including direct and/or indirect ophthalmoscopy, may be completed at

this time; or, if there are suggestions of change, the examiner first may complete the rest of the physical and then perform this part of the eye examination.

Airflow through the nostrils can be quickly assessed using a stethoscope and contralateral compression of the nares or by allowing the pet to breathe onto a metal surface (e.g., a counter top in the examination room).

Examination of the ears, pinnae, and ear canals is expected by the client and is an important part of every veterinary physical examination. This is particularly relevant in the new puppy or kitten examination as a check for ear mites, infection, or odor. An owner may report that a pet has difficulty eating or chewing, but the problem may in fact be caused by pain from one or both ear canals. Discharge, unusual odor, or discoloration of the canal tissue may be noted. Owners are more likely to notice abnormal conditions of the pinnae (e.g., aural hematoma), but even without such information, the pinnae must be examined. Superficial examination of the ear canal can usually be accomplished in the examination room without difficulty, allowing the veterinarian to discuss chronic ear disease with the owners while showing them the abnormality.

The integrity of the jaw bite must be determined, as well as the loss of teeth, or the presence of extra teeth. The color of the mucous membranes, capillary refill time, ulcers, color of the tongue, discolorations, and neurologic integrity are identified. The teeth are examined for calculus, caries, fractures, displacement, or discoloration. Abnormalities are recorded and mentioned to the owner. Signs of dental wear due to fence biting or rock chewing should be noted, as well as any resulting sensitivity. Gingival hyperplasia, masses, gingivitis, or ulcers may correlate with clinical signs. In first-time puppy or kitten examinations, evaluation for cleft palate or other congenital defects is required. With an uncooperative or fractious animal, examination of the oral cavity can be a daunting procedure. When the pet resists such an examination, removal to a treatment area away from the owner often allows further examination without difficulty.

Evaluation of the pharyngeal region is limited during the physical examination to external palpation. In some dogs, depressing the caudal tongue with the index finger allows visualization of the tonsils and oropharynx. However, this is not always the case, and if an indication of an abnormality exists in the pharyngeal or laryngeal region, a more thorough examination under sedation should be encouraged. The tongue should be elevated (using dorsally directed pressure with the thumb between the rami of the mandibles) to assess the sublingual region, such as for linear foreign bodies in cats. The laryngeal region should be checked for sensitivity, pain, or masses or institution of the gag reflex. Detection of visible or palpable deformities and monitoring of the laryngeal apparatus may yet be possible without sedation.

Moving to the ventral cervical region, the veterinarian evaluates for masses, tracheal sensitivity, and enlargement of the lymph nodes or thyroid gland. At the thoracic inlet, the clinician examines for lymph node enlargement, crepitus (subcutaneous air leakage), or other masses. Asymmetry of the thorax (scapula, muscles, rib cage, masses, or fat accumulation) should be correlated with signs, as should kyphosis or sternal deformities. Breathing difficulty can be associated with changes in the appearance of the rib cage. Fluid accumulation in the thoracic cavity, significant pleural or pulmonary disease, and some muscle disturbances cause the rib cage to feel or appear abnormal. Congenital thoracic deformities may cause respiratory signs. Peritoneal-pericardial diaphragmatic hernia (PPDH) may be associated with deformities of the xiphoid region of the sternum, such that the examiner can insert a finger into the thoracic cavity and sometimes actually touch the heart.

My preference is to complete the entire physical examination before auscultating lung and heart sounds. These portions of the physical examination are described in Chapters 54 and 55. When palpating the thorax, the examiner should notice the point of maximal intensity (PMI) of the heart. Normally this is over the left fourth to sixth intercostal space at the level of the costochondral junction. Deviations imply cardiac or thoracic cavity diseases. Similarly, palpation of a cardiac thrill is indicative of an extremely loud heart murmur (greater than grade 4/6).

Cardiac thrills are usually found at the PMI but may be displaced; they should be identified and correlated with the heart sounds and clinical signs.

Progressing caudally to the abdomen, the examiner first should note whether the abdominal wall is pumping rapidly, a possible sign of anxiety, tachypnea, or dyspnea. Tachypnea and dyspnea are observed; they are not recognized through auscultation.

The general appearance of the abdomen is the first thing the clinician should assess. Distended, tucked up, muscular and firm, painful, tense, and soft and doughy are all terms used to describe the abdomen. Abdominal pain should be characterized as coming from the abdomen or from musculoskeletal dysfunction (e.g., disk disease) or just from plain annoyance with being examined. Not all pets are happy to be in the veterinarian's office, and some display their displeasure this way; it should not be mistaken for a pathologic process.

Examination of the abdomen, as with all other parts of the body, should be performed systematically. Examining the outside of the abdomen and spinal column first and then moving deeper with systematic palpation allows the clinician to review body systems in an organized manner.

During either the initial portion of the abdominal examination or at this time, the veterinarian has the opportunity to examine the mammary glands and surrounding tissue. Large lumps in the mammary tissue are usually easily recognized; however smaller, nondiscrete lesions may require more intensive evaluation and palpation. Carefully moving the finger tips up or down the chain on both sides permits the examiner to note discrepancies in the tissue. Likewise, enlargement of the sublumbar lymph nodes may be noted. In the male, changes in and around the prepuce are identified. Preputial discharge may not be readily seen unless the pet is placed in lateral recumbency. Extruding the penis to appreciate changes in the mucosa or sheath of the penis helps explain abnormal findings or a history of licking. In the male cat, evaluation of the penis and its surrounding area is important, particularly in cases of suspected feline urinary tract disease. Neutered tomcats have small to no spines present on the penis, in contrast to intact tomcats.

Palpation of the abdomen is an individually determined technique. I like to examine animals both from behind and from the side. When examining the abdomen from behind, I am able to palpate for bilateral changes, to assess the kidneys more accurately, and to identify midabdominal masses. Lateral palpation provides a clearer indication of hepatomegaly, splenomegaly, bladder stones, or an enlarged bladder. Occasionally it is helpful to pick up the pet and allow it to stand on the hind legs so that the abdominal viscera falls caudally, permitting a more comprehensive examination.

Distention of the abdominal cavity requires differentiation. In general, there are four major causes of abdominal enlargement: fluid or fat accumulation, muscle laxity, and abdominal organ enlargement. The examination begins with gentle ballottement to determine whether the cause is obesity, pregnancy, fluid accumulation, one or more masses, internal obstruction, muscle weakness, or simply poor muscle condition. Correlating the findings of this examination with the weight and temperature allows the veterinarian to consider abnormal results.

It is generally easier to perform a complete abdominal palpation examination on the cat and many smaller dogs than it is on larger dogs. In cats, it is frequently possible to palpate the intestines, spleen, kidneys, and bladder carefully. In larger animals this may not be possible, but there is still much that can be appreciated, such as enlargement of abdominal organs, masses, and fluid collections. In cats, palpation of an enlarged spleen often is a sign suggesting mast cell disease, lymphoma, or another neoplastic process. In dogs, a large, irregular splenic margin strongly suggests hemangiosarcoma, although other causes of splenomegaly must be considered (see Chapters 184 and 276). Differentiation from other abdominal masses may be done initially through the physical examination and later by radiographic and/or ultrasonographic monitoring.

Pain upon palpation of the abdomen is a significant sign. Pain requires distinction between referred spinal pain, abdominal pain, generalized pain, and discomfort. The acute abdomen needs correlation with laboratory tests and clinical signs. Pain should be localized, if possible, as cranial, midabdominal, caudal, or generalized. Palpation for masses and the detection of enlarged viscera comprise an art that is not replaced by more sophisticated, expensive, and complicated tests. Pain in the abdomen is a clear indicator for further testing, including radiography, ultrasonography, and laboratory analyses. It also must be correlated with the clinical history. Malaise, failure to move or change position, fever, and nausea may be explained by abdominal pain, whereas a fractious cat, ears back and pupils dilated, that has a tense abdomen may simply be displeased with being examined.

Distention of the belly must be correlated with clinical signs (e.g., hair loss, polyuria/polydipsia, paper-thin, scaly skin), fluid collection, pregnancy, neurologic changes, and disease, most notably liver and splenic neoplasia. Urinary bladder distention should be palpable and defined. The kidneys often can be palpated bilaterally if enlarged in the dog and are usually palpable normally in the cat. In most dogs and cats, the left kidney normally can be palpated under all circumstances except when the animal is obese. The right kidney of the dog usually can be palpated only when it is enlarged or displaced. The presence of a large or painful prostate should be noted and correlated with clinical signs. Symmetric enlargement of the fat pads and muscles of the lumbar region (love handles) are commonly seen in an older pet, particularly if it is gaining weight.

Palpation of the abdomen is best completed with the dog or cat standing and with the examiner's fingers kept close together. If the thumb is allowed to rest on the spinal tissue and extreme pressure is exerted, the examiner may misinterpret pain as abdominal rather than spinal (induced by the thumb pressure).

The examination of the caudal abdomen is completed by rectal palpation, which is performed in older male dogs or when signs suggest lower bowel dysfunction, possible lower urinary tract problems, or hind end disorders of an orthopedic or neurologic nature. Prostatic abnormalities are likely to be palpated per rectum in all but the largest male dogs. Correct palpation of the prostate is done with the index finger of one hand and simultaneous cupping with the other hand (via dorsocaudal pressure on the caudal abdomen to elevate the prostate gland toward the palpating finger). This is especially useful for larger dogs and/or shorter index fingers. A normal rectal examination identifies a symmetric, bilobed, nonpainful, rubbery-textured prostate gland with a median raphe that clearly separates the two lobes. The peripheral tissue should evoke no pain or irregularity along the canal wall or the bony pelvic structure surrounding the gland.

Upon entering the rectum, the examiner palpates the anal sacs at the 4 and 8 o'clock positions to determine whether they are enlarged and if they can be readily expressed. The ease with which these glands can be expressed and the type of fluid released aids the evaluation for anal sac disease. Many clients worry considerably about “full” anal sacs, and it is important to identify problems if they exist. It also is necessary to establish adequate dietary measures in dogs with problems so that the anal sacs can be expressed regularly when the animal has a bowel movement. Serious anal sac disease does occur in the feline species, albeit uncommonly. The rectal tissue should be neither rough nor painful.

While examining the rectal region and tissue, the clinician should check the animal for evidence of constipation, obstipation, or generally dry, hard stools. Such problems lead to difficulty defecating. The perianal region should be examined for masses and, particularly when straining to defecate occurs, for perineal hernia, either unilateral or bilateral. Perineal hernias are detected by lateral deflection of the index finger immediately after entering the rectum (i.e., no farther than the first or second joint of the inserted finger). If the examiner probes too deeply past that point, this important lesion will be missed. Rectal prolapse must be differentiated from ileal-colic intussusception. Prolapse is associated with the inability to pass a blunt instrument only to the level of the pelvic inlet. During this portion of the examination, the tail is checked for skin lesions and for pain on motion. Animals experiencing tail pain, and

occasionally urinary and/or anal sphincter problems, should be examined with injury to the tail region in mind. Tails that have been caught in doors or pulled aggressively (more common in the cat) may develop neurologic problems involving the urinary bladder, anal sphincter, and/or the ability to move the tail.

The testicles and scrotum should be examined in the intact male for pain, skin lesions, and variability in the size and shape of one or both testicles. The presence of one or no testicles in the intact male is an important diagnostic clue. Retention or neoplasia of one or both testicles may correlate with the presenting clinical signs. In the puppy examination, the presence or absence of testicles may indicate a congenital defect and must be identified to the pet owner because the purchase agreement may need to be reviewed. It is important to note the presence of an inguinal (flanker) testis because showing and breeding would be inappropriate, and the pet may be infertile.

In females, examination of the vulvar region is important in determining the presence of discharges, the state of estrus, or the presence of skin conditions that may be responsible for licking or irritability of the hind region. Asking questions that relate to the timing of the last or latest heat cycle may elicit insightful information relevant to pseudopregnancy or pyometra in the intact bitch. Vaginal swabs taken to evaluate the state of the vaginal mucosa are a quick, easy way to determine the presence of pus or red cells in the canal and the current hormonal status of the bitch.

Prior to examining the limbs, particularly in cases of lameness, the examining veterinarian must evaluate the mobility and flexibility of the head and neck. Particularly in larger breeds of dogs, cervical conditions cause neck guarding and failure to thrive, with nondescript signs of pain, lameness, and malaise. Intermittent or recurrent problems may not be immediately obvious on the physical examination. Dogs that are difficult to examine or animals with acutely painful conditions may be better evaluated under conscious sedation.

Rear leg pain, weakness, and wobbliness may be signs of a neurologic disorder, such as cervical disease, thoracolumbar disease, and/or lumbosacral disease. The physical examination should include compression of the tissues along the spinal canal and the lumbosacral region. Sensitivity alone may be inadequate grounds for making a diagnosis and may only point to one of several conditions that must be considered in the differential diagnosis. Neurologic changes, including postural tone, conscious proprioception, or muscle atrophy, assist the process of evaluating disease states.

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Evaluation and examination of the limbs, including the pulses, lymph nodes, joints, foot pads, and interdigital regions, can reveal important clues to the presence of internal medical problems. Joint disease, often silent or less than immediately obvious, is easily overlooked unless specific attention is paid to joint swelling or discomfort. It is important to observe symptomatic cats out of the carrier, on the floor in a safe, escape-proof room. Swelling, heat, and pain in one or more joints can explain many signs, including lameness, malaise, and fever. Swelling of the peripheral subcutaneous tissues provides reason for further evaluation. Claudication or painful or non-weight-bearing lameness directs the examiner to the affected limb. Thorough examination of the limbs for differentiation of warmth, pulses, or swellings may yield a direct clue to the cause of lameness.

Deep palpation of the bony tissue provides information relevant to both medical and orthopedic problems. Taking into account the age and health of the animal is relevant, because some diseases are specific to young, growing dogs (panosteitis), whereas others would be expected in older, overweight dogs (cruciate rupture, osteoarthritis, bone cancer). Although a general evaluation of the joints is required whenever lameness is present, it is always performed with the realization that only with the animal under conscious sedation or general anesthesia can it be determined with certainty whether a joint problem exists. Cats are usually easier to palpate than dogs, but larger breeds of dogs are often difficult to examine without sedation. With that as a given, it is often advantageous to discuss with the client the benefits of radiology and a joint tap under sedation so that a more complete examination can be done. Palpation of the hips and evaluation for coxofemoral disease must be distinguished from examination for

lumbosacral problems and stifle disorders. The opportunity to evaluate these findings in greater detail may be left to a sedated state accomplished at another time. When radiographs of a limb are to be taken, the examiner should remember the benefit of radiographing both limbs to evaluate the significance of the changes noted. Other orthopedic problems, including patellar disease, may be more easily identified without sedation.

No lameness examination is complete without evaluation of the pads and interdigital regions. It is of paramount importance to examine these tissues carefully for infiltrating problems, particularly where foreign bodies are a possibility, and to distinguish interdigital cysts, digital tumors, and pad burns.

1.3 COMPLETING THE PHYSICAL EXAMINATION

Every hospital has its own set of paperwork. Smaller veterinary clinics may not require much in the way of paperwork, but this is the time to complete a well-written medical record. The traditional “SOAP” method provides the entire hospital and others with a record of the physical examination and history findings and of the plan for moving forward with the pet's care.

No physical examination is complete until the results are listed in the examination report and an assessment is made of the findings. This is the time for the veterinarian to identify in the records his or her recommendations for proceeding with the case. It is here that the client or caregiver can once again participate in the caregiving process. The veterinarian needs to summarize the findings, note the pertinent points, and identify how the case should proceed. Noting the findings alone without recommending a course of action does not complete the process. The owner must be informed of the possible courses of action and the estimated cost of such work. It is recommended that the veterinarian also note in the record, in addition to the subjective and objective findings, the likely rule-outs and tentative clinical assessment. A definitive diagnosis need not be made at this time, but identifying the rule-outs helps to portray a thought process in progress. If the prognosis is potentially poor or guarded, the examining veterinarian should discuss this with the owner at this point. Clients who fail to “hear” bad news may be very surprised to see that the veterinarian had written such news in the record one or more times in the course of record keeping. From a medical-legal point of view, keeping the client informed and up-to-date is very necessary. From the outset, discussing serious findings with the client ensures better practitioner-client communication.

2 CHAPTER • 2 Hyperthermia and Fever of Unknown Origin

James B. Miller

Obtaining a body temperature is part of every physical examination. Too frequently the veterinarian associates any elevation in body temperature with true fever. The assumption is then made that an infectious agent causes the "fever," even if no obvious cause exists. If the animal's fever resolves after giving antibiotics, the assumption is made that it was a bacterial infection. A normal body temperature is often assumed to mean the absence of disease. This approach to hyperthermia, fevers of unknown origin, and normothermia can be misleading and lead to improper diagnosis or therapy (or the lack of therapy).

2.1 THERMOREGULATION

The thermoregulatory center for the body is located in the central nervous system (CNS) in the region of the anterior hypothalamus (AH). Changes in ambient and core body temperatures are sensed by the peripheral and central thermoreceptors, and the information is conveyed to the AH via the nervous system. Thermoreceptors sensing that the body is below or above its normal temperature (normal "set point") will stimulate the AH to cause the body to increase heat production and reduce heat loss through conservation if the body is too cold or dissipate heat if the body is too warm (Figure 2-1). Through these mechanisms, dogs and cats can maintain a narrow core body temperature range in a wide variety of environmental conditions.

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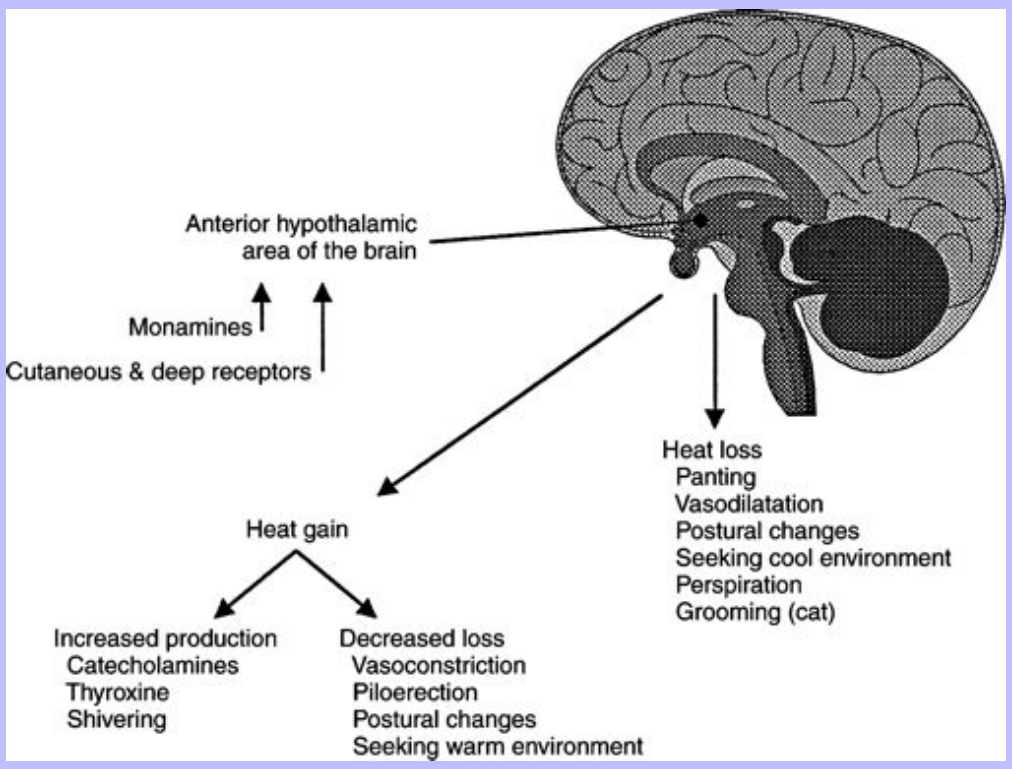
Figure 2-1 Schematic representation of normal thermal regulation.



2.2 HYPERTHERMIA

Hyperthermia is the term used to describe any elevation in core body temperature above accepted normal for that species. Hyperthermia is a result of the loss of equilibrium in the heat balance equation such that heat is produced or stored in the body at a rate in excess of heat lost through radiation, convection, or evaporation. The term *fever* is reserved for those hyperthermic animals where the set point in the AH has been "reset" to a higher temperature. In hyperthermic states other than fever, the hyperthermia is not a result of the body attempting to raise its temperature but is due to the physiologic, pathologic, or pharmacologic intervention where heat gain exceeds heat loss. Box 2-1 outlines the various forms of hyperthermia.

2.2.1 True Fever

2.2.1.1 Exogenous Pyrogens

True fever may be initiated by a variety of substances, including infectious agents or their products, immune complexes, tissue inflammation or necrosis, and several pharmacologic agents including many antibiotics. Collectively, these substances are called *exogenous pyrogens*. Their ability to directly affect the thermoregulatory center is probably minimal, and their action is to cause the release of endogenous pyrogens by the host. Box 2-2 lists some of the more important known exogenous pyrogens.

2.2.1.2 Endogenous Pyrogens

In response to stimuli by an exogenous pyrogen, proteins (cytokines) released from cells of the immune system trigger the febrile response. Macrophages are the primary immune cell involved, although T and B lymphocytes and other leukocytes may play significant roles. The proteins produced are called *endogenous pyrogens* or *fever-producing cytokines*. Although interleukin-1 (IL-1) is considered the most important cytokine, at least 11 cytokines capable of initiating a febrile response have been identified (Table 2-1). Some neoplastic cells are also capable of producing cytokines that lead to a febrile response. The cytokines travel via the blood stream to the AH, where they bind to the vascular endothelial cells within the AH and stimulate release of prostaglandins (PGs), primarily prostaglandin E_2 (PGE_2) and possibly prostaglandin $E_{2\alpha}$ ($PGE_{2\alpha}$). The set point is raised, and the core body temperature rises through increased heat production and conservation (Figure 2-2).

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2.2.1.2.1 Box • 2-1 Classification of Hyperthermia

2.2.1.2.1.1 True Fever

Production of endogenous pyrogens

2.2.1.2.1.2 Inadequate Heat Dissipation

Heat stroke

Hyperpyrexic syndromes

2.2.1.2.1.3 Exercise Hyperthermia

Normal exercise

Hypocalcemic tetany (eclampsia)

Seizure disorders

2.2.1.2.1.4 Pathologic or Pharmacologic Origin

Lesions in or around the anterior hypothalamus (AH)

Malignant hyperthermia

Hypermetabolic disorders

Monoamine metabolism disturbances

2.2.1.2.2 Box • 2-2 Exogenous Pyrogens

2.2.1.2.2.1 Infectious Agents

Bacteria (live and killed)

- Gram-positive
- Gram-negative

Bacterial products

- Lipopolysaccharides
- Streptococcal exotoxin
- Staphylococcal enterotoxin
- Staphylococcal proteins

Fungi (live and killed)

- Fungal products
- Cryptococcal polysaccharide

Cryptococcal proteins

Virus

Rickettsia

Protozoa

Nonmicrobial agents

Soluble antigen-antibody complexes

Bile acids

Pharmacologic agents

Bleomycin

Colchicine

Tetracycline (cats)

Levamisole (cats)

Tissue inflammation/necrosis

Table • 2-1 Proteins with Pyrogenic Activity

ENDOGENOUS PYROGEN	PRINCIPAL SOURCE
Cachectin/tumor necrosis factor-α(TNF-α)	Macrophages
Lymphotoxin/tumor necrosis factor-β(TNF-β; LT)	Lymphocytes (T and B)
Interleukin-1α(IL-1α)	Macrophages and many other cell types
Interleukin-1β(IL-β)	
Interferon-α	Leukocytes (esp. monocyte-macrophages)
Interferon-β	Fibroblasts
Interferon-γ	T lymphocytes
Interleukin-6 (IL-6)	Many cell types
Macrophage inflammatory protein 1α	Macrophages
Macrophage inflammatory protein 1β	
Interleukin-8 (IL-8)	
Adapted from Beutler B, Beutler SM: The pathogenesis of fever. In Bennett JC, Plum F, editors: *Cecil textbook of medicine*, ed 20, Philadelphia, 1996, WB Saunders, p 1535.	

2.2.2 Inadequate Heat Dissipation

2.2.2.1 Heat Stroke

Heat stroke is a common form of inadequate heat dissipation. Exposure to high ambient temperatures may increase heat load at a faster rate than the body can dissipate the heat. This is especially true in larger breeds of dogs and brachycephalic breeds. Heat stroke may occur rapidly in the dog, especially in closed environments with poor ventilation (e.g., inside a car with windows closed), even on moderately hot days. Environmental temperatures inside a closed car exposed to the direct sun may exceed 120°F (48°C) in less than 20 minutes, even when the outside temperature is only 75°F (24°C). Death may occur in less than an hour, especially in the breed types mentioned. Heat stroke will not respond to antipyretics used in true fever. The animal must be treated with total body cooling immediately if a fatal outcome is to be avoided. Water baths and rinses using cool (but not cold) water best accomplish total body cooling. If the water is too cold, a tendency exists for peripheral vasoconstriction, which will inhibit heat loss and slow the cooling process. Cool water, gastric lavage, or enemas have also been suggested. Cooling should be discontinued when body temperature approaches normal to avoid potential hypothermia. In addition to total body cooling, treatment for vascular collapse and shock should be instituted with severe hyperthermia (greater than 107°F [41.6°C]) or when clinical judgement warrants its use. Intravenous crystalloid solutions given at shock doses and glucocorticoids are indicated in an attempt to prevent permanent organ damage and disseminated intravascular coagulopathy (DIC).

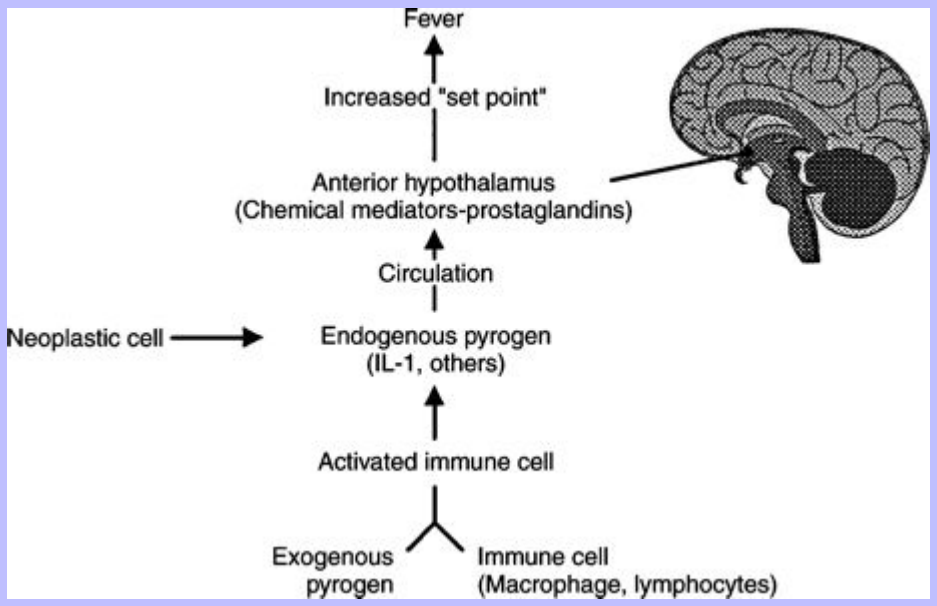
2.2.2.2 Hyperpyrexic Syndrome

Hyperpyrexic syndrome is associated with moderate-to-severe exercise in hot and humid climates. This syndrome may be more common in hunting dogs or dogs that “jog” with their owners. In humid environments, a tendency exists toward a zero thermal gradient for dry heat loss leading to a net heat gain. In addition, severe exercise may cause the cardiovascular system to supply skeletal muscles with adequate blood flow while compromising peripheral heat loss by not allowing proper vasodilation in the skin. Many hunting dogs and dogs that run with their owners will continue to work or run until they become weak, begin to stagger, and then collapse. In suspected cases, owners should obtain a rectal thermometer. If increased, in the future the clinician should evaluate the dogs' rectal temperature at the first sign of weakness or not wanting to continue. Owners should be instructed that rectal temperatures above 106°F (41°C) require immediate total body cooling, and temperatures above 107°F (41.6°C) are an immediate threat to permanent organ damage or death.

2.2.3 Exercise Hyperthermia

The body temperature will slowly rise with sustained exercise because of increased heat production associated with muscular activity. Even when extreme heat and humidity are not factors, dogs will occasionally reach temperatures that would require total body cooling. This is especially true in dogs not accustomed to exercise, overweight, or those with respiratory disease. Puppies seen for vaccinations have often been excited and active during the trip. Activity and probable release of catecholamines results in the increased body temperatures obtained on physical examination. These dogs will display features suggestive of attempting to dissipate excess body heat and are neither febrile nor ill.

Figure 2-2 Schematic representation of the pathophysiology of fever.



Eclampsia results in extreme muscular activity that can lead to significant heat production resulting in severe hyperthermia. Total body cooling should be initiated in conjunction with specific eclampsia therapy if the dog or cat is hyperthermic. Be cautious of lowering body temperature too quickly and of decreases to subnormal levels.

Seizure disorders as the result of organic, metabolic, or idiopathic causes are encountered frequently. Hyperthermia associated with severe muscular activity can be a feature, especially if the seizures are prolonged or occur in clusters. The initial concern of the clinician should be to stop the seizures; however, when significant hyperthermia is present, total body cooling is recommended.

2.2.4 Pathologic and Pharmacologic Hyperthermia

These types of hyperthermia encompass several disorders that lead to impairment of the heat balance equation. Lesions in the hypothalamus may obliterate the thermoregulatory center leading to impaired response to both hot and cold environments. Malignant hyperthermia has been reported in the dog and cat. It leads to a pharmacologic myopathy that is initiated by pharmacologic agents, including inhalation anesthetics (especially Halothane) and muscle relaxants such as succinylcholine. Extreme muscle rigidity results with the production of excess body heat. Removal of the offending causative agent and total body cooling may prevent death. Hypermetabolic disorders may lead to hyperthermic states. Endocrine disorders such as hyperthyroidism and pheochromocytoma can lead to an increased metabolic rate, vasoconstriction, or both, resulting in excess heat production and decreased ability to dissipate heat. These conditions rarely lead to severe hyperthermia requiring total body cooling.

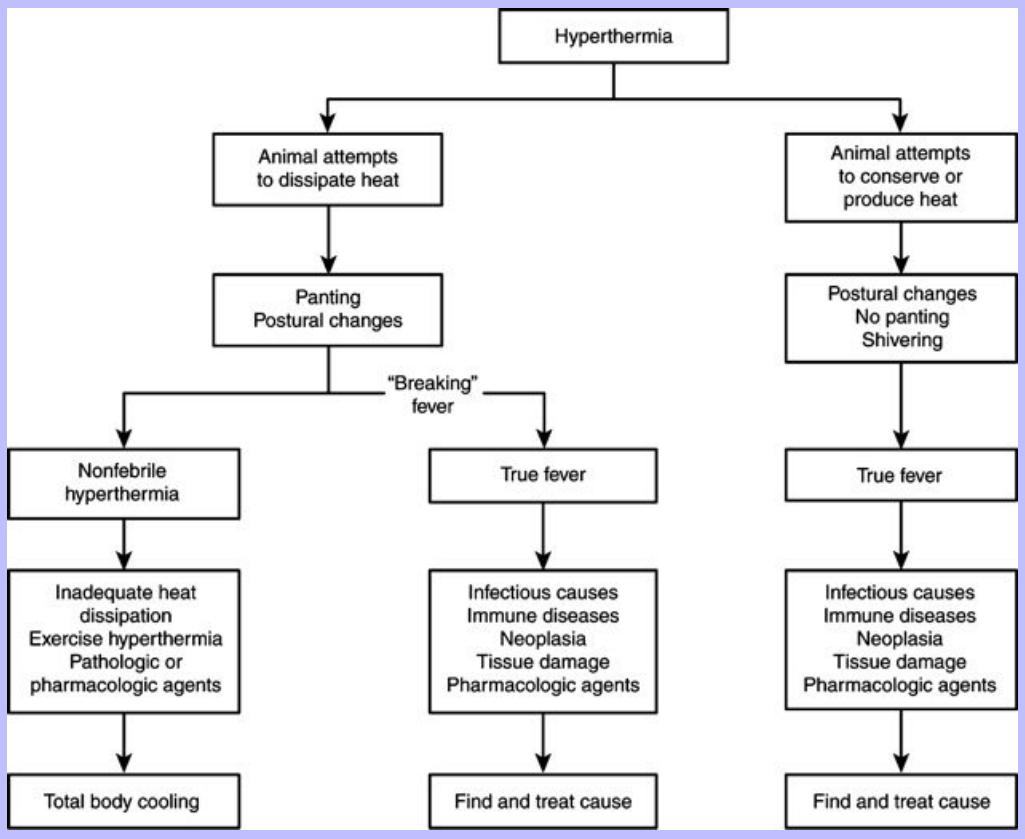
2.2.5 Clinical Approach to the Hyperthermic Patient

When a dog or cat has an increased body temperature, an effort should be made to approach the problem in a logical manner to avoid erroneous conclusions (Figure 2-3). A complete history and physical examination should be performed unless the problem is of extreme nature (temperature greater than 106°F [41°C]) and the animal is obviously attempting to dissipate heat (panting, postural changes) or comatose. In such cases, immediate total body cooling and supportive care should be initiated. In other cases, specific questions concerning previous injuries or infections, exposure to other animals, disease in other household pets, previous geographic environment, and previous or current drug therapy may be beneficial. Through this type of questioning and a complete physical examination, the clinician can frequently decide if the increased body temperature is true fever. Temperatures less than 106°F (41°C), unless prolonged, are usually not life threatening, and caution should be taken on using antipyretics before a proper clinical evaluation.

2.2.6 Fever of Unknown Origin

Fever of unknown origin (FUO) is defined in human medicine as a fever that has lasted 3 weeks and has a cause that has not been determined through laboratory evaluation and radiographs. In veterinary medicine, most clinicians consider any animal that does not have any historical or physical finding that would cause a FUO. Although research involving a large number of patients with FUO has been completed in humans, little veterinary information suggests the most common causes of FUO in dogs or cats. The information given in this chapter is based primarily on clinical experience. Most dogs and cats with FUO probably have an infection or suffer from products of those agents. The prevalence of the causative infectious agent varies depending on the area where the clinician practices and the previous travel history of the pet. Although bacterial infections are probably the most common cause of FUO in the dog, in some geographic locations, systemic fungal diseases or rickettsial infections might be more common. Endocarditis, pyelonephritis, prostatitis, closed pyometra, pyothorax, and other deep abscesses should be considered in a dog with FUO. In the cat, viral diseases such as feline leukemia virus (FeLV), feline infectious peritonitis (FIP) virus, and feline immunodeficiency virus (FIV) are common infectious causes of FUO and may exceed bacterial infections as the leading cause. The next most common cause of FUO in the dog and cat is immune-mediated disease. Most immune-mediated diseases occur in young adult dogs. Immune complexes are a potent stimulator for the release of fever producing cytokines and frequently lead to temperatures of 105°F (40.5°C) or 106°F (41°C). Neoplasia is not as common as immune-mediated disease in causing fevers but should always be considered, especially in the older animal. Another, often overlooked cause of fever, is tissue trauma. Trauma often causes mild fever (103°F to 104°F [39.6°C to 40°C]) 1 or 2 days postsurgery when there has been significant muscle involvement. Most of these animals do not have infections and probably should not be treated with antibiotics without additional evidence of infection.

Figure 2-3 Algorithm for treatment of hyperthermia.



Evaluating for infectious disease, immune-mediated disease, neoplasia, and causes of tissue trauma will usually lead to a final diagnosis, even when no obvious cause for the fever exists.

2.2.7 Nonspecific Therapy for Fever

Mild-to-moderate elevations in body temperature are rarely fatal and may be beneficial to the body. Hyperthermia may inhibit viral replication, increase leukocyte function, and decrease the uptake of iron by microbes, the latter being necessary for growth and replication of many microbes. If a fever exceeds 107° F, a significant risk of permanent organ damage and the initiation of DIC exist. The benefits of nonspecific therapy versus its potential negative effects should be considered before initiating such therapy.

Nonspecific therapy for true fever usually involves the use of inhibitors of prostaglandin synthesis. The compounds most commonly used are the salicylates (acetylsalicylic acid and sodium salicylate) and dipyrone. These products inhibit the chemical mediators of fever production and allow the normal thermoregulation. They do not block the production of endogenous pyrogens. These products are relatively safe, although acetylsalicylic acid is potentially toxic to cats and lower dose and frequency of administration relative to the dog is recommended. Dipyrone may lead to bone marrow suppression, especially when given over a prolonged period, and should be given only for a short period.

Phenothiazines can be effective in alleviating true fever and appear to act on the thermoregulatory center and cause peripheral vasodilation. The sedative qualities and potential for hypotension caused by the phenothiazines should be considered before use in the febrile patient.

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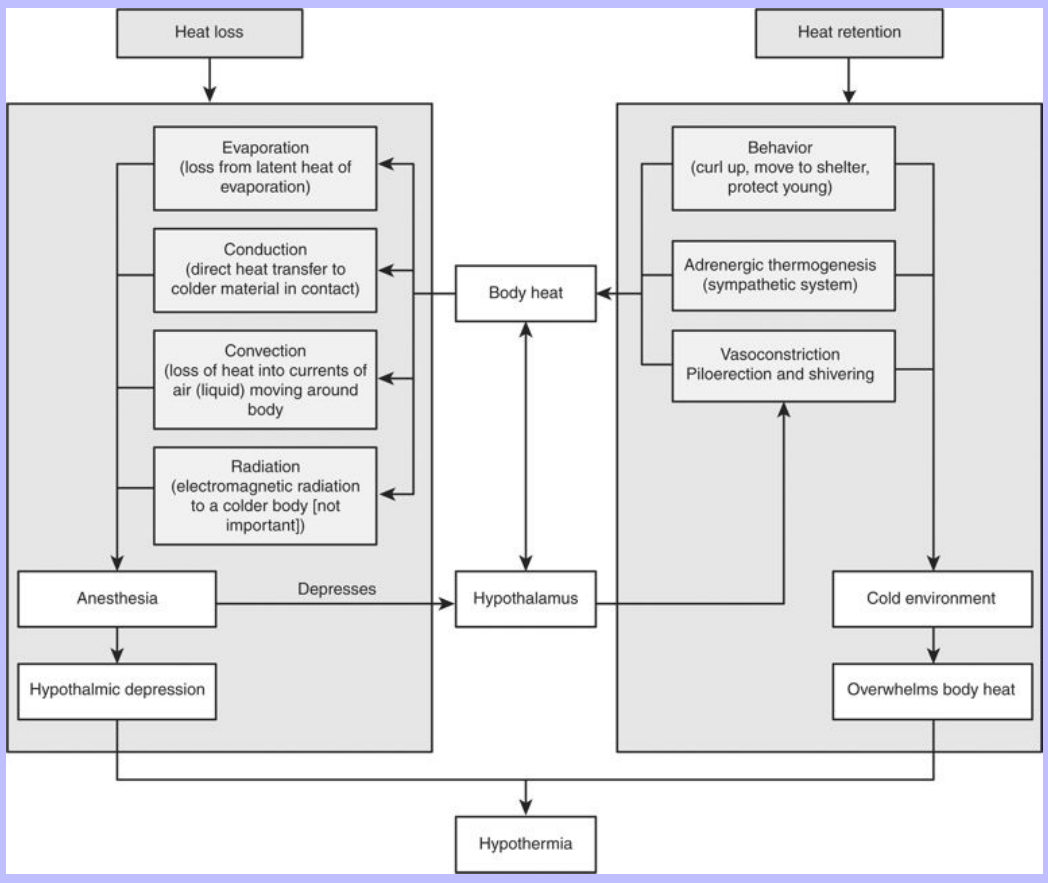
3 CHAPTER • 3 Hypothermia

Polly M. Taylor

3.1 MAINTENANCE OF NORMAL BODY TEMPERATURE

Mammalian body temperature is maintained closely around a constant set point at which cellular function is optimal. A number of complex mechanisms exist to maintain body temperature within tight control. The anterior hypothalamus maintains overall control of body temperature. It responds to local increases or decreases in temperature and also to neural input from warm and cold receptors in the skin, the abdominal viscera, and the spinal cord.

Figure 3-1 How heat is lost from the body.



To maintain constant temperature, heat generated by muscular activity and metabolism is matched to heat loss. Temperature is regulated largely by control of heat lost from the body surface via the classic routes of heat exchange: conduction, convection, evaporation, and radiation (Figure 3-1). Heat is also lost from the respiratory tract through evaporation and in urine and feces. If the body becomes too cold, heat is retained in the body core

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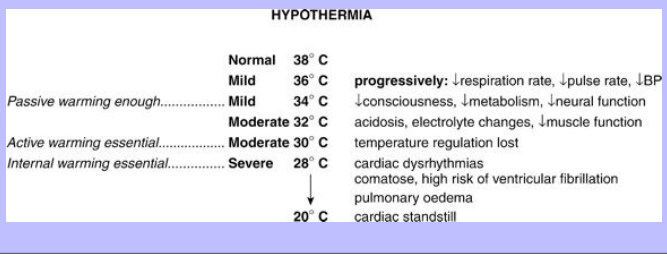
through peripheral vasoconstriction, which prevents warm blood reaching the body surface. Piloerection insulates the skin by trapping a layer of stationary air. Some additional heat is generated through muscle activity, such as shivering and voluntary movement. Chemical thermogenesis (adrenergic) may also play a part. Behavioral responses to cold are important in preventing heat loss; for example, moving into shelter and warmth, curling up, and dams protecting the young. Heat is lost by reversal of these processes, such that vasodilation of superficial blood vessels allows warm central blood to reach the skin. Panting increases evaporation from the respiratory tract. In some species, sweating is stimulated to provide the most effective heat loss through evaporation. Dogs and cats do not sweat from the skin, and loss via the respiratory tract through panting is the most significant form of active heat loss.

3.2 DEVELOPMENT OF HYPOTHERMIA

Hypothermia develops when either the methods of heat production and conservation are overwhelmed by a cold environment or when the mechanisms of heat retention are impaired. Smaller animals, in which the ratio between body surface area and volume are high, are more likely to develop hypothermia. Old, sick, or otherwise debilitated animals are also more likely to become hypothermic as heat generation and temperature control may be impaired. Neonates, with underdeveloped temperature-regulating mechanisms, are particularly susceptible. Hypothermia leads to a progressive failure of body function, ultimately leading to cardiac standstill and death. In man, a core body temperature of 35°C or below is regarded as hypothermia. Although animal temperatures are slightly higher than human temperatures, the definitions of degrees of hypothermia applied in human medicine serve well in other species as a guide to the expected degree of malfunction (Figure 3-2). Initially, as core body temperature falls below 36°C, respiratory rate, pulse rate, and arterial blood pressure fall. As temperature decreases below 34°C, muscular control and neural function begin to fail, consciousness is depressed, and metabolism is slowed. Acidosis and electrolyte imbalance may occur. Below 30°C, cardiac dysrhythmias are likely and temperature regulatory mechanisms fail even in the absence of any drugs. Hence, animals with a body temperature below 30°C are unlikely to regain normal temperature without treatment. Progressive metabolic and respiratory failure takes place when body temperature is below 28°C, with a high risk of ventricular fibrillation; cardiac standstill occurs at around 20°C.

Normal cats and, particularly, dogs withstand a cold environment very well. For instance, dogs immersed in water at 20°C can maintain heat regulation for 5 hours with less than a 1°C fall in body temperature. Hypothermia is most commonly seen when normal control mechanisms are disrupted by sedation and anesthesia, which impair hypothalamic function and behavioral responses. Many anesthetics and sedatives cause some degree of peripheral vasodilation, which itself allows more heat loss. As a consequence, most small animal patients are likely to lose body heat during anesthesia. Exposure to a cold environment or near drowning is a much less common cause of hypothermia in animals. In these circumstances the normal heat retention mechanisms are simply overwhelmed by the environmental conditions. The consequences of cold-exposure hypothermia and the treatment are essentially the same as in anesthesia-induced hypothermia. However, hypothermia is likely to be more severe after cold exposure but has the advantage of being uncomplicated by effects of surgery or drugs.

Figure 3-2 The effects of hypothermia (algorithm).



Anesthetic-associated heat loss and the resultant decrease in body temperature slows drug metabolism and leads to prolonged recovery from anesthesia. If severe, it is possible that cardiac function may be affected sufficiently to cause death. More commonly, postoperative hypothermia causes morbidity or death through the consequences of a slow recovery. A long period of unconsciousness increases the likelihood of unresolved, obstructed airway and prolonged hypoxia. Shivering will worsen this effect through increased oxygen and energy demands. Lack of movement while still under the influence of vasodilating anesthetics and sedatives leads to a vicious circle of further heat loss and reduced drug metabolism prolonging recovery and further increasing the chance of airway obstruction and hypoxia.

3.2.1 Prevention and Treatment

It is a great deal easier to prevent heat loss during anesthesia than to try to restore the temperature of a cold, anaesthetized patient at the end of a long surgical procedure. Effort should be made right from the start of anesthesia to maintain body temperature between 36°to 38°C. Much can be done by passive methods, largely insulation, although active methods using external heat are usually required where body cavities are exposed.

3.2.1.1 Passive Warming

Most heat is lost through conduction to colder surfaces in contact with the animal, such as the operating table, and through evaporation of body fluids and liquids used for surgical preparation. The animal should be insulated from colder surfaces and from the surrounding air, and it should be kept as dry as possible. A warm operating theatre may reduce heat loss into the surroundings, but working in an environment at body temperature is unpleasant; some heat loss by conduction into air circuits flowing around the animal will still occur unless it is insulated. Insulation between the operating table and the animal is easy to achieve with foam padding and other positioning aids. It is also easy to insulate the whole animal by wrapping any exposed parts with bubble wrapping or aluminium foil. A compromise between the ultimate asepsis and the best heat retention must be made by clipping the minimal amount of hair and wetting the smallest area compatible with the proposed surgery. At all costs, excess scrub water must be dried up; the animal should not lie in a pool of scrub liquid during surgery.

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It is impossible to prevent evaporation from the exposed surgical site. Intestinal surgery is the worst in this regard because large surface areas of serous membrane may be exposed. Regular flushing with warm (38° to 40°C) saline helps to reduce the amount of evaporation of body fluid and may help to prevent heat loss. Heat is also lost through the respiratory tract. Use of low-flow rebreathing circuits that retain both heat and moisture are advantageous in this respect. Heat and moisture exchangers placed between the endotracheal tube and the breathing circuit help to retain moisture and hence heat, as evaporation is reduced. These exchangers increase dead space and may be inappropriate for the very small patients that most need the heat retention.

3.2.1.2 Active Warming

Active methods to prevent heat loss are usually required during surgery of the body cavities. These include heated pads, infrared lights, heated gels, and hot-air circulators. Circulating water-heated pads are the safest because they do not become too hot; electrically heated pads may overheat, resulting in burns to the unconscious patient who cannot move off the heat source. Gel pads that are catalysed into an exothermic reaction when changing state to a stiff form are useful in very small patients. The heat generated is not excessive, lasts for 1 to 2 hours, and the stiffened gel bag can be used to position the animal. They are “regenerated” after use by placing in boiling water until the gel state returns. By far the most effective of the

active-heating systems are the hot-air blankets, in which hot air is blown into a perforated blanket that is placed about the animal under the surgical drapes. A very wet animal will initially be cooled as the result of evaporation, but in all other circumstances this method has proved extremely effective.

Treatment of hypothermia depends on its severity and cause. After anesthesia, active warming is required as homeostatic mechanisms are impaired. Where the environment has caused hypothermia, normal heat-generating mechanisms will be more effective, and passive methods such as insulation with warm, dry blankets may be sufficient (see Figure 3-2). Very severe hypothermia (core temperature <30°C) requires internal active warming with intravenous fluids at 40°C and gastric, colonic, or peritoneal lavage with fluids at 40° to 42°C. This is to prevent further core cooling, which occurs when surface warming causes vasodilation, thereby allowing cold, peripheral blood to circulate into the body core.

4 CHAPTER • 4 Pain Identification

Peter W. Hellyer

"Is this patient likely to be in pain, and if so, what is the best way to prevent and manage that pain?" This is an essential question that veterinarians should be asking themselves on a routine basis. When using this approach, the veterinarian has embraced a philosophy of providing the best care possible for the patient—this is practicing good medicine. The importance of measuring pain in patients is exemplified by what has been occurring in human medicine. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) mandated in the year 2000 that human hospitals in the United States must measure pain in their patients and take steps to manage that pain. It is a sad commentary that the human medical community did not recognize that patient comfort is part of good medicine and all important to the patient, necessitating JCAHO to mandate that pain be considered the fifth vital sign (in addition to temperature, pulse, blood pressure, and respiration). In fact, the human medical community has known about the issues of unrelieved pain for almost 30 years, since the landmark study by Marks and Sacher (1973) exposed the practice of withholding effective analgesia from terminally ill patients. In establishing pain as the fifth vital sign, JCAHO acknowledged that treating pain results in quicker clinical recoveries, shorter hospital stays, fewer readmissions, and improved quality of life, leading to increased productivity. Thus pain relief should be considered part of good medicine. In veterinary medicine, pain may be considered as a vital sign, in addition to temperature, pulse rate, and respiratory rate. Pain is similar to other patient parameters in that it is more readily apparent once the clinician looks for it. Unlike the other vital signs, pain is difficult to measure and quantify. The tools to measure pain in veterinary patients will undoubtedly change as more clinical and research information becomes available. This chapter provides a brief summary of the current tools available to evaluate pain in dogs and cats.

4.1 IDEAL PAIN SCALES

Over the past decade, pain scales have been developed and used as part of research studies designed to evaluate specific therapeutic modalities in the treatment of acute or chronic pain in dogs and cats. Nevertheless, the science of accurately measuring pain in animals in general, and dogs and cats in particular, is still in the early stages of development. Because animals cannot tell clinicians that they are in pain, no "gold standard" exists to assess pain in animals. The situation in human medicine provides a useful comparison.

Identifying pain in neonates and young children has been extensively studied over the last 20 years. The results of those efforts have been a proliferation of scales that are used to assess pain in children of different developmental ages and in different settings. Refinement of the scales used in children continues to create tools that are sensitive and specific for pain. The same process needs to occur in veterinary medicine, with the additional challenge of creating scales that are species specific. Criteria for an ideal pain scale are presented in Box 4-1. Because ideal pain scales do not exist for every species and every medical condition, how should the information in Box 4-1 be used? When evaluating a patient for pain, it is essential to be aware of the normal behavior for that species, age, and individual. Deviations from normal behavior suggest pain, anxiety, or some combination of stressors that are inducing a state of distress. If a pain scale was developed to evaluate acute postoperative pain after orthopedic surgery, the scale may be of little help in assessing abdominal pain. Accordingly, pain scales should be used as a guide to identify behavioral changes from normal and as a way to track response to therapy. Pain scales should not be used to deny analgesia based on an arbitrary number.

4.1.1 Box • 4-1 Characteristics of an Ideal Pain Scale

Patient characteristics:

1. Species specific
2. Breed specific (there may be differences in genetic sensitivities to pain)
3. Environmental and rearing specific (e.g., individual animal versus group rearing, home versus clinic)
4. Developmental/age specific (e.g., neonates versus pediatrics versus adult versus geriatric)
5. Gender specific (the role of gender on pain perception is still unclear)
6. Cause of pain specific (e.g., pathology-induced pain, procedural pain, surgical pain)
7. Body region specific (e.g., facial pain, ocular pain, abdominal pain)
8. Character of pain state specific (i.e., acute, subacute, chronic, localized, diffuse)
9. Pain intensity specific (spectrum from none to severe)
10. Recognize individual variations

Pain scale indices and criteria should be:

1. Clearly defined
2. Consistently useable by different individuals
3. Have clearly understood strengths and weaknesses
4. Be able to differentiate differences in the intensity and degree of pain
5. Be straightforward and practical to use
6. Be validated according to carefully considered standards
7. Be a useful tool to guide clinical decision making

4.1.2 Current State of Assessing Pain

Assessing pain in animals on either end of a spectrum from *no pain* to *severe pain* is relatively straightforward, provided the veterinarian and staff are aware of normal behavior for that species and individual. Realistically, many of the most challenging cases involve patients that have varying degrees of pain somewhere between the extremes of *none* and *severe*. Trying to determine the degree of pain and the ability of that animal to cope with its pain can be difficult. In a survey of Canadian veterinarians, Dohoo and Dohoo (1996) found that one of the main factors that determined if veterinarians routinely administered analgesic drugs postoperatively was the veterinarians' perception of the degree of pain felt by animals. The fact that 51.5% of those veterinarians surveyed never used analgesics highlights the clinical importance of being able to recognize pain in the species under a veterinarian's care. Even amongst veterinary personnel committed to treating pain, it can be frustrating at times trying to decide if the benefits (i.e., decreased pain intensity) of the analgesic protocol selected outweigh the side effects (e.g., sedation, nausea). Compounding the decision-making quandary is the fact that many veterinarians and their staff never received any formal training in the recognition of pain. As more studies focus

on species-specific pain behaviors, the ability to recognize and treat pain in animals will improve; however, the assessment of pain in animals will remain a subjective and inaccurate undertaking for the near future. This brings up an interesting question: Is it appropriate to assume that if a procedure is painful in people it will also be painful in an animal? An ever-growing body of scientific literature describes new knowledge and understanding of the anatomy, physiology, and pharmacology of nociception (i.e., pain). The vast majority of those studies are carried out in animals with the information often extrapolated to people, leading to the development of new drugs and techniques and ultimately to clinical trials. From people, clinicians are able to evaluate the efficacy of these new techniques and drugs and often improve the way that pain is treated. In other words, clinicians can ask human patients if the treatment has improved their level of pain. However, if veterinarians apply this pain information gathered from humans to animals, they risk being accused of anthropomorphism. Recognizing that marked differences exist in species pain tolerance, in demonstration of overt signs of pain, and in responses to therapeutic interventions, it nevertheless defies logic and ethics for the scientific community to use animals to understand pain in people while simultaneously denying that pain exists or is important in animals. Thus it is appropriate at this time to assume that if a condition causes pain in people, it will also cause some degree of pain in animals. For animals, pain may be more or less than that experienced by a person; therefore it is incumbent on the veterinarian to determine how well the patient is coping with the pain.

The evaluation methods described in this chapter have been extrapolated from human medicine (i.e., visual analogue scale) or designed to assess acute postoperative pain in dogs. These methods can be adapted to cats and other species provided the veterinarian recognizes that pain behaviors are likely to be different between species. Importantly, all of the methods described are subjective and prone to the error of either underestimating or overestimating the degree of pain. All of the pain scales used in animals rely on the recognition or interpretation (or both) of some behavior. The most useful scales determine the presence or absence of specific behaviors while minimizing the interpretation of those behaviors. Even if the amount of pain is correctly estimated, determining how well the individual animal is coping with the pain may be difficult. In addition, all of the current pain scales are subject to interobserver variability to one degree or another. Finally, it should be recognized that all of these methods are used to assess the effects of physical pain and that none have been designed to evaluate mental or psychologic dimensions of pain that an animal may be experiencing.

4.1.3 Physiologic Assessment of Acute Pain

Physiologic data (e.g., changes in heart rate, respiratory rate, arterial blood pressure, pupil dilation) are useful in assessing responses to a noxious (painful) stimulus in a lightly anesthetized animal. Physiologic responses also occur in conscious patients as a result of acute pain or other stressors but not with the same degree of reliability as in anesthetized patients. Central nervous system (CNS) and cardiopulmonary reflexes control cardiovascular and respiratory function to maintain a state of homeostasis; therefore reflex control mechanisms may dampen the physiologic responses to pain. In addition, physiologic parameters are not specific enough to differentiate pain from other stressors such as anxiety, fear, or physiologic responses to metabolic conditions (e.g., anemia). The reader should note that some pain scales use physiologic data and some do not. In the author's opinion, physiologic parameters are useful in assessing responses to noxious stimuli in patients under general anesthesia or for transient periods in conscious patients. The longer a conscious patient experiences pain, the less useful are physiologic parameters in assessing the degree of pain. When physiologic responses are used to assess pain, it is important to be aware of their limitations and to assess the selected parameter in light of baseline physiologic data. As such, changes in heart rate, respiratory rate, and other physiologic responses may be more useful in assessing the patient than any absolute value for each criterion.

4.1.4 Behavioral Assessment of Acute Pain

Evaluation of pain in animals relies on observation of animal behavior and interpretation of what the behaviors mean by an observer. Pain may be indicated by abnormal behavior that may appear as either an increase or a decrease in activity. In general, pain behaviors are easier to recognize in dogs as compared with cats. For example, dogs in pain may appear restless, agitated, or even delirious. This is particularly true during recovery from anesthesia after surgery. At the other end of the spectrum, dogs may be lethargic, withdrawn, dull, or obtunded. These dogs may not pay attention to environmental stimuli. The normal sleep-wake cycle may be disrupted, such that less sleep than normal is obtained. Normal activity such as grooming or eating may decrease or stop. Dogs may bite, lick, chew, or shake painful areas. Painful dogs may adopt abnormal body postures in an attempt to relieve or cope with pain in a given area. For example, dogs with abdominal pain (e.g., pancreatitis) may assume a posture with a rigid torso and arched back. Dogs with abdominal or thoracic pain may be reluctant to lie down in spite of obvious exhaustion. Although dogs do not have the same degree of motor control over their facial muscles as do primates, changes in facial expression can be used in some dogs to detect pain. The dog may hold its ears back or in a down position. The eyes may be wide open with dilated pupils, or partially closed with a dull appearance. Many dogs will display a “fixed stare” into space, apparently oblivious to their surroundings. Some dogs may display a type of grimace uncharacteristic of the dog when not painful. Disuse or guarding of a painful area is a fairly reliable indicator of pain. The dog's gait may be abnormal, or the dog may appear much more rigid than normal. Vocalization may indicate pain in the dog, however it is an insensitive and nonspecific indicator of pain. Vocalization may occur as a whimper, whine, yelp, groan, grunt, yowl, or any combination. Interactive behaviors are frequently changed in the painful animal. Dogs may become more aggressive and resist handling or palpation. In contrast, they may become more timid than usual and seek increased contact with caregivers. Behavioral changes indicative of pain may be too subtle or take too long to recognize under routine clinical situations. Similarly, sporadic observation of animal behavior may not reveal signs of pain. Except in the most severe circumstances, the signs of pain may be “masked” by behavior that is stereotypic of the species being observed. For instance, dogs may wag their tail and greet an observer at the cage door in spite of being in pain. Cats may simply hide in the back of their cage and demonstrate no behaviors that would suggest to a casual observer that they are in pain. Cats may continue to purr even when painful. Behavioral changes indicating pain may not be what we expect. A cat sitting quietly in the back of the cage after surgery may be in pain; however, pain would not be recognized if the caregiver expects to see more active signs of pain such as pacing, agitation, or vocalizing. Unfamiliarity with normal behaviors typical of a particular species or breed makes recognition of pain-induced behaviors difficult or impossible.

4.1.5 Types of Scoring Systems for Acute Pain

4.1.5.1 Preemptive Scoring System

The preemptive scoring system is a subjective scoring system based on the amount of pain an individual believes the animal will experience after a given procedure. Preemptive scoring systems assign a degree of pain (none, mild, moderate, severe) based on the procedure performed and the amount of tissue trauma involved. In essence, preemptive scoring systems follow the philosophy that if a procedure is likely to cause pain in a human, then it is likely to cause a similar degree of pain in animals. In general, the greater the amount of tissue trauma induced by a procedure the greater the assigned level of pain. Preemptive scoring systems are useful in planning perioperative analgesic strategies. Procedures inducing moderate to severe pain often require the use of multiple analgesic drugs and techniques to adequately manage pain. Preemptive scoring systems are not useful in actually determining the degree of pain felt by an individual patient or in

assessing response to therapy. Therefore it is important to keep in mind that individual patients may experience more or less pain than predicted by the preemptive pain scale.

4.1.5.2

Visual Analog Scale

The visual analog scale (VAS) is typically a straight, horizontal line, 100 mm in length, bracketed with descriptors of pain intensity (e.g., no pain, worst pain possible) on either end of the line (Figure 4-1). The VAS is a semiobjective scoring system. The human patient draws a vertical line across the line in a position that best represents his or her degree of pain. The patient may be asked to assess pain at the current time or the worst pain that occurred since the last assessment. The VAS has been used extensively in people and is generally considered to be a useful tool to assess pain and the response to therapy. The scale avoids the use of imprecise descriptive terms and provides many points from which to choose. In people, bracketing the VAS with phrases such as “no relief of pain” and “complete relief of pain” may provide more clinically useful information because patients do not all start with the same degree of pain. The use of the VAS may result in greater variability of pain scores than a simple descriptive scale. The VAS may erroneously appear as a more sensitive scale compared with other scales resulting in overinterpretation or excessive confidence in the results. The advantages of the VAS are primarily ease of use and that it provides a general sense of whether pain is getting worse or improving. A disadvantage of a standard VAS used to rate pain intensity is that pain is a multidimensional experience, and pain intensity is only one aspect of that experience. Disadvantages of the VAS in veterinary medicine occur primarily because the scale relies on an observer to identify and interpret pain behaviors. Thus observer bias may play a key role in assessing pain, leading to the possibility of over-or underdiagnosing pain. Variability of visual acuity among observers may affect the accuracy of the VAS. Interobserver variability, when more than one observer evaluates an animal, affects the accuracy of the VAS. The sensitivity of the VAS has not been determined in animals; therefore changes in VAS score should be interpreted in light of overall patient appearance. If a VAS is to be used, it is important to have all individuals within the practice that will be assessing pain receive training on the use of the scale. It should not be assumed that an untrained individual would provide a similar assessment of animal pain as would someone with more training and familiarity with the species being observed.

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Figure 4-1 Visual analogue scale (VAS).

4.1.5.2.1

Box • 4-2 Simple Descriptive Scale

- No pain
- Mild pain
- Moderate pain
- Severe pain

4.1.5.3 Simple Descriptive Scale

The simple descriptive scale (SDS) is a semiobjective scoring system that usually consists of four or five categories or descriptions of pain intensity (Box 4-2). Each description is assigned a number, which becomes the patient's pain score. This differs from the preemptive scoring system, in that the SDS assigns a score based on observation of the animal and not the nature of the procedure performed. Advantages of the SDS are that it is simple to use and the results are not affected by visual acuity (no drawing of a line required). Disadvantages of the SDS are that it is not a sensitive scale to assess pain (it consists of only four or five categories); therefore it may overestimate or underestimate the degree of pain and the efficacy of analgesic therapy. As with other assessment tools, observer bias may play a key role in determining pain score.

4.1.5.4 Numerical Rating Scale

The numerical rating scale (NRS) is a semiobjective scoring system that consists of multiple categories in which to evaluate the patient, with descriptive definitions of pain for each category. The NRS generally uses categories that are assigned whole numbers, and the importance of each category is not weighted. The NRS prompts the observer to evaluate certain aspects of the patient that might otherwise go unnoticed (e.g., appearance of the eyes, interactive behaviors, physio-logic parameters). Advantages of the NRS include a more thorough patient evaluation than what is prompted by the VAS or SDS, an easy method to tabulate the score, and numerous categories on which to base an assessment of patient comfort.

Disadvantages of the NRS include lack of accuracy and little improvement over the SDS. Categories are generally scored by whole numbers, suggesting that equal differences exist between categories when in fact that may not be true. Numeric rating scales have been used extensively in the evaluation of postoperative pain in dogs and cats. In spite of numerous categories, painful animals may go undiagnosed. For example, a dog with severe abdominal pain may not receive a high enough number to be considered painful when using a scale designed to assess surgical pain. In the postsurgical patient, NRS may be too insensitive to detect differences in some animals that receive analgesics and those that go untreated. Thus NRS may only be able to identify those animals with extreme pain that overtly demonstrate pain behaviors and would have been identified otherwise.

4.1.5.5 Behavioral and Physiologic Responses Scale

The University of Melbourne Pain Scale (UMPS) is a scale based on specific behavioral and physiologic responses. The UMPS includes multiple descriptors in six categories of parameters or behaviors related to pain. Advantages of the UMPS may include increased accuracy over the Preemptive Scoring System, VAS, SDS, or NRS and an ability to weigh the importance of certain behaviors or parameters. The evaluation of multiple factors increases the sensitivity and specificity of the UMPS. Most importantly the UMPS relies on behavioral observations and evaluates changes in behavior or demeanor, thereby limiting interpretation and observer bias. Disadvantages of the UMPS are limited validation to date; the specific types of patients and procedures in which the UMPS would be expected to be accurate have not been elucidated. As such, the UMPS may not be sensitive enough to detect small changes in pain behaviors, particularly if patient evaluations are performed only periodically. The UMPS was designed to evaluate dogs after surgery, therefore the accuracy of the scale for other uses or for use in cats has not been established. The UMPS requires some knowledge of the demeanor (mental status) of the dog before anesthesia and surgery. Although the veterinary staff usually knows this, the dog's actual mental status when truly comfortable at home will probably not be known. In other words, the mental status of the dog after surgery will be compared with an already altered

mental status that exists simply because the dog is in a veterinary hospital and away from familiar surroundings.

4.1.5.6 Behavioral Response Scale

The Glasgow Composite Pain Tool is a scale based on specific behavioral signs believed to represent pain in the dog. The behaviors included in the scale were derived from a questionnaire of veterinarians. The expressions used to describe pain behaviors were reduced to specific words and expressions using a variety of statistical methods. The advantages of this scale include limited interpretation and bias by the observer providing increased accuracy over the Preemptive Scoring System, VAS, SDS, and NRS. An observer is asked to identify whether or not a behavior is present, rather than to interpret what various behaviors mean. Most importantly, the terms used to describe individual behaviors are specifically defined, thereby decreasing uncertainty in using the scale. Physiologic data are not included, making the scale easier to use than the UMPS and perhaps more accurate. Nevertheless, an evaluation of physiologic parameters can be added when evaluating any patient. Disadvantages of the scale are limited validation in actual animal studies and a lack of a numeric scoring system that would allow for comparison of scores over time.

4.1.5.7 Modified Pain Scale

A modified pain scale used by the Anesthesia Section at Colorado State University is presented in Figure 4-2. This is a composite scale derived from the UMPS and the Glasgow Composite Pain Tool and was developed as part of a study evaluating pain after ovariohysterectomy and castration in dogs (unpublished data). In accordance with the Glasgow Composite Pain Tool, behaviors are identified as either *present* or *absent*. Physiologic data are not included, with the exception of dilated pupils; although changes in heart rate, respiratory rate, and arterial blood pressure can be added. Salivation and vomiting are included as indicators of nausea and as occasional signs of pain. Regardless of the cause, frequent vomiting undoubtedly increases the discomfort of the patient. The modified scale provides a record to track the frequency of behaviors indicative of pain. The frequency of pain behaviors should be low or decreasing with effective analgesic therapy. If a numeric score is desired, behaviors can be assigned the number located in parenthesis. Advantages of this scale are ease of use and minimal interpretation required. Importantly, this scale uses the specific descriptors from the Glasgow scale for individual behaviors. Specific definitions of descriptors decrease interobserver variability and interpretation. Disadvantages of this scale include lack of validation by clinical studies comparing it to other scales and the use of an arbitrary numeric scale when a specific score is required. Another disadvantage is that modifications made in the scale for use in cats have not been validated to date.

Figure 4-2 Modified pain scale.

CSU Modified Pain Scale for Use in Dogs and Cats

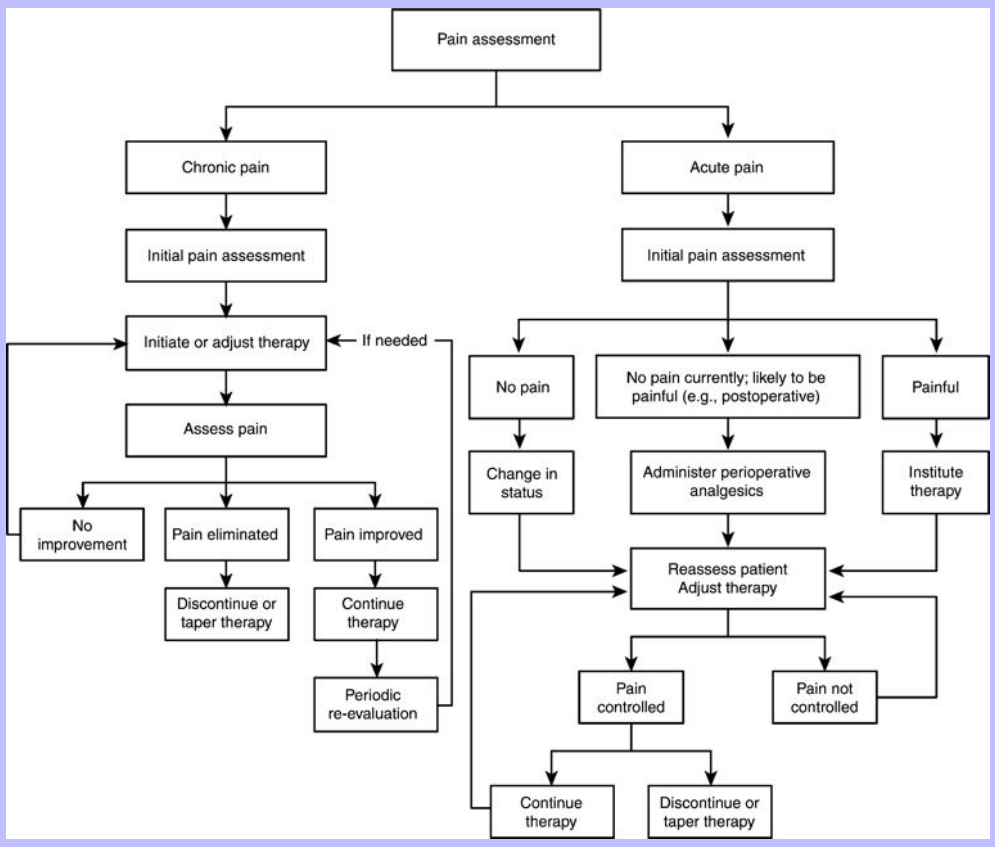
Posture:		
Normal	(0)	_____
Rigid	(1)	_____
Hunched	(2)	_____
Tense	(2)	_____
Abnormal body posture	(3)	_____
Guarding affected area	(4)	_____
Does the dog or cat seem to be:		
At rest	(0)	_____
Comfortable	(0)	_____
Restless	(1)	_____
Uncomfortable	(2)	_____
Rolling, thrashing	(3)	_____
Dilated pupils? (Yes: 1; No: 0)		_____
Salivation? (Yes: 1; No: 0)		_____
Vomiting? (Yes: 1; No: 0)		_____
Vocalization:		
Not vocalizing	(0)	_____
Barking (If abnormal for this dog)	(1)	_____
Crying, whimpering, whining	(2)	_____
Groaning, hissing	(3)	_____
Screaming	(4)	_____
Mental Status:		
Aggressive, obtunded, disinterested, nervous/anxious/fearful, happy/content, happy, bouncy, submissive		
Change in mental status? (Yes: 1; No: 0)		_____
Movement/Walking:		
Assessment not carried out/too sedate (0)		_____
Will not walk/stand	(0)	
None of these	(0)	
Stiff	(0)	
Ataxic	(1)	
Slow or reluctant to rise or sit	(2)	
Lame	(2)	
Palpation:		
When touched, did the dog or cat...		
None of these	(0)	
Look toward wound	(1)	
Appear anxious	(1)	
Cry	(2)	
Flinch	(2)	
Snap/bite/hiss	(3)	
Growl or guard wound	(3)	

If indicated: include additional physiologic parameters:

Heart rate	0	0% to 15% above baseline value
	1	16% to 29% above baseline value
	2	30% to 45% above baseline value
	3	>45% above baseline value
Arterial blood pressure	0	0% to 15% above baseline value
	1	16% to 29% above baseline value
	2	30% to 45% above baseline value
	3	>45% above baseline value
Respiration rate	0	0% to 15% above baseline value
	1	16% to 29% above baseline value
	2	30% to 45% above baseline value
	3	>45% above baseline value

Modified from:
Firth AM, Haldane SL: Development of a scale to evaluate postoperative pain in dogs. *J Am Vet Med Assoc* 214:651-659, 1999.
Holton L et al: The development of a behavioural based pain scale to measure acute pain in dogs. *Vet Record* 148:525-531, 2001. See Holton L et al for complete definition of terms.

Figure 4-3 Algorithm for the assessment of acute and chronic pain.



4.1.5.8

Assessment of Chronic Pain

A number of pathologic states, such as osteoarthritis, cancer, and dental disease may cause chronic pain. The clinical signs of pain will depend on the underlying cause and may range from subtle to obvious. Chronically painful animals may experience acute flare-ups of pain that prompt an owner to seek veterinary assistance. For example, a dog with osteoarthritis may experience an episode of acute pain after excessive strenuous activity. In general, the clinical signs of chronic pain tend to be subtle and may be difficult to recognize during a brief examination in the veterinary clinic. Clinical signs suggestive of pain include decreases in activity, reluctance to get up or play, changes in sleeping patterns, changes in appetite, changes in social interactions and grooming habits, and other behavioral changes (e.g., aggression). Obviously, these clinical signs are also suggestive of numerous other medical conditions. Careful history taking, a thorough physical examination, appropriate laboratory tests, and the occasional response to analgesic therapy are used to diagnose the role that pain is playing in the patient's symptomology. A key aspect of treating the veterinary patient with chronic pain is the absolute requirement to have a close working relationship with the patient's caregiver. As noted in Figure 4-3, periodic reevaluations and possible adjustments in therapy are critical components in managing the chronically painful patient. As noted previously, species-specific pain scales need to be developed that are

sensitive and specific for the type of chronic pain experienced. In the meantime, simply having the caregiver keep a log of daily behaviors may provide useful insight into the efficacy of therapy.

5 CHAPTER • 5 Pain Management

Steven C. Budsberg

The sensation of pain, whether actual or anticipated, triggers a myriad of responses within the body. Pain is a complex experience involving not only the transduction of noxious stimuli from the periphery to the central nervous system (CNS) but also the processing of the stimuli by the higher centers in the CNS. Recent advances have been made in understanding the molecular mechanisms of pain yielding new, important information that is now being incorporated into clinical pain management at all levels. This molecular information coupled with the increasing data supporting the importance of pain modulation on normal systemic physiologic functions has led to increased use of analgesics. Yet despite all the new information, it is humbling to realize how little is known about pain; thus the ability of clinicians to intervene effectively and correctly in this treatment area is still in its infancy.

This chapter will focus on prompting proper use of analgesics in dogs and cats. It must be realized that despite an increased awareness of pain management, many animals are not currently receiving analgesics or are receiving inadequate amounts. The goal of this chapter is to guide the reader through a systematic approach to considering analgesic use in patients. However, the reader must remember that the current discussion is very limited. At least two recent publications have provided excellent compilations on pain and its management (see References). To that end, the present discussion heavily cites these two publications.

First, clinicians must acknowledge that their patients are in pain. In small animal practice, the diagnosis of pain is either observational or presumptive. Several studies have examined the attitudes of veterinarians, physicians, and associated health care providers about pain recognition and management. At best, results of these studies reveal significant knowledge deficits in all groups. These deficiencies contribute to the inconsistent recognition and treatment of pain. In the vast majority of cases the error is undermedication of patients. The paradigm that should be used is to assume the animal is in pain until proven otherwise. Thus the question is not whether analgesia is appropriate but rather what therapy can be instituted to maximize pain relief while minimizing potential side effects and costs. Two common false assumptions about managing pain are that (1) one drug at one dose will work for all patients, and (2) pain management is an “all or none” occurrence. First, each patient may require different drugs, doses, or even a combination of therapies to maximize pain relief. Secondly, a clinician should work toward the goal of pain reduction and subsequent improved patient comfort. Pain management should be individualized to the patient based on the mechanism of pain induction in that patient. Considerations with each patient must include whether the pain is acute or chronic, the type of pain, and the perceived intensity of the pain.

To begin to logically formulate a pain management plan, clinicians need to briefly review the peripheral and central mechanisms of pain. Peripheral sensitization is defined as enhanced sensitivity of nociceptive nerve endings. Nociceptive pain is evoked by activation of peripheral nociceptors. These sensory receptors are often classified by their size and degree of myelination and according to their responses to mechanical, thermal, and chemical stimuli. During inflammation, a high proportion of somatic and visceral peripheral nociceptors can be sensitized by various mediators, including bradykinin, prostaglandin (PG), various leukotrienes, serotonin, histamine, and perhaps free radicals. Tissue injury causes alterations in sodium-and calcium-mediated channels causing the C and A-δ fibers to send action potentials to the CNS. If the injury is persistent, additional recruitment of A-β fibers and silent nociceptors occurs along with alterations in ion activity. The action potentials are propagated to the CNS. Central sensitization is defined as enhanced sensitivity of nociceptive spinal dorsal horn neurons to sensory stimulation. Central sensitization is triggered by impulses in nociceptive C fibers. The neural mechanisms that underlie central sensitization are still being explored. Central sensitization is also evoked by several mediators in the dorsal horn of the spinal cord, including PG, nitric oxide (NO), glutamate and other excitatory amino acids, and substance P. Ascending pathways transmit pain to the brain. In the brain, complex modulation and processing occur at several sites. Finally, a short

discussion of the concept of neuronal plasticity is needed before moving on to treatment. *Neuronal plasticity* refers to changes that occur in the established nervous system. More simply stated, it is the alteration of physiologic response based on previous stimuli. Pain perception by an individual for an identical stimuli may vary each time the stimuli is present. Injury, inflammation, and different diseases can cause neuronal plasticity. A subsequent increase in pain perception takes place by means of either increased excitatory or decreased inhibitory mechanisms. At a molecular level, pain hypersensitivity is the consequence of early posttranslational changes, including phosphorylation of membrane-bound proteins and later transcriptional dependent changes in genes at multiple levels along the nociceptive pathway. Neuronal plasticity can result in short-term changes that last minutes or hours, or it can result in permanent long-term changes.

The management of pain involves a myriad of events (Figure 5-1). Although the complexity of the process can seem overwhelming, it does offer several sites for potential intervention. The first concept to consider is the timing of analgesic initiation. Intuitively one should treat pain as soon as it occurs. The three basic periods to consider in pain management are (1) acute, (2) chronic, and (3) preemptive. Although the first two time periods are self-explanatory, the concept of preemptive analgesia is somewhat new but has already become a staple to the management of pain, especially perioperative pain. In essence, an injury causes central sensitization that leads to a prolonged and amplified hypersensitivity state in the patient. By giving drugs as a "preemptive analgesic," one attempts to prevent the induction of the aforementioned central sensitization, thus preempting the hypersensitivity state after the injury (which is usually surgically induced).

Anatomically, the sites of pain modulation are peripheral and central (both spinal and supraspinal). Attenuation at these sites can be done either by local infusion or systemic administration. As an example, nerve blocks (peripherally or epidurally) using lidocaine block sodium channel propagation of action potentials during painful stimuli. Another underused local administration is direct infusion into joints after arthrotomy. The instillation of local anesthetic agents have been shown to dramatically decrease surgically induced pain. Agents used in local infusions include local anesthetics, opioids, and nonsteroidal antiinflammatory drugs (NSAIDs). Systemic administration can alter both peripheral and central nociception. Interestingly, systemic NSAIDs act peripherally and spinally, whereas opioids can act peripherally, spinally, and supraspinally. Therefore clinicians must be familiar with the drugs to maximize their mechanistic effect and to administer the appropriate drugs according to their pharmacokinetic profiles. Finally, great benefit comes from combining drugs that act on different mechanisms of nociceptive modulation to enhance additive and synergistic effects; this is known as a *multimodal* or *balanced treatment* approach. Multimodal therapy is becoming more commonplace, and its use will continue to increase in small animal analgesia therapy.

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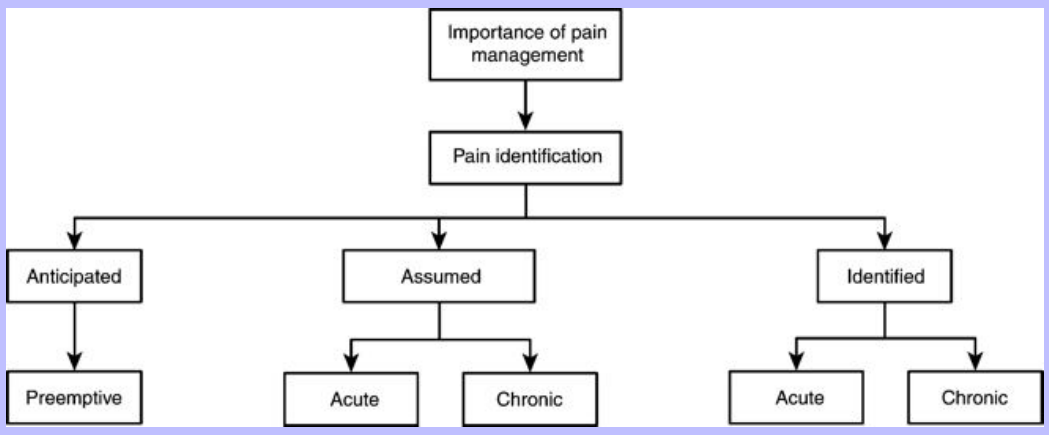
Figure 5-1 Algorithm for pain management.



The following is an overview of the major analgesic drugs that should be considered for use in the management of acute and chronic pain. Morphine and other pure μ-receptor agonists including fentanyl are often the first choice for severe pain (almost always acute pain) because their analgesic efficacy is very high. These drugs act at each target site (peripheral, spinal, and supraspinal). They show a sigmoidal dose and effect relationship that allows their dose to be adapted to the intensity of the acute pain perceived. The analgesic effects of opioids are related to their plasma concentration. Opioid drugs diffuse through the blood-brain barrier in proportion to their lipophilicity and the concentration gradient. Hepatic metabolism of opioids may produce pharmacologically active metabolites (morphine 6-glucuronide [M6G] is 20 to 40 times more potent than morphine). The phenylpiperidine analgesics, including fentanyl, are potent μ-receptor agonists with moderate to high lipid solubility. They diffuse rapidly through lipid membranes. The major pharmacodynamic differences between these drugs are potency and rate of equilibration between plasma and effect site. The next group of opioids to consider is the mixed agonist-antagonist agents. All opioids with mixed agonist-antagonist activity including butorphanol have limited flexibility in dosing in comparison with pure agonists, and they show ceiling effects for analgesia. Finally, partial agonist opioids (e.g., buprenorphine) exist. These compounds show high affinity for the μ-receptor but with low intrinsic activity. These drugs have a dose-response curve that exhibits a ceiling effect at less than the maximal effect produced by a full agonist. Therefore buprenorphine does not provide better analgesia than morphine but it may produce fewer side effects. However these side effects are often overemphasized and have been incorrectly used, more often than not, to justify avoiding the opioids in practice.

NSAIDs are another group of drugs that are rapidly becoming common as use for pain management. These agents are now available in both oral and parenteral formulations. Their analgesic effects result primarily from the inhibition of the cyclooxygenase (COX) isoenzymes (including COX-1, COX-2, and specific gene variants) that synthesize proinflammatory prostanoids. For this discussion, the primary prostanoid is prostaglandin E_2 (PGE_2) in the traumatized and inflamed areas. PGE_2 alters peripheral sensitization by binding to G protein–coupled receptors that increase levels of cyclic adenosine monophosphate (cAMP) within nociceptors, thereby increasing the threshold of activation of the nociceptors. Centrally, PGE_2 likely increases the excitability of dorsal root ganglion (DRG) cell bodies by reducing membrane depolarization needed to initiate action potentials and increase repetitive spiking. This is done by phosphorylation of the channel protein by cAMP-dependent proton kinase. The expression of COX-2 enzyme in the spinal neurons is believed to contribute to neuronal plasticity and central sensitization. NSAIDs are used today for the treatment of postoperative pain, with or without supplemental opioid agents. NSAIDs are useful for achieving multimodal or balanced analgesia given the multiplicity of mechanisms involved in pain. Clinically it must be remembered that NSAIDs are enzyme inhibitors, and their onset of effect is slower than that of opioids. Thus to be clinically relevant it has been recommended that clinicians administer NSAIDs before surgery to enhance their pain-relieving and opioid-sparing effects in the immediate postoperative period.

The α_2-agonists (medetomindine, xylazine) are also commonly used in clinical practice for both sedation and analgesia. These drugs act both peripherally and centrally by activation of α_2-receptor subtypes. The large variations in receptor structure, location, and specificity within and between species are important factors for the clinician to consider and may alter dose and expected effect within a particular patient. This group of drugs does have the potential for significant cardiovascular and respiratory side effects. They are, however, widely used very successfully in small animal practice.

The use of N-methyl-D-aspartate (NMDA)–receptor antagonists (most commonly ketamine) in pain management has begun to rapidly increase in small animal practice. Studies suggest that the spinal dorsal horn NMDA–receptor has an important role in mechanisms underlying central sensitization. NMDA–receptor antagonists lessen the hyperactivity of dorsal horn neurons after prolonged activation of primary afferent neurons and inhibit nociceptive behavior induced by peripheral tissue or nerve injury. Ketamine is a noncompetitive NMDA–receptor antagonist. Analgesia obtained with

ketamine occurs at serum concentrations one tenth to one fifth of an anesthetic dose, with a highly significant correlation between pain relief and serum concentrations of ketamine.

Finally, one should strongly consider local anesthetics in the management of pain. Local anesthetics reversibly block transmission of nerve fibers. Blockade of the sodium channels in the cell membranes causes an inhibition of the generation and conduction of the nerve impulses. The size and the presence of myelination drastically alter different nerve fiber susceptibility to local anesthetic blockade. Examples of local pain management include local tissue infiltrations, direct nerve blocks, or intraarticular administrations. The reader should remember that local blocks are easily combined with systemic analgesics to provide economic and effective mutimodal therapy.

Some key points should be remembered in reference to the management of pain. First, with pain management one must think in terms of mechanism-based, rather than symptomatic, treatment of pain. The clinician must focus on the reason the animal is in pain, not just on the fact that the animal is showing pain or discomfort (or the intensity of that reaction). To do this, one must understand the different types of inciting stimuli, neuronal pathways involved, and most importantly the systemic consequences of pain to the patient. These pathophysiologic considerations should lead the clinician to more multimodal therapy with improved clinical success without considerable increased costs. Finally, from a practical point of view the veterinarian needs to educate clients and staff about the importance of pain management. The use of analgesics should not be an option given to owners, it should be an integral part of each patient's therapy. Clinicians should establish protocols for assessing pain and what drugs to use when pain is encountered or anticipated. This is no different than the different anesthesia protocols each clinic has today. In addition, clinicians should routinely assess and record pain and provide a scoring system chart on each cage that is easy to use and read. This will begin to sensitize the staff to the course of pain in a particular disease or surgical procedure. The bottom line is that as one appreciates the negative side effects of pain and becomes more willing to treat it, everyone benefits—the patient, the client, and the clinician.

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6 CHAPTER • 6 Syncope

Sandra L. Minors

Sudden, transient and unpredictable loss of consciousness has both intrigued and frustrated physicians throughout the ages. Hippocrates is credited with having made the first description of syncope; the medical term for *fainting* is derived from the Greek term *syncoptein* (to cut short). Despite being one of the oldest recorded medical problems, syncope remains an alarming symptom. This is largely because the causes of syncope are diverse, ranging from benign to life threatening. As aptly stated by one observer, “The only difference between syncope and sudden death is you awake from one.”

The definition of syncope is a sudden and brief loss of consciousness with a loss of postural tone, from which recovery is spontaneous. The pathophysiology of all forms of syncope consists of a sudden decrease in or brief cessation of cerebral blood flow and nutrient delivery to the parts of the brain subserving consciousness (i.e., the brain stem reticular activating system, and both cerebral hemispheres) (Figure 6-1). The brain has very limited storage of high-energy phosphates for oxidative phosphorylation and requires continuous delivery of both oxygen and glucose for normal function. Studies in humans have shown that after 5 to 15 seconds of cerebral anoxia, loss of consciousness, pallor, and muscle relaxation occur. More prolonged cerebral ischemia (>15 seconds) is associated with generalized tonic spasms and incontinence. Loss of vascular resistance and decreased cardiac output are responsible for the vast majority of syncopal events as a result of transient systemic hypotension. Episodic weakness or presyncope represent less severe grades of syncope without loss of consciousness, whereas more prolonged hypotension results in shock.

6.1 LOSS OF VASCULAR RESISTANCE

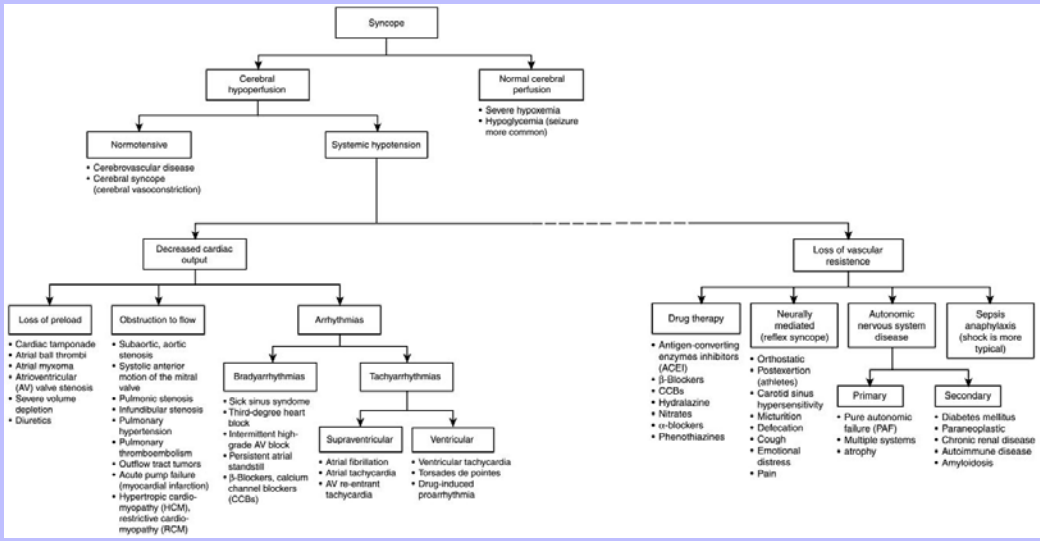
Changes in posture and physical exercise are among many activities that challenge cerebral perfusion. Baroreceptors located in the arterial and cardiopulmonary regions evolved to closely regulate blood pressure. Information from the baroreceptors is relayed to the central nervous system (CNS), where neuronal cell groups regulate reflex cardiovascular activity through changes in sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) outflow. Failure of these homeostatic mechanisms can result in hypotension and syncope. This type of syncope is referred to as *neurally mediated syncope* (NMS), reflex, vasovagal, or neurocardiogenic syncope. This is the most common cause of syncope in humans and is the most likely cause in healthy patients.

NMS is characterized by arterial vasodilation (SNS withdrawal) in the setting of relative or absolute bradycardia (PNS stimulation). Correction of the bradycardia does not necessarily alleviate symptoms of syncope because of the concurrent vasodepressor response. Neurally mediated syncope typically has specific triggers, such as strong emotion, pain, or strong vagal stimulation (e.g., cough, micturition, defecation, swallowing). Patients may experience prodromal signs of autonomic stimulation that include pallor, nausea, mydriasis, hyperventilation, and bradycardia. Complete recovery from NMS tends to be slower than with other causes of syncope. These episodes are believed to represent a hypersensitive autonomic system that overresponds to various stressors in predisposed individuals. The exact cause of NMS has not been elucidated and is likely heterogenous. The risk of sudden death is thought to be very low in NMS. Markedly prolonged periods of asystole may rarely lead to sudden death.

NMS can be classified as postural (associated with the upright position), central (occurring in response to strong emotional stimulation or epileptic discharges), and situational (after specific stimulation of sensory or visceral afferents). In dogs, central and situational NMS is recognized. Examples include syncope induced by hyperexcitability or hyperventilation (or both), vomiting, excessive pulling on a lead, exertion, and cough. Long

periods of ventricular asystole (>8 seconds) have been documented to precede cough-induced syncope. Boxers seem predisposed to NMS. Vigorous exercise, excitement, or both typically precede collapse, which is characterized by the classic pallor, absolute or relative bradycardia, and gradual recovery. In pugs, syncope associated with stimulation of afferent fibers from the laryngeal or nasal mucosa, leading to decreased blood pressure, cardiac standstill, and apnea has been demonstrated.

Figure 6-1 Pathophysiology and differential diagnosis for syncope. *A-V,* Atrioventricular; *RV,* right ventricular; *HCM,* hypertrophic cardiomyopathy; *RCM,* restrictive cardiomyopathy; *CCB,* calcium channel blocker; *ACEI,* angiotensin converting enzyme inhibitor.



NMS represents only one aspect of a broad, heterogenous group of disturbances of the autonomic nervous system (ANS). In contrast to intermittent periods of hypotension seen in reflex syncope, other patients can develop failure of the ANS to function under normal circumstances. In contrast to patients with reflex syncope, patients suffering from ANS failure syndromes have many other complaints relating to ANS disturbances in other organ systems (e.g., disruptions in bladder and gastrointestinal function). Autonomic failure secondary to a wide variety of disorders, including diffuse systemic illnesses, such as renal failure, cancer, and diabetes mellitus may produce varying degrees of disruption in autonomic function, leading to hypotension and syncope.

6.2 REDUCED CARDIAC OUTPUT

In the evaluation of syncope, the presence of structural heart disease (such as cardiomyopathy, congenital and valvular heart disease) has emerged as the most important factor for predicting the risk of death and the likelihood of arrhythmias. Underlying heart disease, irrespective of the cause of syncope, is the factor associated with an increased risk of death.

Malignant causes are more likely if syncope is exertional. Exertional syncope is a common manifestation of all types of heart disease in which cardiac output is fixed and does not rise normally (or falls) with exercise. Systemic vascular resistance normally decreases with exercise because of arteriolar dilatation. This decline in peripheral

vascular resistance normally is compensated for by an increase in cardiac output, thus maintaining arterial pressure and cerebral perfusion. In conditions that cause severe obstruction to flow, cardiac output may not increase, leading to hypotension and syncope. Exertion may also lead to neurally mediated syncope in patients with severe aortic or subaortic stenosis. Heightened SNS stimulation and high intraventricular pressures associated with exercise are thought to stimulate ventricular mechanoreceptors that normally respond to stretch. The resultant afferent neural traffic to the brain stem is thought to mimic conditions of hypertension, leading to a paradoxic sympathetic withdrawal and vagal simulation despite systemic hypotension. Abnormal vascular responses to exercise as a result of altered baroreceptor function have been shown to cause syncope in human patients with hypertrophic cardiomyopathy. Patients who demonstrated vascular instability were also at markedly increased risk of sudden cardiac death.

In patients with CHF, the combination of a low cardiac output, volume depletion caused by diuretic use, and vasodilator therapy likely all play a role in syncope. The propensity for arrhythmias is exacerbated in CHF. In addition, patients with overt pulmonary congestion may be prone to exertional collapse because of hypoxia-induced pulmonary vasoconstriction leading to pulmonary artery hypertension. Many animals with congestive symptoms that collapse will not experience syncope once their heart failure is controlled.

Arrhythmic causes for syncope include tachyarrhythmias and bradyarrhythmias. Tachyarrhythmias lead to collapse as the result of the abrupt reduction in cardiac output related to the marked reduction in diastolic filling. Supraventricular tachyarrhythmias in young dogs without structural heart disease should raise one's suspicion of atrioventricular (A-V) reentrant tachycardias caused by accessory pathways. In the presence of substantial heart disease and concomitant atrial enlargement, atrial tachycardias and atrial fibrillation (sustained or paroxysmal) are common. Supraventricular arrhythmias are less likely to lead to sudden death than ventricular tachyarrhythmias.

Life-threatening ventricular tachyarrhythmias occur most commonly in patients with advanced heart disease of any cause. Boxer and Doberman cardiomyopathies are considered particularly high risk for sudden death, which may be the first manifestation of malignant ventricular arrhythmias in these breeds. Advanced mitral valve disease can result in ventricular arrhythmias and sudden cardiac death. Because exercise can exacerbate subendocardial myocardial ischemia, ventricular tachyarrhythmias may be provoked by exertion in all types of severe heart disease. Exertional sudden death is common in severe subaortic stenosis.

Bradyarrhythmias can lead to very subtle symptoms, such as occasional stumbling, to very dramatic symptoms, such as multiple transient collapses on a daily basis. Seizure activity caused by cerebral hypoperfusion (termed *convulsive syncope*) is most likely to occur in the setting of bradyarrhythmias, as a result of prolonged periods of asystole. Convulsive syncope in patients with intermittent conduction disease is commonly mistaken for neurologic disease. Sick sinus syndrome (SSS) is most commonly associated with the miniature schnauzer but may occur in other breeds. By the time these dogs are syncopal, easily detected abnormalities exist in the rhythm during auscultation and a routine electrocardiogram (EKG). Multiple periods of asystole typically occur, sometimes oscillating with runs of supraventricular tachycardia. Dogs with third-degree heart block may be syncopal with the initiation of their disease, but in some the arrhythmia is an incidental finding. Many dogs with chronic third-degree heart block are not syncopal, presumably as a result of compensatory changes of the cardiovascular system (volume retention) and a stable escape rhythm. Sudden death is surprisingly rare in both SSS and third-degree heart block. Some dogs and cats are syncopal because of intermittent high-grade A-V block characterized by long periods of ventricular asystole. These animals may have extended periods of sinus rhythm, although signs of conduction disease (first-degree heart block, bundle branch block, and intermittent second-degree heart block) should raise one's suspicion of more severe intermittent heart block. It is also worth noting that the symptoms of asystole (opisthotonus, syncope, seizure) are delayed, usually occurring at the termination of the pause, once the rescue rhythm has resumed. Therefore a bradycardic arrhythmia should not be dismissed based on finding a relatively normal heart rate in a recently collapsed patient.

6.3 APPROACH TO THE SYNCOPAL PATIENT

The evaluation of a patient with syncope involves excluding other disorders of consciousness (e.g., presyncope, dizziness, vertigo, sleep disorders, seizure), then determining the cause for the syncopal episode. Causes for episodic weakness should be considered when collapse occurs without loss of consciousness. Dizziness and vertigo do not result in a loss of consciousness or postural tone. Narcolepsy and cataplexy are rare disorders in animals that may mimic syncope. These disorders are characterized by “sleep attacks” in the former and rapid onset and termination of partial to complete flaccid paralysis in the latter. These are heritable disorders in Doberman pinschers, Labrador retrievers, daschunds, and miniature poodles. Seizure is the primary differential for syncope. Distinguishing syncope from seizure can be difficult. Based on the classical features of each, the differentiation seems straightforward; however, in reality the boundaries can be indistinct (Table 6-1).

The generalized epileptic or motor seizure is the classic manifestation of a primary neurologic event; however, complex partial seizure activity is now recognized in veterinary medicine. The primary abnormality of the complex partial seizure is a decrease in consciousness. Motor activity may occur along with autonomic signs such as salivating, urinating, and defecating. In humans, *temporal lobe syncope* is the term used for complex partial seizure in which a loss of consciousness resembles a syncopal episode.

In approximately 40% of patients with syncope, the cause is undetermined. The cause of syncope is difficult to diagnose in many cases because of the transient and often infrequent nature of the events and the fact that syncope rarely occurs in settings where vital functions such as the heart rate, rhythm, and blood pressure can be monitored while symptoms are being displayed. From the foregoing discussion it should be clear that the cornerstone of evaluation of a syncopal patient is thorough history and physical examination. When carefully performed these will have a greater diagnostic yield (45%) than a battery of laboratory tests. This begins with a detailed history, for which veterinarians must rely on witnesses. Because of the distressing nature of these events, owners are often unable to provide an accurate account of the events. For example, their estimation of time is often exaggerated. The frantic struggling to rise after collapse may be interpreted as the tonic clonic limb motions characteristic of generalized seizure. The key questions that should be part of every history taking should extract information about the event (see Table 6-1), age at first episode, frequency of episodes, interepisode duration, symptoms of underlying disease, medications, relation to meals and administration of medications, and relation to exercise. Breed predisposition for cardiac disease or epileptic seizures can also be important.

Table • 6-1 General Features Differentiating Syncope versus Seizure

	SYNCOPE	SEIZURE
Precipitating event	Exertion, pain, micturition, defecation, cough, stressful event	
Prodrome	Seconds	Minutes to days
	Acute weakness, staggering, vocalization, autonomic stimulation	Atypical behavior (e.g., anxious, more withdrawn, attention seeking) (+/–) Vomit
Aura	None	None (epileptic seizure)
		Marks onset of partial seizure, often with secondary generation
Event characteristics	Opisthotonus	Chomping, hypersalivation
	Motionless	Tonic/clonic limb motion
	Flaccid or rigid extension of limbs	Motor activity
	Exception: convulsive syncope	*Exception:* complex partial seizure or akinetic or temporal lobe seizure
	Duration often transient (<1 minute)	Duration often 1 to 2 minutes (>5 minutes suggests seizure versus syncope)
Recovery	Rapid recovery of normal mentation	Slowness returning to consciousness
	Often able to walk within minutes	Disorientation (commonly 10 minutes or longer)*Exception:* recovery can be rapid
	Exception: neurally mediated syncope (NMS) may be a more prolonged recovery	

A thorough physical examination should then be performed. Because cardiac disorders are most likely to result in a risk of sudden death, it is important to search for any evidence of cardiovascular disease. A neurologic examination is also very important to look for evidence for underlying neurologic disease. Interepisode abnormalities may point to the causes for a subacute or chronically reduced cardiac output (e.g., cardiac tamponade, pulmonary thromboembolism), severe systemic disorders (e.g., hemorrhage, severe anemia), or neurologic disease (e.g., abnormal gait or mentation). Once cardiac disease and other malignant causes for syncope (e.g., pulmonary thromboembolism) are excluded, then more benign causes such as NMS and complex partial seizure must be considered. Thus even in the absence of a definitive diagnosis, an owner's mind can be put at ease in most cases.

7 CHAPTER • 7 Weakness

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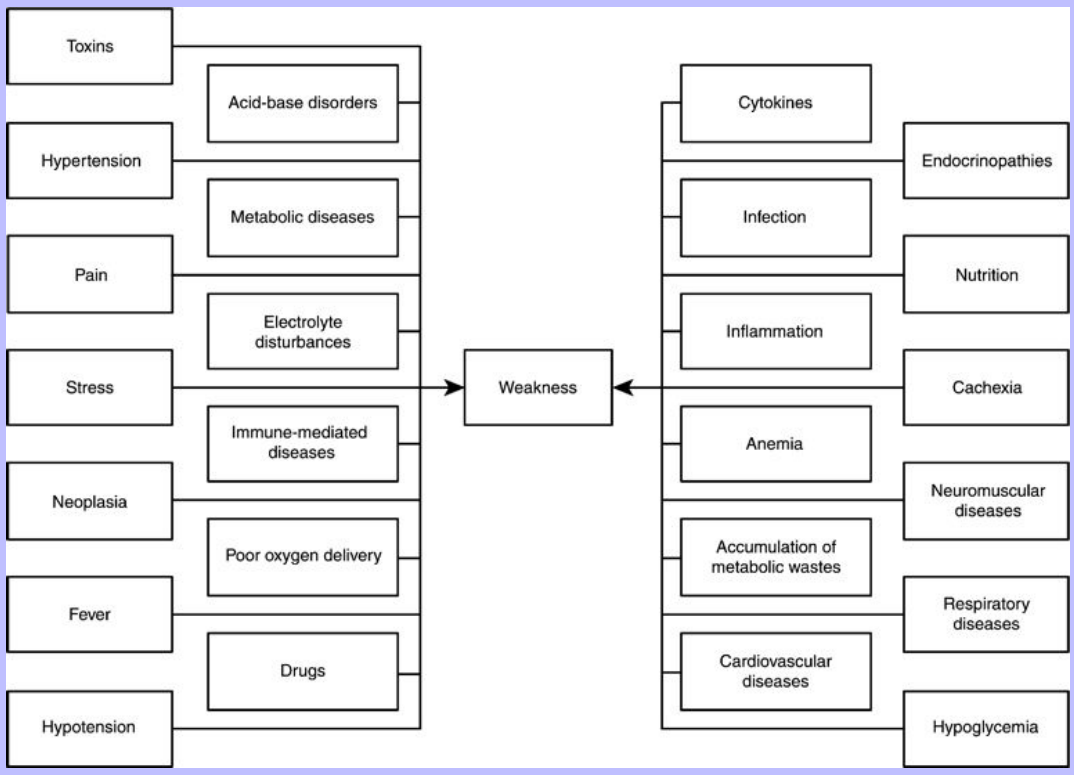
Weakness is a common presenting complaint in small animal medicine. In veterinary medicine, the terms *fatigue* and *lethargy* are often used synonymously with weakness. A multitude of diseases can result in weakness, often making this presenting complaint a diagnostic challenge (Figure 7-1).

The patient's history can provide many important clues as to the cause of the weakness. In addition to routine questions regarding time course, concurrent illness, medications, and familial history, the owners should be asked about any associations with either exercise or time of day. For example, patients with disorders of glucose homeostasis may typically display symptoms either after eating or fasting. Classically, myasthenic dogs exhibit profound weakness after short bursts of normal activity.

Figure 7-1 Causes of weakness.



The patient's signalment will assist in ordering the differential list. Purebred animals are susceptible to breed-specific conditions that can result in weakness. The age of the patient may be more in accordance with some differentials. Puppies and kittens will be more likely to suffer from congenital diseases, portosystemic shunts, hypoglycemia, toxin exposure, and infectious diseases, whereas geriatric patients may present secondary to neoplastic conditions or major organ dysfunction. Immune-mediated diseases are more prevalent in female dogs.

A thorough physical examination is mandatory. Pain on manipulation of joints or long bones may suggest an underlying orthopedic problem, manifesting as weakness. Dermatologic signs such as symmetrical alopecia might indicate an endocrine disorder. Primary cardiovascular disease may be apparent during examination of mucous membranes, capillary refill time, thoracic auscultation, and peripheral pulses. Because many neurologic disorders can also result in weakness, a complete neurologic examination is indicated in the weak patient.

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In some cases a specific finding during the initial physical examination and laboratory analysis results in a definitive diagnosis; unfortunately, many of the conditions resulting in weakness have nonspecific clinical signs and laboratory findings. As a result the initial diagnostic evaluation is used to prioritize differential diagnoses and identify additional diagnostic tests. This chapter discusses the different mechanisms and diseases that result in weakness.

7.1 SPECIFIC MECHANISMS AND DISEASES

7.1.1 Metabolic Diseases

Metabolic diseases are among the most common causes of weakness. Major organ dysfunction can result in weakness through many pathways, such as accumulation of metabolic products, cytokine production, electrolyte imbalances, acid-base disorders, anemia of chronic disease, and nutritional disturbances. Renal and hepatic failure are two examples of metabolic diseases that cause weakness by multiple mechanisms. Biochemical evaluation is essential in the diagnosis of metabolic disorders.

7.1.2 Electrolyte Disorders

Electrolyte imbalances accompany a multitude of conditions and are often the component of the disease that leads to the clinical sign of weakness. Mild changes in electrolyte levels rarely cause weakness. Significant hypokalemia may result from excessive loss (gastrointestinal, urinary) or be iatrogenic in nature (fluid diuresis, diuretics). Hyperkalemia, as is seen with hypoadrenocorticism and urinary tract obstruction or rupture, also results in weakness. Sodium imbalances, both increases and decreases, can result in weakness. Hyponatremia is seen in hypoadrenocorticism, congestive heart failure, liver diseases, and losses through the gastrointestinal system and third space. Hypernatremia may be seen with hyperaldosteronism, salt poisoning, and free-water loss. Perturbations in calcium homeostasis are an important cause of weakness. Hypocalcemia produces excessive excitability of the nervous system, manifested as tetany and possibly seizures. Between bouts of tetany, patients may exhibit weakness. Common causes of hypocalcemia include hypoparathyroidism, renal disease, ethylene glycol toxicity, and eclampsia. Hypomagnesemia may also result in weakness. Hypomagnesemia is prevalent in critically ill patients because of renal and gastrointestinal losses coupled with decreased intake.

7.1.3 Acid-Base Disorders

Disturbances in blood pH can accompany many metabolic conditions and can be seen with pulmonary disease. Drugs and toxins may also lead to acidosis or alkalosis. Weakness can be seen with either disorder.

7.1.4 Inflammatory Conditions

Inflammation accompanies many disease processes such as pancreatitis, hepatitis, neoplasia, infectious disease, and immune-mediated conditions. Systemic inflammation can result in pyrexia, negative energy balance, cytokine production, anemia, and acid-base disorders, all exacerbating signs of weakness. Many of these changes

are mediated by increased cytokine production in response to the inflammatory stimuli. Certain cytokines, such as interleukin (IL)-1, IL-6, and interferon (IFN)-α, directly cause fatigue via central pathways. Cachexins, such as IL-1, IL-6, IFN-γ, and tumor necrosis factor (TNF)-α suppress hunger and promote muscle wasting. Cytokine inhibition of erythropoiesis, resulting in anemia, indirectly contributes to weakness.

7.1.4.1 Infectious Diseases

Bacterial, viral, fungal, rickettsial, protozoal, or parasitic agents can infect any organ or body system. The presenting signs typically indicate the involved organ, such as coughing with respiratory disease or dysuria with prostatitis, as well as nonspecific signs of infection, such as weakness and inappetance. The infecting agent may produce toxins that cause weakness in addition to this being related to the resultant inflammation and organ dysfunction secondary to the infection.

7.1.4.2 Immune-Mediated Diseases

Generalized weakness or exercise intolerance is a common component of many immune-mediated disorders. Immune-mediated diseases may lead to anemia, joint or muscle disease with resultant pain, hepatic or renal dysfunction, and inflammation and chronic wasting. Through any or all of these mechanisms, patients suffering from a variety of immune-mediated diseases will display weakness.

7.1.5 Anemia

Anemia, with the resultant decrease in oxygen delivery to the tissues, can cause weakness. The presence of weakness or exercise intolerance does not specify the pathophysiologic mechanism resulting in the anemic state. Often more severe signs will be seen with acute blood loss than will be noted with more chronic cases, even if the magnitude of the anemia is greater in the chronic case. With chronic diseases, the patient has more time to adapt to the anemia, and clinical signs may be subtle.

7.1.6 Endocrine Diseases

Weakness can be seen with almost every endocrine disease including diabetes mellitus, hypothyroidism, hypoadrenocorticism, hyperadrenocorticism, hypoglycemia, hyperparathyroidism, hypoparathyroidism, and pheochromocytoma. Hyperthyroidism uncommonly manifests as weakness. Until a severe crisis occurs, owners and veterinarians miss early, nonspecific episodes of weakness caused by hypoadrenocorticism. Endocrine disturbances can result in weakness via various mechanisms. Many endocrinopathies, such as hypoadrenocorticism, hypo-and hyperparathyroidism, and diabetes mellitus can produce weakness as the result of electrolyte abnormalities. Neuropathies and myopathies may be seen with diabetes mellitus and hypoglycemia, as well as hyperadrenocorticism and hypothyroidism.

7.1.7 Cardiovascular Disease

The physical examination will often be strongly suggestive of cardiovascular disease if the dysfunction is of sufficient severity to induce exercise intolerance. Heart murmurs will frequently be ausculted in these patients. Crackles may be heard if the patient is suffering from left heart failure. Right heart failure can produce a variety of abnormalities that may be detected on physical exam, including jugular pulses, ascites, and decreased heart and lung sounds secondary to pleural effusion. Often, the biggest diagnostic challenge is establishing that a heart murmur does not signify heart disease of a nature sufficient to induce exercise intolerance. Cardiovascular

disease results in the clinical sign of weakness caused by poor cardiac output leading to diminished oxygen delivery to the tissues or by cardiac cachexia. Valvular disease tends to cause exercise intolerance only when it has progressed to congestive failure. Because of the associated septicemia, bacterial endocarditis usually results in extreme lethargy. Arrhythmias may manifest as intermittent weakness. Diseases resulting in pericardial effusion often produce profound weakness and potentially sudden collapse.

7.1.8 Blood Pressure

Alterations in blood pressure can produce weakness, often episodically. Hypotension can result from cardiac dysfunction, hypovolemia, or decreased vascular tone. Hypotension creates poor perfusion and oxygen delivery. Systemic hypertension damages many organs, including the heart, brain, kidneys, and eyes. Systemic hypertension is usually a secondary problem in veterinary patients, with underlying diseases including heart disease, renal disease, hyperthyroidism, hyperadrenocorticism, and diabetes mellitus. Caution must be exercised when treating hypertension to not create hypotension.

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7.1.9 Respiratory Diseases

Similar to heart disease, respiratory disease may be obvious during the initial physical examination. Historical complaints frequently include coughing, alterations in respiration, or nasal discharge. Changes in lung sounds and respiratory rate or effort will be detected when examining the patient. Respiratory diseases that result in exercise intolerance are commonly infectious or inflammatory in nature. Thoracic radiographs, arterial blood gases, and bronchoalveolar lavage or tracheal wash are often necessary diagnostics. Pulmonary hypertension can also lead to weakness. Pulmonary hypertension may occur secondary to heartworm disease or chronic pulmonary disease and carries a guarded prognosis.

7.1.10 Neuromuscular Diseases

7.1.10.1 Brain

Any disorder affecting the brain can cause weakness. The neurologic exam will localize the problem as being central in origin. Encephalitis caused by infectious agents, inflammatory conditions, or immune-mediated disease; cerebral vascular accidents (embolism or hemorrhage); space-occupying lesions (neoplasia, granulomas, or hydrocephalus); vestibular disease (central or peripheral); and idiopathic epilepsy can present as chronic or intermittent weakness. Additionally, many medications act on the central nervous system (CNS) result in lethargy or exercise intolerance. The minimum data base may help further define the cause. Often more advanced diagnostics such as imaging of the brain or analysis of the cerebrospinal fluid (CSF) will be necessary to fully diagnose the underlying condition.

7.1.10.2 Spinal Cord Disease

Lesions affecting the spinal cord between C1 to T2 can result in quadriparesis. More caudal lesions may cause paraparesis. Causes of spinal cord disease include trauma, degenerative disc disease, vascular accidents, neoplasia, infectious diseases, and inflammatory conditions. Chronic, progressive conditions are more likely to result in the vague presentation of weakness compared with the more recognizable problem of acute paraparesis. In addition to the minimum data base, imaging and CSF analysis may be required to determine the underlying cause of spinal cord disease.

7.1.10.3 Neuropathies

Disorders affecting peripheral nerves can result in generalized weakness. The neurologic examination of these patients will typically reflect lower motor neuron dysfunction with reduced or absent reflexes. Causes of polyneuropathy include polyradiculoneuritis; paraneoplastic disorders; endocrine diseases including diabetes mellitus, hyperadrenocorticism, and hypothyroidism; drugs and toxins (vincristine, lead); infectious agents *(Toxoplasma*, *Neospora)*; and developmental disorders. Weakness may also result from disruption of neuromuscular transmission. Myasthenia gravis can be either acquired or congenital. Severe exercise intolerance is often a hallmark of this disorder. Other neuromuscular disorders include tick paralysis and botulism. Specialized testing such as electromyography, nerve and muscle biopsy, and serology for antibodies to the acetylcholine receptor are often necessary to establish the diagnosis.

7.1.11 Neoplasia

Neoplasia can lead to weakness through many different pathways. Associated inflammation will result in the release of a variety of cytokines that can cause fatigue, cachexia, and anemia. Tumors may specifically release substances such as insulin, corticosteroids, thyroid and parathyroid hormones, catecholamines, and estrogen that cause or exacerbate weakness. Some tumors such as hemangiosarcoma can cause severe, acute blood loss. Cancers can also result in anemia via disseminated intravascular coagulopathy (DIC). Neoplastic invasion or embolization can instigate organ failure. Finally, cancer can produce weakness in patients from pain.

7.1.12 Physical and Psychologic Stress

Stress is the major cause of fatigue in humans. Psychologic causes of lethargy are much harder to evaluate in veterinary patients but should not be completely discounted. Events that can cause clinically significant anxiety (thunderstorms, fireworks, boarding) or chronic stress (social status, deprivation, illness, pain) may result in generalized weakness. Stress of any nature can activate the hypothalamic-pituitary-adrenal axis, with resultant increased levels of corticotropin-releasing hormone (CRH) and cortisol. Hyperactivity of this axis can lead to depression and weakness. CRH may play a specific role in the development of fatigue. It has also been suggested that primary hypothalamic dysfunction may be important in the cause of generalized weakness.

Exercise intolerance may be seen in an animal pushed beyond its physical capabilities. This can occur both in animals that are not used to exercise and in fit animals that overexert themselves during activities such as hunting and racing.

7.1.13 Nutritional Derangements

Nutritional derangements may be the patient's primary problem or may be a reflection of chronic disease. Changes or reduction in protein synthesis, altered glucose homeostasis, or dyslipoproteinemias may all result in weakness. Specific vitamin and mineral deficiencies may also cause weakness. Nutritional disorders may arise from an inadequate diet, either in content or calories. The patient may not be able to use or synthesize nutrients appropriately or may lose them excessively. Liver, pancreatic, kidney, and gastrointestinal disease may all cause weakness via nutritional deficits. Lipid disorders can arise from endocrinopathies such as diabetes mellitus, hypothyroidism, and hyperadrenocorticism; renal disease; liver disease; pancreatitis; diet; or familial causes. Any chronic condition can lead to cachexia. The clinical signs of cachexia are anorexia, weight loss, and muscle

wasting. Cachectic patients suffer from a negative energy balance and metabolic derangements. These changes are often mediated by the same cytokines that cause fatigue.

7.1.14 Drugs

A complete history is essential for the patient with lethargy or weakness. Many medications including anticonvulsants, antihistamines, glucocorticoids, tranquilizers, narcotics, antibiotics, chemotherapeutics, diuretics, and cardiovascular agents can result in side effects, including weakness. If the onset of exercise intolerance coincides with the administration of a new medication, it may be prudent to discontinue that medication or lower the dose.

7.1.15 Pain

Patients may appear exercise intolerant if they are in extreme pain. Animals with spinal, bone, or joint pain are often quite reluctant to move. The physical examination should elucidate musculoskeletal or neurologic pain. Abdominal pain can result from distention, inflammation, or ischemia of organs. These patients may display a hunched appearance and resent abdominal palpation. Visceral pain is less localized and may be harder to pinpoint.

8 CHAPTER • 8 Skin and Subcutaneous: The Skin as a Sensor of Internal Medical Disorders

Sandra R. Merchant

Cutaneous manifestations of internal disease are uncommon. As expertise is strengthened in the field of veterinary dermatology, clinicians continue to discover subtle clues of the skin that alert them to further investigate internal organ systems. In certain diseases the skin may provide the first clinical signs noted. In some conditions, cutaneous and systemic signs occur simultaneously, whereas in others, the skin may reflect a general catabolic and cachectic stage brought about by the primary disease process.

8.1 FUNGAL DISEASES

Deep mycoses are fungal infections of internal organs that can spread hematogenously to the skin. Primary inoculation of the skin is rare. Infections that can cause nodules, plaques, and draining tracts include *Blastomyces dermatitidis, Histoplasma capsulatum, Cryptococcus neoformans,* and *Coccidiodes immitis*. Because of the accessibility of the skin, nodules and draining tracts of the skin can be easily biopsied for culture and histopathology to aid in diagnosis and choice of therapy for treatment of systemic mycotic diseases.

Pithium insidiosum, an aquatic oomycete, primarily affects the gastrointestinal tract but can also cause an ulcerative, draining dermatitis of the skin. With *Pithium*, each organ system is inoculated separately by contact with fresh water containing the infective zoospores.

Lagenidium spp. is a recently recognized oomycete pathogen also causing cutaneous or subcutaneous nodules or ulcerated, thickened edematous draining lesions. In contrast to *Pithium*, most dogs with lagenidiosis have lesions in sites other than the gastrointestinal tract.

8.2 VIRAL DISEASES

Canine distemper can cause hyperkeratosis of the nasal planum and foot pad, “hard pad disease.” Young puppies may develop widespread impetigo.

Feline rhinotracheitis is an infection with an alpha herpes virus. Occasionally, cats will develop oral and cutaneous ulcers that are usually multiple and can occur anywhere on the body. An ulcerative and necrotizing facial dermatitis has been recognized in cats that involves the periocular skin, nasal planum, and bridge of the nose. Exfoliative erythema multiforme has been seen after upper respiratory infections in the cat, and ulceration of the foot pads and perineal skin has been seen with cats infected with *Calicivirus.*

Feline leukemia virus (FeLV) most commonly affects the skin by its cytosuppressive actions. Clinical signs include chronic or recurrent gingivitis or pyoderma, seborrhea, exfoliative dermatitis, pruritus, and cutaneous horns. A facially distributed pruritic crusting dermatosis has been seen secondary to FeLV infection.

Feline immunodeficiency virus (FIV)–infected cats may have chronic or recurrent abscesses, chronic bacterial infection of the skin and ears; and increased incidence of fungal, ringworm, and *Demodex* infections. Generalized papules with crusts, alopecia, and scaling more severely affecting the head and limbs have been associated with FIV-positive cats.

8.3 BACTERIAL DISEASES

Lyme disease is a tickborne disorder of dogs caused by the spirochete *Borrelia burgdorferi*. Arthritis and fever are prominent signs. An expanding annular lesion called *erythema chronicum migrans* can characterize early disease in humans. This clinical sign has been documented in affected dogs in Europe.

Dogs infected with *Rickettsia rickettsii* may have erythema, petechia, edema, and occasional necrosis of the oral, ocular, and genital mucous membranes, as well as the skin of the pinna, nose, ventrum, and scrotum.

Dogs infected with *Ehrlichia* spp., may have crusting of the nasal bridge, pustular and purpuric lesions secondary to vasculitis, and an intensely pruritic papular and crusting dermatitis.

8.4 IMMUNE-MEDIATED DISEASES

Erythema multiforme usually has an acute onset of erythematous macules and papules that spread peripherally and clear centrally. The lesions are most commonly seen at the mucocutaneous junctions, nasal mucosa, pinnae, axilla, and inguinal regions. Erythema multiforme can be associated with infectious diseases and neoplasia and less likely as a manifestation of a drug eruption.

Toxic epidermal necrolysis (TEN) is an acute condition believed to be caused by a lymphocyte-and macrophage-mediated mechanism of immunologic injury. Drugs are the most common known inciting cause, but neoplasia and infection have also been documented. The first signs of TEN are widespread erythema of the skin that may be painful on palpation. Rapid and widespread full-thickness necrosis of the epidermis occurs. The most common areas affected are oral mucosa, footpad, face, and skin of the trunk.

Systemic lupus erythematosus (SLE) produces skin lesions that can be highly variable. They may be nonspecific cutaneous lesions or take the form of cutaneous lupus erythematosus lesions that are specific skin syndromes characterized by certain clinical and histopathologic findings. Cutaneous manifestations of SLE include seborrheic disease, alopecia, diffuse or regional erythema, cutaneous or mucocutaneous vesicles and bullae, footpad ulcers and hyperkeratosis, panniculitis, refractory secondary bacterial infection, and nasal dermatitis. Skin lesions commonly affect nonhaired areas. 31 32

Vasculitis is most commonly believed to be immunologically mediated and the result of a drug reaction. It may be initiated by a hypersensitivity reaction, food allergy, insect sting or arthropod bite reaction, canine mast cell tumor, feline collagenolytic granuloma, rabies vaccine reaction and dermatomyositis in the dog, coexisting disease (e.g., infections, malignancies, lupus), precipitating factors (e.g., drugs, vaccines), or idiopathic in origin. Cutaneous lesions include poorly healing ulcers typically located in the center of the footpads, erosions, ulcerations, and crusting that either affect the pinnal margin or form a linear lesion extending down the center of the concave aspect of the pinna. Some animals experience an urticarial form of vasculitis.

Hemolytic uremia syndrome, a cutaneous and renal glomerular vasculopathy has been described in greyhounds. Greyhounds can have this syndrome (with skin disease alone), systemic signs coincident with typical skin lesions, cutaneous disease before systemic signs, or manifestations of azotemia before cutaneous ulcerations. Cutaneous signs include multiple palpable purpura primarily on the limbs varying from pinpoint to 10 cm in diameter that subsequently ulcerate and discharge a serosanguineous fluid. The ulceration may extend into the subcutaneous tissues.

This syndrome is presumed to be a vasculopathy secondary to a verotoxin elaborated by *E. coli* obtained from eating raw beef products. A genetic predisposition or a propensity for feeding raw beef products to greyhounds may explain the breed susceptibility.

Dermatomyositis is a familial, idiopathic (vascular?) condition of the skin and muscle of collies and Shetland sheepdogs and has been recognized in other breeds of dogs. Skin lesions occur in areas of mechanical trauma and are commonly seen on the face, especially around the eyes, on the tips of the ears, on carpal and tarsal regions, on the digits, and on the tip of the tail. Early lesions include pustules, vesicles, papules, or small nodules progressing to crusting or alopecia. Ulceration can be seen in severely affected dogs. Many of these dogs are left scarred.

8.5 NEOPLASIA

Nodular dermatofibrosis is a disease seen primarily in German shepherd dogs but has also been reported in golden retrievers, boxers, German shepherd crosses, and mix-breed dogs. Clinical signs include numerous firm dermal to subcutaneous nodules that vary in size from a few millimeters up to 5 cm that can coalesce. The epidermis overlying the nodules may be intact but can sometimes be ulcerated and inflamed. Alopecia and hyperpigmentation can be seen over the nodules.

Systemic disease seen in association with these multiple skin tumors include renal lesions varying from polycystic kidneys to cystadenomas to cystadenocarcinomas and uterine leiomyomas in intact females. Most kidney involvement is bilateral. Many dogs have multiple small intestinal polyps that are asymptomatic.

8.5.1 Testicular Tumors

Dermatologic manifestations of testicular tumors are uncommon. Dermatologic manifestation occurs most commonly in the male feminization syndrome associated with Sertoli cell tumors. Dogs with male feminization display dermatologic signs of bilaterally symmetric alopecia that is nonpruritic, usually beginning in the perineal and genital regions and spreading to the ventral abdomen, thorax, flank, and neck. In some cases, the alopecia is restricted to the flanks. Other dermatologic manifestations of testicular tumors include seborrhea, ceruminous otitis externa, macular melanosis of the inguinal and perianal skin, and a linear erythematous or melanotic macular change that is present along the ventral aspect of the prepuce extending to the scrotum. Occasionally a dog will have a papular, pruritic eruption.

8.5.2 Pheochromocytoma

Pheochromocytomas are endocrine tumors arising from the adrenal medulla. The clinical signs associated with pheochromocytomas are quite variable and often subtle. Episodic panting or dyspnea and increased bronchovesicular sounds, weight loss, anorexia, depression, weakness, and collapse are some of the systemic abnormalities noted. The dermatologic manifestation is intermittent flushing, especially of the pinna.

8.5.3 Paraneoplastic Syndromes

Paraneoplastic syndromes consist of clinical signs that are associated with malignancies but not directly related to tumor invasion. In the dog these paraneoplastic syndromes include the crusting and fissuring dermatosis associated with necrolytic migratory erythema, nodular skin disease seen with nodular dermatofibrosis, paraneoplastic pemphigus vulgaris associated with a thymic lymphoma, suspect paraneoplastic pemphigus foliaceus from a Sertoli cell tumor or mammary carcinoma, and necrotizing panniculitis associated with

pancreatic carcinoma or severe pancreatitis. In the cat these paraneoplastic dermatoses include the skin fragility syndrome seen with feline hyperadrenocorticism; exfoliative dermatosis associated with feline thymoma; and a unique bilaterally symmetrical, ventral glistening paraneoplastic alopecia associated with pancreatic carcinoma, bile duct carcinoma, and thymoma.

Paraneoplastic pruritus has been seen associated with lymphosarcoma in the dog, squamous cell carcinoma in a cat, and liver disease or cholangiohepatitis in the cat.

8.6 ENDOCRINOPATHIES

8.6.1 Hypothyroidism

Dermatologic manifestations of hypothyroidism consist of a dry scaly coat, bilaterally symmetrical nonpruritic truncal alopecia, rat tail, variable degrees of hyperpigmentation seen on the ventral neck, abdomen, or in a diffuse truncal distribution; lichenification; myxedema; vesicular mucinosis; haircoat color change; comedones; hypertrichosis; seborrhea oleosa; seborrhea sicca; seborrheic dermatitis; and *Malassezia* dermatitis. Pruritus may be seen with the occurrence of secondary dermatologic diseases of seborrhea, *Malassezia* dermatitis, and staphylococcal pyoderma. Many dogs (with the exception of working and breeding dogs) may be examined when dermatologic abnormalities become evident.

8.6.2 Hyperadrenocorticism

Hyperadrenocorticism or *Cushing's syndrome* refers to the constellation of clinical and chemical abnormalities resulting from chronic exposure to excess glucocorticoids. Dermatologic abnormalities may be quite striking. Classic changes include hair loss that is usually bilaterally symmetrical, but focal hair loss may also be seen. Comedones, especially on the ventral abdomen and thin, inelastic skin, are also usually seen. Other changes include hyperpigmentation, seborrhea sicca, telangiectasia, increased prominence of surgical scars, lack of hair regrowth after shaving, and adult-onset generalized demodicosis. One dramatic manifestation seen in 5% of dogs is calcinosis cutis. Adult dogs that have never had bacterial skin disease may show a marked predisposition to recurrent staphylococcal skin infections.

8.6.3 Hyperthyroidism

The most common endocrine disorder of middle-aged to old cats is hyperthyroidism. Many of these cats have an unkempt haircoat, with excessive shedding and matting of the hair. Changes in hair texture, partial hair loss, and increased nail growth also are features of feline hyperthyroidism. In cats with areas of complete alopecia, behavioral changes associated with excessive grooming have been documented.

8.6.4 Diabetes Mellitus

Cutaneous lesions associated with diabetes mellitus are uncommon. The most common dermatologic manifestations are otitis externa, pyoderma, seborrheic skin disease, demodicosis, thin skin, alopecia, and xanthomatosis.

8.7 PARASITIC DISEASES

Leishmaniasis is a protozoal infection caused by a variety of *Leishmania* spp. endemic in many areas of the world, including the United States. It has been reported in foxhound kennels in 20 states in the United States. Skin lesions occur in over 80% of the dogs with visceral involvement. The most common sign is an exfoliative dermatitis primarily on the head, pinnae, and extremities. Nasodigital hyperkeratosis can been seen. Periocular alopecia is also common. An ulcerative dermatitis, onychogryposis, paronychia, sterile pustular dermatitis, nasal depigmentation with erosion, ulceration, and nodular dermatitis may be seen.

Demodicosis of the dog is most often caused by *Demodex canis*. Demodectic mange of the cat is caused by *Demodex cati* and *Demodex gatoi*. Adult-onset canine generalized demodicosis is most likely caused by suppression of the immune system. Several factors have been suggested or documented as initiating canine generalized demodicosis, including administration of immunosuppressive drugs, serious systemic disease to include hyperadrenocorticism, hypothyroidism, diabetes mellitus, blastomycosis and other deep mycoses, lymphosarcoma, hemangiosarcoma, and mammary adenocarcinoma. In addition, estrus, whelping, heartworm disease, and intestinal parasite infestation have all been associated with the onset of generalized demodicosis.

Because most cases of demodectic mange in the cat have occurred in the adult, immunosuppression as a result of an underlying disease has been proposed as the initiating factor. Generalized demodicosis has been seen in cats with diabetes mellitus, respiratory infection, FeLV infection, SLE, toxoplasmosis, feline endocrine alopecia, FIV infection, hyperadrenocorticism, feline infections peritonitis (FIP), and neoplasia. Immunosuppressive drugs (glucocorticoids and progestational compounds) should also be considered potential initiating factors.

Generalized patchy or diffuse alopecia with erythema, scaling, crusting, and follicular plugging may be seen in the dog. Some animals will have prominent hyperpigmentation in affected areas. In some cases the *Demodex* infection is confined to the feet only.

In the cat, signs of generalized demodicosis secondary to *Demodex cati* include multifocal to generalized patches of alopecia with variable scaling, macules, papules, erythema, hyperpigmentation, crusting, and symmetrical alopecia of the head, neck, legs, and trunk. Pruritus, when present, is either intermittent or mild. Clinical signs associated with *Demodex gatoi* include more severe pruritus, mild erythema, broken hairs, and alopecia of the hind limbs, flank, and ventral abdomen.

8.8 NUTRITIONAL DISEASE

Pansteatitis is caused by a deficiency of vitamin E. It has been reported in cats, usually eating diets containing red fish or excess cod liver oil. Affected cats are usually depressed, febrile, anorectic, and sore or painful on palpation of the skin or abdomen. Subcutaneous and abdominal fat may feel firm or lumpy. Draining tracts may be present.

8.9 NECROLYTIC MIGRATORY ERYTHEMA

Necrolytic migratory erythema (diabetic dermatopathy, hepatocutaneous syndrome, superficial necrolytic dermatitis, metabolic necrolytic dermatopathy, metabolic epidermal necrosis) has been seen in older dogs with glucagon-producing pancreatic endocrine tumor, Cushing's disease, hyperglucagonemia from a glucagon-secreting liver metastasis (primary tumor not found), hepatopathy secondary to ingestion of mycotoxins, hepatopathy secondary to phenobarbital or phenytoin administration, and hepatopathy of unknown origin. The disease has also been reported in the cat.

In the dog, necrolytic migratory erythema is an ulcerative dermatosis, displaying, erythema, crusts, and alopecia. It occurs most frequently periorally, periocularly, on the legs, feet, and external genitalia, and often in the groin region. The foot pads are usually hyperkeratotic and may be fissured and ulcerated. Cutaneous signs may precede evidence of internal disease by weeks or months.

9 CHAPTER • 9 Alopecia

Dominique Heripret

A*lopecia* is defined as a loss of hair, varying from partial to complete. Alopecia can be focal or generalized, diffuse or complete. The causes of alopecia are numerous. However, the major cause of alopecia in the dog, and especially in the cat, is self-trauma associated with pruritus. The hair is damaged from licking and scratching or may be easily removed because of inflammation within the hair follicle, such as in pyoderma and demodicosis. Noninflammatory alopecias are also frequent in dogs (e.g., endocrine alopecia, alopecia X) but are rare in cats.

The diagnostic approach to alopecia should be methodical and involve certain fundamental steps; history and clinical examination should allow formation of a differential diagnosis leading to appropriate diagnostic procedures.

9.1 HISTORY

1. Breed: Congenital hypotrichosis (Burmese, Devon rex, miniature poodles, American cocker spaniel, and other breeds); color mutant alopecia (Doberman pinschers, dachshunds, whippets, Chihuahuas, and other breeds); dermatophytosis (Persian cats, Yorkshire terriers); hyperadrenocorticism (Poodles, Boston terriers, dachshunds, and other breeds); alopecia X (Nordic breeds, poodles, and other breeds); sebaceous adenitis (Akita, Vizla, poodles, Samoyeds, and other breeds).

2. Age of onset of signs: Young animal (congenital or hereditary problems, demodicosis, pyoderma), older animals (neoplasia, endocrinopathy, internal disease).

3. Life-style: Outdoor cats and dogs more likely to have parasitic or fungal dermatoses.

4. Transmission to “in-contact” animals or owners: Dermatophytosis, parasitic dermatoses.

5. General symptoms: Polyuria-polydipsia, asthenia.

6. Initial distribution and aspect of the dermatoses.

7. Pruritus present at the beginning or not: If pruritus began after alopecia, one must carefully look for secondary infections.

8. Evolution: Slow progression of alopecia more indicative of a systemic problem (endocrinopathy); seasonality more indicative of recurrent flank alopecia or flea allergy dermatitis (FAD).

9. Previous treatments: Mainly steroids and megestrol acetate (iatrogenic Cushing's disease, interference with thyroid measurements) and their efficacy.

10. General examination: Pendulous abdomen and hepatomegaly (hyperadrenocorticism), enlarged lymph nodes (Leishmaniasis), abnormal testis, feminization of male dogs.

11. Dermatologic examination: Localized or generalized alopecia that is symmetrical (or not), only on the trunk (or not), aspect of hair shafts (broken or not), epilation, follicular casts (demodicosis, sebaceous adenitis), primary or secondary lesions (papules, pustules, scaling, crusts), skin thickness.

9.2 DIFFERENTIAL DIAGNOSIS

The list of differential diagnoses should be organized so that the most likely diagnoses comprise the top two or three differentials (Tables 9-1 and 9-2).

9.3 DIAGNOSTIC PROCEDURES

In practice the approach should include consideration of costs and owner's willingness to perform diagnostic tests. Diagnostic procedures (or therapeutic recommendations) will be determined from the differential diagnosis list.

1. Routine examinations: Microscopic examination of skin scrapings, direct examination of hair shafts (trichogram), Wood lamp examination (+/− fungal culture), cytologic evaluation of impression smears.

2. Second-intention examinations: Skin biopsies, hematology, biochemistry (FeLV, FIV for cats), endocrine measurements, ultrasonography.

See Figures 9-1 and 9-2.

9.4 OUTCOME

The prognosis of complete return of the haircoat to the normal state is dependent on the presence or lack of hair follicles. In some cases if alopecia is present without abnormal systemic condition (e.g., color dilution alopecia, alopecia X), it is important for the veterinarian to explain to the owner that lack of hair is only a cosmetic problem, and that it may be harmful to prescribe drugs (i.e., hormones) to try to have a normal haircoat.

Table • 9-1 Main Causes of Alopecia in the Dog, Classified as Noninflammatory versus Inflammatory Alopecia

NONINFLAMMATORY ALOPECIA
Congenital/Hereditary Alopecia
Ectodermal dysplasia
Follicular dysplasia
— *Tricorrhexis nodosa*
— Pili torti
— Color mutant alopecia
— Black hair follicular dysplasia
Acquired Alopecia
— Telogen effluvium
— Endocrine alopecia
— Hyperadrenocorticism
— Iatrogenic Cushing's syndrome
— Hypothyroidism
— Sexual imbalance
— Alopecia X
— Recurrent flank alopecia
— Anagen effluvium
— Metabolic imbalance (prot, FA*)
Infectious Alopecia
— Dermatophytosis
— Demodicosis
— Bacterial folliculitis
— Viral infection
— Leishmaniasis
Traumatic Alopecia

	— Hypersensitivity — Pruritic parasitic dermatoses — Scares Traction alopecia **Noninfectious/Immune-Mediated Alopecia** — Sebaceous adenitis — Superficial pemphigus — Alopecia areata — Erythema multiforme — Lupus — Epitheliotropic lymphoma **Atrophic Alopecia** — Dermatomyositis — Cutaneous vasculitis — Postrabies vaccination alopecia

* *FA,* Fatty acids

Table • 9-2 Main Causes of Alopecia in the Cat, Classified as Noninflammatory versus Inflammatory Alopecia

NONINFLAMMATORY ALOPECIA
Congenital/Hereditary Alopecia
— Alopecia universalis (sphinx)
— Congenital hypotrichosis
— Hair shaft dysplasia (Abyssinian)
— Follicular dysplasia (Cornish rex)
— Pili torti
Acquired Alopecia
— Paraneoplastic alopecia
— Hyperadrenocorticism
— Iatrogenic Cushing's—Pruritic parasitic dermatoses syndrome
— Hypothyroidism (rare)
— Hyperthyroidism
— Effluvium
Infectious Alopecia
— Dermatophytosis
— Demodicosis
— Viral infection (FIP*, poxvirus)
Traumatic Alopecia
— Self-induced alopecia
— Anxiety
— Allergy (FAD †)
— Dermatophytosis
— Hypersensitivities
— Scares
Noninfectious Alopecia
— Lymphocytic mural folliculitis

— Paraneoplastic exfoliative derm.

— Pseudopelade

— Epitheliotropic lymphoma

* *FIP,* Feline infectious peritonitis.

† *FAD,* Flea allergy dermatitis.

Figure 9-1 Diagnostic approach to alopecia in the dog. (Adapted from Alhaidari Z: *Prof Med Chir Anim Comp* 26(4): 290–300, 1991.)

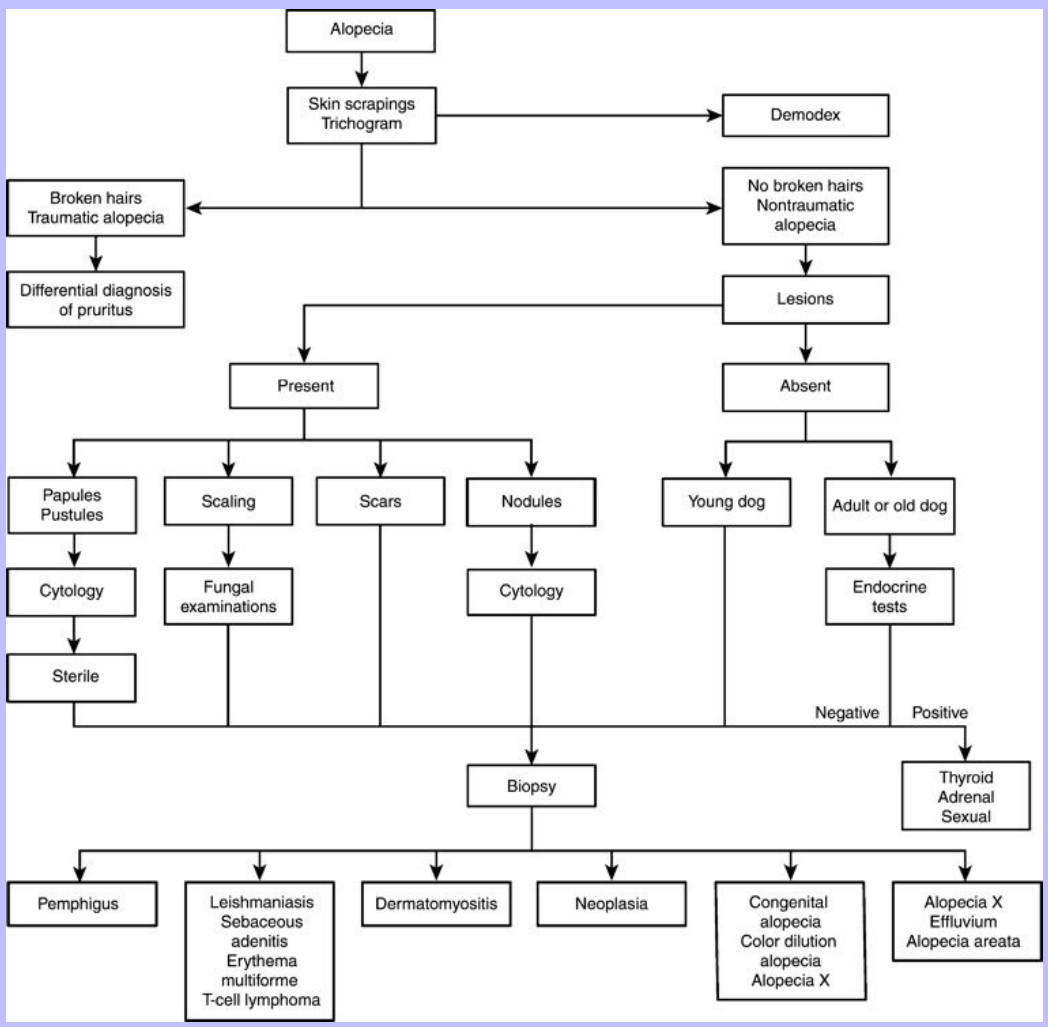
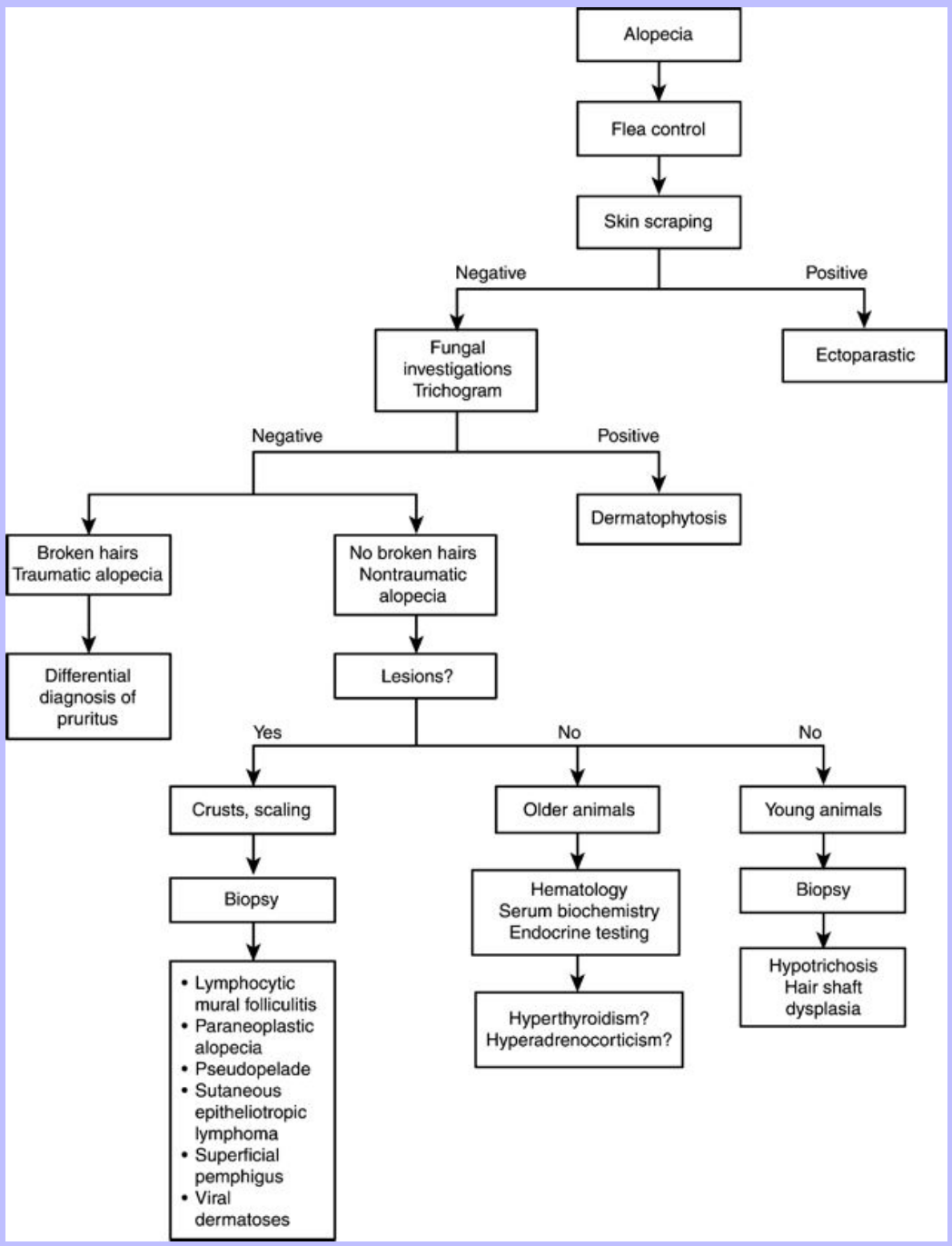


Figure 9-2 Diagnostic approach to feline alopecia. (Adapted from Alhaidari Z: In Guaguere E, Prelaud V, eds: *Feline dermatology*, 2000.)



10 CHAPTER • 10 Pruritus

Peter J. Ihrke

Pruritus can be defined as the sensation that elicits the desire to scratch, chew, or initiate other self-trauma. Pruritus is assumed to occur in animals that have self-trauma or erythema, excoriations, alopecia, lichenification, or hyperpigmentation that results from inflammation and self-mutilation. Licking, chewing, rubbing, hair removal, irritability, and even personality change (lack of tolerance, aggressive behavior) can result from pruritus; it is the most common clinical manifestation of disease that causes owners to bring their pets in for treatment. Because skin changes from self-trauma of any cause are similar clinically, pruritic skin diseases often are diagnostically challenging and frustrating.

10.1 PATHOPHYSIOLOGY

The skin functions as an "external nervous system," providing continuous sensory input to the central nervous system (CNS) through a finely arborized network of free nerve endings responsible for transmitting the sensations of touch, temperature, pain, and pruritus. In humans, "sensory spots" or "itch points" coincide with areas of increased density of free nerve endings. This may be true of domestic animals as well because the face, distal extremities, and groin are common sites of self-trauma in many species. The sensations of pruritus and pain are carried centrally by nonmyelinated slow conducting C fibers and, to a lesser extent, along myelinated A delta fibers. Myelinated ganglion cell axons carry the message of itch from free nerve endings to neurons located in the posterior horn of the spinal cord. Axons of second-order neurons transmit the message across the midline to the lateral spinothalamic tract and upward to the thalamus. Thalamic neurons then carry the signal to the postcentral gyrus of the cerebral cortex, where the message is interpreted as the sensation of pruritus.

Pruritus commonly stimulates self-trauma. The mechanisms by which self-trauma relieves itching are unclear. Self-trauma may disturb the amplified, reverberating spinal pathways that perpetuate the sensation of itch. More severe self-trauma probably substitutes pain for pruritus. Severe self-trauma characterized by deep excoriations is more common in cats than in dogs.

Diffusible chemical mediators induce the sensation of itch. Implicated endogenous mediators include histamine, peptides (endopeptidases, bradykinin, substance P, vasoactive intestinal peptide, neurotensin, secretin, enkephalins, endorphins), proteases (trypsin, chymotrypsin, mast cell chymase, fibrinolysin, kallikrein, cathepsins, plasmin), prostaglandins, leukotrienes (especially LTB_4), monohydroxy fatty acids, and opioid peptides. Proteolytic enzymes are thought to be the most important mediators of pruritus in dogs, cats, and humans. Leukotrienes also play an important role. The hypothesized magnitude of the role of histamine has diminished as the importance of other mediators is recognized. Bacterial and fungal endopeptidases also can initiate pruritus. Chemical mediators present in arthropod saliva, venom, body fluids, and on poisonous hairs or spines include proteolytic enzymes, histamine, cantharidin, apamin, mellitin, histidine decarboxylase, kinins, serotonin, endopeptidases, and proteinases.

A "gate control theory" has been hypothesized to explain how the CNS can amplify or reduce the sensation of pruritus. Stress or anxiety may amplify pruritus in humans by releasing opioid peptides. Boredom or other cutaneous sensations such as pain, heat, cold, or touch also can alter the perception of pruritus. Factors such as increased skin temperature, diminished skin hydration, and low humidity can heighten the sensitivity of the skin to pruritic stimuli.

The concepts of *threshold phenomenon* and *summation of effect* are paramount in understanding and managing pruritus. A certain pruritic load may be tolerated without initiating clinical signs, but a small increase in that load can provoke clinical signs. The itch threshold often is reduced at night in humans and animals when other sensory inputs are diminished. *Summation of effect* occurs when additive pruritic stimuli from coexistent skin diseases raise an animal above threshold. As an example, pruritus from mild flea allergy is additive to pruritus from other skin diseases during flea season, thus exacerbating and perpetuating itch-scratch cycles.

10.2 DIAGNOSIS OF PRURITUS

Signalment, history, physical examination, diagnostic testing, and, occasionally, response to therapy are the cornerstones of diagnosis. Because many pruritic skin diseases are visually similar, clinical history coupled with signalment predilections may offer more direct clues to diagnosis than physical examination. Canine and feline scabies and cheyletiellosis may have increased in frequency during the past 5 years because of the popularity of newer, more narrow-spectrum flea control products that do not kill acarids. The effect of newer flea control products on the incidence of pruritic skin diseases is controversial. Although the frequency of flea allergy dermatitis may have declined in regions where newer products are used, flea allergy dermatitis is still common globally. Effective flea control also may have unmasked formerly undiagnosed cases of canine atopic dermatitis where the pruritus was assumed to be due only to flea allergy dermatitis rather than combined flea allergy and atopic dermatitis. The importance of pyoderma and *Malassezia* dermatitis as frequent causes of pruritus cannot be overemphasized.

10.2.1 Signalment

10.2.1.1 Age

Age provides critical information for prioritizing differential diagnoses. Some skin diseases occur more commonly in young animals, whereas other dermatoses are seen more frequently in middle-aged or older animals. As examples, scabies and demodicosis are pruritic skin diseases seen more commonly in young dogs. Similarly, atopic dermatitis, food allergy, and pyoderma occur more commonly in adult animals.

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10.2.1.2 Breed

Breed predilections for skin diseases are becoming increasingly available. Further, some skin diseases are breed specific. As examples, golden retrievers, Dalmatians, and many small terrier breeds are at increased risk for the development of atopic dermatitis. The West Highland white terrier is at increased risk for secondary *Malassezia* dermatitis and the Chinese Shar Pei seems predisposed to atopic dermatitis, food allergy, pyoderma, and demodicosis.

10.2.1.3 Sex

Sex predilections are not common in pruritic skin diseases. However, pruritus may be seen with Sertoli cell tumors, male-feminizing syndromes, and canine female hyperestrogenism.

10.2.2 Historical Findings

10.2.2.1 General History

General history should be sought referable to diet, environment, use, home skin care, recent exposures, other household pets, and the presence or absence of pruritus in other animals or people in the environment. These data are helpful in prioritizing differential diagnoses.

10.2.2.1.1 Diet.

Food allergy or intolerance can cause pruritus in both dogs and cats. However, adverse reactions to food frequently coexist with other allergic skin diseases such as atopic dermatitis and flea allergy dermatitis. In addition, lipid-deficient diets may exacerbate cornification abnormalities (seborrhea).

10.2.2.1.2 Environment and exposure.

The likelihood of contagious pruritic ectoparasitic skin diseases is affected by environmental exposure. Flea allergy, canine and feline scabies, and less common ectoparasitic skin diseases are all seen more frequently in animals permitted to roam free. Feline scabies is endemic to certain geographic urban areas. Recent exposures such as acquisition of a new pet or sheltering a stray animal increase the likelihood of contagious disease. Grooming establishments, kennels, and veterinary practices offer additional opportunities for contagion.

10.2.2.1.3 Other household pets.

Pruritus or lack of pruritus in other animals may offer clues to contagion. However, even though dogs and cats share the cat flea as a common ectoparasite, flea allergy is much more common in dogs. A seemingly unaffected indoor or outdoor cat is often the source of flea acquisition in indoor dogs with flea allergy dermatitis. Although uncommon, asymptomatic carriers of canine scabies do exist because clinical disease requires hypersensitivity.

10.2.2.1.4 Human contacts.

A pruritic papular rash in an owner with a pruritic pet may suggest zoonotic infestation with canine or feline scabies mites or cheyletiellosis. Annular, erythematous lesions may suggest dermatophytosis.

10.2.2.2 Specific History

Specific history relates to the current pruritic skin disease. The initial site of skin lesion development, onset and progression, intensity of pruritus, seasonality or other pattern (predictability), and response or lack of response to previous therapy may aid in establishing a diagnosis.

10.2.2.2.1 Site, onset, and progression.

Knowledge of the initial sites of skin lesions may be useful, if the disease has generalized before veterinary care is sought. For example, canine scabies often begins on the margins of the pinnae before generalizing. Rapid-onset pruritus should increase suspicion for ectoparasitic diseases and, less commonly, adverse drug reactions. Pruritus of insidious onset is more suggestive of slowly progressive, chronic skin diseases such as atopic dermatitis, food allergy, pyoderma, cornification abnormalities, and Malassezia dermatitis.

10.2.2.2.2 Intensity.

Most animals do not exhibit pruritus in examination rooms. Canine and feline scabies, canine flea allergy dermatitis, and feline food allergy are notable exceptions. Frequency and intensity of pruritus may be inferred from asking the owner how many times the animal will scratch (or chew or lick) if it is ignored while the owner observes the animal at home.

10.2.2.2.3 Seasonality or pattern (predictability).

Atopic dermatitis and flea allergy dermatitis are seasonal in many regions of the world. Malassezia dermatitis may occur more frequently during months of higher humidity. Cyclical pruritus without seasonality can sometimes signify contact dermatitis associated with change of environment. Psychogenic pruritus may began as a predictable, attention-getting device. Pruritus seen with food allergy should be continuous unless the diet is changed.

10.2.2.2.4 Response to previous therapy.

Response or lack of response to previous medications, particularly corticosteroids, antibiotics, or parasiticides, may offer additional clues. Although allergic diseases all respond to corticosteroids to some degree, food allergy may be less responsive to corticosteroids than atopic dermatitis or flea allergy dermatitis. Prior diminished pruritus in response to antibiotics in dogs is often overlooked and indicates the likelihood of pyoderma. Pruritus as the result of pyoderma may also diminish in response to corticosteroids.

10.2.3 Physical Findings

A complete physical examination is extremely important when evaluating any animal with skin disease. Skin disease may be seen secondary to internal medical disorders (see Chapter 8). Proper lighting is of paramount importance. The clinician should observe the animal for general demeanor and signs of pruritus while taking the history. Examination of the skin, mucocutaneous junctions, oral cavity, ears, genitals, and lymph nodes should be emphasized. Objective signs of pruritus include excoriations and broken or barbered hairs with a dry lusterless haircoat. In the dog, worn incisors (buccal surface) and canine teeth (mesial surface) most frequently indicate chronic flea allergy dermatitis.

Pruritus may occur with or without primary skin lesions. If present, primary skin lesions such as papules or pustules may be helpful in establishing a diagnosis. Coexistent alopecia may offer additional clues (see Chapter 9). Unfortunately, self-trauma often leads to the obliteration of initial, more diagnostic primary skin lesions substituting excoriations, lichenification, and alopecia. The concept of “a rash that itches” indicates primary skin lesions that are itchy, and “an itch that rashes” indicates that pruritic patients without primary lesions traumatize

themselves. Ectoparasitic skin diseases, pyoderma, and cornification abnormalities are among the more common pruritic skin diseases where primary skin lesions are identified. Conversely, primary lesions are much less common in atopic dermatitis and food allergy. The distribution of lesions, presence or absence of bilateral symmetry, and major foci of pruritus can be valuable aids to diagnosis. Primary or secondary lesions, if present in a particular site, may be highly suggestive of specific diseases (Tables 10-1 and 10-2).

10.2.4 Diagnostic Plan

Diagnostic plans should be formulated based on prioritization of differential diagnoses using signalment, history, and physical findings. Diagnostic procedures are selected based on the most likely differential diagnoses. The algorithm in Figure 10-1 offers an overview of possible diagnostic plans.

Table • 10-1 Pruritic Canine Dermatoses

DISEASE	SITE	LESIONS
Flea allergy dermatitis A, E, F	Bilaterally symmetric, dorsal lumbosacral, caudal thighs, groin, axilla, caudal half of body	Papules, macules, alopecia, erythema, lichenification, hyperpigmentation, excoriations, fibropruritic nodules
Canine scabies A	Ventrum, pinnae margins, face, elbows, partially bilaterally symmetric	Macules, papules, erythema, alopecia, crusts, excoriations
Demodicosis A	Periorbital, commissures of mouth, forelegs, generalized	Alopecia, erythema, crusts, follicular plugging, hyperpigmentation, secondary pyoderma
Pyoderma A	Groin, axilla, ventrum, interdigital webs, generalized, pressure points	Pustules, crusted papules, erythema, alopecia, target lesions, coalescing collarettes, hyperpigmentation
Atopic dermatitis A, F	Face, periorbital, ears, caudal carpi and tarsi, feet (dorsum), otitis externa, axilla, generalized	Erythema, alopecia, excoriations, lack of primary lesions, lichenification, hyperpigmentation
Malassezia dermatitis A, E, F	Ventral neck, groin, skin folds, face, feet, ventrum	Erythema, exudative or dry, alopecia, hyperpigmentation, lichenification
Cornification defects A, E, F	Generalized, ears, preen body	Scales, crusts, alopecia, erythematous plaques
Acral lick dermatitis A	Anterior carpal, metacarpal, radial, metatarsal, tibial regions	Firm, alopecic plaque, central irregular ulcer, hyperpigmented halo
Food allergy B	Face, feet, ears, generalized	Erythema, alopecia, excoriations, lack of primary lesions
Contact dermatitis C	Hairless areas, feet (ventrum), genitals, groin, axilla, generalized	Erythema, exudation, lichenification, hyperpigmentation, papules
Drug eruptions C	Anywhere, localized or generalized, face, ears, scrotum	Pleomorphic, erythema, papules, coalescing target lesions
Endoparasitic migration in puppies C	Face, feet, generalized	Erythema, alopecia, excoriations, lack of primary lesions
Cheyletiellosis B, E	Dorsum of thorax, generalized	Large scales, crusts, alopecia, erythema
Chiggers B, E, F	Ventrum, legs, anywhere	Erythema, scales, crusts, papules, alopecia
Superficial necrolytic dermatitis C	Footpads, face, mucocutaneous junctions, genitals, groin	Adherent crusts, ulcers, excoriations, erythema, fissured pads
Psychogenic pruritus C	Carpi, tarsi, feet (especially forelegs), perianal, generalized	Erythema, alopecia, excoriations, lack of primary lesions
Pediculosis C, E, F	Dorsum, generalized	Scales, crusts, alopecia, papules
Tail-dock neuroma C	Previously docked tail	Erythema, excoriations, alopecia
Rhabditic dermatitis D, E, F	Ventrum, legs, groin	Erythema, papules, alopecia, crusts, scales

A, Common; *B,* less common; *C,* uncommon; *D,* rare or controversial; *E,* regional; *F,* seasonal.

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10.2.4.1 Skin Scrapings

Multiple skin scrapings should be performed on all pruritic dogs and cats. Affected areas should be gently clipped, and then a no. 10 scalpel blade or spatula, dipped in mineral oil, should be scraped perpendicular to the skin surface in the direction of hair growth. The acquired debris should then be dispersed on a slide, a cover slip applied, and the specimen examined microscopically using low light.

Demodectic mites usually are readily demonstrable (except in chronic pododemodicosis and in the Chinese Shar Pei). Scabies mites are documented in less than half of affected dogs, underscoring the need for trial therapy in suspected cases. Dry scrapings may be stained as smears to look for *Malassezia pachydermatis*.

10.2.4.2 Exfoliate Cytology

Affected skin, intact pustules, or exudates should be smeared, stained with a rapid stain such as Diff Quik®, and examined microscopically for the presence of bacteria, *Malassezia* organisms, and inflammatory cells. Clear tape preparations may demonstrate *Cheyletiella* mites, and stained tape preparations may demonstrate bacteria or *M. pachydermatis*.

Table • 10-2 Pruritic Feline Dermatoses

DISEASE	SITE	LESIONS
Flea allergy dermatitis A, E, F	Neck, dorsum, lumbosacral, caudal and medial thighs, groin, ears	"Miliary dermatitis," erythema, alopecia, eosinophilic plaques
Eosinophilic plaque A, E, F	Ventral abdomen, medial thighs, anywhere	Raised, ulcerated, erythematous alopecic plaques, secondary to allergy (primarily flea allergy dermatitis)
Otodectic acariasis A	Ears, head, neck, rarely generalized	
Food allergy A	Head, neck, ears, generalized	Erythema, excoriations, alopecia, lack of primary lesions, "miliary dermatitis"
Self-induced pruritic hair loss (atopic dermatitis, food allergy, flea allergy) B	Bilaterally symmetric, caudal and lateral thighs, ventral abdomen, perineum	Alopecia, hair stubble, erythema, papules, underlying skin may be normal
Self-induced psychogenic hair loss B	Bilaterally symmetric, stripe(s) on dorsal thorax, caudal and lateral thighs, ventral abdomen, perineum, forelegs	Alopecia, hair stubble, normal underlying skin
Cheyletiellosis B, E	Dorsum of thorax, generalized	Large scales, crusts, seborrhea, "miliary dermatitis"
Demodicosis B, E	Trunk, ventral, generalized	Alopecia, scaling
Mosquito-bite hypersensitivity C, E, F	Bilaterally symmetric, dorsal muzzle, planum nasale, periorbital, pinnae, paw pad margins	Papules, crusts, alopecia, erosion, exudation, fistulation
Pediculosis C, E, F	Dorsum, generalized	Scales, crusts, alopecia
Feline scabies C, E	Head, ears, neck, generalized, partially bilaterally symmetric	Erythema, papules, crusts, excoriations, alopecia
Pruritic dermatophytosis C	Head, neck, ears, generalized	Erythema, alopecia, hair stubble, "miliary dermatitis," hyperpigmentation
Atopic dermatitis B, F	Head, neck, ears, generalized	"Miliary dermatitis," erythema, excoriations, alopecia
Drug eruptions C	Anywhere, localized or generalized, pinnae, face	Pleomorphic, erythema, papules, coalescing target lesions
Pemphigus foliaceus D, E?, F?	Bilaterally symmetric, face, planum nasale, ears, interdigital webs, nipples, generalized	Crusts, vesicopustules, alopecia

A, Common; *B,* less common; *C,* uncommon; *D,* rare or controversial; *E,* regional; *F,* seasonal.

10.2.4.3 Fecal Examination

Fecal examination may document endoparasite infestation in pruritic puppies and may reveal mites or other ectoparasites in any animal.

10.2.4.4 Skin Biopsy

Skin biopsy is especially valuable if primary skin lesions free of self-traumatic excoriations are present. If only self-traumatic lesions are present, definitive diagnosis is less likely, but results may aid in prioritizing or ruling out various differential diagnoses.

10.2.4.5 Fungal Culture

Most dogs and cats with dermatophytosis are not pruritic. However, fungal culture may be warranted because many cases of dermatophytosis are not visually distinctive.

10.2.4.6

Elimination Diets

Animals suspected of having food allergy or food intolerance as a cause of pruritus should be fed a home-cooked diet consisting of one protein and one carbohydrate source for 8 to 12 weeks. Alternatively, newer "limited antigen" or "hydrolyzed" diets are available. Commercial restricted diets are recommended for long-term maintenance. Nothing is specifically "hypoallergenic" about any food source. Foods are selected based simply on lack of previous exposure. Whitefish, rabbit, venison, pork, cottage cheese, or tofu mixed with either potatoes or other novel carbohydrate sources are commonly used in the dog. Mutton, lamb, and chicken are no longer as useful because they are frequently used in commercial dry dog foods. Cats may be fed rabbit, venison, pork, or mutton without an added carbohydrate source, or they may be fed commercial restricted or hydrolyzed diets.

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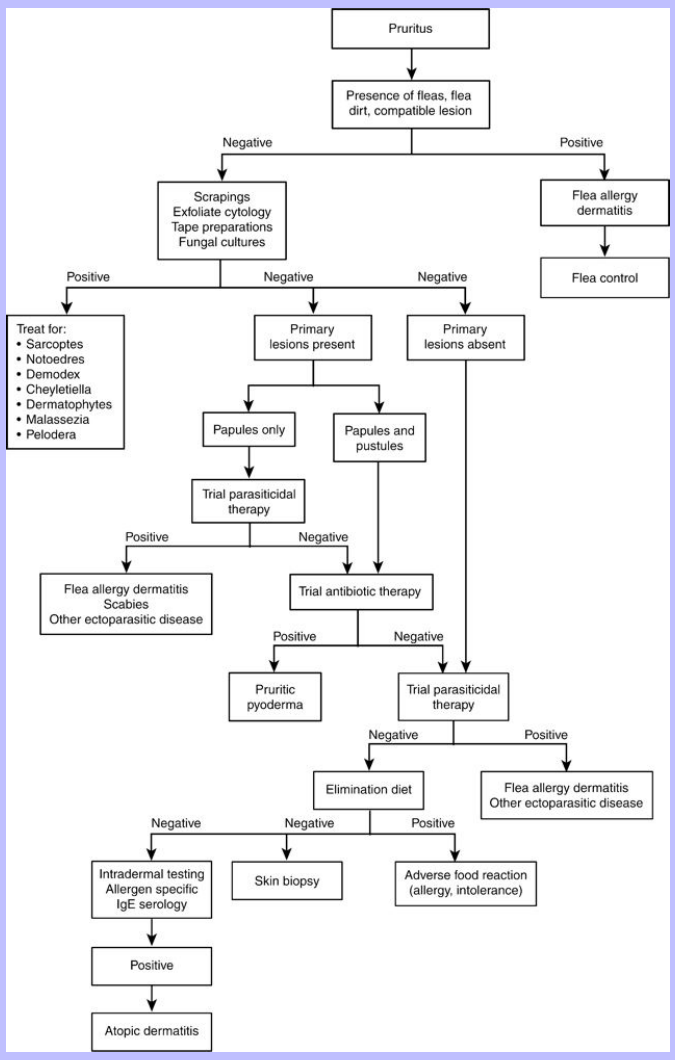
Figure 10-1 Algorithm for diagnosis and management of pruritus.



10.2.4.7 Intradermal Testing

Substantial training is required to select appropriate candidates suspected of having atopic dermatitis, to choose antigens, to develop and maintain a reproducible technique, and to interpret results. Consequently, skin testing is most effective when practiced by dermatologists or other clinicians with a strong interest in dermatology.

10.2.4.8 Allergen-Specific IgE Serology (enzyme-linked immunosorbent assay [ELISA] or radioallergosorbent test [RAST])

In vitro testing for atopic dermatitis offers convenience and accessibility. Reproducibility of test results has increased dramatically over the past decade. However, problems still remain with antigen selection, grouped testing, and standardization of results.

10.2.4.9 Environmental Restriction

If allergic contact dermatitis is suspected, an animal may be housed in a markedly different environment (water-rinsed kennel) for 10 days.

10.2.4.10 Response to Trial Therapy

Trial therapy with parasiticidal agents is used routinely in suspected cases of scabies or flea allergy dermatitis. Flea allergy dermatitis remains the most common cause of canine and feline pruritus despite effective modern products. Because the lesions seen with canine superficial pyoderma may be pleomorphic, trial use of antibiotics may be indicated in undiagnosed pruritic crusted papular dermatoses. Although response to corticosteroids is suggestive of underlying allergic disease, superficial pyoderma will frequently respond partially to corticosteroid therapy.

10.2.4.11 Cost Containment

Skin scrapings, fungal culture, exfoliate cytology, trial therapy for ectoparasites, and, surprisingly, skin biopsy, are the most cost-effective diagnostic procedures for the pruritic animal.

10.3 GOALS OF THERAPY

Successful long-term management of a pruritic dog or cat usually requires definitive diagnosis. Repetitive parasiticidal therapy on a weekly basis for 3 or 4 weeks will rule out most contagious ectoparasitic diseases such as canine or feline scabies. However, management of flea allergy dermatitis is a lifelong endeavor encompassing control of fleas on the affected animal and all in-contact dogs and cats, as well as environmental control. Atopic dermatitis responds best to allergen-specific immunotherapy. Secondary pyoderma and *Malassezia* dermatitis are common sequelae to most pruritic skin diseases and must be assessed for and managed long-term. If corticosteroids are used adjunctively for the long-term management of allergic skin disease, short-acting oral corticosteroids such as prednisone, prednisolone, or methylprednisolone are recommended on an alternate-day basis. Corticosteroids are contraindicated in the treatment of canine demodicosis and pyoderma. Many pruritic animals require long-term adjunctive topical management with shampoos and emollients or antipruritic rinses.

11 CHAPTER • 11 Cutaneous and Subcutaneous Lumps, Bumps, and Masses

Didier N. Carlotti

Cutaneous and subcutaneous lumps, bumps, and masses include hematomas, abscesses, urticaria and angioedema, neoplasms and pseudoneoplasms.

11.1 CLINICAL AND HISTOPATHOLOGIC DEFINITIONS

A hematoma is a focal extravasation of blood with purpura (bruising) and pain, whereas an abscess is a localized collection of pus with pain, heat, and sometimes purpura. Urticaria is referred to as a group of wheals (sharply circumscribed, raised, edematous lesions) that appear and disappear rapidly. Angioedema is a large swelling in a distensible region such as the face and limbs.

Clinically, pseudoneoplasms and neoplasms appear as nodules, plaques, and tumors. Ulceration always indicates a severe pathologic process. Pseudoneoplasms include cysts, nevi, keratoses, granulomas, and pyogranulomas and other lesions. *Pseudoneoplasm* is a better term than *pseudotumor* because the term *tumor* is clinical and should refer to a localized hypertrophy of a tissue or an organ, neoplastic or not. Cysts are epithelial lesions containing grayish keratinous material or serous material, such as apocrine cysts, which appear fluctuant, bluish, and well circumscribed. A hamartoma is a malformation formed by components of a normal organ arranged erroneously. A nevus is a cutaneous hamartoma that may arise from any skin component. Collagenous nevi are single or multiple nodules characterized histopathologically by large areas of collagen hyperplasia. In German shepherds, multiple collagenous nevi may appear, particularly on the limbs, in association with renal adenocarcinomas and uterine leiomyomas (nodular dermatofibrosis syndrome). Organoid (i.e., pilosebaceous) and epidermal nevi are variable in shape and may be linear. Vascular nevi are seen on the scrotum in dogs. Keratoses are solid, elevated, and circumscribed lesions characterized by a hyperproduction of keratin. They show up as greasy nodules and plaques (seborrheic keratoses), squamocrustous plaques (actinic keratoses, lichenoid keratoses on the ear pinnae), or cutaneous horns.

A granuloma is a circumscribed tissue reaction characterized by an organized infiltration of mononucleated phagocytes (histiocytes and macrophages) that may occur when foreign bodies, bacteria, fungi, parasites, or any material penetrates or deposits into the skin. If an acute inflammatory process does not destroy the “invader,” macrophages become epithelioid. A granuloma may persist until the cause has been eliminated. “Pyogranuloma” means granulomatous reaction with many neutrophils.

Lesions of calcinosis circumscripta are pink-colored plaques located on pressure points or in the tongue that contain grayish material. Hard erythematous plaques containing whitish material characterize calcinosis cutis, as seen in canine Cushing's disease. Eosinophilic lesions in the cat are indolent ulcer, eosinophilic plaque, and collagenolytic granuloma (the latter often appearing linear). Nodular sterile panniculitis is characterized by deep nodules that fistulize, expressing an oily material. Canine juvenile cellulitis is characterized by facial swelling. Nodular lesions, particularly on the face, with a “clown nose” appearance, may characterize canine histiocytosis.

Other various pseudoneoplasms include acral lick dermatitis, idiopathic lichenoid dermatitis (coalescent plaques), feline plasma cell pododermatitis or stomatitis, and idiopathic focal mucinosis seen in Doberman pinschers.

11.2 CAUSE AND PATHOPHYSIOLOGY

Hematomas are the result of trauma causing the rupture of blood vessels. They appear frequently after minor trauma in dogs with coagulopathies. Abscesses are the result of the collection of degenerated neutrophils and necrotic tissue cells when an infectious agent has penetrated into and under the skin. Usually a peripheral membrane forms from necrotic tissue and fibrin. Urticaria and angioedema are caused by immediate hypersensitivity reactions generated by insect bites (e.g., hymenoptera); food; drugs; airborne allergens (atopy), and nonimmunologic stimuli such as contact with irritant material (e.g., weeds, such as *Urtica dioica*; insects, such as *Thaumetopoea pityocampa* [caterpillar]; physical stimuli, such as cold, heat, and sunlight; and even psychogenic factors). Cysts may be traumatic (epidermoid), hereditary (dermoid), follicular, or pilar (i.e., trichilemmal) caused by retention of material (i.e., keratin, glandular products) as a result of congenital or acquired loss of follicular orifices. Apocrine cysts are idiopathic. Nevi may be congenital, and the mechanism of their formation is unknown. However, nodular dermatofibrosis is due to an autosomal dominant gene. Keratoses are idiopathic except actinic keratoses and some cutaneous horns, which are associated with various skin neoplasms or feline leukemia virus (FeLV) infection in the cat.

Bacterial granulomas and pyogranulomas include canine furunculosis caused by cocci such as *Staphylococcus intermedius,* botryomycosis (bacterial pseudomycetoma) caused by various bacteria that may cause a granulomatous reaction, and nocardiosis and mycobacterioses (atypical mycobacterial infection, feline leprosy, tuberculosis, which is very rare). Fungal granulomas and pyogranulomas include kerions (inflammatory reaction to a dermatophyte) and pseudo-mycetomas caused by the subcutaneous development of a dermatophyte (*Microsporum canis* in cats, mainly), subcutaneous (intermediate) mycoses (sporotrichosis, pythiosis, mycetomas, phaeohyphomycosis, zygomycosis), and deep (systemic) mycoses (blastomycosis, coccidioidomycosis, histoplasmosis, aspergillosis, cryptococcosis, protothecosis, paecilomycosis, trichosporonosis).

Endogenous or exogenous foreign bodies can cause granulomas. Endogenous foreign bodies are usually hair and keratin (leading to bacterial furunculosis), calcium (calcinosis circumscripta, idiopathic, Cushing's disease), and lipids (xanthomas in case of hyperlipidemia in cats, associated with diabetes mellitus or hereditary). Exogenous foreign bodies include sutures and weed material. Parasitic granulomas include tick bites, canine dracunculosis, canine filariasis, canine leishmaniasis (the nodular form is seen more frequently in short-haired dogs such as the boxer), feline toxoplasmosis, and canine cysticercosis. Arthropod bites (e.g., mosquitoes, spiders) lead to eosinophilic furunculosis (particularly on the face in dogs and cats) with a granulomatous reaction. Some granulomas are idiopathic: lesions of the feline eosinophilic granuloma complex (although most of the cases are caused by flea allergy dermatitis, feline atopic dermatitis, or food allergy or intolerance), canine eosinophilic granuloma, sterile pyogranulomatous dermatosis, nodular sterile panniculitis (the result of an inflammatory process of subcutaneous fat), canine juvenile cellulitis (perhaps viral), canine cutaneous histiocytosis (caused by a proliferation of normal histiocytes), canine erythema nodosum-like granuloma, canine sterile sarcoidal granulomatous skin disease, and amyloidosis. Acral lick dermatitis is often a deep bacterial folliculitis and furunculosis caused by constant licking attributed to an allergic pruritus or behavioral disorder. Lichenoid dermatitis may be idiopathic or an immune-mediated disease such as feline plasma cell pododermatitis and stomatitis sometimes associated with FeLV, feline immunodeficiency virus (FIV)-infection, or both.

Cutaneous and subcutaneous neoplasms include epithelial (epidermal and follicular), glandular (sebaceous, sweat, and hepatoid gland), mesenchymal (fibrocytic, histiocytic, vascular), and melanocytic and round cell tumors (mast cell, histiocytic, lymphoma).

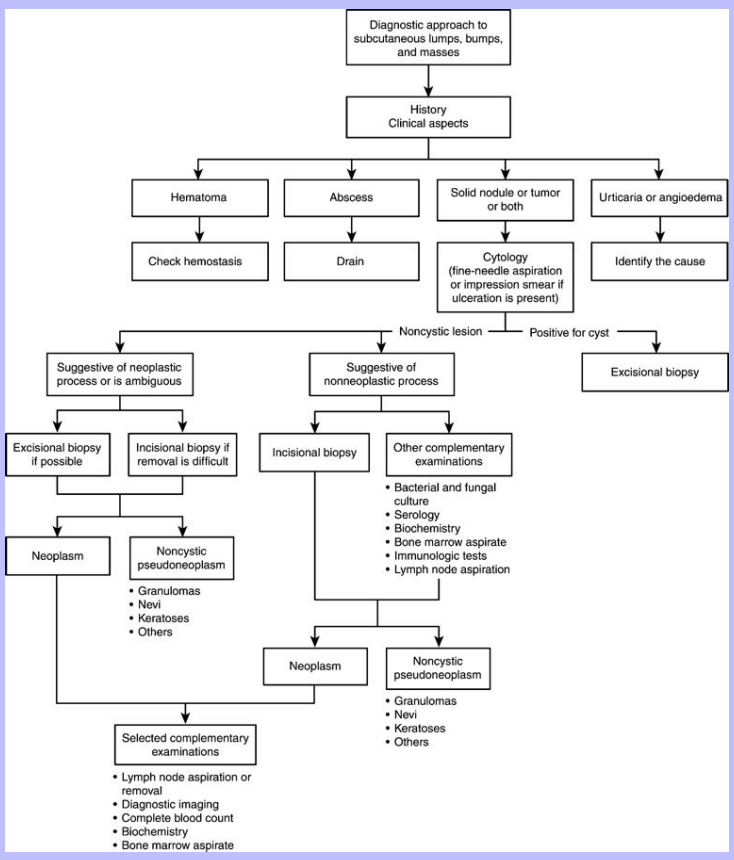
Mammary neoplasms can be considered as subcutaneous. Most of the neoplasms have an unknown cause. Viruses can cause specific tumors such as papillomas in dogs and fibrosarcomas and carcinomas in situ (Bowen's disease) in

cats. Other causes include irritation, trauma, and actinic exposure. The latter is likely to be the cause of squamous cell carcinoma of the face and ears in the cat (particularly of white color). It is not clear whether repeated vaccinations can lead to fibrosarcomas in cats. Benign neoplasms can be harmful if they reach a large size, are located in particular areas (face, eyelids, external ear canal, mouth, feet, genitals, anus), or both. Malignant neoplasms are invasive and will cause the necrosis of surrounding cells, leading to ulceration.

11.3 DIAGNOSIS

Diagnosis of cutaneous and subcutaneous lumps, bumps, and masses is based upon history, physical examination, and complementary aids (Figure 11-1). Signalment of the animal may be of some importance. Neoplastic lesions occur mostly in adults and old dogs. However, viral papilloma and histiocytoma (Langerhans' cell tumor) will be seen mainly in young animals. Intact male cats are prone to develop abscesses as the result of fighting. Mammary tumors and their cutaneous metastases occur in female dogs, whereas perianal gland tumors occur most frequently 44
in intact males. Most neoplasms, however, have no sex predilection. Breed predispositions are recognized for many 45
superficial neoplasms. The boxer is known to be predisposed to many of them, as it is for nodular leishmaniasis. The German shepherd is predisposed to keratinous cysts and nodular dermatofibrosis. Persian cats are predisposed to dermatophytic pseudomycetoma.

Figure 11-1 Algorithm for diagnostic approach to subcutaneous lumps, bumps, and masses.



History of the lesions should be taken into account. Important points are the existence of previous similar lesions, association to general disease, known trauma, and rapidity of onset. Obviously, hematomas, abscesses, urticaria, and angioedema appear rapidly. Some lymphomas can develop rapidly. Feline eosinophilic plaques, urticaria and angioedema, some cases of calcinosis cutis, and mast cell tumors are pruritic. Hematomas, abscesses, and some tumors may be painful.

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Physical examination should include evaluation of the lesions, local lymph nodes, and distant sites such as lungs. This strategy applies to most lumps, bumps, and masses, using the TNM approach (tumor, node, metastasis). The lesions should be characterized by localization, size, shape, pedunculated appearance, consistency, depth, and whether or not they are freely movable, ulcerated, or both. For instance, feline collagenolytic granuloma and canine epidermal nerves can be linear; hematomas and most benign neoplasms are not attached to underlying tissues, whereas most of abscesses and malignant neoplasms are attached. Abscesses evolve from firm to fluctuant stages, whereas most pseudoneoplasms and neoplasms are firm (except apocrine cysts and some angiomas and angiosarcomas). Benign neoplasms can be pedunculated. Feline indolent ulcer, eosinophilic plaques, some malignant neoplasms, and canine acral lick dermatitis ulcerate. Enlargement of local lymph nodes can be caused by inflammation (even in case of a neoplastic process) or metastasis. General lymph node enlargement can result from severe infections and lymphosarcoma. Metastasis can rarely be suspected clinically, except for cutaneous metastasis of mammary neoplasms and when an abnormal abdominal mass is palpated.

Cytologic techniques usable for lumps, bumps, and masses are impression, scrape, swab, and fine-needle aspiration smears. No contraindications exist. Cytology allows rapid identification of cell types. High cellularity and a homogeneous cell population characterize neoplasms. Cytologic criteria of malignancy include pleomorphism, high nucleocytoplasmic ratios, large nucleoli, and atypical mitoses. In many nonneoplastic lesions, the cytologic examination is highly suggestive of the diagnosis (e.g., pyoderma, fungal diseases, eosinophilic plaques). Fine-needle aspiration cytology of a local lymph node can help to differentiate an inflammatory reaction from malignancy.

Histopathology has a fundamental role in establishing specimens' diagnoses. Incisional biopsy specimens can be obtained with a scalpel or a punch, particularly when cytology is ambiguous. Results aid in selecting appropriate medical therapy, surgery, or both. The sample should be biopsied at the margin of the lesion to incorporate some normal-looking tissue, should not be larger than 1 cm, and should be put in 10 times its volume of 10% formalin. No contraindication exists for incisional biopsy because it does not increase risk of metastasis. The wound should be repaired, and the biopsy site should be removed by further surgery. General anesthesia may be required, and wound repair can be difficult. Excisional biopsy can also be performed, particularly when cytology is ambiguous, when the surgical removal of the lesion is easy, and when physical examination suggests a nonneoplastic or benign neoplastic lesion. If lesions are multiple, excisional biopsy of a typical mass should be considered. The removal of a lymph node for histopathologic analysis can be helpful and has no harmful consequence. Radiology, ultrasonography, or both are useful in many instances (e.g., a lesion appearing to be attached to an underlying bone or suspicion of lung or abdominal metastasis).

11.4 PROGNOSIS

The prognosis of cutaneous or subcutaneous (or both) lumps, bumps, and masses is obviously linked to diagnosis, location of the lesion or lesions, and continuing evaluation (TNM). Establishing a prognosis based on physical examination only and clinical neglect (waiting for a possible enlargement of the lesion or lesions), are unacceptable errors.

11.5 TREATMENT

Treatment should be based upon diagnosis and prognosis. Medical treatment of urticaria and angioedema, hematomas, and abscesses is almost always successful. The result of treatment of granulomatous pseudoneoplasms can lead to complete cure, particularly when a bacterial or superficial fungal agent has been identified. Surgical excision of cysts, nevi, keratoses, feline plasma cell podal lesions, and benign neoplasms is usually successful. Treatment for malignancies is rarely curative, but long remissions can be obtained, particularly if the owners wish to cooperate.

12 CHAPTER • 12 Erosions and Ulcerations

Ian S. Mason

Erosions and ulcers are skin defects with a wide range of causes. Erosions are superficial breaks in the continuity of epithelia that fail to breach the intact basement membrane and usually heal without scarring. Ulcers are deeper and extend through the basement membrane into the underlying dermis. They heal slowly and residual scarring is common. It may be impossible to distinguish between ulcers and erosions without histology. In some diseases, ulcers and erosions occur concurrently, whereas in other conditions only one type of lesion may be present.

Ulcers and erosions may result from a variety of conditions (Box 12-1). Trauma, including self-trauma associated with pruritus, may lead to eroded and ulcerated lesions. Infectious diseases can lead to defects in the epithelial surface. In canine skin, bullae and vesicles are thin walled and rupture promptly after formation, leading to erosions and ulcers. Chemical and physical factors such as urine scalding, irritant contact dermatitis and thermal injury may also be responsible for defects in cutaneous continuity.

12.1 Box • 12-1 Differential Diagnosis Of Ulcers And Erosions Affecting Skin And Mucous Membranes

12.1.1 Canine Diseases

Infectious:

Bacterial pyoderma:

Surface:

Acute moist dermatitis (pyotraumatic dermatitis)

Intertrigo

Deep:

Folliculitis/furunculosis (including pyotraumatic folliculitis)

Oral bacterial infections (aerobic/anaerobic)

Fungal:

Yeast infections (*Malassezia pachydermatis, Candida* spp.)

Systemic/subcutaneous

Parasitic:

Demodicosis

Metabolic:

Calcinosis cutis (hyperadrenocorticism)

Uremia/renal failure

Necrolytic migratory erythema/metabolic epidermal necrosis

Neoplastic:

Epitheliotropic lymphoma

Squamous cell carcinoma

Physical, chemical:

Drug reactions

Solar injury

Thermal injury (freeze or burn)

Urine scald

Immune-mediated/autoimmune:

Discoid lupus erythematosus

Pemphigus group

Uveodermatologic syndrome

Miscellaneous autoimmune subepidermal vesiculobullous diseases:

Bullous pemphigoid

Epidermolysis bullosa acquisita

Linear IgA bullous disease

Mucocutaneous pemphigoid

Bullous systemic lupus-type 1

Miscellaneous:

Arthropod bites

Dermatomyositis

Dystrophic epidermolysis bullosa

Idiopathic ulceration of collies

Junctional epidermolysis bullosa

Toxic epidermal necrolysis/erythema multiforme

12.1.2 Feline Diseases

Infectious:

Viral:

Calicivirus and herpesvirus

Bacterial:

Atypical mycobacteriosis

Fungal:

Subcutaneous and systemic mycoses

Cryptococcosis

Sporotrichosis

Metabolic:

Uremia/renal disease

Neoplastic:

Fibrosarcoma

Lymphoma

Squamous cell carcinoma

Physical/chemical:

Drug reactions

Thermal

Immune-mediated/autoimmune:

Bullous pemphigoid

Pemphigus foliaceus

Toxic epidermal necrolysis/erythema multiforme

Miscellaneous/idiopathic:

Arthropod bites

Dystrophic epidermolysis bullosa

Eosinophilic plaque

Idiopathic ulceration of dorsal neck

Indolent ulcer

Junctional epidermolysis bullosa

Erosive and ulcerative diseases in dogs and cats may affect the mucous membranes with or without concurrent cutaneous involvement. Animals with oral lesions usually have halitosis, dysphagia, or both. Clinicians often suspect autoimmune and immune-mediated diseases in animals with erosions and lcerations. However, these diseases are uncommon or rare.

12.2 APPROACH TO THE DIAGNOSIS

Diagnosis may be difficult. Ulcers and erosions have many possible causes. Therefore the diagnostic approach must be carefully planned and thorough (Figure 12-1).

History may yield important clues. Obese or short-legged breeds of dogs are predisposed to intertriginous (or body fold) pyoderma and urine scalding. Older animals are more susceptible to metabolic and neoplastic disorders. Concurrent systemic signs may indicate that lesions are the result of metabolic disease or a drug eruption (assuming the animal has received therapy). Determining whether pruritus is present and at which stage it developed is helpful. If early pruritus is present, then it is possible that this is a primary pruritic disease, such as that caused by hypersensitivity or ectoparasitism, and that the lesions are the result of self-trauma. Late onset of pruritus may be more difficult to assess and may arise in a large number of diseases. Chronic sun exposure, especially of poorly pigmented skin, may lead to actinic lesions including neoplasia.

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General and dermatologic examination will greatly aid the establishment of a differential diagnosis and enable the clinician to identify any concurrent systemic disease. The distribution of lesions may be extremely helpful (Box 12-2). Involvement of mucous membranes indicates that uremia, renal failure, or both; viral, bacterial, or yeast infection; certain immune-mediated disorders (bullous pemphigoid, pemphigus vulgaris), or epitheliotropic lymphoma is present.

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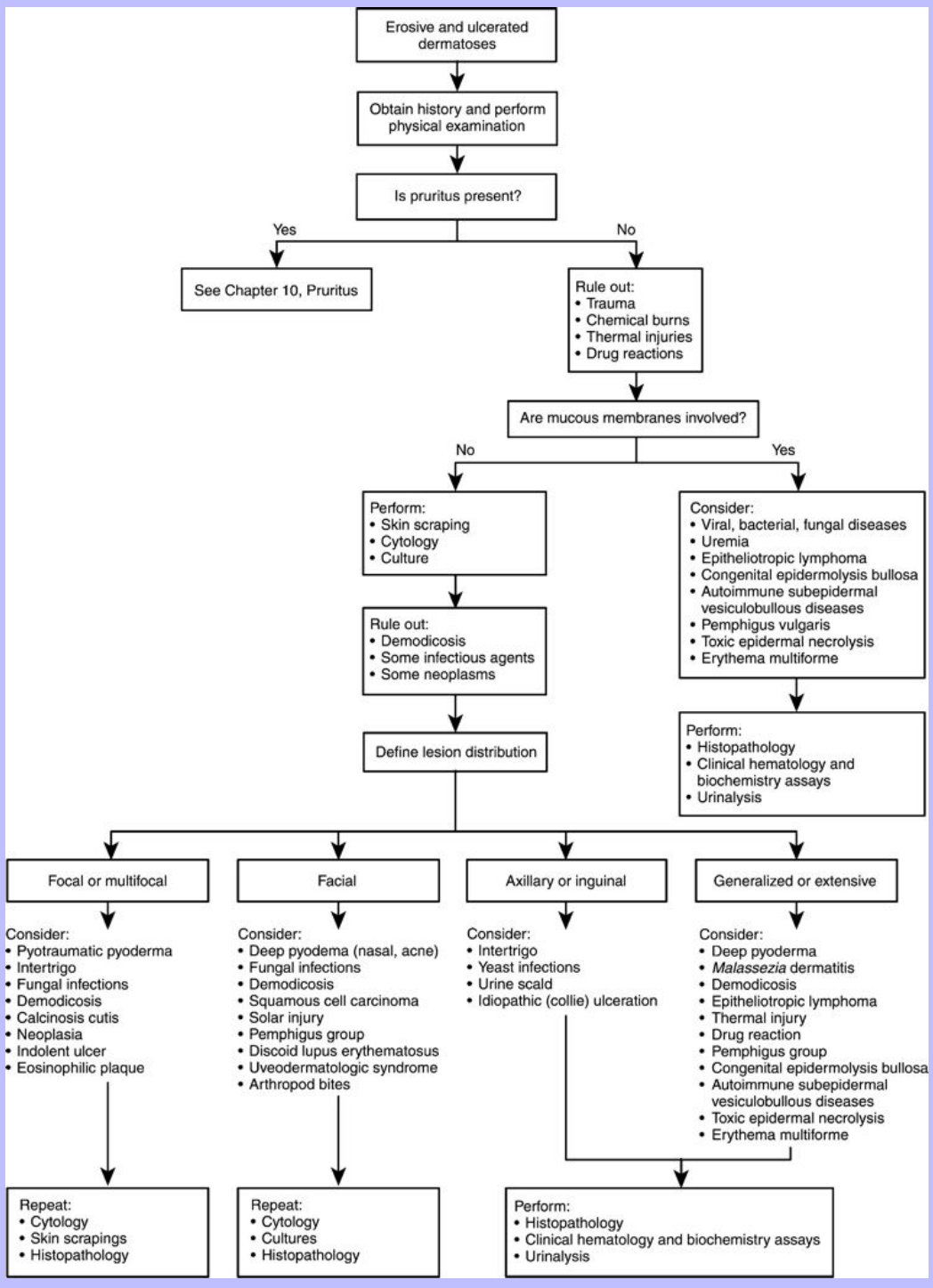
Figure 12-1 Algorithm for evaluation of erosive and ulcerated dermatoses.



Initial diagnostic tests such as cytologic examination of impression smears and microscopy of skin scrapings are useful. However, the majority of causes will be identified by histopathology, and biopsy specimens should be taken early in the development of this group of diseases.

12.3 INFECTIOUS CAUSES OF EROSIONS AND ULCERS

12.3.1 Viral Diseases

Feline calicivirus and feline herpesvirus (FHV) infections usually cause upper respiratory tract disease and conjunctivitis. Rarely, they may lead to cutaneous ulceration, typically on the feet. A tentative clinical diagnosis of feline calicivirus and FHV can usually be based on results of the history and physical examination.

12.3.2 Bacterial Disease

Pyoderma and other bacterial diseases may be difficult to recognize because these infections are pleomorphic. If doubt exists as to whether the lesions are the result of bacterial infection, then histopathology should be performed. Concurrent systemic antimicrobial therapy is indicated while awaiting the pathologist's findings. If histopathology results indicate that the lesions are bacterial in origin but little improvement has been seen after antimicrobial therapy, then it is likely that the infection is secondary. A second biopsy sampling is indicated after antibacterial therapy to allow examination of tissue without secondary infection.

Surface bacterial infections in dogs are characterized by erosion. Intertrigo (skin fold pyoderma) affecting lip, vulvar, facial, tail, or body folds is readily recognized clinically. Impression cytology and culture of the folds may reveal evidence of bacterial infection, usually *Staphylococcus intermedius*, but the yeast *Malassezia pachydermatis* may also be involved. Pyotraumatic dermatitis (“hot spots” or acute moist dermatitis) is another form of canine surface pyoderma that is readily recognized clinically. However, in some cases, the infection is deeper than it would appear on clinical examination (this is termed *pyotraumatic folliculitis*). The distinction between these two forms is made by histopathology and is important because glucocorticoid therapy is contraindicated in the deeper form.

Deep pyoderma in dogs may be characterized by erosion and ulceration; examples include nasal pyoderma and German shepherd dog pyoderma. These may be confused with immune-mediated disorders. As previously discussed, histopathology and antimicrobial therapy may be of value. Aerobic and anaerobic bacterial infection may affect the mucous membranes. Such infections are often secondary to dental disease, immunosuppression, and systemic diseases.

Opportunist or atypical mycobacterial infections may occur when feline skin is inoculated with soil or water harboring the organism via traumatic injury. Affected cats exhibit chronic nonhealing wounds and ulcers with draining tracts. Systemic signs are usually absent.

12.3.3 Fungal Disease

In recent years, infection of the skin surface associated with the yeast *M. pachydermatis* has been recognized in dogs. Ulceration is not a feature, but the affected skin may be eroded. Lesions usually occur in intertriginous regions, particularly in predisposed breeds (Basset hounds, West Highland terriers, and English cocker spaniels). 49
The lesions are characterized by intense erythema, a yellow waxy crust, and malodor. Dermatophytosis may lead 50

to eroded and ulcerated lesions in dogs and cats. Diagnosis is based on cytology, culture, and response to antifungal therapy.

12.3.3.1

Box • 12-2 Distribution of Ulcers and Erosions as a Diagnostic Clue

Axillary/Inguinal:

Fungal (*Malassezia pachydermatis*, *Candida* spp.) (D)

Idiopathic ulceration of collies (D)

Intertrigo (D)

Urine scald (D)

Focal/Multifocal:

Calcinosis cutis (D)

Demodicosis (D)

Eosinophilic plaque (C)

Indolent ulcer (C)

Intertrigo (D)

Neoplasia (D, C)

Pyoderma (principally pyotraumatic dermatitis or folliculitis) (D)

Systemic/subcutaneous mycosis (D, C)

Facial:

Arthropod bites (D, C)

Bullous pemphigoid (D, C)

Deep pyoderma (D)

Demodicosis (D)

Dermatomyositis (D)

Discoid lupus erythematosus (D)

Linear IgA bullous disease (D)

Pemphigus foliaceus/erythematosus (D, C)

Solar injury (D, C)

Squamous cell carcinoma (C)

Systemic/subcutaneous mycosis (D, C)

Uveodermatologic syndrome (D)

Mucocutaneous:

Bacteria (aerobic/anaerobic) (D, C)

Bullous pemphigoid (D, C)

Bullous systemic lupus-type 1

Epidermolysis bullosa aquisita (D)

Epitheliotropic lymphoma (D)

Fungal (*M. pachydermatis, Candida* spp.) (D)

Mucocutaneous pemphigoid (D)

Pemphigus vulgaris (D)

Toxic epidermal necrosis/erythema multiforme (D, C)

Uremia (D, C)

Viral infection (calicivirus/herpesvirus) (C)

Generalized/Extensive:

Bullous pemphigoid (D)

Deep pyoderma (D)

Demodicosis (D)

Drug reaction (D, C)

Epitheliotropic lymphoma (D)

Malassezia dermatitis (D)

Pemphigus group (D, C)

Thermal injury (D, C)

Toxic epidermal necrolysis/erythema multiforme (D, C)

D, Dog; *C*, Cat.

Subcutaneous and systemic fungal infections are far less common. Impression smears and histopathology are indicated. Therapy is dependant on the organism involved.

12.4 OTHER CAUSES OF EROSIONS AND ULCERS

12.4.1 Parasitic Infections

Infestation with mites such as *Sarcoptes scabiei* or *Cheyletiella* spp. may lead to self-induced erosions and ulcers. Severe cases of demodicosis may, less commonly, lead to ulceration. Skin scrapings are diagnostic and mandatory.

12.4.2 Metabolic Disease

Calcinosis cutis is caused by accumulation of calcium in the skin, usually as a result of hyperadrenocorticism (naturally occurring or iatrogenic). Ulcers may develop over these mineral plaques. Histopathology is diagnostic. Treatment of the underlying systemic disease is usually curative.

Hepatic cirrhosis or pancreatic adenocarcinomata may lead to cutaneous ulceration that particularly affects the feet and perineum of older dogs. This disease has a range of synonyms, including hepatocutaneous syndrome, necrolytic migratory erythema, and metabolic epidermal necrosis.

Uremia as the result of renal failure may lead to oral ulceration. In cats, diabetes mellitus and hyperadrenocorticism may also lead to this phenomenon. Signs of systemic disease are usually present (e.g., anorexia, depression, dehydration). Halitosis is a feature. Urinalysis along with clinical biochemistry and hematology are usually diagnostic.

12.4.3 Neoplasia

Squamous cell carcinoma is a common feline neoplasm particularly affecting the extremities of white or lightly pigmented cats (e.g., ear tips, planum nasale). White English bull terriers are also predisposed. The prevalence of squamous cell carcinoma is greater in warmer climates. Waterproof, high sun protection factor cream should be applied to animals at risk. Ideally, access to sunshine should be restricted.

Epitheliotropic lymphoma leads to nodular, scaling, eroded and erythematous skin lesions in older dogs. Oral lesions (erythema, erosion) occur in the majority of cases. The prognosis is grave, with therapy having little influence on survival time.

Diagnosis of cutaneous neoplasia is by histopathology, although cytology of fine-needle aspirates and impression smears may be helpful.

12.4.4 Physical and Chemical Diseases

Such diseases can usually be diagnosed with history: exposure to extreme cold or scalding, recent treatment with medicaments, or (in the case of urine scalding) clinical examination. Solar-induced disease may be more difficult to diagnose because the onset is chronic and some manifestations of solar dermatoses may resemble other diseases.

12.4.5 Immune-Mediated and Autoimmune Diseases

Although this group is ascribed much significance by clinicians, these diseases are uncommon or rare. Lesions arise when tissue is damaged as a result of an inappropriate immunologic response. In autoimmune diseases, antibodies directed against a tissue component elicit an inflammatory response that may lead to cleavage of the epidermis from the underlying dermis (e.g., bullous pemphigoid, epidermolysis bullosa aquisita) or splitting within the epidermis itself (e.g., the pemphigus group). In some diseases, the precise pathologic mechanism is unknown (e.g., discoid lupus erythematosus).

The differentiation of the different immune-mediated diseases is important and made by histopathology. The different diseases respond to different forms of therapy, and the prognosis varies between them. If a definitive diagnosis is not obtained, then there is a risk of treating a benign disease too aggressively with immune-suppressive agents.

12.4.6 Miscellaneous Diseases

Dermatomyositis is a hereditary disorder primarily affecting the face and distal limbs of rough and Shetland collie (shelties) pups, leading to alopecia, erosions, ulceration, and scarring. It probably arises from immune-mediated vasculitis. Idiopathic ulceration is also seen in these breeds; previously it was thought that it may share its cause and pathogenesis with dermatomyositis. However, recent evidence suggests that it may be a form of lupoid dermatitis.

Idiopathic ulceration principally affects the ventral abdomen and groin and usually occurs in middle-aged rough and Shetland collie dogs. The prognosis is guarded because it is refractory to treatment in most cases.

Congenital diseases may affect the basement membrane and lead to ulceration and erosion. Examples include junctional epidermolysis bullosa and dystrophic epidermolysis bullosa.

13 CHAPTER • 13 Pustules and Papules

Edmund J. Rosser, Jr.

Pustules and papules are the most common primary skin lesions in dogs. Bacterial skin diseases are the most frequent cause of these lesions. The discussions will be limited to bacterial skin diseases of the dog because the development of a pyoderma is an extremely rare event in the cat.

13.1 CUTANEOUS BACTERIOLOGY

Bacteria that are isolated from the skin of dogs are commonly divided into three categories: (1) resident organisms, (2) transient organisms, and (3) common pathogenic organisms. Resident bacterial organisms can be routinely and repeatedly isolated and cultured from the surface of the skin, hairshafts, hair follicles, nares, oropharynx, and anal ring of the dog and normally live in harmony with the host without causing clinical disease. The resident bacteria of the canine skin surface include coagulase-negative staphylococci (*Staphylococcus epidermidis, S. cohnii, S. saprophyticus, S. hominis, S. haemolyticus, S. capitis, S. warneri, S. xylosus, S. simulans,* and *S. sciuri*); coagulase-positive staphylococci *(S. intermedius); Micrococcus* spp.; alpha-hemolytic streptococci; *Clostridium* spp.; *Propionibacterium acnes;* and *Acinetobacter* spp. The resident bacteria of canine hairshafts are *Micrococcus* spp., various gram-negative aerobes, *Bacillus* spp., and *S. intermedius. Propionibacterium acnes*, *Micrococcus* spp., streptococci, *Bacillus* spp., and *S. intermedius* have been isolated from within the hair follicles. The resident bacterium of the nares, oropharynx, and anal ring is *S. intermedius*. Transient bacterial organisms are not routinely or repeatedly isolated and cultured from the skin and haircoat of the dog. Under normal circumstances these organisms do not multiply on the dog but occasionally become pathogens by secondary invasion. They include *Escherichia coli, Proteus mirabilis, Pseudomonas* spp., *Corynebacterium* spp., and *Bacillus* spp.

Primary pathogenic organisms are capable of tissue invasion and creating disease. They are usually coagulase-positive staphylococci *(S. intermedius, S. aureus, S. hyicus)*, and *S. intermedius* is the most common isolate from canine skin infections.

13.2 PATHOPHYSIOLOGY

The bacterium *S. intermedius* is a normal resident of healthy canine skin, hairshafts, hair follicles, nares, oropharynx, and anal ring. They are also the most common causative organisms in superficial and deep pyodermas. These skin infections can be classified as *primary* or *secondary*. Secondary infections are undoubtedly the most common and are easily recognized by the tendency of the infection to be recurrent. Recurrence is the result of an underlying disease process allowing *S. intermedius* to become an opportunist and invade the stratum corneum, hair follicle, or both. These underlying disease processes may alter the skin directly as the result of local trauma, irritants, or scratching from parasitic and other pruritic skin diseases (see Chapter 10). Alternatively, the disease may act systemically to decrease resistance to cutaneous infections as in metabolic and immune-mediated skin diseases (see Chapter 269). Primary skin infections are so classified because once they are appropriately treated, they do not recur. However, it seems most likely that some transient insult occurs to the skin that allows *S. intermedius* to become a temporary opportunist and pathogen.

In either primary or secondary pyodermas, *S. intermedius* begins by overcolonizing the surface of the skin and either invading the stratum corneum (as in impetigo) or the hair follicle (as in superficial folliculitis). In cases of impetigo, the invasion of the stratum corneum results in the formation of primarily nonfollicular pustules (i.e., the pustules do not have a hairshaft in the center), which rupture and often form crusts and epidermal collarettes. The

lesions are usually nonpruritic and tend to be associated with minimal inflammation. In cases of superficial folliculitis, the invasion of the hair follicle results in the formation of follicular papules and pustules (i.e., hairshafts are present in the center of the lesions) that also rupture and often form crusts and epidermal collarettes. The lesions are usually pruritic and associated with inflammation and erythema. The older lesions often evolve into annular areas of alopecia and hyperpigmentation.

Deep pyodermas invariably begin as a superficial folliculitis and occur in cases where the underlying disease processes have not been appropriately identified. The infection travels into the deeper portions of the hair follicle and subsequently ruptures the hair follicle into the surrounding dermis, causing a furunculosis. The infection may continue to invade the deeper dermal and subcutaneous tissues, resulting in cellulitis.

13.3 CLINICAL FEATURES

A *pustule* is defined as a small, elevated, purulent fluid-filled cavity in the epidermis that is less than 0.5 cm in diameter. The base of the pustule is often erythematous. Pustules are most commonly associated with a superficial pyoderma. A *papule* is defined as a small, elevated, solid skin lesion up to 0.5 cm in diameter caused by the infiltration of inflammatory cells. They are usually pinkish or reddish in color. When they are oriented around a hair follicle, they usually indicate a superficial bacterial folliculitis. They are also commonly observed in cases of scabies and flea allergy (see Chapter 10). The presence of pustules and papules caused by a bacterial infection is frequently associated with concurrent pruritus owing to the production of proteolytic enzymes by the bacteria present in these lesions (primarily *S. intermedius*). These lesions may then rupture spontaneously or be altered in their appearance as a result of pruritus-induced self-trauma. Therefore these primary lesions may be transient, leaving behind only the presence of secondary lesions such as erosions, crusts, epidermal collarettes, posttraumatic alopecia, and excoriations. As the disease becomes more chronic in nature, additional skin changes may develop, such as hyperpigmentation and lichenification.

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13.4 SUPERFICIAL PYODERMAS

13.4.1 Impetigo (Puppy Pyoderma)

Impetigo is most often observed in young dogs before puberty. This infection is considered to be an opportunistic or secondary pyoderma most frequently associated with poor nutrition, dirty environment, viral infections, ectoparasites, and intestinal parasitism. The disease is associated with the formation of superficial pustules that do not involve hair follicles and affects the inguinal and ventral abdominal regions (and occasionally the axillary region). Minimal erythema is noted, and the puppy is usually nonpruritic. Impetigo is often an incidental finding by the owner or is noticed on routine physical exam.

13.4.2 Superficial Folliculitis

A folliculitis is an inflammation of the hair follicle that can be caused by bacteria (staphylococcal folliculitis), fungi (dermatophyte folliculitis), and parasites (demodicosis, pelodera dermatitis).

Superficial bacterial folliculitis begins with the presence of pustules and papules initially affecting the inguinal and ventral abdominal regions. The papules and pustules are oriented around hair follicles and the dog is usually pruritic. As the disease progresses, epidermal collarettes form with varying degrees of central hyperpigmentation and marginal erythema, and additional areas affected may include the axillary regions and ventrolateral thorax.

When the truncal skin is affected, the haircoat often takes on a “moth-eaten” appearance (especially in short-coated breeds of dogs).

13.5 DEEP FOLLICULITIS AND FURUNCULOSIS

Furunculosis is an inflammation of hair follicles with subsequent follicular rupture extending into the surrounding dermis and subcutaneous tissue. The lesions initially observed include papules, pustules, and epidermal collarettes followed by the presence of exudation, crust formation, and deep draining tracts. As the process of folliculitis and furunculosis continues and the lesions coalesce, areas may become nodular and indurated or a cellulitis may develop. Another lesion occasionally observed in these patients is a hemorrhagic bulla. The lesions are usually first noticed in inguinal, ventral abdominal, and axillary regions as a superficial folliculitis. However, when the underlying disease process is not appropriately treated, deep folliculitis and furunculosis may develop. With this complication, involvement of the entire ventrum or a generalized process may ensue. Occasionally the lesions are most severe over the pressure and wear areas of the body such as the elbows and lateral aspects of the stifle, hip, and chest region. In most cases, the lesions seem to be pruritic or painful.

Signs of systemic involvement may be evident, including anorexia, depression, weight loss, lethargy, and fever. This is often the indication of the development of bacteremia, septicemia, or both. A peripheral lymphadenopathy is also a common finding.

13.6 RECURRENT PYODERMAS

13.6.1 History and Physical Findings

Recurrent pyodermas may appear initially as a superficial folliculitis, deep folliculitis, or furunculosis (or a combination of these symptoms). Invariably, a recurrent pyoderma has some underlying reason for reappearing. Therefore the underlying problem needs to be identified and appropriately treated. One should first make certain that a recurrent pyoderma is not iatrogenic in nature. Iatrogenic recurrent pyodermas may be the result of previously inadequate drug therapy, including inappropriate antibiotic selection; inadequate dose, frequency and duration of antibiotic therapy; and the chronic use of corticosteroids as an adjunct to the treatment of a pyoderma.

13.6.2 Diagnostic Approach

The first part of the diagnostic approach to a patient with a pyoderma is to recognize the various lesions that indicate its presence. One of the commonly misinterpreted lesions on dermatologic examination is the epidermal collarette, especially when its margins are erythematous. It is often thought to be an indication of a dermatophyte (ringworm) infection but is more commonly an indication of a superficial spreading pyoderma. In addition, the presence of papules in patients with pruritus is frequently thought to be associated with primary allergic skin diseases and is treated solely with a corticosteroid. However, in many cases, closer inspection reveals the presence of a pinpoint pustule on top of the papule or a hairshaft exiting the center of the papule, which indicates the presence of a folliculitis. When one is uncertain as to whether the lesion present may be an indication of a bacterial skin disease, a skin biopsy should be performed.

When considering treatment of a dog with an antibiotic-responsive but recurrent pyoderma, the first step is to systematically evaluate the patient for some of the more common causes of a recurrence. One should consider obtaining the following tests: skin scrapings, flea combing, hair plucking and microscopic examination, skin surface impression cytology, cytology of pustules, and acetate (Scotch) tape preparations (Figure 13-1). When

these test results are negative and the cytology or culture of pustules and papules indicate the presence of a pyoderma, an appropriate antibiotic must be selected. Either the antibiotic is empirically chosen (Table 13-1) or, preferably, is chosen based on the results of culture and susceptibility testing. The next step involves the use of the dog's response to therapy as an aid to the definitive diagnosis. In a majority of dogs with a recurrent pyoderma, some degree of pruritus is present. However, at this stage of the workup, the use of a corticosteroid (or any other antipruritic drug) needs to be avoided. The dog is then treated *only* with the appropriate antibiotic and shampoo therapy (benzoyl peroxide shampoo) for a period of 3 consecutive weeks and then reevaluated (Figure 13-2). This initial duration of therapy is usually adequate in cases of superficial folliculitis but may need to be increased to 6 to 8 consecutive weeks in cases of deep folliculitis and furunculosis. If the recheck examination reveals that the pyoderma has noticeably improved or resolved but the pruritus has persisted, the dog needs to be further evaluated for the presence of an underlying primary pruritic skin disease including flea allergy dermatitis, atopic dermatitis, food allergy, scabies, demodicosis, allergic contact dermatitis, and seborrheic dermatitis. On the initial visit the owner should also be advised to observe the areas on the dog's body where the pruritus is persisting or most severe (i.e., the distribution pattern of pruritus) to assist the clinician in establishing the underlying differential diagnosis (see Chapter 10). However, if the recheck examination reveals that the pyoderma has resolved and the dog has become nonpruritic in response to the antibiotic and shampoo therapy alone, then it is necessary to establish whether the pyoderma is truly recurrent. In this case the appropriate antibiotic and shampoo therapy should be continued for a total treatment time of 8 weeks. After having done this, some patients with a history of a recurrent pyoderma will experience permanent resolution of their disease. If the pyoderma recurs after this treatment, then the following diseases should be ruled out: hypothyroidism, Cushing's disease, diabetes mellitus, reproductive hormone imbalances, demodicosis, cheyletiellosis, staphylococcal hypersensitivity, and cell-mediated immunodeficiencies (see Chapter 8).

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Table • 13-1 Systemic Antibiotics Recommended in the Treatment of Staphylococcal Pyodermas

ANTIBIOTIC	RECOMMENDED ORAL DOSE
Clindamycin	5.5 mg/kg q12h, or 11 mg/kg q24h
Erythromycin	15 mg/kg q8h
Cephalexin	22 mg/kg q8h, or 33 mg/kg q12h
Cefadroxil	22 mg/kg q12h
Trimethoprim/sulfadiazine	15–30 mg/kg q12h
Ormetoprim/sulfadimethoxine	55 mg/kg on day 1, then 27.5 mg/kg q24h
Amoxicillin/clavulanate	13.75 mg/kg q12h
Enrofloxacin*	5–20 mg/kg q24h

* Only recommended in instances of recurrent pyodermas when culture and susceptibility testing indicate its required use.

Figure 13-1 Algorithm for diagnosis and treatment of recurrent pyoderma. (From Rosser EJ, Littlewood J: *Practice resource manual: companion animal dermatology*, series I, module 1, Guelph, Ontario, 1996, Lifelearn Inc.)

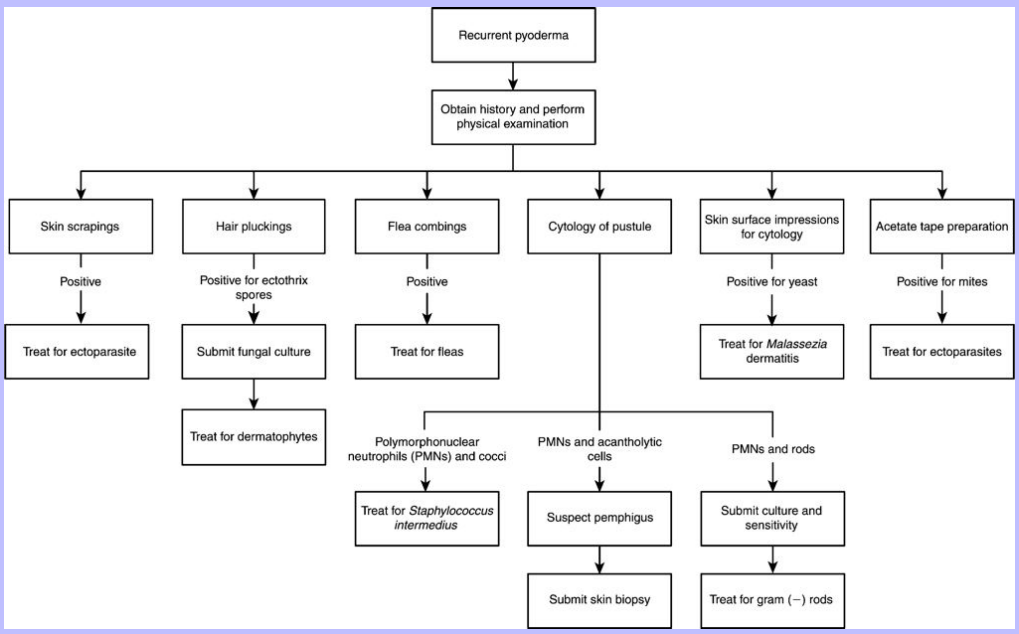
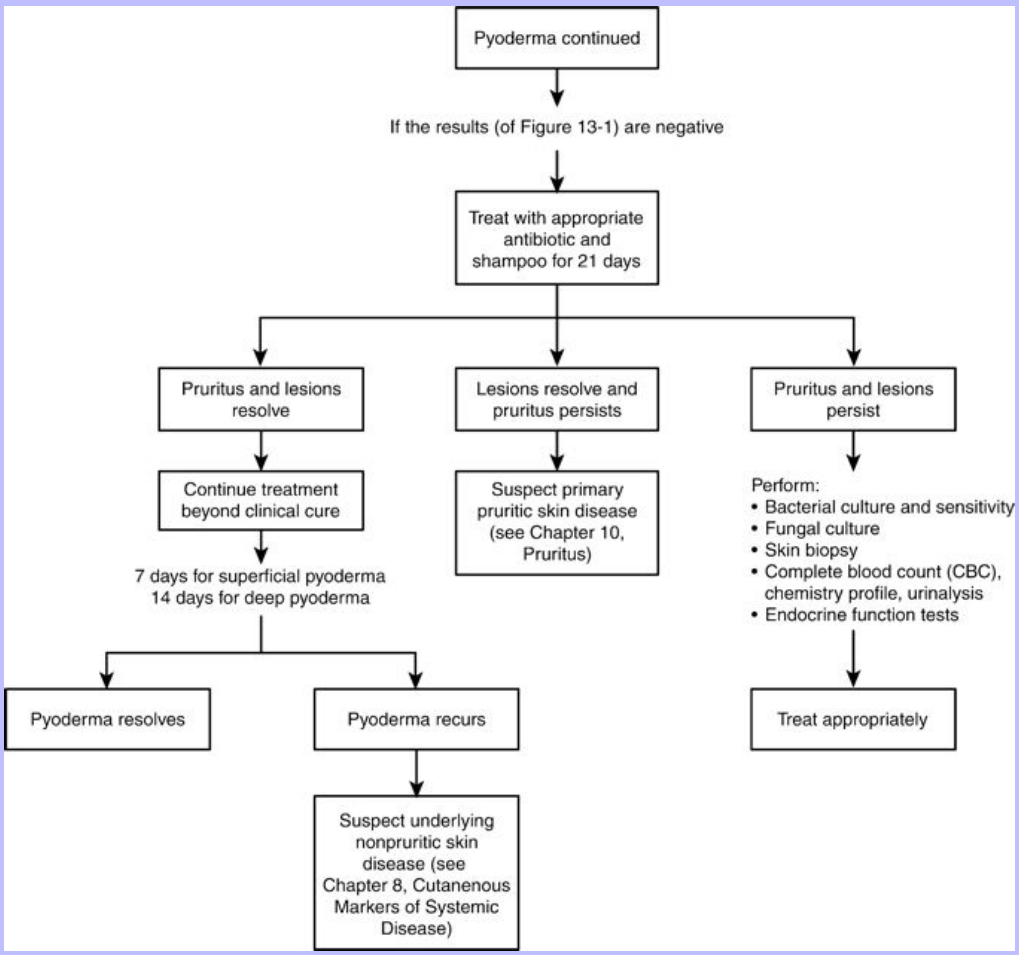


Figure 13-2 Algorithm for pyoderma continued. (From Rosser EJ, Littlewood J: *Practice resource manual: companion animal dermatology,* series I, module 1, Guelph, Ontario, 1996, Lifelearn Inc.)



14 CHAPTER • 14 Scaling and Crusting Dermatoses

Kinga Gortel

Jonathan D. Plant

14.1 PATHOPHYSIOLOGY

Scaling and crusting are common findings in many cutaneous diseases (Table 14-1). Scaling refers to the accumulation of loose fragments of cornified cells on the skin surface. Normal desquamation of cornified cells is not visible to the naked eye, so scales are only seen when loss occurs in larger flakes. Scales are usually secondary lesions in chronically inflamed skin but may also be primary lesions in conditions such as seborrhea and ichthyosis. Crusting occurs when dried exudates or secretions adhere to the surface of the skin. Crusts may be composed of pus, blood, serum, other exudates, or thick scales. They are also usually secondary, occurring on skin traumatized as a result of pruritus or in any pustular dermatosis. Crusts may be primary in some conditions such as miliary dermatitis and zinc-responsive dermatosis.

14.2 SIGNALMENT

14.2.1 Age

Puppies and kittens developing scaling within the first few weeks of life should be evaluated for transmissible infections and congenital dermatoses. Juveniles should be screened for infectious diseases, such as parasites, hereditary dermatoses, nutritional dermatoses, and environmental diseases. Differential diagnoses for similarly affected adult dogs and cats include the diseases listed for younger animals, as well as allergic, immune-mediated, endocrine, and metabolic diseases; keratinization disorders; and cutaneous neoplasia.

14.2.2 Breed

Breeds with an inherited predisposition to the development of primary scaling and crusting disorders include American cocker spaniels, English springer spaniels, West Highland white terriers, Basset hounds, Irish setters, Doberman pinschers, and Labrador retrievers. Breed predispositions are also noted in many other dermatoses that lead to scaling and crusting, including canine atopic dermatitis, hypothyroidism, and sebaceous adenitis.

14.3 HISTORICAL FINDINGS

The history can be helpful in narrowing the list of differential diagnoses in an animal with scaling or crusting. The age of onset should be established. The owner should also be questioned as to the seasonality of the scaling and crusting. An important consideration is the degree of accompanying pruritus. Diseases that are often severely pruritic include sarcoptic acariasis, atopic dermatitis, fleabite hypersensitivity, food hypersensitivity, *Malassezia* dermatitis, and cutaneous lymphoma.

14.4 PHYSICAL EXAMINATION

14.4.1 Lesions

Scaling and crusting are often encountered concurrently. The skin should be examined for pustules, papules, excoriation, erythema, ulceration, and the shape of crusts or scaly areas should be noted (e.g., epidermal collarettes).

14.4.2 Distribution

Scaling and crusting dermatoses may be generalized or have site predilections. Generalized conditions include dermatophytosis, cheyletiellosis, primary seborrhea, and sebaceous adenitis. Site predilections include the nasal planum (e.g., pemphigus foliaceus, discoid lupus erythematosus, squamous cell carcinoma), footpads (e.g., pemphigus foliaceus, zinc-responsive dermatosis, superficial necrolytic dermatitis, plasma cell pododermatitis), and ear pinnae (e.g., sarcoptic mange, ear margin seborrhea).

14.5 DIAGNOSTIC PLAN

Skin scrapings and cytology are simple and often useful for evaluation of dogs and cats with scaling and crusting (Figure 14-1). Skin scrapings are most useful for diagnosing demodectic mange in dogs and *Notoedres cati* in cats. They are less sensitive for canine *Sarcoptes scabiei. Cheyletiella* mites are easiest to find by acetate tape impressions.

Samples for cytologic examination of the skin may be collected directly from the surface of the skin by impression smears if the skin is greasy or moist or after the removal of crusts or adherent scales. If pustules are present, their content should be smeared on a slide. Waxy or dry samples benefit from gentle heat fixing. A modified Wright's stain (e.g., Diff Quick) is used to examine the slides. Cytology is most useful for confirming presence of bacteria and yeast. The inflammatory response of the skin can also be evaluated because neutrophils, eosinophils, and mononuclear cells are easily differentiated. The presence of numerous acantholytic cells among neutrophils suggests pemphigus but is occasionally encountered in other inflammatory conditions.

Examination for fungi should be attempted when dermatophytosis is suspected. Cats with scaling and crusting should always be checked for dermatophytes unless another cause is readily identified. A Wood's light examination should be performed. A dermatophyte test medium (DTM) fungal culture should always be inoculated if dermatophytosis is suspected. Direct examination of hair for dermatophytes is less sensitive.

Skin biopsy is needed to make a definitive diagnosis in some scaling and crusting disorders, including immune-mediated diseases, neoplastic conditions, and primary keratinization disorders. Crust and scale must be included in the biopsy, so the biopsy site should never be cleaned or scrubbed. Hair may be gently cut with scissors without disrupting any surface material.

Table • 14-1 Scaling and Crusting Diseases of Dogs and Cats

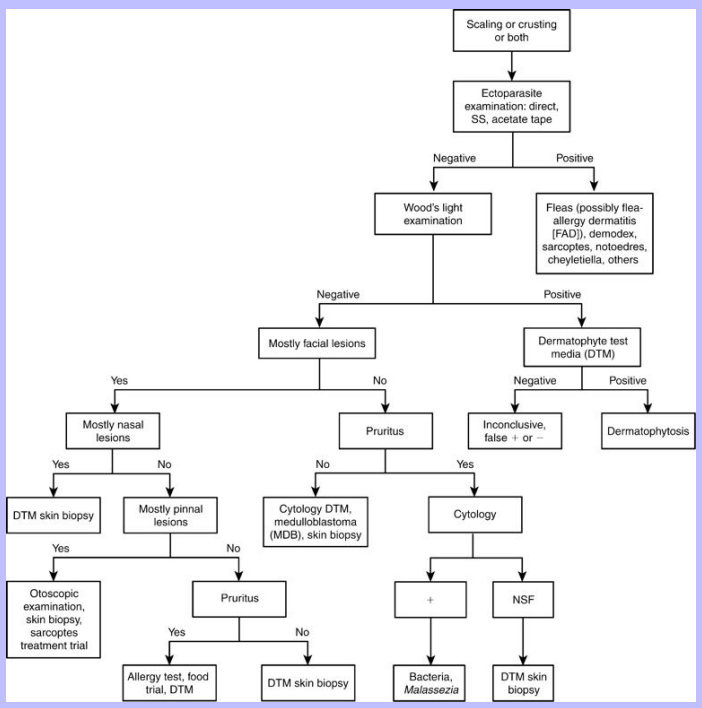
DISEASE	LESIONS	SPECIES	SIGNALMENT	LESION DISTRIBUTION	FREQUENCY	PRURITUS	DIAGNOSIS
Bacterial							
Superficial folliculitis	Crusts, scales, collarettes, pustules	Dog >cat	Varies	Trunk	C	–to ++	CS, Cyt, BC, Bx
Deep pyoderma	Crusts, ulcers	Dog >cat	Varies	Trunk, feet	C	+	CS, Cyt, BC, Bx
Mucocutaneous pyoderma	Crusts, ulcers	Dog	German Shepherd or others	Lips, peribuccal	U	+(painful)	CS, Bx
Pyotraumatic dermatitis	Moist crust, exudation, erythema	Dog	Any (often flea-related)	Face, neck, caudal trunk	C	+++	CS
Fungal							
Dermatophytosis	Crusts, scales, alopecia, erythema	Cat >dog	Young most frequently	Head, extremities, trunk	C	–to ++	DTM, light
Malassezia dermatitis	Crusts, scales, erythema, lichenification	Dog >cat	Adult most frequently	Axillary, groin, interdigital, facial	C	+++	Cyt
Parasitic							
Ctenocephalides felis (flea)	Scales, erythema	Dog >cat	Any	Lumbosacral, neck	C	+	CS, parasite exam
Sarcoptes scabiei	Crusts, scales, excoriations, alopecia, erythema	Dog	Any	Pinnal margins, lateral elbows, ventrum	C	+++	SS, response to therapy
Demodex canis	Crusts, scales, exudation, alopecia, erythema	Dog	Young or immunocompro-mised adults	From single lesions on the head to generalized	C	–to +	SS
Cheyletiella spp.	Scales	Dog, cat	Young most frequently	Dorsal trunk to generalized	U	–to ++	SS, tape impression
Notoedres cati	Crusts, scales	Cat	Any	Head, feet, generalized	U	–to +++	SS
Viral							
Feline leukemia virus (FeLV)	Crusts, scales, erosions	Cat	Any	Face, pinnae, perioral, feet, trunk	U	++	Serology, Bx
Allergic							
Atopic dermatitis	Erythema, alopecia, crusts (excoriation), scales, and others	Dog >cat	All, dogs often 1–5 years old	Face, ears, feet, ventrum	C	+to +++	CS, IDST, IgE
Food hypersensitivity	Erythema, crusts (excoriation), and others	Dog, cat	All, any age	Any	U	+to +++	Food trial
Flea bite hypersensitivity	Erythema, crusts (excoriation), and others	Dog, cat	All	Caudal dorsum, ventrum, thighs	C	++to +++	Response to flea control

Miliary dermatitis	Small hemorrhagic crusts	Cat	All (often associated with fleas)	Dorsum	C	++	CS
Endocrine and Metabolic							
Hyperadrenocorticism	Alopecia, cutaneous atrophy, calcinosis cutis, crusts (pyoderma)	Dog >cat	Middle aged, older	Trunk	C	–(occ. +)	MDB, hormone assays, imaging, Bx
Hypothyroidism	Scaling, dry skin, pyoderma, +/–alopecia	Dog	Middle aged, often large breed	Generalized	C	–	MDB, thyroid assay
Necrolytic migratory erythema	Severe adherent crusting	Dog (cat)	Old	Muzzle, footpads, pressure points	R	+to ++ (painful)	Bx, MDB, liver assays, imaging
Immune Mediated							
Pemphigus foliaceus	Crusts, pustules	Dog, cat	Any age and sex; Akita, chow chow, and others	Nasal planum, muzzle, pinnae, foot pads, trunk	U	–to +	Bx
Discoid lupus erythematosus	Crusts, depigmentation erosions, ulcers	Dog, cat	Collies, Shetland sheepdog, and others	Nasal planum, muzzle	U	–	Bx
Erythema multiforme	Crusts, vesicles erythema, target lesions, erosions, ulcers	Dog, cat	Any	Axillae, groin, mucocutaneous junctions	U	–	Bx
Congenital and Hereditary							
Primary seborrhea	Excessive scaling or greasy skin	Dog (cat)	Onset before 6 months, American cocker spaniel and others	Generalized	U	–to ++, esp. with secondary infections	Bx
Schnauzer comedo syndrome	Comedones that may become crusted	Dog	Miniature schnauzer	Dorsum	C	–	CS, Bx
Familial canine dermatomyositis	Alopecia, scaling, depigmentation	Dog	Onset before 6 months, collie, Shetland sheepdog, and others	Face, pressure points	U	–	Cs, Bx
Keratinization Defects							
Secondary seborrhea	Excessive scaling or greasy skin	Dog, cat	Any age	Depends on primary cause	C	–to +++depending on cause	CS, any appropriate tests for primary disease
Vitamin A—responsive dermatosis	Marked follicular plugging, hyperkeratotic plaques	Dog	Cocker spaniel and others Adult onset	Generalized, more pronounced on ventrum	U	–to ++	CS, Bx
Ear margin dermatosis	Follicular casts and scaling	Dog	Dachshund and others	Ear margins, lateral and medial	U	–, may become painful	CS, Bx
Environmental							

Solar dermatitis	Erythema, scaling, may progress to exudation and crusting	Dog >cat	Light-haired animals, outdoor exposure	Pinnae, nasal planum (cat), bridge of nose, ventrum (dog)	C	–to +	CS, Bx
Nutritional							
Zinc-responsive dermatosis	Crusts, scales, erythema, alopecia	Dog	Siberian husky, Alaskan malamute; young adults	Periocular, perioral, mucocutaneous junctions, pressure points	U	–to +	Bx
Fatty acid deficiency	Scales	Dog, cat	Any	Generalized	U	–to ++	Dietary hx
Other							
Cutaneous lymphoma	Lesions highly variable but may include severe scaling	Dog >cat	Older animals	Generalized or localized	U	–to +++	Bx
Granulomatous sebaceous adenitis	Hyperkeratosis, alopecia, follicular casts, may be erythematous	Dog (cat)	Young to middle-aged, standard poodle, Akita, vizsla, and others	Face, trunk, pinnae, become generalized	C	–to ++	CS, Bx
Otitis externa	Scale, erythema, otic exudate	Dog >cat	Any	Pinnae, ear canal	C	++	Otoscopic examination, Cyt, BC

BC, Bacterial culture; *Bx,* skin biopsy; *C,* common; *CS,* clinical signs; *Cyt,* cytology; *DTM,* dermatophyte test medium fungal culture; *Hx,* history; *IDST,* intradermal skin test; *IgE,* allergen-specific serum IgE assay; *MDB,* minimum database; *NSF,* no significant findings; *R,* rare; *SS,* skin scraping; *U,* uncommon; +, positive; –, negative.

Figure 14-1 Diagnostic approach to scaling and crusting in dogs and cats.



A minimum database is most useful in middle-aged and older animals when endocrine or metabolic causes are suspected. Bacterial culture should be performed when bacteria are identified on cytology or when crusting does not completely resolve after appropriate antibiotic treatment for pyoderma.

14.6 TREATMENT

It is beyond the scope of this chapter to address the specific treatment of each disease that may result in scaling and crusting. In general terms, treatment can be divided into topical and systemic therapeutic approaches.

14.6.1 Topical Therapy

To reduce scaling and crusting, the goal is to normalize cell proliferation, differentiation, and desquamation and to reduce exudation from the skin surface. Active ingredients should be selected based on the underlying condition, and are most frequently applied as shampoos and conditioners. Active ingredients may be keratolytic, keratoplastic, degreasing, antimicrobial, antiparasitic, antiinflammatory, antipruritic, or moisturizing. Most animals with generalized scaling and crusting disorders will benefit from frequent bathing (twice a week or more).

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14.6.2 Systemic Therapy

For secondary scaling and crusting, attempts should be made to correct the underlying cause. For primary scaling and crusting disorders of dogs, vitamin A or synthetic retinoid therapy are variably helpful. Vitamin A is given at a dose of 800 to 1000 mg/kg/day. The synthetic retinoid acetretin has been used to treat primary seborrhea in dogs at a dose of 1 mg/kg/day. The principal effect is to normalize epithelial keratinization. Possible adverse reactions include teratogenicity, keratoconjunctivitis, elevated liver enzymes, and hypertriglyceridemia. Its use is limited by expense.

15 CHAPTER • 15 Changes in Pigmentation

Zeineb Alhaidari

Pigmentation changes are frequently seen in veterinary medicine; they not only have potential cosmetic importance but they could also imply medical or zootechnical consequences because possible causes include systemic diseases, genodermatoses, or both. Evaluation of pigmentation changes requires developing a differential diagnosis (Figure 15-1).

The term *leukoderma* refers to a loss of melanin pigmentation of the skin. The term *leukotrichia* or *poliosis* refers to a loss of melanin pigmentation of the hair. Similarly, *melanoderma* refers to an increased melanin pigmentation of the skin, and *melanotrichia* refers to an increased pigmentation of the hair.

15.1 HYPOPIGMENTATION

15.1.1 History

15.1.1.1 Breed

A marked breed predilection exists for most noninfectious focal hypopigmentation disorders.

- *Vitiligo,* characterized by the symmetrical development of achromic macules on the facial mucocutaneous junctions, has a breed predilection in the Tervueren, Rottweiler, Doberman pinscher, Newfoundland, Collie, German shorthair pointer, Old English sheepdog, (all the breeds, with or without majascule) and Siamese cat.
- The *uveodermatologic syndrome,* an autoimmune disorder targeting ocular and cutaneous melanocytes and resulting in uveitis and skin depigmentation, has been described mainly in northern breeds such as the Siberian husky, Samoyed, and Akita.
- *Acquired idiopathic hypopigmentation of the nose,* an idiopathic gradual loss of nasal planum pigment, is widespread in some canine breeds such as the Labrador retriever, Siberian husky, Samoyed, Poodle, and German shepherd.
- *Discoid lupus,* a presumed autoimmune photoaggravated disorder limited to the skin, affects mainly Collies and German shepherds.
- *Dermatomyositis* is a genodermatosis described in the Collie, Shetland sheepdog, and Beauceron shepherd breed. Crusting, ulceration, and depigmentation of the skin, affecting preferentially the face and extremities, are associated with varying degrees of muscle involvement.

15.1.1.2 Age of Onset

The age of onset is often helpful in the diagnosis of certain depigmenting disorders. An early age of onset usually suggests a genodermatosis. *Dermatomyositis* is classically first observed in 3-to 4-month-old puppies, with variably affected individuals in the litter. Symmetric unpigmented macules involving the mucocutaneous junctions of the face in a young dog, aged 8 months to 3 years, are highly suggestive of *vitiligo. Discoid lupus,*

which has a similar clinical appearance to vitiligo, also affects dogs of a similar age. The old animal is more prone to develop *bullous autoimmune dermatoses* and neoplastic disorders such as *epitheliotrophic lymphomas*.

15.1.1.3 Evolution

Evolution of the hypopigmentation should be carefully documented. Circumstances of onset should be investigated. Local trauma, including physical or chemical causes, must be considered as a potential etiology of melanocyte dysfunction or destruction. Any drug administration preceding the onset of symptoms should be noted.

The nature and location of the initial lesion could be of major interest, especially in the differential diagnosis of nasal depigmentation. Unpigmented macules developing at the junction between the planum nasale and haired skin are highly suggestive of *bullous autoimmune diseases. Contact dermatitis* usually affects the rostral nares. Depigmentation developing on the floor of one nostril and associated with a purulent discharge is highly suggestive of *aspergillosis*.

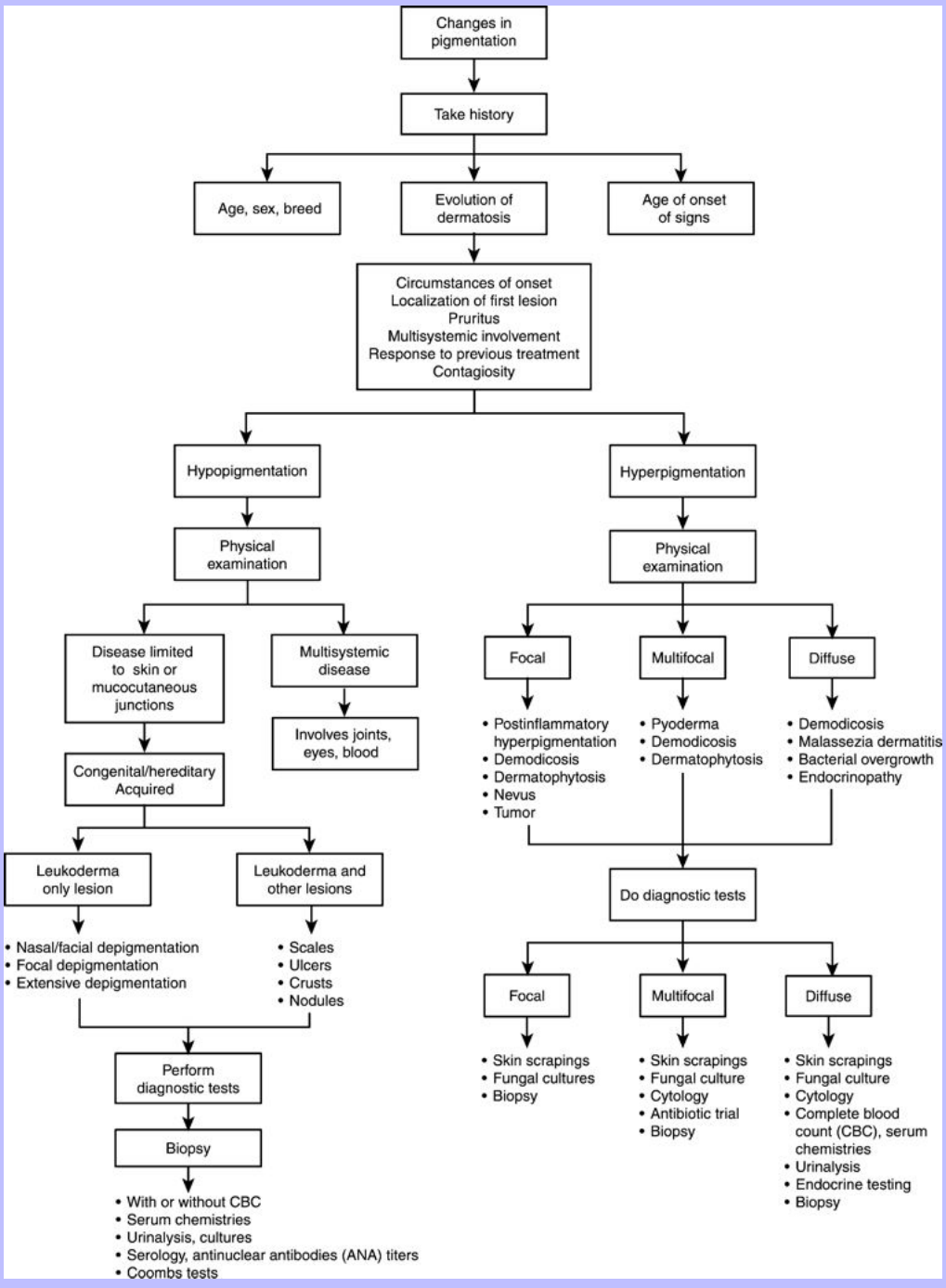
Because *lupus erythematosus* or *pemphigus erythematosus* lesions are exacerbated with sun exposure, seasonality of symptoms is an interesting observation. Reported concurrent clinical signs, such as lameness, can be indicative of *leishmaniasis* or *systemic lupus erythematosus* (SLE). Ocular involvement suggests *uveodermatologic syndrome, leishmaniasis,* or *systemic mycoses,* such as *cryptococcosis* or *blastomycosis*. Weight loss, fever, and anorexia can be manifestations of *neoplastic diseases, SLE, bullous autoimmune disorders, systemic mycoses,* or *leishmaniasis*.

15.1.2 Physical Examination

Physical examination is the second important step in the diagnosis of pigmentary changes. The physical evaluation should help determine whether a disease is limited to the skin or multisystemic (see Figure 15-1). If the disease is limited to the skin and if leukoderma, leukotrichia, or both is the only skin lesion present, then one has to consider the topography of the lesions.

If the depigmentation is limited to the nose or facial mucocutaneous junctions, the persistence of normal nasal surface architecture favors a noninflammatory cause, such as *vitiligo* or *acquired idiopathic hypopigmentation*. Alternatively, if the normal surface architecture has been altered, an inflammatory dermatosis should be suspected. However, ultraviolet radiation associated with sunlight can induce an actinic dermatitis on a lesion that is initially simply unpigmented, with subsequent erythema, ulcers, crusts, and disappearance of cutaneous surface markings.

Figure 15-1 Algorithm for evaluation of changes in pigmentation.



If the unpigmented lesion is focal, then a history of *trauma* should be investigated. Extensive acquired leukotrichia can follow an immunologic attack directed primarily against the hair follicles in *alopecia areata,* resulting in alopecia and occasional regrowth of white hairs.

If leukoderma, leukotrichia, or both is associated with other skin lesions such as scales, ulcers, or crusts, *leishmaniasis* or *autoimmune dermatoses* should be considered.

Infiltrative lesions are usually indicators of *systemic mycoses* or *tumors*.

Multisystemic involvement is seen in *leishmaniasis, SLE, systemic mycoses,* or *tumors*. Arthritis and glomerulonephritis are frequent features of both *SLE* and *leishmaniasis*. Hematologic disorders, such as hemolytic anemia, leukopenia, and thrombocytopenia, can be associated with *SLE*. Nonregenerative anemia, leukopenia, and monocytosis frequently are observed in *leishmaniasis*. In the *uveodermatologic syndrome,* uveitis and subsequent glaucoma usually precede the cutaneous manifestations. The eye is also a frequent target in *leishmaniasis* and in *systemic mycoses,* such as *cryptococcosis* and *blastomycosis*.

15.1.3 Diagnostic Tests

Skin biopsy is the fundamental diagnostic procedure when faced with hypopigmentation (see Figure 15-1). Specimens should be taken both from the center and from the margins of lesions, especially if the disease is active and spreading. Biopsies can demonstrate the presence or absence of an inflammatory infiltrate and the presence or absence of melanocytes. The presence or absence of melanocytes is difficult to ascertain because special stains such as Fontana-Mason or dopa reaction cannot differentiate between nonfunctional and absent melanocytes. If inflammatory infiltrates and melanocytes are absent, one can suspect either *vitiligo* or a *postinflammatory depigmentation* with complete destruction of melanocytes. If melanocytes are present, *acquired idiopathic hypopigmentation* can be suspected. Inflammatory infiltrates are associated with several depigmenting diseases. Of particular interest are lichenoid infiltrates, which are chiefly lympho-cytic in *lupus erythematosus* and *epitheliotrophic lymphomas* and are granulomatous in *uveodermatologic syndrome*. Infectious agents such as leishmania, mycobacteria, or fungal organisms are sometimes demonstrated on histologic sections of inflamed unpigmented lesions. If a pyogranulomatous or granulomatous nodular-to-diffuse infiltrate is observed, special stains should be requested in an attempt to identify the presence of microorganisms.

Depending on biopsy results, diagnosis will be completed by other tests such as complete blood count (CBC), serum chemistry profile, urinalysis, cultures, serologic testing for leishmaniasis or systemic mycosis, antinuclear antibodies dosage, and Coombs' test.

15.2 HYPERPIGMENTATION

15.2.1 History

15.2.1.1 Breed

Demodicosis and most *endocrinopathies* occur more frequently in specific breeds. Doberman pinschers, Shar Peis, West Highland white terriers, Scottish terriers, Boston terriers, Great Danes, and Weimaraners are breeds known to have a high prevalence of *demodicosis*. Great Danes, Irish setters, Doberman pinschers, and Old English sheepdogs are predisposed to *hypothyroidism,* whereas poodles, boxers, Boston terriers, beagles, and dachsunds are predisposed to *hyperadrenocorticism*.

15.2.1.2 Age of Onset

Age of onset is an important clue to the diagnosis of hyperpigmenting disorders. An infectious cause, such as *pyoderma, demodicosis,* or *dermatophytosis*, should be suspected primarily in young animals, whereas older animals may be at risk for endocrinopathies or tumors.

15.2.1.3 Evolution

The evolution of the hyperpigmentation should be carefully investigated. The age of onset and distribution of the initial lesions should be described. Any *trauma* can result in postinflammatory hyperpigmentation. Posttraumatic hyperpigmentation is observed more frequently in certain breeds such as the poodle (especially apricot or gray) or the Siamese cat. Scratching is a common cause of skin trauma. Thus any chronic pruritic skin condition (e.g., *atopy, adverse food reactions, pyoderma, Malassezia dermatitis, sarcoptic mange*) can potentially result in lichenification and hyperpigmentation. This makes pruritus a criterion of primary importance in the differential diagnosis of hyperpigmentation. Response to previous therapeutic trials, including doses and duration of therapy, should be reported. Spread to other animals in the environment or to owners increases the suspicion for contagious diseases such as *dermatophytosis* or *acariasis* (e.g., *scabies, cheyletiellosis*).

15.2.2 Physical Examination

When dealing with hyperpigmentation, the distribution of lesions is of major importance. If the lesion is solitary, the differential diagnosis should include *postinflammatory hyperpigmentation* (carefully review history), *demodicosis, dermatophytosis, nevus,* and *tumor*. If the lesions are multifocal and coin shaped with peripheral expansion, *pyoderma, demodicosis,* and *dermatophytosis* are primary suspects. In cases of diffuse nonpruritic hyperpigmentation, *demodicosis* and *endocrinopathies* should be considered. The latter are usually associated with systemic signs such as lethargy and obesity in the case of hypothyroidism, and polyuria/polyphegia (PU-PD) in the case of Cushing's syndrome.

15.2.3 Diagnostic Tests

Multiple skin scrapings are an extremely important diagnostic aid in almost every dermatologic case. They can give a quick, inexpensive, and easy diagnosis of demodicosis, scabies, or cheyletiellosis, although the latter two mites can be difficult to demonstrate. To confirm or eliminate the diagnosis of dermatophytosis, Wood's lamp examinations, direct examination of hairs or scales, and fungal culture should be performed in every case of focal, multifocal, or diffuse hyperpigmentation. Cytology is another easy test to use when dealing with hyperpigmentation. It can reveal yeast, such as *Malassezia pachydermatis,* or cocci. If the previous diagnostic tests fail to reveal a specific causative agent, an antibiotic trial is indicated when presenting with multifocal coin-shaped hyperpigmented lesions in dogs because pyoderma is common in dogs. Antibiotics with known activity against staphylococci, including beta-lactamase–resistant penicillins; first-generation cephalosporins, macrolides, and related molecules (i.e., lincomycin and clindamycin); potentiated sulfonamides; or fluoroquinolones should be prescribed for 4 to 6 weeks before rechecking the dog. In dogs with diffuse hyperpigmentation, a CBC, serum biochemistry panel, and urinalysis should be performed after skin scrapings have excluded the possibility of demodicosis and cytology has excluded bacterial overgrowth of *Malassezia* dermatitis has been cytologically excluded. These diagnostic tests might provide helpful clues leading to the identification of specific underlying endocrinopathies. For example, increases in serum alkaline phosphatase,

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alanine aminotransferase (ALT), and cholesterol may raise the suspicion of hyperadrenocorticism. Thyroid function can be evaluated by a basal T_4 concentration, endogenous thyroid-stimulating hormone (TSH) level, or TSH response test. Adrenal function can be evaluated using adrenocorticotropic hormone (ACTH) stimulation, low-dose dexamethasone suppression, or urine cortisol: creatinine ratio tests. Sex hormone imbalances can be evaluated by basal estradiol and progesterone concentrations in female dogs and by human chorionic gonadotropin (HCG) stimulation tests in male dogs. The last and least rewarding procedure when dealing with skin hyperpigmentation is skin biopsy. A biopsy generally gives only vague clues or eliminates certain possible causes. It can, however, in conjunction with history and physical examination, furnish a high suspicion index for specific diseases such as *seasonal flank alopecia.* Seasonal flank alopecia is a cyclic follicular dysplasia characterized clinically by recurrent symmetric hyperpigmented alopecic flank lesions and an unpredictable prognosis. Biopsies demonstrate follicular atrophy and infundibular hyperkeratosis, which extend into the ostia of the secondary follicles and sebaceous ducts, mimicking the appearance of a malformed foot.

As always in dermatology, a definitive etiologic diagnosis is a mandatory prerequisite to successful management. Pigmentation changes, including both hypopigmentation and hyperpigmentation, are no exceptions.

16 CHAPTER • 16 Fleas, Flea Allergy, and Flea Control

Candace A. Sousa

Flea infestations of pets and the home environment are a common occurrence. Fleas are responsible for the production and transmission of several diseases of humans and their pets. The flea that causes most of the problems is *Ctenocephalides felis felis*, the common cat flea. In one study it accounted for 92% to 99% of the fleas found on dogs and cats, respectively.[1]

The flea passes through four stages in its life cycle. It undergoes a complete metamorphosis at each stage.[2] At any time approximately 57% of the fleas are eggs, 34% are larva, 8% are pupa, and only about 1% are present as adults. The life cycle can be completed in as little as 12 days or take as long as 174 days and is dependent on the ambient temperature and humidity.[3]

Flea eggs are oval, pearly white, nonsticky, and about 0.5 mm in length.[4] The egg hatches between 1 and 10 days of being deposited on the host and falling off into the environment, depending on the ambient temperature and humidity (ideal conditions are 70% relative humidity and 35°C (95°F).[2–4]

Flea larvae emerge from the eggs after hatching. The larva of *C. felis felis* has three stages or larval "instars." The larvae are about 2 mm long, slender, white, and covered with short hairs. They feed on organic debris and blood-containing feces from adult fleas. The larvae are negatively phototactic (move away from light) and positively geotactic (move toward the ground).[2,4] Therefore when indoors the larvae avoid direct sunlight and move under furniture, appliances, and into carpet fibers. Outdoors, they move into shaded areas under bushes, trees, and leaves. Five to 11 days are required for the larvae to molt twice, during which they grow to about 5 mm in length. The larvae are extremely susceptible to heat and desiccation. They can survive only if the relative humidity is greater than 50% or when soil moisture is between 1% to 20%.[3]

Temperatures greater than 35°C (95°F) and less than 3°C (35°F) for more than 40 hours per month are also deleterious to survival. The mature larvae produce a sticky cocoon in which to pupate. Environmental debris may adhere to the cocoon, which helps it go undetected and provides excellent protection against insecticides. Pupation lasts from 5 to 9 days. Environmental locations suitable for a high rate of larval survival are termed *hot spots* or *source points*.

The preemerged adult flea is the stage that can extend the longevity of the flea. They can survive for up to 140 days in the cocoon if protected from desiccation. In the cocoon they are also protected from most insecticides. Physical pressure and changes in light, temperature, and carbon dioxide are thought to be stimuli for emergence of the adult flea.

Newly emerged fleas can survive in the environment from 10 to 62 days, again depending on the temperature and humidity.[8] Once on the host, the flea begins feeding within seconds and becomes an obligate parasite. The animal's grooming activity is the primary cause of mortality of ectoparasites. The flea feeds by piercing the skin of the host and inserting the tip of the labrum epipharynx to extract capillary blood.[5] Saliva is introduced by way of the salivary pump and used as an anticoagulant.[4] The female flea consumes an average of 14 µl of blood per day (equivalent to 15% of her body weight).[6] About 72 female fleas will remove 1 ml of blood daily. Male fleas consume less blood than females but feed more frequently.[2] Once fleas feed and initiate reproduction, they become dependent on a constant source of blood or they will die within a couple of days. During feeding, female fleas excrete large quantities of incompletely digested blood ("flea dirt") in long tubular coils or fine pellets.[2]

The first of multiple matings occurs on the host within 8 to 24 hours. Egg production begins within 36 to 48 hours of the first blood meal, reaches maximum production between 4 and 9 days, and may continue for more than 100 days. Egg production peaks at 40 to 50 per day and averages 27 eggs per day for the first 50 days. A single female flea may deposit over 2000 eggs during her lifetime.[4,7]

Flea allergy dermatitis (FAD) is the most common veterinary dermatologic condition in the world. It begins with the bite of a flea. The saliva of the flea contains amino acids, aromatic compounds, fluorescent materials, polypeptides, and phosphorus.[9] In the dog the antigenic substances carry a molecular weight of 18,000–45,000Da with the major allergen weighing 30,000–32,000 Da.[10] Dog owners notice scratching, chewing, licking, biting, and other signs of pruritus. Sixty-one percent of flea-allergic dogs develop clinical signs between 1 and 3 years of age.[11] As animals age, with continued exposure to fleas, the degree of hypersensitivity may wane. FAD is uncommon in dogs less than 6 months of age. Patients usually have papules, crusts, salivary stains, excoriations, and erythema in a wedge-shaped pattern over the lumbosacral region, caudal thighs, proximal tail, ventral abdomen, and around the umbilicus. With chronic itching the areas become alopecic, lichenified, and hyperpigmented and the dog develops an odor related to secondary infections with *Staphylococcus intermedius* and *Malassezia pachydermatis*.

Figure 16-1 Dorsal lumbosacral region of an Afghan hound with FAD. Note the distribution of the alopecia. Skin is erythematous and crusted.

A diagnosis of FAD is based on the age of onset of the pruritus, the distribution of the pruritus and clinical signs, and the observation of fleas, flea feces, or both. Many dogs that are allergic to the bite of a flea have very few fleas on them at any time because their excessive grooming activity removes the fleas. Cats are especially efficient at removing fleas. Some of those patients will have recurrent tapeworm *(Dipylidium caninum)* infestations from ingestion of the fleas. The diagnosis of FAD can be confirmed with an intradermal skin test with flea antigen.

Treatment of FAD is a 3-step process. Most important is the elimination of the fleas from the animal and prevention of re-infestation with the use of both on-animal and-premise flea control. The second step involves providing the animal with relief from the allergic reaction and pruritus. Moderate doses of short-acting oral corticosteroids used for 5–10 days will usually be sufficient. Lastly, any secondary infections need to be treated with the appropriate oral and/or topical medications.

The goals of flea control are to eliminate the adult fleas on *all* the animals in the house and immature fleas in the environment. The best approach incorporates mechanical, physical, and chemical measures. Source points should be identified and treated aggressively. Carpets, pet bedding, and resting areas in the home should be well vacuumed using a vacuum with a power head. Pet bedding should be washed. Dead vegetation should be cleaned away from animal resting areas outside. A wide variety of chemicals can be used on pets and in the environment; however, no single, “miracle” flea product exists that can be used on both animals and their surroundings.

Botanical products are the closest things we have to “natural” insecticides. *Pyrethrins* are derived from a certain species of chrysanthemum. Six naturally occurring pyrethrins exist. They are minimally toxic to mammals (oral LD50 in rats, 1500 mg/kg body weight).[12] Because pyrethrins are unstable in the presence of ultraviolet light, moisture, and air, most are found combined with synergists (e.g., piperonyl butoxide) that inhibit oxidative and hydrolytic degradation of the compounds. *Pyrethroids* (e.g., permethrin, sumethrin, resmethrin, d-trans-allethrin, tetramethrin, fenvalerate) are synthetic insecticides derived from the molecular structure or sharing the same mechanism of action of pyrethrins. They are more stable than pyrethrins but are slightly more toxic. The mechanism of action of pyrethroids is based on changes in ion conductance, mainly through delayed closing of the sodium activation gate of the nerve cells.[13]

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Figure 16-2 Same dog as in Figure 16-1. Dermatitis extends onto the caudal thighs.

Figure 16-3 Cat with FAD. Pruritus has resulted in partial alopecia of the entire caudal half of the trunk.

Rotenone is an extract of the root of the derris plant and contains two active ingredients. It is slightly more toxic than pyrethrins and is very toxic to fish.[12] It is safe for use in small animals but not used in many products. *D-limonene* and *linalool* are derived from citrus pulp. They have a solvent action on the cuticular lipids of the exoskeleton of the flea that results in desiccation and death of the flea.[14] They are relatively effective but very short acting, and there have been reports of severe toxic reactions in cats.

Carbamates (e.g., carbaryl, propoxur, bendiocarb) and *organophosphates* (e.g., malathion, ronnel, chlorpyrifos, fenthion, dichlorvos, cythioate, diazanon, propetamphos, phosmet) are cholinesterase inhibitors. They act mainly as adulticides but are potentially very toxic to pets, particularly to cats and young animals. These ingredients are found in a variety of formulations for use on the animal and in the environment. Cythioate and fenthion are also formulated as systemic insecticides.

Nitenpyram (Capstar™, Novartis Animal Health) is a neonicotinoid that acts at the nicotinic acetylcholine receptor of insects. It has a very low mammalian toxicity. It is supplied as an oral medication that can be given to dogs and cats to kill adult fleas within 6 hours after administration. The product is rapidly eliminated in the urine and does not kill new fleas after 24 hours of administration.

Imidacloprid (Advantage™, Advantix™, Bayer) is a topical adult flea killer that acts by binding to nicotinergic receptors in the nervous system of the insect. Claims are that most fleas are killed within 24 hours, before they have a chance to lay eggs. It is used as an on-animal spot treatment once a month and is very safe for use on mammals; however, it can be washed off if the pet is bathed, which will decrease its efficacy.

Fipronil (Frontline®, Frontline Plus®, Merial) is another topical adult flea killer that is found as both a spot treatment and spray. It is a phenylpyrazole and acts by blocking the passage of chloride ions through gamma-aminobutyric acid (GABA)–regulated chloride channels. It is highly specific to invertebrates. One hundred percent of adult fleas are killed within 24 hours. Once used, claims are made that fleas will be killed for up to 3 months and that after 48 hours the animal can be bathed as often as needed without affecting the efficacy of the product because the active ingredient

is incorporated within the sebaceous secretions. Frontline Plus® also contains methoprene, which acts to prevent the production of viable flea eggs and larvae.

Selamectin (Revolution®, Pfizer Animal Health) is an FDA-approved avermectin that is applied as a spot-on product once monthly to dogs or cats. A single application kills more than 98% of the fleas within 24–36 hours. The flea-killing effects persist for 1 month, even with bathing. Selamectin also has ovicidal and larvicidal activity against fleas.

Sodium polyborate (SPB) is a powder that is used in the indoor environment to interrupt the flea life cycle. It is believed that the flea larvae ingest the powder and are killed before they can pupate. Elimination of fleas in the indoor environment may require 3 to 6 weeks. SPB has a high margin of safety around mammals (oral LD50 in rats, 3479 mg/kg).

Insect growth regulators (IGRs) (e.g., methoprene, fenoxycarb, pyriproxyfen) mimic the juvenile hormone that the flea larvae produce during pupation. When the egg and larvae are exposed to this hormone, the egg will not hatch and the larvae will not pupate. These products have no effect on pets and people because these hormones are specific for insects. (Oral LD50 in dogs for methoprene, 5000 to 10,000 mg/kg; oral LD50 for fenoxycarb in rats, 16,000 mg/kg) IGRs are commonly found in both on-animal and in-premises products.

Insect development inhibitors (IDIs) (i.e., lufenuron, Program®, Sentinel®, Novartis Animal Health) are chitin synthesis inhibitors that prevent the flea larvae from hatching from the egg. The product is fed to pets once monthly and deposited in the fat stores of treated animals. It is slowly released from tissues, allowing maintenance of effective blood levels of drug for weeks after administration. The female flea ingests the product when feeding where it becomes incorporated into the flea egg. These products will not kill the adult flea. No known contraindications or side effects exist in mammals, and lufenuron is very safe (oral LD50 in rats >2000 mg/kg).

Many formulations exist for the deliverance of the insecticides to the pet. Shampoos act to mechanically remove the fleas, but because they are rinsed off, they have minimal residual action. This problem with residual flea control can be overcome by using a final rinse (dip) that contains an insecticidal product. Many flea sprays are alcohol-based and quickly kill adult fleas. Unfortunately, most contain pyrethrins, and unless the chemical is microencapsulated, their duration of action is less than 1 day. Powders, foams, concentrated solutions (spot treatments), and collars are all available that are formulated with a variety of chemicals; several of the chemicals are also sold in oral formulations.

In the indoor environment, hand spraying either by a professional or the owner is the preferred method of delivering the chemicals. This allows the product to be applied directly on the areas most frequented by the pets (“source points”). Large pieces of furniture must be moved to ensure that the spray reaches the areas of larval migration.

Outdoors, sprays are very useful and their application should be concentrated in the areas frequented by the animals, especially those that are shaded, have a mild temperature, and contain organic matter.

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17 CHAPTER • 17 Other External Parasites

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External parasites are major causes of distress and disease in dogs and cats. Some parasites cause only mild irritation, whereas others are associated with severe inflammation and secondary infections. Many ectoparasites serve as vectors or intermediate hosts of other diseases. It is important to know the clinical features, identification, and appropriate treatments for external parasites affecting dogs and cats (Table 17-1).

17.1 FAMILY DEMODICIDEA

Demodex spp. live as commensals in the skin of most mammals. Most species (including *D. canis* and *D. felis*) spend their entire life cycle in the hair follicles and sebaceous glands of their host. A few species (including *D. gatoi* and the short-tailed demodectic mite of dogs) are found within the epidermis. It is thought that most follicular infections develop during the early weeks of life, with the commensal population in bitches and queens being transferred to in-contact areas of puppies and kittens. However, the short-tailed forms of the mites may be transferred between adult animals of the same species.

Localized demodicosis in dogs is most common in puppies between 3 to 6 months of age. Skin lesions develop secondary to localized overgrowth of mites on the face or forelimbs and consist of one or more localized areas of alopecia, erythema, and scaling. Clinicians make the diagnosis by doing deep skin scrapings and finding the characteristic “cigar-shaped” mites with short, stubby legs. Counts should be made of all life stages (eggs, larvae, nymphs, and adults). Dogs with normal immune systems will naturally resolve early, localized lesions. Factors that may predispose dogs to *Demodex* overgrowth include other parasites, poor nutrition, immunosuppressive drug therapy, and stress—these factors should be identified and corrected. Specific antimite therapy is rarely warranted. Topical benzoyl peroxide gel or lotion may be applied once daily to help prevent secondary bacterial infections and aid in mite removal from the follicles. Skin scrapings should be repeated in 4 weeks. If lesions are still present and the mite count is still high with a large proportion of immature forms, the condition may be progressing to generalized demodicosis. Rotenone or benzyl benzoate-containing lotions or creams may be applied to the lesions once daily.

Generalized demodicosis in dogs may be classified as juvenile onset (affecting dogs 3–18 months of age) or adult onset (affecting middle-aged to older dogs, often immunocompromised animals with underlying hyperadrenocorticism, hypothyroidism, diabetes mellitus, immunosuppressive drug therapy, or neoplasia). Clinical signs are variable and may start with localized lesions that spread. Patchy to multifocal alopecia, erythema, and silvery-gray scales are common. The affected skin may become lichenified, hyperpigmented, pustular, and crusted or ulcerated. Secondary bacterial infections may progress to life-threatening sepsis. Peripheral lymphadenopathy is common. Deep skin scrapings will reveal numerous demodectic adults, nymphs, and larvae or ova (or both). Mixed infections with *D. canis* plus short-tailed and long-bodied forms of *Demodex* mites may be identified by their characteristic microscopic features. An assessment of the general health of the dog should be made, and any underlying diseases or concurrent infections should be treated.

With the recent withdrawal of Mitaban® (amitraz, Fort Dodge) from sale in the United States, no licensed products are approved for use in treating demodicosis.* It should be noted that amitraz is an Environmental Protection Agency (EPA)-registered pesticide in the United States; although alternative forms of amitraz are available, it is a violation of United States federal law to use an EPA-registered pesticide in a manner inconsistent with its labeling. Both ivermectin and milbemycin are effective alternatives to amitraz in the treatment of generalized demodicosis;

however, high doses and long courses of therapy are required. Ivermectin toxicosis is well recognized in collies and has also been reported in many other breeds of dogs. It is recommended that therapy be initiated with 0.05 mg/kg PO on days 1 to 2, with an increase to 0.1 mg/kg PO on days 3 to 4, and continuing to increase by increments of 0.05 mg/kg until 0.4 mg/kg/day is reached. Ivermectin should be discontinued immediately in any dog showing depression, ataxia, mydriasis, or other signs of toxicity. Collies and other breeds that cannot tolerate high doses of ivermectin may be treated with milbemycin oxime. A recommended protocol for milbemycin is 0.5 mg/kg PO days 1 to 2, with increases of 0.5 mg/kg increments until 2.0 mg/kg/day is reached. Signs of milbemycin toxicosis include mydriasis, ataxia, lethargy, and stupor. Therapy should be continued until two negative skin scrapings have been obtained at monthly intervals.

Localized demodicosis is rare in cats and usually affects the eyelids, periocular region, ear canal, or head and neck. Lesions include patchy alopecia with scaling and crusting or a ceruminous otitis externa (pruritus is variable). Clinicians make the diagnosis by finding mites on superficial and deep skin scrapings, ear swabs, or both. Treatment may include topical rotenone or lime sulfur solution.

Generalized demodicosis is rare and less severe in cats than in dogs. It may be associated with an underlying immunosuppressive or metabolic disease such as feline immunodeficiency virus (FIV), feline leukemia virus (FeLV), toxoplasmosis, systemic lupus erythematosus, or diabetes mellitus. Clinical signs include variable pruritus; multifocal, patchy, or symmetrical alopecia with or without erythema; scaling; crusting; macules; and hyperpigmentation. Clinicians make the diagnosis by finding mites on superficial *(D. gatoi)* or deep *(D. felis)* skin scrapings. Most cats will respond favorably to weekly dips with 2% lime sulfur solution. *D. gatoi* may be contagious, thus in-contact cats should be evaluated and treated if infected.

* In 2004, Pfizer Animal Health acquired the rights to sell Mitaban (amitraz) for the treatment of generalized demodicosis in dogs. This is the only product licensed for use in treating generalized demodicosis in the United States.

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17.2 FAMILY SARCOPTIDAE

Sarcoptes scabiei var *canis* primarily affects dogs but can also cause disease in cats, foxes, and humans. Dogs can be infested with mites from foxes and humans. The life cycle is approximately 21 days and completed on the host. Off-host survival time depends upon the relative humidity and temperature. Adult mites are small (200 to 400 μm), oval, and white with two pairs of short legs. The pretaris have long, unsegmented pedicels. The anus is at the posterior edge of the body. The mites initially affect relatively hairless areas of skin such as the ear pinnae and elbows. Female mites burrow through the epidermis at a rate of 2 to 3 mm/day. They lay their eggs in the resulting tunnel. Eggs hatch into larvae that burrow to the surface of the skin where they feed. Many dogs develop a hypersensitivity reaction to mite antigens. As few as 10 to 15 mites may produce severe clinical signs in a hypersensitive individual. Clinical signs include an intensely pruritic, nonseasonal dermatitis with papules, excoriations, and hair loss. Affected areas typically develop a thick yellowish crust. Lesions may rapidly generalize, but the dorsum is usually spared.

Diagnosis is based on history of a contagious, nonseasonal, intensely pruritic dermatitis involving the pinnal margins, elbows, hocks and ventral abdomen, and chest plus finding mites or mite eggs or feces in superficial skin scrapings. A presumptive diagnosis is made based on response to treatment trials. Effective licensed treatments include weekly applications of 2% lime sulfur solution or monthly applications of 6 to 12 mg/kg selamectin. Effective extra label treatments include ivermectin 0.2 to 0.3 mg/kg PO every 7 days for four to six treatments or milbemycin oxime at 2 mg/kg PO every 7 days for four to six treatments. As in the treatment of demodicosis, it is advisable to initiate treatment with either ivermectin or milbemycin at much lower doses with daily increases until the target dose is reached without evidence of side effects. The target dose is then given once weekly for at least 3

weeks past resolution of clinical signs. In-contact dogs should be treated to eliminate possible asymptomatic carriage of the mites.

Notoedres cati primarily parasitizes cats but may also affect foxes, dogs, rabbits, and humans. Notoedric mange is highly contagious and frequently occurs in epizootics in endemic areas. The mites are smaller than *S. scabiei*, have medium-length unjointed sucker-bearing stalks on their legs, more body striations, and a dorsal anus. Clinical signs include intense pruritus and dry, crusted lesions that first appear on the medial edges of ear pinnae and spread over ears, head, face, and neck. Some cases also involve the feet and perineal regions. Diagnosis is confirmed by finding the mites, nymphs, larvae, and ova in superficial skin scrapings. Traditional therapy is 2% lime sulfur solution applied weekly for 4 to 8 weeks. Other effective treatments include selamectin (6 to 12 mg/kg topically every 30 days), ivermectin (0.3 mg/kg PO or SQ every 14 days for two treatments), or doramectin (0.3 mg/kg SQ once).

17.3 FAMILY PSORPTIDAE

Otodectes cynotis infests the external ear canal and adjacent skin of dogs, cats, foxes, and ferrets. The prevalence in feral cats in the United States has been reported at 25% to 37%. Although ear pruritus and copious production of a dark "coffee grounds-like" cerumen are common, 10% of infested animals may exhibit no clinical signs. Diagnosis is made by finding mites on otoscopic examination or on microscopic examination of material from ear swabs or ear flushes (flushing the ear canal with 1 to 2 ml of mineral oil may have a higher mite yield than use of a cotton swab that traps mites in its fibers). Adult mites are 300 to 400 μm, white, with a terminal anus and four pairs of legs. All legs of the male have short, unjointed stalks with suckers. Only the front two pairs of legs of female mites have suckers; the fourth pair of legs are rudimentary and do not extend beyond the body margin. The mites feed on epidermal debris and tissue fluid. Hosts may develop hypersensitivity reactions to mite antigens. Topical ceruminolytics should be used to remove cerumen and debris from the external ear canal. Topical otic acaricidal products are effective as is topical selamectin. Systemic ivermectin has been used with variable results. Fipronil spray or spot-on may also be effective; however, fipronil should *not* be used in the ear itself. In-contact animals should be evaluated and treated as appropriate for the species.

17.4 GENUS LYNXACARUS

Lynxacarus radovski is a hair-clasping, fur mite of domestic cats. These mites have elongated bodies, 430 to 520 μm long, with a flaplike sternal extension containing the first two legs that are used to grasp the hair of the host. The mites may be found in such large numbers as to give a "salt and pepper" appearance to the haircoat. Some cats develop widespread papular crusts, whereas others show no clinical signs from the infestation. Clinicians make the diagnosis by collecting the mites from acetate tape impressions, hair plucks, or superficial skin scrapings. Effective treatments include topical pyrethrin sprays, 2% lime sulfur dips, or systemic ivermectin. The mite is contagious to other cats and may cause a papular rash in humans; it is not considered contagious to dogs.

17.5 FAMILY CHEYLETIELLA

Cheyletiella spp. mites are easily recognized by their big palpal claws, M-shaped gnathosomal mouthparts, and comblike tarsal appendages. The sensory organs on genu I may be used to identify different species. The sensory organ of *C. yasguri* (primary host is dog) is heart shaped, of *C. blakei* (primary host is cat) is cone shaped, and of *C. parasitovorax* (primary host is rabbits) is globe shaped. These three mite species are freely contagious from one host species to another and can transiently affect humans. The mites do not burrow but move rapidly in pseudotunnels in epidermal debris. The entire life cycle is completed on the host. The ova are smaller than louse nits and are attached to host hairs by fine fibrillar strands. Adult female mites may live up to 10 days in the environment. Clinical signs associated with infestation include a dorsally oriented dry scaling and variable pruritus.

Some cats develop miliary dermatitis. Diagnosis is made by finding mites or ova on acetate tape impressions, on superficial skin scrapings, or in fecal flotations. Affected and in-contact dogs, cats, and rabbits should be treated with topical parasiticides (e.g., 2% lime sulfur dip, fipronil, pyrethrin, selamectin). Systemic ivermectin is also effective. Treatment should be continued for 4 to 8 weeks, and the environment should be also be treated with an acaricidal spray approved for use in homes.

17.6 FAMILY TROMBICULIDAE

Larvae of the family *Trombiculidae* (chiggers) are parasitic, whereas the nymphs and adults are free living. The six-legged larvae are bright red or orange and may be found on the skin or in the ears of dogs and cats. Chiggers remain on the skin for several days, their saliva disintegrates the host skin cells, and a tube called a *stylostome* is formed that holds the mite to the skin until feeding is completed or the mite is dislodged by the host's scratching or biting. Chiggers may be found on skin scrapings. Topical fipronil is an effective treatment.

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17.7 FAMILY IXODIDAE

Ixodid (hard) ticks possess a sclerotized dorsal shield plate on the idiosoma known as a *scutum*. These ticks are intermittent feeders, remaining attached for several days. The number of hosts upon which they feed varies from one to three among the different species of ticks. Ticks are important as vectors of protozoan, viral, and rickettsial diseases. Some are also involved in producing tick paralysis. When animals are infested with a small number of ticks, manual removal can be accomplished by soaking the tick in alcohol, grasping the head with a forceps, and applying firm traction. With heavier infestations the animal may be treated with fipronil or a pyrethrin or pyrethroid (dogs only). Amitraz collars may be used to prevent tick attachment. Environmental control includes mowing and cutting of brush and grass, plus use of environmental pesticides approved for control of ticks.

Rhipicephalus sanguineus is the brown dog tick. It is a three-host tick with all life stages feeding on dogs and occasionally humans, cats, rabbits, and horses. It is identified by its inornate scutum, ventral plates on males, and presence of festoons. *Dermacentor variabilis* is the American dog tick. It is also a three-host tick. The principal hosts of the larvae and nymphs are field mice and other small rodents. The principal host of the adult is the dog, but other mammals and humans may also serve as hosts. Its is identified by its ornate scutum with eyes and festoons. The males lack ventral plates. *Dermacentor andersoni* is the Rocky Mountain wood tick. It is a three-host tick. The adults feed on wild and domestic herbivores. Larvae and nymphs feed on rodents. It is identified by its ornate scutum with legs having the same pattern of brown and gray as the body.

Amblyomma americanum is the Lone Star tick. It has a single white spot on the scutum of the reddish brown adult female. The adult male is small with two pairs of symmetrical spots near the head and pale strips on its sides. It is a three-host tick with larvae and nymphs feeding on rodents, rabbits, and birds. Adult ticks feed on larger mammals. *Ixodes dammini* is the deer tick. It is a three-host tick with larvae and nymphs feeding on rodents and the adults on white tail deer or other mammals. It is a small, inornate tick that lacks eyes and festoons. It is the primary vector of *Borrelia burgdorferi*.

17.8 FAMILY ARGASIDAE

Argasid ticks are soft bodied and lack a scutum. The only argasid tick of importance in small animals is the spinose ear tick, *Otobius megnini*. Adult ticks are not parasitic; however, larvae and nymphs infest the external ear canals of dogs and rarely cats. Clinical signs include an acute onset of otitis externa with severe inflammation and waxy exudate. Diagnosis is made by visualizing the mites and removing them.

17.9 ORDER PHTHIRAPTERA

Lice are highly host specific, with their life cycles completed on the host. Most can only survive a day or two off a host. The body of a louse is divided into a head, thorax, and abdomen. The body is flattened dorsoventrally and has stout legs and claws for clinging tightly to hair, fur, or feathers. Two suborders exist: (1) the sucking lice *(Anoplura)* and (2) the biting lice *(Mallophaga)*.

Sucking lice have mouthparts adapted for sucking the blood of the host. *Linognathus setosus*, the "long-nosed" louse, is the only sucking louse found on dogs. These lice are bluish black and have dark-blue eggs. These lice are relatively slow moving and easy to capture using flea combs or acetate tape. Biting lice have relatively larger heads and ventrally located mouthparts. The claws are smaller than those of sucking lice. The only louse found on cats is *Felicola subrostrata*. The most common biting louse on dogs is *Trichodectes canis*. This louse is short, broad, yellowish in color, and can be a vector for *Dipylidium caninum*. A second biting louse affecting dogs is *Heterodoxus springer*, found only in tropical and subtropical regions. Biting lice can move rapidly and are harder to capture than sucking lice. During a life span of approximately 1 month, female lice lay 200 to 300 operculate eggs ("nits") that are glued to the hair of the host. Light infestations may be asymptomatic. Heavier infestations with *Linognathus* can cause blood-loss anemia, whereas heavier infestations with biting lice produce irritation and pruritus. Pediculosis can result in miliary dermatitis in cats or a pattern of alopecia and excoriations similar to fleabite dermatitis in dogs. Lice are easily killed by 2% lime sulfur dips, pyrethrin or carbaryl powders or sprays, and most other parasiticides used for fleas. Grooming equipment should be thoroughly cleaned.

17.10 ORDER DIPTERA

Diptera is one of the largest orders in class Insecta, with over 120,000 species. All of these species have a complex (complete) metamorphosis. In some species the adults are parasitic on mammals, whereas in other species the larvae are parasitic.

Flies of the genus *Phlebotomus* in the Old World and *Lutzomyia* in the New World are of primary importance as vectors of the protozoan *Leishmania* spp. The fly bites themselves are not associated with significant disease; however, the protozoan often leads to the development of a chronic, exfoliative dermatitis of the face, pinnae, and feet of infected dogs and may also produce severe systemic disease.

Mosquitoes are in the family *Culicidae*. Most animals develop a pruritic papule at the site of a mosquito bite. Some animals (most commonly cats) develop a hypersensitivity reaction to the antigens in mosquito saliva and develop a pruritic, erosive, crusting dermatosis on the bridge of the nose, papular to nodular lesions on ear pinnae, and hyperkeratosis with swelling of footpads. The lesions may be characterized histologically as a diffuse eosinophilic dermatitis, an eosinophilic furunculosis, or an eosinophilic nodular dermatitis with collagen degeneration. Mosquitoes are also important as vectors of *Dirofilaria immitis*.

Flies of the families *Simuliidae* (black flies), *Tabanidae* (horse flies), and *Muscidae* (stable flies, horn flies, houseflies) frequently attack the ear pinnae of dogs housed outdoors. The ear tips, margins, or folds may develop erythema and hemorrhagic crusts. Affected dogs should be housed indoors and treated with topical antibiotic-corticosteroid cream or lotion until the lesions heal and the source of the flies has been eliminated.

Myiasis occurs when fly eggs are laid in damp areas of the skin or haircoat, and the larvae develop in the underlying tissue of the host. True screwworms, *Cochliomyia hominivorax*, can attack healthy tissue. Blowflies (*Calliphora, Lucilia, Protophormia,* and *Phormia*) feed on dead tissue, whereas flesh flies *(Sarcophaga, Wohlfahrtia)* can attack living tissue. Proteolytic enzymes produced by the larvae are highly destructive and can

result in "punched-out" round holes in the skin. Treatment includes débridement of wounds, supportive care, and control of any underlying or predisposing factors (e.g., injuries, urinary incontinence, diarrhea, unkempt haircoat).

Table • 17-1 Scheme for Identification of Arthropod Ectoparasites of Dogs and Cats

Adults with Eight Legs, Two Body Divisions (Cephalothorax, Abdomen), No Antennae, Simple Eyes, and No Wings	**Class *Arachnida***
Flattened dorsoventrally, mouthparts of chelicera, hypostome, palp	Suborder *Metastigmata* (ticks)
Dorsal shield (scutum)	Family *Ixodidae*
Inornate scutum, anal groove forming an arch, lack festoons	Genus *Ixodes*
Inornate scutum, has festoons, basis capituli is hexagonal	Genus *Rhipicephalus*
Ornate scutum, has festoons, basis capituli is rectangular	Genus *Dermacentor*
Ornate scutum, has festoons, mouthparts are longer than basis capituli, the second palpal segment is twice as long as the third	Class *Amblyomma*
Soft bodied	Family *Argasidae*
Mite with respiratory pore in middle of body	Suborder *Mesostigmata*
Chelicerae long and styletlike, 750–1000 µm body, long legs, red color after feeding, found near bird roosts or nests	Genus *Dermanyssus*
Mite without a respiratory pore	Suborder *Astigmata*
Round body 400–430 µm, terminal anus, short stubby legs with long unsegmented pedicels	Genus *Sarcoptes*
Round body 200–500 µm, dorsal anus, legs with medium-length unsegmented pedicels	Genus *Notoedres*
Oval body 300–400 µm, terminal anus, anterior legs are long with short unsegmented pedicels and large suckers, rear legs have suckers in males and are rudimentary with whiplike setae in females	Genus *Otodectes*
430–520 µm elongated body, flaplike sternal extensions, terminal suckers on all legs, found "clasping" hairs on cats	Genus *Lynxacarus*
Mite with stigmata opening on the gnathosoma	Suborder *Prostigmata*
100–400 µm slender "cigar-shaped" body	Family *Demodicidae*
Found in hair follicles of dogs	*Demodex canis*
Found in subcorneal location in dogs, stubby body	*Demodex* unnamed species
Found in hair follicles of cats	*Demodex felis*
Found in subcorneal location in cats, stubby body	*Demodex gatoi*
400 µm oval body with large palpal claws, *M*-shaped gnathosomal mouthpart	Family *Cheyletiellidae*
Found on cats, cone-shaped sensory organ on genu I	*Cheyletiella blakei*
Found on dogs, heart-shaped sensory organ on genu I	*Cheyletiella yasguri*
Found on rabbits, globose-shaped sensory organ on genu I	*Cheyletiella parasitovorax*
Adults with Six Legs, Three Body Parts (Head, Thorax, and Abdomen)	**Class Insecta**
Adults wingless, laterally flattened	Order *Siphonaptera* (fleas)
Head with genal and pronotal combs	Genus *Ctenocephalides*
Flat head (length of head ≥twice height of head)	*Ctenocephalides felis*
Round head (length of head <twice height of head)	*Ctenocephalides canis*
No combs on head, angular forehead	Genus *Echidnophaga*
No combs on head, rounded forehead	Genus *Pulex*
Adults wingless, flattened dorsoventrally, stout legs with claws	Order *Phthiraptera* (lice)
Long nose, sucking mouthparts	Suborder *Anoplura* (sucking lice)
On dog	*Linognathus setosus*
Wide head, biting mouthparts	Suborder *Mallophaga* (biting lice)
On cat	*Felicola subrostrata*
On dog in United States (broad body)	*Trichodectes canis*
On dog in tropics (slender body)	*Heterodoxus spiniger*
Adults with one pair of wings	Order *Diptera* (flies)

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The family Oestridae consists of bot flies. The only bot fly of importance in small animals is *Cuterebra*. The adult fly resembles a bumble bee and lays its eggs along rabbit runs and near rodent burrows. As animals brush past, the

eggs hatch and the larvae crawls onto the host's fur and enters a body opening or wound. Larvae migrate subcutaneously and produce a nonpainful nodular swelling that fistulates. Lesions are most commonly found on the head, neck, or trunk during late summer to early fall. Treatment involves enlarging the hole and carefully extracting the larva.

17.11 HELMINTH PARASITES

Hookworm dermatitis develops when larvae of *Ancylostoma braziliense, A. caninum,* or *Uncinaria stenocephala* enter the skin of areas in direct contact with the ground. Clinical signs include red papules progressing to erythematous, thickened, alopecic areas of skin on the feet, sternum, ventral abdomen, posterior thighs, and tail. Diagnosis is based on history of contact with hookworm ova-containing feces, contaminated soil, or organic material. Treatment involves appropriate anthelmintic treatment of all dogs in the kennel or household, environmental decontamination, and symptomatic treatment.

Pelodera dermatitis occurs when larvae of *Pelodera strongyloides* invade the hair follicles of skin in contact with damp soil or decaying organic debris. Clinical signs include mild-to-intense pruritus with erythema, papules, and crusting of skin in contact with the ground (feet, legs, ventral abdomen, and tail). Diagnosis may be made by finding the 600 to 650 μm larvae on skin scrapings. Treatment involves removal of the contaminated bedding or soil and dipping the dog in a parasitic dip (e.g., 2% lime sulfur).

Dracunculus insignis is a parasite of dogs and wild carnivores. The intermediate host is a *Cyclops* ingested from contaminated water. The larvae develop in the host, and adults are located in subcutaneous tissues of the abdomen and limbs. A nodule forms at the site and fistulates. When the nodule contacts water, the female worm comes to the surface and releases large numbers of larvae. Surgical excision of the worms is the treatment of choice.

18 CHAPTER • 18 Edema

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Jennifer Roberts

18.1 INTRODUCTION

The well-being of cells and tissues depends not only on an intact circulation but also on intercompartmental fluid homeostasis to deliver oxygen and nutrition. Approximately 60% to 70% of lean body weight is water; of this value about two thirds is contained in the intracellular space and one third in the extracellular space. Most extracellular water (approximately 70%) is contained in the interstitium, a matrix of connective tissue and gel-like substrate that is the area between the vascular compartment and the cell membrane.

When this relationship is disturbed, increased water retention in the interstitial compartment often results. Abnormal collection of water in the interstitial space is defined as *edema*. Collection of water in body cavities (hydrothorax, hydropericardium, ascites) and generalized profound subcutaneous swelling (anasarca) are included in the edema category.

18.2 PATHOGENESIS

Under normal conditions, continuous water movement occurs across fluid spaces. Water is shifted from the vascular network into the interstitium; ultimately it crosses cell membranes to become incorporated in the intracellular cytoplasm or is returned back to the vascular network. Water return to the vascular space is controlled by transcompartmental pressure changes induced by the presence of large molecular weight proteins (colloids) in the vascular network. Because of a slight pressure difference between the hydrostatic force displacing water from the arterial-capillary network and the colloidal force promoting water return to the capillary-venous network, residual water remains in the interstitial compartment. This residual volume is drained back into the systemic circulation by lymphatic tributaries. Under normal conditions, no net transfer of water across tissue compartments occurs (Figure 18-1). A defined physiologic relationship governs intercompartmental water balance. This relationship, known as *Starling's law of the capillary*, represents two major factors in water distribution: hydrostatic and oncotic (osmotic) forces. The relationship between hydrostatic and oncotic forces have been extensively investigated and is described as the following mathematical relationship:

$$\text{Net filtration} = Kf[(P_{cap}-P_{if})-(\pi_p-\pi_{if})]$$

where Kf represents net capillary wall permeability, P_{cap} represents hydrostatic pressure generated by the heart, P_{if} represents hydrostatic pressure generated by tissues, π_p represents oncotic forces in plasma, and π_{if} represents oncotic forces in tissues generated by protein and mucopolysaccharides (see Figure 18-1).

Under normal conditions, negative pressure is present in the interstitium. Negative pressure is maintained by the combination of oncotic forces and lymphatic drainage, with a combined drainage capacity that exceeds hydrostatically induced shift of water from the intravascular compartment. When factors associated with this relationship are changed, the outcome is often abnormal interstitial water retention creating a positive interstitial pressure. The conversion from negative to positive interstitial pressure is believed to be a key factor in edema formation (Figure 18-2). Pathophysiologic changes commonly associated with edema formation include increased vascular permeability, decreased protein and mucopolysaccharide concentration in the interstitial matrix, and

reduced lymphatic drainage. Five categories of edema have been described based on changes in Starling's law of the capillary: (1) increased hydrostatic pressure, (2) reduced osmotic pressure, (3) lymphatic obstruction, (4) sodium retention, and (5) inflammation. Specific clinical syndromes associated with each category are listed in Table 18-1.

Figure 18-1 Starling's law of the capillary.

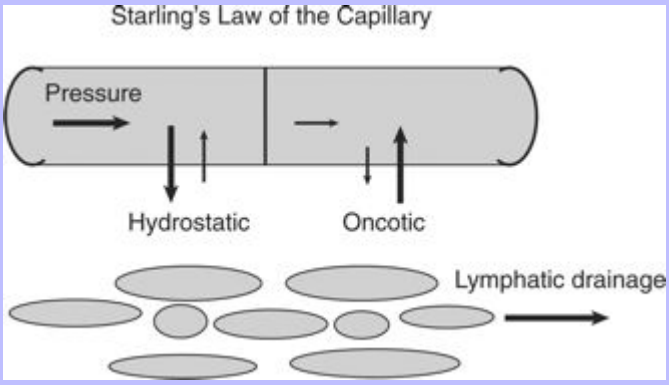

Figure 18-2 Effect of increasing interstitial fluid pressure on volumes of total interstitial fluid, gel fluid, and free fluid.

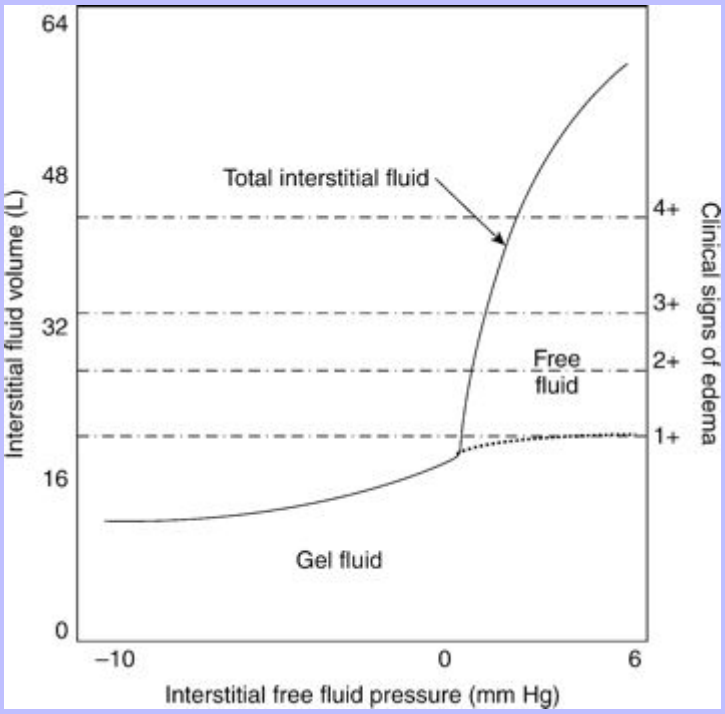

Table • 18-1 Causes of Edema

CAUSE	CONTRIBUTING FACTOR	SPECIFIC CLINICAL SYNDROMES
Increased hydrostatic pressure	Impaired venous return	Congestive heart failure Constrictive pericarditis Ascites (cirrhosis) Venous obstruction or compression (thrombosis, external pressure, extremity inactivity)
	Small-caliber arteriolar dilation	Heat Neurohumoral dysregulation
Reduced plasma osmotic pressure	Hypoproteinemia	Protein-losing glomerulonephropathy (nephritic syndrome) Cirrhosis (ascites) Malnutrition Protein-losing gastroenteropathy
Lymphatic obstruction	Anemia	Various inflammatory Neoplastic Postsurgical Postirradiation
Sodium retention	Excessive dietary intake with renal insufficiency	
	Increased tubular sodium reabsorption	Renal hypoperfusion Increased renin-angiotensin-aldosterone secretion
Inflammation	Acute inflammation Chronic inflammation Angiogenesis	

Modified from Mitchell RN, Cotran RS: Hemodynamic disorders, thrombosis, and shock. In Cotran RS et al, editors: *Robbins pathologic basis of disease*, ed 6, Philadelphia, 1999, WB Saunders.

18.3 CLINICAL PRESENTATION AND DIAGNOSIS

Edema is a secondary feature of many clinical presentations. Historical findings suggestive of edema include limb swelling, increase in abdominal girth, and postural dyspnea. Physical findings include limb swelling in gravity-dependent regions, swelling of the ventral aspect of the mandible, prepuce, scrotum or mammary glands, periorbital swelling, increased breath sounds characterized by rales and rhonchi, and fluid presence in the abdomen or thorax. Superficial edema in subcutaneous tissue can be confirmed by applying digital pressure over the swollen area. Displacement of interstitial water leaves a finger-shaped depression that refills after a short time. This finger-shaped depression is called “pitting edema.”

Diagnostic procedures are focused on confirming edema presence and determining possible cause. Evaluation of the physiologic components of water balance (plasma protein concentration, erythrocyte mass, serum electrolyte levels, and system blood pressure) are important to determine which factor or factors associated with water balance are affected. Evaluation of underlying inflammation (white blood cell [WBC] count, differential, platelet count) is warranted in specific underlying causes. 71

Electrocardiographic and echocardiographic imaging is indicated in cases where edema may be associated with primary or secondary heart failure. Ultrasonographic imaging of the peritoneal space, thoracic space, and pericardial space is warranted if physical finding indicate cavity-based fluid collection. 72

Collection of edema fluid and fluid analysis may be helpful in determining the underlying disease process. The clinicopathologic features of edema fluid are typically a protein-poor transudate with a specific gravity less than 1.012 that has poor cellularity. In inflammation, increased protein content is noted; fluid is generally an exudate with a specific gravity greater than 1.020 and has the presence of inflammatory cell morphology (macrophages, degenerated white blood cells).

18.4 TREATMENT

Treatment of life-threatening edema is an immediate goal irrespective of cause. Typically these presentations are associated with primary heart failure. Administration of parenteral furosemide or vasodilator drugs (or both) is considered the primary step for emergency management. The rationale for furosemide selection includes its known actions producing increased renal sodium excretion facilitating edema mobilization from interstitial sites, pulmonary and systemic vasodilatation, and increased lymph flow in the thoracic duct. All of these responses positively affect transcompartmental water balance and reduce edema formation, especially in the lung. Vasodilators (hydralazine, nitrates) are used to reduce edema; they produce their primary actions through relaxation of systemic arterioles and venules promoting redistribution of central blood volume and reducing hydrostatic pressure. In fulminant cardiac failure, a sympathomimetic such as dobutamine (1 to 5 μg/kg/min constant rate infusion [CRI]) is started and titrated to achieve positive inotropic response. This will improve the Starling's relationship and help to mobilize edema.

Nonemergent edema management is achieved by using goal-directed therapeutic intervention to rebalance the Starling's relationship. Furosemide or other potent loop diuretics (bumetanide, spironolactone, triamterene, amiloride, and thiazide-class) may be used to promote edema mobilization by initiating physiologic responses previously noted for furosemide. Administration of plasma products (fresh plasma, fresh frozen plasma, and cryopoor plasma), hetastarch, or dextran 70 will increase intravascular oncotic pressure and favor water redistribution from the interstitial to intravascular compartment. These products are considered in cases demonstrating decreased oncotic pressure (hypoproteinemia), decreased osmotic balance (anemia), or increased endothelial permeability (inflammation). Decreasing osmotic forces by dietary modification to reduce sodium and chloride intake or through use of loop diuretics to increase sodium and chloride loss is an additional consideration in primary cardiac disease patients.

18.5 PROGNOSIS

The prognosis for successful management of edema is based on the ability to treat and resolve the underlying clinical disorder. Edema secondary to inflammatory states, colloid imbalance, or primary cardiac disease is often successfully managed or resolved. Edema secondary to lymphatic pathology often requires long-term management to successfully correct.

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19 CHAPTER • 19 Hepatocutaneous Syndrome

Catherine A. Outerbridge

Hepatocutaneous syndrome (HS) is an uncommon skin disease associated with systemic metabolic disease. It has also been called *superficial necrolytic dermatitis* (SND), *metabolic epidermal necrosis*, *diabetic dermatopathy*, and *necrolytic migratory erythema* (NME). This disease was first described in a dog in 1968. The first English language reference comparing the disease to the human disease NME was in 1986, when the disease was described in four dogs with diabetes mellitus and was thus first called *diabetic dermatopathy*. The disease has been most commonly described in older dogs, although a histologically equivalent disease occurring in cats and the black rhinoceros has been reported. The etiopathogenesis of this disease is unclear, but it is likely multifactorial. Because different disease processes appear to cause similar histologic skin lesions, it might be more correct to refer to the skin disease as either *SND* or *metabolic epidermal necrosis*.

19.1 COMPARATIVE ASPECTS WITH NECROLYTIC MIGRATORY ERYTHEMA AND THEORIES OF PATHOGENESIS

NME is a histologically similar disease that is seen in humans. Most often NME occurs in association with a glucagon-secreting tumor. Glucagonoma syndrome in humans is characterized by the skin lesions of NME, hyperglycemia resulting from carbohydrate intolerance or diabetes mellitus, weight loss, hypoaminoacidemia, and anemia. Humans with NME usually have a profound hypoaminoacidemia, presumed to result from the catabolic gluconeogenic effects of glucagon. However, NME has been diagnosed in some humans with normal plasma amino acid concentrations, and these have often been patients with nonglucagonoma-associated disease. Nonglucagonoma-associated NME has been reported in humans with celiac disease, chronic malabsorption, cirrhosis, nonalpha islet cell tumors, pancreatitis, hepatitis, inflammatory bowel disease, and heroin abuse. 73

Unlike people with NME, association with glucagonoma has not been consistently demonstrated in the majority of dogs with the skin lesions of SND. Afflicted dogs commonly have a characteristic concurrent hepatopathy, thus the use of the name HS. The hepatic pathology seen in dogs with HS has not been reported to occur in those dogs with confirmed glucagonoma-associated SND. In addition to the association with hepatic pathology, some dogs with the skin lesions of SND have a history of phenobarbital or primidone administration, mycotoxin ingestion, or gastrointestinal signs and malabsorption.

The severe vacuolar liver disease seen in the majority of dogs with the skin lesions of SND and the association in some dogs with concurrent diabetes mellitus suggests that an underlying hormonal or metabolic disturbance is occurring in dogs with HS. Diabetes mellitus has been reported to occur in 25% to 40% of dogs with HS.

Hypoaminoacidemia has been documented to occur in all dogs with SND skin lesions that have, thus far, had concentrations of plasma amino acids measured. Most dogs had nonglucagonoma-associated disease or HS, and only two dogs were confirmed to have a pancreatic tumor. The pattern of the plasma amino acid panels in dogs with SND appears to be significantly different from that seen in dogs with acute or chronic hepatitis.

The liver plays a critical role in amino acid balance. In chronic and acute hepatitis, compromised hepatic metabolism results in increased concentrations of many plasma amino acids. However, this is not seen in dogs with SND because the majority of individual plasma amino acid concentrations are less than 60% of normal. Total amino acid concentrations documented in dogs with SND are approximately 30% of the concentrations documented in healthy dogs or dogs with acute or chronic hepatitis. These differences suggest that the pathogenesis of

hypoaminoacidemia in dogs with SND cannot be explained by compromised hepatic metabolism. The ratio of branch chain amino acids (BCAA) to aromatic amino acids (AAA) has been recognized as an indicator of hepatic insufficiency, and this ratio decreases with the severity of hepatic dysfunction or portal-systemic shunting. The mean BCAA: AAA ratio in dogs with SND in a recent study was 2.6:1.0, which is not indicative of severe hepatic dysfunction. It seems probable that an as yet unexplained increase in hepatic catabolism of amino acids might account for the severity of the hypoaminoacidemia documented in the dogs with SND. Intravenous administration of amino acids initially bypasses the portal circulation resulting in the delivery of amino acids to peripheral tissues before hepatic uptake and catabolism can occur. The fact that some dogs respond better to therapy with intravenous amino acid infusions rather than oral protein hyperalimentation supports the hypothesis that dogs with SND have increased hepatic catabolism of amino acids.

The etiopathogenesis of the hepatic pathology seen in the majority of dogs with SND remains unknown, and it is unclear what metabolic pathway or pathways may link liver or pancreatic disease with the skin lesions seen in SND. Hyperglucagonemia, if it were present, could explain the risk for the development of diabetes mellitus and hypoaminoacidemia seen in dogs with SND. Glucagon secretion can increase threefold without significant increases in peripheral plasma glucagon concentrations. Glucagon is not a hormone routinely measured in dogs, and assays may not detect all biologically active metabolites of glucagon. The catabolism of almost all amino acids is influenced by glucagon except tryptophan. Tryptophan concentrations are not significantly decreased in dogs with SND. It is possible that a disturbance in glucagon metabolism may have a role in the HS form of SND.

The actual etiopathogenesis for the skin lesions seen in dogs with SND or in humans with NME is not known. Humans with NME have had resolution of their lesions after surgical excision of their glucagonoma or after the use of somatostatin analogues. This suggests that hyperglucagonemia may have a direct role in the development of the skin lesions. It has been suggested that in NME, hyperglucogonemia results in increased epidermal arachidonic acid, and the resultant metabolites are responsible for the inflammatory changes in the skin. However, evidence exists that glucagon alone cannot explain the development of NME lesions in all affected humans because some have had resolution of skin lesions despite increased glucagon concentrations. Approximately 50% of humans with nonglucagonoma-associated NME have plasma glucagon concentrations within reference limits. Some patients with nonresectable pancreatic tumors have had NME skin lesions resolve with administration of intravenous amino acids. This finding, along with the hypoaminoacidemia seen in the majority of glucagonoma NME patients has led to the hypothesis that increased gluconeogenesis triggered by hyperglucagonemia results in low plasma amino acid concentrations, epidermal protein depletion, and then the skin lesions of NME. Hypoaminoacidemia was proven to result from increased hepatic clearance in one human patient with a glucagonoma. Essential fatty acid and zinc deficiencies have both been proposed to contribute to the development of NME because the histologic appearance of skin lesions in patients with zinc deficiency or essential fatty acid deficiency shares some similarities to those seen in NME. Some patients have had improvement of their NME skin lesions after zinc or essential fatty acids (EFA) supplementation, but neither has proven to be helpful for long-term resolution of the skin lesions in NME.

In dogs with SND, pancreatic tumor excision or treatment with somatostatin has resolved skin lesions. Because different disease processes appear to be able to produce the same characteristic histologic skin lesion, this suggests that they may perhaps all result in a common metabolic disturbance. The fact that severe hypoaminoacidemia is documented to occur in all cases of SND in which plasma amino acids have been measured, regardless of associated disease, makes it likely that this metabolic derangement is directly contributing to the cutaneous lesions seen in affected dogs.

19.2 CLINICAL PRESENTATION

The disease is typically diagnosed in older dogs. The mean age of affected dogs is 10 years of age, with a range of 4 to 16 years. Male dogs comprise 64% of reported cases. Shetland sheepdogs, West Highland white terriers, Cocker

spaniels, and Scottish terriers may have a predisposition to develop HS because they appear to be overrepresented (Table 19-1).

The most common clinical sign is the development of visually distinctive skin lesions with a characteristic distribution. The skin lesions in dogs with HS may precede any other clinical signs. Skin lesions include erythema, crusting, exudation, ulceration and alopecia involving footpads, periocular or perioral regions, anal and genital regions, and pressure points on the trunk and limbs. A marked crusting, fissuring, and ulceration of the footpads is suggestive of SND (Figure 19-1). Secondary cutaneous infections with bacteria, yeast *(Malassezia, Candidia)*, or dermatophytes, particularly involving the feet, are often present in dogs with SND. Lameness secondary to footpad lesions, inappetence, and weight loss can also be associated with SND. Polydipsia and polyuria may be present when concurrent diabetes mellitus or significant liver dysfunction is present.

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Table • 19-1 Survey of Breeds of Dogs Affected with Hepatocutaneous Syndrome Based on Reported Cases*

	NUMBER		NUMBER
Mixed breed	25	Bichon frise	1
Terrier mix	6	Cairn terrier	1
Shetland sheepdog	11	Cavalier King Charles spaniel	1
Cocker spaniel	11	Golden retriever	1
West Highland white terrier	10	Keeshond	1
Scottish terrier	5	Labrador retriever	1
Jack Russell terrier	5	Maltese	1
German shepherd	5	Miniature poodle	1
Border collie	4	Old English sheepdog	1
Lhasa apso	3	Pomeranian	1
Beagle	3	Rough collie	1
Welsh corgi	3	Samoyed	1
Schipperke	2	Springer spaniel	1
American Eskimo	1	Standard poodle	1
Australian shepherd	1	Yorkshire terrier	1

* 110 compiled cases.

istopathologic findings of representative skin biopsies are unique and confirm the diagnosis. These findings include a marked parakeratotic epidermis with striking inter-and intracellular edema, keratinocyte degeneration in the upper epidermis, and hyperplastic basal cells that create the characteristic “red, white, and blue” histologic lesion. The evaluation of serum biochemistry panels often demonstrates an increase in liver enzyme activities and a decrease in serum albumin concentration. Serum bile acid evaluations are abnormal in about half of affected dogs. A review of reported cases found hypoaminoacidemia in all dogs, elevated glucagon in 4 out of 4 dogs that had a glucagonoma, and increased serum insulin concentrations in 8 out of 11 dogs.

Abdominal ultrasound may demonstrate a unique “honeycomb” pattern to the liver consisting of variably sized hypoechoic regions surrounded by hyperechoic borders. Hepatic histopathology often documents a distinctive vacuolar hepatopathy with parenchymal collapse. Grossly, the liver may appear irregular, have multiple nodules, and be mistaken for being cirrhotic. There exists some contradiction as to whether the hepatic lesions in HS reflect true cirrhosis. Despite some histologic descriptions of micronodular cirrhosis, one study, using special stains, confirmed only a minimal increase in collagen within portal areas. Extensive fibrosis and reduced liver size characteristic of chronic cirrhosis is not seen in HS.

Table • 19-2 Percentage of Reported Cases (101 Dogs) Displaying the Commonly Reported Clinical and Laboratory Finding s in Dogs with Hepatocutaneous Syndrome

CLINICAL FINDINGS	%	LABORATORY FINDINGS	%
Hyperkeratotic and fissured footpads	94%	Elevated serum alkaline phosphatase	98%
Perioral or periocular skin lesions	62%	Elevated serum alanine transferase	71%
Perianal or perineal skin lesions	33%	Anemia	37%
Elbow skin lesions	30%	Hypoalbuminemia	33%
Perivulvar or scrotal or preputial skin lesions	28%	Diabetes mellitus	33%

The prognosis for dogs with SND is generally poor and the majority of dogs have survival times of less than 6 months. However, 20% of the dogs in a recent study were maintained for 12 months or more with oral protein hyperalimentation and periodic parenteral IV amino acid infusions.

19.3 DIAGNOSIS

Diagnosis of HS is based on obtaining skin biopsies with the typical histopathologic changes. The characteristic dermatohistopathology can be focal within a given lesion. Whenever possible, multiple representative samples should be obtained and submitted. Biopsies should be chosen, if possible from easily accessible sites, and attempts to avoid general anesthesia should be taken because these dogs are not often good candidates for anesthesia. The documented occurrence of abnormal laboratory findings as listed in Table 19-2 should increase the clinical suspicion of HS in dogs with compatible cutaneous lesions. If abdominal ultrasound is available, it can provide further support for the diagnosis if the characteristic “honeycomb” pattern is documented. If this ultrasonographic pattern to the liver is not visualized in a dog with a confirmed histologic diagnosis of SND, evaluation for a possible pancreatic tumor is necessary. Pancreatic tumors may not be readily visible with an abdominal ultrasound examination, so measurement of plasma glucagon is also recommended. If plasma glucagon concentrations are abnormally increased or a pancreatic mass is visible on ultrasound, the option for exploratory laparotomy and tumor excision can be considered. However, postoperative morbidity and mortality have been high. Plasma amino acids, if measured, should document a characteristic severe hypoaminoacidemia.

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19.4 MANAGEMENT

The most effective symptomatic or palliative therapy for dogs with HS appears to be the administration of intravenous amino acids. A number of amino acid solutions are commercially available. Administration of a total dose of 25 ml/kg of a 10% Aminosyn (Abbot Labs, N.C. and Ill.) solution, administered over 6 to 8 hours and repeated at 7-to 10-day intervals has been recommended. Both Travasol 8.5% without electrolytes (Baxter Healthcare Corp., Clintec Nutrition Company, Deerfield, Ill.) and ProcalAmine 3% amino acids with 3% glycerin and electrolytes (B. Braun Medical Inc., Irvine, Calif.) can also be used for intravenous infusions in treating dogs with SND. These hypertonic amino acid solutions should be administered via a central vein to diminish the chance of thrombophlebitis. Inducing a hyperosmolar state is possible if administration is too aggressive. Dogs should be watched for neurologic signs, and the infusion discontinued if these occur. If compromised hepatic or renal function is present the administration of intravenous amino acids may exacerbate hepatic encephalopathy or augment increases in blood urea nitrogen (BUN). Such dogs warrant close monitoring with serial measurements of ammonia, BUN, and osmolality during intravenous amino acid administration. Some dogs show dramatic improvement in attitude with resolution of skin lesions after receiving amino acid infusions. As yet no defined protocols exist for the

administration of amino acid infusions in these dogs, and repeat infusions are performed bimonthly, monthly, or when clinical signs return.

Oral nutritional support should include a high quality protein diet that can be additionally supplemented with an amino acid powder such as Promod (Ross Laboratories, Columbus, Ohio), at a dose of one scoop per 10 pounds. Unless significant hepatic dysfunction with hyperammonemia has been documented necessitating a low protein diet, most dogs with HS cannot be fed enough protein to overcome the hypoaminoacidemia occurring in this disease. Zinc and essential fatty acid supplementation is often recommended, in part because of the reported initial improvement in some people with NME. Feeding egg yolks (3 to 6 per day) has been reported to result in clinical improvement in some dogs. This provides some additional protein but may also include micronutrients that may have some role in this disease.

Secondary infections should be treated with appropriate antibiotic and antifungal therapy, with careful consideration of those drugs that may be hepatotoxic or require hepatic metabolism. Topical therapy with antibacterial and antiyeast shampoos can also be of benefit in some dogs in helping to manage secondary infections.

Therapy with glucocorticoids is not recommended. Although antiinflammatory therapy for the skin lesions may be of some benefit, the risk of precipitating or exacerbating diabetes mellitus in these dogs makes the use of glucocorticoids contraindicated.

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20 CHAPTER • 20 Physique: Obesity: A Disease to Be Recognized and Managed

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It is estimated that 24% to 30% of the pet population in the United States seen by veterinarians is overweight or obese. This information, together with an estimated number of pets and veterinarians in the United States, suggests that a single veterinarian may see as many as 840 of these overweight or obese animals per practice. The cause of obesity as a primary disorder is simply that an animal is receiving more calories than it is expending, and body fat mass increases. Obesity may also be a secondary condition in animals with hypothyroidism, hyperadrenocorticism, or insulinomas. Treating these endocrinopathies rarely reduces, so a weight loss program may be necessary. However, the incidence of obesity as a primary disorder exceeds the incidence of the endocrinopathies associated with obesity.

20.1 HEALTH RISKS

Several health risks are associated with obesity as evidenced from long-term studies in cats and dogs. Grossly obese pets have increased prevalence of impaired gaits, traumatic and degenerative orthopedic disorders, and overweight puppies are more likely to develop clinical signs of orthopedic disease. Dogs obese at 1 year of age have a greater risk for developing mammary cancer later in life, and overweight dogs have an increased risk of developing cystic transitional cell carcinoma. Overweight pets have reduced activity, decreased heat tolerance, and they show visible signs of aging earlier than ideal-weight animals. Other health problems commonly noted in obese pets include dyspnea, congestive heart failure, dystocia, and nonallergic dermatologic problems. As we have learned from rodent and canine studies, lean or optimal weight pets may live on average 1 to 2 years longer than overweight pets. Therefore weight control is not only a quality of life issue but also one that may increase longevity. Calorie restriction is the only factor known to increase median life span.

Overweight and obese dogs and cats commonly have primary and secondary health issues. Studies have demonstrated significant weight changes in research dogs and cats using commercially available diets designed for weight loss. These therapeutic weight loss diets are marketed solely to veterinarians.

20.2 RECOGNITION

Body weight alone does not indicate whether that weight is appropriate for the particular patient. Knowing a dog's weight to be 50 lb (23 kg) or a cat to be weighing 12 lbs (5.5 kg) means that animal might be underweight, at optimal weight, or overweight. Writing a body condition score next to the weight puts that weight in perspective, which allows visualization regarding how the weight is carried on that skeletal frame. Scoring body condition is similar to the visual effect of breed (e.g., a 50-lb beagle conjures a very different picture than a 50-lb Newfoundland).

20.2.1 Body Condition Scoring

Body condition scoring (BCS) is a useful tool that estimates an animal's body fat content, taking into account the animal's frame size independent of body weight. Several different numbering systems (using 3-, 5-, or 9-point categories) and wall charts are available. A clinician must learn by experience what visual and palpable characteristics correspond with a given BCS; however, once learned, BCS has been demonstrated to be a reliable indicator for determining body composition. BCS is a useful tool in evaluating weight changes within an individual and as a means of communicating between clinicians.

The 5-or 9-point systems seem to be most commonly used. A 5-point system is most useful to novices using whole numbers (1/5 is emaciated, 3/5 is ideal, 5/5 is grossly obese), but with practice, the scores will be recorded to the nearest half score (e.g., 4.5/5). Experienced clinicians frequently use the 9-point system, in which scores are recorded to the nearest whole number (1/9 is emaciated, 5/9 is ideal, 9/9 is grossly obese). Using the 5-point system scored to the nearest half score actually is the 9-point system.

A pet in optimal body condition has "normal body contours and silhouettes, bony prominences that can be readily palpated but not seen or felt above skin surfaces, and intraabdominal fat insufficient to obscure or interfere with abdominal palpation." Body condition can be defined as the ratio of body fat to nonfat tissues and hence does estimate percent body fat. Fat mass expressed as a percentage of body weight can also be a useful tool in convincing owners their pets are overweight. Body composition studies in dogs and cats suggest that animals assessed to be in optimal body condition have 15% to 25% body fat. Dogs and cats with a BCS of "ideal" will have 15% to 25% body fat, those considered overweight will have 26% to 35% body fat, and those deemed obese will have more than 35% body fat. Some pets may have well more than 40% body fat (e.g., the cat with a 10-lb frame weighing 20 lbs is probably carrying 10 lbs of fat). Therefore it is correct to say that when assigning the maximum BCS, the pet has at least 40% body fat.

Dogs with an ideal BCS of 4 to 5 lived 15% longer than dogs of the same breed, living in the same environment, and eating the same diet but having a BCS of 6 to 7 (using the 9-point system). Hence, weight reduction programs should be discussed and implemented when the BCS is 6/9 or greater because the percent body fat will then be greater than 25%. The benefits derived from controlling body weight and condition are thought to be realized at any time throughout life; hence benefits can be gained by reducing the weight of any pet at any age.

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20.3 MANAGEMENT

Before beginning a weight loss program, it is essential to ensure that the obesity is of primary origin and not the result of an endocrinopathy. Body weight may not naturally correct after such treatments have been instituted. A reduced calorie intake may still be needed after initializing treatment for an underlying endocrinopathy. A complete physical examination, with routine serum, blood, and urine analysis should be done. If necessary, additional diagnostics should be done to further evaluate any abnormal clinical findings of the cardiovascular, gastrointestinal, liver/pancreas, renal/urinary, musculoskeletal, or other organ systems. A dietary history is of limited value because most clients cannot recall the names or amounts of food fed to their pets. The most essential dietary information needed is an estimate of the current amount of calories fed so that appropriate restriction may begin. Most owners of pets with a BCS greater than or equal to 6/9 feed ad libitum, suggesting that a specific feeding amount divided into two meals per day would be an excellent starting point. Some owners requesting a weight loss plan have already begun to limit the pet's calorie intake with no success; hence the first feeding recommendations must be a further restriction of calories. Several different methods can be used to restrict calorie intake.

20.3.1 Short-Term Starvation

Starvation as a method of weight loss cannot be used in cats because of the risk of inducing hepatic lipidosis. Starvation has been used as a form of weight loss in dogs. However, this method creates not only a caloric deficiency but also a deficiency of all other nutrients. Most pronounced would be a protein deficiency (skeletal muscle wasting will occur as a result of the need for synthesis of essential proteins). Body weight lost will then be comprised of fat, muscle, and to a lesser extent bone. Less obvious will be the water-soluble vitamin and trace mineral deficiencies created because little to no body storage of these nutrients takes place, and a daily intake is necessary for ongoing metabolic processes. The goal of weight loss is to reduce the body fat content while

maintaining other body tissues and metabolism. Deficiencies of amino acids, vitamins, and trace minerals are needed to properly and fully catabolize and therefore reduce fat stores. No veterinary protein, vitamin, or mineral supplement exists that will adequately supply 100% of the daily requirement of these essential nutrients. Starvation creates nutritional deficiencies across all metabolic processes and is therefore not an acceptable form of weight reduction from a physiologic perspective. The inhumane aspects of this method are obvious. Additionally, short-term starvation does not teach the owner how to properly feed and manage their pet in the long-term once the proper weight has been achieved.

20.3.2 Feeding Less of Current Food

It is not uncommon to hear a practitioner advocating, “Simply feed less of his regular food,” as a method of weight loss. If the volume of “regular food,” usually an over-the-counter (OTC) pet food product not designed for weight loss, is reduced by 25% or less, there may be little nutritional harm done to a normal healthy overweight adult dog over a short period (weeks), depending on the OTC product used. However, if the volume of regular food has to be reduced by more than 30% to get weight loss, nutritional deficiencies will occur. For example, feeding 30% fewer calories of an OTC adult premium maintenance dog food to a 50-lb overweight dog produces a protein intake 5.6% below current canine feeding recommendations. As the restriction continues, more nutrients become deficient. Therefore when more than a 25% restriction of calories is necessary, changing the pet food product is absolutely necessary. An OTC diet labeled “light,” “lite,” “lean,” “less,” or “reduced calorie or fat” is formulated for weight maintenance, not weight reduction. Some properly formulated OTC “reduced calorie” diets may be fed at 25% less than the recommended feeding; however, unless one is comfortable with the calculations or has some assurance from the manufacturer, it is not advisable as a general rule.

Properly formulated weight loss diets are specifically designed to be low in calories with increased concentrations of all other nonenergy nutrients. In other words, the nonenergy nutrients are in a higher proportion to calories consumed in a weight reduction diet than in the OTC adult maintenance or reduced calorie foods. One only wants to create a caloric deficiency and not other nutrient deficits during weight loss according to Association of American Feed Control Officials (AAFCO) allowances. Feeding fewer or no treats, snacks, or table foods is appropriate because these do not affect the daily nutrient intake balance. Changing treats to high-water (squashes) or fibrous (broccoli) vegetables is also acceptable because they contain no calories to be counted.

20.3.3 Feeding High-Fiber Diets

There has been some debate regarding the effectiveness of diluting dietary calories with dietary fiber, water, and air. Water and air are quickly removed from the gastrointestinal tract and do not contribute substantially to a feeling of gastrointestinal fill; hence they have a minimal sustained effect on decreasing food intake. Dietary fiber has been shown to decrease food intake.

Fibers are complex carbohydrates that cannot be digested by endogenous enzymes within the small bowel but can be fermented to varying degrees in the colon. Fiber is classified by physiochemical and analytic properties. Dietary fiber, including soluble versus insoluble fiber, dilute diet calories, increase satiety, and limit food consumption by increasing digested bulk and prolonged distention of the gastrointestinal tract. The difference between soluble and insoluble fiber is based upon their solubility in water; although the fiber types affect the gastrointestinal rate of transit differently, transit time through the entire gastrointestinal tract is increased approximately the same for both soluble and insoluble fibers. Some dog studies showed no effect on caloric intake when foods contained 12% to 14% of dry matter as soluble or insoluble fibers, but dogs did consume

significantly less of a food containing 21% insoluble fiber. These same dogs also ate less food when offered a second meal 30 to 45 minutes after consuming the high-fiber food. Overall, study results indicate beneficial effects of dietary fiber in foods intended for weight loss. Most commercial weight loss diets contain primarily insoluble fiber at greater than 10% (and sometimes as high as 30%) of the dry matter. Increased fecal bulk is to be expected, and sometimes the increase frequency of defecation is not acceptable to the owner. In this case a lower-fiber diet (10% to 15%) has to be used for weight loss.

20.3.4 Weight Loss Protocol

Several methods can be used to calculate food doses for weight loss. An equation for weight loss must require fewer calories consumed than are currently expended. Different pet food companies offering weight loss products and programs use different methods, and some calculation methods are more successful than others. 77

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Method 1: The daily caloric intake for weight loss is 50% of the maintenance calories at dog's current weight. This method has not produced a rate of weight loss sufficient to meet owner's expectations or inspire interest in continuing the program in clinical trials.

Method 2: The daily caloric intake for weight loss is a percentage (40% to 60%) of the maintenance energy requirements at the target, desired, or optimal body weight. This method has produced a rate of weight loss acceptable to owners.

Method 3: The daily caloric intake is calculated based upon maintenance energy requirement (MER) at the current weight minus a desired percent body fat loss per day, which could be adjusted depending upon individual animal response. This method has been shown to produce a rate of weight loss acceptable to owners. Several pet food manufacturers have these weight loss calculations available in simple, user-friendly programs that can be run on most personal computers (IBM or Macintosh).

Consistently delivering or feeding fewer calories to the pet is of course the responsibility of the owner. Owner (family) compliance is the single most important aspect in an obese pet losing weight; this is simple to say but very difficult to deal with in the single 20-minute office visit. Approximately 55% of the overweight feline and canine patients are not brought back for a recheck weight loss visit. Pets who returned for three or more recheck visits did successfully lose weight. Recheck visits every 4 to 8 weeks are essential because the caloric intake must be reduced (recalculated) to continue weight loss or the weight will stabilize. Some weight loss packages put together by pet food manufacturers aid owner compliance by providing a well-demarcated feeding cup or cans and printed instructions.

In summary, losing excess body fat has been shown to decrease morbidity and increase longevity in pets. BCS systems and computerized weight loss programs are now available as useful clinical tools. Veterinarians should be regularly discussing weight control with owners and helping those with pets with BCS greater than 5/9 because the majority of pets are now neutered and have less exercise and because pet food companies strive to make their OTC products ever more palatable.

21 CHAPTER • 21 Cachexia

Thomas Schermerhorn

A standard definition for cachexia is difficult to provide. In clinical practice, *cachexia* is the term used to describe the weight loss, loss of muscle, and anorexia that accompany many chronic disease conditions. However, it is important to recognize that cachexia is not simply caused by inadequate nutrient intake and that cachexia and starvation are not equivalent physiologic processes. In humans, two biochemical features distinguish malnutrition caused by cachexia from that caused by starvation. First, unlike starvation, cachexia is associated with a pronounced acute phase inflammatory response, characterized by production of proinflammatory cytokines such as interleukins (IL-1 and IL-6, among others) and tumor necrosis factor alpha (TNF-alpha).

Cytokines stimulate the production of ubiquitin, a protein that binds to other proteins and stimulates their metabolism via the cellular proteasome system. Activation of the ubiquitin-proteasome system does not occur during starvation. Increased resting energy expenditure is the second feature of cachexia that distinguishes it from starvation. Resting energy expenditure increases as a consequence of altered protein, fat, and carbohydrate metabolism.

A diagnosis of cachexia should be considered for any dog or cat with marked weight loss, severe muscle loss, and decreased appetite in the setting of a chronic inflammatory response. By this definition, cachexia is not a specific diagnosis but an indication of a state of disordered metabolism that can be caused by a variety of diseases.

When evaluating an emaciated dog or cat, it is important to determine, from diagnostic and therapeutic standpoints, whether the condition has developed as a result of inadequate nutrient intake (maldigestion, malabsorption, or underfeeding, for example) or represents true cachexia.

21.1 HISTORY

Dogs and cats with cachexia may be brought to veterinarians principally for weight loss or for signs associated with an underlying condition. Careful history taking should include questions about appetite, caloric intake, daily exercise, and environment. Some animals with cachexia have weight loss with preservation of appetite; the loss of body condition may be noted before the onset of anorexia in some cases. Dogs and cats with malnutrition as a result of starvation, malabsorption, or maldigestion typically have a good appetite. However, the level of appetite is variable in animals with cachexia, ranging from normal to complete anorexia. Lethargy, weakness, and exercise intolerance may be marked and in some cases are worse than would be expected if simply the result of poor physical condition. The dietary history should be carefully reviewed and include the type and quantity of food offered (including any dietary supplements provided), the possibility that other pets at home might be competing for food, and the pet's level of appetite. It is important to distinguish those animals that have an appetite but cannot prehend or swallow food from those who have no appetite but can chew and swallow normally. Diagnostic considerations suggested by various patient history findings are presented in Box 21-1.

21.2 PHYSICAL AND LABORATORY FINDINGS

Cachexia has few specific indicators other than the marked loss of body condition that is a characteristic finding; muscle may be lost disproportionately to fat in some animals with cachexia. Similarly, laboratory findings are not specific for cachexia. Serum protein levels are variable even in the presence of a systemic inflammatory response. For example, elevated fibrinogen levels (as a component of the acute phase response) in humans with neoplasia may be offset by reduced albumin synthesis. Increases in hormone concentrations, such as cortisol and insulin, may

be observed in animals with cachexia; these changes may result from or be the cause of cachexia-induced alterations in metabolism. In general, an individual patient's physical and laboratory findings will be representative of the underlying disease rather than specific indicators of cachexia. No compelling reasons exist to perform specific laboratory tests to make a diagnosis of cachexia. Instead, cachexia is largely a clinical diagnosis that is made when appropriate physical findings are present in a dog or cat with a disease associated with a chronic inflammatory response.

21.2.1 Box • 21-1 Diagnostic Considerations for Patients with Marked Weight Loss

21.2.1.1 Dietary History—Inadequate

Starvation

Underfeeding

Poor quality food

21.2.1.2 Dietary History—Adequate

Environmental/housing factors

- Competition for food from other pets
- Limited access to food

Oral and dental disease

Impaired use of nutrients

- Specific nutrient deficiency
- Maldigestion of any cause
- Malabsorption of any cause
- Diabetes mellitus
- Protein-losing disease
  - Nephropathy
  - Gastroenteropathy

Cardiac disease*

Elevated metabolism

Hyperthyroidism

Chronic fever of any cause*

End-stage renal disease*

Neoplasia*

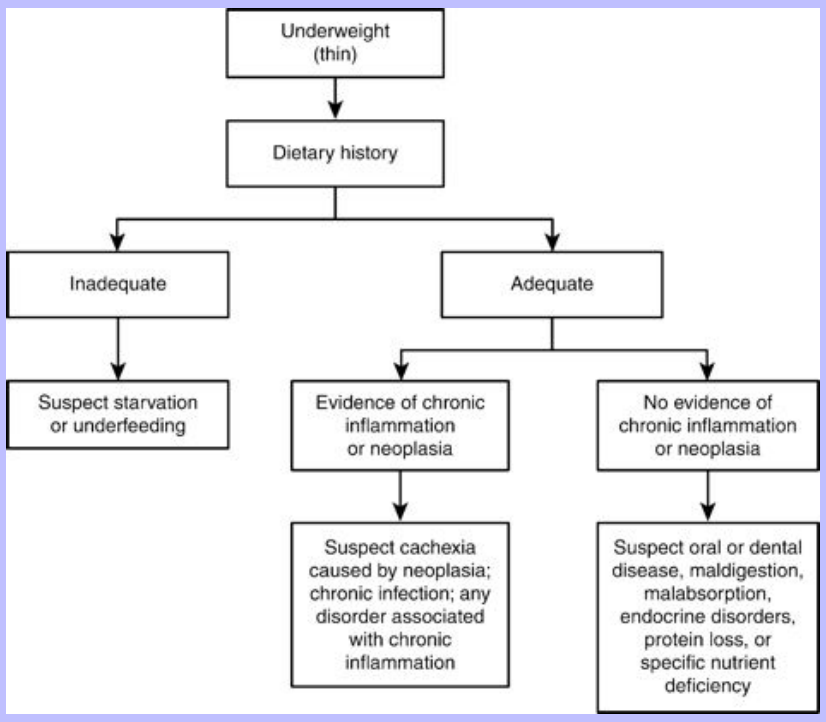
Chronic infection*

Chronic inflammation of any cause (e.g., immunologic disease*)

Note: Patients may present with or without a loss of appetite.

* Diseases typically associated with cachexia in humans and animals.

Figure 21-1 Algorithm for making a diagnosis of cachexia.



21.3 DIAGNOSTIC PLAN

A general algorithm for making a diagnosis of cachexia is shown in Figure 21-1. It is important to recognize cachexia because animals with this condition may not respond as expected to therapeutic interventions and nutritional support.

21.4 THERAPY

Successful therapy of the primary disorder is the most efficacious means of reversing the metabolic abnormalities that underlie the development of cachexia. Nutritional support is the cornerstone of specific therapy for cachexia. Hypercaloric feeding is intended to supply the dog or cat with sufficient calories to meet increased maintenance caloric needs (because of hypermetabolism), prevent additional weight loss, and promote weight gain. Unfortunately, hypercaloric feeding alone may not be sufficient therapy for animals with true cachexia. People with cachexia who receive hypercaloric feeding gain weight, but the increase in body weight is almost exclusively the result of an increase in adipose tissue without change in lean body mass. Thus it appears that simple feeding therapy may not be sufficient in all situations to reverse the abnormal protein catabolism that accompanies cachexia. Additional therapies that have been used for cachexia in humans that may prove useful for the treatment of animals include appetite stimulants, anabolic agents, antiinflammatory drugs, and cytokine inhibitors. Although some of these drugs have been extensively used for other indications in small animals, information is limited about their efficacy when used for cachexia.

22 CHAPTER • 22 Failure to Grow

Sherri L. Ihle

Growth is a complex process that results in an increase in size of an individual. In dogs and cats, growth primarily occurs during the first 6 to 24 months of life. When an animal does not increase in size at the normal rate or to a normal extent, a “failure to grow” is identified. The owner of the affected pet may notice the problem and bring the animal to the veterinarian, or the animal's small size may be first noticed during a routine physical examination. In veterinary medicine, determination of normal growth is sometimes difficult because breed sizes vary and mixed breed pets predominate. Comparing littermates, when possible, can be helpful in making and assessing the individual's growth rate and pattern.

22.1 PATHOPHYSIOLOGY

Genetic, hormonal, metabolic, and nutritional factors influence growth. To meet its full genetic potential, an animal must have growth hormone (somatotropin) to stimulate insulin-like growth factor-I (IGF-I) production, which in turn stimulates skeletal growth, protein synthesis, and cell proliferation. Full IGF-I activity requires the presence of thyroid hormone. The animal must also consume sufficient calories and nutrients; digest, absorb and retain the nutrients; transport the nutrients to the necessary tissues; and be able to use the nutrients for metabolic maintenance and growth. A defect in any of the previously mentioned processes can disrupt, delay, or stop normal growth (Box 22-1; Figure 22-1).

22.1.1 Genetic Abnormalities of Bone Growth

An inherited endochondral ossification defect in chondrodystrophic animals results in angular limb deformities and subnormal height.

22.1.2 Deficient Nutrient Intake

Gastrointestinal parasitism, resulting in a “relative” deficiency in nutrition, is the most common cause of reversible retarded growth in puppies and kittens. If an insufficient amount of food or food of poor quality is consumed, nutrients will not be available to provide substrates and energy for tissue growth. Oral disease may cause pseudoanorexia. Regurgitation or vomiting because of esophageal or gastric disorders results in insufficient food reaching the intestines for digestion and absorption. Maldigestion or malabsorption can result in decreased uptake of nutrients. Renal, hepatic, cardiac, inflammatory, and hypo-adrenal disease can suppress the appetite. Absorption and transport of nutrients from the intestines to other tissues can also be inadequate with cardiac disease.

22.1.2.1 Box • 22-1 Causes of Growth Failure in Dogs and Cats

22.1.2.1.1 Small Stature and Poor Body Condition

Dietary problem

Underfeeding

Poor quality diet

Cardiac disorder

- Congenital anomaly
- Endocarditis

Hepatic dysfunction

- Portosystemic vascular anomaly
- Hepatitis
- Glycogen storage disease

Esophageal disease

- Megaesophagus
- Vascular ring anomaly (e.g., persistent right aortic arch)

Gastrointestinal disease

- Parasites
- Inflammatory bowel disease
- Obstruction (e.g., foreign body, intussusception)
- Histoplasmosis

Exocrine pancreatic insufficiency

Renal disease

Renal failure (congenital or acquired)

- Glomerular disease
- Pyelonephritis

Inflammatory disease

Hormonal disease

- Diabetes mellitus
- Hypoadrenocorticism
- Diabetes insipidus
- Juvenile hyperparathyroidism (dogs)

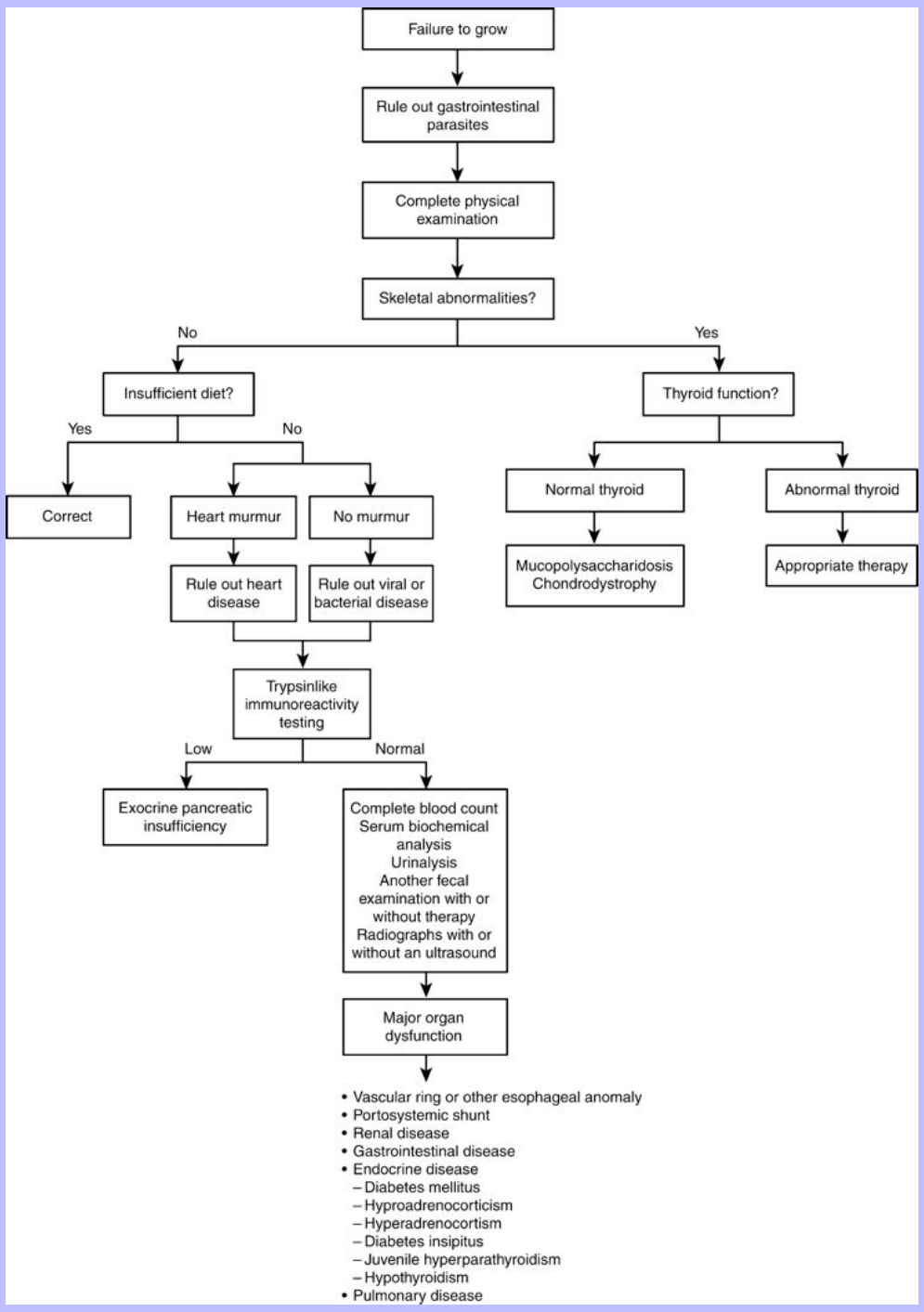
22.1.2.1.2 Small Stature and Good Body Condition

Chondrodystrophy

Hormonal disease

- Congenital hypothyroidism
- Congenital hyposomatotropism (pituitary dwarfism)
- Hyperadrenocorticism

Figure 22-1 Algorithm for diagnostic evaluation of the dog or cat with failure to grow.



22.1.3 Caloric or Nutrient Loss

Fever can result in excess caloric loss as body heat. In diabetes mellitus, glucose is lost in the urine. Protein and salts can also be lost in the urine in animals with glomerular and renal tubular disease, respectively. Several intestinal disorders can result in protein-losing enteropathy. As previously noted, parasitism is the most common cause of “lost” nutrients.

22.1.4 Abnormal Metabolism

Carbohydrate metabolism can be altered in inflammatory disease, renal disease, and hepatic disease. Protein production can also be decreased with hepatic disease. Hypothalamic or pituitary aplasia or neoplasia (e.g., craniopharyngioma) can result in low growth hormone and IGF-I concentrations. Hypothyroidism can decrease the activity of growth hormone. Because insulin has a positive effect on IGF-I production, insulin deficiency caused by diabetes mellitus or malnutrition can slow growth. Cortisol excess, whether endogenous or exogenous in origin, can inhibit the secretion of growth hormone. An extremely rare form of juvenile hyperparathyroidism in German shepherds has also been reported to cause stunted growth.

22.2 HISTORICAL FINDINGS

The animal with subnormal growth may be brought to the veterinarian for that problem or the small body size may be noted during a routine examination. In either case, the owner of the dog or cat should be questioned as to the size of the pet's parents and littermates, if known. If the parents and littermates are also at the lower end of the range of breed size, the small stature of the pet may not be worrisome. However, if the pet is noticeably smaller than its littermates, the problem should be investigated. When the family history is unknown, the pet's size should be compared with others in the breed. For the mixed breed dog, the predominant breed should be determined based on physical characteristics, and that breed's average size should be the standard for comparison.

22.2.1 Duration of the Problem

Determining whether the animal's growth has been slow since birth or whether it was normal and then suddenly seemed to stop can be helpful. In the former case, congenital defects should be strongly considered, whereas in the latter case, acquired disorders must also be considered.

22.2.2 Diet

A detailed nutritional history should be obtained as to type of food, amount of food consumed, appetite, and feeding schedule. A less palatable or poor quality diet may not be eaten well or may be poorly used by the animal. A poor appetite despite the feeding of a palatable, high-quality food suggests the presence of a systemic illness causing inappetence or anorexia. Conversely, if the animal is always hungry and internal parasites have been ruled out or treated, underfeeding (because of inadequate owner knowledge of the pet's nutritional needs), a disorder causing a “relative” lack of calories (e.g., exocrine pancreatic insufficient), or an increased nutrient loss (e.g., diabetes mellitus, renal disease, intestinal disease) should be considered.

22.2.3 Concurrent Clinical Signs

The owner should also be questioned about the presence or absence of other clinical signs, which may help define the cause of the problem. Regurgitation usually indicates a pharyngeal or esophageal problem. Vomiting suggests a gastrointestinal problem or systemic illness (e.g., renal disease, hepatic disease, hypoadrenocorticism). Diarrhea or voluminous stools may be seen with disorders causing maldigestion (e.g., exocrine pancreatic insufficiency) or malabsorption (e.g., severe parasitism, inflammatory bowel disease, histoplasmosis). If polyuria is present, diabetes mellitus, renal disease, hepatic dysfunction, or hypercalcemia (juvenile hyperparathyroidism) should be considered. Seizures, episodic abnormal behavior, vomiting, and diarrhea may be signs of hepatic dysfunction. Exercise intolerance or syncope can suggest a congenital cardiac abnormality. Poor response to housebreaking measures or to obedience training, or a lack of normal puppy play activities can suggest the mental dullness of congenital hypothyroidism, or the encephalopathy of hepatic failure. Poor response to housebreaking measures may also be seen with ectopic ureters or the polyuria of kidney abnormality. Glucocorticoid therapy for an unrelated problem may have slowed the pet's growth. Although the absence of these historical findings does not eliminate these disorders as possible problems, their presence can guide the diagnostic plan.

22.3 PHYSICAL EXAMINATION FINDINGS

Although some animals examined as a result of poor growth will have no other clinical abnormalities, in many animals a thorough physical examination can provide valuable clues as to the organ system or systems responsible for the problem. The animal's general appearance and body condition should be assessed. A short animal with a poor body condition is more likely to have a nutritional, metabolic, or cardiac abnormality, whereas a short animal with a good body condition is likely to have a hormonal problem or be chondrodysplastic (see Box 22-1). Chondrodysplastic animals and many animals with congenital hypothyroidism will also have an abnormal skeletal conformation (e.g., angular limb deformities). Symmetrical truncal alopecia, the prolonged presence of a soft puppy haircoat, or thin scaly skin suggests a thyroid or growth hormone deficiency or cortisol excess. Mental dullness can be seen with hypothyroidism or hepatic encephalopathy. Hepatic failure can also result in cortical blindness.

The head and neck should be examined for pale mucous membranes (anemia of chronic disease), icterus (hepatic disease), oral pain (dysphagia), and lymphadenopathy (inflammatory disease). The thorax should be carefully ausculted for a murmur (congenital cardiac disease, other cardiac dysfunction), bradycardia (hypoadrenocorticism), or abnormal lung sounds (pulmonary disease). On abdominal palpation, enlarged or shrunken kidneys can indicate a renal problem, and hepatomegaly can suggest hepatic disease or dysfunction. Thickened bowel walls may be felt in the presence of inflammatory bowel disease, or a mass lesion may be palpated in the pet with a foreign body or intussusception.

22.4 DIAGNOSTIC PLAN

Decisions concerning the initial diagnostic plan should be based on the animal's body condition and any abnormalities identified from the history and physical examination (see Figure 22-1). Food consumption should always be evaluated (see Historical Findings). If food intake is in question, a brief *feeding trial* can provide information on appetite and caloric consumption in relation to change in body weight. Multiple *fecal examinations* and possible deworming should be performed to eliminate severe parasitism as the cause of malnutrition. If the animal has been given a medication that may have slowed growth, the medication should be discontinued, if possible, and subsequent growth monitored. A *complete blood count* (CBC) should be evaluated for anemia, inflammation, or eosinophilia. Results of a *serum biochemical profile* can suggest renal, hepatic, or gastrointestinal

disease; diabetes mellitus; hypoadrenocorticism; hyperadrenocorticism; hypothyroidism; or hyperparathyroidism. A *urinalysis* may show proteinuria, isosthenuria, hyposthenuria, glucosuria, or inflammatory sediment. *Radiographs* can be used to detect a cardiopulmonary abnormality, organomegaly, a small liver or kidneys, intestinal foreign body, or skeletal abnormalities. *Ultrasonography* may help to further characterize radiographic abnormalities and detect structural abnormalities within an organ. An *electrocardiogram* may be helpful in assessing potential hyperkalemia (in an emergency) and congenital cardiac abnormalities. *Radiographic contrast studies* can be used to characterize congenital cardiac abnormalities, to identify portosystemic vascular anomalies, and to detect partial gastrointestinal obstructions. *Hepatic function tests* can identify the need for further investigation of the liver. *Gastrointestinal function tests* (e.g., serum trypsinlike immunoreactivity, serum cobalamin and folate) can be used to identify occult gastrointestinal disease causing maldigestion or malabsorption. *Biopsy* may be needed if gastrointestinal, hepatic, or renal disease is identified. *Hormonal tests* can be used to detect hypothyroidism, hyperadrenocorticism, hypoadrenocorticism, and hyperparathyroidism; an assay for growth hormone is not currently available on a commercial basis, but an IGF-I assay is available for the dog.

22.5 TREATMENT

Treatment of the animal that exhibits growth failure varies widely based on the underlying pathology. Some disorders can be well managed medically, and others require surgical correction.

23 CHAPTER • 23 Swollen Joints and Lameness

Richard E. Goldstein

Lameness is a common reason for dogs to be taken to a veterinary practitioner. Although lameness has numerous causes, this chapter will address lameness associated with nontraumatic inflammatory disease of the joints. Assessment for swelling or pain of accessible joints should be a routine component of the physical examination of dogs and cats. Arthritis can be categorized based on cause.

Degenerative joint disease is caused by chronic changes to the joint capsule, cartilage, and synovium associated with minimal to no active inflammation. Degenerative joint disease, although painful, is typically not associated with systemic inflammatory signs. Inflammatory joint diseases can be classified as septic or nonseptic (immune mediated). Inflammatory joint disease is typically associated with one or more of the signs consistent with those of systemic disease. These usually include fever, leukocytosis, inappetence, or lethargy. Arthritis can also be classified based on the number of joints involved. Monoarthritis implies involvement of a single joint, whereas polyarthritis involves multiple joints.

23.1 SEPTIC ARTHRITIS

Septic arthritis is defined by presence of bacteria in the synovial or joint fluid, observed on cytologic evaluation or with bacterial culture. Septic arthritis occurs as a result of hematogenous (more common in neonates) spread or external penetrating wounds. It is not always possible to distinguish septic arthritis from immune-mediated arthritis, especially when multiple joints are involved or no obvious penetrating wound is seen. Joint fluid cultures, although worthwhile, are frequently negative even when bacteria are evident on cytologic examination. Neutrophils predominate in the joint fluid of infectious and immune-mediated arthritis. Degenerative changes in neutrophils, however, are more indicative of a septic process. The number and type of joints involved may help the clinician differentiate septic from nonseptic arthritis. Single joint involvement and involvement of proximal joints (hip, shoulder, stifle, and elbow) are usually septic. Multiple, distal joint (carpi, tarsi) involvement, is most commonly seen immune-mediated disease. When a septic process is possible, a period of antimicrobial therapy can be recommended, even if no bacteria are observed on joint fluid cytology and joint fluid cultures are pending or negative.

23.2 IMMUNE-MEDIATED POLYARTHRITIS

Immune-mediated polyarthritis is the most common poly-arthritis in companion dogs and cats. A type III hypersensitivity reaction, in which immune complexes are deposited in the synovial membrane and an inflammatory cascade is initiated, is thought to be the cause. The immune stimulus is frequently unknown, hence the commonly used term “idiopathic polyarthritis.” Immune-mediated polyarthritis can be categorized both radiographically and histologically into the common nonerosive form and the uncommon erosive condition.

23.3 EROSIVE POLYARTHRITIS

Erosive polyarthritis in dogs may have similarities with human rheumatoid arthritis. These similarities include the progressive, severe, deforming course of the disease and the erosive radiographic appearance of affected joints. In humans, specific antibodies, collectively known as *rheumatoid factor* (RF), are commonly identified. An IgM antibody, considered the canine RF, has been identified in some dogs with erosive arthritis. Although the term

rheumatoid arthritis has been used in veterinary medicine, it is preferable to use the descriptive term *erosive arthritis* in dogs. 84

RF is a nonsensitive and nonspecific marker of erosive or immune-mediated arthritis in dogs, making the assay's clinical utility questionable. Radiographic findings commonly seen in dogs with this form of arthritis include erosions involving the articular surface or the loss of trabecular bone density in the epiphyses. The destructive process is progressive. Radiographically, this process appears in the subchondral or juxtaarticular bone as poorly demarcated radiolucent foci. Erosive arthritis has been reported in many breeds but is thought to occur more frequently in small breed dogs, 2 to 6 years of age. A specific form of erosive arthritis has been reported in greyhounds.

Erosive polyarthritis has been reported in cats and has been termed *progressive feline polyarthritis*. This is a disease that occurs more commonly in male cats between 1.5 and 5 years of age. It may be an immune-mediated hypersensitivity type III reaction to chronic viral immune stimulation, secondary to chronic feline syncytium-forming virus infection. Two forms of the disease exist: (1) the deforming type, a severely erosive condition that is similar to canine erosive arthritis, and (2) the more common proliferative form. Both forms can be associated with severe systemic signs of disease, including lymphadenopathy, swollen joints, and muscle wasting.

23.4 NONEROSIVE POLYARTHRITIS

This is the most common form of immune-mediated polyarthritis in dogs and cats. The source of the antigenic stimulation is usually not known. Nonerosive polyarthirtis has been reported to occur secondary to chronic infectious disease, systemic lupus erythematosus (SLE), lymphocytic plasmacytic synovitis, use of certain drugs, and malignancies. It may also be a component of immune-mediated diseases, such as inflammatory bowel disease or chronic hepatitis.

Clinical signs typically include cyclic fever, lethargy, anorexia and varying degrees of pain, lameness and swollen joints. A stiff gait characterized as “walking on egg shells” is frequently observed, but some affected dogs have a normal gait. The distal joints (carpi and tarsi) are most commonly affected. Pain, redness, and swelling range from severe to absent. Some dogs exhibit pain that is difficult to localize. Others have signs of back or neck pain. This could be a result of inflammation of the vertebral articulations or concurrent meningitis. Lymphadenopathy and muscle wasting can be profound. Nonerosive polyarthritis can be seen in any breed at any age but most commonly occurs in young dogs (between 1 and 6 years of age). The condition appears to be overrepresented in German shepherds, Doberman pinschers, collies, spaniels, retrievers, terriers, and poodles. Specific syndromes involving immune-mediated polyarthritis have been identified in certain breeds of dogs, such as swollen hock syndrome in Shar Peis and arthritis in Akitas.

Figure 23-1 A demonstration of the method to grossly assess joint fluid viscosity. A drop is placed on a glass slide. It is gently touched with a fingertip that is then slowly moved away. The reader should note the strand of viscous fluid typical for normal joint fluid viscosity.

Infectious disease can cause a secondary immune-mediated polyarthritis as a result of chronic immune stimulation inducing immune complex deposition in the synovial tissue. Diseases frequently associated with secondary immune-mediated polyarthritis include heartworm disease, rickettsial disease such as ehrlichiosis, Rocky Mountain spotted fever, Lyme disease, and others. Chronic bacterial infections such as discospondylitis, pyelonephritis, prostatitis, and endocarditis can also cause a secondary immune-mediated polyarthritis.

Systemic lupus erythematosus is suspected when polyarthritis is accompanied by immune-mediated hemolytic anemia, thrombocytopenia, glomerulonephritis, or immune-mediated dermatopathies. The value of antinuclear antibody (ANAs) testing is controversial. This syndrome is thought to occur more commonly in females and in German shepherds, collies, Shetland sheepdogs, beagles, and poodles.

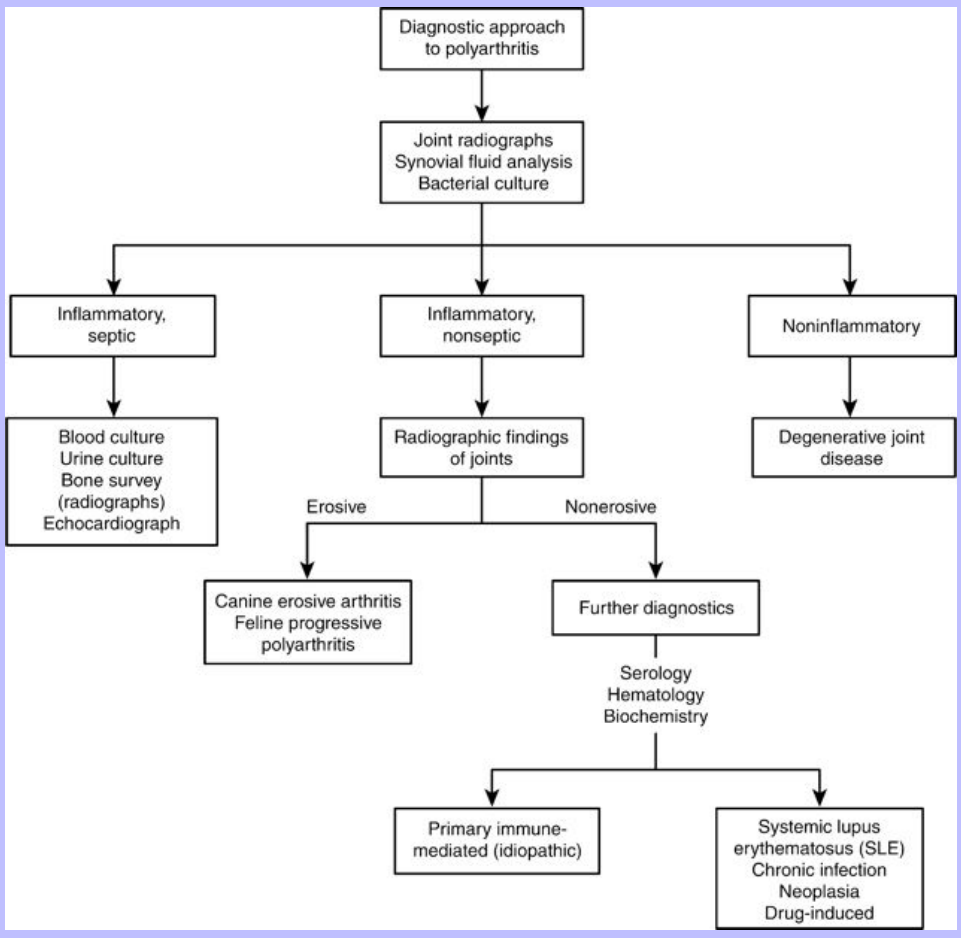
Lymphocytic-plasmacytic synovitis has been reported most commonly in German shepherds and other large-breed dogs. This condition is thought to be associated with degenerative joint disease, such as arthritis in the stifle joint after rupture of the cranial cruciate ligament. The diagnosis can be confirmed with histologic evaluation of the synovium.

Drug-induced immune-mediated polyarthritis appears to be rare. It has been reported to occur as a result of trimethoprim-sulfadiazine therapy in a group of Doberman pinschers. Immune-mediated polyarthritis has been suspected in some cases after vaccinations (e.g., vaccinations for lyme disease).

Inflammatory joint disease (septic or immune mediated) should be suspected in the following instances (Figure 23-2):

- The dog or cat with joint pain, joint swelling, generalized pain, or reluctance to rise.
- Joint pain or swelling that is apparent during the physical examination.
- The dog or cat that has abnormalities that could result from a systemic inflammatory condition: fever or leukocytosis.
- When immune-mediated disease is suspected in other organ systems (i.e., immune-mediated hemolytic anemia, thrombocytopenia, steroid responsive sterile meningitis, glomerulonephritis).

Figure 23-2 Algorithm for diagnostic approach to polyarthritis.



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23.5 ARTHROCENTESIS AND JOINT FLUID ANALYSIS

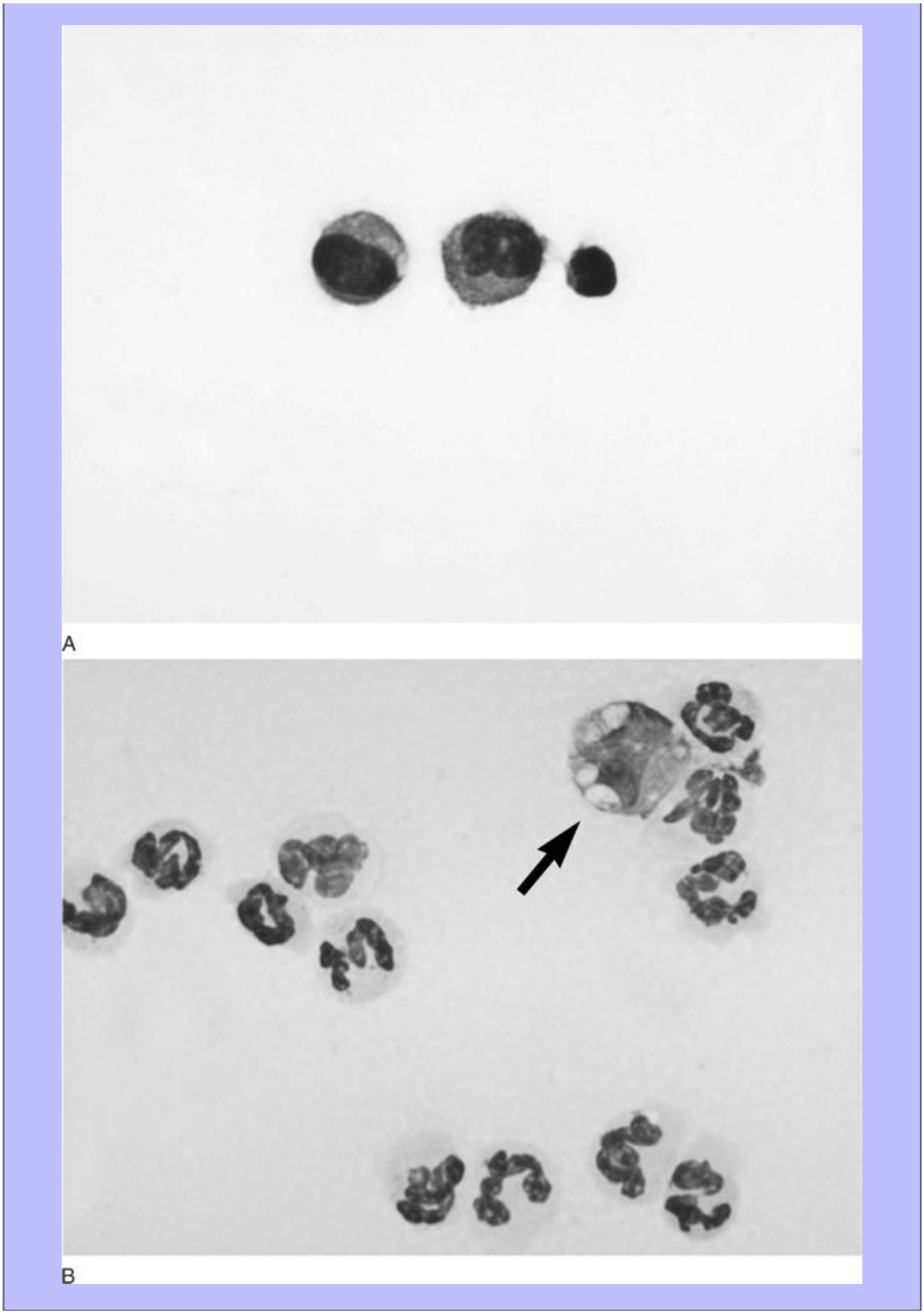
Joint fluid analysis is the single most important test performed in the diagnosis of inflammatory arthritis. Joint taps are usually simple to perform and are associated with minimal morbidity or complications (see Chapter 74). Aspiration of synovial fluid (joint taps) and cytologic analysis are necessary to define the involvement of a joint (Figure 23-3). Affected joints, even severely affected, may not appear swollen or painful. Joint taps should also be performed as part of the diagnostic investigation of a fever or leukocytosis of unknown origin or when other immune-mediated disease is suspected. In a recent study, 20% of dogs with a fever of unknown origin had immune-mediated polyarthritis. Unfortunately, the information clinicians can obtain from joint fluid analysis is limited. Increased numbers of neutrophils appear in joint fluid of both septic and immune-mediated arthritis, making the differentiation between the two difficult, and joint fluid cultures are frequently negative even in the obvious presence of bacteria.

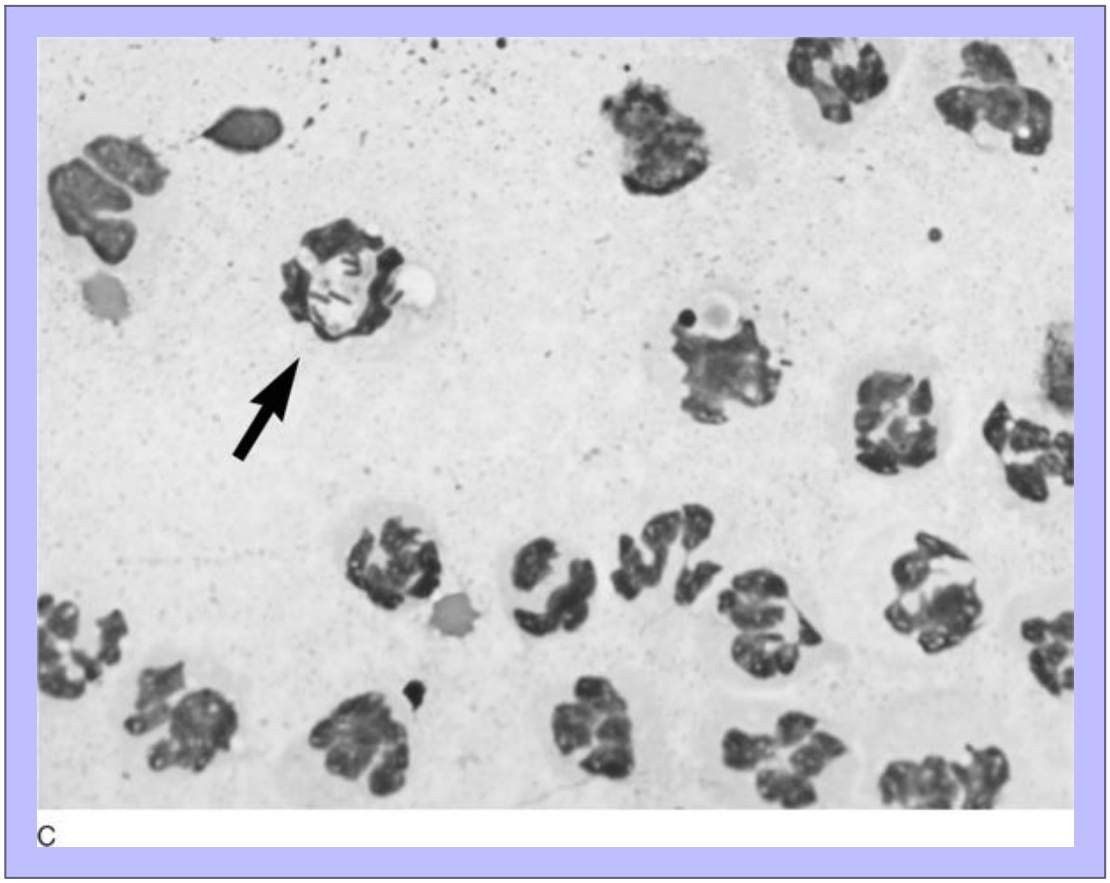
Multiple joints should always be sampled, including those that do not appear to be clinically involved in the disease process. It is recommended that both carpi and both tarsi joints be sampled along with at least one elbow and stifle. Hip and shoulder joints are not commonly tapped unless they appear to be diseased.

23.6 GROSS EXAMINATION

Fluid from a normal joint is clear, light straw colored and has a sticky viscous feel, forming a strand when a drop is paced between a fingertip and the thumb, which are then slowly pulled apart, or between a glass slide and a fingertip, which is slowly moved away from the slide (Figure 23-1). More than a few drops should not be easily obtained from a normal joint. If the fluid is discolored, turbid, lacks viscosity, or is aspirated in excessive amounts, then joint disease is likely. Blood contamination, only partially mixed in with the joint fluid, may occur.

Figure 23-3 **A,** Normal: Two quiescent mononuclear phagocytes *(larger)* and a small mature lymphocyte are seen in this low-cellularity direct smear of normal canine synovial fluid. These are the predominant cell types in health in all species. **B,** Nonseptic arthritis: Numerous well-preserved neutrophils and a macrophage *(arrow)* are seen in this highly cellular direct smear of synovial fluid from a cat with immune-mediated polyarthritis. Neutrophils typically are less than 10% in health. **C,** Septic arthritis: Numerous neutrophils and a few red blood cells (RBCs) are seen in this highly cellular direct smear of synovial fluid from a dog with septic arthritis. The reader should note cellular debris in the background and several degenerate neutrophils, including one that contains several bacterial rods *(arrow)*. (Courtesy Dr. Tracy W. French, Dip. ACVP, Cornell University.)


A
B



23.7 CYTOLOGIC EVALUATION

Normal joint fluid contains less than 2500 to 3000 white blood cells (WBCs) per milliliter and few red blood cells (RBCs). At least 90% of white cells in normal joints are mononuclear. Inflamed joints (septic or immune mediated) will typically have over 5000 WBCs and over 10% neutrophils. The WBC or neutrophil count can be estimated by multiplying the average number of cells seen in each high-power field by 1000. The presence of bacteria or degenerate changes in the neutrophils is suggestive of septic and not immune-mediated arthritis, as is a positive bacterial culture. WBC counts can be markedly increased with septic or immune-mediated disease processes, approaching 100,000 WBC/ml of joint fluid including over 90% neutrophils.

If sufficient joint fluid is obtained, then additional testing of the fluid is possible, including protein content, glucose concentrations, and a mucin clot test. Clinically these tests are not often performed and are thought to have little additional value if cytology and culture have been performed.

23.8 ADDITIONAL TESTING

A minimum data base, including a complete blood count (CBC), a serum biochemistry profile, and a urinalysis is recommended in any dog or cat with suspected inflammatory arthritis. Radiographs of the joint are indicated if septic or erosive arthritis is suspected. A search for possible sources of bacterial infection should be undertaken if

septic arthritis is suspected and no obvious penetrating wound or source of infection is evident. This search could include blood and urine cultures, thoracic and abdominal radiographs, and spinal radiographs to identify discospondylitis, abdominal ultrasound, and possibly cardiac echocardiogram for bacterial endocarditis.

If immune-mediated polyarthritis is suspected, then a search for the source of chronic immune stimulation and additional manifestations of immune-mediated disease should be undertaken. The chronic immune stimulation could be a primary immune disorder (idiopathic) or a result of chronic infection, inflammation, or neoplasia. Additional diagnostics in this case could include the previously mentioned testing listed for septic arthritis, a Coombs' test, and serology for ANAs and RF. Serology for exposure to rickettsial agents such as *Ehrlichia* species, *Borrelia*, systemic fungal infections, and for occult heartworm infestation may be indicated, depending on the prevalence in the region and a possible travel history. Positive results of any of these tests must be taken as part of the entire clinical picture. Positive Coombs' test, RF, and ANA are all nonspecific findings perhaps strengthening the possibility of more general immune-mediated disease or SLE. Positive titers to the previously mentioned infectious agents are likely indicative of exposure and not necessarily active disease. In the case of Lyme disease, if the pet has been vaccinated, then Western blot analysis can differentiate between antibodies produced as a result of the vaccine and those produced by natural exposure.

24 CHAPTER • 24 Body Odors

Karen A. Moriello

***W**ebster's Dictionary* defines odor as "*That characteristic of a substance which makes it perceptible to the sense of smell whether it be pleasant or unpleasant*." From a clinical perspective, the definition of *odor* would have to be expanded to include whether the odor is *normal* or *abnormal*. Whether clinicians realize it or not, the use of smell is an intricate part of the physical examination process. Depending upon the disease process, it can also be involved in the diagnostic, therapeutic, and monitoring process.

24.1 PEOPLE, PETS, VETERINARIANS, AND THE BODY ODOR ISSUE

Body odor has a biologic purpose. In general, smell and body odor for all species are important in species recognition, social interactions, and mate selection. In the animal phylum, changes in body odor and pheromones are driven by genetics and evolutionary trends. In the human species, one other major driving force exists—changing social trends. For example, body odor in one era may be considered normal or even desirable but in another deemed socially unacceptable. The issue of environmental odors (i.e., room odors) is almost equally important to people. Manipulation of personal and environmental odors (out of the "unpleasant" and into the "neutral or pleasant" spectrum) is an important social trend (and a commercial industry). Further complicating this issue is the increased recognition that body odor may be an early warning sign of health issues (e.g., fruity apple odor of ketoacidosis as the result of diabetes mellitus or starvation) or a human health hazard (e.g., mold). Veterinarians increasingly have to navigate the issue of "the pet's body odor" with clients. This is difficult at times because the current norm is "pleasant odor" or "no odor." The clinician's task is to determine whether the body odor in question is a sign of disease or whether it is within the realm of normal for the pet in question. If the latter is true, then clinicians must find a way to make the pet's odor more acceptable to the owner.

24.2 PATHOPHYSIOLOGY OF BODY ODOR

Body odor in animals varies with species, breed, sex, age, and overall health. In the healthy dog or cat, skin secretions contain insignificant amounts of odorous substances. Skin odor is the result of bacterial decomposition of secretions from sebaceous glands, epidermal lipids, and epitrichial and atrichial sweat glands. Epitrichial glands are present on haired skin just below sebaceous glands and open onto the surface via the piliary canal. These glands are largest and most numerous in mucocutaneous junctions, interdigital spaces, and over the dorsal back and lumbosacral areas. Not surprisingly this is often where odor concentrates in pets. Atrichial glands are located only on footpads. Sweat contains unsaturated fatty acids, ammonia constituents, and their volatile salts. Sebum and epidermal lipids on the skin surface are degraded by lipases of gram-positive bacteria to glycerol and unsaturated fatty acids, which are further metabolized to odorous compounds. It is these by-products that give sebum its antibacterial and antifungal properties. Some of the acids produced by the degradation of these lipids, butyric and caproic acids, are quite volatile and emit a cheesy rancid odor. Oral odor may be associated with systemic illnesses, such as uremia, diabetes mellitus, or periodontal disease. Malodor associated with periodontal disease is due to the production of volatile sulfur components. Oral odors are most often the result of by-products of bacterial metabolism resulting from bacteria colonization of plaque, gingival sulci, and the dorsal surface of the posterior tongue. Oral odors may also be the result of something the pet has ingested (e.g., fecal material).

24.3 CLINICAL APPROACH TO THE PROBLEM OF BODY ODOR

The starting point of any medical visit is the owner's complaint. In general, pets with the problem of body odor fall into one of four broad categories (see the following) as determined by the history and physical examination. In the case of body odor, what the clinician simply sees and smells may accomplish the initial sorting. After this, the clinician can then determine how best to proceed (see Box 24-2). In most cases the veterinarian needs to determine if underlying cause is due to a systemic disease, pure dermatologic disease, external factors, or lack of client education.

"Normal pets" are considered to be malodorous by the client but not by the clinician. In general, the clinician's initial assessment is that the pet's body odor is within the normal range for the *species* (e.g., cat owners first acquiring a dog may not be aware of species differences), *age* (e.g., puppies have a unique odor), *sex* (e.g., intact tom cats are more odorous than neutered male cats), *breed* (e.g., hound dogs' odor versus poodles'), *hair length*, etc. Furthermore, a thorough literal "sniff exam" (nose to tail, dorsum to ventrum, feet, and ears) of the patient reveals no unusual odors. Finally, no evidence of a dermatologic or medical disease exists. The *key sorting aspect* of this group is that the veterinarian considers the animal to smell normal, and no history or physical evidence of illness or skin disease exists. In these situations, client education and suggestions for bathing routines that are tolerable and safe for the pet are indicated.

The clinician should be aware of two subsets in the normal pet group. The first is a subset of normal pets with owners who complain of odors that "come and go." In these situations the cause may be anal sac expression, something the dog ate (e.g., onions, garlic), flatulence, "wet dog" smell, a change in the dog's regular dog food (some specialty diets, especially fish based, cause the dog to "smell fishy"). In warm weather, many dogs will drool excessively, and this will mat the haircoat around the face, chest, and forelegs, leading to an offensive odor. Warm weather often results in increased moisture on the skin, and this can lead to bacterial degradation and odor. In addition, many owners of dogs with allergic skin disease report acute episodes where the skin becomes warm, the dog "literally sweats" and then is very odorous.

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The second subset includes those pets that smell normal to the clinician, but the owner reports that there has been a change in how the dog smells. It is critical to carefully examine these patients for evidence of subtle signs of skin disease because these owners may be reporting a valid finding. A recent study found that 86% of owners that were blindfolded and only allowed to use their sense of smell were consistently able to differentiate their dog's body odor from that of another simply by sniffing a blanket. This finding amazed both owners and investigators. What is pertinent to veterinarians is that owners may very well "know" what their dog smells like when it is normal and when it is not.

24.3.1 Malodorous Pet with an Obvious Cause

These are patients with unmistakable odor from urine, feces, skunk, flatulence, and "I rolled in the compost heap" odors. This group could also include the pets with obvious skin or medical problems, where the source of the odor (infected fracture, ears, seborrheic skin, pyotraumatic dermatitis, and so on) is easily found. Animals with severe halitosis are also included here (Box 24-1). The *key sorting aspect* of this group is that the clinician immediately knows where the odor is coming from, what is causing it, what needs to be done to eliminate it, and whether or not further medical or dermatologic diagnostics are needed. In these situations, client education may be as simple as recommendations on how to remove the odor (e.g., skunk) or more complicated discussions on the need to treat existing infections and perform appropriate diagnostic tests to investigate the underlying cause.

24.3.2 ## Malodorous Pets with Obvious Systemic Illnesses

These are patients that are malodorous, but more importantly are systemically ill. This might be determined by historical or physical examination findings (or both); changes in body odor might have been what prompted the client to finally bring the animal for examination. The *key sorting aspect* of this group is an obvious state of ill health associated with the body odor. In general, cats rarely are presented for the problem of body odor. When they are, it is usually for one of three reasons. First, a strong odor emanates from an ear, mouth, or body region. This should prompt the clinician to look for infections, injuries, neoplasia, myiasis, etc. Second, the cat is soiling itself with urine, feces, or both or not removing it from the haircoat. This could be for any number of reasons, such as physical inability to groom (e.g., obesity, arthritis) or neuromuscular injury. Third, the cat could just be generally odorous to the client. These cats usually have stopped grooming themselves, and their haircoat is matted or greasy. This situation should prompt the clinician to look for a systemic illness (e.g., hyperthyroidism, diabetes mellitus, neoplasia). Dogs with systemic illness may be mildly or severely malodorous. Mild odors are usually caused by concurrent skin infections triggered by debilitation. The skin odor in these patients usually is not noticeable to the clinician until the dog is physically examined. Severely odorous dogs almost always have the odor localized to one area (e.g., mouth odor caused by uremia), a site of injury and infection (open fracture with secondary infection), or excrement on their haircoat because of some cause of immobility. In these situations, client education must focus on a need to aggressively pursue the cause of the illness, whereas the odor issue is addressed as part of the therapy for the health and well-being of the patient (e.g., treatment of urine or fecal soiling).

24.3.2.1 24.3.2.1 Box • 24-1 ***Common Causes of Halitosis in Dogs and Cats***[*]

24.3.2.1.1 ### Oral Diseases

Periodontal disease (gingivitis, periodontitis, abscessation)

Neoplasia (melanoma, fibrosarcoma, squamous cell carcinoma)

Foreign body or trauma (fractures, electrical cord injury)

Pharyngitis

Stomatitis, lymphocytic-plasmacytic feline stomatitis

24.3.2.1.2 ### Respiratory Diseases

Rhinitis and/or sinusitis

Neoplasia

Pneumonia or pulmonary abscess

24.3.2.1.3 ### Dermatologic Diseases

Lip fold pyoderma

Ulcerative mucocutaneous pyoderma

Feline or canine eosinophilic granulomas

Pemphigus complex, bullous pemphigoid, lupus erythematosus

Drug eruptions

Cutaneous lymphoma

Exposure to dimethyl sulfoxide (DMSO)

24.3.2.1.4 Metabolic Diseases

Renal failure/uremia

Diabetic ketoacidosis

24.3.2.1.5 Gastrointestinal Diseases

Megaesophagus

Inflammatory bowel disease

Exocrine pancreatic insufficiency

24.3.2.1.6 Neoplasia

Constipation (cats)

24.3.2.1.7 Dietary

Aromatic foods (onions, garlic)

Fetid foodstuffs (e.g., ingestion of carrion)

Coprophagy

24.3.2.1.8 Grooming Behavior

Anal sacculitis

Vaginitis/balanoposthitis

Lower urinary tract infections

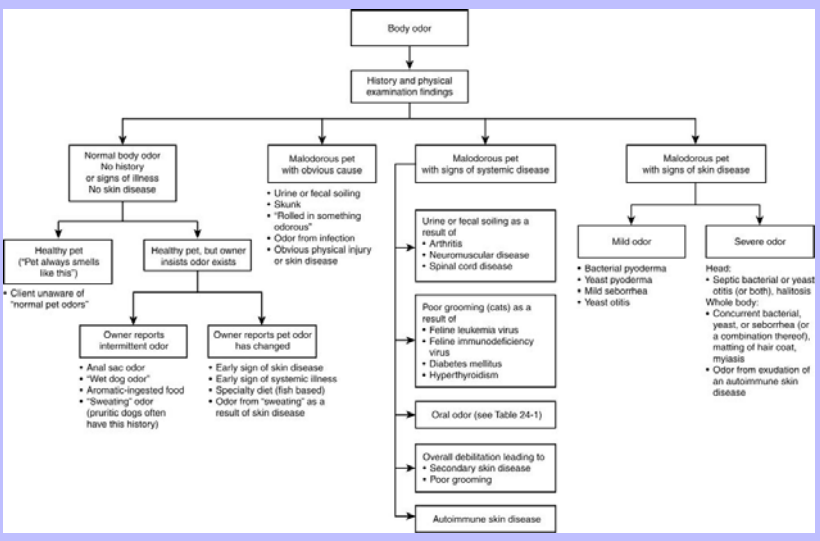
* Adapted from *Veterinary Guide to Odor and Disease, The Oral Cavity and Dermatology*, Veterinary Learning Systems, 1997.

24.3.3 Malodorous Pets with Skin Disease

Without a doubt, most obviously odorous animals will fall into this group. For the vast majority of patients, the *key sorting aspect* of this group is an otherwise healthy pet with a history of skin disease, blatantly obvious skin disease, skin disease found during the examination, or a combination of these factors. When working with these patients, the clinician should remember several key points: 89 91

- The most common causes of body or ear odor is almost always some combination of bacterial pyoderma, *Malassezia* pyoderma, and seborrhea (usually oily).
- Many of these patients are severely pruritic. The pruritus is most likely caused by a combination of the microbial infections, inflammatory degradation products of oily seborrhea, the presence of an underlying pruritic disease (e.g., atopy), or a combination of these factors.
- The duration of the skin problem, presence or absence of underlying primary seborrhea, and severity of the skin infections (superficial or deep) mostly determine the severity of the odor. Other factors such as length of the haircoat, presence or absence of hair mats, and exposure to moisture can also affect the severity of the odor.
- The odor will most likely resolve with appropriate systemic and topical treatment of the superficial microbial infections and seborrhea; it may or may not return. This depends on whether the underlying trigger of microbial infections is still present, whether the patient has a previously undiagnosed primary disorder of keratinization, and whether the pruritus has resolved. If not, the return of the body odor is almost guaranteed because it will trigger secondary microbial infections and seborrhea.
- Recurrent otic or skin odor always means an underlying skin disease is present. Whether or not diagnostics beyond skin scrapings, flea combing, skin and ear cytology, and possibly a fungal culture are indicated in malodorous pets with skin disease depends on the patient's history and physical examination.

Figure 24-1 Algorithm for presenting complaint of body odor.



24.3.3.1

Box • 24-2 General Recommendations for Control of Odor

24.3.3.1.1

Normal Pets without Skin Disease

- Client education for the owner.
- Keep the haircoat short; no feathering haircuts.
- Clip hair from inner pinnae.
- Avoid cloth dog collars that can become impregnated with the pet's body odor.
- Bathe pet in a veterinary hypoallergenic shampoo only as often as to keep odor free.
- Dry pet after exposure to rain or after swimming to avoid wet-dog smell.
- Use veterinary coat deodorizers only.

24.3.3.1.2

Skunk Odor

- Liberal application of “Skunk Off”
- Keep pet dry to prevent reemergence of skunk odor (it may take several weeks for the odor to dissipate completely).

24.3.3.1.3

Urine, Fecal Matter, and Odors Associated with “Rolled in Something Dead”

- Clip any mats from haircoat.
- Bathe pet in grooming or flea shampoo first to remove gross debris, and rinse well.
- Bathe a second time in a degreasing shampoo such as benzoyl peroxide; odors are often held in skin and hair lipids.

24.3.3.1.4

Pets with Odor and Skin Disease

- Complete appropriate diagnostics, and begin appropriate systemic therapy.
- Administer appropriate sedation, analgesia, or anesthesia, if needed.
- Clean or flush ears as needed.
- Grooming recommendations:
  - Clip haircoat from inner ear pinnae and around ears, if necessary.
  - Clip hair mats and areas of lip fold pyoderma.
  - Clip haircoat of medium-or long-haired dogs.

- Bathing recommendations:
  - Always prebathe pet with grooming or flea shampoo to remove gross debris before using a medicated shampoo; rinse well (this step facilitates efficacy of medicated-shampoo product).
- Bathe pet in antimicrobials or antiseborrheic shampoo (it may work best if the client alternates between two shampoos).
- Severely odorous pets should be bathed daily until client deems pet acceptable.
- Most pets require two to three baths per week during medical treatment.
- Warnings:
  - Some shampoos are irritating; do not use if pet seems uncomfortable after use.
  - If haircoat becomes excessively dry, decrease frequency of bathing.
  - Dogs with primary seborrhea will require aggressive bathing for life to control disease and odor.

Note: A subgroup of malodorous pets exists with skin disease and signs of systemic illness (e.g., anorexia, persistent or waxing and waning fevers, depression, reluctance to walk, weight loss, dehydration). This triad (odor, skin disease, illness) should alert the clinician to the possibility that the patient has a severe life-threatening condition such as deep pyoderma with or without demodicosis, drug reactions, immune-mediated diseases, deep fungal infections with cutaneous manifestations, or toxic epidermal necrolysis. An immediate aggressive dermatologic evaluation is needed: skin scrapings, bacterial cultures, impression smears of exudate, and skin biopsy, in addition to appropriate medical diagnostics and supportive care pending diagnosis.

25 CHAPTER • 25 Ocular Manifestations of Systemic Disease

David J. Maggs

Clinicians tend to consider the eye and adnexa as unique structures that are dissimilar to nonocular tissues. This can lead to omission of the ophthalmic examination in patients with systemic disease or omission of the general physical examination in patients presented with ophthalmic disease. In fact, the eye is a complex aggregate of tissues with marked anatomical and functional similarities to tissues found in most other organ systems. Viewed in this manner, the eyes provide a unique opportunity for direct observation of tissue types that are otherwise not visible without invasive techniques or special instrumentation.

The major correlations between ocular and nonocular tissues are summarized in Table 25-1. This table identifies ocular tissues that should be examined carefully in animals with systemic disease and nonocular tissues that should be examined in those with ocular disease. For example, in a dog or cat with generalized lymphadenopathy, the conjunctiva, third eyelid gland, and uveal tract should be closely examined because they are also composed of lymphoid tissue. Likewise, a thorough general physical examination of the pet with retinal disease may reveal more widespread vascular, neurologic, or hematologic disease.

The following is a description of specific ocular conditions, arranged by affected ocular tissue, often associated with systemic disease. This chapter highlights the correlation between ocular and systemic tissues. It does not provide an exhaustive description of the diagnostic approach or therapies.

25.1 SURFACE OCULAR DISEASE

The eyelids, conjunctiva, cornea, and sclera are intimately related, physiologically and anatomically. They provide a protective surface for the eye, and all three tissues are susceptible to the same insults that cause surface (dermatologic) disease elsewhere. Therefore a thorough dermatologic history and a complete dermatologic examination may be helpful in animals with surface ocular disease. The diagnostic approach to lesions involving eyelids, conjunctiva, or cornea is identical to that used for skin. It includes incisional or excisional biopsy, scrapings, and viral, fungal, chlamydial, and mycoplasmal or bacterial culture.

Table • 25-1 Correlations between Ocular and Nonocular Tissues

Tissue Type	Visible Ocular Correlates
Mucous membrane	Conjunctiva
Vascular tissue	Conjunctiva, uvea, retina
Neural tissue	Retina, optic nerve
Lymphoid tissue	Uvea, conjunctiva, third eyelid
Glandular tissue	Meibomian glands, conjunctival goblet cells, third eyelid gland
Connective tissue	Sclera, cornea
Smooth muscle	Iris, upper eyelid third eyelid
Interstitial space	Anterior chamber, subretinal space, vitreous
Hematologic	Conjunctiva, uvea, retina

Ocular surface tissues may also be affected as “innocent bystanders” in more serious orbital disease or intraocular conditions such as uveitis or glaucoma. Retropulsion of the globe and thorough intraocular exam with measurement of intraocular pressure (IOP) will identify such animals.

25.1.1 Eyelids

Although blepharitis may represent more widespread dermatitis, special consideration should be given to unique palpebral anatomy. Meibomian glands are specialized sebaceous glands that can be primarily infected; particularly with *Staphylococcus* and *Demodex* spp. Altered immune responses can exacerbate clinical signs at this site. Immunodeficiency may encourage colonization by organisms such as dermatophytes or *Demodex* spp., whereas an exuberant immunologic response such as hypersensitivity to *Staphylococcus* spp. may cause more severe inflammation. Eyelid margins represent a clearly visible mucocutaneous junction that could be involved in primary immune-mediated dermatitis such as the pemphigoid diseases or systemic lupus erythematosus (SLE). Other immune-mediated diseases such as vasculitis or uveodermatologic syndrome (also known as Vogt-Koyanagi-Harada [VKH] or VKH-like syndrome) may also be more obvious or more severe in periocular skin.

Altered lid position, with or without altered pupil size or globe deviation can also represent central, peripheral, or disseminated neurologic disease, specifically dysfunction of cranial nerve (CN) III or VII or decreased sympathetic tone (Horner's syndrome). Clinical localization of the lesion or lesions is important, particularly for Horner's syndrome—the triad of enophthalmos (with protrusion of the third eyelid), ptosis, and miosis. Because of the circuitous, three-neuron route by which sympathetic neurons course from the hypothalamus to the eye, Horner's syndrome can result from disease involving the brain, spinal cord, brachial plexus, thorax and mediastinum, neck, temporal bone and tympanic bulla, or orbit. Diagnostic procedures should be directed at each specific area to eliminate definitive causes. However, even with intensive diagnostic testing, approximately 50% of cases of Horner's syndrome are idiopathic and usually resolve within 2 months.

25.1.2 Conjunctiva

Conjunctival disease is seen alone, with blepharitis or keratitis, or may reflect inflammation of deeper structures such as the sclera, meibomian glands, orbital contents, third eyelid gland, or intraocular tissues. The rich vascularity of conjunctiva and its almost transparent epithelium also make it an excellent site for detection of hematologic (cyanosis, anemia, icterus) or vascular disease. 92 93

Feline herpesvirus (FHV-1) and *Chlamydophila felis* (formerly *Chlamydia psittaci*) are primary conjunctival pathogens of cats. Although cats undergoing primary FHV-1 exposure generally demonstrate concurrent signs of upper-respiratory infection, cats infected with *C. felis* and those undergoing a recrudescent FHV-1 episode may demonstrate few or mild nonocular clinical signs. Despite an apparent lack of systemic signs, recent evidence confirms that cats harbor and shed *C. felis* from nonocular sites. Studies also suggest that systemic therapy is more effective than topical therapy at decreasing clinical signs and shedding of *C. felis*.

Conjunctivitis in dogs is usually not associated with systemic disease. Ligneous conjunctivitis is an uncommon but important exception. This is a chronic, membranous conjunctivitis in which gross thickening of conjunctiva occurs bilaterally. Younger, female Doberman pinschers may be predisposed. Other mucous membranes may also be involved, and the majority of affected dogs also have evidence of upper-respiratory or urinary tract disease. Histology reveals a characteristic amorphous, eosinophilic hyaline material throughout the subconjunctiva.

25.1.3 Cornea and Sclera

Corneal clarity is important for normal vision. Attentive owners may often note early or subtle corneal pathologic changes. Although altered corneal appearance may represent primary keratitis or intraocular disease (particularly uveitis or glaucoma), corneal opacification that begins at or is most notable at the limbus is often an indicator of systemic disease. For example, lymphosarcoma (LSA) tends to cause a homogenous, creamy-pink discoloration of the peripheral corneal stroma. Corneal lipidosis is an important differential diagnosis in these cases and may occur secondary to any disease causing systemic hyperlipidemia. Hypothyroidism is one of the most common causes; however, hyperadrenocorticism, diabetes mellitus, and familial hypertriglyceridemia should also be considered. Serum triglycerides and cholesterol should both be assessed in animals with corneal lipidosis. Rarely, corneal opacification in dogs or cats will be caused by mucopolysaccharidosis.

Although hyperadrenocorticism and diabetes mellitus are associated with prolonged corneal wound healing, dogs with diabetes mellitus have also recently been shown to have significantly decreased corneal sensitivity relative to normal dogs. This may represent a manifestation of diabetic neuropathy, making dogs less likely to blink and produce reflex tears to protect their corneas. In addition, multiple growth factors are transferred to the cornea by sensory nerves, and these are likely to be reduced in such dogs. This likely contributes to the poor wound healing observed in these pets. Therefore therapy and monitoring of corneal disease, especially ulceration, should be more intense in diabetic dogs.

25.1.4 Keratoconjunctivitis Sicca

Decreased aqueous tear production with subsequent keratoconjunctivitis sicca (KCS) is common in dogs but uncommon in cats. In dogs it is usually caused by idiopathic lymphocytic-plasmacytic dacryoadenitis. Rarely, cats or dogs with KCS have immune-mediated destruction of the salivary glands and associated xerostomia (Sjögren's-like syndrome), sometimes clinically apparent as dysphagia. KCS in association with xeromycteria (dry nose) should prompt investigation of neurogenic KCS caused by damage to afferent or efferent pathways of lacrimal innervation. Lacrimal stimuli are transmitted by CN V, and efferent (parasympathetic) fibers are carried first by CN VII and peripherally by CN V. Because these same neural pathways are involved in the production of moisture for the nasal mucosa, ipsilateral xeromycteria evidenced by a dry crusty nostril may be seen. Diagnostic efforts should be directed at disease processes along the paths of CN V and VII, particularly in the region of the tympanic bullae.

KCS may also occur as a result of drug therapy. Drugs incriminated in decreased tear production include systemically or topically administered atropine, systemically administered sulfa drugs, etodolac, and general anesthesia within the preceding 2 days. Dogs with marginal tear production before administration of these drugs, and those weighing less than 12 kg (in the case of trimethoprim sulfa), appear to be at increased risk of developing KCS. Dose and duration of therapy are less relevant. Restoration of tear production and corneoconjunctival health does not always occur upon discontinuation of the offending drug; therefore Schirmer tear test (STT) results should be monitored before and during therapy.

Finally, KCS may occur as a component of systemic disease but may be overlooked unless a STT test is performed. Systemic infection with canine distemper virus (CDV) or FHV-1 is associated with usually transient KCS. Dysautonomia (Key-Gaskell syndrome) can cause bilateral reduced aqueous tear secretion, nonresponsive dilated pupils, and protrusion of the third eyelids. Associated systemic signs of autonomic dysfunction including urinary and fecal incontinence, bradycardia, hypotension, dysphagia, and dry nose are usually more noticeable

than the ocular signs; however, ocular signs may help to confirm the diagnosis. Association between hypothyroidism and KCS has not been substantiated by recent studies.

25.2 UVEAL TRACT

Uveal pathology is commonly seen with systemic disease. The uveal tract includes the iris, ciliary body and choroid and is the major vascular supply for the avascular components of the eye (cornea, lens, outer retina). It is composed of a large network of arterioles, venules, and fine capillaries and therefore is a sensitive indicator of vascular or hematologic conditions, such as vasculitis, hypertension, anemia, and hyperviscosity (see Fundus). Loss of vascular integrity may be apparent in the anterior chamber as breakdown of the blood-aqueous barrier. This appears differently, based on the extent of breakdown and the presence or absence of inflammatory mediators within the anterior chamber and surrounding tissues. With minimal breakdown, albumin and other small serum proteins are detectable in the anterior chamber as aqueous flare. The aqueous humor may be thought of as a directly visible area of interstitial space, and if serum contents are seen within this space, the possibility of similar plasma “leakage” in other less visible nonocular interstices should also be considered.

Detection of aqueous flare requires that a beam of light emanating from a bright and focal source be viewed transversely, preferably with some magnification, as it traverses the anterior chamber. This examination should be done with dim ambient light. A slit lamp biomicroscope provides the optimum combination of these conditions; however, a direct ophthalmoscope turned to the smallest spot of light and held within 1 cm of the corneal surface provides a focal light source and can be used in general practice to detect flare. By definition, albumin, and therefore aqueous flare, will be approximately evenly distributed throughout the anterior chamber. Cellular debris (hyphema, dispersed white blood cells [WBCs], or hypopyon) or larger proteins, particularly fibrin in the anterior chamber suggests more major vascular compromise or potent, cytokine-mediated extravasation of cells. These blood constituents are more likely to settle into the ventral anterior chamber. Depressing the pet's nose so that the eyes are elevated within the orbits will often assist in seeing this region.

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Fine uveal capillary beds can act as a biologic “filter” that traps organisms, particularly fungi, or metastatic neoplastic cells. It is frequently involved in systemic infectious disease or as a site of metastatic neoplasia. The uvea also contains the major intraocular lymphoid tissue and is therefore a common site for LSA. It is also frequently involved in specific or nonspecific ocular inflammatory responses (uveitis) that may reflect broader immunopathology such as infectious or neoplastic disease. The list of organisms that have been associated with uveitis is expanding and is somewhat species specific. In cats, feline infectious peritonitis (FIP), feline immunodeficiency virus (FIV) (principally a retinochoroiditis), feline leukemia virus (FeLV) (principally via LSA), *Toxoplasma gondii,* Mycobacteria, and the systemic mycoses (principally a chorioretinitis) have traditionally been associated with uveitis. More recently, intraocular detection of other organisms such as FHV-1, *Bartonella* spp., and some *Ehrlichia* spp. has led to suggestions that these organisms also warrant consideration as causative agents in feline uveitis. Despite this expanding list of differential diagnoses and thorough diagnostic testing (sometimes including enucleation and histopathology), a definitive cause of uveitis is not identified in 50% to 70% of affected cats.

The list of infectious organisms causing uveitis in dogs includes fungal organisms, *Leishmania donovani*, *Ehrlichia platys* or *canis*, *Rickettsia rickettsii*, *Brucella canis*, *Toxoplasma gondii*, Canine adenovirus, and *Leptospira* spp. In addition, dogs appear to be more susceptible to immune-mediated uveitis than cats. One example is lens-induced uveitis, in which lens proteins leak from a cataractous or ruptured lens and overwhelm normal immune tolerance of these proteins. Another example is uveodermatologic (VKH-like) syndrome in which the immunopathology is directed at melanocytes throughout the body. Because of the preponderance and visibility of melanin-containing cells in the uveal tract and skin, clinical manifestations of disease in these two tissues are most dramatic.

It is incorrect to suggest that the clinical appearance of uveitis can be used to determine a definitive cause. However, noting whether the uveal inflammation appears more cellular or granulomatous, blood tinged, or proteinaceous may help prioritize diagnostic efforts (Figure 25-1).

Finally, the iris (anterior uvea) forms the pupil and therefore often provides clinical evidence of neurologic disease. Pupillary abnormalities suggestive of systemic disease include feline "spastic pupil syndrome" in which intermittent periods of anisocoria are seen without obvious iridal or afferent neurologic defects. Most cats are FeLV positive or become so soon after diagnosis but may not have other systemic signs of infection when pupil abnormalities are noted. A virally induced neuropathy of CN III is suspected. Pupilomotor abnormalities with normal vision and without ocular inflammation are also seen with dysautonomia (mydriasis) and Horner's syndrome (miosis).

25.3 LENS

The two most common conditions affecting the lens are cataract and lens dislocation (subluxation or luxation). Lens dislocation usually occurs secondary to severe intraocular disease, particularly uveitis, which may be a sign of systemic disease. Although lens dislocation may also occur as a primary event in predisposed dog breeds such as terriers, these pets do not have evidence of the generalized connective tissue disorders seen in some humans.

Although the majority of canine cataracts are hereditary in origin, almost all dogs with diabetes mellitus will develop cataracts within 12 months of diagnosis. By contrast, the most common cause of feline cataracts is uveitis. Cats with diabetes rarely develop cataracts. Other systemic causes of cataracts include altered nutrition (especially orphan animals raised on milk replacement products), hypocalcemia with or without hyperphosphatemia (as seen with hypoparathyroidism), electric shock, lightning strike, and senility.

25.4 FUNDUS

The ocular fundus is not a single structure. Rather, it is a collective term describing all structures in the posterior portion of the globe that can be viewed with the ophthalmoscope. Visible structures will vary but may include retinal pigment epithelium (if pigmented), neurosensory retina, optic nerve head, retinal vasculature, sclera, tapetum, or choroid. The fundic examination therefore provides a unique opportunity to directly visualize a large cranial nerve (optic nerve), sensitive neural tissue (retina), large venules and arterioles (retinal vessels), and a massive capillary bed (choroid). For this reason, a fundic examination should be performed in all animals with systemic disease.

The choroid is perhaps the fundic tissue most commonly affected in animals with systemic disease. Because of its position immediately subjacent to the retina and its critical role in retinal nutrition and function, signs of choroidal disease are frequently first noted once they affect the retina. The classic example is retinal detachment, which may be caused by primary retinal disease but frequently reflects choroidal effusion. As a result of these close anatomic and physiological relationships, the terms *chorioretinitis* and *retinochoroiditis* are used to reflect inflammation of these two tissues. The difference between these two terms is subtle, with the intent that the first-mentioned tissue is the one believed to be primarily involved. For example, the systemic mycoses have a predilection for the choroid and so cause a marked chorioetinitis. By contrast, CDV targets neurologic tissue in general and, within the eye, retinal tissue specifically. Insults to the subjacent choroid usually also occur, and the disease is typically referred to as a *retinochoroiditis*.

25.4.1 Optic Nerve and Retina

Although primary dysfunction of the optic nerve or retina occurs, altered appearance of these tissues often represents disease of the adjacent central nervous system (CNS) or subjacent choroid (see Uveal Tract). Optic neuritis and retinitis may therefore reflect more widespread meningoencephalitis or uveitis. Causes include infectious agents (CDV, systemic mycoses, or *Toxoplasma gondii*), immune-mediated diseases such as granulomatous meningoencephalitis, or neoplasia involving the CNS, meninges, orbit, or choroid. Diagnosis frequently involves cerebrospinal fluid (CSF) analysis and advanced imaging. Optic nerve edema without hemorrhage, exudates, or blindness is termed *papilledema* and is seen in association with increased intracranial pressure. Therefore fundic examination is recommended in all animals suspected of having CNS disease, especially when a CSF tap is planned.

Taurine deficiency in cats has been associated with retinal degeneration that begins as a focal rhomboid area of subtle increased granularity of the area centralis, progresses to involve retina on both sides of the optic papilla, and ultimately affects the whole retina. Affected cats should also be screened for dilated cardiomyopathy. This syndrome is sometimes called *feline central retinal degeneration* (FCRD) because abnormal dietary or tissue taurine concentration is not always established.

Sudden acquired retinal degeneration (SARD) describes a rapid onset of complete blindness in middle-aged to older dogs with initially normal fundic examination findings. Generalized retinal degeneration becomes clinically evident within 4 to 6 weeks of blindness. Complete and irreversible loss of photoreceptor function takes place without any clinically or histologically detectable inflammation. Female dogs appear overrepresented and many are moderately overweight. Many have a history suggestive of hyperadrenocorticism and some may have clinical signs, blood work, or both that support the diagnosis. The cause of the apparent hyperadrenocorticism is unknown, but unlike the vision loss, systemic signs typically resolve without treatment. This disease must be differentiated from blindness as the result of optic nerve or CNS disease (particularly a functional pituitary tumor with blindness secondary to pressure effects at the optic chiasm). This can be accomplished with advanced imaging under general anesthesia; however, it is completed more simply, safely, and inexpensively by demonstrating an extinguished electroretinogram in the dog with SARD. Sight is never regained; however, owners should be reassured that this is a nonpainful disease that does not involve other ocular tissues.

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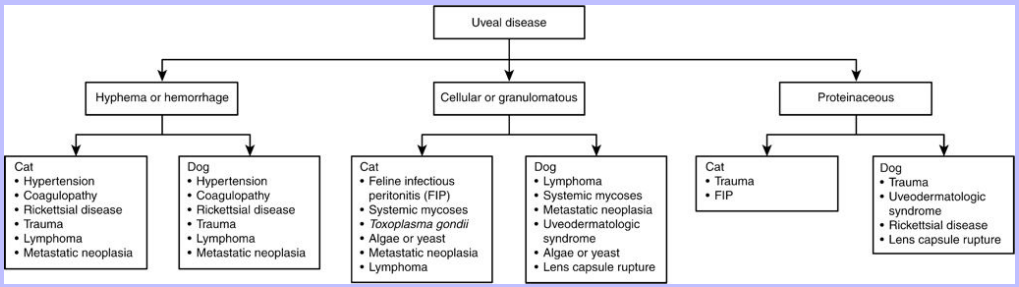
Figure 25-1 The nature of the exudates in patients with uveitis can be used to prioritize differential diagnoses.



25.4.2 Vascular and Hematologic Disease

Direct visualization of retinal (and sometimes choroidal) blood vessels permits assessment of many hematologic abnormalities, including anemia (where obvious attenuation or paleness of vessels exists), hyperlipidemia (where retinal vessels take on a creamy orange hue), and hyperviscosity (where increased vessel tortuosity sometimes is noted). Anemia, hyperviscosity, and systemic hypertension also alter tissue perfusion and vessel wall viability and can be associated with segmental vascular constriction and sacculations of retinal vessels (so-called "box-carring"), "sludging," and extravasation of blood or plasma into the choroid, retina, and subretinal space. This is clinically apparent as intraretinal or subretinal edema or hemorrhage or as retinal detachment. Some hypertensive cats also have iridal aneurysms and hyphema. A recent retrospective study of hypertensive cats established that concurrent chronic renal failure, hyperthyroidism, diabetes mellitus, hyperaldosteronism, and cardiac or neurologic abnormalities were common; however, the majority of cats with systemic hypertension are brought to veterinarians after owners observe apparent vision loss.

26 CHAPTER • 26 Acute Vision Loss in Small Animals

Teresa R. Tucci-Prošek

Vision loss is seldom truly acute; more commonly it is a sudden recognition of blindness in a pet by the owner. Multiple lesions in the visual system and central nervous system (CNS) can result in bilateral blindness. Acute vision loss is more apparent to the owner compared with progressive vision loss. Gradual vision loss enables the dog or cat to acclimate and memorize its surroundings. Many times the owner may not realize their pet is blind until an abrupt change takes place in the pet's environment, such as rearranging the furniture or moving the pet to another location. The goal of this chapter is to provide the proper guidelines for a comprehensive ophthalmologic examination, which enables the veterinarian to accurately assess acute vision loss in a dog or cat. (Please see Figure 26-1 in the e-dition.)

26.1 ABNORMALITIES RESULTING IN BLINDNESS

Blindness is a bilateral functional complete loss of vision to which attributing causes are numerous. Three categories are listed in the initial approach to locate a lesion that has caused blindness:

1. Lesions interfering with formation of an image onto the retina
2. Lesions preventing transmission of an image (peripheral → central)
3. Lesions inhibiting image interpretation (central)

Lesions limiting the formation of the image onto the retina are caused by the absence of a normally clear ocular media (cornea, aqueous humor, lens, and vitreous humor). Disruption of this media results in varying degrees of blindness (Boxes 26-1 and 26-2). Lesions affecting the retina and its ability to transmit images to the brain or visual pathway (optic nerve, optic chiasm, optic tract, lateral geniculate nuclei [LGN] and optic radiations) are listed (Box 26-3). Central blindness, also known as *cortical blindness*, results when interpretation of an image is absent (Box 26-4).

26.1.1 Box • 26-1 Ocular Media Abnormalities Causing Blindness

26.1.1.1 Cornea

- Edema (glaucoma, endothelial dystrophy, immune-mediated keratitis such as keratouveitis caused by cainine adenovirus-1, neurotropic keratitis, trauma, persistent papillary membranes)
- Cellular infiltrate (bacterial, fungal, viral)
- Vascular invasion (exposure keratitis)
- Fibrosis (scar formation)
- Dystrophies (lipid, genetic)

26.1.1.2 Aqueous Humor

- Fivrin (anterior uveitis—numerous causes)

- Hyphema (trauma, neoplasia, blood-clotting deficiencies)

26.1.1.3 Lens

- Cataracts (genetic, nutritional, metabolic/diabetic, toxic, traumatic)

26.1.1.4 Vitreal Humor

- Hemorrhage (trauma, systemic hypertension, retinal detachment, neoplasia, clotting deficiency)
- Hyalitis (numerous infectious diseases such as feline infectious peritonitis [FIP], penetrating injury causing cellular infiltrate)

26.1.2 Box • 26-2 Retinal Lesions Causing Blindness

26.1.2.1 Retinopathies

- Glaucoma
- Sudden acquired retinal degeneration syndrome (SARD)
- Progressive retinal atrophy (rod-cone dysplasia, rod dysplasia, progressive rod-cone degeneration)
- Central progressive retinal atrophy
- Feline central retinal degeneration
- Toxicity (fluoroquinolone administration in cats)

26.1.2.2 Retinal Detachment Syndromes

- Exudative/transudative retinal detachment (systemic hypertension, mycoses, viral, bacterial, rickettsial)
- Neoplasia
- Retinal dysplasia
- Hereditary/congenital (collie eye anomaly)

26.2 VISUAL ASSESSMENT

Obtaining a complete and proper history is an essential component of completing an ophthalmologic examination. Discerning information, such as previous developmental, hereditary, traumatic, or systemic disease problems, should assist in accurate diagnosis of the dog or cat's acute blindness. In addition, a history of prior neurologic disturbances or drug usage will many times confuse lesion localization of visual deficits. A unique feature of the eye is that its structures can be directly observed and interpreted without clinical pathology or invasive tests. Orderly sequence of examination is essential for a thorough, detailed analysis of the ocular structures and is

typically performed by examining the superficial structures and then proceeding to deeper structures. Characterization of blindness will assist in lesion localization. For example, day blindness with good night vision (hemeralopia) could be an indication of the pet having cataracts. In dim light the pupil dilates, allowing sight around the cataract. Good day vision with poor night vision (nyctalopia) may be an indication of progressive retinal atrophy (PRA). Blindness with no cause (amaurosis) or mechanical blindness (exophthalmia, facial nerve paralysis, elevated third eyelid [Horner's syndrome]) will give the examiner an area of focus when deciphering the clinical findings.

26.2.1 Box • 26-3 Abnormalities Resulting in Failure to Transmit the Visual Message

26.2.1.1 Viral Diseases

- Canine distemper
- Feline infectious peritonitis (FIP)

26.2.1.2 Systemic and Ocular Mycoses

- Blastomycosis, cryptococcosis, histoplasmosis, and coccidiodmycosis
- Neoplasia
- Tramautic avulsion of optic nerves
- Granulomatous meningoencephalitis (GME)
- Hydrocephalus
- Optic nerve hypoplaysia
- Immune-mediated optic neuritis

26.2.2 Box • 26-4 Abnormalities Resulting in Failure to Interpret the Visual Message

- Viral (canine distemper virus and feline infectious peritonitis [FIP])
- Canine distemper virus and FIP
- Granulomatous meningoencephalitis (GME)
- Systemic mycoses
- Trauma
- Heatstroke
- Hypoxia
- Hydrocephalus

- Hepatoencephalopathy
- Neoplasia
- Storage diseases
- Postictal
- Meningitis

26.2.3 Motion Detection

Evaluation of motion detection in animals is done by tossing an object (cotton balls) across the animal's field of view and monitoring the response, such as a head or eye movement following the object. The presence of tactile hairs, especially in cats, makes it important not to touch or create air currents or sound if stimulation of these hairs would create a similar response.

26.2.4 Obstacle Course

Creating an obstacle course in an exam room will allow the examiner to determine if the dog or cat is able to navigate an unknown environment. Any large solid object can be used (chairs, wastebasket, or cones). It is important to perform this test in both bright and dim light and to perform several trials. Neurologic deficits or animals who are unwilling to walk are not good candidates for this test. The animal should be able to walk through the course and avoid walking into the obstacles. If the dog or cat is unable to visualize objects and hesitates or bumps into them, that animal is likely blind.

26.2.5 Menace Response

Before testing the menace response, a palpebral reflex should be elicited to assess if the dog or cat is capable of blinking (intact facial nerve CN VII and eyelid function). Severe buphthalmia, exophthalmia, or blepharospasm will prevent blinking and obtund the menace testing. A menace response is elicited by waving a hand or an object toward the animal's head and eyes. The normal response is an avoidance motion, such as moving the head away from the object or blinking the eyes. The response is “learned” and therefore not typically present in dogs or cats less than 12 weeks of age. An intact menace response requires an intact visual cortex, whereas a dazzle reflex and corneal reflex are strictly subcortical responses. Dazzle reflex is mediated by reflex centers in the rostral colliculi and can evaluate optic nerve function while not stimulating the trigeminal nerve.

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26.2.6 Visual Placing and Postural Reactions

This test is performed by holding the animal cradled in a horizontal position with its front legs free to move and then moving toward the edge of a tabletop. A visual animal will respond by lifting the legs before touching the table. A blind animal will move the legs after they touch the table. Stairs can be used to perform this test on dogs too large to hold.

26.2.7 Pupillary Light Reflex

Pupillary light reflex (PLR) is not a test of vision but rather a starting point in lesion localization. No special equipment is needed for this test. Using a focal light source in a dimly lit room, the examiner can adequately assess the PLR in a dog or cat. Brachycephalic patients such as Boston terriers and pugs can sometimes be more difficult to examine because of their lateral globe position. A nervous animal may require a few minutes for the sympathetic nervous system (SNS) response to lessen. Stimulation of the SNS causes mydriasis, giving the examiner the illusion of absent or diminished PLR. Before testing the PLR, the examiner should ensure that the pupils are equal size in both dim and ambient light. Unequal pupil size (anisocoria) is usually pathologic in small animals.

The PLR pathway requires normal optic nerve function, optic chiasm, optic tracts, pretectal and accessory oculomotor nuclei (Edinger-Westphal), oculomotor nerves (parasympathetic portion), and functional iridal muscles (iridal sphincter mm). The retinas are also required for the PLR pathway, although there can be marked retinal pathology and a PLR may still be present. Iris atrophy, synechia, and opacification of the cornea or anterior chamber are additional complications that can diminish the PLR or prevent observation of the pupil. In this situation the lesion may or may not be localized in the globe.

26.3 SPECIAL DIAGNOSTIC TESTS

Electroretinography (ERG) is a highly sensitive test interpreted by specialists to evaluate the function of the photoreceptors (rods and cones) using light stimulation. The ERG is beneficial in dogs and cats with acute vision loss when ophthalmoscopic examination proves normal because of its ability to differentiate between photoreceptor disease verses optic nerve or CNS lesions.

Ocular ultrasonography is a useful tool in diagnosis of intraocular or retrobulbar lesions when opacification of the ocular media such as corneal edema, cataracts, or severe enophthalmos is present.

Computed tomography (CT) and magnetic resonance imaging (MRI) scans are excellent diagnostic imaging tools used to localize lesions in animals with acute vision loss. When other tests are unremarkable, they suggest a retrobulbar, optic nerve, or central lesion.

27 CHAPTER • 27 Urogenital: Vaginal-Vulvar and Preputial Discharge

Claudia J. Baldwin

27.1 VAGINAL-VULVAR DISCHARGE

When veterinarians examine a female animal with genital discharge, it is usually a vulvar discharge, composed of fluid, cells, and/or tissue, that originates from the uterus, vagina, urinary tract, vestibule, or vulva. Such discharges may occur in both intact and neutered females. Other sources or causes that need to be considered, because their manifestations may present as a vaginal-vulvar discharge, are sex hormone-producing ovarian disorders (neoplasia or remnant), generalized mucosal disease, exudative perivulvar dermatitis, and bleeding diathesis arising from disorders of blood coagulation.

Normal physiologic vaginal-vulvar discharges, which originate from the uterus, are expected in the intact bitch and queen during the reproductive cycle. During proestrus, the bitch produces a serosanguineous discharge of varying volume. During estrus, the discharge becomes less bloody and usually is straw colored. During early diestrus, the discharge is scant and, if present, is mucoid to dark red. The queen does not normally exhibit appreciable discharge. During late gestation, both the queen and the bitch may display a mucoid discharge. At parturition, both produce a clear to green-black discharge that signifies amniotic fluid and separation of placentas, respectively. Normal lochia is red/green/brown; it diminishes to undetectable levels by 3 weeks post gestation in the bitch but may not be appreciable in the queen. The etiology of a *pathologic vaginal-vulvar discharge* (Table 27-1) can be considered using the DAMNITT diagnostic method. This broad scheme allows the clinician to consider the origin and potential causes of discharge in both intact and ovariohysterectomized (OHE) females. (*D* stands for degenerative or developmental, *A* stands for allergic or autoimmune, *M* for metabolic, *N* for neoplastic or nutritional, *I* for iatrogenic, idiopathic, or inflammatory [infectious or immune related], *T* for toxic or traumatic.)

Table • 27-1 Source and Etiology of Pathologic Vaginal-Vulvar Discharges

	SOURCE		ETIOLOGY	
ORGAN OR DISORDER	**DEVELOPMENTAL/DEGENERATIVE ORIGIN**	**NEOPLASTIC**	**INFLAMMATORY/INFECTIOUS OR IATROGENIC**	**TRAUMATIC/TOXIC**
Uterus/stump	Healing failure post-OHE, SIPS	Various	CEH/pyometra, metritis,	Parturient
Vagina	Vaginal bands/septa	Various	Primary and secondary	Breeding, postpartum, FB
Urinary tract	Ectopic ureter, sphincter laxity Vaginal abnormality	TCC	Cystitis/urethritis Iatrogenic	Calculi
Vestibule	Vulvovestibular stricture	Various	Primary or secondary	Breeding, postpartum, FB
Vulva	Ventral displacement/agenesis Infantile/intersex	Various	Clitoral enlargement	FB
Generalized mucosal disease			Immune mediated Infectious	Irritant
Ovarian disorders	Cystic disease/remnant	E2-secreting tumor	Ovarian remnant	
Perivulvar dermatitis			Pyoderma	Irritant
Bleeding diathesis	Inherited deficiency		Iatrogenic platelet dysfunction	Vit K antagonism

OHE, Ovariohysterectomy; *CEH,* cystic endometrial hyperplasia; *SIPS,* subinvolution of placental sites (etiology is nondegeneration of trophoblastic cells); *FB,* foreign body; *TCC,* transitional cell carcinoma; *E2,* estradiol; *Vit,* vitamin.

27.1.1 History

The history is important in determining the age, breed, and reproductive status of the female. Information on the date of the OHE or the last estrus, pregnancy, or parturition may assist the clinician in choosing diagnostics. When there is a question as to whether an OHE has been performed, the clinician should inspect the skin for a surgical incision line.

The history may include a continuous or intermittent discharge, licking, and scooting. Developmental or inherited conditions likely would manifest in a younger female, whereas neoplastic disease would be more common in an older female. Clinical signs of systemic illness (e.g., fever, anorexia) would be expected with inflammatory, infectious, disseminated neoplastic, traumatic, or toxic disorders. A drug administration history is important.

27.1.2 Physical Examination

A complete physical examination should be performed, including abdominal palpation to detect organomegaly (uterine or bladder) or discomfort. Inspection of the vulva and perineal region may reveal edema, often associated with estradiol influence, inflammation, or trauma; primary or secondary dermatitis; or anatomic abnormalities (e.g., enlarged clitoris, infantile vulva, or ventral vulvar displacement). A rectal examination in bitches allows palpation of the cranial vestibule, the urethra, and a variable portion of the vagina.

27.1.3 Cytology

Further reproductive evaluation should include collection of discharge from the vestibule with a cotton swab (or in a container if copious). Cytologic evaluation is important to characterize the discharge further. Typically, large amounts of *clear* discharge are relatively acellular and most often of urinary bladder origin. Analysis of fluid to determine compatibility with urine (chemical and microscopic) is indicated, as is comparison of results with those from a voided sample or one obtained by cystocentesis. A *mucoid* discharge displays few cells cytologically, usually healthy appearing neutrophils. With *mucopurulent to purulent* discharges, neutrophil numbers have increased and an increasing number of cells have degenerated. *Serosanguineous to sanguinous* discharges contain red blood cells with either healthy appearing neutrophils or degenerate neutrophils, indicating inflammation. Discharges that are *greenish-black or a mixture of red, green, and brown* derive this coloration from red blood cell breakdown pigment and tissue particles when associated with abortion.

27.1.4 Vaginal-Vulvar Examination

Once fluid has been collected, a *digital vaginal examination* is indicated. Examination may not be possible without sedation in a juvenile small breed dog or in a cat or if pain or discomfort is present. The digital examination should be performed before vaginoscopy, because structural abnormalities can easily be "passed by" if the clinician is relying only on what is seen.

Digital examination allows evaluation of the vulva, vestibule, urethral papilla, vaginovestibular region, and possibly the vagina. Normal anestrous or OHE females have narrowing at the vulvovestibular junction and also at the vaginovestibular junction (the *cingulum*). Abnormal findings such as circumferential strictures or vaginal septa or bands (commonly at the cingulum) or narrowing of the lumen and altered mucosal texture should be noted, as should straining or discomfort. Digital examination may elucidate the cause of the discharge.

Vaginoscopy can be performed in many dogs without sedation. A rigid pediatric proctoscope can be used in medium to large dogs. Other instruments (e.g., a rigid endoscope) allow visualization in cats and smaller dogs. Insufflation and adequate lighting are essential. Shorter instruments with a light source can be used to examine the vestibule, clitoris, and fossa.

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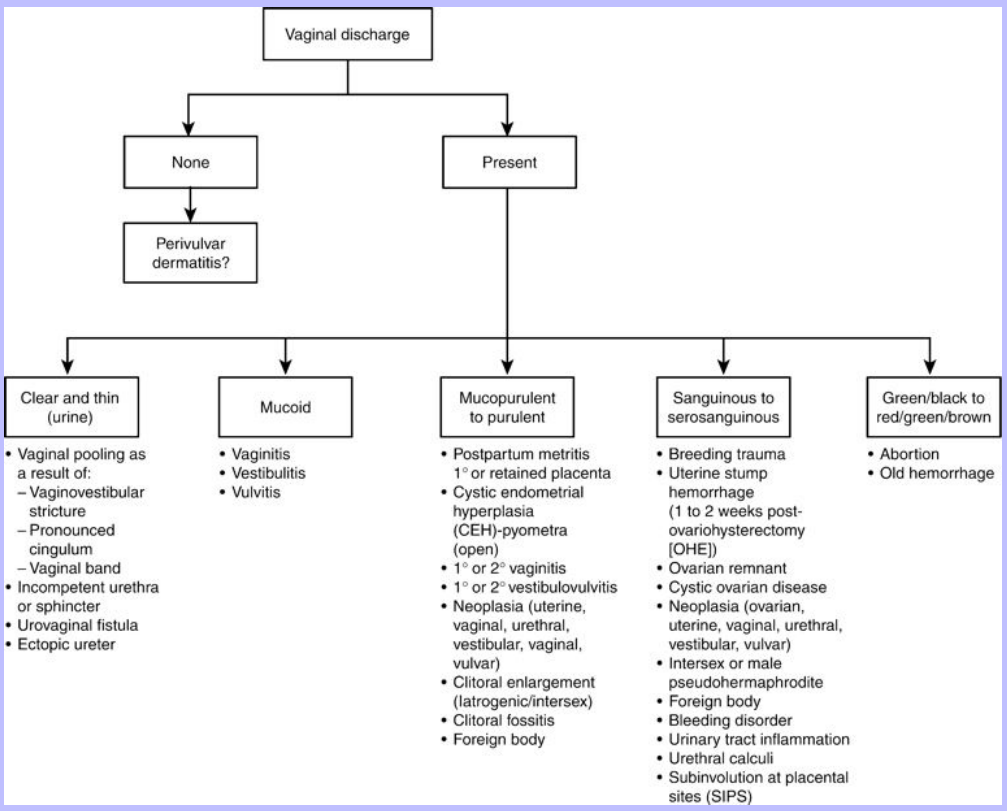
Figure 27-1 Algorithm for assessment of pathologic vaginal-vulvar discharge based on character of discharge and digital examination.



With the information gained from these examinations, the clinician may approach the problem with more clarity (Figure 27-1). (See Artificial Insemination and Vaginoscopy and Vaginal Disorders for further detail on these procedures.)

Other diagnostic testing may be indicated. If the dog or cat has signs of systemic illness, a *complete blood count (CBC), serum biochemistry,* and *urinalysis* should be performed. If the abdomen is painful, the uterus enlarged, and/or the discharge is characterized as purulent, a pyometra should be considered and cystocentesis should be avoided to prevent contamination of the abdomen. *Bacterial culture* of the discharge (collected with a guarded or sheathed culturette to avoid contamination) is indicated for a systemically ill animal or if an infectious process is suspected. Susceptibility testing of the cultured organisms is indicated to determine the appropriate therapy. *Imaging of the abdomen and urogenital system* by means of plain and contrast radiology (i.e., vaginogram, vagino-urethrogram), as well as ultrasound, may be indicated.

Assessment of *reproductive hormonal status* is important when evaluating both intact and OHE females. Increased estradiol concentrations and vaginal cytology suggestive of estradiol influence (keratinization of vaginal cells) is consistent with normal proestrus or estrus, follicular cysts, ovarian secreting neoplasia, or ovarian remnant, although estradiol concentrations may fluctuate. *Stimulation tests* using human chorionic gonadotropin or gonadotropin-releasing hormone, which induce ovulation with resultant increases in the progesterone concentration, may be diagnostic for follicular cysts or ovarian remnant (see the section on Ovarian and Estrous Cycle Abnormalities). Measurement of serum progesterone for evidence of the luteal phase of the reproductive cycle may also be helpful with suspected cystic endometrial hyperplasia (CEH)/pyometra in both intact and OHE females, because the majority of females with this disorder have an elevated progesterone concentration or have received exogenous progestational therapy (see the section on Cystic Endometrial Hyperplasia and Pyometra).

Histology of masses found in the reproductive tract can further characterize them and allow prognostication. *Coagulation system testing* should be considered in a female with a serosanguineous to sanguinous discharge. Mucosal hemorrhage is characteristic of a primary system (platelet and vascular) defect but may also be associated with a coagulation factor abnormality. Iatrogenic, inherited, and acquired disorders should be considered.

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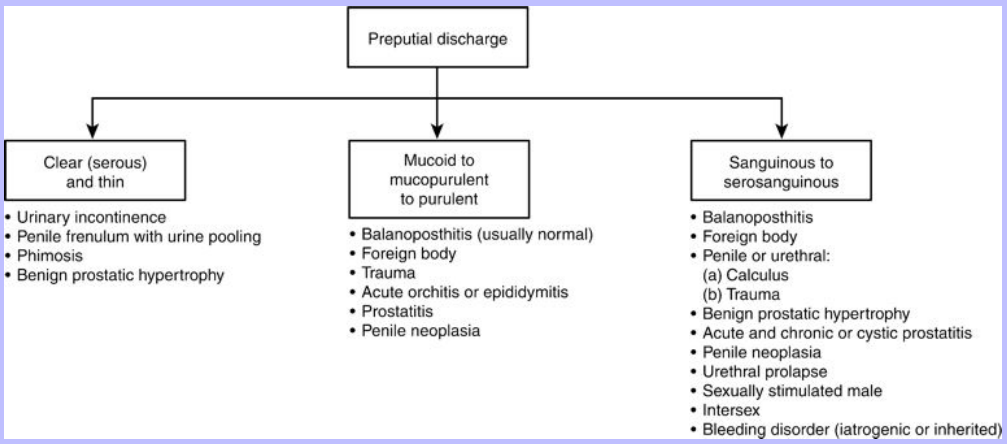
Figure 27-2 Algorithm for assessment of pathologic preputial discharge based on character of discharge and examination.



At times no cause may be apparent for a vaginal-vulvar discharge. Common causes of chronic vaginitis include morphologic abnormalities of the reproductive or urinary tract, resulting in urinary incontinence or pooling. Juvenile vaginitis, seen in the prepubertal bitch, is almost always self-limiting. Vaginitis in the queen is unusual. (See Vaginal Disorders.)

27.2 PREPUTIAL DISCHARGE

Preputial discharges are composed of fluid and cells that originate from the urinary bladder, prostate gland, testes and epididymis, urethra, and mucosa of the penis and penile sheath. Discharges may be present in both intact and neutered males, and they are much more common in the dog than in the cat. Other causes that should be

considered are sex hormone–induced conditions (e.g., hermaphroditism), generalized mucosal disease, or bleeding diathesis caused by disorders of blood coagulation.

Normal discharge in the male is typified as a small amount of grayish-white to yellow material that may be seen at the preputial orifice as moist or dried exudate. It may be difficult to determine, upon inspection of the preputial orifice and surrounding skin and haircoat, whether the volume present is normal. Careful examination of the genitalia is indicated. *Abnormal discharge* in the male may be investigated by means of the source of origin and the gross appearance of the discharge. Abnormal discharge may be characterized grossly as clear or serous, mucoid to mucopurulent to purulent, and sanguinous or serosanguineous (see the section Cytology, above, for the cytologic characteristics).

27.2.1 History

It is important to determine the age, breed, and reproductive status of the animal. It also should be ascertained whether the male has been castrated and if so, whether one or both testes were removed. Reproductive activity may be important. The duration and historical character of the discharge should also be noted. The presence of systemic signs that precede or are associated with discharge would be expected with inflammatory or infectious disease, neoplasia, and traumatic or toxic causes.

27.2.2 Physical Examination

A complete physical examination should be performed, with particular attention given to the scrotum, testes (if present), and prepuce. Edema of the scrotum or enlargement or asymmetry of testicular or epididymal tissues is important. The prostate gland can be evaluated by simultaneous abdominal and rectal palpation for size, symmetry, and pain. The size of the urinary bladder can also be evaluated by abdominal palpation. The prepuce and penis should be palpated, and the prepuce then should be retracted, caudal to the bulbus glandis, to allow visual inspection of the entire penis. Digital and visual inspection of the preputial space (using a blunt instrument) may be indicated.

27.2.3 Other Diagnostic Testing

Based on the appearance of the discharge, the historical information, and the physical examination findings, a list of differential diagnoses can be generated (Figure 27-2). Further evaluation might include a *CBC, serum biochemical profile,* and *urinalysis,* as well as *imaging* of the testicles, prostate, or urinary bladder by means of ultrasound or radiology. Evaluation of testicular or prostatic secretions may be possible through *semen collection* or *prostatic massage*. Additional diagnostics may include *bacterial culture with susceptibility determination, fine needle aspiration, or biopsy*. (See Cystocentesis; Bladder, Urethral, Vaginal, Prostatic Mass Aspiration/Biopsy; and Urethral Catheterization and Cystoscopy.) *Coagulation system testing* should be considered for a male with a serosanguineous to sanguinous discharge. Mucosal hemorrhage is characteristic of a primary system defect but may also be associated with a coagulation factor abnormality; iatrogenic, inherited, and acquired disorders should be considered.

The above evaluation may well lead to a definitive diagnosis. In the absence of definite findings, the male should be re-evaluated at a later date. Comparison of subsequent findings with the original data may lead to a definitive diagnosis or management plan.

28 CHAPTER • 28 Polyuria and Polydipsia

Edward C. Feldman

Concerns about a pet's atypical or unusual urination habits are a common reason for owners to seek veterinary assistance. For example, a dog or cat may urinate excessive volumes, urinate more frequently than “normal,” appear to be incontinent, urinate for an unusually long time, or urinate in atypical or unacceptable locations. Some owners seek veterinary care because they think their pet is drinking too much water, but this is a less common concern than those previously mentioned.

28.1 PHYSIOLOGY OF WATER METABOLISM

Water consumption and urine production are controlled by complex interactions between plasma osmolality, fluid volume in the vascular compartment, the thirst center, the kidneys, the pituitary gland, and the hypothalamus. Dysfunction in any of these can result in the clinical signs of polyuria (PU) and polydipsia (PD). Vasopressin (antidiuretic hormone [ADH]) plays a key role in the control of renal water resorption, urine production, urine concentration, and water balance. In the presence of ADH and dehydration, the average healthy dog or cat has the capacity to produce urine with an osmolality well above 2000 mOsm/kg. If a dog or cat is chronically deficient in ADH or is chronically unable to respond to ADH at the renal tubular level, the urine may be as dilute as 20 mOsm/kg.

Plasma osmolality and its principal determinant, the plasma sodium concentration, normally are maintained within remarkably narrow ranges. This stability is achieved through the adjustment of total body water concentrations to maintain balance with the plasma sodium concentration. Water balance is controlled by an integrated system that involves precise regulation of water intake via thirst mechanisms and control of renal water loss via ADH secretion and action. Water is continuously lost through the urine, respiratory tract, and feces. Lost water is replaced by that consumed. The urine concentrating capacity can reduce but not eliminate water loss.

ADH, a nonapeptide, is synthesized in the hypothalamus and secreted from the posterior pituitary gland. The primary sites of ADH activity are epithelial cells in the renal distal tubules and collecting ducts. Here, ADH acts to increase the hydro-osmotic permeability of these cells. The fluid in the tubular lumen normally is dilute, and the fluid in the interstitial space, through which the tubules traverse, is concentrated. Therefore, if water is allowed to diffuse passively along concentration gradients, it flows from the lumen of the nephron in which the fluid is dilute into the hypertonic milieu that normally exists in the interstitial space of the renal medulla. If ADH is present, the volume of fluid in the nephron decreases, the osmolality of that fluid increases, and water is conserved. Thus the “normal” animal has the capacity to secrete ADH in response to appropriate stimuli (increasing plasma osmolality, decreasing plasma volume) and the ability to respond to ADH at the level of the renal tubules and collecting ducts. In the absence of ADH (central diabetes insipidus) or if renal tubular cells are resistant to the action of ADH (nephrogenic diabetes insipidus), the cells lining this portion of the nephron are resistant to diffusion of both water and solutes. Hence, the hypotonic filtrate formed in the more proximal portion of the nephron passes unmodified through the distal tubule and collecting duct. This *water diuresis* is associated with large volumes of urine that has a low osmolality.

It should be noted that 85% to 90% of the fluid filtered by the glomerulus is reabsorbed isosmotically with sodium and glucose in the proximal portion of the nephron. Sodium then is selectively reabsorbed from the remaining fluid, making the fluid in the distal nephron hypotonic. However, if a poorly reabsorbed solute, such as urea or glucose, is present in excess in the glomerular filtrate, fluid resorption from the proximal tubule is impaired.

Because of this physiologic process, an abnormally increased volume of fluid reaches the distal nephron and can overwhelm its capacity to reabsorb water. Consequently, urine volume increases despite the presence of ADH. This type of polyuria is called *solute diuresis*.

28.2 DIAGNOSTIC APPROACH TO POLYURIA, POLYDIPSIA, AND OTHER ABNORMALITIES IN URINATION

28.2.1 The First Step: Collecting the Urine

It may be difficult for a veterinary hospital staff member to distinguish “inappropriate” urination (frequency with or without straining or hematuria) from polyuria at the time an owner phones the hospital to make an appointment. Therefore, it is strongly recommended that all cat and dog owners with any “chief complaint” that resembles those mentioned here, be encouraged to catch a urine sample from their pet (Figure 28-1). That urine (even if only a few drops) should be collected in a clean container with a lid and brought with the pet at the time of initial evaluation. Owners of medium-to-large breed dogs rarely have difficulty collecting urine in a small relatively flat container if they approach their pet slowly and discreetly. Owners of small dogs, especially female dogs, may find success in collecting urine if the container lid is used for collection. Owners of cats can try placing plastic wrap on top of their cats' litter and collecting urine after the cat uses the litter box. Alternatively, owners can replace absorbable litter with non-absorbable litter (using any type of gravel, such as that used in an aquarium). In this situation, the urine can simply be poured into a container.

28.2.2 The Next Step: Evaluating the Urine

When the owner arrives at the veterinary hospital, the urine they collected can be evaluated prior to their pet being examined. The urine specific gravity should be noted and a “dip stick” test completed. Urine is usually considered normally “concentrated” if the specific gravity is 1.025 to 1.035 or greater. Since the owner has collected the urine sample from the pet while that animal was in its home environment, problems in interpretation associated with water being withheld prior to an automobile trip or a pet not consuming typical amounts of water due to nervousness or fear are not encountered. The truly polyuric dog or cat will almost always have dilute urine (specific gravity <1.012), “relatively” dilute urine (specific gravity >1.012 but <1.022), or it will have glucose in the urine.

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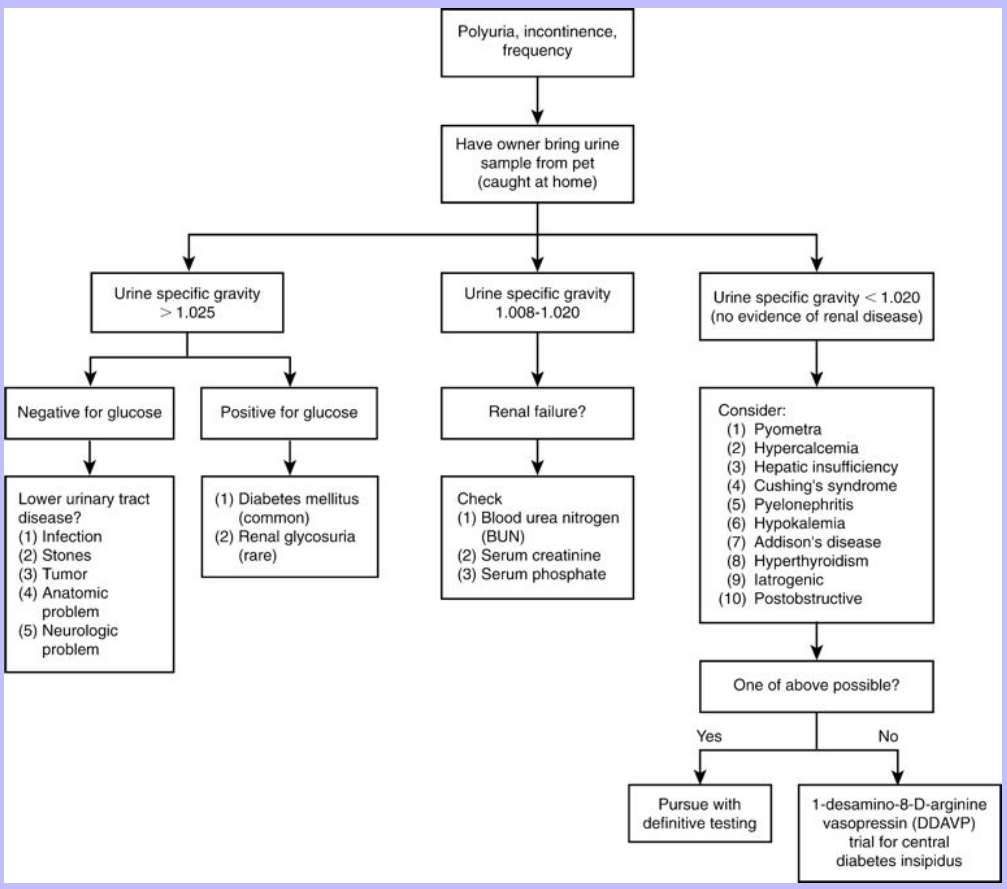
Figure 28-1 Algorithm for polyuria, incontinence and frequency.



28.2.3 Concentrated Urine without Glucose

If the urine bought to the hospital by the owners is concentrated (specific gravity >1.025 to >1.035) and it has no glucose, it is likely that the animal has a lower urinary tract condition. In this situation the veterinarian must consider the possibility of urinary tract infection, bladder calculi, bladder mass, anatomic or neurologic problems that may explain the owner's observations. Appropriate testing for these conditions (culture, abdominal imaging, etc.) can be recommended if the history and physical examination support such an approach.

28.2.4 Concentrated Urine with Glucose

Most dogs and cats with diabetes mellitus are first examined after an owner has observed polyuria. These animals frequently also have polydipsia, polyphagia, and weight loss. Less commonly, a diabetic dog is brought in for veterinary examination after an owner notes that it has become acutely blind due to cataract formation. A dog or cat also may be brought in for treatment of vomiting, diarrhea, anorexia, listlessness, or other systemic

signs secondary to developing diabetic ketoacidosis. Regardless, almost all diabetic dogs and cats have a urine specific gravity of 1.025 to 1.045 and glycosuria. The diagnosis of diabetes mellitus can be strongly suspected simply by noting a positive reaction in the glucose reagent portion of the urine test strip within seconds of removing the strip from the urine. Thus diabetes mellitus can be diagnosed in dogs and cats before the pet is ever examined by the veterinarian. This diagnosis can be confirmed by the finding of hyperglycemia. In cats, stress may result in glycosuria; also, two uncommon causes of hyperglycemia and glycosuria are Cushing's syndrome and acromegaly. In the rare case in which the blood glucose concentration is within reference limits, the veterinarian should consider the possibility of renal glycosuria, a congenital renal tubular defect in the basenji and Norwegian elkhound. Renal glycosuria, however, can occur in any dog or cat.

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28.2.5 Isosthenuric Urine (Urine Specific Gravity of 1.008 to 1.012): Chronic Renal Failure

The term *isosthenuria* usually implies that the urine specific gravity or osmolality is the same as that of serum or plasma. Using this criterion, urine with a specific gravity of 1.008 to 1.012 is *isosthenuric*. However, for clinical purposes, it is important to remember that a dehydrated animal typically has a plasma osmolality greater than normal due to loss of water and abnormal retention of solutes (e.g., urea). In this setting, urine with a specific gravity of 1.013 to 1.020 may be “isosthenuric” despite being greater than the classic 1.008 to 1.012. In other words, what happens if a cat or dog is examined and is thought to be 3% to 10% dehydrated? If the animal has a normal hypothalamus, pituitary, and kidneys, it should have responded to this degree of water loss by secreting maximum amounts of ADH (it has been demonstrated repeatedly that a 3% to 5% decrease in body weight due to water loss is associated with this response). The urine of such an animal, therefore, should reflect maximum release of ADH, and the specific gravity should be well in excess of 1.035. If the dog or cat has a urine specific gravity of 1.018, for example, it should not be considered to have responded appropriately to the dehydration.

The primary concern a veterinarian should have when an animal has polyuria and a urine specific gravity within the isosthenuric range is renal insufficiency or failure. In chronic renal failure, the number of functioning nephrons progressively decreases. A compensatory increase in the glomerular filtration rate by surviving nephrons occurs, and a commensurate increase in fluid volume is presented to the distal renal tubules. The increase in the tubular flow rate causes less urea and sodium to be reabsorbed. The result is an osmotic diuresis, which may be exaggerated by a reduction in the renal medullary concentration gradient. For an animal with this type of urine specific gravity, a serum chemistry evaluation is the first step toward determining the presence or absence of renal disease as the cause of the polyuria. Specifically, the blood urea nitrogen (BUN), serum creatinine, and serum phosphate concentrations should indicate whether the pet has renal disease.

28.2.6 Urine Specific Gravity < 1.020: Pyometra

It has been stated that any ill, intact female dog or cat should be considered a candidate for having pyometra until proven otherwise. This is an appropriate approach because of the serious nature of uterine infection. Animals with pyometra can quickly deteriorate as a result of overwhelming sepsis. Dogs and cats that may have pyometra typically have a history of being in estrus 2 to 10 weeks previously, and most have a purulent vaginal discharge. For any animal in which pyometra is suspected, a complete blood count (CBC) should be done to assess for evidence of systemic infection; abdominal radiographs or ultrasound scans also should be obtained and examined for uterine enlargement. Dogs and cats with pyometra may develop polyuria and dilute urine because of the effects of endotoxin from *Escherichia coli,* the bacteria most commonly associated with pyometra. Because this endotoxin interferes with the action of ADH at the level of the renal tubules, these animals have a reversible form of nephrogenic diabetes insipidus.

28.2.7 Urine Specific Gravity < 1.020: Hypercalcemia

Hypercalcemia has several common causes. Some, but not all, of the conditions associated with this biochemical abnormality are lymphosarcoma, chronic renal failure, hypoadrenocorticism, primary hyperparathyroidism, vitamin D toxicosis, granulomatous disease (histoplasmosis, blastomycosis), multiple myeloma, and apocrine gland carcinomas of the anal sac. Therefore, if a dog or cat has a urine specific gravity of less than 1.020, it would be appropriate to obtain a serum biochemistry profile to assess the serum calcium concentration. If the serum calcium concentration is abnormally increased, tests needed to rule in or rule out the various causes of hypercalcemia can be considered. An increased serum calcium concentration may interfere with the action of ADH at the renal tubular level, causing a reversible form of acquired nephrogenic diabetes insipidus. This is the most likely explanation for the polyuria and secondary polydipsia noted in hypercalcemic animals. Other possible explanations for this polyuria are damage to ADH receptors in the renal tubules, inactivation of adenyl cyclase, or decreased transport of sodium and chloride into the renal medullary interstitium.

28.2.8 Urine Specific Gravity < 1.020: Hepatic Insufficiency

Although the condition is not extremely common, some dogs with severe hepatic insufficiency also have an inability to concentrate their urine. One possible owner concern, therefore, would be polyuria. In these dogs, a decrease in one or more of the following “liver function” tests usually is seen on routine serum biochemical profiles: albumin, BUN, cholesterol, or glucose. In addition, an afflicted dog may have microhepatica or a liver that appears otherwise abnormal on radiography or ultrasonography. A dog with some or many of these abnormalities could be further assessed with pre-and post-prandial bile acid, a radio-labeled liver scan, or hepatic biopsy. There are several explanations for the polyuria and dilute urine. Although not well understood, one plausible explanation is loss of renal medullary hypertonicity secondary to impaired BUN production. BUN is an important component of the renal medullary concentration gradient. Decreases in this gradient result in polyuria with compensatory polydipsia. Other potential explanations are hypokalemia and impaired metabolism of cortisol.

28.2.9 Urine Specific Gravity < 1.020: Canine Cushing's Syndrome

Polyuria is an extremely common clinical sign in dogs with canine Cushing's syndrome (CCS) (excess cortisol concentrations do not commonly cause polyuria in cats). The urine specific gravity in at least 75% of dogs with iatrogenic or naturally occurring CCS is less than 1.020 and can be as low as 1.001. The cause of this polyuria remains obscure, although most of these dogs appear to have secondary and reversible ADH deficiency (central diabetes insipidus). Dogs with CCS typically have additional clinical signs, such as polydipsia, polyphagia, panting, muscle weakness, alopecia, pot belly, and thin skin. Routine laboratory abnormalities commonly include increases in serum alkaline phosphatase and alanine amino transferase activities, increased serum cholesterol concentration, and a decreased or low-normal BUN. Confirmation requires appropriate pituitary-adrenocortical function tests.

28.2.10 Urine Specific Gravity < 1.020: Pyelonephritis

Infection and inflammation of the renal pelvis can destroy the countercurrent mechanism in the renal medulla. This results in isosthenuria, polyuria, secondary polydipsia and, eventually, renal failure. A dog or cat with bacterial pyelonephritis may have nonspecific signs of lethargy, anorexia, and fever. Neutrophilic leukocytosis

may be noted on the CBC. Urinalysis may reveal white blood cells, casts, bacteria, and red cells. Recurrent urinary tract infection may increase suspicion of pyelonephritis. Urine cultures should be performed on cystocentesis samples, but these may or may not be positive for bacteria. Abdominal ultrasonography or urography usually is required to confirm this diagnosis.

28.2.11 Urine Specific Gravity < 1.020: Hypokalemia

Hypokalemia is thought to interfere with the action of ADH in the renal tubules, creating a reversible form of nephrogenic diabetes insipidus. This electrolyte disturbance is more common in cats than in dogs, more commonly causes muscle weakness than polyuria, and usually occurs secondary to other disorders (see Chapter 65).

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28.2.12 Urine Specific Gravity < 1.020: Hypoadrenocorticism (Addison's Disease)

Most dogs with Addison's disease are young to middle-aged females. Despite normal kidney function and severe hypovolemia, animals in an Addisonian crisis frequently have a urine specific gravity of less than 1.030 due to the hyponatremia caused by mineralocorticoid deficiency. Hyponatremia reduces the renal medullary concentration gradient, impairing the ability to produce concentrated urine. Although “relatively” dilute urine is typical of addisonian dogs and cats, signs of polyuria or polydipsia are quickly overshadowed by the more worrisome and obvious signs of vomiting, diarrhea, listlessness, weakness, anorexia and weight loss. The combination of signalment and findings of hyperkalemia and hyponatremia should raise suspicion of Addison's disease. Confirmation requires a finding of an abnormally suppressed plasma cortisol concentration after administration of ACTH.

28.2.13 Urine Specific Gravity < 1.020: Hyperthyroidism

Polyuria and polydipsia are common in hyperthyroid cats and dogs. Although the exact mechanism of the polyuria is unclear, it is likely that increases in renal blood flow cause a decrease in renal medullary concentration. This impairs water resorption from the distal nephron. Concurrent renal insufficiency may also contribute to these signs. The tentative diagnosis of hyperthyroidism is based on palpation of a thyroid nodule or mass. Confirmation requires a finding of abnormally increased serum total or free thyroxine concentrations.

28.2.14 Urine Specific Gravity < 1.020: Iatrogenic

Several drugs may cause polydipsia and polyuria, including some that are commonly used, such as glucocorticoids, diuretics, and anticonvulsants.

28.2.15 Urine Specific Gravity < 1.020: Postobstructive Diuresis

Postobstructive diuresis is most often encountered after a urethral obstruction has been relieved in cats, but it may occur in dogs. These animals often show dramatic increases in BUN secondary to the obstruction, which accounts for a marked osmotic diuresis after the obstruction has been relieved.

28.3 CENTRAL DIABETES INSIPIDUS, NEPHROGENIC DIABETES INSIPIDUS, AND PSYCHOGENIC (PRIMARY) POLYDIPSIA

It should be emphasized that most dogs and cats with polyuria and polydipsia have one of the conditions described in the previous sections of this chapter. Most causes of polydipsia and polyuria can be identified from the signalment, history, physical examination, urinalysis (especially if the urine is caught by the owner before leaving the home environment), CBC, and serum biochemistry profile. *Primary nephrogenic diabetes insipidus (NDI)* is an extremely rare condition. However, secondary and often reversible NDI accounts for the polyuria in many of the conditions previously discussed. Both *central diabetes insipidus (CDI)* and *psychogenic (primary) polydipsia (PP)* are quite uncommon (although CDI is much more common than PP). If an animal has dilute urine and does not appear to have any of the previously discussed conditions, it is appropriate to assume that the animal does not have primary NDI, but it may have CDI or PP.

The veterinarian then can ask the following question: Does this animal drink a lot because it urinates a lot (CDI), or does it urinate a lot because it drinks a lot (PP)? If CDI is present, the serum osmolality should be high-normal or increased. If PP is present, the serum osmolality should be low-normal or decreased. Thus the serum osmolality becomes a reasonable, cost-effective, and simple test to run. Because the veterinarian has reached a point where it is likely that one of these two conditions may exist and because CDI is much more common than PP, trial therapy at home is recommended using oral DDAVP (synthetic ADH, which is commercially available as 0.1 or 0.2 mg tablets). The dose is empirical. It is recommended that a 20 kg dog be given 0.1 mg three times a day for about 7 days and that a 40 kg dog be given 0.2 mg three times a day for about 7 days. The dosage for dogs and cats weighing more or less than this can be so-adjusted. The response in dogs or cats with CDI is quick and obvious. Owners can collect urine on a daily basis during the trial to substantiate their clinical impressions regarding response. If the pet responds, CDI (Cushing's syndrome remains a possibility) is diagnosed, and dose of DDAVP can be slowly tapered to determine the minimum required for long-term treatment. The use of nasal drops placed in the eyes is no longer recommended. The water deprivation test is considered dangerous and is never warranted.

29 CHAPTER • 29 Micturition Disorders

Mary Anna Labato

Micturition is a two-stage process involving the passive storage and the active voiding of urine. Processes that interfere with the storage and voiding of urine are termed *micturition disorders*. Micturition disorders may lead to unresponsive urinary tract infection, resulting in an ascending pyelonephritis and ultimately renal disease. Neurogenic disorders, typically functional obstructions, include lower motor neuron disorder, or atonic bladder, with overflow incontinence; upper motor neuron disorder, or automatic bladder; detrusor-urethral dyssynergia, and dysautonomia. Non-neurogenic disorders, typically mechanical obstructions, include such processes as infection, inflammation, calculi, and neoplasia.

29.1 ANATOMY AND PHYSIOLOGY OF THE URINARY BLADDER

The body of the bladder is composed of smooth muscle, which is referred to as the *detrusor*. The *outlet conduit* consists of the trigone and proximal urethra. The smooth muscle fibers of the detrusor continue into the proximal urethra, forming a functional internal urethral sphincter. The distal urethra is composed of striated skeletal muscle and functions as an external sphincter. During the storage phase of micturition, the bladder functions as a low-resistance, high-capacity vessel. The urethra functions as a high-resistance barrier. The reverse is true during the voiding phase, at which time the bladder acts as a muscular pump and the urethra as a low-resistance vessel.

29.2 NERVOUS CONTROL OF MICTURITION

Nervous control of the bladder and urethra is a combination of autonomic and somatic interactions. Parasympathetic innervation is supplied to the detrusor by the pelvic nerve, which arises from sacral spinal cord segments S1 to S3. Sympathetic innervation is supplied via the hypogastric nerve, which is composed of preganglionic fibers that exit the lumbar spinal cord (L1 to L4 in dogs and L2 to L5 in cats) and synapses in the caudal mesenteric ganglion. Sympathetic innervation, which is supplied both to the detrusor and the urethral smooth muscles, characterizes the storage phase of micturition. Alpha-adrenergic fibers synapse in smooth muscles in both the trigone and proximal urethra. Stimulation results in contraction of these muscles and forms a functional internal urethral sphincter. Beta-adrenergic fibers synapse in the detrusor muscle; stimulation results in relaxation. Somatic innervation is supplied via the pudendal nerve, which arises from sacral spinal cord segments S1 to S3 and provides stimulation to the striated urethral musculature. For voluntary control of micturition to occur, the actions of the cerebral cortex, pons, and reticulospinal tract must be integrated. A second pathway, from the cerebral cortex to the sacral nuclei, coordinates voluntary sphincter control.

29.3 HISTORY AND DIAGNOSIS

When an animal is presented for a urine retention problem, it is of utmost importance to obtain a complete history, including reproductive status; age at neutering; age at the onset of the problem; previous medical problems, especially those involving the urogenital system; previous history of trauma; and an accurate description of the abnormality (Figure 29-1). If the animal is having difficulty urinating, two other questions are important: How frequent is urination? Is there stranguria, and if so, is any urine being passed?

A *complete physical and neurologic examination* should be performed, with particular attention paid to the urogenital system. The bladder should be palpated carefully before and immediately after voiding to evaluate the extent of distension, tone, and the ease with which the bladder may be expressed manually. Lower motor neuron

lesions generally are associated with easy manual expression and reduced sphincter tone. Upper motor neuron lesions generally are associated with difficult manual expression and increased sphincter tone. In the neurologic examination, the innervation of the urogenital system should be evaluated. The perineal reflex evaluates the pudendal nerve. Pricking or pinching the skin of the perineum results in contraction of the anal sphincter. The bulbospongiosus reflex evaluates the integrity of both the pudendal nerve and the sacral spinal segments. Squeezing the distal portion of the penis or the edges of the vulva causes the anal sphincter to contract.

A *rectal examination* should be done to evaluate the prostate gland, pelvic diaphragm, and anal tone. The veterinarian should try to observe the animal urinating to verify the micturition abnormality. Also, the residual urine volume should be measured. The animal is allowed to void until urine is no longer passed, the bladder is catheterized, and the volume of any remaining urine is measured. In a normal animal, the residual volume should not exceed 0.4 mL/kg. Catheterization of the bladder also assesses the patency of the urethra.

The *minimum database* should include a *complete blood count (CBC), serum biochemical profile,* and *urinalysis and culture*. In most cases the CBC and chemistry profile are within normal limits, unless a post renal azotemia has developed from an obstructive process. The urinalysis may reflect evidence of infection, inflammation, or neoplasia or a combination of these.

Survey and *specialized radiographic studies* may be useful. Survey radiographs should be checked for any obvious abnormalities in the bladder, urethra, pelvis, or spine. Contrast radiographic studies (intravenous urography, retrograde urethrocystography, vaginourethrography) are evaluated for bladder wall thickening, calculi, prostatic enlargement, urethral strictures, and skeletal abnormalities in the pelvis. An abdominal ultrasound examination may be useful for evaluating bladder wall thickness, the prostate, and the sublumbar lymph nodes and for checking for calculi or masses. A myelogram may be indicated to evaluate for spinal cord compression, as with cauda equina syndrome, or intervertebral disk disease. Magnetic resonance imaging may be indicated to evaluate for diseases of the spinal cord and vertebrae.

Urodynamic studies to evaluate micturition disorders routinely consist of a cystometrogram and urethral pressure profile; electromyography also may be a part of the study. The cystometrogram is a pressure-volume recording that measures bladder tone and volume, threshold volume and pressure, maximum contraction pressure, and the detrusor reflex. The urethral pressure profile measures intraurethral resistance and identifies and localizes areas of increased or decreased resistance. Electromyography can evaluate coordination of muscular activity between the detrusor and the urethral sphincter. Electromyography usually is performed on the anal sphincter; however, with specialized catheters that incorporate electrodes, it also can be performed directly on the urethral sphincter.

29.4 CAUSES OF MICTURITION DISORDERS

Micturition disorders have a number of causes, which may be categorized as *neurogenic* or *non-neurogenic*.

29.4.1 Neurogenic Causes

The four types of neurogenic disorders are lower motor neuron disorder, upper motor neuron disorder, detrusor-urethral dyssynergia, and dysautonomia.

29.4.1.1 Lower Motor Neuron Disorder (Detrusor Areflexia with Sphincter Areflexia)

Lower motor neuron disorder, or *atonic bladder,* results from lesions involving the sacral spinal cord segments or pelvic nerve, including intervertebral disk disease, cauda equina syndrome, sacroiliac luxations,

sacrococcygeal fracture/separation, and tumors (e.g., spinal lymphoma). This type of disorder causes both detrusor and sphincter areflexia. Dribbling of urine with the bladder remaining full often is referred to as *overflow incontinence*. The bladder typically is large, distended, and easily expressed. The incontinence is continuous, and a loss of perineal, bulbospongiosus, and detrusor reflexes is noted.

Treatment involves manual expression of the bladder three or four times daily. Long-term therapy for this disorder has not been successful. Complications include urine scalding, decubital ulcers, and recurrent urinary tract infections. Bethanechol, a parasympathomimetic, may be administered to increase detrusor contractions.

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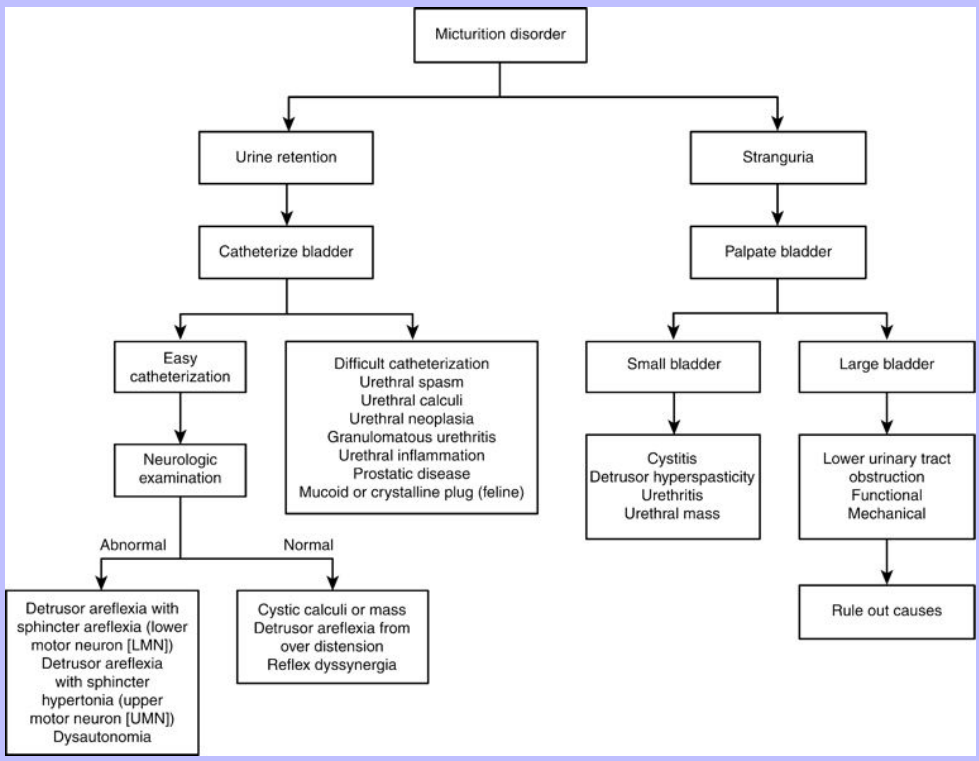
Figure 29-1 Algorithm for diagnostic approach to micturition disorders. *LMN,* Lower motor neuron; *UMN,* upper motor neuron.



29.4.1.2

Upper Motor Neuron Disorder (Detrusor Areflexia with Sphincter Hypertonus)

Upper motor neuron disorder, or *automatic bladder,* results from a lesion involving the spinal cord above the sacral spinal cord segments, such as intervertebral disk disease, tumor, or trauma. This disorder causes incomplete reflex detrusor contraction and spasticity of the urethral sphincter, the result being incomplete emptying of the bladder. The bladder is large, turgid, and initially extremely difficult to express. The animal has a history of inability to urinate, and concomitant hindquarter paresis or paralysis frequently is seen.

Voluntary control is lost, and manual expression is difficult if not impossible. After a period of days to weeks, the spinal reflexes resume. Involuntary micturition is initiated when the threshold capacity of the

bladder is reached (automatic bladder). Initially it is difficult to express the bladder manually. Because of the risk of bladder rupture, this maneuver should not be attempted until manual evacuation of the bladder is tolerable. Instead, the patient should be catheterized aseptically at least three times daily to empty the bladder completely. An indwelling catheter should not be used because of the risk of urinary tract infection. Frequent urinalyses with culture and sensitivity should be performed.

Concurrent administration of antibacterial agents may be indicated, especially with long-term intermittent catheterization. Baclofen, a skeletal muscle relaxant, decreases muscle tone by exerting a depressive effect on the central nervous system. It inhibits medullary interneurons and spinal reflexes, and it decreases spasticity by reducing the activity of gamma efferent neurons.

29.4.1.3 Detrusor-Urethral Dyssynergia

In detrusor-urethral dyssynergia, initiation of the detrusor reflex that results in voiding is followed by involuntary contraction of the urethral sphincter. The term *detrusor-urethral dyssynergia* refers to involuntary contraction of the external urethral sphincter in the distal urethra (detrusor-striated sphincter dyssynergia) or contraction of smooth muscle in the bladder neck and proximal urethra (detrusor-smooth sphincter dyssynergia) during detrusor contraction. The condition is caused by lesions or partial lesions (masses, degeneration) of the reticulospinal tract. Increased sympathetic activity of both the smooth and striated urethral musculatures may arise from a lesion cranial to or involving the caudal mesenteric ganglion. Treatment involves decreasing sympathetic tone or the use of muscle relaxants (Table 29-1.

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Table • 29-1 Pharmacologic Agents Used in the Treatment of Micturition Disorders

AGENT	ACTION	DOSAGE	ADVERSE EFFECTS	CONTRAINDICATIONS
Baclofen	Skeletal muscle relaxant	*Dog:* 1–2 mg/kg PO q8h *Cat:* Not recommended	Weakness, pruritus, GI upset	
Bethanechol	Parasympathomimetic effect	*Dog:* 5–25 mg PO q8h *Cat*: 2.5–10 mg PO q8h	Vomiting, anorexia, cramping, ptyalism	Urethral obstruction, GI disease, hyperthyroidism
Dantrolene	Skeletal muscle relaxant	*Dog:* 1–5 mg/kg PO q8-12h *Cat:* 0.5–2 mg/kg PO q8h	Weakness, GI upset, sedation, hepatotoxicity	Cardiopulmonary disease
Diazepam	A benzodiazepine; skeletal muscle relaxant	*Dog:* 2–10 mg/dog PO q8h *Cat:* 1–2.5 mg/cat PO q8h	Sedation, polyphagia, paradoxic excitement, hepatotoxicity	Hepatic disease, pregnancy
Phenoxybenzamine	An alpha antagonist; urethral smooth muscle relaxant	*Dog:* 0.25 mg/kg PO q12-24h *or* 2.5–20 mg/dog PO q12-24h *Cat:* 1.25–7.5 mg/cat PO q12-24h	Hypotension, GI upset, tachycardia	Cardiac disease, glaucoma, diabetes mellitus, renal failure
Prazosin	Same as phenoxybenzamine	*Dog:* 1 mg/15 kg PO q8h *Cat:* 0.5 mg/cat PO q12-24h	As for phenoxybenzamine	As for phenoxybenzamine
Terazosin	Same as phenoxybenzamine	*Dog:* 0.5–5 mg/dog PO q12-24h *Cat:* Not established	As for phenoxybenzamine	As for phenoxybenzamine

GI, Gastrointestinal.

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Alpha-adrenergic blocking agents (e.g., phenoxybenzamine, prazosin, and terazosin) can be used to decrease internal sphincter resistance. In addition to its alpha-1 antagonism in urethral smooth muscle, prazosin can cause a centrally mediated decrease in somatic input to the external urethral sphincter. Skeletal muscle relaxants (e.g., baclofen, diazepam, and dantrolene) can be used to decrease external sphincter resistance.

29.4.1.4

Dysautonomia

Dysautonomia is a result of dysfunction of the autonomous nervous system. The cause is unknown. It is a rare disease seen mostly in cats in Great Britain, but it has been recognized in dogs and cats worldwide. The clinical signs are acute in onset and involve many autonomic abnormalities. Urine dribbl-ing and dysuria often are presenting clinical signs due to an atonic bladder. Treatment options include administration of bethanechol and frequent bladder emptying by means of catheterization or manual expression.

29.4.2 Non-Neurogenic Causes of Micturition Disorders

As mentioned previously, non-neurogenic disorders, which typically involve mechanical obstructions, include such processes as infection, inflammation, calculi, and neoplasia.

29.4.2.1 Detrusor Atony from Overdistention

Detrusor atony from overdistention results from a mechanical or functional outflow obstruction that causes the tight junctions of the detrusor muscle to separate. Subsequent contractions of the detrusor muscle are weak and ineffectual. A functional outflow obstruction may have a neurogenic component. It usually is the result of excessive sympathetic stimulation to the urethra, which effects an increase in urethral tone. Common examples of mechanical obstruction are urethral obstruction (especially in cats from mucoid or crystalline plugs), cystic and urethral calculi, neoplasia of the trigone or urethra, severe urethritis, stricture of the urethra, and prostatic disease.

As a result of a functional or mechanical obstruction, urine volume increases until the intravesicular pressure can overcome the urethral resistance. Once the urethral pressure has been overcome, dribbling of urine occurs because of ineffectual detrusor contractions.

With detrusor atony from overdistention, the animal has a history of continuous incontinence and urine outflow obstruction. Abdominal palpation reveals a large, flaccid bladder. Neurologic examination reveals intact perineal and bulbospongiosus reflexes, yet the detrusor reflex is weak or absent. There is a large residual urine volume. Urodynamic studies may help rule out a neurogenic component.

Detrusor atony from overdistention is the one disorder in which indwelling urinary catheterization for up to 7 to 14 days is indicated, because the bladder must be kept as small as possible to re-establish tight junction connections in the detrusor muscle. It is imperative that the obstruction be removed or the primary cause resolved. Occasionally anti-inflammatory therapy is indicated. Frequent urinalyses should be performed, and the appropriate antibiotics, based on susceptibility results, should be given. The cholinergic drug bethanechol has been used successfully to stimulate detrusor contractions in both neurogenic and non-neurogenic atonic bladders. It also is effective for postobstructive atony; however, care must be taken to ensure urethral patency. When the overdistention is caused by increased urethral resistance, an alpha-adrenergic blocker is given before the administration of bethanechol.

29.5 OUTCOME

The prognosis for return to normal function depends on the underlying cause of the micturition disorder. The prognosis is good for acute mechanical obstruction associated with resolving obstructive or irritative disease, acute reversible neurologic lesions, and detrusor atony from overdistention. The prognosis is less favorable for chronic detrusor atony or idiopathic functional obstructive disorders. A complete return to normal voiding may not occur, and long-term treatment may be necessary.

30 CHAPTER • 30 Urinary Incontinence

S. Dru Forrester

***U**rinary incontinence* is the inability to voluntarily control the passage of urine through the urethra. *Enuresis* is urinary incontinence that occurs during sleep; it is a common finding in dogs with urethral incompetence. Dogs and cats with urinary incontinence may also have *nocturia* (excessive urination at night), although this probably is more likely in pets with *polyuria* (increased urine volume). *Dysuria* (painful or difficult urination) most often is characterized by *pollakiuria* (increased frequency of urination attempts) or *stranguria* (straining to urinate); however, it may be associated with incontinence caused by increased urgency to urinate.

30.1 PHYSIOLOGY OF MICTURITION

Control of micturition is centered in the lumbosacral spinal cord and is modified by higher neurologic structures. Sympathetic input originates from lumbar spinal cord segments and projects to beta-adrenergic receptors in the urinary bladder and alpha-adrenergic receptors in the urinary bladder neck and internal urethral sphincter. Parasympathetic input is derived from sacral spinal cord segments and travels through the pelvic nerve to cholinergic receptors in the urinary bladder. The pudendal nerve originates from sacral spinal cord sements and provides somatic input to the external urethral sphincter.

Urine storage is maintained primarily by sympathetic activity, whereas voiding is initiated and maintained by parasympathetic input. Sympathetic input stimulates beta-adrenergic receptors in the urinary bladder, causing detrusor relaxation. Sympathetic input also stimulates alpha-adrenergic receptors in the urethra, causing contraction of the internal urethral sphincter. Voluntary contraction of the external urethral sphincter contributes to increased outlet resistance, which helps maintain continence. Filling of the urinary bladder stimulates stretch receptors, which send impulses through the pelvic nerve and spinal pathways to the brain stem and cerebral cortex. Parasympathetic impulses are transmitted from the micturition center through spinal pathways and the pelvic nerve to stimulate cholinergic receptors and initiate detrusor contraction. During detrusor contraction, concomitant inhibition of sympathetic and somatic input to the urethra allows urethral opening. In normal animals, complete voiding occurs, and the urinary bladder returns to a relaxed state.

30.2 CAUSES OF URINARY INCONTINENCE

30.2.1 Neurogenic Disorders

Any neurologic lesion that affects the micturition reflex may cause abnormal micturition. Incontinence is most likely to occur with lower motor neuron disorders (i.e., S1 to S3 segments or peripheral nerves), such as congenital malformation of the sacrum in Manx cats, sacral fractures, trauma affecting the pelvic nerve, and lumbosacral disease (e.g., rupture of an intervertebral disk, neoplasia, and stenosis). Upper motor neuron disorders (e.g., lesions cranial to S1) usually are characterized by urinary retention; however, if the urinary bladder is overdistended, urine may leak through the urethra once intravesicular pressure exceeds outlet resistance, causing overflow incontinence.

30.2.2 Non-Neurogenic Disorders

Incontinence may be associated with functional or anatomic disorders of the urethra or urinary bladder. Urethral incompetence is a functional disorder associated with incontinence; it occurs most often in neutered dogs but has also been observed in dogs with ectopic ureters and cats with feline leukemia virus infection. A less common functional cause of incontinence is detrusor instability, a disorder characterized by failure of the urinary bladder to relax during the storage phase. Anatomic abnormalities such as ectopic ureters, patent urachus, and vaginal stricture also may cause incontinence. Lower urinary tract disorders (e.g., urinary tract infection, urolithiasis) most often cause pollakiuria; however, incontinence may occur secondary to an increased urge to urinate. Animals with partial urinary outlet obstruction (e.g., small uroliths) may have incomplete voiding and a distended urinary bladder, but they also may have periods of paradoxical incontinence as urine escapes past the obstructive lesion.

30.3 DIAGNOSTIC EVALUATION

In the evaluation of dogs and cats with abnormal micturition, it is helpful to determine whether failure of urine storage or of voiding (or both) is present. Urinary incontinence is the hallmark of urine storage disorders; however, some animals with primary urine retention may also have incontinence. In addition to the information gained from the signalment, history, and physical examination, it is helpful to determine whether neurologic deficits, which may be a cause of incontinence, are a factor (Figure 30-1). Additional diagnostic tests (e.g., imaging studies) may be needed to identify the underlying cause and to help determine the appropriate treatment.

30.3.1 Signalment

Congenital disorders (e.g., ectopic ureters) are more common in younger animals, whereas acquired diseases (e.g., hormone-responsive incontinence) are more likely in older dogs and cats. Ectopic ureters occur most frequently in female, large breed dogs. Hormone-responsive incontinence is most common in neutered female dogs that weigh more than 20 kg.

30.3.2 History

Owners should be asked about previous urogenital tract problems in their pets, including trauma or surgery. Dogs and cats with ectopic ureters usually have incontinence from birth, whereas hormone-responsive incontinence often occurs in dogs several months to years after neutering. Animals with urethral incompetence often dribble urine while sleeping or lying down. If polyuria exists, it may worsen clinical signs in dogs predisposed to incontinence. It should be determined whether the incontinence is intermittent or continuous. Continuous incontinence occurs with bilateral ectopic ureters and severe urethral incompetence; intermittent incontinence may be observed with mild to moderate urethral incompetence, unilateral ectopic ureters, and disorders that cause paradoxical incontinence. The presence of dysuria, stranguria, or pollakiuria suggests lower urinary tract disorders (e.g., urinary tract infection, urolithiasis), which may cause urge incontinence.

A description of the pet's urination should be obtained from the owner; if this is not possible, the veterinarian should observe the animal urinate. The ability to voluntarily initiate and maintain urination until voiding is complete indicates normal detrusor reflex activity. Absence of this ability occurs with neurogenic diseases. Animals with urethral incompetence and those with anatomic abnormalities (e.g., ectopic ureters) can initiate and maintain urination.

30.3.3 Physical Examination

A thorough physical examination should be completed before the urogenital tract is examined. The urinary bladder should be palpated to detect masses and to determine whether it is full or empty, spastic or flaccid, and easy or difficult to express. Upper motor neuron disorders are associated with a firm, distended urinary bladder that is difficult to express. However, if urinary retention is prolonged, the urinary bladder may become overdistended and flaccid. Lower motor neuron diseases result in a flaccid, distended urinary bladder that is easily expressed. After the animal has voided, the bladder should be palpated again to allow estimation of the residual urine volume, which should be less than 0.4 mL/kg in normal animals. A rectal examination is indicated for evaluation of the caudal urinary bladder, urethra, and prostate gland. Vaginal palpation should be done in female dogs to detect strictures and urethral masses. The perineal area should be inspected for anatomic abnormalities and evidence of urine staining or scalding, which may occur with incontinence.

30.3.4 Neurologic Examination

A neurologic examination should be completed to detect deficits caused by neurogenic disorders. A decrease in or the absence of anal tone, perineal sensation, and the bulbospongiosus reflex are consistent with lower motor neuron disease. Pain on palpation over the lumbosacral area or when the tail is lifted and decreased tail tone occur in patients with lumbosacral disease. Animals with intervertebral disk disease may have ataxia, proprioceptive deficits in the rear limbs, and/or pain on palpation of the vertebral column. 110

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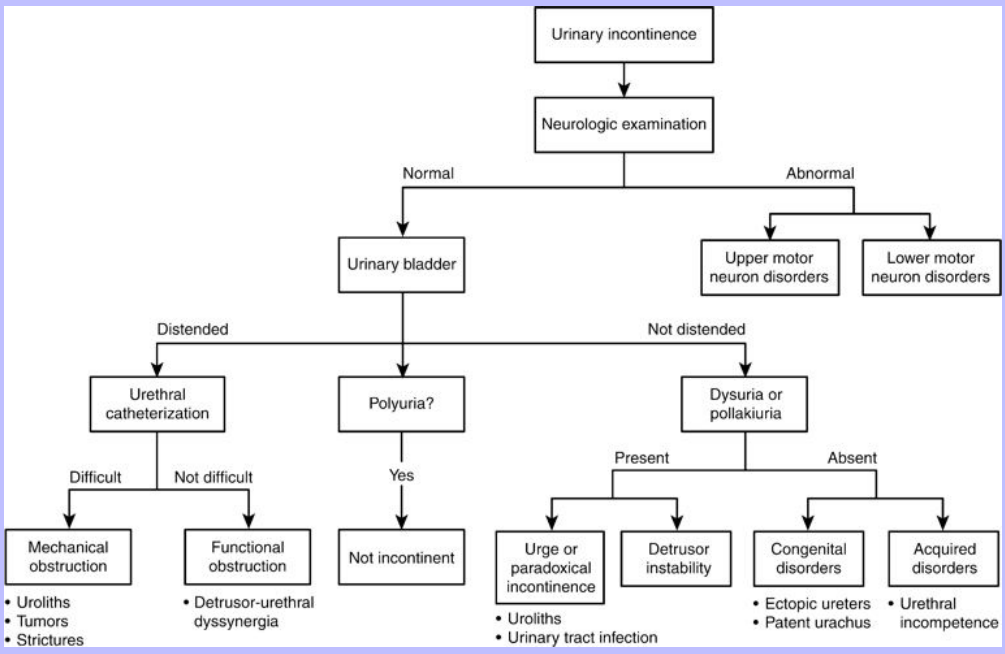
Figure 30-1 Algorithm for diagnosis and treatment of urinary incontinence.



30.3.5 Laboratory Tests

A urinalysis should be done and urine should be collected for culture in all animals with incontinence; other tests, such as serum chemistries, are indicated when systemic signs of illness are present (e.g., inappetence, vomiting, polyuria, polydipsia). Cystocentesis is the preferred method of collecting urine. The presence of pyuria is consistent with urinary tract inflammation, which may cause urge incontinence. Hematuria may be the predominant finding in feline lower urinary tract disease and in animals with urinary tract neoplasia. Bacteriuria found in urine collected by cystocentesis is highly suggestive of urinary tract infection. Although urinary tract infection may cause urge incontinence, it also may occur secondary to abnormal host defenses in animals with incontinence.

30.3.6 Diagnostic Imaging

Radiography and ultrasonography are helpful when anatomic or structural abnormalities are suspected to be the cause of incontinence. Abdominal radiographs provide information about the size and location of the urinary bladder and also help identify radiopaque uroliths and prostatomegaly. Ultrasonography is helpful for identifying structural abnormalities of the urogenital tract. If the results of noninvasive imaging are normal, contrast studies should be considered. Cystourethrography and vaginography are indicated for identifying abnormalities of the lower urinary tract and vagina, respectively. Excretory urography may be helpful for detecting ectopic ureters. In animals with neurogenic disorders, additional imaging studies (e.g., spinal films, myelography, computed tomography) may be indicated.

30.3.7 Endoscopy

Endoscopy of the lower urogenital tract may be helpful in female dogs suspected of having congenital or anatomic abnormalities. Vaginal strictures should be identified through digital examination of the vaginal vault, and urethral masses can be identified by vaginoscopy. Cystoscopy may be used to evaluate the flow of urine through the ureteral openings into the urinary bladder in normal dogs; the absence of urine flow through one or both ureteral openings is consistent with ectopic ureters.

30.3.8 Urodynamic Tests

Urodynamic studies measure pressure, volume, and flow in the urinary bladder and urethra. Because specialized equipment is needed, these tests generally are available at referral centers. In most cases, urodynamic testing is not needed; however, it may be helpful when the diagnosis is uncertain or when the response to treatment is inadequate.

30.4 OUTCOME

The outcome depends in part on the underlying cause of the urinary incontinence. The outcome in dogs and cats with structural abnormalities that can be corrected is good to excellent. Surgical correction of ectopic ureters may be successful; however, incontinence may persist due to concomitant urethral incompetence in these animals. Dogs with hormone-responsive incontinence respond well to treatment but may have periods of worsening signs that require adjustments in dosage.

31 CHAPTER • 31 Discolored Urine

Joseph W. Bartges

31.1 NORMAL URINE

Normal urine is typically transparent and yellow or amber upon visual inspection. Two pigments impart the yellow coloration: urochrome and urobilin. Urochrome is a sulfur-containing oxidation product of the colorless urochromogen. Urobilin is a degradation product of hemoglobin. Because the 24-hour urinary excretion of urochrome is relatively constant, highly concentrated urine is amber, whereas dilute urine may be transparent or light yellow. The intensity of the color is partly related to the volume of urine collected and the concentration of urine produced; therefore color should be evaluated in the context of the urine specific gravity. Care must be taken not to overinterpret the significance of urine color as part of a complete urinalysis. Significant disease may exist when urine is normal in color. Abnormal urine color may be caused by the presence of several endogenous or exogenous pigments. Although the abnormal color indicates a problem, it provides relatively nonspecific information. Causes of abnormal coloration should be investigated with appropriate laboratory tests and examination of urine sediment. Detection of abnormal urine color should prompt questions related to diet, administration of medication, environment, and collection technique. A knowledge of urine color may also be important in interpreting colorimetric test results, because the color may induce interference with the test.

Table • 31-1 Potential Causes of Discolored Urine

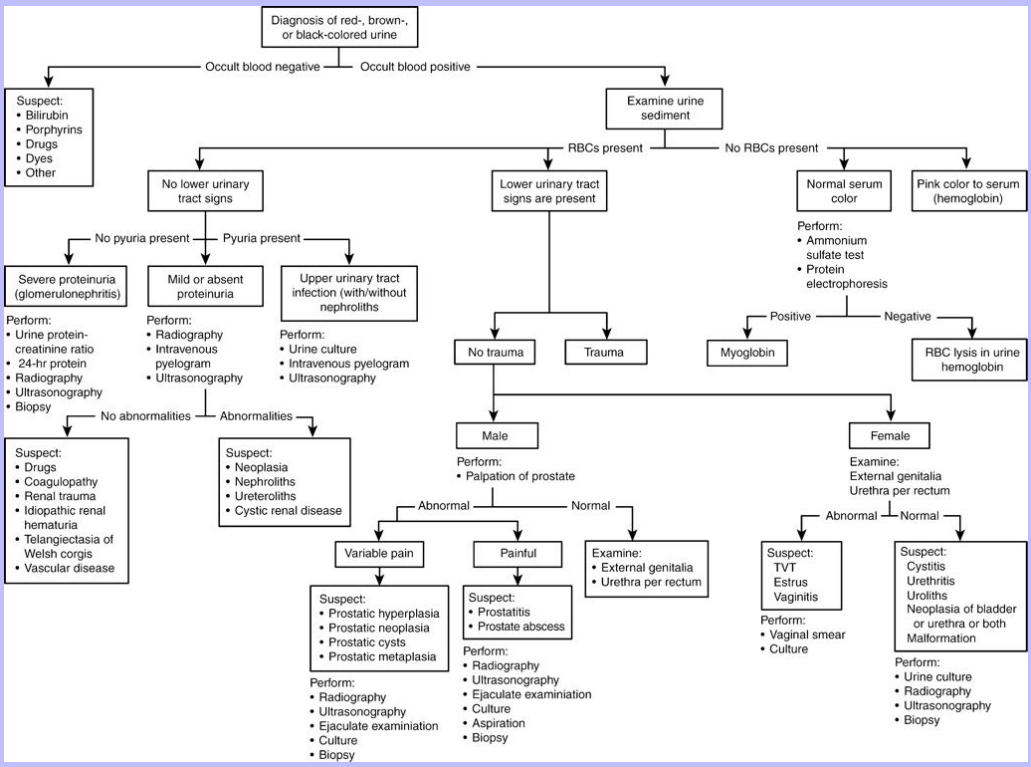
URINE COLOR	CAUSES
Yellow or amber	Urochromes, urobilin
Deep yellow	Highly concentrated urine, quinacrine,* nitrofurantoin,* phenacetin,* riboflavin (large quantities),* phenolsulfonphthalein (acidic urine)*
Blue	Methylene blue, indigo carmine and indigo blue dye,* indicans,* *Pseudomonas* infection,* water-soluble chlorophyll,* rhubarb,* toluidine blue,* triamterene,* amitriptyline,* anthraquinone,* blue food dye*
Green	Methylene blue, dithiazanine, urate crystalluria, indigo blue,** bilirubin, biliverdin, riboflavin,* thymol,* phenol,* triamterene,* amitriptyline,* anthraquinone,* green food dye*
Red, pink, red-brown, red-orange, or orange	Hematuria, hemoglobinuria, myoglobinuria, porphyrinuria, Congo red, phenolsulfonphthalein (after alkalinization), neoprontosil, warfarin (orange),* food pigments (rhubarb, beets, blackberries),* carbon tetrachloride,* phenazopyridine, phenothiazine,* diphenylhydantoin,* bromsulphalein (after alkalinization), chronic heavy metal poisoning (lead, mercury),* rifampin,* emodin,* phenindione,* eosin,* rifabutin,* acetazolamide,* red food dye*
Orange-yellow	Highly concentrated urine, excess urobilin, bilirubin, phenazopyridine, sulfasalazine,* fluorescein sodium,* flutamide,* quinacrine,* phenacetin,* 2,4-d,* acetazolamide,* orange food dye*
Yellow-brown or green-brown	Bile pigments
Brown to black (brown or red-brown when viewed in bright light in a thin layer)	Melanin, methemoglobin, myoglobin, bile pigments, thymol,* phenolic compounds,* nitrofurantoin,* nitrites,* naphthalene,* chlorinated hydrocarbons,* aniline dyes,* homogentisic acid*
Brown	Methemoglobin, melanin, sulfasalazine,* nitrofurantoin,* phenacetin,* naphthalene,* sulfonamides,* bismuth,* mercury,* feces (rectal-urinary fistula), fava beans,* rhubarb,* sorbitol,* metronidazole,* methocarbamol,* anthracin cathartics,* clofazimine,* primaquine,* chloroquine,* furazolidone,* copper toxicity
Colorless	Very dilute urine (diuretics, diabetes mellitus, diabetes insipidus, glucocorticoid excess, fluid therapy, overhydration)
Milky white	Lipid, pyuria, crystals

* Only observed in human beings.

31.2 DISCOLORED URINE

Urine color that is anything other than yellow or amber is abnormal. Discolored urine has many potential causes (Table 31-1). The most common abnormal urine color in dogs and cats is red, brown, or black, which may be caused by hematuria, hemoglobinuria, myoglobinuria, and bilirubinuria (Figure 31-1). 112 114

Figure 31-1 Algorithm for diagnosis of red, brown, or black colored urine.



31.2.1 Pale Yellow Urine

Urine that is pale yellow or clear may be normal or indicative of a polyuric state. Urine may be appropriately dilute if associated with recent consumption or administration of fluids, consumption of a diet containing low amounts of protein or high amounts of sodium chloride, glucocorticoid excess, or administration of diuretics. Urine concentration would be considered inappropriate if it were dilute in the presence of dehydration. Diseases that may be associated with persistently dilute urine include renal failure, diabetes insipidus, hyperadrenocorticism, hypoadrenocorticism, hypercalcemia, diabetes mellitus, and hyperthyroidism. If the urine is pale yellow or clear, the urine specific gravity often is less than 1.015. A simple test of whether polyuria is persistent is to determine the urine specific gravity of a sample collected in the morning. Other tests should include serum biochemical analysis and a complete urinalysis. Additional testing may include measurement of the serum thyroxine concentration, adrenal function testing, or monitoring of the urine specific gravity after several days of vasopressin administration.

31.2.2 Red, Brown, or Black Urine

Urine that is red, brown, or black suggests the presence of blood, hemoglobin, myoglobin, or bilirubin (see Figure 31-1). A positive occult blood reaction is obtained when urine contains any of these substances. Discoloration of urine may also result in false-positive reactions on other urine dipstick test pads. Analysis of

urine sediment reveals the presence of red blood cells if the discoloration is due to hematuria. If no red blood cells are present on microscopic examination of the urine sediment, hemoglobin, myoglobin, or bilirubin should be suspected. Examination of plasma color may help differentiate these. If the discoloration of the urine is due to myoglobin, the plasma is clear, because myoglobin in plasma is not bound significantly to a carrying protein and the result is filtration and excretion of myoglobin. Pink coloration of the plasma is suggestive of hemoglobin. A yellow plasma color is suggestive of bilirubin; the serum bilirubin concentration should also be increased. Myoglobinuria is indicative of muscle damage, and serum creatine kinase activity often is increased in this setting. Hemoglobinemia is indicative of intravascular hemolysis resulting from immune-mediated, parasite-mediated, or drug-mediated destruction of red blood cells. Hyperbilirubinemia may result from liver disease, posthepatic obstruction, or hemolysis.

31.2.3 Milky White Urine

A milky white color may be due to the presence of white blood cells (pyuria), lipid, or crystals in the urine. The more concentrated the urine sample is, the more opaque it may appear. The presence of pyuria secondary to a bacterial urinary tract infection is the most common cause of milky white urine; however, pyuria may occur as a result of inflammation and may not be associated with an infection. Lipiduria may be observed in healthy animals but is frequently observed in cats with hepatic lipidosis. Crystalluria, if heavy and present in a concentrated urine sample, may also result in milky white urine. Microscopic examination of the urine sediment aids differentiation of these causes.

32 CHAPTER • 32 Proteinuria

Gregory F. Grauer

Normal canine and feline urine contains only a small amount of protein. The permselectivity of the glomerular capillary wall hinders filtration of most plasma proteins, primarily on the basis of weight and, to a lesser extent, charge. Proteins with a molecular weight greater than 60,000 to 65,000 daltons are not usually filtered because of their size. Negatively charged proteins of glomerular capillary walls further restrict the filtration of other negatively charged proteins, such as albumin. Smaller molecular weight proteins, as well as the positively charged proteins that are filtered, are largely resorbed from the glomerular filtrate by proximal tubular epithelial cells. Resorbed proteins may be catabolized by the epithelial cells or returned to the circulation. Protein resorption by tubular epithelial cells has a transport maximum and, if that maximum is exceeded, proteinuria may result.

Another source of urine protein is the secretion of enzymes, mucoproteins, and immunoglobulins by renal tubular and lower urinary and genital tract epithelial cells. These secreted proteins may account for as much as 50% of the protein typically present in urine.

When examining a dog or cat with proteinuria, it is important that the veterinarian try to identify the source of the urine protein. Proteinuria may be caused by physiologic or pathologic conditions (Table 32-1). Physiologic or benign proteinuria often is transient and abates when the underlying cause is corrected. Strenuous exercise, seizures, fever, exposure to extreme heat or cold, and stress are examples of conditions that may cause physiologic proteinuria. The process by which physiologic proteinuria occurs is not completely understood; however, relative renal vasoconstriction, ischemia, and congestion likely are involved. Decreased physical activity may also influence urine protein excretion in dogs; one study demonstrated that dogs confined to cages had a higher urine protein loss than dogs with a normal level of activity.

Pathologic proteinuria may be caused by urinary or non-urinary abnormalities. “Nonurinary” disorders associated with proteinuria often involve excessive production of small molecular weight proteins, which are freely filtered by the glomerulus and which subsequently overwhelm the resorptive capacity of the proximal tubule. Examples of this excessive production include the production of immunoglobulin light chains (Bence-Jones proteins) by neoplastic plasma cells or the release of hemoglobin and myoglobin from damaged red blood cells and muscle tissue. Hemoglobin and myoglobin in plasma are bound by haptoglobulin, and glomerular filtration of these proteins does not occur until the binding capacity of haptoglobulins has been exceeded. Renal vascular congestion secondary to heart failure may also result in pathologic nonurinary proteinuria, as can genital tract inflammation (e.g., prostatitis or metritis).

Table • 32-1 Diagnostic Criteria for Different Types of Proteinuria

TYPE AND POSSIBLE CAUSES OF PROTEINURIA	DIAGNOSTIC TESTS/SIGNS
Physiologic/Benign Proteinuria	
Change in exercise level, seizure activity, fever, exposure to temperature extremes, stress	• UP/C usually <0.5 • Compatible history • Intermittent/transient proteinuria
Pathologic Proteinuria	
Nonurinary	• UP/C not indicated
Congestive heart failure	• History/PE/thoracic radiographs/echocardiogram
Hemoglobinuria/myoglobinuria	• Urine remains red after centrifugation
Paraproteinuria	• Serum/urine electrophoresis
Genital tract inflammation/hemorrhage	• PE/imaging/urine sediment changes
Urinary—nonrenal	
Lower urinary tract inflammation (e.g., bacterial cystitis, cystoliths, polyps, neoplasia)	• UP/C not indicated • History/PE • Urine sediment changes • Imaging • Urine culture
Urinary—renal	
Renal parenchymal inflammation (e.g., pyelonephritis, renoliths, neoplasia)	• UP/C not indicated • Urine sediment changes • Imaging
Tubular proteinuria	• UP/C usually 0.5–1.0 • Can be associated with normoglycemic glucosuria and excessive urinary loss of electrolytes
Glomerular proteinuria	• Persistent UP/C ≥ 1.0 • Inactive urine sediment except for possible hyaline casts

PE, Physical examination; *UP/C*, urine protein/creatinine ratio.

"Urinary" proteinuria may arise from renal or nonrenal sources. Nonrenal proteinuria most frequently is associated with lower urinary tract inflammation or hemorrhage. Changes in the urine sediment often suggest the underlying cause (e.g., urolithiasis, neoplasia, trauma, or bacterial cystitis). Glomerular lesions are the most common causes ofrenal proteinuria. Glomerulonephritis and amyloidosis alter the selective permeability of the glomerular capillaries and frequently result in proteinuria greater than 40 mg/kg/24 hours or urine protein/creatinine ratios greater than 2.0. Persistent proteinuria of this magnitude with a normal urine sediment or a urine sediment that contains hyaline casts is suggestive of glomerular disease. In addition to glomerular disease, renal proteinuria may be caused by inflammatory or infiltrative disorders of the kidney (e.g., neoplasia or pyelonephritis) or by tubular abnormalities that result in decreased resorption of filtered protein (e.g., Fanconi syndrome) (see Table 32-1).

Proteinuria is routinely detected by semiquantitative methods, including the dipstick colorimetric test and the sulfosalicylic turbidimetric test. The dipstick test is inexpensive and easy to use; amino groups of proteins bind to the indicator incorporated in the filter paper on the dipstick and cause a color change. The color change is graded by subjective comparison to a standard. The dipstick test is most sensitive to albumin, inasmuch as albumin has more free amino groups compared with globulins or Bence-Jones proteins. False-positive results are common and may be seen with alkaline urine or urine that has been contaminated with quaternary ammonium compounds, or with excessive urine contact time, which causes the citrate buffer to leach out of the filter paper pad. False-negative results may occur with Bence-Jones proteinuria or dilute or acidic urine. The sensitivity of the dipstick test is approximately ≥30 mg/dL.

The sulfosalicylic acid test can be performed by mixing equal amounts of urine and 5% sulfosalicylic acid. The turbidity that results from the acid precipitation of protein is graded on a scale of 0 to 4+. The advantages of this test, compared with the dipstick test, are increased sensitivity and the ability to detect proteins other than albumin (e.g., Bence-Jones proteins). False-positive results are rare but may be obtained if urine contains radiographic contrast agents, penicillin, cephalothin, cephalodine, sulfisoxazole, or thymol preservatives. The protein content may be overestimated with the sulfosalicylic acid test if uncentrifuged urine or turbid urine is analyzed. False-negative results may be obtained with highly alkaline or dilute urine. Similar to the dipstick test, the varying degrees of turbidity are not standardized, and variability in results may be seen among laboratories. The sensitivity for this test is approximately ≥5 mg/dL.

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Proteinuria detected by these semiquantitative methods should always be interpreted in light of the urine specific gravity (USG) and urine sediment findings. Significant proteinuria may be overlooked if the urine is dilute and voluminous. Conversely, a protein reaction of trace or 1+ may be normal in concentrated urine. For example, a 2+ proteinuria with a 1.010 USG suggests much greater urine protein loss on a 24-hour basis than does a 2+ proteinuria with a 1.040 USG. In addition, the urine protein concentration is frequently increased in dogs or cats with urinary tract inflammation and/or hemorrhage. Proteinuria, therefore, should also be assessed in relation to changes in the urine sediment that are compatible with inflammation or hemorrhage (e.g., bacteria and increased numbers of white and red blood cells and epithelial cells in the urine sediment).

Recently an enzyme-linked immunosorbent assay (ELISA) for detecting low levels of albumin in canine and feline urine *(microalbuminuria)* has become commercially available (E.R.D.-Screen, Heska Corp., Fort Collins, CO). Microalbuminuria usually is defined as a urine albumin concentration between 1.0 and 30 mg/dL. These concentrations are too small to be detected routinely by standard dipstick screening tests. It is interesting to note that microalbuminuria has been shown to be an accurate predictor of subsequent renal disease in human beings secondary both to systemic hypertension and to diabetes mellitus and that it has also been observed in human beings with systemic diseases associated with glomerulopathy. Studies in dogs have shown the prevalence of microalbuminuria in apparently healthy dogs to be 19% and in dogs brought to veterinarians because of illness to be 36%. In addition, high prevalence rates of microalbuminuria have been reported in soft-coated wheaten terriers (SCWT) and SCWT/crosses (76%); in dogs experimentally infected with heartworm disease (100%); and male dogs with X-linked hereditary nephropathy (97%). Each of these models is associated with glomerulopathy, and in all three studies microalbuminuria, when it occurred, appeared to be progressive and preceded the onset of overt proteinuria. These results suggest the utility and importance of microalbuminuria as an early marker of renal disease in the dog.

Prerenal (physiologic and pathologic-nonurinary), postrenal (pathologic urinary-nonrenal), and inflammatory renal proteinuria usually can be identified on the basis of the history, physical examination, and urine sediment changes (see Table 32-1). Renal proteinuria caused by abnormal tubular resorption may be accompanied by glucosuria and excessive urinary loss of electrolytes, which helps differentiate tubular proteinuria from glomerular proteinuria. Identification of the source of the proteinuria is important, because quantitation of glomerular proteinuria can be a helpful prognostic tool, although it is not useful in patients with prerenal or postrenal proteinuria.

When glomerular proteinuria is suspected, urine protein excretion should be quantitated. Quantitation of renal proteinuria aids evaluation of the severity of renal lesions, as well as the response to treatment or the progression of disease. The trichloroacetic acid-N-Ponceau S, Coomassie brilliant blue, or benzethonium chloride tests are the methods most commonly used to quantify urine protein and are available at referral centers and reference laboratories. Collection of urine for 24 hours and measurement of urine protein excretion in milligrams per kilogram per 24 hours has been the time-honored method of quantitating proteinuria, because errors caused by variation in urine volume are minimized by 24-hour collection. However, such collections require the use of a metabolism cage, an indwelling urinary catheter, or repeated urinary catheterization, all of which make the procedure cumbersome and

expensive. In addition, incomplete collection of all urine produced over the 24-hour period results in errors. Alternatively, the urine protein concentration (in milligrams per deciliter [mg/dL]) in a single, random urine sample may be divided by the urine creatinine concentration (also in mg/dL). This ratio negates the effect of urine volume on the urine protein concentration.

Calculation of the urine protein/creatinine ratio from canine and feline urine samples has been shown to accurately reflect the amount of protein excreted in the urine over a 24-hour period. This test has greatly facilitated the diagnosis of glomerulonephritis in small animals. Most studies suggest that normal urine protein excretion in dogs and cats is less than 10 to 20 mg/kg/24 hours. A regression line equation allows the urine protein/creatinine ratio, when multiplied by approximately 20, to be converted to milligrams of protein per kilogram per 24 hours. A urine protein/creatinine ratio of less than 0.5 to 1.0 is usually considered normal in dogs and cats. A complete urinalysis should always be obtained before or along with the urine protein/creatinine ratio, because hematuria or pyuria may indicate significant nonglomerular proteinuria. If evidence of inflammation is present (e.g., pyuria, bacteriuria), the protein determination should be repeated after successful treatment of the inflammatory disorder. The urine protein/creatinine ratio cannot be used to differentiate glomerular proteinuria from proteinuria associated with lower urinary tract inflammation or hemorrhage.

Urine and serum protein electrophoresis may be helpful both in identifying the source of the proteinuria and in establishing a prognosis. Proteinuria associated with hemorrhage into the urinary tract has an electrophoretic pattern similar to that of the serum. Early glomerular damage usually results principally in albuminuria; however, with progression of the glomerular disease, an increasing amount of globulin may be lost as well. Marked hypoalbuminemia and increased concentrations of larger molecular weight proteins in the serum suggest severe glomerular proteinuria and are often associated with nephrotic syndrome.

The consequences of glomerular proteinuria may include loss of plasma oncotic pressure, sodium retention, formationof edema and/or ascites, hypercoagulability, muscle wasting, and weight loss. With progressive renal disease and nephronloss, proteinuria tends to diminish as the number of affected glomeruli decrease. However, the remaining viable nephrons that have undergone compensatory hypertrophy exhibit intraglomerular hypertension and hyperfiltration. Protein loss remains increased in these individual nephrons. Evidenceis accumulating in many species, including the dog and cat, that proteinuria can contribute to progressive nephron loss through tubulointerstitial damage and exacerbation of glomerular lesions.

33 CHAPTER • 33 Gastrointestinal: Anorexia

John P. Hoover

William E. Monroe

In general, a good appetite for food is associated with health, whereas *anorexia,* or loss of appetite, is associated with illness. Reduced food consumption is a common manifestation of disease. When accompanied by observable weight loss, anorexia often prompts pet owners to seek veterinary attention. Anorexia may be the result of decreased appetite (true anorexia) or may occur secondary to other factors that do not affect appetite *(pseudoanorexia)*. Anorexia can range from partial to complete and can reflect the severity or cause of disease.

33.1 PATHOPHYSIOLOGY

Appetite was once simplistically thought to be controlled by a "hunger" or "feeding center" in the lateral (hypothalamic) nuclei (LHN) as modulated or inhibited by a "satiety center" in the ventromedial nuclei (VMN) of the hypothalamus. Chemical mediators produced by vagal or sympathetic stimulation of central and peripheral receptors provide LHN and VMN input that alters appetite. *Satiety* is associated with the absence of hunger during the absorptive phase after food ingestion, when metabolic fuels are supplied by nutrients assimilated from the gastrointestinal tract. *Hunger* is associated with the postabsorptive phase before food ingestion when energy must be derived from mobilization of stored nutrients such as glycogen, triglycerides, and proteins to provide glucose, fatty acids, and amino acids. Current evidence suggests that in addition to the LHN and VMN, the amygdala, the solitary nuclei, arcuate nuclei, paraventricular nuclei (PVN), and suprachiasmic nuclei, the anterior piriform cortex, and the telencephalon play important roles in facilitating or inhibiting appetite by means of a plethora of peripheral and central neurochemical mediators or transmitters.

33.2 HISTORICAL FINDINGS

Environmental or psychologic factors that an owner may not perceive as significant (e.g., fear, dominance) may lead to pseudoanorexia. The addition of animals that are threatening or aggressive may interfere with eating. A new baby or other individuals who make an animal feel threatened or ignored, or a change of housing, may also affect appetite. Changing the diet to one that is less palatable may lead to anorexia or a reduced appetite.

Animals that lack a sense of smell *(anosmia)* may have difficulty finding their food, and animals with severe nasal disease, especially cats, may find food unpalatable. Pets with lingual, pharyngeal, or esophageal dysfunction or those with neurologic disorders that affect swallowing (e.g., trigeminal neuritis) may show interest in food but may drop it and be unable to eat. Others with painful retrobulbar abscesses, masticatory myositis, mandibular fractures, temporomandibular joint disease, maxillary or nasal fractures or masses, severe periodontal or dental disease, or oral foreign bodies may attempt to eat only to stop, cry out, and drop food. Some may show no interest in eating. There may be a history of trauma, feeding of bones, or chewing on sticks or other potential sources of self-trauma. Animals with respiratory disease and marked dyspnea or orthopnea may be unable or unwilling to eat or drink due to compromise in breathing during prehension and deglutition.

The historical findings in animals that do not eat because of systemic disease are variable and depend on the disease present. In general, animals that are anorectic because of systemic disease have no interest in food. Pain, lameness, motor dysfunction, urination abnormalities, vomiting, diarrhea, coughing, and dyspnea all may be signs

of disease that leads to anorexia. Animals with neurologic disease that results in decreased eating because of reduced cerebral arousal may have a history of behavioral changes or stupor.

Medications also may cause partial or complete anorexia through direct effects on appetite centers. Chemotherapeutic agents may inhibit appetite by inducing nausea. Opioid peptides inhibit the orexigenic network and suppress appetite. Supplying glucose, fatty acids, and amino acids by intravenous infusion may promote satiety and decrease hunger similar to that seen after eating, in the absorptive state.

33.3 PHYSICAL FINDINGS

Animals that are anorectic because of psychologic causes, such as environmental stress or unpalatable diet, usually are normal on physical examination. Bite or fight wounds may be present in pets that are not eating because of the presence of another dominant animal or excessive competition. The veterinarian can determine if an animal is having trouble finding food because of a poor sense of smell by blindfolding the pet and placing aromatic food near its nose. If the animal shows no sniffing behavior, it may not be able to smell. Observing the animal walk around the examination room where other animals have been may also reveal whether it has a sense of smell, because most pets exhibit sniffing behavior in these circumstances.

An animal that is unable to eat because of pain or dysfunction of the oral area may resist or cry out when the mouth is opened for examination. Skull fractures, soft tissue trauma, neoplasia, craniomandibular arthritis or osteoarthropathy, masticatory myositides, and retrobulbar masses all may be associated with pain when attempts are made to open the mouth. Asymmetry of the face, mandible, nose, mouth, or skull may be apparent. Evidence of dental disease may be noted, such as severe calculus, loose or broken teeth, pain, or exudation when applying pressure to or tapping on the teeth. Ulcers, wounds, stomatitis, gingivitis, masses, or foreign bodies such as sticks, rocks, or bones may be noted when the mouth and pharynx are examined. If nasal disease is the cause of poor appetite, nasal swelling, epistaxis, mucopurulent discharge, masses, or ulceration of the mucocutaneous junctions of the nares may be seen. Exophthalmos often is noted with retrobulbar abscesses or tumors and masticatory myositides. Trigeminal neuritis or trauma to the jaw may be associated with a dropped jaw and inability to eat.

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Physical examination abnormalities associated with systemic diseases that cause anorexia are as varied as the potential causes of disease. Fever, pallor, jaundice, ocular abnormalities, abdominal pain, abnormally small or large organ size, abdominal distention from fluid accumulation, spinal or limb pain, masses or swellings, cardiac murmurs, dyspnea with muffled heart and lung sounds, and adventitial breath sounds all are signs of diseases that can lead to anorexia.

33.4 DIAGNOSTIC PLAN

A thorough history is the essential diagnostic tool for psychologic or iatrogenic causes of anorexia. A thorough physical examination, in conjunction with the history, is essential to help determine physiologic causes of anorexia (Figure 33-1). Pets that are anorectic, particularly those that seem interested in food but are unable or refuse to eat, should receive a thorough oral, dental, and cranial examination. If the dog or cat is uncooperative, sedation or anesthesia may be necessary. In addition to the more routine physical examination procedures, the spine should be carefully palpated for pain (e.g., discospondylitis), and a careful rectal examination should be performed in all dogs to determine prostate size (in males), to detect pelvic masses, or to assess for unsuspected abnormalities, such as hematochezia or perineal hernias. When respiratory distress due to pleural space disease is present, thoracocentesis can provide symptomatic relief, and fluid analysis may prove diagnostic. A fundic examination after pupil dilatation should be included in the examination, because systemic diseases such as feline infectious

peritonitis, lymphoma, deep mycoses, toxoplasmosis, and rickettsial infections may have characteristic ocular changes.

For pets without a history that supports a psychologic cause for anorexia and that also have no physical examination abnormalities to indicate a physiologic cause, a minimum data base should be compiled that includes a complete blood count, serum chemistry profile, urinalysis with microscopic examination of the sediment, a heartworm test in dogs, and feline leukemia virus and immunodeficiency virus serology in cats. These tests may suggest inflammatory, degenerative, endocrine, metabolic, neoplastic, or toxic disorders that can lead to anorexia. If systemic disease appears to be the probable cause of anorexia, further diagnostic testing should be directed toward abnormalities identified by the history, physical examination, and minimum data base. For cases in which no historical, physical, or data base abnormalities can be found, thoracic and abdominal radiographs or ultrasonography may reveal evidence of occult disorders, such as thoracic masses, gastrointestinal foreign bodies or masses, or pericardial, pleural, or abdominal fluid. When these procedures reveal no abnormalities, gastrointestinal endoscopy, contrast radiographic studies, or a computed tomography (CT) scan may be indicated to rule out the possibility of neoplasia or other infiltrative diseases. Multiple joint centesis may also be indicated to rule out the possibility of polyarthritis.

33.5 GOALS OF TREATMENT

The first goal of therapy for anorexia should be to correct any underlying causes, such as oropharyngeal or systemic inflammatory disease. Although definitive treatment requires a definitive diagnosis, animals that have been anorectic for longer than 3 to 5 days should receive nutritional support through enteral or parenteral feeding (see Chapters 92 and 161) until the definitive diagnosis can be made.

Appetite stimulation by drug therapy focuses on agents that affect central nervous system serotonin and dopamine receptors. Benzodiazepines and the serotonin antagonist cyproheptadine induce hunger and inhibit physiologic sati-ety. Megestrol acetate may stimulate appetite by centralinhibition of anorexigenic hormones, such as corticotrophin-releasing hormone, as in human cancer patients. The efficacy of gastrokinetic agents in stimulating appetite in anorecticanimals hasn't been established, but metoclopramide, cisapride, and the peripheral dopamine D2 receptor antagonist domperidone have yielded positive results in some human beings.

34 CHAPTER • 34 Polyphagia

Ellen N. Behrend

***P**olyphagia* is the consumption of food in excess of normal caloric intake. Hunger and satiety and, consequently, feeding behavior are primarily controlled by certain regions in the central nervous system (CNS), but many factors affect the function of these areas. Thus polyphagia can be classified as *primary* (i.e., a CNS abnormality) or *secondary* (i.e., a systemic problem affecting the CNS). Secondary polyphagia is by far more common and usually is accompanied by clinical signs of the underlying disease. Determining whether weight gain or loss has occurred should be the first step in formulating a list of differential diagnoses and a diagnostic plan.

34.1 PHYSIOLOGY

Food intake is controlled by a variety of factors, including gastrointestinal, environmental, and CNS phenomena. The CNS, mainly the hypothalamus, controls eating behavior. The lateral hypothalamic nuclei represent the "feeding center"; their stimulation causes an animal to eat, and their destruction results in severe, fatal anorexia. Conversely, the ventromedial nuclei are the "satiety center," because their stimulation causes a refusal to eat even highly appetizing food, and their ablation leads to polyphagia and obesity. The feeding center is constantly active unless inhibited by the satiety center (e.g., postprandially). Lesions of the amygdala or paraventricular nuclei also can increase feeding behavior.

Gastrointestinal components that affect feeding include gastric distention, the rate of gastric emptying, the release of gastric hormones, and absorption of nutrients, such as fatty acids, glucose, and amino acids. The gut hormones can act locally on the gastrointestinal tract and centrally on the CNS. Insulin, glucagon, and cholecystokinin secreted in response to a meal decrease feeding signals from the CNS. Leptin, a polypeptide released from adipose tissue, may also help to create a sense of satiety. Decreased serum concentrations of glucose, amino acids, or lipid metabolites cause hunger by stimulating neural centers so as to re-establish normal levels. Feeding behavior also can be incited by increased nutrient utilization (i.e., an elevated metabolic rate).

Normal control of feeding, therefore, is complex and works to maintain energy stores and body weight through an interplay of central and peripheral inputs. Pathologic conditions that affect the CNS can increase feeding behavior even in the presence of normal energy stores *(primary polyphagia)*. *Secondary polyphagia* exists when feeding behavior is stimulated by non-neural factors and can be caused by an increased metabolic rate or decreased nutrient supply (Box 34-1). An augmented metabolic rate can be physiologic (e.g., pregnancy) or pathologic (e.g., hyperthyroidism) in origin. Diabetes mellitus is an unusual case of decreased nutrient supply. Due to an inability to respond to or a lack of insulin, the body does not recognize glucose and reacts to a perceived hypoglycemia. Certain diseases (e.g., hyperadrenocorticism and liver disease) lead to polyphagia by unknown mechanisms. Secondary polyphagia can also be caused by certain drugs.

34.2 HISTORY

Any change in body weight is an important differentiating feature of the various causes of polyphagia (Figure 34-1). Primary or drug-induced polyphagia typically results in weight gain, because nutrients are adequate and feeding is inappropriately increased. Pathologic secondary polyphagia is more commonly associated with weight loss, because the nutrient supply usually does not meet physiologic demands. However, some causes, such as acromegaly, hypoglycemia caused by an insulinoma, sudden acquired retinal degeneration syndrome (SARDS), and hyperadrenocorticism (HAC), lead to weight gain. Physiologic polyphagia can result in weight gain (e.g.,

pregnancy, growth) or maintenance of weight (e.g., lactation, cold environment, increased exercise). An animal with HAC or in the early stages of any of these states, however, may show no weight change.

Certain causes of polyphagia may be diagnosed on the basis of the history. The possibility of exposure to a cold environment, increased exercise and, for intact females, pregnancy and lactation should be ascertained. Polyphagia is commonly associated with anticonvulsant and glucocorticoid therapy but has been observed with other medications as well (see Table 34-1). Psychogenic polyphagia has been noted after introduction of a more palatable diet or in response to a stressful event, most commonly introduction of a new pet into the household. Feeding of a low-calorie diet may also be diagnosed on the basis of a complete dietary history.

An animal with primary polyphagia caused by destruction of the satiety center may have a history of trauma or clinical signs associated with CNS disease. Depending on the extent of a hypothalamic lesion, upper motor neuron signs may be seen in all four limbs or unilaterally. A midbrain lesion often leads to incessant pacing, circling, and blindness; polyuria/polydipsia may also be present. Disorders caused by diffuse or multifocal CNS disease will have other clinical signs as well, depending on the areas affected.

Perturbation of hypothalamic control of the pituitary can lead to reproductive, thyroidal, and adrenal hypofunction and associated clinical signs. Hypothyroidism secondary to pituitary dysfunction is clinically identical to primary thyroidal failure. If adrenal insufficiency occurs secondary to a lack of adrenocorticotropic hormone (ACTH), vague, nonspecific signs of lethargy and gastrointestinal disease usually are seen. Serum electrolyte concentrations (e.g., sodium and potassium) are normal because aldosterone secretion is not affected by pituitary disease. This type of hypoadrenocorticism is referred to as *atypical*.

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Historical findings associated with secondary polypha-gia can be highly varied. Animals with diabetes mellitus, acromegaly, HAC, SARDS, and hyperthyroidism usually are polyuric and polydipsic. Feline acromegaly is seen in middle-aged to older males, and naturally occurring canine acromegaly is seen almost exclusively in intact bitches. In dogs of either sex, progestin administration can lead to acromegaly, and use of this medication should be historically evident. Owners may note inspiratory stridor or a change in body conformation, such as increased interdental spaces, skin folds, or head size in acromegalic animals. It should also be noted that progestin administration to dogs and cats can increase appetite without causing acromegaly. A multitude of historical details can be associated with HAC, including abdominal enlargement, persistent panting, failure to regrow hair after clipping, lethargy, and muscle weakness. Animals with SARDS typically have the presenting complaint of sudden-onset blindness. Hyperthyroidism commonly leads to increased activity but can be associated with depression and lethargy. Gastrointestinal signs (e.g., vomiting and diarrhea) may also be present.

34.2.1

Box • 34-1 Differential Diagnoses of Polyphagia

34.2.1.1

Primary Polyphagia

Destruction of satiety center

- Trauma
- Mass lesion (e.g., neoplasia)
- Infection

Psychogenic causes

- Stress
- Introduction of a more palatable diet

34.2.1.2 Drug-Induced Polyphagia

Glucocorticoids

Anticonvulsants

Antihistamines

Progestins

Benzodiazepines

Amitraz

Cyproheptadine

34.2.1.3 Reported Specific Disorders Associatedwith Polyphagia

Feline infectious peritonitis

Lymphocytic cholangitis (feline)

Spongiform encephalopathy (feline)

Foreign body encephalitis (feline)

34.2.1.4 Secondary Polyphagia

Physiologic increase in metabolic rate

- Cold temperature
- Lactation
- Pregnancy
- Growth
- Increased exercise

- Pathologic increase in metabolic rate
  - Hyperthyroidism
  - Acromegaly
- Decreased energy supply
  - Diabetes mellitus
  - Malassimilation syndromes
    - Pancreatic exocrine insufficiency
    - Infiltrative bowel disease
    - Parasites
    - Lymphangiectasia
  - Decreased intake
    - Megaesophagus (congenital)
    - Low-calorie diet
    - Hypoglycemia
  - Unknown
    - Hyperadrenocorticism
    - Portasystemic shunt/hepatoencephalopathy
    - Sudden acquired retinal degeneration (SARDS)

Hypoglycemia has a number of causes. Of these, insulinoma is the most likely to lead to polyphagia, but other neoplasias and insulin overdose may also do so. Hypoglycemic patients may exhibit weakness, trembling, ataxia, disorientation and, possibly, grand mal seizures. Malassimilation can be caused by a number of problems such as pancreatic exocrine insufficiency (PEI), infiltrative bowel disease, parasites, and lymphangiectasia. Malassimilation syndromes and PEI generally cause large-volume, malodorous, soft stools. PEI is more common in younger dogs (i.e., those less than 2 years of age), and the German shepherd breed shows a predisposition for this disorder. In older dogs and cats, PEI is rare but, if seen, is most commonly associated with chronic pancreatitis. The category of infiltrative disease encompasses processes such as inflammatory bowel disease, neoplasia, and infections such as histoplasmosis. Historical details vary according to the underlying disease.

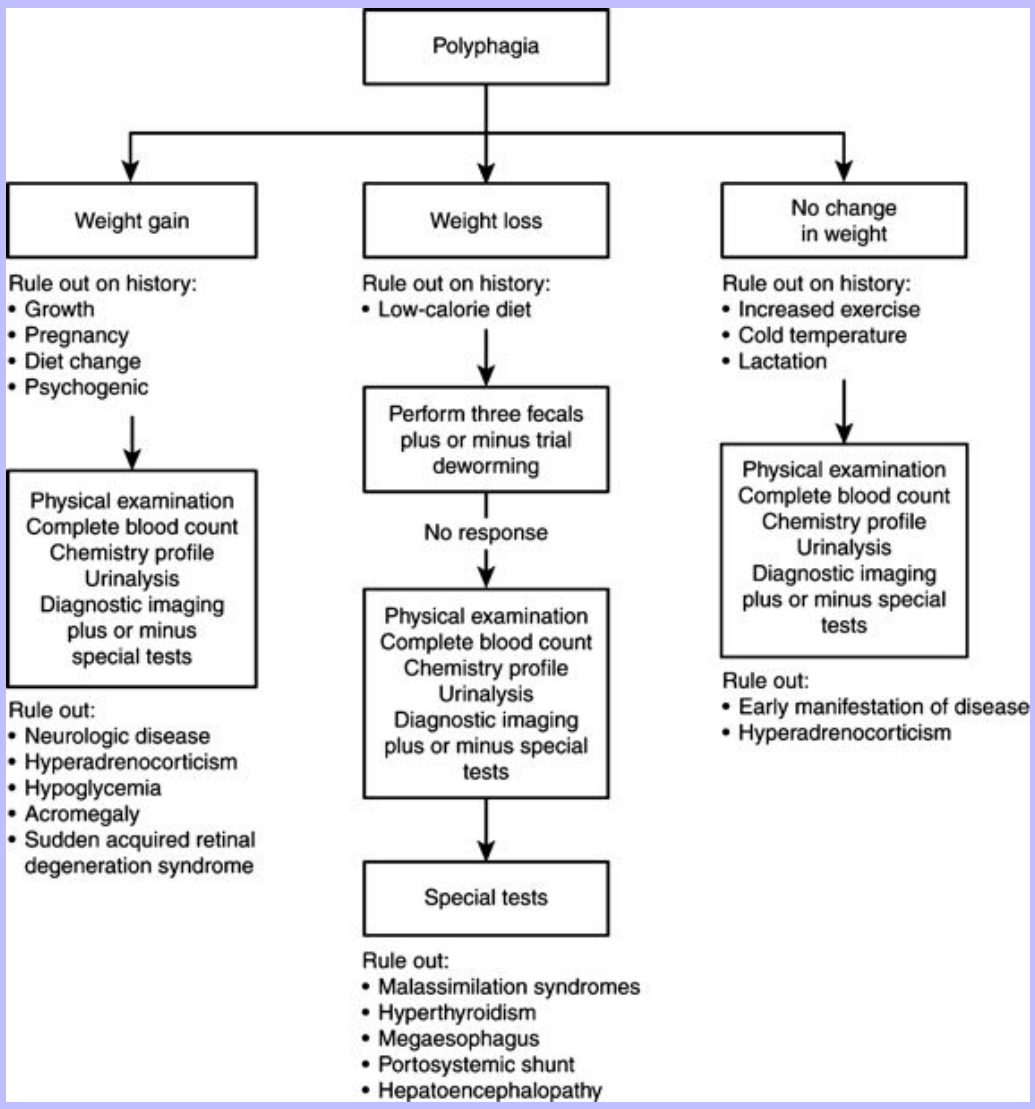
Acquired esophageal disease often leads to anorexia, but animals with congenital megaesophagus may be polyphagic and typically have a history of regurgitation. Although anorexia is more common in animals with a portacaval shunt, polyphagia has been reported in approximately 10% of cases. Depression, vomiting, weight loss, polydipsia, and neurologic signs may also be noted. Polyphagia has been reported rarely in cases of hepatoencephalopathy; other clinical findings are the result of hepatic failure and may be similar to those in an animal with a portasystemic shunt.

34.3 PHYSICAL EXAMINATION

Physical examination findings in polyphagic animals vary, depending on the underlying disease. With primary polyphagia, neurologic abnormalities such as ataxia and proprioceptive deficits may be present. A complete neurologic and fundic examination should be performed. With acute causes of central blindness, however, the fundus appears normal.

If unclear from the history, pregnancy potentially can be diagnosed by abdominal palpation and lactation by inspection of the mammae. Approximately 80% of cats with hyperthyroidism have a palpable thyroid nodule, and approximately 50% have tachycardia or a gallop rhythm. Hyperthyroidism is rare in dogs, and a cervical mass usually is palpable. Hyperadrenocorticism can have a variety of physical examination findings, including abdominal and hepatic enlargement, muscle wasting, bilaterally symmetric alopecia, cutaneous hyperpigmentation, areas of poor hair regrowth or calcinosis cutis. Even when not noted by an owner, the physical changes associated with acromegaly can be documented on physi-cal examination; a degenerative polyarthropathy may alsobe present.

Figure 34-1 Algorithm for diagnostic approach to polyphagia.



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Examination findings in a dog with SARDS may be unremarkable, because in the early stages of the disease, the retinas appear normal on fundic examination. Dogs or cats with PEI, an insulinoma, megaesophagus, hepatoencephalopathy, a portasystemic shunt, or a malassimilation syndrome may have no abnormal physical findings other than the associated weight change. In rare cases, polyneuropathies may accompany an insulinoma. Aspiration pneumonia may be presentin animals with megaesophagus. Neurologic abnormalities may be detected in an animal with a portasystemic shunt, and ascites is noted in approximately 20% of afflicted dogs. Neurologic findings associated with hepatoencephalopathy may be episodic, and other examination findings vary with the cause of liver disease. Depending on the cause of malassimilation, the intestines may feel thickened. Lymphangiectasia may lead to ascites.

Occasionally, polyphagia may be a clinical sign of a disease with which it is not usually associated. For example, one cat with feline infectious peritonitis (FIP), one with foreign body encephalitis, and one with spongiform encephalopathy have been reported as being polyphagic, as have 18 cats in Great Britain with lymphocytic cholangitis. Other historical and clinical signs are present depending on the cause.

34.4 DIAGNOSTIC PLAN

The first step in diagnosis is to ascertain what change has occurred, if any, in the animal's weight (see Figure 34-1). After as many differential diagnoses as possible have been ruled out on the basis of the history, further testing is warranted. In all cases a minimum data base (MDB), including a serum biochemistry profile, complete blood count (CBC), and urinalysis, should be submitted.

For dogs and cats with weight gain, pregnancy must be ruled out. To diagnose primary polyphagia, a complete neurologic examination should be performed, any abnormalities localized, and appropriate tests obtained. A cerebrospinal fluid analysis or diagnostic imaging, such as radiography, computed tomography (CT), or magnetic resonance imaging (MRI), may be necessary.

Hypoglycemia caused by an insulinoma usually can be diagnosed by measuring paired blood glucose and insulin serum concentrations when the animal is hypoglycemic. Rarely, provocative testing may be required (see Chapter 240). The diagnosis of SARDS can be made on the basis of appropriate history, physical examination findings, an MDB that rules out other causes and, if necessary, an electroretinogram (ERG). Although certain changes in the MDB are typical of hyperadrenocorticism, they do not confirm the diagnosis and further adrenal testing must be performed; an ACTH stimulation test or low-dose dexamethasone suppression test should be performed to confirm the diagnosis (see Chapter 242). Diagnosis of acromegaly can be difficult because of the lack of a commercial assay for growth hormone, but measurement of insulin-like growth factor-I (IGF-I) may be helpful (see Chapter 235). The history, together with conformational changes, can provide evidence of the underlying disease. Acromegalic cats consistently have insulin-resistant diabetes mellitus, and imaging of the pituitary may reveal a tumor.

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If weight loss is associated with polyphagia, the MDB should be preceded by three fecal examinations. If the results of these are negative, the MDB does not provide the diagnosis, and the animal is stable, trial therapy with antiparasiticides may be warranted. If deworming does not resolve the problem, additional tests must be done. Hyperthyroidism often can be diagnosed on the basis of a single serum thyroxine measurement; however, other tests, such as measurement of the free thyroxine concentration by equilibrium dialysis, may be required (see Chapter 238).

Malassimilation syndromes cover myriad differential diagnoses (see Table 34-1). Protein-losing enteropathies can be associated with hypoalbuminemia and hypoglobulinemia. Depending on the suspected cause, measurement of serum folate or cobalamin, assessment of fat absorption, abdominal radiography or ultrasonography, and/or biopsy either by endoscopy or exploratory surgery may also be considerations. For verification of PEI, serum trypsin-like immunoreactivity (TLI) should be determined. Thoracic radiographs with a positive contrast esophagram should be used to diagnose megaesophagus; this imaging may also aid in the determination of the cause. Determination of preprandial and postprandial serum bile acid concentrations can document hepatic dysfunction, but a biopsy may be required to document the cause of hepatic failure. Ultrasonography or a radionuclide scan may be used to identify a portacaval shunt.

If the disease is in the early stages, weight change may not yet have occurred, and the list of differentials may be difficult to narrow. However, a good history and physical examination combined with an MDB can eliminate

many possibilities. Although animals with HAC may not have a weight change, abdominal enlargement may create the impression of weight gain. All diseases suspected as possible differential diagnoses in this situation should be diagnosed as discussed above.

34.5 MANAGEMENT

The management of polyphagia depends on the cause. Physiologic causes of polyphagia are transient. If the condition is drug induced, the polyphagia may be temporary, as is usually seen with anticonvulsants. Psychogenic polyphagia may be corrected by removing the instigating element, if possible, or by behavioral therapy (e.g., paying more attention to the animal). If the polyphagia persists with ongoing drug therapy or if the inciting agent (stress or medication) cannot be removed, food intake should be limited to that necessary to satisfy caloric requirements. Low-calorie, high-fiber foods, such as carrots, can be added to the diet to assuage hunger and prevent obesity. Polyphagia caused by dietary factors can be managed as needed. In cases of SARDS, the poly-phagia usually is self-limiting. For all other conditions, appropriate therapy should be initiated to resolve the underlying disease.

35 CHAPTER • 35 Ptyalism

Sandra Manfra Marretta

***P**tyalism* is the excessive production and secretion of saliva. *Pseudoptyalism* is the drooling or dribbling of saliva because of an inability or reluctance to swallow, which results in an overflow of saliva from the oral cavity.

35.1 PATHOPHYSIOLOGY

Saliva is continuously produced by the salivary glands. The production of saliva may be increased by excitation of the salivary nuclei, located in the brain stem, after taste and tactile stimuli are received from the tongue and other areas in the oral cavity. Higher centers in the central nervous system (CNS) may also have an excitatory or inhibitory affect on the salivary nuclei. Increased production of saliva is a normal physiologic occurrence associated with imminent feeding, hyperthermia, and purring in cats.

Oral lesions and central nervous system disorders may stimulate an increase in the production of saliva. Diseases of the pharynx, esophagus, and stomach also may stimulate the production of excessive amounts of saliva. In some cases this excess may be clinically evident not as drooling but as frequent episodes of swallowing.

Anatomic abnormalities of the oral cavity may cause saliva to drip from the mouth even when normal amounts of saliva are produced. Drooling is evident with diseases in which the animal is unable or reluctant to swallow because of pain associated with swallowing.

35.2 HISTORICAL FINDINGS AND THEIR MEANINGS

35.2.1 Age and Breed

Young animals with congenital anomalies, including porto-systemic shunt and megaesophagus, may hypersalivate. Jaw abnormalities, such as severe retrognathism, may cause excessive drooling. In some giant breed dogs, the shape and size of the lower lip may predispose to drooling. Young animals are more indiscriminant in their eating habits, which results in a higher incidence of ingestion of foreign bodies, constipation, consumption of caustic materials, and biting on electrical cords.

35.2.2 Diet

High-protein diets can precipitate excessive salivation in animals with a portosystemic shunt. Animals with painful oral lesions may refuse to eat hard food, preferring bland, soft diets.

35.2.3 Eating Behavior

If ptyalism is caused by oral pain, the animal may drop food when attempting to eat or chew on one side.

35.2.4 Anorexia and Weight Loss

When anorexia and severe weight loss accompany ptyalism, the potential for acute or chronic oral lesions, systemic diseases, and gastrointestinal disorders should be considered.

35.2.5 Drugs and Toxins

Various drugs and toxins can cause adverse reactions, including hypersalivation, in animals. Unpleasant-tasting drugs may cause excessive salivation. Administration of higher than normal therapeutic levels of organophosphates may cause cholinergic signs including ptyalism. Overdoses of other drugs that may cause hypersalivation include: pyrethrin and pyrethroid insecticides, D-limonene (citrus oil insecticide), ivermectin, fluids containing a benzoic acid derivative, caffeine, amphetamines, cocaine, and opiates. Toxins that irritate the oral cavity include thallium, metaldehyde, and cresol. The secretions of various toads and newts and the venom of black widow spiders can cause ptyalism. Plants, including *Amanita* mushrooms, nettles, dumb cane, philodendron, dieffenbachia, poinsettia, and Christmas trees, can cause increased salivation. Household cleaning products can irritate the oral mucosa, resulting in hypersalivation.

35.2.6 Anesthesia

A potential complication of anesthesia is reflux esophagitis. Clinical signs, including hypersalivation and regurgitation, may develop 1 to 4 days after anesthetic episodes.

35.2.7 Swallowing Difficulty

Evaluation of dysphagia as a potential cause of excessive drooling can be supported by observing the dog or cat eating and drinking. Pharyngeal lesions, neuromuscular disease, and abnormally large retropharyngeal lymph nodes can cause dysphagia.

35.2.8 Regurgition

Excessive salivation may occur in animals that regurgitatesecondary to esophageal disease. In cases of chronic reflux esophagitis, hypersalivation, regurgitation, and vomiting often occur soon after eating. Regurgitation and hypersalivation may also be seen in animals with esophageal foreign bodies or tumors.

35.2.9 Vomiting

Nausea is the first stage in the complex process of vomiting, which may be accompanied by hypersalivation and frequent episodes of swallowing.

35.2.10 Behavioral Changes

Animals with oral pain may show behavioral changes, including depression and/or aggressiveness. These changes may also be associated with hepatic encephalopathy and rabies.

35.2.11 Hepatic Encephalopathy Signs

Animals with CNS signs, behavioral changes, and signs of hepatic failure including anorexia, weight loss, lethargy, polydipsia, polyuria, nausea, ptyalism, vomiting, and diarrhea should be evaluated for hepatic encephalopathy.

35.2.12 Seizures

During a seizure, ptyalism may occur secondary to autonomic discharge, reduced swallowing of saliva, and clonic movements of the jaw.

35.3 PHYSICAL FINDINGS AND THEIR INTERPRETATION

35.3.1 Halitosis

Halitosis usually is associated with oral pathology, including periodontal disease, oral ulcers, cheilitis, stomatitis, or neoplasia. Esophageal and gastric disorders less frequently may cause halitosis.

35.3.2 Oral Cavity

35.3.2.1 Oral Trauma

Animals that are drooling after a traumatic event should be carefully evaluated for oral trauma. Fractured teeth, with pulpal exposure or jaw fractures, cause significant pain and may result in secondary hypersalivation. With bilateral mandibular fractures, the rostral mandible drops and excessive drooling occurs.

35.3.2.2 Periodontal Disease

Severe periodontal disease may cause significant gingival and oral mucosal inflammation. Severe contact ulcerations may occur on the mucosa in contact with the teeth, causing extreme oral pain and ptyalism.

35.3.2.3 Stomatitis

Stomatitis, which frequently is associated with ptyalism, has many underlying causes, including local factors, immune-mediated diseases, systemic infections, toxins, and immunologic or nutritional deficiencies.

35.3.2.4 Oral Masses

Neoplasms, eosinophilic granulomas, and granulomatous lesions may occur in the oral cavity. Ulcerated masses may be painful and cause ptyalism. Caudal oral masses or those that interfere with tongue movement may cause difficulty with swallowing, resulting in excessive drooling.

35.3.2.5 Glossitis

Lingual ulcers often are painful and may result in hypersalivation. Irritation of the tongue may be caused by chemical or environmental substances, viral infections, metabolic disorders (uremia), immune-mediated diseases, and tumors.

35.3.2.6 Base of the Tongue

The base of the tongue should be examined thoroughly, with the animal under sedation if necessary, to rule out the presence of a mass or foreign body. Linear foreign bodies may be trapped around the base of the tongue, and penetrating foreign bodies may cause severe inflammatory responses and pain, resulting in hypersalivation.

35.3.2.7 Faucitis

Severe inflammation and ulceration of the glossopalatine arch occurs primarily in cats. Severe faucitis is painful, and affected cats exhibit severe discomfort when the mouth is fully opened.

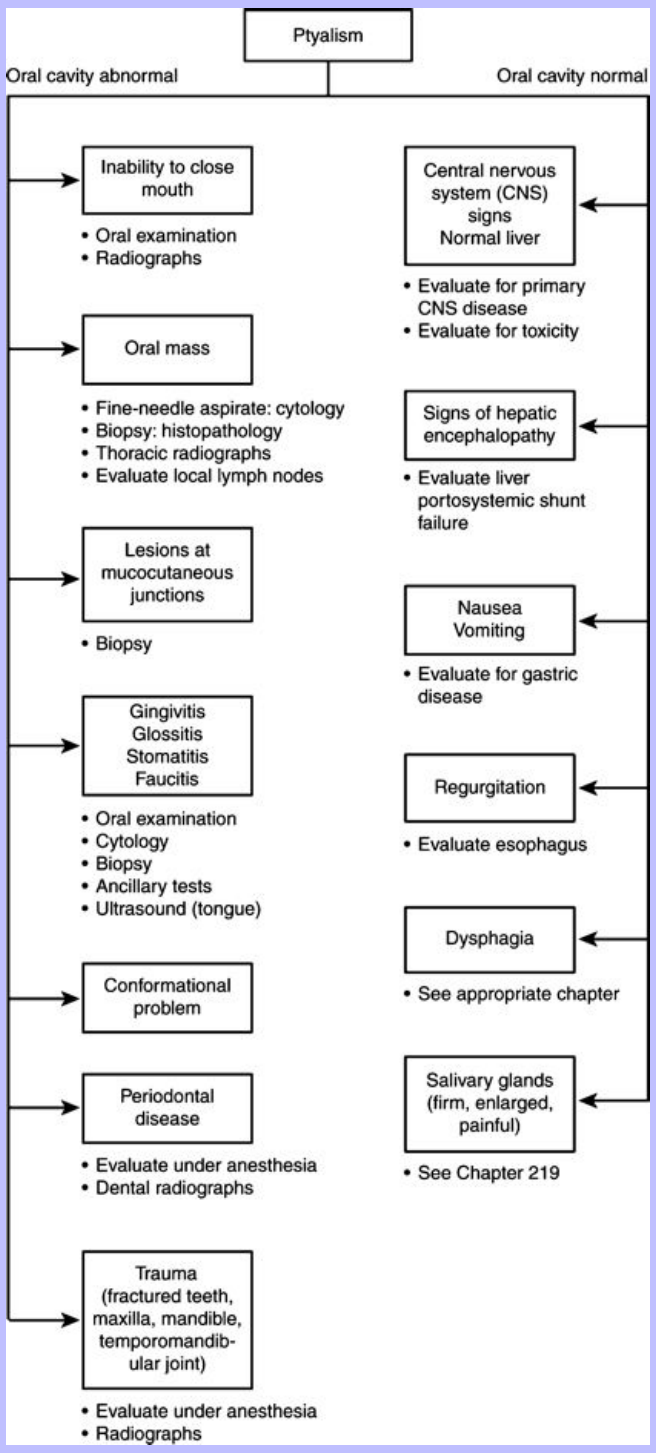
35.3.3 Blood-Tinged Saliva

Blood-tinged saliva most frequently is indicative of bleeding from the oral cavity. Less frequently, it may be associated with bleeding from the upper intestinal tract, nasal passages, or lungs.

35.3.4 Mucocutaneous Junction Ulcerations

When ulcerative stomatitis is associated with ulcerations at the mucocutaneous junctions, the possibility of an immune-mediated disease should be considered.

Figure 35-1 Algorithm for differential diagnosis of ptyalism.



35.3.5 Facial Pain

Ptyalism may occur secondary to pain associated with oralor pharyngeal disease, and these patients may resist oralexamination.

35.3.6 Dysphagia

Space-occupying lesions and severe inflammatory lesions in the pharyngeal region may cause dysphagia and excessive drooling.

35.3.7 Cranial Nerve Deficits

Lesions of the trigeminal nerve (cranial nerve [CN] V) can cause drooling secondary to an inability to close the mouth. Facial nerve palsy (CN VII) may cause drooling from the affected side because of inability to move the lip. Glossopharyngeal (CN IX), vagus (CN X), and hypoglossal (CN XII) nerve lesions can cause loss of the gag reflex or inability to swallow and secondary drooling.

35.3.8 Dropped Jaw

Trigeminal nerve (CN V) paralysis prevents voluntary closure of the mouth. The differential diagnoses in these cases include idiopathic trigeminal neuritis, bilateral mandibular fractures, and infectious diseases, such as rabies.

35.3.9 Inability to Close Mouth with Assistance

Animals with acute sustained inability to close the mouth, even with assistance, will hypersalivate. Foreign bodies or displaced teeth may interfere with normal occlusion and closure of the mouth. Displacement of the coronoid process lateral to the zygomatic arch or temporomandibular luxations may resultin intermittent or sustained locking of the jaw in an openposition.

35.3.10 Muscle Atrophy

Muscle atrophy may occur secondary to cranial nerve deficits or muscular disorders, such as myositis, that may result in difficulty swallowing.

35.3.11 Lymph Nodes

Retropharyngeal lymph node enlargement or regional lymphadenopathy may cause dysphagia.

35.3.12 Salivary Glands

Ptyalism rarely may be associated with salivary gland enlargement or necrosis.

35.4 DIAGNOSTIC PLAN

A systematic approach is required for diagnosing the underlying cause of ptyalism in animals. The initial plan in all dogs and cats should include a thorough history and physical examination, followed by appropriate diagnostic procedures based on the history and physical findings (Figure 35-1).

36 CHAPTER • 36 Gagging

William Gengler

***G**agging* is defined as the swallowing-vomiting reflex activity of the elevation of the soft palate followed by a reverse peristalsis of the upper digestive tract. *Swallowing* is the taking in of a substance through the mouth and the pharynx and into the esophagus. It is a combination of a voluntary act and a series of reflex actions. Once begun, the process operates automatically. The swallowing reflex is a rigidly ordered sequence of events that propels food from the mouth to the stomach while concurrently inhibiting breathing and preventing food from entering the trachea.

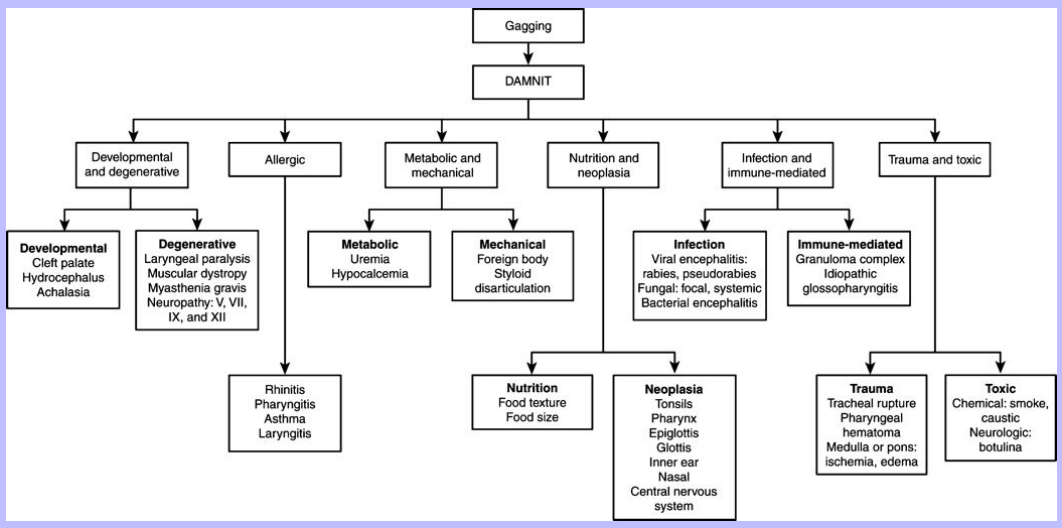
The nerves involved with swallowing are the sensory and motor branches of the trigeminal nerve (CN V), the hypoglossal nerve (CN XII), the facial nerve (CN VII), and the glossopharyngeal nerve (CN IX). The afferent limb of the swallowing reflex begins with tactile receptors, most notably those near the opening of the pharynx. Sensory impulses from these receptors are transmitted to certain areas in the medulla. The central integrating areas for swallowing lie in the medulla and lower pons, called the *swallowing center*. Motor impulses travel from the swallowing center to the musculature of the pharynx and upper esophagus via various cranial nerves.

The process of swallowing, called *deglutition,* can be divided into three phases in the dog and cat (and also in human beings): (1) the oral (or voluntary) phase, (2) the pharyngeal phase, and (3) the esophageal phase (Figure 36-1). The *oral phase* is initiated by separation of a bolus of food from the mass in the mouth with the tip of the tongue. The bolus is moved in a dorsocaudal direction in the mouth by pressing first with the tip of the tongue and then with the more caudal tongue segment against the hard palate. The bolus is forced into the pharynx, where it stimulates the tactile receptors that initiate the swallowing reflex. In the cat the oral phase is much longer, marked by bolus accumulation in the valleculae.

The *pharyngeal phase* of swallowing occurs in less than 1 second. During this phase, breathing is reflexly inhibited. The soft palate is pulled dorsally and the palatopharyngeal folds move medially, preventing reflux of food into the nasopharynx. The pharyngeal passage narrows, directing the bolus caudally. Concurrently, the vocal cords move medially and the epiglottis covers the opening of the larynx, preventing food from entering the trachea. The cranial esophageal sphincter relaxes to accept the bolus. The dorsal constrictor muscles of the pharynx contract strongly to force the bolus deep into the pharynx. Peristalsis of these muscles initiates the movement of the bolus caudally through the cranial esophageal sphincter into the esophagus.

The *esophageal phase* of swallowing is partly controlled by the swallowing center. The cranial esophageal (pharyngoesophageal) sphincter, or cricopharyngeus muscle, reflexly constricts after the bolus passes caudal to the sphincter, preventing regurgitation of the bolus. A peristaltic wave, which begins just caudal to the cranial esophageal sphincter, traverses the entire esophagus in approximately 10 seconds. The initial peristaltic wave is termed *primary peristalsis* and is controlled by the swallowing center. If primary peristalsis is insufficient to clear the bolus from the esophagus, distension of the esophagus stimulates *secondary peristalsis,* which is mediated in part by the swallowing reflex and by local stretch receptors.

Figure 36-1 Algorithm for gagging.



During primary and secondary peristalsis, the caudal esophageal (gastroesophageal) sphincter relaxes to receive the bolus into the stomach. In human beings and dogs, the cranial one third of the tunica muscularis of the esophagus is composed predominantly of striated muscle, the caudal one third is composed predominantly of smooth muscle, and the middle one third is a mixture of these two muscle types. In the cat, the esophagus changes abruptly from striated to smooth muscle at the heart. Somatic nerve fibers from the vagus nerve (CN X) form motor endplates on striated muscle fibers. Visceral motor nerves are preganglionic parasympathetic fibers that innervate the smooth muscle cells.

Gagging often is associated with retching. *Retching* is an involuntary and ineffectual attempt at vomiting, and the causes of retching are similar to those that cause vomiting. Another physical sign that resembles gagging is *expectoration,* which involves clearing the airway of mucus and discharges without nausea. For cats, expectoration can be a normal means of clearing the airway of hair after grooming.

36.1 SUGGESTED READINGS

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2. CE Harvey, PP Emily: In *Small animal dentistry*. 1993, Mosby, St Louis.

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37 CHAPTER • 37 Dysphagia and Regurgitation

Emilie Fleming

Dysphagia and regurgitation are both manifestations of swallowing disorders. Close attention to the history, clinical signs, and physical examination findings can help localize the disease process responsible (Figures 37-1 and 37-2).

37.1 DYSPHAGIA

Dysphagia, defined as difficult or painful swallowing, may be due to pain during the swallowing process, mechanical obstruction of the oral cavity or pharynx, or neuromuscular dysfunction that results in weak or uncoordinated swallowing (Box 37-1). Dysphagia generally is broken down into three types: *oral dysphagia* is difficulty prehending and forming a bolus of food at the base of the tongue; *pharyngeal dysphagia* is a malfunction of the involuntary movement of a food bolus through the oropharynx; and *cricopharyngeal dysphagia* is failure of relaxation *(achalasia)* or closure of the cricopharyngeal sphincter or cricopharyngeal asynchrony (Figure 37-1).

37.1.1 Clinical Signs

Clinical signs vary depending on the location or severity of the swallowing defect. Oral dysphagia is expressed by difficulty prehending food and by modified eating behavior, such as tilting or throwing back the head while eating. With pharyngeal dysphagia, prehension of food generally is more normal, but repeated efforts to swallow often are seen, generally accompanied by flexing and extending of the neck. With cricopharyngeal dysphagia, patients make repeated efforts to swallow and may gag or cough. They also may regurgitate immediately after or during swallowing.

37.1.2 History

Very young affected animals are more likely to suffer from congenital defects. For example, cricopharyngeal achalasia generally is seen at the time of weaning from milk to solid food. Young to middle-aged animals are more prone to ingestingforeign bodies, which may become lodged in the esophagus, or caustic substances. Older dogs, or dogs with chronic signs (e.g., weight loss, reluctance to eat) have an increased likelihoodof systemic disease. Acute signs are more consistent with a mechanical obstruction, such as a foreign body, mass, or inflammation. The presence of other cranial nerve signs in conjunction with dysphagia suggests central nervous system (CNS) disease.

37.1.3 Diagnosis

A complete physical examination is essential to enable the clinician to localize the source of the dysphagia. A thorough oral examination, often requiring sedation, is important to evaluate for foreign bodies, masses, stomatitis, and tooth root abscesses. A neurologic examination, including cranial, gait, and peripheral nerves, is essential. It also is important to evaluate the patient as a whole, focusing on body condition, the presence or absence of weight loss, and interest in food. These help narrow down the list of differential diagnoses. Because rabies is a differential diagnosis, caution must be exercised in all cases with any index of suspicion for this disease.

A diagnostic plan begins with survey radiographs of the head, neck, and thorax to evaluate for foreign bodies and evidence of aspiration pneumonia. If other systemic signs are present, a complete blood count, chemistry screen, and urinalysis should be done. If warranted, contrast fluoroscopy motion study or endoscopy can be considered. Also, further blood studies may be indicated to rule out specific disease processes.

37.1.4 Treatment

Treatment of dysphagia involves identification and elimination of the underlying disorder, which may involve medical or surgical treatment. Management with tools such as feeding tubes may be necessary. Treatment of any complications, such as aspiration pneumonia, also is important.

37.2 REGURGITATION

Regurgitation is the passive retrograde expulsion of gastric or esophageal contents (Box 37-2). Regurgitation may occur immediately or minutes to hours after eating. The regurgitant may be either undigested or digested food or liquid. The first important clinical distinction is to differentiate regurgitation from vomiting. This is done by taking a detailed and careful history, by clinician observation of the patient, or by having the owner videotape the event. Regurgitation is differentiated from vomiting by the lack of forceful abdominal contractions. In addition, the regurgitant should not be yellowish green.

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Figure 37-1 Dysphagia.

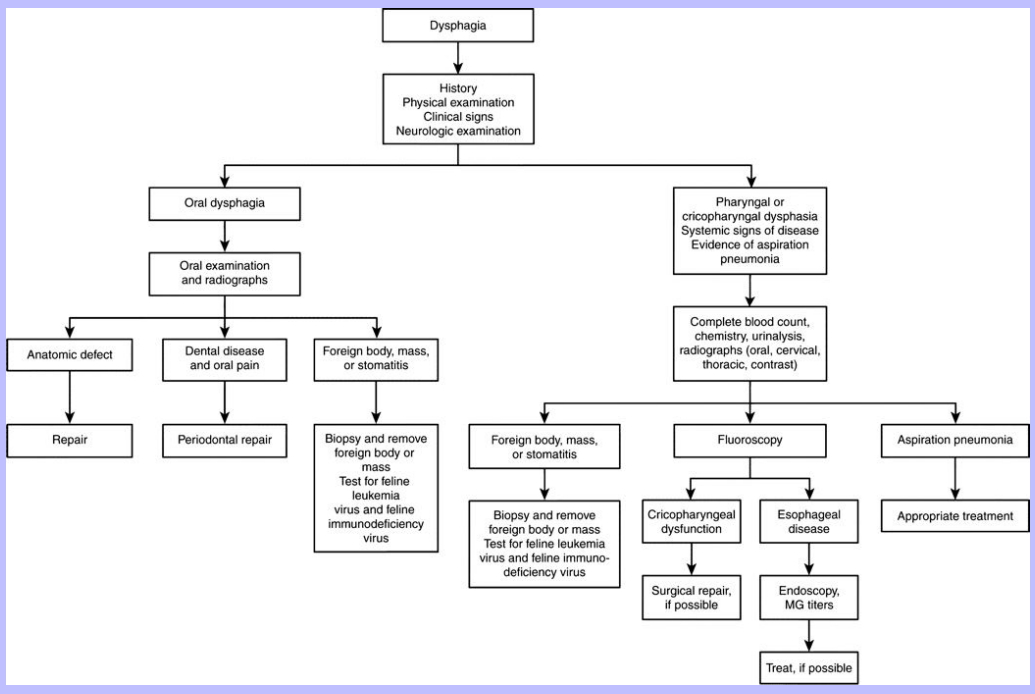
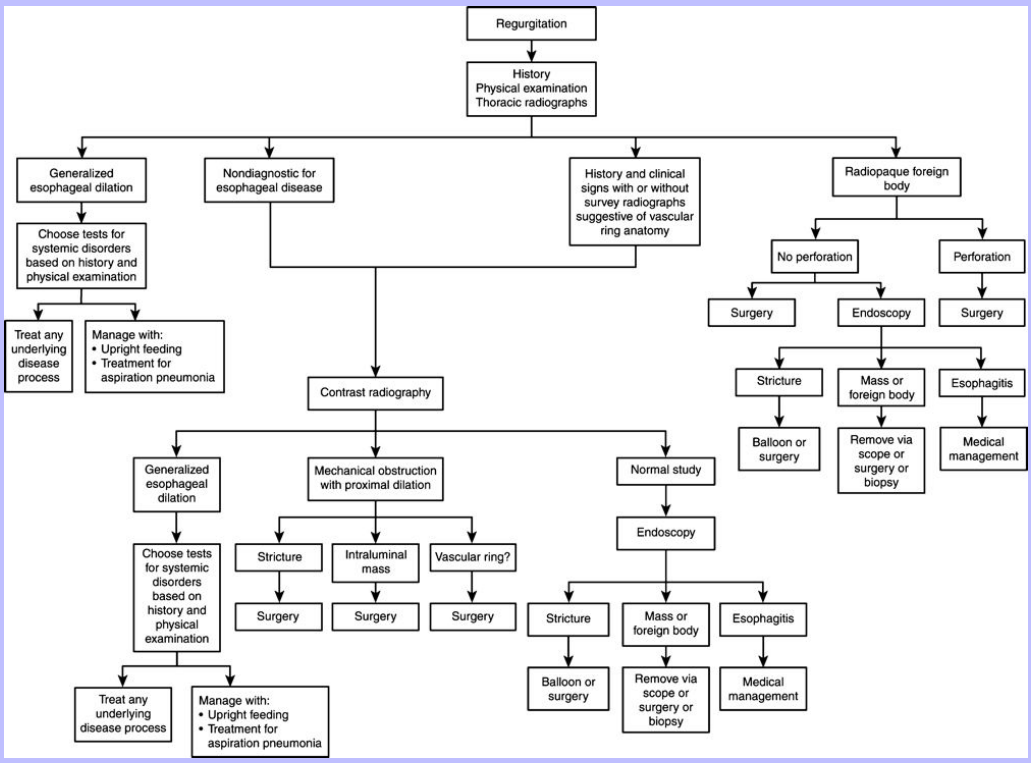


Figure 37-2 Regurgitation.



37.2.1 Box • 37-1 Causes of Regurgitation

37.2.1.1 Anatomic or Mechanical Lesions

Pharyngeal inflammation (e.g., abscess, inflammatory polyps, oral eosinophilic granulomas)

Foreign body obstruction (oral, pharyngeal, nasopharyngeal, proximal esophagus)

Neoplasia

Retropharyngeal lymphadenomegally

Sialocele

Mandibular fracture

Lingual frenulum disorder

Cricopharyngeal achalasia or asynchrony

TMJ disorder (e.g., luxation, fracture)

Cleft palate

Pharyngeal trauma

37.2.1.2 Pain

Stomatitis/glossitis/pharyngitis (FIV, FeLV, immune-mediated disease, uremic glossitis, ingestion of a caustic substance)

Tooth-related problems (tooth root abscess, fracture, periodontitis)

Trauma

Electric cord burns

Retrobulbar abscess

37.2.1.3 Neuromuscular Disorders

Myasthenia gravis (focalized or generalized)

Acute polyradiculitis

Masticatory myositis

Tick paralysis

Botulism

Polymyositis

TMJ disease

37.2.1.4 Neurologic Disorders

Rabies

Trigeminal paralysis or neuritis

Neuropathies of cranial nerves VII, IX, X, or XII

CNS disease (brain stem lesion)

37.2.2 Clinical Signs

Clinical signs may include weight loss accompanied by an increased appetite. Regurgitating animals often present with signs of aspiration pneumonia. Systemic signs of underlying disease processes that can cause regurgitation also may be noted, such as the weakness associated with myasthenia gravis.

37.2.3 Diagnosis

A complete physical examination is essential. A neuro-logic examination can help reveal a possible neuropathy or neuromuscular dysfunction. Auscultation is important to evaluate for aspiration pneumonia and other respiratory or cardiovascular abnormalities.

37.2.3.1 Box • 37-2 Causes of Regurgitation

37.2.3.1.1 Esophageal Disease

Megaesophagus (primary or secondary)

Esophagitis

Mechanical obstruction (foreign body, stricture, vascular ring anomaly)

37.2.3.1.2 Alimentary Disorders

Pyloric outflow obstruction

Gastric dilatation volvulus

Hiatal hernia

37.2.3.1.3 Neuropathies

Peripheral (polyradiculitis, giant cell axonal neuropathy, polyneuritis, lead poisoning)

Central (distemper, brain stem lesion, neoplasia, trauma)

37.2.3.1.4 Neuromuscular Junction Abnormalities

Myasthenia gravis (focalized or generalized)

Botulism

Tetanus

Acetylcholinesterase toxicity

37.2.3.1.5 Immune-Mediated Causes

Systemic lupus erythematous

Polymyositis

Dermatomyositis

37.2.3.1.6 Endocrine

Hypothyroidism

Hypoadrenocorticism

Thoracic radiographs should be examined for generalized esophageal dilatation, radiopaque foreign bodies, focal esophageal dilatation or other evidence of vascular ring anomalies, and evidence of aspiration pneumonia. Contrast radiography may be necessary for evaluation of the size and shape of the esophagus and any vascular anomalies. Endoscopy of the esophagus is useful for evaluating for foreign bodies, strictures, or esophagitis. Fluoroscopy can be used to characterize motility during swallowing.

When clinical signs suggest systemic disease or with evidence of megaesophagus, laboratory data are an important tool in ruling out underlying disorders. The initial workup includes a complete blood count, chemistry screen, and urinalysis. Depending on clinical suspicion, a thyroid hormone deter-mination, adrenocorticotropic hormone (ACTH) stimu-lation test, acetylcholine receptor antibody test, lead level determination, and antinuclear antibody (ANA) test can be considered.

37.2.4 Treatment

Treatment is aimed at any underlying disease process and at complications, such as aspiration pneumonia. Considerable effort can be put into the management of a regurgitating animal. Management of megaesophagus, for example, often includes feeding small, frequent meals from an elevated level.

38 CHAPTER • 38 Vomiting

David C. Twedt

Vomiting is a common clinical sign observed in small animals. It occurs secondary to gastrointestinal and nongastrointestinal disorders.

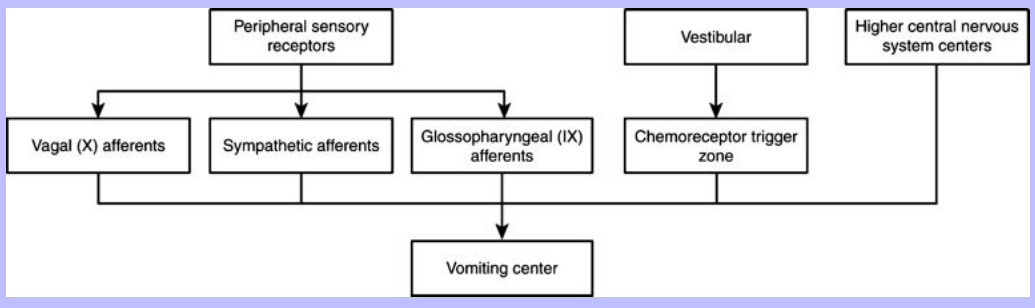
In its evolution, vomiting began as a rather primitive protective means of removing toxic or noxious ingested substances. Vomiting mechanisms then progressed to prevention of further adsorption of toxin after a toxic substance had entered the bloodstream. A mechanism that stimulates vomiting then evolved so that an animal could feed ingested food from a hunt to an offspring; this reflex is more developed and arises from higher centers in the central nervous system (CNS).

An important fact to remember is that vomiting is a clinical sign, not a disease per se. Clinically, vomiting results from a variety of disorders of the gastrointestinal system, as well as from disorders such as abdominal conditions, systemic or metabolic disease, and drug toxicity. This chapter covers basic pathophysiology, etiologies, and a practical clinical approach to evaluation of a patient with vomiting.

38.1 PATHOPHYSIOLOGY

The clinical act of vomiting is divided into three phases: nausea, retching, and vomiting. *Nausea* precedes vomiting and is associated with an episode that defies complete definition in animals. Outward signs of nausea may include depression, shivering, hiding, yawning, and licking of the lips. Increased salivation and swallowing occur; this lubricates the esophagus with bicarbonate-rich saliva that neutralizes gastric acid as it passes through the esophagus. Next, there is a reduction in gastric, lower esophageal sphincter, and esophageal motility, which is followed by increased retrograde motility of the proximal small intestine. *Retching,* the second phase of vomiting, consists of forceful contractions of the abdominal muscles and diaphragm to produce negative intrathoracic pressure and positive intra-abdominal pressure. These pressure changes are associated with movement of gastric contents into the esophagus. *Vomiting,* the third phase, occurs when the gastric contents are forcefully expelled from the mouth by the driving force generated by contraction of the abdominal muscles and diaphragm, which causes intra-thoracic pressure to change from negative during retching to positive during vomiting. As the vomit passes through the pharyngeal cavity, respiration is inhibited and the nasopharynx and glottis close to prevent aspiration.

Figure 38-1 Factors that activate the vomiting center.



Vomiting is a complex and poorly understood clinical sign that is best described as a neurologically mediated reflex act initiated by stimulation of the conceptualized *vomiting* or *emetic center* in the medulla oblongata of the brain. Activation of the vomiting center occurs either through a humoral pathway initiated by blood-borne substances or through activa-tion of various neural receptors and the pathways leading to the vomiting center (Figure 38-1). Adjacent to the vomiting center are areas for controlling respiration and salivation, which both are integrated into the vomiting process.

Neural stimulation of the vomiting center arises through either afferent vagal, sympathetic, vestibular, glossopharyngeal, and cerebrocortical pathways. Activation of peripheral receptors found throughout the body can stimulate these neural pathways. Particularly important are receptors located throughout the abdominal viscera. The duodenum contains the highest concentration of these receptors and hence has been referred to as the "organ of nausea." Disease or irritation of the gastrointestinal tract, other abdominal organs, or peritoneum can directly stimulate vomiting through vagal afferent pathways. Receptors found in the kidneys, uterus, and urinary bladder send afferent impulses via sympathetic nerves. Receptors located in the pharynx and tonsilar fossae transmit impulses thorough afferent fibers of the glossopharyngeal nerve. There is evidence that vagal receptors are located in the great vessels in the thorax.

CNS disease may directly stimulate the vomiting center through extension of inflammatory stimuli, hydrocephalus, or space-occupying CNS lesions. Supramedullary receptors may also influence the reactivity of the vomiting center. For example, psychogenic vomiting appears to arise from the cerebral cortex and may occur as the result of fear, stress, or pain. Cyclic vomiting in the dog has been associated with autonomic or visceral epilepsy arising from the limbic region in the CNS.

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The vomiting center may also be stimulated indirectly via humoral pathway activation of the chemoreceptor trigger zone (CRTZ) in the area postrema. The blood-brain barrieris less effective in this area, which allows the CRTZ to be exposed to chemical stimuli found in the circulation. Blood-borne substances that stimulate the CRTZ include certain drugs, uremic toxins, and electrolyte, osmolar, and acid-base disorders, as well as a number of metabolic derangements. Drugs such as apomorphine, cardiac glycosides, and bacterial toxins are examples. The cat has poorly developed CRTZ dopaminergic receptors and fails to respond adequately to apomorphine as an emetic agent. However, xylazine, an alpha$_2$-adenergic agonist, effectively stimulates the CRTZ in cats. There is evidence that vestibular stimulation passes through the CRTZ before activating the vomiting center. Motion sickness, inflammation of the labyrinth, or lesions in the cerebellum may result in vomiting via this pathway.

38.1.1

Box • 38-1 Common Causes of Vomiting

38.1.1.1

Metabolic/Endocrine Disorders

Uremia

Hypoadrenocorticism

Diabetes mellitus

Hyperthyroidism

Hepatic disease

Endotoxemia/septicemia

Hepatic encephalopathy

Electrolyte disorders

Acid-base disorders

38.1.1.2 Intoxicants

Lead

Ethylene glycol

Zinc

Strychnine

38.1.1.3 Drugs

Cardiac glycosides

Erythromycin

Chemotherapy agents

Apomorphine

Xylazine

Penicillamine

Tetracycline

Nonsteroidal antinflammatory drugs (NSAIDs)

38.1.1.4 Abdominal disorders

Pancreatitis

Peritonitis

Neoplasia

Hepatobiliary disease

38.1.1.5 Dietary Causes

Indiscretions

Intolerances

Allergy

38.1.1.6 Gastric Disorders

Gastritis

Helicobacter infection

Parasites

Ulceration

Neoplasia

Foreign bodies

Dilatation-volvulus

Hiatal hernia

Obstruction

Motility disorders

38.1.1.7 Disorders of the Small Intestine

Inflammatory bowel disease

Neoplasia

Foreign body

Intussusception

Parasites

Parvovirus

Bacterial overgrowth

38.1.1.8 Disorders of the Large Intestine

Colitis

Obstipation

Parasites

38.2 CAUSES OF VOMITING

Vomiting has a vast number of etiologies. Box 38-1 presents some of the more common causes of vomiting in small animals.

38.3 CLINICAL APPROACH

A complete history is the first step in establishing a correct diagnosis of vomiting. The signalment and history, as well as a description of the vomiting episodes, are important. It also is important to glean from the history whether the animal actually is vomiting. The veterinarian should differentiate the owners' report of vomiting from gagging, coughing, dysphagia, or regurgitation. The signalment may be helpful in that young, unvaccinated pets, for example, are more susceptible to infectious disease, such as parvovirus. Vaccination status, travel history, previous medical problems, and the medication history should be determined. Certain drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), may cause serious gastrointestinal ulceration. The clinician should also investigate the possibility of toxin or foreign body ingestion and should look for other, concurrent signs that often arise with systemic or metabolic disease. For example, polydipsia, polyuria, and weight loss are typical of vomiting associated with diabetic ketoacidosis or chronic renal failure.

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The history should then focus on the actual vomiting episodes. The duration, frequency, and relationship of the episodes to eating or drinking should be determined, and a complete physical description of the vomitus should be elicited. A dietary history, including the type of diet or recent dietary changes, is equally important, because vomiting may be associated with an adverse reaction to food. Vomiting of an undigested or a partly digested meal more than 8 to 10 hours after eating, a point at which the stomach normally would be empty, suggests a gastric outflow obstruction or gastric hypomotility. Gastric outflow obstructions can be caused by foreign bodies, mucosal hypertrophy, tumors, or polyps.

A description of the vomitus should include the volume, color, consistency, odor, and the presence or absence of bile or blood. Undigested food suggests gastric origin, whereas digested vomitus containing bile suggests an intestinal origin. Vomitus with a fecal odor suggests a low intestinal obstruction or bacterial overgrowth in the small intestine. The presence of blood in the vomitus *(hematemesis),* either as fresh, bright red blood or as digested blood with the appearance of coffee grounds, indicates gastrointestinal erosion or ulceration. Gastric ulceration is caused by metabolic conditions such as hypoadrenocorticism or uremia, by drug-induced ulceration, and by clotting abnormalities, gastritis, or neoplasia.

A complete physical examination should include careful evaluation of the mouth and oral cavity. This examination may reveal icteric membranes, uremic breath and ulceration, or the presence of a linear foreign body around the base of the tongue. The presence of a fever would suggest an infectious or inflammatory process. Bradycardia or cardiac arrhythmias in a vomiting animal may be a sign of a metabolic disturbance, such as hypoadrenocorticism. The abdomen should be carefully palpated for distention and tympany (e.g., gastric dilatation-volvulus syndrome), effusion (e.g., peritonitis), masses or organomegaly (e.g., neoplasia, intussusception, or foreign body), and pain (e.g., peritonitis, pancreatitis, or intestinal obstruction). The presence of gas-and fluid-filled intestines suggests obstruction, whereas plication of the bowel is characteristic of linear foreign body obstruction. A rectal examination provides characteristics of colonic mucosa and feces. Melena suggests upper gastrointestinal bleeding, and the presence of foreign material in the feces supports foreign body etiology. Animals that have colitis or that are severely obstipated may also vomit.

Finally, investigation of the CNS should be considered when the cause of the vomiting is not obvious. Vomiting is seen in some animals with vestibular disease (e.g., nystagmus, head tilt, and/or ataxia). Other CNS disease may be less obvious and usually requires a thorough neurologic evaluation. Occasionally dogs with intervertebral disk disease vomit because of pain or secondary intestinal ileus.

38.4 DIAGNOSTIC PLAN

Based on the history and physical examination, the animal should be classified as having either acute or chronic vomiting. The diagnostic and therapeutic approaches differ considerably based on this clinical classification (Figures 38-2 and 38-3).

If the vomiting episodes are acute and of short duration, they may be self-limiting and can be treated with symptomatic therapy. Most often, acute vomiting is associated with gastro-enteritis secondary to dietary indiscretions, and signs resolve quickly. A routine fecal examination for parasites should be performed in all animals with gastrointestinal signs to eliminate the possibility of parasitism. Investigation for environmental intoxicants is imperative. Young, unvaccinated dogs should always be evaluated for parvovirus because the disease frequently begins with vomiting prior to the onset of diarrhea. Radiographic studies may be necessary to confirm gastric dilatation-volvulus (GDV) syndrome, gastrointestinal foreign bodies, or obstructions. Severe acute vomiting or vomiting with concurrent systemic signs requires laboratory diagnostic evaluation and radiographic testing. Common systemic and metabolic diseases that can cause vomiting usually can be identified with basic diagnostic testing, beginning with a complete blood count (CBC), biochemical blood screen, urinalysis, and fecal examination.

Chronic vomiting generally is characterized as vomiting that has persisted for longer than 5 to 7 days or that has failed to respond to initial symptomatic therapy and requires in-depth investigation. In the majority of chronic vomiting cases, routine laboratory and survey radiographs either provide an etiology or direct the next step in diagnostics or therapy.

Vomiting may result in significant fluid, electrolyte, and acid-base changes. The most common electrolyte disturbance is hypokalemia. Acid-base changes generally are minimal in vomiting animals. However, if metabolic alkalosis is found to be associated with hyponatremia, hypochloremia, and hypokalemia, the cause is most likely to be frequent vomiting, gastric outflow, or a high duodenal obstruction.

When routine diagnostic testing fails to identify an obvious etiology, additional tests are required based on the appropriate clinical circumstances of the case. These tests may include viral or heartworm serology, a thyroid evaluation, adrenocortical testing, bile acid determinations, toxologic testing (e.g., lead poisoning), and a neurologic examination.

If laboratory testing fails to identify a nongastrointestinal cause of vomiting, the focus should move to investigation of gastrointestinal disease as a possible cause. The diagnostic approach includes contrast radiography, ultrasonography, endoscopy, or laparotomy. Frequently, inflammatory gastro-intestinal lesions are a cause of chronic vomiting; these conditions include gastritis, inflammatory bowel disease (IBD) of the small intestine, and colitis. The diagnosis should be confirmed with gastrointestinal biopsies. In cats with inflammatory bowel disease, vomiting often is the predominate clinical sign, with diarrhea being a minor component of the disease. Conditions such as gastric antral pyloric mucosal hypertrophy, antral polyps, foreign bodies, or neoplasia can cause gastric outflow obstruction, with gastric retention and vomiting. These gastric lesions usually are easily identified endoscopically or by contrast radiography.

Obstructive intestinal lesions, such as foreign bodies, intussusception, and neoplasia, usually require radiographic contrast studies or ultrasonography for diagnosis. The diagnosis of gastrointestinal motility disorders should be considered when clinical signs support abnormal gastric retention and a failure to identify inflammatory or obstructive gastrointestinal lesions. Specialized contrast studies that evaluate motility, or possibly a clinical response to gastrointestinal prokinetic agents, may support a diagnosis of gastric hypomotility.

In summary, vomiting is a complex clinical sign that is associated with a vast number of clinical conditions. Frequently, only through a complete and systematic approach is the cause of the vomiting identified. The veterinarian who understands the mechanisms of vomiting is able to select the appropriate diagnostics or therapy for this clinical sign.

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Figure 38-2 Algorithm for the diagnosis of acute vomiting.

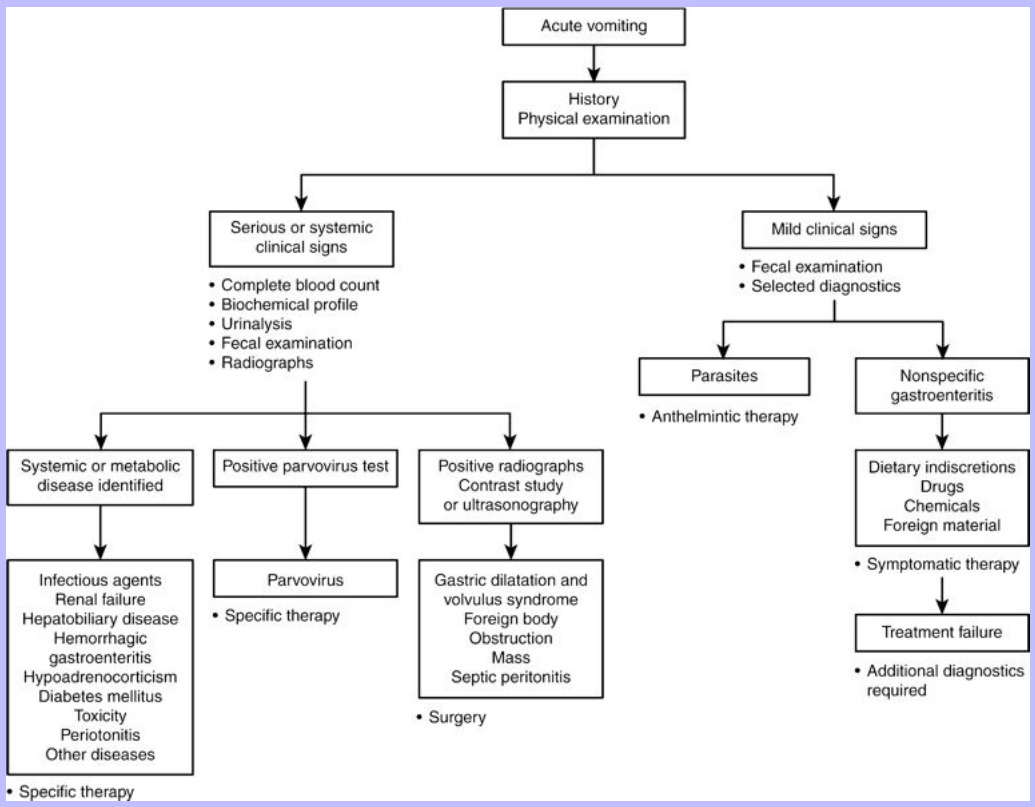
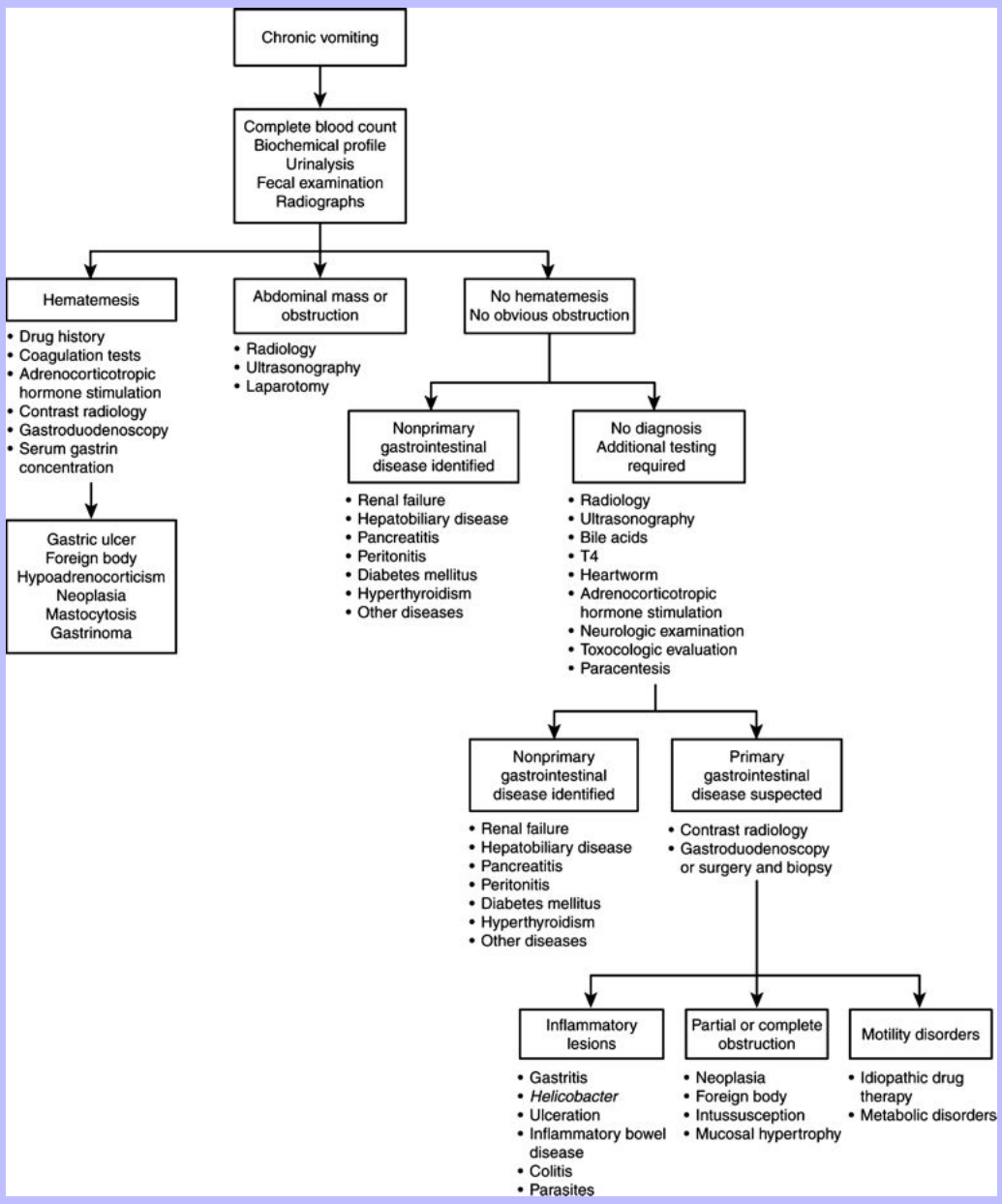


Figure 38-3 Algorithm for the diagnosis of chronic vomiting.



39 CHAPTER • 39 Diarrhea

Jörg M. Steiner

Fecal consistency depends on several factors, including diet, digestion, absorption of nutrients and water, and gastrointestinal milieu and motility. An abnormality of any one of these factors can lead to a change in fecal consistency. However, it is important to note that the compensatory reserve of the gastrointestinal tract is large, and minor changes in one or more of these factors often are compensated for by other components of the system. Only when the compensatory mechanisms are overwhelmed does diarrhea occur. Yet, diarrhea is one of the most common clinical signs seen in dogs and cats. Most cases of diarrhea consist of an isolated episode that does not appear to affect the animal systemically. These dogs and cats are rarely brought to a veterinarian. If they are, they do not pose a diagnostic or therapeutic challenge because no therapy is required, therefore any therapy used will lead to apparent treatment success.

Other cases of diarrhea are also mild, not associated with systemic clinical signs, and resolve naturally after only a few days. These animals require only a minimum amount of diagnostic testing to ensure that systemic complications are not present and in some cases to rule out specific causes, suchas infection with *Giardia sp*. Necessary therapeutic effortsare also minimal because remission ensues without treatment or with symptomatic therapy alone. Withholding food for24 to 48 hours and then introducing small amounts of an easily digestible diet usually is followed by remission of the diarrhea.

A third group of animals, mostly dogs and only rarely cats, have acute or even peracute severe disease. Although gastrointestinal disease is clearly present, the primary disease process is less of a concern than the animal's overall health status. Therefore the clinical approach to these dogs and cats is the same as for any others with a severe condition. The focus is on supportive care, aggressive monitoring for systemic complications, and early intervention against such complications. Finally, there is a large group of dogs and cats that have chronic diarrhea (arbitrarily defined as lasting for more than 3 weeks) that might benefit from a full medical workup. The following discussion pertains to this large group, which is commonly seen in veterinary practice.

39.1 CHRONIC DIARRHEA

The workup of chronic diarrhea in dogs and cats can be approached in many different ways. Differences may be due to certain diagnostic modalities that may or may not be readily available. Differences may also be due to the clinical expertise of the veterinarian. In addition, differences may be due to a particularly common problem in a geographic region. For example, fungal disease is more common in some geographic regions than in others, requiring a high degree of suspicion leading to the use of specific diagnostic tests in some areas. Finally, differences in evaluation may be due to a difference of opinion between clinicians.

The workup of a dog or cat with chronic diarrhea also needs to be guided by the severity of illness. Rapid weight loss, emaciation, systemic clinical signs, hypoalbuminemia, or acid-base and electrolyte disturbances all require an aggressive diagnostic approach. The workup and successful treatment of animals with chronic diarrhea could take anywhere from a few days to several months. It is important to establish realistic expectations early during client communication to avoid disappointment later on.

39.2 DIFFERENTIATION OF PRIMARY AND SECONDARY GASTROINTESTINAL DISEASE

As for any clinical problem, a careful history is important. It should include questions about the pet's current and past clinical history. Owners should be asked about the environment, husbandry (especially as it relates to the diet), and the clinical history of other pets in the household (see Figure 39-1).

If the history does not reveal any specific indicators for a cause of the diarrhea, a reasonable initial approach includes careful fecal examination (direct smear and zinc sulfate floatation) for evidence of parasitic infestation. This should befollowed by treatment with a broad-spectrum anthelmintic agent such as pyrantel pamoate or fenbendazole, regardless of the findings on the fecal examination. Fecal examination is warranted even though anthelmintic therapy will be used because evidence of a specific parasite may alter the choice of treatment. The yield of fecal examination and anthelmintic therapy varies, but the veterinarian should not dismiss the possibility of parasites being the cause of the diarrhea.

An important step for proper diagnosis and treatment is determining whether the diarrhea is caused by a primary gastrointestinal disease or by a disorder of another organ system. In most animals this determination can be made using the history and physical examination findings and performing a complete blood count, serum chemistry profile, and urinalysis. In cats older than 7 to 8 years of age, this minimum data base also should include measurement of a serum total thyroxine (T_4) concentration. If possible, additional serum should be collected and frozen for future analyses.

Central nervous system disease rarely causes chronic diarrhea, and in most cases these dogs and cats have severe neurologic signs that are apparent on physical examination.

Chronic diarrhea rarely occurs in dogs and cats with heart failure. Heart failure can be ruled out by lack of historical findings, such as shortness of breath, exercise intolerance, or coughing and by lack of appropriate abnormalities on physical examination, especially during thoracic auscultation.

Liver failure or portosystemic shunts can cause chronic diarrhea. Dogs and cats with liver failure should have additional clinical signs, such as anorexia, vomiting, weight loss, or even neurologic signs. These animals may have increased serum hepatic enzyme activities and serum bilirubin concentrations and/or decreased serum urea nitrogen, cholesterol, or albumin concentrations. Finally, a decreased urine specific gravity may be noted on urinalysis. Liver failure or portosystemic shunt usually can be ruled out by the minimum data base. However, if suspicion remains, other diagnostic tests, such as measurement of preprandial and postprandial bile acid concentrations, abdominal radiographs, abdominal ultrasono-graphy, or even hepatic biopsy may be necessary to definitively rule out hepatic failure.

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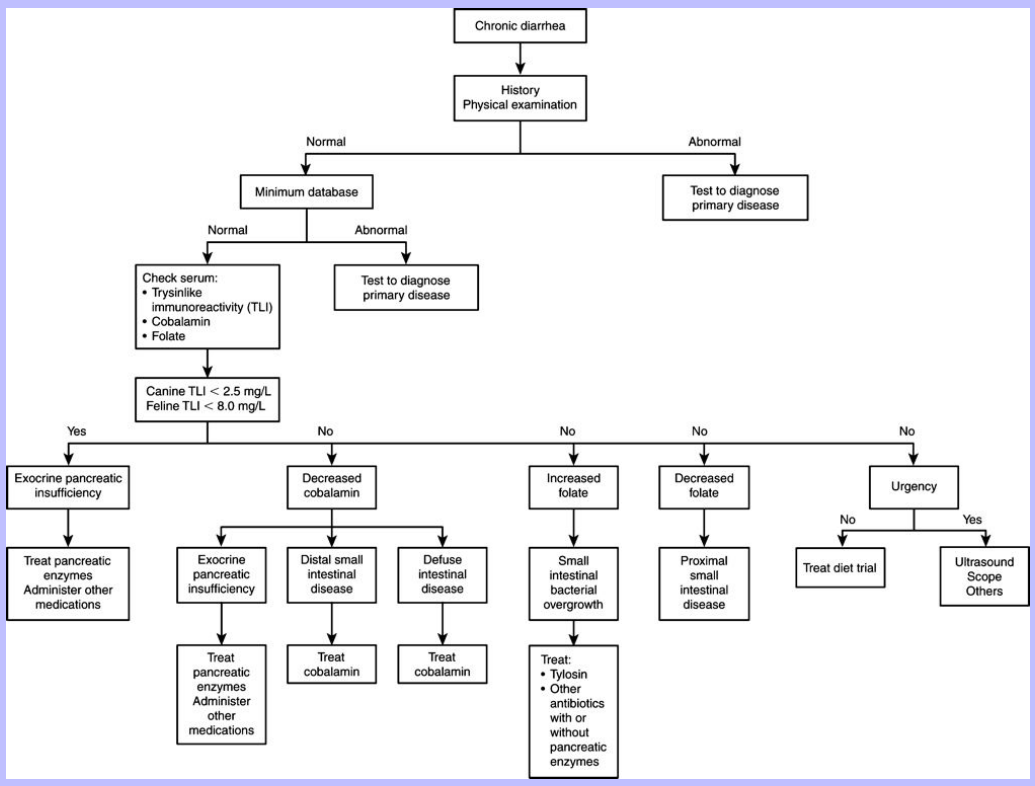
Figure 39-1 Chronic diarrhea.



Hypothyroidism may cause chronic loose stools or diarrhea. Dogs with hypothyroidism may have a history of weight gain, decreased exercise activity, or heat-seeking behavior. They may also be anemic and have an increased serum cholesterol concentration. If hypothyroidism is suspected, the total serum T_4 concentration should be measured. If the total serum T_4 concentration is decreased, it may be necessary to measure the serum free T_4 concentration (only equilibrium dialysis methods are reliable) and/or the serum thyroid-stimulating hormone (TSH) concentration to differentiate sick-euthyroid dogs from those with true hypothyroidism. If any suspicion remains, a therapeutic trial with thyroid hormone supplementation may be instituted to confirm the diagnosis.

Hyperthyroidism in cats usually is ruled in or out after careful palpation of the neck and determination of the serum total T_4 concentration. In some cats, definitive diagnosis may require repeat testing several weeks later or the use of other diagnostic tests, such as a triiodothyronine (T_3) suppression test.

Renal failure may cause chronic diarrhea in some pets. The most important parameters for ruling out renal failure arethe serum creatinine and urea nitrogen concentrations and the specific gravity on urinalysis.

Hypoadrenocorticism (Addison's disease) is another potential cause of chronic diarrhea, mainly in dogs. Dogs with Addison's disease may have waxing and waning clinical signs that include diarrhea, vomiting, and/or weakness. The serum chemistry profile for these animals may show hyperkalemia and hyponatremia. Dogs (rarely cats) with so-called atypical Addison's disease lack only glucocorticoids and thus are able to regulate the serum sodium and

potassium concentrations. The differential white cell count may provide a clue foridentifying these animals. Ill animals typically have a stress leukogram characterized by neutrophilia, lymphopenia, eosinopenia, and monocytosis. Dogs with glucocorticoid deficiency cannot respond appropriately and thus cannot develop a stress leukogram. Therefore most dogs with Addison's disease, typical or atypical, display a lack of a lymphopenia. Only a few actually show a lymphocytosis, but an elevated, high-normal, or even mid-normal lymphocyte count should raise suspicion of the possibility of hypoadrenocorticism. If the slightest degree of suspicion for hypoadrenocorticism exists, an adrenocorticotropic hormone (ACTH) stimulation test should be performed.

Finally, exocrine pancreatic disease often causes chronic diarrhea. Exocrine pancreatic insufficiency (EPI) in both dogs and cats leads to loose stools or diarrhea. Pancreatitis can also lead to chronic diarrhea but most often is accompanied by other clinical signs. However, cats with chronic pancreatitis may show only chronic diarrhea, possibly because they often have concurrent disease of the small intestine. Exocrine pancreatic disease cannot be ruled out by the history, physical examination, and minimum data base alone. The serum trypsin-like immunoreactivity (TLI) concentration is the test of choice to rule out EPI in both dogs and cats, and it should be performed if the workup has not led to a definitive diagnosis. A canine TLI less than or equal to 2.5 μg/L is diagnostic for canine EPI, and a feline TLI (fTLI) less than or equal to 8 μg/L is diagnostic for feline EPI. If chronic pancreatitis is suspected as a cause of the chronic diarrhea, a serum pancreatic lipase immunoreactivity (PLI) concentration should be evaluated.

39.3 WORKUP FOR PRIMARY GASTROINTESTINAL DISEASE

Once secondary disorders have been ruled out, the type of diarrhea should be characterized. In general, small and large bowel diarrhea can be distinguished. Animals with small bowel diarrhea have an increased fecal volume but only a mildly increased frequency of defecation. Blood, if present, is digested, causing melena. In contrast, pets with large bowel diarrhea often strain to defecate and have fresh blood and an increased amount of mucus covering the feces. Also, weight loss does not usually occur in dogs and cats with large bowel diarrhea, whereas those with small bowel diarrhea may or may not show weight loss. These differences, however, are not absolute, and most dogs and cats with clinical signs of large bowel diarrhea have diffuse disease with significant small bowel involvement. In contrast to human beings, isolated colitis is rare in dogs and uncommon in cats. Therefore, although it is useful to characterize the type of diarrhea, the clinician would be ill advised to make a definitive assessment based on the type alone.

Many animals with chronic diarrhea have a normal minimum data base or only nonspecific changes, such as a mild increase in hepatic enzyme activities. These animals should be worked up for primary gastrointestinal disease. As previously mentioned, fecal examination for parasitic infestation and therapy with a broad-spectrum anthelmintic agent should be attempted before any further steps are taken. Also, repeated testing (zinc sulfate floatations or enzyme-linked immunosorbent assay [ELISA]) should be performed to rule out giardiasis.

The serum cobalamin and folate concentrations are of great diagnostic importance and, in the case of cobalamin, also of therapeutic importance and should be measured together with the serum TLI concentration. The serum folate concentration may be decreased in disorders of the proximal small intestine, whereas the serum cobalamin concentration may be decreased in disorders of the distal small intestine and in EPI. In animals with diffuse small intestinal disorders, both the serum folate and cobalamin concentrations may be decreased. Decreases in the serum cobalamin concentration and increases in the serum folate concentration may be seen in dogs with small intestinal bacterial overgrowth (SIBO). The significance of the increased serum cobalamin concentration is unknown. Folate and cobalamin are both plentiful water-soluble vitamins in canine and feline diets. However, dietary folate is poorly absorbed, because it occurs as folate polyglutamate and needs to be deconjugated to folate monoglutamate by folate deconjugase, a brush border enzyme. Folate monoglutamate is absorbed by specific carriers in the proximal small intestine, therefore, longstanding and severe disorders of the proximal small intestine can lead to

depletion of folate body stores and ultimately to a decreased serum folate concentration. However, it should be pointed out that a severely decreased serum folate concentration does not commonly occur in either dogs or cats with chronic diarrhea. In SIBO, microorganisms in the small intestine synthesize folic acid, which can lead to an increase in folate absorption and in turn to an increased serum folate concentration.

Dietary cobalamin is tightly bound to dietary protein. In the stomach, dietary protein is partly digested by pepsin and hydrochloric acid (HCl), and cobalamin is released. However, cobalamin immediately binds to R-protein, which in turn is digested by pancreatic proteases in the small intestine. Free cobalamin binds to intrinsic factor, released mostly in pancreatic juice. These cobalamin–intrinsic factor complexes are absorbed through specific receptors in the ileum. Therefore severe and longstanding disorders of the distal small intestine, as well as exocrine pancreatic insufficiency, can lead to depletion of cobalamin body stores and ultimately to a decreased serum cobalamin concentration. Approximately half of all dogs with EPI have cobalamin deficiency, whereas almost all cats with EPI have cobalamin deficiency. Finally, microorganisms, present in excessive numbers in the small intestine in animals with SIBO utilize cobalamin and compete with the host for dietary cobalamin. A low serum cobalamin concentration combined with an increased serum folate concentration is specific for SIBO, and a therapeutic trial with an antimicrobial agent is indicated. Currently, the antibiotic agent of choice is tylosin (15 to 25 mg/kg given twice a day for 6 weeks). An increased serum folate concentration alone also is indicativeof SIBO, and a trial therapy is appropriate. In both situations dogs should respond within approximately 1 week of starting therapy. Failure to show at least a partial response within that period should stimulate further diagnostic workup.

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Serum cobalamin is of therapeutic interest. Cobalamin deficiency in human patients has been shown to cause systemic neuropathies, dementia, compromise of the immune system, and gastrointestinal changes, such as villous atrophy, inflammatory infiltrates of the intestinal mucosa, and cobalamin malabsorption. Experimental cobalamin deficiency in cats has led to similar changes, with clinical signs of weight loss, anorexia, and an unkempt haircoat. In a recent study, cobalamin deficiency was present in more than 60% of cats with chronic diarrhea. Clinical experience would further suggest that both cats and dogs with severe cobalamin deficiency often do not respond to therapy of the underlying gastrointestinal disorder until cobalamin is supplemented. Because cobalamin deficiency causes cobalamin malabsorption, oral supplementation is not efficacious in patients with cobalamin deficiency. Also, multivitamin preparations do not contain sufficient amounts of cobalamin. Furthermore, pure cobalamin is needed for therapy. Based on body size, 250 to 800 μg is given subcutaneously in dogs and 150 to 250 μg in cats. Injections should be administered once weekly for 6 weeks, every other week for 6 weeks, one more dose a month later, and a recheck a month after that. Re-evaluation is important in deciding whether further cobalamin supplementation is indicated.

For all dogs and cats that do not have secondary chronic diarrhea, parasitism, or SIBO, additional testing or a therapeutic trial may be chosen. The choice depends on many factors but ultimately on the condition of the pet and the goals of the owner. If the pet does not have any systemic clinical signs and does not deteriorate, a dietary trial is reasonable. Many animals with chronic diarrhea are suspected of having dietary intolerance or dietary hypersensitivity. Clinically, it is not feasible to differentiate between the two. Although those with dietary intolerance would benefit from an easily digestible diet, others with dietary hypersensitivity may benefit from a hypoallergenic diet. A diet with a novel protein and a novel carbohydrate source is one option for a hypoallergenic diet. Note that diets containing a novel protein and a novel carbohydrate source are not intrinsically hypoallergenic but are unlikely to elicit an allergic response in a patient that has not been previously exposed to them. Another option is to usea diet that contains hydrolyzed proteins. Dogs and cats should show some response to a dietary trial 1 to 2 weeks after initiation, but complete remission may take up to 6 to 8 weeks. Depending on the urgency of the situation, several different diets could be introduced to identify the optimal diet for a particular pet.

If a dog or cat is not stable or is quickly deteriorating, or if the owner wants to do anything possible regardless of cost or prognosis, more diagnostic tests should be performed immediately. Some clinicians prefer to do abdominal

ultrasonography first because it is not invasive. Abdominal ultrasonography can be useful for identifying neoplastic or fungal lesions or partial obstructions by foreign bodies or an intussusception, or for visualizing mesenteric lymph nodes. However, it must be pointed out that diagnostic yields differ significantly, depending on the quality of the equipment and the expertise of the ultrasonographer. Other clinicians prefer to perform a gastroduodenoscopy first, because the diagnostic yield for this procedure is usually better than that for abdominal ultrasonography. However, it is more invasive and does not allow visualization of other abdominal structures. It should alsobe pointed out that gastroduodenoscopy may appear more definitive than it is in most cases. Although a definitive answer may be found in some dogs and cats with gastrointestinallymphoma, parasitism, or fungal disease, most animals show varying degrees of lymphocytic-plasmacytic inflammation that may or may not be normal.

A special scenario is the dog or cat with panhypoproteinemia or hypoalbuminemia with or without chronic diarrhea. These animals need to be carefully screened for hepatic disease and protein-losing nephropathy (PLN). Hepatic disease should be ruled out by a serum chemistry profile and determination of preprandial and postprandial bile acid concentrations; PLN should be ruled out by determination of a urine protein/creatinine ratio. In dogs, if there is no evidence of hepatic disease or PLN, protein-losing enteropathy (PLE) can be confirmed by measuring the fecal $alpha_1$-proteinase inhibitor ($alpha_1$-PI) concentration. This test is also useful for assessing fecal protein loss in dogs that have not yet developed panhypoproteinemia. For example, soft-coated Wheaten terriers with familial PLE/PLN often have increased fecal $alpha_1$-PI before clinical signs develop.

Other diagnostic tests may be useful in specific cases. Culture of fecal material for *Salmonella spp., Clostridium spp.,* and *Yersinia spp*. may be useful for a select group of animals, mostly those immunocompromised by concurrent disease or chemotherapy or dogs with bloody diarrhea. However, indiscriminate bacterial culture of fecal material is of little diagnostic value. Measurement of serum unconjugated bile acids and breath hydrogen can be useful for supporting a diagnosis of small intestinal bacterial overgrowth in dogs. Finally, gastrointestinal permeability and mucosal function testing in dogs is extremely sensitive for altered gastrointestinal integrity and function and shows abnormalities long before histopathologic changes are apparent.

40 CHAPTER • 40 Melena and Hematochezia

Karen M. Kelly

40.1 HEMATOCHEZIA

Hematochezia is the term used to describe bright red blood on the surface of or admixed into the stool. The origin of the red blood most commonly is the anus, rectum, or descending colon.

40.1.1 Clinical Signs

It is important to take a thorough history. The owner should be asked if there is any fresh blood in the stool, mucus, straining, or difficulty defecating. It should be determined whether the pet has been given medications, has had a dietary indiscretion or a recent diet change, or has been subjected to trauma (e.g., pelvic trauma), toxin exposure (e.g., rodenticides), or stress (e.g., boarding). In addition, it should be determined whether this is a recurrent problem and if it has respondedto previous treatments. Any travel history (e.g., parasite and fungal exposure) should be noted. The veterinarian should observe the animal's demeanor and ask the owner if the animal is lethargic, has been vomiting, or has had a loss of appetite or recent weight loss. Owners often are very concerned when they see blood in the stool, but hematochezia is rarely life threatening. Animals with hematochezia rarely have any other clinical signs aside from the blood with the stool. Exceptions to this are more serious causes, such as neoplasia and hemorrhagic gastroenteritis; for these cases, the physical examination and history can reveal weight loss, shock, lethargy, cachexia, anorexia, or inappetence, along with large volumes of fresh blood. Causes of hematochezia are listed in Box 40-1.

40.1.2 Diagnostics

A physical examination and complete rectal examination should be done. A rectal examination is performed to confirm hematochezia, to obtain a stool sample for fecal examination, and to detect polyps, strictures, neoplasia, or perianal diseases (e.g., fistulas). The anal gland should be palpated and expressed to detect infection, impaction, or neoplasia. The extent of the workup should be based on the severity and duration of the problem and the physical examination findings. For example, an animal that has a normal physical examination, other than hematochezia, could be treated conservatively with a trial course of metronidazole, a broad-spectrum wormer, and a diet with a fermentable fiber. For more persistent and recurrent cases of hematochezia, a more extensive workup is indicated, such as abdominal radiographs, a complete blood count, a serum chemistry profile, colonoscopy, and abdominal ultrasonography.

40.2 MELENA

Melena is the presence of dark, tarry, often foul-smelling stools, the result of digested blood in the intestinal tract. Melena is always a more serious clinical sign then hematochezia and demands a more extensive workup. The blood can originate from the pharynx, lungs (coughed up and swallowed), esophagus, stomach, small intestine, or upper large bowel if transit time is sufficiently slow. It is the duration of the stool in the intestinal tract, not the origin, that determines the ultimate color. Blood must be present in the intestine for some time before the bacteria can break down the hemoglobin, resulting in melena. Also, a sufficient amount of blood must be present before melena can occur. It is important to note that large-volume, upper gastrointestinal bleeding can result in short transit times and can appear as fresh blood. Not all dogs with dark stools have melena.

40.2.1 Box • 40-1 Causes of Hematochezia

40.2.1.1 Anal Disease

Perianal fistulas

Anal sacculitis or abscess

Stricture

Neoplasia (e.g., anal sac tumor)

Trauma (e.g., bite wound)

Perianal hernia

Foreign body

40.2.1.2 Rectum and Colon

Proctitis (inflammation of the rectal mucosa)

Colitis

- Idiopathic
- Inflammatory bowel disease
- Stress
- Infectious
  - *Campylobacter*
  - *Clostridium perfringens*

Parvovirus

Parasitism

- Hookworms
- Whipworms

Coccidia

Roundworms

Neoplasia

Rectal polyp

Adenocarcinoma

Lymphoma

Prolapsed rectum

Mucosal trauma

Movement of foreign material (e.g., hairballs)

Iatrogenic (e.g., thermometers, enemas, fecal loops)

Automobile trauma

Ileocecocolic area: intussusception

NOTE: Constipation often can cause excessive straining, which can result in formed stools with blood on the surface.

Modified from Tams TR: Gastrointestinal symptoms. In *Handbook of small animal gastroenterology,* Philadelphia, 1996, WB Saunders.

As with hematochezia, a detailed history should be taken and a thorough physical examination performed. The clinician should ask specifically about administration of nonsteroidal anti-inflammatory drugs and corticosteriods, both of which may cause gastrointestinal bleeding, especially when used concurrently. Any potential exposure to toxins should be addressed. Spurious dark stools can be caused by salicylates, bismuth (e.g., Pepto-Bismol), charcoal, and diets high in iron. A history of coughing (may indicate swallowed blood from pulmonary disease), gagging, and regurgitation (esophageal disease), behavioral changes (hepatic encephalopathy), and polyuria and polydipsia (renal disease) should be noted. A thorough examination of the nares and oropharynx for sources of bleeding should be included. Causes of melena are listed in Box 40-2.

40.2.2 Diagnostics

A rectal examination can help confirm the presence ofmelena and at the same time allows collection of a stool sample (Figure 40-1). In-house packed cell volume and total solids testing should be done to assess for anemia, especially in shocky, debilitated animals. A fecal examination for hookworms should not be overlooked. A

complete blood count with a reticulocyte count helps differentiate regenerative from nonregenera-tive anemia. Regenerative anemia often is present after a few days except with iron-deficiency anemia, which is common with chronic gastrointestinal bleeding characterized by a hypochromic, microcytic anemia and bone marrow disease. A chemistry panel helps in the evaluation for metabolic disease, such as liver and kidney disease. If liver disease is suspected, a bile acid determination may be helpful. A coagulation profile and platelet counts also are indicated to rule out thrombocytopenia and rodenticide intoxication. Survey radiographs of the abdomen and thorax aid detection of esophageal disease, pulmonary disease and evidence of bleeding elsewhere (e.g., ascites and pleural fluid), neoplasia, foreign bodies, and trauma to the pelvic canal.

If additional tests are required to determine the cause of bleeding, abdominal ultrasonography should be preformed. Ultrasound scanning is an easy, noninvasive test that can aid the detection of lesions. If a lesion detected by ultrasound is accessible by endoscopy (e.g., a proximal mass or diffuse small intestinal thickening), biopsies should be taken and submitted. If no lesion is detectable by ultrasound, which often is the case, there are two options. The first is endoscopy with biopsies. Endoscopy is noninvasive and allows the clinician to visualize the mucosal surfaces of the proximal gastrointestinal tract while simultaneously obtaining biopsy samples. A disadvantage is that the lower gastrointestinal tract is not visualized, and a lesion could easily be missed. The second option is exploratory abdominal surgery. The advantage is full examination of the serosal surfaces of all the gastrointestinal tract, full-thickness biopsy samples, and surgical excision of identifiable bleeding lesions. The disadvantages are inability to visualize the mucosal surface and the invasiveness of the procedure. Surgery can be combined with endoscopy to allow visualization of the mucosal surface intraoperatively as an aid to locating a lesion. When the above tests and procedures fail to provide an answer, more specialized tests can be performed, such as scintigraphy using technetium-labeled red blood cells to locate the site of bleeding and arteriography to diagnose gastrointestinal blood vessel malformations.

40.2.2.1 **Box • 40-2 Causes of Melena**

40.2.2.1.1 **Ingested Blood**

Oral lesions

Nasopharyngeal lesions

Pulmonary lesions

Diet

40.2.2.1.2 **Parasitism**

Hookworms

40.2.2.1.3 **Neoplasia**

Adenocarcinoma

Lymphoma

Leiomyoma or leiomyosarcoma

Mast cell tumor

Gastrinoma

40.2.2.1.4 Coagulopathies

Disseminated intravascular coagulation (DIC)

Rodenticide intoxication

40.2.2.1.5 Drug Administration

Nonsteroidal anti-inflammatory drugs

Glucocorticoids

40.2.2.1.6 Miscellaneous

Liver failure

Pancreatitis

Renal failure

Inflammation (e.g., foreign body, acute gastritis, hemorrhagic gastroenteritis, inflammatory bowel disease)

Hypoadrenocorticism

Gastrointestinal ischemia (e.g., shock, volvulus, intussusception)

Foreign bodies

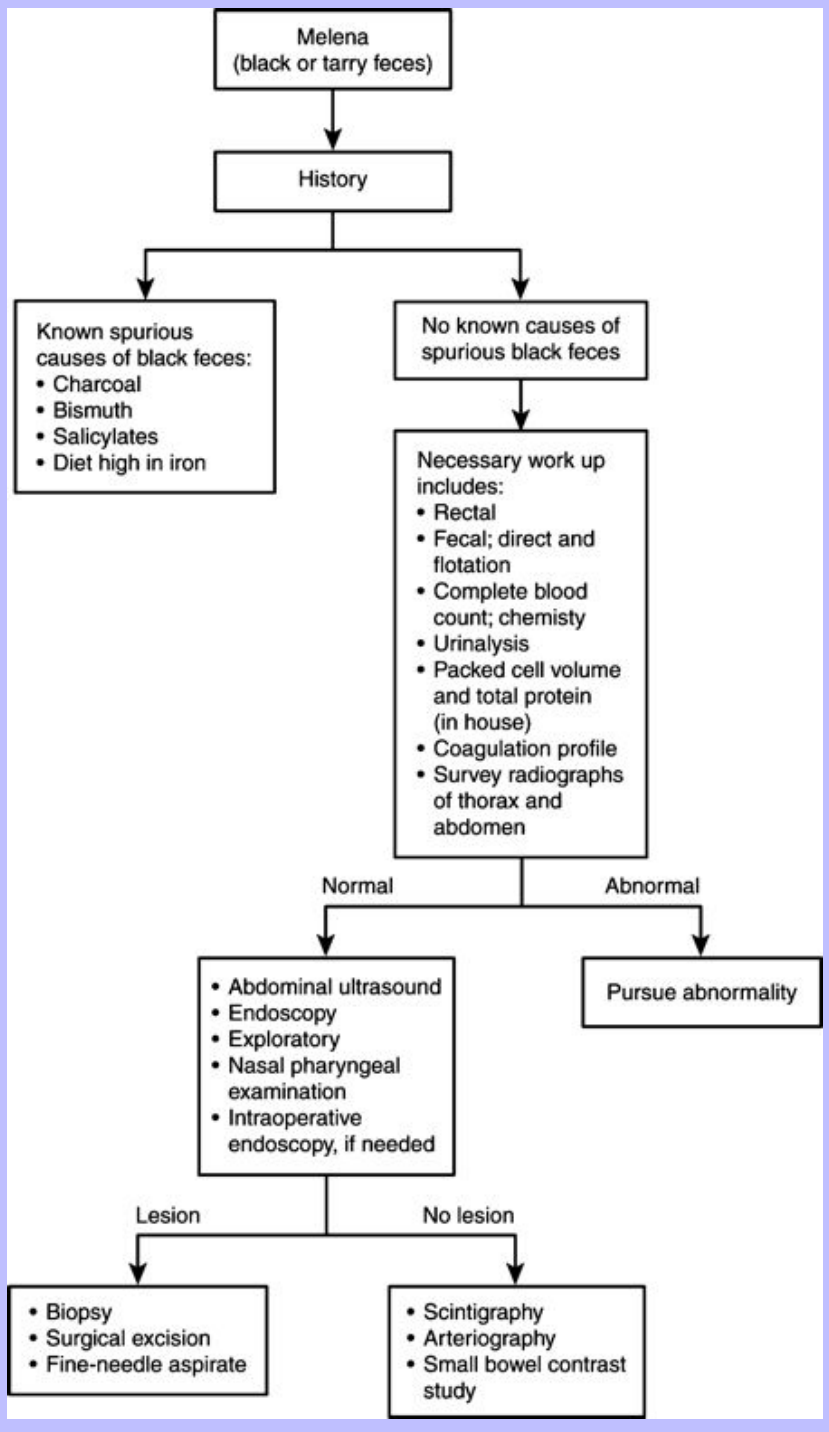
Gastrointestinal blood vessel malformations (e.g., arteriovenous fistula)

Polyps

40.2.3 Treatment

The treatment of melena largely depends on the underlying cause. For animals in shock, hospitalization with intravenous fluid therapy is indicated. Depending on the duration and volume of bleeding, a blood transfusion may be necessary. If a coagulopathy is suspected, plasma or whole blood may be indicated. Gastric acid inhibitors (e.g., famotidine and omeprazole) can be helpful. Antiemetics are indicated if nausea and vomiting are factors.

Figure 40-1 Diagnostic approach to a patient with melena.



41 CHAPTER • 41 Constipation, Tenesmus, Dyschezia, and Fecal Incontinence

Kenneth R. Harkin

41.1 DEFINITIONS

Constipation is the infrequent or difficult evacuation of feces, typically characterized by the presence of dry, hard feces.

Obstipation is intractable constipation, characterized by an inability to evacuate the mass of dry, hard feces, which can result in an impaction extending from the rectum to the ileocolic valve.

Megacolon is a pathologic condition of hypomotility and dilatation of the large intestine that results in constipation and obstipation.

Tenesmus is ineffectual and painful straining at defecation or urination.

Dyschezia is difficult or painful defecation that arises exclusively from disease of the anal and perianal tissues.

Fecal incontinence is the involuntary passage of feces and flatus as a result of dysfunction of the internal and external anal sphincters.

41.2 NORMAL PHYSIOLOGY OF THE LARGE INTESTINE

The primary functions of the large intestine are absorption of water and electrolytes, which occurs predominately in the proximal half, and storage of fecal matter until expulsion, which is the primary function of the distal half.

Movement of contents through the large intestine normally is sluggish and consists of *haustral contractions* and *mass movements*. Haustral contractions, which are combined segmental contractions of the circular and longitudinal layers of smooth muscle of the large intestine, result in focal accumulation of contents in unstimulated segments. These contractions primarily serve to mix the contents of the large intestine, increasing the exposure to the luminal surface for maximal absorption of water and electrolytes. They also serve to propel material slowly from the level of the cecum through the ascending colon.

Mass movements carry fecal material from the transverse colon to the rectum; however only a few of these occur daily, compared with the continuous action of the haustral contractions. Mass movements are maximized after a meal, facilitated by the gastrocolic and duodenocolic reflexes, which are conducted through extrinsic nerves of the autonomic nervous system. Contraction of circular smooth muscle begins at an area of distention or irritation, forcing the mass of feces into the rectum, where the desire for defecation is felt. These mass movements persist for 10 to 30 minutes. Irritation in the colon also can initiate mass movements, which may become continuous.

The stimulus for defecation is initiated by the movement of feces into the rectum. Continence is maintained by tonic contractions of the internal anal sphincter, which is composed of smooth muscle and is under the control of the autonomic nervous system, and by the external anal sphincter, whichis composed of striated muscle and is under voluntary con-trol and innervated by the pudendal nerve. Defecation is accomplished by a weak intrinsic defecation reflex (IDR) and a more powerful parasympathetic defecation reflex (PDR). The IDR is initiated when distention of the rectum activates the myenteric plexus and initiates a peristaltic wave and reflex relaxation of the internal anal sphincter. The PDR is stimulated by nerve endings in the descending colon, rectum, and anus, which

activate the parasympathetic nervous system (PNS). Motor nerves of the PDR, which arise from the pelvic nerve, intensify the peristaltic wave. Activation of the PNS also stimulates the deep breath, closure of the glottis, and contraction of the abdominal muscles that constitute the abdominal press. Defecation then depends on voluntary relaxation of the external anal sphincter. If the external anal sphincter remains voluntarily closed, the defecation reflexes are terminated after a few minutes. These reflexes can be voluntarily initiated later, but they are less effective than the intrinsic reflex. Frequent voluntary termination of the defecation reflex commonly results in constipation.

Bowel activity can be inhibited by the peritoneointestinal reflex, which is activated by the presence of peritoneal irritation; by the renointestinal and vesicointestinal reflexes, which are activated by irritation of the kidney or urinary bladder, respectively; and by the somatointestinal reflex, which is activated when the skin over the abdomen is intensely irritated.

41.3 CONSTIPATION

Although tenesmus is the most common clinical sign for an animal with constipation, vomiting, depression, anorexia, and various degrees of abdominal discomfort may also be reported. Animals may be misdiagnosed as having diarrhea when passage of liquid feces around fecal impaction occurs and consequently a complete physical examination is not performed.

Constipation can occur as a result of extraintestinal disorders or primary intestinal and anorectal disorders. Extraintestinal disorders may inhibit normal neural impulses or muscular function; they may interfere with the PDR through weakness, pain, or dyspnea; they may affect fecal consistency through dehydration; or they may cause mechanical obstruction through compression. Extraintestinal disorders include hypothyroidism, hypercalcemia, hypokalemia, chronic renal failure, myopathies, and thoracic cavity disease. Intestinal and anorectal diseases result in constipation through obstruction, inhibition of the defecation reflex because of pain, and loss of motility.

41.3.1 Clinical Evaluation

41.3.1.1 History

Detailed information regarding the duration of constipation and influencing factors may help determine the cause. The clinician should determine if there is a history of ingestion of indigestible material (e.g., bone, hair, plastic, sticks, or branches) that may increase fecal bulk or cause pain that can terminate the defecation reflex. Other historical factors that may be relevant include recent surgery, previous pelvic trauma and, possibly, radiation therapy.

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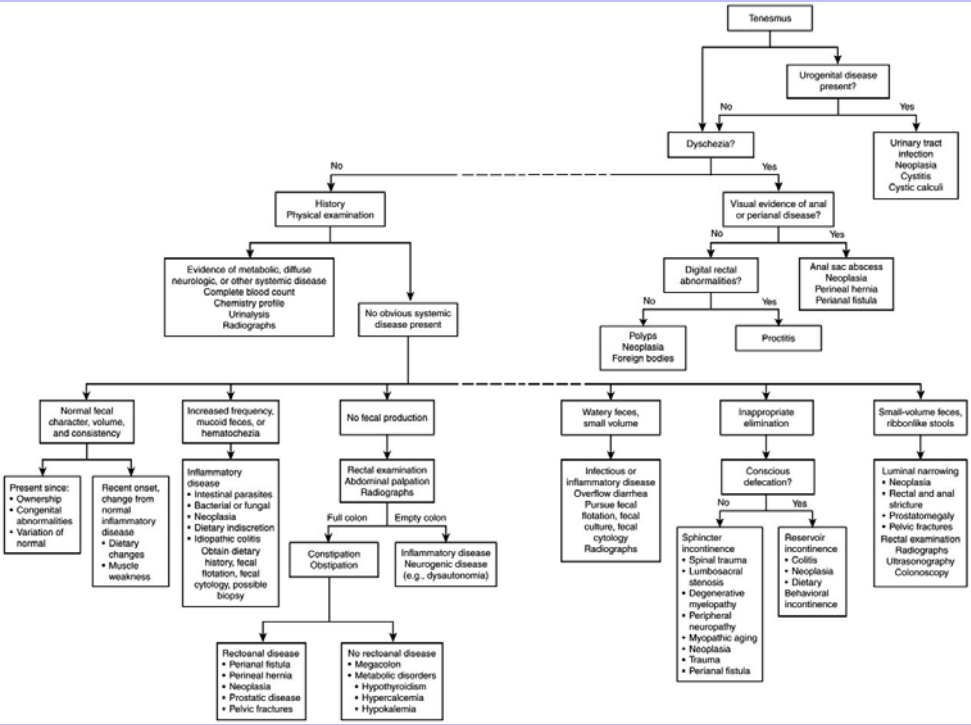
41.3.1.2 Signalment

In the feline, megacolon is a common disease. Specifically, sacral spinal cord deformities are seen in the Manx cat. Intact male dogs should be carefully evaluated for prostate disease, such as abscesses or cysts, and perineal hernia. Aged and large breed dogs should be screened for orthopedic disease, such as hip dysplasia. Juvenile dogs and cats should be evaluated for congenital abnormalities, such as imperforate anus. Dysautonomia has been diagnosed primarily in dogs from Kansas and Missouri and in cats primarily from Great Britain. The German shepherd dog should be carefully evaluated for perianal fistulas.

41.3.1.3 Physical Examination

In addition to a careful examination of all other body systems, which may yield clues to extraintestinal disease, particular attention should be given to examination of the anorectal area. Visual inspection may identify perianal fistulas or tumors, and careful digital examination may identify prostatic disease, strictures, masses, perineal hernia, foreign material, or pain.

Figure 41-1 Diagnosis and treatment of constipation, tenesmus, dyschezia, and fecal incontinence.



41.3.1.4 Diagnostic Evaluation

Routine laboratory work usually is of minimal value, except when systemic disease is suspected. Survey and contrast radiography, ultrasonography, and colonoscopy may be helpful when the diagnosis cannot be determined from the history and physical examination.

41.4 TENESMUS AND DYSCHEZIA

Tenesmus and dyschezia are clinical signs that often overlap and occasionally are difficult to distinguish. The difference is that dyschezia occurs exclusively as a result of disease of the anal and perianal tissues. Tenesmus, a result of disease of the large intestine, is seen with obstruction, inflammation, and constipation (Figure 41-1).

41.4.1 History

It is important for the clinician to determine whether tenesmus is the result of urinary tract or intestinal tract disease. Cats with lower urinary tract signs frequently are described by their owners as straining to defecate or constipated, which may result in a misguided diagnostic workup. Female dogs adopt similar postures when straining to defecate or urinate. The timing of the event may also be helpful, because tenesmus prior to defecation suggests obstruction, and tenesmus after defecation suggests irritative disorders. The character of the feces may provide further clues to the diagnosis. The presence of fresh blood or mucus suggests an inflammatory component, such as with infectious colitis, idiopathic colitis, dietary indiscretion, or neoplasia. Small volumes of ribbonlike stool suggests luminal narrowing, such as with a stricture or prostate disease.

41.4.2 Signalment

There are a few breed-specific disorders, such as histiocytic ulcerative colitis in the boxer and perianal fistulas in the German shepherd dog. Other inflammatory conditions can be seen in a variety of breeds. Infectious and inflammatory disease is suspected in young animals, whereas neoplastic disease is a primary concern in the aged animal.

41.4.3 Physical Examination

The principles of a complete physical examination are identical to those outlined for constipation. Absence of fecal material may be suggestive of an inflammatory condition. Additional care must be given to examination of the urinary tract, particularly palpation of the urinary bladder transabdominally and the urethra per rectum.

41.4.4 Diagnostic Evaluation

Routine laboratory work provides few clues to the diagnosis. Radiography, ultrasonography, fecal flotation, fecal culture, fecal cytology, colonoscopy/proctoscopy, and biopsy usually provide the information necessary to confirm a diagnosis.

41.5 FECAL INCONTINENCE

Incontinence occurs as a result of dysfunction in the ability of the anal sphincters to prevent involuntary leakage (sphincter incontinence) or the loss of the storage ability of the large intestine (reservoir incontinence).

Animals with reservoir incontinence are aware of their need and act of defecation. As a result of small intestinal or colorectal disease, which can result in irritation, loss of storage capacity or compliance, overwhelming fecal volume, or disturbances of motility, voluntary inhibition of external anal sphincter relaxation is lost.

Sphincter incontinence typically is a result of a neuromuscular disorder affecting the *continence reaction,* the reflexive and conscious contraction of the external anal sphincter. Sphincter incontinence occurs with denervation or damage to the external and internal anal sphincters or the muscles that support the pelvic canal or, possibly, with loss of sensory function. Patients with sphincter incontinence are plagued by the involuntary passage of feces. Disease of or damage to the levator ani and coccygeus muscles, damage to the pudendal nerve or sacral spinal cord, and disease or trauma to the perianaltissues can result in sphincter incontinence.

41.5.1 Clinical Evaluation

41.5.1.1 History

If the animal is conscious of defecation, characterized by posturing and possibly tenesmus, the clinician can focus on causes of reservoir incontinence. Frequent defecation, fresh blood in the stools, and mucoid stools also are clues to reservoir incontinence. Other information that may be important includes a dietary history, a history of trauma or orthopedic problems, previous dystocia, previous surgery, and the duration of disease. Behavioral problems can be mistaken as reservoir incontinence, and attempts should be made to distinguish the two. Dogs with behavior problems usually do not display the tenesmus and urgency of reservoir incontinence and defecate at inappropriate times and places. The animal's ability tourinate normally should give clues as to the integrity of the nervous system.

41.5.1.2 Signalment

Large breed dogs have a higher incidence of lumbosacral stenosis and degenerative myelopathy, older dogs may have neoplastic disease or geriatric incontinence, and younger dogs and cats may have congenital abnormalities, such as vertebral malformations.

41.5.1.3 Physical Examination

In addition to a complete physical examination, careful visual and digital examination of the perianal, anal, and rectal areas may provide clues to the diagnosis. Anal sphincter tone should be carefully evaluated; however, it is not a reliable indicator of anal sphincter function. The clinician should also assess urinary bladder tone and tail tone, as well as hindlimb function and reflexes and whether paresthesia is present. Hyperesthesia or paresthesia of the pelvic limbs is supportive evidence of lumbosacral stenosis. Depressed pelvic limb reflexes are seen with lumbosacral cord lesions, lumbosacral stenosis, peripheral neuropathies and, possibly, myopathies.

41.5.1.4 Diagnostic Evaluation

Routine laboratory work is of limited value except when systemic disorders are present. Radiography, myelography, computed tomography (CT) or magnetic resonance imaging (MRI), colonoscopy, and electromyography may be performed as needed based on suspicion of disease localization.

42 CHAPTER • 42 Flatulence

Michael E. Matz

The term *flatulence* refers to excessive accumulation of gas in the gastrointestinal tract. It may be associated with eructation, borborygmus, or flatus. *Eructation* is the expulsion of gas from the stomach. *Borborygmus* is a rumbling noise caused by the propulsion of gas through the gastrointestinal tract. *Flatus* is the anal passage of intestinal gas.

Flatulence is more commonly observed in dogs than cats and is most often noted in inactive indoor dogs. It usually results from dietary intolerances but occasionally can signal more serious gastrointestinal disease, particularly of the small bowel or pancreas. Most owners accept flatulence and borborygmus in their pets as normal and are unconcerned about its consequences.

42.1 PATHOPHYSIOLOGY

The major gastrointestinal gases are nitrogen and oxygen, which are derived from swallowed air and diffusion from blood, and hydrogen, carbon dioxide, and methane, which are primarily products of bacterial metabolism and fermentation and nonbacterial reactions (e.g., pancreatic bicarbonate interacting with acid to produce carbon dioxide) that occur in the bowel lumen. In human beings, and probably in dogs and cats, as much as 99% of flatus is composed of these odorless gases. The remaining 1% is composed of odoriferous gases, including hydrogen sulfide, methanethiol, dimethylsulfide, ammonia, skatole, mercaptans, volatile amines, and short chain fatty acids. These odoriferous gases also result from bacterial metabolism and fermentation. Sulfur-containing gases, particularly hydrogen sulfide, have been shown to be a major determinant of the malodor of canine flatus.

Most of the gas that enters the digestive tract is thought to come from swallowed air. Aerophagia mainly occurs during the ingestion of liquids and solids and can be exacerbated by rapid or competitive eating situations. Most swallowed air is subsequently eliminated by eructation from the stomach and esophagus. If not eructated, the nitrogen contained in swallowed air travels through the gastrointestinal tract with minimal absorption and subsequently is passed. It is noteworthy that the transit time for gas is considerably shorter than that for liquids or solids. Air entering the intestinal tract can be passed out the rectum rapidly (within minutes). Gases can also be removed by diffusion into blood or consumption by bacteria.

The composition and volume of flatus are affected by the quantity and variety of nutrients eaten, as well as by the type and abundance of bacterial flora. A significant amount of gas is formed from the bacterial fermentation of both dietary (e.g., fiber and poorly digestible carbohydrates and proteins) and endogenous (e.g., mucin, bile acids) substrates. Foods such as legumes (soybeans, beans, peas) that contain large amounts of indigestible oligosaccharides are apt to produce large amounts of intestinal gas. The oligosaccharides are fermented to hydrogen and carbon dioxide by *Clostridium* organisms and other bacteria. Variations in the metabolic capacity of the bacteria flora may explain the different responses animals may have to nonabsorbable carbohydrates. Fiber-containing pet foods may contribute to flatulence directly, if the fibers are fermentable by colonic bacteria, and/or indirectly through reduced dry matter digestibility. Pectins and most gums are rapidly fermentable fibers found in pet foods. Sulfur-reducing bacteria convert dietary sources of sulfur, including sulfate and sulfur-containing amino acids, to the odoriferous gases hydrogen sulfide, methanethiol, and dimethylsulfide. The production of these gases usually is increased by foods containing increased amounts of sulfate (cruciferous vegetables, onions, nuts, carrageenan) or protein.

Maldigestion due to exocrine pancreatic insufficiency or malabsorption resulting from small intestinal diseases often leads to excessive intestinal gas caused by the fermentation of malassimilated substrates. Lactose intolerance also can cause flatulence.

42.2 CLINICAL EXAMINATION FINDINGS

Owners may describe an increase in the frequency of flatus, an objectionable odor associated with flatus, the presence of borborygmus, or abdominal distention. Occasionally these signs are associated with concurrent abdominal pain, vomiting, diarrhea, or weight loss, any of which suggest more serious gastrointestinal disease. The owner may report that the pet has a hunched posture, exhibits unsettled behavior, or adopts a praying position. These signs may result from excessive intestinal gas, motility disorders that disrupt the passage of gas through the bowel, or increased visceral sensitivity to bowel distention. The animal's temperament may be important. Excessive aerophagia in a nervous animal, or animals with aggressive or competitive eating habits, can increase gastric gas, although it is unclear whether ingested air contributes significantly to intestinal gas or flatus.

A complete dietary history is essential. Owners should be questioned about any recent dietary change or dietary indiscretion. An assessment of specific foods, food ingredients, treats, and supplements, as well as the potential for dietary indiscretion, should be made. In human beings, diets high in soybeans, whole wheat products, bran, and fats can cause flatulence. Similar associations appear to occur in some dogs and cats. Spoiled food and diets high in protein or fat are more likely to yield odoriferous gases. Milk products can cause flatulence in animals with lactase deficiency. The feeding method should also be thoroughly evaluated. The amount fed, feeding frequency, how the food is offered, access to other food, and the relationship of feeding to exercise should be determined.

With the exception of borborygmus, the physical examination of an animal with flatulence usually is unremarkable unless concomitant gastrointestinal disease is present. Additional diagnostic tests are warranted in the latter animals.

42.3 MANAGEMENT

The management of flatulence begins with changing the diet (Figure 42-1). Feeding a highly digestible diet reduces the food residues available for bacterial fermentation. The diet should not contain excessive amounts of rapidly fermentable fiber. Vegetarian-based diets should be avoided because these products often have sulfur-containing vegetables and legumes. Optimally, the diet should be lactose deficient. Changing sources or amounts of dietary protein, carbohydrate, and fat may benefit individual animals. Diets containing rice as the primary carbohydrate source may produce less intestinal gas than diets containing other sources of carbohydrate. Suitable commercial foods are available from most major pet food manufacturers. Dietary trials may be necessary to find a food that reduces flatulence or objectionable flatus. Vitamin-mineral supplements may increase intestinal bacterial activity and probably should be avoided.

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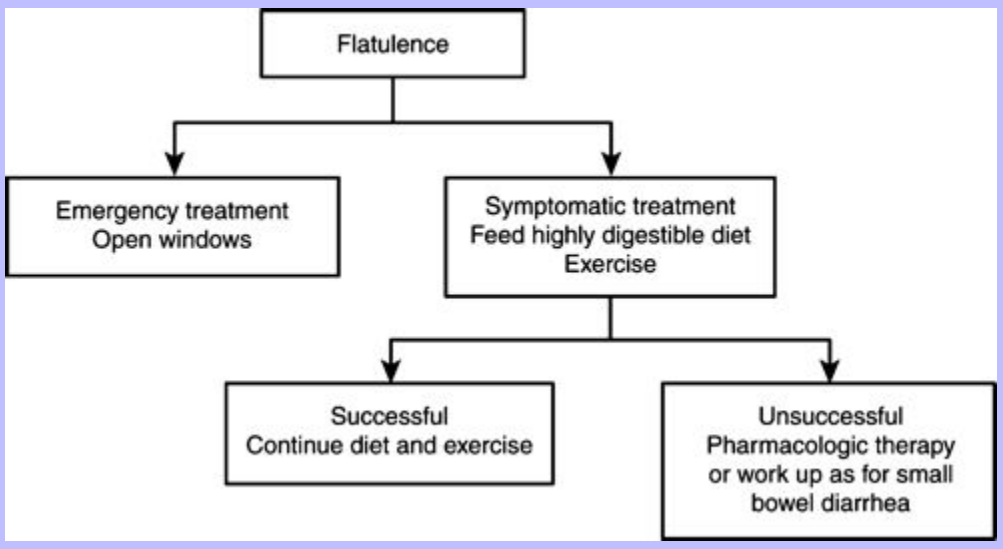
Figure 42-1 Algorithm for management of flatulence.



Reducing aerophagia, by avoiding situations that provoke nervousness and discouraging rapid or competitive eating, may also be helpful. Feeding several small meals daily may alleviate some of these problems.

Regular exercise also is beneficial, presumably because exercise stimulates gastrointestinal motility and defecation. In the event that dietary manipulation and regular exercise are not successful, symptomatic pharmacologic intervention should be considered.

Pharmacologic management involves reducing or controlling the amount of flatulence and/or the objectionable odor of flatus. Substances that can be used include simethicone, activated charcoal, *Yucca schidigera* preparations, zinc acetate, bismuth subsalicylate, alpha-galactose, and pancreatic enzyme supplements.

Simethicone (25 to 200 mg per dose, given every 6 hours) frequently is used as a treatment for borborygmus, gaseous colic, and flatulence in human beings. It is an antifoaming agent that reduces surface tension, allowing bubbles to coalesce so that they can be passed more easily. Simethicone is not absorbed from the gastrointestinal tract and can be safely used in dogs and cats at or near the dosage for human beings. Its effectiveness as an antiflatulent in dogs and cats is unknown. Both veterinary and human (over the counter) products containing simethicone are commercially available.

Activated charcoal is one of the more commonly used adsorbent antiflatulents in human beings. Its absorbency results from its porous structure, which confers a tremendous internal surface area. Charcoal is of questionable benefit for the relief of flatulence, but it may be effective in absorbing small amounts of sulfur-containing gases, which are primarily responsible for malodorous flatus. Commercial treats containing activated charcoal are available for dogs.

Y. schidigera, zinc sulfate, and bismuth subsalicylate also may be effective in reducing the unpleasant odor of flatus. The efficacy of *Y. schidigera* appears to be related to its ability to bind hydrogen sulfide and/or to decrease the numbers or activity of sulfate-reducing bacteria that generate hydrogen sulfide. Poorly absorbed divalent cations (e.g., zinc, bismuth) bind sulfhydryl compounds such as hydrogen sulfide and methanethiol to form

insoluble salts, and this effectively prevents the liberation of these gases. To be of benefit, bismuth subsalicylate probably needs to be given multiple times per day, which can make it impractical to use. Like charcoal, these agents do not appear to be particularly effective in reducing flatulence. The efficacy of the agents may be improved if administered together.

Anecdotal reports indicate that alpha-galactosidase and pancreatic enzyme supplements may be effective in reducing flatulence in some dogs and cats. Alpha-galactosidase works by improving digestion of nonabsorbable carbohydrates found in legumes. Both veterinary and human products containing alpha-galactosidase are available. Pancreatic enzyme preparations are claimed to assist the digestion of fermentable nutrients that are digested poorly by the gastrointestinal systems of monogastrics.

In most dogs and cats, flatulence can be controlled successfully, often through dietary management alone. Relapses in controlled animals often are due to dietary indiscretion. If dietary management, exercise, and supplementary therapy are unsuccessful in reducing or controlling flatulence, an investigation similar to that for a dog or cat with small bowel diarrhea (see Chapters 39 and 222) should be considered.

43 CHAPTER • 43 Abdominal Distention, Ascites, and Peritonitis

Stephen A. Kruth

Abdominal distention is potentially a serious sign of disease and should be evaluated reasonably quickly, especially when associated with discomfort, restricted breathing, fever, weakness, or other clinical signs. The initial diagnostic goal should be to identify obesity, pregnancy, a distended urinary bladder, obstipation, or gastric dilatation. If these are not the cause of the distention, the clinician should determine whether hepatomegaly, splenomegaly, or some other mass is present or whether the predominant abnormality is the accumulation of fluid in the peritoneal cavity (i.e., an effusion). In some cases both a mass and an effusion may be present. Distinguishing between organ enlargement or masses and effusion is accomplished through physical examination and abdominal imaging.

When organomegaly or a mass is the predominant abnormality, a specific diagnosis usually can be made through needle biopsy. When an effusion is present, a sample should be obtained by paracentesis and characterized as a transudate, modified transudate, exudate, chyle, or blood. If the effusion is a *transudate* (low to moderate cellularity and a low protein concentration), modified transudate, or chyle, the animal is said to have *ascites*. If the effusion is an *exudate* (high cellularity and a high protein concentration), the animal has *peritonitis*. Exudates can be septic or nonseptic (e.g., feline infectious peritonitis, bile, urine, pancreatitis).

43.1 PATHOPHYSIOLOGY OF ABDOMINAL ORGAN ENLARGEMENT

Distention of the stomach or intestines usually is due to the accumulation of gas and fluid in the lumen of the affected organ. Gas can accumulate as a consequence of aerophagia (usually secondary to respiratory disease), gastric dilatation, ileus, or obstruction. Obstipation can cause abdominal enlargement, especially in cats with megacolon. Renal or urinary bladder enlargement can follow ureteral or urethral obstruction; bladder enlargement can also be associated with neurologic dysfunction. Enlargement of the liver can be a consequence of venous congestion secondary to right heart failure; splenic enlargement can be caused by venous congestion secondary to splenic torsion. Gross organ enlargement often is due to infiltrative disorders (especially lymphosarcoma and other neoplasms), which may cause either diffuse or localized enlargement of the involved organ. Hyperadrenocorticism can also cause remarkable hepatomegaly, abdominal wall weakness, and abdominal distention.

43.2 PATHOPHYSIOLOGY OF ABDOMINAL EFFUSIONS

The peritoneum is a serous membrane consisting of mesothelial cells overlying a connective tissue stroma. The parietal portion covers the transversalis fascia of the abdominal wall, and the visceral portion envelops the abdominal viscera. The peritoneal cavity formed by these two layers is almost nonexistent in normal animals, containing only a small volume of fluid, which serves to lubricate the parietal and visceral peritoneal surfaces. Normally, peritoneal fluid (lymph) is formed at the arteriolar end of capillaries and reabsorbed both at the venous end of capillaries and by means of lymphatic uptake (predominately via the large lymphatic vessels of the diaphragm). In the normal animal, fluid movement is balanced; a large exchange of fluid and solute occurs, but a low and stable volume is maintained.

The primary event leading to the development of an effusion is an alteration in one or more of the Starling forces governing fluid movement across membranes. Increased portal hydrostatic pressure caused by obstruction of venous flow, decreased plasma colloidal oncotic pressure associated with hypoalbuminemia, and/or increased permeability of the capillary endothelium secondary to inflammation can all lead to the development of an

effusion. Decreased lymphatic uptake, usually due to reduced flow of lymph from the peritoneal cavity, can also cause effusion.

An important consequence of the redistribution of extracellular fluid into the peritoneal cavity is a decreased effective plasma volume and reduced cardiac output. This stimulates the renin-angiotensin-aldosterone system, resulting in sodium and water retention. Antidiuretic hormone levels increase in response to sodium retention, leading to isotonic expansion of the extracellular fluid space. In heart failure, elevations in the levels of endothelin and insensitivity to circulating atrial natriuretic peptide contribute to sodium retention. The net effect in any ascitic condition is an increase in total body water and sodium, which perpetuates the ascitic state if the underlying cause is not resolved.

Ascites caused by portal hypertension can be classified as *prehepatic* (restriction of blood flow into or through the portal vein), *hepatic*, or *posthepatic* (from the level of hepatic vein tributaries, through to the right ventricle) in origin, and to some extent the effusion characteristics are determined by where the abnormality lies. Ascites caused by prehepatic disorders is rare as recruitment of collateral portosystemic vessels often occurs when portal pressure increases. Portal vein obstruction due to compression by a mass, or increased circulation and thus increased hydrostatic pressure in the portal system caused by a *hepatic artery–portal venous fistula* are possible causes. With prehepatic portal hypertension, the elevated hydrostatic pressure causes increased lymph formation from the intestinal serosa, and the effusion typically is a pure transudate (at least initially; the presence of any fluid in the peritoneal cavity irritates the peritoneum, causing protein loss, increased cellularity, and formation of a modified transudate).

The most common posthepatic cause of portal hypertension is *right-sided heart failure* (which can be caused by cardiac disease or can occur secondary to tamponade resulting from pericardial effusion). Ascites secondary to right heart failure is more common in dogs than cats because the hepatic veins of dogs are more likely to act as postsinusoidal sphincters, which increase portal pressure. Rare causes of posthepatic ascites include *obstruction of the caudal vena cava* by a thrombus, compression by a mass, or anatomic changes associated with a diaphragmatic hernia. In posthepatic portal hypertension, excess lymph is formed primarily in the hepatic sinusoids and then diffuses across the liver capsule. Hepatic lymph is relatively high in protein compared with lymph formed from the intestinal capillaries, and the typical effusion of posthepatic disease is a modified transudate.

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Ascites secondary to hepatic disease is due largely to portal hypertension, and the effusion can be either a transudate or a modified transudate, depending on the type of pathology and its distribution. In human beings, the mechanism of effusion formation in cirrhosis is complex and not completely understood. Three theories have been invoked to explain this form of ascites: the underfill theory proposes that the primary abnormality is a decrease in effective circulating volume (underfilling), which occurs when fluid is sequestered in the splanchnic vascular bed secondary to portal hypertension. Secondary renal sodium and water retention occurs, and an increase in hydrostatic pressure in hepatic sinusoids and splanchnic capillaries leads to increased lymph formation, which exceeds the drainage capacity of the lymphatic system. Alternatively, the overfill theory suggests that the primary abnormality is renal retention of sodium and water in the absence of volume depletion (by an unknown mechanism), leading to an increase in extracellular fluid volume (overfilling). In the presence of pre-existing hepatic venous outflow obstruction and portal hypertension, ascites develops. The third hypothesis proposes that the primary abnormality is splanchnic arteriolar vasodilatation (possibly mediated by nitric oxide), leading to underfilling of the systemic arterial vascular space and baroreceptor-mediated stimulation of the renin-angiotensin-aldosterone system. Concurrent hypoalbuminemia and decreased colloidal oncotic pressure may contribute to the formation of ascites in all of these situations.

Abdominal effusion can be caused by mechanisms other than portal hypertension. Severe hypoalbuminemia secondary either to *glomerular disease* or to severe *protein-losing enteropathies* can lead to ascites (usually a

transudate). Widespread miliary *carcinamatous* seeding of the serosa *(carcinomatosis),* as well as other cancers, can induce the formation of modified transudate or exudate through obstruction of capillaries and inflammation. With any form of inflammation, mediators increase endothelial permeability and recruit neutrophils and other phagocytic cells, which may lead to the formation of an exudate. Septic exudates usually are caused by bacterial infections and are relatively small in volume. Nonseptic exudates can be caused by *neoplasia, bile, urine,* or *feline infectious peritonitis. Chyle* (lymph of intestinal origin with a high lipid content) can leak into the peritoneal cavity from lymphatics; the causes of *chylous ascites* in dogs and cats include neoplasia, trauma, infection, and right heart failure. Rupture of blood vessels, the ureters, bladder, or biliary tree can occur secondary to *trauma*. Bleeding caused by coagulopathies (usually affecting the clotting cascades) or tumors (especially splenic or hepatic *hemangiosarcoma*) can cause hemoabdomen.

43.3 CLINICAL SIGNS

Owner concerns for a dog or cat with abdominal enlargement can include weight gain, decreased activity and decreased exercise tolerance, inappetence, or increased respiratory rate. The rate of abdominal enlargement is variable, and the condition may develop over hours to weeks, depending on the underlying cause. The history should include a review to identify signs suggestive of pathology of the cardiac, renal, hepatic, or other organ systems. Abnormalities identified by abdominal palpation can include hepatomegaly, splenomegaly, or one or more mass lesions. Low-volume effusions can give the impression of a “slippery” feel when the small bowel is palpated, and a fluid wave usually can be appreciated with large-volume effusions. Tachypnea can result from restricted ventilation caused by cranial displacement of the diaphragm by an enlarged liver or by fluid. Signs of abdominal pain may be present with peritonitis of any cause.

A careful general examination may reveal signs that direct the diagnostic approach. For example, cardiovascular abnormalities, such as jugular distention or pulsation, murmurs, or arrhythmias, are suggestive of right heart failure, and muffled heart sounds are consistent with pericardial effusion and tamponade. Jaundice is consistent with liver failure or rupture or obstruction of the biliary system, fever is suggestive of an inflammatory disorder, and generalized lymphadenopathy is consistent with lymphosarcoma.

43.4 DIAGNOSTIC APPROACH

Radiographs can be used to help differentiate organomegaly, other mass lesions, and effusions. Ultrasonographic examination of the abdomen is more useful for identifying specific organ enlargement, and alterations in organ echogenicity may be suggestive of some types of neoplasia, hepatic lipidosis, or other pathology. Abdominal ultrasound is also useful for identifying low-volume effusions. Ultrasound-guided needle biopsies and/or fluid aspiration can be performed, and cytologic diagnosis may be possible. However, histopathologic evaluation of biopsy tissue may be more reliable in terms of making a specific diagnosis. Tissue samples can also be submitted for bacterial culture, if indicated. The animal's hemostatic ability should be evaluated prior to biopsy: platelet number and function (as evaluated by mucosal bleeding time) are important considerations, along with assays of the coagulation cascades (activated clotting time or activated partial thromboplastin and prothrombin times).

A sample of effusion can be safely obtained by aspirating the peritoneal cavity using a 22-gauge needle attached to a 12 mL syringe. After aseptic skin preparation, the needle is placed through the body wall at the ventral midline slightly caudal to the umbilicus, avoiding the liver, spleen, and urinary bladder. The animal can be standing or in lateral recumbency, and local anesthesia usually is not necessary. Nondiagnostic samples are obtained when blood is aspirated from the liver or spleen or when only small amounts of effusion are present. Other than coagulopathies, there are few contraindications for paracentesis. Complications include laceration of the liver, spleen, or, if present, a tumor, and bacterial contamination of the peritoneal cavity.

The specific gravity, protein content, and cell count of the effusion should be determined, and cytologic evaluation should also be performed. Depending on the situation, creatinine, cholesterol, triglyceride, and bilirubin levels or other assays may be indicated. Smears of aspirated fluid should be made immediately, and the remaining fluid split into ethylenediamine tetra-acetic acid (EDTA) and clot tubes so that additional smears can be made from a centrifuged pellet or, preferably, as a cytospin slide. If the fluid is bloody, the packed cell volume should be determined and compared with that of peripheral blood. Blood obtained from the spleen or other organs contains platelets and usually clots, whereas blood from previous abdominal hemorrhage usually does not contain platelets and does not clot. A sample should be saved for bacterial culture if indicated. The characterization of an effusion as a transudate, modified transudate, exudate, chyle, or hemorrhage is presented in the algorithm (Figure 43-1). In human beings, characterization of effusion often is based on the serum ascites-albumin gradient, which correlates directly with portal hypertension; however, the utility of this test has not been adequately determined in dogs and cats.

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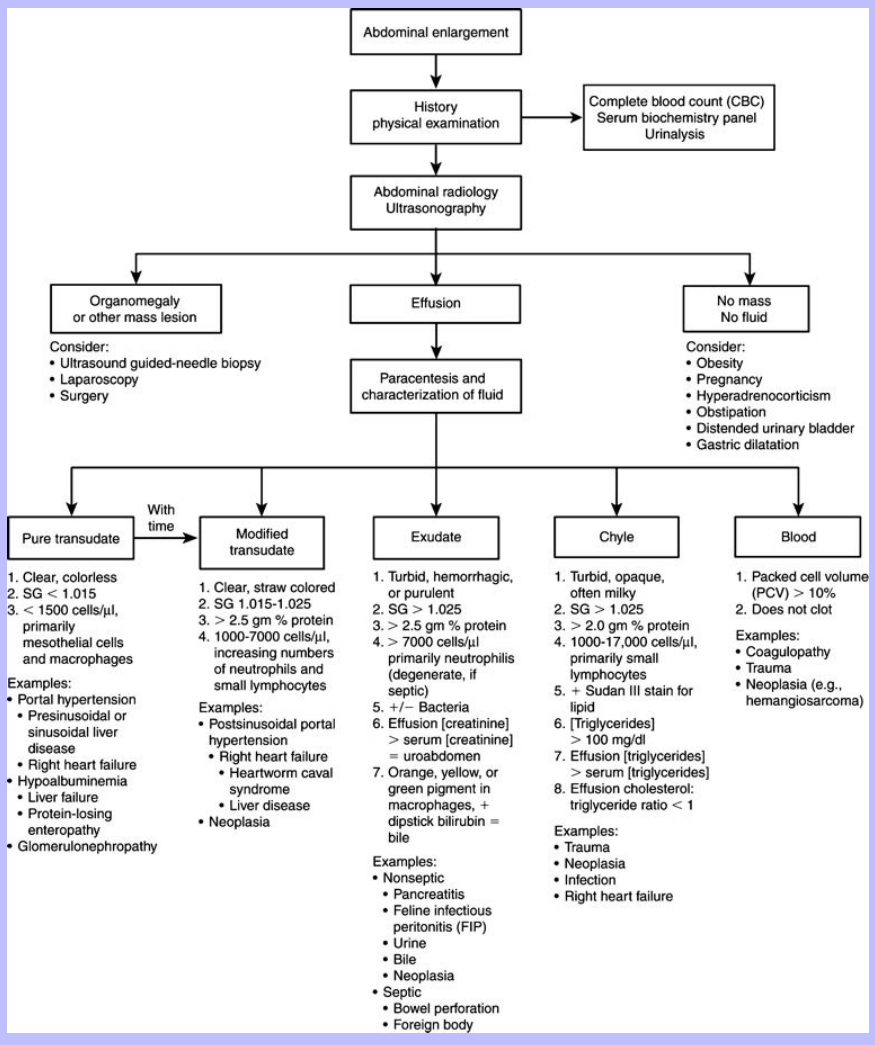
Figure 43-1 Algorithm for diagnostic approach to abdominal enlargement.



A complete blood count (CBC), serum biochemistry panel, and urinalysis are indicated for any animal with abdominal effusion. Although animals with effusions have an increase in total body water and sodium, hyponatremia sometimes is present, likely caused by increased thirst and water consumption and by impaired free water excretion. Hyperkalemia may also be present due to decreased renal distal tubular function. These animals usually have normal adrenal function (i.e., do not necessarily have hypoadrenocorticist. For animals with proteinuria, a urine protein/creatinine ratio should be determined, and an ultrasound-guided renal biopsy can be performed to diagnose and characterize glomerulonephropathies. Animals with signs of right-sided heart failure should be evaluated with thoracic radiographs, echocardiography, and electrocardiography (ECG), and tested for heartworm. Dogs or cats that may have cancer should have thoracic radiographs evaluated for pulmonary metastases. External masses or enlarged lymph nodes should be aspirated for cytology; core biopsies can be obtained for histopathology.

43.5 MANAGEMENT OF ABDOMINAL EFFUSIONS

Animals with hemoabdomen (due to trauma or hemangiosarcoma), rupture of the urinary bladder or biliary tree, or chylous effusion usually require surgical management. Dogs and cats with exudative effusions associated with pancreatitis or bacterial peritonitis should also be considered as surgical candidates, and septic effusions must be managed with appropriate antibiotics and supportive therapy. Cats with the effusive form of feline infectious peritonitis (FIP) can be made more comfortable with large-volume paracentesis while medical management of FIP is considered. Large-volume paracentesis is also indicated as a palliative measure for animals with carcinomatosis, when there is significant respiratory distress secondary to any effusion of any cause, or when diuretics are not effective for controlling ascites. Large-volume paracentesis appears to be well tolerated by most animals with abdominal effusions. The management of malignant effusions is dictated by the type of cancer and the clinical stage of the animal. Colloid therapy with plasma, albumin, hetastarch, or pentastarch may be useful for short-term management of effusions secondary to hypoalbuminemia.

The management of ascites caused by cardiac failure is based on improving cardiac performance as dictated by the primary disorder. Animals with portal hypertension of any cause (e.g., right-sided heart failure, liver disease) should be managed with diuretic therapy (furosemide, 1 mg/kg PO, IV, IM given twice daily, and/or spironolactone, 1 mg/kg PO given twice daily, increasing the dosage as necessary; these drugs can be administered concurrently to minimize electrolyte abnormalities). As total body sodium increases in ascitic disorders, a sodium-restricted diet is indicated.

44 CHAPTER • 44 Neurologic: Neurologic Manifestations of Systemic Disease

Karen L. Kline

The evaluation of a dog or cat with neurologic dysfunction is based on two questions: (1) Does this patient have disease of the nervous system? and (2) If so, is it brain, spinal cord, or neuromuscular in origin? The neurologic examination can reveal whether the animal has evidence of focal, diffuse, or multifocal, central or peripheral nervous system disease. From these findings, a differential list can be formulated and the appropriate diagnostics performed. What is essential, however, is a thorough physical examination to help determine if the signs observed are primarily of neurologic origin or are secondary to underlying systemic or metabolic disease. At times this distinction can be difficult until further diagnostics are performed; it is determining which diagnostics are appropriate that can be confusing to the clinician. Underlying systemic or metabolic illness can have a dramatic effect on the nervous system. The diagnosis and treatment of the diseases responsible for these effects are discussed in greater detail in Chapter 190. This chapter concentrates on categories of these diseases, areas of the nervous system affected, and the diseases' common neurologic presentations.

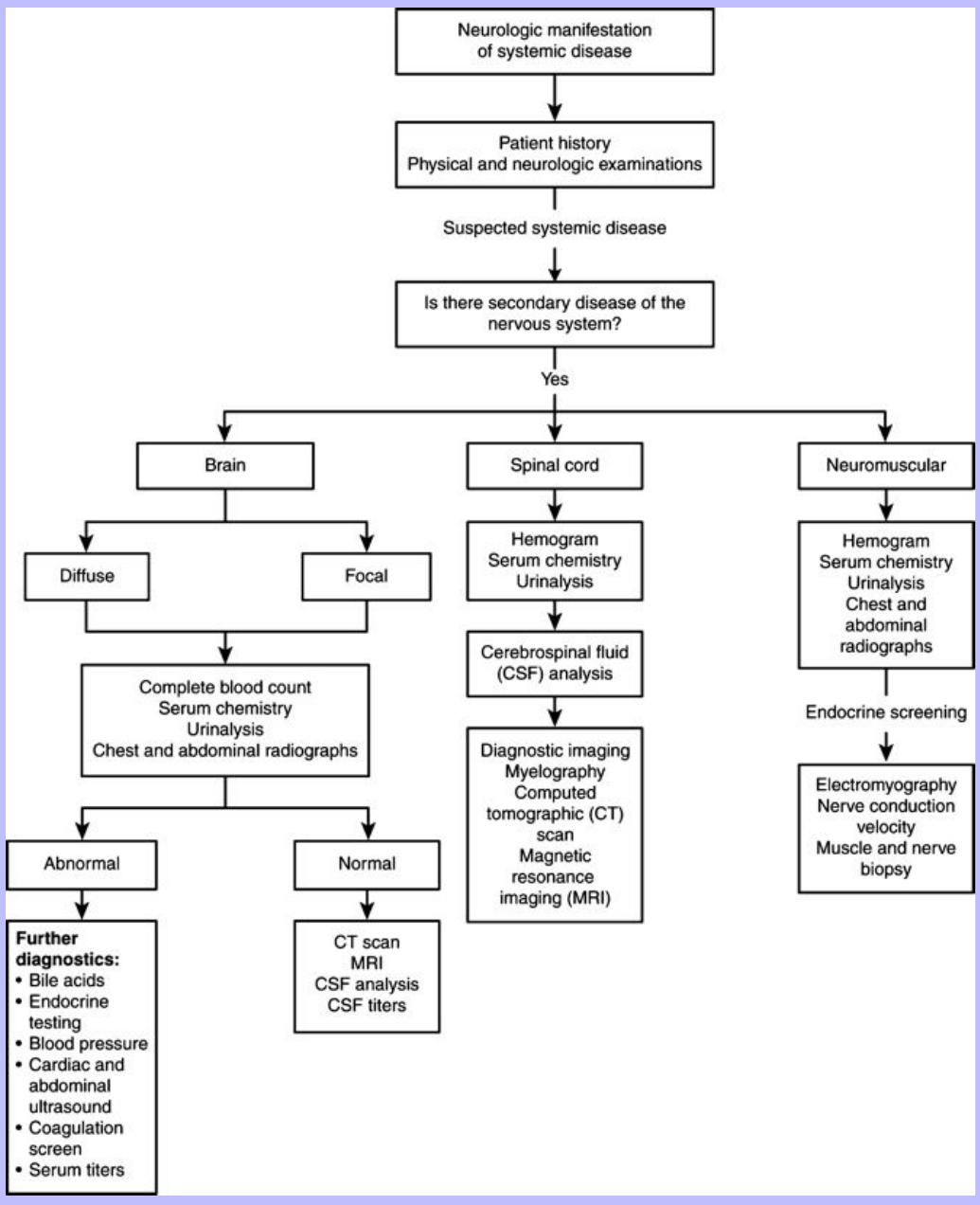
The different categories of diseases that affect the nervous system can include disorders of energy supply, ionic or electrolyte disturbances, endocrine dysfunction, metabolic dysfunction, hematologic disorders, infectious agents, immune dysfunction, and paraneoplastic syndromes (Figure 44-1).

In general, the neurologic target areas for these disturbances are the cerebral cortex and the peripheral nervous system (peripheral nerves and muscle), although other portions of the central nervous system (CNS) can be affected. These two regions tend to have a high demand for energy supply, and even subtle changes can instigate neurologic manifestations.

44.1 CENTRAL NERVOUS SYSTEM EFFECTS

Signs of CNS dysfunction vary with the location of the insult. Changes in energy supply, electrolyte disturbances, and endocrine and metabolic dysfunction tend to cause more diffuse neurologic signs, such as behavior changes, seizures, circling in either direction, pacing, partial cranial nerve and visual deficits, and generalized weakness. Hematologic, infectious, immune-mediated, and paraneoplastic disorders tend to cause more focal or asymmetric signs, although exceptions do occur. The cerebral cortex and thalamus are two areas especially prone to even subtle changes in energy supply. The brain stem and cerebellum, however, are not immune to these changes. Examples of fuel deprivation include (1) hypoxemia secondary to underlying cardiopulmonary disease, anesthetic-related injuries, bleeding diatheses, or cerebrovascular ischemic disease; (2) hypoglycemia resulting from sepsis, endogenous or exogenous hyperinsulinism, or lack of glucose production as a result of severe hepatic dysfunction or increased metabolic demand; and (3) nutritional deficiencies, the most recognized of which is thiamine deficiency, which can result in both cerebrocortical and central vestibular dysfunction.

Figure 44-1 Algorithm for the evaluation of neurologic manifestations of systemic disease.



Aberrations in water and electrolyte balance can result in secondary cerebrocortical dysfunction. Examples include hypernatremia and hyponatremia that result in shifts in the brain osmolality and that have an acute or chronic course. Changes in ion balance, such as those that occur secondary to hypercalcemia or hypocalcemia and

hyperkalemia or hypokalemia, have a direct effect on ion channels in the CNS and can lead to excitatory or inhibitory neurotransmission.

Metabolic disorders that have secondary effects on the CNS and, more specifically, on the cerebral cortex and thalamus are those that liberate endogenous neurotoxins that affect the blood-brain barrier and neurotransmission and that alter the brain's neurochemical balance. Examples of such disorders include (1) hepatic encephalopathy caused by portosystemic shunting, microvascular dysplasia, hepatic cirrhosis, hepatic neoplasia, or inflammatory or infectious causes of hepatic dysfunction (the major causative agents involved in these diseases are hyperammonemia and false neurotransmitter production); and (2) uremic encephalopathy as a result of end-stage renal dysfunction. Exogenous neurotoxins, including strychnine, metaldehyde, illicit drugs, and lead, all can cause secondary CNS effects that, left untreated, can result in death.

Endocrine dysfunction can result in a wide range of CNS effects. Examples of such diseases include hypothyroidism, hyperthyroidism, hyperadrenocorticism, and hypoadrenocorticism. Each of these diseases can disturb the normal resting metabolic energy requirements of the brain and can cause structural changes in the brain parenchyma (pituitary macroadenoma) and vessels (atherosclerosis secondary to hypothyroidism and cerebrovascular accidents secondary to hyperthyroid toxicosis).

44.2 HEMATOLOGIC DISORDERS

Diseases associated with thromboembolism and polycythemia (relative and absolute) have a direct effect on brain function secondary to resultant infarction, changes in cerebral blood flow, and vascular sludging. Thromboembolism often is a sequela to cardiac disease, hyperadrenocorticism, glomerulopathies, immune-mediated disease, and sepsis and results in focal infarction of the surrounding brain parenchyma. Absolute polycythemia, either primary or secondary, results in an increased red blood cell mass that causes an increase in blood viscosity and resultant vascular hindrance, decreased microcirculation, and local hypoxia.

44.3 IMMUNE-MEDIATED DISEASE

Systemic lupus erythematosus (SLE) has been recognized as causing CNS signs in human beings as a result of immune complex deposition and plaque formation. Although this has not been recognized in the dog, evidence is strong that the same sequelae can occur in this species.

44.4 INFECTIOUS DISEASE

Disseminated fungal infections (histoplasmosis, blastomycosis, cryptococcosis), viral infections (canine distemper virus, rabies, and feline infectious peritonitis), and protozoal infections (toxoplasmosis, neosporosis) tend to have a neurotropism and can cause severe CNS dysfunction. In these cases, all portions of the CNS can be affected, and resolution of disease can be difficult because the organisms cause secondary, sometimes permanent, neuronal necrosis and death.

44.5 PARANEOPLASTIC SYNDROMES

Two of the most common paraneoplastic CNS effects are hypoglycemia induced by insulin-secreting tumors and hypercalcemia secondary to lymphoma and apocrine gland adenocarcinoma. Although the peripheral nervous system (PNS) is more prone to the effects of hypercalcemia, animals with this electrolyte disturbance can manifest CNS signs secondary to the effect on ion pumps and neurotransmission. Metastasis to the central nervous system from a distant site (hemangiosarcoma, feline renal lymphoma) is also an important sequela in this disease category.

44.6 PERIPHERAL NERVOUS SYSTEM

The components of the peripheral nervous system are the nerve root, peripheral nerve, neuromuscular junction, and muscle. Clinical signs vary according to the region affected; most commonly, the peripheral nerve, junction, and muscle are affected.

44.7 PERIPHERAL NEUROPATHIES

Clinical signs associated most commonly with peripheral neuropathies include weakness (either diffuse or focal) with or without normal proprioception, decreased or absent reflexes, and a voice change (if the lesion involves the laryngeal innervation). Common causes of neuropathies that occur secondary to changes in energy supply include (1) hypoglycemia, in which peripheral nerve degeneration and demyelination have been reported; (2) hyperglycemia (e.g., feline diabetic neuropathy manifested in a plantigrade stance), in which increased serum glucose concentrations are thought to impede axonal transport; and (3) hypoxia, which is observed in cases of aortic or iliac thromboembolism in the dog or cat and in cases of chronic cardiovascular disease.

Endocrine causes of peripheral neuropathies include (1) hypothyroidism, which can cause both focal clinical signs (most commonly cranial nerves VII and VIII are affected) and diffuse clinical signs, secondary to axonal degeneration, necrosis, and demyelination; and (2) hypoadrenocorticism, in which sudden shifts in electrolyte balance can affect axonal health and result in hyporeflexia and profound weakness.

Other examples of diseases that cause secondary peripheral neuropathies include (1) the infectious protozoan *Neospora caninum,* which causes a lumbar intumescence neuritis in puppies; (2) paraneoplastic syndromes associated with multiple types of cancer; and (3) immune-mediated polyradiculoneuritis, which is theorized to occur secondary to immune destruction of the myelin sheath.

44.8 JUNCTIONOPATHIES

Junctionopathies are characterized by either complete lower motor neuron paralysis or progressive exercise intolerance with normal reflexes. Examples of the former condition include tick paralysis and botulism, in which an endogenous toxin binds to the presynaptic membrane at the endplate and blocks acetylcholine (ACh) release. Examples of the latter condition include acquired myasthenia gravis, in which ACh is blocked from its reception at the postsynaptic membrane by immune complexes bound to the ACh receptor site.

44.9 MYOPATHIES

The previously described causes of neuropathies can also affect the muscles. The clinical signs associated with myopathies include weakness with normal proprioception; normal to decreased myotatic reflexes; voice change; a stiff, stilted gait, and ventral neck flexion (observed most commonly in the cat). Decreased energy supplies, including glucose and oxygen, can lead to abnormal muscle oxidative metabolism and resultant weakness. Endocrine disturbances, such as hypothyroidism and hyperthyroidism, have been implicated, because thyroid hormone is very tightly regulated within the muscle membrane, and even subtle changes result in aberrant oxidative metabolism. Hyperadrenocorticism results in abnormal glycogen deposition in the muscle and may have permanent effects, even with treatment for the disease, whereas the weakness induced by hypoadrenocorticism is reversible with therapy. Electrolyte disturbances, most importantly hypokalemia and hypocalcemia, can result in severe muscle weakness and tetany, respectively, due to the importance of these two electrolytes in the regulation of muscle ion channels. Other causes of secondary myopathies include the infectious agent *Toxoplasma gondii*,

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hematologic aberrations such as absolute polycythemia, immune-mediated diseases such as masticatory myositis, the polymyositis associated with SLE, and paraneoplastic syndromes (cancer cachexia).

45 CHAPTER • 45 Tremor Syndromes

Dominik Faissler

45.1 DEFINITIONS

Tremor is a common presentation in dogs and cats. The terms *tremble, shake, quiver,* and *shiver* are used interchangeably to describe this involuntary, rhythmic, and oscillatory movement. Tremor results from simultaneous or alternating contractions of agonist and antagonist muscle groups. Electromyographically, biphasic rhythmic bursts can be recorded. Clinically, tremor syndromes present with continuous, rapid, back-and-forth movements of the head, hind legs, or whole body; these movements cease with sleep.

Tremor must be distinguished from myoclonus, fasciculations, tetany, dyskinesia, and seizures. *Myoclonus* is defined as a sudden, short, jerky, shocklike, involuntary movement caused by an abrupt muscular contraction. Myoclonic jerks arise from electrical discharge of the central nervous system and can involve the head, limbs, or trunk. *Fasciculations* are arrhythmic, involuntary, visible contractions of groups of muscle fibers that indicate pathologic discharge of spinal motor neurons. *Tetany* is characterized by skeletal muscle rigidity and spasm. *Dyskinesias* are rare disorders of the central nervous system that result in involuntary, ticlike, repetitive, and episodic movements of individual muscle groups. The terms *dystonia, atheosis, chorea,* and *ballism* are used in human neurology to describe various clinical manifestations of dyskinesia.

45.2 PHYSIOLOGIC TREMOR

Physiologic tremors are difficult to see in normal animals, but they are present at low-amplitude movements, at rest or with posture. Shivering is a normal response to hypothermia, and a fast-rising body temperature in the course of a febrile process may lead to trembling. In both cases, the caudal hypothalamus plays an important role in the induction of muscle oscillations. Fear, stress, joy, and anger are the manifestations of a complex response processed in the limbic system, prefrontal cortex, and hypothalamus. These emotional conditions produce a complex pattern of reactions, including increased muscle tone, adrenergic stimulation, and physiologic muscle tremor. Trembling may also be seen after heavy exercise as a result of metabolic exhaustion and weakness.

45.3 PATHOLOGIC TREMOR

Tremor is considered pathologic when it impairs the patient's normal function. Abnormal tremor has a more synchronous activation and larger amplitude and is more easily visualized. No classification system has been devised for pathologic tremor in animals, and little information is available on the etiology and pathogenesis of this condition.

45.3.1 Type

A *kinetic tremor* (or, as it is commonly called, an *intention tremor*) is evident when the patient performs a voluntary movement, and it is most obvious when the movement is goal oriented. *Intention tremor* usually presents with slow, high-amplitude, to-and-fro movements. *Resting tremor* is most visible at rest and diminishes with voluntary movement; the amplitude of these oscillations is much lower, and the frequency is midrange. A fine, fast *action tremor* occurs when parts of the body are activated in certain positions; this type of tremor may

occur when the animal is attempting greater precision of movement. *Static tremor* is manifested when antigravity muscles are activated.

45.3.2 Distribution

Involuntary movements can be restricted to the head, and intention tremor is the most common presentation. Head bobbing in either a vertical or horizontal direction also is possible. Localized tremor may be confined to the lumbosacral area and hind legs. *Generalized (whole body) tremors* seem to be more common than focal tremors.

45.4 LOCALIZATION OF THE PACEMAKER

Lesions in the lateral cerebellar hemispheres, nucleus interpositus, and cerebellar vermis are associated with intention tremor. Experimental lesions in the rubro-olivo-cerebellar system of cats can induce either intention tremor or resting tremor. In general, except for intention tremor, anatomic localization of the pacemaker is uncertain in dogs and cats.

45.5 PREDOMINANCE OF CLINICAL SIGNS

Some diseases may cause trembling accompanied by other signs. Another group of selective, functional disorders presents with tremor syndromes in which shivering is the predominant complaint.

45.6 DISORDERS IN WHICH TREMBLING IS ACCOMPANIED BY OTHER SIGNS

45.6.1 Metabolic Disorders

In addition to other signs, head or whole body tremors may be present in renal disease, hypoglycemia, hypocalcemia, and hypoadrenocorticism.

45.6.2 Intracranial Diseases

A large number of brain diseases may cause tremors, most often with cerebellar involvement. Head tremors, intention tremors and, less frequently, whole body tremors may be part of the syndrome. Other signs often are more obvious than the tremors, such as ataxia, hypermetria, paraparesis or tetraparesis and, less frequently, broad-based stance, abnormal behavior, cranial nerve deficits, opisthotonos, and seizure-like activity. Tremors are reported to be a possible sign in multisystemic inflammatory disease in borzois and in cerebellitis caused by *Neospora caninum;* cerebellar hypoplasia due to mutation or intrauterine panleukopenia viral infection; fibrinoid leukodystrophy; the late course of neuraxonal dystrophy and Labrador retriever axonopathy; spongiform encephalopathy; neuronal abiotrophies; subacute necrotizing encephalopathy; and several lysosomal storage diseases.

45.6.3 Hind End Weakness

Tremor may be part of the clinical presentation in various disorders, including degenerative lumbosacral stenosis; lumbosacral disc herniation, tumors, or discospondylitis; and nerve root compression. In some

peripheral neuropathies, synaptic dysfunction, and certain myopathies, shivering may be an additional sign. This static tremor is most pronounced when the animal is standing. Weakness and pain are possible causes.

45.7 DISORDERS IN WHICH TREMBLING IS THE PREDOMINANT SIGN

45.7.1 Corticoid-Responsive Tremor Syndrome

A generalized tremor syndrome first was reported in white Maltese dogs. However, the widely used term *white shaker syndrome* turned out to be misleading, because a recent study showed that one half of affected dogs had no or only a par-tial white haircoat. The disease is reported in young to middle-aged West Highland terriers, Maltese dogs, poodles, dachshunds, miniature pinschers, Pekingese, and mixed-breed dogs. An inflammatory process of the central nervous system is suspected. Histopathologically, mild, diffuse meningoencephalitis, characterized by lymphocytic infiltrates and perivascular cuffing, is reported. Immune-mediated disruption of neurotransmitter metabolism, resulting in reduced conversion of tyrosine to dopamine, has been proposed as a mechanism, but this hypothesis appears less likely in light of the high number of nonwhite dogs. The most consistent clinical sign of generalized tremor syndrome is a whole body tremor that worsens with excitement. Other abnormal findings include, in rare cases, spontaneous nystagmus, head tilt, ataxia, and reduced menace response. Cerebrospinal fluid analysis reveals a mild mononuclear pleocytosis and, in some dogs, an elevated protein level. Most patients respond well to treatment with prednisone and propranolol.

45.7.2 Hypomyelination

An inherited genetic defect results in hypomyelination or dysmyelination in the central nervous system but normal peripheral nerves. In shaking pup syndrome, for example, quantitative studies have shown normal axonal diameters but a marked reduction in the number of oligodendrocytes and decreased myelin volume and thickness. Brain structures are affected more than the spinal cord white matter. Failure of precursor cell division and insufficient migration, abnormal maturation, and early cell death of oligodendrocytes are suspected. The origin of the tremor in animals with this developmental myelin disorder is not well understood.

Clinical signs correlate with the degree of myelin deficiency. Affected puppies start to show signs within the first weeks and months of life. Hypomyelinated or dysmyelinated animals have a whole body tremor that worsens when the puppy begins to move (intention tremor may be present in some cases). Exercise or excitement worsens the tremor, which resolves with sleep. Severely affected animals show a “rocking horse” stance or a bunny hop gait or are unable to stand or ambulate. A perpendicular nystagmus is possible. In some mildly affected animals, the tremor plateaus at the end of the first year of life and improves later. There is no known therapy.

In springer spaniels and Samoyed pups, hypomyelination is transmitted by a sex-linked recessive trait. An autosomal recessive mode of transmission is suspected in the dysmyelination syndrome of the chow chow. Hypomyelination also has been reported in the weimaraner, Bernese mountain dog, lurcher, and Dalmatian and in two Siamese kitten littermates.

45.7.3 Spongy Degeneration

The histologic feature of a spongy appearance of the central nervous system has been reported in several breeds. A congenital disorder of amino acid metabolism is suspected but has not been proved in dogs and cats.

A generalized tremor syndrome is reported in the Samoyed, silky terrier, Scottish terrier, and Malinois shepherd –cross puppies. No treatment is available.

45.8 TREMORGENIC TOXINS

Numerous toxins are reported to cause generalized tremor. The mycotoxins penitrem A and roquefortine are produced by *Penicillium* spp. growing on garbage, moldy dairy foods, bread, nuts, grains, or blue cheese. Clinical signs of ingestion of these mycotoxins include generalized tremors, ataxia and, in rare cases, seizures. Metaldehyde, a slug and snail poison, causes generalized tremors. Hyperesthesia, salivation, and seizures vary from mild to severe (see Chapter 70). Hexachlorophene, bromethalin, organophosphates, carbamates, chlorinated hydrocarbons, zinc phosphide, methylated xanthines (caffeine, theophylline, theobromine), pyrethroids, macadamia nuts, and strychnine are other toxins that can cause generalized tremors and ataxia. Strychnine induces severe seizures. Therapy is limited to supportive care.

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45.9 IDIOPATHIC HEAD TREMOR IN DOBERMANS AND BULLDOGS

A localized tremor of the head is reported in Dobermans and bulldogs. The head movement may be in a vertical direction, similar to the affirmation tremor seen in human beings. Head bobbing in the horizontal plane also occurs. The underlying mechanism is unknown.

45.10 IDIOPATHIC TREMOR OF THE HIND LEGS

A tremor of the hind legs has been described in geriatric dogs, particularly in terrier breeds. No weakness or other neurologic abnormalities are noted. A similar syndrome has been observed in young Leonberger dogs. In this breed, a dysfunction of serotonin metabolism is suspected.

46 CHAPTER • 46 Ataxia, Paresis, and Paralysis

Donald C. Levesque

All levels of the nervous system, from the brain to the peripheral nerves, have neurons that in some wayare associated with sensory, motor, or integrative functions of locomotion. Disturbances of these pathways cause some degree of ataxia, paresis, or paralysis. However, because some orthopedic and systemic diseases can mimic thesesigns, the first goal of a neurologic examination is to deter-mine whether the signs observed in the patient actually are due to neurologic dysfunction. Once neurologic deficits havebeen confirmed, the next goal becomes localization of the lesion or lesions. A general algorithm for localization of nervous system lesions, based on the presence of ataxia, is presented in Figure 46-1. Accurate interpretation of clinicalsigns, consistent use of terminology, and an awareness of the ways in which various disease processes can affect the nervous system are essential for the most effective use of any algorithm for localization of nervous system lesions. Recognition of the various forms of ataxia and of the significance ofparesis in association with ataxia is important in lesion localization and may aid in the determination of the etiology and prognosis.

46.1 TERMINOLOGY

Ataxia, paresis, and *paralysis* are terms ascribed to neuro-logic deficits. These conditions must be distinguishedfrom limb lameness and weakness caused by non-neurologic manifestations of gait abnormalities. Ataxia is an abnormality of movement, particularly gait, characterized by a degree of sway and incoordination; it may affect the head, trunk, or limbs. Paresis is a partial loss of voluntary movement andusually is accompanied by conscious proprioceptive deficits. Paralysis is the absence of voluntary motor function andis described as flaccid or spastic. Prognostically, it is important to determine whether pain sensation is present orabsent. Paralysis is not be confused with nonambulatoryparesis.

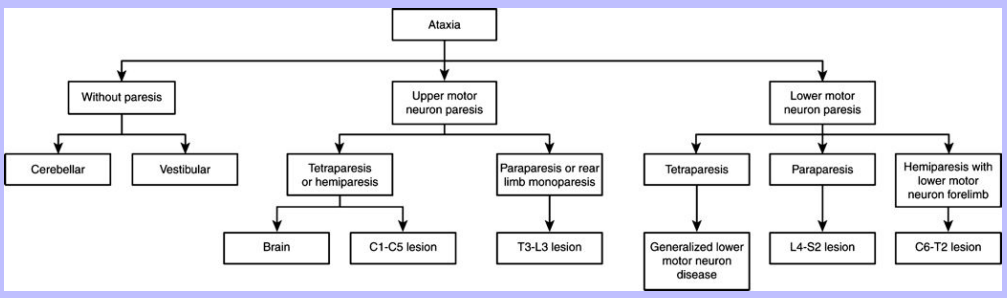
Ataxia, paresis, and paralysis are characterized as generalized or localized. Ataxia and paresis are graded on a scale ranging from mild to severe. Ataxia is further categorized as proprioceptive, vestibular, or cerebellar.

46.2 SIGNS BASED ON THE NEUROANATOMIC LOCATION OF LESIONS

46.2.1 Forebrain (Diencephalon, Basal Nuclei, Cerebral Hemispheres)

In the conscious patient, forebrain disease generally causes relatively mild limb paresis and ataxia. Unilateral lesions usually cause contralateral conscious proprioceptive deficits with minimal gait disturbance. Generalized forebrain disease (e.g., encephalitis, hydrocephalus, midline thalamic lesions) often causes generalized ataxia and mental dullness with only mild to moderate paresis. Although ataxia and paresis often are present in forebrain disease, other signs, such as seizures, disorientation, behavioral changes, circling, and visual deficits, usually predominate. Paralysis is seen only during deep stupor or coma. In general, forebrain disease has less profound effects on locomotion than do lesions of the brain stem, cerebellum, spinal cord, and peripheral nerves.

Figure 46-1 Algorithm for localization of nervous system lesions based on presence of ataxia with or without paresis.



In some instances, cerebral dysfunction mimics thoracolumbar myelopathy by causing rear limb ataxia and paraparesis without detectable forelimb deficits. This apparent paradox can be seen postictally; it also occurs secondary to side effects of anticonvulsant medications, particularly potassium bromide, in some patients. In nearly all these cases, mentation and forelimb dysfunction likely are present but subclinical. Postictal paraparesis can be differentiated from myelopathic paresis by its transient nature. Recovery from postictal paraparesis usually occurs within minutes to hours, compared with days to weeks in patients with myelopathies.

46.2.2 Brain Stem

In the conscious patient, brain stem disease can cause moderate to marked ataxia, hemiparesis, or tetraparesis but rarely paralysis. Unilateral lesions caudal to the pyramidal decussation in the medulla affect ascending sensory and descending motor pathways, causing marked ipsilateral hemiparesis. Vestibular nuclei are commonly affected, causing superimposed vestibular ataxia, head tilt, and nystagmus. The ataxia of central vestibular disease, although sharing many similarities with peripheral vestibular disease, is distinguished by the presence of ipsilateral conscious proprioceptive deficits. Other cranial nerve signs, such as facial paralysis, head muscle atrophy, or dysphagia, may also be present. Hemiplegia and tetraplegia can occur, but lesions severe enough to cause paralysis usually result in respiratory arrest.

46.2.3 Peripheral Vestibular System

Unilateral lesions of the membranous labyrinth or cranial nerve VIII can cause ataxia ranging from mild and barely perceptible to profound and extremely debilitating. Head tilt, horizontal or rotatory nystagmus, positional strabismus, and abnormal oculovestibular eye movements are nearly always present to some degree. Bilateral peripheral vestibular disease most often causes symmetric, generalized ataxia with characteristic wide, swaying head excursions in both directions; oculovestibular eye movements, including pathologic nystagmus, are absent.

Peripheral vestibular disease does not cause paresis or paralysis, therefore proprioceptive deficits are not present. However, because of the strong influence of the vestibular system on limb muscle tonus, vestibular dysfunction results in an increase in contralateral and a decrease in ipsilateral extensor muscle tone, often making it difficult for the examiner to interpret proprioceptive reactions in severely affected patients.

46.2.4 Cerebellum

Because the cerebellum functions as modulator rather than as a site of initiation of motor function, cerebellar disorders cause mild to marked ataxia without paresis or paralysis. Unilateral lesions of the cerebellum cause ipsilateral limb ataxia with dysmetria, usually hypermetria. The flocculonodular lobe of the cerebellum modulates posture and movement based on vestibular input; consequently, lesions at this location cause disequilibrium and ataxia.

46.2.5 Cervical Spinal Cord

Cervical spinal cord disease can cause mild to marked ataxia and forelimb monoparesis, hemiparesis, or tetraparesis. Forelimb monoplegia, hemiplegia, or tetraplegia also can occur. Deep pain sensation is always present in tetraplegic animals with normal respiratory function, because functional transection of the cervical spinal cord cranial to the sixth spinal cord segment results in loss of innervation of the diaphragm and intercostal musculature, with subsequent apnea. Cervical cord lesions caudal to C6 disrupt innervation of the intercostal musculature, leaving only diaphragmatic respiration.

Lesions affecting spinal cord segments C6-T2 cause forelimb hyporeflexia owing to injury of the cell bodies of lower motor neurons that innervate forelimb musculature. Forelimb reflexes are preserved with lesions cranial to C6. Cervical spinal cord disease most often causes injury to ascending and descending axons serving the rear limbs and results in rear limb ataxia with normal to exaggerated rear limb reflexes.

In unusual cases, very focal spinal cord lesions (usually a vascular or contusive type) selectively affect grey matter and spare ascending and descending white matter tracts. If such lesions affect spinal segments C6-T2, flaccid forelimb paresis or paralysis without rear limb deficits can result. Conversely, chronic caudal cervical spinal cord compression, such as can occur in cervical spondylolisthesis, may selectively affect descending and ascending white matter tracts serving the rear limbs, resulting in rear limb ataxia and paresis and no detectable forelimb deficits.

46.2.6 Thoracolumbar (T3-L3) Spinal Cord

Thoracolumbar spinal cord disease can cause mild to marked rear limb ataxia, paraparesis, paraplegia, monoparesis, or monoplegia. Rear limb reflexes are normal to exaggerated. The panniculus reflex generally is reduced or absent two to three spinal segments caudal to the site of a thoracolumbar lesion. Mildly to moderately compressive injuries generally result in ataxia with paraparesis. More severely compressive lesions can cause paraplegia. Contusive or vascular injuriesare usually more acute but cause similar signs. Cranial thoracic spinal cord lesions often cause a more “lumbering,” swaying rear limb ataxia than do more caudal lesions as a result of paresis of the thoracic paraspinal musculature. Nonambulatory paraparetic and paraplegic patients with cranial thoracic lesions often are laterally recumbent and unable to rise to a sternal position. Focal spinal cord ischemia can selectively affect only a portion of the spinal cord, causing monoparesis or monoplegia. Examples of this condition are seen in patients with fibrocartilaginous embolization or ischemia secondary to vasculitis.

Shiff-Sherrington sign, an increase in extensor tone of forelimb musculature after acute thoracolumbar spinal cord injury, is an indicator of severe spinal cord injury but does not necessarily carry a grave prognosis. Generally, the more cranial the lesion, the more exaggerated the forelimb hypertonia.

46.2.7 Lumbosacral (L4-S2) Spinal Cord

Lumbosacral spinal cord disease causes mild to marked rear limb ataxia, paraparesis, paraplegia, or monoplegia with reduced to absent rear limb reflexes. Lesions that affect segments L4 and L5 cause decreased to absent knee-jerk reflexes. Lesions that affect segments L6 through S2 cause decreased withdrawal reflexes of the rear limbs, as well as bladder hypotonia and bladder and anal sphincter hypotonia.

46.2.8 Peripheral Nerve

Peripheral nerve lesions also can cause mild to marked ataxia, paresis, or paralysis of one or more limbs. Hyporeflexia is a consistent finding.

Nerve root avulsion or severance of a major peripheral nerve to a limb results in areflexia and paralysis of the affected muscle or muscles as a result of loss of sensory and motor innervation. Degenerative, inflammatory, and toxic neuropathies generally affect all peripheral nerves and result in varying degrees of ataxia, paresis, and paralysis. Hyporeflexia is a common denominator in these patients. Gait disturbances of patients with polyneuropathy can vary from marked paresis to paralysis to almost cerebellar-appearing dysmetria. Even though the histopathologic changes in nerve fibers and affected muscles may be similar in the forelimbs and rear limbs, it is not unusual for gait abnormalities to be more obvious in the rear limbs. Presumably, this phenomenon is due to the longer distance from the brain to the motor endplates and sensory receptors in the rear limbs, which allows for greater dispersion of motor and sensory action potentials.

Most polyneuropathies in dogs and cats appear to preferentially affect motor fibers, causing ataxia, paresis, and paralysis with preservation of superficial pain sensation and, often, conscious proprioception. With very few exceptions, therefore, a patient presenting with tetraplegia, hyporeflexia, and preservation of superficial pain sensation has a neuromuscular disorder (neuropathy, junctionopathy, myopathy). A notable exception is focal myelomalacia, in which descending motor tracts are affected but ascending superficial and deep pain fibers are preserved.

47 CHAPTER • 47 Altered States of Consciousness: Stupor and Coma

Karen L. Kline

47.1 DEFINITIONS

Stupor and coma are pathologic abnormalities caused by an interruption in the structural, metabolic, and/or physiologic integrity of the brain stem or cerebral cortex. *Stupor* is characterized by a state in which the animal appears to be asleep or unconscious but can be aroused by a noxious stimulus. Once the stimulus is withdrawn, however, the animal may lapse back into the sleeplike state. *Coma* is characterized by a state of unconsciousness in which the animal cannot be aroused even by a noxious stimulus. A strong toe pinch, for example, may elicit a flexion reflex or increased extensor tone but does not cause a behavioral response, such as crying or biting. In either case, prompt action is required to attempt to reverse these signs and correct the underlying cause.

47.2 PATHOPHYSIOLOGY

Consciousness is maintained by sensory stimuli that act through the ascending reticular activating system (ARAS) on the cerebral cortex. Decreasing levels of consciousness indicate abnormal cerebrocortical function or interference with cortical activation by the ARAS. The cerebral cortex controls the content of consciousness, whereas the brain stem controls the level of consciousness. In a sense, the cerebrum is the light bulb, and the brain stem is the rheostat that regulates its brightness. All sensory pathways have collateral input to the ARAS in the pons and the midbrain, and this information is projected diffusely to the cerebral cortex, where cholinergic synapses communicate constantly with cortical neurons. Balance is maintained between the ARAS and the adrenergic (sleep) system, which projects from the midbrain and diencephalon (thalamus). Signs ranging from hyperexcitability to coma can be observed if imbalance exists between the two systems.

The causes of stupor and coma are numerous. The three most important are (1) increased intracranial pressure, (2) cerebral edema, and (3) herniation of brain tissue. Increased intracranial pressure can occur secondary to an increase in the volume of tissue or fluid (e.g., cerebrospinal fluid, edema, or blood) within the cranial vault; even small shifts in these volumescan have dramatic consequences. Causes of increased intracranial pressure include encephalitis, meningitis, mass lesions (e.g., neoplasia, granulomas, or abscesses), vascular events, traumatic injury, or underlying metabolic disturbances, such as hypertension.

Cerebral edema is an abnormal accumulation of fluid in the brain parenchyma. It is classified into three types: (1) vasogenic, which is most commonly associated with brain masses and is due to a breakdown in blood-brain barrier integrity; (2) cytotoxic, which is most commonly associated with metabolic disturbances, such as hypoxia and neuroglycopenia, that cause cell or neuronal death; and (3) interstitial, which is most likely associated with hydrocephalus. The end result of progressively increased intracranial pressure and/or cerebral edema is brain herniation.

There are four different types of herniation, two of which can induce stupor or coma: (1) caudal transtentorial herniation, in which portions of the temporal lobe shift ventral to the tentorium cerebelli and cause midbrain compression; and (2) foramen magnum herniation, the most common form, which occurs when the caudal cerebellar vermis moves through the foramen magnum, causing a compression of the displaced cerebellum and the medulla oblongata. In these cases, injury to the respiratory center, descending motor pathway tracts, and cardiovascular centers in the caudal brain stem can lead to midbrain and cerebral hypoxia and coma, which can be irreversible.

47.3 APPROACH TO THE PATIENTWITH STUPOR OR COMA

After the pet's initial presentation, close attention must be paid to immediate life-threatening injuries and their sequelae, such as hemorrhage, hypoxia, or shock. The ABCs of critical care medicine—airway, breathing, and cardiovascular status—are paramount. Concurrently, a thorough history, including onset and progression of signs, previous illness or injury, and drug use or toxin exposure, should be ascertained. Thorough physical and neurologic examinations should be performed, with emphasis placed on the cardiac rate and rhythm and the respiratory pattern. Simply observing the patient for a short time can yield considerable information. An anatomic diagnosis can be ascertained on the basis of the following: (1) mental status and level of consciousness; (2) neuro-ophthalmologic signs (vision, pupil size and symmetry, and ocular movements); (3) alterations in respiratory pattern; and (4) skeletal motor responses. Following these trends can aid prognostication and the development of treatment protocols and is essential for patient management.

47.3.1 Mental Status and Level of Consciousness

Consciousness is maintained by the midbrain ARAS, which acts as a rheostat, projecting diffusely to the cerebral cortex. Consequently, diffuse cerebral disease or midbrain disease can result in stupor, coma, or other alterations in consciousness, such as dementia. Differentiation between stupor and coma can be achieved with the application of a noxious stimulus, such as a hemostat or needle. Care must be taken to follow trends when evaluating the patient, and hasty prognostication should be avoided. In general, stupor has a better initial prognosis than coma, but exceptions can occur. Other factors include the patient's age, the underlying medical history, and the cause of the alteration in consciousness.

47.3.2 Neuro-Ophthalmologic Signs

47.3.2.1 Pupillary Reactions

Pupil size and reactivity to light can be normal in the comatose patient; alterations in these parameters can aid in neurolocalization and prognostication. Integrity of the retinae, optic nerves, and chiasm and of the rostral brain stem is consistent with pupils that are equal in size and that respond well to light and darkness. In general, lesions of the cerebral cortex andthalamus result in normal or constricted pupils that respond to both darkness and light. Lesions in the brain stem can result in unilateral or bilateral pupillary constriction (pons) or dilatation (midbrain), depending on the location. Peripheral lesions involving cranial nerve (CN) III usually result in dilated pupils with normal vision. Pupils that are bilaterally dilated (fixed) and unresponsive to light imply a guarded to grave prognosis.

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47.3.2.2 Ocular Movements

The pathways that mediate ocular movements lie adjacent to the brain stem regions responsible for consciousness, making it clinically useful to evaluate ocular movements in the stuporous or comatose patient. Physiologic nystagmus or conjugate eye movements (the oculocephalic and doll's eye reflexes) are normal and require integrity of CN VIII (vestibulocochlear nerve), the brain stem (vestibular nuclei, medial longitudinal fasciculus), the cerebellum (flocculonodular lobe), and the nuclei of CN III, IV, and VI. Any disruption in this pathway results in pathologic nystagmus (rotary, horizontal, or vertical downbeat). Ocular movements are evaluated by moving the head in a slow or rapid fashion from side to side while it is held in a fixed position. In the normal animal, this movement results in several beats of horizontal nystagmus (with

the fast component toward the direction of the head movement) that stops once the head movement stops. If the nystagmus continues after the movement stops, if it occurs spontaneously, or if it changes with position, a lesion in the vestibular system is likely to exist. If there is absence of ocular movements in the comatose patient, severe brain stem injury should be suspected, and the prognosis for return to function is guarded to grave.

47.3.3 Alterations in Respiratory Pattern

Severe or progressive brain injury can result in changes in breathing patterns. *Cheyne-Stokes respiration* is characterized by hyperpnea alternating with apnea and can be an indication of a bilateral cerebral hemisphere or diencephalic lesion. Central neurogenic breathing or hyperventilation is associated with lesions in the midbrain pneumotaxic center, whereas lower pontine and medullary lesions result in apneustic or ataxic (gasping) respirations, respectively. When a change in breathing patterns is noted, aggressive therapy may need to be instituted to counteract herniation.

47.3.4 Skeletal Motor Responses

The examination of motor function in the comatose patient provides valuable localizing information. Trends must be monitored in order to follow the disease course. Injury to the descending motor systems can result in either increased or decreased extensor and flexor tone, depending on where the injury occurs. Involuntary movements, such as twitching or paddling, may indicate seizure activity. Decerebrate posture (all four limbs extended) indicates a lesion in the midbrain or pons and can occur primarily or secondary to cerebrocortical herniation; decerebrate posture indicates that the motor pathways that aid in flexion are damaged, and stupor or coma is present. Decerebellate posture (forelimbs extended with alternating hind limb flexion and extension) indicates a rostral cerebellar lesion, and the level of consciousness may not be impaired. Flaccid paralysis due to injury to the descending motor pathways implies a grave prognosis, especially when the patient is stuporous or comatose.

47.4 DIAGNOSTIC PLAN

The causes of stupor and coma are numerous (Figure 47-1). Routine laboratory data (hemogram, serum chemistries, urinalysis) can aid in determining a metabolic cause of the alteration in consciousness. Inflammatory, infectious, or toxic agents may cause changes in the hemogram, whereas metabolic or endocrine disorders may result in changes in the blood chemistries, which would suggest the need for other diagnostic tests, such as evaluation of blood ammonia levels and serum bile acids, adrenocorticotropic hormone (ACTH) stimulation, and thyroid profiles. Chest and abdominal diagnostic imaging (radiographs, ultrasonography) may also be indicated if metastatic or infectious disease is suspected. If minimal changes are noted in these parameters, a primary or intracranial cause of stupor or coma should be considered. Noninvasive methods used to determine the cause of intracranial disease include electroencephalography (EEG) and brain stem auditory evoked response (BAER). These methods are useful for evaluating the integrity of the cerebral cortexand brain stem, respectively, and they can be performed without general anesthesia. Ophthalmic evaluation may help to determine whether high intracranial pressure or infectious disease is present. Computed tomography (CT) and magnetic resonance imaging (MRI) are quite useful for confirmingthe presence and character of intracranial lesions, such as tumors, hydrocephalus, and vascular injuries. If the dog or cat is comatose, general anesthesia may not be necessary. Spinal fluid analysis typically is useful for determining whether the animal has an inflammatory or a neoplastic intracranial process; general anesthesia is required and does carry some risk if high intracranial pressure exists.

47.5 TREATMENT GOALS

Most dogs and cats with stupor or coma have life-threatening injuries that require immediate attention. Establishing a patent airway and maintaining respirations and cardiovascular status (in particular blood pressure) are critical to stabilization, regardless of the underlying cause of the insult. Bloodwork should be evaluated, and intravenous administration of fluids, anticonvulsants, osmotic diuretics and, in some cases, corticosteroids can be instituted to aid patient stabilization. Elevation of the head may help reduce excessive cerebral blood flow, and body temperature should be continuously monitored, especially in the case of seizures. Cerebral edema can be treated using injectable corticosteroids (once the blood pressure has stabilized), osmotic and loop diuretics (mannitol and furosemide, respectively), and hyperventilation. Seizures can be controlled using injectable anticonvulsants such as diazepam, phenobarbital, and pentobarbital. These treatments are discussed in more detail in the chapters on specific brain diseases. Intensive nursing care is paramount. Frequent turning (to avoid hypostatic lung congestion), bladder evacuation, ocular lubrication, optimal nutrition, and proper bedding are imperative.

47.6 PROGNOSIS

The prognosis for animals with stupor or coma depends on the cause of the insult, other underlying disease processes, the location of the injury, the signalment of the patient, and the response to therapy. Serial neurologic evaluations that concentrate particularly on the level of consciousness, ocular movements, pupillary size, motor tone, and breathing patterns can guide the practitioner in terms of treatment options and prognostication. Patience is necessary, especially in cases of brain trauma, and trends in improvement or deterioration need to be followed. If the patient survives the immediate injury, sequelae such as seizures, permanent neurologic deficits, and long-term nursing care should be addressed with the client.

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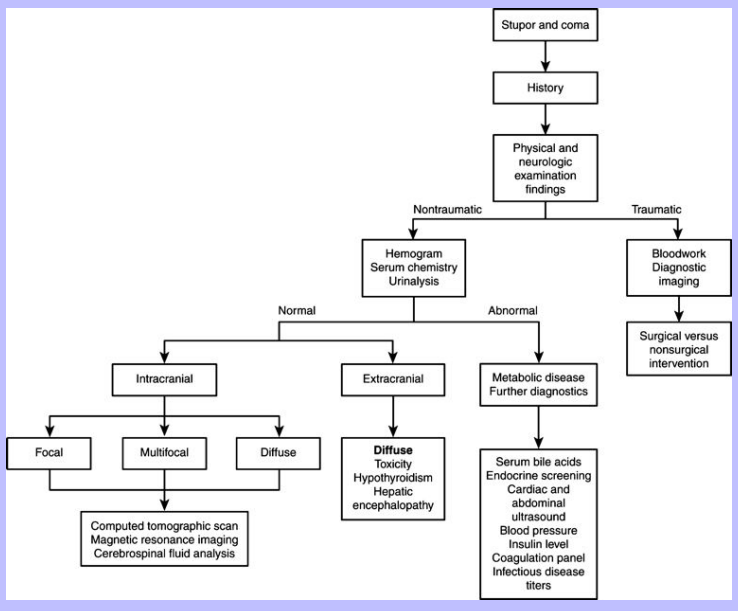
Figure 47-1 Algorithm for diagnostic approach to stupor and coma.



48 CHAPTER • 48 Seizures

Andrée D. Quesnel[†]

***A** seizure* is the clinical manifestation of an excessivedischarge of hyperexcitable cerebrocortical neu-rons. Depending on the location and extent of the seizure discharge, the clinical appearance of seizures can vary a great deal.

Without the use of electroencephalography, seizures can be classified only according to their clinical manifestations. *Generalized seizures* have a widespread onset within both cerebral hemispheres and manifest with loss of consciousness, recumbency, and generalized symmetric motor signs. Most generalized seizures manifest with violent motor activity that involves the whole body (convulsions), such as *tonic* (sustained) and/or *clonic* (repetitive) muscle contractions, limb paddling, and trembling. Jaw chomping and facial twitching are frequently observed. Signs of autonomic hyperactivity (e.g., pupillary dilatation, salivation, piloerection, micturition, defecation) are common. Rarely, the seizures may be atonic ("drop-attack") and must be differentiated from syncope and narcolepsy-cataplexy.

Partial seizures have a focal onset in one cerebral hemisphere and limited spreading within the brain. Their occurrenceindicates the presence of a focal acquired structural brain lesion. Partial seizures may be simple or complex, depending on whether consciousness is disturbed. *Simple partial seizures* arise from and are confined to neocortical structures of one cerebral hemisphere. These do not cause consciousness alterations. Unilateral motor signs such as facial twitching, tonic or clonic movements of one or both limbs, and spasmodic turning of the head to one side are often observed and are contralateral to the side of the seizure focus.

In *complex partial seizures,* the spread of the seizure involves allocortical structures and often continues bilaterally. Consciousness is either impaired or lost. There may be contralateral or bilateral asymmetric or symmetric motor signs, usually limited to some parts of the body. Bizarre activity, both stereotypical (e.g., circling) and behavioral (e.g., startling, growling, hissing, chasing and attacking imaginary or real objects, running in a panic), may also be observed, particularly in cats.

Some seizures thought to be mild generalized seizures are likely complex partial seizures. In the latter type, consciousness is impaired or lost and there is bilateral motor activity that usually does not result in recumbency; however, there is an arrest of the animal's ongoing activities (e.g., it stops if moving and may sit if standing). Motor signs are limited to bilateral facial twitching, jaw chomping, or lip smacking, sometimes with mild generalized trembling or spasms of the neck and front end. Occasionally, there may be decreased motor function that causes stumbling, crawling, or inability to get up and walk. The dog or cat may still be aware and responsive to varying degrees. Because these seizures are not manifested by complete loss of consciousness and generalized motor signs, the underlying neuronal discharge likely has a limited spread within the brain, which is a feature of partial seizures.

A third class of partial seizures are those that secondarily evolve to generalized seizures. Secondary generalization may occur so quickly that no features of partial seizures may be observed clinically.

Another hallmark of partial seizures is an *aura*. An aura is considered to be the initial portion of the seizure, experienced before the consciousness is altered and for which memory is retained in people. It corresponds to the onset of a simple partial seizure before it evolves into a complex partial or a generalized seizure. In animals, it is most often manifested by behavioral changes within a few seconds or minutes of the apparent seizure onset (e.g., attention seeking or withdrawal, depression or agitation, pacing, whining, howling). Mood changes that precede seizures for several hours or even longer should not be confused with an aura. This is rather a prodrome and is not the

result of the onset of cerebral epileptic activity. It may be observed before many seizure types and has no diagnostic value.

Localized postictal motor deficits also indicate that a partial seizure has occurred. This phenomenon, referred to as *Todd's paralysis* in human beings, consists of a transient (minutes to hours) localized loss of motor function that follows some partial seizures. It may be attributed to neuronal exhaustion or increased inhibition in the region of the seizure focus. It is observed contralateral to the focus.

Seizures may occur as brief, isolated events (usually lasting 2 minutes or less), cluster seizures (two or more over a 24-hour period), or status epilepticus (sustained or serial seizures lasting at least 30 minutes and without intervening periods of full recovery). They can be convulsive with generalized and violent motor activity (e.g., tonic-clonic generalized seizures) or nonconvulsive with milder and often subtle motor signs (e.g., partial seizures limited to facial twitching).

The term *epilepsy* should be restricted to seizure disorders with inactive intracranial causes. *Primary epilepsy* (functional, asymptomatic) is the result of functional cerebral disturbances for which there would be no underlying cause other than a hereditary predisposition (e.g., canine idiopathic epilepsy). *Secondary epilepsy* (structural, symptomatic) is caused by acquired but inactive brain lesions (e.g., posttraumatic, postischemic, and postencephalitic gliosis). The term *cryptogenic epilepsy* may be used when evidence exists of a structural brain lesion (e.g., partial seizures), but this cannot be further documented, and the etiology remains unknown.

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48.1 GENERAL PATHOPHYSIOLOGY

The neuronal hyperexcitability that underlies the generation of seizures is the result of an imbalance between normal excitatory and inhibitory mechanisms. This may be due to an intracranial or an extracranial disease process. Intracranial causes of seizures include primary brain disorders, either functional disturbances of neurons (e.g., idiopathic epilepsy) or structural brain lesions that irritate the surrounding neurons. Structural brain lesions can be active (e.g., neoplasms, encephalitides) or inactive (e.g., glial scars). Extracranial causes of seizures alter the brain biochemical homeostasis in favor of excitation and may be exogenous (seizurogenic toxins) or endogenous (severe metabolic disturbances).

It is important to appreciate that seizures enhance the likelihood of further seizures, regardless of their cause. The development of progressive and refractory seizure disorders correlates well with the cumulative number of seizures, especially when they have a high rate of recurrence, and the seizures may occur relatively early in some cases. Such self-perpetuating phenomena may also be involved in acutely recurring seizures (cluster seizures and status epilepticus), which often become more difficult to control the longer interval from their onset. Rapidly recurring seizures may recruit adjacent as well as remote areas of the brain into the epileptic discharge *(kindling phenomenon)* and may also produce neuronal damage. These factors likely contribute to the development of progressive and refractory seizure disorders. Early diagnostic and therapeutic procedures, especially aggressive antiepileptic drug therapy, are crucial for optimal seizurecontrol in both acute and chronic seizure disorders.

† During the preparation of this manuscript, Dr. Andrée Quesnel died at the age of 44 after fighting lung cancer for a year.

Neurology was a great passion in her life. She had been a Diplomate in the specialty of neurology since 1994. Her main interests were seizure disorders and feline diseases.

As a professor at the University of Montreal, she was instrumental in building the neurology department. She made neurology understandable and even enjoyable for her students. As a friend and colleague, she taught us much. Not surprisingly, she was the recipient of many teaching awards.

She was rigorous, independent, and a perfectionist, but all of those who knew her will remember her laugh and her friendship more than anything.

She will be greatly missed.

—Dr. Veronique Sammut, Former Resident in Neurology, University of Montreal. February 2004.

48.2 DIAGNOSTIC APPROACH

48.2.1 Historical Findings

Careful scrutiny of the seizure history (age at the first seizure, seizure type, and initial frequency) often brings to light critical information about the underlying cause. An overview of this process appears in Figure 48-1.

In dogs, idiopathic epilepsy should be excluded if the first seizure did not occur between the ages of 6 months and 5 years, if all seizures are not primarily generalized tonic-clonic, if aura or localized postictal motor deficits have been observed, or if the first few seizures occurred at less than 4-to 6-week intervals. High-frequency seizures may develop with idiopathic epilepsy in many medium or large breeds of dogs (e.g., Border collie, Dalmatian, German shepherd, golden retriever, Siberian husky, Saint Bernard), but this usually occurs several months after the seizure onset. Another cause should be suspected in some breeds of dogs (e.g., Doberman pinscher, rottweiler, Newfoundland, brachycephalic breeds) and in cats, which are less likely to suffer from idiopathic epilepsy.

48.2.2 Physical Findings

Physical and fundic abnormalities may be related to seizures, revealing the existence of a multisystemic infectious, metabolic, hypoxic (e.g., polycythemia), or neoplastic disease.

In the neurologic examination, particular attention should be paid to tests that evaluate the thalamocortex (e.g., menace response, facial [nasal septum] sensation, and postural reactions [proprioceptive positioning and hopping]). Postictal disturbances may include bilateral and systemic deficits and should not be interpreted as evidence of structural brain disease. Subtle unilateral or bilateral but asymmetric deficits are frequently found in patients with a seizure disorder; these can be overlooked if the response obtained on both sides is not carefully compared. Such deficits indicate the presence of a structural lesion in the contralateral cerebral cortex or thalamus. Neurologic deficits that cannot all be attributed to a focal cortical or thalamic lesion indicate multifocal central nervous system involvement, which is usually caused by infectious or noninfectious (immune mediated) encephalitides.

48.2.3 Diagnostic Plan

Once the seizure history has been scrutinized and the clinical examinations performed, the likelihood of an intracranial or extracranial cause can often be established, and a rational diagnostic evaluation can be planned (see Figure 48-1).

Despite extensive diagnostic investigation, an etiology is often difficult to establish in seizure disorders with intracra-nial causes. However, the main objective is not necessarily toreach a precise diagnosis, but rather to rule out conditions thatwould require or benefit from specific medical treatment (e.g., encephalitides) and/or

surgical treatment (e.g., neoplasms). Once this has been done, symptomatic antiepileptic drug therapy is the only treatment option.

48.3 TREATMENT

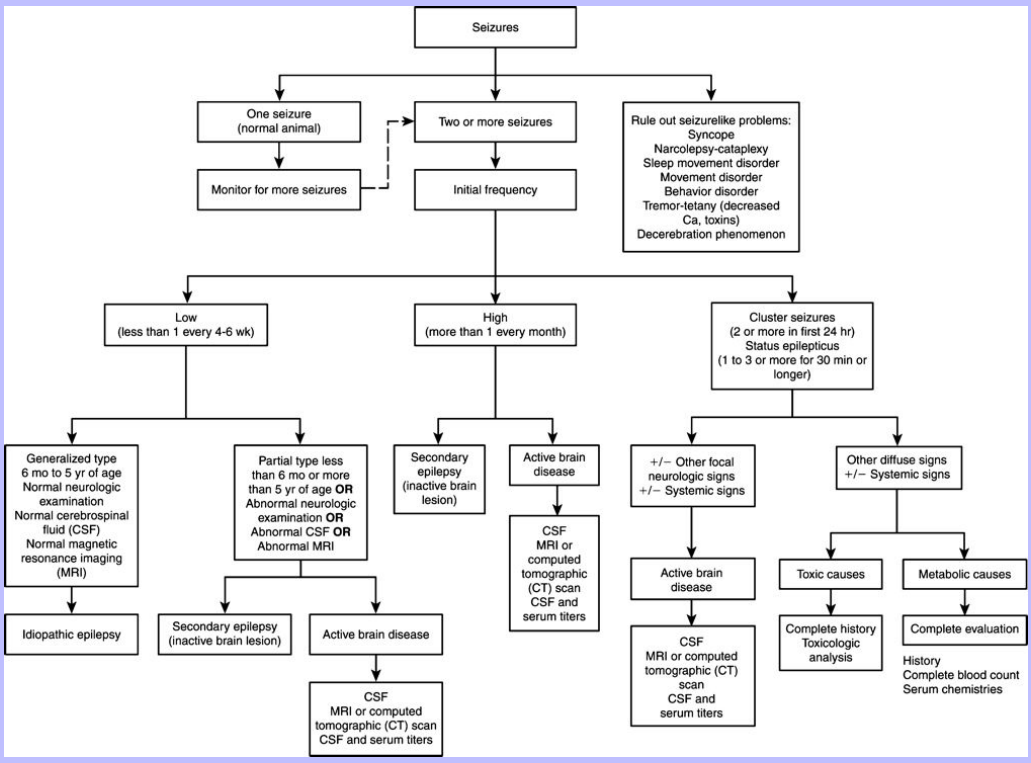
Status epilepticus and cluster seizures, whether convulsive or nonconvulsive, are emergencies. Their management is outlined in Box 48-1.

Oral maintenance antiepileptic (AED) drug therapy should be initiated as soon as two consecutive seizures have occurred in an interval of less than 6 to 8 weeks; this includes cluster seizures and status epilepticus, even the first occurrence of seizures. The importance of early, aggressive, and rational treatment cannot be overemphasized. Guidelines for oral maintenance therapy are presented in Boxes 48-2 and 48-3. The goal of treatment is to reduce the seizure frequency to less than one single seizure every 6 to 8 weeks as soon as possible.

Potassium bromide has replaced phenobarbital as the first-choice antiepileptic drug for dogs. It offers the advantage of being eliminated by the kidneys with no risk of hepatic toxicity and minimal drug interactions. When used as a first-line drug, potassium bromide seems to be as effective as phenobarbital, yet has no toxicity potential other than causing excessive side effects with overdosing or individual intolerance. Also, it can be administered once daily; it is not expensive; precise therapeutic guidelines have been devised; serum bromide concentration testing is available in most veterinary laboratories at the same cost as for phenobarbital; and it is not a controlled drug. The main inconvenience of potassium bromide is its very long half-life (3 to 4 weeks), with the resulting long delay (4 to 5 months) before steady state and maximal antiepileptic effect for a given dosage are obtained. In cases of high seizure frequency, therefore, treatment must be initiated with a loading dose in order to reach a low therapeutic serum concentration within 24 to 48 hours. However, a long half-life is an advantage for minimizing both serum concentration fluctuations between dosing intervals and the effect of missed doses.

Adverse effects of potassium bromide are similar to those of phenobarbital (polydipsia, polyuria, polyphagia). Gastrointestinal disturbances (vomiting, diarrhea, loss of appetite) are also occasionally observed and may be due to the hypertonic and osmotic nature of bromide formulations. Medicating with food or dividing the daily dosage into two doses may alleviate this problem. Signs of an excessive bromide serum concentration include sedation and hindlimb paresis that is strikingly more marked than ataxia. These are usually seen with serum concentrations above 15 mmol/L (1.5 mg/mL), although many dogs tolerate well levels up to 25 to35 mmol/L, which may provide additional antiepileptic protection in some cases. Rare idiosyncratic reactions to bromide include pruritic dermatitis, paradoxical hyperactivity, and pancreatitis. The point is unclear, but some speculate that the pancreatitis may be due to marked polyphagia and dietary indiscretion, mainly when bromide is used in combination with phenobarbital.

Figure 48-1 Algorithm for diagnostic approach to seizures.



48.3.1

Box • 48-1 Emergency Treatment of Cluster Seizures and Status Epilepticus in Dogs and Cats

I. **The animal is not seizing** at the time of presentation but has had cluster seizures (CS) or status epilepticus (SE) within the previous 12 to 24 hours.

A. Perform a complete physical and neurologic examination.

B. Collect appropriate samples for eventual laboratory testing: complete blood count (CBC), biochemical profile, urology and, in patients already on maintenance therapy, determination of the serum antiepileptic drug concentration ($[AED]_s$).

C. In naive patients, initiate oral maintenance AED therapy with a loading dose.

1. *Dogs*: Potassium bromide (KBr) 450–600 mg/kg.

a. Divide into 4 subdoses to be administered with food q 3-4h. Continue with the maintenance dosage (40–50 mg/kg q24h) the next day. If marked side effects (e.g., difficulty walking) develop within the nextfew days, administration of the daily maintenance dose may be stopped for a few days.

b. Measure $[Br]_s$ on day 3. If it is <12–15 mmol/L, especially if seizure recurrence is likely in the next few weeks (e.g., more than 1 seizure/1–2 weeks before treatment onset), give another oral mini-loading dose of 250 mg/kg for each desired 5 mmol/L increment of the [Br]s.

c. Measure $[Br]_s$ again 3 weeks later. If it is lower than on day 3 or if it is suboptimal (<15–20 mmol/L), increase the maintenance dosage accordingly. A mini-loading dose may also be given if more than 1 seizure has occurred since the treatment onset.

d. Measure $[Br]_s$ 3 months after treatment initiation or modification and adjust the dosage accordingly (see Box 48-2).

2. *Cats*: Phenobarbital (PB) 15–20 mg/kg slow IV. This should immediately provide a therapeutic serum PB concentration ($[PB]_s$) of 80–110 µmol/L.

a. Continue with a maintenance dosage (2.0–2.5 mg/kg q12h) 12 or 24 hours later, depending on the degree of sedation.

b. [PB]s may be measured just before administration of the first oral dose. A mini-loading dose of 1 mg/kg IV may be added for each 5 µmol/L to be added to the $[PB]_s$.

c. Measure $[PB]_s$ 2 weeks later and adjust the dosage if necessary, aiming at an optimal $[PB]_s$ of 100–130 µmol/L.

D. In patients already treated with AED, measure $[AED]_s$ (this first can be estimated based on the administered dosage). Add a mini-loading dose and increase the maintenance dosage if $[AED]_s$ is suboptimal, or add another AED (initial loading dose) to the treatment regimen if the $[AED]_s$ is optimal (see Boxes 48-2 and 48-3).

E. If the animal has 2 or more seizures or a prolonged seizure during the 24 hours after its presentation, continue tosection II, *A,* below.

II. **The animal is seizing** at the time of presentation (convulsive or nonconvulsive seizures).

A. Immediately stop the ongoing seizures.

1. Give a diazepam (DZ) IV bolus of 1.0 mg/kg in dogs and 0.5 mg/kg in cats. If seizure activity does not subside within 1–2 minutes, repeat the DZ bolus (can be repeated 1–2 times without significant risk of cardiorespiratory depression).

2. Restore and maintain homeostasis.

a. Maintain patent airway and administer oxygen if necessary.

b. Maintain body temperature between 38° C and 39.5° C.

c. Do not give glucose or calcium unless a deficiency is documented by laboratory testing (or is highly suspected and laboratory testing is not readily available).

d. Continuously monitor vital signs and look for potential complications (e.g., signs of increased intracranial pressure, neurogenic pulmonary edema, cardiac arrhythmias, intravascular disseminated coagulation). Provide intensive supportive care to a markedly sedated or stuporous patient.

3. Obtain samples for laboratory analysis as soon as possible (see section I, *B,* above).

B. Prevent seizure recurrence over the following hours.

1. If a maintenance PB treatment will be started (first-choice AED in cats or add-on drug in dogs), administer an IV loading dose of 15–25 mg/kg in dogs and 15–20 mg/kg in cats (see section I, *C,* step 2, above).

a. Maximal antiepileptic effect after IV administration of PB is obtained only after 20–30 minutes (slow brain penetration). If ≥ 1 seizure occurs before that time, administer another DZ bolus.

b. If maintenance PB therapy is not to be initiated or if 1 or more seizure occurs despite the administered IV boluses of DZ and PB, continue to the next step (II, *B,* no. 2).

2. Administer a continuous IV infusion of DZ at the rate of 0.5–1.0 mg/kg/h in dogs and 0.5 mg/kg/h in cats.

a. Add the DZ to maintenance fluids in an in-line burette. Avoid using saline in patients treated with KBr (this would rapidly lower $[Br]_s$ and possibly precipitate withdrawal seizures). Prepare only 1–2 hours of solution at a time (DZ is rapidly adsorbed into the administration set plastic and is inactivated by light).

b. If more than 20 minutes have elapsed since administration of the last DZ bolus, give another one at the beginning of the infusion to rapidly return to a therapeutic serum benzodiazepine concentration ($[BZ]_s$) that will be maintained by the infusion afterward.

c. If no other seizures occur within the first 4–6 hours of the infusion onset, progressively decrease the infusion concentration by 25%-steps every 4–6 hours. If 2 or more seizures occur at any time during the infusion, continue to section II, *C,* below.

3. If it is absolutely impossible to administer an IV infusion (e.g., prohibitive cost for the owners, unavailable continuous in-hospital monitoring, no possibility for referral), administer repeated IV boluses as a “salvage procedure.”

a. After an initial bolus (1 mg/kg in dogs and 0.5 mg/kg in cats), give other boluses of 0.5 mg/kg q20min for a total of 4–5 boluses, even if no other seizures have yet occurred. A therapeutic $[BZ]_S$ should be maintained for several hours.

b. Marked sedation should subside within a few hours.

4. Oral maintenance AED therapy should be initiated (loading dose protocol), or continued but improved to provide adequate long-term antiepileptic protection.

a. In patients that cannot swallow safely due to marked sedation, administer the AED scheduled doses parenterally (PB and DZ by the IM route and KBr per rectum).

C. Control refractory seizures.

1. If ≥2 seizures occur during the DZ infusion, administer another DZ bolus and increase the infusion rate (up to 1.5 mg/kg/h in dogs and 1.0 mg/kg/h in cats) for 6–8 hours before attempting to progressively decrease it.

a. In patients naive to PB, an IV loading dose may also be given (give only 15 mg/kg to avoid the risk of cardiorespiratory depression with combined IV administration of DZ and PB).

b. If ≥2 seizures recur, discontinue the DZ infusion and administer a propofol infusion (see next step [II, *C,* no. 2], below).

2. Propofol

a. Give an initial bolus of 1.0–3.5 mg/kg or more, to effect.

b. Initiate a constant-rate infusion of 0.01–0.25 mg/kg/min (use an automated syringe) and administer for at least 6–12 hours before progressively decreasing the infusion rate. If seizures recur when the infusion rate is decreased, increase the rate. Up to 24–48 hours of treatment may be necessary to control very severe CS and SE. In cats, proceed to frequent evaluation of the hematocrit and red blood cell morphology to detect Heinz body formation and possible hemolytic anemia.

c. If frequent seizures persist, proceed to general anesthesia.

3. General anesthesia

a. Propofol (dogs only): IV bolus of 4–6 mg/kg followed by an infusion of 0.1–0.3 mg/kg/min, to effect.

b. Isoflurane

c. Pentobarbital: IV bolus of 2–5 mg/kg, to effect, followed by an infusion of 5 mg/kg/h for several hours. Do not confuse dysphoric anesthetic recovery (e.g., paddling, stiffness) with seizure recurrence.

d. Always provide optimal anesthetic monitoring and supportive care (e.g., intubate, ventilate, prevent or correct hypothermia and hypotension).

III. Treatment of cluster seizures at home.

A. For dogs known to have CS, provide injectable DZ (in its original vials, not in a plastic syringe) to be administered per rectum at home: 1 mg/kg after the second or third seizure has occurred within 12 to 24 hours. This should be repeated 3–4 times at 20-minute intervals to obtain and maintain therapeutic $[BZ]_s$ for several hours. If ≥2 seizures recur despite this treatment, emergency in-hospital IV administration of AED is necessary.

48.3.2

Box • 48-2 Guidelines for Maintenance Oral Antiepileptic Drug Therapy in Dogs

I. Perform a complete blood count (CBC), serum biochemistry profile, and urology to establish pretreatment values.

II. First-choice antiepileptic drug (AED): Potassium bromide (KBr).

A. Initial dosage: 40–50 mg/kg q24h

B. Contraindication: Renal insufficiency

C. Follow-up

1. Measure $[Br]_s$ 3 weeks after initiation of therapy (50% of steady state is reached at that time) and adjust dosage accordingly, aiming at an optimal $[Br]_s$ of 20–25 mmol/L (2.0–2.5 mg/mL) at steady state (practically reached 3 months after treatment initiation or modification).

2. Measure $[Br]_s$ again at steady state and adjust the dosage using the following formula:

$$\text{Optimal daily dose} = \frac{\text{Desired } [Br]_s}{\text{Actual } [Br]_s} \times \text{Actual daily dose}$$

$[Br]_s$ may be increased up to 25–30 mmol/L as long as this does not cause excessive side effects while significantly improving the seizure control.

3. Monitor $[Br]_S$ and renal function at least once a year in young adults and every 6 months in older dogs.

4. As soon as adequate seizure control (less than 1 seizure/6-8 weeks) is not obtained or is no longer maintained despite $[Br]_s$ of 20–25 mmol/L, add a second AED (phenobarbital) to the treatment regimen. Continue KBr and maintain the $[Br]_s$ in the optimal range.

D. Other considerations

1. Initiate KBr therapy with an oral loading dose (450–600 mg/kg) if the interval is <3–4 weeks between successive seizures, including recent cluster seizures (CS) or status epilepticus (SE) (see Box 48-1 for treatment protocol).

2. Ensure a stable dietary chloride intake (brand and amount of food and treats) to avoid $[Br]_s$ fluctuations (renal elimination of bromide is directly proportional to the chloride intake). Seizure breakthrough may occur if $[Br]_s$ decreases, or excessive side effects may

develop if $[Br]_s$ increases. If a dietary change must be made, monitor $[Br]_s$ 6 weeks and then 12 weeks later and adjust the dosage if necessary.

III. Second-choice antiepileptic drug: Phenobarbital (PB).

A. Initial dosage: 2.5–4 mg/kg q12h. Increase the dosage by about 50% in puppies (possibly in kittens also) because of their higher metabolic rate.

B. Contraindication: Liver disease

C. Follow-up

1. Always measure PB serum concentration ($[PB]_s$) 2 weeks (1 week in immature animals) after treatment onset and dosage modification. Adjust the dosage to reach an optimal $[PB]_s$ of 100–130 µmol/L (23–30 µg/mL). Use the following formula:

$$\text{Optimal daily dose} = \frac{\text{Optimal } [PB]_S}{\text{Actual } [PB]_S} \times \text{Actual daily dose}$$

Also perform a CBC to detect rare but possible PB-induced blood dyscrasias (e.g., neutropenia, thrombocytopenia).

2. As soon as adequate seizure control (less than 1 seizure/6–8 weeks) is not obtained or is no longer maintained despite an optimal $[PB]_S$ and $[Br]_S$, add a third AED to the treatment regimen. Continue PB and KBr and maintain their serum concentrations within the optimal ranges.

D. Other considerations

1. Initiate PB therapy with an IV loading dose of 15–25 mg/kg if seizures are occurring at intervals of less than 7 days, including recent CS or SE (see Box 48-1 for treatment protocol).

2. PB often causes a progressive and marked liver enzyme induction that stabilizes after the first 4–6 months of treatment in dogs. This increases the metabolism of PB to the point that $[PB]_S$ may significantly decrease and may not even increase after dosage increment during the first months of treatment. Ideally, $[PB]_s$ should be monitored, and the dosage increased if necessary, at 2 and 6 weeks, then at 3 and 6 months after treatment initiation. Liver enzyme induction also leads to a mild increase of the serum alanine aminotransferase (ALT) (4–5 times the upper reference limit) and a marked elevation of ALP (sometimes >1000 U/L). This should not be interpreted as liver toxicity unless there are other laboratory abnormalities (e.g., hypoalbuminemia, elevated preprandial and postprandial bile acids), accompanied or not by clinical signs suggestive of liver failure.

IV. Third-choice antiepileptic drugs: Several human AEDs may be tried. Consult a veterinary neurologist for the most suitable AED, its recommended dosage, follow-up schedule, and so on.

V. Client communication (verbal and written)

A. Define the treatment goals and side effects/toxicity.

B. Emphasize the importance of complying with drug administration regimens, of keeping a seizure calendar (dates, duration, and intensity), and of consulting as soon as adequate seizure control has not been obtained within the expected time or is no longer achieved, as well as for any treatment modification.

C. Insist on the importance of initial determinations of $[AED]_s$ and periodic blood analysis (CBC, biochemistry and $[AED]_s$) every 6–12 months.

D. Define emergency situations and establish a precise emergency plan.

E. Recommend that intact females be spayed as soon as a diagnosis of epilepsy is made.

VI. Drug interactions and contraindications

A. Do not administer drugs that may lower the seizure threshold: acepromazine, xylazine, ketamine, estrogens, tricyclic antidepressants (e.g., amitriptyline), and bronchodilators (e.g., aminophylline, terbutaline, theophylline).

B. Do not administer drugs that interfere with the metabolism of PB (may result in rapid accumulation of a toxic $[PB]_s$): chloramphenicol, cimetidine, ranitidine, and tetracyclines.

VII. Only if no seizures have occurred for 6–12 months, consider slow weaning of AED over a period of a few months. If more than 1 seizure/6–8 weeks recurs during or after weaning, resume therapy, probably for life.

48.3.3

Box • 48-3 Guidelines for Maintenance Oral Antiepileptic Drug Therapy in Cats

Recommendations are the same as for dogs (see Box 48-2) with the following differences:

I. First-choice antiepileptic drug: Phenobarbital (PB).

A. Initial dosage: 2.0–2.5 mg/kg q12h.

B. Hepatic toxicity and enzymatic induction has not been documented in cats; significant elevation of liver enzymes should be investigated.

II. Second-choice antiepileptic drug: Diazepam (DZ).

A. Initial dosage: 0.5–1.0 mg/kg q12h.

B. Measure serum total benzodiazepine concentration ($[BZ]_s$) 5 days after onset of therapy and adjust the dosage (use the same formula as for PB), to reach a therapeutic range of 500–800 nmol/L (500–800 ng/mL). Evaluate liver enzymes at the same time to detect rare but possible idiosyncratic acute hepatic necrosis; if elevated, discontinue DZ and add potassium bromide.

III. Third-choice antiepileptic drug: Potassium bromide (KBr).

A. Initial dosage: 30–40 mg/kg q24h.

B. Because the half-life of KBr is shorter in cats (slightly less than 2 weeks), first monitor the $[Br]_s$ at 2 weeks (50% of steady state reached) and then at steady state (2 months).

C. Bromide has been reported to induce bronchial asthma in up to one third of treated cats. The onset is often acute, 2 weeks to 2 years after treatment initiation, and sometimes is life-threatening. KBr is therefore contraindicated in cats with past or actual asthmatic problems. Although glucocorticoids may alleviate clinical signs in some cats, it is preferable to discontinue treatment to avoid possible life-threatening deterioration.

Phenobarbital is the first-choice antiepileptic drug for cats. In dogs it is the drug of second choice, to be added to the treatment regimen when adequate seizure control cannot be obtained despite achievement of an optimal or supraoptimal serum bromide concentration. Phenobarbital is effective; safe when adequate follow-up is assured; and inexpensive. Although the therapeutic range is reported to be 65 to175 μmol/L (15 to 40 μg/mL), levels below 100 μmol/L(23 μg/L) are often insufficient to obtain and maintain adequate seizure control, and levels higher than 140 μmol/L (32 μg/mL) are more likely change in behavior, to cause excessive side effects and hepatic toxicity on a long-term basis. Rare hypersensitivity reactions attributed to phenobarbital include hyperactivity in dogs and pruritic dermatitis, neutropenia, and thrombocytopenia in both species.

48.4 OUTCOME

The prognosis of seizure disorders depends mainly on the nature of the underlying cause and on the response to therapy. Idiopathic epilepsy often progresses to refractoriness despite adequate treatment in some large breed dogs; this is less common in small breeds. Although seizure disorders of cats are almost always the result of structural brain lesions, these are most often inactive or self-limiting. Even if cats have severe seizures at some point during the course of the disease, the seizures can most often be well controlled or even completely stopped with adequate therapy. Refractoriness to antiepileptic drug therapy appears to be less common in cats.

49 CHAPTER • 49 Deficits of Function Due to Peripheral Cranial Neuropathies

Vince Pedroia

Signs of the most common peripheral cranial neuropathies in animals are acute blindness, Horner's syndrome, jaw drop, unilateral facial paralysis, loss of balance, dysphagia and regurgitation, and stridor (Figure 49-1 to 49-6). The same clinical scenario may introduce either a benign, self-limiting condition or a relentless, hopeless disease. Therefore it is crucial to evaluate these dogs and cats appropriately so that hasty decisions regarding euthanasia are not made, nor are useless pursuits undertaken. Furthermore, the dysfunction in question may be due to neuropathy, but the same dysfunction may be due to abnormality of the effector organ, such as the eye, vestibule, neuromuscular junctions, or muscles. In general, dogs and cats presenting with these disorders can be managed along the guidelines below. Otherwise, referral for evaluation would be recommended.

49.1 DISCOVERY AND THE NEUROLOGIC EXAMINATION

Clinical scenarios involving peripheral cranial neuropathies can be dramatic and disturbing to dog or cat guardians. These problems have a tendency to be noticed suddenly. However, they also can be incidental discoveries made during the physical examination. As always, it is important that clinicians remain attentive during the physical examination so that incidental neurologic deficits are not missed. Any of these presentations would be reason for a neurologic examination. The expression “complete neurologic examination” is often heard; this is redundant. The presence of any of these conditions would dictate that the entire nervous system be surveyed, because some signs may be very difficult to detect. For example, a patient with a balance disorder may have conscious proprioceptive deficits that may be subtle or difficult to detect, depending on the severity of the disturbance. Also, some disorders may be multifocal, and that discovery would be crucial to the differential diagnosis. Because some nerves, such as the trigeminal nerve, serve multiple functions and multiple areas, it is important to survey all its realms. In this example, there may be deficits of one sensory area but not another. It is important to tax the nervous system to reveal some signs. For example, the animal should be inverted to evoke and detect positional nystagmus.

Figure 49-1 Acute blindness with pupil light reflexes.

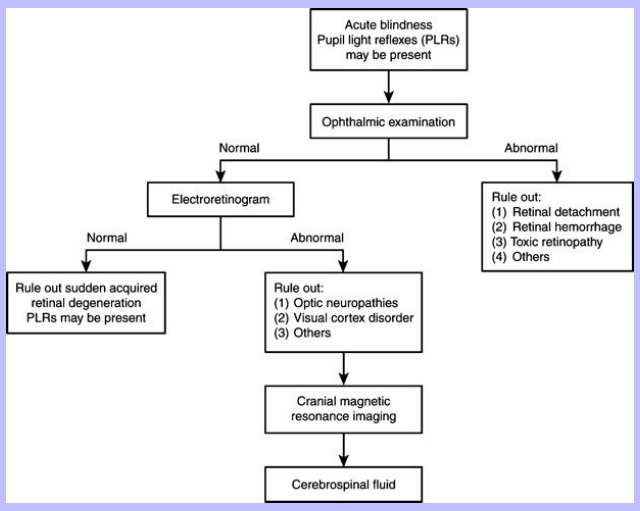


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Figure 49-2 Acute Horner's Syndrome.

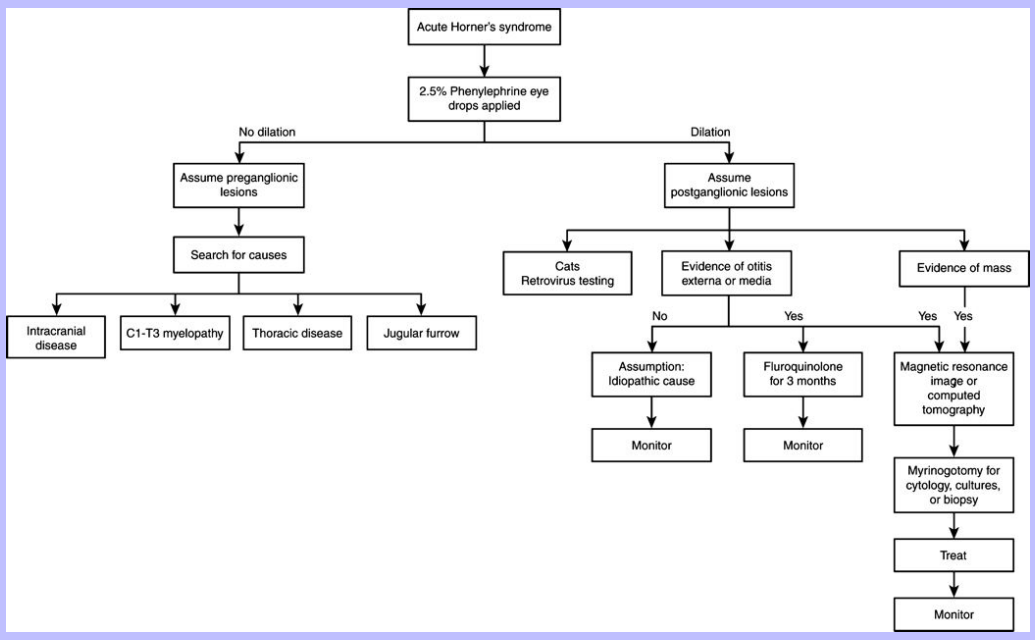

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Figure 49-3 Acute urilateral facial paralysis.

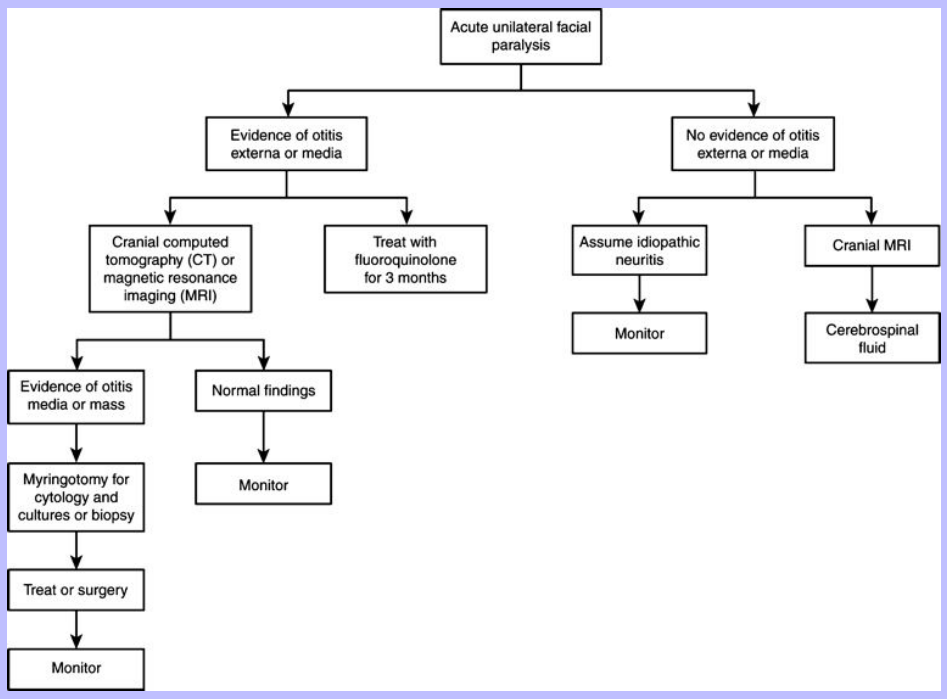

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Figure 49-4 Acute loss of balance.

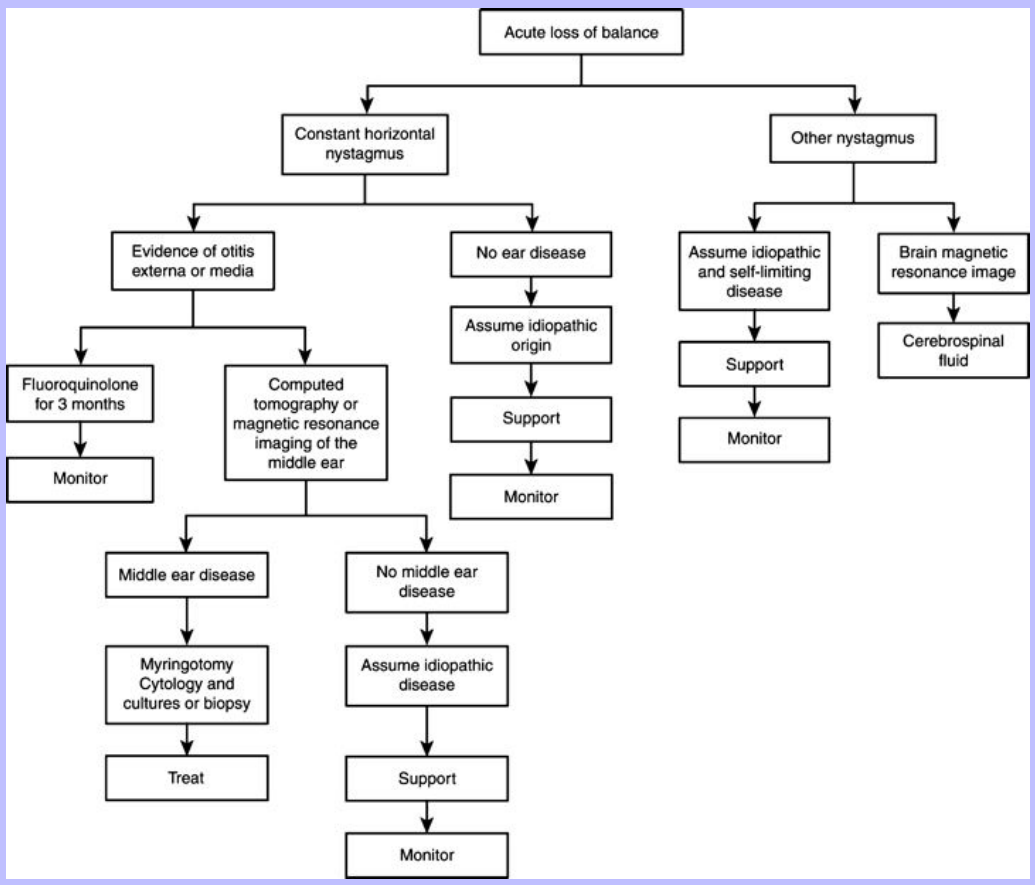

Figure 49-5 Dysphagia or regurgitation.

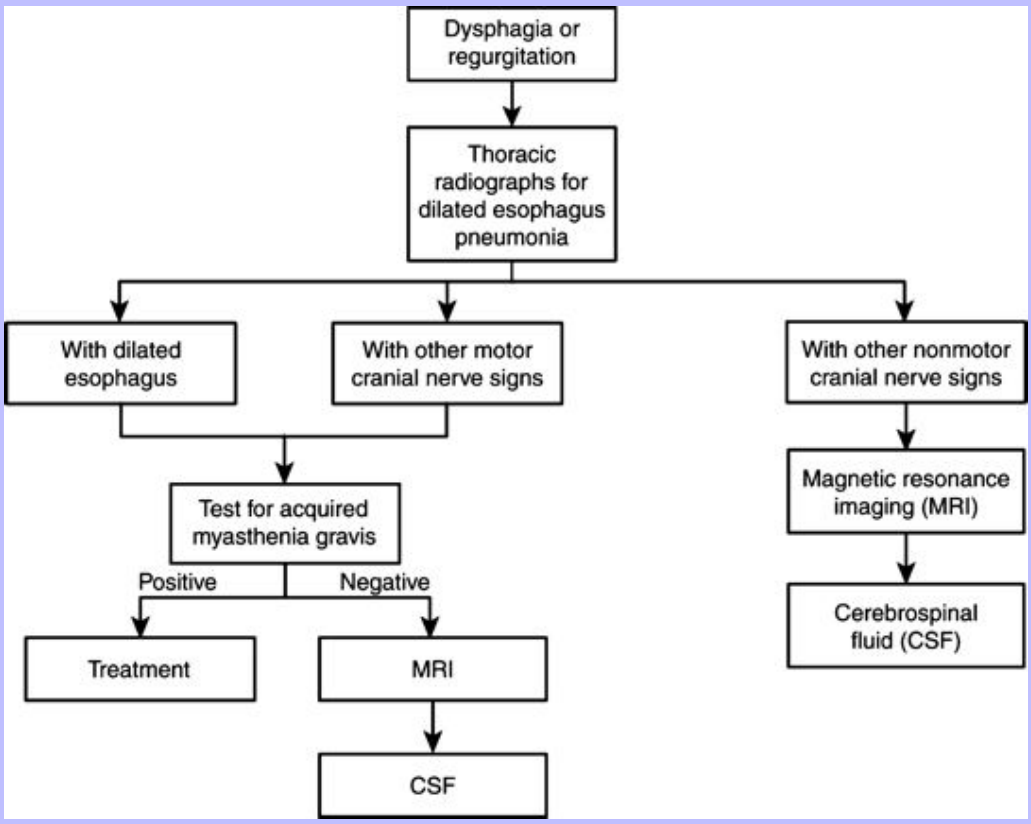

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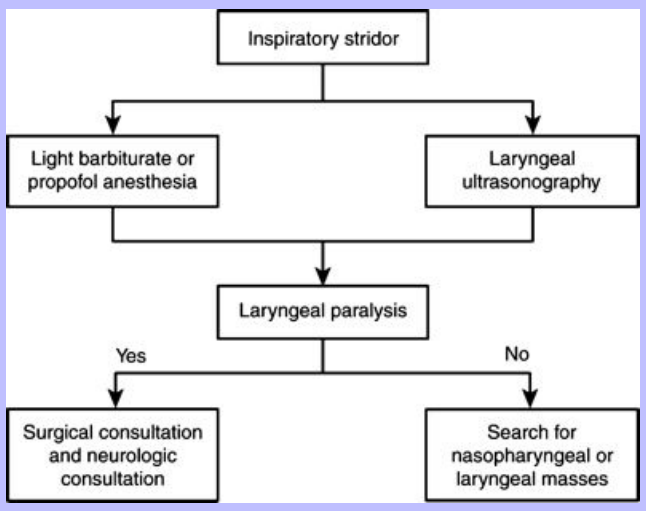
Figure 49-6 Algorithm for inspiratory stridor.



49.2 LOCALIZATION AND CLASSIFICATION

First, no neurologic discussion is complete, or worthy of notice, without a repetition of the rule that localization is foremost. Differential diagnosis, hence prognostication, cannot ensue without localization. Because cranial nerves have their origins in the brain, because they may serve afferent, efferent, or both afferent and efferent functions, and because they may also serve autonomic functions, the basic neuroanatomy must be remembered or reviewed. For example, if the palpebral reflex is absent, it must be remembered that the deficit may be on the trigeminal afferent side of the reflex arc (rather than the facial efferent side or the brain stem), where this reflex is integrated. In general, a catalog of deficits is created as the first step in the assessment process. Some constellations of signs have powerful localizing value. For example, any combination of Horner's syndrome, facial palsy, and peripheral vestibular disorder suggests a lesion in the middle ear region.

Second, the problem should be defined from the history as chronic, acute, progressive, static, or improved.

Finally, a unifying statement about the problem is made, such as “an acute left facial paralysis and left peripheral vestibular syndrome.” This leads to a differential diagnosis. For example, using the condition described, the differential diagnosis list would include all causes of simultaneous otitis media and interna, neoplasms of the petrous region, and idiopathic cranial neuritides.

49.3 DIFFERENTIAL DIAGNOSIS

Several generalities can serve as useful guidelines:

- The causes of peripheral cranial neuropathies usually fall into three pathologic categories: idiopathic inflammation, infectious inflammation, and neoplasia.
- Afferent or autonomic abnormalities exclude myasthenia gravis and other skeletal myopathies. Facial paralysis, for example, is a common feature of acquired myasthenia gravis. However, if Horner's syndrome or vestibular signs are present, myasthenia gravis would be eliminated from the differential list.
- Deficits of facial sensation exclude a diagnosis of masticatory myopathies.
- Most of the common peripheral cranial neuropathies are idiopathic and self-limiting. Included in this list are Horner's syndrome, facial paralysis, acute jaw drop, and acute peripheral vestibular syndromes. The neuropathies leading to laryngeal paralysis, pharyngeal paralysis, and megaesophagus are likely also self-limiting, but the consequences are more severe than for the other conditions.
- Some cranial neuropathies can originate peripheral to the brain but within the cranial vault (e.g., in the cavernous sinus syndrome), usually as a result of tumors.
- Trauma is rarely a cause of cranial neuropathy in dogs and cats, except for facial nerve injury associated with surgery of the ear and Horner's syndrome as part of the brachial plexus avulsion syndrome.
- Hypothyroidism has not been proven to have a role in these conditions.

49.3.1 Acute Blindness

In general, it is important to know that most acute disturbances of vision without ophthalmoscopic abnormalities represent sudden acquired retinal degeneration. Pupillary responses may not be definitively abnormal. An electroretinogram is the test of choice. If visible fundoscopic abnormalities are present, alternative differential diagnoses must be entertained. Optic neuritis is the second most likely differential diagnosis.

49.3.2 Horner's Syndrome

Horner's syndrome can be preganglionic or postganglionic, and the differentiation can be made with topical application of 2.5% phenylephrine; this will cause a denervated iris to dilate, confirming a postganglionic localization. A few days must elapse before denervation sensitivity develops. Without other neurologic signs or physical findings, most postganglionic lesions are idiopathic and benign. Establishing the presence of preganglionic Horner's syndrome may be more problematic because the lesions may be in areas where occult disease may difficult to confirm.

49.3.3 Acute Jaw Drop

Trigeminal neuropathies are common, and the condition often diagnosed is the acute jaw drop syndrome. This syndrome is usually idiopathic, presumed to be an acute neuritis, but it can be caused by infections (e.g., *Neospora caninum*) and by lymphoma. Unilateral trigeminal neuropathy may manifest as sensory impairment and, eventually, atrophy, but bilateral involvement is required to produce masticatory dysfunction. It is reasonable to assume a diagnosis of acute, self-limiting, presumed immune-mediated trigeminal neuritis in acute jaw drop if the signs are limited to trigeminal dysfunction. Whether corticosteroids benefit these animals has not been proven. Typically, the animals can eat and drink, with assistance, until recovery ensues in a few weeks.

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49.3.4 Acute Unilateral Facial Paralysis

Facial neuropathy is probably the most common cranial neuropathy. Most cases are idiopathic, and deficits are limited to the muscles of facial expression. The onset, or at least guardian notice, is usually abrupt. The disorder is presumed to be a peripheral neuritis. Central causes are implied by the presence of other deficits, such as a central vestibular syndrome or deficits of ipsilateral limb function. Facial muscle paralysis can be due to acquired myasthenia gravis, which should always be included in the differential diagnosis. Suspects should be tested for serum antiacetylcholine receptor antibodies. Other peripheral causes include disorders of the middle ear and the petrous temporal region, including otitis media and neoplasms.

Animals with facial paralysis and any evidence or history of ear disease should undergo diagnostic imaging. Bullae radiographs can be useful, but either computed tomography (CT) or magnetic resonance imaging (MRI) is an ideal means of imaging the middle ear. If any evidence of middle ear disease is found, sampling from within the bullae is indicated. Careful cleaning of the outer ear, followed by myringotomy, should be performed. Cytology and cultures also should be performed. Ideally, all dogs and cats with facial paralysis that do not have evidence of middle ear disease should have a cranial MRI that explores both the peripheral and central realms. If a diagnosis of idiopathic facial paralysis is made, there is no proof of benefit from

corticosteroids. Keratitis sicca due to poor production of tears is not usually a problem, but dryness due to exposure may be, and treatment or monitoring should be recommended.

49.3.5 Acute Loss of Balance

Unilateral hearing loss can be difficult to detect, but loss of function of the vestibular component of the vestibulocochlear nerve produces a dramatic set of signs. In general, it is not possible to distinguish clinically between a lesion in the nerve and one in the sensory organ, whether auditory or vestibular. However, the neurologic ground rule that differentiates peripheral from central vestibular syndromes is reliable: Peripheral syndromes produce a constant horizontal or rotary nystagmus, and central syndromes cause all the others. Most acute vestibular disorders are idiopathic, presumably an acute neuritis or vestibulitis, and these are self-limiting. An idiopathic disorder is distinguished from a relentless disorder by the presence of other historical, physical, or neurologic evidence that suggests the latter. A dog or cat with an acute peripheral vestibular disorder should be managed in the same fashion as for facial palsy if evidence of any ear disease is present. As with facial paralysis, all pets with a vestibular syndrome ideally should have a cranial MRI. However, because signs often abate rapidly, resolution in a short time may be used as proof that a relentless disorder is not present. If a diagnosis of idiopathic vestibular syndrome is adopted, there is no proof of benefit from corticosteroids.

49.3.6 Dysphagia and Regurgitation

Dysphagia may be due to disturbances of the glossopharyngeal and vagus nerves, but specific pathologic disorders have not been well defined. Acquired myasthenia gravis should be included in the differential diagnosis, and testing should ensue. These patients should have thoracic radiographs to detect esophageal dilatation and aspiration pneumonia. Except for acquired myasthenia gravis, these patients represent a mysterious group and often have a poor prognosis.

49.3.7 Stridor

Inspiratory stridor can be caused by various conditions, such as neoplasia or polyps of the larynx, but most cases are due to laryngeal paralysis, presumed to be the result of neuropathy of the vagus nerve or recurrent branches. The cause can be confirmed using light anesthesia achieved with a short-acting barbiturate or propofol; failure of arytenoid abduction confirms the diagnosis. These cases are treated surgically. Although solitary laryngeal paralysis has not been a feature of acquired myasthenia gravis, that diagnosis should be given consideration.

50 CHAPTER • 50 Sleep Disorders

Joan C. Hendricks

Sleep-associated problems in cats and dogs are uncommon owner complaints. Owners and clinicians cannot easily assess subjective disorders of sleep such as pathologic hypersomnolence and insomnia. Slight-to-moderate disruption of daily behavior patterns that accompany many changes in sleep do not substantially alter an animal's ability to function as a pet. The disorders that prompt an owner to bring a pet for veterinary treatment tend to be those that dramatically change the animal's overt behavior, such as sleep-associated epilepsy or narcolepsy with cataplexy. Other disorders, such as sleep apnea or cardiac arrhythmias, can be triggered by sleep and may have profound consequences for an animal despite being overlooked by most owners. It is interesting to realize that relatively minor changes in sleep behavior may herald future manifestations of abnormal central nervous system (CNS) function.

Sleep is a complex physiologic state with two distinct stages in normal mammals. During the first of these, the animal seeks a quiet, secure resting place and takes a characteristic relaxed species-specific posture. A few minutes after closing its eyes and becoming immobile, changes in CNS activity occur in the electroencephalogram (EEG): the cerebral activity alters from the rapid, desynchronized neural firing patterns of waking to synchronous discharges that produce high-voltage, slow (approximately 5 to 12 per second) wave activity. The pulse and respiratory rates slow, blood pressure decreases, and reflex arcs maintain homeostasis in autonomic systems. After a specific duration of uninterrupted slow-wave sleep (approximately 30 minutes in cats and dogs), behavioral and physiologic signs of a second stage appear. The observer notes a further relaxation of muscle tone, as a powerful postsynaptic inhibitory influence descends fromthe pontine brain stem along a ventral reticulospinal tractto the spinal motor neurons to produce postural muscle atonia. Several seconds to minutes after this atonia begins, volleys of distal small muscle twitching occur, producingrapid movements of the eyes, facial muscles, paws, and tail. Irregular respiration, heart rate, and blood pressure surges accompany these phasic bursts of small muscle movements. These small movements are the external manifestation of a highly activated brain: the flaccid musculature and lack of responsiveness belie a high rate of neural discharge throughout virtually all areas of the brain. During this second phase, most commonly known as rapid-eye movement (REM) sleep, the autonomic systems are driven by cerebral and brain stem influences during the bursts of twitching activity, which override reflex control. REM lasts as long as 10 to 15 minutesin normal cats and dogs. In humans this stage can last 20 to35 minutes and represents the sleep period when most dreams occur.

Sleep is thus a complex CNS and somatic syndrome that normally has an orderly progression. The atonia of REM sleep has the important function of preventing overt movements during the sleep period when the cerebrum is highly active.

50.1 SLEEP-ASSOCIATED AGGRESSION

An abnormal behavior that seems to occur relatively commonly is sleep-associated aggression. Owners report that a normally calm and friendly or attacks suddenly if disturbed while sleeping. Although owners may perceive this behavior as unpredictable and unprovoked, these attacks seem to be expressions of aggression—both dominance aggression related to the pet's sense of vulnerability upon arousal and territorial aggression related to defense of the resting place. No cases have been reported or documented in the literature in which animals displayed aggressive behavior directed at their owners while still asleep. Unfortunately, because this behavior is typically episodic and occurs in the home environment, it is difficult to observe directly. However, many or most dogs respond to behavioral approaches to treat aggression.

50.2 TRUE SLEEP DISORDERS

In general, true sleep disorders can be classified into two categories: (1) those in which the CNS mechanisms of sleep are normal (Figure 50-1) but other CNS or physiologic abnormalities are unmasked or triggered by sleep and (2) those in which the CNS mechanisms of sleep itself are abnormal. Knowing the physiology of sleep, augmenting a careful history with observation or (preferably) videotapes of behavior, and taking a rational approach to assessing the signs facilitates the differential diagnosis of these problems.

50.3 EXACERBATION OR UNMASKING OF ABNORMALITIES WITH SLEEP

50.3.1 Physiologic Abnormalities

Serious cardiovascular and respiratory disorders associated with sleep have been well documented in the literature and further studied in laboratory colonies of affected animals. Several families of German shepherds with histories of sudden cardiac death in apparently normal pups were identified. These dogs have an inherited predisposition to cardiac arrhythmias that are most common during sleep, especially during the REM stage. Abnormalities during standard clinical cardiac evaluation were relatively subtle, but ventricular tachycardia could be detected if pups were monitored by Holter monitors. Implanted pacemakers appear to have been successful in preventing sudden death in at-risk dogs. The mode of inheritance is complex, apparently either a polygenic or a dominant trait with incomplete penetrance. A colony of these dogs has been established, and studies of the underlying cellular abnormalities are in progress. In addition to the relevance of this basic research, it is significant that several families from widespread geographic regions were found to share a trait that can be transmitted by unaffected carriers. Thus although the syndrome is well described in German shepherds descended from a single common ancestor, the possibility exists that similar abnormalities could occur in other families and in other canine breeds.

Sleep apnea has been described in English bulldogs. Even if they have normal arterial blood gases during waking, virtually all bulldogs exhibit episodes of apnea (pauses in breathing) and hypoxia during sleep, especially in REM sleep. These dogs normally compensate for their narrowed upper airways by augmenting the activity of upper airway dilating muscles during waking and much of non-REM sleep. However, during REM sleep, when muscle activity is reduced by normal atonia and reflexes are intermittently overridden by phasic cerebral influences, intermittent upper airway obstruction occurs. In laboratory studies, these pauses have been documented to occur at rates ranging from six per hour to over 100 per hour. The oxygen saturation can fall as low as 70% but most commonly falls to 85% to 90% from the normal 94% to 95%. As is true for humans with sleep apnea, these dogs are hypersomnolent and exhibit obvious snoring. However, these signs in themselves do not usually present difficulties for owners or pets. Based on other experimental evidence, it is likely that the episodic drops in oxygen saturation lead to hypertension and cardiovascular consequences in both dogs and humans, but the clinical importance of these abnormalities for dogs has not been proved.

Although it is not clear whether sleep apnea alone warrants treatment, surgery is often performed in English bulldogs to relieve waking signs of upper airway obstruction, and this surgery appears to be partially effective in relieving obstructive sleep apnea as well. The usual treatment in humans is to prescribe a face mask to be worn nightly. This constant positive airway pressure mask forces air through the nares to the pharynx to maintain a patent airway; this is obviously not feasible in canine patients. Pharmacotherapy is being investigated, and at present, some approaches that alter serotonin appear to have promise.

As in the case of the sudden cardiac death syndrome of German shepherds, it seems likely that this type of disorder, well described in the laboratory in one breed, may exist in other predisposed animals. Any anatomic narrowing of the upper airway could lead to the same signs. Thus brachycephalic conformation in any cat or dog, or an acquired narrowing caused by tumor or traumatic injury, could predispose to sleep apnea. Owners do not commonly complain of snoring, hypersomnolence, or gasping respiratory patterns in bulldogs; but they often describe these signs in response to direct questions. Owners of Shar Peis, pugs, beagles, and an obese, hypothyroid miniature poodle with obvious upper airway narrowing due to fat accumulation have described similar signs. In the latter case, treatment of the hypothyroidism resolved the profound sleepiness and sleep-induced apnea noted by the owners. This anecdotal evidence suggests that sleep apnea exists in several canine breeds. In addition, some owners of brachycephalic cats have described obvious snoring and irregular breathing, but none of these animals has been available for further laboratory assessment.

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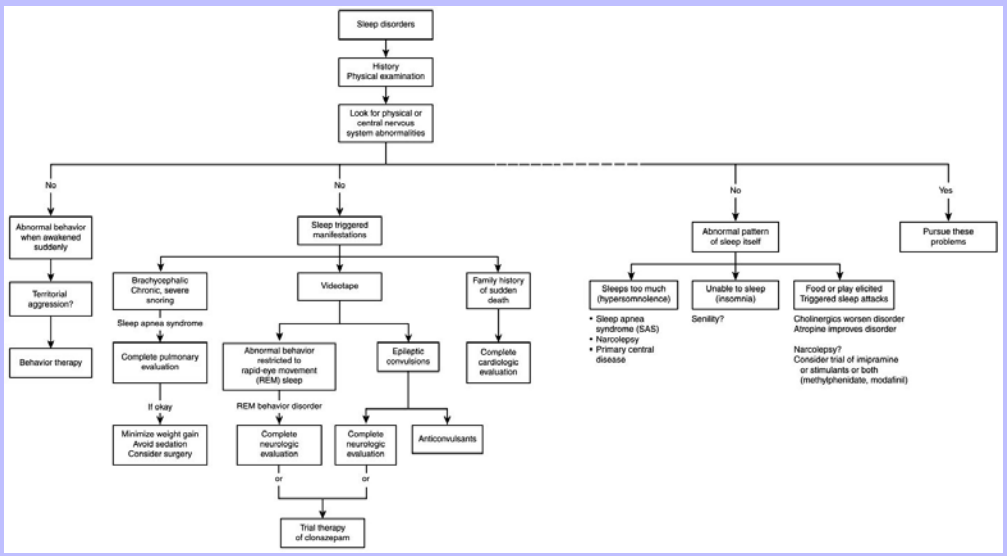
Figure 50-1 Algorithm for clinical evaluation of sleep disorders.



Diagnosis of sleep apnea requires continuous pulse oximetry and respiratory movement recordings, together with documentation of the sleep stage. This assessment can be noninvasive but is labor-intensive and impractical in a clinical setting. At present, the recommendation to a clinician who sees a pet with signs suggestive of sleep apnea is to treat the animal based largely on its waking signs.

50.3.2 Central Nervous System Abnormalities

Abnormal movements seen during sleep are often evidence of an underlying CNS disorder. The systematic changes in CNS activity that accompany normal sleep can unmask CNS disorders. Epilepsy from any cause, including idiopathic epilepsy, can be triggered by the rhythmic discharges of slow-wave sleep; however, seizures are rarely confined to sleep. Indeed, as part of the diagnostic workup of human epilepsy, the EEG is recorded during slow-wave sleep in an effort to trigger the epileptic charges. During the REM stage, abnormal movements can occur when the inhibitory pathway that normally produces atonia during REM sleep is disrupted. This pathway, which arises in the pons and descends in the spinal cord, can be interrupted by a

number of brain stem or spinal cord abnormalities, including traumatic injuries. Interrupting this inhibitory pathway permits the expression of the ongoing cerebral activity. Humans with this disorder (REM behavior disorder [RBD]) report that the observed behaviors represent the motor behavior appropriate to their dream content. Thus a patient may stand up, run, and clutch an invisible object while dreaming of playing football; or a patient may sit up and begin attacking his spouse and later describe that he was defending himself against a dream attacker. Dogs and cats with RBD, which (judging by referrals) appears to be the most common sleep disorder in pets, typically lift their heads and exhibit dramatic but intermittent paddling or locomotor activity during REM sleep. They can easily be aroused from these episodes, which occur during every REM period andcan often be recognized by an experienced observer viewing videotapes of the behavior. Although many of these animals are completely normal at all other times, in some cases it is obvious that CNS damage is correlated with the disorder, as in the case of a kitten that suffered a traumatic injury to the cervical spinal cord before the onset of signs. Even individuals that have an unremarkable physical examination may have an underlying CNS disorder. In humans with RBD and no other abnormalities at diagnosis, 38% developed overt Parkinson's disease an average of 3.7 years after the diagnosis of RBD. At the present time, the author has followed two cats with apparent congenital RBD for 10 or more years and observed no progression of signs. One of these cats eventually died and underwent a complete necropsy, and no gross or microscopic CNS abnormalities were identified.

Clonazepam, a benzodiazepine tranquilizer, reduces the level of activity during RBD in the vast majority of humans and was partially effective in the two cats. Routine anticonvulsant agents are not effective because they initially suppress REM sleep, with an eventual rebound of REM and recurrence of the behavior. Even if the disorder is not associated with other evidence of CNS disease, it can be life threatening for cats and dogs because some pets suffer urinary incontinence during the episodes, which is intolerable for some owners. In one cat treated for 10 years with clonazepam, the intensity of the behavior was reduced but not abolished. Withdrawing the clonazepam after the first 6 years resulted in an increase in motor behavior and related urination during REM, which was again partly controlled by reinstituting the treatment. Thus chronic treatment is feasible in pets with this disorder, but no improvement of the underlying abnormality should be expected based on experience to date.

In summary, evidence of abnormal movements during sleep should be assessed in view of the possibility that these movements may reveal otherwise occult CNS disease. However, some individuals (only cats identified to date) appear to have a congenital abnormality of the REM motor inhibitory pathway, perhaps caused by a biochemical change in the neural systems that normally maintain atonia.

50.4 DISORDERS OF SLEEP MECHANISMS

50.4.1 Effects of Systemic Disease

Sleep itself is affected by many systemic disorders. Systemic changes in immune function may alter sleep. It is now clear that prostaglandin D and interleukin-1-beta produce the increase in sleep that occurs with many febrile illnesses, accounting for this common symptom. One specific condition that alters sleep in humans is infection with human immunodeficiency virus (HIV), and a recent study documented that cats with feline immunodeficiency virus (FIV) show reduced sleep and disproportionately reduced REM sleep. The only owner complaints the author received regarding reduced sleep, or insomnia, involved elderly dogs who pace throughout the night. These dogs may be like humans with senile dementia, in whom the quantity and pattern of sleep become abnormal in association with increasing dementia. The opposite condition, increased sleep or pathologic hypersomnolence, can occur with sleep apnea and has also been described as an isolated idiopathic

abnormality in humans and in one case report of a dog. However, the best-described syndrome in which sleep mechanisms are abnormal is narcolepsy.

50.4.2 Narcolepsy

Narcolepsy is a fascinating but rare disease that is well documented in humans and dogs. It has also been reported in a cat, a bull, and several horses. The abnormality appears to be in the CNS trigger mechanisms of the REM sleep state. The abnormalities that appear are caused by the sudden eruption ofcomponents of REM sleep, including unconsciousness, muscle atonia, and dream imagery, into wakefulness. Without the normal temporal insulation of non-REM sleep, such manifestations are disruptive to normal life. In animals, the sudden loss of muscle tone (cataplexy) is almost always the sign noted by owners. However, in one dog, a sleepy appearance led the owners to seek veterinary advice. Although some individual cases of human and canine narcolepsy are caused by organic brain disease, the vast majority has no obvious CNS abnormality. Several subtle changes in CNS pharmacology have been documented in canine narcoleptics. An inherited form of the disease has been best documented in a colony of Doberman pinschers. The gene responsible for inherited narcolepsy in dogs was found to be an abnormality in the receptor for a previously poorly understood neuropeptide named *orexin* or *hypocretin*. The normal function of this neuropeptide is not known, but abnormalities of this system have now been shown to produce narcolepsy in mice, humans, and dogs. This is the first genetic basis of a sleep disorder to be described in any species.

The diagnostic process includes ruling out organic brain disease, and the diagnosis is best made when the behavior can be observed to be triggered by play or by food presentation, as is typical of canine narcoleptics. Fortunately, the disorder in dogs usually has only a moderate effect on their ability to lead normal lives, and in many cases it may be transient. In a colony of Doberman pinschers, the signs were maximal in pups at 4 to 7 months of age and then waned in severity. One case has been reported, however, in which the food-triggered cataplexy was so severe that complete anorexia resulted in a 20 kg weight loss and long-term treatment was required. The biochemical control of muscle atonia is well characterized, but proven pharmacotherapeutic agents in dogs are limited to imipramine. However, initial reports on treating dogs with orexin, hypocretin, or both suggest that treatments based on this new information hold considerable promise. Arousal-promoting agents can be used to relieve the hypersomnolence if necessary.

51 CHAPTER • 51 Cognitive Dysfunction in Aged Dogs

Elizabeth Head

Gary M. Landsberg

Advanced age in dogs may be associated with behavioral changes including separation anxiety, the onset of new fears and phobias, increasing irritability and aggression, stereotypic disorders, night waking, and house soiling.[1] Some of these behaviors are attributable to existing, possibly age-associated, medical conditions (including other neurologic conditions) and some may be due to primary behavior problems arising from changes in the household. However, once these have been excluded, remaining behavioral signs may be a consequence of pathologic brain aging.

51.1 COGNITIVE DYSFUNCTION: CLINICAL SIGNS

Until recently, clinicians had regarded this constellation of behavioral symptoms to indicate senility associated with advanced age. Cognitive dysfunction is not an inevitable consequence of aging in dogs, and striking individual differences are more likely the rule than the exception. Some aged animals show little or mild behavioral decline. However, a subset of aged dogs develops severe cognitive deficits that may disrupt normal function to a level prompting euthanasia. Ruehl and colleagues have identified a more general cognitive dysfunction syndrome (CDS).[2] The clinical signs have been described using a simplified acronym DISHA, which refers to *disorientation*, *interaction* changes with owners or other pets, *sleep-wake cycle* alterations, *house soiling*, and *activity* changes (which might be increased, stereotypic, or reduced). Additional signs such as increasing agitation and anxiety, altered responsiveness to stimuli (which might be heightened or reduced), altered interest in food (which might be increased or reduced), and decreased ability to perform learned tasks (which might be most obvious in working dogs) may also be seen. The number of dogs affected by CDS has been assessed in a number of survey-based studies. Approximately 48% of pet owners report that their senior dogs (7 years or older) exhibit at least one clinical sign of CDS. However, only 17% of these owners reported these signs to their veterinarian (proprietary market research, 1999; pet owner sample size: 150; data on file, Pfizer Animal Health). In another study, 180 owners of dogs aged 11 to 16 with no identifiable medical problems reported that 28% of the dogs between 11 and 12 years and 68% of the dogs between 15 and 16 years had at least one sign that might be consistent with CDS.[3] Further, CDS may be a progressive disease as aged dogs with impairments in one category were later found to have impairments in 2 or more categories.[4] Thus clinical signs of cognitive dysfunction in senior and geriatric pet dogs occur in a significant number of animals and potentially signals a progressive neurologic disorder.

51.2 COGNITIVE DYSFUNCTION: LABORATORY STUDIES

Questionnaire-based tools used in the clinic to identify dogs with CDS provide a measure of global brain dysfunction. However, these behavioral checklists are insensitive to early and subtle changes in learning and memory associated with pathologic aging in dogs. In fact, cognitive dysfunction is generally recognized as a syndrome in dogs 11 years of age and older, and signs may not be apparent until the last 18 to 24 months of a dog's life.[1] At this time no biomarker exists for CDS in aged dogs. An alternative technique to detect cognitive dysfunction in aged dogs involves the use of neuropsychologic tests that provide quantitative measures of cognitive function without reliance on questionnaires.[5] These tests are systematic, standardized, objective and a

more sensitive measure of age-related cognitive decline. In fact, they can identify age-related deficits in learning and memory from as early as 7 years of age.[4] Although these tests are too lengthy and complex to be applicable for clinic use, a number of cognitive functions assayed with these laboratory-based tasks are also likely to be contributors to the clinical signs that might be noted by pet owners.

In studies using a battery of reward-motivated neuropsychologic tests, several cognitive domains or functions can be evaluated in aged dogs. These tests involve teaching dogs to use visual information to solve different problems. Simple learning problems include discrimination tasks that involve showing dogs two objects that are different in appearance. Dogs must learn that only one of the two objects covers a food reward. Aged dogs can learn these problems, as can younger dogs. Once dogs have learned this visual discrimination problem, the reward can be switched to the previously incorrect object. This is called *reversal learning* in which dogs must be able to change a previously learned behavior, a type of cognitive ability that depends upon the intact function of the prefrontal cortex. Aged dogs have difficulty learning to switch to selecting the previously incorrect object, suggesting a lack of ability to modify learned behaviors. These laboratory tests depend on cognitive abilities that would be involved with modifying previously learned behaviors; thus aged dogs may be slower to modify problem behaviors. Other behaviors that are consistent with prefrontal cortex dysfunction include pacing, stereotypic behaviors, and an inability to inhibit behaviors (e.g., house soiling).

The aging process can also significantly affect memory. Spatial memory is defined as the ability of dogs to remember *where* they had last obtained a hidden food reward and is compromised in a subset of aged animals.[6] Functionally this type of memory impairment may be reported in companion animals as disorientation, wandering, and getting lost. Dogs also show age-dependent impairments in their ability to recognize objects seen previously.[7] This type of dysfunction may be reflected in decreased recognition of familiar people or animals.

Age-related differences have also been demonstrated in behavioral reactivity tests. The curiosity test, for example, allows the dogs to examine and play with a variety of toys to assess an animal's reaction to novel objects. In this brief 10-minute test, young dogs show significantly more exploration and contact with novel objects than old dogs, with cognitively impaired aged dogs showing the least object contact. Further, cognitively impaired aged dogs show higher levels of locomotion during a curiosity test than their age-matched unimpaired peers. The curiosity test measures exploratory behavior and is more amenable to clinical use because it requires brief 10-minute testing sessions and a small test area, suggest-ing that it may be a useful clinical screen for aged animals with cognitive dysfunction.[8]

51.3 COGNITIVE DYSFUNCTION: NEUROBIOLOGIC BASIS

Cognitive dysfunction that is not attributable to other systemic or central disease may reflect underlying age-associated neuropathology. A number of morphologic features of aging are found in the canine brain.[9] For example, cortical atrophy and ventricular widening occur with age in dogs.[10] The abnormal accumulation of proteins within and around neurons with age may be toxic to the brain. One form of pathology, the accumulation of diffuse plaques, contains a number of proteins, of which the primary constituent is the β-amyloid peptide (Aβ). The extent and location of Aβ deposition in the aged dog brain is linked to the severity of cognitive deficits.[11,12] For example, aged dogs that are severely impaired on a reversal learning task have the most extensive prefrontal cortexAβ pathology.[13] Another key feature of the aged canine brain is the progressive accumulation of oxidative damage to proteins and lipids[14] and a reduction in endogenous antioxidant activity. Damaged proteins and lipids can lead to neuronal dysfunction, which may subsequently compromise cognitive function. In support of this

hypothesis, a diet rich in antioxidants and mitochondrial cofactors can significantly improve cognitive function in aged but not young dogs.[15]

51.4 TREATMENT OPTIONS

Age-dependent cognitive impairments in companion animals, as mentioned previously, may reflect systemic or a CNS disease. Once other contributing factors are eliminated, the appropriate treatment can be implemented. Currently, one pharmaceutical is approved for the treatment of cognitive dysfunction in aged dogs in North America. Anipryl© is a monoamine oxidase B inhibitor that can improve cognitive signs in aged dogs.[16] Its mode of action appears to be to enhance catecholamine transmission, as well as decrease the production and increase the clearance of toxic free radicals. In Europe, two drugs are presently licensed for the treatment of cognitive decline in senior dogs that are purported to enhance cerebral vascular blood flow. Nicergoline is an alpha 1 and alpha 2 adrenergic antagonist, whereas propentofylline may improve blood flow by inhibiting platelet aggregation and thrombus formation. Alternatively, a specially formulated senior canine food isalso available (Prescription Diet® Canine b/d™) that contains antioxidants and mitochondrial cofactors that significantly improve cognition in both laboratory and clinical studies.[15]

51.5 SUMMARY

Aged dogs, like aged humans, are vulnerable to the development of progressive brain pathology that is associated with clinical signs of cognitive dysfunction. However, it is important to rule out other contributing systemic diseases or other central nervous system (CNS) disorders that can also cause cognitive impairments. Along with behavioral therapy, a variety of medical and dietary treatment options have been licensed; however, availability varies among countries.

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52 CHAPTER • 52 Behavioral Disorders

Andrew Luescher

Behavior problems of pets are extremely common. According to a variety of studies the prevalence of behavior problems in dogs and cats lies between 40% and 80%. In an epidemiologic study, approximately 40% of dogs had growled at their owners, and 15% had bitten their owners. Around one third of cats appear to have at least an occasional problem with inappropriate elimination. Behavior problems jeopardize the human-animal bond and are a main cause of relinquishment and euthanasia of healthy dogs and cats. Therefore pet owners, pets, and the veterinary profession benefit from the prevention and treatment of behavior problems in patients.

Behavior services in a small animal practice may include prepurchase counseling, counseling of new pet owners, puppy classes, behavioral intervention, and clinical behavior service. Counseling of new pet owners for problem prevention is a service that is performed routinely, but not always effectively or appropriately, at the first puppy or kitten visit. These first visits set the stage for all future doctor-patient and doctor-client relationships. If handled effectively, they can bond a client and patient to the clinic. Inappropriate actions such as rough handling or frightening (“dominating”) the young pet can cause continuous problems with fear or aggression at future visits. Client counseling is best performed with use of a check sheet inserted into the pet's file. Problem prevention includes socialization and exposure to varied environments, house training or litter-box training, consistent interaction and training, encouraging appropriate play, teaching a bite and claw inhibition, and teaching the “leave-it” and “drop-it” commands. To prevent food guarding in puppies, treats should be added to the food while the puppy eats. Puppy and (where available) kitten classes should be recommended. It is advantageous to offer these at the clinic.

Behavioral intervention refers to recognition of a behavior problem that underlies a medical problem. In cases of wounds inflicted by another dog, for example, the aggression between the dogs should be addressed. In cases of self-inflicted wounds, information that relates to possible separation anxiety or panic attacks should be sought. Furthermore, information on management and behavioral issues should be solicited at every yearly visit. For example, it would be important to find out if a dog had been relegated to the garage. This would indicate a high risk of imminent relinquishment, and preventive behavioral intervention would be urgent.

If clinical consults are offered, they should be performed in a methodical way in special appointments. The diagnosis should be based on a minimal medical database (i.e., physical exam with basic neurologic exam, CBC, chemistry profile including a thyroid panel, urinalysis, and additional tests as indicated), a thorough history and direct observation and/or observation from videotapes. The history may involve collection of general information regarding early history; housing, feeding, exercising, and training the pet; the animal's behavior in various situations to assess temperament; and the specific problem. The latter information should include triggers of the behavior; the behavior itself, including body language; and consequences of the behavior. Because behavior problems often change over time, this information should be gathered for the earliest incidents in addition to the most recent few. Observations need to include normal dog-owner interactions. Particular attention should be paid to behavior that results from motivational conflict or frustration.

Treatment modalities include changes in management (housing, feeding, exercise, training methods), behavior modification (e.g., systematic desensitization, counter-conditioning, and response substitution), and pharmacologic treatment.

While behavior modification is being addressed, exposure to the natural stimulus must be avoided. Systematic desensitization involves training the patient to a relaxed down-stay, and exposing the patient to the stimulus at a low intensity. The patient is rewarded for staying relaxed. The stimulus intensity is increased incrementally, and the

patient always is rewarded for relaxation. If the dog shows a reaction, the owners have progressed too quickly and need to go back a few steps in the training. Systematic desensitization requires identifying the stimulus, reproducing the stimulus, and having control over the stimulus intensity. If these requirements cannot be met, or the natural stimulus cannot be avoided for the duration of behavior modification, drug desensitization may be necessary. In this case, the patient is put on an effective dose of an appropriate drug and exposed to the natural stimulus as often as possible. He is rewarded for desirable behavior. Over time, the patient is weaned from the drug.

The term *counter-conditioning* is used inconsistently in the literature. This author uses it for a technique based on Pavlovian conditioning. It involves association of a situation that previously evoked fear and/or aggression with something pleasant. The pleasant stimulus can be food or play, for example. It is very unlikely that fear is reinforced by giving food but could easily be reinforced by picking the animal up or sheltering it (avoidance conditioning).

Response substitution is a technique by which an animal is trained to perform an appropriate behavior in a situation in which it used to perform an unacceptable behavior. The animal first needs to be trained to perform the desired behavior on a cue. Then, whenever the animal shows any inclination to perform the unacceptable behavior, the owner distracts it, gives the command, makes the animal do the appropriate behavior, and reinforces that behavior with a reward. They need to either supervise the animal constantly, or put it in a situation in which it will not perform the inappropriate behavior when not supervised. The animals may not be given any chance to perform the inappropriate behavior.

Often these techniques are used in combination. Variations of these techniques are used depending on the situation or problem. The instructions given here are examples, not the only correct form, of behavioral treatment of the specific problem.

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52.1 CANINE BEHAVIOR PROBLEMS

52.1.1 Aggression

Depending on the author, some dozen different types of canine aggression are recognized, including conflict-related, dominance, possessive, territorial aggression, interdog, play-induced, excitement induced, fear induced, pain-induced, redirected, maternal, and predatory aggression.

They fall into the three major groups of affective aggression, predatory behavior (part of feeding behavior), and play aggression. Redirected and learned aggression are not really diagnoses but imply a mechanism of modification of a type of aggression.

52.1.1.1 Aggression to Household Members

Aggression to household members is often exhibited in situations in which the dog is threatened or "challenged." This type of aggression has generally been diagnosed as dominance aggression. Dominance aggression would be expected primarily in adult dogs and intact males. Dogs would be expected to have a self-confident personality and show offensive body language when aggressive. However, recent research showed that the majority of cases start at a very young age. Typically, initial aggression is shown in response to discipline or over food within the first 2 months of ownership. The affected dogs have a different disease history (severe early disease, dermatologic disease) than nonaggressive dogs. They are more excitable as puppies and more excitable and fearful (shy of people) as adults. Their body language before and during an attack is ambivalent and indicates a motivational conflict. Frequently, in the initial incidents the dog shows defensive body language, but over time it becomes more and more offensive. There is a breed predisposition;

Spaniels, Terriers, and toy breeds are more likely to bite. Dogs most likely to be aggressive are neutered males, neutered females and intact males are less likely, and intact females are least likely to be aggressive (although in small breeds, females are more likely to bite than males). Neutering can make females more aggressive. Dogs that are aggressive to their owners are also likely to be aggressive to strangers, which indicates this aggression is not confined to the dogs' social group.

It appears that the aggressive dogs are in a motivational conflict (approach-withdrawal conflict) relative to people. When a person approaches, aggressive dogs' anxiety level increases and they show aggression. As the person responds by backing off, the threat diminishes. The dogs thus learn that they can resolve their conflict and reduce their anxiety by showing aggression. Thus aggression becomes conditioned through avoidance conditioning; this type of conditioning produces persistent behavior. Based on this putative pathogenesis, we have proposed the term *conflict-related aggression*.

Treatment should address the dog's basic disposition (e.g., fearfulness, hyperexcitability), the way in which the dog is managed, and the cause of conflict (i.e., the inconsistency in the owner-dog interaction).

Recommended management changes include twice daily meal-feeding (as opposed to *ad lib* feeding) and regular twice-daily exercise. The situations in which confrontations are likely should be avoided. This may imply that the dog needs to be confined (e.g., in a separate room or exercise pen) unless being trained. Confinement is also indicated when the owners are afraid of the dog, when smaller children are involved, or when the owner is unable to ignore the dog. A head halter with a leash attached is placed on the dog, so that the owner can control all aggression-inducing situations in a safe, nonconfrontational, and consistent way. Toys or other assets that have caused confrontations should be removed. The dog is not to be let on furniture *if* that caused a problem. The dog should be reintroduced to situations in which he showed aggression only in the context of systematic desensitization and response substitution.

Owners are instructed to avoid all casual interaction (i.e., ignore the dog most of the time) and only interact with the dog in a command-response-reward format. This ensures that all interactions with the dog are consistent and thus predictable. Highly structured obedience exercises, especially ones that desensitize the dog to owner-behavior perceived as threatening, are very useful. Clicker training is especially helpful when dealing with these dogs, because it is a hands-off method of training and avoids confrontations between owner and dog. No punishment, choke chain, or scolding are to be used. A head halter assists the owner in training and walking the dog. Punishment or the “alpha roll-over” are *not* appropriate in dealing with aggression. Situations in which the dog still shows aggression are addressed by systematic desensitization, counter-conditioning and response-substitution.

Food guarding can be addressed through management, that is, by feeding the dog in a separate room and calling the dog out of the room once he is finished eating. It can also be treated through systematic desensitization. In the latter case, the dog is tied in a different place than where he is normally fed, and fed from a different food bowl (preferably a saucepan with a long handle). The ration is measured out into yet another dish that is placed out of the dog's reach. The dog is asked to sit and a few kibbles are placed into the food bowl, and the dog is offered the food. This is repeated until all the food is fed, and all meals are fed in this way for about a week. Then, the amount of food given at one time is increased. Next, the amount of food is decreased again to a few kibbles, but the owner lets go of the food bowl while the dog eats. The amount is then increased again. Eventually, a third of the food can be placed into the food bowl, and the owner adds the remainder of the ration gradually with a ladle. Once this goes well, all the food can be placed in the food bowl, and the owner tosses treats into it while the dog eats. This should be done occasionally throughout the dog's life (in very mild cases, this last step is all that needs to be done).

No drugs have been proven effective in the treatment of any type of canine aggression, although there is anecdotal evidence of positive effects with SSRIs.

52.1.1.2 Possessive Aggression

Guarding of food and objects is a natural but unacceptable canine behavior. It becomes exacerbated if the dog is afraid of a confrontation over the item (it may therefore be regarded as a special case of conflict-related aggression). It can be addressed by management or through training. The latter option includes training “leave-it” and “drop-it” commands, or exchange exercises (a form of systematic desensitization). For exchange exercises, the dog is tied to an immovable object, initially away from where he most commonly shows aggression. The dog is asked to lie down and stay. A toy that the dog does not value much is laid down at some distance from the dog, the leave-it command is given, the toy is picked up, and the dog is rewarded for staying relaxed. At subsequent trials, the distance is reduced. The exercise is repeated with increasingly valuable toys.

52.1.1.3 Territorial Aggression

Territorial aggression is exhibited to strangers or strange dogs either on the owner's property or in the owner's proximity. It is a normal but unacceptable canine behavior. Treatment involves training the dog to sit near the door and staying while the door is opened, while the doorbell is rung, or while a stranger stands at a distance and progressively closer to the door. It is important to prevent the dog from ever showing aggression until the training program is completed.

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The dog should be walked twice daily off the property on head halter and leash. Whenever a person approaches, the owner should go out of the way and keep the dog busy with fast-paced obedience, reinforcing appropriate behavior with ample food treats. Once the other person has passed, they can continue their walk. Each time, the distance to the other person can be reduced (depending on the response of the dog), until the owner can heel the dog by the other person, and then reward the dog for having passed without aggression. This method can also be used with a volunteer who stands still while the owner performs obedience training with the dog at decreasing distance. The dog can also be systematically desensitized to a stranger approaching.

52.1.1.4 Aggression Between Dogs

Aggression to strange dogs or *interdog aggression* can be status-related, territorial, fear-based, or even predatory. Treatment is similar to that of territorial aggression and includes the same exercises on walks, systematic desensitization to a dog passing by or approaching, response substitution (having a helper with a dog stand still and doing obedience with the patient at decreasing distances, rewarding frequently), and counterconditioning (making the situation when another dog is in sight very pleasant). Punishment is contraindicated with any form of aggression, in this case in part because the patient would learn that the presence of another dog means he will likely get punished.

Aggression between dogs living in the same household, often referred to as “sibling rivalry” (a misnomer because they are not usually siblings), can have various reasons as well but most cases are either status-related or related to owner attachment (sometimes called “alliance aggression”). Fights are usually severe, especially among females.

Status-related aggression may occur between dogs that are close in social status. Fighting may also begin when a younger dog reaches adulthood, or when an older dog is no longer able to maintain his position. Treatment of status-related aggression involves deciding which dog will likely end up dominant and treat him as such (giving attention or food first, giving this dog privileges that the other dog does not have), and treating the other dog as subordinate (ignoring, cutting privileges, possibly confinement, rewarding subordinate behavior). Furthermore, systematic desensitization and response substitution (as for interdog aggression) can be used. The dogs may need to be separated and/or muzzled when exposed to each other. The times the dogs are exposed to each other should be as positive as possible (counterconditioning).

Alliance aggression is aggression to another dog in the same household shown only in the proximity of the owner. It is usually, but not always, the lower-ranking dog that initiates the aggression. The aggressive dog is usually overdependent on the owner and becomes very anxious if the other dog gets close to the owner. He may also feel much more confident in the presence of the owner.

The most important aspect of treatment is to ignore both dogs for 3 to 4 weeks, except when working with them. The dogs should be exposed as much as possible to each other. If there is any indication that the dogs will be aggressive, the owner should distract them with a loud noise (clapping hands, rape alarm) and immediately leave. In some cases the dogs will need to be muzzled when exposed to each other. It should be determined which of the two is the dominant dog (from a videotape taken when they are on their own, without owner present), and that dog should be treated as such.

The aggressive dog can be desensitized to the owner paying attention to the other dog. While the aggressive dog is tied and in a down-stay, the owner interacts with the other dog at decreasing distance and rewards the aggressive dog frequently for staying relaxed. Dogs that exhibit alliance aggression are often not aggressive to each other in other places, or out in the yard. In this case, they can be exposed to each other initially on neutral ground, then kept together in the backyard, and then gradually allowed access to increasing parts of the house.

52.1.1.5 Predatory Aggression

Predatory aggression is highly genetically controlled and may therefore be difficult to treat. It is a particularly dangerous form of aggression because there is no warning and the bite is not inhibited. Systematic desensitization and response substitution (in combination) can be successful. The owner is instructed to do obedience training at a distance from the “prey” (e.g., horses, cars going by), using a head halter and food rewards. Gradually, the owner reduces the distance. Confinement and control, as well as a muzzle, are useful in managing the behavior. A good recall can help to control dangerous situations. Socialization of the puppy to the species that it should not consider as prey (e.g., children) is essential. Selection of a breed with little predatory behavior helps in prevention.

52.1.2 Separation Anxiety

Separation anxiety is a common problem. Among these cases, dogs obtained from shelters are overrepresented. Affected dogs are usually very friendly and dependent on the owner, and more highly trained than dogs with other behavior problems. Because of their owner attachment, these dogs become anxious when separated form the owner (i.e., when the owner is either not home with the dog, or not accessible to the dog) and express this anxiety in a variety of ways (e.g., by destroying property, barking, salivating, pacing, urinating or defecating, self-mutilation). Diagnostically it is important to note that these behaviors start within a short time of the owner

leaving. First line treatment may include two daily walks to reduce anxiety; ignoring the dog for approximately 30 minutes before leaving, and after coming home until the dog settles; giving a hollow toy containing food treats some 5 to 10 minutes before leaving; and ignoring attention-getting behavior at any time. In addition, owners may want to train the dog to a long down-stay and then use that command to prevent the dog from following them all the time, and when doing planned departures (see below). Mixing up the order of predeparture cues makes departure less predictable, and desensitization to these same cues (by presenting them frequently without leaving) will reduce the dog's response to them. Drug treatment concomitant with behavior treatment is often indicated. The drug clomipramine (Clomicalm, Novartis) is the only drug licensed in the United States for the treatment of separation anxiety.

If necessary, the owner can do planned departures, leaving the dog for initially very short and increasingly longer times, while giving the dog a safety cue (e.g., the sound of the radio). If at all possible, dogs with separation anxiety should not be confined when left alone, because usually this makes the anxiety worse. If the owners keep the dog confined and do not want to risk leaving him loose, they may want to use the planned departure technique with the dog loose in the house during practice departures. In this way they can find out without great risk if it is safe to leave the dog loose (if done this way, being loose becomes a safety cue for the dog).

52.1.3 Fear

Fear is a combination of physical, emotional, and physiologic responses to a threatening stimulus or situation that, in the wild, would protect the animal from harm. Fear may become a maladaptive *"phobia"* when the response is out of proportion to the threat. The dog may be afraid of specific stimuli or be globally fearful. The cause of fearfulness may be genetic, or early experience (lack of socialization and exposure before 14 weeks of age, or an adverse experience in the fear period 8 to 10 weeks of age). Specific fears are usually learned. 185 186

Learning can exaggerate any fear. Learning is most easily achieved through avoidance or escape conditioning. However, it is very difficult to reinforce fear with food. Giving food to a fearful dog is therefore not contraindicated, but recommended, because it may make the situation more pleasant (counterconditioning).

Specific fears can usually be treated very effectively with systematic desensitization, counterconditioning, and response substitution. For generalized fear or when fear-evoking stimuli cannot be avoided, or if the stimulus cannot be replicated (e.g., thunderstorms), drug desensitization is indicated. The dog is given a large enough dose of a drug with anxiolytic effects to reduce fear to the point at which the dog is capable of habituation to the stimuli (the above behavior modification techniques should be used simultaneously). Once the dog functions well at that dose, the dose is slightly reduced. When the dog no longer shows fear on the lower dose, the dose is further reduced, and the dog is thus gradually weaned off the drug. Throughout the procedure, the dog should be rewarded for acting confidently. Even after successful treatment, the dog should be periodically exposed to the fear-inducing stimuli and rewarded for not responding fearfully, to prevent spontaneous recovery of the fear response. A fear response is not ever to be punished.

52.1.4 Hyperexcitability

A high level of activity may be normal for a certain breed and age of dog. Although there are various physiologic and environmental reasons for abnormally high activity or excitability, the most common cause is inadvertent conditioning with owner attention. Consequently, the first treatment strategy is to ignore the dog, especially when excitable. Relaxed, calm behavior should be rewarded. Obedience training, especially a long, relaxed down-stay, and regular twice-daily walks will also help in most cases.

52.1.5 Canine House Soiling

Before a diagnosis of house soiling is made, medical causes, urine marking, separation anxiety, and other anxiety-related disorders have to be ruled out. Causes of house soiling include insufficient initial house training, long periods of cage confinement during puppyhood so that the dog learned to soil his bed, and various other factors that can result in the loss of house training.

To treat house soiling, the factors that affect elimination have to be understood. Elimination is most likely after rest, eating, and physical activity. It is also stimulated by the smell of previous elimination. The dog should be fed two to three times a day (depending on his usual number of stools per day) and walked thereafter to the same location. The dog should also be taken to that location when first waking from sleep, after play, and frequently in between. When the dog eliminates at that location, he should be rewarded. If he does not eliminate this time, he can be brought back to the house but should be taken out again within 10 minutes or so. Indoors, the dog should be under constant supervision (crate confinement or on leash with the owner). The soiled areas should be treated with a high-quality enzymatic cleaner and can then be made aversive with bi-weekly application of pine-oil cleaner or citrus-scented liquid, or small amounts ($^1/_4$ teaspoon) of mothball powder brushed into the pile of the carpet *(mothball crystals are toxic)*.

52.1.6 Canine Urine Marking

Canine urine marking can be a territorial behavior, greatly facilitated by testosterone in intact males (especially in the presence of other intact dogs or bitches in heat), or related to anxiety. It involves deposition of small amounts of urine in specific places, usually on or near vertical objects. The strongest stimulus is environmental competition of other males and freshly voided urine from other dogs.

Stimuli that elicit urine marking should be identified and, if possible, eliminated. If urine marking is anxiety-related, then the cause of the anxiety has to be addressed. The marked areas should be cleaned and deodorized as described for house soiling. Castration reduces leg lifting in the house in about 60% of cases.

Behavior modification involves constant supervision in the house, possibly with the dog tied to the owner with a leash (umbilical cord technique). Whenever the dog shows any signs of wanting to mark a place, the leave-it command (it will have to be taught in advance) or response substitution should be used. Punishment generally does not work as it is usually not applied consistently, and because the dog may learn to lift the leg only when the owner is absent.

52.1.7 Compulsive Disorder in Dogs

Compulsive disorder is expressed as repetitive or sustained, apparently abnormal behaviors performed out of context. Compulsive behaviors could be categorized as related to locomotion, oral activity and grooming, aggression, vocalization, and hallucinatory behaviors. In dogs, locomotory behaviors include circling, tail chasing, pacing, jumping in place, chasing light reflexes, and freezing. Oral behaviors and behaviors related to grooming manifest, among others, as leg or foot chewing, licking, flank sucking, scratching, chewing objects, pica, and snapping in the air (“fly-snapping”). Compulsive behaviors related to aggression include self-directed aggression, attacking the food bowl or other inanimate objects, and possibly unpredictable aggression to people. Vocalization may be rhythmic barking or whining. Hallucinatory behaviors may be staring at “shadows,” chasing light reflexes, and startling. Dogs that wake up suddenly without any discernible trigger and jump or are aggressive may suffer from hallucinatory compulsive disorder.

Compulsive behaviors may be considered an expression of stress, frustration, and/or motivational conflict. Frustration refers to the situation in which an animal is motivated to perform a behavior, but prevented from doing so. Motivational conflict results from two opposing, similarly strong motivations (such as approach and withdrawal). Prolonged and particularly repeated frustration and conflict may result in conflict behaviors developing into compulsive disorder. A genetic predisposition is probably present in any case of compulsive disorder. Physical lesions or irritations, such as ones caused by allergy, may trigger CD in some cases by increasing stress and by directing the compulsive behavior towards a particular body site. Owner attention may reinforce existing compulsive behaviors, or condition normal conflict behaviors to the extent that they appear compulsive. Disease that increases stress and/or irritability may contribute to CD, as may other stressful behavioral problems (e.g., interdog aggression or separation anxiety) or certain temperament traits (e.g., fearfulness).

A diagnosis of CD is based primarily on a detailed history and on ruling out other possible behavioral and medical causes for the observed behavior. One aspect of the history that is particularly important for the diagnosis is the development of the problem. In many cases (especially locomotory behaviors), compulsive behaviors are first shown in a specific conflict situation but later may generalize to other contexts in which the animal experiences a high level of arousal. Once established, compulsive behaviors are displayed outside of their natural context and are often excessive. The animal is in full consciousness while performing the behavior and aware of its surroundings (although in some cases they may not respond to any stimuli in their environment, and may even run into furniture, etc.). The behavior can usually be interrupted, albeit often with difficulty, and the animal does not exhibit a postictal phase. Their performance is not dependent on the owner's presence.

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The differential diagnosis has to consider various behavioral, neurologic, dermatologic, and other medical conditions. To exclude other possible causes for the behaviors, a minimal medical database consisting of a physical exam including a basic neurologic exam, and CBC, chemistry profile, thyroid panel, and urinalysis should be obtained. Additional tests may be needed in specific cases.

Behavioral differentials include acute conflict behavior only shown in specific contexts, and conditioned behavior only shown in a person's presence. Neurologic rule-outs are seizures, forebrain and brain stem lesions, lesions of the vestibular system (circling), lumbosacral stenosis (tail chasing), hydrocephalus, sensory neuropathies, and neuromas (self-mutilation).

Any dermatologic lesion, skin-gland disease, or endocrine disease that results in itching or pain can cause licking. Preexisting wounds or pressure point granulomas can also direct compulsive licking towards a particular area.

Treatment is directed at identifying and removing the cause of conflict, frustration, and stress. In cases in which the cause of stress cannot be removed, it may be possible to desensitize the animal to the stressful situation. Casual (i.e., inconsistent) interaction should be avoided and replaced with highly structured interactions in a command-response-reward format. Formal obedience sessions allow for such consistent interaction. Punishment should not be used at all. A consistent feeding and exercise schedule provide for a consistent routine. Sufficient exercise helps reduce anxiety. Rotating toys and providing food-dispensing toys are also recommended.

In most cases, drug therapy may prove necessary or will at least facilitate treatment. Pharmacologic intervention is most likely achieved with serotonin re-uptake inhibitors such as clomipramine (Clomicalm, Novartis Animal Health US, Greensboro, NC) at 3 mg/kg bid, or fluoxetine (Prozac, Eli Lilly, Indianapolis) or

paroxetine (Paxil, GlaxoSmithKline, Pittsburgh) at 1 mg/kg sid-bid. It may take more than 4 weeks to see a drug effect. The author usually gives the drug until at least 3 to 6 weeks after the drug appears to have a satisfactory effect and then weans off gradually over at least three weeks, by reducing dose but maintaining dosing frequency. If during the weaning process the behavior reappears, the dose is increased again and maintained at the effective level for some time before resuming weaning. Weaning is important to avoid a rebound effect.

The above behavioral treatment with or without drug treatment is likely to reduce the frequency of the behavior. If the dog still performs the behavior occasionally, consistent response substitution can be highly effective in the treatment of compulsive disorder.

52.2 FELINE BEHAVIOR PROBLEMS

52.2.1 Inappropriate Urination and Defecation

Cats that are house-soiling with urine may be differentiated from those that are urine marking by the amount of urine that is released. When marking, a cat eliminates small amounts of urine at a time, usually on vertical objects, whereas a house-soiling cat tends to empty his bladder, which results in a large spot. The exception is cats that mark with full urination and/or defecation on human's concentrated body odor (e.g., beds, bath mats, dirty clothes). In these cases, the cat has a conflict with the person on whose smell he marks with urine or feces.

Cats may stop using their litter-box for a variety of reasons. They may have developed an aversion to the litter, the pan, an odor or the location; they may have developed a preference for certain substrates or locations; they may be under some environmental stress; or they may have underlying disease, most commonly urinary tract infection or cystitis, and in older cats also arthritis or cognitive dysfunction.

The first step in treatment is to identify which cat of a multicat household is the culprit (Figure 52-1). To differentiate disease-related from behavioral house soiling, a physical exam, CBC, profile, urinalysis, and urine culture are indicated. Then litter-box factors need to be addressed. The number of boxes should equal the number of cats plus one. Owners should scoop the box daily and wash it out regularly with warm water only. Many cats do not like covered boxes. Location of boxes is crucial. Laundry rooms and basements are usually not preferred areas, whereas hallways and closets are most suitable. In a multicat household, a core area for each cat should be established, containing food, water, lying area, scratching post and litter-box, in the cats' preferred locations. The most important factor that determines litter acceptance is particle size; most cats prefer small particle size. Litter material should not be scented. A variety of litter materials can be offered. Litter-box liners are often aversive to cats and should not be used. Soiled areas should be cleaned and made aversive as described under canine house soiling.

If cats have established a substrate preference (e.g., for carpet) the cat can be retrained by confining it to a room with different flooring. A piece of carpet is placed in the litter-box. Each day, a somewhat smaller piece of carpet is provided, and a little more litter material is sprinkled on it, until the cat is completely switched over to litter. The cat can then be taken out of the room daily for short and increasingly longer periods of time, under close supervision. It is recommended to feed the cat free choice food and to change its water frequently.

52.2.2 Feline Marking or Spraying

Spraying is a form of territorial marking with small amounts of urine, or rarely, small amounts of feces. It is most common in intact males or males that produce steroids from other sources (check penis for barbs). Among

neutered animals, males are twice as likely to spray than are females. Spraying usually occurs in only a few specific areas, most commonly on prominent vertical objects, and often near windows and doors. Spraying is usually related to stress resulting from the presence of other cats, changes in the environment, changes in schedule, food and water restriction, or other factors. Some cats mark with full urination or defecation on concentrations of body odor of a specific person. This usually indicates some conflict related to that person, such as fear or overattachment. The smell of previously soiled areas will compel a cat to re-mark the same area.

In a multicat household it is important to determine which cat is marking. Although disease is not a common cause for urine marking, it should always be ruled out first. Intact animals (especially males) should be neutered. Environmental and social stressors should be addressed. In multicat households, different core areas for the cats, with food, water, lying area, scratching post, and litter-box should be established. Provision of cat trees enables cats to use the third dimension to get out of each other's way. Outside cats may need to be kept away, or the patient needs to be prevented from seeing them. The sprayed areas should be cleaned with a good enzymatic cleaner. Making the sprayed areas aversive is controversial. Application of a feline pheromone analogue (Feliway, Veterinary Products Laboratories, Phoenix), as a spray or by diffuser, may reduce spraying. The temporary use of an anxiolytic drug such as paroxetine (Paxil, GlaxoSmithKline) or clomipramine (Clomicalm, Novartis) may be necessary. It is recommended to offer free-choice food and provide fresh water frequently.

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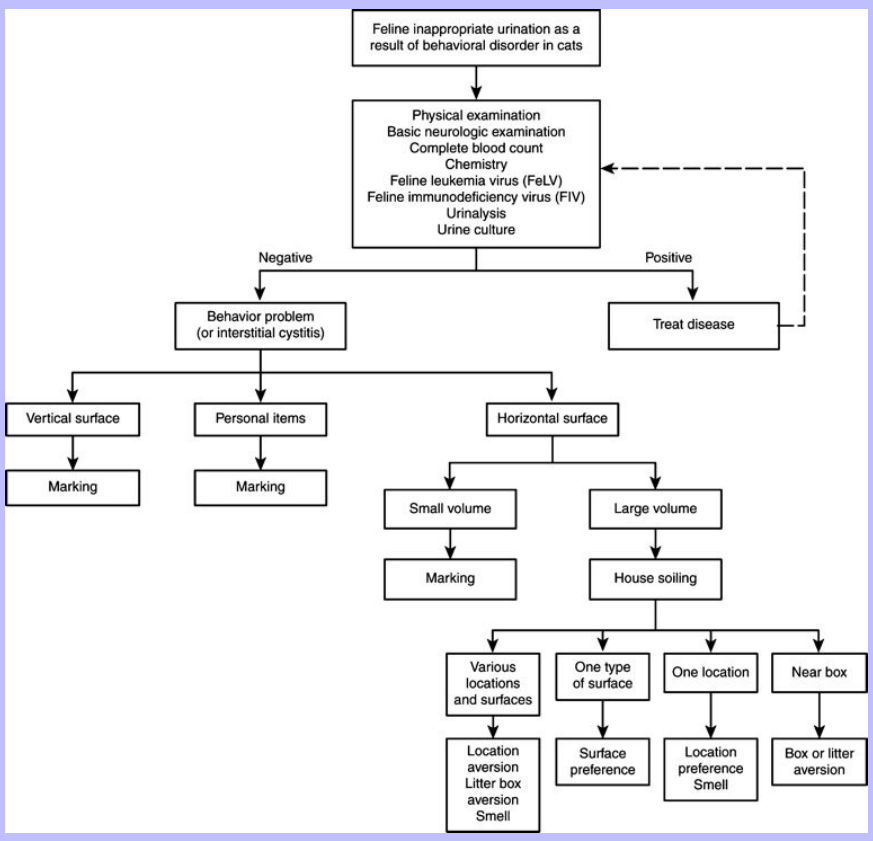
Figure 52-1 Algorithm for diagnosis and treatment of feline inappropriate urination.



52.2.3 Territorial Aggression, Intercat Aggression

This type of aggression is seen most frequently when a new cat is introduced to the household, or when a resident cat is reintroduced after a stay at the veterinary hospital or boarding. One cat may stalk the other cat, and the victim usually shows fear, which increases the probability of an attack.

Letting the cats “fight it out” does not work. Systematic desensitization and counterconditioning are recommended. Cats can be exposed to each other in carriers at a decreasing distance. Each time, the carriers are swapped, so the cats are exposed and take on each other's smell. While exposed to each other, they get their favorite food to eat. They can also be exposed to each other on leashes. While exposed, the owners should play with the cats and give them their favorite treats, gradually reducing the distance. When not systematically exposed to each other, the cats should be separated with only the bare necessities provided, and ignored. The rooms in which the cats are kept can be swapped after each exposure, so the cats are exposed and take on each other's smell. The smell can also be transferred between cats by rubbing a towel alternately on either cat. Drugs are often used on both cats (in the aggressor to reduce aggression, in the victim to reduce fear).

52.2.4 Petting Aggression

Some cats get very aggressive when petted for a prolonged time. The reasons are not well understood. Treatment involves avoiding prolonged petting or systematically desensitizing the cat to tolerate petting.

52.2.5 Redirected Aggression

This is not a diagnosis, but it describes aggression that is redirected to an alternate target, when the intended target is not accessible. It is often triggered by the view of outside cats. The cat that is indoors redirects its territorial aggression to another resident cat (which results in intercat aggression) or a person. *188* *189*

52.2.6 Play Aggression

Play aggression becomes a problem if the cat delivers uninhibited bites and causes injury. Affected cats are usually young, are living as the only cat in a household, and were taken early from their mothers. Often, owners contribute to the problem by playing roughly with the cat when it is a little kitten, and failing to teach a bite and claw inhibition. Play aggression is not usually preceded by a threat. The cat often hides behind some furniture and waits until a person walks by and then dashes out and attacks the person's ankles. Hands dangling over the armrest of a chair are also favorite targets.

To prevent further injury, the cat should wear a collar with as many bells as possible, so the owner becomes aware when the cat approaches. Some protective device or a canister of compressed air may also be effective. The cat should be distracted with the compressed air, and its behavior can then be redirected by tossing a toy. Teaching a bite and claw inhibition by immediately interrupting play as the cat gets rough is also important. Interesting toys that are rotated daily, and hiding food will keep the cat busy. A companion kitten may also help. The owner should teach the cat appropriate play by engaging it daily in play with interactive toys. They can also train their cat to obey commands and to do tricks.

52.2.7 Compulsive Behavior

In cats, examples of compulsive behavior include overgrooming (psychogenic allopecia), wool-chewing, vocalization, hallucinatory behavior, aggression to self, and many cases of the hyperesthesia syndrome. The diagnostic procedure and differentials are the same as described for dogs. Differentials for neurologic signs include FIV. Dermatologic differentials are particularly important in overgrooming cats. Skin scraping, dermatophyte culture, and trichogram are indicated. The patient should be treated for fleas and mites, undergo a food trial for 8 to 12 weeks, and undergo a trial of corticoid therapy before being treated with an anticompulsive drug.

The treatment is basically the same as in dogs. In multicat households, various core areas with food, water, a litter-box, a soft lying area, and a scratching post should be established, because social tension often contributes to stress. Cat trees allow cats to make better use of the third dimension and get out of each other's way. In some cases, an area needs to be provided where only the patient can go (e.g., electronically controlled cat door in a door). Feeding of dry food should always be ad libitum. It can be distributed around the house so that the cat is kept busy foraging for longer times. A large variety of interesting toys that are rotated may serve as an unspecific means of decreasing arousal. Particularly attractive toys such as food dispensing toys can be given at times when the performance of the compulsive behavior is likely.

Drug therapy is usually necessary as part of the treatment. Response substitution can also be used for cats. The cat is continuously supervised or placed in a situation in which it will not perform the behavior. Every time the cat is about to perform the compulsive behavior, it is distracted (startled), and then its attention reoriented by throwing a toy. If the cat is clicker trained, the same procedures as described above for dogs can be used.

53 CHAPTER • 53 Cardiorespiratory: Coughing

Kelly Anderson-Wessberg

A cough is a sudden, forceful expiration against a closed glottis. Sudden opening of the glottis and turbulent airflow create the noise identified as a cough. Coughing may occur as a conscious action or as a reflex. The coughing reflex is stimulated by mechanical or chemical irritation of the pharynx, larynx, trachea, bronchi, and smaller airways. Less commonly, disease processes involving the pleura, pericardium, diaphragm, nose, nasal sinuses, and mediastinum may also stimulate the coughing reflex.

Coughing may be the first indicator of a serious disease. On the other hand, coughing may be confused with other symptoms such as sneezing, gagging, panting, labored breathing, reverse sneezing, retching, and vomiting. The presence of a terminal retch is often misinterpreted as vomiting. Reverse sneezing has a characteristic sound with audible inspiratory and expiratory components. Failure to differentiate a cough from these other signs results in misdiagnosis and treatment failure.

The causes of coughing in small animals may be divided into the following categories (Box 53-1): inflammatory, neoplastic, cardiovascular, allergic, traumatic and physical factors, parasitic, and fungal.

53.1 DIAGNOSTIC APPROACH

53.1.1 Signalment and Historical Findings

The age and breed of the animal will influence the likelihood of certain conditions. Puppies and kittens are more likely to suffer from infectious respiratory diseases. Toy and miniature breeds such as Chihuahuas, Pomeranians, toy poodles, Yorkshire terriers, Shih Tzus, and Lhasa apsos are predisposed to collapsed trachea. Lungworm typically occurs in dogs less than 2 years of age, although it may occur in older animals. The history should focus on the general health of the pet, previous medical problems, recent diagnostics performed (heartworm testing, general blood profile, fecal examination, radiographic studies), vaccination status, heartworm prevention, exposure to other animals, and other symptoms the pet is experiencing. The history should include all recent and current medications, dosages, length of treatment, and response to each medication. Environmental history may provide important additional information. Exposure to dog parks, grooming facilities, kennels, and stray animals increases the likelihood of contagious disease. Any changes in the animal's environment should be noted along with the health of the other pets in the household. An accurate travel history should be obtained. Certain respiratory diseases are common in specific geographic areas and unlikely to occur in others. Coughing is a side effect reported in as many as 15% of human patients receiving ACE inhibitors. The cough is due to increased sensitivity of the cough reflex resulting in a dry, nonproductive cough. Increased bradykinin levels are thought to play a role. In dogs, coughing as a side effect from ACE inhibitors does not seem to be a common problem.

53.1.1.1 Box • 53-1 Causes of coughing in dogs and cats

53.1.1.1.1 Inflammatory

Pharyngitis

Tonsillitis

Tracheobronchitis

Chronic bronchitis

Bronchiectasis

Pneumonia—bacterial, viral, fungal

Granuloma

Abscess

Chronic pulmonary fibrosis

Collapsed trachea

Hilar lymph node enlargement

Secondary to esophageal dysfunction

Inhalation

Foreign body

53.1.1.1.2 Neoplastic

Primary

Mediastinal

Metastatic

Tracheal

Laryngeal

Ribs, sternum, muscle

Lymphoma

53.1.1.1.3 Cardiovascular

Left heart failure—pulmonary edema

Cardiomegaly—especially left atrium

Heart failure

Pulmonary emboli

Pulmonary edema—vascular origin

53.1.1.1.4 Allergic

Bronchial asthma

Eosinophilic pneumonitis

Eosinophilic pulmonary granulomatosis

Pulmonary infiltrate with eosinophilia (PIE)

Immune disease

Sinusitis (?)

Reverse sneeze (post nasal drip?)

53.1.1.1.5 Parasitic

Larval migration (*Toxocara* spp., *Ancylostoma caninum*, *Strongyloides stercoralis*), *Filaroides* spp. (dog), *Aelurostrongylus abstrusis* (feline lungworm), *Paragonimus kellicotti* (dog, cat), *Dirofilaria immitis* (dog, cat), *Capillaria aerophilia* (dog, cat), *Crensoma vulpis* (dog)

53.1.1.1.6 Protozoal

Toxoplasmosis (cat)

Pneumocystis (dog)

53.1.1.1.7 Fungal

Blastomycosis

Histoplasmosis

Coccidiomycosis

Cryptococcosis

Aspergillosis

53.1.2 Nature of the Cough

A description of the cough provides additional diagnostic clues. Specific questions regarding the cough should include the following: how does the cough sound, is it productive or nonproductive, what stimulates the cough, when does it occur, how often does it occur, is the cough worse at night or during the day, is it stimulated by exercise, is the timing of the cough related to eating or drinking, and does the cough respond to diuretics or other medications? Cardiac disease initially results in nocturnal coughing, but advanced cardiac disease may result in coughing during any time of day or night. Tracheal collapse typically produces a characteristic “goose-honk” sound easily recognized by most owners and experienced clinicians. Coughing due to tracheal

collapse or tracheal irritation is stimulated by excitement, drinking water, and by pulling on the collar. A productive cough may be produced by the following conditions: chronic bronchitis/bronchiectasis, pneumonia, pulmonary edema, esophageal dysfunction, and hemoptysis. A nonproductive cough may be produced by the following conditions: bronchitis, early cardiac disease, left atrial enlargement without pulmonary edema, lymphadenopathy, allergic lung disease, and tracheal irritation or collapse. These lists are not meant to be all-inclusive and some diseases may produce both types of cough. Also, some animals may be experiencing more than one disease process at a time, thus having multiple reasons for a cough.

53.1.3 Physical Examination

As with other body systems, a thorough physical examination is required for obvious reasons. Emphasis is placed on the cardiorespiratory system. Careful auscultation will reveal the presence or absence of a murmur, crackles, wheezes, rales, upper airway noises, or evidence of pleural effusion. In the presence of tracheal sensitivity or collapsing trachea, palpation of the extrathoracic trachea may stimulate the coughing response.

53.1.4 Radiographs

Thoracic radiographs may provide information leading to a diagnosis, but they are not necessary in every case. Radiographs should be analyzed for evidence of cardiac enlargement, pulmonary disease, pulmonary edema, and narrowing of the trachea. If pulmonary edema is identified, left heart enlargement is expected. Right heart enlargement alone does not typically result in a cough. It is important to distinguish coughing due to cardiac enlargement and coughing due to pulmonary edema. Left atrial enlargement may result in compression of the mainstem bronchi. Although some findings may be obvious, it may be impossible to distinguish between neoplasia, fungal infection, and pneumonia on radiographic examination alone. An algorithm for a general approach to interpreting thoracic radiographs in the presence of a cough is presented in Figure 53-1.

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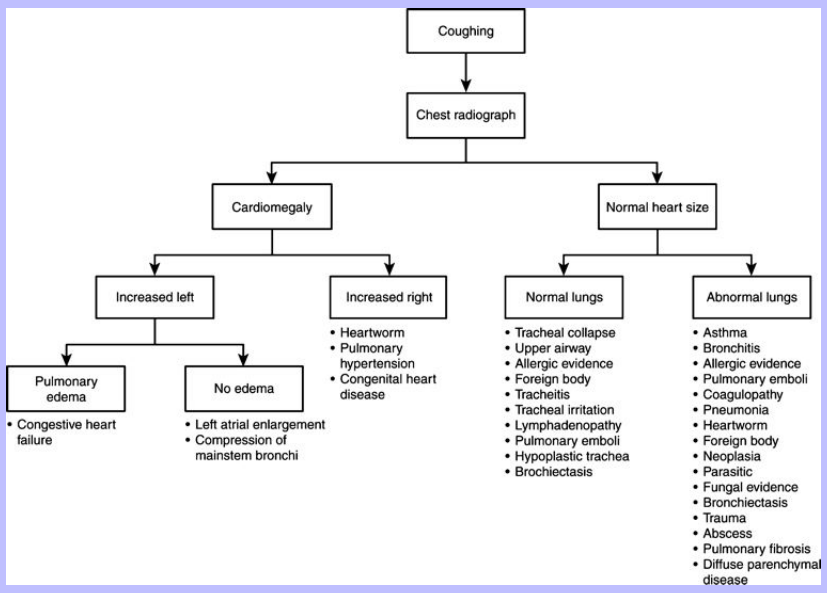
Figure 53-1 Algorithm for interpretation of thoracic radiographs in the presence of a cough.



53.1.5 Further Diagnostics

In some cases, it may be necessary to perform further diagnostics in an effort to obtain a diagnosis and proper treatment plan. A complete blood cell count, general chemistry profile, fecal examination, and heartworm test (in endemic regions) should precede further diagnostics. Descriptions of further diagnostics involving the cardiac and respiratory systems can be found elsewhere in this textbook.

53.2 TREATMENT GOALS

The ideal treatment for a cough is based on a definitive diagnosis and treatment of the underlying problem. However, it is not always possible to obtain a definitive diagnosis, and in such cases, treatment options must be based on clinical assumptions or a preliminary diagnosis. If no specific diagnosis has been made, there is no underlying problem identified, or the cough persists despite treatment of the underlying problem, the use of antitussives should be considered. Table 53-1 outlines commonly used antitussive agents. As a general rule, antitussive agents are contraindicated in cases when suppressing a cough masks important clinical symptoms or when a cough is actually encouraged as part of therapy. Specific treatment of underlying disorders can be found elsewhere in this textbook.

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Table • 53-1 Drugs Commonly Used for Canine and Feline Coughing

GENERIC NAME	TRADE NAME	DOSAGE
Bronchodilator		
Aminophylline	Many names	Dog: 10 mg/kg PO, IV tid Cat: 5 mg/kg PO bid
Theophylline	Many names	Dog: 6 mg/kg PO tid
Slow release	Theo-Dur	Dog: 20 mg/kg PO bid
Slow release	Slo-bid	Dog: 25 mg/kg PO bid
Antitussive		
Hydrocodone	Hycodan, Tussigon	Dog: 0.22 mg/kg PO bid-qid
Hydrocodone/Chlorpheniramine	Tussionex	Dog: 0.5 to 1 tsp PO sid-tid
Butorphanol	Torbutrol	Dog: 0.5 mg/kg PO bid-qid
Antiinflammatory		
Prednisone		Dog: 0.5 mg/kg PO bid, then taper dose
Prednisone/trimeprazine	Temaril-P	Dog: 1 tablet/20 lbs PO bid
Expectorant/Antitussive		
Guafenesin/dextromethorphan	Robitussin-DM	Dog: Similar to adult children dosages

54 CHAPTER • 54 Dyspnea and Tachypnea

Dianne Mawby

D*yspnea* is defined as labored or difficult breathing. The human patient is likely to communicate this to the physician as "air hunger." *Respiratory distress* is a similar term. *Tachypnea* is defined as an increased rate of respiration. *Panting* is a method of heat regulation and does not imply respiratory difficulty in the dog; however, panting in the cat usually indicates stress or hyperthermia. *Orthopnea* describes the inability to breathe except in an upright position.

The pathophysiology of respiratory distress usually stems from the lack of oxygen or excess of carbon dioxide in the body. Hypercapnea and acidemia are sensed in the central respiratory center and hypoxia is sensed through the peripheral chemoreceptors located in the carotid and aortic bodies. The body tries to resolve the problem with either increased ventilatory rate or increased ventilatory depth or both.

54.1 HISTORICAL FINDINGS

History should include geography and environment, recent exposure to other animals, past illnesses, past injuries, and vaccination and heartworm preventative status. The current complaint should be addressed regarding duration, progression, previous treatment, and response to therapy. The owner can also supply information involving upper respiratory problems such as nasal discharge, sneezing, noisy breathing, abnormal breathing patterns, and recent exposure. Coughing is discussed in Chapter 53. Other relevant history includes exercise intolerance, change in appetite, and general demeanor.

54.2 CLINICAL SIGNS

Dyspnea can result from physical obstruction of the nares and upper airways. Animals with complete nasal passage obstruction breathe through the mouth, whereas patients with upper airway obstruction usually have inspiratory dyspnea. Lower airway or bronchial disease is accompanied by expiratory dyspnea because normal expiratory forces increase pressure on diseased airways. Bronchospasm and decreased luminal size due to excretions results in wheezes. Lung parenchymal disease decreases air-blood interaction resulting in dyspnea with increased ventilatory rate and depth. Gas exchange is affected by thickened alveolar-capillary membrane due to inflammatory or neoplastic cells, edema, hemorrhage, or through capillary shunting of blood through unventilated alveolar capillaries. Another cause of ventilation-perfusion mismatch is pulmonary thromboembolism (PTE), which can also result in severe dyspnea.

Pleural space expansion causes decreased lung compliance and will result in shallow tachypnea. Dyspnea can result when the capacity of the restricted lungs is further challenged, such as with exercise or stress.

Other diseases can be reflected by the respiratory system. With severe acidosis, the body attempts to restore acid-base balance by exhaling carbon dioxide. This can cause tachypnea, which may be interpreted as dyspnea. Infectious, neoplastic, vascular, or traumatic damage to the central nervous system can result in abnormal rate or rhythm of ventilation, which may be mistaken for pulmonary tachypnea or dyspnea.

54.3 PHYSICAL FINDINGS

Physical examination of the dyspneic patient can be quick and efficient but should not be pursued until the patient is stable. Oxygen supplementation using a face mask is suggested but, if not tolerated, the oxygen hose alone may

prove to be effective. However, the animal may need to recover from the stress of transport and continued stress of handling may be harmful. In these circumstances the patient should be left undisturbed in an oxygen cage.

Body condition and general appearance should be evaluated. The integument is examined for signs of trauma or tumors. Enlarged peripheral lymph nodes can indicate underlying inflammatory, infectious, or neoplastic disease. The musculoskeletal system may also give clues to the cause of respiratory distress if lameness is due to fungal infection or hypertrophic pulmonary osteoarthropathy, or if it indicates trauma (such as fractures). Cats have a propensity for metastasis of primary bronchogenic carcinoma to the digits.

The cardiovascular system is intimately associated with the respiratory system. The mucous membranes can indicate anemia, shock, or cyanosis. The heart is auscultated to evaluate arrhythmias, murmurs, or decreased intensity. Characterization of peripheral pulses indicate perfusion, pulse pressure, and cardiac arrhythmias. Abdominal palpation can reveal abnormal masses, organomegaly, or ascites, which can cause secondary respiratory problems through metastasis or physical compromise. A complete neurologic and ocular examination may reveal diseases that also affect the respiratory system.

The upper airway consists of the nasal passages, pharynx, larynx, and trachea. External nares can be stenotic from cartilage malformation and unilateral or bilateral discharge could indicate upper airway disease. The nasal cavities may not be patent as a result of obstruction with soft tissue or excessive discharge. *Stertor* describes the snoring noise that is made with partial obstruction of the nasal or nasopharyngeal area. The bridge of the nose and the hard and soft palate are examined for abnormalities that may affect the nasal passage. Masses at the back of the throat cause airway obstruction. Everted laryngeal saccules and elongated soft palate occur in the brachiocephalic complex and result in inspiratory dyspnea. The oropharynx may be visualized but examination of the larynx may require heavy sedation or anesthesia. Laryngeal paralysis can cause dyspnea, especially with exercise, excitement/stress, or hyperthermia. The inspiratory dyspnea resulting from upper airway obstruction causes a harsh, high-pitched sound on inspiration, which is called *stridor* (Figure 54-1). Tracheal collapse may cause coughing and may progress to obstruction. The collapse may be in the cervical or intrathoracic trachea and may also involve mainstem bronchi. The characteristic “goose-honk” cough usually historically precedes complete airway collapse.

The lower respiratory tract is examined by observing breathing patterns, palpation, percussion, and auscultation. Breathing patterns may help localize the problem. The obstructive pattern usually has increased rate and depth. Upper airway obstruction results in difficulty with inspiration and lower airway obstruction causes expiratory difficulty. Mixed patterns of increased inspiratory and expiratory effort can occur. Restrictive breathing pattern implies decreased lung compliance, which results in decreased depth and increased rate such as with pleural effusion.

Palpation of the thorax can reveal masses or trauma such as rib fractures. Young cats have an easily compressible thorax, which can be compromised by mediastinal masses or pleural effusion. Feline bronchitis can obstruct outflow of air from the lower airways resulting in a barrel-chested appearance over time.

Percussion of the thoracic wall can help localize areas of increased or decreased resonance. Pneumothorax results in increased resonance on percussion and decreased lung sounds with auscultation. A fluid line may be percussed with pleural effusion when the animal is standing or in sternal recumbency. Fluid or hernias cause decreased resonance with percussion and muffled heart and lung sounds with auscultation.

Normal respiratory sounds with auscultation are termed *bronchovesicular* and are produced by tissue vibration and air movement. Increased bronchovesicular sounds result from increased air flow or turbulence. Upper airway noises can be referred to the thorax due to the direction of air flow; therefore purring, stertor, and stridor can be

ausculted in the chest and must be distinguished as such. Abnormal lower airway sounds are termed *continuous* or *discontinuous*. Continuous sounds include rhonchi and wheezes that result from partial obstruction of airways from bronchoconstriction or secretions. Discontinuous sounds usually occur during inspiration and are referred to as *crackles* or *rales*. These sounds result from the opening of alveoli and small airways that are otherwise collapsed or partially filled with fluid. Absence of respiratory sounds may indicate pleural effusions, pneumothorax, diaphragmatic hernia, or masses.

54.4 DIAGNOSTIC AND THERAPEUTIC PLAN

To increase oxygen delivery to the dyspneic patient, either mask, nasal tubing, or oxygen cage can be used. Oxygen concentration of 100% can only be tolerated for a few hours before toxicity develops; therefore long-term therapy is usually limited to 40% oxygen. If the animal is dyspneic, cyanotic, and frantic, sedation is essential. Control of upper airway problems may require general anesthesia and placement of an endotracheal tube, during which any obstruction can be visualized and bypassed. If the problem is identified and not readily resolved, a tracheostomy can be performed as a short-or long-term solution.

If the dyspnea is of a mixed or expiratory pattern, then evaluation for lower airway or parenchymal disease is indicated. Crackles heard with auscultation indicate edema or exudate. Wheezes can indicate lower airway disease. Blood can be obtained from the stable patient to determine blood gases and to evaluate for anemia, thrombocytopenia, coagulopathy, and metabolic or infectious causes of disease. A pulse oximeter reading may provide information on hemoglobin saturation. Radiology is an important diagnostic tool for prioritization of differential diagnoses of parenchymal disease, if it can be done without excessive stress. Diuretics are indicated for pulmonary edema. Cardiogenic edema may need to be initially managed with a diuretic plus a venodilator such as topical nitroglycerin. Bronchodilators are used for lower airway and parenchymal disease to increase airflow. If indicated and the patient is stable, transtracheal wash or bronchoalveolar lavage may provide diagnostic information. Fine needle aspiration of diseased lung parenchyma can also be done if inflammatory, infectious, or neoplastic etiologies are suspected. This procedure and complications of FNA are described elsewhere in this text. If an inflammatory process is suspected, corticosteroids are indicated after diagnostic samples are obtained. This may not always be possible with a severely dyspneic animal.

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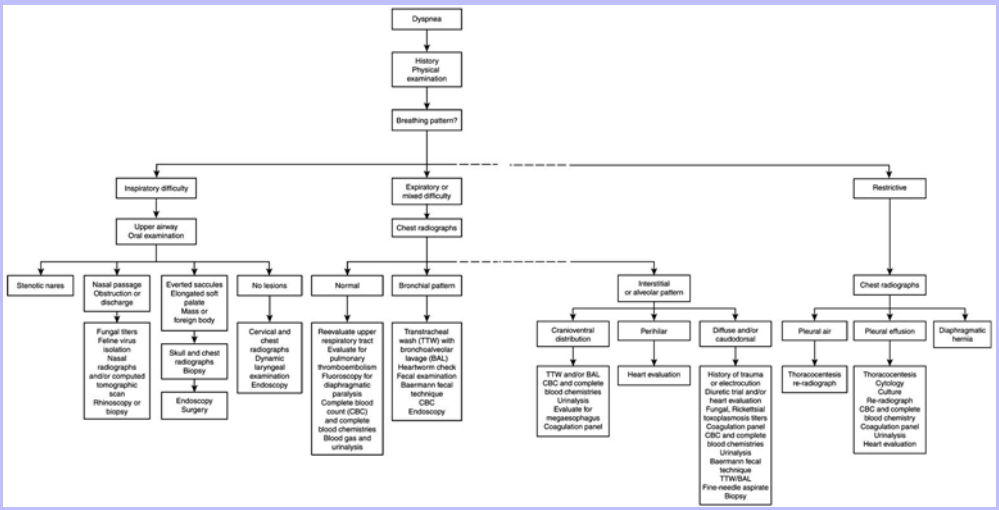
Figure 54-1 Algorithm for inspiratory stridor.



Pulmonary thromboembolism (PTE) patients can be severely dyspneic and have normal radiographs. Definitive diagnosis of PTE involves selective angiography or nuclear medicine scans. Supportive care with efforts directed towards resolution of the underlying disease is the best treatment for PTE. Patients with severe parenchymal disease may benefit from mechanical ventilation, which requires general anesthesia.

Thoracic imaging is useful in identification of problems of the pleural space, but thoracocentesis may be needed first for therapeutic and diagnostic purposes. If air or fluid is obtained, evacuation of the pleural space will resolve the dyspnea and allow radiologic examination for underlying disease. If a diaphragmatic hernia is present, then surgery is necessary for complete resolution.

55 CHAPTER • 55 Abnormal Heart Sounds and Heart Murmurs

Robert Prošek

Cardiac auscultation is an important tool in the clinician's armamentarium. Interpretation of heart and lung sounds is predicated on the clinician's understanding of their genesis in health and a variety of clinical disorders. Cardiovascular sounds of short duration are referred to as *transient heart sounds* and include the normally heard first heart sound (S_1) and second heart sound (S_2). Heart murmurs are auditory vibrations of longer duration created when laminar flow is disrupted.

Implementing good technique with a quality stethoscope is fundamental. During auscultation the animal should be standing or sitting in a quiet environment. Both sides of the thorax should be carefully auscultated with the stethoscope's diaphragm and bell with special attention to the areas overlying the cardiac valves. The clinician should correlate the various heart sounds to the events of the cardiac cycle. A good orientation is the palpation of the precordial impulse (left apex beat) that occurs just after S_1, and the arterial pulse that is felt between S_1 and S_2.

55.1 TRANSIENT HEART SOUNDS

55.1.1 The First (S_1) and Second (S_2) Heart Sounds

The first heart sound is associated with closure and tensing of the atrioventricular valves (mitral and tricuspid) at the onset of systole coinciding with the QRS complex on the electrocardiogram. S_1 is longer, louder, and lower pitched than the second heart sound. Causes of increased intensity of S_1 include thin chest wall, tachycardia, high sympathetic tone, systemic arterial hypertension, and anemia. Diminished intensity of S_1 may be auscultated in animals with obesity, pleural or pericardial effusion, diaphragmatic hernia, dilated cardiomyopathy, hypovolemia, emphysema, or a prolonged P-R interval. Splitting of S_1 is occasionally auscultated at the cardiac apex in healthy, large breed dogs or may result from electrical disturbances (ectopic beats, bundle branch blocks, cardiac pacing) or mechanical factors (tricuspid or mitral stenosis).

The second heart sound is associated with closure of the semilunar valves (aortic and pulmonic) at the end of systole following the T wave on the electrocardiogram. In dogs and cats, pulmonic valve (P_2) closure follows aortic valve (A_2) closure by a very short interval, which causes S_2 to be heard as a single sound. On occasion an audible split second heart sound may be seen in healthy, large breed dogs during inspiration due to a longer right ventricular ejection period. Pathologic splitting of S_2 due to delayed closure of the pulmonic valve is most commonly auscultated in dogs with pulmonary hypertension as occurs with heartworm disease and right-to-left patent ductus arteriosus. Delayed closure of P_2 also occurs with left-to-right intracardiac shunts (atrial septal defects), pulmonic stenosis, right bundle branch block, ectopic beats, and ventricular pacing. Premature A_2 closure can on occasion be noted with mitral insufficiency and mitral stenosis. Paradoxic splitting of S_2 results from delayed closure of the aortic valve and is sometimes audible in dogs with aortic stenosis, left bundle branch block, ectopic beats, and systemic hypertension.

55.1.2 The Third (S_3) and Fourth (S_4) Heart Sounds

The third and fourth heart sounds occur during diastole and are not audible in normal dogs and cats. S_3 and S_4 heart sounds are of lower frequency than S_1 and S_2 and are usually best heard with the bell of the stethoscope. When heard, S_3 or S_4 may sound like the triple cadence of a galloping horse. The term *gallop rhythm* should probably be avoided because the presence of an audible S_3 or S_4 has nothing to do with the heart's underlying electrical rhythm.

Rapid ventricular filling generates the S_3 sound, also known as *S_3 gallop*, *protodiastolic gallop,* or *ventricular gallop*. An audible S_3 is most commonly heard with diastolic volume overloading as in dilated cardiomyopathy, patent ductus arteriosus, and mitral insufficiency. In dogs with mitral insufficiency, the S_3 gallop may be mistaken for the second heart sound if a loud pansystolic murmur extends through the second heart sound. Protodiastolic gallop sounds in cats are most commonly associated with dilated cardiomyopathy, anemia, and hyperthyroidism.

The presystolic gallop, also called *S_4 gallop* or *atrial gallop,* is heard just before S_1 and occurs just after the P wave on the electrocardiogram. This low-frequency sound is generated by blood flow into the ventricles during atrial contraction; hence the absence of S_4 gallops with atrial fibrillation. An audible S_4 in the cat and dog is usually associated with increased ventricular hypertrophy and stiffness and is sometimes audible in animals with third-degree atrioventricular block.

At fast heart rates, rapid ventricular filling and atrial systole transpire very close together, which makes differentiation between S_3 and S_4 impossible. The resulting single accentuated sound is referred to as a *summation gallop*.

55.1.3 Ejection Sounds, Systolic Clicks, Opening Snaps, and Pericardial Knocks

Ejection sounds are left basilar high-frequency sounds generated by opening of the semilunar valves or dilatation of the great vessels during early systole. These sounds are occasionally noted in pulmonic stenosis, aortic stenosis, tetralogy of Fallot, and heartworm disease. Systolic clicks are mid to late high-frequency sounds usually heard best over the mitral valve area. Systolic clicks are occasionally associated with degenerative valvular disease, mitral valve prolapse, and mitral dysplasia. The genesis of the sound in dogs is uncertain but is likely caused by the sudden tensing of redundant valve leaflets or elongated chordae tendineae as they buckle into the left atrium. A systolic click should be differentiated from a split or gallop heart sound. Pericardial knocks are uncommon early diastolic sounds caused by restrictive pericardial disease. Timing of the sound is similar to S_3 and appears to be generated by abrupt restriction to ventricular filling by a diseased pericardium. (See Figure 55-1 for timing of transient heart sounds and description of murmurs.)

55.2 CARDIAC MURMURS

Cardiac murmurs represent sounds of longer duration than the transient heart sounds. Cardiac murmurs are caused by turbulent blood flow in the heart or adjacent blood vessels created upon disruption of normal laminar flow. The development of turbulent blood flow can be created by high-velocity flow, flow from narrow restricted area into a larger area, or low blood viscosity. The relationship of cardiac murmurs with flow velocity, vessel size, and blood

viscosity is defined by the Reynold's number. When the number reaches a critical high level, blood flow becomes turbulent.

$$\text{Reynold's number} = \frac{(\text{Radius})\ (\text{Velocity})\ (\text{Density})}{\text{Viscosity}}$$

Murmurs can be characterized and described by their timing within the cardiac cycle (systolic, diastolic, portions thereof), location (point of maximal intensity), radiation, intensity (loudness), shape, and frequency (pitch).

55.2.1 Timing

Systolic murmurs may start immediately at the first (S_1) heart sound and last through the second (S_2) heart sound (pansystolic murmur), may start immediately after S_1 and last until S_2 (holosystolic), or may occur in early (protosystolic), mid (mesosystolic), or late (telesystolic) systole. Diastolic murmurs most commonly occur in early diastole (protodiastolic), throughout diastole (holodiastolic), or can occasionally be audible only at the end of diastole (presystolic).

55.2.2 Location and Radiation

The location of a murmur refers to the valve area at which the murmur is heard best (point of maximal intensity). Alternatively, location can be described simply by the terms *apex* or *base* (e.g., left apex or mitral valve area). Some murmurs may also radiate to other areas, yielding important clues as to the source of the murmur. For example, the murmur of subvalvular aortic stenosis (PMI at left heart base) may radiate to the ventral neck area due to turbulence in the carotid arteries and may also be heard on the right cranial thorax.

55.2.3 Intensity (Loudness)

The intensity of the murmur is commonly graded on a 1 to 6 scale, with grade 1 murmur the softest and grade 6 the loudest (Box 55-1). A grade 1 murmur is the faintest murmur and is heard in a quiet environment with particular effort, whereas grade 5 and 6 murmurs are associated with palpable vibrations on the chest wall (palpable thrill). The intensity of the murmur at its origin is determined by blood flow velocity and the rate of flow (velocity × flow = force). The intensity of the murmur at the body surface is affected by direction of the turbulent jet, character of tissue between auscultation area and the turbulent jet, and the frequency of the murmur. Often the intensity of a heart murmur is not directly correlated with the severity of a lesion. However, describing the loudness of a murmur is important for serial examinations, and in certain heart diseases at least a rough correlation exists.

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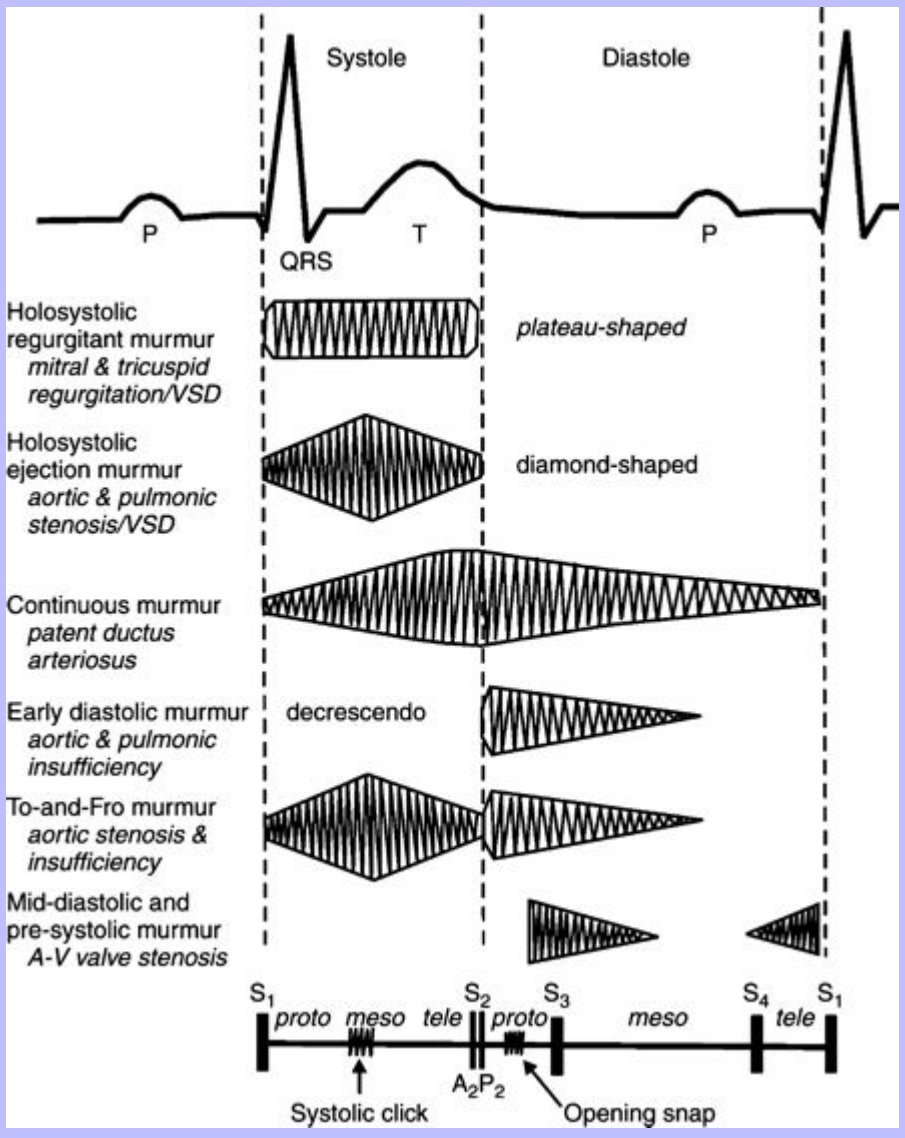
Figure 55-1 Murmur shapes and descriptions with some common examples. Also depicted are normal and abnormal transient heart sounds and their location within the cardiac cycle. *Proto,* Early; *meso,* mid; *tele,* late; A_2, aortic valve closure; P_2, pulmonic valve closure; S_1, first heart sound; S_2, second heart sound; S_3, third heart sound; S_4, fourth heart sound.



55.2.4 Pitch (Frequency)

A murmur's quality and pitch relate to its frequency components, which may be high, medium, low, or of mixed frequency. Most murmurs consist of midrange mixed-frequency sounds. On occasion high-frequency musical tones or low-frequency “honks” are auscultated. Musical murmurs are most commonly identified in dogs with modest mitral valve disease.

55.2.5 Shape

Heart murmurs are often described by their frequency profile within the cardiac cycle in relation to their shape on a phonocardiogram. Terms that are commonly used include *plateau-* or *band-shaped murmurs* for those murmurs of equal intensity throughout their duration; decrescendo for murmurs that gradually taper off from an initial peak; and crescendo decrescendo (diamond-shaped, ejection murmur) for murmurs that build up to a peak intensity and then taper in intensity.

55.3 SYSTOLIC HEART MURMURS

55.3.1 Mitral Insufficiency

The murmur of mitral insufficiency is best heard at the left apex (mitral valve area) and commonly radiates dorsally and to the right thorax making reliable diagnosis of tricuspid regurgitation difficult. The characteristic murmur is plateau (band-shaped) and holosystolic; however, in its early stages the murmur may develop in mid-to late-systole. Mitral insufficiency murmur is typically of mixed frequency and harsh sounding, but it may be high-pitched or musical (whooping) in quality. Mitral insufficiency can be caused by chronic degenerative valvular disease (endocardiosis), endocarditis, hypertrophic obstructive cardiomyopathy, congenital malformations, and diseases that cause left heart enlargement and dilation of the mitral annulus (e.g., patent ductus arteriosus, dilated cardiomyopathy).

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55.3.1.1 Box • 55-1 Grading of Cardiac Murmurs

55.3.1.1.1 Grade 1

Very soft, localized murmur detected in a quiet room after intently listening for a few minutes

55.3.1.1.2 Grade 2

Soft murmur but easily heard after a few seconds

55.3.1.1.3 Grade 3

Moderate intensity murmur

55.3.1.1.4 Grade 4

Loud murmur but not accompanied by a palpable thrill (vibration)

55.3.1.1.5 Grade 5

Loud murmur accompanied by a palpable thrill

55.3.1.1.6 Grade 6

Very loud murmur that produces a palpable thrill still audible after stethoscope is removed from the chest

55.3.2 Tricuspid Insufficiency

The murmur of tricuspid insufficiency sounds similar to that of mitral insufficiency but is loudest over the right apex (tricuspid valve area). It is often difficult to distinguish tricuspid insufficiency from a radiating murmur of mitral insufficiency. Tricuspid murmurs might be a different pitch compared with a radiating mitral murmur and can be accompanied by jugular pulsations. Tricuspid insufficiency can result from congenital malformations of the valve, chronic degenerative valve disease, or any disorders that cause marked right heart enlargement and valve annulus distention, such as pulmonary hypertension, and arrhythmogenic right ventricular cardiomyopathy). Tricuspid valve endocarditis is extremely rare in dogs and cats.

55.3.3 Aortic Stenosis

Valvular and subvalvular aortic stenosis (SAS) produce a systolic ejection (crescendo-decrescendo) murmur that is usually best heard at the left heart base. The murmur is usually of mixed frequency and harsh, and it sometimes radiates towards the right cranial thorax and up the neck along the carotid arteries. Mild obstructions cause soft murmurs that are difficult to distinguish from innocent or functional murmurs. Murmurs that vary dramatically in intensity with exercise or excitement should prompt consideration of a dynamic left ventricular outflow tract obstruction. Dynamic outflow tract obstruction is the most common type of ejection murmurs in cats with hypertrophic cardiomyopathy and its onset and duration coincide with systolic anterior motion of the mitral valve. Dynamic left ventricular outflow tract obstruction occurs uncommonly in dogs as an isolated abnormality or in association with mitral valve dysplasia or hypertrophy of interventricular septum.

55.3.4 Pulmonic Stenosis

Pulmonic stenosis murmur is typically a high-frequency crescendo-decrescendo (ejection) holosystolic murmur, best heard at the left heart base over the pulmonic valve. The murmur can be very similar to aortic stenosis murmur described above but should not radiate along the carotid arteries. As the pressure gradient between the right ventricle and pulmonary artery increases, the murmur intensity becomes louder and peaks later in systole.

55.3.5 Ventricular Septal Defect

Ventricular septal defects (VSDs) produce murmurs that vary tremendously in shape and quality. Most often the murmur is a harsh, mid-to high-frequency holosystolic murmur best heard on the right cranial thorax. Murmur intensity may be reduced when the VSD is large and as pulmonary hypertension develops. With severe pulmonary hypertension, the murmur may be entirely absent and splitting of the second heart sound is noted.

55.3.6 Atrial Septal Defect

Heart murmurs in dogs and cats with an atrial septal defect (ASD) result from increased flow across the pulmonic valve as a result of the left to right shunting. This murmur resembles that of mild pulmonic stenosis but is often accompanied by a fixed splitting of the second heart sound. Flow across the atrial septal defect is usually not audible.

55.3.7 Physiologic and Innocent Murmurs

Functional (physiologic) murmurs are usually caused by decreased blood viscosity or increased cardiac output. Physiologic murmurs are most often noted in animals with anemia, fever, pregnancy, hyperthyroidism, and increased sympathetic tone. These murmurs usually are proto to mesosystolic, soft to moderate intensity (grade 1/6 to 3/6), and loudest at the left heart base. They tend not to radiate extensively.

Innocent murmurs should disappear as the dog matures and appear to be the result of larger stroke volumes in puppies for the size of their great vessels in comparison with adult dogs. In some cats, turbulent blood flow can be noted in the region of the right ventricular outflow tract, often causing a soft systolic apical sternal murmur ranging in grades from 1 to 3/6, with no evidence of structural heart disease and little clinical consequence.

55.4 DIASTOLIC HEART MURMURS

55.4.1 Aortic Insufficiency

The murmur of isolated aortic insufficiency is typically a decrescendo murmur starting at the time of S_2 and extending variably into diastole. In young dogs, aortic insufficiency can occur as an isolated defect or in combination with subaortic stenosis or a ventricular septal defect. Detection of aortic insufficiency in an adult dog or cat should prompt consideration of bacterial endocarditis.

When the regurgitant volume is large, the diastolic murmur is often accompanied by a soft mesosystolic ejection murmur, creating a distinct *"to-and-fro"* murmur. The systolic ejection component tapers off in late systole and allows recognition of S_2 and differentiation from a continuous murmur. Other causes of "to-and-fro" murmurs include ventricular septal defects that cause loss of aortic root support and pulmonic valve stenosis and significant pulmonic insufficiency (rare). Occasionally massive aortic regurgitation causes premature closure of the mitral valve producing functional mitral stenosis and a diastolic murmur referred to as an *Austin Flint murmur*.

55.4.2 Pulmonic Insufficiency

The murmur of pulmonic insufficiency is similar to that of aortic insufficiency; however, clinically significant pulmonic insufficiency is uncommon. It is sometimes detected in animals with pulmonary hypertension, pulmonic valve dysplasia, or idiopathic dilation of the pulmonary artery.

55.4.3 Mitral Stenosis

The diastolic murmur of mitral stenosis is difficult to recognize in dogs and cats. This low-frequency murmur begins in mesodiastole and has presystolic accentuation due to atrial contraction. Mitral stenosis might be

accompanied by other cardiac malformations, which causes murmurs such as valvular or subvalvular aortic stenosis. In dogs, mitral stenosis may be more common in breeds that are prone to congenital mitral valve malformations such as the bull terrier breed, in which it is often associated with aortic stenosis.

55.5 CONTINUOUS MURMURS

The most common cause of a continuous murmur at the left heart base is patent ductus arteriosus (PDA). This classic "machinery-like" murmur of a PDA is usually audible throughout the cardiac cycle with peak intensity near S_2. The intensity of the murmur is diminished in late diastole in dogs with very slow heart rates and the diastolic component can also disappear with the development of pulmonary hypertension. Less common causes of continuous murmurs include aorticopulmonary windows, ruptured aneurysms of sinus of Valsalva, and coronary arteriovenous fistulas.

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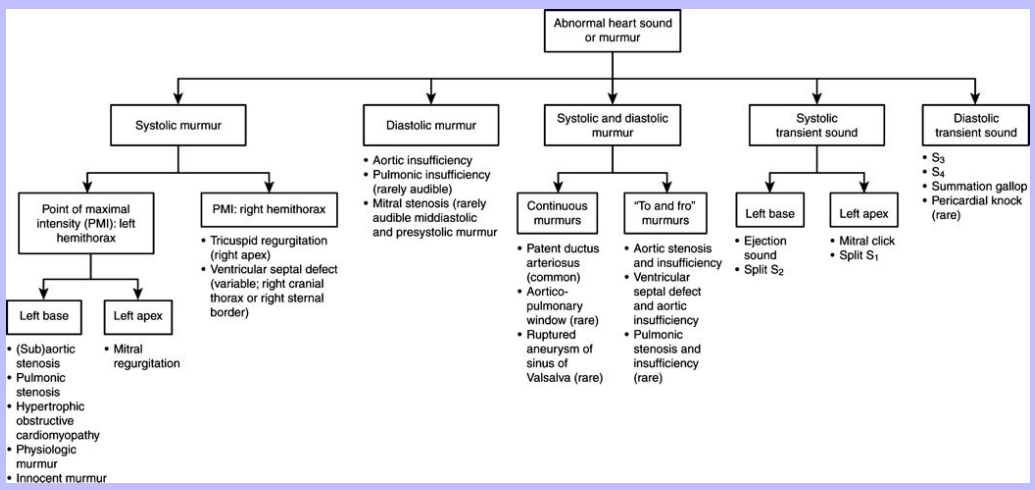
Figure 55-2 Algorithm for differentiating causes of abnormal heart sounds and murmurs. *PMI,* Point of maximal intensity; *PDA,* patent ductus arteriosus; *AP,* aorticopulmonary.



55.6 AUSCULTATION AND BEYOND

Historical findings may suggest underlying heart disease; however, a thorough auscultation with identification and understanding of abnormal heart sounds and their genesis will permit recognition of the most likely cause (see Figure 55-2). As important a tool as cardiac auscultation is, it should be one part of a complete physical exam that integrates evaluation of lung fields, jugular veins, arterial pulses, and peripheral circulation. Increasingly the affordability and availability of next generation electronic stethoscopes will allow the clinician to pick up difficult-to-hear heart sounds and other body sounds.

Additionally, other diagnostic tests might be needed to further classify and define the animal's abnormality, and in some cases differentiate a pathologic from a physiologic murmur (especially cats).

56 CHAPTER • 56 Pulse Alterations

Richard Kienle

Assessment of arterial and venous pulse characteristics is an integral component of the physical examination. However, the findings from these exams should not be used in isolation but integrated with findings from other exams and diagnostic tests. Arterial pulse qualities (rate, rhythm, symmetry, and strength) provide important information regarding the status of the cardiovascular system, specifically cardiac output and perfusion. Evaluation of venous pulse qualities (distention or pulsation) provides insight regarding right-sided cardiac pressures and the status of venous return. Abnormalities of arterial and/or venous pulse characteristics may be present in any cardiovascular disease state and may also be present in other systemic and metabolic states that affect cardiac output and systemic pressure or venous return. Detection of these changes often facilitates selection of additional diagnostics and allows for monitoring of patient status and response to therapy. The clinician should be familiar with the common abnormalities detected and their significance (Figure 56-1).

56.1 THE ARTERIAL PULSE

56.1.1 Genesis of the Arterial Pulse

Systolic arterial blood flow and pressure are generated by the contractile force of the left ventricle and to a lesser extent by elastic recoil of the aorta. During systole, aortic pressure rises rapidly as left ventricular pressure exceeds aortic pressure and ventricular ejection begins. Later in systole, as ventricular pressure declines and the blood flows into the distal vasculature, aortic pressure decreases. During ventricular diastole, when left ventricular pressure drops below aortic pressure and the aortic valve closes, diastolic blood pressure is maintained by elastic recoil of the aorta. Diastolic blood pressure gradually decreases as elastic recoil is consumed and blood continues to flow distally.

56.1.2 Assessment of the Arterial Pulse

The femoral pulse should be evaluated carefully in every patient (Figure 56-2). This evaluation is performed preferably with the patient standing but may also be done in recumbent patients. The femoral arteries should be palpated high on the limb so that the artery is palpated within or just below the femoral triangle, where the least amount of fat and muscle overlie the artery. The index finger, the middle finger, or both should be placed over the artery lightly to start. Digital pressure should then be applied with sufficient strength to occlude arterial flow so that no pulsation directly beneath the fingers is identified. Digital pressure should then be gradually decreased until the maximum pulsation is felt. The maximum pulsation occurs when digital pressure is equal to mean arterial blood pressure.

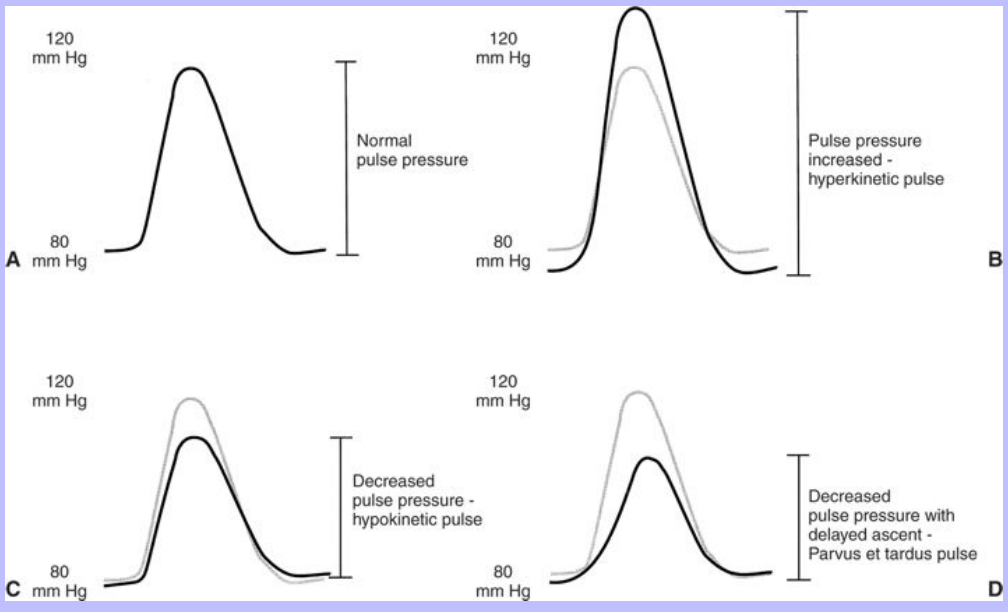
The intensity of the peripheral arterial pulse is determined by the difference between the systolic blood pressure and the diastolic blood pressure, termed the *pulse pressure*. Consequently, absolute blood pressure cannot be determined by digital palpation of artery. In addition to pulse pressure, body condition affects the perceived strength of the arterial pulse. Arterial pulses are usually more prominent in thin animals, whereas they may be difficult to palpate in obese animals. The clinician should take into account the animal's body condition when pulse strength is assessed.

56.1.3 Arterial Pulse Alterations

Pulse pressure can be decreased or increased or it can have an altered configuration (see Figure 56-1). Three physiologic factors are important in determining arterial pulse pressure: (1) heart rate, (2) stroke volume, and (3) peripheral vascular resistance. An increase in heart rate may result in a mild increase in diastolic arterial pressure, as there is less time for diastolic pressure to decline. This will result in a decrease in pulse pressure and an increase in mean arterial pressure generally leading to what is perceived as a weak peripheral pulse. Bradycardias, on the other hand, may lead to excessive run off during diastole as well as a greater strength of contraction due to greater diastolic filling, leading to a stronger than normal pulse.

A decrease in pulse pressure can occur if stroke volume is decreased, as in patients with heart failure or hypovolemia. This is termed a *hypokinetic* pulse. In most patients with a decreased stroke volume, arterial resistance increases and arterial compliance decreases to keep systemic blood pressure within the normal range. Patients with a decreased stroke volume commonly have normal pulses until the stroke volume becomes markedly reduced.

Figure 56-1 Schematic illustration of femoral artery pulse contours. **A,** Normal pulse. There is a rapid rise in pressure followed by a more gradual descent to diastolic pressure. The pulse pressure is indicated by the bar. **B,** Hyperkinetic pulse. Elevation in systolic pressure and decrease in diastolic pressure have widened the pulse pressure, resulting in a strong or hyperkinetic pulse. **C,** Hypokinetic pulse. Pulse pressure is reduced because of decreased systolic pressure. **D,** Parvus et tardus pulse. This is a type of hypokinetic pulse characterized by a slow ascent and is typical for subaortic stenosis.



Pulse pressure may also decrease if peripheral vascular resistance (PVR) is decreased or if arterial compliance is increased. Peripheral vascular resistance is a function of vessel tone and arterial wall compliance. When PVR is increased, there is an increase in diastolic blood pressure and a corresponding decrease in pulse pressure. PVR is increased in older animals as a result of loss of arterial wall compliance and in some animals with heart failure.

An increase in pulse pressure, known as a *hyperkinetic* pulse, can occur because of an increase in systolic blood pressure, a decrease in diastolic blood pressure, or both. In cardiovascular disease, an increase in systolic blood pressure is usually caused by an increase in stroke volume. A decrease in diastolic blood pressure is usually due to excessive runoff of blood into some other portion of the cardiovascular system during diastole. Consequently, dogs with shunting lesions such as a patent ductus arteriousus or dogs with aortic insufficiency commonly have a significant increase in pulse pressure, leading to a "bounding" pulse. Bounding pulses can also be felt in patients with arteriovenous fistula, severe bradycardia, thyrotoxicosis, fever, and anemia.

Alterations in pulse conformation may also occur. Dogs with severe subaortic stenosis may have a "weak" pulse or may have a pulse pressure that increases more slowly and peaks later during systole (pulsus parvus et tardus) (see Figure 56-1). This occurs because the velocity of shortening and the ejection time may be longer in severe subaortic stenosis. Dogs with mitral regurgitation, conversely, commonly have a brisk pulse that rises more rapidly in systole and lasts a shorter time because the left ventricle ejects blood at a higher velocity and the ejection time is shorter.

Other pulse abnormalities include pulsus paradoxus, pulse deficits, and pulsus alternans. Pulsus paradoxus is an increase in pulse pressure on expiration and a decrease on inspiration. This occurs normally but is exaggerated in pericardial tamponade. Pulse deficits occur with cardiac tachyarrhythmias in which beats occur so rapidly that the ventricle does not have time to fill enough to result in ejection of blood. Pulsus alternans is alternating strong and weak pulses and is rare. In patients with atrial fibrillation, pulse pressure alternates erratically and pulse deficits are also present.

Systemic thromboembolism, a complication of feline cardiomyopathy, is often characterized by a complete loss of arterial pulsations of the femoral arteries. Systemic thromboembolism may also occur in dogs and cats secondary to hypercoagulable sates such as renal amyloidosis, hyperadrenocorticism, and infective endocarditis.

56.2 VENOUS PULSES

Jugular venous pressures correlate with right atrial and ventricular pressures. Because the tricuspid valve is open in diastole and because the tricuspid valve annulus provides very little resistance, right ventricular diastolic pressure and right atrial pressures are approximately equal. Whatever pressure is present in the right atrium is also present in the systemic veins that are at the same height as the right atrium. The pressure in the vessels higher than the RA will have lesser pressure and the veins will be less distended. Because of this, as right atrial pressure increases, the jugular veins become distended farther and farther up the neck.

Figure 56-2 Algorithm for arterial pulse evaluation.

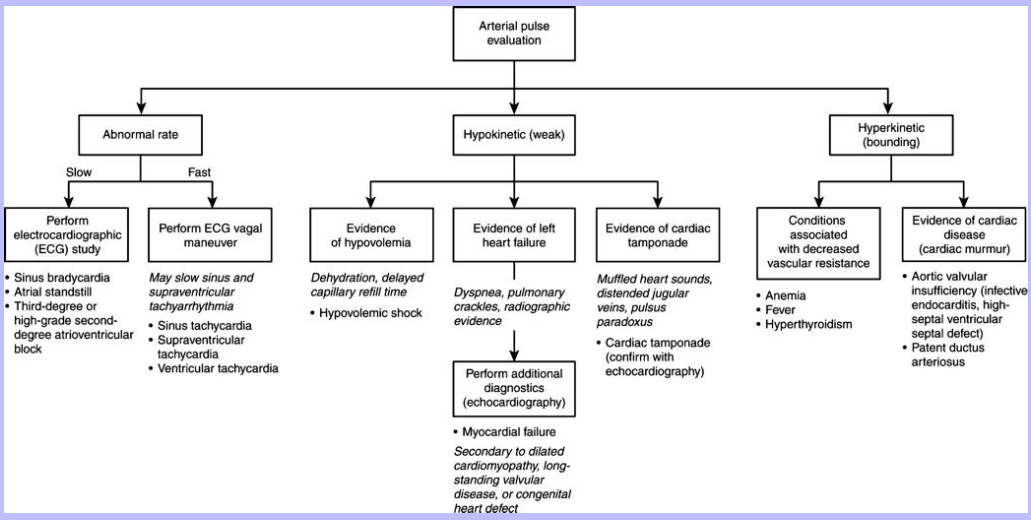
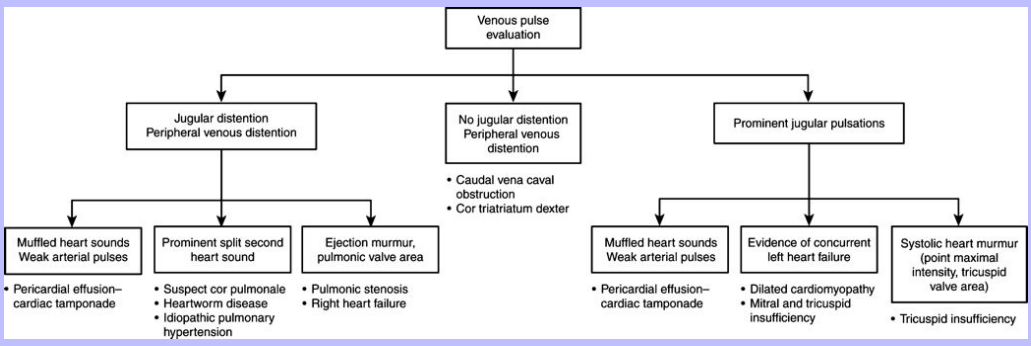


Figure 56-3 Algorithm for venous pulse evaluation.



56.2.1 Components of the Normal Venous Pulse

When jugular waveforms are analyzed, several components can be detected. The most prominent deflection is the A wave corresponding to right atrial contraction. During right atrial relaxation, a slight dip in pressure is noted (Z point). Immediately following the Z point, a second wave (C wave) corresponding to right ventricular isovolumetric contraction occurs. This wave is produced by bulging of the tricuspid valve into the right atrium and transmission of this pressure into the jugular veins. During right ventricular ejection, the tricuspid valve is displaced downward producing a prominent negative deflection, the X descent. Late in systole, a third positive deflection, the V wave, occurs resulting from increased blood volume and pressure within the right atrium. Immediately following the V wave, right atrial emptying occurs as a result of relaxation of the right ventricle producing a second prominent dip in jugular venous pressure, the Y descent.

56.2.2 Assessment of the Venous (Jugular) Pulse

The jugular veins should be examined carefully in any case suspected of having cardiac disease (Figure 56-3). Neck hair may need to be clipped or wetted to identify the jugular veins in dogs and cats with thick or long neck hair (see Figure 56-3). A jugular vein should be initially identified with the animal in a sitting or standing position with the head moderately extended. In a normal animal the vein should be distended by placement of enough pressure at the thoracic inlet to occlude jugular vein flow, which results in jugular vein distension. Thoracic inlet pressure should then be released and the vein observed to determine the rate of vein collapse. In normal animals, jugular pulsations should not extend more than one third the distance up the neck from the thoracic inlet. Pulsations from the underlying carotid arteries may mimic jugular venous pulsations. If pulsations continue despite occlusion of jugular vein, they are arterial in origin. In an animal with cardiac disease, the vein may be distended or pulsating, in which case the vein should be observed with-out occlusion. More subtle jugular vein alterations may be detected by performing the hepatojugular or abdominojugular reflux test. This test is performed by application of sustained pressure to the abdomen with one or both hands for 30 to 60 seconds during observation of the jugular veins. This technique results in increased venous return (increased right ventricular preload), which in the presence of underlying right heart disease will elevate right atrial pressure and impede jugular venous return, which leads to distention or pulsation of the jugular veins. This technique is generally accepted as a test for detecting right heart failure. Most likely this test is an indication of increased blood volume in the peripheral venous system and can be positive with either left or right heart failure.

56.3 VENOUS (JUGULAR) PULSE ALTERATIONS

Distended jugular veins indicate increased systemic venous pressure or occlusion of the venous system between the jugular veins and the right heart. An increase in systemic venous pressure is most commonly secondary to an increase in right ventricular diastolic pressure.

Jugular vein pulsation may also be observed. Jugular vein pulsation may be due to exaggerated “a” waves, cannon “a” waves, or prominent “v” waves. Exaggerated “a” waves may occur secondary to decreased right ventricular compliance. A decrease in right ventricular compliance may occur with such conditions as right ventricular hypertrophy, restrictive right ventricular disease, and constrictive pericarditis. The deceased right ventricular compliance must be severe to result in jugular vein pulsations and a severe decrease in right ventricular compliance generally results in an overall increase in right ventricular diastolic pressure with resultant jugular vein distension. Cannon “a” waves may occur with A-V dissociation when the atria contract against a closed tricuspid valve, as in third degree A-V block. Prominent “v” waves occur secondary to tricuspid regurgitation. The “v” wave occurs during ventricular systole and is increased in tricuspid regurgitation when the atrial volume is increased by the regurgitation of blood into the right atrium. Patients with overt right heart failure from any cause may have obviously distended jugular veins.

57 CHAPTER • 57 Pleural Effusion

O. Lynne Nelson

57.1 DEFINITION OF PLEURAL EFFUSION

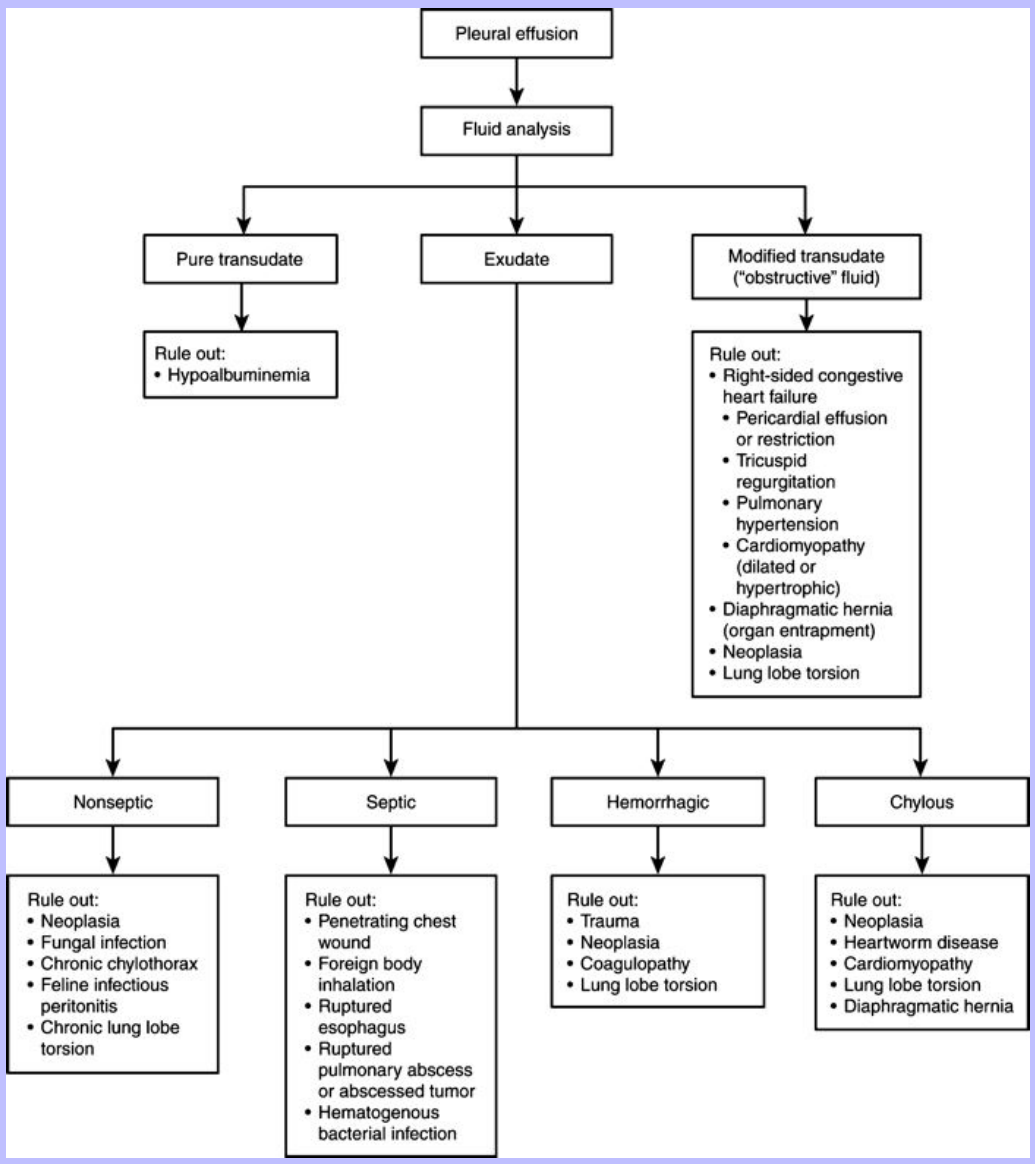
The pleura surround the lung lobes (visceral pleura) and line the thoracic cavity (parietal pleura). Normally, the pleural space contains 3 to 5 mL of a low-protein fluid that lubricates the pulmonary tissue for respiratory motion. Normal pleural fluid is in a constant state of flux much like fluid flow across capillary membranes. The same Starling forces that determine fluid movement across capillary walls are responsible for fluid movement in and out of the pleural space. Abnormal accumulations of pleural fluid may occur due to increased capillary hydrostatic pressure or permeability, decreased intravascular oncotic pressure, or impaired lymphatic drainage. The mediastinum of the dog and cat is fenestrated or incomplete, therefore pleural effusions are usually bilateral.

Pleural effusion is typically a secondary phenomenon; therefore recognition of pleural effusion is not analogous to diagnosis of a dog or cat's underlying condition. A thorough investigation should reveal the primary disease (Figure 57-1). 205

57.2 CLINICAL SIGNS OF PLEURAL EFFUSION

Clinical signs associated with pleural effusion are most often related to the respiratory system. Severity of signs is determined by the amount of the effusion and how quickly the effusion developed. The respiratory pattern caused by pleural effusion results from the interference of normal lung expansion. This observed pattern of ventilation is often called *restrictive respiration*. The respiratory effort is characterized by a labored inspiratory phase, often with a pronounced abdominal component, and an easy expiratory phase. The increased inspiratory effort associated with pleural effusion can be difficult to differentiate from the inspiratory effort of airway disease by observation alone. As a general rule, dogs and cats with pleural effusion will have decreased lung sounds, particularly ventrally, on thoracic auscultation. The presence of a fluid line may be determined by auscultation of a definitive point on the chest wall, where respiratory sounds shift from muffled to normal or slightly increased. By contrast, dogs and cats with airway disease often have abnormal inspiratory airway sounds such as crackles and wheezes. Most animals with significant pleural effusion are tachypneic as a compensatory measure because total lung capacity is reduced (secondary to reduced inspiratory capacity). Coughing is occasionally noted. 205 206

Figure 57-1 Algorithm of differential diagnosis of pleural effusion.



57.3 DIAGNOSTIC EVALUATION OF PLEURAL EFFUSION

A thorough physical examination often provides clues to the underlying cause of pleural effusion. For example, the presence of uveitis may alert the clinician to possible systemic inflammatory conditions such as viral disease (e.g., feline infectious peritonitis), rickettsial disease, fungal infection, or sepsis or systemic neoplasia (e.g., lymphosarcoma). Lymphadenopathy may suggest systemic inflammatory process or lymphosarcoma. Jugular distension and pulsation suggests increased right heart filling pressures that may be associated with

cardiomyopathy, pericardial effusion, tricuspid regurgitation, pulmonic stenosis, or any of the many causes of pulmonary hypertension (e.g., heartworm disease, thromboembolic disease). Jugular distension without pulsation is more likely to be associated with occlusion of right heart inflow, due to mediastinal masses or severely increased intrapericardial pressues. Many cats with large mediastinal masses will have decreased compressibility of the anterior thorax. A thorough palpation of the skeleton and the abdomen may uncover masses or painful regions associated with inflammatory disease.

Dogs and cats with severe respiratory distress from pleural effusion may be quite fragile. Unnecessary handling should be avoided until the animal is sufficiently stable. In these cases, oxygen therapy may be provided and thoracocentesis should be performed before additional diagnostics are planned. Although thoracocentesis is invasive, the potential therapeutic benefit far outweighs the small chance of complications. Patients that present in stable condition may have chest radiographs taken to confirm presence of pleural effusion before thoracocentesis.

Thoracic radiography can confirm pleural effusion and often identifies the underlying cause (i.e., cardiac disease, mediastinal mass). In many cases, critical evaluation of the chest cannot be performed because the fluid silhouettes with the normal thoracic structures, which obscures their borders. Repeating chest radiographs after thoracocentesis may aid in identification of thoracic pathology.

Fifty to 100 milliliters of fluid must be present for pleural effusion to be recognized radiographically. A minute amount of effusion may be detected as pleural fissure lines on the radiograph. These radio-opaque lines arc from the periphery toward the hilar region and outline individual lung margins. As effusions progress, lung lobes retract from the chest wall and lung borders become rounded. With large volumes of effusion, the lungs appear to float on the fluid line and the trachea is displaced dorsally, which mimics cardiomegaly or cranial mediastinal mass. The fluid often obscures cardiac margins interfering with cardiac size interpretation. The cardiac silhouette may not be visualized at all on the dorsoventral radiograph. Lung lobes may appear abnormally dense due to incomplete expansion, collapse, or lung lobe torsion. Pockets of fluid accumulation or unilateral effusions should alert the clinician to the possibility of inflammatory lesions and pleural adhesions.

Analysis of the pleural fluid obtained by thoracocentesis provides important clues in determination of the cause. The thoracocentesis technique is described in detail elsewhere in this text. Samples should be placed into anticoagulant tubes (EDTA) for cell counts, clot tubes for possible biochemical analysis, and culture devices in the event septic processes are identified by cytologic evaluation. Measurement of protein concentration, a total cell count, and cytologic analysis may reveal a specific diagnosis or at minimum, assist in formulating a diagnostic plan. Pleural effusions can generally be categorized as transudates and modified transudates; septic and nonseptic exudates; or chylous, hemorrhagic, or neoplastic effusions.

57.4 TRANSUDATES AND MODIFIED TRANSUDATES

Pure transudates are fluids characterized by low protein concentration (less than 3 gm/dl) and low nucleated cell counts (less than 1000/µl). Macrophages, lymphocytes, and mesothelial cells are the primary cell types. Modified transudates have slightly higher protein concentration of up to 3.5 gm/dL and cell counts of up to 5000/µl. In addition to the above cell types, neutrophils are a common finding. Pure transudates are classically transparent, whereas modified transudates may have very slight turbidity.

The most common cause of a pure transudate is decreased oncotic pressure from hypoalbuminemia. The finding of a pure transudate should alert the clinician to assess serum albumin concentration and to screen for underlying causes of hypoalbuminemia (impaired hepatic production, or albumin loss via gastrointestinal or renal lesions). Occasionally, pleural effusions of hypoalbuminemia will be modified transudates in long-standing cases.

The most common cause of modified transudates is increased hydrostatic pressure of the vascular system or lymphatics. Pleural effusion due to increased intravascular hydrostatic pressure is typically referred to as *right-sided congestive heart failure*. Cardiomyopathy (dilated and hypertrophic), severe tricuspid regurgitation, pulmonary hypertension, and pericardial effusion or restriction are some common examples of diseases that may result in right heart failure. Pleural effusion from lymphatic obstruction can be caused by neoplasia or strangulation of intrathoracic tissue such as with diaphragmatic hernia or lung lobe torsion.

57.5 SEPTIC AND NONSEPTIC EXUDATES

Exudates are usually the result of inflammation and increased vascular permeability. Exudates have a higher protein content and cell count than transudates. Protein concentrations are classically greater than 3 gm/dL and cell counts are greater than 5000/µl. These fluids appear turbid as a result of the higher cellular content. The cell types are similar for septic and nonseptic exudates (neutrophils, macrophages, eosinophils, lymphocytes), but septic processes usually have extremely high nucleated cell counts, that is, greater than 50,000/µl. In septic exudates, degenerate neutrophils predominate and bacteria can also be observed within the neutrophils or free fluid. However, the absence of bacteria does not rule out an infectious process and all exudative fluids should be submitted for gram stain and aerobic/anaerobic culture. Prior antibiotic therapy can alter the cellular concentration of the pleural fluid and diminish bacterial numbers; therefore cytology (and culture) should ideally be performed prior to initiation of treatment. In some cases the septic exudates will have a foul odor. Septic pleural effusions are also called *pyothorax*. Penetrating chest wounds, penetrating esophageal or airway lesions, migrating foreign material such as grass awns, and extension of bacterial pneumonia are relatively common causes of pyothorax in the dog and cat.

Nonseptic exudates may be difficult to differentiate from septic processes. The cell count is usually lower for nonseptic effusions. Although macrophages and lymphocytes may appear activated, neutrophils are typically nondegenerate. As stated earlier, the absence of obvious bacteria in fluid does not guarantee a nonseptic process. Culture and sensitivity testing should be performed. Differential diagnoses for patients with nonseptic exudates include neoplasia, resolving sepsis, chronic diaphragmatic hernia and lung lobe torsion, fungal infection, feline infectious peritonitis, and long-standing chylothorax.

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57.6 HEMORRHAGIC EFFUSIONS

Hemorrhagic effusions are grossly red with red blood cells and may appear similar to frank blood. A packed cell volume (PCV) should be determined on the fluid and compared with a peripheral blood sample. PCV of similar values suggest active bleeding into the chest cavity, whereas effusions with lower PCV than the peripheral blood suggest other factors are responsible for the bloody effusion. Hemorrhagic effusions due to active inflammatory causes often have increased numbers of neutrophils and macophages compared with the peripheral blood sample, and erythorphagocytosis is commonly present. Hemorrhagic effusions may result from trauma, neoplasia, lung lobe torsion, and systemic coagulopathies such as rodenticide ingestion.

57.7 CHYLOUS EFFUSIONS

Chylous pleural effusion (chylothorax) results from leakage of material from the thoracic duct. These effusions may occur from increased lymphatic hydrostatic pressure or obstruction. Common causes include cardiac disease, pericardial disease, dirofilariasis and pulmonary hypertension, lung lobe torsion, diaphragmatic hernia, neoplasia, and trauma. Idiopathic cases of chylothorax are suspected to be secondary congenital or acquired defects of the thoracic duct.

Chylous effusion is usually milky white due to the presence of chylomicrons, but it may be clear if the animal has fasted. Occasionally, the effusions are blood-tinged and resemble tomato soup. These fluids must be differentiated from exudative processes, as protein concentration and cell counts are similar. The predominant cell type in chylous effusion is the mature lymphocyte. With chronic effusions, increasing numbers of nondegenerate neutrophils and macrophages may be seen. A definitive diagnosis of chylothorax may also be made by comparing the triglyceride content of the effusion to that of serum. The triglyceride content of chyle is classically greater. Occasionally, this test may need to be repeated if an animal has been anorectic.

57.8 NEOPLASTIC EFFUSIONS

Thoracic neoplasia can cause any type of pleural effusion with the possible exception of pure transudates. Neoplastic cells may or may not exfoliate into the effusion for cytologic identification. Repeat thoracic radiography after thoracocentesis (particularly with mediastinal neoplasia), thoracic ultrasonography or computed tomography may uncover masses, but definitive diagnosis requires fine needle aspiration or biopsy.

57.9 TREATMENT AND PROGNOSIS OF PLEURAL EFFUSION

Recognition of pleural effusion is not analogous to diagnosis of the patient's underlying condition. A thorough investigation should reveal the primary disease process. Initial treatment for patients with respiratory distress from pleural effusion is thoracocentesis. Thoracocentesis provides therapeutic as well as diagnostic benefit. The prognosis for pleural effusion is directly related to the underlying condition.

58 CHAPTER • 58 Sneezing and Nasal Discharge

Kirsten Cooke

Sneezing and nasal discharge are common problems in companion animals. Nasal discharge may result from nasal or paranasal (sinus) disorders or from systemic disease (Box 58-1). Sneezing and reverse sneezing localize the problem to the nasal cavity or nasopharynx. Although increased frequency of sneezing is often readily apparent, many owners may not notice nasal discharge immediately because most animals clear these secretions by licking. However, clients may report other clinical signs associated with nasal disease, including increased respiratory sounds, increased respiratory effort, gagging, epiphora, and/or nasal deformity. Alternatively, they may notice signs of systemic disease such as lethargy and weight loss.

Signalment, history, and physical exam including characterization of the nasal discharge can help narrow the list of differential diagnoses and thus the diagnostic focus.

58.1 DIAGNOSTIC APPROACH

58.1.1 Signalment

Younger animals are more likely to have congenital, infectious, or toxicity-related disorders, whereas nasal discharge in older animals is more likely to be due to neoplasia, metabolic, or dental disease.

58.1.2 History

Acute disease results most commonly from trauma, foreign body, acute viral infections, and coagulopathies. If other pets in the household are affected, an infectious process should be suspected. Chronic disease is usually caused by neoplasia, fungal infection, dental disease, or chronic foreign bodies. Outdoor pets are prone to trauma and foreign bodies in addition to parasitic and fungal infections. Owners should also be questioned about clinical signs such as polyuria, polydipsia, or melena that may support systemic disease. Environment and travel history should be determined as both rickettsial and fungal infections have regional predilections.

58.1.3 Physical Exam

A complete physical exam should be performed to try to differentiate nasal disease from systemic disease (Table 58-1). Patency of each nostril should be evaluated with the use of a glass slide to look for condensation or a wisp of cotton and looking for movement with respiration. Cats with polyps may have a head tilt, nystagmus, or otic discharge. Systemic disease is associated with clinical signs that involve other organs such as ocular lesions (hypertension) or petechia (coagulopathy).

58.1.3.1 Box • 58-1 Causes Of Sneezing And Nasal Discharge

58.1.3.1.1 Nasal and Paranasal Diseases

Congenital

- Cleft palate
- Ciliary dyskinesia
- Foreign body
- Dental disease
  - Tooth root abscess
  - Oronasal fistula
- Neoplasia
  - Carcinoma (adeno-, squamous cell)
  - Sarcoma (fibro-, osteo-, chondro-)
  - Round cell (lymphoma, transmissible venereal tumor)
- Infectious
  - Viral
    - Herpesvirus (C)
    - Calicivirus (C)
  - Fungal
    - *Aspergillus* (D)
    - *Penicillium* (D)
    - *Rhinosporidium* (D)
    - *Cryptococcus* (C)

Parasites

Pneumonyssus caninum (nasal mite) (C)

Eucoleus böehmi (formerly *Capillaria* sp.) (C, D)

Cuterebra sp. (C, D)

Inflammatory

Lymphocytic-plasmacytic rhinitis

Allergic rhinitis

Acquired nasopharyngeal stenosis

Nasopharyngeal polyps (C)

Trauma

58.1.3.1.2

Systemic Disease

Hypertension

Hyperthyroidism

Hyperadrenocorticism

Renal disease

Pheochromocytoma

Infectious

Canine infectious tracheobronchitis (kennel cough)

Canine distemper

	Pneumonia
Coagulopathy	
	Thrombocytopenia
	Vitamin K rodenticide toxicity
	DIC
Vasculitis	
	Ehrlichia
	Rocky Mountain spotted fever
Hyperviscosity	
	Multiple myeloma
	Lymphoma

D, Dogs; *C,* cats.

A thorough oral exam to evaluate the teeth, gums, palate, and tonsils is essential. However, this may be difficult or impossible in the conscious animal. A cursory exam may be done during the initial physical and a more complete exam done under sedation or anesthesia prior to other, more invasive, diagnostics.

58.1.4 Characterization of Nasal Discharge

Unilateral nasal discharge is usually indicative of intranasal rather than systemic disease. Neoplasia, fungal infection, foreign bodies, and dental disease often present with unilateral nasal discharge. However, the discharge may become bilateral as the disease progresses. Therefore establishing whether bilateral nasal discharge began as unilateral discharge can be an important piece of historical information.

Bilateral nasal discharge can be due to lymphocytic-plasmacytic rhinitis, allergic rhinitis, and chronic fungal or neoplastic diseases. Systemic diseases such as hypertension, coagulopathy, or infectious diseases usually result in bilateral nasal discharge as well. However, systemic diseases such as coagulopathies can occasionally be associated with unilateral nasal discharge.

Nasal discharge can be characterized as serous, mucoid, purulent, or hemorrhagic (or a combination of types). The character of the discharge may change as acute disease becomes chronic. For example, a serous discharge may become purulent as the result of a secondary bacterial infection.

Serous discharge is clear and often intermittent. It is most commonly associated with allergic rhinitis, lymphocytic-plasmacytic rhinitis, nasal parasites, foreign bodies, and early viral infections. If the disease is associated with paroxysmal sneezing, the discharge may become blood-tinged.

Purulent nasal discharge is thick, opaque, and yellow to green and is associated with bacterial infection. However, bacterial infections are almost always secondary to some other disease that has damaged the nasal mucosa. Mucopurulent nasal discharge can also be seen in patients with bacterial pneumonia. As with a serous discharge, it is not uncommon for purulent discharge to be tinged with blood due to mucosal irritation.

Systemic diseases, including coagulopathies or vasculitis, can lead to epistaxis or hemorrhagic nasal discharge. Intranasal diseases that erode major blood vessels (neoplasia, fungal disease) should also be included on the list of differential diagnoses for epistaxis. Hemorrhagic nasal discharge can be differentiated from blood-tinged nasal discharge by the volume. Epistaxis is generally copious and has a hematocrit similar to peripheral blood.

Mucoid nasal discharge is clear and gel-like. It may be copious and may be blood tinged. It is uncommon but when seen, is most commonly associated with nasal adenocarcinoma.

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Table • 58-1 Physical Exam Findings Associated with Sneezing

LOCATION	FINDINGS	DIFFERENTIAL DIAGNOSIS
Face	Asymmetry (swelling, deformity)	Neoplasia
		Fungal rhinitis
		Tooth root abscess
Nose	↓Air movement	Neoplasia
	Depigmentation Mass	Fungal rhinitis
Submandibular lymph nodes	Enlargement	Neoplasia
		Infection
		Dental disease
Oral cavity	Dental disease	Oronasal fistula
	Cleft palate	Tooth root abscess
	Swelling	Neoplasia
Eyes	Exophthalmos	Neoplasia
		Trauma
		Abscess
	Retinal hemorrhage/detachment	Vasculitis
	Tortuous vessels	Hypertension
		Coagulopathy
	Ocular discharge	Viral infection
		Lacrimal duct obstruction (neoplasia)
Skin	Petechia	Vasculitis
Mucous membranes	Ecchymoses	Coagulopathy
Thoracic auscultation	Crackles	Pneumonia

The presence of food particles in nasal discharge suggests a cleft palate in a young animal or an oronasal fistula in an adult.

58.2 DIAGNOSTIC PLAN

Evaluation of the signalment, history and physical exam findings should allow initial prioritization of differential diagnoses and selection of the most appropriate diagnostic tests (Figure 58-1).

Routine laboratory evaluation (CBC, chemistry profile, urinalysis) is unlikely to establish a diagnosis for intranasal disease. However, these tests may support a systemic cause of nasal discharge and prompt investigation along these lines. Additionally, these values may provide information on the patient's overall health prior to general anesthesia, which may be required to arrive at a definitive diagnosis.

Indirect blood pressure can be measured to determine if the patient is hypertensive. If vasculitis is suspected, serology for *Ehrlichia* species and Rocky Mountain spotted fever should be done. A platelet count, buccal mucosal bleeding time, prothrombin time, and partial thromboplastin time are indicated to rule out a coagulopathy in a patient with epistaxis. It is also a good idea to assess coagulation parameters prior to nasal biopsy.

Fungal serology for aspergillosis, penicilliosis, and cryptococcosis may be evaluated. Both false positive and false negative results occur. Results are interpreted in light of other findings, including imaging, rhinoscopy, histopathology, and fungal culture.

Cytology of nasal secretions or tissue specimens is of limited value. Neutrophils, bacteria, and even fungal elements may be present in normal animals or as part of a secondary infection and are not diagnostic of a primary bacterial or fungal rhinitis. Cytology can be useful in the diagnosis of cryptococcal rhinitis as well as nasal lymphoma.

58.2.1 Imaging

Imaging of the nasal cavity, whether via conventional radiography, computed tomography, or magnetic resonance imaging, requires general anesthesia to provide the most accurate study. Imaging should be done *prior* to invasive diagnostic procedures such as rhinoscopy, nasal flushing, or nasal biopsy. These procedures can lead to hemorrhage in addition to alterations in bony and soft tissue structures, which can obscure subtle pathologic lesions and make it difficult to determine if abnormalities are pathologic or iatrogenic.

Immediately following induction of anesthesia for imaging studies is the perfect time to complete the oral exam. Palpation of the hard and soft palate and evaluation of the tonsils, teeth, and gums, including periodontal probing, should be done at this time.

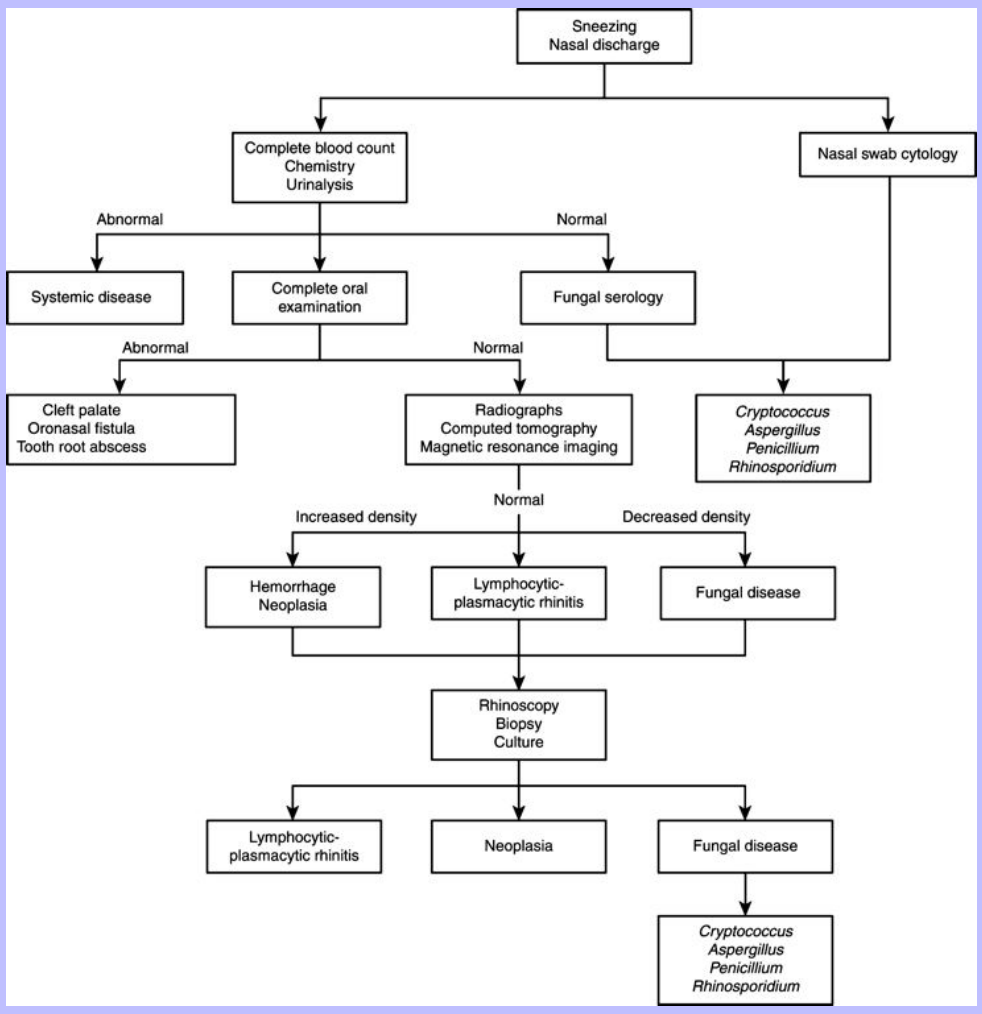
58.2.1.1 Radiography

Radiography of the nasal cavity and sinuses can be useful for determining the location and extent of disease. Radiographs should be evaluated for changes in soft tissue opacity in addition to osteolytic or osteoproductive changes. Nasal and sinus films can be challenging to interpret under the best of circumstances due to the complexity of the anatomy as well as superimposition of overlying structures. Proper positioning requires general anesthesia and is critical to obtaining diagnostic films.

58.2.1.2 Computed Tomography

Computed tomography (CT) allows a more complete examination of the nasal cavity and sinuses than conventional radiography. Because cross-sectional images are obtained, superimposition of structures is eliminated. Where available, it has largely replaced radiography for evaluation of nasal disease. The use of contrast agents can help to distinguish vascularized tumors from mucous accumulation. The ability of CT to localize nasal lesions can help direct other procedures, including rhinoscopy and biopsy.

Figure 58-1 Algorithm for sneezing and nasal discharge.



Although imaging provides information regarding the location, extent, and character of a nasal lesion, it generally does not provide a definitive diagnosis.

58.2.1.3 Rhinoscopy

Rhinoscopy provides direct visualization of the anterior nasal cavity, the nasopharynx, and the choanae. It allows sample collection directly from visible lesions and foreign body removal in addition to diagnosis of nasal mites and nasopharyngeal polyps. Tissue samples should be submitted for histopathology and fungal culture.

58.2.2 Histopathology

Histopathology remains the gold standard in the diagnosis of most cases of nasal disease. Biopsies are obtained rhinoscopically. Alternatively, “blind” biopsies can be obtained with or without the use of radiography or CT to localize the lesion. It is extremely important that the biopsy instrument be passed no further than the distance from the tip of the nose to the medial canthus of the eye to avoid penetration of the cribriform plate.

58.2.3 Treatment and Outcome

Successful treatment of sneezing and nasal discharge hinges on the determination of a definitive diagnosis. Although antibiotic therapy may lead to some improvement, clinical signs will return unless the underlying problem can be resolved.

59 CHAPTER • 59 Hematologic/Chemical: Pallor

Wallace B. Morrison

The term *pallor* is defined as the absence of skin color. Clinically, the term *pallor* is most associated with paleness of mucous membranes. Pale mucous membranes originate from either shock or anemia (Figure 59-1). A severely anemic patient may progress to shock as an end-stage event. A patient experiencing shock will be anemic only if blood loss is a part of the clinical disorder. However, severe blood loss may lead to both shock and anemia. Neutrophil and platelet counts are unaffected by shock and many causes of anemia. Anemia with other and concurrent cytopenias is common. Anemic patients that are not in shock should have a normal capillary refill time (CRT) of 1 to 2 seconds. Patients in shock will have a prolonged CRT; however, unless blood loss is also present, they should have a normal packed cell volume (PCV). Evaluation of mucous membrane color and CRT becomes progressively more difficult as the PCV falls below about 20% because not enough hemoglobin is present to impart any color through mucous membranes to make evaluation of these parameters possible.

Metabolically and biochemically, shock is a complex event characterized by poor tissue perfusion that leads to decreased or uneven O_2 delivery to tissues, altered cell metabolism that may in turn result in cell death, organ failure, or a combination. Shock usually has a readily apparent cause and either responds to intervention or results in death. Shock is a peracute state. It is not a chronic condition, although the primary disorder that ultimately culminated in shock may itself have been chronic in duration.

Causes of shock include hypovolemia and disruptions in blood flow (noncardiogenic shock), as well as poor cardiac activity (cardiogenic shock). The primary causes of shock are trauma, hypovolemia, hypotension, severe acute blood loss (internal or external), severe chronic blood loss (flea infestation, gastrointestinal loss), severe heart disease causing underperfusion of peripheral tissues, and sepsis. Most cardiac conditions that result in shock are secondary to decreased myodynamic ventricular function, conditions that compromise ventricular filling, disruption of valve structures that result in severe regurgitation of blood, severe arrhythmias, or conditions that block outflow of blood from the heart (Table 59-1). The physical consequences of inadequate tissue perfusion relate directly to the production of proinflammatory mediators as a result of cellular ischemia and inadequate oxygen delivery to tissues. The origins and clinical consequences of proinflammatory mediators in shock are listed in Table 59-2.

Anemia has many origins and is initially classified as either being regenerative or nonregenerative (see Figure 59-1). Anemia can be further characterized with erythrocyte indices. The terms *normocytic*, *microcytic*, and *macrocytic* characterize the size of red blood cells (RBCs). The terms *normochromic* and *hypochromic* characterize the hemoglobin-related properties of RBCs.

Nonregenerative anemia lacks a normal reticulocyte response (reticulocyte count <60,000/μL). It occurs when selective erythropoietic depression, decreased RBC survival time from an extramarrow chronic disease, or insufficient erythropoietin release (or a combination of these factors) exist, as well as if the bone marrow fails to respond to normal or increased amounts of erythropoietin. Simple, nonregenerative anemia that is due to hyporesponsiveness of bone marrow to erythropoietin alone will have normal platelet and leukocyte production. Bone marrow disorders affecting more than erythrocytes will have other and concurrent cytopenias (Table 59-3). Nonregenerative anemias are usually normocytic and normochromic.

A regenerative anemia is usually the result of blood loss (bleeding) or hemolytic disease (Table 59-4). A regenerative anemia has a normal bone marrow response to erythropoietin in an effort to replace the lost red cells. A regenerative anemia is characterized by a reticulocytosis (reticulocyte count >60,000/μL), polychromasia, and perhaps the

presence of nucleated RBCs. It takes 5 to 7 days from the time of the blood loss for the maturation process of red cells to develop such that polychromasia and reticulocytosis is detectable.

Table • 59-1 Classification and Examples of Causes of Shock

CARDIOGENIC	NONCARDIOGENIC
Decreased myodynamic ventricular function	Trauma
Dilated cardiomyopathy	
Myocarditis	
Myocardial infarction	
Compromised ventricular filling	Hypovolemia
Cardiac tamponade	Severe blood loss
Hypertrophic cardiomyopathy	Severe dehydration
	Hypoadrenocorticism
Disruption in valvular function	Disruptions in blood flow
Severe endocardiosis	Sepsis and endotoxemia
	Hypotension
Outflow obstruction	
Intracardiac tumors	
Aortic stenosis	
Hypertrophic obstructive cardiomyopathy	
Heartworm disease	
Thrombosis	
Severe arrhythmia	

Figure 59-1 Algorithm for pallor.

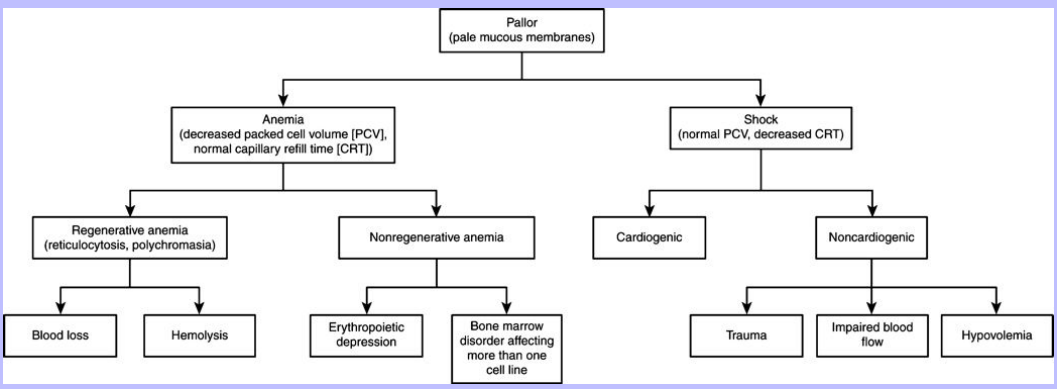


Table • 59-2 Cytokine and Chemical Mediators of Shock

CYTOKINE OR CHEMICAL MEDIATOR	CLINICAL CONSEQUENCES
Histamine	Released from mast cells and results in vasodilation, increased capillary permeability, and bronchoconstriction
Bradykinin	Released from many cells and kallikrein; it causes pain, vasodilation, and edema; it also stimulates prostacyclin production
Serotonin	Causes bronchoconstriction, platelet aggregation, and increased vascular permeability
Prostaglandins	Prostaglandin E_2 results in vasodilation, erythema, hyperalgesia, and edema; prostaglandin F_2 results in vasoconstriction
Thromboxane A_2	Causes vasoconstriction, platelet aggregation, and leakage of lysosomal enzymes
Leukotrienes C_4, D_4, and E_4	Causes bronchoconstriction, vasodilation, increased vascular permeability, and cardiodepression
Tumor necrosis factor	Stimulates the production of many inflammatory mediators and cytokines; it promotes the production of adrenomedullin, vasodilation, myocardial depression, increased capillary permeability, edema and disseminated intravascular coagulation
Platelet-activating factor	Produced by most inflammatory cells, the endothelium, and platelets; it can result in vasodilation and increased capillary permeability
Endothelins	Causes vasoconstriction and increased capillary permeability
Nitric oxide	Causes vasodilation, increased capillary permeability, hypotension, and the production of oxygen free radicals
Oxygen free radicals (O_2^-, H_2O_2, OH^-)	Free radicals promote production of peroxynitrite and peroxynitrous acid, destroy cell membranes, and cause cell lysis

Modified from Muir WW: Shock, *Compend Cont Ed* 20:549, 1998.

Table • 59-3 Nonregenerative Anemia

CAUSE	KEY POINTS
Erythropoietic Depression	
Anemia of chronic disease	This is a poorly understood disorder that accompanies many chronic diseases. It is normochromic and normocytic, the survival time of red blood cells (RBCs) is decreased, increased tissue iron stores exist, and apparent bone marrow hyporesponsiveness to erythropoietin occurs. Packed cell volume (PCV) is usually only mildly depressed and rarely requires treatment. Neutrophil and platelet counts are unaffected.
Anemia with renal failure	Common in dogs and cats in chronic renal failure. It is due to inadequate renal erythropoietin release and a shortened survival of RBCs. It may be mild to severe in magnitude. Neutrophil and platelet counts are unaffected.
Feline leukemia virus (FeLV)–associated	Approximately 70% of anemic cats will test positive for FeLV. Nonregenerative anemia may be due to simple erythropoietic depression and/or associated hemolysis, but concurrent neutropenia and/or thrombocytopenia often result from the myelodysplasic, myeloproliferative, or myeloaplastic effects of infection with FeLV.
Endocrine	Mild anemia is often associated with hypothyroidism and hypoadrenocorticism in dogs, but the mechanisms are poorly characterized.
Bone Marrow Disorders	
Myeloaplasia (aplastic anemia)	Characterized by severe bone marrow cell depopulation and peripheral cytopenias. Because bone marrow aspirates are often diluted with blood and therefore difficult to interpret, it is advisable to collect a bone marrow core biopsy for histologic examination to establish a diagnosis. Myeloaplasia can be associated with FeLV infection, ehrlichiosis, trimethoprim-sulfadiazine use, estrogen toxicity, phenylbutazone toxicity, chemotherapy, and chloramphenicol toxicity. It occasionally occurs without a known cause.
Myelodysplasia	Bone marrow of affected individuals is often normal or hypercellular, but associated maturation defects result in cytopenias. Myelodysplasic anemia is most recognized in cats where the anemia is attributed to maturation defects in RBCs.
Myeloproliferative and lymphoproliferative disorders	This disorder is characterized by the proliferation of abnormal cells within bone marrow at the expense of normal hematopoiesis. If the anemia appears to be regenerative, a low-grade hemolytic process may be occurring concurrently.
Myelofibrosis and osteosclerosis	These disorders may be terminal lesions in myeloproliferative disorders or a response to bone marrow injury. Myelofibrosis can be a consequence of pyruvate kinase (PK) deficiency in dogs.

Table • 59-4 Regenerative Anemia

CAUSE	KEY POINTS
Hemolysis	An absolute reticulocytosis is not present in up to 30% of cases. Spherocytosis is expected in dogs. Cats rarely show spherocytosis with immune-mediated hemolytic anemia because they have relatively small red blood cells (RBCs) and lack central pallor when compared with dogs.
Immune mediated	
Extravascular	
Intravascular	
Parasites of Erythrocytes	These organisms are known to cause hemolytic disease and include *Hemobartonella*, *Babesia*, and *Cytauxzoon* spp.
Fragmentation (Microangiopathic)	Fragmentation anemia may occur with disorders like disseminated intravascular coagulation, heartworm disease, hemangiosarcoma, vasculitis, hemolytic-uremic syndrome, and diabetes mellitus. Anemia results from mechanical shearing of red cells by intravascular strands of fibrin across small vessel lumina. Often the rate of hemolysis is subclinical. RBC fragments are called schistocytes.
Hereditary Nonspherocytic Hemolytic Anemia	Hereditary nonspherocytic hemolytic anemia has been reported in poodle and beagle dogs, but it may not be the same disease in each breed. It is very rare.
Pyruvate Kinase (PK) Deficiency	Lack of normal red cell PK activity impairs normal adenosine triphosphate (ATP) generation from glucose. The result is chronic, severe hemolysis without spherocytosis. PK deficiency affects basenjis and beagles and is very rare.
Phosphofructokinase (PFK) Deficiency	This is intravascular hemolysis as a result of vigorous exercise or panting from overheating. It involves erythrocyte fragility to alkaline pH caused by impaired synthesis of 2, 3, diphosphoglycerate (2, 3, DPG). Spherocytosis is absent. It is very rare.
Feline Porphyria	This is a rare autosomal dominant disorder of Siamese cats that is characterized by porphyrin accumulation that causes reddish discoloration of teeth and bones, fluorescence with ultraviolet light, and mild-to-severe anemia.
Hemolysis in Abyssinian and Somali Cats	This is a very rare hereditary hemolytic anemia secondary to severe increased osmotic fragility of erythrocytes.
Copper Toxicity	Intravascular hemolysis has been rarely associated with hepatic necrosis in Bedlington terriers.
Neonatal Isoerythrolysis	Although rare in dogs and cats, this results from colostrum passage of an antibody capable of lysing RBCs.
Oxidative Injury (Heinz Body)	A variety of agents will cause oxidative injury to hemoglobin. Exposure to oxidants can denature hemoglobin into aggregates known as *Heinz bodies*. Cats are more sensitive to Heinz body formation than are dogs. Eccentrocytes may form in dog RBCs after oxidant-induced membrane fusion that causes hemoglobin to shift to one side of the cell, lack of central pallor, and a clear zone outlined by a membrane. They are associated with Heinz body formation in dogs. Oxidant damage to hemoglobin can also result in methemoglobin formation.
Onion ingestion (usually dogs)	
Acetaminophen ingestion(usually cats)	
Zinc ingestion (pennies mintedpost-1982, zinc oxide ointment, zinc-plated bolts and screws)	
Benzocaine ingestion vitamin K3(dogs)	
D-L methionine ingestion (cats)	
Phenolic compounds (moth balls)	
Phenazopyridine (cats)	

Blood Loss Anemia External blood loss Blood loss to a body cavity Coagulopathy (factors, platelets, disseminated intravascularcoagulopathy [DIC]) Endoparasites GI loss	Occult GI loss of blood may not be obvious. Body iron is stored as hemoglobin, and iron deficiency anemia is a late feature of chronic blood loss. Iron deficiency anemia is usually characterized as being microcytic and hypochromic. Red cell fragmentation may be seen after microcytosis is well established owing to increased stiffness of the RBC membrane and increased membrane fragility to normal intravascular trauma.

Hemolysis can be triggered by immune-mediated and nonimmune-mediated mechanisms. Immune-mediated hemolytic anemia is often highly regenerative. However, in up to 30% of cases, the anemia is not regenerative because it is either too acute and the bone marrow has not yet had time to respond or because there may be antibodies also directed at bone marrow stem cells that inhibit the normal regenerative response. Primary immune-mediated hemolytic anemia occurs when immunoglobulins (usually IgG or IgM) develop against normal or altered RBC membrane antigens. Primary immune-mediated hemolytic anemia is common in dogs but rare in cats. Infectious agents like *Ehrlichia, Hemobartonella*, *Babesia*, and *Leptospira* organisms and feline leukemia virus (FeLV) can alter normal surface antigens on RBCs and result in secondary immune-mediated hemolytic disease. Adsorbed immunoglobulins on RBC membranes cause intravascular hemolysis, extravascular hemolysis, or both. Extravascular hemolysis occurs when RBCs are removed by macrophages of the reticuloendothelial system (primarily in the spleen and liver) at an accelerated rate. Intravascular hemolysis occurs when adsorbed immunoglobulins activate complement and the cells spontaneously lyse. Some immunoglobulins (IgM) have greatest activity below normal body temperature and cause intravascular agglutination at cold temperatures (cold-agglutinin disease). Clinical effects may first be noticed in devitalized areas of the ear tips, feet, and tip of the tail after exposure to cold temperatures has caused plugging of small vessels and capillaries with agglutinated RBCs.

Nonimmune-mediated mechanisms of hemolysis include Heinz body formation after oxidative damage to hemoglobin, congenital defects in erythrocyte metabolism, intracellular parasites of erythrocytes, fragmentation across intravascular strands of fibrin, and copper toxicity. Common causes of blood loss include trauma, external blood loss, blood loss to a body cavity, coagulopathy, endoparasites and ectoparasites that suck blood, and gastrointestinal loss from nonparasite causes.

Clinical signs of severe anemia and shock may be similar and may include pallor (pale mucous membranes), cool mucous membranes, polypnea, tachycardia, weakness, and signs referable to the primary disease. Distinguishing shock from anemia should be uncomplicated. A patient in shock will usually have a history of trauma or a preexisting and serious systemic disease. Previously nonanemic patients with shock from any acute cause (including acute bleeding) should have a normal PCV. A time delay exists for acute blood loss to be reflected as a lower PCV because it takes several hours to complete fluid shifting from the extravascular space to the intravascular space to compensate for lost blood volume. Patients with shock and anemia will have a low PCV, but a careful history and physical examination and other diagnostic texts should reveal the underlying disorder.

Table • 59-5 Guidelines for Interpreting Anemia

CRITERIA	PCV DOG	PCV CAT
Normal	40%–50%	30%–40%
Mild anemia	35%–39%	25%–29%
Moderate anemia	20%–34%	20%–24%
Severe anemia	<20%	<20%

PCV, Packed cell volume.

An anemic patient will have a PCV below the reference range and will either be unstable if the blood loss is acute and severe or stable if the blood loss is mild, moderate, or of slow onset over a prolonged period of time (up to a critical end point). Patients with sudden blood loss will become unstable because of hypovolemia and the reduced oxygen carrying capacity of blood. Anemia that develops slowly over time allows for each red cell to increase the relative amounts of oxygen it carries in hemoglobin through increases in intracellular 2, 3, diphosphoglycerate (2, 3, DPG). Increases in 2, 3, DPG increases the amount of oxygen that hemoglobin can carry so that the clinical manifestations of a decreased red cell mass are minimized. The speed of the blood loss will in part determine how stable the anemic patient is relative to the degree of anemia present (Table 59-5). The detection of anemia after acute blood loss cannot be done until several hours has passed and the normal circulating blood volume is reestablished.

60 CHAPTER • 60 Polycythemia

Andreas H. Hasler

60.1 DEFINITIONS AND PATHOPHYSIOLOGY

Polycythemia denotes the finding of an elevated cell count in the blood and is a medical composite term of the Greek words *polys* (many), *cytos* (cell), and *haima* (blood). In veterinary medicine most often only the erythrocyte number is increased, whereas the other cell lines (leukocytes, thrombocytes) are not. Some authors prefer the term *erythrocytosis*, but the term *polycythemia* is historically well established.

It is important to recognize that normal upper values of erythrocyte parameters for dogs are different from those for cats. Upper limits for dogs versus cats are packed cell volume (PCV) of 55% versus 45%, red blood cell (RBC) count of $8.5 \times 10^6/\mu L$ versus $10 \times 10^6/\mu L$, and hemoglobin concentration (Hb) of 18 versus 14 g/dl. Certain breeds such as greyhounds and dachshunds generally have higher PCV values than other breeds.

60.2 PATHOPHYSIOLOGY

Polycythemia is classified as relative or absolute (Figure 60-1). Relative polycythemia is defined as an increased PCV with a normal total RBC mass resulting from a decrease in plasma volume. The most common causes of relative polycythemia are external losses of body fluids such as in diarrhea or burns. Less common causes are shifting of body fluids from the vascular space into the interstitial space or inadequate fluid intake (water deprivation). Signs of dehydration are usually present. Splenic contraction can lead to a temporary increase of circulating red cells in dogs but not in cats.

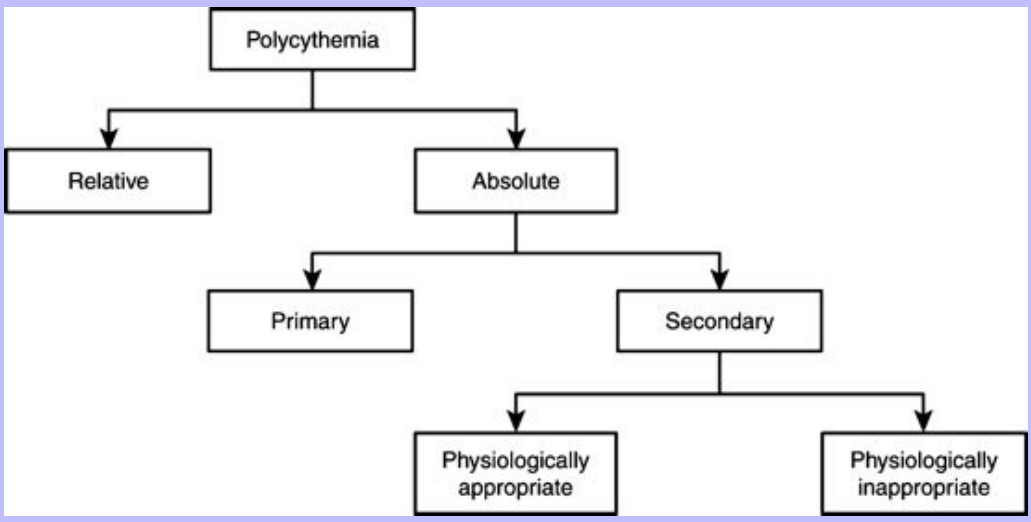
An increase in total RBC mass defines the absolute polycythemias. Absolute polycythemia is further divided into primary and secondary polycythemia, and the latter is further classified as physiologically appropriate or inappropriate (see Figure 60-1).

Under normal circumstances, the erythropoiesis and hence red cell mass is tightly regulated. The principal hormone that regulates erythropoiesis is erythropoietin (EPO). Renal hypoxia, but not the number or mass of circulating red cells, mediates the production of the hypoxia-inducible factor-1 (HIF-1). HIF-1 is a physiologic factor and the major factor of EPO gene transcriptional activation. The cellular site of EPO production in the kidney has been localized to interstitial renal cells in the inner cortex lying in immediate proximity to the proximal tubules. The number of cells that are recruited parallels the degree of hypoxia. As a consequence, EPO is released and its plasma level increases. The interaction of EPO with the EPO receptor results in stimulation of mitosis, differentiation, and prevention of apoptosis of erythroid progenitor cells. The resulting increase in circulating red cells enhances the oxygen-carrying capacity and, as a consequence, improves renal oxygenation. The oxygen sensor is turned off, HIF-1 and EPO levels decrease, and the regulatory loop is complete. The classification of absolute polycythemia is based on this physiology. In primary polycythemia an autonomous (i.e., EPO independent) production of red cells takes place, whereas in secondary polycythemia the red cell production is EPO dependent.

In veterinary medicine the term *primary polycythemia* is used synonymously with polycythemia vera. To the author's knowledge no attempts have been published to further characterize primary polycythemia in dogs or cats. Conversely, in human medicine polycythemia vera is one of several forms of primary polycythemia. The

underlying molecular basis of polycythemia vera has yet to be determined. Despite being considered a myeloproliferative disorder, the erythroid precursors mature into normal RBCs.

Figure 60-1 Classification of polycythemia.



Secondary appropriate polycythemia is a consequence of persistent hypoxia. This may be a physiologic response to living at high altitude. The most common cause of appropriate polycythemia is congenital heart defect with right-to-left shunting of blood. The mixing of venous and arterial blood causes systemic hypoxemia and activation of EPO production. Lung disease may cause hypoxia due to abnormal ventilation or ventilation-perfusion mismatch. The author is aware of one case of eosinophilic bronchitis in a cat with a PCV of 55% and mildly elevated serum EPO levels, but in general, respiratory disease causes mild polycythemia.

Hemoglobin function abnormalities that cause polycythemia are extremely rare in cats and in dogs. One cat with methemoglobinemia due to methemoglobin-reductase deficiency was noted to have moderate polycythemia (PCV 55%). Alterations of hemoglobin structure or decreases in 2,3-biphosphoglycerol that lead to polycythemia have been described in humans but not in cats or dogs.

Secondary inappropriate polycythemia refers to disease processes leading to elevated serum EPO levels without systemic hypoxia. Malignancies can produce EPO as a paraneoplastic syndrome; in a case of cecal leiomyosarcoma, immunohistochemistry and mRNA assays found the neoplastic cells to be the source of EPO origin. Renal disease (e.g., renal neoplasia, amyloidosis, infection, inflammation) may cause local hypoxia and trigger EPO synthesis.

Regardless of the cause, the consequence of an increased PCV is an increase in viscosity. As the red cells occupy the largest fraction of volume, hematocrit is a major determinant of blood viscosity. The rise in viscosity is not linear and becomes more pronounced above a PCV value of 50% to 60% (for dogs). Viscosity is elevated about twofold at a PCV of 70%. Depending on the degree of viscosity and local or systemic vascular hindrance, microcirculation decreases and may lead to local hypoxia or thrombosis. Most likely the neurologic symptoms seen in patients with absolute polycythemia are caused by impaired microcirculation in the brain. Thrombosis of cortical arteries associated with seizures and secondary polycythemia has been reported in a dog.

60.3 PRESENTING COMPLAINT AND PHYSICAL FINDINGS

The signs of relative polycythemia are usually obvious and depend on the severity of dehydration and the underlying disease process. The hematocrit generally is mildly increased (i.e., in dogs 55% to 65%) and returns to normal with fluid therapy. Depending on the amount of concomitant protein loss or shift, the plasma protein concentration will be low, normal, or high. Patients with absolute primary polycythemia have mainly signs related to hyperviscosity. More than half of the cases with primary polycythemia are presented for neurologic complaints such as seizures, ataxia, blindness, tremor, or behavior changes.

Animals with secondary polycythemia can have signs referable to hyperviscosity, to the underlying disease process, or both. Mucous membranes are typically hyperemic, and differentiation from cyanosis can be difficult.

60.4 DIAGNOSTIC PLAN

Treatment of a polycythemic animal is dependent on the cause; hence the type of polycythemia should be determined. Primary polycythemia is a diagnosis by exclusion; therefore all diagnostic steps are used to identify a relative or secondary cause of polycythemia (Figure 60-2).

60.4.1 Minimal Data Base

A complete blood count (CBC), a chemistry panel, and urinalysis are the minimal data base. This enables the clinician to distinguish absolute from relative polycythemia, to assess the degree of polycythemia, and to determine therapeutic success. In clinical practice it is rarely necessary or feasible to determine total red cell mass. On the other a hand, an absolute reticulocyte count is an inexpensive method to gauge the erythropoietic activity.

Appropriate polycythemia will show signs of dyspnea or cyanosis. In the latter case, signs might be restricted to caudal body parts, as seen with reversed patent ductus arteriosus (rPDA). Although an arterial blood gas (ABG) value should detect systemic hypoxia, the high viscosity can hamper sampling and reading. Hence it is recommended to stabilize the patient first (phlebotomy). Normal values are expected in all but appropriate polycythemia (exception: hemoglobinopathies where pO_2 is normal). If hypoxia is the cause of polycythemia, the changes are usually marked. Pulse oximetry can be used if ABG determination is not available. A low saturation (<80%) with a reliable recording and repeatability suggests hypoxia.

Abdominal ultrasound is used to detect renal disease, abdominal neoplasia, or both. Unspecific signs such as hyperechoic kidneys may be found in primary polycythemia. Splenomegaly is detected in up to 25% of cats and about 10% of dogs with primary polycythemia and might suggest primary polycythemia.

Thoracic radiographs and cardiac ultrasound examinations are directed toward identifying pulmonary and cardiac abnormalities. Mild changes such as myocardial hypertrophy or bronchointerstitial changes can be found in primary polycythemia and may be the result of hyperviscosity.

Routine bone marrow examination cannot distinguish primary from secondary polycythemia and hence are not useful. In either case the myeloid-erythroid ratio is normal or decreased. Growth performance of erythroid precursors in EPO-free culture medium can be helpful because erythroid cells of patients with polycythemia vera show normal growth, whereas erythropoiesis in secondary polycythemia is EPO dependent. However, this method is restricted to research laboratories, and few cases have been published in veterinary medicine.

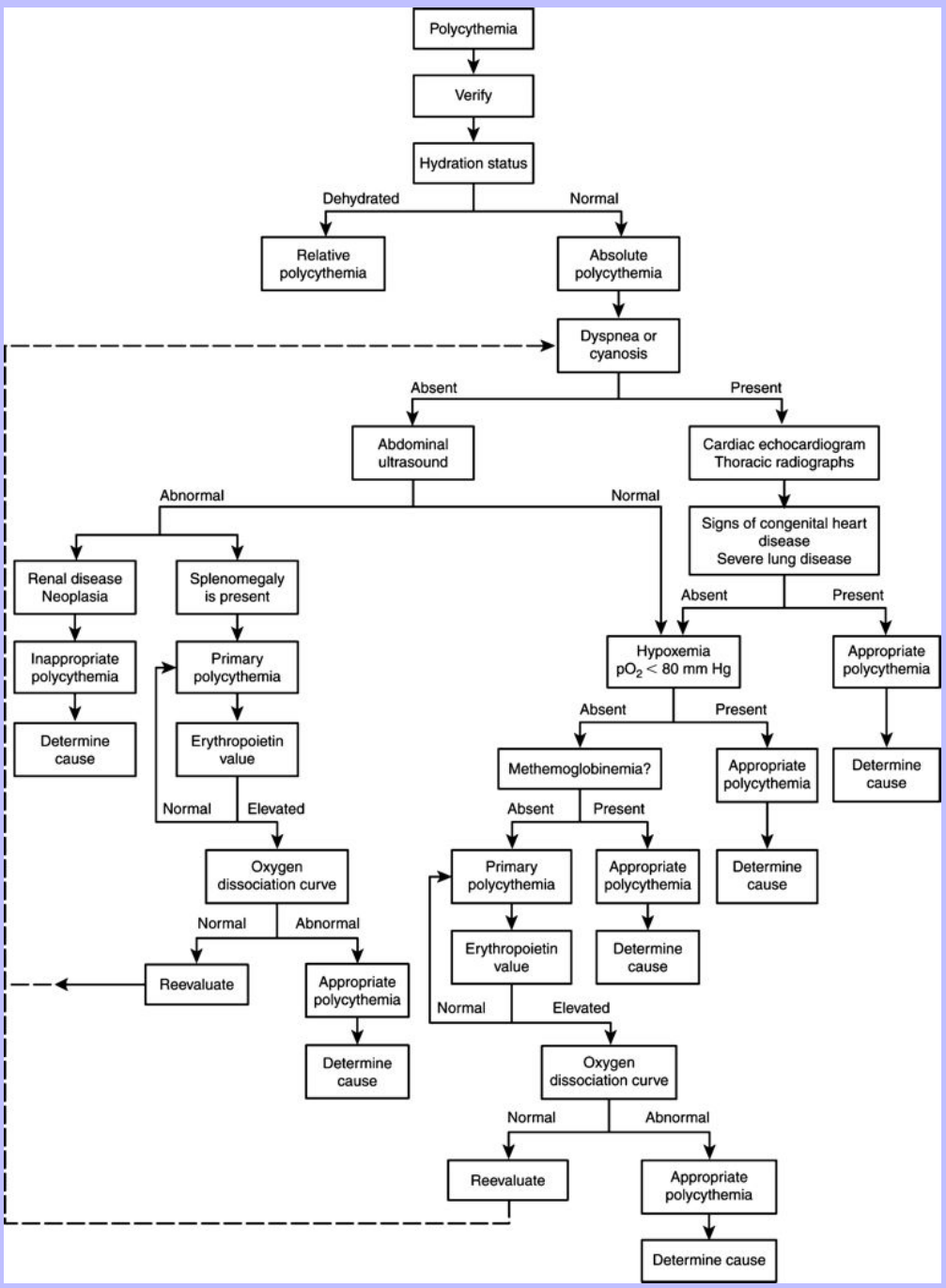
As primary and secondary polycythemia are EPO independent and EPO dependent respectively, it would appear that measurement of serum EPO levels is an appropriate test to differentiate the two forms. Several human test kits using either an enzyme-linked immunosorbent assay (ELISA) or radioimmune assay (RIA) method have been validated for animals. Although an increased serum EPO level is diagnostic for secondary polycythemia and values up to fiftyfold elevation have been found in secondary polycythemia, a low or normal serum EPO value occurs in about 50% of secondary polycythemia. This finding reduces the diagnostic accuracy of serum EPO level's determination.

60.4.2 Treatment and Prognosis

Relative polycythemia is treated with intravenous fluids and addressing the underlying cause. Phlebotomy is contraindicated in cases of relative polycythemia. Independent of the cause, absolute polycythemia is treated initially with blood-letting. This can be done by phlebotomy or by leeching. The latter has been used successfully in a cat as initial treatment when phlebotomy was not feasible. Four leeches reduced the hematocrit from 79% to 56% within 48 hours. Serial phlebotomies of 10 to 20 mL/kg blood are withdrawn until clinical symptoms have resolved or the target hematocrit is reached. In primary polycythemia the target hematocrit is below 55% for dogs and below 50% for cats. In cases of secondary appropriate polycythemia such as in rPDA the aim of treatment is resolving clinical signs of polycythemia and a higher hematocrit (60% to 70%) can be acceptable. A higher hematocrit might provide higher oxygen carrying capacity without causing hyperviscosity problems. If blood letting is inadequate, the myelosuppressing drug hydroxyurea is the treatment of choice. Multiple-dose regimens have been suggested in the literature. Some regimens use a loading dose starting with 30 to 50 mg/kg orally once a day; after 1 week the dose is reduced to 15 mg/kg/d, then titrated to effect. Other regimens propose using a maintenance dose such as 50 mg/kg every other day and titrating to effect. Side effects are reversible and include myelosuppression (thrombocytopenia), hair loss, and gastrointestinal (GI) upsets.

The prognosis for primary polycythemia is guarded, but survival for more than 6 years has been achieved in treated animals. The prognosis for secondary polycythemia depends on the cause. In cases of rPDA, survival of more than 4 years has been reported.

Figure 60-2 Algorithm for diagnostic approach to polycythemia.



61 CHAPTER • 61 Cyanosis

Jean-Paul Petrie

Cyanosis is a bluish discoloration of the skin and mucous membranes. It occurs due to an increased amount of reduced hemoglobin (RHb) within the erythrocytes and can be broken down into *central* and *peripheral* causes. In central cyanosis an unsaturation of arterial blood or the presence of a hemoglobin (Hb) derivative is seen. Peripheral cyanosis is a desaturation of blood due to a regional reduction in blood flow. It is not a sensitive indicator of the state of oxygenation, often not being recognized until the percent saturation of Hb in arterial blood (SaO_2) falls below 80%. Cyanosis is an emergency condition necessitating early recognition and careful diagnostic planning.

61.1 PATHOPHYSIOLOGY

Cyanosis can usually be detected when the mean capillary concentration of RHb is greater than 5 g/100 mL. An animal with a normal packed cell volume (PCV) must have an SaO_2 between 73% and 78%, or an arterial oxygen tension (PaO_2) of 39 to 44 mm Hg to have clinically detectable cyanosis. In general, the lower the total Hb concentration, the more SaO_2 may fall before the detection of cyanosis. An animal with a PCV of 18% (total Hb 6 g/dl) must have a PaO_2 of less than 30 mm Hg before cyanosis is detectable. This degree of arterial saturation is not compatible with life; therefore cyanosis is only detectable in this patient after death!

Secondary polycythemia is frequently seen with chronic arterial unsaturation contributing to the development of cyanosis at a higher SaO_2 compared with animals with a normal PCV. An animal with a PCV of 60% may appear cyanotic when their SaO_2 falls below about 87% or a PaO_2 of 55 mm Hg. Cyanosis can also be observed when nonfunctional Hb such as methemoglobin (MetHb) is present within the blood.

Peripheral cyanosis is due to a slowing of blood flow and a relative increased oxygen extraction from normally saturated arterial blood. Vasoconstriction, diminished peripheral blood flow, peripheral vascular disease, or venous obstruction can result in cyanosis. Peripheral vasoconstriction occurs as a compensatory mechanism with decreased cardiac output secondary to congestive heart failure or shock. Blood is diverted from the skin to more vital organs such as the brain, lungs, and heart.

61.2 DIFFERENTIAL DIAGNOSIS

Cyanosis is a clinical sign with many possible causes. Box 61-1 lists the common causes and classifications of central and peripheral cyanosis. Peripheral cyanosis results when a regional reduction of blood flow or venous obstruction exists. Causes of reduced capillary arterial blood flow include vasoconstriction (e.g., hypothermia, shock, low cardiac output), arterial thromboembolism (e.g., saddle thrombus, neoplasia, hypercoagulant states, arteritis), and low cardiac output (e.g., cardiac disease, arrhythmias, hypovolemia). Obstruction of venous drainage can be seen secondary to a tourniquet, venous thrombosis, or right-sided heart failure.

Central cyanosis occurs when SaO_2 decreases due to a reduced PaO_2. Reduced PaO_2 is seen with right-to-left shunting congenital cardiac disease, pulmonary disease, and when nonoxygen carrying Hb (e.g., methemoglobinemia) is present. When cyanosis is present in younger animals, congenital cardiac disease should be strongly suspected. Right-to-left shunting cardiac defects result in unoxygenated venous blood bypassing the lungs into the systemic circulation. Systemic vascular resistance normally decreases with exercise augmenting the degree of right-to-left shunting. Right-to-left shunting patent ductus arteriosus (PDA) may occur in the presence of

pulmonary hypertension and is associated with *differential* cyanosis. *Differential* cyanosis occurs when unoxygenated blood is delivered to the caudal portion of the body and oxygenated blood is delivered to the cranial portion of the body due to the anatomic location of the ductus. Severely impaired pulmonary function secondary to hypoventilation, airway obstruction, or poorly ventilated portions of the lung results in central cyanosis. This may occur acutely as with pneumonia, pulmonary edema, pleural effusions, and pulmonary thromboembolism, or it may occur with chronic pulmonary disease. Cyanosis resulting from primary pulmonary disease may occur at any age.

Increased amounts of nonoxygen carrying MetHb can result in cyanosis. MetHb is a normal product of Hb oxidation and is maintained at a normal concentration, approximately 1% of the total Hb concentration, by the enzyme MetHb reductase within the erythrocytes. Congenital MetHb reductase deficiency can occur but is rare in dogs and cats. Methemoglobinemia more frequently results from exposure to oxidants. Common oxidants associated with the production of MetHb include acetaminophen, benzocaine, phenazopyridine, and nitrates. If the MetHb content increases to 10% or greater, the patient's blood should have a noticeably brown coloration compared with bright-red blood.

61.3 APPROACH TO THE PATIENT WITH CYANOSIS

Initial clinical differentiation of cyanosis into central or peripheral causes is based on history, physical examination, and diagnostic testing (Figure 61-1). Peripheral vasoconstriction can occur with primary pulmonary pathology (e.g., pulmonary edema), and a mixture of both types of cyanosis may be present. Therefore all animals with peripheral cyanosis should be closely evaluated for central cyanosis.

History can sometimes provide useful information leading to the cause of the cyanosis. Recent exposure to oxidants (e.g., acetaminophen) or other toxic agents should be determined. The duration of the cyanosis may be helpful. Chronic cyanosis in a young animal is more likely associated with congenital heart disease. Information related to either chronic cardiac disease or pulmonary disease should be determined (e.g., coughing, labored breathing, fatigue, syncope, medications). Peripheral cyanosis may be associated with a history of acute pain, paresis, or lameness in the affected area.

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61.3.1 Box • 61-1 Causes of Central and Peripheral Cyanosis

61.3.1.1 Central Cyanosis

Cardiac (right-to-left shunting)

- Intracardiac
  - Fallot's tetralogy
  - Atrial or ventricular septal defect with pulmonic stenosis or pulmonary hypertension
- Extracardiac
  - Reversed patent ductus arteriosus (PDA) (differential cyanosis)

Pulmonary arteriovenous fistulas

Pulmonary

Hypoventilation

Pleural effusion, pneumothorax

Respiratory muscle failure (e.g., fatigue, myopathy, or neurologic abnormalities)

Toxicity (e.g., sedative or anesthetic overdose)

Primary neurologic disease (e.g., neoplasia, inflammatory)

Obstruction

Laryngeal paralysis

Foreign body (e.g., laryngeal, tracheal)

Mass lesion of large airways (e.g., neoplasia, parasitic, inflammatory)

Inadequate oxygen concentration of inspired gas (e.g., high-altitude, anesthetic complication)

Ventilation-perfusion mismatch

Pulmonary thromboembolism

Pulmonary infiltration

Edema

Inflammation

Neoplasia

Acute respiratory distress syndrome (ARDS)

Chronic obstructive pulmonary disease or pulmonary fibrosis

Nonoxygen carrying hemoglobin (Hg) (e.g., methemoglobinemia)

61.3.1.2 Peripheral Cyanosis

Central cyanosis (e.g., congestive heart failure)

Decreased arterial supply

Peripheral vasoconstriction (e.g., hypothermia, shock)

Arterial thromboembolism

Low cardiac output

Obstruction of venous drainage

Tourniquet or foreign object (i.e., rubber band)

Venous thrombosis

Right-sided heart failure

Peripheral versus central cyanosis is often determined based on physical examination. Typically, peripheral cyanosis involves the extremities and skin, and central cyanosis is most readily apparent in the mucous membranes and tongue. An exception to this rule is differential cyanosis seen with a right-to-left shunting PDA as described earlier in the chapter. Causes for peripheral cyanosis can frequently be determined by careful examination of affected areas. Generalized peripheral hypothermia may be secondary to vasoconstriction. Massaging or gentle warming of a cyanotic extremity will increase blood flow and may abolish the cyanosis. Mechanical venous obstructions or deformities (e.g., rubber band, tumor) may be readily apparent. Typical findings associated with arterial thromboembolism include pain, pulselessness, paresis, pallor, and palpable coolness of the affected area.

Other physical examination findings including respiratory pattern, lung sounds, murmurs, arrhythmias, jugular venous distension, ascites, weakness, and pulse quality may provide information that is useful in differentiating a cardiac or respiratory cause for the cyanosis.

Arterial blood gases (ABGs) or pulse oximetry can be a reliable method to evaluate central cyanosis, suggesting the type of altered physiology present (Table 61-1). Specimens for ABG analysis should be compared on room air and 100% oxygen. Pulse oximetry can be used in clinics where immediate blood gas analysis is not available. If a satisfactory signal is recorded, there can be a good correlation for SaO_2 between pulse oximetry and ABG.

Radiographic analysis provides valuable information in determining the extent of pulmonary disease if present. Radiographs can differentiate the presence of common respiratory abnormalities including pulmonary edema, pleural effusion, pneumonia, pneumothorax, neoplasia, bronchiole disease, and potentially pulmonary thromboembolism. The cardiac silhouette and pulmonary vasculature can also be evaluated. Animals suspected of having congenital cardiac disease should have an echocardiogram and electrocardiogram performed as soon as possible.

61.4 THERAPY

Successful therapy of cyanosis relies on understanding the cause. Peripheral cyanosis can be indicative of a very serious condition but is not itself life threatening. Therapy should be directed toward resolution of the underlying disease process and supportive care.

Central cyanosis is often a life-threatening emergency. Immediate determination of airway patency is critical. If airway obstruction is present, either removing the obstruction (e.g., foreign body) or intubation by means of a tracheostomy or endotracheal tube should be performed bypassing the obstruction. Oxygen administration should be instituted as soon as possible via an oxygen mask, nasal cannula, oxygen cage, or tracheal intubation. Significant pleural effusion and pneumothorax require thoracocentesis. If primary pulmonary parenchymal disease is present, direct treatment aimed at relieving the disease process is required (e.g., diuretics should be administered to animals assessed as having cardiogenic pulmonary edema). Chronic obstructive pulmonary disease and pulmonary fibrosis are chronic conditions with limited treatment options. Oxygen supplementation in the home environment is impractical, and chronic management includes weight loss, exercise restriction, and bronchodilators. Future vasodilator therapies (i.e., oral prostacyclins) may provide more hopeful outcomes in these patients.

Right-to-left shunting congenital cardiac disease does not respond well to oxygen administration. In some cases where severe pulmonary hypertension is present, oxygen administration can result in pulmonary artery vasodilation and improve pulmonary blood flow resulting in less ventilation-perfusion mismatch. Cage rest is recommended. Polycythemia can be treated by phlebotomy or medications (e.g., hydroxyurea). In some cases of cyanotic heart disease, surgical palliation may be an option.

Figure 61-1 Algorithm for the differential diagnosis of cyanosis. All tentative diagnoses should be confirmed with appropriate specific testing.

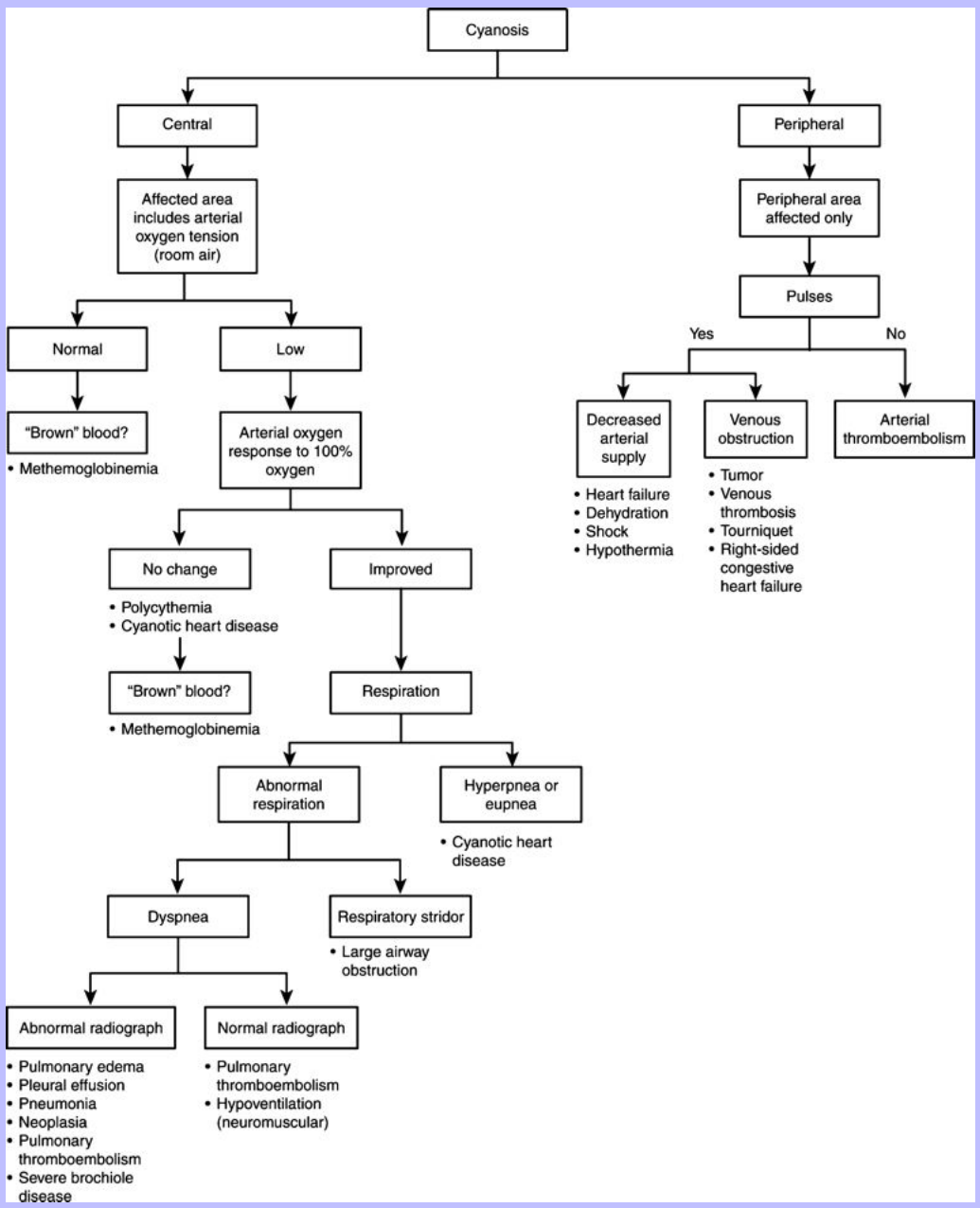

Table • 61-1 Arterial Blood Gas Patterns with Various Central Cyanotic Causes

PROBLEM	SaO_2 (ROOM AIR)*	PaO_2 (ROOM AIR)*	$PaCO_2$*	PaO_2 RESPONSE TO 100% O_2
Right-to-left shunting cardiac defect	↓↓	↓↓	Normal	–
Pulmonary parenchymal disease	↓↓	↓↓	↑	↑
Hypoventilation	↓	↓	↑↑↑	↑
Systemic hypoperfusion	↓	↓	Normal/↑	↑
Ventilation-perfusion mismatch	↓	↓	Normal/↓	↑
Methemoglobinemia	↓	Normal	Normal	–

* Normal SaO_2 (room air), ~97%; normal PaO_2 (room air),~100 mm Hg;normal $PaCO_2$ (room air), ~40 mm Hg.

Mild methemoglobinemia does not require specific therapy, but oxidant exposure should be eliminated. After elimination of oxidant exposure, erythrocytes can convert most of the MetHb back to Hb within 24 hours. MetHb cannot bind to oxygen; therefore supplementation with oxygen has limited value. In some cases where the exposure is more severe, the use of N-acetylcysteine or methylene blue may be indicated.

Neurologic or musculoskeletal causes of hypoventilation may require respiratory support including oxygen supplementation with or without mechanical ventilation. Temporary causes (e.g., sedative overdose, respiratory muscle fatigue) may only require short-term treatment. Therapy for pulmonary thromboembolism (PTE) includes oxygen supplementation and fluid therapy. Other more controversial therapies for PTE include anticoagulants and plasma.

In all causes of cyanosis, patients should be monitored for response to therapy by serial assessments of mucous membrane color, oxygen saturation, radiographs, blood gas values, and respiratory rate and effort.

62 CHAPTER • 62 Jaundice

Susan M. Eddlestone

***J**aundice* or icterus is a syndrome characterized by hyperbilirubinemia and deposition of bile pigment in the skin, mucous membranes, and sclera with resulting yellow appearance. Visually detectable jaundice may begin to occur when serum bilirubin exceeds 1.5 mg/dl, with most cases being clinically detectable closer to 2 mg/dl. Obvious jaundice is seen at serum bilirubin concentrations of 4 to 5 mg/dl or greater. Inspection of nonpigmented body surfaces including sclera, gingiva, sublingual tissues, soft palate, pinnae, periumbilical area, and mucosal surface of the penis or vagina allows easy recognition. Urine and feces may be a bright orange-gold to dark brown color due to increased excretion of bilirubin. The differential diagnoses of jaundice includes (1) prehepatic conditions such as hemolytic anemia, (2) hepatic diseases causing intrahepatic cholestasis, and (3) posthepatic causes such as biliary obstructive disease.

62.1 BILIRUBIN METABOLISM

Bilirubin is a waste product formed during the catabolism of hemoglobin (Hg) from aging or damaged erythrocytes or ineffective erythropoiesis, myoglobin, and a small portion of other hemoproteins in the body. Hg from erythrocytes contains more than 90% of all heme in the body. Aging erythrocytes are phagocytized by macrophages in the liver, spleen, bone marrow, and lymph nodes. Hg is released into the circulation and binds with haptoglobin, an $alpha_2$-globulin and acute-phase reactant that serves as a carrier protein. The Hb-haptoglobin complex is taken up by the reticuloendothelial (RE) system. Both Hg and the carrier proteins are degraded.

After degradation, heme is released from globin and transferred to heme oxygenase in the endoplasmic reticulum of the RE cell and in hepatocytes. Globin is degraded to amino acids and recycled by the body. Ferric (Fe^{3+}) heme is reduced to ferrous (Fe^{2+}) heme and then modified to a ferric iron-biliverdin complex. Released iron binds to iron-carrying proteins, transferritin, and ferritin for storage or recycling. Biliverdin is converted to unconjugated bilirubin via biliverdin reductase available in most mammalian cells, with highest concentration in liver, spleen, and kidney. The lipid soluble unconjugated bilirubin is released into the circulation and must bind with albumin for circulatory transport.

Albumin-bound unconjugated bilirubin binds to receptors on hepatocytes and is taken up and converted to the water-soluble conjugated bilirubin diglucoronide. This occurs by the reaction of bilirubin and two UDPEA molecules catalyzed by glucoronyl transferase to form bilirubin diglucoronide. Approximately 70% of bilirubin in the liver is in the unconjugated form due to the rate-limiting factors of enzymatic activity and availability of glucuronic acid needed for bilirubin conjugation. Conjugated bilirubin is excreted from the hepatocyte into the canaliculi to enter the bile by an active transport process that occurs against a large concentration gradient. This is the rate-limiting step in bilirubin metabolism in the dog and probably the cat.

The liver has a large reserve capacity for bilirubin excretion and can accommodate a thirtyfold to sixtyfold increase above normal. Only a small percent of conjugated bilirubin is refluxed into the circulation, with only a small percentage (<2%) filtered through the glomerulus. Conjugated bilirubin is carried in bile via the common bile duct and emptied into the duodenum. Colonic bacteria deconjugate and hydrogenate the conjugated bilirubin to unconjugated bilirubin. This produces the colorless pigment mesobilirubinogen that is oxidized to a group of colorless tetrapyrolles called *urobilinogens*. Urobilinogens are oxidized to urobilin, which has a yellow-orange color and stercobilin that gives the brown fecal pigment. Small amounts (10% to 20%) of urobilinogen are absorbed from the intestine, with 95% circulating back to the liver for hepatic uptake and 5% excreted through the

kidneys. Conjugation of bilirubin inhibits small intestinal absorption, thus impeding the enterohepatic circulation. Increased deconjugation occurs during bacterial overgrowth of the small bowel with colonic anaerobes, leading to increased enterohepatic turnover of bilirubin pigments. Feces lacking brown pigment are referred to as *acholic* and may be caused by decreased bile flow or deficient intestinal bacterial activity. Complete biliary obstruction would be required for development of acholic stools due to the small amount of bile pigments necessary to impart normal color. Absence of fecal pigment develops 7 to 10 days after complete bile duct occlusion by which time clinical jaundice is obvious.

62.2 DIFFERENTIAL DIAGNOSIS

Prehepatic jaundice is caused by intravascular or extravascular hemolysis (see Figure 62-1). The greatly increased rate of erythrocyte destruction and subsequent catabolism of Hg causes an increased production of bilirubin. Serum unconjugated bilirubin is increased transiently, with both unconjugated and conjugated bilirubin increased by the time the dog or cat is clinically jaundiced. An increased production of bilirubin accompanied by reduced hepatic clearance has been shown to be present in dogs with severe Coomb's-positive hemolytic anemia. In general, hyperbilirubinemia due to hemolytic anemia without underlying hepatic disease is usually mild with serum bilirubin values below 10 mg/dl.

Hepatic causes of jaundice may occur when disruption takes place in any step of bilirubin hepatocellular transport. Inflammatory conditions of the liver can impede bile flow causing swelling and occlusion of canaliculi, bile ductules, and small bile ducts. Membrane permeability is increased with bilirubin refluxing into the sinusoidal space in conjunction with bilirubin back diffusing into hepatocytes. In addition, canalicular excretion of bilirubin may become compromised.

Chronic inflammation occurring in periportal areas (zone 1) can cause occlusion of smaller bile ducts. Chronic inflammation within bile ducts leading to bile duct hyperplasia or biliary cirrhosis may also cause mechanical obstruction. *Cholestasis* is the term applied to conditions in which bile flow is impaired. Paranchymal lesions occurring away from periportal areas (zone 3) tend not to cause hyperbilirubinemia until later in the disease, when hepatocellular transport of bilirubin fails as opposed to the mechanical occlusion of bile flow. Formation of regenerative nodules due to hepatic injury may cause hyperbilirubinemia in severe cases. Bile flow may be impaired due to compression by fibrotic tissue that results in disruption of normal hepatic architecture. Congenital portosystemic vascular anomalies causing hepatic atrophy do not usually cause hyperbilirubinemia even though other indicators of liver function may become affected (hypoalbuminemia, hypoglycemia, decreased blood urea nitrogen [BUN]).

Primary conditions associated with jaundice in the dog and cat include sepsis. Sepsis causes hyperbilirubinemia due to the production of cytokines that interfere with the transport of bilirubin across the canalicular membrane. Heritable disorders of bilirubin metabolism have not been reported in the dog or cat.

Posthepatic or obstructive jaundice may be caused by intraluminal or extraluminal mechanical occlusion of the larger ducts of the biliary tree. The most common causes are pancreatitis and neoplasia in and around the gallbladder, cystic duct, and common bile duct. Less frequent causes are primary disorders of the walls of the biliary system that obstruct the flow of bile. Inspissated bile and choleliths formed secondary to biliary wall inflammation can obstruct bile flow. Bile duct rupture with bile spillage into the peritoneal cavity can cause extrahepatic jaundice.

62.3 CLINICAL SIGNS

The canine or feline patient with prehepatic jaundice due to hemolytic anemia may have anorexia, pale mucous membranes, increased respiratory rate, lethargy, weakness, or collapse. Mucous membranes may be slightly yellow to orange in color due to the combination of pallor and hyperbilirubinemia. Early intravascular hemolysis may cause a port wine-colored urine due to hemoglobinuria if the presence of bilirubin in the urine has not yet occurred. Historical and clinical findings in canine and feline liver disease are nonspecific but may include anorexia, weight loss, vomiting, diarrhea, and abdominal pain. Severely affected animals may be dehydrated, hypovolemic, or have neurologic signs. Posthepatic diseases causing biliary obstruction may have anorexia, depression, weight loss, vomiting, or diarrhea occurring 1 to 3 weeks prior to presentation.

62.4 DIAGNOSTIC PLAN

Clinical assessment of the jaundiced dog or cat begins with historical and physical exam findings described previously. Laboratory analysis can distinguish prehepatic jaundice from hepatic and posthepatic jaundice by the presence of severe anemia (packed cell volume [PCV] <20%) and evidence of hemolysis. In the absence of blood loss, hemogram changes consistent with hemolysis and regenerative anemia include low PCV and hematocrit (HCT) (< 20%), low erythrocyte number, increased mean corpuscular volume (MCV), reticulocytosis, poikilocytosis, anisocytosis, regenerative leukocytosis, nucleated erythrocytes, and enlarged platelets. In primary immune-mediated disease causing erythrocyte destruction, spherocytes, and autoagglutination may be seen, as may a delayed regenerative response. Hepatocellular disease occasionally results in hemolysis associated with erythrocyte membrane alterations, but this rarely causes severe anemia or contributes significantly to increased serum bilirubin concentration.

Once hemolysis is ruled out, hepatic and posthepatic diseases need to be considered. Serum biochemical analysis allows evaluation of serum total bilirubin and liver enzymes. Increased liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], gamma-glutamyltransferase [GGT]) are found in primary hepatic disease, in secondary hepatic diseases (sepsis, pancreatitis), and in posthepatic diseases. Therefore these enzymes do not allow differentiation between these categories. Measurement of unconjugated (indirect) and conjugated (direct) bilirubin to distinguish between prehepatic, hepatic, and posthepatic causes of jaundice is not useful in dogs and cats. Serum bile acids will be simultaneously increased with bilirubin in jaundiced animals due to the interruption of the enterohepatic circulation of bile acids noted in hepatic and posthepatic diseases. Urinalysis can confirm the presence of bilirubinuria in discolored urine. Male dogs and occassionally female dogs may normally have small amounts of bilirubin present in urine; however, large amounts in conjunction with hyperbilirubinemia are diagnostic for jaundice. Bilirubinuria in the cat is always significant and indicates hyperbilirubinemia due to a higher renal threshold and an inability of the cat to conjugate bilirubin at the renal tubule, as compared with the dog. Hemoglobinuria may be seen in patients with intravascular hemolysis.

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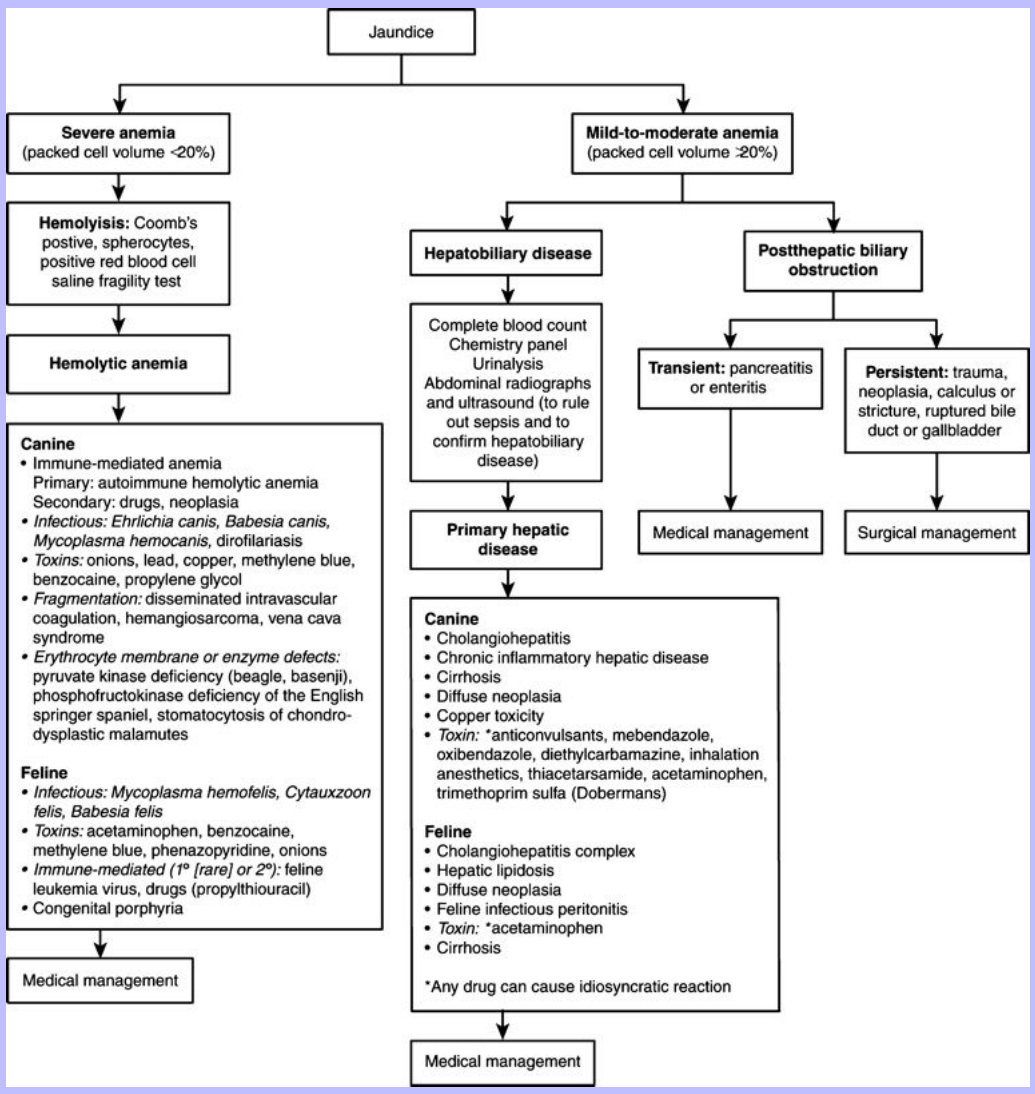
Figure 62-1 Algorithm for differential diagnoses of jaundice.



The initial diagnostic approach to differentiate hepatic from posthepatic disease is the noninvasive use of abdominal radiographs and abdominal ultrasound to identify any obvious structural changes in the biliary tract that may suggest posthepatic biliary obstruction such as an enlarged gallbladder or a tortuous, dilated common bile duct. Duodenal and pancreatic masses and pancreatitis may be suggested on ultrasound. Hepatomegaly, hepatic masses, or changes in hepatic echogenicity on ultrasound examination may indicate liver disease. Ultimately, exploratory celiotomy or laparotomy may be indicated to examine the liver and biliary tract and to biopsy the liver for histologic diagnosis of hepatic disease. Celiotomy may also be indicated when corrective surgery for obstructive masses or biliary reconstruction to preserve bile flow is needed.

62.5 TREATMENT AND PROGNOSIS

The specific treatment for jaundice is dependent on the underlying cause. Treatment for hemolytic anemia is directed at the primary initiator of hemolysis. Toxic, infectious, or immune-mediated causes are treated with specific therapies that include specific antidotes, antibiotics, and immunosuppressive therapies, respectively. Supportive care including red blood cell (RBC) or Hg transfusion may be needed in severe cases of anemia. Prognosis is good for toxic and infectious causes of hemolysis if treated appropriately. Prognosis for immune-mediated disease is guarded due to the resistant and relapsing nature of the disease in dogs.

Treatment of specific hepatic diseases requires a liver biopsy for definitive diagnosis. Infectious, toxic, canine copper storage disease; chronic immune-mediated liver disease; feline hepatic lipidosis; and cholangiohepatitis carry fair-to-good prognoses when treated with appropriate therapy. Hepatic neoplasia and cirrhosis carry a much poorer prognosis. Supportive therapy of liver disease may include intravenous fluids to rehydrate the dog or cat and promote forward bile flow, vitamin K1 to replace deficiencies due to cholestasis, vitamin E for antioxidant properties, vitamin B complex, and S-adenosyl for replacement of intrahepatic glutathione levels to restore mechanisms of hepatocyte metabolism.

Treatment of chronic cholestasis associated with chronic hepatic or posthepatic disease may include the use of the cholerectic, ursodeoxycholic acid, a hydrophilic bile acid that displaces the more toxic hydrophobic bile acids from the bile acid pool that can cause hepatocyte membrane damage. Posthepatic obstructive disease is almost always surgically managed except for pancreatitis, which is usually responsive to medical therapy. Prognosis of postobstructive diseases is good if appropriately managed, except for necrotizing pancreatitis and neoplasia that carry a poorer prognosis.

63 CHAPTER • 63 Bleeding Disorders: Epistaxis and Hemoptysis

Tracy Gieger

63.1 EPISTAXIS

Epistaxis is defined as hemorrhage originating from the nose. The following areas should be emphasized when evaluating a patient with epistaxis (Figure 63-1).

63.1.1 Signalment

Young animals that roam are susceptible to trauma, infections, and foreign body (FB) inhalation. Intact dogs that roam are susceptible to transmissible venereal tumors. Purebred dogs may be affected with von Willebrand's disease (vWD) or coagulation factor deficiencies. Immune-mediated diseases occur most commonly in middle-aged animals. Nasal tumors are more common in animals over 8 years of age, although nasal lymphoma may occur in younger cats. Nasopharyngeal polyps occur more often in young cats. Brachycephalic cats are more susceptible to chronic viral respiratory infections.

63.1.2 Environment

Outdoor pets are more susceptible to nasal trauma, parasitic and fungal infections, rodenticide toxicity, and FB inhalation. The owner should be questioned about travel to areas endemic for fungal and rickettsial organisms, leishmaniasis, and hepatozoonosis.

63.1.3 Time Course

Nasal trauma results in acute-onset and often severe bleeding that resolves with supportive measures and does not recur. FB inhalation, most commonly wood splinters or grass awns, often causes an acute onset of epistaxis, sneezing, and pawing at the face; however, if foreign objects remain lodged in the nasal cavity, chronic nasal discharge secondary to granuloma formation may result. Chronic or intermittent epistaxis is more common with oronasal fistulas, fungal rhinitis, and nasal tumors; often these diseases begin with mucoid nasal discharge that progresses to epistaxis later in the course of disease. Allergic rhinitis may cause seasonal epistaxis.

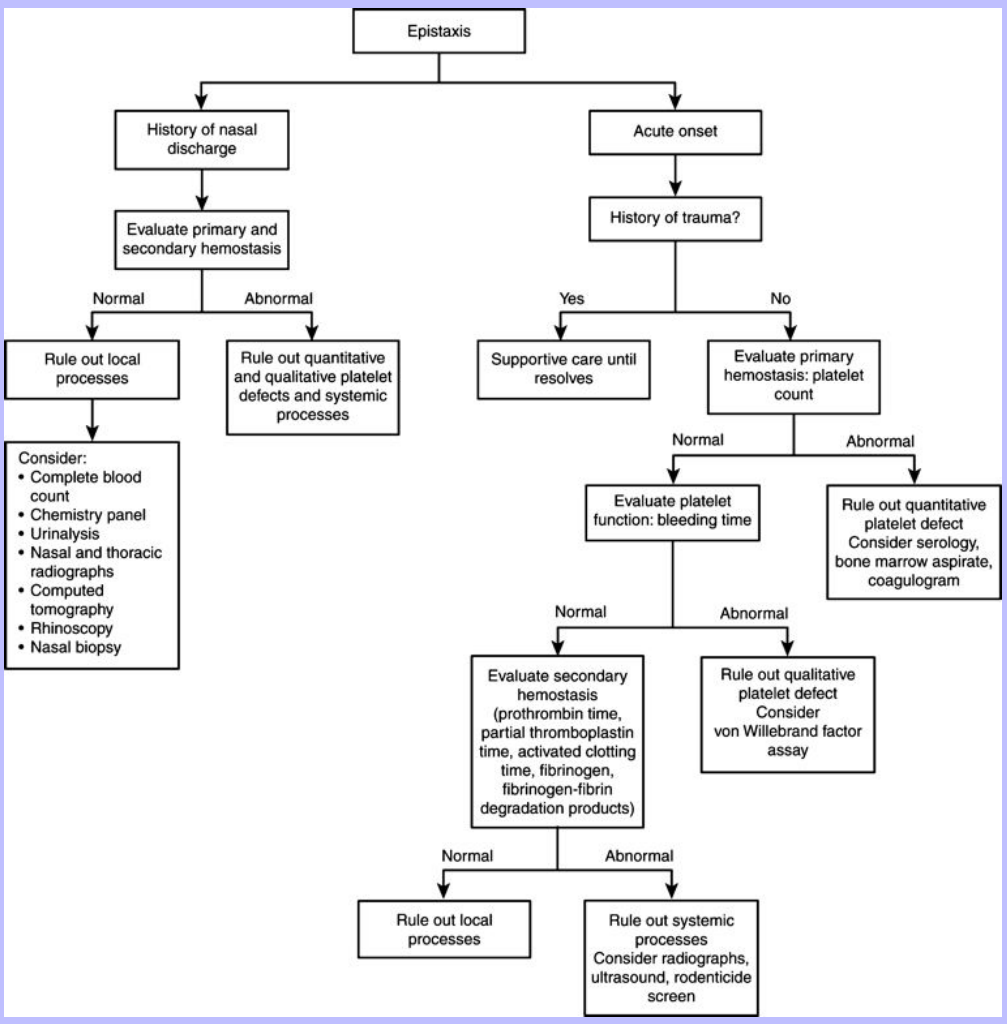
63.1.4 Characterization of Epistaxis

Many intranasal diseases such as nasal tumors begin with unilateral epistaxis that becomes bilateral as the disease progresses, disrupting the nasal septum. Bilateral epistaxis often indicates “extranasal” causes such as coagulopathies, hypertension, thrombocytopenia, and thrombocytopathia (a defect in platelet function).

63.1.5 History of Bleeding from Other Sites

Historical bleeding after tooth loss or elective neutering may indicate a congenital coagulation factor defect or platelet disorder. Animals with petechia, mucosal bleeding, melena or fundic hemorrhages are likely to have a defect of primary hemostasis (platelets), whereas those with hemarthrosis, hematomas, or bleeding into body cavities are likely to have a defect of secondary hemostasis (coagulation factors). Melena and hematemesis may occur when blood from the nasopharynx is swallowed.

Figure 63-1 Algorithm for epistaxis.



63.1.6 Concurrent Problems Not Related to the Nasal Cavity

Central nervous system (CNS) dysfunction may occur with hyperviscosity syndromes or nasal tumors invading the brain. Polyuria and polydipsia are seen with hyperadrenocorticism, chronic renal failure, and hyperthyroidism which uncommonly cause epistaxis secondary to hypertension. A history of dental disease may support oronasal fistula formation as a cause of epistaxis.

63.1.7 History of Drug and Vaccine Administration

Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit platelet function; trimethoprim sulfa and other antibiotics may induce an immune-mediated platelet destruction, whereas chemotherapeutic agents, estrogens,

and phenylbutazone may cause myelosuppression and thrombocytopenia. Immune-mediated thrombocytopenia is an uncommon sequela to vaccination.

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63.2 PHYSICAL EXAMINATION

The clinician should examine the face for visual or palpable asymmetry, which is most commonly secondary to neoplasia. A glass slide may be held up to the nose to document airflow through the nostrils by the presence of condensation on the slide. Ulceration and depigmentation of the nasal planum may be seen with aspergillosis or squamous cell carcinoma. Polypoid masses extending from the nares are seen with rhinosporidiosis and cryptococcosis. Cats with nasal cryptococcosis often have a characteristic convexity of the nose ("Roman nose"). The mouth should be examined for palate deformity, masses, oronasal fistulas, or loose teeth. Nasal tumors often cause facial or hard palate deformity, inability to retropulse the globe, or epiphora. A fundic examination may reveal chorioretinitis, signs of hypertensive retinopathy, or hyperviscosity. Regional lymph nodes should be examined for enlargement secondary to infectious organisms, inflammation, or metastatic neoplasia. Evaluation of the skin, body cavities, and joints will help to eliminate evidence of a coagulopathy.

63.3 DIFFERENTIAL DIAGNOSIS

The differential diagnosis for epistaxis can be divided into *systemic* and *local* causes (Box 63-1). Local diseases may progress and develop systemic complications that can exacerbate bleeding.

63.4 SYSTEMIC PROCESSES

Hemostatic defects or increased capillary fragility are mechanisms of epistaxis. Primary hemostatic defects (platelet plug formation) include thrombocytopenia or thrombocytopathia. Mechanisms of thrombocytopenia include decreased production, increased destruction, sequestration, and increased consumption. Spontaneous bleeding is uncommon unless the platelet count is less than or equal to 50,000/μL. Decreased production of platelets can occur secondary to viral, rickettsial, protozoal, parasitic, or bacterial infections; to neoplastic conditions resulting in myelophthisis; to drug administration; or to immune-mediated phenomena. Increased destruction of platelets may be immune mediated (primary or secondary) or related to microangiopathy (seen with hemangiosarcoma). Sequestration of platelets in the spleen, liver, or large vascular tumors results in thrombocytopenia. Increased platelet consumption is seen with disseminated intravascular coagulopathy (DIC), vasculitis, and hemorrhage. Thrombocytopathia may be primary, such as in vWD, or secondary to uremia, dysproteinemias (associated with ehrlichiosis, multiple myeloma, among others), or drugs such as NSAIDs. Secondary coagulation (coagulation factor) defects such as Hemophilia A and B are uncommon congenital abnormalities that vary in severity. Acquired coagulopathies include anticoagulant rodenticide toxicity and hepatic failure (with decreased coagulation factor production). Increased capillary fragility with subsequent rupture can result from hypertension, neoplasia invading blood vessels, hyperviscosity syndromes, hyperlipidemia, and thromboembolic disease.

63.5 LOCAL PROCESSES

Local processes ("intranasal" causes) are the most common cause of epistaxis. Nasal adenocarcinomas are more common in dogs, whereas cats are more often affected with nasal lymphoma and benign polyps. Bacterial rhinitis is almost always secondary to inflammation or damage to the nasal mucosa, although *Bordetella, Pasteurella,* and *Mycoplasma* spp. may be primary pathogens. Aspergillosis is more common in dogs, and nasal cryptococcosis is seen more frequently in the cat. Animals with oronasal fistulas may have nasal discharge or epistaxis. Nasal

parasites are highly irritating and can cause severe epistaxis and intractable head rubbing and itching. Viral diseases rarely result in epistaxis in dogs, and cats with upper respiratory infections uncommonly develop chronic nasal discharge and sneezing that results in intermittent epistaxis. Allergic (eosinophilic) and lymphoplasmacytic rhinitis are uncommon immune-mediated phenomena that are often steroid responsive. Arteriovenous malformations can rupture, causing sudden-onset epistaxis.

63.6 DIAGNOSTIC PLAN

63.6.1 Complete Blood Count Including Platelet Count

Regenerative anemia indicates a bone marrow response to bleeding, but with chronic epistaxis, iron deficiency and a nonregenerative anemia may occur. Schistocytes are observed with microangiopathies that occur with hemangiosarcoma and DIC. Leukocytosis is anticipated with chronic inflammation or infection, and leukopenia suggests chronic ehrlichiosis, cytotoxic drug administration, or sepsis. Thrombocytopenia is the result of increased destruction or consumption, sequestration, or decreased production of platelets. Evaluation of a blood smear may be useful while awaiting laboratory results: normal dogs and cats have 8 to 29 platelets/100X oil immersion field. If the platelet count is 20,000/μL, approximately one platelet per oil immersion field is present. Macroplatelets suggest regeneration associated with peripheral platelet destruction or consumption; these platelets may be more functional than normal, explaining why dogs with platelet counts less than 10,000/μL often do not bleed.

63.6.2 Chemistry Profile

Panhypoproteinemia may develop with chronic blood loss. Hyperglobulinemia is associated with neoplasia or chronic infections, and serum protein electrophoresis helps to dis-tinguish between monoclonal or polyclonal gammopathy. Monoclonal gammopathies occur with multiple myeloma, chronic ehrlichiosis, lymphoma, leukemias, and macro-globulinemia. Evidence of renal, hepatic, or endocrine disease identifies general causes of disease that can cause or exacerbate epistaxis.

63.6.3 Urinalysis

Indirectly, the urine samples provide clues to potential causes of epestosis, such as bladder mucosal bleeding, and hematuria or glomerulonephropathies may be seen with thrombocytopenia and thrombocytopathia.

63.6.4 Hemostatic Studies

Buccal mucosal bleeding time (BMBT) is a useful in-hospital test of platelet function and is reliable if the platelet count is >100,000/μL. If this test is abnormal, searching for a cause of thrombocytopathia is indicated, including a von Willebrand's titer and evaluation for secondary causes of platelet function defects. Coagulation studies such as partial thromboplastin time (PTT), prothrombin time (PT), and activated clotting time (ACT) can be abnormal if the platelet count is <10,000/μL and should be considered in cases of epistaxis in which platelet abnormalities have been ruled out. If these coagulograms are abnormal, tests for specific clotting factors and a PIVKA (proteins inhibited by vitamin K antagonists) should be considered. A coagulogram should also include fibrinogen, fibrin degredation products (FDPs), and an antithrombin III level to examine for evidence of DIC.

63.6.4.1

Box • 63-1 Causes of Epistaxis

63.6.4.1.1

Systemic Processes ("Extranasal" Disease)

Thrombocytopenia (quantitative platelet abnormality)

- Decreased production
  - Infectious: Ehrlichiosis, feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), Rocky Mountain spotted fever, hepatozoonosis, septicemia, endotoxemia, leishmaniasis
  - Drugs: Cytotoxic drugs, modified live virus vaccines, estrogens
  - Neoplasia: Myelophthisis secondary to myeloproliferative or lymphoproliferative diseases
  - Immune-mediated: Antibodies against megakaryocytes
  - Other: Bone marrow aplasia, cyclic thrombocytopenia, myelofibrosis, hyperestrogenism (secondary to Sertoli cell and granulosa cell tumors), myelodysplasia, toxins, osteosclerosis, idiopathic
- Increased destruction
  - Immune mediated: Idiopathic or secondary to drugs, neoplasia, infection
  - Microangiopathy: Shearing of platelets; associated with hemangioma/hemangiosarcoma
- Sequestration
  - Neoplasia: Large vascular tumors
  - Splenomegaly or splenic torsion
  - Hepatomegaly
- Increased consumption

Disseminated intravascular coagulopathy (DIC)

Vasculitis: Rocky Mountain spotted fever, endotoxemia, neoplasia, heartworm disease, bacteremia

Hemorrhage-induced thrombocytopenia

Thrombocytopathia (qualitative platelet defect)

Congenital: von Willebrand's disease (vWD), platelet procoagulant activity deficiency in German shepherd dogs, Glanzmann's thrombasthenia in Great Pyrenees, Basset hound thrombopathia

Acquired: vWD (associated with hypothyroidism), uremia, dysproteinemia (associated with multiple myeloma, ehrlichiosis, leishmaniasis), drugs (NSAIDs)

Coagulation factor deficiency

Congenital: Hemophilia A and B, others

Acquired: Anticoagulant rodenticide toxicity, liver failure, DIC

Increased capillary fragility

Hypertension: Primary or secondary to chronic renal failure, glomerulonephropathies, pheochromocytoma, hyperadrenocorticism, hyperthyroidism, heart disease

Hyperviscosity syndrome: Secondary to multiple myeloma, ehrlichiosis, polycythemia (primary or secondary to hypoxia or neoplasia), leukemias

Hyperlipidemia

Thromboembolic disease

Neoplasia invading blood vessels

63.6.4.1.2 Local Processes (“Intranasal” Disease)

Trauma

Neoplasia

Epithelial: Adenocarcinoma, undifferentiated carcinoma, squamous cell carcinoma, polyps

Mesenchymal: Chondrosarcoma, fibrosarcoma, hemangiosarcoma, osteosarcoma, melanoma

Round cell: Lymphoma, transmissible venereal tumor, mast cell tumor

Infection

Fungal: *Cryptococcus*, *Aspergillus, Penicillium*, *Rhinosporidium*, *Exophiala jeanselmi*, phaeohyphomycosis

Parasitic: *Pneumonyssus, Eucoleus, Cuterebra*, *Linguatula*, *Capillaria*

Bacterial: Primary *(Bordetella, Pasteurella, Mycoplasma)* or secondary

Viral: Canine infectious tracheobronchitis, canine distemper, feline viral rhinotracheitis, calicivirus

Inflammation

Lymphoplasmacytic: Primary or secondary

Eosinophilic: Allergic rhinitis

Dental disease

Tooth root abscess

Oronasal fistula

Foreign body (FB)

Vascular malformation

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63.6.5 Serology

Ehrlichiosis and Rocky Mountain spotted fever are diagnosed with serology. *Aspergillus* titers are nonspecific and seldom useful. Latex agglutination tests for *Cryptococcus* capsular antigen are useful for diagnosis and therapeutic monitoring. Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) tests are indicated if the viral status is unknown. Thyroxine levels should be part of the minimal data base for cats over 6 years of age.

63.6.6 Imaging

Imaging studies are performed prior to rhinoscopy to avoid difficulties in interpreting iatrogenic lesions (i.e., bleeding induced by biopsy). Images should be examined for asymmetry and bone lysis, which can localize the disease, determine the severity of involvement, and guide biopsy procedures. Nasal radiographs should include lateral, oblique, open-mouth, ventrodorsal, intraoral, and frontal sinus views. Computed tomography (CT) is superior to radiographs for nasal disease because it allows visualization of bony and soft tissue lesions and it images all areas including turbinates, nasal septum, cribriform plate, and sinuses. Uptake of contrast material by tumors can distinguish them from mucus collections.

63.6.7 Rhinoscopy

If a coagulopathy has been ruled out as a cause for epistaxis, rhinoscopy is performed under general anesthesia (with a cuffed endotracheal tube in place) after imaging studies are completed. The least affected side should always be examined first, and the evaluation should begin ventrally and move dorsally in case of iatrogenic hemorrhage. Thorough evaluation of the oropharynx and oral cavity should be performed. Instruments including dental mirrors, spay hooks, and otoscopes provide limited visualization of the nasal cavity but may assist in the diagnosis of foreign bodies and large tumors. Rigid or flexible endoscopes are required for a full examination. The entire nasal cavity including the frontal sinuses (if possible) should be examined for masses, foreign bodies, fungal or inflammatory plaques, and polyps. The distance from the medial canthus to the end of the nostril should be marked on the instrument prior to entry into the nose to avoid penetrating the cribriform plate.

63.6.8 Nasal Swabs, Flushing, and Biopsy

Cryptococcus can be identified on cytology of nasal discharge with use of India ink. Flushing or biopsy of the nasal cavity is performed after the oropharynx has been packed with gauze sponges and the head is positioned ventrally to avoid aspiration of blood or fluid. A flexible endoscope or red rubber catheter retroflexed behind the soft palate may be used to flush saline through the nose. FBs may be retrieved, and parasitic ova may be evident on examination of the fluid. Biopsy should be performed after rhinoscopy, and it may be performed "blindly" if visualization of the nasal cavity is not possible. If lesions are not seen on imaging or rhinoscopy, multiple biopsies throughout the nose should be obtained. Biopsy instruments include alligator or pituitary-cup forceps, and should not be advanced past the medial canthus. Incisional biopsy or aspiration of hard palate defects or areas of facial deformity may be useful. Complications of nasal biopsy that should always be anticipated include life-threatening hemorrhage, aspiration of blood, and neurologic signs if the cribriform plate is violated.

63.6.9 Culture

Primary bacterial rhinitis is rare, but secondary infection is common. Nasal cultures may be obtained through nasal swabs, flush, or tissue culture; the latter is most likely to yield true representation of the nasal cavity flora. A superficial nasal swab is likely to yield growth of normal flora, including *Escherichia coli, Streptococcus* spp., *Pasteurella* spp., and others. The growth of only 1 to 2 species is more likely to represent an abnormality, whereas growth of multiple bacteria is usually normal flora; therefore, the laboratory should be advised to report all growth. Treatment with antibiotics may improve clinical signs and can give a false sense of disease resolution to the veterinarian. The growth of *Aspergillus* and *Penicillium* should be interpreted in light of other

findings such as fungal plaques and radiographic evidence of bony destruction to make a diagnosis of fungal rhinitis because these organisms may represent normal flora.

63.6.10 Blood Pressure

Blood pressure evaluation is indicated if hypertension is suspected as a contributing cause for epistaxis; it is commonly performed using indirect Doppler or oscillometric methods (see Chapter 28).

63.6.11 Exploratory Rhinotomy

If all other diagnostic procedures have failed to obtain a diagnosis or if an FB cannot be removed via rhinoscopy, exploratory rhinotomy may be indicated. Potential benefits of surgery must outweigh potential complications, including hemorrhage, subcutaneous emphysema, inadvertent entry into the brain, and recurrent nasal cavity infections.

63.7 TREATMENT

The goal of treatment is to control epistaxis until a definitive diagnosis and therapeutic plan can be determined. Treatments include cage rest, ice packs, and application of pressure. Sedation may aid in controlling hemorrhage. Sedatives such as diazepam and butorphanol at low doses may help to relieve anxiety, but caution should be used to avoid causing hypotension. In animals that have suffered trauma or are obtunded, suctioning blood from the oropharynx is indicated to prevent aspiration of blood. In severe cases, general anesthesia and packing the nasal cavity and oropharynx with dilute epinephrine-soaked (1:100,000) sponges or tampons, ligation of the external carotid artery on the affected side, or both might help to control bleeding. If a coagulopathy is suspected, transfusions are indicated. In thrombocytopenic animals, transfusions very rarely supply adequate platelet numbers to stop bleeding.

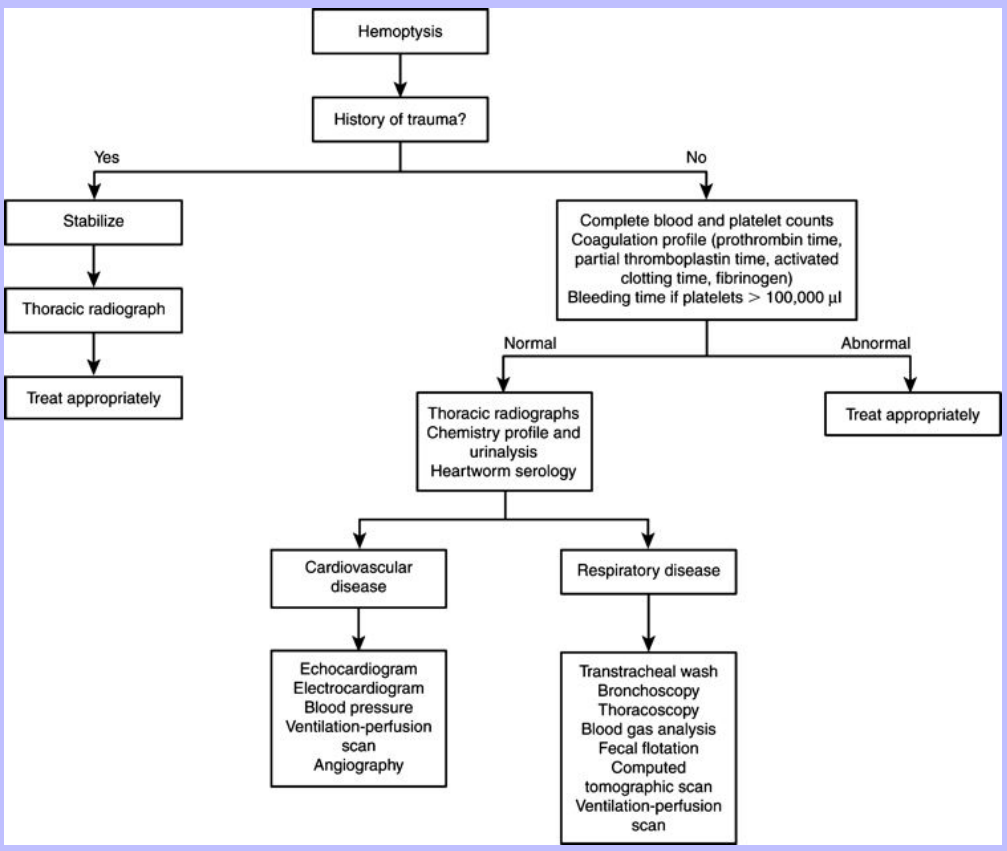
63.8 HEMOPTYSIS

Hemoptysis (from Greek *hamia,* "blood" + *ptysis,* "spitting") is defined as expectoration of blood or bloody mucus from the respiratory tract at or below the larynx. Detection and confirmation of hemoptysis may be difficult in dogs and cats because they do not expectorate after coughing. To direct the diagnostic and therapeutic process, it must be determined that the coughed up material is actually blood, the blood was coughed up and not regurgitated or vomited, and the blood originated from the lower respiratory tract. Hemoptysis is generally a serious condition that requires aggressive management. The following areas should be emphasized when evaluating a patient with hemoptysis (Figure 63-2).

63.8.1 History

Information regarding cardiac and pulmonary abnormalities, medications (including heartworm preventative), toxin exposure, and travel history are essential. The owner should be questioned regarding exercise intolerance, dyspnea, syncope, and cough in the patient. Animals that swallow blood from the upper gastrointestinal or respiratory tracts may experience hematemesis, which can be mistaken for hemoptysis. Prior bleeding episodes suggest a primary or secondary coagulopathy. Animals with a history of cough prior to onset of hemoptysis may have chronic diseases such as bronchitis, neoplasia, heartworm disease, or left-sided heart failure.

Figure 63-2 Algorithm for hemoptysis.



63.8.2 Signalment

Older dogs and cats are more likely to suffer from primary lung and metastatic neoplasia.

63.8.3 Environment

Dogs and cats in specific geographic areas are more susceptible to infections with heartworms and lungworms. Outdoor animals are more susceptible to trauma, anticoagulant rodenticide ingestion, and FB inhalation. Specific fungal diseases are endemic in limited regions.

63.8.4 Nature of the Expectorated Material

If the blood is mixed with sputum, suppurative lesions such as bronchopneumonia are likely; pulmonary edema often appears as blood mixed with pink frothy material; and bright-red blood is likely from an artery.

63.9 PHYSICAL EXAMINATION

A thorough evaluation of the cardiovascular and respiratory systems is essential to localize the condition. Care should be taken to avoid undue stress, and supportive measures such as oxygen therapy may need to be instituted prior to examination. Examination for coagulopathies should be performed as for epistaxis. Animals with systemic mycosis often have cutaneous or bony lesions.

63.10 DIFFERENTIAL DIAGNOSIS

Heartworm disease can cause hemoptysis in dogs and cats (Box 63-2). In dogs, exercise after adulticide therapy may result in worm embolization, inciting inflammatory lesions in the pulmonary vasculature and parenchyma and resulting in hemoptysis. Coagulopathies and platelet defects uncommonly result in airway mucosal bleeding. Cardiogenic pulmonary edema can result in expectoration of blood and pink froth. Pulmonary thromboembolism (PTE) (secondary to cardiac, endocrine, immune-mediated, gastrointestinal, and neoplastic disease) and 230
pulmonary hypertension (secondary to congenital or acquired cardiac malformations that result in abnormal 231
shunting of blood) uncommonly cause hemoptysis. Parasites including *Capillaria, Aelurostrongylus,* and *Paragonimus* species cause cavitated pulmonary lesions that rupture and bleed into airways. Chronic inflammatory conditions of the lung including heartworm disease, chronic bronchitis, bronchiectasis, and pulmonary infiltrate with eosinophils can result in inflamed and edematous mucosa that bleeds easily during coughing. Bacterial and fungal (*Blastomyces, Histoplasma, Coccidioides* spp.) pneumonia and lung abscesses may result in hemoptysis. Hemorrhage is a reported complication of transtracheal wash, lung biopsy, and bronchoscopy, and animals should be appropriately monitored after these procedures. Primary or metastatic neoplasia can result in erosion of pulmonary vessels. Blunt trauma or FB inhalation into the trachea or airways can result in hemoptysis. Rarely, ruptured arteriovenous malformations, bacterial endocarditis, and lung lobe torsions cause hemoptysis.

63.10.1 Box • 63-2 Causes of Hemoptysis

63.10.1.1 Pulmonary

Pulmonary thromboembolism: Secondary to neoplastic, endocrine, cardiac, metabolic disease

Pulmonary hypertension: Secondary to heartworm disease, congenital or acquired cardiac defects that result in shunting of blood

Chronic bronchitis/bronchiectasis

Bacterial pneumonia

Nocardiosis

Pulmonary abscess

Kennel cough (rare)

Fungal pneumonia: Blastomycosis, histoplasmosis, coccidiomycosis

Parasites: *Paragonimus kellicotti, Capillaria aerophila, Aelurostrongylus abstrusus*

Pulmonary infiltrate with eosinophils

Neoplasia: lung: Primary adenocarcinoma, undifferentiated carcinoma, squamous cell carcinoma, chondrosarcoma; metastatic; primary tracheal tumors

Lung lobe torsion

63.10.1.2 Cardiovascular

Heartworm disease

Cardiogenic pulmonary edema

Arteriovenous fistula

Bacterial endocarditis

63.10.1.3 Systemic

Coagulopathies: Primary (quantitative or qualitative platelet defects) or secondary hemostatic (factor deficiencies, anticoagulant rodenticide toxicity, disseminated intravascular coagulopathy [DIC]) abnormalities

Trauma: Pulmonary contusion, tracheal rupture, foreign body (FB)

Iatrogenic: Endotracheal intubation, complication of lung biopsy/aspirate, transtracheal wash, or bronchoscopy

63.11 DIAGNOSTIC PLAN

Measures must be taken to stabilize the animal and avoid undue stress during diagnostics. The minimum data base includes a complete blood count (CBC) with platelet count, chemistry profile, urinalysis, and three-view thoracic radiographs. The blood work should be evaluated for evidence of chronic bleeding, inflammation, infection, and systemic disease. Thoracic radiographs should be carefully evaluated for evidence of cardiac enlargement, pulmonary edema or contusions, pleural effusion, pneumonia, primary or metastatic neoplasia, signs of thoracic trauma such as broken ribs, foreign objects, and evidence of heartworm disease. A heartworm antigen test (and antibody test in cats) should be performed in animals not receiving heartworm preventative. Occasionally, malignant cells or fungal elements may be seen on microscopic evaluation of sputum. Examination of feces, sputum, or both for evidence of parasites may be indicated. Once the patient is as stable as possible, bronchoscopy may be performed if indicated to directly examine the upper airway, trachea, and bronchi, remove foreign objects, and perform bronchoalveolar lavage (BAL) and culture. Additional testing might include pulmonary arterial catheterization, ventilation-perfusion scan, arterial blood gas, coagulation giocardiogram fine needle aspiration or open biopsy of the lung, thoracoscopy, and CT scan of the thorax.

63.12 GOALS OF TREATMENT

Establishing a patent airway and intravenous fluid (once cardiogenic causes are ruled out), oxygen, or blood product administration should be instituted as needed until the underlying disease process can be identified. Most

commonly, hemoptysis is scant and self-limiting with cage rest and avoidance of stress. Antitussives may be indicated to decrease airway trauma from coughing, but sedation should be avoided because it increases the risk of aspiration of blood. If radiographs can localize bleeding to one lobe, the patient should be positioned with that side dependent. Broad-spectrum antibiotic therapy such as ampicillin and enrofloxacin or amoxicillin and clavulanic acid should be considered if bacterial infection is suspected (while cultures are pending) or as a prophylactic therapy to prevent pneumonia. If hemorrhage is uncontrollable, general anesthesia with suctioning of the airway, ventilatory support, or surgical intervention (or a combination of these treatments) may be indicated.

64 CHAPTER • 64 Petechiae and Ecchymoses

Mary Beth Callan

Superficial bleeding into the skin or mucous membranes is referred to as *purpura*. Purpura can be categorized as petechiae and ecchymoses. Petechiae are small pinpoint hemorrhages (<3 mm) resulting from extravasation of blood from capillaries, whereas ecchymoses are larger areas of hemorrhage resulting from leakage of blood from small arterioles and venules. Petechiae and ecchymoses are observed in primary hemostatic defects (i.e., platelet-vessel abnormalities). They represent a mild form of surface bleeding without external blood loss but may be associated with more serious hemorrhage. Both are commonly seen in dogs but rarely in cats.

64.1 PATHOPHYSIOLOGY

The vasculature is lined by a layer of endothelial cells that are linked by continuous and well-organized tight junctions varying in width from 0 to 4 nm. This provides a selectively impermeable membrane that prevents the passive transfer of blood into the extravascular space. The subendothelial matrix and additional layers of the vessels (media and adventitia) also act as barriers against extravasation of blood. Vascular integrity is influenced by many factors, one of which is platelets. Ultrastructural and functional changes develop in the vascular endothelium of thrombocytopenic animals, and these abnormalities are promptly reversed by a rise in the platelet count. However, the molecular basis for the observed changes remains unclear.

Thrombocytopenia (reduced platelet numbers), either as a sole hemostatic defect or as part of a combined hemostatic disorder, is the most common cause of petechiae and ecchymoses in dogs and cats. However, thrombopathias and vascular disorders may also cause capillary bleeding.

64.1.1 Thrombocytopenia

Thrombocytopenia may be a result of decreased platelet production by the bone marrow or increased platelet destruction, consumption, or sequestration. Frequently more than one mechanism is involved. For example, bone marrow suppression, consumption of platelets secondary to vasculitis, splenic sequestration, increased destruction of platelets by both immune-mediated and nonimmune-mediated mechanisms, virus-associated myelodysplasia, and myeloproliferative disorders may contribute to thrombocytopenia in dogs and cats with infectious diseases (e.g., ehrlichiosis, babesiosis, Rocky Mountain spotted fever, leishmaniasis, feline leukemia virus [FeLV], feline immunodeficiency virus [FIV]). In addition to infectious diseases, common underlying causes for thrombocytopenia include neoplasia, drug reactions, and immune-mediated disorders.

The most common cause of petechiae and ecchymoses in the dog is increased platelet destruction associated with immune-mediated thrombocytopenia (IMT), a disorder in which antibodies bound to the surface of the platelet results in premature removal by the reticuloendothelial system.

The bone marrow typically has normal to increased numbers of megakaryocytes. However, antibodies may also be directed against the megakaryocytes, resulting in decreased platelet production. Dogs suspected of having IMT should also be evaluated for hemolytic anemia, proteinuria, and polyarthritis. If any of these signs exist, systemic lupus erythematosus (SLE) should be considered. IMT occurs rarely in cats.

Increased sequestration of platelets resulting in thrombocytopenia has been observed in dogs with splenomegaly, hepatomegaly, and endotoxemia, as well as in experimental hypothermia. However, petechiae and ecchymoses are not typically observed as a result of sequestration of platelets.

64.1.2 Thrombopathia

Thrombopathias may be classified as inherited or acquired defects. Inherited disorders of platelet function have been identified in several breeds of dogs (e.g., Glanzmann's thrombasthenia of otter hounds and Great Pyrenees, δ-storage pool disease of American cocker spaniels) and a few cats. Spontaneous formation of petechiae and ecchymoses, mucosal surface bleeding, and excessive bleeding after surgery or trauma are common features of these disorders, and fatal hemorrhage has been observed in some affected dogs. Platelet function, as assessed by the bleeding-time test and various in vitro tests, may be affected by various systemic and hematologic disorders (e.g., uremia, liver disease, dysproteinemias) and by a large number of drugs. Although drugs of nearly every classification have been associated with acquired platelet dysfunction in humans, fewer drugs have been evaluated for adverse effects on platelet function in dogs and cats. Platelet dysfunction induced by aspirin, cephalothin, and acepromazine has been documented in vitro in the dog, but the in vivo effects of these drugs on platelet function are less clear. Nevertheless, it would seem prudent to avoid use of such drugs in dogs with known bleeding disorders.

von Willebrand disease (vWD), the most common inherited bleeding disorder in the dog, results from a reduction in the amount of functional plasma von Willebrand factor (vWF), leading to impaired platelet-vessel adhesion. vWD rarely causes petechiae, although ecchymoses may be observed in some dogs with vWD after trauma and surgical procedures. As with other primary hemostatic defects, typical signs of vWD include bleeding from mucosal surfaces (e.g., epistaxis, melena, hematuria) and excessive bleeding after surgery or trauma.

64.1.3 Vascular Disorders

In the absence of a quantitative or qualitative platelet abnormality, the presence of purpura suggests a vascular disorder. Vasculitis, secondary to infectious, inflammatory, immune-mediated, or neoplastic diseases or drug reactions, is the most common cause of vascular purpura. Some dogs with Cushing's disease are also prone to develop ecchymoses after minor trauma (e.g., cystocentesis), possibly as a result of increased protein catabolism leading to dermal and connective tissue atrophy and thus altered dermal vascular support.

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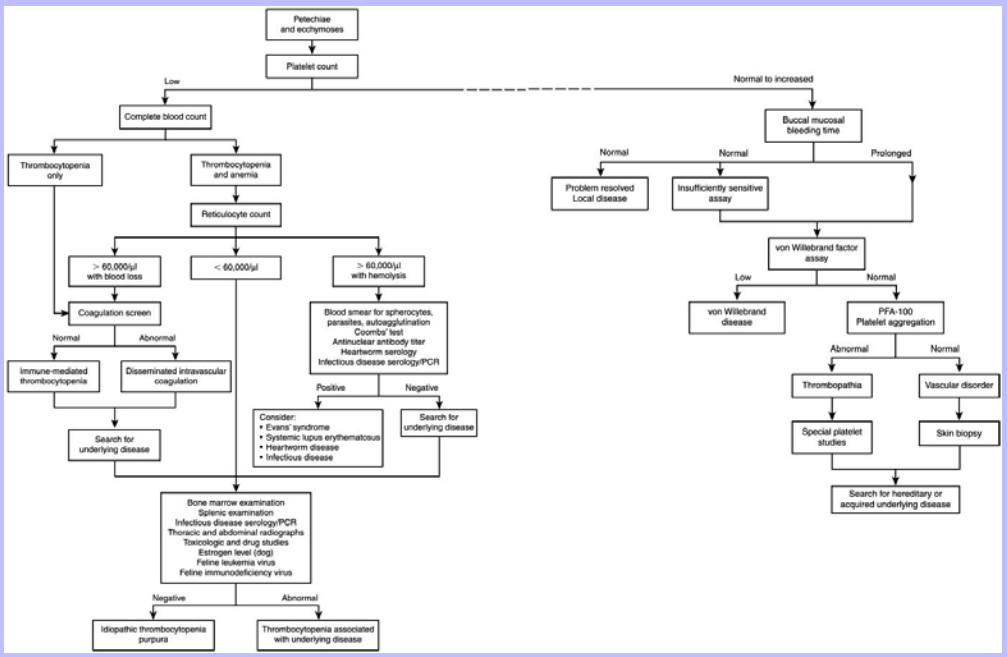
Figure 64-1 Algorithm for diagnostic approach to petechiae and ecchymoses.



64.2 PATIENT HISTORY AND PHYSICAL EXAMINATION

In a dog or cat with petechiae, ecchymoses, or both, the history may provide important clues as to the cause of the disorder. Given the many possible effects of various drugs on primary hemostasis (bone marrow suppression, immune-mediated thrombocytopenia, platelet dysfunction, and vasculitis), a complete medication history is imperative. Likewise, recent vaccinations, tick exposure, and previous or concurrent medical problems are relevant. A history of previous episodes of mucosal surface bleeding or purpura in an otherwise healthy animal or a family history of similar bleeding may be suggestive of an inherited thrombopathia.

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Given that thrombocytopenia, thrombopathia, and vascular disorders may be associated with an underlying disease, a complete physical examination is essential. Peripheral lymphadenopathy, hepatomegaly, or splenomegaly (or a combination of these abnormalities) may indicate an underlying infectious, inflammatory, or neoplastic disease. Petechiae are most readily found on mucous membranes of the gingiva, prepuce, and vulva, as well as on sparsely haired skin of the ventral abdomen and pinnae. After phlebotomy, ecchymoses are commonly observed around the venipuncture site.

64.3 DIAGNOSTIC APPROACH

Because thrombocytopenia is the most common cause of petechiae and ecchymoses, the initial laboratory evaluation should always include a platelet count (Figure 64-1). Although electronic particle counters can quickly and accurately perform platelet counts in dogs, blood smears should also be evaluated. However, cell-counting instruments with a threshold function to separate platelets and red blood cells (RBCs) by volume may not be accurate in the cat (considerable overlap exists between erythrocyte and platelet volumes), resulting in spuriously

low platelet counts. In addition, feline platelets tend to clump. A manual platelet count and evaluation of a blood smear are recommended for all cats (although platelet clumping may also lead to inaccurate manual counts) and for dogs in which the automated platelet count is low. In an emergency situation, evaluation of a blood smear to obtain an estimate of platelet number is sufficient; 10 to 20 platelets per oil immersion field are deemed adequate. Platelet counts are often less than 10,000/μL in dogs with IMT. In addition to providing an estimate of platelet number, evaluation of a blood smear may reveal evidence of RBC regeneration (polychromasia, anisocytosis, and macrocytosis), blood parasites, RBC agglutination, spherocytosis, or RBC fragments.

If the dog or cat is thrombocytopenic, evaluation of the complete blood count (CBC) to determine if other cytopenias are present will aid in formulation of a list of differential diagnoses and a focused diagnostic plan. Pancytopenia is most suggestive of bone marrow disease, whereas concurrent anemia and thrombocytopenia may be the result of blood loss anemia due to thrombocytopenia, immune-mediated destruction of both RBC and platelets, or bone marrow disease. Newly synthesized or reticulated platelets can be identified using the ribonucleic acid (RNA)–binding fluorescent dye thiazole orange and flow cytometry. Reticulated platelets lose RNA within 24 hours after entering the peripheral circulation. The percentage of reticulated platelets is typically increased in dogs with IMT. However, the absolute numbers may be within reference range because of the low total number of platelets. The assay for measurement of reticulated platelets is rapid and less invasive than obtaining bone marrow samples to evaluate thrombopoiesis and may be readily available through commercial diagnostic laboratories in the future.

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A bone marrow aspirate or biopsy is indicated in dogs and cats with pancytopenia, nonregenerative anemia and thrombocytopenia, persistent thrombocytopenia despite therapy, or atypical cells noted in the peripheral blood. A bone marrow aspirate is not necessary in all patients with IMT but should be considered when the platelet count has not increased within 5 to 7 days of initiating immunosuppressive therapy. Despite severe thrombocytopenia, excessive bleeding is rarely a complication of bone marrow aspiration or biopsy.

The buccal mucosal bleeding time (BMBT) evaluates only primary hemostasis or the platelet-vessel interaction. A BMBT is indicated in animals with petechiae and ecchymoses that are not thrombocytopenic. The BMBT is performed using a spring-loaded device that is standardized to produce uniform incisions. Simplate devices (Organon Tecknika Corp., Durham, NC) are available with one or two blades and produce incisions approximately 5 mm long and 1 mm deep (clinicians should not use blades with only 0.5 mm depth). Single-blade devices are recommended for cats and small dogs. Normal BMBT in the dog is less than 4 minutes and in the cat is less than 2 minutes. The effect of a low hematocrit (HCT) on bleeding time is often neglected, but ample evidence in the literature indicates an inverse relationship between HCT and bleeding time (the lower the HCT, the more prolonged the bleeding time) in humans with HCTs less than 25%. Altered rheologic properties of the blood and a reduced source of adenosine diphosphate (ADP) (RBCs release ADP) to activate platelets are mechanisms proposed for the prolongation of bleeding time in severely anemic patients. A prolongation of the BMBT in an animal with a normal platelet count and HCT suggests a thrombopathia, vWD, or a vascular disorder. Because vWD is much more common in the dog than intrinsic platelet function defects or vascular disorders, measurement of plasma vWF concentration is recommended before platelet function testing, particularly in dogs being evaluated for development of ecchymoses after surgery rather than for spontaneous formation of petechiae.

A point-of-care platelet function analyzer, the PFA-100 (Dade Behring, Miami, FL), assesses platelet adhesion and aggregation in citrated whole blood (800 μL per test sample) and provides results in less than 10 minutes. As with the BMBT, results of the PFA-100 are dependent on platelet count and HCT. This instrument, now available at a few veterinary teaching hospitals, has been useful in quickly identifying dogs with vWD and some thrombopathias, although measurement of plasma vWF concentration is necessary to differentiate these primary hemostatic disorders.

The cuticle bleeding time assesses both primary and secondary hemostasis and thus cannot differentiate between a thrombopathia and a coagulopathy. In addition, clipping the nail too short is painful. Finally, it is difficult to standardize this bleeding-time test, potentially providing misleading results. Therefore the BMBT is preferred to the cuticle bleeding time in the evaluation of animals with suspected disorders of primary hemostasis.

An activated clotting time (ACT), which assesses the intrinsic and common pathways of the coagulation cascade and thus provides similar information to the activated partial thromboplastin time (aPTT), is useful in ruling out a concurrent coagulopathy. Normal ACT in the dog is 60 to 110 seconds and in the cat is 50 to 75 seconds. In patients with severe thrombocytopenia (<10,000/μL), the ACT may be slightly prolonged by approximately 10 seconds because of decreased availability of platelet phospholipid to support coagulation.

64.4 TREATMENT

Medical management of patients with petechiae and ecchymoses varies widely. Treatment is aimed at the underlying disorder (e.g., rickettsial infections, neoplasia, immune-mediated diseases). Because IMT is the most common cause of severe thrombocytopenia in dogs with resultant formation of petechiae and ecchymoses, most thrombocytopenic dogs should be initially treated with doxycycline and prednisone pending results of diagnostic tests. In some cases, discontinuation of medications (e.g., methimazole, sulfonamides) may be all that is necessary to resolve the primary hemostatic disorder.

Dogs and cats with petechiae and ecchymoses as the sole form of bleeding rarely require blood transfusion support. However, if concurrent mucosal surface bleeding exists, particularly into the gastrointestinal tract, leading to anemia, transfusion of packed RBCs may be indicated to provide additional oxygen-carrying support. Platelet transfusions in the form of fresh whole blood, platelet-rich plasma, or platelet concentrate are indicated in life-threatening or uncontrolled bleeding. A small amount of bleeding into the brain, myocardium, lungs, or oropharynx could have devastating consequences without resulting in anemia. Platelet transfusions are generally not recommended in patients with IMT (unless uncontrolled or life-threatening bleeding occurs) because the transfused platelets have a short life span (typically destroyed within minutes to hours).

65 CHAPTER • 65 Electrolyte Disorders

David Church

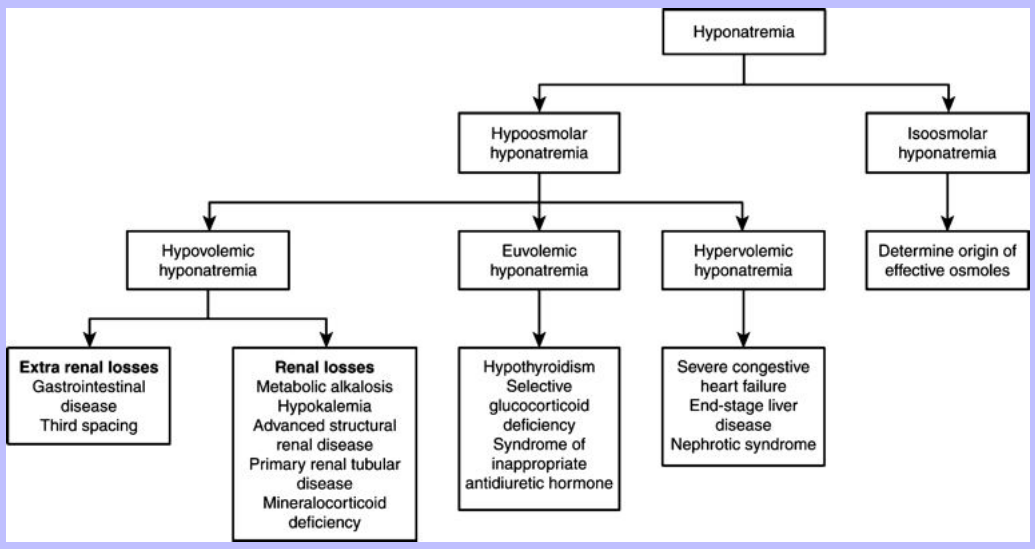
Disorders of electrolyte homeostasis are among the most frequently encountered challenges in small animal practice. An understanding of the underlying physiologic interactions is essential for a logical approach to their recognition and management (Figure 65-1).

65.1 DISORDERS OF CALCIUM METABOLISM

Only about 1% of total body calcium is freely exchangeable with the extracellular fluid (ECF). Maintenance of normal serum calcium concentration in the ECF is controlled by calcium itself through a specific receptor along with a number of hormones, the most influential of which are parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D_3 (1,25 D_3).

Calcium circulates in the ECF in three fractions. Approximately 50% exists in a biologically active, ionized form and 40% is protein bound, predominantly to albumin, although this proportion can be increased in alkalosis and decreased with acidosis. Additionally, factors that lower albumin can lower total serum calcium concentration without actually lowering the biologically active serum calcium concentration. For these reasons, measurement of serum ionized calcium is recommended in all patients suspected of having a clinically significant perturbation of serum calcium.

Figure 65-1 Algorithm for electrolyte disorders.



65.1.1 Hypercalcemic Disorders

The signs associated with hypercalcemia generally correlate with the magnitude and rate of change in serum calcium and include weakness, lethargy, polydipsia and polyuria, inappetence, and vomiting. Diarrhea, constipation, arrhythmias, seizures, and muscle fasciculations are uncommon.

Mild hypercalcemia can be present in young, large breed dogs and is a reflection of accelerated calcium turnover associated with rapid bone growth. Various degrees of hypercalcemia may occur artifactually (lipemia or sample contamination with detergent). It can be transiently associated with hemoconcentration, hyperproteinemia, hypoadrenocorticism, or severe hypothermia. Hypercalcemia can be a persistent, pathologic abnormality secondary to a number of diseases including malignant neoplasia, primary hyperparathyroidism, and renal failure. Other less frequently encountered associations include vitamin D intoxication, granulomatous inflammatory disease, and marked osteolysis. Over 50% of hypercalcemic cats reportedly have associated renal failure or malignancy; however, no explanation for the hypercalcemia could be found in 12% of these animals. Approximately 70% of hypercalcemic dogs are azotemic, with azotemia uncommon in those with primary hyperparathyroidism.

In cats and dogs with renal failure, hypocalcemia rather than hypercalcemia is generally observed. However, whenever hypercalcemia is present in a renal failure patient, one must determine if the impaired renal function is *due to* the hypercalcemia or the renal failure has *resulted in* the hypercalcemia. Hypercalcemia impairs renal function by reducing renal sensitivity to antidiuretic hormone (ADH). The reduction in ECF volume decreases glomerular filtration rate (GFR), which is exacerbated by calcium's direct vasoconstrictive effect on afferent glomerular arterioles. Furthermore, decreased renal tubular delivery of sodium increases tubular resorption of calcium and aggravates hypercalcemia. Consequently, any hypercalcemic scenario will tend to impair renal function by reversible processes that do not affect renal structure nor necessarily cause irreversible nephron loss.

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Hypercalcemia does, however, result in nephron destruction through tubular calcium phosphate deposition (so called nephrocalcinosis). Once sufficient nephrons are destroyed, this loss of functional renal mass will further impair renal function. Consequently, persistent hypercalcemia will eventually lead to significant structural renal disease.

Malignancy may cause hypercalcemia through secretion of calcemic factors by malignant cells. Many tumors produce either PTH or parathyroid hormone–related peptide (PTH-rP), which binds to PTH receptors and has similar bioactivity to PTH. Primary hyperparathyroidism is another recognized cause of hypercalcemia and is generally diagnosed by finding a mild-to-moderate hypercalcemia in dogs and cats with normal renal function and an inappropriately increased (midreference range to increased) intact serum PTH concentration. Granulomatous diseases may produce hypercalcemia due to granulomatous tissue conversion of 25 D_3 to 1,25 D_3.

Vitamin D toxicosis and hypercalcemia may be observed in animals oversupplemented with vitamin D analogues. Vitamin D intoxication can also occur with ingestion of cholecalciferol rodenticides, calcipotriol-containing psoriasis preparations, or plants containing calcitriol glycosides.

Hypercalcemia may also result from exposure to aluminum salts, vitamin A intoxication, various nonmalignant skeletal lesions, hyperthyroidism, and the administration of thiazide diuretics.

65.1.2 Hypocalcemic Disorders

Hypocalcemia occurs when calcium is lost from the ECF, often through renal mechanisms, in greater quantities than can be replaced by accelerated absorption from the intestine or bone depots. As with hypercalcemic disorders, falsely low levels of serum calcium due to hypoalbuminemia should be excluded by measuring serum ionized calcium concentration.

The clinical signs of hypocalcemia generally correlate with the magnitude and rapidity of the fall in serum calcium concentration. Manifestations of neuromuscular irritability predominate and include generalized muscle weakness with or without muscle fasciculation, which in severe cases may progress to tetanic spasms and even seizures. Cardiac manifestations include a prolongation of the QT interval that may progress to ventricular tachydysrythmias or various degrees of heart block.

Causes for hypocalcemia are extensive. Because calcium phosphate has a low solubility quotient, any condition that increases serum phosphate concentration such as release of large amounts of cellular phosphorous or acute impairment of renal function may result in a reduction in serum calcium concentration. In idiopathic disease after removal of a PTH-secreting tumor, a deficiency of PTH leads to increased renal calcium excretion and decreased intestinal calcium absorption, the latter secondary to reduced 1,25 D_3 production.

Hypocalcemia and hypomagnesemia frequently coexist and are often due to decreased absorption of dietary divalent cations. Hypomagnesemia impairs both PTH secretion and activity. A loss of extracellular calcium leading to hypocalcemia can occur with pancreatitis through the release of pancreatic lipase, degradation of retroperitoneal and omental fat, and binding of calcium in the peritoneum. Hypomagnesemia and hypoalbuminemia may also contribute to the hypocalcemia associated with acute pancreatitis. Other infrequent causes of hypocalcemia include endotoxic shock and dietary deficiency of vitamin D.

65.1.3 Disorders of Phosphate Metabolism

Plasma phosphate concentrations are relatively increased in young animals, decreasing to adult values by approximately 1 year of age. Phosphorous is predominantly absorbed from the gut by passive transport processes, although active transporters are stimulated by 1,25 D_3. Phosphorous is freely filtered by the glomerulus and more than 80% of the filtered load is reabsorbed in the proximal tubule. Proximal reabsorption occurs by passive transport coupled to sodium and is regulated mainly by phosphorous intake and serum PTH. Acute adaptation to a low-or high-phosphorous diet involves the insertion or retrieval of Na-P transporters from the brush border membranes of the renal proximal tubules, whereas chronic adaptation involves the synthesis of new transport proteins. PTH induces phosphaturia by inhibition of the Na-P cotransporters, thus its phosphaturic effect is diminished in phosphate deficiency. In addition, the renal tubules respond to dietary phosphate intake, although this effect is independent of plasma phosphate and PTH levels. The precise nature of the dietary phosphate signal is uncertain. In parallel with the antiphosphaturic effect of reduced dietary phosphate, an increase in bone resorption takes place leading to mobilization of phosphate and calcium from the skeleton. This renal tubular response to dietary phosphate means dietary restriction of phosphorous rarely leads to hypophosphatemia. However, hypophosphatemia can occur through internal redistribution, increased urinary excretion, decreased intestinal absorption, or combinations of all three.

65.1.4 Alterations in Sodium Metabolism

Although characterized by an abnormal sodium concentration, hypo-and hypernatremia generally reflect abnormalities in water balance that may or may not be accompanied by changes in sodium balance. Despite marked fluctuations in water intake and excretion, stable plasma sodium concentration is maintained by a complex interplay between osmoreceptors and baroreceptors, both of which control secretion of ADH, the primary physiologic determinant of the rate of free water excretion. The major stimuli to ADH secretion are hyperosmolality and depletion of the effective circulating volume. ADH-induced water retention lowers plasma osmolality and raises effective circulating volume. It is important to remember the physiologic response to hyperosmolality includes a second mechanism for modifying free water—the sensation of thirst mediated through the satiety centre. Although thirst is regulated centrally, it is sensed peripherally through sensory oropharyngeal receptors. The cessation of thirst is also mediated initially in the periphery by oropharyngeal mechanoreceptors that are stimulated by swallowing relatively large volumes of fluid.

65.1.5 Modification Due to Altered Osmolality

The osmoreceptors that govern ADH release are located in the hypothalamus and are activated by changes in intracellular water content and consequent alterations in intracellular osmolality. These changes in intracellular water content are determined by the levels of so called effective osmoles in both the intracellular and 237
extracellular compartment. Effective osmoles are those determinants of serum osmolality that do not readily 238
cross cell membranes. Because sodium has poor cell membrane permeability and is by far the most abundant cation in the ECF, the serum sodium concentration with its accompanying anions generally accounts for nearly all of the effective osmotic activity of the plasma and is the primary osmotic determinant of ADH release. An increase in serum sodium invariably predicts a hyperosmolar state. However, a subnormal serum sodium concentration does not always reflect hypo-osmolar conditions because the presence of significant amounts of other osmotically active substances can modify osmolality with resultant variable effects on serum sodium concentration. In these situations the hyponatremia is a reflection of translocation of intracellular water rather than an indication of hypo-osmolality.

65.1.6 Modification Due to Altered Effective Circulating Volume

The carotid sinus baroreceptors are pressure receptors that induce secretion of ADH from cells in the paraventricular nuclei of the hypothalamus. The relationship between mean arterial blood pressure and plasma volume means they also function indirectly as volume receptors. They are much less sensitive than osmoreceptors, although once activated they produce marked increases in ADH secretion that exceed those induced by hyperosmolality. Potential exists for interaction between the osmoreceptors and volume receptors. Volume depletion will potentiate the ADH response to hyperosmolality but can also prevent inhibition of ADH release normally induced by a fall in the plasma osmolality. Volume depletion is also a potent stimulus to the thirst center, with hypovolemic patients having persistent activation of the thirst center even in the presence of hyponatremia. In other words, volume and tissue perfusion are maintained at the expense of plasma osmolality.

65.1.7 Hypo-Osmolar Hyponatremia

Underlying all hypo-osmolar hyponatremic states is a limitation of urinary water excretion due either to secretion of ADH through nonosmolar mechanisms despite serum hypo-osmolality or impaired renal diluting ability. Consequently in animals with hyponatremia, once hypo-osmolality has been established, assessment of

the extracellular fluid volume allows each pet to be classified as hypovolemic, hypervolemic, or euvolemic. This classification can provide possible explanation or explanations for the hyponatremia.

Hypovolemic hyponatremia occurs with concurrent deficits of both total body sodium and total body water, with the former exceeding the latter. This occurs as a result of persistent ADH secretion in response to marked volume depletion with continued oral or parenteral hypotonic fluid intake. The reasons for the sodium depletion can be broadly divided into *extrarenal* or *renal* sodium losses. Extrarenal sodium losses are invariably due to gastrointestinal (GI) or third-space losses and are characterized by concentrated urine with minimal natriuresis.

The causes for renal sodium losses are more extensive. Some individuals with GI disease resulting in vomiting and metabolic alkalosis may have both extrarenal and renal sodium loss. Renal sodium losses may occur in these animals for a number of reasons. In a proportion of cases there may be an appreciable bicarbonaturia that, despite severe volume depletion, leads to natriuresis through attempts to maintain tubular electroneutrality. Furthermore, these dogs and cats may have concurrent hypokalemia that will interfere with renal sodium resorption and reduce osmoreceptor and thirst receptor sensitivity. The mineralocorticoid deficiency of hypoadrenocorticism will result in hypovolemic hyponatremia with marked natriuresis along with moderate to marked hyperkalemia and azotemia. In primary hypoadrenocorticism both the hypovolemia and the markedly increased secretion of ACTH provide a dual stimulus for ADH release regardless of the serum sodium concentration. Animals with advanced renal disease, primary renal tubular disorders, and osmotic diuresis all may have hypovolemic hyponatremia.

In hypervolemic hyponatremia, although total body sodium is increased, total body water is increased even more. This is an unusual occurrence in veterinary medicine, although it may be associated with severe cardiac or hepatic failure, nephrotic syndrome, and oliguric and anuric renal failure.

Euvolemic hyponatremia is an uncommon finding in small animal medicine, although theoretically it may occur in dogs and cats with glucocorticoid deficiency through nonspecific cosecretion of ADH with ACTH, as well as ADH-independent, glucocorticoid-mediated disturbances in renal hemodynamics. In man, euvolemic hyponatremia has been associated with hypothyroidism, postsurgical stress with overzealous hypotonic fluid administration, and the syndrome of inappropriate ADH secretion (SIADH) in which defective osmoregulation of ADH secretion through heightened osmoreceptor sensitivity takes place. In the most common form of SIADH in man, ADH release varies appropriately with serum sodium concentration; however, the threshold for ADH secretion occurs at an abnormally low osmolality.

The clinical signs induced by hyponatremia depend upon its severity and the rate of development. Although sodium remains above 130 nmol/L clinical signs are rare. When the serum sodium concentration decreases to <130 m/q/L, animals may have inappetence, vomiting, muscular weakness, and ataxia, whereas severe or acute hyponatremia may result in seizures and irreversible central nervous system (CNS) damage. Animals with an acute hyponatremia are at risk of developing permanent CNS damage through marked cerebral edema, whereas those animals with chronic hyponatremia are at risk of osmotic demyelination if the hyponatremia is corrected too rapidly.

65.1.8 Hypernatremia

The presence of hypernatremia represents a hyperosmolar state and may develop when water loss exceeds loss of sodium and potassium. Free water can only be lost from one of three places: (1) through the skin and respiratory tract (so called insensible water loss), (2) through the urine, or (3) through the gut. Urinary water loss requires impairment of either ADH secretion or end-organ sensitivity. Water loss through diarrhea is more variable. With diseases resulting in secretory diarrhea the fluid that is lost is iso-osmotic with plasma and is

almost entirely composed of sodium and potassium salts. Although the animal may become profoundly volume depleted, the plasma sodium concentration will remain relatively unaffected. In conditions resulting in osmotic diarrhea the fluid lost is again iso-osmotic; however, the nonreabsorbed solute accounts for most of the osmolality. Consequently, water loss markedly exceeds sodium and potassium loss, and hypernatremia and volume depletion occurs. Similar considerations may apply to urinary water loss induced by osmotic diuretics such as glucose or mannitol, although the tendency for hypernatremia to develop will be offset by the translocational effect of these effective ECF osmoles.

As the thirst center will normally be concurrently activated by the increasing osmolality, any hypernatremic tendency should be offset by increased water consumption. Consequently, hypernatremia usually requires not only increased loss of free water but also reduced water consumption. The latter is generally due to either reduced availability of water to an appropriately thirsty animal or impaired activation of the thirst center through neurologic pathology or dysfunction in the hypothalamic region that may be either a primary problem or secondary to intercurrent illness.

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65.2 DISORDERS OF POTASSIUM METABOLISM

Although sodium is primarily located extracellularly, roughly 98% of total body potassium is located within cells. Localization of sodium and potassium to the different fluid compartments is maintained by the Na-K ATPase cell membrane pump that actively pumps sodium from the cell and potassium into it in a ratio of two potassium ions for every three sodium ions.

65.2.1 Potassium Homeostasis

The plasma potassium concentration is predominantly determined by various homeostatic mechanisms controlling both internal and external balance, although total body potassium levels may have a modifying influence.

Internal potassium balance determines the ratio of intracellular to extracellular potassium and is influenced by many factors including extracellular pH, bicarbonate, insulin, glucagon, catecholamines, and osmolality. Acidosis and alkalosis are potentially potent influences on the internal balance of potassium. As H^+ ions move relatively freely across cell membranes, potassium tends to move in the opposite direction to maintain electrical neutrality. Consequently, ECF acidosis results in intracellular movement of H^+ ions and extracellular movement of K^+. The opposite occurs with alkalosis. Acidosis also inhibits Na-K ATPase activity, although this hyperkalemic effect is countered to some degree by an associated acidosis-induced reduction in the cell membrane's permeability to potassium.

Equally alkalemia, either metabolic or respiratory, promotes intracellular potassium entry although the effect tends to be relatively mild. A more potent hypokalemic effect may be seen with bicarbonate administration because plasma bicarbonate directly promotes intracellular potassium movement.

Various hormones including insulin, the catecholamines, and thyroxine may modify normal transcellular potassium balance. Insulin promotes potassium influx and sodium efflux from the cell through insulin's activation of the electroneutral Na^+/H^+ exchanger. Na-K ATPase then removes the resultant increase in intracellular sodium, with a consequent intracellular shift of potassium. In contrast, catecholamines lower plasma potassium by β_2 activation of membrane-bound adenylate cyclase and subsequent stimulation of Na-K

ATPase. Synthesis of Na-K ATPase is stimulated by thyroid hormone, and this effect can contribute to the hypokalemia of hyperthyroidism.

External potassium balance is predominantly determined by renal modification of kaliuresis based on a complex array of factors. Although the majority of filtered potassium is resorbed actively in the proximal tubule, regulation of potassium excretion predominantly occurs in the cortical collecting duct (CCD). The cells lining the CCD contain high numbers of Na-K ATPase pumps on their basolateral membranes and abundant numbers of potassium channels on their luminal surface. Altering the activity of the basolateral Na-K ATPase pumps or changing factors that encourage diffusion of intracellular potassium into the CCD through the luminal potassium channels can modify renal potassium excretion.

The most potent modifiers of renal potassium excretion include potassium intake, aldosterone, ADH, and the animal's acid-base status. In man, a chronic high potassium intake increases the number of basolateral Na-K ATPase pumps in the CCD (and in the colon), thereby facilitating increased renal and colonic potassium excretion. Aldosterone, ADH, and alkalosis increase kaliuresis by activation of both basolateral Na-K ATPase pumps and luminal potassium channels. Additionally the mechanism by which potassium and hydrogen may exchange for one another in the CCD favors renal potassium wasting in alkalosis and retention in acidosis. Luminal fluid flow rate and sodium content in the CCD will also influence renal potassium excretion. Sodium ions in the CCD tubular fluid are resorbed through luminal sodium channels down their concentration gradient, making the tubular fluid more electronegative and consequently increasing the tendency for intracellular potassium, through its luminal potassium channels, to move down both its concentration and electrical gradients into the CCD tubular fluid. This effect will be enhanced with increased tubular fluid delivery to the CCD.

65.2.2 Hypokalemia

Hypokalemia may develop as a postcollection artifact in some animals with a marked leukocytosis due to excess potassium uptake by the nucleated cells. Generally, however, hypokalemia reflects a breakdown in normal homeostatic mechanisms resulting in marked intracellular shifts or excessive losses of potassium.

A syndrome of fluctuating muscle weakness with concurrent hypokalemia has been reported in Burmese cats. The underlying cause for this condition is poorly understood, although it may be a result of dramatic intracellular shifts in potassium similar to the syndrome of familial hypokalemic periodic paralysis in man.

Insulin, catecholamines, and thyroxine all increase intracellular uptake of potassium, whereas accidental ingestion of barium compounds may cause hypokalemia by blocking potassium membrane channels and hence extracellular potassium movement. However, most commonly, hypokalemia is the result of either abnormal kaliuresis or GI losses associated with vomiting or diarrhea. As discussed previously, renal potassium loss will occur in any metabolic alkalosis, particularly if induced by selective chloride depletion due to vomiting, hypersecretory disorders of the upper GI tract, or both. The association is further enhanced because hypokalemia itself may play a role in the development and maintenance of metabolic alkalosis.

Additionally, primary hyperaldosteronism and various genetic abnormalities that influence the activity of renal ion transporters or activation and deactivation of cortisol in renal tubules may be rare causes of metabolic alkalosis and hypokalemia.

Increased urinary loss of potassium will also occur in several forms of metabolic acidosis in which concurrent increased distal tubular sodium delivery and flow takes place, as is seen with the osmotic diuresis associated with diabetes mellitus. The acidosis will tend to increase plasma potassium concentration and mask the tendency for depletion of total body potassium through kaliuresis. By increasing distal tubular sodium delivery,

the thiazide and loop diuretics, as well as larger doses of the intravenous penicillins, may cause hypokalemia. Aminoglycoside antibiotics, cisplatin, and amphotericin B all cause renal potassium loss through magnesium depletion. Hypomagnesemia can lead to potassium depletion and hypokalemia because it not only reduces intracellular potassium movement through impairment of Na-K ATPase activity but also leads to decreased potassium resorption in the loop of Henle and the CCD.

Hypokalemia can result in varying degrees of muscle weakness and enhanced myocardial excitability through activation of the normally inactive cell membrane sodium channels. Potassium depletion also may interfere with renal function. Diminished urinary concentrating capacity is a reversible consequence of hypokalemia and is due in part to impaired renal responsiveness to ADH through reduced expression of aquaporin-2 and decreased renal countercurrent function caused by impaired NaCl transport in the loop of Henle. In addition, these changes will result in an increased delivery of tubular fluid to the CCD and a consequent reduction in GFR.

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65.2.3 Hyperkalemia

Hyperkalemia may occur as a postcollection artifact. This is a particular problem in the Japanese Akita breed, although rare changes in plasma potassium concentration occur in other dogs or cats. Although the presence of hyperkalemia is a common finding in many diseases, it invariably reflects impaired renal function together with varying degrees of nonspecific tissue damage, cell destruction, and intracellular potassium release into the ECF. Conditions characterized by hyperkalemia include hypoadrenocorticism, primary hypoaldosteronism, malignant hyperthermia, thromboembolic disorders resulting in marked myonecrosis, and idiosyncratic reactions to angiotensin converting enzyme inhibitors and nonsteroidal antiinflammatory agents. Hyperkalemia can be associated with any form of renal failure although it tends to be more profound in conditions resulting in either acutely impaired renal function, or urethral obstruction.

The clinical signs that are directly referable to hyperkalemia include varying degrees of muscular weakness and disturbances in cardiac conduction. These signs are due to changes in neuromuscular conduction caused by reduced membrane excitability, a result of further inactivation of cell membrane sodium channels.

The clinical consequences of hyperkalemia are uncommon unless plasma potassium exceeds 7.5 mmol/L. However, substantial interpatient variation occurs because factors such as the plasma calcium concentration and acid base status can modify the toxicity of hyperkalemia.

65.3 DISORDERS OF MAGNESIUM METABOLISM

Magnesium is predominantly an intracellular cation, with only 1% of total body magnesium found extracellularly. Although the majority of filtered magnesium is resorbed in the proximal tubule and loop of Henle, magnesium regulation occurs through variable resorption in the distal tubule. Many hormones can influence renal handling of magnesium; however, the major regulator of reabsorption is the plasma magnesium concentration itself.

Depletion of total body magnesium can occur through GI losses associated with acute or chronic diarrhea, malabsorption, and/or steatorrhea. Some evidence suggests that Yorkshire terriers, collies, and German shepherds are more prone to developing hypomagnesemia with these types of enteropathies, and a recent report suggested hypomagnesemia was a common finding in Cavalier King Charles spaniels. Many other factors may contribute to hypomagnesemia, including increased intracellular movement of magnesium induced by alkalosis or insulin, impaired renal resorption, and the pharmacologic actions of various drugs.

Urinary magnesium loss is often the basis for magnesium depletion. Tubular resorption is related to urine flow, so long-term parenteral fluid therapy and volume expansion may result in magnesium deficiency. Hypercalcemia and calciuria reduce tubular resorption of magnesium, as does glucosuria or any cause for osmotic diuresis.

A close link exists between magnesium and potassium concentrations. Potassium depletion is associated with reduced distal tubule resorption of magnesium, magnesuria, and hypomagnesemia. Furthermore, hypomagnesemia produces secondary cellular potassium depletion, kaliuresis, and hypokalemia as a result of increased potassium secretion in the loop of Henle and the CCD. Finally, reversible hypocalcemia due to impaired PTH secretion and target tissue PTH insensitivity is a consistent finding with hypomagnesemia. Consequently, otherwise unexplained hypocalcemia and hypokalemia is highly suggestive of underlying magnesium depletion.

66 CHAPTER • 66 Intoxication versus Acute, Nontoxicologic Illness: Differentiating the Two

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Any acutely ill animal can present a diagnostic challenge if toxicosis is suspected but a clear recent history is not available. Common examples of such a situation include the pet that disappears and returns home with clinical signs or the found stray dog or cat that is ill. To address this challenge, this chapter presents common clinical problems that often are due to either intoxication or naturally occurring disease, and it highlights features of each to help elucidate the problem's cause in the absence of a medical history.

The categorization of toxicants and illnesses presented in this chapter is based solely on the patient's predominant clinical sign or abnormality. For management of suspected intoxications prior to the onset of overt signs or for details of specific diseases or intoxications, the reader is referred to the chapters indicated in each section and the references listed at the end of the chapter.

In general, intoxications probably are more likely in individuals known to be susceptible to ingestion (dogs or cats that are known to chew or swallow foreign material). Whether this behavior exists should be established as an initial part of the history whenever possible.

66.1 CENTRAL NERVOUS SYSTEM ALTERATIONS AND SEIZURES

Many intoxications are systemic and thus produce diffuse effects, such as central nervous system (CNS) alterations and seizures (see Chapter 48). Therefore in general, an interictal neurologic exam that reveals asymmetrical CNS deficits is inconsistent with ongoing toxicity.

With *lead* toxicity, such as from ingestion of paint chips, lead ornaments, or fishing weights, the onset of CNS signs and seizures may begin within a few days after the ingestion. Other signs of lead toxicity can include anorexia, vomiting, diarrhea, or constipation. Due to poor bioavailability, lead that is not ingested (e.g., gun pellets embedded in the tissues) almost never causes toxicity. In lead toxicity, basophilic stippling (25%) and nucleated red blood cells (RBCs) (54%) occur more often than anemia (8% of cases) and radiographic signs of metal in the gut (20%). Seizures that occur with *metaldehyde* (snail and slug bait) toxicity are distinctive in their speed of onset (30 minutes to 6 hours after ingestion) and in the prominent muscle tremors they generally produce, often resulting in marked hyperthermia (>106° F) that should be treated with cooling measures, not antipyretic drugs. A sweet, acetone-like smell of the vomitus or the whole animal may be apparent to some clinicians. Metaldehyde-induced seizures tend to respond well to antiseizure medications (high doses may be necessary). Clinical signs generally last 1 to 2 days, but acute hepatic damage can occur 24 to 48 hours later. Seizures induced by such *tremorgenic mycotoxins* as penitrem A or roquefortine occur within a few hours of consumption of moldy refrigerated foods or organic debris. Hypersalivation and vomiting commonly precede the seizures, and severe muscle tremors causing hyperthermia are also common. Uncomplicated cases resolve in 2 to 3 days. A similar syndrome occurs with ingestion of certain *blue-green algae* (see following discussion of acute hepatic damage). *Organophosphate*-and *carbamate*-induced of seizures very often occur with concurrent cholinergic signs, including vomiting, profuse diarrhea, hypersalivation, and increases or decreases in muscle tone, heart rate, or pupil size (though pupils remain symmetrical). Onset of signs is usually within minutes to a few hours of ingestion. Low blood cholinesterase levels (human or veterinary laboratory) are diagnostic. In dogs, *chocolate* toxicity that leads to seizures usually

does so within 12 hours of ingestion. Signs that precede the seizures commonly include polydipsia (PD), vomiting (brown color), tachycardia, and restlessness. *Marijuana* toxicity typically first produces CNS depression; vomiting, hypersalivation, and vocalization also occur. Rapid confirmation of toxicity is possible with over-the-counter (OTC) illicit drug test kits or by submitting a urine sample to a human hospital. The presence of anuria, azotemia, or a high osmole gap raises the possibility that seizures could be due to *ethylene glycol* toxicity (see discussion of acute renal failure that follows). Large ingestions of *ethanol* or *methanol* (distilled alcohol; fermented foods or grains) may terminally cause seizures, often preceded by vomiting, CNS depression, ataxia, disorientation, and coma.

Naturally-occurring illnesses that cause CNS alterations and seizures include *head trauma* (signs of blunt or penetrating injury should be present if trauma alone is causing seizures), *meningitis* (asymmetrical deficits during interictal period, neck pain, or papilledema on fundic exam would increase likelihood; cerebrospinal fluid [CSF] tap for diagnosis), *hydrocephalus* (persistent fontanelle may or may not be an indicator but allows transcranial ultrasound for diagnosis), *intracranial neoplasia* (more likely than intoxication if asymmetrical neurologic deficits are present during interictal period), *congenital portosystemic shunts* (PSS); (majority of symptomatic patients <6 months of age; concurrent cryptorchidism suggestive of PSS; liver commonly small on radiographs; pre-and post-prandial bile acid levels with or without skilled ultrasonography are most valuable for diagnosis, but if icterus, ascites, or very high liver enzyme elevations are present, PSS alone is unlikely), *rabies* (unvaccinated status, endemic area, and possible exposure to wildlife increase likelihood; fresh bite wounds are not usually relevant to seizures because rabies virus incubation period is at least 2 weeks), and *canine distemper* (fundic lesions, “hard pad disease” increase likelihood; if present, signs of conjunctivitis, rhinitis, or gastroenteritis are *not* usually from distemper once seizures are occurring; indirect fluorescent antibody [IFA] test for diagnosis). 242
Hypocalcemia (measure blood calcium) and *hypoglycemia* (measure blood glucose) should be ruled out 243
immediately in all seizuring patients because they are common, rapidly controllable causes of seizures. Sustained, profound *bradycardia* (e.g., <40 beats/minute for large dogs, <80 beats/minute for cats or small dogs) may cause syncope, progressing to cerebral hypoperfusion and seizures; heart rate should be measured during examination and on an electrocardiogram (ECG) if necessary. *Idiopathic epilepsy* remains the diagnosis of exclusion for recurrent seizures of unidentifiable cause.

66.2 MUSCLE WEAKNESS, PARESIS, AND FLACCID PARALYSIS

Weakness, paresis, and paralysis caused by intoxications tend to be symmetrical and diffuse, whereas a regional distribution may be observed with nontoxic causes. When it occurs, progression from weakness to paresis and paralysis is often quite rapid (hours) and uninterrupted with intoxications; it may be much slower or even chronic or malingering (e.g., wax-wane) with nontoxic causes. (For more on muscle weakness, paresis, and flaccid paralysis, the reader is referred to Chapter 46.)

Coral snakes (Southwestern, Southern United States and southward) can inflict a bite that produces paresis and paralysis within hours. Concurrent dysphagia and dyspnea are common, causing overlap in signs with botulism. However, coral snake bites usually cause swelling at the site of envenomation and may cause such additional signs as muscle fasciculations, vomiting, hypersalivation, and anemia with hemoglobinuria due to hemolysis. Bites of *black widow spiders* (*Latrodectus* spp.) throughout the United States typically cause an onset of signs within 8 hours of the bite. Muscle fasciculations, salivation, and generalized weakness, followed by flaccid paralysis can be observed. Such *phenoxy herbicides* as 2,4 D can cause muscle weakness and paresis within 24 hours of exposure. These common household herbicides can be absorbed by animals walking through wet, recently-treated lawns and usually cause other signs including vomiting, diarrhea, occasionally hepatic damage, and possibly may induce muscle rigidity. Dogs that ingest *macadamia nuts* (>1 to 2g/kg body weight) may show diffuse muscle weakness

and ataxia within 12 hours of ingestion and for 1 to 2 days' duration. Vomiting commonly occurs first, and depression, muscle fasciculations, and hyperthermia may occur concurrently.

Medical differential diagnoses for diffuse muscle weakness, paresis, and flaccid paralysis include *acute polyradiculoneuritis/coonhound paralysis* (diffuse muscle pain fairly common), *tick paralysis* (ticks may or may not be present [e.g., *Dermacentor* spp. in North America, *Ixodes* spp. in Australia]), *botulism*, and *myasthenia gravis* (acetylcholine receptor antibody test required for diagnosis; edrophonium test less commonly rewarding; weakness may classically be exercise induced and rest responsive, or it may be profound and continuous). Disorders not affecting the neuromuscular system directly, such as *joint pain* (suggested by joint swelling, resentment to manipulation of joints, and radiographic and cytologic abnormalities) or *aortic thromboembolism* (more likely if cyanosis of nail beds, absent pulse, cool extremity of affected limb, heart murmur, gallop sound, or cardiac arrhythmia are present) may also produce clinical signs appearing to suggest weakness. Such systemic disorders as *hyperviscosity* (evaluate hematocrit, serum globulins), marked *hyponatremia* (measure serum sodium), and *hypokalemia* (measure serum potassium) may also cause these signs. Diffuse muscle weakness can be caused by *profound anemia* (measure hematocrit) or such systemic disorders as *severe hypovolemia* (more likely if poor pulse quality, cool extremities, and tachycardia are present), or *marked hypo-* or *hyperthermia* (body temperature should be checked), all of which can alter mental alertness along with the weakness. Finally, degenerative spinal cord diseases such as *degenerative myelopathy* may cause ataxia and weakness; however, in most cases the hindlimbs are predominantly (or solely) affected and patients tend to be older, larger dogs, often with evidence of chronicity (e.g., worn dorsal toenails) if signs are severe.

66.3 ACUTE BLINDNESS

With massive ingestion of *salt,* severe mentation changes (profound mental depression, seizures) are expected simultaneously if blindness is present, as well as extreme hypernatremia (serum Na >180 mEq/L). Accidental ingestion of *horse dewormers* containing ivermectin or similar compounds (moxidectin) by dogs can cause acute blindness that is usually reversible, may last for a few days, and is accompanied by ataxia, tremors, shaking, CNS depression, or seizures. Differentiation from nontoxic causes is difficult and relies on the possibility of exposure (e.g., rural setting, horses in region); resolution is possible with supportive care. (For more on acute blindness, the reader is referred to Chapter 26.)

Medical differential diagnoses for acute blindness include *trauma* (more likely if signs of blunt or penetrating injury to the head or face, or obvious corneal, conjunctival, or scleral lesions are present); *retinal hemorrhage* or *detachment* (fundic exam; blood pressure measurement; assessment of coagulation if signs of coagulopathy); *glaucoma* (tortuous conjunctival vessels and corneal haze are common; intraocular pressure >30 mm Hg is diagnostic); acute onset of *cataracts* (presence of diabetes mellitus increases likelihood; ocular exam); *optic neuritis* (fundic examination; possibly CSF tap); *other disorders of the optic nerves, optic chiasm, optic radiation, or occipital cortex* (increased likelihood with other intracranial signs; CSF tap, imaging for diagnosis, or both); and *sudden acquired retinal degeneration* (electroretinogram for diagnosis).

66.4 ORAL MUCOSAL LESIONS

Ingestion of such substances as *corrosive acids* (e.g., some toilet cleaners, drain openers, antirust compounds), *alkalis* (e.g., alkaline batteries, bleaches, homemade soaps), *cationic detergents* (e.g., disinfectants, fabric softener sheets), *liquid potpourri* (more commonly in cats), or *formaldehyde* can cause mucosal injury and oral ulcers when ingested. Induction of vomiting is usually contraindicated, to avoid chemical esophagitis. (For more on oral mucosal lesions, the reader is referred to Chapter 219.)

Medical differential diagnoses for oral mucosal lesions include *uremic stomatitis* (more likely with abnormal kidneys on palpation, especially if azotemia and inadequately concentrated urine also are present), *periodontal disease* (usually concurrent with severe dental calculus; distribution of lesions more along gingivae and cheeks than tongue), *trauma* (e.g., persistence of foreign body such as porcupine quills), chewing on *electrical cord* (often including other signs of electrocution, such as mentation changes, dyspnea from noncardiogenic pulmonary edema; oral lesions commonly linear or regional, rather than multifocal), *systemic lupus erythematosus* or other autoimmune diseases (ulcerations most commonly at mucocutaneous junction; other cutaneous and systemic signs common), *feline calicivirus* infection (unvaccinated cats more susceptible; often, concurrent nasal congestion or purulent nasal with or without ocular discharge), *candidiasis* (cytology), or *feline leukemia virus* (FeLV) or *feline immunodeficiency* virus (FIV) infection (other signs possible; serologic tests).

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66.5 ACUTE RENAL FAILURE

Ethylene glycol intoxication may first manifest with signs mimicking drunkenness, followed by weakness, ataxia, vomiting, recumbency, and seizures. Metabolic acidosis may be detectable within 1 to 2 hours of ingestion, hyperglycemia by 3 to 9 hours, and hyperkalemia and hypocalcemia by 6 to 9 hours. Serum urea and creatinine (CR) elevations are usually first apparent only 12 hours postingestion. Ethylene glycol intoxication can be suspected with an osmole gap greater than 15 mOsm/μL (osmole gap = measured serum osmolality – [2X (Na+K) + blood urea nitrogen (BUN)/2.8 + glucose/18]; for Système International Units [outside United States], osmole gap = measured serum osmolality – [2X (Na+K) + BUN + glucose]); an elevated osmole gap typically is detectable within 1 to 2 hours of ingestion of ethylene glycol. Confirmation is with a veterinary test kit or by submitting a urine or blood sample to a veterinary or human hospital laboratory for ethylene glycol analysis. In dogs, acute renal failure caused by ingestion of *grapes* or *raisins* typically manifests with vomiting within a few hours of ingestion, followed by polyuria (PU) and PD, depression, anorexia, and signs of abdominal pain. The vomitus can be informative (visible traces of grapes or raisins). Signs of renal failure occur in the subsequent 24 hours, and some have responded to supportive treatment (a few days to 3 weeks). Pancreatitis can occur concurrently. In cats, ingestion of *lilies* (Easter lily *[Lilium longiflorum]*, tiger lily *[L. tigrinum]*, *L. rubrum*, Japanese showy lilies *[L. speciosum*, *L. lancifolium]*, or day lily [*Hemerocallis* spp.]) can cause acute renal failure. Vomiting, anorexia, and depression occur 2 to 4 hours postingestion, and azotemia and isosthenuria occur 24 to 72 hours later.

Medical differential diagnoses for acute renal failure include *renal infiltration* as with lymphoma (kidneys often enlarged on palpation; ultrasound and cytology [and/or biopsy] for diagnosis), *renal thromboembolism* (more likely with procoagulant states; Doppler ultrasound of renal vessels to assess), *pyelonephritis* (urinalysis may reveal evidence of urinary tract infection; ultrasound, urine culture indicated), and *end-stage chronic renal failure* (azotemia, nonregenerative anemia, isosthenuria, and negative urine culture are needed to make this diagnosis). (For more on acute renal failure, the reader is referred to Chapter 258.)

66.6 ACUTE HEPATIC DAMAGE

Mushroom poisoning (e.g., *Amanita phalloides*) may cause acute hepatic damage in dogs 1 to 2 days postingestion; these signs usually follow acute vomiting, diarrhea, signs of abdominal pain, and anorexia that begin a few hours after ingestion. Similarly, ingestion of *blue-green algae*, usually from drinking pond water, produces acute vomiting, diarrhea, and signs of abdominal pain within 6 hours, progressing to intrahepatic hemorrhage, hypovolemic shock, and acute liver failure in hours to days depending on dose and type of algae. The patient's muzzle should be inspected because in some cases the exposure and diagnosis are strongly aided by the finding of algae around the lips or nose. *Iron* toxicity, most commonly from the ingestion of an overdose of

multivitamins, may first produce signs of gastrointestinal (GI) disturbance, followed by apparent recovery for a few hours, and then progressive weakness and possibly shock. Signs of liver failure occur 1 to 2 days later. The iron in vitamins is not radiographically detectable as metal. Iron toxicity produces elevated serum iron levels, usually more than the total serum iron–binding capacity. Ingestion of any part of the *sago palm* or *cycad palm* (*Cycas* spp.), native to the Southwestern United States, can cause acute GI disturbances, followed by signs of acute liver failure 1 to 3 days after ingestion. Some dogs also show such neurologic signs as weakness, ataxia, depression, or seizures. All parts of the plant are considered toxic, especially the seeds (1 to 2 of which can be lethal to an average-sized dog), and mortality in dogs in general is high (33%). (See also Chapters 227, 228, and 230.)

Medical differential diagnoses for liver failure include acute systemic processes such as *sepsis* (suggested by the presence of a focus of infection, elevated white blood cell [WBC] count, left shift and toxic changes on complete blood count [CBC]); *heat stroke* (elevated body temperature); *leptospirosis* (renal failure often concurrent; serology); *heartworm caval syndrome* of dogs (likelihood dependent in part on geographic location; heartworm antigen test positive; heartworms may be seen in right heart or cavae on echocardiogram); *trauma* (more likely with signs of trauma elsewhere on patient; hemoabdomen, fractures possible); and advanced cases of primary hepatobiliary disorders including *hepatic lipidosis* of cats (more common in obese cats; abdominal ultrasound shows diffusely hyperechoic liver; biopsy should be done to confirm); *cholangitis, cholangiohepatitis,* and *lymphocytic portal hepatitis* of cats; *chronic hepatitis* of dogs (in advanced stages, microhepatica possible on radiographs or ultrasound; ascites possible [pure transudate]; see previous discussion of CNS alterations.) In general, ultrasound evidence of marked microhepatica, a markedly nodular liver, or ascites that is a pure transudate (or a combination of these factors), are suggestive of chronic liver disorders or infiltrative liver disease rather than acute toxicity. Similarly, normal liver enzyme values (alanine aminotransferase [ALT], aspartate transaminase [AST], alkaline phosphatase [ALP]) may occur with liver failure originating from longstanding, naturally occurring liver disorders (e.g., PSS, chronic hepatitis) but are inconsistent with acute, toxic causes of liver failure. Ultimately, in the absence of a medical history, persistent signs of hepatopathy for more than several days despite supportive care warrant a liver biopsy to further pursue the diagnosis.

66.7 SEVERE ANEMIA

Ingestion by dogs of *onions* or *garlic* (as little as 3.5 oz of minced onions in a 25 lb [11 kg] dog), *zinc* (ingestion of U.S. pennies minted in 1983 or thereafter or galvanized nuts or cage wires), or *naphthalene mothballs* (one mothball for a medium-sized dog can cause signs; breath may smell like mothballs can all acutely produce GI signs), followed by Heinz body hemolytic anemia and hemoglobinuria within 1 to 2 days of ingestion. In cats, *acetaminophen* causes methemoglobinemia, Heinz body anemia, and hemolysis. Severe anemia of toxic origin may also come from blood loss caused by *anticoagulant rodenticide* ingestion, in which case overt signs of hemorrhage (e.g., melena, epistaxis, hematuria) may be present, or dyspnea (pulmonary hemorrhage, airway hematoma) or lethargy (hypovolemia, anemia) may be dominant features. Suspicion of the latter diagnosis comes from these signs together with failure of blood to clot in vitro or bruising after venipuncture or handling. Hematocrit may or may not be decreased depending on acuity and severity of blood loss. A markedly increased prothrombin time (PT) is highly suggestive of anticoagulant rodenticide toxicity. (For more on severe anemia, the reader is referred to Chapters 59, 270, and 271.)

Medical differential diagnoses for severe anemia include traumatic overt blood loss (physical exam); GI blood loss (more likely in presence of feces with melena; hematochezia; or vomitus with black flecks of digested blood or strong positive reaction on blood square of urine dipstick); bleeding abdominal mass (more common in larger breed, older dogs; palpable abdominal mass or abdominal fluid wave [or both]; ultrasound and abdominocentesis for confirmation); immune-mediated hemolytic anemia (IHA) (spherocytosis, positive Coombs' test, in-saline

autoagglutination are all more suggestive of IHA); immune-mediated thrombocytopenia (thrombocytopenia often marked [<30 k]); ehrlichiosis (anemia classically with neutropenia, thrombocytopenia, and hyperglobulinemia, but variable; titers or polymerase chain reaction [PCR] to pursue the diagnosis); *Mycoplasma hemofelis* infection in cats (formerly *Hemobartonella felis;* seen on blood smear; may be incidental finding only); feline leukemia (FeLV test); hookworms (fecal flotations; evidence of regeneration, iron loss; empiric deworming); chronic renal failure (often small kidneys; azotemia with isosthenuria); and other neoplasia (thoracic radiographs may reveal mass, effusion, or metastases; abdominal palpation or ultrasound may reveal intestinal thickening or mass; if present, biopsy should be considered to confirm). With the exception of intoxications causing aplastic anemia, anemias of toxic origin tend to be regenerative, whereas anemias of several days' duration or more that show no evidence of regeneration are unlikely to be caused solely by ingestion of the toxins listed previously.

66.8 CARDIAC ABNORMALITIES

Substances with toxic effects on the heart include the plants *foxglove* (*Digitalis* spp.), *lily of the valley* (*Convallaria* spp.), *oleander (Nerium oleander)*, *azalea* and other *Rhododendron* spp., *mistletoe (Phoradendron)*, and yew (*Taxus* spp.); as well as bufo toads (*Bufo* spp.). These toxins produce cardiac effects that manifest mainly as cardiac arrhythmias such as premature atrial or ventricular complex, as opposed to causing structural heart disease like valvular regurgitation. Therefore physical abnormalities from the previously listed intoxications commonly include lethargy or weakness associated with an irregular pulse and heart rhythm, perhaps a weak pulse, or syncope and collapse; monitoring of these patients begins with continuous ECG. Signs of structural heart disease such as valvular regurgitation (e.g., heart murmur) are almost never due to intoxication alone. (For more on cardiac abnormalities, the reader is referred to Chapter 202.)

Medical differential diagnosis for cardiac arrhythmia would include *automobile trauma* (physical exam or radiographic evidence of recent trauma); *gastric dilatation* and *volvulus* (physical examination; abdominal radiographs); such metabolic disturbances as *anemia*, *hypokalemia*, *acidosis*, or *hypoxia; abdominal mass* (palpation, radiographs, ultrasound), and *primary heart disease* including cardiomyopathy, advanced valvular heart disease, congenital heart disease, or heartworm (heart murmur, cardiomegaly on radiographs, or congestive heart failure would increase likelihood of primary heart disease as cause of arrhythmia).

66.9 GASTROINTESTINAL (GI) SIGNS

Many intoxications provoke vomiting as an initial manifestation before producing additional clinical signs. (The reader is referred to the previous sections of this chapter for information on GI signs occurring jointly with chief complaints or problems already discussed). In addition, ingestion of *arsenic* (in some ant baits and some herbicides; urinary arsenic concentration >1 ppm is diagnostic [human hospital laboratory]); *castor beans* (*Ricinus communis*: colorful, 6 mm seeds often incorporated into jewelry as beads; vomiting usually begins within 6 hours of ingestion); nitrogen-phosphorus potassium [NPK] *fertilizers; calcium oxalate-containing plants* (e.g., elephant's ear [*Caladium* spp.], dumb cane [*Dieffenbachia* spp.], and peace lily [*Spathiphyllum* spp.]; oral mucosal swelling a common occurrence with ingestion); *zinc oxide* (skin ointment either licked off the skin or eaten from a chewed tube); or *zinc phosphide* (gopher bait; concurrent pulmonary edema common; onset of signs within 15 minutes to 4 hours of ingestion; odor of rotting fish [phosphine gas] suggests hazard to veterinary personnel) may all initially produce GI abnormalities. (For more on GI signals, the reader is referred to Chapters 33, 35, 38, and 39.)

Medical differential diagnoses include *gastroenteritis* of unknown cause (self-resolving in 24 to 72 hours with minimal supportive care); *parvoviral enteritis* (fecal parvovirus test positive; leukopenia common; dog often unvaccinated); *small intestinal infiltration* (more likely if intestine is palpably thickened or with weight loss; abdominal lymph nodes may be enlarged; ultrasound may show bowel thickening; biopsy should be done for

diagnosis); *GI obstruction* such as with a foreign body, mass, or intussusception (palpable mass with or without discomfort; abdominal radiographs may suggest obstruction; *pancreatitis* (ultrasound can show abnormal pancreatic echogenicity with or without apparent abnormal size); *intestinal parasites* (serial fecal flotations; empiric deworming); *hypoadrenocorticism* (most dogs are young to middle-aged adults; usually hyperkalemia and hyponatremia are seen when GI signs are present; adrenocorticotropic hormone [ACTH] stimulation test for confirmation); *peritonitis* (ascites almost always present [may be small amount, only on radiographic or ultrasound]; cytology of fluid is diagnostic; penetrating injury around abdomen highly suggestive); *renal failure* (small kidneys on physical exam, uremic halitosis are suggestive; azotemia with isosthenuria highly consistent); *liver failure* (icterus with normal hematocrit very suggestive; liver enzymes, bile acids, hepatobiliary ultrasound abnormalities suggestive); *hypovolemic shock* (physical exam shows depression, recumbency, poor pulse, often tachycardia [or bradycardia in cats]); or *right-heart failure* (ascites, pleural effusion possible with normal serum albumin; echocardiogram shows right-heart disease or pericardial disease causing tamponade).

66.10 RECOMMENDED READING

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67 CHAPTER • 67 Venomous Bites and Stings

Patrick M. Burns

Venomous bites by snakes, spiders, and other species account for 1% to 1.3% of calls to poison information centers and approximately the same proportion of deaths in pets. The practitioner must know which venomous creatures inhabit the local area and the various treatments for envenomation.

A number of misconceptions exist about the treatment of envenomation, and new therapies are being developed for several of the conditions discussed here. In general, two important requirements are to keep the animal calm and quiet and to transport it quickly to the nearest veterinary facility. Administration of antivenin and supportive care are the mainstays of treatment for most envenomations, and this requires accurate identification of the toxin.

67.1 CROTALIDS (PIT VIPERS)

Nearly all snake bite envenomations in the United States are caused by snakes of the Crotalidae family. The three genera of crotalids in the United States are *Crotalus* (rattlesnakes) (Figures 67-1 67-3, 67-8), *Sistrurus* (pygmy rattlesnakes and massasauga) (Figure 67-7), and *Agkistrodon* (copperheads, cottonmouth water moccasins) (Figure 67-2). *Crotalus catalinensis* is the only rattlesnake that does not have a keratinized rattle on the end of the tail.

A single bite may produce as many as six puncture marks. The maxillary teeth are rotated forward at the time of the bite. Pit vipers have characteristic retractable rostral maxillary fangs (Figure 67-4). They can control the amount of venom delivered with each bite, and the first, defensive bite often is “dry.” Bites to the torso tend to develop more severe clinical signs, and bites are more serious during the spring and summer months.

Cats are more resistant than dogs to crotalid venom, but they often present with more severe clinical signs because of their small size relative to the amount of venom. Also, the interval between the occurrence of the bite and administration of medical therapy frequently is longer because of the hiding behavior of sick cats.

Crotalid venom is a mixture of enzymatic and nonenzymatic proteins. The enzymatic proteins (hyaluronidases and collagenases) cause local tissue injury and help the venom enter the systemic circulation. Different toxins found among the various species affect the clotting cascade through different mechanisms and result in impaired platelet function, thrombocytopenia, activation of clotting factors, fibrinolysis, and vasculitis. The venom of some crotalid species can cause neurologic signs, such as convulsions and alterations in mentation. The severity of the local reaction does not correlate with the severity of the systemic signs.

Clinical signs include localized pain, salivation, weakness, fasciculations, hypotension, alteration in respiratory pattern, regional lymphadenopathy, mucosal bleeding, prolonged bleeding times, echinocytosis of erythrocytes, obtundation, and convulsions.

Hematologic changes suggestive of envenomation include hemoconcentration followed by anemia, stress leukogram findings, and echinocytosis. The coagulation panel may show prolongation of the prothrombin time and partial thromboplastin time, with a reduction in fibrinogen and an increase in fibrin degradation products. Rhabdomyolysis may also be seen, especially with envenomation by Mojave, canebrake and tiger rattlesnakes. Urinalysis can reveal proteinuria, hemoglobinuria, and myoglobinuria. Electrocardiographic abnormalities occur in more severely affected victims.

Antivenin is indicated in moderate-to-severe cases of envenomation. Some first aid procedures are not efficacious, including application of ice or hot packs; incision and suction on the wound; the use of tourniquets; and electric shock therapy at the bite site. Most patients require one to two vials of the polyvalent antivenin given intravenously over 30 minutes. The antivenin reverses the coagulopathy, electrocardiographic findings, and neurologic changes. Tissue necrosis cannot be reversed by antivenin; however, the extent of the damage is limited. The practitioner should monitor the hemolysis and coagulation profile in order to judge the amount of venom required. Administration of blood products to reverse the coagulopathy without neutralization of the antivenin may result in further fibrinolysis.

Hypotension, hemolysis, and rhabdomyolysis are reasons for aggressive fluid therapy. Administration of antihistamines and corticosteroids usually is not necessary and tends to increase morbidity. Slow infusion of the antivenin reduces the chance of anaphylactoid reactions. Prior administration of an antivenin does not appear to increase the chance of a reaction. Broad-spectrum antibiotics and analgesics are indicated in patients with severe envenomation.

67.2 ELAPIDS (CORAL SNAKES)

Most elapids are found in the southern and southeastern United States (i.e., *Micrurus fulvius tenere* [Texas coral snake]; *M. fulvius fulvius* [Eastern coral snake]; *M. fulvius barbouri* [South Florida coral snake]; and *Micruroides euryxanthus euryxanthus* [Sonoran coral snake]). The incidence of elapid envenomation is extremely low compared with that from crotalids, and the percentage of dry bites is high because these snakes must “chew” on their victims to inject venom. Another difference between the elapids and crotalids is the lack of proteolytic enzymes in elapid venom (and therefore the lack of a local reaction). The neurotoxic venom of elapids affects the nervous system mainly by means of a nondepolarizing postsynaptic neuromuscular blocking activity, similar to the effect of curare. Some reports have mentioned an intravascular hemolysis, which is speculated to be mediated by phospholipase A.

The clinical onset of symptoms commonly is delayed 10 to 18 hours. In the dog, emesis, salivation, agitation, and central depression, followed by quadriplegia, hyporeflexia, intravascular hemolysis and, finally, respiratory paralysis, are seen. Cats show a loss of cutaneous nociception and hypothermia but not hemolytic anemia. Hematologic studies in dogs reveal erythrocyte membrane damage, such as burr cells and spherocytes.

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Application of a compression bandage, where possible, has been shown to be helpful. The definitive treatment is with *Micrurus fulvius* antivenin (Wyeth Laboratories, Marietta, Pennsylvania). However, this antivenin is not effective against the Sonoran coral snake. Early administration of the antivenin produces the maximum effect. It should be administered slowly intravenously to help reduce the chances of anaphylactic and anaphylactoid reactions. (A new ovine Fab antivenin with fewer side effects may become available in the near future.) Subcutaneous injections at the bite site are ineffective. Initially, one to two vials of antivenin may be given, and the clinical signs are closely monitored to gauge the requirement for more antivenin. In severe cases of envenomation, respiratory support by means of artificial ventilation may be required for several days. Broad-spectrum antibiotics are recommended for local wound infections. Treatment of Sonoran coral snake envenomation is supportive at this stage. Tick paralysis, botulism, polyradiculoneuritis, myasthenia gravis, and certain drugs can have clinical signs similar to those of elapid envenomation.

67.3 *LATRODECTUS* spp. (WIDOW SPIDERS)

The widow spiders belong to the genus *Latrodectus. Latrodectus mactans* (black widow), *L. variolus, L. bishopi* (red widow), *L. hesperus* (western black widow), and *L. geometricus* (brown widow) are the five species found in all the U.S. states except Alaska. The cat seems more susceptible to *latrodectism,* or envenomation by a widow spider, than does the dog. Alpha latrotoxin is the major active component of the venom. The lethal dose (LD_{50}) of the venom varies, depending on the species of widow spider. The brown widow is the most potent, with an LD_{50} of 0.43 mg/kg body weight. The LD_{50} of the black widow is 1.39 mg/kg body weight. Alpha latrotoxin causes an initial release of neurotransmitters from nerve endings throughout the nervous system and ultimately causes depletion of these transmitters, resulting in a blockade. It affects both motor and sensory fibers.

Clinical signs are commonly detected within 8 hours of envenomation, with most occurring in the first hour. The toxin does not cause a significant local reaction at the bite site. Small, young, and geriatric patients are most susceptible to the venom. Hyperesthesia, muscle fasciculations, and cramping occur, and somatic abdominal pain is a characteristic clinical sign. The motor signs may give way to a flaccid paralysis within 24 hours of the bite. An acute abdomen, rabies, or intervertebral disk disease are differential diagnoses. Respiratory compromise, hypertension, tachycardia, and seizures may also occur. Cats also show vocalization, salivation, agitation, muscle cramping, and ataxia leading to paralysis. Severe bites tend to occur in the autumn.

The diagnosis is based on the clinical signs and historical exposure to the spider habitat. Occasionally cats may vomit up a spider. A stress leukogram with hyperglycemia is often seen. The muscle cramping may lead to a rise in creatinine phosphokinase. Urinalysis may reveal concentrated urine, casts, and an elevated albumin level. The reduction in urine output occurs secondary to dehydration and urinary retention.

The main treatment modality consists of administration of the antivenin (Lyovac antivenin, Merck, Sharpe & Dohme). This may be give intramuscularly or intravenously. One vial is usually enough, but at times a second is required. Relief of clinical signs is usually seen within 30 minutes. Slow administration reduces the risk of anaphylactoid reactions. Blood pressure monitoring is advantageous because of the hypertension that occurs. Intravenous fluids to correct dehydration and oliguria should be administered only after the hypertension has been corrected. Pulmonary edema has also been seen with latrodectism. In the early stages of the clinical signs, calcium gluconate 10% theoretically may help reduce muscle cramping and pain; however, the effect is short-lived, and this therapy is not a substitute for the antivenin. Muscle relaxants such as methocarbamol and diazepam may be of some help, but results from clinical trials have not been supportive of their efficacy.

67.4 LOXOSCELIDAE (RECLUSE OR BROWN SPIDERS)

Recluse spiders are members of the family Loxoscelidae, genus *Loxosceles*. Five species (*L. reclusa, L. refuscens, L. arizonica, L. unicolor,* and *L. laeta*) found in the south-central United States are capable of causing necrotic arachnidism. Two forms of *loxoscelism* (envenomation by recluse or brown spiders), cutaneous and viscerocutaneous, have been described. The cutaneous form, which is more common, starts with a bull's-eye lesion at the bite site. A pale center, caused by localized thrombosis, is surrounded by an area of erythema. Within 24 to 72 hours, a hemorrhagic bulla with an underlying eschar develops in the center. The eschar eventually sloughs, leaving an ulcer that may take months to heal. The severity of these lesions depends on the response of the immune system to the toxin.

The viscerocutaneous form involves the development of a Coombs'-negative hemolytic anemia that may last for 7 days, thrombocytopenia, and disseminated intravascular coagulopathy. The extent of the cutaneous lesion and the

severity of the systemic signs do not appear to be correlated. A single bite can be lethal but in most cases results in dermonecrosis and prolonged wound healing (2 to 3 months). The bite itself is painless. Renal failure from the hemolytic anemia is the major cause of death from *Loxosceles* envenomation.

Figure 67-1 **A,** *Crotalus molossus*, blacktail rattlesnake; **B,** Color variant.

Figure 67-2 *Agkistrodon contortrix*, broad banded copper snake.

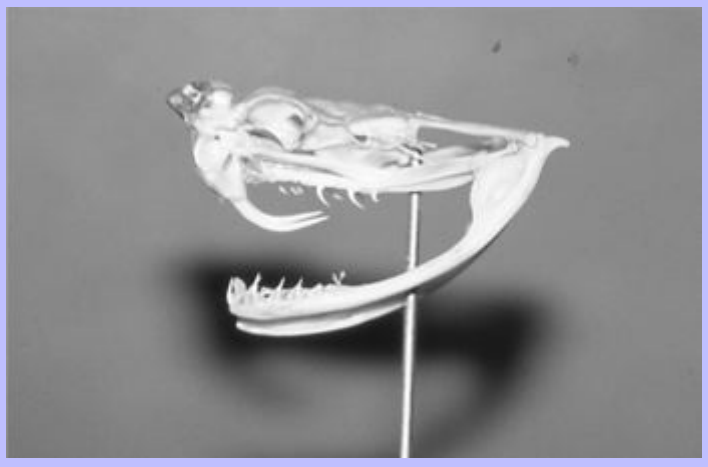
The exact mechanism of loxoscelism is unknown; however it is likely the result both of the toxin and the immune response to the toxin. An immune-mediated vasculitis, hemolysis, and platelet abnormalities all play a part in the mechanism. Sphingomyelinase D is the major toxin. The venom causes rapid coagulation and thrombosis of the capillaries. Depletion of clotting factors VIII, IX, XI, and XII also occurs, with resultant prolongation of the activated partial thromboplastin time.

No definitive test for *Loxosceles* envenomation exists. The diagnosis is based on the history and clinical signs and on laboratory findings of a Coombs'-negative hemolytic anemia, hemoglobinemia, hemoglobinuria, and a prolonged activated partial thromboplastin time. Hemolysis usually is seen only in the early stages and is followed by the cutaneous lesions. Systemic signs may be used to monitor the response to therapy. Other diagnostic possibilities include necrotizing fasciitis, mycobacterial infection, a burn wound, or a decubital ulcer.

Antivenin has had disappointing results when given after the lesions became obvious. Dapsone (1 mg/kg given orally for 14 days) has shown some efficacy in reducing the size of the cutaneous lesions. Dapsone inhibits chemotaxis, thereby minimizing the vasculitis caused by polymorphonuclear cells. Some evidence suggests that the use of hyperbaric oxygen (2 atmospheres twice daily) may be beneficial. Corticosteroids and surgery have not been shown to be efficacious in these cases. Viscerocutaneous symptoms may require intravenous fluids or blood products, and systemic antibiotics and analgesics may be necessary. Any analgesic that interferes with renal function should be avoided.

Figure 67-3 Crotalus horridus, timber rattlesnake.

Figure 67-4 *Crotalus* spp. skull.



67.5 TICK PARALYSIS

Dermacentor andersoni, D. variabilis, and *Haemaphysalis cinnabarina* are found in the western United States and British Columbia, and *D. variabilis* is found in the central and eastern United States and in southern portions of Canada. However, tick paralysis does not occur at all locations, which suggests a variation in the potency of the toxin. This is also true for the transmission of tick-borne diseases. Tick paralysis is more likely to occur in the spring and summer months.

Holocyclotoxin, a presynaptic neurotoxin at the neuromuscular junction, is secreted in the saliva of *Ixodes holocyclus*. It is similar to the toxin isolated from *D. andersoni*. The toxin inhibits the release of acetylcholine. The *Dermacentor* toxin can cause mortality, if left untreated, by means of a progressive, ascending paralysis that results in respiratory failure. Local effects of paralysis may be noted before the generalized form is seen. This is

most evident when the tick bite occurs close to the eye, resulting in ptosis or lack of a palpebral reflex. In such cases exposure keratitis may develop, requiring a temporary tarsorrhaphy. Recent studies on *I. holocyclus* have shown that toxin to have a direct effect on the heart, causing a reduction in the fractional shortening and a prolongation of the QT interval. Aspiration pneumonia secondary to megaesophagus is not uncommon in severely affected animals.

Clinical signs usually first appear 5 to 9 days after tick attachment. The diagnosis is based on the clinical signs and a history of exposure to ticks. Most ticks are found around the head, neck, and forelegs, and clipping of the patient sometimes is necessary to find them. Recovery from the paralysis usually occurs spontaneously 3 days or more after removal of the tick. Treatment is supportive during this time, which in severe cases may mean artificial ventilation for respiratory failure. Fiprinol sprays are a good alternative to organophosphates for eliminating other ticks. The main differential diagnoses for tick paralysis are polyradiculoneuritis and botulism.

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Figure 67-5 *Heloderma horridum*, beaded lizard.

67.6 HYMENOPTERAN STINGS (INSECT BITES)

The bites and stings of some winged insects and fire ants (*Solenopsis* sp.) have the potential to cause serious toxic or allergic effects. Toxic reactions are dose dependent unless hypersensitivity to the toxin is a factor. The venoms of this group have three broad components: low molecular weight toxins, peptides, and high molecular weight toxins. Low molecular weight toxins consist of histamine, dopamine, noradrenaline, amino acids, epinephrine, and acetylcholine and are involved only in the local reaction. Peptides (melittin, apamin, kinins, hemolysin, mast cell degranulating factors, and chemotactic factors) cause cytolysis and can act as neurotoxins, inducing hyperexcitability. High molecular weight toxins consist of phospholipase A and B, hyaluronidase, and proteases and cause allergic reactions. Dialkydpiperidine is the main cytotoxic alkaloid found in fire ants.

Allergies are mediated by immunoglobulin E (IgE) and usually occur after a period of sensitization. The common bee *(Apis mellifera)* has the greatest propensity to cause an allergic reaction. Reactions to hymenopteran stings can include localized angioedema, urticaria, emesis, diarrhea, hematochezia, respiratory distress, and death. The most significant stings occur around the head and neck.

The diagnosis of hymenopteran stings is based on historical evidence of contact with stinging insects and clinical signs. Certain breeds of dogs (boxers, Staffordshire terriers, and bull terriers less than 18 months of age) have a

higher chance of a severe reaction to the stings. Other diagnostic possibilities include skin testing, specific IgE or IgG antibodies, histamine release assay, and sting challenge. Treatment consists of administration of corticosteroids and antihistamines and supportive care. In severe cases, prednisolone sodium succinate may be administered intravenously; however, most cases respond to dexamethasone sodium phosphate given intravenously or intramuscularly. Severe cases may require supportive care with oxygen therapy, intravenous fluids, gut protectants, positive inotropes, and vasopressors. Patients with airway obstruction or bronchial constriction may require a tracheostomy or the use of bronchodilators.

Figure 67-6 *Heloderma suspectum*, Gila monster.

Figure 67-7 *Sistrurus catenatus*, Eastern massauga.

Figure 67-8 *Crotalus atrox*. **A,** Western diamondback rattlesnake tail; **B,** Western diamondback rattlesnake.

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Table • 67-1 Toxins of the Gila Monster

TOXIN	ACTION
Gilatoxin	Acts as a neurotoxic protein
Helothermine	Reduces body temperature
Hyaluronidase	Damages local tissue, allowing toxins to spread
Phospholipase A_2	Causes release of histamine, serotonin, acetylcholine, kinins, and other slow-release substances
Helodermatine	Causes vasodilatation, increased permeability and edema
Arginine hydrolase	Causes release of bradykinin
Helospectin and helodermin	Have activity similar to that of vasoactive intestinal peptides

67.7 HELODERMATIDAE LIZARD (GILA MONSTER)

The genus *Heloderma* includes two species of lizard that are venomous to humans (*H. suspectum* and *H. horridum*) (see Figures 67-6 and 67-5, respectively). The venom of the helodermatids is a mixture of proteins and peptides. The intravenous LD_{50} of the crude toxin is 0.4 to 2.7 mg/kg in mice; the toxic dose in dogs and cats is unknown.

Bite wounds typically are obvious and commonly are found around the face or forelegs. Clinical signs include salivation, lacrimation, emesis, tachypnea, respiratory distress, tachycardia, hypotension, and shock. Coagulopathies have not been reported, although a coagulation profile and minimum data base are indicated to help rule out snake envenomation. Treatment is symptomatic and may include intravenous fluids, respiratory support, debriding of the wound, and administration of broad-spectrum antibiotics and analgesics. An antivenin has been produced by the Poisonous Animal Research Laboratory at Arizona State University, but it is not yet commercially available.

67.8 SUGGESTED READINGS

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68 CHAPTER • 68 Plant Toxicities

Lynn R. Hovda

Plant toxicity continues to account for about 10% of all companion animal exposures reported to poison control centers. Pets less than 1 year of age make up about 50% of the cases, with dogs having significantly higher exposure rates than cats.[1] Ingestion usually occurs secondary to playfulness, boredom, or confinement; although the number of pets poisoned by well-meaning owners is increasing.

Veterinarians and pet owners are often faced with determining whether or not a plant ingestion is responsible for poisoning. This is rarely an easy task because most ingestions are not witnessed and many pet owners do not know the names of plants in their house, garden, or yard. Several reliable sources of plant identification aid the veterinarian, as does some baseline knowledge of toxic plants indigenous to the local area.

Very few antidotes are available for plant poisoning. Treatment generally consists of symptomatic and supportive care. Unless contraindicated, emesis or gastric lavage followed by activated charcoal with a cathartic should be performed. Identification of the specific plant, the quantity and parts ingested, the time of ingestion, and the age and breed of animal all are necessary for formulating a treatment plan. Examination of stomach contents (seeds, bulbs, flowers) may confirm ingestion, assist in plant identification, guide therapy, and offer a prognosis.[1]

68.1 NEWER PLANT TOXICITIES

68.1.1 Grapes and Raisins

Ingestion of grapes and raisins has just recently been associated with the onset of acute renal failure in dogs. Literature is sparse, and signs and treatment are based on case reports with no firm scientific research as a backup.[2] No specific breed predilection or geographic location has been noted. Neither the toxin nor the mechanism of action has been identified. Toxicity varies and has been reported with ingestion of just a few raisins or grapes up to several pounds. Homegrown grapes or raisins appear to be just as toxic as those purchased in stores. Vomiting partially digested grapes or raisins occurs 1 to 3 hours after ingestion and is followed by anorexia, severe abdominal pain, and diarrhea with partially digested grapes or raisins in feces. Later signs include central nervous system (CNS) depression and decreased urine output. Results of serum chemical analysis taken 24 to 36 hours after ingestion are consistent with acute renal failure. Treatment is symptomatic and includes early and aggressive intravenous (IV) fluid diuresis or peritoneal diuresis in anuric dogs. Signs may last from a few days to many weeks. Prognosis is good if treated early, although sporadic deaths have occurred in well-treated cases.

68.1.2 Macadamia Nuts

Reports of dogs poisoned by ingesting macadamia nuts have increased over the past 3 to 4 years.[3] Macadamia nuts, produced by *Macadamia integrifolia* and *Macadamia tetraphylla* trees in Hawaii, can be found in most grocery stores throughout the United States. Both the toxin and mechanism of action remain unknown. Generally, signs occur within the first 2 to 12 hours after ingestion, with the most frequently reported signs associated with locomotor disturbances. Almost all dogs have difficulty walking, with the gait best described as drunken or staggering. Tremors, ataxia, and weakness (hind end > front end) have also been reported.[3] Other

reported signs include depression, vomiting, abdominal pain, and hyperthermia.[3] Laboratory analysis shows a mild increase in serum alkaline phosphatase and lipase, as well as a delayed increase in serum triglycerides. No antidote exists, and treatment is mainly supportive. Prognosis is excellent, with signs generally resolving over 24 to 48 hours with appropriate care.

68.2 COMMON PLANT TOXICITIES

68.2.1 Plants Affecting the Blood

Ingestion of raw or cooked onion (*Allium* spp.) is well associated with toxicity in dogs and cats.[1] A hereditary abnormality makes Akitas and Shibas more susceptible to toxicity than other dogs.[4] Most recently, reports have surfaced of cats poisoned by eating baby food with onion powder as an ingredient.[5] The primary toxin is *n*-propyl disulfide, an alkaloid found in onions, wild onions, leeks, garlic, and chives. The toxin oxidizes free sulfhydryl groups on hemoglobin, and the oxidized hemoglobin precipitates Heinz bodies in red blood cells (RBCs).[1] Anemia occurs when the spleen removes affected RBCs. Onset of action varies from a few hours to several days. Signs are consistent with anemia and include increased heart and respiratory rates, pale mucous membranes, fatigue, weakness, exercise intolerance, and collapse.[4] Laboratory findings include hemoglobinuria, decreased hematocrit, decreased hemoglobin, Heinz bodies in RBCs, and mild methemoglobinemia. Treatment depends on the hematocrit; some animals need a transfusion.

68.2.2 Plants Primarily Affecting the Cardiovascular System

Plants with cardiac glycoside activity include the common oleander *(Nerium oleander)*, yellow oleander *(Thevetia peruviana)*, foxglove *(Digitalis purpurea)*, lily of the valley *(Convalleria majalis)*, and kalanchoe *(Bryophyllum* spp.).[1] Five different types of cardiac glycosides have been identified in common oleander. The seeds, stems, and roots are toxic. Yellow oleander contains the cardiac glycosides thevetin A, thevetin B, and peruvoside. All parts of the plant are toxic, with seeds having the highest concentration. Digoxin, digitoxin, and digitonin are the most common toxins in foxglove, with seeds again having the highest concentration. Lily of the valley contains at least 15 toxins, with convallatoxin, convallarin, and convallamarin the most common. Seeds contain the highest concentration, whereas the fruit flesh is minimally toxic. Kalanchoe contains bufadienolides, with most poisonings occurring during the plant's flowering season. The mechanism of action for all cardiac glycosides occurs at the cellular membrane level. Inhibition of the sodium-potassium ATPase pump causes slowed electrical conductivity with decreased active transport of sodium and an efflux of potassium.

Signs associated with cardiac glycoside-containing plants are generally related to either the cardiovascular system or gastrointestinal (GI) tract.[1] Vomiting and abdominal pain begin several hours before deterioration in myocardial function. Marked bradycardia with first-, second-, or third-degree atrioventricular (AV) block, ventricular arrhythmias, asystole, and sudden death can occur. Hyperkalemia is usually prominent, although scattered reports of hypokalemia exist. Sap from oleander plants has caused contact dermatitis and blistering of the nose and footpads. Diagnosis depends on physical identification of the plant. Digoxin assays could aid in identification of oleander and foxglove.[1] Serum digoxin levels might be a screening tool, but the correlation between the level and degree of toxicity is very poor.

Treatment varies from case to case but may include correction of potassium abnormalities, appropriate antiarrhythmic drugs, implantation of a temporary pacemaker, and antidigitalis antibody fragments (Fab).

Prognosis is generally poor unless intervention is early and aggressive. An extremely bitter taste and spontaneous vomiting help limit the number of deaths from oleander.

Azaleas (*Rhododendron* spp.) are associated with severe toxicity and death.[1] The precise mechanism of action is unknown, but it appears that grayanotoxins act by binding to closed sodium channels. Slower opening and increased sodium permeabilities cause a decreased resting membrane potential in Purkinje's fibers. Clinical signs include severe weakness, hypotension, dyspnea, and respiratory failure. GI signs unrelated to grayanotoxins include salivation, vocalization, vomiting, and diarrhea. Sodium channel–blocking drugs like quinidine and procainamide have been used successfully.

The yew (*Taxus* spp.) is a common ornamental shrub found in the United States and Canada.[1] Common species include the Japanese yew *(T. cuspidata)*, English yew *(T. baccata)*, Florida yew *(T. floridana)*, and ground hemlock *(T. canadensis)*. Bark, leaves, and seeds are toxic but not the fleshy part of the bright-red fruit. Taxine, a cardiotoxic alkaloid, causes conduction disturbances by direct effect on cardiac muscle ion channels. In dogs, bradycardia, vomiting, diarrhea, weakness, and seizures have been reported. Sudden death may occur. Caged birds may be poisoned by bark or other shrub pieces placed in their cages. Clinical signs in birds include crop regurgitation, ruffled feathers, dyspnea, weakness, ataxia, and sudden death. Treatment is supportive and symptomatic. Prognosis is poor, and once clinical signs have occurred, further treatment is of limited value.

68.2.3 Plants Primarily Affecting the Gastrointestinal System

Oxalate-containing plants (family Araceae) are the most frequently reported household exposures.[1] Common household plants containing insoluble crystals include dumbcane *(Dieffenbachia* spp.), philodendron (*Philodendron* spp.), peace lily (*Spathiphyllum* spp.), and devil's ivy (*Epiprennum aureum*). Crystals are usually concentrated within a raphite structure in the stalk. Chewing on the stalk releases oxalate crystals and other as yet unidentified enzymes. Clinically, stomatitis and glossitis, ocular, or systemic scenarios can occur.

68.2.3.1 Stomatitis and Glossitis

Irritation to the mucous membranes of the mouth and throat causes immediate and intense pain, local swelling, and profuse salivation. These may be accompanied by head shaking, loss of vocalization, and rarely airway compromise. Treatment is symptomatic. The mouth should be thoroughly examined and any remaining plant pieces removed. Cool fluids, ice chips, and analgesics increase comfort until signs resolve. Most typically, it takes 30 to 90 minutes for this to occur, but signs can be prolonged for hours in animals with airway compromise.

68.2.3.2 Ocular

Eye exposures, although rare in animals, cause severe burning pain and swelling. Left untreated, conjunctivitis, abrasions, and corneal ulcers develop. Treatment includes a 10-to 15-minute eye irrigation followed by a thorough eye examination with fluorescein dye staining or slit lamp examination. Ophthalmic protectant medications are used as indicated.

68.2.3.3 Systemic

Systemic effects occur primarily in cats exposed to *Philodendron* spp. Signs are referable to the renal system and CNS and include hyperexcitability, tetany, and seizures. Treatment is symptomatic and supportive.

Rhubarb (*Rheum* spp.) contains soluble oxalate crystals concentrated in the leaf. The stalk is edible and generally causes no systemic effects. When leaves are ingested, soluble oxalates can be absorbed and bind to circulating calcium ions. Symptoms include diffuse GI tract irritation and infrequently systemic hypocalcemia. Oral calcium hydroxide is used to bind oxalates in the GI tract. If systemic signs are noted, IV calcium gluconate or chloride should be administered.

The chinaberry tree *(Melia azedarach)* can be found throughout temperate regions of North America. All parts of the tree are toxic, although dogs are generally poisoned by eating fruit fallen from trees.[6] Toxicity has been reported in rabbits, guinea pigs, rats, and other species. Many potential toxins have been isolated, with meliatoxins found in highest concentration in the fruit. Clinical signs usually occur within 1 to 2 hours after ingestion. Vomiting and diarrhea (with or without blood) are the most common signs along with anorexia, severe abdominal pain, hypersalivation, and straining to defecate.[6] Neurologic effects are similar to nicotine, and signs include depression, ataxia, seizures, and coma. Other reported signs include hyper-or hypothermia, tachycardia or bradycardia, mydriasis or miosis, and muscle rigidity.[6] Death generally occurs from respiratory depression and arrest. Treatment is symptomatic and supportive. Prognosis for recovery decreases significantly with the onset of neurologic signs.

Cycad palms or sago palms (*Cycas and Macrozamia* spp.) are subtropical to tropical houseplants known to cause toxicity in dogs.[7] All plant parts are toxic, with the seeds containing the greatest concentration. The plants contain three toxins: (1) cycasin, which causes GI effects and liver necrosis; (2) β-methylamino-L-alanine, which causes neurologic effects; and (3) an unknown toxin associated with neurologic effects. The onset of action is variable, with signs occurring from a few hours to a day or so. The most commonly reported signs are vomiting and diarrhea (with or without blood) followed by lethargy, depression, liver failure, and death.[7] Laboratory work shows an increase in liver enzymes (alanine transferase and alkaline phosphatase) and bilirubin. Treatment includes multiple-dose activated charcoal and supportive care with special emphasis on the liver.

English ivy *(Hedera helix)*, a common houseplant and ground cover, contains hederagenin, a saponin associated with GI irritation.[1] Other *Hedera* spp. of ivy with suspected toxicity include Persian ivy, Irish ivy, Atlantic ivy, and Nepal ivy. Ingestion of leaves and berries causes profuse salivation, abdominal pain, vomiting, and diarrhea. Treatment is symptomatic and supportive.

Abrus precatorius, the jequirity bean, has been used for centuries in Latin American necklaces and jewelry. It has long been illegal to import this jewelry into the United States, yet it frequently shows up at flea markets and garage sales. Abrin, the toxin, is a toxalbumin similar to botulinum, cholera, and diphtheria.[1] The castor bean plant *(Ricinus communis)* has similar toxic principals. Castor bean plants are widely used as an ornamental shrub throughout North America. Ricin, the toxin, is present in all parts of the plant but is most concentrated in seeds. Abrin and ricin are among the most deadly poisons in the world but must be released from their shell to be absorbed. Dogs are most often poisoned by chewing on the hard outer shell and ingesting the contents. Once absorbed, abrin and ricin enter cells and inhibit protein synthesis resulting in cell death. Signs of toxicity occur within 6 hours of ingestion and include severe abdominal pain, vomiting, diarrhea, seizures, and cerebral edema.[1] Treatment is supportive. Prognosis for recovery is poor once clinical signs develop.

Ornamental holiday plants include holly (*Ilex* spp.), poinsettia *(Euphorbia pulcherrima),* and mistletoe *(Phoradendron flavescens)*. Well over 300 species of holly are found in the United States alone, making

actual plant identification difficult. The toxin remains unidentified but may be ilicin (ilexanthin and ilex acids), a saponin causing GI effects. Poinsettias produce only mild toxicity. The unidentified toxin in the latex sap, thought to be a diterpenoid ester, rarely causes more than mucous membrane irritation or contact dermatitis. Clinical signs include salivation, mild GI irritation, and occasional diarrhea. Mistletoe has the potential for more serious effects, although few animal case reports exist.[8] The toxin is a phytotoxin or toxalbumin that can cause severe gastroenteritis with prolonged emesis. Signs occur up to 18 to 24 hours after ingestion of leaves, berries, or tea made from berries. Treatment associated with any of these plants is symptomatic and supportive. Demulcents and antacids are often of great benefit.

Several varieties of poisonous plants grow from bulbs, tubers, or corms. Included are amaryllis, jonquil, and daffodil (family *Amaryllidaceae*); tulip (family *Liliaceae*); and iris (family *Iridaceae*).[1] The toxic principal is unknown, but ingestion of the bulb has been associated with only mild-to-moderate gastroenteritis. Treatment is symptomatic and supportive.

Autumn crocus *(Colchicum autumnale)* and glory lily (*Gloriosa* spp.) contain colchicine, a toxic alkaloid that concentrates in the tuber and seeds. Colchicine causes cell death by inhibiting normal cell division.[9] Clinical signs include vomiting and diarrhea (with or without blood), hypersalivation, abdominal pain progressing to depression, weakness, ataxia, and collapse. Signs progress further to include several organ systems and finally, multiple organ system collapse. Treatment is supportive. Prognosis is poor if multiple organ systems are affected.

Solanine-containing plants are members of the Solanaceae family. Included are the tomato *(Solanum lycopersicon)*, potato *(S. tuberosum)*, eggplant *(S. melongena)*, bittersweet *(S. dulcamara)*, deadly or black nightshade *(S. nigrum)*, and Jerusalem cherry *(S. pseudocapsicum)*.[1] The primary toxin is solanin. Some plants also produce tropane belladonna (deadly nightshade) or solanocapsine (Jerusalem cherry). Solanine is poorly absorbed orally, and most members of this family act only as GI irritants. Systemic absorption only occurs when substantial GI mucosa damage exists. Systemically, solanine causes CNS depression and cardiac arrhythmias. Deadly nightshade may cause a mixed picture, depending on which toxin is prevalent. Solanine usually predominates, but anticholinergic signs occasionally occur and physostigmine may be indicated. Solancapsine affects cardiac muscle, causing decreased heart rate and conductive changes. Treatment is symptomatic and supportive.

Life-threatening mushroom ingestions include amanitin poisoning *(Amanita virosa, Amanita phalloides, Conocybe filaris)*, orellanine poisoning *(Cortinarius orellanus*, *Cortinarius rainierensis)*, and monomethylhydrazine *(Gyromitra esculenta)*. Of these, amanitin toxicity is the most widely reported in dogs. *A. phalloides* are found in wooded areas throughout the United States and Canada. Signs usually do not develop for 6 to 24 hours after ingestion. Typically, signs include a 24-to 36-hour GI phase, followed by 24 hours of remission, then a late hepatic phase characterized by jaundice, coma, and death. Survivors of the hepatic phase may ultimately die from renal tubular necrosis. Diagnosis is difficult. Liver enzymes are marked early in the process and blood urea nitrogen (BUN) and creatinine increase later. Occasionally, spores are found in GI contents or feces. A few commercial laboratories are able to perform amatoxin tests on urine. If a sample mushroom is available, the Meixner blue test is a useful qualitative test for amatoxins. Early treatment includes gastric lavage and activated charcoal with a cathartic. Charcoal hemoperfusion is perhaps the most helpful therapeutic agent but rarely performed on animals. Further treatment is supportive and symptomatic. Experimentally, high-dose penicillin, silymarin, *S* Adenosylmethionine, thioctic acid, N-acetylcysteine, cimetidine, and cytochrome-*c* have all been used with mixed success. Liver transplant remains the proven therapy.

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68.2.4 Plants Primarily Affecting the Neurologic System

Animals ingest tobacco *(Nicotiana tobacum)* from cigarettes, chewing tobacco, cigars, or pipe tobacco.[1] Nicotine is a rapidly acting toxin that stimulates and then depresses the autonomic ganglia. Centrally mediated emesis often occurs before significant absorption, and no further signs develop. Animals with severe poisoning show signs of CNS involvement and cardiac abnormalities. Death is from paralysis of the muscles of respiration. Treatment is first aimed toward assisting respiration and then removing residual tobacco from the GI tract.

Many plants are associated with hallucinogenic effects. Poisoning may be accidental or intentional. Diagnosis is often difficult because many owners are reluctant to cooperate. Sporadically reported in dogs are poisonings from psilocybins or "magic mushrooms."[1] Muscle weakness, ataxia, abnormal mutation, vocalization, and temperature changes occur 20 to 30 minutes after ingestion. Marijuana *(Cannabis sativa)* poisoning is infrequently reported in dogs. Dogs become glassy eyed, ataxic and hyperactive, or comatose. Other less common hallucinogenic plants are jimsonweed *(Datura stramonium)*, thorn apple *(Datura metaloidyl)*, blue morning glory *(Ipomoea violacea)*, nutmeg *(Myristica fragrans)*, and peyote (family Cactaceae). Signs vary from plant to plant; however, in general all of these plants cause changes in the CNS. Treatment is supportive and signs generally resolve in 24 to 48 hours.

Nettle toxicity (family Urticaceae) is seen primarily in hunting or field dogs.[1] Some species of nettles contain hairs that break off when an animal rubs against them, allowing injection of the contents into the animal. The toxic agents are histamine, acetylcholine, serotonin, and formic acid. Clinical signs are variable and depend on which toxin predominates. Muscle weakness is the most common sign but may be accompanied by salivation, vomiting, pawing at the mouth, tremors, dyspnea, and a slow, irregular heartbeat. Atropine in large doses, antihistamines, and sedation are useful. Generally, animals respond to treatment in less than 24 hours.

68.2.5 Plants Primarily Affecting the Renal System

All parts of the Easter lily *(Lilium longiflorum)* and day lily (*Hemerocallis* spp.) are toxic to cats.[10] Tiger lilies *(L. tigrinum)*, Japanese showy lily *(L. speciosum)*, and Asiatic lilies have also been implicated.[10] The toxic agent and mechanism of action are unknown. Clinical signs generally occur within 2 hours and include vomiting, depression, and anorexia, followed in 1 to 3 days by acute renal failure.[1,10] Laboratory work shows an increase in BUN, creatinine, potassium, and phosphorous. Epithelial casts have been found in the urine as early as 18 hours after ingestion. Early intervention is necessary for survival. Treatment includes aggressive GI decontamination with multiple doses of activated charcoal and fluid diuresis until BUN and creatinine have returned to normal. Peritoneal dialysis may be helpful in anuric cats. Prognosis is poor if treatment is delayed past 18 to 24 hours or anuria is present. Renal tubular epithelial cell necrosis precedes death.

68.2.6 Plants Primarily Resulting in Respiratory Signs

All above-ground parts of the avocado tree *(Persea americana)* are toxic to caged birds, rabbits, and mice.[11,12] The toxin is unknown but is suspected to be persin.[12] The mechanism of action is unknown. Onset and duration of signs vary from species to species. In caged birds, signs occur 12 to 29 hours after ingestion and consist of acute respiratory distress, ruffled feathers, abnormal wing posture, and sitting in the bottom of the cage. Death

is from respiratory arrest. Rabbits develop acute cardiac arrhythmias, mammary gland enlargement, and sudden death.[12] Treatment is symptomatic and supportive. Prognosis is poor once respiratory or cardiac signs occur.

68.2.7 Plants Resulting in Sudden Death

Seeds and leaves from many fruit trees (apple, apricot, cherry, peach, plum) contain cyanogenic glycosides.[13] The glycosides concentrate in the seed and, depending on the tree, as few as 5 to 25 fruit seeds can cause toxicosis. Cyanide binds to cytochrome oxidase and inhibits cellular respiration. Onset of signs occurs within 30 to 90 minutes after ingestion; once signs occur, death follows in just a few minutes.[13,14] The most common clinical sign is sudden death although this may be preceded by ataxia, dyspnea, and tremors. Many treatment modalities have been tried, but the use of IV sodium nitrite followed by IV sodium thiosulfate is still the most successful and widely used.[14] Repeated doses of IV sodium thiosulfate and administration of 100% humidified oxygen[14] may be helpful.

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69 CHAPTER • 69 Topical Toxins

Patrick M. Burns

According to poison information centers throughout the United States, topical toxins are a major cause of death in companion animals. Synthetic pyrethrins, organophosphates, and carbamates are discussed in chemical toxicities. This chapter focuses on some of the more commonly encountered topical toxins.

When dealing with these types of intoxications, practitioners must protect themselves from exposure by wearing gloves. Washing the patient with a mild soap is adequate for most poisons, although a degreaser may sometimes be necessary. Long-haired patients may require clipping of the coat. Care must be taken in handling any skin that has been burnt. Analgesia and or a general anesthesia may be required to handle these animals humanely. A thorough endoscopic examination may also be required in some cases.

69.1 TOAD POISONING

The two main species of toads found in the United States are *Bufo marinus* (the marine or cane toad) and *Bufo alvarius* (the Colorado River toad). These Hawaiian natives are introduced species that are found mainly in Arizona, Colorado, Florida, and Texas. Intoxications tend to occur more often in spring and summer, especially after a period of rain. The peak time of exposure ranges from late afternoon to around midnight. In a common scenario, the pet is allowed out at night briefly and then is found acutely drooling and having seizures.

The most common signalment is a young male terrier weighing approximately 5 kg. The smaller the pet, the more toxin that is absorbed on a body weight basis. In the toad, the toxin is secreted by two large parotid glands just caudal to the eyes and then is spread over the rest of the body. The toxins are absorbed via mucosal membranes. Swallowing of toads is very rare because the toxins have a bitter taste. However, they are still active even if the toad has died and the body has dried up.

Toad toxins contain a variety of catecholamines, along with digitalis-like substances (bufagenins and bufotoxins) and a hallucinogen (bufotenin) that is similar to the hallucinogen lysergic acid diethylamine (LSD). A synergism exists between these groups of toxins. The bufagenins and bufotoxins also have potent local anesthetic properties.

Major clinical signs of intoxication are disorientation, ataxia, stupor, seizures, nystagmus, profuse drooling, brick-red mucous membranes, mydriasis, cardiac arrhythmias, and death. The onset of clinical signs occurs within minutes of exposure. Laboratory changes may consist of the following: a stress leukogram, mild fluid loss, mild elevation in serum alkaline phosphatase activity and mild increase in serum potassium concentration, whereas serum sodium, phosphorous, and total protein concentration tend to decrease. It is also possible to confirm exposure with a digoxin serum immunoassay, although practically not required. Geographic differences exist in the severity of clinical signs; the worst are seen in Florida.

Clients should be advised to flush the animal's mouth with water for at least 10 to 15 minutes prior to transportation to the veterinarian's office. Charcoal is thought to be of some benefit because some of the toxins enter the enterohepatic circulation. Seizures may be controlled with diazepam given nasally, rectally or intravenously. Propofol and pentobarbital also can be used to treat the seizures. Control of the seizures allows further flushing of the mouth and eyes. In severe cases, cerebral edema may occur secondary to the seizure activity and may need to be treated with short-acting corticosteroids, mannitol, and furosemide.

Table • 69-1 Toad Poisoning: Treatment of Electrical Disturbances

TYPE OF ARRHYTHMIA	TREATMENT OPTIONS
Bradycardia and heart blocks	Atropine, 0.02 mg/kg intravenously (IV)
Sinus tachycardia	Esmolol, 0.5 mg/kg IV, then a constant-rate infusion (CRI) of 50 to 200 µg/kg/min. Propranolol, 0.5 to 2.0 mg/kg IV +/−CRI 60 µg/kg/min.
Ventricular tachycardia	Lidocaine, 1 to 2 mg/kg IV bolus, followed by CRI 40 to 80 µg/kg/min. Procainamide, 6 to 8 mg/kg IV, then CRI 25 to 40 µg/kg/min. Correction of hypomagnesemia if present.

As soon as possible, an electrocardiogram should be analyzed to determine the type of electrical disturbance present. Bufagenins and bufotoxins can cause any type of digoxin-like arrhythmia. Also, any type of bradydysrhythmia or tachydysrhythmia may be seen, and these should be treated with the appropriate drug (Table 69-1). Most of the arrhythmias improve with flushing of the mouth and control of the seizures.

A novel therapy that may prove very useful in counteracting the deleterious effects of the digoxin-like toxins is administration of digoxin immune Fab. These anti-digoxin antibodies have been shown to cross-react with bufagenins and bufotoxins. This therapy would be useful for plant-derived cardiac glycoside intoxications.

Administration of intravenous fluids may be indicated in severe cases. Most animals respond favorably to this therapy within 1 to 2 hours. Of patients that reach veterinary care, the vast majority survive. The differential diagnoses for toad poisoning include heat stroke; metaldehyde, organophosphate, carbamate, oleander, or theobromine poisoning; and contact irritants. A good history helps in the differentiation of the diagnosis.

69.2 NEW GENERATION INSECTICIDES

Topical agents such as fipronil, imidacloprid, lufenuron, and selamectin all have wide margins of safety; the only reported side effect has been one unverified case of localized dermatitis. However, all these drugs have the potential to cause hypersensitivity reactions. The clinical signs seen with overdoses are caused by the carrier vehicle rather than the active ingredient. Mild gastrointestinal upset is usually seen, and symptomatic therapy may be required. Ocular exposure is best treated with saline lavage and fluorescein staining to assess the extent of any damage. Hypersensitivity reactions require shampooing with a mild soap and the use of glucocorticoids if indicated. Lufenuron appears to reduce fertility in the dog in high doses (Table 69-2).

69.3 ANTIBIOTICS

The antibiotics found in dermatologic preparations are well tolerated orally; extremely high dose rates over a prolonged period (on the order of months) are required to produce any serious effects. In general, antibiotics cause signs of gastrointestinal upset, such as nausea, anorexia, vomiting, and diarrhea. Neomycin, polymyxin B, bacitracin, and ampicillin, to name a few, are antibiotics used in topical preparations that have low bioavailability, hence the high oral tolerance. It should also be remembered that with any antibiotic preparation, an anaphylactic reaction is possible. Anaphylaxis to bacitracin-neomycin-polymyxin ointments in cats has been reported when the ointments were used prophylactically with routine surgeries.

69.4 TOPICAL GLUCOCORTICOSTEROIDS

Ophthalmic and dermatologic preparations of glucocorticoids usually contain hydrocortisone, betamethasone, or triamcinolone. Oral intoxication from ingestion of these preparations may result in mild gastrointestinal signs caused by the carrier vehicle. Overdoses usually are self-limiting and require only supportive care. Clinical signs are caused by the local and systemic effects of glucocorticoids. Long-term use of these preparations may result in a cushingoid patient.

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Table • 69-2 Topical Pesticides and Their Mode of Action

DRUG	VETERINARY PRODUCT LD_{50}	MODE OF ACTION
Fipronil (Frontline; Merial Laboratories)	>2000 mg/kg (rabbit dermal)	Noncompetitive blocker of gamma aminobutyric acid-gated chloride channels +/−glutamate-gated channels
Imidacloprid (Advantage; Bayer Animal Health)	2000 mg/kg (rat dermal)	Competitive inhibitor of nicotinic receptors in postsynaptic nerves
Lufenuron (Program; Novartis Animal Health)	Tested in dogs using 20 times the recommended dose and in cats using 10 times the recommended dose; no ill effects seen	Inhibitor of chitin synthetase
Selamectin (Revolution; Pfizer Animal Health)	Safe in doses up to 10 times the recommended dose	Inhibitor of glutamate-gated channels

69.5 ANTIFUNGALS — ZINC UNDECYLENATE

Sunscreens, diaper rash ointments, and antifungals can all contain zinc. Acute ingestion of zinc oxides usually results in a self-limiting emesis that rarely requires treatment. These episodes do not usually result in zinc toxicosis. Prolonged use of sunscreens and antifungals may cause zinc toxicosis, manifesting as gastrointestinal disturbances, hypotension, hemolytic anemia, jaundice, and pulmonary edema. Milk or water given orally helps reduce intestinal absorption of zinc, and calcium ethylenediamine tetra-acetic acid (EDTA) chelates the zinc that has been absorbed systemically. In severe cases of zinc toxicosis, the use of blood products may be indicated.

69.6 CLEANING PRODUCTS

In the United States, the number of animals that die of poisoning from cleaning products is more than three times the number that die of bites and stings from poisonous insects. This discussion focuses on chemicals that are directly irritating to the skin or that are absorbed through the skin and cause systemic signs of intoxication. Acids and alkalis are commonly found throughout the household (Box 69-1.)

Acids induce intense pain, which limits the duration of contact with these chemicals. Acids cause rapid protein coagulation, resulting in a localized necrotic lesion. Full-thickness mucosal lesions are rare. Alkaline substances tend to be more damaging to the skin and alimentary tract. Chemicals with a high pH have a greater propensity to cause full mucosal thickness injuries, with a resultant liquefactive necrosis.

69.6.1 Box • 69-1 Examples of Household Acids and Alkalis

69.6.1.1 Acids

Antirust compounds

Toilet bowl cleaner

Gun barrel cleaning fluid

Automobile batteries

Swimming pool cleaning agents

69.6.1.2 Alkalis

Drain and toilet bowl cleaners

Liquid cleansers

Washing detergents and powders

The formulation of the preparation also affects the extent and location of the lesions. Solids tend to cause more buccal cavity and upper esophageal injuries, whereas liquids cause more lower esophageal and stomach lesions. However, this is a generalization, and it should be remembered that up to 30% of esophageal burns show no oral lesions. A full inspection of the entire upper alimentary tract is always indicated for complete evaluation of the extent of injury. A thoracic radiograph may reveal signs of esophageal perforation, as indicated by a pneumomediastinum.

Neutralization of any acid or alkali is contraindicated, because the resultant exothermic reaction may cause a thermal burn. Charcoal is ineffective, and gastric lavage is contraindicated with corrosive substances. Washing the affected area with copious amounts of water or administering milk helps dilute the effects of these corrosive substances on the alimentary tract. Ocular lavage may also be necessary. These measures must be taken as quickly as possible to have any effect. If any evidence suggests esophageal perforation (e.g., signs of bleeding), a full endoscopic examination may be prudent; however, it must be done with caution. Stricture formation may not be evident until some time after the injury. Glucocorticoids may help reduce the amount of fibroblastic activity early in the healing process; however, their efficacy is unproven. Caution should be used if gastric ulceration has occurred. Prophylactic antibiotics may be necessary with severe mucosal damage or extensive dermal burns, but their use is controversial, especially if no signs of infection are present at the time this therapy is instituted. In severe cases of buccal cavity or esophageal injury, an esophagostomy or a gastrostomy tube feeding regimen may be indicated.

69.6.2 Phenols

Phenols can be found in disinfectants, soaps, shampoos and detergents. These compounds are rapidly absorbed via the oral, respiratory and dermal routes. The phenol LD_{50} in the dog is approximately 0.5 g/kg body weight. Limitations in glucuronide transferase activity in the cat make this species more susceptible to intoxication. Dermal burns have resulted from concentrations greater than 1%; however, the severity of dermal absorption

depends more on the area of contact than on the concentration. Phenols cause intense pain followed by local anesthesia to the affected skin. The coagulative necrosis discolors the skin white, and a dry eschar eventually forms over several days. Corrosive burns to the mouth and esophagus occur with oral ingestion. Severe burns are seen with ocular exposure.

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Initially, with phenol intoxication, vomiting, hypersalivation, apprehension, panting, and ataxia may be seen, with progression to muscle fasciculations, shock, cardiac arrhythmias, and death. Phenols cause methemoglobinemia. Histopathologically, both hepatic fatty degeneration and necrosis and renal tubular degeneration and necrosis are seen.

Demulcents such as milk or eggs, rather than water, should be given as soon as possible, because some evidence suggests that water may enhance phenol absorption. For dermal exposure, the area should be washed first with polyethylene glycol or glycerol and then with a mild, soapy solution, followed by a final rinse with water. Gloves must be worn during this procedure. Any wounds should be bandaged with dressings soaked with sodium bicarbonate 0.5%. Oily dressings enhance dermal absorption. Ocular lesions must be flushed with saline for 20 to 30 minutes and treated appropriately. Aggressive fluid therapy is needed to correct any acid-base disturbance, to support hepatic and renal function and to reverse any signs of shock. Hepatic and renal function may also be supported by use of N-acetylcysteine for the first 3 days after intoxication. Methylene blue and ascorbic acid may be indicated for methemoglobinemia. Tube feeding is necessary for severe injuries to the oral cavity and upper alimentary tract.

69.6.3 Essential Oils

Essential oil extracts, which are incorporated into products such as insecticide sprays, collars, shampoos, soaps, fragrances, and cleaning solutions, are generally thought by the general public to be nontoxic. Two commonly used essential oils are citrus oil (*Citrus* spp.) and tea tree oil *(Melaleuca alternifolia)*.

The main active ingredients are *d*-limonene and linalool oils (citrus oil) and terpenes (tea tree oil). Cats appear to be more susceptible to essential oils than dogs, partly because they metabolize these oils poorly and because their grooming habits increase oral exposure. The lipid nature of essential oils allows them to be absorbed rapidly via the dermal and oral routes, especially when mixed with organic solvents or surfactants. Urinary excretion is the main route of excretion.

The exact mechanism of intoxication by essential oils is unknown, and the LD_{50} varies. Clinical signs can develop within 6 to 8 hours of exposure. Central and peripheral vasodilatation tends to occur with exposure. Transient hypersalivation is seen in the cat. Muscle tremors may occur in response to the mild-to-severe hypothermia that can develop. Mydriasis, weakness, collapse, and paralysis are seen in advanced cases. In the dog, lesions similar to toxic epidermal necrolysis have been documented and were followed by disseminated intravascular coagulopathy and death. Tea tree oil has caused transient paresis in small dogs when applied as a flea treatment to the backline. With severe exposure, hepatic failure may result, especially in the cat because of the need for glucuronide conjugation. Induction of the cytochrome P-450 system may also occur.

Decontamination of the skin with a mild soap and symptomatic treatment of other clinical signs are necessary. Gut decontamination, through the use of emesis, gastric lavage, charcoal, or enemas, may be performed, especially in cases of recent exposure. Emesis should not be performed if the level of consciousness is altered or if aspiration pneumonia is a concern. No specific antidote exists for essential oil intoxication. In humans, N-acetylcysteine has been used for pennyroyal toxicosis. The prognosis is guarded, depending on the severity of clinical signs, which may last several days; however, with supportive care most animals recover.

70 CHAPTER • 70 Chemical Toxicities

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Hazardous chemicals are found throughout the home, and a significant potential exists for poisoning after exposure to these agents. Most veterinary toxicology cases are the result of accidental dermal or oral exposure arising from improper storage or handling of these chemicals within the home. Timely decontamination through bathing, gastric lavage, or use of emetics, activated charcoal, and cathartics serve to reduce systemic absorption acutely after exposure. However, risks associated with these procedures (e.g., handling, aspiration, sedation) must be weighed against potential therapeutic benefits. This chapter provides brief synopses of commonly involved chemicals, both active and vehicle ingredients. Its purpose is to provide a framework for appropriate case management of the poisoned small animal patient. For success, management must always be tailored to the animal's initial, and ever changing, clinical signs.

70.1 PETROLEUM DISTILLATES AND OTHER ALIPHATIC HYDROCARBONS

70.1.1 Sources

Kerosene, gasoline, and mineral seal oil are prototypical hydrocarbons.[1] Turpentine, a similar hydrocarbon product, is derived from pine oil. Hydrocarbons are found in lubricants, degreasers, waxes, varnishes, cleaning fluids, lamp oil, and starting fluids.

70.1.2 Signs

Most commonly the pulmonary system, central nervous system (CNS), and gastrointestinal (GI) system are involved.[1] Some animals emit a characteristic hydrocarbon odor, and many develop vomiting or diarrhea. Hepatotoxicity, renal toxicity, and cardiac arrhythmias may also occur. Of note, aspiration and chemical-induced pneumonitis are especially common after exposure to low-viscosity or highly volatile hydrocarbons. Aspiration is less common with higher viscosity hydrocarbons such as tar, oil, and grease. Nevertheless, owing to the risk of aspiration during drug-induced emesis or gastric lavage, these procedures are generally not recommended. Because volatile hydrocarbons may displace oxygen when aspirated, transient hypoxia and respiratory dysfunction may occur within minutes of exposure. Other signs related to aspiration pneumonitis include cough, hyperthermia, dyspnea, and cyanosis.

70.1.3 Management

Thoracic radiographs may reveal changes consistent with aspiration pneumonia. Oxygen and positive end-expiratory pressure therapy may prove necessary in cases where alveolar collapse and cyanosis are evident. Animals that remain asymptomatic for 6 to 12 hours after exposure are unlikely to develop pneumonitis. For dermal contamination with thick tarry or asphalt materials, mild detergents and fur clipping is most useful. Vegetable oil may be used to soften the material prior to removal. Of note, solvents or other hydrocarbons should never be used in an attempt to “dissolve” these compounds. Prophylactic antibiotics and steroids are generally not recommended.

70.2 NAPHTHALENE

70.2.1 Source

The primary source of naphthalene is moth balls.

70.2.2 Signs

Ingestion of large quantities of naphthalene may be associated with vomiting, lethargy, seizures, acute hemolytic anemia (reportedly at “doses of” 411 mg/kg), Heinz body formation, methemoglobinemia, hemoglobinuria, and renal failure.

70.2.3 Management

Treatment is largely based on GI decontamination and supportive care (i.e., fluid therapy, warming, control of methemoglobinemia with ascorbic acid or methylene blue) until recovery.

70.3 ETHANOL

70.3.1 Sources

Sources of ethanol[2] are ethanol-containing beverages, consumer products, and fermenting materials (e.g., raw sourdough, uncooked pizza dough, rotting apples[3]). The oral lethal dose is 5 to 8 g/kg.

70.3.2 Pathogenesis

Ethanol is metabolized by alcohol dehydrogenase to acetaldehyde, which is subsequently metabolized to acetate by aldehyde dehydrogenases. Metabolic acidosis resulting from acetate accumulation has been reported.

70.3.3 Signs

Intoxication generally develops within 1 hour of ingestion and may result in CNS depression, behavioral changes (e.g., vocalization, excitability), ataxia, hypothermia, and respiratory or cardiac arrest.

70.3.4 Management

Blood alcohol levels can confirm a diagnosis. Treatment is largely based on GI decontamination and supportive care (i.e., fluid therapy, warming, assisted ventilation) until recovery.

70.4 METHANOL (WOOD ALCOHOL)

70.4.1 Sources

Sources of methanol (wood alcohol[2]) are methanol-based automotive windshield fluid, antifreezes, and related consumer products. The oral lethal dose of methanol in the dog is 4 to 8 g/kg.

70.4.2 Pathogenesis

Methanol is metabolized to formaldehyde and formate. Unlike people, formate accumulation and subsequent blindness does not occur in dogs or cats exposed to methanol.

70.4.3 Signs

Clinically, methanol toxicosis resembles that of ethanol poisoning; it is therefore treated similarly.

70.5 ETHYLENE GLYCOL

70.5.1 Sources

Sources of ethylene glycol are automobile radiator antifreeze, heat exchange fluids, and some photographic solutions. A lethal dose of 95% ethylene glycol is 1.4 mL/kg in cats and 4.4 mL/kg in dogs. It remains one of the most common causes of poisoning in small animals.[4]

70.5.2 Pathogenesis

The initial metabolism of ethylene glycol to glycoaldehyde by alcohol dehydrogenase is rate limiting. Other major metabolites include glycolic acid, glyoxylic acid, and oxalic acid. An anion gap metabolic acidosis typically develops due to formation of these organic acids, in particular glyoxylic acid. Most of the oxalic acid is excreted in the urine; however, some may be retained as calcium oxalate. Calcium oxalate and hippuric acid crystals often precipitate in the renal tubules and in other organ vasculature systems.

70.5.3 Signs

Ethylene glycol toxicosis is best described as a triphasic syndrome.[4] Initially (within 1 hour of exposure), the animal appears ataxic or “drunk,” followed by a relatively asymptomatic period. Secondly (12 to 24 hours after ingestion), cardiopulmonary involvement inconsistently develops (e.g., cardiac failure). Thirdly (1 to 3 days later), animals commonly develop oliguric renal failure with renomegaly. These animals are depressed, anorexic, and often develop vomiting, renal pain, hypothermia, coma, and ultimately death. Unfortunately, many companion animals are not presented until this third phase.

70.5.4 Management

Urinalysis with polarized light microscopy may reveal the presence of calcium oxalate crystalluria. In addition, blood and tissue ethylene glycol levels can confirm a diagnosis. For recent exposure (≤2 hours), treatment consists of administering an emetic followed by activated charcoal and a cathartic. If the animal is presented within 8 to 12 hours after ingestion, treatment with ethanol or fomepizole (4-methyl-pyrazole [4-MP]) is indicated to inhibit further ethylene glycol metabolism.[5] Ethanol is given intravenously (IV) as a 20% solution in saline at a dose of 5 to 5.5 mL/kg every 6 hours for 5 to 6 treatments. The dose should be titrated to produce CNS depression but not semicoma. Alternatively, in dogs, 4-MP may be administered as a 5% solution, given as a slow IV bolus using a decreasing dose regimen. Initially, 4-MP is given at 20 mg/kg; followed by 15 mg/kg at 12 hours and again at 24 hours; and then 5 mg/kg at 36 hours.

Additional 4-mp doses of 3 mg/kg every 12 hours may be required if the animal has yet to fully recover or if ethylene glycol blood levels are still detectable. The advantage to using 4-MP is that it has minimal depressive side effects; however, it is not effective in cats.[5,6] Sodium bicarbonate may be given intraperitoneally to dogs and cats to control acidosis. In addition, diuresis with furosemide, mannitol, or dopamine may be necessary to correct unresponsive anuria or pulmonary edema. Peritoneal dialysis may also be used to manage acute oliguric renal failure. In general, with aggressive and appropriate therapy, exposed animals that have been examined before developing overt renal insufficiency would be expected to recover. Symptomatic animals have a poorer prognosis as a result of associated renal damage; however, renal tubular regeneration is still possible because the tubular basement membrane remains relatively unaffected.

70.6 PROPYLENE GLYCOL

70.6.1 Source

The source of propylene glycol is automotive radiator antifreeze. The acute oral lethal dose is approximately 9 mL/kg (dogs).

70.6.2 Signs

This toxic syndrome is similar to that observed during the acute phase of ethylene glycol toxicosis (i.e., ataxia, CNS depression).

70.6.3 Management

Treatment largely consists of supportive care and early GI decontamination. Alcohol dehydrogenase inhibitors are not required because propylene glycol is metabolized to lactic and pyruvic acid, both of which have low renal toxicity.

70.7 PHENOL PRODUCTS

70.7.1 Sources

The sources of phenol products[7,8] are household cleaners, disinfectants, and some antiseptic and germicidal agents. They are also used, in lesser concentrations, as preservatives. The oral LD_{50} of phenol in dogs is estimated to be only 0.5 g/kg. Cats are even more sensitive because of their limited glucuronyl transferase activity. Toxicosis induced by phenolic compounds is considered a medical emergency.

70.7.2 Pathogenesis and Signs

Phenols are very cytotoxic. Dermal exposure may result in coagulative dermal necrosis accompanied by intense pain. Ocular exposure may lead to significant corneal damage. Ingestion is associated with severe corrosion of the upper GI tract. Systemic effects include ataxia, weakness, tremors, coma, seizures, methemoglobinemia, and respiratory alkalosis. Liver and kidney damage may develop within 12 to 24 hours after exposure.

70.7.3 Management

N-acetylcysteine administration (140 mg/kg orally [PO] or IV initially; then 50 mg/kg every 4 hours for 3 days) may be partially effective to reduce hepatic and renal injury. Resultant methemoglobinemia should be treated with ascorbic acid or methylene blue.

70.8 ANTICOAGULANT RODENTICIDES

70.8.1 Sources

Anticoagulant rodenticides[9] include short-acting (e.g., warfarin) and long-acting (e.g., bromadiolone, brodifacoum, chlorophacinone, diphacenone, valone, pindone) agents.

70.8.2 Pathogenesis

These compounds principally interfere with vitamin K_1 hydroquinone recycling and thus inhibit clotting factor synthesis. A coagulopathy affecting the intrinsic, extrinsic, and common pathways ensues. Lethal doses vary considerably depending primarily on the anticoagulant involved but also on patient predisposing factors such as age, concurrent disease, and exposure history (single dose versus repeated ingestions). The acute oral toxic dose of warfarin in the dog or cat is 5 to 50 mg/kg; whereas repeated daily ingestion of as little as 1 mg/kg may result in severe toxicosis. The toxic dose of brodifacoum in dogs and cats is 0.2 to 4 and 25 mg/kg, respectively. Secondary or relay toxicity arising from the ingestion of poisoned rodents is uncommon.

70.8.3 Signs

Typically, signs develop within 2 to 5 days after exposure and may vary considerably depending upon the site and volume of blood loss. Signs may include petechiae and ecchymosis of the skin and mucous membranes,

hematomas, weakness, pallor, respiratory distress, and CNS depression. Hematemesis, epistaxis, melena, ataxia, paresis, seizures, and sudden death have also been reported.

70.8.4 Diagnosis

Significant prolongation of the activated clotting time (ACT), prothrombin time (PT), and activated partial thromboplastin time (aPTT) occurs. Elevated levels of the carboxylated forms of the vitamin K dependent coagulation factors also occur in exposed animals, and the proteins inhibited by vitamin K antagonists (PIVKA) test can help identify a vitamin K_1–responsive coagulopathy. Poisoned animals exhibiting respiratory distress should be radiographed to establish the presence of pleural, mediastinal, or pericardial fluid. Necropsy findings often include hemoperitoneum, hemothorax, and pulmonary hemorrhage. Postmortem samples for chemical analysis should include unclotted blood, liver, and GI contents.

70.8.5 Treatment

Vitamin K_1 is antidotal, with a recommended oral dose of 2.5 to 5.0 mg/kg given every 8 to 12 hours for either 2 or 4 weeks depending upon whether the ingested anticoagulant was a short-or long-acting agent. Synthesis of new clotting factors takes at least 12 hours. In the interim, clinically ill patients may need life-support measures (e.g., whole blood, fresh-frozen plasma transfusions) to prevent further blood loss. Coagulation screening tests should be reassessed 48 to 72 hours after cessation of vitamin K_1 therapy to determine whether additional K_1 supplementation is warranted. Restricting movement and exercise and providing a warm, safe environment is essential in preventing trauma-induced hemorrhage.

70.9 ZINC PHOSPHIDE

70.9.1 Source

Zinc phosphide[9,10] is a rodenticide. The lethal dose in dogs and cats is 20 to 50 mg/kg. Secondary toxicity is rare.

70.9.2 Pathogenesis

Within the acidic environment of the stomach, ingested zinc phosphide is converted to phosphine gas that in turn damages capillary endothelium and erythrocyte membranes within the lung, liver, and kidney.

70.9.3 Signs

Anorexia, lethargy, weakness, abdominal pain, and vomiting commonly occur within 1 to 4 hours of ingestion. 258
Signs may progress to recumbency, whole-body tremors, seizures, cardiopulmonary collapse, and death. Gross 259
and microscopic findings may include pulmonary edema and hemorrhage, as well as mild hepatic and renal necrosis.

70.9.4 Management

No specific antidote exists; however, supportive therapy including antacids (containing magnesium or aluminum hydroxide) is considered beneficial.

70.10 CHOLECALCIFEROL (VITAMIN D)

70.10.1 Sources

The sources of cholecalciferol (vitamin D[9,11]) are certain rodenticides and vitamin D–based creams and medications. The toxic dose of cholecalciferol in dogs is 1.5 to 8 mg/kg. Cats are likely equally sensitive.

70.10.2 Pathogenesis

Cholecalciferol and other vitamin D metabolites abnormally increase intestinal absorption of calcium, stimulate bone resorption, and increase the renal tubular reabsorption of calcium, thereby resulting in persistent hypercalcemia (serum calcium >12 mg/dl). Soft tissue mineralization may occur and when severe can be apparent radiographically. Death is usually due to cardiac failure, renal failure, or both. Serum phosphorus, ionized calcium, parathyroid hormone, and 25-hydroxycholecalciferol levels may serve to rule out other causes of hypercalcemia.

70.10.3 Signs

Signs of cholecalciferol toxicity typically appear within 3 to 5 days after ingestion and include anorexia, CNS depression, vomiting occasionally with hematemesis, muscle weakness, constipation, bloody diarrhea, polyuria, and polydipsia.

70.10.4 Treatment

Prompt GI decontamination is indicated as soon after ingestion as possible. Ancillary therapy is directed at increasing renal calcium excretion via furosemide administration (5.0 mg/kg IV followed by 2.5 mg/kg PO three times a day (tid) or four times a day (qid) in combination with aggressive fluid therapy (physiologic saline at rates up to two times maintenance). In addition, prednisone (2 to 3 mg/kg PO once a day [qd] to twice a day [bid]) aids in decreasing both osteoclastic activity and GI calcium absorption. Calcitonin (4 to 6 IU/kg subcutaneously [SQ] every 2 to 3 hours) may serve to further reduce serum calcium concentrations; however, some animals become refractory. Vomiting and anorexia are common adverse side effects. Pamidronate disodium IV (1.3 to 2.0 mg/kg in 0.9% saline) has been shown to reverse cholecalciferol-induced hypercalcemia.[6] Prolonged treatment (up to 4 weeks in some cases) may be required. Periodic reassessment of serum calcium, phosphorus, potassium, blood urea nitrogen (BUN), and creatinine levels is prudent. Once serum calcium and phosphorus levels have been normalized and the patient appears stable, most animals can be treated on an outpatient basis.

70.11 BROMETHALIN RODENTICIDES

Cats are especially sensitive to bromethalin rodenticides,[8,12,13] with toxic doses of 0.3 and 2.5 mg/kg in cats and dogs, respectively.

70.11.1 Pathogenesis

Bromethalin uncouples oxidative phosphorylation, resulting in myelin edema in the brain and spinal cord.

70.11.2 Signs

Relatively high-dose acute exposure results in severe muscle tremors, hyperexcitability, vocalization, running fits, seizures, hyperesthesia, vomiting, and dyspnea. More commonly, however, this toxic syndrome has a delayed and insidious onset (>12 to 24 hours); with clinical signs characterized by progressive ataxia, paresis, hind limb paralysis, and progressive CNS depression that may culminate in semicoma or coma.

70.11.3 Management

Treatment consists of (1) GI decontamination using repeated administration of oral activated charcoal; (2) control of cerebral edema with mannitol, dexamethasone, and furosemide; and (3) supportive care including effective control of seizures. Animals ingesting mild-to-moderate doses may improve over a 2-to 3-week period with aggressive supportive care. Prognosis is poor for severely affected animals.

70.12 PYRETHRINS AND PYRETHROID INSECTICIDES

Pyrethrins and pyrethroid insecticides[14,15] are lipophilic insecticides used for the control of ectoparasites. They are rapidly metabolized and excreted and rarely cause adverse effects in dogs and cats when used according to label instruction. Excessive or inappropriate administration, however, may result in clinical toxicity.

70.12.1 Signs

Most commonly, affected animals develop an acute onset of CNS depression, hypersalivation, muscle tremors, vomiting, ataxia, dyspnea, and anorexia. Less commonly, hyperthermia, hypothermia, weakness, and seizures may occur. Death is rarely observed. Of note, neither pyrethrins nor pyrethroid insecticides are inhibitors of acetylcholinesterase. Gross and microscopic changes are nonspecific.

70.12.2 Management

Treatment is aimed at reducing dermal or GI absorption and providing supportive care. Diazepam may be used to control muscle tremors and seizure activity. Atropine, although not a true antidote, can be used at low doses to control hypersalivation. The overall prognosis is very favorable, and the majority of animals recover within 1 to 3 days.

70.13 ORGANOPHOSPHOROUS AND CARBAMATE INSECTICIDES

Organophosphorous (OP) and carbamate insecticides[15] are lipophilic insecticides that are well absorbed from the skin and GI tract. Toxicity due to these agents is highly variable (Box 70-1).

70.13.1 Box • 70-1 National Pesticide Telecommunications Network

The National Pesticide Telecommunications Network is a useful source of toxicity data for pesticides (phone: 800-858-7378; website: http://ace.orst.edu/info/nptn). ASPCA-Animal Poison Control Center is another valuable resource that is provided on a fee-for-service basis. (phone: 888-426-4435).

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70.13.2 Pathogenesis

Carbamate insecticides are reversible acetylcholinesterase inhibitors. Most OP insecticides irreversibly inhibit this enzyme. In fact, most OP insecticides covalently bind this enzyme (i.e., aging) within 24 hours of exposure.

70.13.3 Signs

Toxicity results in a "cholinergic crisis" that is marked by muscarinic (i.e., salivation, lacrimation, bronchial secretion, vomiting, diarrhea), nicotinic (i.e., muscle tremors, respiratory paralysis), and mixed (i.e., CNS depression, seizures, miosis, hyperactivity) signs.

70.13.4 Diagnosis

Determination of reduced cholinesterase activity (<50% normal activity) in blood, brain, and retinal tissues is highly supportive of a diagnosis.[16] The prognostic value of this test is difficult to assess, especially in cats, where the very sensitive pseudocholinesterase enzyme comprises a large percentage of total blood esterase activity.

70.13.5 Treatment

Life-saving symptomatic therapy should be instituted immediately. Atropine sulfate (0.1 to 0.2 mg/kg, repeated as needed) is useful to alleviate severe bradycardia and excessive bronchiolar constriction and mucus hypersecretion. The reader should note, however, atropine will not abolish muscle tremors and other signs related to excessive nicotinic stimulation. Atropine doses should be adjusted to provide the minimum amount that alleviates dyspnea, bradycardia, and other signs of cholinergic stress. However, if tachycardia, GI stasis, hyperthermia, or severe behavioral changes (e.g., aggressiveness, delirium) occur, atropine should be decreased or discontinued. Enzyme reactivators may be used for treatment of OP insecticide toxicosis. Reactivators act on the OP insecticide-acetylcholinesterase complex to free the enzyme and restore normal function. Reactivators are most effective if "aging" has not yet occurred. Of the enzyme reactivators, pralidoxime chloride has received the widest clinical use. Pralidoxime chloride is given (20 mg/kg intramuscularly, repeated every 12 hours) to relieve tremors and other nicotinic signs and should be continued until these signs are alleviated or until additional benefit is no longer observed. Pralidoxime chloride generally has low toxicity; however, overdoses can cause tachycardia and cardiac arrhythmias. It is critical that further exposures to OP and carbamate insecticides be avoided until the animal is fully recovered. Complete recovery is ultimately dependent on the resynthesis of sufficient quantities of acetylcholinesterase enzyme—which may require up to 4 to 6 weeks.

70.14 2,4-DICHLOROPHENOXYACETIC ACID

70.14.1 Source

Animals are occasionally poisoned with the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D).[17,18] The approximate lethal dose of 2,4-D in dogs is 100 mg/kg. Poisoning is not expected to occur after exposure of pets to treated lawns.

70.14.2 Pathogenesis

The mechanism of action of 2,4-D is poorly understood.

70.14.3 Signs

Moderate exposure can result in an acute onset of anorexia, vomiting, and diarrhea with signs of toxicity typically abating within 48 hours. Greater exposures may result in CNS depression, ataxia, and hind limb myotonia.

70.14.4 Management

The diagnosis often relies on a known history of exposure, development of compatible clinical signs, typical electromyogram changes (e.g., fibrillation potentials), and residue analysis of urine samples. Treatment is nonspecific and includes the general principles of decontamination and maintaining normal fluid and electrolyte status. Fortunately, affected animals typically recover within a 24-to 72-hour period.

70.15 LEAD

Lead poisoning continues to be a significant toxicologic problem in companion animals.

70.15.1 Sources

A common cause of lead poisoning is ingestion of paints found in the interior of older buildings.[19] Veterinarians should warn owners of lead-poisoned animals that exposure of children may occur in the same environment. Other lead sources include batteries, linoleum, solder, plumbing supplies, and fishing line weights.

70.15.2 Signs

Chronic low-level lead poisoning is most commonly associated with GI signs, as evidenced by vomiting, abdominal pain, anorexia, diarrhea, and megaesophagus.[20] Constipation occurs less frequently. Acute, high-level lead exposure results most commonly in CNS signs, including behavioral changes, hysteria, ataxia, tremors, opisthotonos, blindness, and seizures.[21,22] In cats, GI signs appear to be more common than CNS signs.

70.15.3 Diagnosis

Nucleated erythrocytes may be found in peripheral blood smears of affected dogs without evidence of severe anemia.[22] Basophilic stippling is sometimes observed in red blood cells (RBCs). In cats, nucleated erythrocytes and basophilic stippling is found only occasionally. Toxicosis may be confirmed definitively by chemical analysis with blood lead concentrations ≥0.20 ppm being considered diagnostic.

70.15.4 Treatment

The cornerstone of treatment is the use of chelators to enhance metal elimination.[23] In general, chelator therapy should be initiated as soon after metal exposure as possible. However, prior to chelator use one should attempt to eliminate the source of lead within the GI tract. Surgery is indicated for removal of large lead-containing objects. For dispersed lead-laden material (e.g., paint dust, paint chips), oral administration of magnesium sulfate or sodium sulfate may serve to precipitate lead within the intestinal tract, thereby limiting further absorption. Of note, chelator administration may initially aggravate the clinical signs, and one should be prepared to control aggressiveness or seizures. Furthermore, to safely mobilize lead in patients with relatively high-dose exposures, several "courses" of chelator therapy may be warranted (i.e., 5 days of chelator therapy followed by 5 days of no therapy and so forth). Of the available agents, succimer (meso-2, 3-dimercaptosuccinic acid) is an orally active agent that appears quite effective in dogs and cats.[6,24] It has recently been approved for use in children and will likely emerge as the primary drug of choice in veterinary medicine. It is administered at 10 mg/kg, three times a day for 10 to 17 days. To date, it has been associated with few side effects. Alternatively, calcium disodium EDTA is an effective metal chelator. It should be diluted to 10 mg/ml with 5% dextrose, then administered subcutaneously at 25 mg/kg, qid, for 2 to 5 days. Another agent, D-penicillamine has also been used, most commonly as a follow-up agent after treatment with calcium disodium EDTA. D-penicillamine is administered orally at 110 mg/kg/day (divided every 6 to 8 hours) for 1 to 2 weeks. If toxicity to D-penicillamine develops, as evidenced by vomiting, CNS depression, and anorexia, the dose should be reduced.

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70.16 ZINC

70.16.1 Sources

Sources of zinc include zinc nuts, pennies minted after 1981, and zinc oxide-containing products (e.g., diaper rash ointments, cosmetics).[25,26]

70.16.2 Signs

Acute zinc oxide poisoning results in severe vomiting, CNS depression, and lethargy, with diarrhea occurring less commonly. Subacute or chronic elemental zinc poisoning may result in anorexia, vomiting, diarrhea, CNS depression, pica, hemolysis, regenerative anemia, spherocytosis, an inflammatory leukogram, icterus, and renal failure.

70.16.3 Diagnosis

Diagnosis is based on the history of exposure, development of compatible clinical signs, and the presence of radiodense material within the GI tract. Hypocupremia may be present, presumably from zinc antagonism of the GI absorption of copper. Blood and tissue levels may confirm a clinical diagnosis, but care should be taken to collect samples in containers appropriate for trace mineral analysis.

70.16.3.1 Treatment

As with lead ingestion, removing the source of zinc, either through emesis or surgery, is important. Supportive care and chelation therapy with calcium disodium EDTA are also indicated.[26] Of note, animals with zinc poisoning appear to have high postoperative complication rates. One should also anticipate that serum zinc concentrations would decrease rapidly after removal of the source.

70.17 IRON

70.17.1 Sources

Sources of iron are multivitamins and other iron-containing medications. Animals should be monitored for possible clinical signs of iron toxicosis if elemental iron has been ingested in excess of 60 mg/kg. Potentially lethal doses of iron are in the range of 200 to 250 mg/kg.

70.17.2 Signs

Clinical signs observed shortly after ingestion are characterized by certain acute GI effects: vomiting, abdominal pain, diarrhea, hematemesis, and melena. These signs may resolve within 6 to 24 hours after ingestion. Many poisoned animals do not progress beyond this stage; however, life-threatening signs associated with multisystem failure may occur 1 to 3 days after ingestion.

70.17.3 Management

Treatment of animals that have ingested large amounts of iron includes the use of an emetic if ingestion was less than 2 hours. This is followed by administration of activated charcoal plus a saline or osmotic cathartic. If potentially toxic amounts (>60 mg/kg) of iron were ingested, gastric lavage with magnesium hydroxide at 5 to 10 times the dose of elemental iron has been shown to be effective. Whole-bowel irrigation with a polyethylene glycol electrolyte solution may also be effective for decontaminating the GI tract after iron ingestion. Finally, deferoxamine, a chelating agent, should be considered after large ingestions of iron. It is administered 15 mg/kg/hour IV.[27]

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71 CHAPTER • 71 Clinical Genetics

Urs Giger

Recent developments in molecular and human genetics have increased the interest in using this tool in the diagnosis, management, and control of hereditary disorders. Genetics has emerged as an important discipline in small animal practice for several reasons. Effective preventative measures have reduced the frequency of infections, nutritional disturbances, and intoxications. Furthermore, life-saving advances in medicine and surgery have increased the chance of survival of companion animals and thus tend to raise the recognition of genetic defects. Inbreeding practices to preserve desirable traits in certain breeds favor the occurrence of recessively inherited diseases. Technologic advances have allowed the recognition and characterization of the clinicopathologic, biochemical, and molecular basis of many hereditary diseases. In the past, genetics played a large role in a few patients; however, today hereditary disorders and genetic predispositions to diseases are critical in small animal practice for most patients. Specific hereditary disorders are covered under chapters of individual organ systems. This chapter on clinical genetics reviews the general characteristic clinical features of hereditary diseases in small animals, the various modes of inheritance, the screening of specific tests used to reach a diagnosis, as well as the management of these diseases and control in future generations. The importance of genetic counseling is addressed (i.e., providing information for pet owners and breeders of animals afflicted with hereditary disorders, concerning the consequence of such disorders and the ways in which they can be prevented by informed breedings). Furthermore, the recent completion of the human and canine genome sequence and initiative for a feline genome sequence have greatly facilitated the research of single-gene and complex inherited diseases. The field of *genomics* is the study not only of single genes but also of the organization, function, and interaction of all genes in the genome, including their interaction with environmental factors.

71.1 FREQUENCY

Because of the increased awareness (on the part of breeders, pet owners, and veterinarians) of genetic defects and improved diagnostic abilities in clinical practice, the number of reported hereditary diseases in small animals is rapidly growing. Originally, diseases with apparent clinical manifestations affecting the appearance and gait of an animal were recognized. Thus it is not surprising that skeletal malformations, skin and eye abnormalities, and neuromuscular defects were more frequently reported than disorders involving internal organs. Furthermore, clinicians now recognize that animals with recurrent or chronic infections or immune-mediated diseases may have a genetic defect that dysregulates one of their immune functions. Other genetic predispositions of certain animals, families, or breeds to develop disorders such as hip dysplasia, gastric torsion, adverse drug reactions, and cancer have been clearly established.

At present, approximately 430 hereditary diseases in dogs and 180 disorders in cats have been adequately documented. By comparison, several thousand hereditary disorders have been accumulated in the compendium known as *Online Mendelian Inheritance in Man* (OMIM) by Victor McKusicks. Practically all hereditary diseases described in small animals have also been seen in humans and generally represent close homologues.

Although any genetic defect may occur in any animal, many have been documented only in one family or breed. In some breeds, the frequency of a particular disorder and the mutant allele may reach high proportions. This may be due to a “founder” effect in which one or more of the founders of a small ancestral group was a carrier or even affected, or it may be as observed in several smaller breeds in which a “popular sire” was later determined to be a carrier of a mutant gene. Unfortunately, genetic disease frequencies are generally not available or are severely biased because of data collection. For instance, the prevalence of hip dysplasia may differ greatly depending on

methods used to reach a diagnosis and whether a registry requires or only encourages recording of every examined animal. Large-scale randomized screening programs and open registries with data on genetic diseases in certain breeds have rarely been established. In people, a disease occurrence of 1 in less than 500 individuals is considered a high-frequency disorder. In companion animals, many hereditary diseases appear to occur in 1% to 10% of certain breed populations. Recently, resources have become available to obtain genetic information. In addition to the list of hereditary diseases and associated breeds in the appendices of this book, other published lists organized by breed or disease are available. A list of genetic diseases in all species with references assembled by Frank W. Nicholas, known as *Mendelian Inheritance in Animals* (MIA), can be obtained online on Cambridge University's website. The most comprehensive and updated searchable information on canine hereditary traits, however, is Donald F. Patterson's *Canine Genetic Disease Information System*, available in book format.

71.2 INHERITANCE

Genetic diseases are caused by chromosomal alterations or gene mutations. Disease-causing mutations are heritable changes in the sequence of genomic deoxyribonucleic acid (DNA) that alter the expression, structure, and function of the coded protein. The *genotype* refers to the animal's genetic makeup (reflected by its DNA sequence), whereas the *phenotype* relates to the entire makeup of an animal (determined both genetically and environmentally). The molecular genetic defect is now known for more than 40 hereditary disorders in small animals (Table 71-1). Among the disorders caused entirely or partly by genetic factors, three main types are recognized: (1) chromosomal, (2) single gene, and (3) complexor multifactorial disorders. For approximately half of the disorders suspected to be of a genetic nature, however, the mode of inheritance remains unknown. These molecular genetic changes include point mutations, deletions, and insertions in the DNA sequence that result in a missense or nonsense sequence with an altered codon sequence. A codon is a three base sequence of DNA or RNA that specifies a single amino acid.

Table • 71-1 Examples of Hereditary Disorders Characterized at the Molecular Genetic Level

DISORDER	BREED
Hematologic Disorders	
Elliptocytosis (band 4.1) deficiency	Mixed breed dog
Pyruvate kinase (PK) deficiency	Basenji, West Highland white terrier, Cairn terrier, Beagle, Eskimo toy, Dachshund, Abyssinian, Somali, DSH cat
Phosphofructokinase (PFK) deficiency	English springer and American cocker spaniel, mixed breed dog
Hemophilia A (Factor VIII)	Mixed breed, Irish setter
Hemophilia B (Factor IX)	Airedale terrier, Labrador retriever, mixed breed
von Willebrand disease	Doberman, Manchester terrier, Pembroke Welsh Corgi, Bernese mountain dog, Kerry Blue, Poodle, Papillon
vWD type 1	
vWD type 2	German shorthair, wirehair pointer
vWD type 3	Dutch Kooiker, Scottish terrier, Shetland sheepdog
Severe combined immunodeficiency (SCID)	Basset, Pembroke Welsh corgi
Leukocyte adhesion deficiency (LAD)	Irish setter, red and white setter
Complement component 3 deficiency	Brittany spaniel
Hereditary Eye Diseases	
Progressive retinal atrophy	Irish setter, red and white setter
PRA dominant	Bull mastiff, English mastiff
PRA type A	Miniature schnauzer
PRA X-linked	Samoyed, Siberian husky
PRA red 1	B phosphodiesterase
PRA red 1a	Sloughi
PRA red 3 (pred)	Cardigan Welsh Corgi
Progressive cone dysplasia	Chesapeake Bay and Labrador retriever, English cocker spaniel, Portuguese water dog, Australian cattle dog, Miniature and toy poodle, Entlebuchers,
PRA pred (linkage)	American Eskimo, Nova Scotia Duck Tolling Retrievers
Stationary night blindness	Briard
Con (retinal) degenerative	German short haired pointers
Neuromuscular Diseases	
Shaking puppy syndrome	English springer spaniel
Dystrophin muscular dystrophy	Golden retriever, Rottweiler, DSH cat, mixed breed
Mucopolysaccharidosis type I	Plott hound
type IIIA	Wirehaired dachshund, New Zealand Huntaway dog
type IIIB	Schipperke
type VI	Siamese cat (two mutations), Miniature pinscher, miniature Schnauzer
type VII	German shepherd, mixed breed, DSH cat
Alpha mannosidosis	Persian, DSH cat
Gangliosidosis GM1	Siamese, Korat cat, Portugese water dog
GM2	Korat cat
Globoid cell leukodystrophy (Krabbe)	West Highland white and Cairn terrier
Glycogenosis type IV	Norwegian forest cat
Alpha fucosidosis	English springer spaniel
Neuronal ceroid lipofuscinosis	English setter
Myotonia congenital	Miniature schnauzer
Narcolepsy	Doberman, Labrador retriever, dachshund
Ivermectin toxicity (MDR-1 gene)	Collie, Sheltie, Australian cattle dog
Deafness	German short haired pointers
Hepatic Diseases	
Congenital hypothyroidism with goiter	Toy fox terrier
Hyperchylomicronemia	DSH cat

Glycogenosis type Ia	Maltese
Copper toxicosis	Bedlington terrier
Cobalamin malabsorption	Giant Schnauzers
Renal Diseases	
Cystinuria type I	Newfoundland, Labrador retriever
Renal adenocarcinoma and nodular dermatitis	German shepherd (linkage)
X-linked nephropathy	Samoyed
Polycystic kidney disease	Persian and other cats
A list of test laboratories is available at www.vet.upenn.edu/penngen.	

The dog has 76 autosomes (38 pairs) and 2 sex chromosomes (78XX or 78XY), whereas the cat has 38XX or 38XY. The human genome project has facilitated progress in canine and feline gene mapping. Furthermore, the canine genome sequence is nearing completion. Through physical and genetic mapping strategies, genes have been assigned to and localized along a chromosome, and new genes can be identified.

71.2.1 Chromosomal Disorders

Chromosomal disorders are caused by an excess or deficiency of genes contained in a chromosome or chromosomal segment. Understandably, such defects may result in severe, often lethal clinical syndromes. Although alterations of autosomes have only rarely been reported in small animals—some had syndromes with multiple defects—they are commonly reported in infants and are often responsible for fetal losses. In contrast, abnormalities involving the X and Y chromosomes leading to sex development disorders are well recognized. The best example is the tricolored (calico, tortoiseshell) male cat with testicular hypoplasia and an XXY chromosome set. However, not every sex developmental disorder is due to a defect in the sex chromosomes (e.g., XX sex reversal reported in various canine breeds).

71.2.2 Single-Gene Traits

The inheritance of a single-gene defect is often called *Mendelian trait* and involves one mutant gene (allele) at a single locus. When an animal has a pair of identically mutant genes (alleles), it is said to be *homozygous* (a homozygote), whereas when only one of the alleles is mutated, it is said to be *heterozygous* (a heterozygote) at that gene locus. The pattern of inheritance depends mainly on two factors: (1) whether the mutation is located on an autosome (autosomal) or on the X chromosome (X linked) and (2) whether the phenotype, the observable expression of a genotype as a disease trait, is dominant (i.e., expressed when only one chromosome of a pair carries the mutation) or recessive (i.e., expressed when both chromosomes of a pair carry the mutation). Therefore it is the phenotype rather than the mutant gene or protein that is dominant or recessive. In humans most diseases are dominantly inherited, whereas recessive traits resulting from inbreeding practices are more commonly been in small animals.

71.2.3 Autosomal Recessive Inheritance

Autosomal recessive inherited traits are common in small animals. The parents of affected animals must carry the mutant allele. Because they are generally asymptomatic carriers (heterozygotes), they are called *obligate carriers*. Typically one fourth of males and females in a litter are likely to be affected. Phenotypically normal offspring may be in a ratio of 2:1, either carriers (heterozygotes) or free of the mutant allele (“clear,” homozygous normal). Although the parents could also be affected, diseased animals generally are not used for breeding, unless they remain unrecognized because signs do not develop until later in life (late-onset diseases).

71.2.4 X Chromosomal Recessive Inheritance

In X chromosomal recessively inherited disorders, males who are hemizygous for the X chromosome are either affected or normal, whereas females are typically carriers (one normal and mutant allele on X chromosome). When heterozygous females (carriers) are mated to a normal male, half of their male offspring will be affected and half of their female offspring will be phenotypically normal carriers (whereas the other males and females will be "clear"). The mutant X chromosomal gene is never passed on from the sire to a male offspring but is transmitted by an affected male to all of its female offspring (obligate carriers). Affected females would occur only if a carrier female is mated with an affected male. Heterozygous females are usually unaffected, although some manifestations may occur because of X chromosomal inactivation. In addition, an X-linked dominant trait may need to be considered but has been reported only in Samoyeds with a specific glomerulonephropathy. X-linked disorders should not be confused with sex-limited disorders, such as diseases related to the primary and secondary sex organs. Y chromosomal diseases have not been reported in animals.

71.2.5 Autosomal Dominant Inheritance

In autosomal dominant conditions, the disease appears in every generation. An affected animal generally has one affected parent unless this animal has a new mutation in the gamete of a phenotypically normal parent or when the disease is variably expressed (nonpenetrant in parent). *Penetrance* refers to the likelihood that an animal carrying a particular mutation will exhibit an altered phenotype. Males and females are equally likely to transmit the disease to an offspring of either sex. Because affected animals are generally heterozygous, half of all offspring will be affected. Affected animals generally are not used in breeding programs, hence rapidly eliminated. Furthermore, homozygous states of dominant traits are often lethal and thus result in fetal loss or stillborns.

71.2.6 Mitochondrial Inheritance and Imprinting

Mitochondrial inheritance is a rare and atypical hereditary disorder involving mitochondrial DNA. Because all mitochondrial DNA is transmitted from the ova (mother), all offspring from an affected female (but none from an affected male) will be diseased. In humans, several neuromuscular diseases are known to be associated with mutations in mitochondrial DNA. In dogs, some myopathies may be caused by a mitochondrial defect.

Imprinting is another non-Mendelian mechanism for single-gene disorders. Here the effects of certain genes depend on whether they are inherited through the maternal or paternal parent. In companion animals this phenomenon has not yet been documented.

71.2.7 Complex or Multifactorial Inheritance

A number of developmental disorders resulting in congenital malformations are caused by complex or multifactorial inheritance, as well as other disorders in adult animals. Rather than having one single-gene error, several major and minor gene defects (polygenic) in the genetic information, together with certain environmental factors, can produce or predispose to a serious illness. Hip and other dysplasias and certain congenital heart defects (conotruncal defect) are examples, and the degree to which a trait (e.g., hip dysplasia) is genetically determined may greatly vary between breeds (heritability). Thus the hereditary nature of a particular disease may be suggested or established by a certain familial occurrence, breed predilection, breeding studies, established mode of inheritance, identified gene defect, or a combination of these factors.

71.3 CLINICAL SIGNS

Hereditary defects can involve any gene and hence, any organ. Therefore the clinical signs of hereditary diseases are extremely variable and may mimic acquired disorders. Some typical features, however, may raise our suspicion of a genetic disorder. In contrast to infectious diseases, intoxications, and nutritional imbalances that generally affect an entire litter, hereditary diseases often involve only a few in a litter. Furthermore, the age of onset of clinical signs for a particular gene defect is rather specific and independent of environmental factors.

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Most genetic defects cause clinical signs early in life. Fetal resorptions, late abortions, and stillborns may be caused by genetic traits but are rarely determined. Most puppy and kitten losses occur during the first week of life, shortly after the maternal homeostatic system can no longer compensate for an endogenous defect and are generally not shown to the veterinarian as they are considered of the usual losses by breeders. Some neonatal kitten losses have recently been attributed to blood type incompatibility: Type A and AB kittens born to Type B queens develop life-threatening neonatal isoerythrolysis when nursing and absorbing anti-A–containing colostrum during the first day of life. Certain congenital malformations may also not be compatible with life, such as severe cleft palates and hernias. The term *congenital* only implies that the disease is present at birth, however, and does not necessarily mean it is hereditary.

A common problem in puppies or kittens that have problems due to hereditary conditions is *failure to thrive*. These animals lag behind their healthy littermates in their development; they do not gain weight at a normal rate and are generally lethargic. They often fade (hence the term *fading puppy or kitten syndrome)* and finally die. Failure to thrive should not be confused with *growth retardation*, which refers to a proportionally stunted growth that may or may not be associated with other clinical signs. In addition to these relatively unspecific clinical signs, some hereditary defects may cause specific clinical manifestations. Easy to recognize are malformations that involve any part of the skeleton and can lead to disproportionate dwarfism, gait abnormalities, facial dysmorphia and other malformitives. A large number of hereditary eye diseases have been described in dogs, some of which are not recognized until adulthood. Neuromuscular signs may vary from exercise intolerance to ataxia and seizures. Defects of many other internal organs are associated with unspecific clinical signs. Many disorders cause an isolated typical sign, whereas others produce a characteristic overall pattern of anomalies known as specific *syndromes*.

Clinical manifestations of hereditary diseases are extremely variable, ranging from benign to debilitating and lethal. They are usually chronic, progressive (i.e., once an animal shows signs, it probably will not recover), and often cause death at an early age. A few hereditary defects, however, result in intermittent or recurrent problems, such as hereditary bleeding disorders and primary immunodeficiencies.

71.3.1 Diagnostic Tests

Diagnostic tests generally are required to support or confirm the diagnosis of a genetic disorder. Radiology and other imaging techniques may reveal skeletal malformations or cardiac anomalies. Ophthalmologic examination may further define an inherited eye disease; although some are not recognized before several years of age. Routine tests such as complete blood count (CBC), chemistry screen, and urinalysis may suggest some specific hematologic or metabolic disorders or rule out many acquired disorders. Furthermore, clinical function studies may better define a GI, liver, kidney, or endocrine problem. Histopathology or electron microscopy of a tissue biopsy (or both) from an affected animal or from the necropsy of an affected littermate or relative may give the first clue as to a genetic defect.

A few laboratories provide special diagnostic tests that allow a specific diagnosis of an inborn error of metabolism. *Inborn errors of metabolism* include all biochemical disorders due to a genetically determined, specific defect in the structure, function, or both of a protein molecule. Aside from the classical enzyme deficiencies, genetic defects in structural protein receptors, plasma and membrane transporters, and other proteins covered by this definition will result in biochemical disturbances. The laboratory approach is to detect the failing system or to determine the specific protein or gene defect. Disorders of intermediary metabolism typically produce a metabolic block in a biochemical pathway leading to product deficiency, accumulation of substrates, and production of unusual substances via alternative pathways. The most useful specimen to screen for biochemical derangements is urine because abnormal metabolites in the blood will be filtered through the glomeruli but fail to be reabsorbed (because no specific renal transport system exist for most abnormal metabolites).

Once the failing system has been identified, the defect can be determined at the protein level. These protein assays include the classic enzyme function tests and immunologic assays. Because most enzymes are present in abundant amounts, no major functional abnormalities are generally observed unless the enzyme activity is severely reduced, usually to less than 20% of normal value. Thus homozygously affected animals have very low-protein activity, quantity, or both, often in the range of 0% to 10%. These tests may also be used to detect carriers (heterozygotes) that typically have intermediate quantities at the protein level (30% to 70%) but no clinical signs. Unfortunately, protein assays are labor intensive and require submission of appropriate fresh tissue or fluid (and a control sample) under special conditions to specialized laboratories. The section of Medical Genetics at the School of Veterinary Medicine of the University of Pennsylvania performs tests to diagnose known conditions and to study potential new disorders (www.vet.upenn.edu/penngen).

The molecular defect has been identified for over three-dozen hereditary diseases in companion animals; thus DNA screening tests have been developed. These tests are mutation specific and can therefore only be used in animals suspected of having the exact same gene defect. Small animals within the same or a closely related breed will likely have the same disease-causing mutation for a particular disease (e.g., phosphofructokinase deficiency in English springer and American Cocker spaniels), as will mixed breed dogs due to mother-son or father-daughter matings with one parent. However, dogs, cats, and unrelated breeds of species with the same disorder will likely have different mutations, as shown with X-linked muscular dystrophy and erythrocyte pyruvate kinase deficiency in various breeds of dogs and cats.

DNA tests have several advantages over other biochemical tests. The test results are independent of the age of the animals; thus tests can be performed long before an animal is placed in a new home and before clinical signs become apparent. DNA is stable, and only the smallest quantities are needed. Therefore no special shipping arrangements are necessary as long as one follows the specific instructions for biologic products. DNA can be extracted from any nucleated cell (e.g., blood, buccal mucosa [cheek swabs], hair follicle, semen, formalinized tissue). For instance, blood can be sent in an EDTA tube, or a drop of blood can be applied to a special filter paper for DNA extraction. Buccal swabs can be obtained with special cytobrushes. This method should not be used in nursing animals, or only hours after nursing and rinsing the oral cavity with water. The DNA segment of interest is amplified with appropriate forward and reverse primers and polymerase chain reaction (PCR). The mutant or normal allele (or both) is identified by DNA size difference directly on a gel (in case of deletions or insertions) or after restriction enzyme digestion for point mutations or other suitable test systems to differentiate normal and mutant allele. These tests are generally simple and accurate as long as appropriate techniques and controls are used, but human errors in identifying samples can still occur. Furthermore, they can be used not only for the detection of affected animals but also for carriers. Such testing is extremely valuable to select breeding animals that will not cause disease or further spread the disease-causing allele. For instance, phosphofructokinase deficiency was recognized to cause intermittent anemia and myopathy

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in English springer spaniels, and a DNA-based test became available in the early 1990s. There were still 4% and 1% carriers in the field trial and conformation lines, respectively, in the first randomized survey performed in 1998. If an animal with all the desirable qualities is found to be a carrier, it could be bred to a clear animal (homozygous normal) because this would not result in any affected offspring. However, offspring would need to be tested, and only clear animals would be used in subsequent breedings.

For many inherited disorders the defective gene remains unknown; however, for a few, a polymorphic DNA marker that is linked to the disease-causing mutant allele has been discovered (see chapter on genome). Such linkage tests were first developed for copper toxicosis in Bedlington terriers and are now available for some forms of retinopathy, in various breeds and renal carcinoma with nodular dermatitis in German shepherds. They are accurate for a particular animal as long as an affected animal is in its family (informative family). At present, mutation-specific and linkage tests are available only for single-gene defects in small animals. However, complex genetic traits may also soon be approached by these methods.

71.3.2 Prognosis and Therapy

Because the clinical consequences of the many hereditary disorders vary greatly, it is not surprising that the prognosis for survival and quality of life ranges from excellent to grave. The clinical course and outcome for a particular defect is rather similar among affected animals. Some defects are recognized as a breed characteristic (e.g., fold ear in Scottish folds and lack of tail in Manx [both dominant traits]) or an incidental finding (e.g., microcytosis in Akitas), whereas others are progressive and lead to severe organ dysfunction and death (e.g., many lysosomal storage diseases).

At present the therapeutic options in the treatment of hereditary diseases are limited, and ethical principles need to be carefully considered. Although several structural malformations can be surgically corrected (e.g., cryptorchism, hernias, hepatic shunts, patent ductus arteriosus [PDA]), these animals should not be shown or bred. In a few cases a deficient protein, cofactor, substrate, or metabolite can be supplemented to correct the defect. For instance, vitamin B_{12} deficiency in cachectic and lethargic giant schnauzers and Border collies with an ileal receptor defect can be helped by monthly cobalamin injections. Pancreatic enzyme supplementation and daily insulin injections are used to manage animals with exocrine or endocrine pancreatic insufficiency, respectively. Fresh frozen plasma is administered in the treatment of hereditary coagulopathies and von Willebrand's disease whenever animals excessively bleed. Other enzyme and protein replacements are also experimentally attempted.

Although kidney transplants have been established in clinical practice for chronic renal failure in cats, they have not been applied in animals with hereditary (juvenile) renal disorders. Several hereditary disorders of hematopoietic cells have been experimentally corrected by bone marrow transplantation (e.g., pyruvate and phosphofructokinase deficiency, cyclic hematopoiesis, and interleukin-2 [IL-2] receptor defects). Furthermore, bone marrow transplantation is being attempted to deliver functional cells or active proteins to other tissues including liver, bone, and brain (e.g., in lysosomal storage disease). Finally, gene therapy, the integration of a functional gene into the patient's own defective cells, will likely be clinically feasible in the twenty-first century. Experiments in rodent models have provided encouraging results. However, effective gene therapy has proven more difficult in larger mammals, and the technology needs to be further improved to achieve persistent and regulated gene expression in larger mammals including humans, dogs, and cats. One of the first and most promising canine gene therapy experiments has been the correction of mucopolysaccharidosis type VII in neonatal puppies with a retroviral vector carrying the beta-glucuronidase gene; these treated animals remain ambulatory, whereas affected animals become tetraparetic by a few months.

71.3.3 Control

Much more important than the treatment of hereditary disorders is the control of these traits in breeding programs. Thus to reduce the frequency or altogether eliminate a genetic defect, the further spread of the mutant gene has to be prevented in a family or entire breed. It is obvious that affected animals of any genetic disease should not be used for breeding. This approach is simple and effectively eliminates disorders with a dominant trait. For recessively inherited disorders, however, the elimination of affected animals is not sufficient to markedly reduce the prevalence of a defect within a breed, kennel, or cattery. It may be safest not to breed any related animals of affected animals, as requested by some kennel clubs; however, this practice may (because of inbreeding and narrow gene pools in some breeds) eliminate all breeders in an entire kennel or cattery and severely reduce the genetic diversity of a breed. Thus it will be pivotal to detect carriers (heterozygotes) and truly “clear” animals (homozygous normal). Obligate carriers can be readily identified for autosomal (both parents of affected) and X chromosomal recessive (mother of affected) disorders. As mentioned previously, for some diseases, reliable carrier detection tests are available, and many breeders know about them and inform the veterinarian. For instance, carriers have half-normal (~ 50%) enzyme activity by functional assays or have a normal *and* mutant DNA sequence for the diseased gene on a DNA test. Breeders should therefore be encouraged to screen their animals before breeding for known genetic diseases whenever carrier tests are available. Their availability is also listed on several websites including www.vet.upenn.edu/penngen. Unfortunately, many breeders mistrust these newer tests; either they were disappointed by inaccuracy of early tests, such as the radiographic examination for hip dysplasia, or they fear that the results may become public and could hurt their business. Thus breeders need to be educated by well-informed veterinarians. If a particular carrier needs to be used because of a narrow gene pool and many desirable traits, it should only be bred with a homozygously normal (clear) animal; all its offspring need to be tested, and only clear animals should be used in future breedings. If no carrier tests are available, a test mating between the dog in question and a known affected or carrier could be performed, and as long as no affected offspring and at least 5 healthy puppies or 11 healthy kittens, are born to “clear” an animal of a carrier state. For many breeders this approach is ethically unacceptable because it may produce affected animals.

In conclusion, it is exciting to learn about recent advances in the understanding of hereditary disorders and genetic predispositions in small animal practice, be it the advances in diagnostic approach to a hereditary disease, understanding of its pathophysiology, or its control. In addition to the clinician's responsibility to suspect a genetic disease and to appropriately diagnose it with modern, specific techniques, clinicians must become involved in the control of these disorders in the breeders' kennels or catteries. Practitioners thus can make an important contribution toward controlling the further spread of mutant genes and reducing future suffering of animals.

72 CHAPTER • 72 Abdominocentesis and Diagnostic Peritoneal Lavage

Elke Rudloff

Sterile procedure: There should be no gross evidence of intra-abdominal mass lesions, and the urinary bladder must be empty before the procedure. If the animal is unable to void voluntarily, careful manual expression or urinary catheterization is performed.

Surgical scrub required: The ventral abdominal skin from the xyphoid to pubis region is clipped free of hair and surgically prepared.

Conscious sedation: The clinician uses intravenous butorphanol 0.4 mg/kg or hydromorphone 0.2 mg/kg and diazepam 0.2 mg/kg; this is more important for diagnostic peritoneal lavage (DPL) than for centesis.

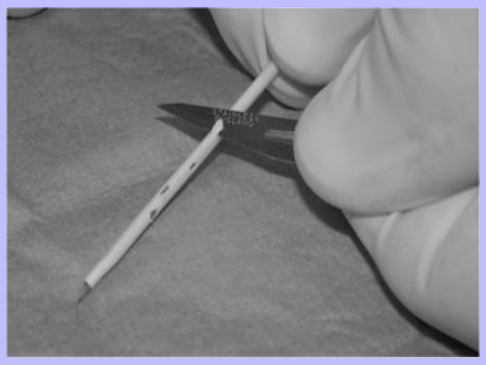
Local anesthesia required: Up to 4 mg/kg of lidocaine is used in the region where the needle or catheter is placed.

If an *abdominocentesis* is to be performed, the animal can be standing or in lateral recumbency. Ultrasound-guided centesis of any fluid pocket is the preferred method for fluid collection. If ultrasound is unavailable, a four-quadrant tap should be performed. In each of the four abdominal quadrants, an 18 to 22 gauge 1-inch needle or over-the-needle catheter is percutaneously inserted. Sample yield is maximized if fluid is allowed to flow out of the needle under the influence of gravity and not aspirated. A negative tap *does not* rule out the presence of intra-abdominal pathology.

If a DPL is to be performed, the animal should be placed in left-lateral recumbency or in a ventrodorsal position to avoid traumatizing the spleen.

Catheter placement for DPL: When using an over-the-needle catheter (Figure 72-1), the clinician should make a small skin incision at the site of the skin block and insert the catheter just through the body wall. There will be a slight pop as the peritoneum is penetrated. The catheter should then be rotated and advanced over the needle until it is fully inserted. If the catheter does not advance easily, it may still be in the subcutaneous tissue or against an organ and should be repositioned.

Figure 72-1 Over-the-needle abdominal catheter. Small side holes (two to four) are carefully cut into a 14-to 18-gauge 2-inch catheter 2 mm apart with a scalpel blade. The edges of the holes are kept smooth to prevent the catheter from barbing and possibly breaking.



Peritoneal lavage catheters (Figures 72-2 and 72-3) are usually placed using a Seldinger technique, with instructions contained in the kit. The kits contain all the materials necessary (except for the fluid to be infused), including local anesthetic, drapes, and disinfectants.

When placing a catheter, the following points should be kept in mind:

- If fluid freely drains from the catheter, samples should be collected (Figure 72-4).
- If no fluid drains, the clinician should infuse 20 mL/kg of warmed isotonic replacement crystalloid (e.g., 0.9% sodium chloride, Ringer's lactate solution) and clamp the infusion set. Then the animal should be gently rolled back and forth and turned on its side. The infusion set should then be opened, and the first few milliliters should be allowed to drain out of the catheter before collecting samples.
- If an abdominal bleed is suspected, the catheter can be sutured in place to permit evaluation of follow-up samples. If septic peritonitis is suspected, the catheter can be left in place until surgical intervention to permit periodic lavage to dilute and drain septic material. If an aseptic peritonitis or pancreatitis is suspected, the catheter can be left in place to permit periodic abdominal lavages to dilute and drain inflammatory mediators.

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- Complete removal of the fluid is not always possible or necessary; it may be used to partially replace calculated fluid deficits when peritonitis is not present.
- If the catheter is to be removed, the skin is pinched around the catheter while it is removed and a temporary dressing is placed on the area.
- Cytology: The presence of vegetable or meat fibers, intracellular bacteria, or toxic neutrophils is an indication for surgical exploration and culture submission.
- Special laboratory tests required: The packed cell volume (PCV) of the abdominal fluid can be compared with the peripheral PCV and serially monitored if abdominal hemorrhage is suspected. A white blood cell (WBC) count greater than $1000/mm^3$ is diagnostic for peritonitis. If chemical analysis reveals that the creatinine or potassium level (or both) in the abdominal fluid is higher than the peripheral blood, a urinary tract rupture is suspected. If the total bilirubin of the fluid is greater than that of peripheral blood, a leaking biliary system is suspected.

Figure 72-2 Manufactured abdominal drains. *Top to bottom:* Arrow abdominal drainage catheter, Arrow peritoneal lavage catheter, pediatric peritoneal dialysis catheter. (Arrow, International, Reading, PA.)

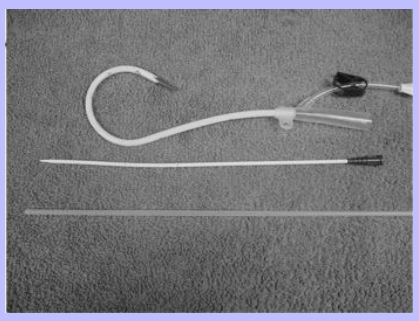

Figure 72-3 **A,** Placement of an abdominal drain via Seldinger technique. The animal is placed on its back and the ventral abdomen surgically prepared. Local administration of 2% lidocaine is injected lateral to the umbilicus at the site of catheter insertion. **B,** Placement of an abdominal drain via Seldinger technique. A sterile 1½-to 2-inch needle is placed into the peritoneal cavity at the locally anesthetized site. **C,** Placement of an abdominal drain via Seldinger technique. The J-wire is fed through the needle into the abdomen and the needle is removed leaving the J-wire in place. **D,** Placement of an abdominal drain via Seldinger technique. The catheter is fed over the J-wire into the abdomen. The J-wire is grabbed as it comes out of the proximal end of the catheter, and the catheter is fed into the abdomen until all the holes are contained within the abdominal cavity. **E,** Placement of an abdominal drain via Seldinger technique. The J-wire is removed and the catheter secured to the skin.

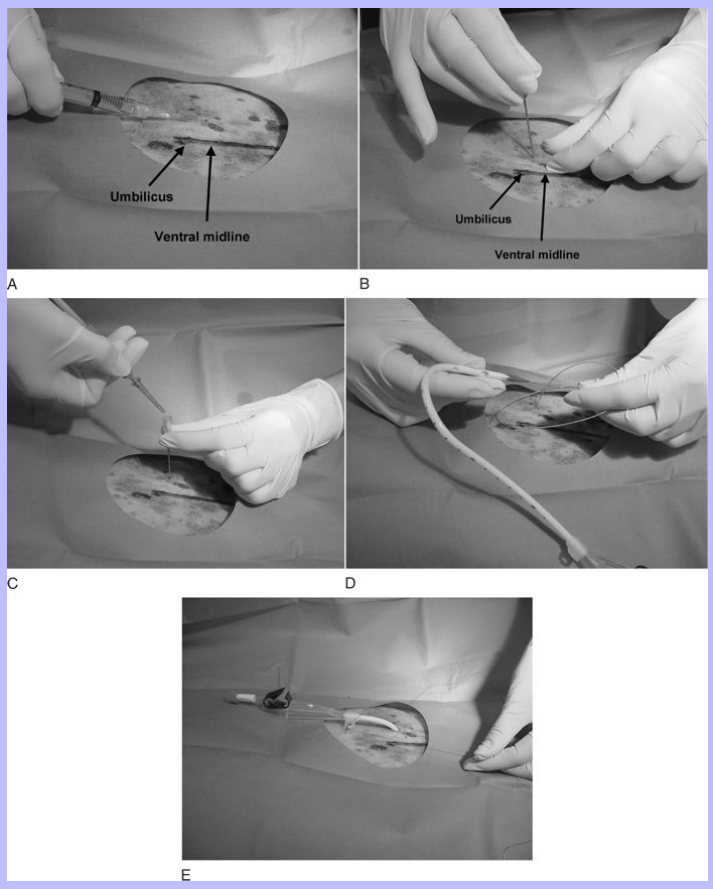

Figure 72-4 Collection of abdominal fluid samples for cytologic and chemical analysis.

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73 CHAPTER • 73 Abdominal Ultrasound: Aspirations and Biopsies

Wendy D. Fife

73.1 INTRODUCTION

Ultrasonography has many advantages, including its ability to detect parenchymal changes within organs and define the origin and extent of lesions. Abnormalities detected with ultrasonography are often nonspecific, with a great deal of overlap in the appearance of various disease processes. Ultrasound-guided fine needle aspirates or tissue-core biopsies are therefore often required for cytology or histopathology to reach a definitive diagnosis. The use of ultrasound guidance when obtaining diagnostic samples allows for real-time monitoring of needle placement so that a selected portion of an organ or a focal mass lesion may be sampled. Ultrasonography allows for the assessment of nearby vessels or other structures to be avoided and can be used to reassess the patient after the biopsy procedure for evidence of complications, such as hemorrhage. Ultrasonography and ultrasound-guided biopsies are noninvasive and rarely require general anesthesia when compared with surgery.

73.2 INDICATIONS

Percutaneous ultrasound-guidance may be used to obtain diagnostic samples or to provide therapeutic intervention. Fine needle, large-gauge needle, or tissue-core biopsies are chosen based on the size and type of lesion to be sampled. Biopsy samples of a specific organ may be warranted in cases of diffuse parenchymal abnormalities, (focal loss of parenchymal homogeneity) or mass lesions, or in the case of a normal ultrasonographic appearance of an organ when the results of other diagnostics indicate organ dysfunction. Therapeutic uses of ultrasonography include the drainage of intra-abdominal or intrathoracic cysts, abscesses, or fluid, or to instill local chemotherapeutics or other chemical therapy.

73.3 MATERIALS

Sector or linear-array transducers may be used, depending on the depth of the structure to be biopsied. Linear-array transducers provide superior resolution for more superficial structures, whereas sector transducers are used to biopsy deeper tissues. The lesion to be biopsied should be placed within the focal zone of the transducer to allow for the best resolution. Some transducers are equipped with biopsy guides, and separate guides are available for attachment to conventional transducers. The guides function to keep the needle in the plane of the ultrasound beam (Figure 73-1).

Dedicated biopsy transducers and those equipped with biopsy guides often display electronic markers on the display screen. The lesion or tissue to be biopsied is placed between the markers and the needle is inserted with its position continuously monitored. Dedicated biopsy transducers are more expensive and specialized than conventional transducers or transducer biopsy guides and are rarely used in veterinary medicine.

The size and type of needle to be used depends on the size of the lesion being sampled and the type of sample desired. The smallest needle that will provide a diagnostic sample should be used because larger needles may be associated with higher complication rates, such as hemorrhage. Fine needle samples most commonly yield samples for cytology, whereas histologic evaluation requires a tissue-core biopsy. Fine needle samples are commonly obtained when the organ being sampled has a diffusely abnormal appearance or when a small lesion (<1 cm) is being sampled. Tissue-core biopsies may be preferred in the case of a large mass or when

histopathology is necessary. In many cases, a fine needle aspiration may be obtained first and a tissue-core biopsy pursued if the sample is inconclusive or nondiagnostic.

For fine needle aspiration, 20-to 25-gauge needles are typically used. In the case of the freehand technique, standard injection needles are used. A longer needle (e.g., 3½ inch) is required if a transducer guide is used. This length is necessary to pass through the biopsy guide and into the tissue. In the case of a tissue-core biopsy, a 14-to 18-gauge needle is used. Manual and automated biopsy devices are available. A manually operated Tru-Cut® needle requires two hands to operate, so two people are required for the procedure: one to place the transducer and another to operate the biopsy device. The operator is able to control the depth of the needle and the length of tissue to be sampled. Several types of semiautomatic and automatic biopsy devices have been developed. The inner cutting needle is manually advanced to the desired depth with a semiautomatic device. The outer cutting shaft, which is spring loaded, is then triggered. The exact depth of tissue biopsied is manually controlled. The inner cutting needle and outer shaft of an automatic device are initially advanced manually, 1.5 to 2.0 cm superficial to the tissue to be biopsied. Automatic biopsy guns automatically advance the cutting needle and external shaft when triggered. Caution is advised when using an automatic biopsy gun; the inner cutting shaft advances a specific distance (15 to 20 mm) beyond the external shaft to acquire the tissue sample when it is triggered. Most automatic biopsy guns accept disposable needles of varying sizes, and the distance the cutting shaft will advance can be adjusted to control the length of tissue sampled. This is particularly useful in cats and in the case of small lesions. This gun is reusable and can be sterilized. Individual disposable spring-loaded automatic and semiautomatic biopsy needles are available in various sizes.

73.4 TECHNIQUE

The needle should not enter more than one organ or pass through an organ, and a separate needle should be used for each organ sampled. Multiple samples of an organ or lesion are usually obtained.

The freehand technique can be used, in which case the transducer is operated with one hand and the needle with the other (Figures 73-2 and 73-3). This allows for greater flexibility in the approach to the structure of interest but requires hand-eye coordination and practice. The entire length of the needle must be kept within the ultrasound beam, and the tip must be localized. Moving the needle gently up and down while fanning the region with the ultrasound probe may aid in locating the needle tip. Under no circumstances should the location of a needle be determined by moving the needle side to side within an organ. This causes unnecessary tissue trauma. Roughening the outer needle shaft prior to introduction will create an irregular interface to increase sound reflection and sonographic visualization. Commercially available Teflon or other highly reflective-coated needles are available to enhance visualization. Use of a larger-gauge needle will facilitate visualization but may increase the risk of complication. The needle tip should be placed at the focal zone of the transducer to enhance resolution. Injection of a small amount of air or sterile saline may help localize the needle tip. After needle placement, and stylet removal in the case of a spinal needle, a syringe or extension tubing and syringe are attached to the needle. If the lesion is fluid filled, fluid is then aspirated. If large amounts of fluid are to be aspirated, a three-way stopcock is attached. For cytologic samples, aspiration is performed as the needle is moved slightly up and down within the tissue or lesion. Some individuals prefer to simply move the needle up and down within the tissue, without aspiration, to obtain a cytologic sample. This technique may provide less blood contamination within the sample and has been shown to yield diagnostic results. Fine needle samples may be obtained with the stylet in place as the needle is advanced (Figures 73-4 and 73-5). Once the needle is placed at the desired depth, the stylet is removed and the sample is acquired. This may be particularly useful in the case of traversing fat within the falciform ligament to obtain a liver aspirate in the cat. Without a stylet, the sample may consist of fat only, which may be improperly interpreted as hepatic lipidosis.

Use of a needle guide requires less dexterity, but once the needle enters the skin, the probe cannot be moved. Transducer guides also cause the angle of the needle relative to the ultrasound beam to be fixed, thereby limiting the angle at which the surface of the patient can be approached and prohibiting biopsy of superficial structures.

73.4.1 Patient Preparation

The patient is usually placed in dorsal recumbency on a padded trough. An intravenous catheter is placed in the case of a tissue-core biopsy so that intravenous sedatives can be administered. In the case of a very small lesion or a lesion in close proximity to large vascular structures, general anesthesia may be required. The use of some drugs should be avoided, including those that cause splenic enlargement or panting.

Depending on the tissue being sampled, the patient's clinical status, and the type of biopsy being performed, screening of the patient's coagulation status is recommended. For fine needle aspirations, coagulation-screening profiles are not routinely performed unless the lesion to be sampled is extremely vascular or the patient is at an increased risk of bleeding.

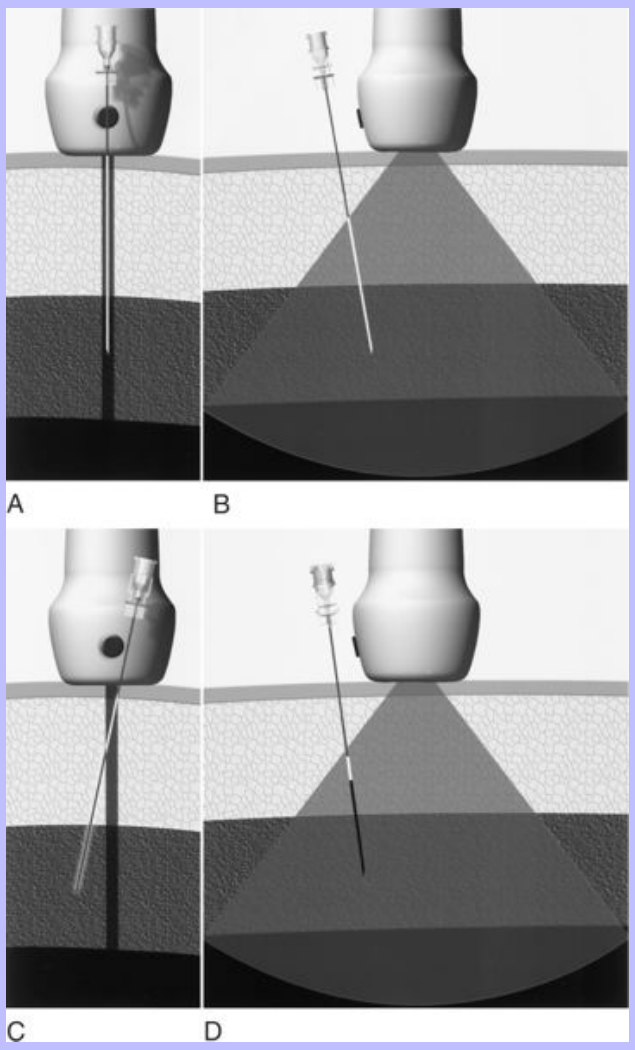
73.4.2 Specific Biopsy Sites

Fine needle aspiration and tissue-core biopsies of the liver are commonly done. Fine needle aspiration is performed when sampling focal masses that are complex or highly vascular, whereas a tissue-core biopsy is preferred in the case of a focal solid–appearing mass. In cases of diffuse hepatic disease, a fine needle aspirate may be done first and often yields a diagnosis in cases of specific diseases, such as lymphoma or hepatic lipidosis. Other diffuse hepatic diseases may require a tissue-core biopsy for a definitive diagnosis. The left-lateral aspect of the liver is generally the safest area to sample because it is the largest and the gallbladder and hilar vessels can be avoided. If a focal lesion is in a different location, or if the liver is small, sampling of another portion of the liver may be warranted. If the liver is small or located cranially, an intercostal approach is sometimes used, being cautious to avoid lung tissue. General anesthesia and positive pressure ventilation may also be used to displace the liver caudally for easier access. Multiple biopsies are routinely obtained.

The gallbladder may be sampled in cases of acalculous cholecystitis for culture and cytology. A transhepatic approach and a 22-gauge needle are used. The transhepatic approach is reported to decrease the risk of bile leakage.

Diffuse infiltrative splenic diseases, such as lymphoma and mast cell disease, and focal splenic masses are common indications for aspiration. Needle biopsy without aspiration may decrease the potential for blood contamination in splenic samples. If the aspiration technique is used, aspiration should be discontinued if blood appears in the hub of the needle. Complications due to splenic aspirates are extremely rare, but caution should be used when sampling complex, cavitary masses, such as those seen in splenic hemangiosarcoma. If fine needle samples of the spleen are nondiagnostic, a tissue-core biopsy of a solid mass lesion or the solid portion of a complex lesion may be indicated.

Figure 73-1 The angle of the biopsy instrument relative to the plane of the ultrasound beam is essential to visualize the tissue being sampled with the freehand method. **A** and **B,** Proper alignment of the biopsy instrument and ultrasound beam, with the two remaining parallel the entire length of the needle. **C** and **D,** Improper alignment of the needle relative to the ultrasound beam. Only a small segment of the length of the needle can be seen as it intersects the plane of the beam. The tip of the needle and therefore the tissue being sampled cannot be seen. The white portion of the needle represents that which transects the path of the scanning plane and is therefore visualized.



Renal biopsy may be performed in cases of diffuse renal disease or focal renal masses. Fine needle aspirates are usually performed if diffuse disease such as lymphosarcoma is suspected, whereas tissue-core biopsies are required to diagnose glomerular and tubular diseases and renal mass lesions. Sampling of the left kidney is preferred in cases of diffuse bilateral renal disease due to its relatively caudal location and easier access. The caudal cortex of the kidney should be sampled (including glomeruli but avoiding the medulla and hilar vessels). The biopsy plane should be directed laterally to avoid puncturing the renal hilus, caudal vena cava, or aorta. Feline renal biopsies are commonly done by manually stabilizing the kidney close to the ventral or lateral skin surface while performing a core biopsy of the lateral cortex with or without direct ultrasound guidance. Complications are rare and in most cases self-limiting but may include intra-abdominal hemorrhage or hemorrhage manifested as hematuria. Small dogs and cats may have an increased risk of hemorrhage and cats with hypertension are at particular risk. The animal's packed cell volume (PCV) should be monitored for several hours after the procedure. Renal biopsies should not be performed indiscriminately because fatal hemorrhage can occur.

Urinary bladder masses are commonly identified ultrasonographically. They are usually readily accessible for aspiration with a 21-or 22-gauge needle. In cases of transitional cell carcinoma, percutaneous biopsy often yields a diagnostic sample, but seeding of the tumor into the abdomen and subcutaneous tissues can occur. Ultrasound-guided urinary catheter placement and vigorous suction is a viable diagnostic alternative and avoids the potential for seeding of tumor cells.

Percutaneous biopsy of the prostate may be indicated when parenchymal abnormalities or prostatomegaly are identified. Fine needle aspiration of fluid-filled cysts or cavities within the prostate may be obtained for culture and cytology. These lesions may occur in association with prostatitis or neoplasia. If neoplasia is suspected, a tissue-core biopsy should be performed. The biopsy is obtained from the caudal abdomen, lateral to the prepuce. Adjacent vascular structures, such as the aorta and caudal vena cava, should be avoided. If the prostate is small or caudally located, the pubic bone may interfere.

The pancreas may be aspirated to differentiate between pancreatitis and pancreatic neoplasia. Secondary pancreatitis is an uncommon complication. Infection may develop in conjunction with pancreatic neoplasia, so false-negative diagnoses may occur.

Other abdominal structures that may be aspirated or biopsied include enlarged intra-abdominal lymph nodes and gastrointestinal (GI) masses. Aspiration of adrenal masses has been reported in veterinary medicine but is uncommonly performed; blood pressure alterations and severe hemorrhage may occur in the case of pheochromocytoma. Close proximity to the caudal vena cava and aorta are additional risks.

Ultrasound-guided percutaneous drainage of intra-abdominal abscesses is performed in people as an alternative to surgical treatment. This technique may be useful in veterinary patients. With the patient under sedation, the abscess cavity is drained using a 20-gauge or larger needle. Samples are submitted for culture and cytology. Follow-up ultrasound examinations, possibly in conjunction with repeated abscess drainage, are done. The procedure may reduce morbidity and mortality associated with abdominal abscesses treated surgically.

73.4.3 Contraindications and Complications

Complications related to ultrasound-guided biopsy procedures are uncommon. The risk of complication varies based upon the size of the needle being used and the location of the lesion. A 22-to 25-gauge needle should be used when possible, and larger gauge and tissue-core biopsies pursued if samples are nondiagnostic. 273
Hemorrhage is minor and self-limiting in most instances. The results of physical examination and laboratory 274

testing when necessary will identify patients at increased risk for hemorrhage. Color Doppler imaging is recommended when available to assess the vascularity of tissues and adjacent structures before the biopsy is performed and to monitor for hemorrhage in the postbiopsy period. The risk of peritonitis associated with penetration of the bowel is small in cases of fine needle aspiration, but bowel should be avoided with larger-gauge needles and tissue-core biopsies. Seeding of a tumor along a needle tract is also rare but has been reported in cases of transitional cell carcinoma in the canine urinary bladder. As with any procedure, adequate restraint and sedation are necessary to minimize risk to the patient.

Figure 73-2 Freehand biopsy technique. The ultrasound probe is held in one hand and the biopsy instrument in the other hand. The biopsy instrument must be maintained within the plane of the ultrasound beam. **A,** Proper alignment of biopsy instrument relative to ultrasound beam. **B,** Improper alignment, with the biopsy instrument angled relative to the ultrasound beam. This will not allow proper visualization of the biopsy instrument within the scan plane.

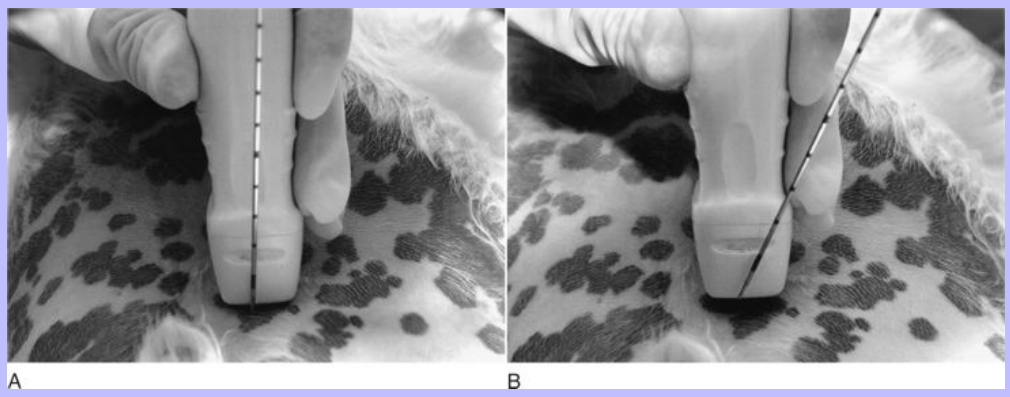
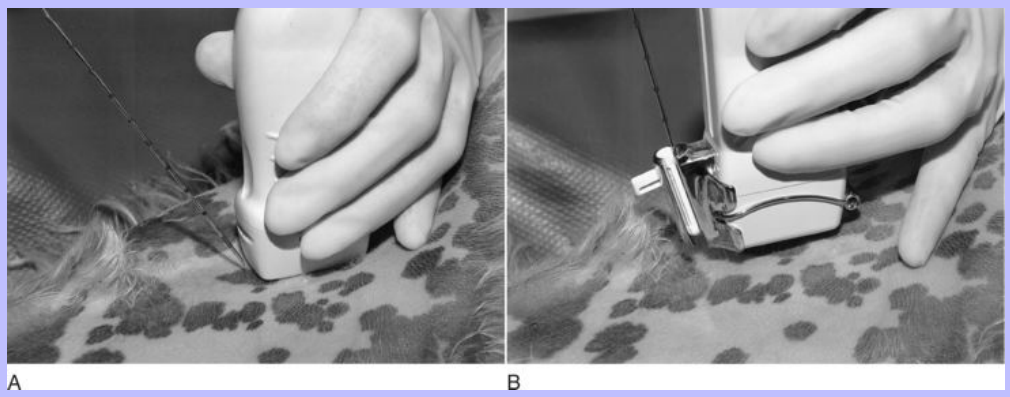


Figure 73-3 **A,** Freehand biopsy technique. The instrument is held with one hand and the biopsy instrument, in this case a Biopty® gun, is held with the other. The angle of the biopsy needle relative to the transducer is not fixed. **B,** Biopsy with guide attached to transducer. In this case, an external metal guide is attached to this sector transducer. The angle of the biopsy needle relative to the probe is fixed.



73.5 FUTURE TRENDS

Ultrasonographic-guided percutaneous antegrade pelography has been used to confirm obstructive uropathy and the site of obstruction in the dog and cat. This procedure does not require the intravenous administration of iodinated contrast medium as it does with excretory urography (EU). A 22-gauge spinal needle is introduced into the renal pelvis via the lateral cortex, to avoid hilar vessels, and nephropyelocentesis is performed by withdrawing 4 to 6 ml of urine. The clinician then injects 2 to 4 ml of iodinated contrast medium into the renal pelvis and radiographs are performed. This procedure is useful in animals with poor renal function and resultant inadequate pyelogram phase during EU to diagnose a ureteral obstruction. The possible nephrotoxic effects associated with intravenous contrast administration are decreased. Transcutaneous pyelocentesis can also be used to collect urine for culture when pyelonephritis is suspected and cystocentesis samples yield a negative culture.

Figure 73-4 Fine needle aspirate of the liver using a sector transducer. **A,** Color Doppler identifies blood flow in hepatic vessels, which are to be avoided by the path of the biopsy needle. **B,** The entire length of the needle can be seen coursing through the hepatic parenchyma as a linear hyperechoic structure *(arrows)*.

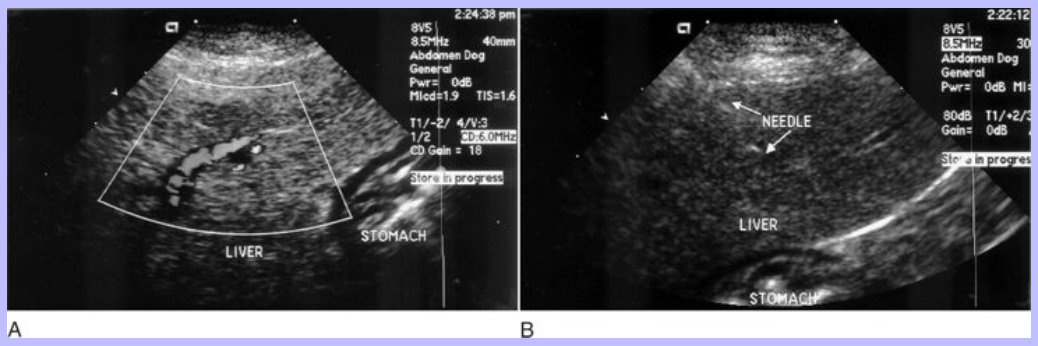
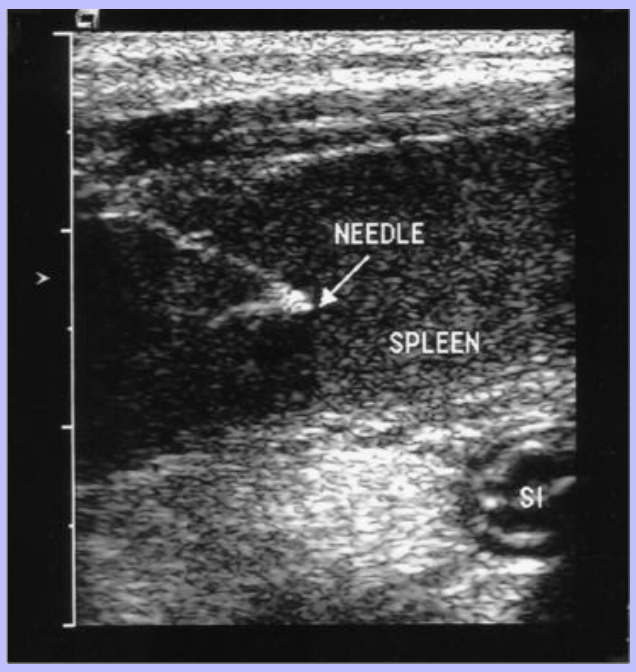


Figure 73-5 Fine needle aspirate of the spleen using a linear transducer in a cat with splenomegaly. A linear transducer is useful for biopsy of superficial structures. The entire length of the needle can be seen. The needle tip is causing distal acoustic shadowing due to its high degree of echogenicity. *SI,* Small intestinal segment.



Local administration of pharmaceuticals can be performed with ultrasound guidance. Percutaneous injection of ethanol has been used to treat thyroid and parathyroid disease in veterinary patients. Local chemotherapeutics have been placed with ultrasound guidance in cases of abdominal neoplasia.

Endoscopic and laparoscopic ultrasonography are being used in people to evaluate structures more directly and to obtain aspirates and biopsies. These procedures are less invasive and quicker than open surgical biopsies. The necessary equipment is expensive and not yet widely available in veterinary medicine.

74 CHAPTER • 74 Arthrocentesis and Arthroscopy

Mark C. Rochat

74.1 ARTHROCENTESIS

Synovial fluid is a dialysate of plasma combined with hyaluronic acid produced by type 2 (B) synoviocytes. The viscosity of normal synovial fluid provides lubrication, shock absorption, and joint stability. Arthropathy results in loss of integrity of the synovial membrane and introduction of inflammatory mediators into the joint. Inflammatory cells and infectious agents release hyaluronidase and other matrix metalloproteinases, resulting in breakdown of hyaluronic acid. Loss of normal hyaluronic acid leads to loss of synovial fluid viscosity, improper cartilage nutrition, and decreased shock absorption.

Arthrocentesis is the process of withdrawing synovial fluid from a joint by use of a hypodermic needle and syringe. Arthrocentesis is a secondary diagnostic tool that should be preceded by a thorough history, physical and orthopedic examination, and diagnostic imaging studies. Diagnostic imaging studies should be performed prior to arthrocentesis because artifacts such as hematomas may be created, leading to difficulty in interpreting the diagnostic images.

Arthrocentesis is indicated for characterizing the nature of arthropathies. The source of lameness can usually be isolated to a specific joint by history, as well as physical and orthopedic examination. Rarely, joint effusion, pain, or other signs of arthropathy cannot be readily identified, and the animal has vague and often diffuse lameness. This is common in immune-mediated polyarthropathies. In these situations, arthrocentesis is indicated as a screening tool when historical information supports a diagnosis of polyarthropathy. Multiple joints should be aspirated to enhance the likelihood of identifying the arthropathy. The carpus and hock are commonly involved in immune-mediated disease but can be difficult to aspirate due to their small size. On occasion, arthrocentesis yields a definitive diagnosis. For example, the presence of *Ehrlichia* morulae in intra-articular monocytes is diagnostic for joint sepsis due to ehrlichiosis. More often, arthrocentesis reveals the general cellular pattern and characteristics of the synovial fluid and joint environment, allowing broad classification of the arthropathy. Arthrocentesis is also the primary method of monitoring response to therapy for immune-mediated polyarthropathies.

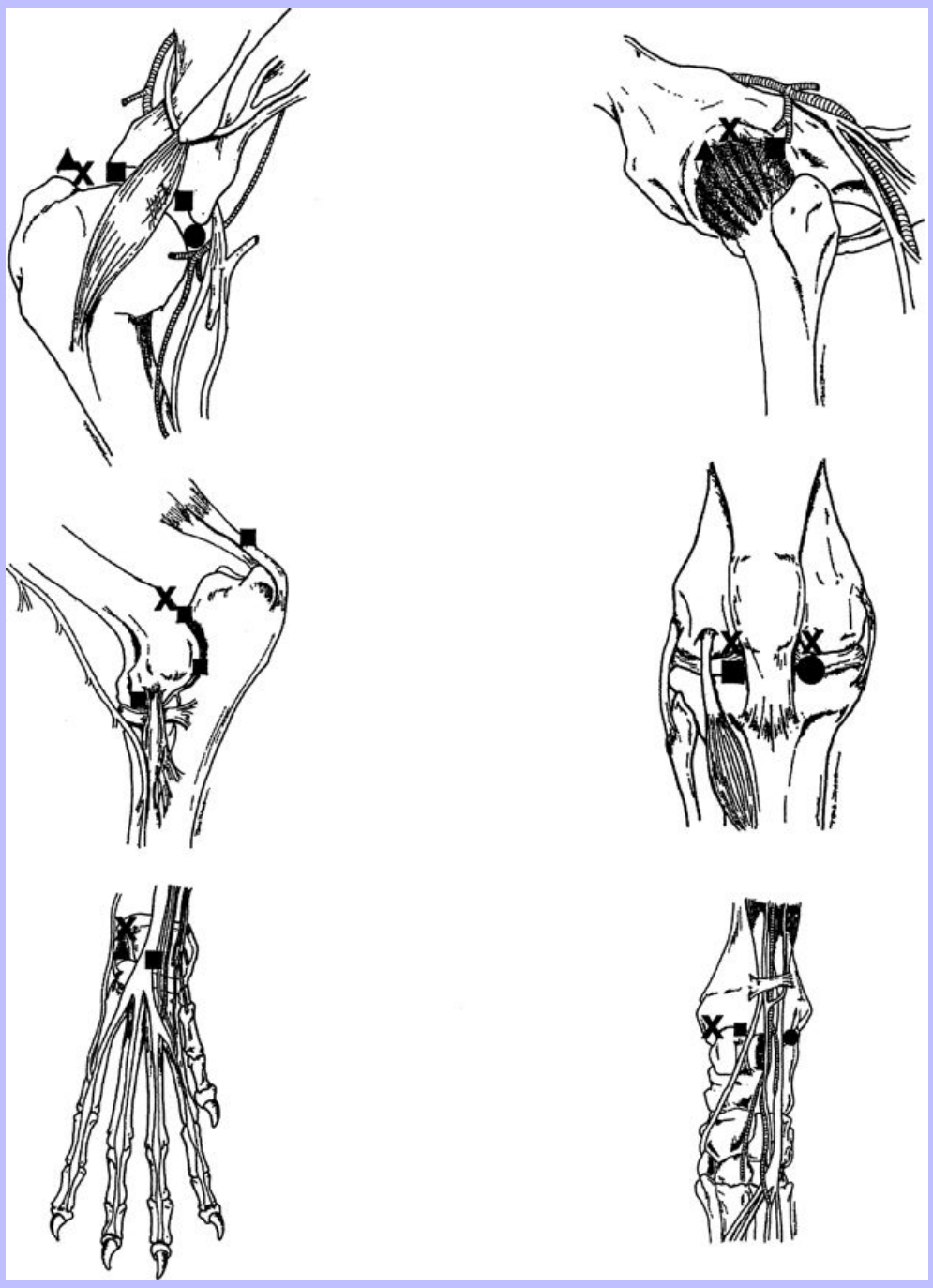
Arthrocentesis may require brief heavy sedation or anesthesia to allow safe aspiration of synovial fluid while minimizing the risk of injury to intra-articular structures or articular cartilage if the animal is fractious, painful, or energetic. Aseptic technique is required. To perform arthrocentesis, the animal is positioned in lateral recumbency with the affected limb uppermost. A 20-to 25-gauge needle attached to a 3-to 5-cc syringe is inserted with the clinician's dominant hand, while the opposite hand stabilizes the limb and joint. Proper orientation of the needle to safely enter the joint is facilitated by palpation of the joint during flexion and extension, reviewing diagrams illustrating proper needle placement (Figure 74-1), or by viewing skeletal specimens. The needle is inserted and gentle vacuum applied with the hand that inserts the needle and syringe. The needle is advanced until synovial fluid enters the syringe. Use of a 3-to 5-cc syringe allows the operator to achieve an adequate degree of suction while using one hand to insert the syringe and needle. The needle should be withdrawn if blood is encountered, and a new needle and syringe should be used for a second aspiration attempt. Hemarthrosis secondary to trauma does occur in small animals but is uncommon. Aspirated blood is usually a contaminant and should clot. Generally as much as 1 to 2 ml of fluid should be aspirated if possible, but the application of excessive negative pressure or aspiration of large volumes of fluid may increase the risk of aspirating blood, thereby ruining the sample. After the fluid is collected, negative pressure is released and the needle withdrawn. If no synovial fluid is obtained, the

needle is redirected after reviewing the angle of placement. If the needle is properly aligned but little or no synovial fluid is obtained, the needle may be plugged with soft tissue or hematomas or there may be insufficient fluid for aspiration as is true with normal joints.

Aspirated fluid should be immediately transferred to an EDTA tube, if a sufficient amount of fluid was aspirated (0.5-cc fluid for a 3-cc EDTA tube). Smears of the synovial fluid should also be made and air-dried prior to submission. If sufficient synovial fluid remains for bacterial culture and susceptibility, it can be inoculated at room temperature for 24 hours in a sterile red tube top with blood culture media at a 9:1 ratio. If only a small amount of fluid (1 drop) remains in the needle hub, 0.5 cc of blood culture media can be aseptically aspirated in a separate syringe, the needle with residual synovial fluid placed on the syringe, and the media flushed through the needle into a sterile red top tube and incubated as previously described.

Prepared slides and the EDTA tube should be submitted to a clinical pathology laboratory for evaluation. Synovial fluid characteristics that should be evaluated include volume, color, turbidity, total protein, total cell count, cell differential, viscosity, mucin clot test, and cytologic exam for cellular characteristics, infectious organisms, neoplastic cells, crystals, and other abnormalities (see Figure 74-2). Synovial fluid characteristics for cats are extrapolated from dogs. If immediate results are needed, some aspects of synovial fluid analysis can be determined in the clinical setting. Some appreciation of color, turbidity, and viscosity can be made when the fluid is expelled onto the glass slide. Cytologic examination of the fluid will provide a rough estimate of the cellularity of the sample, the types of cells present, and specific cellular characteristics such as inclusions or organisms, cytoplasmic granules, nuclear changes, phagocytosed cellular debris, and vacuolation. Other findings such as crystals may be identified. Cytologic examination is the single best test for determining the nature of the arthropathy if the amount of fluid obtained limits the extent of the fluid analysis. Complications are rare and generally limited to articular cartilage injury, hemorrhage, and iatrogenic infection.

Figure 74-1 Sites for arthrocentesis (X), egress portal (▲), arthroscope portal (■), and instrument portal (•) for the large joints of the appendicular skeleton.



74.2 ARTHROSCOPY

Arthroscopy is the process of examining and treating joint disorders by use of a small fiber-optic telescope. The advantages of arthroscopy are a minimal degree of invasiveness, decreased recovery times from surgery, visualization of a greater percentage of the joint surfaces than what is possible by arthrotomy, and improved visualization of joint pathology. The disadvantages of arthroscopy are the expense of the associated equipment, steep learning curve to master the technique, and limitation of the technique to the shoulder, elbow, carpus, hip, stifle, and hock joints of medium to large breed dogs.

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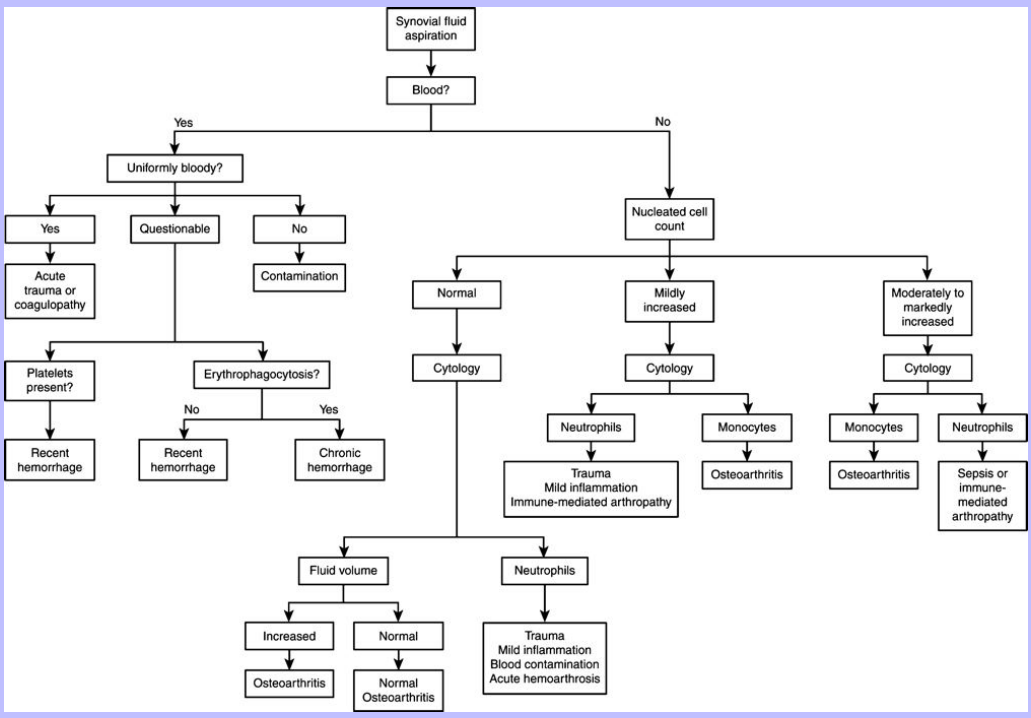
Figure 74-2 Algorithm for synovial fluid aspiration.



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Arthroscopy is indicated for characterizing ill-defined arthropathies of the previously mentioned joints by synovial biopsy and visualization of the pathology. Arthroscopy is also indicated for treating a limited number of joint diseases including osteochondritis dissecans, bicipital tenosynovitis, fragmented medial coronoid process disease, cranial cruciate ligament disease, and stifle meniscal injury. As the science and instrumentation of arthroscopy improves, other techniques for addressing various arthropathies may also be treated by arthroscopic methods.

The basic principles of surgery are observed whenever arthroscopy is performed. Canine arthroscopy must be performed with the patient under general anesthesia. The patient is clipped and prepared in the same fashion as for an arthrotomy. Strict adherence to principles of aseptic technique should be observed throughout the procedure. Perioperative antibiotics are unnecessary due to the minimally invasive nature of the procedure and the continuous irrigation of the joint surfaces. The instrumentation required for arthroscopic surgery in dogs is not extensive but

somewhat delicate and very expensive. A complete discussion of arthroscopic instrumentation and technique is presented elsewhere.

Complications observed with arthroscopy include failure to properly create an arthroscopic or instrument portal, damage to intra-articular structures, premature dislodgement of the arthroscope, collapse of the joint capsule secondary to excessive fluid extravasation, hemorrhage from inadvertent puncture or injury of periarticular vessels or the stifle intra-articular fat pad, damage to the arthroscope from excessive bending forces applied to the arthroscope, neurologic injury, infection, and inability to adequately explore or treat the joint disease. The incidence of complications is, for the most part, directly related to the experience of the participating arthroscopist.

75 CHAPTER • 75 Artificial Insemination in the Dog

Catharina Linde-Forsberg

Success rates in having dogs conceive after artificial insemination (AI) are dependent on a number of factors. These include the timing of the AI relative to the time of ovulation, how many times during estrus the AI is performed, the quality of the freshly ejaculated semen, how that semen was handled, and the AI technique used. This chapter will only deal with AI techniques.

75.1 AI TECHNIQUES IN THE DOG

Methods for AI in bitches include vaginal deposition of semen and transcervical intrauterine deposition, surgical intrauterine deposition, and intrauterine insemination by laparoscopy. The canine vaginal tract consists of the vulva, the vestibule, the vagina, the narrow paracervical region, the cervix, and the fornix (Figure 75-1).

Significantly higher whelping rates (range, 30% to 50%) are obtained with both fresh, chilled, and frozen-thawed dog semen when inseminated into the uterus, as opposed to when it is deposited in the vaginal tract. For frozen-thawed semen, litter size is also significantly increased by intrauterine AI. It has been estimated that 10 times as many spermatozoa are required to obtain similar results by vaginal AI as by intrauterine AI. For these reasons intrauterine AI should always be attempted in the dog. The problems faced in attempting to catheterize the canine cervix relate to its relative inaccessibility.

75.1.1 Palpation of the Cervix

To obtain good results using AI in the bitch, it is absolutely essential to learn location of the cervix by abdominal palpation so that semen can be deposited correctly and so that the bitch is not injured during the insemination procedure. The bitch should have an empty stomach and bladder to facilitate palpation. While training to palpate the cervix, the rigid single-use plastic canine AI catheter is introduced into the vagina of the patient. The introduction of the catheter is facilitated if the vulva is elevated to just below the anus (such as when the bitch stands for the male dog). By inserting the catheter along the left or right side of the vestibulum, the centrally located urethral opening can be avoided. Because the urethral opening of the bitch is located at the pelvic brim, it is surprisingly easy for the plastic AI catheter, or a thin rigid endoscope, to be unintentionally introduced into the urinary bladder. Apart from the hazards of perforating the bladder with the catheter, it is obvious that no pregnancy would follow AI of the bladder. Thus the correct position of the catheter should always be checked by palpation before depositing a semen dose. If the catheter is in the urinary bladder, the cranial part of the vagina and the cervix can be palpated above the catheter. The walls of the urinary bladder usually are thinner than the walls of the vagina and the tip of the catheter stands out more distinctly, therefore, than if it were in the vagina. When the tip of the catheter is introduced just cranial to the pelvic brim, its position should be checked by palpation. Cranially the vagina in most bitches slopes slightly downward. However, in some breeds, especially the sight hounds that have a very arched loin, the vagina may have a more dorsal direction (see Figure 75-1). The cranial end of the catheter should now be lowered closer to the abdominal wall to make it more accessible to palpation. In large or obese bitches and in bitches with large and pendulous mammary glands, it may be easier to grasp the cervix by palpation via the flank, which is usually thinner than the ventral abdominal wall. The tip of the catheter should then be lowered and also deflected toward the left flank (if the left hand is used for palpation). When the catheter tip can be palpated and its correct position in the vagina thus checked, it is carefully introduced further, under continued palpatory control, until it reaches the paracervical area. This is the narrow, cranial portion of the vagina created by the dorsal, median

postcervical fold that can be palpated as a 1-to 2-cm long, usually somewhat firm structure. It ends at the cervix, which in a bitch in estrus is a 0.5-to 1.5-cm hard, rounded-to-ovoid, freely movable structure (see Figure 75-1). The rigid plastic AI catheter, which has a diameter of 5 mm, may be too wide to be introduced into the paracervical area in some bitches, especially those of the smaller breeds or those that have not given birth to a litter of pups. Consequently, it is usually not possible to pass the outer protecting sheath of the Scandinavian catheter, which has a diameter of 10 mm, into the paracervical area (Figure 75-2). Once the cervix has been identified, the corpus uteri and the uterine horns can be palpated in front of this structure. This can be achieved by lowering the tip of the catheter and closing the tip of the thumb against that of the index finger above the catheter, then lifting the cranial end of the catheter in such a way that the cervix and the uterine horns are pulled upward between the fingers. Their size and consistency then become evident. (This method of palpating the uterus is also useful for early pregnancy detection and to examine bitches with suspected pyometra.)

Figure 75-1 Schematic drawing of the canine caudal reproductive tract. **1,** Plicate area of vagina; **2,** rugose area of vagina; **3,** dorsal median fold of paracervix (number is placed on caudal tubercle of dorsal median fold); **4,** vaginal cervix; **5,** paracervix and paracervical area (*v,* single permanent ventral median fold in vestibule; *c,* cingulum at vaginovestibule junction). (From Lindsay FEF: The normal endoscopic appearance of the caudal reproductive tract of the cyclic and non-cyclic bitch: post-uterine endoscopy, *J Small Anim Pract* 24:1, 1983, with permission.)

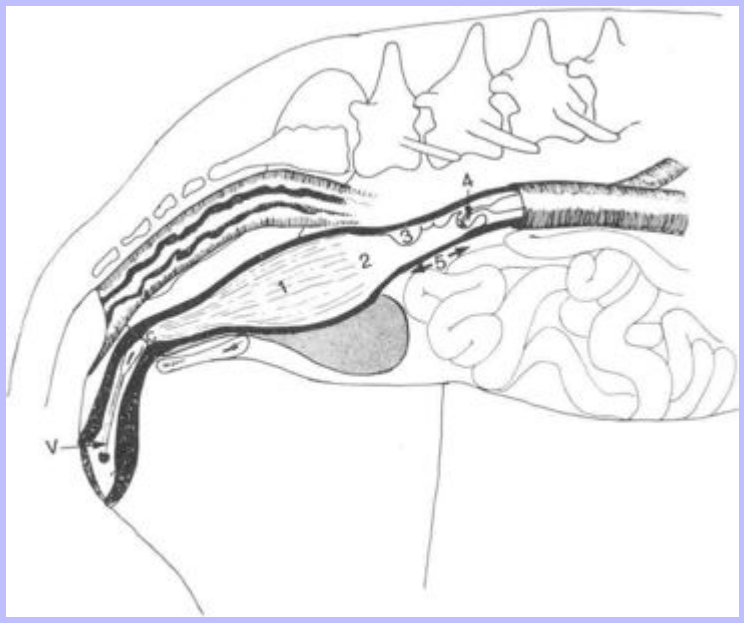
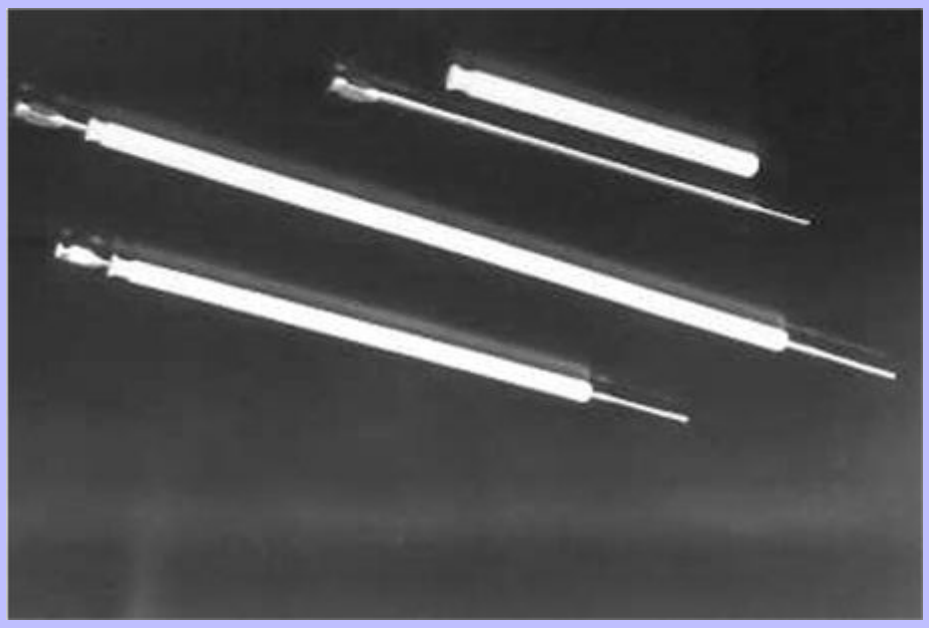


Figure 75-2 The three sizes of the Scandinavian AI catheter for dogs. (The Scandinavian catheters can be obtained from the Norwegian Fur Breeders' Association, PO Box 136, Økern, N-0509 Oslo 5, Norway. Phone: +47-23-25 81 00; Fax: +47-22-64 35 91.)



75.2 VAGINAL INSEMINATION

Vaginal AI involves using a rigid plastic single-use catheter (20-to 45-cm long and 5 mm in diameter) that is introduced into the cranial vagina and as close to the cervix as possible. With the catheter in place in the cranial vagina, the syringe containing semen is attached and the hindquarters of the bitch then elevated before infusing the semen. After deposition of the semen dose, the catheter is withdrawn and the bitch is held with elevated hindquarters for 5 to 10 minutes to facilitate the transport of spermatozoa toward the oviducts. The bitch should also be feathered around the vulva and perineal region to stimulate uterine contractions. Spermatozoa may reach the tip of the uterine horn within 30 seconds to 1 minute during a natural mating and within about 30 seconds to 2 minutes after a vaginal AI if the bitch is held with elevated hindquarters. Vaginal AI with the bitch standing horizontally may prevent the transport of spermatozoa into the uterus and oviducts.

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75.3 INTRAUTERINE INSEMINATION USING THE SCANDINAVIAN CATHETER

The Scandinavian catheter consists of a 3-mm wide steel catheter with a 1-to 2-mm diameter tip. It comes in three different lengths (20, 30, and 40 cm) and is used together with an outer protecting nylon sheath that is 10 mm in diameter (see Figure 75-2). The medium sized catheter fits most small-and medium-sized bitches.

Intrauterine AI with the Scandinavian catheter is performed with the bitch standing on the floor or on a table. Sedation is rarely needed. On the contrary, most bitches in estrus freely accept this type of handling. If light

sedation is necessary (in a large, obese, or nervous bitch), 1-to 3-mg/kg xylazine intramuscularly or intravenously can be used. The nylon sheath is first introduced into the vagina as far as possible. If lubrication should prove necessary, a small amount of liquid paraffin or Vaseline, which are not spermicidal, can be used. If the nylon sheath is introduced together with the inner steel catheter, the tip of the steel catheter must be placed so that it is completely protected by the nylon sheath. The cranial end of the nylon sheath is palpated in front of the pelvic brim as previously described. If the tip of the sheath is lowered closer to the abdominal wall, the cervix usually can be palpated a few centimeters in front of and above the catheter. In large or obese bitches it may be easier to palpate and grasp the cervix via the flank. The steel catheter is then introduced through the sheath until its tip reaches the ventral fornix. The cervix is fixed between the thumb and the index finger and, by applying a slightly downward traction at the corpus uteri, it is tilted so that the angle of the cervical canal becomes more horizontal. The tip of the steel catheter is then carefully withdrawn while pushing it repeatedly against the surface of the cervix in search of the opening of the cervical canal. In most cases the sensation when this opening is found can be described as the sensation of touching cartilage (i.e., “crispy”). Once the opening has been found, the catheter should be fixed and the cervix worked against the catheter. The cervical canal is 5-to 10-mm long and not always completely straight (see Figure 75-1). Thus slight pressure may have to be applied, while rotating the catheter to ease it through. In most bitches the tip of the catheter can easily be felt in front of the cervix in the corpus uteri. In some bitches, however, the sensation is not as distinct. In a few bitches the catheter can only be introduced halfway through the cervix, which is usually sufficient. The syringe containing semen is firmly connected to the catheter, and the semen is slowly infused into the uterus while pressure is applied with thumb and index finger around the cervix to prevent backflow. Sometimes a resistance to infusion occurs because the opening of the catheter may be pressed too hard against the endometrial mucosa. Slight downward traction at the corpus uterior of the cervix usually alleviates resistance and allows semen to be infused. (To check that the catheter really is in the uterus, 1 to 2 ml of physiologic saline can be infused. If the catheter is in the right position in the uterine body, the fluid can easily be infused. If, on the other hand, the catheter is in the paracervical region, there will be an almost immediate backflow of saline between the catheter and the nylon sheath). After intrauterine deposition of the semen, the catheter is withdrawn; to minimize backflow of semen and to facilitate uterine transport of spermatozoa toward the oviducts, the bitch should be held with elevated hindquarters for 5 to 10 minutes after the AI while being feathered around the vulva and perineal region to stimulate uterine contractions and sperm transport.

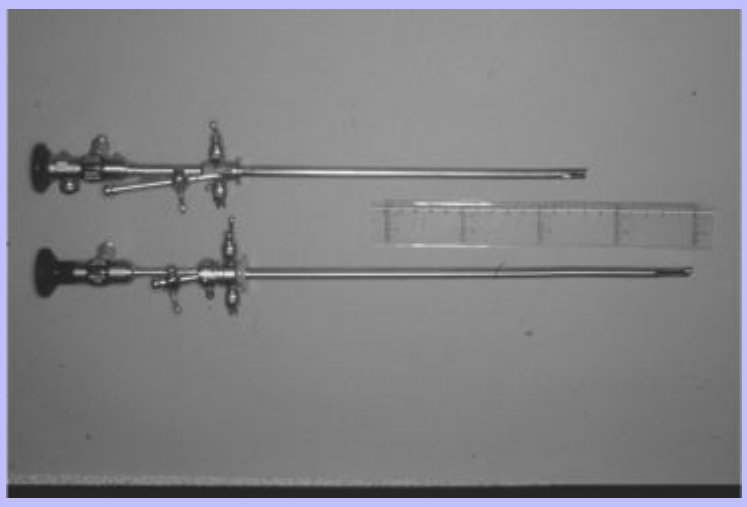
To learn this technique requires some practice, but once learned it is a quick procedure, usually being accomplished within minutes. Once learned, less than 5% of attempts are unsuccessful. It is recommended that, initially, organ specimens be obtained for training purposes and anatomic study. It is also advised that first attempts be made in medium-sized, calm, lean bitches that have given birth to one or more litters. They are usually considerably easier to catheterize. Perforations may occur if the catheter is introduced blindly or with force. Provided that the catheterization is performed under careful palpatory control, however, the technique is completely safe. (This technique can also be used for procedures such as intrauterine infusion of contrast medium for hysterographic examinations of the bitch with suspected pyometra.) Some bitches are more difficult to catheterize, particularly those belonging to some of the giant breeds, as well as obese or nervous animals. Should transcervical catheterization fail and the decision be made to deposit the semen in the vagina, a change should be made to the single-use vaginal catheter to avoid a backflow of semen between the nylon sheath and the steel catheter.

75.4 INTRAUTERINE INSEMINATION USING ENDOSCOPIC VISUALIZATION OF THE CERVIX

Transcervical intrauterine insemination on the standing, nonsedated bitch can also be accomplished with the aid of a rigid fiber-optic endoscope (i.e., a cystourethroscope) that is 23 to 29 cm in length and 4 mm in diameter with an oblique viewing angle of 25 to 30 degrees, together with a stainless steel sheath (23 French gauge) (Figure 75-3).

A dog urinary catheter, 6 to 8 French gauge, is passed through the operating channel of the sheath. The endoscope is introduced into the vagina and advanced past the vaginal folds and into the narrow paracervical area until the external os of the cervical canal can be visualized. To guide the endoscope through the sometimes tortuous vaginal vault, it can be quite helpful to let the urinary catheter lead the way by a few centimeters, thus indicating the right direction. Similar to use of the Scandinavian catheter, it can also be established (by abdominal palpation) whether the tip of the endoscope is correctly positioned in relation to the cervix. If the lumen in the paracervix is very narrow, the catheter may have to be introduced along one side of the dorsal median fold. The urinary catheter is then manipulated into the cervical opening and further into the uterus by a pushing and twisting movement. If the 281
opening of the cervical canal is directed away from the endoscope and thus out of sight, the cervix can be 282
manipulated by pushing it with the tip of the rigid endoscope or with the catheter while moving the instrument from side to side below the cervix. After semen has been deposited into the uterus, the catheter and the endoscope should be removed and the bitch kept with elevated hindquarters for 5 to 10 minutes.

Figure 75-3 Transcervical intrauterine insemination can also be accomplished with the aid of a rigid fiber-optic endoscope connected to a cold light source and a canine urinary catheter (6 to 8 French gauge). The endoscope comes in different lengths.



A significant advantage of this technique is that it allows direct visualization of the cervical opening. However, it involves manipulation of the scope and catheter and requires some practice. Although the equipment is expensive, it should be a good investment for practitioners specializing in canine reproduction and AI to obtain at least one endoscope of medium size, which will fit most breeds. The endoscope is also a great help when training to perform transcervical catheterization with the Scandinavian catheter.

75.5 INTRAUTERINE INSEMINATION USING SURGERY

Surgery to effect intrauterine insemination is still widely used. The bitch should be under general anesthesia and in dorsal recumbency. The ventral abdomen is clipped, and after routine surgical preparation a 4-to 6-cm incision is made midway between the pubis and the umbilicus through the linea alba. The uterus is elevated through the incision, and the needle of the syringe containing the semen is inserted into the lumen of the uterine body at a

45-degree angle with the bevel of the needle up. The semen is slowly injected into the uterus. It should flow easily with obvious distention of the uterine horns. If it does not, the needle should be repositioned. A piece of saline-moistened gauze is held over the injection site after the needle is withdrawn. After 1 minute the gauze is removed, the uterus replaced into the abdomen, and the wound closed using routine methodology. To avoid backflow of semen the bitch should be positioned with its rear elevated as she recovers from anesthesia. Whether it is ethically acceptable to resort to surgery to achieve pregnancies is debatable. The method, although advocated by some, is considered by many to be unethical and unacceptably stressful for the bitch. Two obvious disadvantages are (1) the general risks for infection and other complications associated with surgery and (2) the limited number of surgical AIs that can be performed in a given bitch. The method is also costly and time consuming.

75.6 INTRAUTERINE INSEMINATION USING LAPAROSCOPY

Abdominal laparoscopy should offer a somewhat more acceptable alternative to full surgery for AI in the dog; however, this method has not met with acceptance from practitioners, most likely because they are more used to the surgical technique.

76 CHAPTER • 76 Diagnostic Blood Pressure Measurement

Rebecca L. Stepien

Acute blood pressure (BP) measurement is required to diagnose hypertension or hypotension or to exclude these diagnoses as a cause for clinical signs in a patient. Multiple BP measurement techniques are available; each is associated with advantages and disadvantages.

76.1 PATIENT SELECTION

Blood pressure measurements are assessed as one part of a clinical evaluation that includes the patient history, physical examination findings, results of other diagnostic testing, and evaluation of concomitant medications, including anesthetics and sedatives. Many BP measurement techniques have test characteristics that require low diagnostic cutoff values for maximum sensitivity to hypertension (maximum opportunity to correctly identify an abnormally high value). Unfortunately, low diagnostic cutoff values also are associated with increased numbers of false-positive diagnoses. As a result, many BP measurement techniques are best able to correctly identify truly hypertensive patients as abnormal when the test is applied to patient populations with clinical signs or diseases likely to be associated with systemic hypertension. Routine "screening" BP measurements in clinically normal patients may assist the clinician in establishing a typical baseline BP value for an individual patient, but abnormally high BP values obtained from clinically normal patients must be viewed with caution due to the high incidence of false-positive readings in this patient population.

76.2 INDICATIONS FOR BLOOD PRESSURE ASSESSMENT

Blood pressure assessment is indicated in cats suspected of having or already diagnosed with diseases commonly associated with systemic hypertension (i.e., renal insufficiency or thyrotoxicosis); in cats presenting with clinical signs consistent with systemic hypertension; and in cats that have unexplained left ventricular hypertrophy. The most common reason for clinical presentation of hypertensive cats is ophthalmologic abnormalities. Although other causes of intraocular hemorrhage (e.g., coagulopathy) and retinal detachment (e.g., inflammatory disease) should be ruled out, immediate measurement of systemic BP guides the course of the diagnostic evaluation in these patients. For cats with neurologic signs in addition to ophthalmologic signs, diagnosis of critical levels of hypertension and immediate therapy can lead to rapid improvement in BP and relief of clinical signs.

Systemic BP should be assessed in cats whenever auscultatory cardiac abnormalities (e.g., gallop rhythms, left-sided systolic murmurs) and radiographic, electrocardiographic, or echocardiographic findings are consistent with hypertrophic myocardial disease involving the left side of the heart. Systemic hypertension (and hyperthyroidism in cats over 8 years of age) should be excluded by appropriate testing before a diagnosis of idiopathic hypertrophic cardiomyopathy is made. Early recognition of abnormal BP typically leads to evaluation for other systemic diseases, especially renal insufficiency.

Ophthalmologic abnormalities may also be seen in cases of canine hypertension, but systemic hypertension in dogs is most often diagnosed when BP is evaluated as part of the clinical workup of dogs with systemic diseases known to be associated with hypertension. In dogs, the diseases most frequently associated with elevations in BP are protein-losing renal diseases or chronic renal failure of any etiology, hyperadrenocorticism, diabetes mellitus, and pheochromocytoma. As with cats, systemic hypertension should be ruled out as a cause of left ventricular thickening of unknown etiology. Lastly, BP should be evaluated in cats or dogs with intracranial neurologic signs.

Dogs and cats that present with clinical signs of low cardiac output (e.g., weak peripheral pulses, cold extremities), shock, blood loss, or obtundation should be evaluated for hypotension. In some cases, hypotension is diagnosed clinically based on the constellation of history, presenting signs, and suspected clinical diagnosis (see Shock, Chapter 124). Accurate measurement of BP is important in any hypotensive patient to confirm the diagnosis and to provide baseline data for monitoring the response to therapy. BP evaluation methods differ in their sensitivity to low BP. Automated noninvasive techniques (i.e., oscillometric techniques) may fail to detect a pulse when hypotension is present, and operator-reliant techniques for pulse detection (e.g., Doppler sphygmomanometry) can be unreliable if the pulse signal is difficult to discern. Of the methods typically used in acute BP measurement, arterial cannulation is the most accurate method of documenting hypotension.

76.3 CHOOSING A BLOOD PRESSURE MEASUREMENT TECHNIQUE

76.3.1 Acute Diagnostic Blood Pressure Measurement

Detection of systemic hypertension may lead to additional testing for an underlying disease condition. In such cases, it is advantageous to perform BP measurement acutely (i.e., during a clinical examination or diagnostic evaluation), rather than hospitalizing patients and placing indwelling arterial catheters. When a technique to measure BP in a particular animal is chosen, specific issues to be considered include the availability of equipment, the availability of "normal" values to use for comparison, the skill and experience of the person making the measurement, and specific issues related to the animal (e.g., size, obesity, temperament).

The accuracy and usefulness of the measurement technique chosen ultimately depends more on attention to detail and use of applicable normal values (i.e., generated with the same technique as the one in use) than on which technique is used. Although multiple studies have addressed correlation or lack of correlation between invasive and noninvasive techniques in both dogs and cats, few studies are available that address the ability of these techniques to discern "normal" from "abnormal" in a conscious clinical population. Therefore assessment of BP values obtained may involve comparisons with normal values or comparison with values known to be associated with clinical signs.

76.3.2 Continuous Blood Pressure Monitoring: Conscious Patients

The monitoring of BP over time requires either continuous measurement (arterial catheterization) or repeated measurements, recorded automatically (oscillometric or photoplethysmographic techniques) or manually (Doppler sphygmomanometric methods). Arterial catheterization has the greatest number of advantages in conscious patients. Blood pressure obtained via arterial cannulation is accurate when the technique is used correctly and the values obtained are objective and repeatable (no manual pulse detection is required). A particularly important advantage is that the system can be secured to continue BP measurement when the animal moves. The major disadvantages are the technical skills and equipment required to maintain an arterial catheter and transducer system. Noninvasive methods are commonly used to take serial BP measurements in conscious animals. Although noninvasive BP measurements appear to be technically simple to obtain, they are subject to marked inaccuracy with animal movement, poor pulse pressure, arrhythmia, or inconsistent technique. When repeated BP measurements are obtained using these methods, cuff size and positioning, as well as limb position, should be identical for the repeated recordings.

76.3.3 Continuous Blood Pressure Monitoring: Anesthetized Patients

Blood pressure monitoring by most clinical methods is accurate and repeatable in anesthetized animals. The primary confounding problem of patient movement is absent in these patients, which renders them ideal subjects for BP measurement. Nonetheless, differences between values obtained by invasive methods (arterial catheterization) and noninvasive methods have been documented in numerous studies of dogs and cats. These studies indicate that numeric values obtained by means of noninvasive methods often underestimate true BP. In the case of anesthetized animals, this may result in an erroneous diagnosis of hypotension, but it seldom leads to the more dangerous error of overestimating BP in these patients.

76.4 BLOOD PRESSURE MEASUREMENT TECHNIQUES

76.4.1 Arterial Puncture or Arterial Cannulation ("Invasive" or "Direct" Technique)

Direct BP measurement involves advancing a needle attached to a pressure transducer directly into an artery to measure BP. This procedure may be performed acutely to obtain instantaneous BP readings, or BP can be measured over time through the use of an indwelling arterial catheter instead of a needle. Invasive BP measurements are typically used during anesthetic procedures, in critical care patients when ongoing BP information is desired, or to document or exclude hypertension acutely as a clinical diagnosis in dogs. Acute arterial puncture is seldom used for clinical diagnosis of hypertension in cats.

Direct BP measurement is usually performed by means of puncture of the femoral artery in dogs. Use of local anesthesia is strongly recommended for this procedure and is well tolerated by most dogs. The patient is gently restrained in lateral recumbency. Approximately 5 minutes prior to arterial puncture, 1 to 2 mL of 2% lidocaine hydrochloride is injected subcutaneously over the area in which the femoral pulse is palpated. A 22-gauge, 1-inch needle is attached to a transducer and flushed with heparinized saline, ensuring that no bubbles remain in the transducer. The transducer is zeroed at the level of the sternum in the laterally recumbent dog. The femoral 283
pulse is palpated in the femoral triangle, and the needle is carefully advanced into the femoral artery (Figure 284
76-1) until a satisfactory pressure waveform is recorded on the monitor screen. A sample of the tracing is recorded, and the needle is withdrawn. Firm pressure is applied to the area of arterial puncture for a minimum of 5 minutes after measurement. The patient should be monitored for at least 1 hour after the procedure for any complications related to hematoma formation. Systolic, diastolic, and mean BP values from five consecutive cardiac cycles during normal sinus rhythm are averaged to obtain a representative value for the patient. When use of an arterial catheter is preferred, the catheter is usually inserted into the dorsal pedal artery. A local anesthetic may be used as described previously.

76.4.2 Oscillometric Technique

Oscillometric BP measurement involves the use of an automated detection system and a cuff that is wrapped around a limb or tail over an artery. The cuff is inflated automatically to a pressure that causes occlusion of the artery and then slowly deflated. The machine detects oscillations in the vessel wall as the occlusion is eased, and the pressure at which oscillations are maximal is recorded as the mean arterial pressure. Systolic and diastolic pressures are then calculated by the monitor using algorithms specific to the technique. This technique uses data from many cardiac cycles to render a single reading and is therefore unsuitable for use in animals with rapidly changing BP.

Oscillometric BP measurement methods are more accurate in dogs than in cats. This measurement method may return inaccurate results if the patient is not motionless (e.g., trembling), has a weak or irregular pulse, or has a small artery (i.e., most cats). Use of a cuff of appropriate size is extremely important to ensure accurate measurements. Cuff width should be approximately 40% of the circumference of the limb or tail in dogs and approximately 30% of the appendage circumference in cats. When used on the tail, the cuff is wrapped snugly high on the tail head with the dog in sternal or lateral recumbency. Although tail cuffs can be used in standing animals, animal movement often interferes with accurate measurement. Limb cuffs are wrapped around the forelimb distal to the elbow or around the mid-metatarsus at the level of the superficial plantar arterial arch (Figure 76-2).

Figure 76-1 Invasive BP measurement via direct arterial puncture in a dog. A 22-gauge needle (with an attached pressure transducer, previously flushed with heparinized saline and zeroed) is advanced into the femoral artery at the level of the palpable pulse in the femoral triangle.

To maximize accuracy, the cuff should be at the level of the heart during readings; therefore lateral or sternal recumbency is preferred, and use in standing patients is not recommended. In cats, tail cuffs return more repeatable measurements than limb cuffs, but the accuracy of oscillometric BP measurements obtained by this method is questionable. Typically, the cat rests in sternal recumbency during readings (Figure 76-3).

In all cases, best results are obtained when the patient is minimally restrained and soothed during the procedure. A short acclimation period prior to measurement is recommended. A series of at least five readings are obtained at approximately 1-minute intervals. Any readings that are clearly erroneous are discarded. The multiple readings are then averaged to obtain a representative result.

Oscillometric techniques are valuable in anesthetized dogs and cats to monitor trends in BP. Because the animal is immobilized and BP shows less variability over time, repeatable and accurate readings can be obtained over time in both dogs and cats.

76.4.3 Doppler-Ultrasonic Technique (Doppler Sphygmomanometry)

Doppler ultrasonic flow detection through the use of a piezoelectric crystal allows detection of flow in a peripheral artery. Hair is clipped just proximal to the palmar metacarpal pad at the level of the superficial palmar arterial arch for forelimb measurement; over the dorsal pedal artery for hindlimb measurement; or on the ventral aspect of the tail for tail measurement. An occluding cuff (sized as outlined for oscillometric techniques) is placed proximal to the point of flow detection (mid-radius in the forelimb, proximal to the hock in the hindlimb, or proximal to transducer placement on the tail), and measurements are obtained with the cuff at the level of the heart. Ultrasonic coupling gel is placed on the concave surface of the Doppler transducer, and the transducer is held in position during measurements (Figure 76-4) or fixed in position using adhesive tape. An audible pulse signal is obtained, and the cuff is inflated with a bulb attached to a pressure gauge. The cuff is inflated to a pressure no less than 40 mm Hg above the audible cutoff point of the signal. The cuff is then slowly deflated, and the pressure at which the Doppler signal is again audible is recorded as the systolic pressure. The cuff is deflated further, and the pressure at which the audible signal abruptly changes in pitch or becomes muffled is recorded as the diastolic pressure.

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Figure 76-2 Correct cuff placement for oscillometric measurement of BP via the dorsal pedal artery in a dog. The cuff tubing is attached to the oscillometric BP monitor for readings.

Figure 76-3 Correct placement of a tail cuff for oscillometric readings in a cat. The cat is relaxed and minimally restrained in sternal recumbency.

The Doppler flow detection system of BP measurement is considered the most accurate and repeatable of studied noninvasive BP measurement techniques in conscious cats. It is frequently used in dogs but may provide spurious high readings in some individuals. When abnormal readings are obtained by this method from dogs, care should be taken to make sure the abnormal readings are repeatable over multiple measurement periods. The advantages of this technique include flexibility with regard to motion, low pressure, small vessels, or the presence of arrhythmias, as well as speed of measurement. The rapidity of the measurement techniques allows for prompt assessment of changing BP, but meticulous attention must be paid to obtaining strong, audible signals in order to obtain the most accurate BP readings. This technique is also the most operator dependent of the techniques discussed. Accurate identification of diastolic pressures improves with operator practice, and BP measurement using Doppler ultrasonic flow detection techniques is most accurate if a few well-trained individuals in a practice are responsible for this diagnostic test and perform the test frequently.

Figure 76-4 Measurement of BP via Doppler sphygmomanometry from the forelimb of a cat. Note that the inflatable cuff is at the same level as the heart in the sternally recumbent animal.

76.4.4 Photoplethysmography

Photoplethysmographic techniques measure blood volume by attenuation of infrared radiation. The blood volume is held constant by a microcomputer-based servosystem so that cuff pressure equals intra-arterial pressure. The cuff is positioned distal to the hock or at the tail head, and a visible waveform is used to assess the strength of the signal. Because the equipment is designed for use on the human finger, it is most suitable for cats or small dogs. Skin pigment may interfere with readings. This technique has not been studied extensively in conscious dogs and cats but appears to be as accurate as other noninvasive techniques in anesthetized animals.

77 CHAPTER • 77 Techniques for Bone Marrow Aspiration and Biopsy

Leo J. “Ty” McSherry

Peripheral blood abnormalities are the most common indications for the evaluation of bone marrow. These include poorly or nonregenerative anemia, persistent or unexplained neutropenia, unexplained thrombocytopenia, or any combination of peripheral cytopenias. A persistent leukocytosis or thrombocytosis, dysplastic changes, or the inappropriate presence of immature hematopoietic cells in the peripheral circulation are additional indications for bone marrow evaluation. Bone marrow can be used to stage neoplasia, evaluate lytic bone lesions, or determine the cause of unexplained hypercalcemia or hyperproteinemia, especially hyperglobulinemia, as may relate to lymphoma, multiple myeloma, or some systemic infections. Less commonly, bone marrow can be evaluated to help determine the cause of fever of unknown origin or evaluate total body iron stores.

Contraindications to bone marrow aspiration or biopsy are few and are generally related to the use of sedation or restraint. Hemorrhage is an uncommon complication, even in severely thrombocytopenic animals, and severe or unexplained thrombocytopenia is a common indication for marrow evaluation. Peripheral neutropenia is also a common indication for marrow evaluation; however, infection is unlikely because the aspirate, biopsy, or both is performed as a sterile procedure. The potential complications associated with hemorrhage or infection are minimal and should not dissuade the clinician from evaluating the marrow if indications to do so are present.

With the possible exception of a Petri dish or watch glass, most hospitals will have the necessary materials for bone marrow aspiration and biopsy. These include aspiration or biopsy needle, sedation or anesthesia, microscope slides, anticoagulant, scalpel blade (no. 11, no. 13), Petri dish or watch glass, 12-cc syringe, hematocrit capillary tubes, 2% lidocaine, and surgical scrub.

77.1 BONE MARROW ASPIRATION

Three types of aspiration needles are available: (1) the Illinois sternal, (2) the Jamshidi, and (3) the Rosenthal. These are available in 15-and 18-gauge sizes, 1 to 1½ inches in length. The 18-gauge needles are typically used in cats and small dogs, whereas the 15-gauge needles are reserved for dogs greater than 20 pounds. The Illinois sternal needles have a removable plastic cap (designed to hold the stylet in place during placement of the needle) and a removable needle guard. However, the plastic cap and needle guard necessitate the use of gas sterilization. The Jamshidi needles are stainless steel, durable, and may be heat sterilized; however, they lack a removable cover or needle guard.

The use of adequate sedation or general anesthesia will greatly facilitate the collection of bone marrow. Many authors describe collection with nothing more than a local anesthetic, and this may be all that is necessary or permissible in stoic animals or those at a high risk of anesthetic complications. Aspiration is a painful procedure, however, and a struggling or anxious animal will likely interfere with collection of an adequate sample. Sedation or anesthesia is suggested.

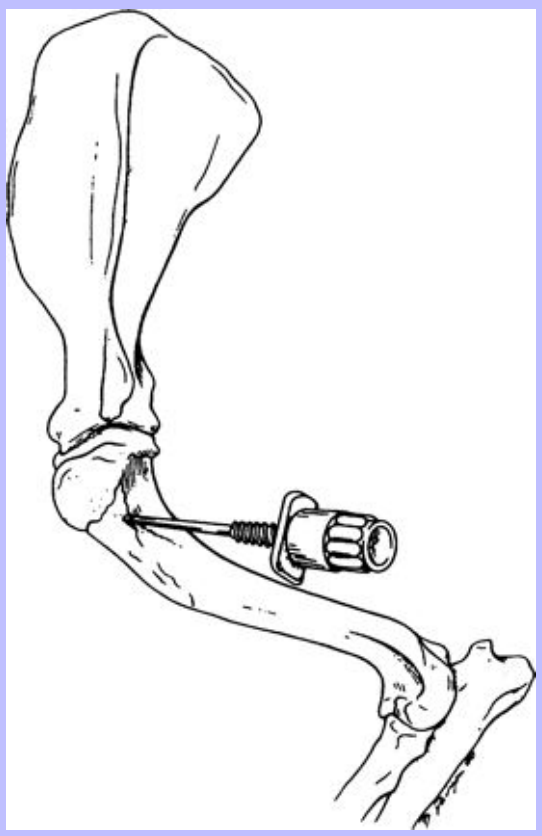
The use of an anticoagulant, although not necessary, is recommended and allows for the preparation of high-quality slides. It also allows time to complete the procedure before slides need to be prepared. Anticoagulant can be prepared by injecting 0.35 cc of sterile saline into a 3-ml lavender top tube containing EDTA, withdrawing the solution, and then reinjecting it into a second EDTA tube. This should yield approximately 0.5 cc of a 2.5% EDTA solution. Alternatively, a 5% solution of EDTA may be prepared using the dry reagent by a local or compounding pharmacy. The dry reagent is inexpensive and available through many pharmaceutic companies.

This is a practical and recommended alternative for hospitals that regularly perform bone marrow aspiration. A volume of 0.5 to 1.0 ml is recommended per collection.

Three sites are commonly used for the collection of bone marrow: (1) the proximal humerus, (2) the iliac crest, and (3) the trochanteric fossa. The proximal humerus is an easily accessible site in dogs and cats of all sizes. It has little overlying tissue and provides a fairly large area for placement of the needle. Its disadvantages include its proximity to the head and the thick, rounded cortex. The greater tubercle is easily palpated, and the needle is inserted into the flat area of the craniolateral aspect of the humerus distal to the greater tubercle. The needle is inserted perpendicular to the long axis of the humerus (Figure 77-1).

The iliac crest is easily accessible in thin dogs or those in good body condition, as well as in large cats. It should be avoided in large or obese animals because it may be difficult to palpate or to seat the needle due to a large amount of overlying tissue. The iliac crest is the widest and most dorsal aspect of the wing of the ilium (Figure 77-2). The trochanteric fossa may be used in cats or small dogs. The trochanteric fossa is medial to the greater trochanter. The greater trochanter is palpated, and the needle inserted medial to it (into the trochanteric fossa). The needle is inserted parallel to the long axis of the femur (see Figure 77-2). The trochanteric fossa is generally avoided in well-muscled or obese animals due to a significant amount of overlying tissue.

Figure 77-1 The needle is inserted perpendicular to the long axis of the humerus. (From Grindem CB: Bone marrow biopsy and evaluation, *Vet Clin North Am Small Anim Pract* 19:669, 1989.)



After sedation the animal is placed in lateral recumbency for collection from the proximal humerus, or it can be placed in either lateral or sternal recumbency for collection from the iliac crest. In nonsedated animals, lidocaine is used to block the surgically prepared site, beginning with the periosteum. The needle is then slowly withdrawn while blocking the overlying tissues and finally the skin. The sterile aspiration needle, scalpel blade, and 12-cc syringe are placed on the sterile glove field. Sterile gloves are worn, and 0.3-to 0.5-cc of anticoagulant is drawn into the 12-cc syringe that is then placed again on the sterile field. A small stab incision is made in the skin. The incision only need be wide enough for the aspiration needle.

The site of collection can be localized using one hand. The aspiration needle should be firmly seated in the palm of the hand and the needle held securely between the thumb and index finger. The plastic needle guard on the Illinois sternal needle has a small lip on which the thumb and index finger can be placed to grip the needle securely and to apply firm pressure. A tendency exists to hold the needle as if it were a pen. This should be avoided because it does not allow sufficient pressure to be applied to advance the needle through the cortex. In addition, if using the Jamshidi aspiration needle, pressure should be applied to the top of the stylet to prevent it from being dislodged while placing the needle. This is accomplished by holding it firmly in the palm of the hand.

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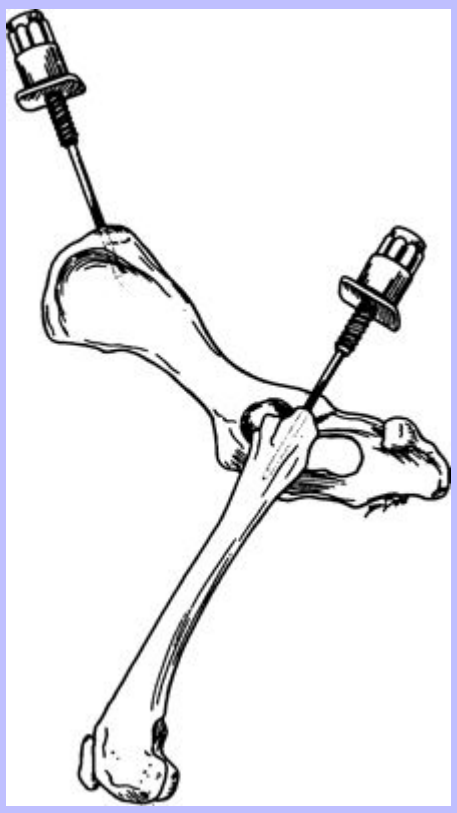
Figure 77-2 The needles are inserted medial to the greater trochanter and parallel to the long axis of the femur. (From Grindem CB: Bone marrow biopsy and evaluation, *Vet Clin North Am Small Anim Pract* 19:669, 1989.)



The aspiration needle is placed through the stab incision down to the periosteum. With the needle seated on the bone, firm clockwise-counterclockwise rotational pressure is applied to advance the needle. Frequently a slight decrease in resistance occurs when the needle enters the marrow cavity. When approaching the proximal humerus in cats, the needle may suddenly "pop" into the marrow cavity. When the needle has been properly positioned, it should feel very firmly seated, as might a nail in a block of wood. During advancement, the needle may occasionally and suddenly slide off the cortex into the surrounding soft tissue. This is especially common when approaching the proximal humerus and to a lesser degree the iliac crest. The needle will be freely movable in the subcutaneous tissues and not be firmly seated. Should this occur, the clinician should simply withdraw the needle to the level of the cortex, again seat the needle, and begin rotational pressure. When approaching the iliac crest, it is useful to have an assistant place counterpressure against the distal femur at the level of the stifle.

Once the needle is seated, the clinician should remove the top (if using an Illinois sternal needle) and stylet and place them on the sterile field. Next, a 12-cc syringe should be attached. While holding both the aspiration needle and syringe with one hand, the clinician should make several firm aspirations by rapidly pulling the plunger back. Marrow can appear after the first attempt at aspiration; however, several attempts could be necessary before marrow appears in the syringe. A total volume of 1 or 2 cc is collected if possible. If anticoagulant has been used, the syringe is removed from the needle and gently rocked to mix the marrow and anticoagulant. The sample may then be set down and the needle removed before preparing slides. Should no marrow appear in the syringe after vigorous aspiration, the syringe is removed from the needle and the stylet replaced. The needle is then advanced slightly using the same pressure with which it was placed, and aspiration is reattempted. Occasionally while approaching the iliac crest, the needle may be advanced too far into the opposite cortex. Unsuccessful attempts at aspiration will result. The needle should then be slightly withdrawn before again attempting aspiration.

After mixing the marrow and anticoagulant, the sample is expelled into a Petri dish or watch glass. The Petri dish or watch glass may be gently shaken or tilted to allow visualization of the marrow spicules. Marrow spicules appear as small, irregular white or gray particles that may adhere slightly to the dish or glass. These are collected using a hematocrit capillary tube or pipette. Only a small amount of sample needs to be collected in the capillary tube to prepare an adequate slide. The sample is placed on one end of a glass slide. A second slide is overlain on the bottom slide and the sample permitted to spread briefly between the slides. Digital pressure on the top slide is typically not necessary and is discouraged because cell lysis can result. The top slide is then smoothly but rapidly pulled down the length of the bottom slide and the sample air-dried.

If anticoagulant is not used, the slide must be prepared immediately after successful aspiration. Bone marrow clots very rapidly, and a clotted sample will not allow adequate slides to be prepared. As soon as marrow appears in the syringe, negative pressure is released and both the aspiration needle and syringe are removed. It is important to have several clean glass slides laid out prior to collection. The clinician should rapidly place a few drops of sample near the top of each of the slides. An assistant should then follow closely, preparing slides as the clinician goes down the row. It is difficult to prepare several slides by oneself because the marrow is likely to clot before the smears can be prepared. Several slides should be prepared and submitted. The preparation of 12 to 15 slides should result in several diagnostic slides and would permit additional testing or special staining should this be necessary to identify a poorly differentiated leukemia. In addition, accurate interpretation of the marrow is dependent upon the findings of a concurrent complete blood count (CBC), and a CBC (or current CBC results) should always be submitted with the aspirates.

77.2 BONE MARROW BIOPSY

Bone marrow biopsy is indicated if repeated attempts at aspiration are unsuccessful, if evaluating for metastatic neoplasia, or if evaluating lytic bone lesions resulting from neoplasia, inflammation, or infection. Unsuccessful

aspiration resulting in a dry tap may result from myelofibrosis, myelophthisis, hypoplasia or aplasia, or technical error. Bone marrow may be collected immediately after aspiration and may be collected from the same site or a distant site. Collection from separate sites may increase the likelihood of identifying metastatic neoplasia. Concurrent aspiration and biopsy is beneficial in that aspirated samples may occasionally be insufficient, necessitating histologic evaluation. Additionally, marrow biopsy immediately after aspiration may prevent the need for an additional anesthetic procedure should the aspirates be insufficient for a diagnosis.

Patient preparation, sites of collection, and approach are similar to those described for aspiration. Biopsy is considerably more painful, and good sedation or (preferably) anesthesia should be used. Jamshidi bone marrow biopsy needles are 11 to 13 gauge and 3 to 4 inches long. The 13-gauge needles are typically used in cats and dogs less than 20 lb. Due to the larger size of these needles, the wing of the ilium may be too thin to be used in cats or very small dogs.

The biopsy needle is seated on the cortex and advanced using the same clockwise-counterclockwise rotational pressure that is used to place the aspiration needle. It is beneficial to lay the index finger along the shaft of the needle while advancing the needle to stabilize it while it is rotated. With the needle firmly imbedded, the stylet is removed and the needle is advanced an additional inch or more using the same rotational pressure to collect an adequate sample. The biopsy fragment must be broken loose using several 360-degree twists in both directions, and the needle is withdrawn. The biopsy fragment is pushed out the top of the needle in a retrograde fashion using the wire that accompanies the needle. The biopsy needle is tapered, and attempting to push the sample out the tip will crush it and damage the sample. The collection of a sufficient sample will allow the core to be sectioned and part submitted for culture if an infectious process is suspected. The biopsy fragment is typically submitted in formalin; however, consulting the surgical pathology service may be beneficial because other fixatives are occasionally preferred. Biopsy samples should not be submitted in the same packaging as cytology preparations because the formalin vapors can interfere with the staining quality of cytologic preparations.

78 CHAPTER • 78 Brain Biopsy

Peter J. Dickinson

Richard A. LeCouteur

Neoplastic, vascular, infectious, or inflammatory diseases of dogs and cats frequently result in focal brain involvement. In affected animals, results of ancillary diagnostic investigations, such as cerebrospinal fluid (CSF) analysis and electroencephalography, may be within normal limits or may provide only "indirect" evidence of the presence of a brain lesion. The use of computed tomography (CT) and magnetic resonance imaging (MRI) has enabled accurate detection of many focal brain lesions. Although CT and MRI are sensitive in determining location, extent, and relationships to adjacent structures of brain lesions, both have limited specificity. Non-neoplastic lesions (such as those seen in association with infectious, inflammatory, or vascular diseases) may mimic the CT or MRI appearance of a neoplasm. In most instances, results of CT or MRI provide only a broad list of differential diagnoses for a focal brain lesion. An accurate histologic diagnosis of an intracranial lesion is critical before recommending a specific management or treatment strategy, and the need remains to obtain an intraoperative neuropathologic diagnosis from tissue samples obtained from the lesion.

78.1 OPEN BRAIN BIOPSY

Open brain biopsy may be appropriate in certain clinical situations in which cortical architecture needs to be preserved, for leptomeningeal sampling, for superficially located lesions, and when a decompressive craniectomy with good cortical visualization may be helpful in addition to obtaining a biopsy sample.

For superficial brain lesions, a craniectomy is performed, the dura is opened, the lesion is located, and a specimen of affected brain is excised using a no. 11 scalpel blade. For more deep-seated brain lesions, freehand fine needle (22 gauge) aspiration, or Tru-Cut® biopsy (using a 14-gauge Tru-cut biopsy needle, Travenol Laboratories Inc., Deerfield, IL), CT-guided freehand Field-Lee needle biopsy (using a 13-gauge Field-Lee brain biopsy needle, V. Mueller, Chicago, IL), or ultrasound-guided Menghini needle brain biopsy techniques (using a 16-gauge Menghini biopsy needle, Miltex Corp., Lake Success, NY) have been reported for use in dogs after a limited craniectomy.

Although open brain biopsy techniques usually are accompanied by low morbidity and mortality, these techniques are no longer recommended for deep-seated brain lesions. Stereotactic brain biopsy procedures are preferred, as they have been shown to work safely and effectively in a consistent manner in a large number of cats and dogs.

78.2 STEREOTACTIC BRAIN BIOPSY

With the advent of CT and MRI, and the development of CT-guided stereotactic frames, closed stereotactic brain biopsy has become the standard of care in people. Essentially all closed methods rely on the three-dimensional CT-generated coordinates identifying the lesion location. These coordinates are used to plot the optimal trajectory and depth needed for a biopsy needle to reach a target and obtain a diagnostic tissue sample.

Technical impediments exist to the direct application of most human stereotactic systems to dogs and cats. Most commercially available systems use a cumbersome head-frame, designed specifically for the human skull, and require dedicated, expensive computer software for the planning phase. Several different systems for image-guided stereotactic brain biopsy have been reported for use in dogs and cats.

Stereotactic biopsy begins with proper patient selection. The possibility of non-neoplastic disorders such as infection, cerebral infarction, or vasculitis, must be considered and investigated with other tests in appropriate patients prior to biopsy. When the differential diagnosis list is long and may include neoplasms and inflammatory lesions, the appropriate handling of tissue samples should be discussed with a neuropathologist in advance of the procedure. All patients should be tested for coagulation parameters (prothrombin time [PT], partial thromboplastin time [PTT]) prior to the procedure and should have a platelet count greater than 100,000. Patients should not receive aspirin products for 1 week before surgery.

General anesthesia is required for stereotactic brain biopsy. Biopsy generally is done on the CT-scanner table. For those lesions not well identified on CT images, MRIs that demonstrate a lesion may be used for comparison to localize the lesion on CT images, using well-defined anatomic landmarks (e.g., lateral ventricles). Axial CT images are used to define the CT coordinates of reference markers and the biopsy target. Dorsal or sagittal images may be used for trajectory planning. An entry point should be selected that is associated with a low risk for neurologic deficit or hemorrhage (e.g., avoidance of dorsal sagittal sinus). Ependymal puncture should be avoided where possible. A small craniotomy (2-to 4-mm diameter) is made by means of a twist drill, the dura mater is punctured with an 18-gauge needle, and biopsies may be done with a side-cutting aspirator biopsy needle (using a T 19. S biopsy needle, Ohio Medical Instruments, Cincinnati, OH) with a 10-mm side opening. On average, two or three specimens are removed. It is important to biopsy several regions of the intracranial lesion using a single trajectory.

The intraoperative goal should be to confirm by means of smear or touch preparations whether tissue satisfactory for an eventual diagnosis has been obtained. A specific histologic diagnosis may require routine formalin fixation and paraffin embedding of the biopsy tissue. At the conclusion of the biopsy procedure, the needle is withdrawn in increments to assess any possibility of hemorrhage. In the case of hemorrhage, blood should be permitted to egress from the needle spontaneously until the bleeding stops. An immediate postoperative CT scan should be obtained.

Although stereotactic brain biopsy is minimally invasive (compared with open biopsy techniques) and designed for low risk, complications may rarely occur. Morbidity may include seizures, hemorrhage, new neurologic deficits, brain infection, tumor seeding, and lack of a definitive diagnosis.

78.2.1 Handling the Intraoperative Specimen

The intraoperative specimen must be processed rapidly and carefully to provide timely and accurate diagnostic information. For large specimens, cytologic analyses (touch imprints, smears) may be done in conjunction with frozen sections. Cytologic analyses alone may be done in situations where access to frozen sections is difficult or when the biopsy specimen is small.

The clinician can make a smear (or “squash”) preparation by placing a small fragment of tissue at one end of a standard glass microscope slide. The end of another glass slide is placed over the tissue, mild pressure is applied to the slides, and the slides are gently and rapidly pulled apart to produce a smear. The slides are fixed immediately in 95% alcohol and stained with a rapid hematoxylin and eosin stain. Other techniques include fixation of the specimen in alcohol followed by toluidine blue, Giemsa, or Papanicolaou staining, or air-drying the specimen prior to Romanovsky or Wright's staining.

The clinician may take touch imprints by pressing a glass slide briefly to the surface of the fresh (unfixed) biopsy specimen. Small fragments first may be blotted to remove excess blood or fluid. The slides are fixed and stained in a similar manner to the smear preparations.

Frozen sections provide superior architectural detail for the intraoperative interpretation of biopsy specimens. They are done by placing carefully oriented tissue fragments on a cryostat chuck and freezing them in a viscous freezing medium (such as OCT), either within the cryostat with use of coolant spray and a metal heat extractor or by snap freezing in super-cooled isopentane or 2-methylbutane. Frozen sections are cut and thaw mounted on glass slides. They may be either fixed immediately in alcohol or air-dried before fixation. The sections then are stained with a rapid hematoxylin and eosin stain.

With results of one of the rapid tests outlined previously, a decision may be made regarding the need for further biopsy specimens to define the exact nature of the lesion (e.g., if results from an initial specimen are inconclusive) or the need for additional specimens for completion of specialized techniques (e.g., culture and sensitivity testing for a suspected inflammatory or infectious disorder).

Most intracerebral biopsy specimens may be safely fixed in 10% neutral buffered formalin and processed for hematoxylin and eosin staining. Small samples (1 to 2 mm) may be adequately fixed in 1 to 2 hours, whereas larger specimens may require overnight fixation. If any doubt exists as to the appropriateness of the fixative, a neuropathologist should be consulted immediately. Although technical improvements in immunohistochemical staining permit accurate assessment of samples after formalin fixation and paraffin embedding, assessment of ultrastructural detail using electron microscopy requires fixatives containing glutaraldehyde.

78.3 CONCLUSION

Treatment options based on empiric observations of brain lesions in dogs and cats may compromise clinical outcome. Regardless of lesion location, size, or appearance, a histologic diagnosis is necessary for optimal treatment. Although stereotactic brain biopsy techniques require specialized equipment and instrumentation, they should be considered a standard option in the diagnostic workup of dogs or cats with definable brain lesions on CT or MRI.

79 CHAPTER • 79 Muscle and Nerve Biopsy

Peter J. Dickinson

Richard A. LeCouteur

Biopsy of muscle and nerve is an essential consideration in the diagnosis and therapy of neuromuscular diseases in small animals. Examination of the specific components of the motor unit, as well as of sensory and autonomic nerves, permits definition and classification of the underlying pathology.

79.1 MUSCLE BIOPSY

Conventional biopsy and formalin fixation techniques, as used with most organ systems, severely limit the quantity and quality of information that may be obtained from muscle specimens. The development of specialized enzyme histochemical techniques, using frozen skeletal muscle biopsy specimens, has greatly increased the understanding both of normal muscle and of the underlying pathologic processes of many neuromuscular diseases.

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79.1.1 Selection of Muscle

The selection of a muscle for biopsy is guided by a number of criteria:

1. The muscle should be affected by the disease process but should not be end-stage. This choice may be based on electrophysiologic data, including abnormal electromyographic (EMG) results and clinical abnormalities suggesting muscle involvement (atrophy, hypertrophy, apparent pain, weakness).
2. The muscle should be easily identified surgically, with low associated morbidity, and with fibers oriented in a single direction.
3. Specimens should be harvested from muscles for which there is previous interpretive experience. Standard muscles include the lateral head of the triceps brachii (distal third), vastus lateralis (distal third), cranial tibial (proximal third), and temporalis muscles. Biopsy specimens from both a thoracic and a pelvic limb muscle, or other distant locations, are necessary to permit diagnosis of generalized neuromuscular disease.
4. Muscle biopsy specimens should be harvested from a site remote to tendinous insertions and aponeuroses.
5. Specimens should be free of artifacts induced by previous disease, intramuscular injections, and EMG needle insertion.
6. Some specialized procedures may require biopsy specimens from specific muscles or regions within muscles. For example, diagnosis of congenital myasthenia gravis is based on the demonstration of decreased numbers of acetylcholine receptors in biopsies of external intercostal muscle.

79.1.2 Open Muscle Biopsy Procedure

Open biopsies are done most often under general anesthesia following electrodiagnostic investigations. After routine surgical preparation, the skin and fascia overlying the muscle are incised, allowing visualization of the

orientation of the myofibers. A sample for fixation is harvested first. Two incisions are made with a No. 11 scalpel blade, parallel to the direction of the myofibers and approximately 2 cm long, 0.25 cm apart, and 0.5 cm deep. Specialized muscle clamps are placed at either end of the incised strip of muscle (to minimize myofiber contraction), and the isolated muscle is freed from the surrounding muscle with a scalpel blade or scissors. This specimen is immersed immediately in fixative, usually glutaraldehyde (either sodium phosphate–buffered glutaraldehyde or Karnovsky's fixative). Clamps may be removed after 24 hours following fixation. If a specialized muscle clamp is not available, the specimen may be sutured to the wooden stem of a cotton-tipped applicator. Samples for freezing and routine histochemical staining (approximately 0.5 to 1 cm in cross section and 1 to 1.5 cm long) may be harvested from adjacent muscle. It is not necessary to maintain these specimens in a stretched position. Handling of the specimen should be kept to a minimum to reduce artifact. Wound closure is routine. External dressings are not necessary. Complications (infection, hematoma) are uncommon and usually are the result of animals interfering with the biopsy site. Collection of a muscle biopsy specimen may be contraindicated in patients with significant coagulopathies.

79.1.3 Percutaneous Muscle Biopsy Procedure

Percutaneous needle or punch muscle biopsy is not recommended routinely due to the limited size and poor orientation of the biopsy specimens obtained.

79.1.4 Specimen Processing and Transport

Ideally, muscle biopsy specimens should be frozen immediately or transported to specialized laboratories for processing and interpretation. Specimen blocks are mounted on thin cork squares using tissue-embedding media, with the muscle fibers oriented vertical to the cork, and frozen for approximately 20 seconds in isopentane (2-methylbutane) cooled to approximately −150°C in liquid nitrogen. Proper freezing of the sample is critical for preservation of morphologic detail and prevention of artifacts. Frozen blocks may be stored in airtight containers at −80°C or in liquid nitrogen storage vessels. For biopsy specimens that are to be transported to specialized laboratories for processing, one fact cannot be overemphasized: *the quality of the information that will be obtained depends on the quality of the biopsy specimen that arrives at the laboratory*. Before a biopsy procedure is performed, the laboratory's specific instructions for selection, handling, and transportation of the specimen should always be obtained. Nonfrozen specimens should be wrapped in saline-moistened swabs that have been thoroughly wrung dry; the specimens then should be placed in an airtight container and maintained at 4°C using cold packs. The specimen container should be wrapped in a layer of newspaper to insulate it from the cold packs to prevent partial freezing of the specimen. Specimens should be shipped so as to reach the laboratory within 30 hours and should not arrive at the laboratory during a weekend. Muscle specimens to be used for biochemical analysis, such as carnitine quantitation, and glutaraldehyde-fixed specimens may be transported in a container separate from the chilled biopsy specimen. Many laboratories request that 5 cc of the animal's serum be shipped with the muscle biopsy specimen.

79.2 NERVE BIOPSY

79.2.1 Selection of Nerve

As with muscle selection, certain guidelines should be followed in the selection of a nerve for biopsy:

1. The nerve should be affected by the disease process, as evidenced by abnormal results on electrophysiologic investigations or by neurologic abnormalities in areas innervated by the nerve (atrophy, hypotonia, hyporeflexia, paresis, sensory deficits).

2. If the disease process is generalized, a nerve should be selected that (1) is easily biopsied with low morbidity, (2) has established normal electrophysiologic and morphometric data available, and (3) innervates a muscle that may be routinely biopsied.

Biopsy of the mixed (motor/sensory/autonomic) common peroneal nerve is recommended when generalized neuromuscular disease is suspected. This nerve is relatively easy to identify and biopsy because it is flat and contains prominent fascicles. Other mixed nerves that may be biopsied easily are the tibial nerve (pelvic limb) and the ulnar nerve (thoracic limb). When a predominantly sensory neuropathy is suspected, biopsy of cutaneous sensory nerves, such as the caudal cutaneous antebrachial nerve or the caudal cutaneous sural nerve, may be appropriate. Biopsy of nerve roots via laminectomy may be necessary when pathology is restricted to the most proximal portions of the peripheral nervous system. If both dorsal and ventral nerve roots are affected, biopsy of the dorsal nerve root is preferred. Biopsy of cranial nerves is infrequently done, largely due to the inaccessibility of these nerves.

79.2.2 Nerve Biopsy Technique (Common Peroneal)

The common peroneal nerve may be palpated on the lateral aspect of the distal femur just caudal to the proximal tibia. A 6 to 8 cm incision is made over this region, exposing the fascia of the biceps femoris muscle. After the nerve has been palpated through the fascia, a small incision (4 to 5 cm) is made in the fascia while the fascia is elevated with a pair of rat-toothed forceps to prevent inadvertent damage to the nerve. The nerve may be seen as it passes over the lateral head of the gastrocnemius muscle. A 5-0 or 6-0 silk suture is placed through the caudal one fourth to one half of the nerve at the proximal end of the biopsy site, allowing minimal gentle traction as a 3 to 4 cm fascicular biopsy is excised using fine iris scissors. Severely diseased nerves may be markedly reduced in size and may appear almost translucent. Care should be taken to dissect as much fat and fascia from around the nerve as is possible. Wound closure is routine. External dressings normally are not required. Some animals may exhibit proprioceptive deficits, with knuckling of the distal pelvic limb on the side of the biopsy. This usually resolves within 3 to 4 days, and long-term deficits are uncommon.

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79.2.3 Nerve Specimen Processing

The nerve should be placed immediately into fixative (usually glutaraldehyde). Contraction artifact is minimized by (1) pinning the nerve at either end to a piece of balsa wood; (2) suturing the nerve at either end onto the wooden stem of a cotton-tipped applicator; or (3) suspending the nerve in fixative with a stainless steel weight. The sample then may be transported to the laboratory in a sealed screw-top bottle. A nerve specimen also may be frozen in liquid nitrogen if specialized biochemical analysis is required. Specimens collected in this manner may be used for plastic embedding, teased fiber preparations, or electron microscopy.

80 CHAPTER • 80 Buccal Mucosal Bleeding Time

Catharina Brömel

Examination of the patient with a suspected bleeding disorder includes assessment of vascular response and platelet function with formation of the platelet plug (primary hemostasis) and of the coagulation cascade leading to formation of fibrin and stabilization of the plug (secondary hemostasis). Persistent hemorrhage from superficial cutaneous injuries and mucosal surfaces (nasal, gingival, gastrointestinal, genitourinary) and formation of petechiae or ecchymoses are characteristic indicators of abnormalities in primary hemostasis. Primary hemostasis can be evaluated through quantitative measures (platelet estimate from blood smear, platelet count, mean platelet volume) and qualitative measures (von Willebrand factor [vWF] concentration and in vitro platelet function tests, such as aggregometry, aperture closure time, and flow cytometry). The buccal mucosal bleeding time (BMBT) is an in vivo, easily performed screening test for evaluation of primary hemostasis in dogs and cats.

Abnormalities in secondary hemostasis can cause hematomas, hemarthrosis, and bleeding into the pleural and peritoneal cavities. These abnormalities are identified by coagulation screening tests (prothrombin time, activated partial thromboplastin time, activated coagulation time, fibrinogen), proteins induced by vitamin K absence or antagonism (PIVKA), and individual coagulation factor assays.

Determination of the BMBT requires two people and can generally be performed without sedation in dogs. The materials needed are (1) a bleeding time device, such as the Simplate II R (Organon Teknika Corp., Durham, North Carolina), shown in Figure 80-1; (2) a gauze strip approximately 5 cm wide; (3) circular filter paper; and (4) a stopwatch.

The animal is placed in lateral recumbency. The upper lip facing the examiner is everted to expose the buccal mucosa, and the gauze strip is tied around the maxilla and mandible to cause moderate venostasis of the buccal mucosa (in sedated cats, the gauze strip can be tied through the open mouth around the cranium). The tear-away tab (see Figure 80-1) of the single or dual-blade spring-loaded bleeding time device is removed. The device is placed evenly against the exposed mucosal surface rostral to the gauze, with care taken to avoid visible blood vessels. The trigger is depressed, resulting in one or two standardized 5 mm by 1 mm mucosal incisions. The stopwatch is started at the time of trigger activation, and the device is removed from the mucosa. The filter paper is used to blot the blood in 5 second intervals about 2 mm from the incision; care is taken to avoid disrupting platelet plug formation by touching the incision (Figure 80-2). The blood should be prevented from reaching the animal's mouth, because this causes agitation. Blotting and the stopwatch are stopped upon complete cessation of hemorrhage, when blood is no longer absorbed by the filter paper. The BMBT is the time elapsed between mucosal incision and cessation of hemorrhage. If two incisions are made, bleeding generally stops at the same time at both sites. If not, the time should be recorded when the first incision ceases to bleed.

Published reference ranges for the BMBT are 1.4 to 3.5 minutes in dogs and 1.5 to 2.5 minutes in cats. For clinical purposes in dogs, a BMBT of less than 4 minutes is considered normal.

BMBT measurement is not indicated in animals with thrombocytopenia (less than 70,000/μL), because an abnormal result would be expected. Other causes of a prolonged BMBT are von Willebrand's disease (vWD), thrombocytopathies, and vascular disorders. Impaired platelet adhesion and aggregation are present in vWD, a hereditary deficiency of vWF that is reported in various dog breeds but is rare in cats. In a patient with a normal plasma vWF concentration and absence of thrombocytopenia, a prolonged BMBT suggests a defect in platelet function that can be congenital or acquired. Inherited thrombocytopathies (intrinsic platelet function defects) are rare. They include disorders of platelet membranes (e.g., Glanzmann's thrombasthenia in otter hounds and Great Pyrenees

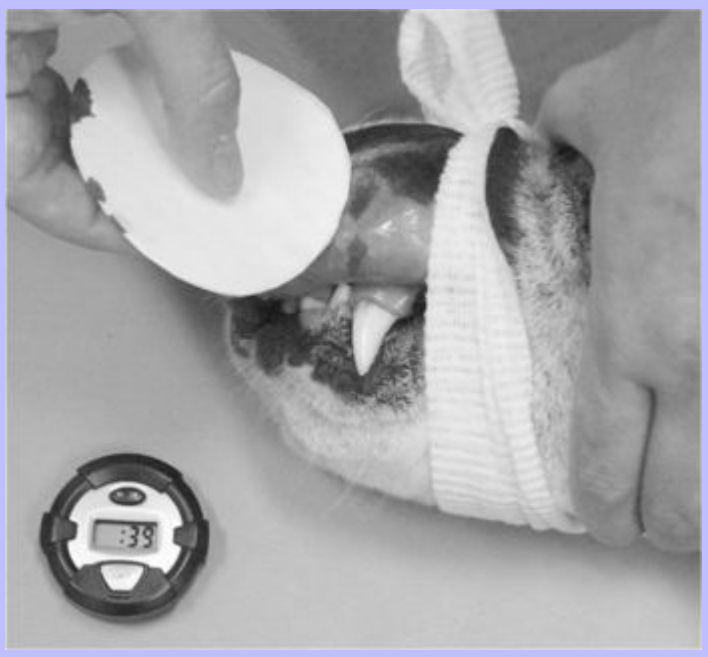
dogs) and disorders of platelet secretion (e.g., spitz and basset hound thrombopathy and platelet granule storage pool deficiency in American cocker spaniels and feline Chédiak-Higashi syndrome). These defects have been associated with a prolonged BMBT. However, not all conditions or agents that cause a platelet dysfunction are reported to result in an abnormal BMBT. 292

Figure 80-1 Disposable bleeding time device (Simplate II R). *Top,* Entire device. *Bottom,* Device with front cover removed, after tear-away tab has been removed and trigger pressed.

Acquired thrombocytopathies are seen in uremic animals, in whom the prolonged BMBT is primarily due to defective platelet adhesion. Platelet aggregation is not consistently altered in uremic animals. Uremic toxins are

thought to play a role in the pathogenesis of this condition. A prolonged BMBT was noted after infusion of dextran 70 in dogs. Nonsteroidal anti-inflammatory agents interfere with platelet function through inhibition of cyclooxygenase 1 (COX-1), leading to decreased synthesis of thromboxane A2, a plateletaggregating and vasoconstricting factor. Aspirin was found to prolong the canine BMBT. Indomethacin did not prolong the BMBT in dogs; the same results were found for the weak COX-1 inhibitors carprofen and meloxicam. Reports on ketoprofen have been conflicting. Acquired thrombocytopathies associated with dysproteinemias and with disseminated intravascular coagulation (DIC) are thought to result from platelet coating by paraproteins and fibrin degradation products. Other causes of a prolonged BMBT include infectious diseases (feline retrovirus–induced thrombocytopathy, canine leishmaniasis and ehrlichioses e.g., *Ehrlichia canis, Ehrlichia platys*), myeloproliferative diseases, and vasculopathies, e.g., vasculitis and inherited vascular defects. Coagulation factor deficiencies do not produce an abnormal BMBT because functional primary hemostasis leads to the formation of an unstable platelet plug; however, rebleeding can occur.

Figure 80-2 Determination of the buccal mucosal bleeding time in a dog.



The BMBT is a quick, useful cage-side test for evaluation of primary hemostasis. It requires minimal preparation and few materials, and it is fairly noninvasive, safe, cost-effective, and easy to perform. Results are available immediately, which allows efficient presurgical screening and repeated evaluation to assess response to treatment. The test can be used as a complement to in vitro function tests, which may not fully reflect platelet function in vivo. However, the BMBT procedure is affected by iatrogenic variables that could normalize the result. Reports on sensitivity and specificity for the detection of primary hemostatic disorders vary. A normal result does not eliminate a diagnosis of vWD or a platelet function defect, especially if the degree of dysfunction is mild. No correlation was found between the BMBT and plasma vWF concentration in dogs. The BMBT test is not standardized (e.g., degree of venostasis) and not reproducible. For any two readings in the same dog, the BMBT may differ by up to 2 minutes with one observer or between two observers. However, it is a valuable tool for the initial assessment of the patient with a suspected bleeding disorder, together with the signalment, medical history (e.g., congenital versus acquired

thrombocytopathy), drug history, physical examination findings, and results of other hemostatic, biochemical, and hematologic parameters.

81 CHAPTER • 81 Jugular Catheterization and Central Venous Pressure

Darlene L. Riel

Catheterization of the jugular vein is a common method of achieving central venous access. Of the four general categories of intravenous access devices (winged needle, over-the-needle, through-the-needle, and multilumen catheters), the through-the-needle and multilumen catheters are favored for jugular catheterization. These catheters are available in a variety of lengths and diameters.

81.1 THROUGH-THE-NEEDLE CATHETERS

Through-the-needle catheters are catheters that are passed through a needle. The catheter is packaged in a protective plastic sleeve to prevent contamination. After catheter placement, the needle is withdrawn and a needle guard is applied to prevent trauma to the dog or cat and to protect the catheter from shearing.

81.2 MULTILUMEN CATHETERS

Multilumen catheters have two to five separate lumens in one catheter and are available in both the over-the-needle and through-the-needle designs. They are useful for administering two or more continuous infusions at the same time and/or for monitoring central venous pressure. Catheter placement is accomplished with the aid of a guide wire and a vein dilator.

81.3 JUGULAR CATHETERIZATION

81.3.1 Supplies and Patient Preparation for All Catheters

The catheterization supplies (Box 81-1) are gathered and arranged so as to be ready for use on a clean tray or countertop close to the patient. An appropriate-size catheter for the dog or cat is selected. The tip of the jugular catheter should reach the vena cava, close to the right atrium. The length to which the catheter should be inserted is determined by measuring from the expected catheter insertion site to the caudal edge of the triceps muscles.

81.3.1.1 Box • 81-1 Jugular Catheterization Supplies

Clippers and antiseptic preparation solutions

Through-the-needle catheter or multilumen catheter kit

Antimicrobial ointment

Sterile 2 × 2 gauze sponge

Heparinized saline syringes

Surgical drapes, if necessary

Sterile gloves

Small utility surgical set

Suture material

Injection cap (or caps) or T-port

Bandage material

Tape

Proper positioning of the dog or cat, usually in lateral recumbency, is crucial. An assistant should extend the patient's head and direct the front limbs caudally. The assistant should hold off the vein by pressing into the thoracic inlet. Placement of a bag of fluids, a sandbag, or rolled towels under the neck may help stabilize the vein. If the vein is not properly stabilized, it may roll laterally or crumple longitudinally. Hair should be clipped wide enough to prevent contamination during the catheterization procedure. Aseptic technique is used, and the site is prepared as would be a surgical site. Sterile drapes should be used if necessary.

81.3.2 Through-the-Needle Catheterization Technique

The operator should first inspect the through-the-needle catheter to make sure the catheter is retracted back into the needle and is not visible at the needle bevel. Grasping the needle firmly, with the needle bevel up, the operator inserts the needle through the skin and advances it subcutaneously parallel to the vein for at least 1.25 cm before it is introduced into the vein. Venipuncture is confirmed when a flash of blood is seen within the catheter. The operator then advances the needle well into the vein, holds the needle with one hand, and threads the catheter with the other hand by pushing the catheter hub within the protective plastic sleeve until the catheter hub is advanced into the needle hub. Pressure is applied at the catheter puncture site; the needle is backed out from the skin, and the plastic sleeve is disconnected from the needle. The needle is secured with a needle guard. If a wire stylet is present, it is removed from the catheter. The catheter then is capped with an injection cap or T-port. Placement is confirmed by successful aspiration of blood, and the catheter is then flushed with heparinized saline. The catheter is sutured close to the insertion site, and care is taken not to kink the catheter. The insertion site is covered with a sterile dressing. Finally, the catheter is secured with a stabilizing wrap.

81.3.3 Multilumen Catheter Technique

All the “pigtail” ports of the multilumen catheter are flushed with sterile heparinized saline, and injection caps are applied to all the ports *except* the most distal one. A No. 11 scalpel blade is used to make a full-thickness stab incision large enough to accommodate the vessel dilator (too small an incision makes it difficult to pass the dilator). The catheter introducer (usually an over-the-needle style catheter) is inserted, and the guide wire is fed through the catheter introducer and into the jugular vein. A length of wire is left exposed that is equivalent in length to the multilumen catheter. It is important that the operator control the wire so as to prevent contamination outside the sterile field and to prevent the wire from slipping down the jugular vein. The catheter introducer is then withdrawn from the vein over the guide wire, leaving the guide wire in the vein. The vein dilator is threaded over the guide wire and advanced into the jugular vein to its full length. Some resistance is expected, and the dilator may need to be rotated or twisted to insert it into the jugular vein. Digital pressure is applied to minimize bleeding, and the dilator is removed from the vein and then withdrawn over the guide wire. *Care must be taken not to remove the guide wire!* The catheter is threaded over the guide wire until the operator can grasp the guide wire from the open pigtail injection port. The operator holds the guide wire and advances the catheter into the jugular vein to the predetermined length. Once the catheter is in place, the guide wire is removed, leaving the multilumen catheter in the vein. An injection cap is placed on the pigtail of the distal port, air is aspirated, and the port is flushed with heparinized saline. The catheter is then sutured in place, and the insertion site is covered with a sterile dressing. Finally, the catheter is secured with a stabilizing wrap.

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81.4 CENTRAL VENOUS PRESSURE MEASUREMENT BY WATER MANOMETER

Central venous pressure (CVP) is a luminal pressure measurement taken from the intrathoracic portions of the cranial vena cava. The accepted normal range for CVP is 0 to 10 cm H_2O.

81.4.1 Supplies Needed for Central Venous Pressure Measurement

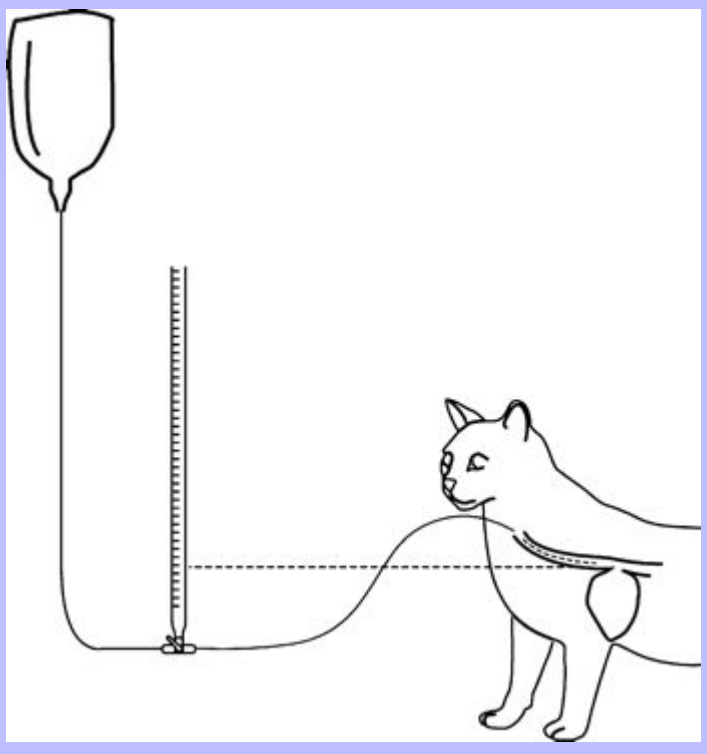
A catheter with the tip properly placed in the intrathoracic vena cava is required. The materials needed include a sterile bag of fluids with an attached fluid administration set, an intravenous fluid extension set, a three-way stopcock, and a water manometer.

81.4.2 Procedure

The dog or cat should be positioned in lateral or sternal recumbency. A water manometer is placed in the fluid line via a three-way stopcock and the extension set (Figure 81-1). The fluid administration set and the extension set are primed with sterile fluids from the fluid bag while the stopcock is in the “Off” position to the water manometer. There must be no air bubbles in the fluid lines. The primed extension set is attached to the patient's catheter. The stopcock at the bottom of the manometer should rest on the table or cage floor. The administration set is opened, again with the stopcock in the “Off” position to the manometer, to allow fluid to flow into the patient's catheter, thus ensuring that the catheter is patent. If fluid does not flow freely into the patient's catheter, a valid CVP measurement will not be obtained. Next, the stopcock is turned so that the “Off” position is now to the patient. The fluid will now fill the manometer, which is allowed to fill about three-quarters full. The stopcock then is turned “Off” to the fluids, allowing a pathway only from the fluid-filled manometer and the patient's catheter.

The level of fluid in the manometer falls until the hydrostatic pressure of the column of fluid reaches equilibrium with the hydrostatic pressure of the blood at the end of the catheter. Therefore it is essential to know where the catheter tip lies in relation to the manometer fluid column. When the animal is in lateral recumbency, the cranial vena cava lies near the midline, and the manubrium is a good reference point. When the animal is in sternal recumbency, the cranial vena cava is about at the level of the point of the shoulder or the scapulohumeral joint. With the stopcock resting on the tabletop or cage floor, a *zero reference point* is determined by a horizontal line drawn between the manometer and the appropriate external anatomic landmark (manubrium or scapulohumeral joint). The centimeter mark where the horizontal line intersects the manometer is the zero reference point. A carpenter's level fastened to a taut string is an excellent guide for the horizontal line from the anatomic landmark to the manometer. The difference between the equilibrium point reading and the zero reference point is the CVP measurement. For example, if the initial reading is 15 cm H_2O (where the fluid level stopped falling) and the zero reference point is 10 cm H_2O (horizontal line drawn between the external anatomic landmark and the manometer), the CVP is 5 cm H_2O. The presence of a well-placed, unobstructed catheter can be verified by the fluid column in the manometer, which will slightly oscillate up and down as the animal's heart beats or as the animal breathes. Readings are taken between ventilatory excursions. Trends in central venous pressure are more informative than single values. Each time a CVP measurement is obtained, the patient should be in the same recumbent position. The goal is to be consistent in taking the readings and to monitor the trends.

Figure 81-1 Setup for central venous pressure (CVP) assessment.



82 CHAPTER • 82 Cerebrospinal Fluid Collection, Myelography, and Epidurals

Scott M. Anderson

82.1 CEREBROSPINAL FLUID COLLECTION

Cerebrospinal fluid (CSF) can be collected from the cerebellomedullary (CM) cistern or from the lumbar subarachnoid space. A larger volume of fluid is more easily obtained from the former, with less risk of iatrogenic hemorrhage.

82.1.1 Cerebellomedullary Cistern Collection

With the animal under general anesthesia, the operator clips and prepares the region for aseptic sample collection. If elevated intracranial pressure is suspected, the dog or cat is hyperventilated.

The animal is placed in lateral recumbency, with the neck flexed so that the long axis of the head is perpendicular to the spine. The spine and median plane of the head should be parallel to the table. Care should be taken to avoid hyperflexion of the neck, which can partially occlude the endotracheal tube and increase intracranial pressure by reducing jugular venous flow.

The midline is identified through palpation of the occipital crest. On the midline, just ahead of a line between the cranial edge of the wings of the atlas, a 22-gauge, 3.75 to 7.5 cm styletted spinal needle is inserted perpendicular to the long axis of the spine. In thick-skinned animals, a stab incision is made in the skin at the needle entry site so that the needle does not plunge into the spinal cord after being forced through the skin.

The needle is advanced slowly, in 1 to 2 mm increments. A pop and decreased resistance may be felt as the needle penetrates the dura. In cats and smaller dogs, this may be difficult to feel. The stylet then is withdrawn, and the operator checks for CSF flow. If none is seen, the stylet is replaced and the needle again is advanced in 1 to 2 mm increments, with the operator checking each time for CSF flow. If the needle strikes the occipital bone, it is “walked” off the caudal edge of the bone until it enters the CM cistern.

If no CSF flow is seen after further advancement, the operator should remove the stylet and withdraw the needle slowly, observing for CSF flow. If two unsuccessful attempts are made at CM cerebrospinal fluid collection, the operator should consider performing a lumbar tap rather than risking trauma to the cervical spinal cord.

If whole blood flows from the needle at any time, the needle should be withdrawn and the procedure repeated using a fresh needle.

Once CSF flow is seen, 0.5 to 2 mL is collected, depending on the animal's size, and the pressure is measured if desired. The jugular veins may be occluded to increase CSF flow. Aspiration with a syringe should be avoided, because this increases the risk of blood contamination. Only as much CSF as needed should be collected; removing a large volume of CSF may increase the risk of brain herniation (shift in intracranial contents), which is often fatal.

Blood in the CSF may be iatrogenic or pathologic. If blood is seen, the stylet is replaced for 1 minute, and sample collection is then resumed. Often the bleeding will have diminished. Iatrogenic hemorrhage often decreases as the fluid is collected. Therefore the first and second portions of the sample must be collected in

separate tubes. If the degree of blood contamination is severe, an ethylenediamine tetra-acetic acid (EDTA) tube may be used to prevent clotting. Red blood cell contamination does not significantly correlate with the nucleated cell count or protein concentration.

If fluid analysis cannot be performed immediately, the addition of 30 μL of autologous serum per 250 μL of CSF has been shown to help preserve the structure of the cells in refrigerated CSF for up to 48 hours. If this process is used, a sample of unaltered CSF should also be submitted for determination of the protein concentration and total cell count.

If no flow can be obtained, the dog or cat may have suffered a brain herniation that is obstructing CSF flow. Attempts at CSF collection should be discontinued and hyperventilation instituted.

82.1.2 Lumbar Collection

For lumbar CSF collection, the animal is placed in lateral recumbency, with the hind legs pulled forward to flex the lumbar spine. A median or paramedian needle insertion site may be used. For a median puncture, the needle is inserted perpendicular to the spine just cranial to the L6 dorsal spinous process. For a paramedian placement, the needle is inserted slightly caudolateral to the L6 dorsal spinous process. The needle then is directed cranioventrally at an angle parallel to the plane of the dorsal intervertebral articulation (approximately 45 degrees to the spine). Fluoroscopy is helpful in confirming needle position.

The needle is advanced into the spinal canal. Aspiration of CSF from the dorsal subarachnoid space avoids needle-induced trauma to the spinal cord and is preferable, but obtaining fluid from this level is more difficult than obtaining it from the ventral subarachnoid space. Once the needle is felt to pass the articulation, the operator withdraws the stylet to check for CSF flow. If none is seen, the stylet is replaced and the needle is advanced in 1 to 2 mm increments, with the operator checking for CSF flow after each advance. Alternatively, the needle can be advanced until the tip contacts bone, and CSF then is withdrawn from the ventral subarachnoid space. The pathologist must be informed of the collection site: lumbar CSF has a slightly higher protein concentration and fewer cells than CSF collected from the CM cistern.

If no CSF is obtained, the needle is withdrawn in 1 mm increments, with the operator observing for CSF flow. If none is seen, collection at the L4 to L5 level can be attempted.

82.2 MYELOGRAPHY

Myelography (radiography after subarachnoid injection of a contrast medium) may be performed by either cervical (CM cistern) or lumbar injection. Cervical injection allows more contrast medium to flow cranially into the cerebral ventricular system. In addition, a lesion causing severe cord swelling or compression may not allow the contrast medium to pass, resulting in only the cranial edge of the lesion being outlined. Lumbar injection, however, can be performed under pressure, forcing contrast medium past the lesion to outline the entire lesion and the full length of the spinal cord. For these reasons, a lumbar injection site is preferred.

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The needle is placed as described above for CSF collection. Lumbar injection is typically done in the ventral subarachnoid space, because it can be difficult to position the needle tip in the dorsal subarachnoid space. Fluoroscopic guidance facilitates proper needle placement. CSF is collected prior to injection of the contrast media, because the CSF protein concentration and neutrophil count typically increase after myelography.

Use of a nonionic contrast medium (iohexal or iopamidol, 180 to 240 mg/mL) is advised. Metrizamide should not be used, because it poses a higher risk of complications, including seizures. A test injection of 0.2 mL of contrast

medium should be performed, with fluoroscopic or radiographic confirmation that subarachnoid injection has occurred. The needle hub and injection set should be filled with contrast medium prior to commencing injection; this minimizes the appearance bubbles in the subarachnoid space, which may hamper interpretation.

Epidural leakage of contrast medium obscures the subarachnoid dye columns. If this is seen, the operator should withdraw the needle 1 to 2 mm and perform another test injection. If this does not produce opacification of the subarachnoid space, the operator should consider withdrawing the needle and selecting another injection site. Further incremental withdrawal could result in contrast medium being injected into the spinal cord parenchyma, with deleterious results.

After cervical injection and needle removal, the front half of the dog or cat is elevated to maximize the flow of contrast medium into the thoracic and lumbar subarachnoid space; lateral and ventrodorsal spinal radiographs are then obtained. Oblique views and dynamic studies may be helpful in some cases.

Transient exacerbation of neurologic impairment may be seen after myelography, particularly in large breed dogs, dogs with degenerative myelopathy, and dogs with chronic neurologic conditions. This usually resolves within a few days.

82.3 EPIDUROGRAPHY

Because the subarachnoid space typically does not extend to the lumbosacral junction, myelography is an unreliable means of assessing lesions caudal to L5. For this area, magnetic resonance imaging (MRI) scans are preferred. If MRI is not available, epidurography may be performed.

The tail base and dorsal sacral region are clipped and aseptically prepared. At any level from S3-CD1 through CD4-CD5, a 22-gauge, 2.5 to 7.5 cm styletted spinal needle is inserted on the midline perpendicular to the spine. With the needle tip on the floor of the spinal canal, 0.15 to 0.2 mL/kg of contrast medium is injected. With the needle in place, flexed, neutral, and extended lateral radiographs of the lumbosacral region are obtained. Supplemental injections of 0.1 mL/kg are given as needed for follow-up views. The needle then is removed, and a ventrodorsal radiograph is obtained.

Epidurography has no significant complications.

82.4 EPIDURAL ANESTHESIA

Epidural anesthesia may be administered as a single dose or may be given continuously through an indwelling catheter. To administer a single dose, a 20-to 22-gauge, 2.5 to 7.5 cm needle is inserted on the midline, perpendicular to the spine and slightly caudal to the L7 dorsal spinous process. A pop and decreased resistance are felt as the needle passes through the interarcuate ligament.

To verify that the needle tip is in the epidural space, sterile saline solution can be injected. There should be no resistance to injection if the needle tip has been properly placed. Alternatively, 3 to 4 mL of air may be injected. The bubbles produced do not significantly decrease the efficacy of the local anesthetic to be injected.

If CSF flow is obtained, the needle tip is in the subarachnoid space. This is uncommon, because the subarachnoid space typically does not extend to the L7 to S1 level. In this situation, a second attempt may be made to insert the needle into its proper epidural location. Alternatively, subarachnoid injection of a reduced dose of anesthetic may be performed (1 mL/10 kg body weight; that is, 50% of the epidural dose).

If blood flow is obtained, the needle should be withdrawn and another attempt made at proper placement. A local anesthetic should not be injected in this situation. Intravascular injection is contraindicated due to the risk of toxicity.

The selected local anesthetic can now be administered. Details of specific agents and dosages are beyond the scope of this chapter, but in general, approximately 1 mL/5 kg body weight is administered, to a maximum of 20 mL. For cesarean section, 1 mL/6 kg is reported to be sufficient. The anesthetic should be warmed to body temperature and injected over a 1-minute interval to minimize discomfort.

For continuous epidural anesthesia, a 17-or 18-gauge, 7.5 cm Touhy or Crawford needle is inserted and directed 30 degrees cranial, rather than perpendicular to the spine. The bevel is directed cranially. The catheter is advanced through the needle at least 3 cm into the epidural space, or farther, to the desired level in the lumbar or thoracic spine. If the catheter cannot be advanced, the operator injects a small amount of saline solution while again attempting to advance the catheter. If this fails, the needle and catheter are withdrawn simultaneously; if the catheter is withdrawn alone, it could be severed by the needle tip. If this occurs, most authors agree that surgery to retrieve the catheter fragment is not indicated.

Paresis of the nictitating membrane (the sympathetic innervation of which originates from T1 to T3) indicates blockade of spinal sympathetic outflow due to thoracic epidural anesthesia. This may produce hypotension, Horner's syndrome, and hypoglycemia. If the agent affects the cervical spinal cord, respiratory muscle paralysis can occur. In these cases, the thorax, neck, and head are elevated to decrease forward flow of the anesthetic agent and the patient is ventilated if necessary.

Other reported complications of epidural anesthesia include infection, seizures, insufficient or delayed onset of anesthesia, circulatory depression, Schiff-Sherrington–like reflexes, unilateral hind limb paresis, and partial anesthesia of the tail and perineum.

83 CHAPTER • 83 Veterinary Diagnosis of Bacterial, Fungal, and Viral Disease

Janet E. Foley

83.1 INDICATIONS FOR TESTING

Infectious disease testing may be performed for a number of reasons; for example, to identify the etiology of an inflammatory disease, to follow up on a dog or cat with an infectious disease, to obtain an isolate for further testing (such as for antibiotic susceptibility), or to determine the risk of transmission of an infection to other animals or to people. Tests and interpretation vary, depending on the clinician's intent, therefore it is helpful to clarify the purpose for testing in each case. For example, if the goal is to determine whether an animal poses a risk to an immunocompromised human member of a household, it would be important to document active infection; thus culture or antigen-based tests would be used, not serology. It is important to evaluate test results in the context of the whole patient evaluation; documenting the presence of a pathogen does *not* prove that the pathogen is the cause of the animal's clinical signs.

83.2 TYPES OF TESTS: PROS, CONS, AND LIMITATIONS

Tests for infectious agents are either direct or indirect (Figure 83-1). *Direct tests* detect a pathogen, its nucleic acids, or its antigens. These tests include culture, polymerase chain reaction (PCR), antigen tests, and direct visualization. Direct methods may either document living (active) infection or may pick up an infection that no longer is active. Only culture documents that the infection is active at the time of sample acquisition, although cytology or histopathology can be suggestive. PCR or antigen tests may remain positive after effective treatment has been initiated; that is, after the target agent has died. For example, the blood of a bacteremic animal could be PCR positive for bacterial DNA for a few days after administration of antibiotics and after the animal has become culture negative. *Indirect tests* seek evidence of exposure to a pathogen by evaluating host response; these tests consist primarily of serology for specific host antibodies.

Good tests should be *sensitive* (high likelihood of detecting the infectious agent) and *specific* (low likelihood of a positive result if the agent is not present). Culture often is insensitive but highly specific. Bacterial culture often is negative in samples from animals recently started on antibiotics, and some agents may require days to weeks to grow in vitro. However, culture should be highly specific, depending on how well “positives” are further characterized in the laboratory. Culture has the additional advantages of providing an isolate for testing antibiotic, antifungal, or antiviral agents, molecular epidemiologic studies, and possible experimental infections. Culture sensitivity depends on sample handling (discussed below). *Many agents cannot be cultured,* therefore alternative methods for these organisms are critical and may be useful for improving sensitivity even for agents that can be cultured.

The “most direct” test is direct visualization, which also is insensitive, sometimes like looking for a needle in a haystack. Inflammation may be helpful in directing the attention of the clinical pathologist or microbiologist to the area containing organisms. Gram stains are useful in bacterial processes, because culture virtually always underestimates the number and diversity of bacteria, whereas a semiquantitative Gram stain can reveal both. Special stains, such as silver-based stains or calcofluor white (a fluorescent stain), can enhance spirochetes, some bacteria, fungi, and other organisms. Immunohistochemical stains use monoclonal or polyclonal antibodies raised against the pathogen to target areas in tissue where a pathogen is present, coupled with a technique for flagging the pathogen (usually either a fluorescent dye or a chemical chromogen).

PCR is emerging as a diagnostic powerhouse for bacterial, fungal, and viral infectious diseases. PCR is an iterated biochemical reaction performed in a *thermal cycler,* a machine that cycles repeatedly through a temperature series, so that a few target DNA fragments in a sample can yield millions of copies. Millions of same-size DNA fragments can be visualized on an electrophoretic gel. The trick to PCR is to find primers to start the reaction that anneal to a particular target and only that target. Thus *Hemobartonella felis* (now *Mycoplasma hemofelis*) primers should anneal only to *M. hemofelis* DNA and feline coronavirus primers only to feline enteric coronavirus (FECV) cDNA. There are several *universal primers,* which anneal to all bacteria or all filamentous fungi. After PCR is performed, the resulting fragment can be sequenced and the results checked against a data base to identify the bacterium or fungus present in the sample.

Even carefully designed PCR reactions occasionally have been found to amplify nontargets (when by chance, some other organism has a region of DNA to which the primers anneal), therefore it is important to verify PCR results with DNA sequencing, a DNA probe, a second PCR in another region of DNA, or some other method. Two other limitations of PCR are the feasibility of obtaining sufficient quality RNA or DNA from the clinical sample and inhibitors in the sample. RNA in viruses such as FECV, canine distemper, and others is prone to RNAse degradation and must be kept as cold as possible and processed rapidly in a laboratory using special techniques to protect the RNA. Delays in sample handling increase the rate of false-negative PCR results. DNA is more stable and can be shipped dried, frozen, at room temperature, in paraffin-embedded tissue, and so forth. Some pathogens are harder to "crack," in terms of obtaining DNA, particularly mycobacteria and many fungi. Blood, feces, ascitic fluid, ticks, and other samples have inhibitors that can make the reaction less sensitive. Also, PCR can become cross-contaminated with DNA in the laboratory, therefore positive results should be trusted only if the laboratory has excellent quality control and makes stringent use of negative controls.

Antigen tests are available for a few veterinary pathogens associated with high levels of antigen in a sample; some of these pathogens are feline leukemia virus (FeLV), *Cryptococcus neoformans,* and canine parvovirus. In other infections, such as feline immunodeficiency virus (FIV), antigen is insufficient to make such a diagnostic modality feasible.

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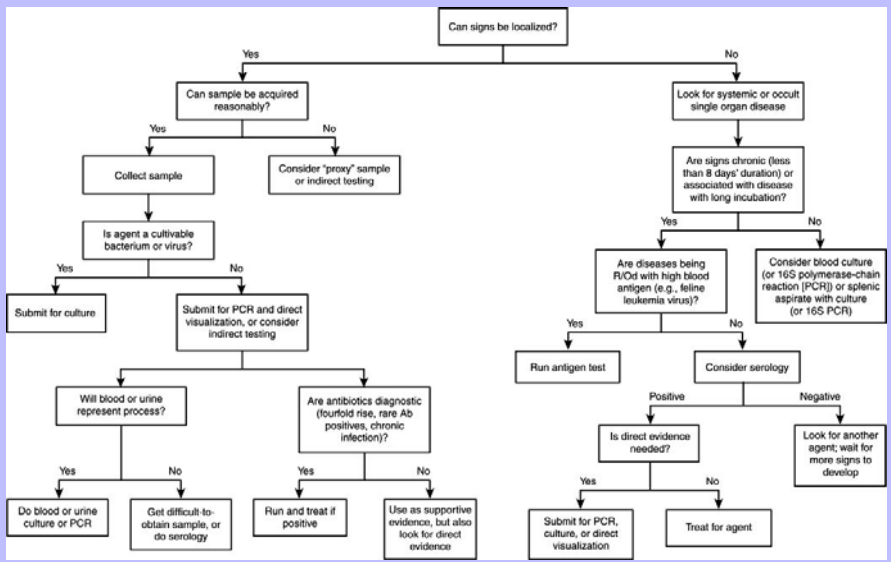
Figure 83-1 Algorithm for the diagnosis of bacterial, fungal, and viral diseases.



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Antibody testing has several advantages. The sample typically is serum, which may be easier to obtain than, for example, tissue, and animals may remain seropositive for months after exposure, providing a larger window for testing. However, this large window may be a drawback as well, because the animal remains seropositive long after infection has resolved. In diseases that do not resolve (e.g., FIV), antibody testing documents infection; however, in other diseases, such as ehrlichiosis, serology only documents previous exposure. Serology has two other drawbacks: there is no detectable immunoglobulin G (IgG) early in infection (up to 10 to 14 days), and vaccines induce cross-reacting seropositivity in some diseases, such as feline herpesvirus, calicivirus, and canine parvovirus. Twofold or fourfold rises in titer over 2 to 4 weeks are helpful for documenting recent infection in some diseases (and are part of the human case definition for ehrlichiosis) but are not helpful in others (e.g., feline infectious peritonitis [FIP]). Negative titers in a disease process that has been ongoing for at least 2 weeks are extremely informative in terms of ruling out some infections.

83.3 SAMPLE COLLECTING, HANDLING, AND SUBMISSION

The packaging and transport of samples depend on the tests to be run. The requirements are:

- *Direct visualization, pathology, or immunohistochemistry:* Rapid transport, room temperature, and room air (unless formalin fixed)
- Virus isolation, PCR, or antigen and antibody tests: Frozen
- Aerobic and fungal culture: Cooled with room air
- Anaerobic or microaerophilic bacteria: Cooled with special atmospheres

Although each institution has a different configuration of laboratories, infectious disease diagnosis could involve clinical pathology, virology, immunology, microbiology, parasitology, biochemistry, and/or molecular biology. Clinicians should verify, through contact with the laboratory, how much sample and what paperwork are required to route the sample to all desired laboratories.

84 CHAPTER • 84 Urogenital Diagnostic Procedures

S. Dru Forrester

84.1 CYSTOCENTESIS

Cystocentesis is indicated to collect urine for diagnostic evaluation and also to temporarily decompress the urinary bladder in animals with urethral obstruction. Obtaining urine from the urinary bladder bypasses contamination from the lower urogenital tract and is the preferred technique when samples are to be submitted for bacterial culture. When performed correctly, cystocentesis is a safe procedure. In most dogs and cats, a 22-gauge, 1.5-inch needle attached to a 12-mL syringe is used. For large or obese dogs, a 22-gauge, 3-inch spinal needle may be needed. If the urinary bladder cannot be palpated, ultrasound guidance is helpful for localizing it.

Cystocentesis can be done with the dog or cat standing or in dorsal or lateral recumbency. The bladder is palpated to determine the site for puncture. Usually the needle is inserted into the ventral or ventrolateral aspect of the urinary bladder. Hair can be clipped over the site and the skin prepared aseptically. However, in almost all situations this is unnecessary, and alcohol can simply be used to wipe the skin over the puncture site. The urinary bladder is immobilized with one hand, and the other hand is used to insert the needle through the abdominal wall (Figure 84-1). If the urinary bladder contains a small amount of urine or if cystocentesis is done therapeutically, the needle should be inserted near the urinary bladder neck, rather than at the apex, so that urine can be removed continually as the urinary bladder becomes smaller. Urine is aspirated by pulling back on the plunger to create negative pressure. If urine is not obtained, the needle is not redirected; rather, the needle is removed from the abdomen and the procedure is begun again. Excessive pressure on the urinary bladder during and immediately after aspiration should be avoided to prevent leakage of urine into the abdominal cavity.

Figure 84-1 During cystocentesis the urinary bladder is immobilized with one hand while the other hand is used to insert the needle into the urinary bladder and aspirate urine.

If the urinary bladder cannot be palpated and ultrasound is not available, cystocentesis can be done "blindly." Although this technique may not be as effective, it can be attempted if a dog or cat cannot be hospitalized during the day or is likely to void frequently due to pollakiuria. The pet is positioned in dorsal recumbency, and a puncture site is selected on the midline, halfway between the umbilicus and pelvic brim (this is often the point where alcohol pools when dripped onto the area in female dogs). In male dogs, the penis and prepuce should be retracted laterally so that the needle can be inserted into the abdomen on the midline. Urine is aspirated as described above. If a sample is not obtained, the needle is removed and aspiration is attempted at a site just cranial or caudal to the original puncture. If urine is not obtained after a total of three attempts, cystocentesis should be delayed until the urinary bladder can be palpated.

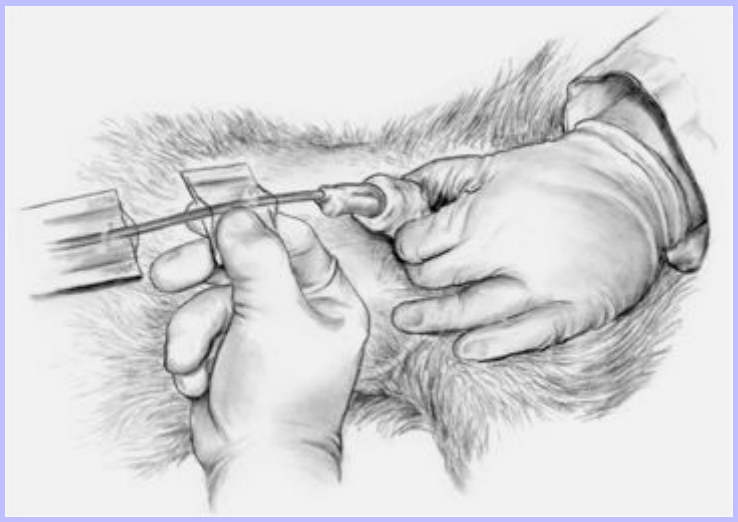
84.2 URETHRAL CATHETERIZATION

Transurethral catheterization is indicated to collect urine for analysis or bacterial culture (primarily in male dogs), to measure urine output, to inject radiographic contrast material, and to relieve urinary retention secondary to functional or anatomic urethral obstruction. Potential complications include iatrogenic urinary tract infection (more likely in females) and urethral or urinary bladder trauma. Catheterization should always be performed aseptically using a sterile catheter. Flexible catheters (e.g., rubber) are appropriate for the collection of urine for diagnostic purposes and are less traumatic than polypropylene catheters. Urethral catheters with an inflatable balloon near the tip (e.g., Foley catheters) are useful for indwelling catheterization in female dogs. Catheters are available in a variety of sizes and lengths. Catheter diameter is most often expressed in French (F) units (3F = 1 mm). For male dogs, depending on the animal's size, catheter diameters of 3.5 to 5F (<10 kg), 8 to 10F (10 to 25 kg), and 10 to 12F (>35 kg) are appropriate. Catheters ranging from 5 to 14F are adequate for most female dogs.

Male dogs should be restrained in lateral recumbency, and an assistant should retract the prepuce to expose the penis. The tip of the penis should be cleansed with a mild antiseptic solution. The length of catheter needed to reach from the distal end of the penis to the neck of the urinary bladder should be estimated; this helps avoid overinsertion of the catheter, which could damage the urinary bladder mucosa. The tip of the catheter should be lubricated with a sterile, water-soluble lubricant from a single-use packet. The urinary catheter should be maintained in sterile condition during catheterization; this may be accomplished by using a sterile hemostat, wearing sterile gloves, or using a cut portion at the end of the catheter package to advance the catheter (Figure 84-2). The tip of the catheter is inserted into the external urethral opening and gently advanced. Some resistance may occur as the catheter is advanced through the area of the os penis and again at the ischial arch. If the catheter has been inserted to the appropriate level and urine is not observed, a syringe is attached to the catheter to aspirate urine. After urine collection, the catheter is gently removed from the urethra.

Urethral catheterization is more technically difficult in female dogs, and sedation may occasionally be helpful in some cases (e.g., with small or fractious dogs). Catheterization may be performed using a speculum (e.g., human nasal speculum, otoscope cone) to visualize the urethral orifice or blindly, with or without digital palpation. Selection of technique depends on the preference and experience of the clinician and the temperament of the dog or the size of the vagina. It is helpful to insert a lubricated, sterile, metal stylet or 3.5F polypropylene catheter through the lumen of the Foley catheter to increase its rigidity and facilitate its passage. The stylet should be advanced to the tip of the Foley catheter to prevent it from exiting the eye of the catheter and causing urethral damage during placement.

Figure 84-2 Urethral catheterization of a male dog. A portion of the catheter's package is used to aseptically advance the catheter through the urethra.



Female dogs are most easily catheterized while standing or in sternal recumbency with the rear legs hanging over the end of a table; an assistant should hold the tail to one side. Excessive hair around the vulva should be clipped, if necessary, and the area should be cleansed with antiseptic soap. A lubricated tuberculin syringe is inserted into the vagina, and 0.25 to 0.5 mL of local anesthetic (e.g., 0.5% lidocaine or topical ophthalmic anesthetic) is instilled in the area of the urethral orifice (approximately 3 to 5 cm cranial to the vulvar opening). While sterile conditions are maintained, the tip of the catheter is lubricated with water-soluble lubricant.

For the visual technique, the vaginal speculum is lubricated and the tip is gently inserted dorsally through the vulva and then directed cranially to avoid the clitoral fossa. The blades of the speculum are opened gently so that the urethral orifice can be visualized. The handles of the speculum should be directed dorsally so that they do not interfere with visualization. A sterile glove is worn to pick up the catheter; the tip is inserted through the urethral orifice, and the catheter then is gently advanced into the urinary bladder. If the catheter is to remain in place, air or saline is injected to inflate the balloon at the catheter tip.

For the digital technique, the person passing the catheter should wear sterile gloves. A lubricated index finger is inserted into the vagina, and the urethral orifice is palpated. The other hand is used to insert the catheter ventral to the finger in the vagina; the catheter is guided ventrally on the midline so that it enters the urethral orifice (Figure 84-3). If a finger cannot be inserted into the vagina, the catheter can be passed blindly. After the catheter has been inserted through the vulva, it is directed ventrally along the midline of the vestibular floor and advanced cranially. If resistance is encountered, the catheter has most likely advanced past the urethral orifice to the cervix. If this occurs, the catheter is withdrawn and the procedure is repeated. If urine is not noted from the catheter, a syringe is attached and urine is obtained through aspiration.

Figure 84-3 Urethral catheterization of a female dog. An index finger is placed over the urethral orifice to guide the catheter ventrally into the urethra.

84.3 ASPIRATION/BIOPSY OF UROGENITAL MASSES

Tissue specimens may be obtained from urogenital masses (i.e., vagina, prostate gland, urethra, and urinary bladder) for cytologic and histologic evaluation by a variety of methods, including endoscopy, ultrasound-guided aspiration, and catheter-assisted biopsy. Catheter-assisted biopsy can be performed without the need of special diagnostic equipment. Sedation may be helpful in fractious dogs. The location of the mass should be confirmed by physical examination or diagnostic imaging studies (e.g., ultrasound, contrast urethrography). As described above, a flexible urinary catheter with side openings (eyes) on the distal end should be passed into the urinary bladder and all urine removed. The tip of the catheter should then be withdrawn to the level of the mass (Figure 84-4). The location of the catheter tip can be confirmed by digital palpation per rectum or by radiographs if a radiopaque catheter is used. A 12-mL syringe containing sterile saline is attached, and all but 1 mL is injected through the catheter. The plunger is pulled back to create negative pressure, and mucosal pieces are aspirated into the side openings of the catheter. If the mass is located in the prostate gland, vigorous palpation of the prostate per rectum during aspiration may facilitate collection of prostatic tissue.

Figure 84-4 Passage of a flexible rubber catheter through the urethra of a male dog to aspirate tissue samples from a mass at the trigone of the urinary bladder.

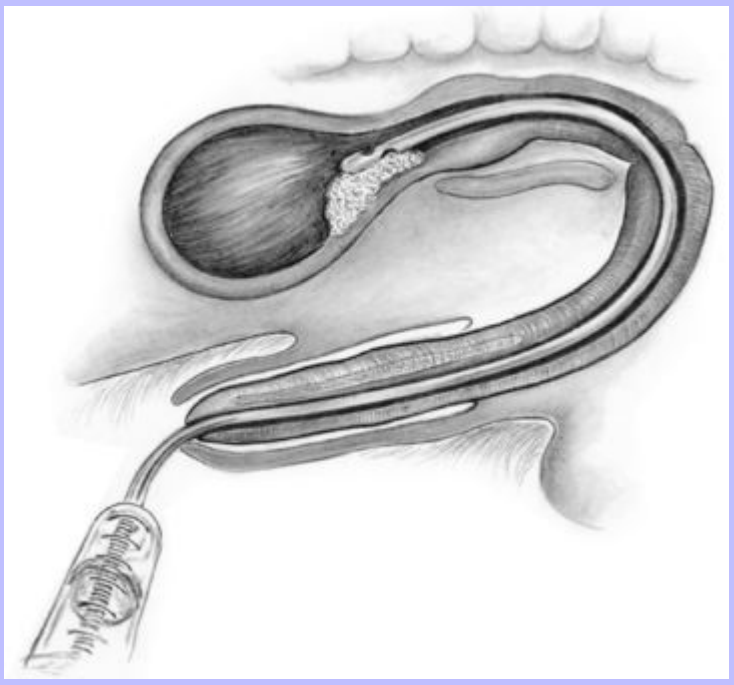
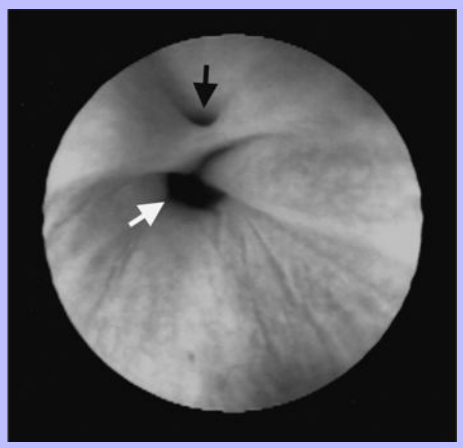


Figure 84-5 Urethroscopy of female Labrador retriever with incontinence since birth. Note the urethral lumen *(white arrow)* and the ectopic ureter entering the urethra *(black arrow)*. (Courtesy Dr. Patti Sura, Virginia Tech.)



After the sample has been collected, negative pressure is released and the catheter is removed from the urethra. The tip of the catheter is placed in a vial, and additional saline is injected through the catheter to remove tissue samples. Any solid pieces of tissue should be placed in formalin and submitted for histologic evaluation. The remaining saline, containing small fragments of tissue, should be evaluated cytologically.

84.4 CYSTOSCOPY

Cystoscopy may be indicated for the evaluation of dogs or cats with hematuria, signs of lower urinary tract inflammation, recurrent urinary tract infections, urinary bladder or urethral masses, urolithiasis, and urinary incontinence. Procedures that can be performed include visualization of the urethral and urinary bladder mucosa, collection of tissue samples from masses or other lesions, removal of uroliths, collection of urine from individual ureters for diagnosis of renal hematuria or pyelonephritis, and identification and location of ectopic ureters (Figure 84-5). Rigid or flexible cystoscopes can be inserted through the urethra of female dogs and cats; however, only flexible endoscopes can be used in males.

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Cystoscopy is performed under general anesthesia with the dog or cat in lateral or dorsal recumbency. Hair should be clipped around the vulva, and the area should be gently scrubbed with antiseptic solution. Sterile gloves should be worn to assemble the cystoscope. The tip of the cystoscope is lubricated and then gently inserted into the vestibule. Sterile saline is infused through the fluid port of the cystoscope to distend the mucosa and allow visualization of the urethral orifice (Figure 84-6). The scope then is inserted through the urethral orifice and advanced slowly, allowing the urethra to be distended so that it can be examined thoroughly. After the cystoscope has been advanced into the urinary bladder, urine is drained completely and the bladder is distended with sterile saline. The entire urinary bladder mucosa should be examined. It may be helpful to examine the urinary bladder when it is distended at low pressure and also at high pressure. After cystoscopy an antimicrobial (e.g., ampicillin) should be given for 5 days to prevent urinary tract infection secondary to bacterial contamination.

Figure 84-6 Urethral orifice on the ventral floor of the vagina in a female dog undergoing cystoscopy.

85 CHAPTER • 85 Cytology of Internal Organs

Amy L. MacNeill

A. Rick Alleman

Cytologic evaluation of internal organs is a powerful diagnostic technique. It is imperative that samples be collected and processed properly and that a well-maintained microscope is used. This chapter briefly describes proper sample handling and some diseases of internal organs that can be diagnosed cytologically.

85.1 ASPIRATE COLLECTION AND PREPARATION

Ultrasonography is recommended to guide sample collection and to monitor the dog or cat for bleeding. It is possible to obtain some samples without sedation. Aspiration of internal organs must be considered a sterile procedure. The center of large masses should be avoided, because this area is often necrotic. Multiple samples should be taken so that different areas of the lesion are represented. If fluid is collected, some should be smeared directly onto a slide, and the rest should be saved for determination of cell counts and protein content and concentration. If the fluid is bloody, it should be placed in an ethylenediamine tetra-acetic acid (EDTA) tube. Also, cytologic examination of touch preparations from nonfixed biopsy samples can be informative.

If generalized splenomegaly or hepatomegaly is detected, blinded aspiration can be performed but is not recommended. The animal should be placed in dorsal recumbency. A 6-to 12-cc syringe is attached to a 20-to 22-gauge, 1.5-inch needle. The needle is introduced into the caudodorsal aspect of the spleen or liver to avoid piercing the diaphragm. The plunger is pulled back to create 1 cc of vacuum. The needle position is carefully redirected within the organ. The pressure on the plunger is released, and the needle is withdrawn. The sample is placed near the frosted edge of a clean slide and smeared by placing a second slide flat onto the sample slide and pulling the second slide from the frosted edge to the open edge of the sample slide in one continuous, smooth motion. The weight of the second slide is sufficient to smear the sample. It is important not to pull the sample off the end of the slide.

Once a sample has been collected, it should be air dried and stained for cytologic examination. New methylene blue and Romanowsky-type stains are commonly used. If a slide is sent to a laboratory, it should be shipped separately from histology samples.

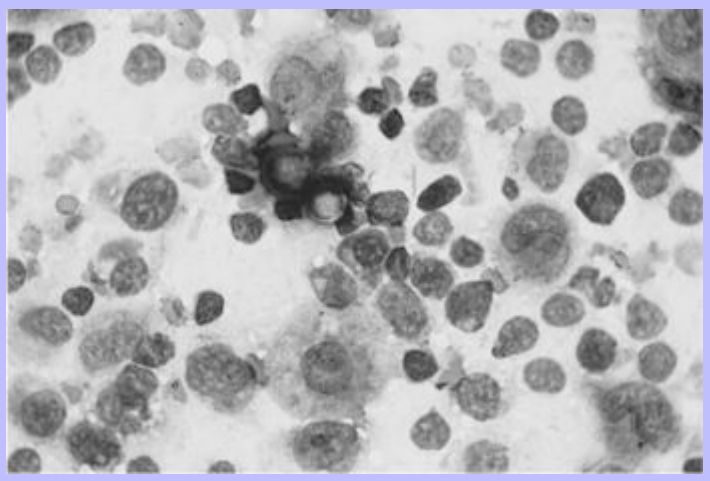
85.2 THORACIC ORGAN CYTOLOGY

85.2.1 Pulmonary Aspirates

Aspirates from normal pulmonary tissue tend to be hemodilute and contain low numbers of respiratory epithelial cells and macrophages. Inflammation caused by most bacterial agents is purulent, whereas fungal infections cause pyogranulomatous disease. Culture is recommended with most inflammatory samples. Several specific fungal diseases can be diagnosed cytologically, including blastomycosis (Figure 85-1). Carcinomas tend to exfoliate as sheets of epithelial cells with visible cell junctions, basophilic cytoplasm, and round nuclei. Acinar structures or punctuate cytoplasmic vacuoles may be observed with adenocarcinomas (Figure 85-2). Metastatic carcinomas can rarely be distinguished from primary lung tumors. As with most malignant lesions, features such as anisocytosis, anisokaryosis, prominent nucleoli, an increased nuclear to cytoplasmic ratio (N:C), mitotic figures, coarse chromatin, and multinucleation must be observed for diagnosis. Also,

inflammation can cause epithelial cells to have characteristics of malignancy; neoplasia, therefore, often cannot be reliably diagnosed if inflammation is observed.

Figure 85-1 Blastomycosis. Several round organisms, approximately 15 µm in diameter and having a nonstaining capsule, are characteristic of *Blastomyces* infection. Infiltrating macrophages and lymphocytes are also noted. (Wright-Giemsa stain, ×250.)



85.2.2 Heart-Based Tumors

Echocardiography and anesthesia are necessary to obtain aspirates of heart-based masses. Hemangiosarcomas exfoliate poorly and are hemorrhagic with low numbers of basophilic, spindle-shaped cells with large pleomorphic nuclei, multiple prominent nucleoli, and other features of malignancy. Erythrophagia may be noted within neoplastic cells and macrophages. Neuroendocrine tumors, including chemodectomas and aortic body tumors, contain aggregates of pale blue cytoplasm with indistinct cell borders that are associated with round “naked” nuclei (Figure 85-3). Minimal characteristics of malignancy are seen with large heart-based masses because these tumors tend to be benign.

Figure 85-2 Adenocarcinoma, lung. Epithelial cells arranged in an acinar structure are pictured. Note the marked anisokaryosis and prominent nucleoli. (Wright-Giemsa stain, ×250.)

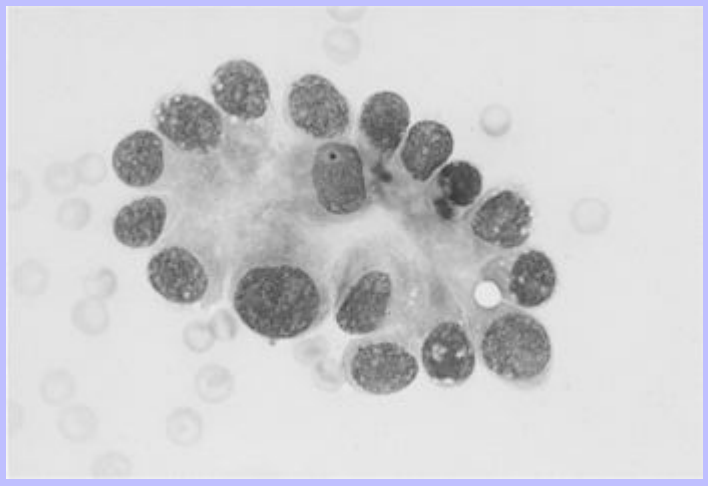
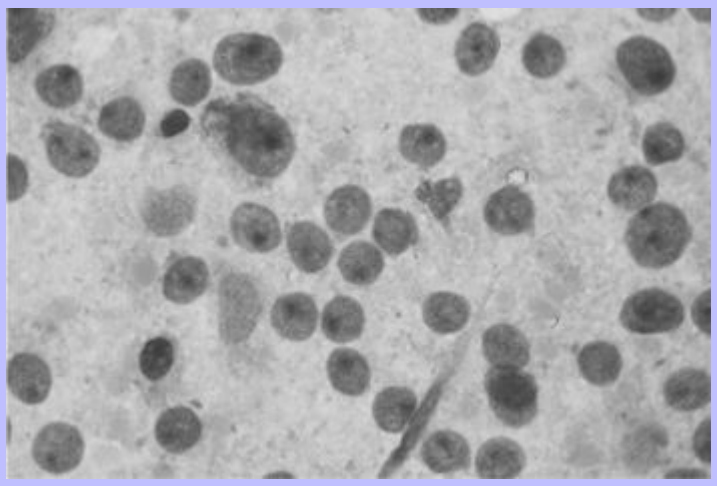


Figure 85-3 Heart-based neuroendocrine tumor. Round “naked” nuclei with single prominent nucleoli can be seen. (Wright-Giemsa stain, ×250.)



85.2.3 Thymus

Thymic enlargement can be caused by a thymoma or thymic lymphoma. Thymomas contain large clusters of thymic epithelial cells, large numbers of small lymphocytes, low numbers of intermediate to large lymphocytes, and mast cells (Figure 85-4). Thymic epithelial cells have a moderate amount of blue-grey cytoplasm and single round nuclei. Eosinophilic material may be associated with the cells. Thymic lymphomas have a predominant

population of intermediate or large lymphocytes with scant, deeply basophilic cytoplasm, round to pleomorphic nuclei, and prominent nucleoli.

85.3 ABDOMINAL ORGAN CYTOLOGY

85.3.1 Liver

Normal hepatocytes are large cells that occur in clumps with distinct cytoplasmic borders and abundant, basophilic cytoplasm (Figure 85-5). The nuclei are round and contain a distinctive, large, single nucleolus. 303
Vacuolar degeneration is a common cytologic finding and is classified as either glycogen or lipid accumulation. 304
Glycogen accumulation appears as a diffuse cytoplasmic clearing that is most prominent in the periphery of the cytoplasm (Figure 85-6). Glycogen accumulation is seen in dogs with steroid hepatopathy, nodular hyperplasia, or idiopathic vacuolar degeneration. Hepatocytes with lipid accumulation contain discrete, clear cytoplasmic vacuoles (Figure 85-7). Severe lipid degeneration is almost exclusively seen in cats with hepatic lipidosis syndrome. However, mild to moderate lipid degeneration can be seen as a secondary response to diseases such as diabetes mellitus, pancreatitis, cholangiohepatitis, or hepatic lymphoma. Hepatic cholestasis is characterized by the presence of dark blue bile pigment within the cytoplasm of hepatocytes or in casts between adjacent hepatocytes. This is a common finding in hepatobiliary disorders and precedes the onset of icterus.

Figure 85-4 Thymoma. A cluster of thymic epithelial cells with a moderate amount of cytoplasm and large round nuclei are shown. Several small lymphocytes, low numbers of large lymphocytes, a neutrophil, and a mast cell are also present. (Wright-Giemsa stain, ×250.)

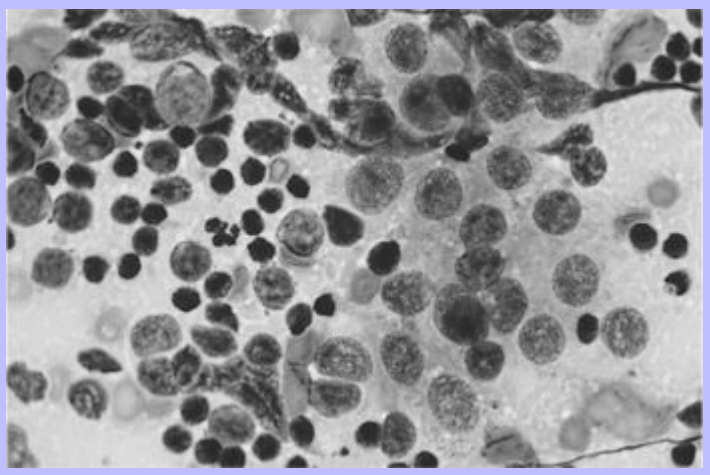
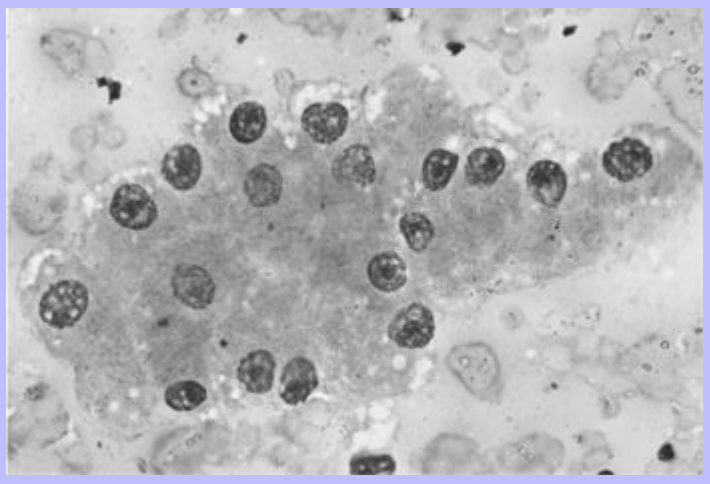


Figure 85-5 Normal liver. Hepatocytes have abundant cytoplasm, round nuclei, and single prominent nucleoli. (Wright-Giemsa stain, ×250.)



Due to the focal nature of many inflammatory lesions, cytologic identification of inflammatory liver disease may be difficult. Tumors commonly found in the liver include hepatocellular carcinoma (HCC), bile duct carcinoma, lymphoma, and hemangiosarcoma. The diagnosis of HCC is made when anaplastic cells with differentiation toward mature hepatocytes are aspirated from a hepatic mass. These cells have a cytoplasm similar to that of hepatocytes with nuclear features of malignancy, particularly a high N:C, anisokaryosis, and extremely prominent nucleoli. Bile duct carcinomas contain dense clusters of epithelial cells that are smaller than hepatocytes and have a very high N:C and scant, basophilic cytoplasm. Nuclear features of malignancy are usually present with the exception of nucleoli.

Figure 85-6 Steroid hepatopathy. Indistinct cytoplasmic vacuoles concentrated at the borders of hepatocytes indicate excess glycogen storage in the liver. (Wright-Giemsa stain, ×250.)

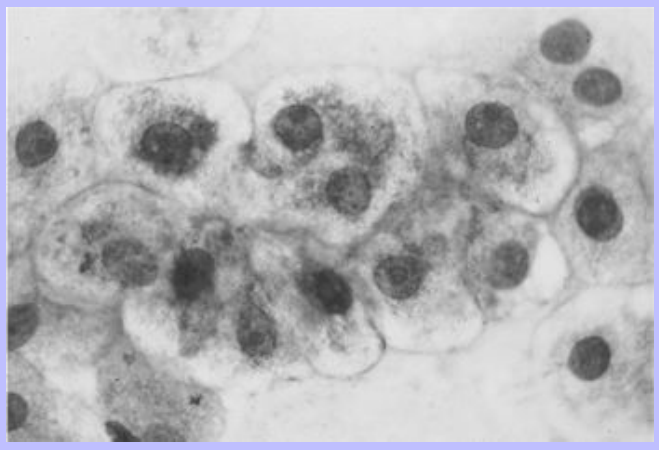
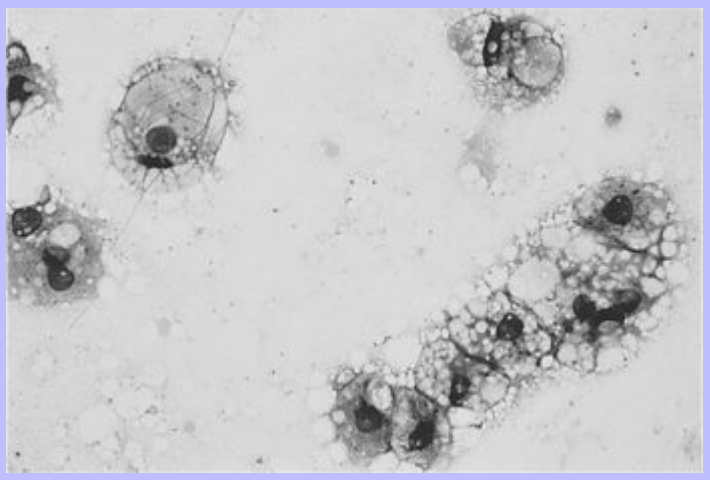


Figure 85-7 Hepatic lipidosis. The cytoplasmic vacuoles observed with lipid accumulation in the liver are large and distinct. (Wright-Giemsa stain, ×125.)



85.3.2 Spleen

Aspirates from normal spleen are hemodilute with clusters of splenic reticular elements, large numbers of small lymphocytes, moderate numbers of intermediate to large lymphocytes, and low numbers of plasma cells and mast cells. Common cytologic diagnoses associated with generalized splenomegaly are extramedullary hematopoiesis (EMH) and lymphoma. EMH may be observed when the peripheral demand for erythroid or myeloid cells exceeds production in the bone marrow. All stages of erythroid and myeloid precursors, as well as megakaryocytes, can be present. Splenic lymphoma is difficult to diagnose due to the mixed population of lymphocytes in a normal spleen. If a monomorphic population of either intermediate or large lymphocytes makes up greater than 70% of the cells, splenic lymphoma can be suspected. The most common cause of splenic nodules is nodular hyperplasia, which is indistinguishable from normal spleen when aspirated. Hemangiosarcomas, hemangiomas, or hematomas cause large hemorrhagic splenic nodules that can be difficult to differentiate cytologically.

85.3.3 Intestinal Tract

Intestinal aspirates tend to be poorly cellular with low numbers of epithelial cells. Lymphocytes may be seen due to lymphoid tissue associated with the intestine. Inflammatory bowel disease and lymphoma also have lymphocytes. In all of these cases, small lymphocytes can predominate, which prevents a definitive cytologic diagnosis. However, large granular lymphoma is easily diagnosed cytologically. Infectious diseases may also be observed. Figure 85-8 is an example of intestinal pythiosis. Intestinal carcinomas contain dense clusters of epithelial cells with deeply basophilic cytoplasm, round to pleomorphic nuclei, prominent nucleoli, an increased N:C, and other features of malignancy. Acinar formation is observed with adenocarcinomas (Figure 85-9).

85.3.4 Kidney

Aspirates of enlarged kidneys require anesthesia and ultrasonography. Renal aspirates are hemodilute with rare clusters of renal tubular epithelial cells that have abundant blue cytoplasm, distinct cell borders, and round nuclei. Clear cytoplasmic vacuoles may be seen. A diagnosis of lymphoma is made if increased numbers of lymphocytes are observed. Inflammatory lesions may be purulent or pyogranulomatous and should be cultured. Renal carcinomas are rare.

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Figure 85-8 Pythiosis, intestine. *Pythium* organisms cause severe pyogranulomatous inflammation with increased numbers of eosinophils. Septate branching hyphal structures stain black with silver stain. (Grocott's methenamine silver [GMS] stain, ×250.)

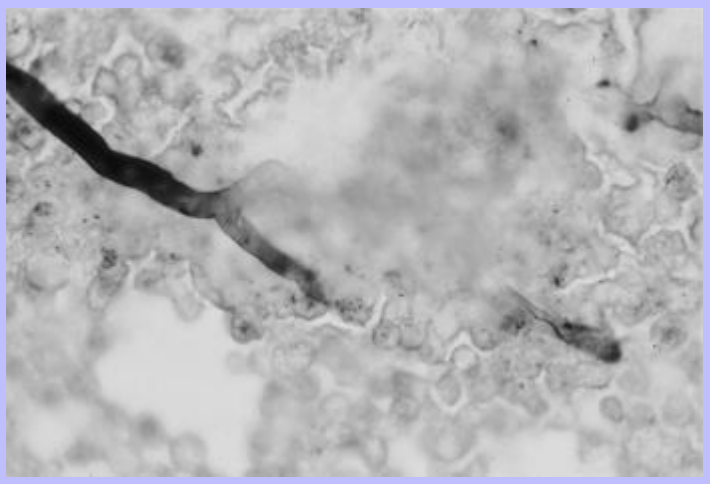
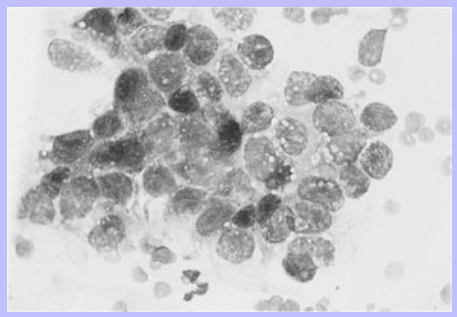


Figure 85-9 Adenocarcinoma, intestine. A cluster of intestinal epithelial cells with distinct cell borders, variably sized nuclei, an increased N:C, and multiple nucleoli are shown. Acinar formation is observed. (Wright-Giemsa stain, ×250.)



86 CHAPTER • 86 Cytology of the Skin and Subcutaneous Tissues

Deborah C. Bernreuter

Cytology should be regarded as a *rapid screening test* to determine if a biopsy, culture, or surgical excision is necessary. Quite often cytologic examination is the only test needed to arrive at a diagnosis, prognosis, and treatment plan. A representative cytologic sample at least can yield a short list of possible diagnoses. If the cytologic evaluation is not completely diagnostic, a biopsy is required to rule out or to confirm various differential diagnoses. When the cytologic results are considered in conjunction with the patient's history; the location, description, and duration of the lesion; the physical examination results; diagnostic imaging findings; and other laboratory determinations, the list of differential diagnoses becomes quite short.

86.1 REQUIRED EQUIPMENT

The following equipment is required for obtaining an adequate representative sample for cytologic evaluation:

- 22-gauge needle (21-to 23-gauge needles also can be used)
- 12-cc syringe
- Unused glass slides, preferably with frosted ends for ease of labeling
- Lavender-top tube (for fluid)
- Sterile swab (for fistulous tracts and mucous membranes) and saline
- Paper towel (for impression smears)

If the cytologic evaluation is to be done in-hospital, a good quality, well-maintained binocular microscope, a “quick” type of Romanowsky stain, and distilled water are also required.

86.2 PROCEDURE FOR SAMPLE COLLECTION

86.2.1 Samples from Solid Masses or Fluid-Filled Lesions

For solid masses and fluid-filled lesions, a 22-gauge needle on a 12-cc syringe is usually used to collect and transfer cells or fluid (or both) to several glass slides. Sedation or anesthesia can be used if required to reduce risk and unnecessary pain. Local anesthesia is not used on superficial lesions, because the pain associated with aspiration of a sample is no greater than the pain felt during injection of the local anesthesia. Skin preparation is the same as that required for a venipuncture or an injection. If the lesion will also be sampled for micro-biologic culture, surgical preparation should be done on the collection site.

Before the sample is collected, four glass slides should be made ready to receive it. This minimizes clotting of the sample in the needle, which can occur while slides are located to receive the sample. It is not necessary to submit more than four smears; even a single smear can be adequate if it is representative.

The needle is attached to the syringe while the plunger is depressed. One hand is used to grasp the lesion firmly to stabilize it, and the other hand is used to insert the tip of the needle deep into the mass. Inserting the needle

deeply into the mass yields a larger sample than inserting the needle only superficially. When the tip of the needle is in a representative location, the plunger of the syringe is pulled back as far as possible and *held* for a few seconds. *The plunger is never pumped!* The pumping action that is useful in the collection of bone marrow samples is harmful for cells in all other anatomic sites. It causes excessive tissue damage, and encourages bleeding and clotting (release of tissue thromboplastin). The direction of the needle within the mass should be changed only when the needle has been almost completely withdrawn so as to avoid excessive tissue destruction and subsequent lysis of cells, which would occur with an attempt to change the direction of the needle while it is still embedded in the mass. Aspiration can be done in two or three different orientations in the mass to collect the most representative sample. The hub of the needle where it is attached to the syringe must be watched; *blood must not be allowed to flow into the syringe*. Blood dilutes a previously representative sample and causes clotting. If blood appears while the plunger is withdrawn, the plunger (and thus the vacuum pressure) is released immediately. A needleful of cells is sufficient to make a dozen smears if necessary.

Only after the vacuum in the syringe has been released is the needle removed, first from the lesion and then from the syringe. A small amount of air is then drawn into the syringe, the needle is reattached, and the plunger is rapidly advanced *while the needle's tip is close to a glass slide* (i.e., not from a great height). In this way, the sample is expelled onto the slide intended, and it does not inadvertently shed a few cells onto the adjacent slide. On several occasions this author has identified misdiagnoses made because a few tumor cells or organisms were inadvertently sprayed onto adjacent slides, which, because they grossly appeared to be unused slides, were then used to prepare smears from a different patient. When slides are prepared to receive cytology samples, they should not be placed close to each other, to avoid overspray.

86.2.2 Liquid Samples

If the sample is liquid, only one drop of sample should be placed on each slide so that when the sample is smeared *rapidly* to make a feathered edge (and thus a monolayer of cells), *the entire smear will be one half to three fourths the length of the slide*. If too large a drop is accidentally expelled onto a slide, the excess is immediately reaspirated into the syringe. It is helpful if an assistant who can make a feathered edge is available to smear out the drop of sample as soon as one is placed on a slide, while additional drops are being placed on additional slides. If the sample consists of a large amount of fluid, a couple of feathered edge smears are made, and the remaining fluid is expelled into a lavender-top tube. *Watery fluid* is smeared correctly by raising the angle between the sample slide and the spreader slide to 50 to 60 degrees and smearing very quickly. *Thick fluid* is smeared to a monolayer by lowering the angle to 25 to 30 degrees and smearing slightly more slowly. Normal blood is smeared with a 45-degree angle. Any remaining fluid should be expelled into a lavender-top tube and mixed well to avoid clotting so that accurate cell counts can be attained and smears of concentrated cells can be prepared. The ethylenediamine tetra-acetic acid (EDTA) in the lavender-top tube is the preservative of choice for accurate cell morphology. Heparin can distort cells. Both the fresh smears and the fluid are submitted to the laboratory. At the laboratory, some of the fluid can be placed in a cytocentrifuge for production of concentrated smears. Cytocentrifuges concentrate the cells directly onto a small area of a glass slide, which is especially useful with fluids of low cellularity. In addition, some of the fluid can be centrifuged and a drop of sediment (or buffy coat smear, if the sample is very hemorrhagic) can be prepared, stained, and examined.

86.2.3 Semisolid Samples

If the sample is semisolid, another slide should be placed flat on top of the sample and the two slides should be gently pulled apart to make monolayers on both slides. With either the direct smear or the “pull” technique, *all smears should be thin enough to air dry within 1 minute*. The smears should be double-checked to ensure that they are completely dry before they are encased in a slide holder for transportation to a laboratory.

An *impression smear* can be useful with a biopsy sample. Before the biopsy sample is placed in formalin, its cut surface can be blotted with a paper towel to remove surface blood and tissue fluid and then touched to a glass slide several times to make an impression smear.

86.2.4 Samples from Mucous Membranes of the Vagina, Conjunctiva, and Mouth and from Fistulous Tracts

For sampling the mucous membranes of the vagina, conjunctiva, or mouth or for sampling fistulous tracts, a sterile swab moistened with saline can be used to swab the lesion. If the lesion is already moist, the saline is not needed. The tissue is swabbed, and the swab then is *rolled* onto a glass slide. *Never rub the swab on the slide;* it causes disruption of the cells.

86.3 COMMON MISTAKES TO AVOID IN COLLECTION AND PREPARATION OF CYTOLOGY/FLUID SAMPLES

The following common mistakes should be avoided in sample collection and preparation:

1. *Pumping the syringe plunger during collection*. This causes tissue destruction and lysis of cells and also increases the risk of clotting due to release of tissue thromboplastin.

2. *Using a syringe with a capacity of less than 10 cc*. If the syringe is too small, the vacuum pressure it creates is too weak, and the sample is often too small for adequate evaluation.

3. *Placing too large a sample on one slide*. If the drop of sample is too large, the consequences are (1) the largest cells are pushed off the end of the smear, resulting in a nonrepresentative sample; (2) a monolayer is not formed, and the smear will be too thick for evaluation; and (3) thick smears dry slowly, causing cell lysis and distortion.

4. *Failing to smear out the sample*. A drop of sample left in one place on the slide dries slowly, causing lysis, and forms a thick jumble of cells, which cannot be evaluated. If two cells are on top of each other, neither can be evaluated. If excessive cell fragility is present (as in some lymphomas and other tumors), the cells might not be able to survive smearing, and a biopsy would be necessary for evaluation.

5. *Refrigerating the smears*. When smears are placed in slide holders and then refrigerated, the ambient humidity from the room air in the holder condenses, causing droplets of water to fall onto the smears. Water is hypotonic and causes cell lysis; only a homogeneous, proteinaceous background is observed on cytology.

6. *Placing the slides in the slide holder before they are completely dry*. Slow drying causes lysis of cells. If cells are lysed and then placed near an ice pack while liquid, the cells crystallize into shapes of long spears, preventing evaluation.

7. *Submitting samples for cytology or fluid analysis without including the signalment, patient history, and other physical findings, as well as the anatomic location, a description, and the duration of the lesion.* Without these other parameters, only a description, not an interpretation, is possible.

8. *Submitting fluid without EDTA*. Fluid is always submitted for analysis in an EDTA tube, and a fresh smear is submitted as well for accurate cell counts (without clots).

86.4 DETERMINING THE CHOICE OF CYTOLOGY OR BIOPSY

The choice of cytology or biopsy depends on the type and location of the lesion. For discrete masses in the intradermal and subcutaneous tissues, a fine needle aspiration biopsy is often diagnostic. It is useful for identifying the mass as a site of inflammation, a cyst, or a solid tumor. In addition, if the lesion is a site of inflammation, the etiology (e.g., bacteria, fungal elements, yeast, parasites, or keratin debris from a ruptured epithelial cyst) can often be observed. Bacteria can be identified as cocci, rod shaped, spirochetes, possible anaerobes, mycobacteria, or a mixed population, which can be helpful in choosing an appropriate class of antibiotic while awaiting results of a culture and sensitivity test. If Gram stain is also available, additional samples can be used to determine Gram positivity or negativity. If the lesion is a solid tissue tumor, an experienced cytologist can further classify it as epithelial or mesenchymal in origin and list any criteria of malignancy observed. If it is a round cell tumor, cytology is often sufficient for diagnosis.

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If the lesions are vesicular, however, such as pemphigus lesions, cytology is not useful. Instead, an intact vesicle (or at least the edge of a vesicle if none is intact) is gently excised, and the tissue is placed in formalin for biopsy. For other superficial lesions (e.g., ulcers) that are not associated with a mass, a biopsy of the edge of the lesion is usually more helpful than cytology. If a dermal mass has an ulcerated surface, impression smears of the lesion will contain only the secondary inflammatory cells and organisms; they will not be representative of the primary lesion underneath. For this reason, an aspirate of the deeper layers of the mass would probably be more representative.

87 CHAPTER • 87 Ear Flushing

Kinga Gortel

Most cases of acute otitis externa in cats and dogs can be managed by treatment with topical medications and ear cleaning administered by owners. There are, however, many instances in which in-clinic ear flushing is essential for the successful resolution of otitis. The most common indication for ear flushing is failure of owner-administered therapy to clear an infection within a reasonable period (2 to 4 weeks). Ears containing exudate that cannot be removed by simple cleaning respond poorly to topical medications, which are unable to reach the target tissue and pathogens. Another common indication is the presence of purulent exudate associated with Gram-negative bacteria, such as *Pseudomonas*. Ear flushing is also recommended when there is a suspicion of otitis media, a foreign body, or otic neoplasia.

Ear flushing allows evaluation of the ear canal and tympanic membrane, and myringotomy if necessary. It permits cleaning of the tympanic bulla and its sampling for culture and cytology. It also facilitates removal of foreign bodies and visualization and sampling of masses.

Complications from ear flushing are infrequent in dogs but more common, although usually transient, in cats. These include vestibular symptoms, deafness, Horner's syndrome, and facial nerve paralysis. The possible need for myringotomy to fully evaluate and treat a diseased ear should be explained to the owner. Owners are often unaware that the tympanic membrane usually heals after myringotomy. Ear flushing, however gentle, during another anesthetic procedure should be avoided unless the owner has been forewarned of possible side effects. It is important to understand the anatomy of the external and middle ear, because it may be severely altered by chronic inflammation.

If ear canal stenosis, glandular hyperplasia, or edema prevent passage of an otoscope tip, ear flushing should be postponed until the canal can be rendered more accessible by a 1-to 2-week course of topical and systemic corticosteroids (e.g., prednisone, 1 mg/kg given orally daily for dogs). If severe stenosis persists, surgical intervention is more likely to result in a favorable outcome than ear flushing and medical therapy.

Sedation suffices for ear cleaning only when minimal exudate is present; general anesthesia is required for full cleaning or myringotomy. An endotracheal tube with an inflated cuff is used to prevent lower respiratory tract contamination via the auditory tubes.

Bulla radiographs or computed tomography is recommended prior to the ear flush when otitis media is suspected. These procedures allow evaluation of otic structures, including the bulla.

Various ear flushing techniques utilizing hand-held and video-otoscopes have been described. The procedure should allow removal and sampling of exudate in the outer ear canal, a myringotomy if needed, and sampling and cleaning of the bulla.

Ear flushing in dogs utilizing a hand-held otoscope may be performed as follows. While the patient is prepared for anesthesia, swabs for culture and cytology are collected from each ear. The ear canals are then filled with a mild ceruminolytic ear cleaner. Once the dog has been anesthetized and intubated, an ear bulb syringe and warmed irrigation saline solution are used to gently remove the exudate and ear cleaner. All the ceruminolytic agent must be removed from the ear canal to prevent irritation. The ear canal must not form a tight seal with the bulb syringe in order to avoid tympanic rupture. A new bulb syringe should be used for each patient. Once the flushing yields clear fluid, the canal can be suctioned with an 8 French polypropylene catheter (cut to the desired length) on a 12-cc

syringe introduced through the otoscope. The tip of the catheter may be heated over a flame to smooth sharp edges. The ear should then be examined, and flushing should continue via the catheter until the canal appears clean. Repeated flushing, suctioning, and re-evaluation may be needed. An ear curette can be used to remove tenacious exudate, and grasping tools, such as alligator forceps, can be used to remove hair, wax balls, or foreign bodies. Finally, the ear canal should be thoroughly suctioned.

Ear flushing in cats is performed similarly. Pretreatment with a ceruminolytic agent is not recommended due to the higher incidence of complications from ear flushing in this species.

Video-otoscopy facilitates ear flushing procedures and permits documentation. Video-otoscopes provide greater magnification and resolution than hand-held units. Working channels allow simultaneous flushing and visualization. In contrast, when a hand-held otoscope is used, the visual field may be obscured by instruments and fluids.

Also, the stream of saline from the flushing catheter can be directed more effectively at adherent material using a video otoscope. A relatively simple technique uses a 5 French polypropylene catheter attached to a 20-cc syringe. An assistant flushes warmed saline solution in pulses while the tip of the catheter is moved within the ear canal by the operator. Pretreatment with a ceruminolytic agent and cleansing with an ear bulb syringe are still helpful but less necessary. Alternatively, a three-way stopcock may be attached by intravenous tubing to a 1 L bag of saline solution for flushing and to a syringe or suction apparatus for removing saline from the ear. A dual-port attachment may also be used for simultaneous infusion and suction.

After thorough cleaning, the area of the tympanic membrane can be evaluated. Obliteration of the tympanum in cases of chronic otitis is common but may be confusing unless one has extensive experience in observing the normal location of this structure. If the otoscope tip has been advanced as far as possible and the tympanum is not seen, it is likely absent. The intense light source in video-otoscopy may make the lining of the tympanic cavity appear reflective and white, confusing the operator by its similarity to the tympanum. If the tympanum is absent or partially ruptured, material from the middle ear is obtained by passing two sterile swabs into this area, preferably through a sterile otoscope cone. The first swab is cultured, and the second is used for cytologic evaluation. The middle ear cavity should be gently flushed to remove exudate or ceruminolytic agent.

Diagnostic and therapeutic myringotomy should be performed if otitis media is suspected, because the tympanum is frequently intact despite a middle ear infection. Otitis media should be suspected in cases of chronic, relapsing, or unremitting otitis, when the tympanum appears abnormal, when neurologic signs are present, or when radiographic evidence is present. Myringotomy allows collection of samples from, and thorough flushing of, the middle ear. After the ear canal has been cleansed and dried, the myringotomy incision may be made using a 5 French polypropylene catheter, an open-ended tomcat catheter, or a calcium alginate swab or with a short CO_2 laser pulse. The incision should be made in the caudoventral quadrant of the tympanic membrane to minimize the damage to the tympanic germinal epithelium and middle ear structures. The middle ear should be sampled and flushed as described above, using a catheter passed through the myringotomy incision.

Essential to the successful outcome of the ear flush is the ability to keep the ear clean, therefore topical and oral antimicrobial agents should immediately be initiated based on cytology. Once or twice daily ear cleaning by owners is prescribed, and a 1 week follow-up is scheduled. Saline solution may be used in an ulcerated ear or immediately after myringotomy. Oral corticosteroids are recommended to facilitate at-home treatment and to reduce the production of inflammatory exudate in painful or ulcerated ears. At the 1 week follow-up, topical and oral antimicrobial agents may be changed, based on the culture results, and a more effective ear cleaner prescribed.

88 CHAPTER • 88 Ear Vein Blood Glucose Monitoring

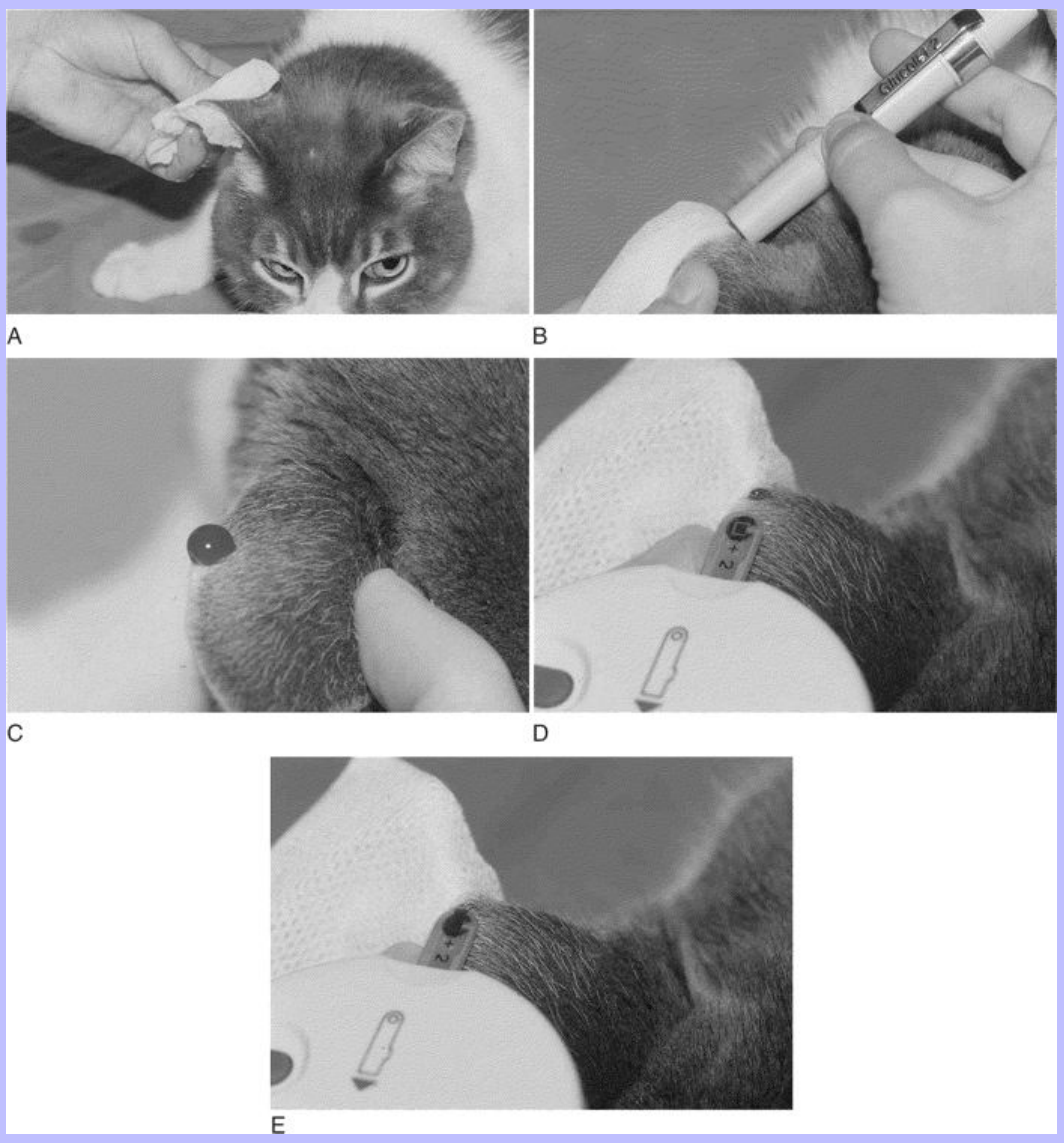
Melanie D. Thompson

In dog and cats with diabetes mellitus, owner observation of clinical signs and in-hospital evaluation of serial blood glucose curves are common methods both of assessing glycemic control and of determining the dosage and type of insulin to be used and the frequency of administration. For these blood glucose curves, affected dogs and cats are typically hospitalized and blood samples are collected at 1-or 2-hour intervals by means of direct venipuncture of a peripheral vein. Hospitalization, restraint for blood sample collection, and venipuncture have all been associated with stress hyperglycemia (especially in cats), and some hospitalized pets may not eat. This can complicate interpretation of the resulting blood glucose curve.

Most human diabetics perform self-monitoring of blood glucose concentrations using a portable blood glucose meter (PBGM) and capillary blood, which is collected by pricking a fingertip with a lancet device. Portable blood glucose meters are being used more frequently to generate serial blood glucose curves in diabetic dogs and cats. These meters are inexpensive, require only a single drop of blood for analysis, and provide results rapidly. In addition, the results obtained with these meters have been shown to correlate with those obtained by reference laboratories. When only a small amount of blood is required for analysis, use of an ear vein for blood sampling can minimize patient discomfort, preserve the integrity of peripheral veins, and decrease the need for physical restraint during sample collection. Recent studies have shown that the marginal ear vein nick technique is a reasonable alternative to venous blood collection for serial measurement of blood glucose concentrations. Studies have also shown good correlation between the glucose concentration of capillary and venous blood. Two methods of capillary blood sampling from the ear of dogs and cats are described here. Both methods are fast and easy to perform.

The first technique utilizes conventional lancet devices designed for pricking the fingertips of human beings. A device with a variable needle depth should be chosen. This allows the appropriate depth to be selected in order to provide an adequate amount of blood for the test (dogs usually require greater depth compared to cats). Although any portion of the inner pinna can be sampled, the marginal ear vein (MEV) usually results in the best sample. First the MEV is identified, then a warm, damp gauze sponge (or warm washcloth) is applied to it to increase perfusion as needed (Figure 88-1, *A*). A thin film of Vaseline can be placed over the sampling site in longhaired pets to allow the drop of blood to form without dissipating into the fur. The automatic lancing device should then be placed over the vein (Figure 88-1, *B*); the ejected needle will nick the ear, causing a drop of blood to form (Figure 88-1, *C*). The person performing the test should place a folded gauze sponge between the ear and the individual's finger to avoid an inadvertent nick. The PBGM with the test strip already inserted is then applied to the drop of blood to measure the blood glucose concentration (Figure 88-1, *D* and *E*).

Figure 88-1 **A,** A warm, damp gauze sponge is applied to the ear vein to increase perfusion. **B,** The automatic lancing device is placed over the ear vein. Note that the gauze is folded so that the individual performing the test does not inadvertently get nicked. **C,** After the ejected needle nicks the ear, a drop of blood will form. **D,** The PBGM with the test strip already inserted is applied to the drop of blood. **E,** The drop of blood is aspirated by capillary action into the reaction chamber after contact with the test strip.



The second technique utilizes a vacuum lancing device, the Microlet Vaculance (Bayer Diagnostics, Tarrytown, New York), to facilitate collection of an adequate drop of blood (Figure 88-2, *A*). The device was designed to allow blood collection from body sites other than the fingertips in human beings. It also has variable needle depth. This technique allows sampling of the inner pinna in dogs and cats. The tip of the ear is held between the thumb and index finger, and the surface of the pinna is held flat by the rest of the fingers (Figure 88-2, *B*). The lancet device then is set on a nonhaired area of the ear. An airtight seal between the device and the ear is obtained by pushing the outer ear against the device with the tip of one finger. The entire edge of the endcap must be in contact with the skin (Figure 88-2, *C*). The site is lanced by pressing the plunger cap down until it comes to a complete stop. While pressure is maintained between the endcap and the skin, the plunger is slowly released. This creates a negative pressure, and the skin slightly bulges up into the endcap. The negative pressure is maintained until there is an adequate drop of blood (Figure 88-2, *D*). When an adequate drop of blood has formed, the plunger is pressed three fourths of the way down to release the vacuum and remove the device. The PBGM with the test strip already inserted is then applied to the drop of blood to measure the blood glucose concentration.

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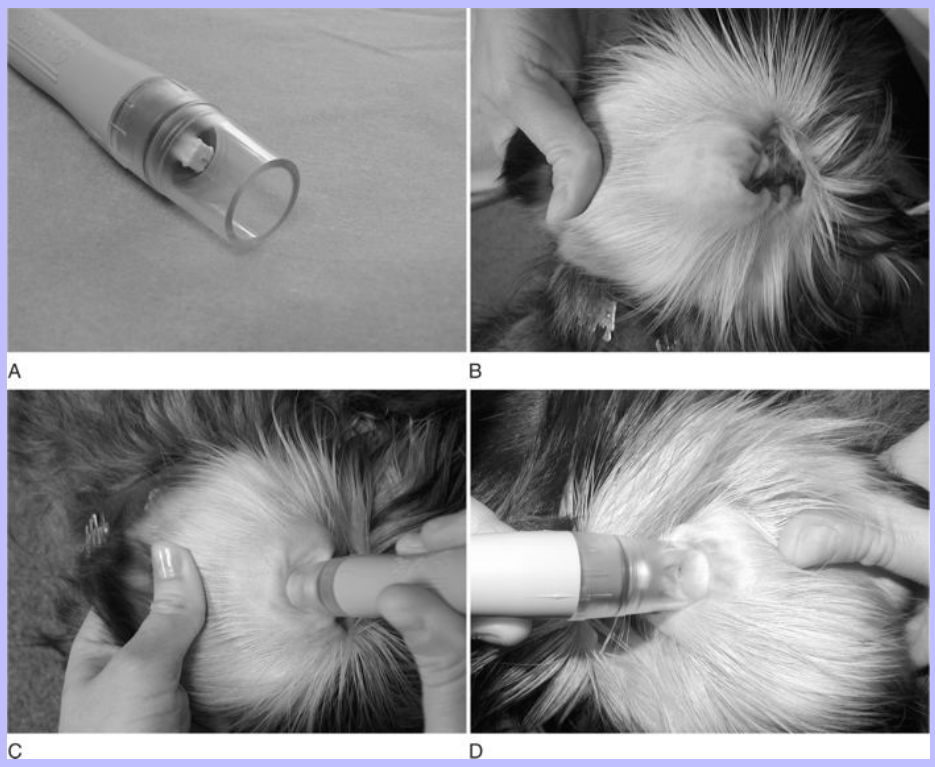
Figure 88-2 **A,** The Microlet vaculance (vacuum lancing device). **B,** The tip of the ear is held between the thumb and index finger. The surface of the pinna is held flat by the rest of the fingers. **C,** The lancet device is set on a nonhaired area of the ear. The outer ear is pushed against the device to form an airtight seal. **D,** After lancing the ear, pressure is maintained and the plunger is slowly released. Negative pressure causes the skin to bulge up into the endcap.



Clinicians should be aware that there are some important limitations to the use of a PBGM. In particular, several factors can affect the accuracy of the blood glucose concentrations obtained with these meters, including the level of training of the user, whether the meter is properly maintained, whether appropriate quality control checks are performed, whether the animal has any concurrent diseases, and the hematocrit of the animal. All PBGMs overestimate the blood glucose concentration of anemic animals. Dehydration results in falsely lower blood glucose concentrations. Other factors may also affect results, such as altitude, environmental temperature and humidity, hypotension, hypoxia, and the triglyceride concentration.

The Bayer Glucometer Elite (Bayer Diagnostics) is one of the easiest PBGMs to operate. It has no buttons to press. The meter automatically turns on when the test strip is inserted and turns off when the test strip is removed. It requires only 2 μL of blood, which is automatically aspirated by capillary action into the reaction chamber after contact with the test strip. The result is displayed in 30 seconds. It is important that the operator make sure the test strip is filled to the mark, because this meter starts the measuring process even if the test strip chamber is only partially filled with blood; this can result in an erroneously low blood glucose value.

A PBGM that is simple to operate should be chosen. Portable blood glucose meters are constantly being improved, and the result is greater precision, faster measurement, decreased blood volume, and decreased operator dependence. It is important to become familiar with the PBGM and perform routine maintenance. With practice, veterinarians, veterinary technicians, and veterinary students can become proficient in the techniques outlined here, and errors can be minimized. Ear vein sampling can become the routine method of generating serial blood glucose curves in the hospital. These techniques can also be taught to clients for home monitoring of blood glucose concentrations.

Owners also can be directed to web sites dedicated to diabetic pets, which contain information on home monitoring of glucose. In the search field, type “home monitoring of diabetic pets.”

89 CHAPTER • 89 Echocardiography

Marie-Claude Bélanger

Cardiac ultrasonography has become a powerful diagnostic tool in the noninvasive evaluation of the size, structure, function, and blood flow dynamics of the canine and feline heart. This chapter is designed to guide the practitioner through veterinary transthoracic echocardiography.

89.1 BASICS OF CARDIAC ULTRASONOGRAPHY

Propagation of sound waves is favored by fluids and soft tissue and inhibited by bone, metal, and air. The operator must therefore obtain a suitable air-free window between the ribs of the animal and ventral to the lungs. A *window* is described as a transducer location or region where the heart contacts the intercostal muscles, allowing adequate imaging of cardiac structures.

The basic idea of any ultrasound technique is that the probe emits a pulse of sound that penetrates the target tissue. A portion of that emitted ultrasound goes through the organ and is lost; another portion is reflected back to the probe. If considerable sound is reflected back (as occurs with the myocardium, for example), the structure is said to be *hyperechoic;* a hyperechoic structure appears on the screen as a whiter image. When very little of the sound is reflected back (as with blood or blood vessels), the structure is *hypoechoic* and appears dark on the screen.

Echocardiographic transducers are made of piezoelectric crystals that generate sound waves, which travel in cycles. The frequency of a probe is determined by the number of cycles sent out per minute. High-frequency transducers emit more cycles per time unit and thus have shorter wavelengths. These transducers reflect sound from smaller structures and therefore produce better image definition and resolution, but less tissue penetration, than low-frequency transducers.

Figure 89-1 **A,** Typical examination setting for echocardiographic studies in veterinary medicine. Rectangular or circular cutouts allow the transducer to be introduced from the bottom of the scanning table. **B,** The animal is held in lateral recumbency with the shaved thoracic window over the hole. The examiner is scanning from the right parasternal location.

89.1.1 Equipment

The quality of images obtained from echocardiographic studies depends on the sophistication and technology of the ultrasound machine, the skill and experience of the operator, and the individual patient's characteristics. Echocardiograms can be obtained from an upright position, but lateral recumbency on a table with an opening that allows examination from beneath the animal is optimal, because this arrangement creates a larger echo window. Sector scanning transducers are recommended for cardiac studies in veterinary medicine, because the small intercostal space of our patients limits the size of the available acoustic windows. The choice of transducer is directed by the size of the patient, because tissue penetration is inversely proportional to the frequency of the probe. In other words, the higher the frequency of the probe, the less the tissue penetration. Cats and small dogs usually require a 7.0 MHz transducer. A 5.0 MHz probe is appropriate for most dogs. For very large dogs, a 3.5 MHz transducer may be required to obtain optimal tissue penetration.

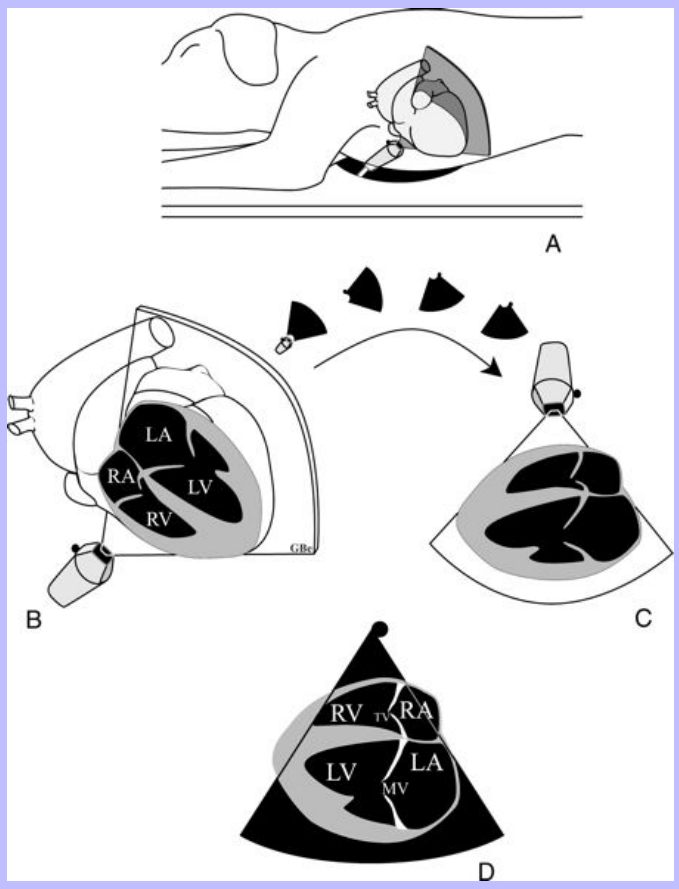
89.1.2 Technique

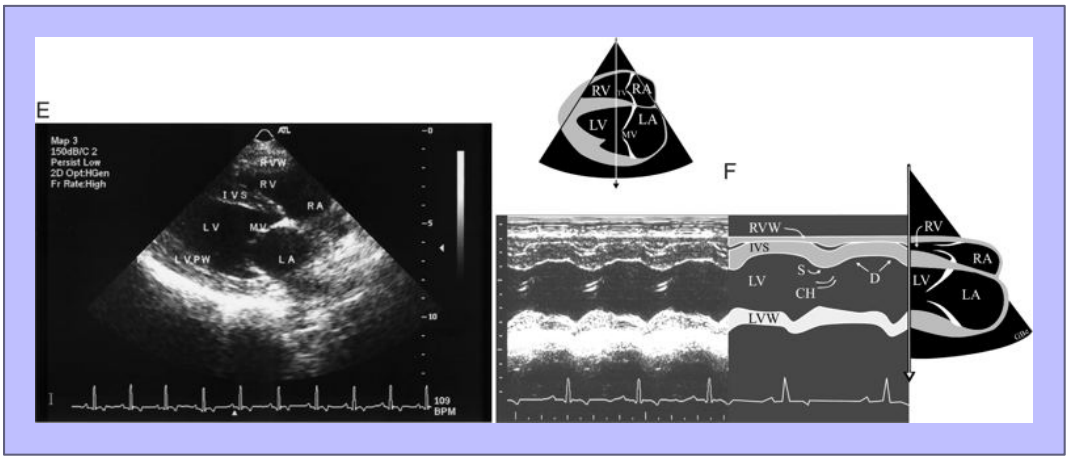
In animals, the hair is usually clipped to improve skin contact and image quality, and coupling gel is applied over the right or left precordial impulses. However, shaving may not be required for dogs with very short hair. Also, one should always warn breeders before shaving a show dog! Application of alcohol or water can sometimes replace the coupling gel; either of these provides good but briefer contact. The animal is restrained in lateral recumbency on a special table with an imaging opening (Figure 89-1). The patient's forelimbs should be gently pulled cranially by a technician to keep the elbows out of the acoustic window. The probe is placed 311
on the prepared area and twisted, tilted, or slid as needed to find a good window for optimizing the quality of 312
images from the cardiac structures. A complete echocardiographic study includes two-dimensional (2-D), M-mode, and Doppler examinations.

An echocardiogram can usually be performed in animals with minimal or no chemical restraint. On the other hand, sedation has the advantage of minimizing stress and poor image quality in squirmy patients. Low doses of ketamine hydrochloride (2 to 5 mg/kg given intravenously [IV] or intramuscularly [IM]), alone or with midazolam (0.1 to 0.2 mg/kg given IV or IM), can be used on asymptomatic fractious cats. A combination of butorphanol (0.2 mg/kg IM) and midazolam (0.1 to 0.2 mg/kg IM) is a good alternative when one wishes to avoid the positive chronotropic effect of ketamine or when sedation is necessary in a cat with congestive heart failure. An opiate (buprenorphine, 0.0075 to 0.01 mg/kg IV) with acepromazine (0.03 mg/kg IV) can be helpful in uncooperative dogs. Oxymorphone (0.05 mg/kg IM) with midazolam (0.2 mg/kg IM) is the protocol used by the author when sedation is needed in a cardiac dog, although other options are also utilized.

The potential influence of the sedation used must be considered in the interpretation of echocardiograms. For example, an increased heart rate, a decreased left ventricular (LV) internal diameter in diastole, an increased septal and left ventricular wall thickness, and a decreased fractional shortening are observed in most cats sedated with ketamine. Also, the potentially hazardous side effects of some sedatives must be considered in the decision on whether to chemically restrain a compromised cardiac patient.

Figure 89-2 **A,** Typical positioning of the animal for visualization of the right parasternal long axis view. In the dog, the long axis of the heart is parallel to an imaginary line connecting the shoulder to the xiphoid. **B,** Spatial orientation of the right parasternal location, long axis four-chamber view. **C,** Spatial orientation of the right parasternal location, long axis four-chamber view as observed on the ultrasound monitor. **D,** Illustration of the different cardiac structures observed with this window. **E,** Real-time 2-D image of the right parasternal location, long axis four-chamber view. **F,** Corresponding M-mode image obtained from this window. The heart is seen as it fills and empties (diastole and systole). *CH,* Chorda tendineae; *D*, diastole; *IVS,* interventricular septum; *LA,* left atrium; *LV,* left ventricle; *LVPW,* left ventricular posterior wall; *MV,* mitral valve; *RA,* right atrium; *RV,* right ventricle; *RVW,* right ventricular wall; *S*, systole; *TV*, tricuspid valve.





89.2 NORMAL CARDIAC ULTRASONOGRAPHIC EXAMINATION

89.2.1 2-D Echocardiography

Two-dimensional echocardiography is used to evaluate the cardiac structural changes resulting from congenital defects or cardiac diseases. It produces a real-time anatomic evaluation of the heart throughout the cardiac cycle. A complete 2-D study involves imaging of all valves and great vessels, as well as the relative size and wall thickness, of the cardiac chambers.

89.2.1.1 Common 2-D Echocardiographic Positions

The animal is first imaged from its right side. The transducer is placed on the right side of the chest wall just dorsal to the sternum at the fourth or fifth intercostal space. This typical position is called the right parasternal location. The views routinely performed from the right parasternal location are the long axis four-chamber view, the long axis left ventricular outflow view, and the different short axis views described in Figures 89-2 and 89-3. Conventionally, echocardiographic views are named from the positioning of the transducer and the structures that are examined (e.g., right parasternal long axis view). The right and left parasternal positions are used most often, but a multitude of planes can be obtained to better visualize a distinct part of the heart. The subcostal or subxiphoid position is an example of another window used to specifically evaluate the left ventricular outflow tract (LVOT) in the dog. The long axis view is obtained by an imaging plane that transects the heart parallel to its long axis from apex to base; a perpendicular imaging plane is performed to obtain the short axis view (see Figures 89-2 to 89-4). Technically, this means that the short axis views can be obtained from the long axis views by a 90-degree rotation of the probe.

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The second half of the echocardiographic study consists of the left-sided views. As opposed to the right parasternal location, there are two acoustic windows on the left side. The left cranial parasternal views are obtained at the level of the fourth intercostal space, and the left caudal (apical) parasternal views are best visualized from the fifth to sixth intercostal spaces (see Figure 89-4). Table 89-1 presents useful tips for optimizing the imaging of the canine and feline heart in some situations.

Table • 89-1 Tips for Optimizing Small Animal Echocardiography

REQUIREMENT/PROBLEM	OPTIMAL IMAGING
The view required is the right parasternal long axis view.	Make sure the dot on the probe points toward the shoulder of the animal.
The view required is the right parasternal short axis view.	Make sure the dot on the probe points toward the elbow of the animal.
Structures from the right side of the heart are difficult to image.	Image the right side of the heart from the left parasternal location.
A specific cardiac structure is difficult to visualize.	Remember the three ways the probe can be moved: twisting, tilting, and sliding.
The right parasternal location must be used in a brachycephalic breed.	Position the probe closer to the sternum than is done in other breeds.
Optimal image of one extremity of the heart (apex or base) cannot be obtained.	Slide one intercostal space cranially or caudally.
Horizontal lines with a hazy image are observed.	Add coupling gel to improve poor transducer contact.
Resolution of the structures in the lateral field is decreased.	Decrease the overall gain.
Near-field resolution is poor in very small patients.	Change to a higher frequency probe.

89.2.2 M-Mode Echocardiography

The term *M-mode* refers to real-time *motion-mode*. M-mode echocardiography is used to evaluate the phasic motion of the cardiac structures during the cardiac cycle. M-mode echocardiography complements the 2-D echocardiogram, because it has a higher sampling rate, which allows good resolution of rapidly moving structures. It is especially useful for recording subtle changes in wall and valve motion and for performing accurate measurements of chamber diameters and wall thicknesses. The M-mode image is viewed on a video screen, on which the depth of the structures is plotted on the *Y* axis and time is shown on the *X* axis. Only the structures transected by the cursor are seen on the M-mode images. The steerable cursor scrolls across the heart, and the associated changes in thickness or position of the structures are recorded on the screen as the heart fills and contracts (see Figure 89-2, *F*).

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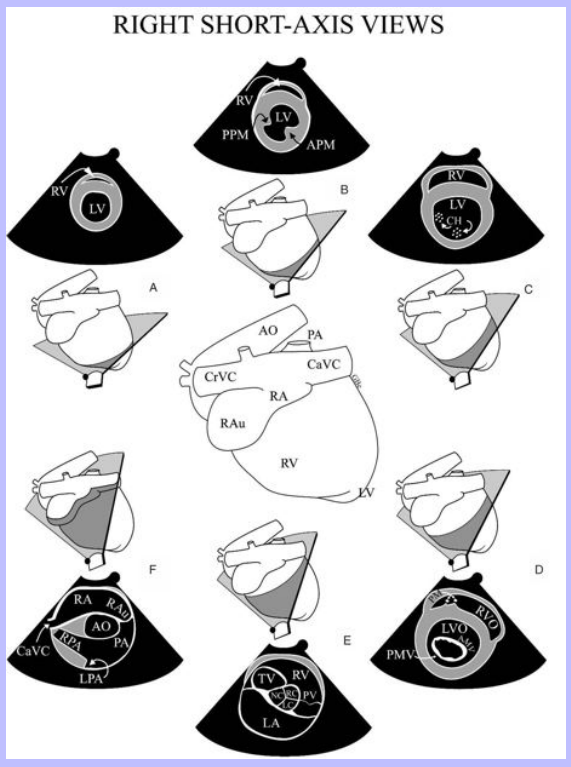
Figure 89-3 Standard 2-D echocardiographic study obtained from the right parasternal transducer location; short axis views are at the level of the apex **(A),** the papillary muscles **(B),** the chordae tendineae **(C),** the mitral valve **(D),** the aorta **(E),** and the pulmonary arteries **(F).** *AMV,* anterior mitral valve cusp; *APM,* anterior papillary muscle; *CaVC,* caudal vena cava; *CH,* chorda tendineae; *CrVC,* cranial vena cava; *LA,* left atrium; *LC*, left coronary aortic cusp; *LPA,* left pulmonary artery; *LV,* left ventricle; *LVO,* left ventricular outflow; *NC,* noncoronary aortic cusp; *PA,* pulmonary artery; *PM*, papillary muscle; *PMV,* posterior mitral valve cusp; *PPM,* posterior papillary muscle; *PV,* pulmonary valve; *RA,* right atrium; *Rau,* right auricle; *RC,* right coronary aortic cusp; *RPA,* right pulmonary artery; *RV,* right ventricle; *RVO,* right ventricular outflow; *TV,* tricuspid valve. (Modified from Thomas WP, Gaber CE, Jacobs GJ: Recommendations for standards in transthoracic two-dimensional echocardiography in the dog and cat, Echocardiography Committee of the Specialty of Cardiology, American College of Veterinary Internal Medicine, *J Vet Intern Med* 7:247–252, 1993.)



In veterinary medicine, M-mode echocardiography is generally performed only from the right parasternal location. The usual M-mode echocardiogram includes an evaluation of the left ventricle (see Figure 89-2, *F*) and of the mitral valve and aortic root (Figure 89-5). As recommended by the American Society of Echocardiography (ASE), end-diastolic measurements are taken at the onset of the QRS complex, and end-systolic measurements are taken at the level of the maximal excursion of the interventricular septum. The *leading edge method* is used; that is, the measurements of each echo line are made beginning at the edge that is closest to the transducer. The sonographer should be aware that a tremendous potential exists for artifactual measurements when the M-mode image is obtained in a suboptimal plane (e.g., tangential slices).

The left ventricular M-mode study provides absolute measurements of the left ventricular walls and chamber during systole and diastole. It can be performed using the right parasternal long axis four-chamber view (see Figure 89-2, *F*) or the right parasternal short axis view at the level of the papillary muscles (see Figure 89-3, *B*). Tables 89-3, 89-4, and 89-5 describe the normal M-mode echocardiographic values used in cats and dogs. These M-mode measurements are also used to evaluate the left ventricular systolic function by calculation of the ejection phase indices (as described later in the chapter under Evaluation of Cardiac Function).

89.3 DOPPLER ECHOCARDIOGRAPHY

Spectral and color flow Doppler imaging techniques are used to evaluate blood flow velocity and direction in the heart and great vessels. The transducer generates ultrasound waves, which are reflected off the red blood cells. The change in frequency between the sound transmitted by the transducer and the sound received by it is called the *Doppler shift* (Δf). Because velocity = frequency × wavelength, the magnitude of the Doppler shift is directly proportional to red blood cell (RBC) velocity:

$$\Delta f = \frac{2f_0 \times V \times \cos\Theta}{C}$$

Where f_0 is the frequency transmitted by the transducer; V is the flow velocity of RBC in meters per second (m/sec); Θ is the intercept angle; and C is the speed of sound in blood (1540 m/sec).

Doppler echocardiography assesses the direction and velocity of blood flow. Blood moving toward the transducer creates a positive frequency shift encoded in red on color Doppler and is displayed above the baseline of spectral Doppler. Blood flow moving away from the transducer is blue and is inversely displayed as a negative flow profile under the baseline (Figure 89-6).

89.3.1 Spectral Doppler

Cardiac spectral Doppler study uses imaging planes that align the sound beam along the blood flow. A marker is represented on the cursor line that corresponds to the sampling volume or *gate* where the flow is interrogated. The parallel beam positioning is in contrast to the M-mode, in which the beam is oriented in a perpendicular manner to visualize the cardiac structures. When Doppler studies are performed, care must be taken to align the Doppler beam with the jet flow (intercept angle <20 degrees) to minimize underestimation of the flow velocity.

Flow signals are displayed with time on the horizontal axis and velocity on the vertical axis. Two types of spectral Doppler are used clinically, *pulsed wave (PW) Doppler* and *continuous wave (CW) Doppler*. An intermediate between PW and CW Doppler, called *high pulse-repetition frequency (HPRF),* is another type of spectral Doppler, one that is used less frequently. Spectral Doppler is helpful in the assessment of pressure

gradients, intracardiac chamber pressure, regurgitant fractions, shunt ratios, valve area, effective orifice area, and cardiac output.

In veterinary medicine, spectral Doppler is often used to calculate *instantaneous pressure gradients* (ΔP) across a stenotic area or regurgitant valve. The maximal pressure gradient is calculated from the maximal flow jet velocity *(v)* using the modified Bernoulli equation:

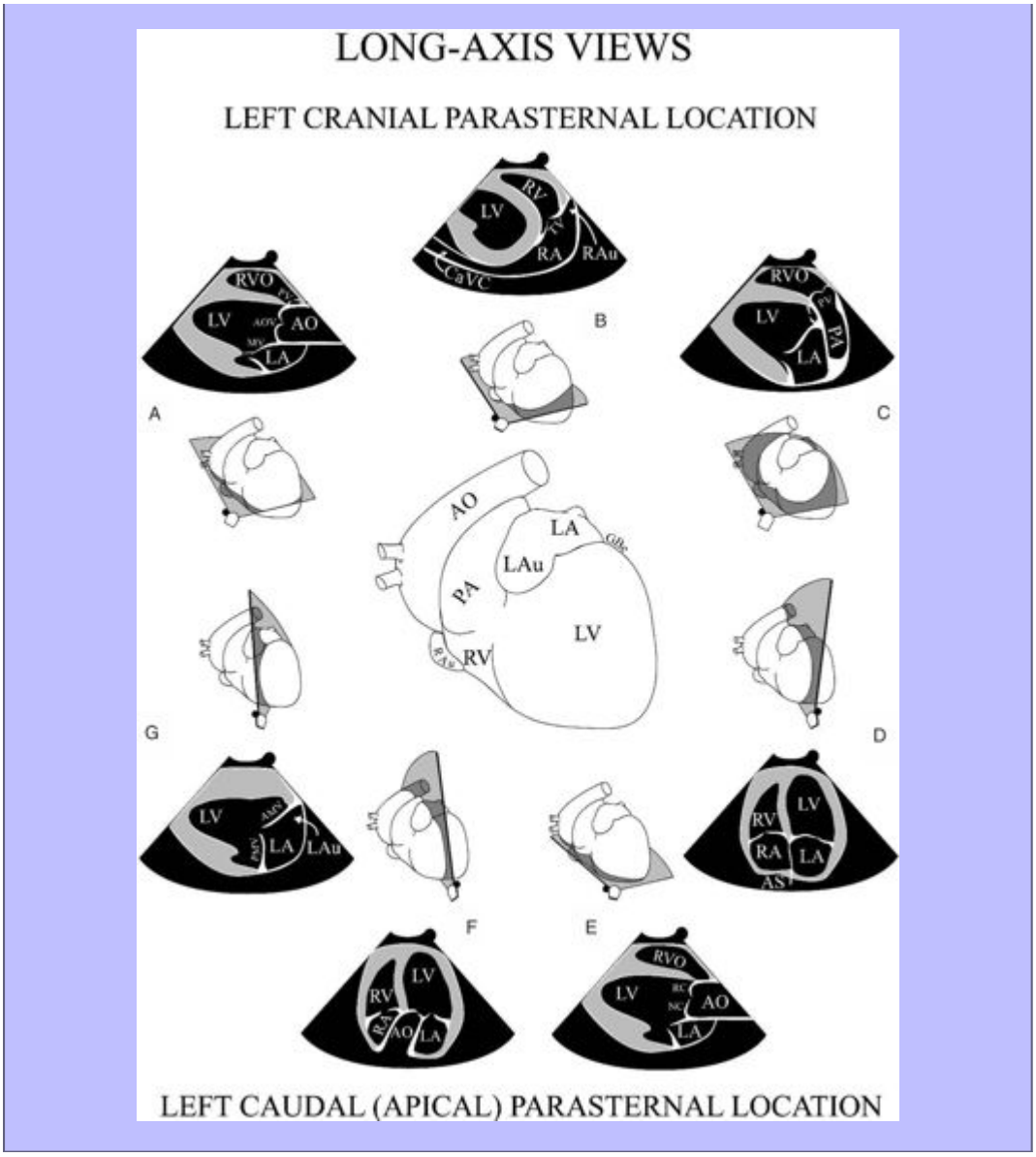
$$(\Delta P) = 4v^2$$

The peak pressure gradient, along with the determination of the effective orifice area and other 2-D and M-mode echocardiographic findings, is used in the clinical assessment of the severity of stenosis.

89.3.2 Pulsed Wave Doppler

PW Doppler uses a single crystal transducer that transmits and receives the Doppler signal. Short pulses of ultrasound are produced, and the returning echoes from a specific sample volume are analyzed. The main advantage of PW Doppler is the possibility of interrogation of the direction, velocity, and spectral characteristics (laminar versus turbulent) of the blood flow from a distinct anatomic region of the heart or blood vessels. Laminar flows are characterized by the similitude of the velocities within the flow profile, which creates a Doppler signal with less disparity in velocity and little spectral broadening (see Figure 89-6). 315
Turbulent flow profiles are broad, and the area under the curve is filled in because the transducer is receiving 318
many frequency shifts associated with variable velocities. The disadvantage of PW Doppler lies in a maximal measurable velocity, called the *Nyquist limit,* that cannot be exceeded because of a limited pulse-repetition frequency. In other words, PW Doppler is only accurate when measuring low velocities.

Figure 89-4 Standard 2-D long axis views. **A,** Left cranial parasternal view optimized for the aortic root. **B,** Left cranial parasternal view optimized for the right atrium and auricle. **C,** Left cranial parasternal view optimized for the right ventricular outflow tract and main pulmonary artery. **D,** Four-chamber inflow view from the left caudal (apical) parasternal position. **E,** Left caudal (apical) parasternal view optimized for visualization of the left ventricular outflow tract. **F,** Five-chamber left ventricular outflow view from the left caudal (apical) parasternal position. **G,** Left caudal (apical) parasternal location, two-chamber view optimized for visualization of the left ventricular inflow and left auricle. **H,** Left ventricular outflow view from the right parasternal position. **I,** Four-chamber right parasternal long axis view. *AO*, aorta; *AOV,* aortic valve; *AMV,* anterior mitral valve cusp; *AS,* atrial septum; *CaVC,* caudal vena cava; *CH,* chorda tendineae; *CrVC,* cranial vena cava; *IVS,* interventricular septum; *LA,* left atrium; *LAu,* left auricle; *LPA,* left pulmonary artery; *LV,* left ventricle; *LVO,* left ventricular outflow; *LVW,* left ventricular wall; *MV*, mitral valve; *NC,* noncoronary aortic cusp; *PA,* pulmonary artery; *PM*, papillary muscle; *PMV,* posterior mitral valve cusp; *PV,* pulmonary valve; *RA,* right atrium; *Rau,* right auricle; *RC,* right coronary aortic cusp; *RMPA*, right main pulmonary artery; *RV,* right ventricle; *RVO,* right ventricular outflow; *TV,* tricuspid valve. (Modified from Thomas WP, Gaber CE, Jacobs GJ: Recommendations for standards in transthoracic two-dimensional echocardiography in the dog and cat, Echocardiography Committee of the Specialty of Cardiology, American College of Veterinary Internal Medicine, *J Vet Intern Med* 7:247–252, 1993.)


LONG-AXIS VIEWS
LEFT CRANIAL PARASTERNAL LOCATION
RV
LV
RA
RAu
CaVC
RVO
LV
AO
LA
A
B
RVO
LV
PA
LA
C
AO
LA
LAu
PA
LV
RV
G
D
LV
LA
LAu
RV
LV
RA
LA
F
E
RV
LV
AO
LA
RVO
LV
AO
LA
LEFT CAUDAL (APICAL) PARASTERNAL LOCATION

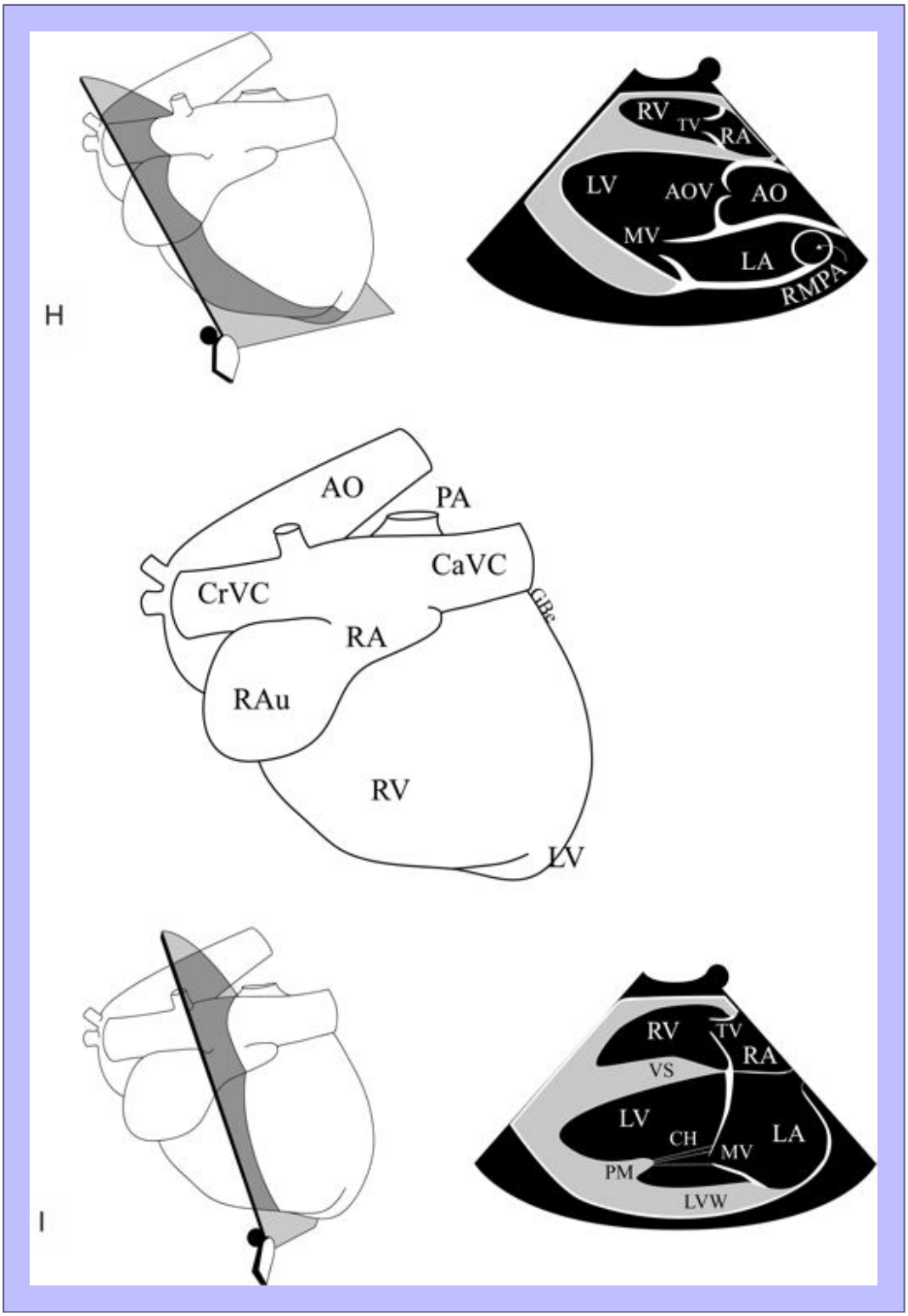

H
RV
TV
RA
LV
AOV
AO
MV
LA
RMPA
AO
PA
CaVC
CrVC
GBs
RA
RAu
RV
LV
I
RV
TV
RA
VS
LV
CH
MV
LA
PM
LVW

Figure 89-5 Standard M-mode views obtained at the level of the mitral valve *(A)* and the aortic valve *(B)*. **A,** The mitral valve is seen as an M shape. During rapid ventricular filling (early diastole), the mitral valve is forced to open up toward the interventricular septum. As ventricular filling progresses, the pressure in the left atrium equalizes with the left ventricular pressure and the mitral leaflets move toward each other. The mitral leaflets open again during atrial contraction. Closure of the mitral valve occurs after atrial systole. **B,** During diastole, the line in the middle of the aorta represents the closed aortic cusps. During systole, the aortic valve opens toward the walls of the aorta, remains open during the systolic ejection of blood, and then rapidly closes at the end of systole. *AO,* Aorta; *AOV,* aortic valve; *D,* diastole; *IVS,* interventricular septum; *LA,* left atrium; *LV,* left ventricle; *LVW,* left ventricular wall; *MV,* mitral valve cusp; *RA,* right atrium; *RV,* right ventricle; *RVW,* right ventricular wall; *S,* systole.

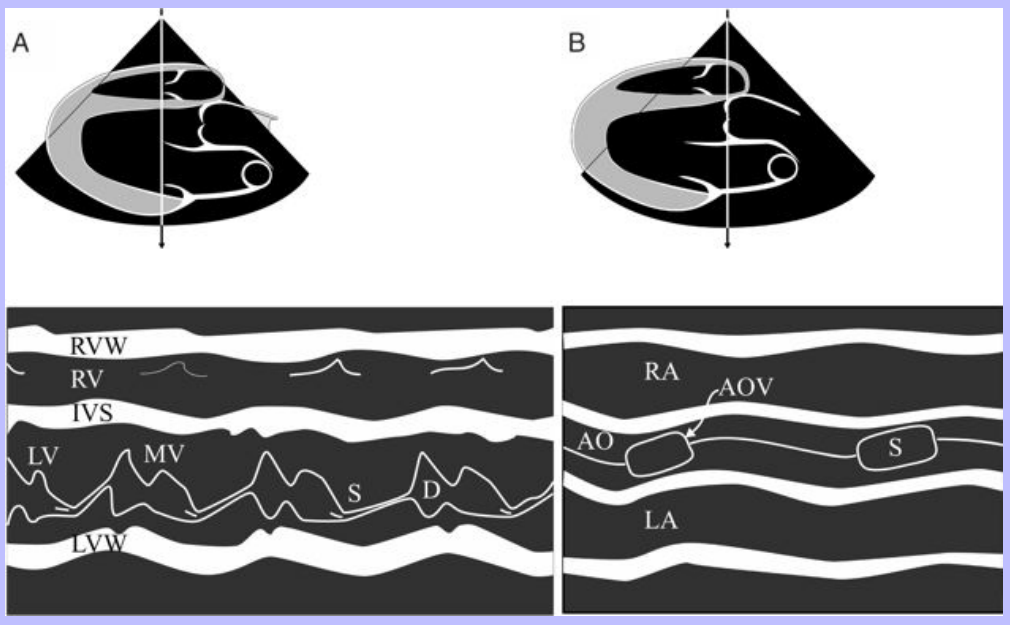
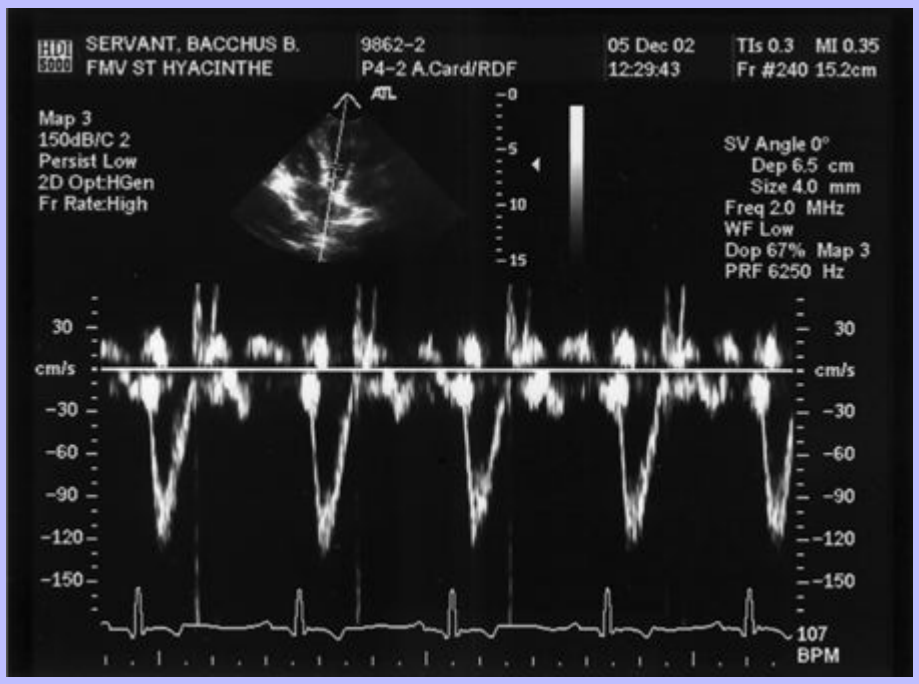


Figure 89-6 Normal left ventricular systolic outflow signal measured from the apical five-chamber view with PW Doppler.



PW Doppler is very useful in the evaluation of valvular blood flow patterns. Diastolic flows across the atrioventri-cular valves have similar patterns, which are characterized by an initial high-velocity signal associated with the rapid ventricular filling known as the *E wave*, followed by a lower velocity signal produced by the atrial contraction, or *A wave* (Figure 89-7). The flow patterns across the semilunar valves are characterized by a rapid acceleration during ejection followed by a more gradual deceleration. The variance of these valvular flow patterns is studied to identify different valvular diseases as described elsewhere. Table 89-6 describes the normal values for valvular spectral doppler echocardiographic velocities in dogs and cats.

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89.3.3 Continuous Wave Doppler

CW Doppler uses dual crystals for simultaneous transmission and reception of the Doppler signal. Very high velocity flows can be recorded with CW Doppler, because there is no Nyquist limit. The disadvantage of CW Doppler is that the specific location and characteristic of flow cannot be documented, because all velocities are measured along the cursor line.

PW and CW Doppler, therefore, are complementary, and both techniques are used to accurately describe the location, quality, and maximal velocity of an abnormal flow jet.

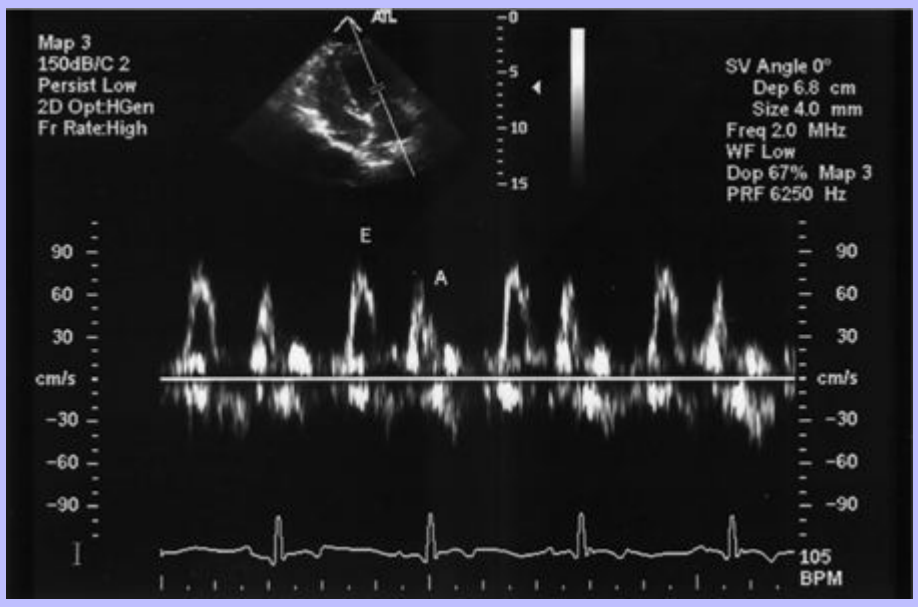
89.3.4 Color Flow Doppler

Color flow Doppler is a form of PW Doppler. Its primary clinical use is the detection of flow disturbances. The Doppler shift is encoded with a color map, which usually uses red, blue, and green to produce other color shades such as cyan, yellow, and white. Conventionally, blood moving away from the probe is blue, whereas blood moving toward the probe is red. This color map configuration is called the BART display (Blue/Away and Red/Toward). Color Doppler is very helpful for appropriately aligning with flow jets, searching for modest insufficient jets, describing the size and shape of regurgitant jets, identifying areas of turbulent flow, and confirming some cardiac shunts seen on 2-D echocardiograms. Turbulent flow is characterized by disparate velocities within the sampled area, which appears as a disorganized flow with a mosaic pattern. Several transducer positions and planes are used to find the optimal color flow imaging of a specific cardiac structure.

89.4 SPECIAL ECHOCARDIOGRAPHIC TECHNIQUES

Other echocardiographic techniques can provide useful information in the imaging of the canine and feline heart. These techniques include transesophageal and three-dimensional (3-D) echocardiography. Although useful in the clinical setting, these imaging methods have limited application in veterinary medicine, because they require expensive equipment. Transesophageal echocardiography requires general anesthesia, which increases the time and cost of the procedure.

Figure 89-7 Spectral Doppler recording of a normal mitral flow obtained from the left apical position with the PW Doppler gate located in the left ventricular inflow tract. The E point represents the rapid ventricular filling. The A wave corresponds to the atrial contraction.



Contrast echocardiography is another useful imaging method in the clinical evaluation of the cardiovascular system. It now is mostly used when Doppler echocardiography is unavailable. Microbubbles (obtained from the agitation of a syringe filled with 3 to 10 mL of physiologic saline) can be injected in a peripheral vein to assist in the diagnosis of right-to-left intracardiac shunting. The microbubbles reflect ultrasound and do not cross pulmonary or systemic capillaries, and they are reabsorbed by the pulmonary capillaries. In a normal patient, therefore, microbubbles injected into the cephalic vein stay on the right side of the heart. When right-to-left shunting is present, microbubbles are also observed in the left side of the heart.

89.5 EVALUATION OF CARDIAC FUNCTION

89.5.1 Cardiac Size and Chamber Dilatation

Cardiac chamber dimensions are determined by M-mode echocardiography and sometimes by 2-D echocardiography. Table 89-2 summarizes the most common etiologies for anomalies in chamber size.

The *E point to septal separation (EPSS)* is a very useful parameter in the assessment of left ventricular dilatation and systolic dysfunction. EPSS measures the distance from the maximal opening of the mitral valve (E point) to the endocardial aspect of the interventricular septum (Figure 89-8). In the normal heart, the mitral valve opens in diastole, and its anterior leaflet almost contacts the interventricular septum. In dilated hearts with decreased contractility (e.g., dilated cardiomyopathy), the mitral valve does not reach the septum. Reports in human medicine have shown that the size of the left ventricle alone does not alter the EPSS unless systolic dysfunction is present.

The *left atrial to aortic ratio (LA: Ao ratio)* is used to estimate the degree of left atrial enlargement. It compares the M-mode diameter of the left atrium in systole to the diameter of the aorta in diastole. This ratio is best obtained from the right parasternal short axis view but may also be evaluated from the right parasternal long axis view. The M-mode LA: Ao method has often been criticized because of the subjectivity of the cursor placement. This method underestimates left atrial size if the cursor does not reach the body of the left atrium. Conversely, it overestimates the relative left atrial size if a tangential plane of the aorta is performed. The reported LA: Ao ratio in normal dogs and cats is less than 1.3.

Table • 89-2 Common Etiologies for Anomalies in Cardiac Chamber Size

ANOMALY	ETIOLOGY
Left ventricular dilatation	Volume overload
	Mitral regurgitation
	Right-to-left shunting
	Aortic insufficiency
	Dilated cardiomyopathy
	High output stage
	Hyperthyroidism
	Anemia
Left ventricular reduction	Volume depletion
	Severe dehydration
	Hypoadrenocorticism
	Hypovolemic shock
	Inadequate blood return to the left heart
	Dirofilariasis
	Tetralogy of Fallot
Left ventricular hypertrophy	Pressure overload
	Aortic stenosis
	Hypertension
	Hypertrophic cardiomyopathy
	Infiltrative myocardial disease
Right ventricular dilatation	Volume overload
	Tricuspid regurgitation
	Atrial septal defect
	Dilated cardiomyopathy
Right ventricular reduction	Cardiac tamponade
	Volume depletion
Right ventricular hypertrophy	Pressure overload
	Pulmonic stenosis
	Tetralogy of Fallot
	Cor pulmonale
	Pulmonary hypertension
	Dirofilariasis
	Feline hypertrophic cardiomyopathy
	Feline restrictive cardiomyopathy
Left atrial enlargement	Chronic degenerative mitral valve disease
	Dilated cardiomyopathy
	Left-to-right shunting
	Mitral stenosis
	Mitral dysplasia
Right atrial enlargement	Tricuspid regurgitation/dysplasia
	Dilated cardiomyopathy
	Dirofilariasis
	Right-to-left shunting
	Tricuspid stenosis
	Cor pulmonale
	Pulmonary hypertension

Rishniw reported a more accurate 2-D echocardiographic method for estimating left atrial size in adult dogs. This method measures the LA: Ao ratio from the right parasternal short axis view of the aorta and left atrium when the aortic valve is closed. The internal diameter of the aorta is measured along the commissure between the noncoronary and right coronary aortic valve cusps after aortic valve closure (Figure 89-9). The left atrial

internal diameter is measured from a line parallel to the commissure between the noncoronary and left coronary aortic valve cusps to the distant margin of the left atrium. A LA: Ao ratio greater than 1.6 suggests left atrial dilation.

89.5.2 Left Ventricular Volumes

Many experimental models and formulas have been described in the canine patient to assess left ventricular volumes (LVV) by use of M-mode and 2-D echocardiography. Left ventricular end-diastolic and end-systolic volumes can be estimated by the Teichholz method; the bullet method; or the disk summation method (i.e., Simpson's rule). The disk summation method is considered the more accurate echocardiographic method in veterinary medicine. The Teichholz method is considered the more accurate M-mode method in the assessment of LVV, but one must realize that much of the volumetric estimates calculated from only one-dimensional measurements are less accurate, especially with an abnormal heart. The Teichholz method calculates the volume as follows:

$$LVV_{ES} = \frac{7(ESD^3)}{2.4 + ESD} \qquad LVV_{ED} = \frac{7(EDD^3)}{2.4 + EDD}$$

Where *ESD* is the left ventricular internal dimension at the end of systole, *EDD* is the left ventricular internal dimension at the end of diastole, LVV_{ES} is the left ventricular volume at the end of the systole, and LVV_{ED} is the left ventricular volume at the end of the diastole. This formula takes into consideration that the short axis of the left ventricle widens more than the long axis when the heart dilates.

Because of the inaccuracy of M-mode calculations for ventricular volumes in the diseased heart, the American Society of Echocardiography recommends the use of 2-D methods involving fewer geometric assumptions, such as the disk summation method (Figure 89-10). This method is especially more accurate when the heart has an irregular, enlarged, or asymmetric shape, as is the case in many of the canine and feline cardiomyopathies.

89.5.3 Ejection Phase Indices

Ejection phase indices are used to evaluate cardiac performance, especially the left ventricular systolic function. These indices, which are calculated from linear M-mode measurements, include the fractional shortening, the velocity of circumferential fiber shortening, the stroke volume, and the ejection fraction. The *end-systolic diameter,* by itself, is also a good indicator of left ventricular performance and is a more specific index of myocardial contractility than the fractional shortening. Although M-mode methods of volume determination have a poorer correlation with more invasive methods, these indices are still useful in the clinical setting, especially in the normal heart. It should be remembered that these indices are significantly influenced by ventricular loading conditions (preload and afterload).

Fractional shortening (FS) is the percent change in diameter of the ventricular cavity from diastole to systole. It provides a rough index of cardiac function. In veterinary medicine, the FS is the clinical index used more commonly in the evaluation of global inotropism and systolic function. Normal values in dogs range from 27% to 48%. FS is calculated as follows:

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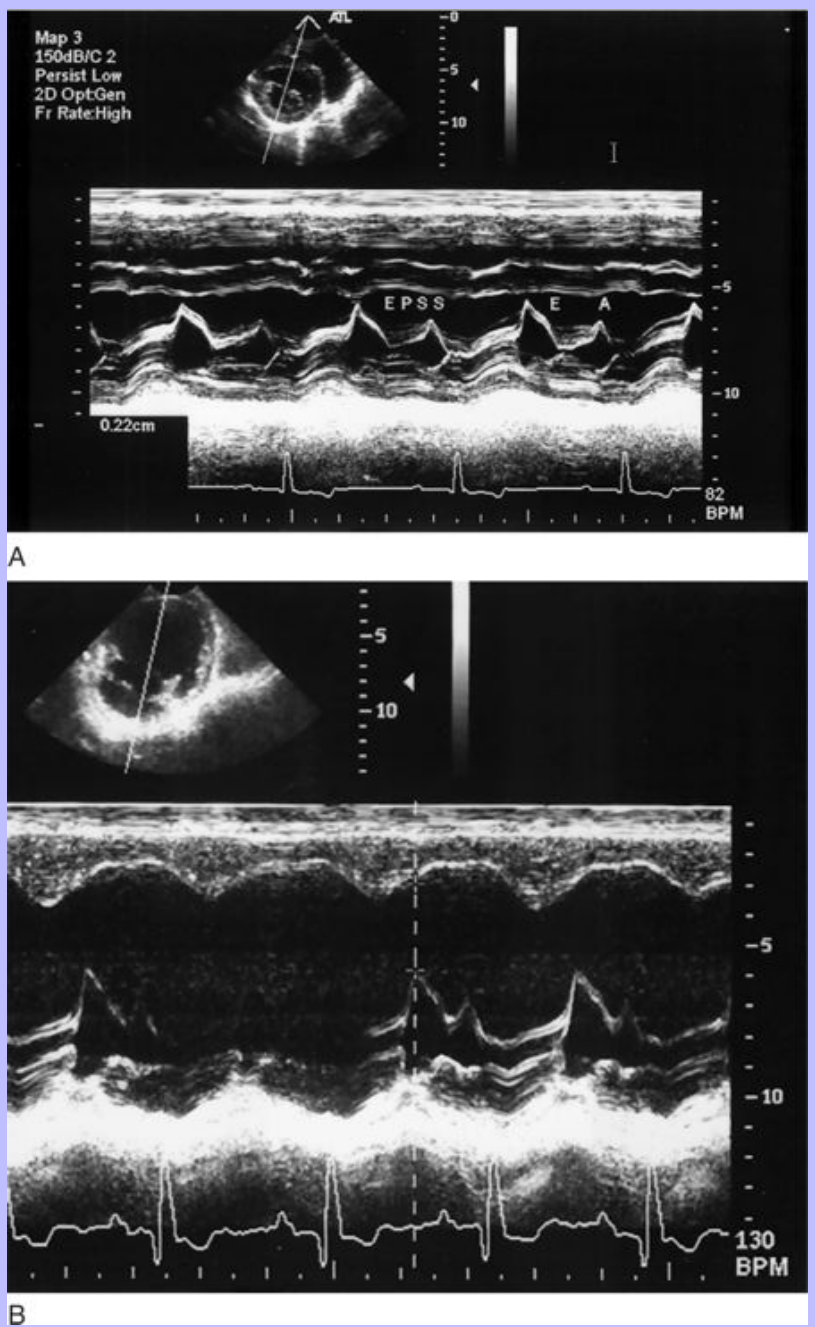
$$FS\,(\%) = \frac{EDD - ESD}{EDD} \times 100$$

Figure 89-8 **A,** EPSS measurement in a normal dog. A line is drawn between the interventricular septum and the maximal initial opening of the mitral valve (E point). **B,** Increased EPSS (2.9 cm) in a dog with dilated cardiomyopathy.



where, as noted previously, *EDD* is the left ventricular internal dimension at the end of diastole, and *ESD* is the left ventricular internal dimension at the end of systole. The *velocity of circumferential fiber shortening* (V_{cf}) measures the rate of change in the circumference *(circ)* of the left ventricle during systole. It is calculated as follows:

$$V_{cf}(\text{circ/sec}) = \frac{EDD - ESD}{EDD \times LVET}$$

where *LVET* is the left ventricular ejection time (see Systolic Time Intervals, below). Normal values for V_{cf} are 1.6 to 2.8 circ/sec in dogs and 1.3 to 4.5 circ/sec in cats.

The *stroke volume (SV)* and ultimately cardiac output can be calculated from M-mode measurements or more accurately by Doppler echocardiography (see Hemodynamic Parameters, below). M-mode SV is computed as follows:

$$SV\ (mL) = LVV_{ED} - LVV_{ES}$$

where, as noted previously, LVV_{ED} is the left ventricular volume at the end of diastole, and LVV_{ES} is the left ventricular volume at the end of systole.

The *ejection fraction (EF)* is a rough index of LV cardiomyocyte shortening, because it is the percentage of the LVV_{ED} ejected with each heartbeat. It also corresponds to the 3-D volumetric equivalent of the FS. The EF is the ratio of the left ventricular SV to the LVV_{ED} as calculated here:

$$EF\ (\%) = \frac{LVV_{ED} - LVV_{ES}}{LVV_{ED}} \times 100$$

89.5.4 Systolic Time Intervals

Systolic time intervals (STI) are other indices used in the assessment of global LV function. They are obtained by simultaneous recording of the electrocardiogram (ECG) and M-mode echocardiogram of the aortic valve (Figure 89-11). The following three intervals are routinely measured during systole:

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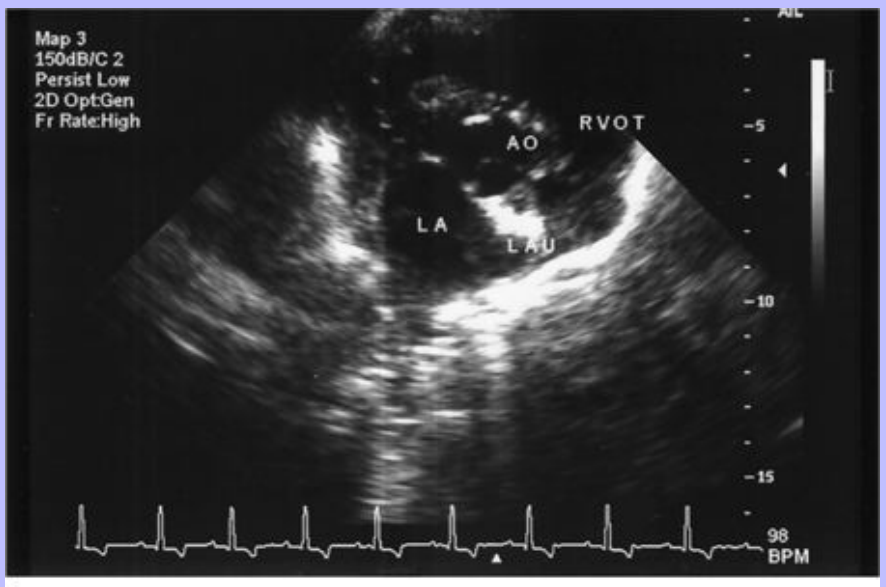
- The *pre-ejection period (PEP),* which is the time between ventricular depolarization (initial deflection of the QRS) and the onset of LV ejection, which corresponds to the opening of the aortic valve. PEP represents the isovolumetric contraction time.
- The *left ventricular ejection time (LVET),* which is the time required for aortic valve opening, which is measured from the opening of the aortic valve to its closure. The LVET is determined by the SV and the rate of flow. Generally, improvement of LV systolic performance is characterized by a shortening of the PEP or a decreased isovolumetric contraction time and a prolongation of the LVET, which corresponds to an improved SV.
- The *total electromechanical systole (QAVC),* which is the interval between the beginning of the Q wave and aortic valve closure. In other words, QAVC is the summation of PEP + LVET.

Figure 89-9 Two-dimensional measurement of the left atrium to aortic root ratio. **A,** Right para-sternal short axis view of the aorta and left atrium. **B,** Measurement of the internal diameter of the aorta and left atrium. (See text for details.) *AO*, aortia; *LA*, left atrium; *LAU*, left auricule; *RVOT*, right ventricular outflow tract.



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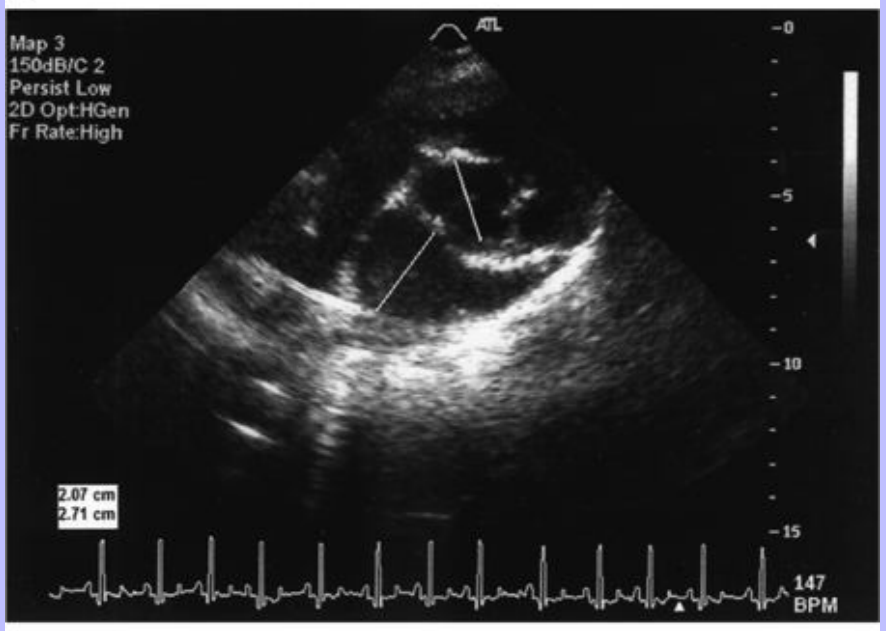


B

Figure 89-10 Disk summation method for estimating left ventricular volumes.

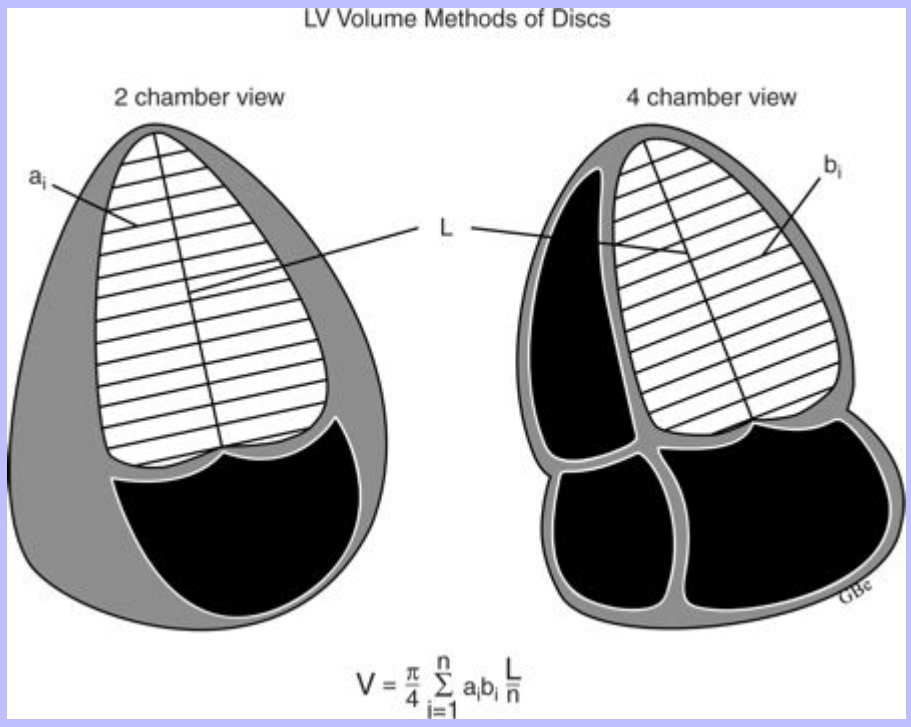


Table • 89-3 Normal Mean M-mode Echocardiographic Values in Dogs

BODY WEIGHT (kg)	$LVID_{ED}$ (cm)	$LVID_{ES}$ (cm)	IVS_{ED} (cm)	LVW_{ED} (cm)	EPSS (cm)	Ao_D (cm)	LA_S (cm)
3	2.0	1.1	0.5	0.6	0.1	1.1	1.3
5	2.4	1.3	0.6	0.7	0.1	1.3	1.5
10	3.0	1.8	0.7	0.8	0.2	1.6	1.8
15	3.4	2.1	0.8	0.8	0.2	1.9	2.0
20	3.8	2.4	0.9	0.9	0.3	2.1	2.2
25	4.0	2.6	0.9	0.9	0.3	2.2	2.4
30	4.3	2.8	1.0	1.0	0.4	2.4	2.5
35	4.5	3.0	1.0	1.0	0.4	2.5	2.6
40	4.7	3.1	1.0	1.0	0.5	2.6	2.7
45	4.9	3.3	1.1	1.1	0.5	2.7	2.8
50	5.0	3.4	1.1	1.1	0.6	2.8	2.9
55	5.2	3.6	1.2	1.1	0.6	2.9	3.0
60	5.3	3.7	1.2	1.1	0.7	3.0	3.1
65	5.5	3.8	1.2	1.2	0.7	3.1	3.1
Formula	1.44 BW	0.69 BW	0.36 BW	0.46 BW	0.03 BW	0.72 BW	0.90 BW
R value	0.97	0.95	0.89	0.81	0.94	0.96	0.98
Number of dogs	350	328	309	309	175	204	204

Ao_D, Aortic root diameter in diastole; *BW*, body weight; EPSS, E point to septal separation; *IVS_{ED}*, interventricular septal thickness at the end of diastole; *LA_S*, left atrial diameter in systole; *$LVID_{ED}$*, left ventricular internal diameter at the end of diastole; *$LVID_{ES}$*, left ventricular internal diameter at the end of systole; *LVW_{ED}*, left ventricular posterior wall thickness at the end of diastole.

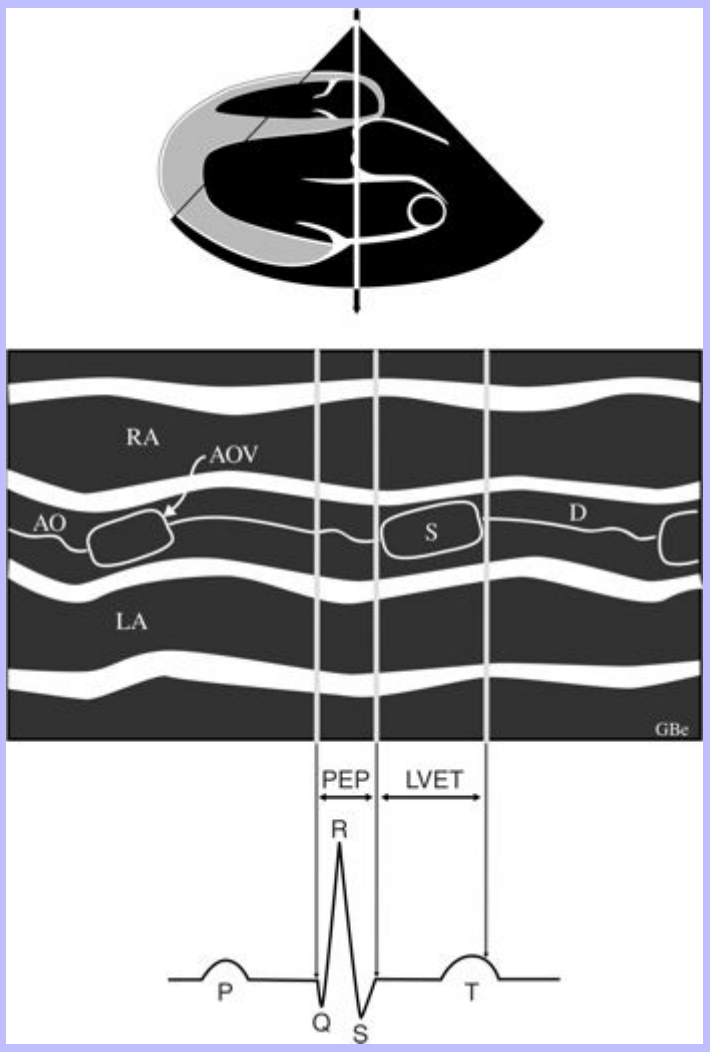
Table • 89-4 M-Mode Echocardiographic Reference Values for Certain Canine Breeds

VALUE	MINIATURE POODLE	BEAGLE	COCKER SPANIEL	AFGHAN HOUND	GOLDEN RETRIEVER	DOBERMAN	NEW-FOUNDLAND	GREAT DANE	IRISH WOLFHOUND
$LVID_{ED}$ (cm)	1.6–2.8	1.8–3.3	3.1–3.7	3.3–5.2	3.7–5.1	3.5–4.6	4.4–6.0	4.4–5.9	4.9–5.9
$LVID_{ES}$ (cm)	0.8–1.6	0.8–2.7	1.9–2.5	2.0–3.7	1.8–3.5	2.6–3.7	2.9–4.4	3.4–4.5	3.0–4.0
IVS_{ED} (cm)	0.4–0.6	0.5–1.1	0.7–1.0	0.8–1.2	0.8–1.3	0.8–1.1	0.7–1.5	1.2–1.6	0.6–1.0
IVS_{ES} (cm)	0.6–1.0	0.6–1.2	—	0.8–1.8	1.0–1.7	1.3–1.6	1.1–2.0	1.4–1.9	1.0–1.7
LVW_{ED} (cm)	0.4–0.6	0.6–1.3	0.7–0.9	0.7–1.1	0.8–1.2	0.6–1.0	0.8–1.3	1.0–1.6	0.7–1.2
LVW_{ES} (cm)	0.6–1.0	0.7–1.7	—	0.9–1.8	1.0–1.9	0.8–1.4	1.1–1.6	1.1–1.9	1.2–1.8
EPSS (cm)	0–0.2	—	—	0–1.0	0.1–1.0	0–0.8	0.3–1.4	0.5–1.2	0–1.0
FS (%)	35–57	20–70	30–39	24–48	27–55	21–38	22–37	18–36	30–40
LA_S (cm)	0.8–1.8	—	—	1.8–3.5	1.6–3.2	2.4–3.0	2.4–3.3	2.8–4.6	2.8–4.0
Ao_D (cm)	0.8–1.3	—	—	2.0–3.4	1.4–2.7	2.5–3.5	2.6–3.3	2.8–3.4	2.7–3.5

Ao_D, Aortic root diameter in diastole; *EPSS*, E point to septal separation; *FS*, fractional shortening; *IVS_{ED}*, interventricular septal thickness at the end of diastole; *IVS_{ES}*, interventricular septal thickness at the end of systole; *LA_S*, left atrial diameter in systole; *$LVID_{ED}$*, left ventricular internal diameter at the end of diastole; *$LVID_{ES}$*, left ventricular internal diameter at the end of systole; *LVW_{ED}*, left ventricular posterior wall thickness at the end of diastole; *LVW_{ES}*, left ventricular posterior wall thickness at the end of systole.

It should be remembered that STI are affected by heart rate and preload or afterload variations. The PEP/LVET index is therefore recommended because it is less influenced by these loading parameters. Normal values for STI are shown in Table 89-7.

Figure 89-11 Illustration of the method used to evaluate the systolic time intervals. *AO*, aorta; *AOV*, aortic valve; *D*, diastole; *LA*, left atrium; *LVET,* left ventricular ejection time; *PEP,* Pre-ejection period; *RA*, right atrium; *S*, systole.



89.5.5 Hemodynamic Parameters

Doppler echocardiography is used to calculate the cardiac output (CO). The cardiac index is the CO indexed for body surface area (BSA), which takes into account body size variation among animals. The BSA is calculated from body weight using the following formula:

$$BSA = (10.1 \times w^{2/3}) \times 10^{-4}$$

where *w* is the body weight in grams. Cardiac output is calculated from the product of the heart rate (HR) and stroke volume:

$$CO = HR \times SV$$

The continuity equation is used to evaluate the CO. This equation is based on the theory of conservation of mass that is applied to fluids, which specifies that flow through a given area of a conduit must equal flow through an adjacent area over a given time. Accordingly, SV ejected through a valvular orifice during systole is equal to the flow that passes through the valve, as expressed by the following equation:

$$SV = A \times VTI$$

Table • 89-5 Normal M-Mode Echocardiographic Values in Cats*

$LVID_{ED}$ (mm)	$LVID_{ES}$ (mm)	LVW_{ED} (mm)	LVW_{ES} (mm)	IVS_{ED} (mm)	IVS_{ES} (mm)	LAS (mm)	Ao_D (mm)	FS (%)	EPSS (mm)
12–18	5–10	3–5	4–9	3–5	5–9	8–13	8–11	30–55	≤ 4

Ao_D, Aortic root diameter in diastole; *EPSS*, E point to septal separation; *FS*, fractional shortening; *IVS_{ED}*, interventricular septal thickness at the end of diastole; *IVS_{ES}*, interventricular septal thickness at the end of systole; *LA_S*, left atrial diameter in systole; *$LVID_{ED}$*, left ventricular internal diameter at the end of diastole; *$LVID_{ES}$*, left ventricular internal diameter at the end of systole; *LVW_{ED}*, left ventricular posterior wall thickness at the end of diastole; *LVW_{ES}*, left ventricular posterior wall thickness at the end of systole.

* These measurement guidelines are based on the author's experience and published data.

where *A* is the cross-sectional area of the orifice calculated from the diameter of that orifice (O) measured by 2-D echocardiography, and *VTI* is the velocity-time integral of the PW Doppler signal across the valvular orifice.

$$A = D^2 \times (\pi/4)$$
$$CO = HR \times D^2(\pi/4) \times VTI$$

Virtually any valve or area in the heart can be used to estimate the CO, but the left ventricular outflow tract and the aortic valve are used most often.

89.5.6 Diastolic Function

Historically, the assessment of diastolic function has received little attention in veterinary medicine. The diastolic function should be evaluated when abnormal ventricular compliance or abnormal diastolic filling patterns are suspected. Doppler echocardiographic study of the transmitral flow profiles (E and A waves) is useful in the characterization of diastolic function. In general, with a decrease in ventricular compliance, the passive filling velocity (E wave) is decreased, and the active atrial contraction velocity (A wave) is increased; thus the E/A ratio is less than 1, representing a delayed relaxation pattern in diastole. This finding has been recognized inconsistently in dogs suspected of having depressed diastolic function. The E/A ratio is even more difficult to evaluate in the cat, owing to its high heart rate, which often causes a fusion of the E and A waves. A *restrictive pattern* has also been described in some cardiomyopathies; in this pattern, the peak E wave velocity is increased and the A wave velocity is decreased. A number of other diastolic indices have been described elsewhere, including the isovolumetric relaxation period, relaxation time index, duration of rapid filling phase, time to peak filling rate, rate of change in LV dimension, and peak rate of ventricular wall thinning in diastole.

89.6 NORMAL VALUES

M-mode measurements vary with body size, body surface area, breed, and sedative drugs used. They are also modified by factors such as fear and stress, which significantly affect heart rate and contractility in veterinary patients. Therefore reported normal values should always be regarded as approximate. Kienle collected values from the literature to establish mean normal M-mode values for dogs ranging from 3 to 68 kg (Table 89-3). Normal dogs generally have values within a range of 10% of either side of the mean. Figure 89-12 shows the typical echocardiography report used in veterinary medicine.

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Figure 89-12 Typical echocardiography report.

ECHOCARDIOGRAPHY REPORT

Date _____

File # _____

Patient _____ Owner _____

Diagnosis: _____

M-MODE MEASUREMENTS (mm)

	Feline	Min. Poodle	Cocker	Afghan	Golden	Wolfhound
IVS_{ED} _____	3-5	4-6	6.9-9.5	8-12	8-13	6.1-9.9
IVS_{ES} _____	5-9	6-10	-	8-18	10-17	10.3-17.1
$LIVD_{ED}$ _____	12-18	16-20	30.5-37.1	33-52	37-51	48.7-59.1
$LIVD_{ES}$ _____	5-10	8-16	19.4-25	20-37	18-35	30.4-40
LVW_{ED} _____	3-5	4-6	6.8-9	7-11	8-12	7.4-11.6
LVW_{ES} _____	4-9	6-10	—	9-18	10-19	11.7-18.3
FS (%) _____	30-55	35-57	34-39	24-48	27-55	30-40
EPSS _____	<4	<6	—	<10	<10	<10
Ao_D _____	8-11	8-13	—	20-34	14-27	26.5-34.5
LA_S _____	8-13	8-18	—	18-35	16-32	27.8-39.8
LA:Ao _____	<1.3	<1.6	—	<1.6	<1.6	<1.6
LVEF _____						
CI _____						

2D-STUDY

Pericardial effusion none mild moderate severe

Cardiac masses none observed Location: _____ Size: _____

Blood clots/smoke effect none observed Location: _____ Size: _____

Intraluminal anomalies none observed Location: _____

Valvular anomalies _____

Myocardial anomalies _____

COLOR DOPPLER STUDY

Normal Other: _____

Spectral DOPPLER STUDY

Normal Other: _____

Sedation

NO YES Protocol: _____

Comments _____

Veterinarian's signature: _____

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Table • 89-6 Normal Values for Spectral Doppler Echocardiography Velocities in Dogs and Cats*

VALVE	CANINE (m/sec)	FELINE (m/sec)
Mitral Valve		
Peak E wave	0.8–1.0	0.55–0.77
Peak A wave	0.5–0.7	0.44–0.6
Tricuspid Valve		
Peak E wave	0.8–0.9	—
Peak A wave	0.5–0.6	—
Aortic Valve		
Peak systolic velocity	≤2.0	≤1.2
Pulmonic Valve		
Peak systolic velocity	≤1.5	≤1.2

* These guidelines are based on the author's experience and published data.

Table • 89-7 Normal Values for Left Ventricular Systolic Time Intervals in Dogs* and Cats†

SYSTOLIC TIME INTERVALS (ms)	CANINE	FELINE
PEP	54 ± 7	46 ± 5
LVET	159 ± 15	116 ± 19
PEP/LVET	0.34 ± 0.05	0.40 ± 0.05
QAVC	214 ± 18	162 ± 24

Atkins IE, Snyder PS: Systolic time interval and their derivatives for the evaluation of cardiac function. *J Vet Intern Med* 1992;6:55–63. *PEP*, Pre-ejection period; *LVET*, left ventricular ejection time; *QAVC*, total electromechanical systole.

90 CHAPTER • 90 Electrocardiographic (ECG) Techniques

Kelly Anderson-Wessberg

The heart is an electrical field created by the flow of current through individual cardiac muscle cells. These cells are connected by intercalated discs, which allows for rapid spread of electrical activity throughout the heart. The arms and legs are linear extensions of this electrical field. When electrodes are connected to the extremities, an electrocardiograph machine can record electrical activity within the heart.

A *dipole* generates an electrical force by having a positive pole and a negative pole, which are separated by a small distance. The sum of multiple dipoles in the heart is measured at the body surface by the electrocardiograph. The *equivalent dipole theory* assumes that all cardiac cells summate to one dipole on the body's surface.

90.1 LEAD SYSTEMS

Each lead evaluates the heart at a specific angle and in a certain plane. The augmented unipolar leads and the standard bipolar leads relate to the frontal plane. They provide information about current flowing right, left, inferior, and superior (head and tail). Chest leads are in the horizontal plane and provide information about current flowing right, left, anterior, and posterior (ventral and dorsal). Bipolar leads use a positive and a negative electrode on that lead. Unipolar leads use a single electrode and a neutral reference point. The letter V indicates a unipolar lead.

90.1.1 Bipolar Leads

Leads I, II, and III are standard bipolar limb leads (Table 90-1). They were devised by Willem Einthoven in 1902 and were the first fixed lead system to be used. The position of these leads forms an approximate equilateral triangle, called *Einthoven's triangle*.

90.1.2 Augmented Unipolar Leads

Leads aVR, aVL, and aVF are augmented unipolar leads (“a” stands for augmented) (Table 90-2). These leads record only half the voltage of the other leads, and the electrocardiograph must amplify, or augment, the deflections to make the size of the complexes comparable to those of the other leads. Because these leads are unipolar, they have a positive electrode and a neutral reference point. The neutral reference point is the average of the other two limb electrodes.

Table • 90-1 Electrode Placement for Standard Limb Leads

LEAD	POSITIVE	NEGATIVE
I	Left front limb	Right front limb
II	Left hind limb	Right front limb
III	Left hind limb	Left front limb

Table • 90-2 Electrode Placement for Augmented Unipolar Leads

LEAD	POSITIVE ELECTRODE	NEUTRAL REFERENCE POINT
aVL	Left front limb	Right front limb, left hind limb
aVR	Right front limb	Left front limb, left hind limb
aVF	Left hind limb	Right front limb, left front limb

90.1.3 Precordial Chest Leads

In humans, chest leads are used most often for their ability to identify myocardial infarctions. In animals, chest leads are most helpful for identifying P waves not easily seen in other leads; bundle branch blocks; and heart enlargement patterns. Right heart enlargement, in particular, may be identified only through the use of chest leads. In animals, the leads are connected as indicated in Table 90-3. Chest leads are unipolar leads. The neutral reference point is the sum of electrical activity at the left arm (LA), left leg (LL), and right arm (RA). This neutral reference point is essentially the center of the heart.

90.1.4 Other Lead Systems

The orthogonal lead system was designed to measure the heart's electrical activity in three dimensions. This system uses three axes, X, V, and Z, and the three leads are perpendicular to each other. Lead I approximates the X axis; lead aVF approximates the Y axis; lead V_{10} approximates the X axis; lead aN/F approximates the Y axis; and lead V approximates the Z axis. The vectorcardiogram is derived from these leads. This system is not commonly used today because it is cumbersome and usually does not provide additional information.

90.2 RECORDING THE ELECTROCARDIOGRAM

The canine patient is placed in right lateral recumbency. This position is recommended because the majority of reference data were obtained from dogs in this position. Metal tables should not be used, nor should the animal be positioned directly on the ground. With the patient's head to the right, the handler may place the right arm over the patient's neck and the left arm over the hindquarters. The patient's legs are held perpendicular to the body and parallel to each other. It is essential that each pair of limbs remain parallel to each other and that enough space remains between the limbs to avoid contact between limbs or electrodes. Patient movement is restricted without discomfort. Figure 90-1 shows proper patient positioning.

Table • 90-3 Electrode Placement for Unipolar Chest Leads

CURRENT LEAD NAME	ELECTRODE LOCATION	OLDER LEAD NAMES	HUMAN EQUIVALENT
rV_2	Right side, 5th ICS, near sternum	CV_5 RL	V_1
V_2	Left side, 6th ICS, near sternum	CV_6 LL	V_2, V_3
V_4	Left side, 6th ICS, at costochondral junction	CV^6 LU	V_4, V_5
V_{10}	Over dorsal spine of 7th thoracic vertebra	CV_{10}	V_6

ICS, Intercostal space.

Figure 90-1 Proper patient positioning.

The electrodes are attached directly to the skin. It is not necessary to clip the hair or prepare the skin. Electrodes may be alligator clips, adhesive patches, or wire. If alligator clips are used, patient discomfort can be minimized by filing or blunting the teeth and relaxing the spring. Alternatively, a gauze pad can be placed between the alligator clip and the skin. Limp electrodes are placed just proximal to the caudal surface of the elbow (LA, RA) and just proximal to the stifle on the cranial surface of the hind limbs (LL, RL). Chest leads are placed according to their respective locations (see Table 90-3). To maintain electrical contact, the electrodes are saturated with 70% isopropyl alcohol or covered with ECG electrode gel.

A 1-millivolt pulse should be recorded at the beginning of every ECG to ensure standardization. A minimum of three complexes of each lead, at 50 mm/sec, is recorded. A rhythm strip is obtained by recording lead II at 25 or 50 mm/sec. The ECG is labeled with the patient's name and medical record number, the date, and the paper speed.

Inaccurate ECG recordings may lead to misdiagnosis and inappropriate treatment. Improper patient positioning, electrical interference, and breathing artifacts are the most common causes of inaccurate ECG recordings. Small changes in limb or electrode placement can result in significant changes on the ECG. Lead aVL has been shown to be the lead most affected by forelimb malposition. Electrical interference may occur because of loose connections between the alligator clips and cable tips or because of nearby operation of electrical equipment.

In feline patients or dyspneic dogs, an ECG recorded in a sternal position is adequate. If restraining the animal at all presents a danger, a rhythm strip may be obtained in any position. An ECG recorded in a nontraditional position may yet provide vital information, particularly about the rhythm, while avoiding any harm to the patient.

91 CHAPTER • 91 Electromyography and Nerve Conduction Velocity Studies

David Lipsitz

Diseases involving any part of the neuromuscular system (peripheral nerve, muscle, neuromuscular junction) may be clinically identical, and the neurologic examination may not always reveal which part of the neuromuscular system is affected. Electrodiagnostic testing may extend the examiner's capabilities in these disorders, by supplementing clinical findings and localizing lesions within the neuromuscular system. They may also aid in selecting and guiding nerve and muscle biopsies. To avoid movement, discomfort, and lack of cooperation, dogs and cats are usually placed under general anesthesia when examined.

91.1 ELECTROMYOGRAPHY

Electromyography (EMG) is a method for detection and display of insertional, spontaneous, and voluntary electrical activity of skeletal muscles. EMG deals primarily with the electrical activity of a single muscle fiber or groups of muscle fibers. EMG is based upon the inherent excitability of normal skeletal muscle and on changes in this excitability during disease. Normal muscle is electrically and mechanically silent except during voluntary contraction. Denervated muscle fibers and muscle fibers damaged due to primary disease will spontaneously depolarize, causing readily detectable spontaneous activity.

EMG is most useful in defining mononeuropathies, polyneuropathies, and myopathies and for differentiating neurogenic from disuse atrophy. Disuse atrophy and diseases of neuromuscular transmission do not induce EMG abnormalities. EMG abnormalities are not specific for a particular neuromuscular disease, but a distinction can frequently be made based on neurologic examination, distribution of affected muscles, and results of nerve conduction studies. EMG can also be used to select a biopsy site in diseases where only specific muscles are involved, such as masticatory muscle myositis.

The most commonly used EMG electrodes are concentric (coaxial) needle electrodes, which measure the potential difference between a nichrome silver or platinum wire and the surrounding stainless steel shaft. Factors to consider when performing an EMG examination are the amount of electrical interference in the room from extraneous sources (heating pads, electrical outlets) and patient-monitoring equipment. The dog or cat must be properly grounded and the machine set to filter 60 Hz interference and radio interference to obtain proper recordings. The sensitivity of the EMG examination can be increased by performing multiple insertions into a specific muscle group and by examining multiple muscle groups. EMG abnormalities may be patchy in their distribution within a muscle or within muscle groups.

Normal muscle is electrically silent, but electrical activity may be detected in normal skeletal muscles. These are as follows:

- Insertional activity is caused by mechanical stimulation and disruption of both muscle fibers and membranes by the EMG needle; it should subside in a few hundred milliseconds.
- Miniature endplate potentials (MEPPs) are caused by spontaneous release of single quanta of acetylcholine causing partial depolarization of the postsynaptic membrane.
- Endplate spikes are associated with MEPPs when enough acetylcholine is released to completely depolarize a single muscle fiber. They should not be confused with fibrillation potentials.

- Motor unit action potentials (MUAPs) are large action potentials caused by summation of action potentials of one or several motor units. They are present during contraction. They are not routinely evaluated in veterinary electrophysiology.

The spontaneous activity of abnormal skeletal muscles are as follows:

- Increased and prolonged insertional activity is due to mechanical irritation of firing muscle fibers.
- Fibrillation potentials and positive sharp waves arise from depolarization of the T-tubular system or depolarization of the surface sarcolemma. They result from the same type of pathologic process but have a different morphology due to their orientation with respect to the EMG electrode.
- Giant MUAPs are large polyphasic potentials that suggest reinnervation of muscle fibers.
- Myotonic discharges result from delayed relaxation of single muscle fibers due to ion channel defects; the discharges have a distinct waxing and waning firing rate and produce the classic “dive bomber” sound.
- Complex repetitive discharges are the spontaneous firing of groups of muscle fibers; they do not wax and wane like myotonic discharges. They have previously been termed *pseudomyotonia* and *bizarre high-frequency discharges*.

91.2 MOTOR AND SENSORY NERVE CONDUCTION

Nerve conduction and nerve conduction velocities are affected by various neuropathies, and methods have been developed for testing nerve conduction of both motor and sensory nerves. Nerves commonly tested are the peroneal, tibial, radial, and ulnar. Clinicians can evaluate motor nerves by stimulating a peripheral nerve and recording the stimulated compound muscle action potential (CMAP). They can evaluate sensory nerves by stimulating cutaneous nerves (which have no motor axons) and recording the sensory nerve action potentials (SNAP) while the electrical potential conducts along the nerve.

Regardless of which nerves are stimulated, certain aspects of neurophysiology must be considered. Insulated stainless steel needle electrodes (except for the tip) are commonly used for stimulating and recording. Stimulating electrodes should be placed such that the negative pole (cathode) is more proximal to the recording site than the positive pole (anode) to avoid conduction block. The negative charges at the cathode depolarize the nerve, whereas the positive charge at the anode hyperpolarizes the nerve. Supramaximal stimulus strength is necessary to ensure that all axons are activated. A ground electrode is imperative, usually placed between stimulating and recording electrodes. Motor nerve conduction velocities are calculated by measuring the latency difference between the CMAP responses from two sites along the nerve and by measuring the distance between these sites, using the following formula:

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$$\text{MNCV (m/s)} = \text{Distance (mm)}/\text{Latency}_{\text{proximal}} - \text{Latency}_{\text{distal}}\text{(ms)}$$

Using only one stimulation site results in inaccuracies of MNCV because it takes into account neither the neuromuscular transmission time nor the muscle fiber depolarization time. Sensory nerve action potentials are recorded directly from the nerve itself, so only one stimulation site is necessary to calculate the conduction velocity. SNAPs are quite small compared with CMAPs (μV versus mV), so signal averaging is necessary to obtain recordings, thereby avoiding background noise and muscle artifact.

Abnormalities of both motor and sensory nerve conduction studies include the following:

- Slowing of conduction velocity without a significant decrease in CMAP amplitude is caused by demyelination with the axons remaining intact.
- Temporal dispersion and polyphasia of action potentials occur normally due to axons with different conduction velocities but may be prolonged with demyelination.
- The number of muscle fibers activated determines the amplitude of the CMAP. Decreased amplitude of CMAPs without temporal dispersion is caused by axonal degeneration, myopathies, or disorders of neuromuscular transmission.
- Many neuropathies cause both segmental demyelination and axonal degeneration; therefore all of the previously mentioned abnormalities may be seen together.

92 CHAPTER • 92 Nasoesophageal, Esophagostomy, and Gastrostomy Tube Placement Techniques

Stanley L. Marks

The enteral route is the preferred method of nutritional support in animals with a functional gastrointestinal (GI) tract. Many techniques for obtaining enteral access are available, and the approach used depends on several issues, including anticipated duration of enteral support, aspiration risk, condition of the GI tract, the animal's temperament, and the level of local expertise. The reader is advised to review Chapter 161 in the Dietary Considerations of Systemic Problems section for a comprehensive overview of diet selection and feeding implementation for the anorectic or sick animal.

92.1 ENTERAL FEEDING ACCESS DEVICES

Most feeding tubes today are made of polyurethane or silicone. These materials have tended to replace the older polyvinyl chloride feeding tubes that stiffened when exposed to digestive juices and are more irritating, necessitating frequent tube replacement. Silicone is softer and more flexible than other tube materials with a greater tendency to stretch and collapse. Polyurethane is stronger than silicone, allowing for a tube of the same French size to have thinner walls and a larger internal diameter. The flexibility and decreased internal diameter of silicone tubes may lead to clogging or kinking of the tube. Both polyurethane and silicone do not rapidly disintegrate or embrittle in situ, providing a longer “wear.” The French (F) unit measures the outer lumen diameter of a tube (each F unit is equal to 0.33 mm).

92.1.1 Nasoesophageal Tube Placement

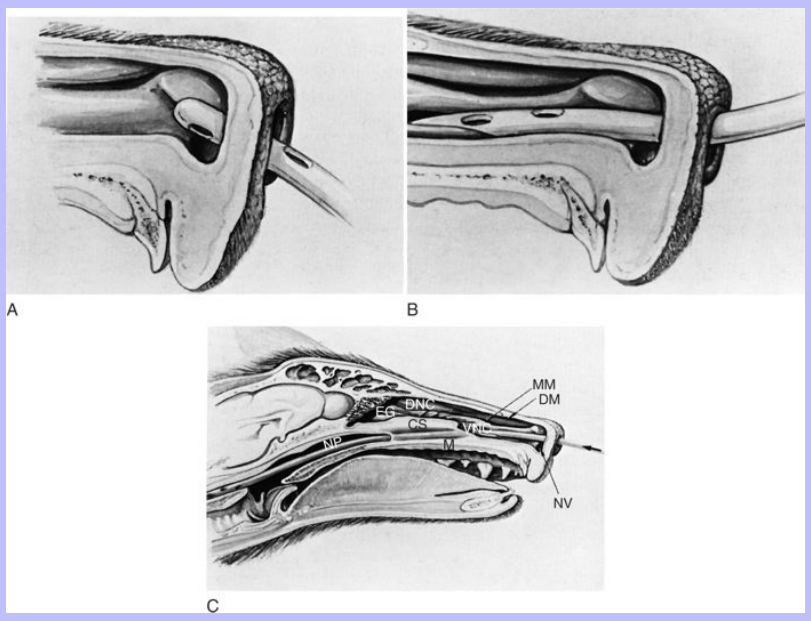
Nasoesophageal tubes are a simple and efficient choice for the short-term (less than 10 days) nutritional support of most anorectic hospitalized animals that have a normal nasal cavity, pharynx, esophagus, and stomach. Nasoesophageal tube feeding is contraindicated in animals that are vomiting, comatose, or lack a gag reflex. Polyvinyl chloride (Infant Feeding Tube, Argyle Division of Sherwood Medical, St. Louis, Mo.) or red rubber tubes (Sovereign Feeding Tube, Monoject Division of Sherwood Medical) are the least expensive tubes for dogs and cats, although the polyvinyl chloride tubes may harden within 2 weeks of insertion and cause irritation or ulceration of the pharynx or esophagus. Tubes made of polyurethane (MILA International, Inc., Florence, Ky.) or silicone (Global Veterinary Products, Inc., New Buffalo, Mich.) are more expensive; however, they are less irritating and more resistant to gastric acid, allowing prolonged usage. An 8 to 10 F × 43-inch tube (preferably with a guide wire) is suitable for dogs weighing more than 15 kg. A 5 to 8 F × 22-to 43-inch tube is recommended for dogs weighing less than 15 kg and for cats.

The length of tube to be inserted into the distal esophagus is determined by measuring the distance from the tip of the pet's nose to the eighth or ninth rib. This will help verify the correct placement of the tube in the distal esophagus rather than the stomach and decrease the likelihood of reflux esophagitis. Desensitization of the nasal cavity with four or five drops of 0.5% proparacaine hydrochloride is recommended. The tube tip should be lubricated with a water-soluble lubricant or 5% lidocaine ointment to facilitate passage. The tube is passed by maintaining the animal's head in the normal angle of articulation and gently directing the tip of the tube in a ventromedial direction. The tube should move with minimal resistance through the ventral meatus and nasopharynx and into the esophagus. In dogs, the presence of a small ventral ridge at the proximal end of the nasal passage necessitates directing the tip of the tube dorsally initially to allow passage over the ventral ridge and into the nasal vestibule (Figure 92-1). Nasoesophageal intubation is more difficult to perform in dogs

because of their long, narrow nasal passages and extensive turbinate structures. In the dog, the tube is directed in a ventromedial direction while pushing the external nares dorsally. This maneuver opens the ventral meatus and guides the tube into the oropharynx.

If the tube is unable to be passed with minimal resistance into the oropharynx, it should be withdrawn and redirected because it could be positioned in the middle meatus with its tip encountering the ethmoid turbinate. Once the tube has been passed to the level of the attached "butterfly" tape, it should be secured as close to the nostril as possible, with either suture material or glue (Superglue, Loctite Corp., Cleveland, Ohio). A second tape tab should be secured to the skin on the dorsal midline between the eyes (Figure 92-2). An Elizabethan collar is usually required for dogs to prevent inadvertent tube removal; however, most cats do not require such a device. The clinician can remove the tube by clipping the hair that is attached to the glue.

Figure 92-1 Parasagittal section showing step-wise insertion of a nasoesophageal tube through the ventral meatus of a dog. **A,** The presence of a small ventral ridge at the rostral end of the nasal passage necessitates directing the tip of the tube dorsally to clear the protuberance. **B,** Once past the protuberance, the tube is aimed medially and ventrally and advanced into the ventral meatus. **C,** Tube through ventral meatus and nasal pharynx *(NP)*. Structures identified: nasal vestibule *(NV)*, cartilaginous septum *(CS)*, maxilla *(M)*, dorsal meatus *(DM)*, middle meatus *(MM)*, ethmoidal conchae *(EC)*, ventral nasal conchae *(VNC)*, dorsal nasal conchae *(DNC)*, and alar fold *(AF)*. (Reprinted with permission from Crowe DT: Clinical use of an indwelling nasogastric tube for enteral nutrition and fluid therapy in the dog and cat, *J Am Anim Hosp Assoc* 22:675, 1986.)



After placement the tube position is checked by injecting 5 to 10 mL of air while auscultating the cranial abdomen for borborygmus, or it is done by infusing 3 to 5 mL of sterile saline or water through the tube and observing for a cough response. Correct tube placement can also be confirmed with a lateral survey thoracic radiograph and observing the position of the radiopaque tube in the esophagus. The most common complications associated with the use of nasoesophageal tubes include epistaxis, dacryocystitis, rhinitis, tracheal intubation and secondary pneumonia, and vomiting.

92.1.2 Pharyngostomy Tube Placement

The increasing availability of endoscopic equipment and the superior benefits of esophagostomy and percutaneous gastrostomy tube placement have resulted in pharyngostomy tubes becoming virtually obsolete. Nevertheless, the introduction of placement modifications has resulted in a dramatic reduction in complications associated with the interference of epiglottic movement and partial laryngeal obstruction. The indications for pharyngostomy tube placement are similar to those for nasoesophageal tube placement; however, the procedure requires general anesthesia. Pharyngostomy tubes are specifically indicated for pets requiring long-term nutritional support with bypass of the oral cavity or oropharynx.

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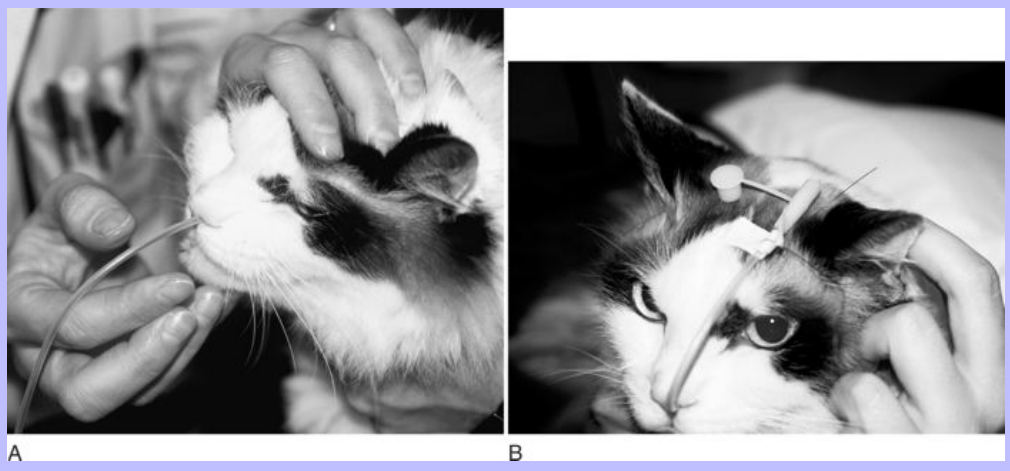
Figure 92-2 **A,** The tip of the nasoesophageal tube has been lubricated and passed into the ventral meatus by positioning the animal's head in a normal angle of articulation. **B,** The nasoesophageal tube can be secured to the skin on the dorsal midline between the eyes with tape “butterflies.” A second tape tab should be secured as close to the nostril as possible, using either suture material or glue.



For tube placement, the animal is anesthetized with either a short-acting injectable or inhalant anesthetic, intubated, and placed in lateral recumbency. The tube can be placed on either the right or left side of the oral pharynx. An area of skin caudal to the mandible over the hyoid apparatus is aseptically prepared. A 14 to 20 F red rubber, latex, silicone, or polyurethane tube can be used and is premeasured as described for nasoesophageal intubation, to avoid entering the stomach. A mouth gag is placed and an index finger is used to palpate the hyoid apparatus from inside the patient's mouth. Caution should be exercised to palpate dorsally and

caudal to the stylohyoid and epihyoid bones, as close to the cervical esophagus as possible. This will help avoid creating the stoma site rostral to the hyoid apparatus and causing obstruction or interference with epiglottic function. The pulsating carotid artery is palpated and avoided while a 1 cm skin incision is made over the finger that is pushing the pharyngeal wall outwards. The landmarks for the incision include the hyoid apparatus and the bifurcation of the external jugular vein into the maxillary and linguofacial veins. The incision is made caudal to the hyoid in a direction that bisects the angle created by the bifurcation of the external jugular vein. Curved Kelly forceps are used to bluntly dissect soft tissue to create a stoma from the skin incision to the inside of the pharynx in a caudal direction. Blunt dissection will help prevent damage to the external carotid artery, vagosympathetic trunk, and hypoglossal nerve in the dissection field. The flared end of the tube should be cut and grasped with the curved hemostats before inserting the tube into the esophagus by way of the oral cavity and tunneling the cut end of the tube out through the stoma. Alternatively, the tube can be advanced through the tunnel created by blunt dissection and passed down the esophagus. The tube should run straight into the esophagus without kinking to avoid interference with the epiglottis or glottis. The clinician secures the tube by placing adhesive tape in a butterfly configuration around it and suturing the tape to the skin or by placing friction (Chinese finger-tie) sutures. Antibiotic ointment should be applied to a cut gauze sponge that is placed around the tube at the stoma-skin edge. A protective circumferential bandage is used to keep the tube against the patient's neck.

Complications of pharyngostomy tube placement include airway obstruction, aspiration of food, vomiting or reflux, epiglottic entrapment, laryngeal obstruction, recurrent laryngeal nerve injury, tube displacement, chewing of the tube, esophagitis, and infection of the wound site. Large diameter tubes (larger than 24 F) are not recommended due to the increased risk of interference with epiglottic movement or obstruction of the glottis. Displacement of the tube secondary to vomiting or regurgitation necessitates replacement of the tube by opening the animal's mouth and redirecting the tube down the esophagus. If the tube is damaged due to chewing, a new tube may be passed through the old stoma, provided it has had at least 5 days to form.

92.1.3 Esophagostomy Tube Placement

Esophagostomy feeding tubes are easily inserted, and insertion only requires light general anesthesia with isoflurane, or heavy sedation and intubation with a cuffed endotracheal tube. The technique is minimally invasive, and no specialized endoscopic equipment is needed. The dog or cat should be placed in right lateral recumbency, and the left lateral cervical region clipped and aseptically prepared for tube placement. A 14 to 20 F red rubber catheter, (Sovereign Feeding Tube, Sherwood Medical) silicone catheter (Global Veterinary Products) or polyurethane catheter (MILA International) should be premeasured from the midcervical esophagus to the eighth rib and marked with a permanent marker to ensure the distal end of the catheter terminates in the distal esophagus.

Three basic techniques for placement of a midcervical esophagostomy tube have been described:

1. Technique using right-angled forceps (Carmalt, Mixter, Schnidt or Kantrowitz) forceps: The clinician should advance the right-angle forceps into the midcervical esophagus from the oral cavity and use the angle of the jaw and the point of the shoulder for landmarks to help ensure that the tip of the forceps can be palpated externally in the midcervical region. Then the curved tips of the Carmalt forceps should be pushed laterally at the midcervical esophagus, so they can be palpated below the skin. A No. 11 scalpel blade should be used to make a stab incision through the skin only, exposing the subcutaneous tissue and muscle layers of the esophagus. The clinician should be careful to avoid the jugular and maxillofacial veins when selecting the stoma site. The tip of the forceps should be exteriorized from the esophageal lumen through the skin incision, and the advancing forceps should be guided through the esophageal muscle layers; then the clinician should carefully dissect the esophageal mucosa off the tip of the forceps

with a scalpel blade. The tip of the forceps should be used to grasp the distal end of the feeding tube, and the tube should be drawn out of the oral cavity. Next, the clinician should secure the distal end of the feeding tube using the forceps to ensure that the tube remains exteriorized while the proximal end of the tube is pulled out of the animal's mouth. The proximal tip of the feeding tube should be retroflexed and advanced in an aboral direction across the pharynx and down the esophagus, while the external end of the tube is slowly retracted 2 to 4 cm. A wire guide can be used to facilitate pushing the proximal tip of the feeding tube into the esophagus. The exteriorized portion of the tube will be observed to rotate in a cranial direction while the tube moves down the esophagus, indicating correct placement of the tube in the esophagus. Retention sutures (Chinese finger-knot suture) using 3-0 polypropylene are used to secure the distal end of the tube to the skin. An additional method of securing the tube involves passing a heavy suture on a taper needle through the skin next to the tube and into the periosteum of the wing of the atlas.

Antibiotic ointment and gauze dressing is placed at the incision site, and the tube and entrance site is loosely bandaged with conforming gauze wrap. The correct placement of the tube in the mid-to distal esophagus should be confirmed radiographically. It is important to ensure that the tube does not traverse the lower esophageal sphincter, because the tube can cause irritation and predispose the pet to vomiting and gastroesophageal reflux. Feeding can be instituted once the animal has recovered from anesthesia. The tube esophagostomy and skin interphase should be examined at least daily during the first week for evidence of infection or leakage of food or saliva. The stoma site can be kept clean with a topical antiseptic solution (1:100 Betadine solution in 0.9% saline). Once nutritional support is no longer needed, the tube can be easily removed by cutting the Chinese finger-trap anchoring suture and pulling the tube. The wound should be allowed to heal by second intension.

2. Percutaneous feeding tube applicator technique: An alternative tube esophagostomy technique using an (ELD) percutaneous feeding tube applicator or similar device can be used. The applicator is inserted into the midcervical esophagus via the oral cavity. The distal tip is palpated, and an incision is made through the skin and subcutaneous tissue over the tip of the ELD. The trocar is advanced through the esophageal wall and directed through the incision. The distal end of the feeding tube is secured to the eyelet of the trocar with suture material. The ELD device and attached feeding tube are retracted into the esophagus and exteriorized out of the oral cavity. The feeding tube is redirected into the midcervical esophagus after inserting a wire stylet into the distal tip of the feeding tube. The tube is secured to the skin as previously mentioned.

3. Percutaneous needle catheter technique: This method incorporates the use of an esophagostomy introduction tube (Van Noort oesophagostomy tube set, Global Veterinary Products) (Figure 92-3) that is introduced into the midcervical esophageal area. The slot in the distal portion of the tube is palpated, and a peel-away® sheath needle (Global Veterinary Products) is introduced into the distal portion of the tube. The needle is removed from the sheath, and a 10 F catheter is introduced through the sheath to the distal third of the esophagus. The sheath is peeled away and the esophagostomy tube is carefully removed. The feeding tube is secured as described previously. This technique has limitations because the small diameter of the feeding tube (10 F) only allows for the administration of fluids and liquid enteral formulas.

Despite the potential for esophageal scarring and stricture formation, esophageal stricture or a persistent esophagocutaneous fistula has not developed. The most common minor complication is peristomal inflammation, with peristomal abscessation occurring infrequently. Most of the inflammatory reactions are mild and respond to thorough cleansing with topical antibiotics. Other less common complications include vomiting of the tube into the oral cavity.

92.1.4 Gastrostomy Tube Placement

Gastrostomy tube feeding is indicated for long-term (weeks to months) nutritional support of anorectic or dysphagic animals. Gastrostomy feeding tubes are relatively large in diameter (20 to 24 F), allowing administration of blended pet foods and medications. Gastrostomy tube feeding is contraindicated in animals with persistent vomiting, decreased consciousness, or GI obstruction. Caution should be exercised in conditions under which the stomach cannot be apposed to the body wall (severe ascites, adhesions, space-occupying lesions).

Gastrostomy tubes can be placed percutaneously or during laparotomy. Placement is usually accomplished with a percutaneous endoscopic gastrostomy (PEG) technique or a blind percutaneous gastrostomy (BPG) technique. There are a variety of feeding tubes that can be used for gastrostomy feeding including latex, polyurethane, and silicon tubes with French-Pezzer mushroom, balloon, bumper, or silicone dome tips (Figure 92-4). The silicone catheters can be purchased from Global Veterinary, Inc. (New Buffalo, KY) and US Endoscopy (Mentor, OH); polyurethane from MILA International, Inc. (Florence, KY); and latex catheters from BARD Urological Division (Murray Hill, NJ). One can modify the catheters by cutting off and discarding the flared, open end of the catheter and cutting off two 2 cm pieces of tubing (to be used as internal and external flanges) from the same end of the catheter. The end of the catheter opposite the mushroom tip is trimmed to facilitate its introduction into the larger opening of a disposable plastic micropipette. The clinician should make a small stab incision through the center of each flange, and fit one flange over the cut end of the catheter—sliding it down until it rests against the mushroom tip. The other 2 cm piece of tubing will be used as an external flange that lies against the abdominal wall. Cutting the small nipple on the mushroom tip to enhance the flow of food through the tube is *not* recommended. Removing the tip of the mushroom compromises the integrity of the mushroom and hinders percutaneous removal of the tube.

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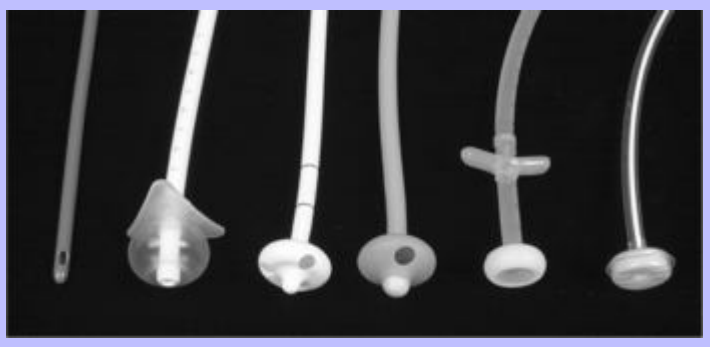
Figure 92-3 Photograph of the esophagostomy tube set, illustrating the esophagostomy introduction tube, 10 gauge, 5.0 cm long needle with Peel-away® sheath needle, and a 10 F silicone catheter.

Figure 92-4 Gastrostomy tubes illustrating the various mate-rials and catheter tips. *Left to right:* French red rubber catheter, silicone balloon catheter, silicone mushroom catheter, latex mushroom catheter, silicone catheter with dome, polyurethane catheter with bumper.



92.1.4.1

Percutaneous Endoscopic Gastrostomy Technique

Endoscopic and blind placement of gastrostomy tubes necessitates brief anesthesia. The animal should be placed in right lateral recumbency so that the stomach tube can be placed through the greater curvature of the stomach and the left body wall. Preparation for both percutaneous procedures is identical and involves a surgical prep of the skin caudal to the left costal arch. The endoscope is introduced into the stomach, and the stomach is carefully inflated until the abdomen is distended but not drum tight. The left body wall is transilluminated with the endoscope to ensure that the spleen is not positioned between the stomach and body wall. An appropriate site for insertion of the tube is determined by endoscopically monitoring digital palpation of the gastric wall. A small incision is made in the skin with a scalpel blade, and an intravenous catheter (16 to 18 G, 1.5 to 2 inches) is stabbed through the body wall into the lumen of the stomach (Figure 92-5, *A*). The stylet is removed and nylon or polyester suture is threaded through the catheter into the lumen of the stomach. The suture material is grasped with the endoscopic biopsy forceps (Figure 92-5, *B*), and the endoscope and forceps are carefully withdrawn through the esophagus and out of the mouth. The suture material is secured to the feeding tube, and gentle traction is applied to the suture material at its point of exit from the abdominal wall (Figure 92-5, *C*). The feeding tube is pulled out through the body wall, allowing the mushroom end to draw the stomach wall against the body wall (Figure 92-5, *D*). The feeding tube is anchored in this position by the external flange placed over the catheter at the skin surface (Figure 92-5, *E*). The endoscope is then reinserted into the stomach to verify the correct placement of the mushroom against the gastric mucosa. If blanching of the mucosa is observed, less tension should be applied to the tube, otherwise ischemic necrosis of the gastric wall may ensue. A plastic clamp is placed over the tube, and the tube is capped with a Y-port connector. A jacket made from stockinette (San Jose Surgical Supply, Inc., San Jose, CA) is fitted to protect the tube (Figure 92-5, *F*).

Complications related to PEG tubes include those associated with placement of the tube (splenic laceration, gastric hemorrhage, and pneumoperitoneum), and delayed complications such as vomiting, aspiration pneumonia, tube extraction, tube migration, and stoma infection. Clinicians can minimize splenic laceration by insufflating and transilluminating the stomach prior to placement of the needle or catheter into the abdominal wall. The authors have recognized a discordant number of large breed dogs that have had major

complications secondary to the stomach "falling off" the silicone dome at the end of the gastrostomy tube. The stoma appeared normal in all dogs, with the unfortunate consequence that several dogs were fed through the gastrostomy tube. This complication occurred despite the placement of an internal flange between the dome and the gastric mucosa. For this reason, it is recommended that all dogs heavier than 30 kg do not have a PEG procedure and instead have a gastrostomy tube placed surgically. Minor complications include pressure necrosis at the stoma site and cellulitis.

92.1.4.2 Blind Percutaneous Gastrostomy Technique

An alternative technique for nonendoscopic and nonsurgical gastrostomy tube placement has been described. The gastrostomy tube placement device can be prepared with a length of vinyl or stainless steel tubing (diameter 1.2 to 2.5 cm) purchased from a hardware store, or an ELD gastrostomy tube applicator (Jorgensen Laboratories, Loveland, Colo.) or gastrostomy tube introduction set (Global Veterinary) can be used. The ELD gastrostomy tube applicator is the only device that uses an internal trocar, whereas the Cook gastrostomy tube introduction set contains a wire that is threaded through an introduction needle. The distal tip of a stainless steel tube can be flared and deflected 45 degrees to the long axis of the tube to help displace the lateral body wall. The lubricated tube is passed through the mouth and into the stomach. The tube is then advanced until the end of the tube displaces the stomach and lateral abdominal wall. Positioning the animal with its head over the edge of the table and lowering the proximal end of the tube will facilitate identifying the tube tip through the body wall. For the Cook gastrostomy introduction set or similarly prepared device, a percutaneous needle is introduced into the lumen of the tube while the assistant firmly holds the distal tip of the tube between two fingers. A skin nick is made over the end of the tube and a 14-gauge over-the-needle catheter advanced into the lumen of the tube. Proper positioning of the catheter is confirmed by moving the hub from side to side and feeling the catheter tip strike the inside of the tube. A guide wire prepared from a banjo string is attached to suture material that is 60 cm longer than the stomach tube. The guide wire is threaded through the catheter, into the tube, and out the mouth of the patient. The attached suture is pulled through the tube and cut from the wire at the mouth. The tube and catheter are removed, and the suture is attached to a gastrostomy tube that is secured in an identical fashion to the PEG tube procedure.

The reported complication rate for BPG is similar to that of PEG; however, the risk of penetrating the spleen, stomach, or omentum is greater when the stomach is not insufflated with air prior to positioning the tube against the lateral abdominal wall. Contraindications to using the "blind" technique include pets with esophageal disease and those that are severely obese (which would preclude accurate palpation of the tube against the abdominal wall). Such animals should have gastrostomy tubes placed surgically.

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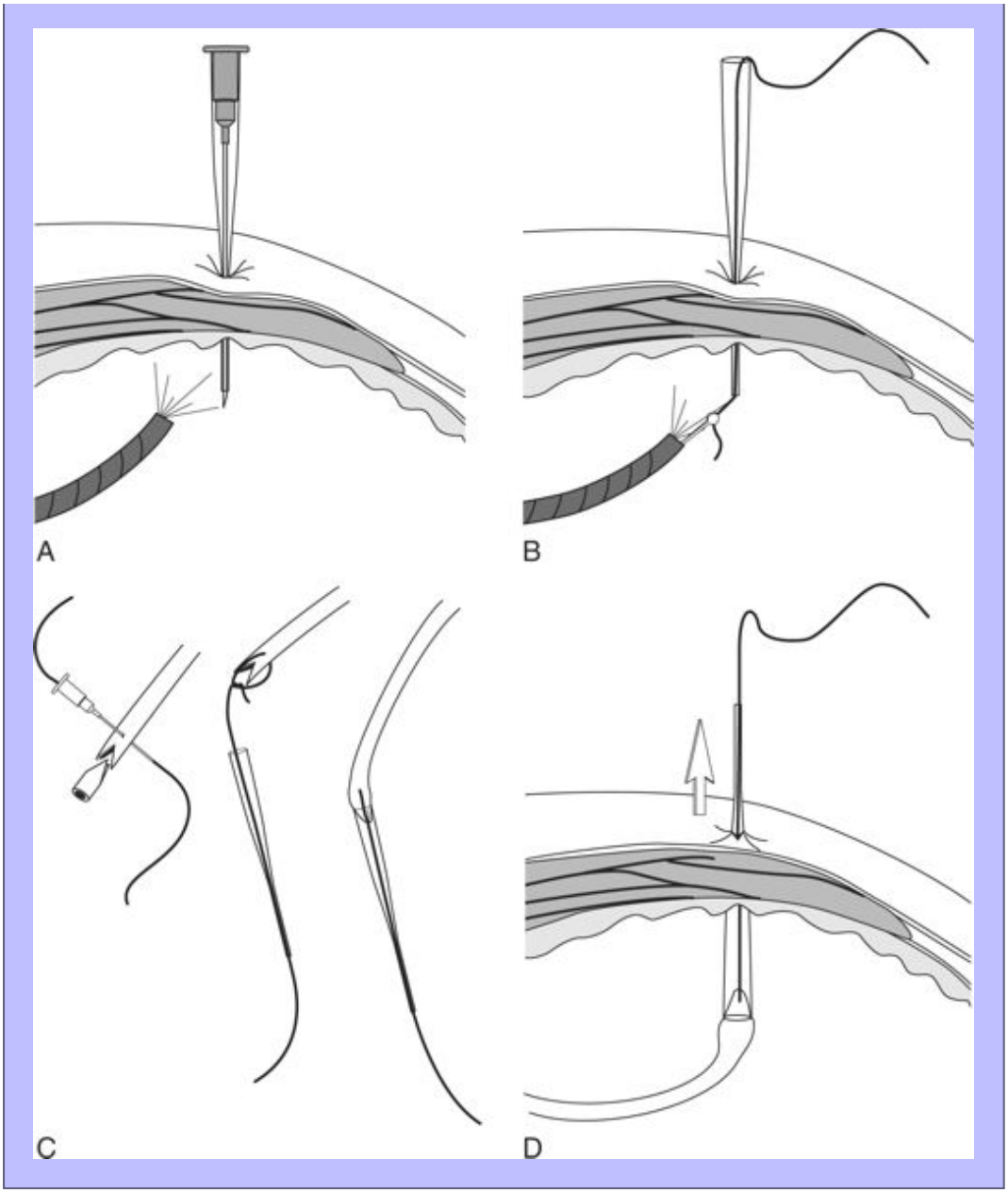
92.1.5 Gastrostomy Tube Removal

For percutaneously placed tubes, it is recommended that the tube be left in place for a minimum of 14 days. Animal's receiving immune-suppressive therapy or those that are severely debilitated may require longer for a peritoneal seal to form. The tube should only be removed when oral food intake is sufficient to meet the pet's caloric requirement. One of two methods of Pezzer tube removal can be applied: The tube can be cut at the body wall and the mushroom tip pushed into the stomach to be passed in the feces. This method is safe in medium to large size dogs, because the mushroom and internal bumper should be easily passed in the stool. Alternatively, a stylet can be inserted into the tube to flatten the mushroom tip, while exerting firm traction on the tube. This method is recommended for cats and small dogs, because the mushroom can cause intestinal obstruction. Removal of the MILA catheter is accomplished by deflating the bumper, which occurs once the Y-port adapter is removed. Catheters with a dome (US Endoscopy) are removed by gentle, but firm traction on the tube. The gastrocutaneous tract should seal with minimal or no leakage within 24 hours.

Figure 92-5 Percutaneous endoscopic gastrostomy (PEG) technique. **A,** With the dog in right lateral recumbency, the endoscope is introduced into the stomach, and the stomach is insufflated with air. The left body wall is transilluminated with the endoscope to ensure that the spleen is not between the stomach and the body wall. A 16 to 18 G sheathed catheter is pierced transabdominally into the insufflated stomach lumen. **B,** The catheter stylet is removed, and nylon suture is advanced through the catheter until it can be grasped with endoscopic retrieval forceps. The nylon suture is pulled out through the mouth while the endoscope is withdrawn. **C,** The suture material is secured to the feeding tube and water-soluble jelly is applied liberally to the catheter sheath and the mushroom tip catheter. **D,** The lubricated catheter is drawn down the esophagus and into the stomach while the assistant applies traction on the suture exiting the abdominal wall. **E,** The catheter is advanced until the mushroom tip rests gently against the gastric mucosa. Endoscopy should be repeated to confirm the correct position of the mushroom tip. An external flange is fitted down the tube against the skin to prevent the tube from slipping into the stomach. **F,** Gastrostomy feeding tube in place with the clamp in the open position. The stockinette jacket is pulled over the gastrostomy tube once feeding is completed.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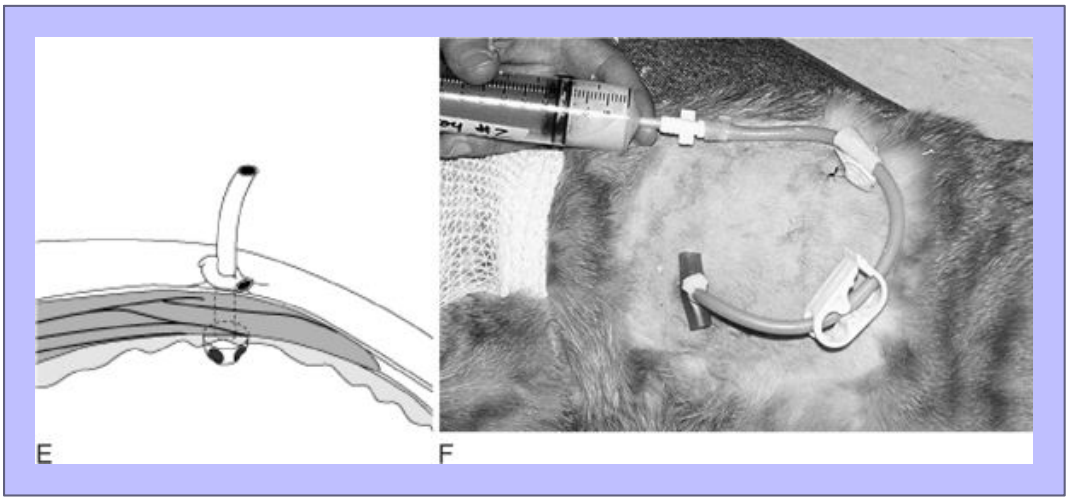

92.1.6 Gastrostomy Tube Replacement

The PEG tube may malfunction or be prematurely removed by the dog or cat, requiring replacement. If the gastrostomy tube is removed within 14 days of placement (before establishment of the gastrocutaneous tract), a PEG procedure should be performed to evaluate the gastric mucosa and verify correct positioning of the replacement gastrostomy tube. If the tube is inadvertently removed once the gastrocutaneous tract is well healed, one can replace the original catheter with a balloon-type catheter (Flexiflo Gastrostomy tube, Ross Laboratories, Columbus, OH) or a low-profile gastrostomy device (LPGD, Bard Interventional Products Division) (Figure 92-6, *A*). Neither of these catheter types require an endoscopic procedure or anesthesia for placement. The gastrostomy "button" is a small, flexible silicone device that has a mushroomlike dome at one end and two small wings at the other end that lie flush with the outer abdominal wall (Figure 92-6, *B*). A one-way antireflux valve prevents reflux of gastric contents through the top of the tube. There are two types of LPGDs: (1) obturated and (2) nonobturated. The obturated device has an enlarged mushroom tip that must be stretched for placement in the stomach by using a special introducer (Figure 92-6, *C*). The nonobturated tube works like a Foley catheter and does not require forceful entry into the gastrostomy stoma. The length of the gastrocutaneous fistula must be precisely determined to guide correct selection of the appropriate "button" shaft length. This is accomplished with a special stoma-measuring device provided with the kit. The main advantages of the LPGD include their durability due to their silicon material, decreased likelihood of inadvertent removal by the pet, and their aesthetically pleasing appearance to the owners.

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92.2 COMPLICATIONS OF ENTERAL FEEDING

92.2.1 Gastric Pressure Necrosis

Gastric pressure necrosis can occur from either the mushroom of the PEG tube or flange eroding the mucus layer of the stomach due to excessive tension being exerted on the PEG tube during placement. In addition, overzealous traction of the PEG tube followed by placement of the external flange flush against the skin of the patient can also cause pressure necrosis characterized by redness, swelling, and moistness of the skin. To reduce the chance that this problem will occur, the clinician should ensure that the PEG tube can be rotated after its placement and leave a 5 mm space between the external flange and the skin.

92.2.2 Feeding Tube Displacement

This is a relatively common problem, particularly with nasoesophageal tubes. Displacement of the tube can lead to aspiration, diarrhea, or in the case of gastrostomy tubes, peritonitis. Gastrostomy tubes should be marked with tape or a marking pen at the level of the skin to help verify the position of the tube. Detachment of the stomach from the abdominal wall with consequent intraperitoneal leakage of gastric contents can occur in large breed dogs, and an internal flange should be placed in these animals to minimize chances of tube dislodgement.

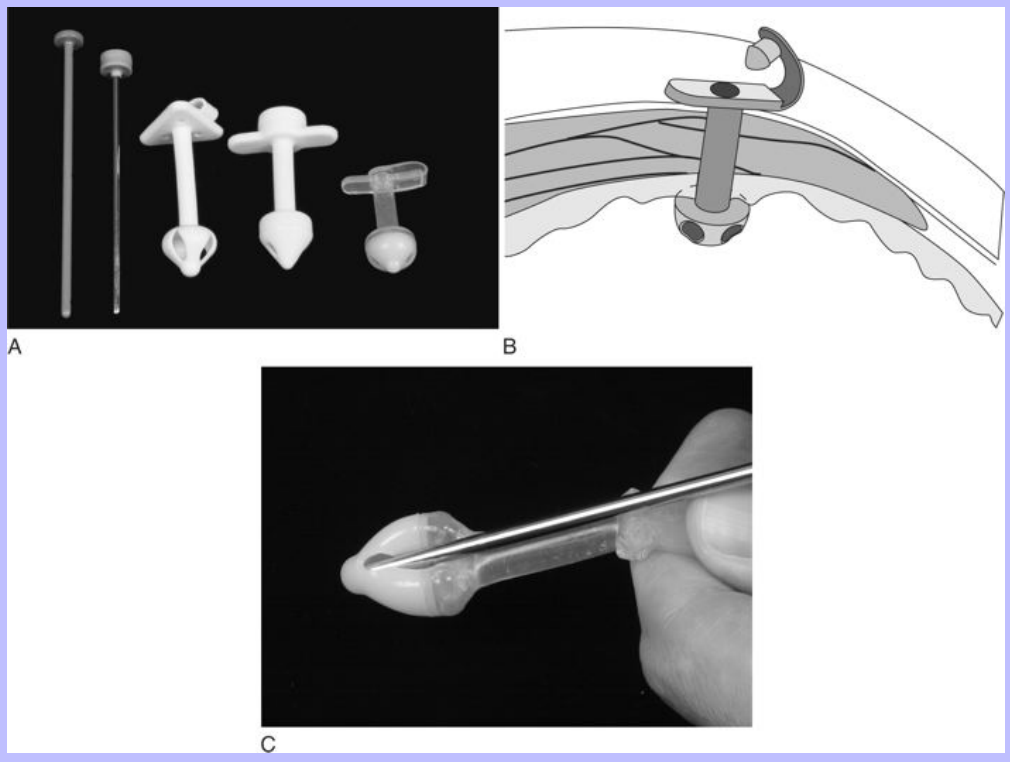
92.2.3 Tube Obstruction

Obstruction of the feeding tube is one of the most common complications of enteral feeding. Most obstructions are secondary to coagulation of formula, although obstruction by tablet fragments, tube kinking, and precipitation of incompatible medications can also result in tube obstruction. Nasoesophageal tubes are prone to obstruction because of their small diameters, and obstruction also occurs up to three times more frequently in patients fed by continuous versus bolus feedings. Sucralfate and antacids have been reported to precipitate with enteral formulas and cause tube obstruction. Several “remedies” have been advocated to relieve tube obstruction. Warm water injected with gentle pressure and suction will relieve most obstructions. For more unyielding obstructions, carbonated water is instilled into the tube and allowed to sit for one hour before applying gentle pressure and suction. Pancreatic enzyme infusions and meat tenderizer have also been advocated to dissolve tube obstructions. On rare occasions, the passage of an angiographic wire down the lumen is needed to unclog the tube. Clinicians can minimize obstructions by flushing the feeding tube with warm water before and after administering medications or enteral feedings. The tube should also be flushed after checking for gastric residuals, because the acid pH will cause the formula to coagulate in the tube. Elixir forms of medication should be used rather than crushed tablet forms whenever possible. Tablets should be crushed and dissolved in water prior to administration through the feeding tube, if no alternative form of medication is available.

92.2.4 Leakage Through Ostomy Sites

Mild leakage at the stoma site can occur for the first few days after placement of the feeding tube. Persistent leakage may indicate tube dysfunction, peristomal infection, or a stoma site greater than necessary for the tube. Signs of inflammation with or without discharge or fever may indicate infection of the stoma site. This must be differentiated from fasciitis. A simple wound infection can usually be treated locally with dilute Betadine solution, topical Betadine antibacterial ointments, and more frequent dressing changes. Systemically administered antibiotics are usually reserved for animals with systemic signs of infection.

Figure 92-6 **A,** Low-profile gastrostomy devices and obturators used for stretching the dome-shaped tip of the device. *Left to right:* The Ross Laboratories Stomate low-profile device, the Cook low-profile device, and the Bard "Button"® low-profile device. **B,** Low-profile gastrostomy device with small outer wings of the device lying flush against the skin of the abdominal wall. For feedings, the small plastic plug is removed and a feeding adapter is connected to a syringe. **C,** Correct technique for stretching the dome-shaped tip of the low profile gastrostomy device with an obturator. The dome should not be stretched by passing the obturator through the lumen of the device as it will compromise the integrity of the anti-reflux valve located adjacent to the dome.



92.2.5 Aspiration

Pulmonary aspiration is a common complication of enteral feeding, although the actual incidence of this complication is difficult to determine due to the lack of consistency in how aspiration is defined. Risk factors for aspiration include impaired mental status, neurologic injury, absence of a cough or gag reflex, mechanical ventilation, and previous aspiration pneumonia. The source of the aspirated material should be identified

because withholding gastrostomy feedings or placing a jejunostomy feeding tube will have no benefit if the pet aspirated oropharyngeal secretions. Although controversial, most authors agree that postpyloric feeding reduces the risk of aspiration. In addition, the use of continuous feedings has been shown to induce less gastroesophageal reflux than bolus feedings.

92.2.6 Diarrhea

Diarrhea is the most common complication associated with tube feeding in humans and animals. The incidence range is from 2.3% to 63%. The clinical implications of enteral feeding-related diarrhea are significant. Severe diarrhea leads to fluid, electrolyte, and nutrient loss, and it can cause considerable distress. Diarrhea in tube-fed individuals occurs due to multiple factors, including hypoalbuminemia, hyperosmolar or high-fat diets, infected diets, and concomitant antibiotic therapy. The incidence of diarrhea in enterally fed patients taking antibiotics far exceeds the incidence in those normally fed taking the same antibiotics. Antibiotic-associated diarrhea may arise from overgrowth of enterobacteria *(Klebsiella, Proteus, Pseudomonas)* or from proliferation of *Clostridium difficile*. Antibiotic administration is also associated with decreased concentrations of fecal short-chain fatty acids, occurring as a result of decreased colonic carbohydrate fermentation.

93 CHAPTER • 93 Gastric Lavage

Roger Gfeller

Gastric lavage is widely used as a gastrointestinal (GI) decontamination technique in small animals poisoned by ingestion of toxins. Removal of the stomach contents by gastric intubation and irrigation can be performed rapidly by trained staff members and does not require a cooperative patient. However, experts are beginning to question the value of gastric lavage; studies fail to confirm its value as a practical clinical procedure. Even when gastric lavage can be performed within minutes of ingestion, recovery of the toxin is limited. If the procedure is not completed before 1 hour has passed, recovery of many toxins is less than 15%. In small animal veterinary medicine, it is rare that gastric lavage would be completed within this period.

The volume of lavage fluid has also become a focus of attention. Using previously recommended volumes often results in gastric distention and complications (including fluid and electrolyte imbalances). Hypernatremia has been reported when large volumes of saline were used, whereas hyponatremia has been reported when water was the lavage solution. Further, one study found that when the volume administered resulted in gastric distention, as much as 25% of the lavage fluid passed into the small intestine carrying the ingested toxin with it. This knowledge has led experts to recommend two changes in gastric lavage protocols.

First, because a possibility exists that lavage solution may carry toxin into the duodenum, experts have begun to advise administration of activated charcoal before initiating the lavage procedure. In at least one study, administration of activated charcoal before (and after) gastric lavage resulted in reduced plasma levels of the toxin. Second, experts now agree that more attention should be paid to the degree of gastric distension allowed during lavage. It is advisable to have one staff member responsible for monitoring the amount of distension. Although visual observation of the abdomen is acceptable, it is better if one repeatedly palpates the stomach during lavage.

Additional complications of gastric lavage include aspiration pneumonia; traumatic injury of the oropharynx, esophagus, or stomach; hypoxemia; hypercapnia; and hypothermia. Gastric lavage is contraindicated in patients with an unprotected airway. Ingestion of caustic or corrosive toxins (e.g., acids, alkalis) or toxins with a high risk of aspiration (e.g., hydrocarbons) is also a contraindication to gastric lavage. A relative contraindication to gastric lavage is ingestion of a foreign body that could cause physical damage to the alimentary tract.

Gastric lavage has risks, it is messy, and it may not decontaminate the GI tract as efficiently as once thought. Before the veterinary team commits to this procedure, a scout radiograph of the stomach can be obtained. If the radiograph reveals an empty stomach, little evidence suggests that gastric lavage will decontaminate the patient more than administration of activated charcoal alone.

93.1 PROCEDURE

The patient must be anesthetized and intubated with a cuffed endotracheal tube (See Box 93-1). The cuff should be inflated just enough to create a seal between the tube and the trachea. The pop-off valve should be closed, and the rebreathing bag squeezed while filling the cuff. The clinician should listen for air escaping around the cuff and stop filling the cuff immediately when no further leakage of air occurs. The anesthetist should be able to inflate the lungs to a pressure of 15 to 20 cm of water without air leaking between the trachea and the endotracheal tube. The patient is maintained on an appropriate gas or injectable anesthetic. If injectable anesthesia is used instead of gaseous agents, the patient should be maintained on oxygen. If the patient is at risk for hypoventilation, the staff should consider ventilating the patient.

The clinician should prepare two tubes for use. The first tube is the *egress* tube. The egress tube should be as large as possible to allow rapid and complete removal of stomach contents. It should have additional side fenestrations in the end that will be inserted into the stomach. The tube should be marked with a piece of tape at a distance equal to the distance from the incisors to the xiphoid. The second tube is the *ingress* tube, through which activated charcoal and lavage solution will be instilled into the stomach. This tube should be smaller in diameter to allow the egress tube to be as large as possible. The distance from the incisors to the last rib should be measured and marked on the ingress tube with a piece of tape.

The patient is secured in right lateral recumbency. The patient's head should be positioned lower than the chest. The clinician should apply an appropriate lubricant (e.g., KY Lubricating Jelly, Johnson & Johnson, Arlington, Tex.) and insert the egress tube into the esophagus. The tube should be advanced into the stomach but not farther than the mark established previously. As much of the stomach contents as possible should be allowed to drain from the tube. If nothing drains from the stomach, the clinician should confirm that the tube is in the stomach. This can be done by several methods. In small animals, direct observation of the tube entering the esophagus and advancement of the tube to the measured distance is usually sufficient. Alternatively, one can push air through the tube while listening over the stomach. A gurgling sound can be heard in the stomach if the tube is properly positioned. A radiograph may be rarely required for confirmation.

If nothing comes from the egress tube after it has been confirmed to be in the stomach, the clinician should lubricate and insert the ingress tube. After confirming the ingress is in the stomach, the manufacturer's recommended dose of activated charcoal should be instilled. The egress tube should be clamped while the activated charcoal is infused so that the charcoal will be retained in the stomach long enough to mix with the contents. Gentle external agitation of the stomach will help the charcoal to mix with stomach contents. The egress tube should be opened to begin evacuation of the stomach contents.

Whether water or saline is to be used as the lavage solution, it should be warmed. Warming the lavage solution will slow gastric emptying and help prevent patient hypothermia. The clinician should attach the stomach pump to the ingress tube, begin to infuse the lavage solution slowly, and monitor gastric distension. Gentle external agitation of the stomach will help mix and remove stomach contents. If the egress tube does not allow free flow of fluid from the stomach, the tube should be withdrawn slowly. If flow begins, the lavage should continue. If no flow can be established, a small amount of water or air should be infused through the large bore tube to dislodge material. If flow is still not established, the clinician should remove the tube and check for a plug, then gently reinsert the tube to establish flow.

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93.1.1

Box • 93-1 Materials Needed for Gastric Lavage

1. Large-bore stomach tube with additional fenestrations in one end (egress tube)
2. Small-bore stomach tube (ingress tube)
3. Lubricant
4. Stomach pump or funnel
5. Activated charcoal
6. Lavage solution (water or saline)
7. Container appropriate for laboratory submission of gastric contents, if desired

8. Disposal area for large quantities of lavage solution

The procedure should be continued until the effluent is clear. In some cases, this may take large volumes of lavage solution and a great deal of time. *At no time should the patient's stomach be distended.* The patient should be lavaged in both left and right lateral recumbency. In some cases it is helpful to move the egress tube gently back and forth to help mix and dislodge stomach contents. If this is necessary, it must be done gently to avoid trauma to the pharynx, esophagus, and stomach.

When the stomach is emptied, the clinician should crimp or clamp the egress tube and remove it. He or she should ensure that the endotracheal tube is still properly placed and sealed and instill activated charcoal through the remaining tube. Then the ingress tube should be crimped or clamped and removed.

To minimize the chances of aspiration, the patient should be recovered with the endotracheal tube in place and the cuff inflated until the swallowing reflex returns. The oropharynx should be carefully checked for fluid, activated charcoal, or stomach contents and suctioned clean before the endotracheal tube is removed.

94 CHAPTER • 94 Transcervical Catheterization in the Bitch

Autumn P. Davidson

Bruce E. Eilts

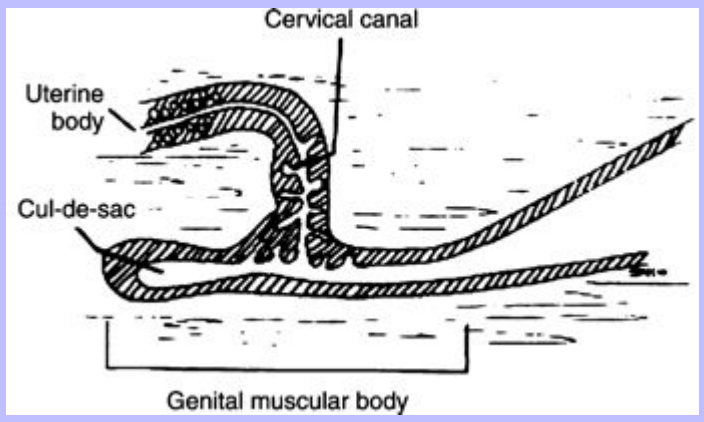
The anatomy of the vaginal vault and cervix in the bitch has hampered access to the canine uterus. Historically, both intrauterine diagnostic sampling (for endometrial biopsy, cytology, and culture) and intrauterine insemination have required an invasive procedure (laparotomy or laparoscopy) in the bitch. In addition to an invasive approach, laparotomy requires general anesthesia, factors some clinicians and breeder clients find objectionable for an elective procedure such as artificial insemination (Figure 94-1). A laparoscopic approach to the canine uterus has been used infrequently, especially in the practice setting, because of its invasive nature and because it requires special equipment, expertise, and anesthesia. Cryopreservation and subsequent thawing diminish semen quality, necessitating special insemination technology. The process and resultant quality of canine cryopreservation have improved with time; however, insemination techniques remained suboptimal until transcervical intrauterine access was developed.

94.1 ANATOMY

The vagina of the bitch is relatively long compared with other domestic animals; the total length from the cervix to the vulva (including the vestibule) has been reported to be 10 to 14 cm in an 11 kg bitch. The canine cervix is not accessible by digital palpation per vaginum, nor can it be visualized with an ordinary vaginal speculum or otoscope. Consequently, equipment for visualizing and approaching the canine cervix must be long (e.g., up to 29 cm for larger breeds). In addition, the presence of vaginal mucosal folds and the position of the cervix in the bitch require the use of rigid equipment to access the cervix.

Figure 94-1 Injection of thawed semen into the lumen of the uterine horn in a bitch during laparotomy.

Figure 94-2 Graphic representation of the canine vagina, cervix, and paracervix.



The *paracervix,* the most cranial portion of the vagina, surrounds the cervix and is dominated dorsally by a well-defined mucosal ridge, the *dorsal median fold (DMF)*. Cranially, the paracervical region ends in the *fornix,* a dead-end space cranio-ventral to the vaginal portion of the cervix that appears as a blind pocket when viewed endoscopically. The DMF extends from just distal to the vaginal portion of the cervix to the mid-vaginal region. It narrows the paracervix, necessitating the use of smaller diameter equipment to access the cervical area.

The DMF forms a distinct caudal tubercle where it ends in the mid-vagina. The cervix is approximately 2.5 cm cranial to the caudal tubercle of the DMF. The canine cervix is difficult to access blindly. It lies diagonally across the uterovaginal junction, with the canal of the cervix directed craniodorsally from the vagina to the uterus (Figure 94-2). The vaginal portion of the cervix appears as a large tubercle when viewed endoscopically. The internal (uterine) os of the cervical canal faces almost directly dorsally, whereas the external (vaginal) os is directed toward the ventral vaginal floor. The vaginal os is often located ventrally or laterally in the cervical tubercle, in the center of a rosette of distinct mucosal furrows. The cervical canal varies in diameter with the stage of the estrous cycle and parity; nonestrual and maiden bitches are expected to have a narrower cervical lumen. The actual appearance and general orientation of the vaginal cervix can vary from day to day during the estrous cycle.

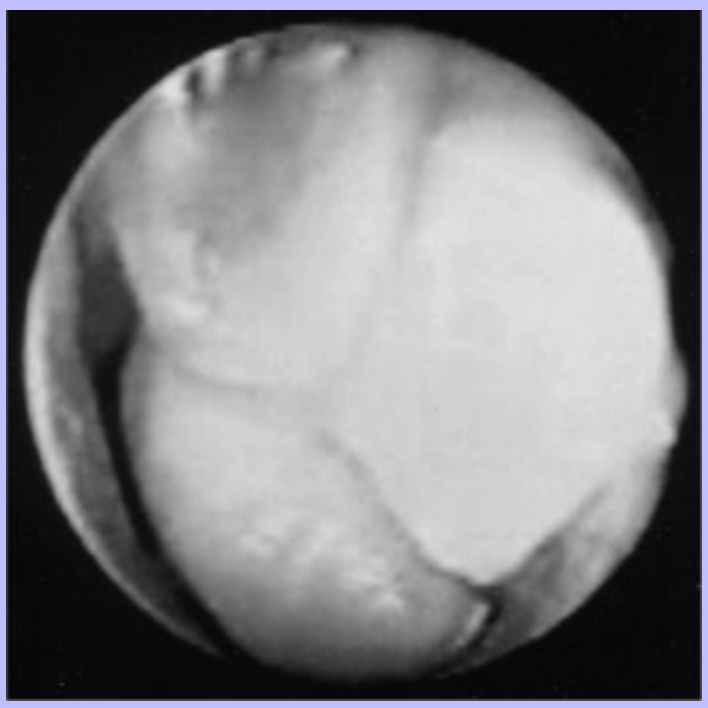
The mid-vaginal region is characterized by a somewhat narrowed, crescentlike lumen. When viewed through a speculum, the caudal tubercle and narrowed middle vaginal lumen give the misleading appearance of tissue with an opening; this is the *false cervix* (Figure 94-3). When rigid insemination pipettes are introduced blindly into this area, often some resistance is felt, followed by advancement; this may lead some clinicians to believe they have accomplished an intrauterine insemination. In reality, insemination into the cranial vagina is more likely, often into the paracervical area.

94.2 EQUIPMENT AND METHODOLOGY

Endoscopically guided transcervical catheterization requires the use of a rigid cystourethroscope,* the components of which are a 3.5 mm forward oblique telescope with 30-degree viewing angle; a 22 French (22 F) protective sheath with two Luer-Lok adapters and an obterator; a telescope bridge with one 10F instrument channel; and a cold light source (Figure 94-4). The working length of the scope is 29 cm. The 30-degree angle is essential for visualization of the dorsally oriented cervix. A video camera can be attached to the endoscope, permitting enlarged imaging of the procedure. Video-endoscopy is preferred because it also allows the audience (e.g., the client) to

watch the entire insemination procedure. Unlike with gastrointestinal endoscopy, electronic air pumps for insufflation and suction are not generally necessary. Adequate air insufflation or suction can be achieved, if needed, by connecting intravenous tubing and a syringe with a three-way stopcock to one of the working channels; this arrangement is sometimes useful for insufflation for routine vaginoscopy in a nonestrous bitch and occasionally for suctioning of copious estrual fluid to improve visualization of the vaginal lumen.

Figure 94-3 Endoscopic appearance of the false cervix.



Transcervical catheterization is best accomplished with the bitch standing under light restraint and with gentle sling support of the abdomen to inhibit sitting (Figure 94-5). The operator should work from a sitting position, with the arms raised to the level of the vulva. An adjustable chair can facilitate operator comfort. Bitches tend to tolerate transcervical catheterization well, especially during estrus. With proper restraint and table setup, the procedure can be accomplished by one operator. However, the participation of the breeder client for restraint and observation generally is rewarding.

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Figure 94-4 Rigid cystourethroscope: *From left,* bridge, sheath, telescope, and light source/cable.

Figure 94-5 Bitch restrained lightly for transcervical endoscopy.

An 8 F urinary catheter is an appropriate size for most bitches for cervical catheterization, although a 6 F catheter sometimes is required for small or maiden bitches. The largest catheter accommodated offers the best rigidity for manipulation through the cervix. A smaller catheter can be placed inside a catheter if increased rigidity is required. Routine endoscopic biopsy and (guarded) culture instruments can be used for intrauterine sample acquisition.

Lubrication of the endoscope is seldom necessary. If a lubricant is used, it should be nonspermicidal and should be applied to the midportion of the sheath. Care must be taken to avoid contact with the lens, which would obscure visibility.

The endoscope is introduced through the vulva along the dorsal commissure, through the vestibule, over the brim of the pelvis, and into the vagina in a dorsal direction. To avoid the clitoral fossa and urethral orifice (Figure 94-6), the end of the endoscope must be directed dorsally. It is surprisingly easy to enter the urethra, which can be differentiated from the vagina by the characteristic smoother, more vascular appearance of the mucosa. The scope is then advanced between the vaginal folds by observing and following the direction of the vaginal lumen. During estrus, the vaginal lumen is cavernous in appearance until the false cervix is approached. Here the caudal tubercle of the DMF is commonly seen as a prominent landmark. Following the DMF facilitates passage into the cranial vagina. The vaginal portion of the cervix appears as a distinct tubercle with a cobblestone appearance due to a rosette of mucosal furrows converging at the os (Figure 94-7). The false cervix, by comparison, is smooth and has a single horizontal fissure. The actual cervical os sometimes can be identified by serosanguineous to hemorrhagic fluid of uterine origin flowing from the cervical canal.

Figure 94-6 Directing the scope dorsally when entering the vestibule avoids entry into the urethra, facilitating passage into the vaginal lumen.

The vaginal cervical os can be difficult to visualize, because it tends to be located ventrally or laterally on the cervical tubercle. The scope can be used to manipulate the somewhat moveable cervix into a position that permits better visualization of the os. If a large amount of estrual fluid impedes visualization of the cranial vagina, removal of the scope and having the bitch sit for a few moments can be helpful. The tip of the polypropylene catheter or

endoscopic instrument is advanced into the cervical os by simultaneous manipulation of the cervix using the endoscope and catheter (Figure 94-8). The rigidity of the endoscope permits manipulation of the cervical tubercle to access the os and start insertion of the catheter. If access to the cervical os is difficult because of its position, bending the tip of the polypropylene catheter beforehand may be helpful.

Figure 94-7 Catheterization of the vaginal cervical os, showing the rosette appearance of the cervix.

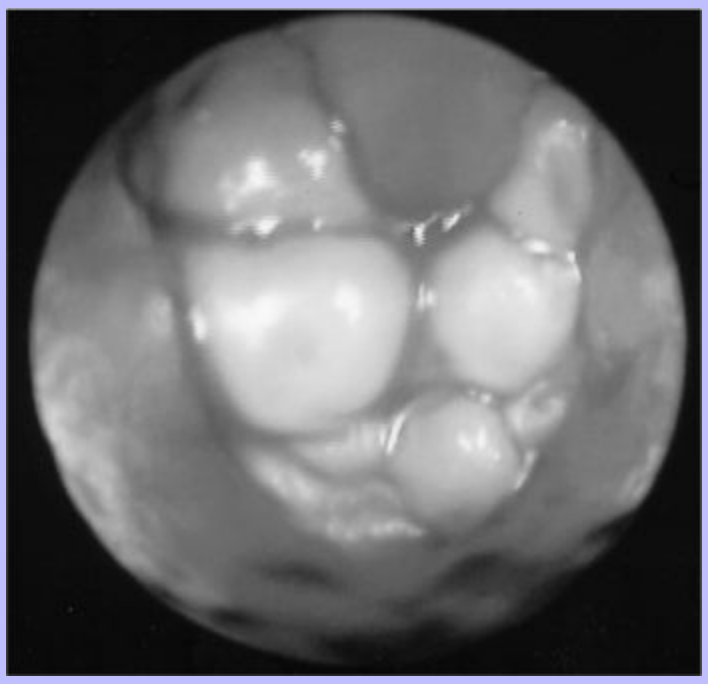

Figure 94-8 Passage of the catheter into the uterine lumen is accomplished by having one hand on the cystourethroscope and the other on the catheter.

After insertion of the tip of the catheter, the viewing end of the scope should be dropped significantly to align the catheter parallel to the direction of the cervical canal. Once the scope position is parallel to the cervical canal, the catheter can be steadily advanced through the cervix with a twirling motion. For intrauterine insemination, the catheter is passed in as far as possible without meeting resistance. The uterine lumen of the average-sized bitch in estrus can accommodate approximately 2 mL of semen, and semen has been shown to distribute throughout both horns even when inseminated into only one. Minimal backflow of semen occurs with proper catheter placement. In the event of semen backflow, the insemination should be stopped and the catheter repositioned cranially or caudally. Minimizing the amount of air introduced into the uterine lumen before semen reduces backflow. A small amount of air (1 to 2 mL) is used to flush all the semen from the catheter into the uterus (Figure 94-9). For intrauterine diagnostics, culture and biopsy instruments are similarly advanced until contact is made with the uterine mucosa. Saline can be infused in and out of the uterine lumen through a polypropylene catheter for cytologic specimen acquisition.

The ease of transcervical catheterization can be recorded for each bitch (1 = very easy, less than 5 minutes; 5 = not achievable). Rarely, access to the cervical canal cannot be achieved. A repeat attempt should be made in 24 hours, because the morphology of the cervix changes under hormonal influence. For this reason, frozen semen should not be thawed until successful catheterization of the cervix has been accomplished. The practitioner and client should

agree on a plan for vaginal or alternate intrauterine insemination beforehand, in the rare event that catheterization cannot be accomplished by the end of the bitch's fertile window. Repeat inseminations may provide better semen availability during the fertile period of the estrous cycle and may improve conception and litter size. The minimal inseminant dose in the dog has not been established.

Figure 94-9 Injection of semen through the catheter; afterward, a small amount of air is injected to clear all fluid from the catheter lumen.

Concerns about the introduction of vaginal flora into the uterine lumen through transcervical catheterization have not been realized. Normal vaginal flora can be found transiently in the uterus during proestrus and estrus, and vaginal flora is known to be introduced into the uterine lumen with natural breeding with no impact on fertility.

Unless rigid endoscopy is already a part of their practice, clinicians must make a substantial investment in equipment for video-endoscopic transcervical catheterization. However, the investment is soon returned, because the transcervical approach is popular with breeder clients who prefer to avoid surgery and anesthesia for intrauterine inseminations. Additional use of the equipment for diagnostic procedures, such as endometrial biopsy and intrauterine culture and cytology, may enhance its value.

Maintenance of the equipment is minimal; a 10-minute soaking of the immersible parts in 0.2% chlorhexiderm in solution, and through rinsing with distilled water followed by air drying, is optional. Techniques for sterilization are described by the manufacturer. The use of stronger disinfectants raises concern because of their spermicidal potential. Sterility does not appear to be necessary, because the vagina harbors normal flora.

Published pregnancy results for endoscopic insemination are not abundant, but some reported conception rates have been 100% when breeding twice with 200×10^6 sperm/breeding; 85% using as few as 50×10^6 sperm/breeding; and 57% using a total of 452×10^6 sperm in 2.4 breedings/cycle. The wide acceptance of frozen insemination by practitioners implies acceptable conception rates in field situations. As with all reproductive procedures, success is greatly influenced by the dogs' inherent fertility, by the timing of ovulation in the bitch, and by the quality of the semen. Collaborative multicenter studies to determine the minimal inseminant dose for

conception in the bitch, as well as the utility of intrauterine diagnostic and therapeutic efforts, will be facilitated by the endoscopic transcervical technique.

* Storz Extended Length Cysto-urethroscope: Hookins Telescope, 30 degrees 325 B, 3.5 mm (width); 36.5 cm (length); sheath, 027KL; bridge, 0278NL. Karl Storz Veterinary Endoscopy, Galeta, Calif.

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95 CHAPTER • 95 Laparoscopy

Keith Richter

95.1 INTRODUCTION

The use of laparoscopy for diagnostic and therapeutic purposes has increased tremendously in human medicine during the last 10 years. This acceptance of laparoscopy stems from technologic advances in equipment and impressive results achieved with this noninvasive modality. Though many procedures performed in human beings will have little appli-cability in veterinary medicine, many of the procedures will gain acceptance due to their ease, effectiveness, and lack of morbidity.

95.2 EQUIPMENT

Light is transmitted from a remote light source via a fiber-optic light cable to the rigid fiber-optic laparoscope (telescope). Size and viewing angles of laparoscopes vary. A forward-viewing (0 degrees), 5.0 to 10 mm outer diameter, 35 cm long scope is preferred. Smaller scopes have a smaller image with less field of view. In addition, a greater light intensity is needed for smaller scopes. A 6.5 mm scope is suitable for examining any dog or cat. Scopes are available in various degrees of angulation of view, including zero degree (direct forward viewing) up to 70 degree. The zero-degree angle is easier to use and generally preferred for most procedures. A 30-degree angle scope can be used to view structures to the side of the tip, and through rotation, to expand the field of view. Angled scopes are more difficult for inexperienced operators. Most scopes have no biopsy channel. Operating scopes have a 5 or 6 mm channel, with an eyepiece extending from the proximal end. These scopes allow introduction of instruments through the same puncture as the scope. The disadvantage of operating scopes is the limited ability to manipulate instruments passing through the channel. Usually the accessory or secondary puncture technique is preferred.

Video capabilities can be achieved with a handheld charged coupling device (CCD) video camera mounted on the eyepiece. These cameras have high resolution, magnify images 5 to 15 times, and provide a clear image. Three-chip cameras are superior to one-chip cameras in terms of clarity, light sensitivity, and color. The use of video is essential for operative laparoscopy. A bright light source (usually 150 to 300 watts) is required to adequately illuminate the abdomen.

To visualize abdominal structures, a pneumoperitoneum must be created to lift the abdominal wall away from the viscera. This is accomplished by insufflating gas through tubing attached to a Veress needle. The latter has a spring-loaded blunt inner portion and an outer cannula with a sharp point. The sharp point is used to penetrate the abdominal wall; then the inner blunt portion is protruded past the sharp point and left in that position to avoid traumatizing abdominal viscera. Gas can then be continually insufflated as needed throughout the procedure.

Three gasses can be used: carbon dioxide (CO_2), nitrous oxide (N_2O), or room air. Carbon dioxide is recommended because it has the advantage of being rapidly absorbed, and thus the risk for air embolism is minimized. The latter is a reported complication of laparoscopy using room air (the gas absorbed most slowly). The disadvantage of CO_2 is that it is slightly more irritating to the peritoneal surface and therefore requires a slightly higher plane of anesthesia. Nitrous oxide is intermediate in its rate of absorption. Gas is infused with an automatic insufflator. These devices regulate flow rate and intra-abdominal pressure. Ideally, intra-abdominal pressure should not exceed 15 mm Hg. Excessive pressure decreases venous return to the heart and causes decreased ability to ventilate.

The laparoscope is introduced into the abdomen with the use of a trocar/cannula assembly. The cannula is a metal or hard plastic sleeve with a one-way valve that permits passage of instruments (such as the trocar and laparoscope) and prevents the escape of gas. The trocar is a sharp-pointed stylet that is used to penetrate the abdominal wall. It is then removed leaving the cannula in place so that the laparoscope can then be introduced. Accessory puncture sites are made for introduction of additional trocar/cannula assemblies. This allows the introduction of blunt metal probes, suction tips, cautery instruments, grasping forceps, "spoon," or "clamshell" style biopsy forceps, and a wide variety of surgical instruments. These instruments are elongated, narrower versions of standard surgical instruments. The use of stapling equipment has enabled surgeons to perform procedures such as vessel ligation and bowel resection.

95.3 TECHNIQUE

It is preferred to perform laparoscopy with the animal under general anesthesia. The position of the dog or cat and location of the various puncture sites will depend on the procedure and organ being examined. Because the liver is the most common organ examined and biopsied, this procedure will be described in detail.

95.4 LAPAROSCOPY-GUIDED LIVER BIOPSY

The main advantage of laparoscopy-guided biopsy is the ability to obtain large biopsy samples and to visualize the liver, biliary tree, and other abdominal organs. With experience, the gallbladder can be examined, palpated with a blunt probe, and the bile duct traced to its entry into the duodenum. In this manner it can be determined whether a common bile duct or cystic duct obstruction exists. In addition, because focal lesions of the liver can be directly visualized, an appropriate biopsy site can be selected while avoiding other intrahepatic structures (gallbladder and portal vessels). Hemorrhage can be observed and, when excessive, controlled with direct compression with a blunt probe over the biopsy site. Alternatively, electrocautery or application of a hemostatic material (Gel-Foam®) can be used to control hemorrhage. Compared with laparotomy, much less anesthetic time exists. A complete laparoscopic examination can be completed and multiple hepatic biopsies obtained in 10 to 15 minutes. Because only a 1.0 cm incision is made, less risk exists for wound dehiscence.

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The animal is placed in left dorsal oblique recumbency at a 45-degree angle. This position allows visualization of both sides of the liver, gallbladder, bile duct, pancreas, duodenum, and much of the abdominal viscera, and avoids the falciform ligament (which may be encountered with a midline approach). The puncture sites should be surgically prepared and draped. The Veress needle (for insufflation) is inserted through a small incision (using a No. 11 blade) on the midline near the umbilicus. Prior to insufflation, the Veress needle is aspirated to confirm that no viscus has been entered. Saline (6 to 8 cc) is then infused to ensure free flow into the abdominal cavity. The abdomen is then insufflated with gas to an appropriate pressure. This amount can be determined by a pressure gauge on an automatic insufflator (usually 10 to 15 mm Hg) or when the abdominal wall is tympanic to the touch. Overdistension should be avoided so as not to decrease venous return or cause impairment in ventilation. Once the desired degree of pneumoperitoneum is reached, a 1.0 cm skin incision is made on the right side between the last rib and the flank. The incision is adjusted in a cranial direction for larger animals, in a caudal direction for smaller animals, and should take into account the size of the liver. The trocar and cannula assembly is then "popped" into the abdominal cavity with a twisting motion. Grasping the cannula ~3 cm from the tip with the free hand will prevent inadvertent insertion of the assembly too far into the abdomen. The trocar is removed and laparoscope inserted into the abdominal cavity through the cannula. The remote light source is connected to the laparoscope with a fiber-optic cable and the liver examined. If a video camera is available, this should be placed on the eyepiece of the laparoscope. A secondary puncture site is made to the left of midline at the level of the umbilicus. Through this site, a second cannula can be introduced so that a blunt probe can be used to palpate the liver and

gallbladder. The probe should also be used to lift up each lobe of the liver to examine the dorsal surface and to get the omentum out of the way so the bile duct can be traced to its entry into the duodenum. The pancreas should also be examined.

Once the abdomen has been examined, a suitable place on the liver is selected for a biopsy site. The author prefers using a laparoscopic spoon or clamshell type of biopsy instrument. This can be placed through the same accessory cannula as the blunt probe, thus avoiding an additional puncture site. These types of instruments result in less hemorrhage than biopsy needles. Repeated twisting of the shaft or retracting the closed jaws into the cannula will prevent ripping of liver tissue and result in less bleeding. If a laparoscopic biopsy instrument is not available, an automated needle biopsy instrument can be used to obtain hepatic tissue. This is inserted into the abdominal cavity just caudal to the xiphoid cartilage and can be directly visualized to enter the liver. It is then operated in the standard manner under direct visualization to obtain hepatic tissue. The number of biopsies obtained depends on the risk of bleeding and the anticipated need of adequate tissue. Multiple samples from various areas of the liver are recommended (observing for hemorrhage after each sample). If excessive bleeding occurs, the blunt metal probe is used to put direct compression over the biopsy site. Suction can also be applied to clear the field if bleeding cannot be adequately assessed. If bleeding is not controlled, an electrocautery probe can be used to stop the bleeding. Alternatively, laparoscopic forceps can be used to place a piece of a hemostatic material (Gel-Foam®) on the bleeding biopsy site. Once the biopsy samples are obtained, the clinician completes the procedure by removing all instruments, evacuating all the gas through opened cannula valves, and suturing the puncture sites.

Potential complications of the procedure include those related to a general anesthetic, excessive bleeding, inadvertent organ damage during instrument introduction, overdistention of the abdomen with gas, air embolism, and a tension pneumothorax if the diaphragm is inadvertently punctured (as abdominal gas enters the thoracic cavity). Meticulous attention to details of technique together with experience will minimize the probability of these complications. Postoperative pain should be anticipated, and this should be addressed with appropriate analgesics.

95.5 OTHER USES OF DIAGNOSTIC LAPAROSCOPY

Laparoscopy can be used to diagnose and stage abdominal tumors through direct visual assessment and allowing directed biopsies. Laparoscopy can detect lesions less than 1 mm in diameter on the peritoneal surface. Laparoscopy can be also used to examine and biopsy the pancreas, an organ that can be difficult to image with radiographs and ultrasound. Other organs that can be biopsied via laparoscopy include the kidney, spleen, prostate, intestine, mesentery, omentum, and the parietal peritoneum. Laparoscopy can guide aspiration of the gallbladder, loculated ascites, and abdominal cysts or abscesses. Laparoscopy can guide transabdominal intrauterine artificial insemination. Laparoscopy can also be used in evaluation of abdominal trauma. Such injuries as hepatic and splenic laceration, diaphragmatic hernia, bladder rupture, renal rupture, and abdominal hernia can be assessed.

95.6 LAPAROSCOPIC SURGERY

Many laparoscopic surgical procedures are currently being performed on humans. These include cholecystectomy, ovariectomy and hysterectomy, adrenalectomy, appendectomy, bile duct exploration, hernia repair, bowel resection, gastropexy, pyloromyotomy, and others. Many of these are applicable to veterinary medicine. Limitations of laparoscopic surgery include the two-dimensional image, restricted freedom of movement of the instruments, restricted sense of touch, and the need for extensive training. Controlled studies are necessary to substantiate the role of all laparoscopic procedures in veterinary medicine. As clinicians and equipment

manufacturers address technical limitations, many surgical procedures performed within a body cavity should be amenable to laparoscopic surgery.

96 CHAPTER • 96 Fine Needle Aspiration and Lung Biopsy

Lynelle R. Johnson

Airway samples are often valuable in determining the underlying cause of respiratory signs in dogs and cats. They can be collected by means of tracheal aspiration, bronchoalveolar lavage, fine needle aspiration, or lung biopsy. The use of a particular technique depends on the results of the physical examination, the animal's stability for procedures that require anesthesia, the type and distribution of radiographic infiltrates, and the list of most likely differential diagnoses.

Fine needle aspiration (FNA) and lung biopsy are most useful for investigating the etiology of diffuse interstitial disease, mass lesions, or focal infiltrates. In general, fine needle aspiration or surgical lung biopsy should be performed when bronchoscopy or other noninvasive tests have failed to yield a diagnosis or to provide sufficient information to guide therapy.

Fine needle lung aspiration can be performed in a conscious animal, under light sedation, or during anesthesia. The technique may be done blindly or with ultrasound guidance. Lung biopsies are performed under general anesthesia and can be accomplished percutaneously with ultrasound guidance, via thoracoscopy, with a keyhole surgical approach, or during thoracotomy. Typically, thoracoscopic and keyhole biopsies provide evaluation of peripheral lung segments only. Focal histologic abnormalities or lesions in more central regions of the lung can be missed. Diagnostic yield can be improved by using preoperative computed tomography to identify and localize appropriate regions for aspiration or biopsy.

Contraindications for FNA include bleeding disorders, intractable tachypnea or hyperpnea, and mechanical ventilation. Standard contraindications for general anesthesia would preclude lung biopsy.

96.1 FINE NEEDLE LUNG ASPIRATION

In animals that are relatively eupneic, percutaneous FNA of the lung can be performed without sedation. Local anesthesia generally is not helpful, because infiltration with lidocaine often causes more discomfort than the single pass of the aspiration needle through the skin. The equipment for FNA includes a 23-to 27-gauge needle ¾ to 1½ inches long and a 6-to 10-cc syringe. Microscope slides should be readily accessible for preparation of the sample for cytologic evaluation, and aspirated material can be applied to culture swabs for microbiologic analysis if sufficient quantity is obtained.

For FNA, a small region of the chest is shaved and minor surgical preparation is completed. The needle is passed through the skin and subcutaneous tissue and into the thoracic cavity cranial to the border of the rib. With respiration halted, the needle is directed swiftly into the lung perpendicular to the lesion. It is inserted back and forth gently and quickly, and one or two gentle aspirations are applied to the syringe. The needle and syringe are removed together for preparation of cytologic specimens.

A second method uses an inverse aspiration technique. The needle (attached to syringe) is inserted through the rib muscles until it is close to the pleural cavity. To enter the lung, the barrel of the syringe is advanced toward the chest wall while the plunger is held stationary. Release of the plunger aspirates material into the hub of the needle. The syringe and needle are removed for preparation of the sample.

Generally, only a small aspiration sample is visible in the hub of the needle. The syringe is detached from the needle and filled with air, and the contents of the needle hub then are gently sprayed onto a slide or cover slip for

cytologic examination and Gram staining. Additional material can be applied to a culturette swab. If aspiration with an empty syringe fails to yield material, the syringe can be filled with 1 to 2 mL of sterile saline. The aspirated material in the hub of the needle is drawn back into the syringe to create a suspension of the aspirant. A cytospin preparation can be done; however, this technique may result in excess dilution of the sample.

For more central or focal lesions, ultrasound-guided percutaneous aspiration is performed with the animal under heavy sedation or anesthesia. Balanced anesthetic protocols that maintain cardiopulmonary support are preferred, and narcotic agents are often used. If a larger instrument (18 to 21 gauge) is used, the aspiration biopsy needle is preferred over a cutting biopsy needle because the former technique has a lower incidence of complications.

96.2 LUNG BIOPSY

Lung biopsy can be achieved through video-assisted thoracoscopic surgery (VATS), keyhole biopsy, or thoracotomy. Samples are submitted for histology and bacterial cultures (aerobic and anaerobic). Fungal cultures should be considered in some cases, and impression smears of biopsy samples may be helpful for early assessment of cytologic lesions.

Thoracoscopy is the least invasive surgical technique that provides an opportunity for visualized lung biopsy or lung lobectomy. General anesthesia with endotracheal intubation is used, and close anesthetic monitoring is required because a moderate pneumothorax is induced during the procedure. VATS is performed more commonly in dogs than cats because of their larger body size. This technique requires specialized rigid telescopes, trocars, and endoscopic instruments, a light source, and a video monitor. Formal training is required to develop expertise in this procedure. Peripheral biopsies of a distal lung segment can be obtained with a stapling instrument or an endoscopic loop ligature. Alternatively, a lung lobe can be resected. The most serious complication of thoracoscopic biopsy is hemorrhage.

Lung biopsy of a peripheral segment can also be obtained through a modified (keyhole) thoracotomy. The animal should be placed under general anesthesia and surgically prepared. An intercostal thoracotomy is performed, and a wedge of lung is exteriorized. A biopsy is obtained by applying loop ligatures around the segment or by using a stapling device.

In an animal with a solitary mass lesion, consolidated lung lobe, central pulmonary infiltrate, or focal abnormality, exploratory thoracotomy with lung biopsy, partial lobectomy, or lung lobectomy may be required to obtain a diagnosis. A lateral intercostal approach on the side of the lesion provides the best access to structures in the immediate area and usually has the advantage of an uncomplicated approach and closure. The technique is associated with less postoperative discomfort than a sternotomy; however, it does not allow access to the entire contents of the chest cavity. Median sternotomy is performed when a complete thoracic cavity exploratory is required, but it is difficult to perform lung lobectomy by this approach. In addition, access to hilar structures through a median sternotomy is limited in large, deep-chested dogs.

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96.3 COMPLICATIONS

The most common complications of fine needle lung aspiration and percutaneous lung biopsy are pneumothorax and hemorrhage, although seeding of the pleural cavity with neoplastic cells is also of theoretical concern. Complications can occur when the technique is done either blindly or with ultrasound guidance, but the occurrence rate is substantially lower when small needles are used. Proper patient selection is also of critical importance, because animals with marked tachypnea and/or pronounced respiratory distress are more likely to develop pneumothorax. Highly agitated or fractious dogs or cats that are difficult to restrain are prone to hemorrhage, as

are animals with coagulopathies or pulmonary hypertension. Sedation or anesthesia of fractious animals might improve the safety of the procedure. After a lung aspiration procedure, the animal should be encouraged to lie on the side of the aspiration to promote the development of a seal at the site. Radiographs should be taken if an increase in respiratory rate or effort develops or if an absence of lung sounds is noted, which could suggest pneumothorax.

Complications of open lung biopsy are those associated with duration of anesthesia or respiratory depression. Chest tubes are placed after surgery, thus limiting the occurrence of pneumothorax. Hypotension, hypoxemia, and poor ventilatory recovery are potential postoperative problems.

97 CHAPTER • 97 Lymph Node Aspiration and Biopsy

David M. Vail

Lymph node aspirates, biopsies, or both are indicated when lymph nodes are clinically enlarged or are suspected of being involved in a disease process where their histologic assessment would be helpful in diagnosis or staging the extent of disease involvement. Whether a fine needle aspirate, incisional, or excisional biopsy is chosen depends on the disease process under consideration, the tissue volume requirements for assessment, and the condition of the dog or cat.

97.1 LYMPH NODE ASPIRATION

This simple, rapid, and low-morbidity assessment of lymph nodes can be performed several ways; the technique used will depend on operator preference and location of the node in question. For peripheral lymph nodes, sedation is rarely necessary; however, sedation or general anesthesia may be necessary if a dog or cat is fractious, or an intracavitary node is to be aspirated either by palpation or by ultrasound guidance.

For most accessible nodes, the author prefers the “needle without the syringe” approach to fine needle aspiration. This technique is well suited for lymph nodes because, in general, they readily exfoliate their cells. This allows the operator to experience a fingertip feel of the node texture; it also decreases blood admixture and cellular disruption secondary to vacuum aspiration (Figure 97-1). Alternative techniques for lymph node aspiration include aspiration with the needle attached to a 10-cc syringe. In this case, upon insertion of the needle (20 gauge) into the node, suction is created by rapid, repetitive aspiration of the syringe. Metal or plastic commercially available mechanical aspiration devices can also be used to create vacuum, but they are rarely necessary for lymph node samples.

No preparation is necessary for peripheral lymph nodes other than swabbing the site of penetration with alcohol. If the node is within a body cavity, then surgical preparation of the site of entry is recommended. Instrumentation includes a 20-gauge needle, a 10-mL syringe, and cytology slides. The process is as follows (see Figure 97-1, *A* and *B*).

While holding the node in an off hand, the operator holds the needle with one finger over the hub. The needle is passed once through the skin and into the node, followed by several quick thrusts in and out of the node without exiting the skin each time. The needle is then removed from the node, placed on an air-filled 10-cc syringe, and the contents are gently expressed onto several slides. The sample is smeared out and submitted for appropriate staining and analysis.

97.2 LYMPH NODE BIOPSY (INCISIONAL)

If a larger sample for histopathology is required, a needle core biopsy (e.g., Tru-Cut®) is recommended and outlined in Figure 97-2. Usually, only sedation and local anesthesia is required. Rarely, intravenous or gaseous anesthesia is necessary if a dog or cat is fractious or an intracavitary node is to be biopsied. Mechanical, spring-loaded needle biopsy instruments are also commercially available.

Instrumentation includes a No. 11 blade to make a stab incision for needle biopsy entry, a Tru-Cut® biopsy instrument, a specimen cassette, and suture material (only necessary if entry hole is large or if excessive hemorrhage occurs).

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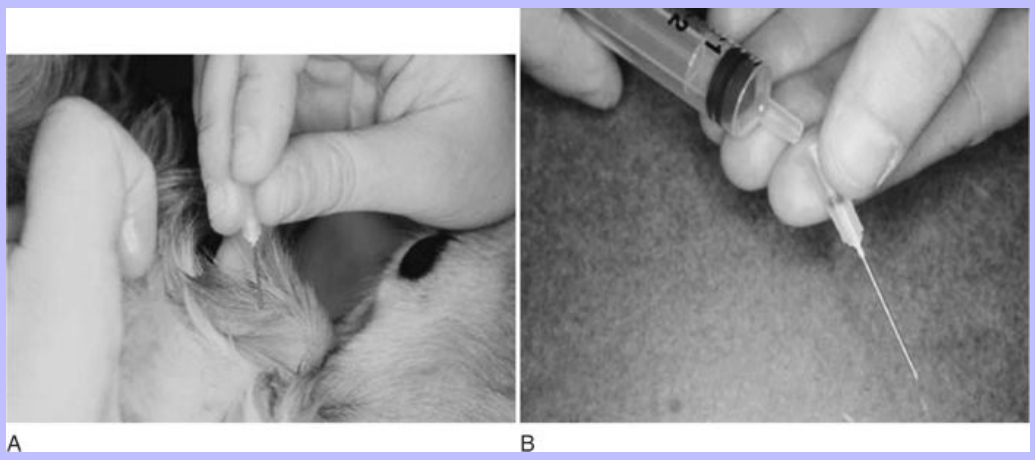
Figure 97-1 Fine needle aspiration—lymph node.



The Tru-Cut® core biopsy instrument can be set in one of two positions (see Figure 97-2, *A*): The first, the *closed* or sheathed position, has the inner canula within the outer sheath. This is the position used when placing the needle into the node. The second, or *open* position, occurs when the outer sheath is held in place and the inner cannula is thrust forward by pushing the handle plunger (indicated by the thick arrow in Figure 97-2, *A*) forward. This opens the specimen or sample trough (indicated by the narrow arrow in Figure 97-2, *A*).

After a No. 11 blade is used to make an entry hole in the surgically prepped area, the biopsy needle is passed through the skin just into the node while in the *closed* position (see Figure 97-2, *B*).

Next, the operator thrusts the plunger forward to place the instrument in the *open* position (see Figure 97-2, *C*), thereby allowing nodal tissue to fill the needle trough. While the biopsy plunger is held in a steady position, the operator slides the outer sheath forward over the inner cannula, thereby cutting the core sample off within the specimen trough (i.e., the biopsy instrument is again in the *closed* position); the entire instrument is then withdrawn from the node while in the *closed* position (see Figure 97-2, *D*). The biopsy needle is then *opened*, and the specimen (i.e., core sample) is placed in a biopsy cassette for processing (see Figure 97-2, *E*).

97.3 LYMPH NODE BIOPSY (EXCISIONAL)

In the case of low-grade lymphoma in dogs or when lymphoma is considered in cats where several well-documented benign lymphadenopathies may mimic lymphoma, the entire lymph node should be removed for histologic assessment. This is important for the pathologist to determine architectural changes and capsular invasion. The reader is referred to a general surgical textbook for techniques for whole-node extirpation.

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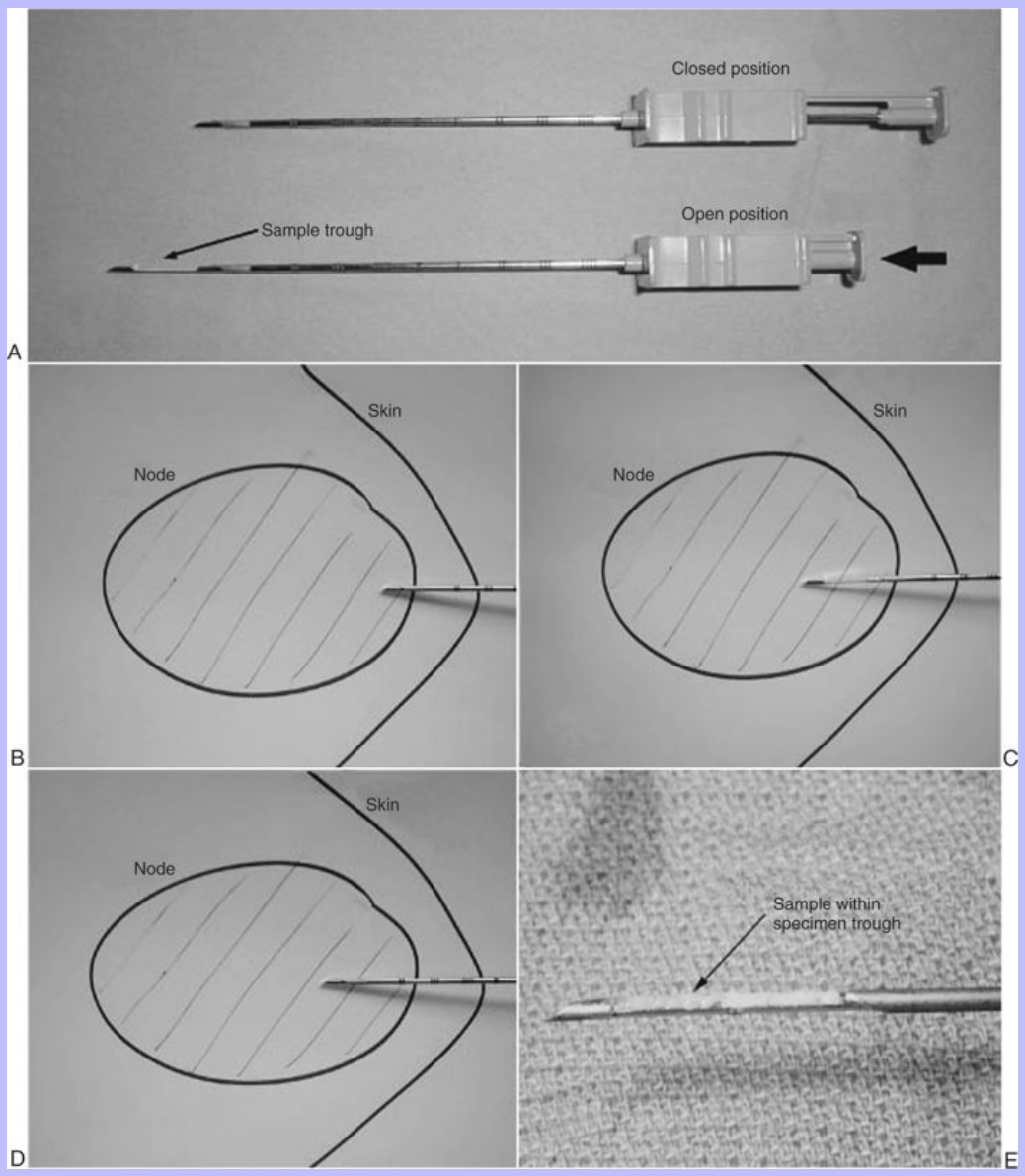
Figure 97-2 Needle core biopsy—lymph node.



98 CHAPTER • 98 Pacemaker Implantation

Daniel F. Hogan

98.1 INTRODUCTION

Artificial pacing (AP) for the treatment of symptomatic bra-dyarrhythmias in veterinary medicine began over 30 years ago and is now considered the standard level of care for such patients. The most common conditions requiring AP include third-degree (complete) atrioventricular block (3AVB) and sinus node dysfunction (sick sinus syndrome [SSS]). Other less common conditions include high-grade second-degree atrioventricular block (2AVB), persistent atrial standstill, vasovagal syncope, reduction of obstruction gradient in hypertrophic obstructive cardiomyopathy (HOCM), and biventricular pacing in congestive heart failure patients. Pacing systems are varied and can range from simple to complex, depending on what the requirements are for the individual patient. The vast majority of pacing systems implanted today consist of single-chambered systems where one pacing lead is placed, usually into the right ventricle (RV), and programmed to deliver an electrical stimulus when intrinsic electrical activity is absent. A single-chambered system could also use a lead placed within the right atrium (RA), as sometimes used to treat SSS, but this requires a competent atrioventricular node (AVN). However, it is well recognized that maintenance of atrioventricular synchrony in pacemaker patients is preferable and results in increased cardiac output, improvement in neuroendocrine profile, and reduced incidence of the pacemaker syndrome. For these reasons, there has been increased use of dual-chambered systems in veterinary medicine over the past 5 years. These systems usually consist of two leads: one in the RA and one in the RV. Dual-chambered pacing can be established by use of a special single lead where free-floating electrodes reside within the RA that sense intrinsic atrial electrical activity. However, atrial pacing is precluded in this system.

98.2 PACING COMPONENTS

The pacing system consists of (1) a pulse generator that contains a lithium-iodide power source and magnetic switches that determine how and when the electrical stimulus is delivered and (2) lead or leads that deliver the electrical stimulus and sense intrinsic electrical activity. These components must be compatible; the clinician can determine this by consulting with a local pacemaker representative, by reading publications such as the *Pacemaker* and *Connector Encyclopedia*, or by obtaining the components from the Companion Animal Pacemaker Registry and Repository (CANPACERS).*

Pulse generators have two main categories: (1) single or dual chambered and (2) unipolar or bipolar. Dual-chambered generators have two channels or connectors for the leads. Unipolar generators serve as the anode to complete the electrical circuit and are only compatible with unipolar leads. The noninsulated surface of the unipolar generator must be in contact with body tissues to allow pacing. Bipolar generators can be programmed as unipolar, allowing compatibility with unipolar and bipolar leads that results in greater flexibility of such systems. Generators also differ with respect to their programmability, with the newer generators having more functions that can be modified by the user.

Leads are classified as (1) endocardial or (2) epicardial. Endocardial leads contact the endocardial surface of the RV or RA and are implanted by the transvenous route, whereas epicardial leads are implanted by thoracotomy or celiotomy and contact the epicardial surface of the left ventricle (LV). As already mentioned, leads are classified as unipolar (epicardial leads are always unipolar) or bipolar, and this will influence compatibility issues. The clinician can identify bipolar leads by the distal ring electrode on the lead that functions as the anode or by the two ring electrodes on the connector pin. In addition, the size of the connector pin on the lead can vary, but this must

match the connector size of the generator. Older leads can have connector sizes of 5 or 6 mm, whereas newer components have been standardized (these leads are listed as IS-1 UNI or IS-1 BI for unipolar and bipolar, respectively). However, adapter sleeves can be used to allow a smaller-diameter lead connector to fit into a larger generator channel. Leads also have two different types of fixation to the myocardium. Active fixation leads penetrate the myocardial wall with a corkscrew mechanism, whereas passive fixation leads have silicone or polyurethane tines that become entangled within the trabeculae of the endocardial surface. Epicardial leads must have some form of active fixation either through a corkscrew mechanism, suture disc, or both. Either fixation technique can be used for endocardial leads, because the dislodgement rates from the ventricle are similar. However, the author prefers to use active fixation for atrial leads for more secure myocardial engagement. Most of the newer leads have steroid-eluting tips that reduce the risk of excessive fibrosis around the contact site that could result in exit block and loss of pacing.

It is important to have access to a pacing system analyzer (PSA) on site, through a pacemaker representative, or from a local hospital. However, most PSAs are only compatible with generators from the same manufacturer as the PSA, and compatibility needs to be confirmed prior to pacemaker implantation. The PSA allows programming of user-modified parameters through the application of a magnet over the generator. After implantation, the magnet can be applied on the skin surface overlying the generator, allowing noninvasive programming of the pacing system.

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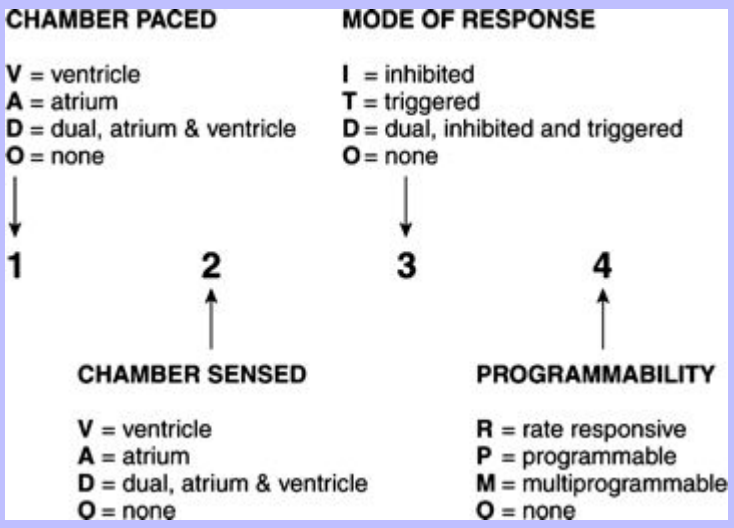
Figure 98-1 Pacemaker programming code.



Pacing systems in veterinary medicine are most commonly coded by a four-letter system (Figure 98-1). The first letter represents the chamber paced, the second letter the chamber sensed, the third letter is the mode of response to sensed intrinsic electrical activity, and the fourth letter indicates the programmability of the generator. In veterinary medicine, the most common pacing modality is VVI, with a fixed pacing rate ranging from 70 to 100 pulses per minute (ppm). However, over the last 5 years there has been increased use of dual-chambered pacing systems where DDD or VDD pacing modalities are used. A PSA is used prior to implantation to estimate battery life and to program nominal pacing parameters. During implantation the PSA allows evaluation of the surface ECG, atrial or ventricular electrograms (or both), determination of lead impedance, and optimal pacing parameters. Postimplantation, the PSA is used to interrogate the pacing system for changes that occur over time that could require the pacing parameters to be altered. In addition, the PSA can program in-stock generators to

nonpacing modes such as OAO or OVO to prolong the battery life of the generator prior to implantation. If a PSA is not routinely available, then a pulse generator can be programmed to the following parameters: pace amplitude 5 V, pacing pulse width 0.5 ms, sensitivity 2.5 mV, ventricular refractory period 250 ms, and pacing rate 70 to 100 ppm within a VVI pacing system. The author does not recommend implanting a dual chambered pacing system without having a PSA readily available because these systems are more complex and often require multiple adjustments during implantation.

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98.3 PREIMPLANTATION DIAGNOSTIC EVALUATION

Preimplantation diagnostics should include a complete blood count, serum chemistries, and urinalysis to identify possible underlying causes of the rhythm disturbance and determine overall health of the animal. An electrocardiogram is necessary to accurately diagnose the arrhythmia. Thoracic radiographs and echocardiograpy should be performed to identify any possible underlying causes of the rhythm disturbance and any concurrent cardiac disease and to assess baseline cardiac function. It is important to determine baseline cardiac function because a small subset of animals with 3AVB develop myocardial failure after pacemaker implantation, either from an adverse effect of the pacemaker or extension of the disease process that resulted in the arrhythmia requiring pacemaker implantation (Figure 98-2). Additional diagnostics may be performed to identify diseases that have been associated with arrhythmias requiring pacemaker implantation such as Lyme disease and myasthenia gravis.

98.4 PACEMAKER IMPLANTATION

Perioperative antibiotics are routinely used on a prophylactic basis. First-generation cephalosporins such as cefazolin (22 mg/kg IV q 2 hours) are most commonly used. However, the use of antibiotics does not replace good aseptic techniques. Controversy exists as to whether a temporary pacing system should be placed prior to general anesthesia for permanent pacemaker implantation. The procedural time is increased, there is no significant decrease in adverse events and no clear consensus from cardiologists if temporary pacing systems should be placed on a routine basis. However, it is generally agreed that animals with unstable escape rhythms should be temporarily paced. The author routinely uses temporary pacing in all cases with propofol anesthesia, which allows a more controlled and relaxed environment for permanent pacemaker implantation.

The vast majority of pacing systems use endocardial leads placed via the transvenous approach. However, epicardial leads are routinely placed in cats due to complications with transvenous systems and in the rare instances of persistent single left cranial vena cava in dogs.

98.5 TEMPORARY PACEMAKER IMPLANTATION

When implanting a temporary pacemaker, the clinician can use the following as a guide:

- A large area over the left or right jugular vein is clipped and surgically prepared.
- Anesthesia is induced with propofol intravenously to effect (4 to 6 mg/kg), and the animal is intubated and given oxygen.
- A 5 or 6 F vascular introducer is placed in the jugular vein via percutaneous technique.

- A 4 to 6 F temporary pacing lead is advanced into the RV under fluoroscopic guidance.
- The lead is attached to the external generator and paced as VVI with 5 V amplitude, 0.5 ms pulse width duration, 2.5 mV sensitivity, and 60 to 90 ppm.

Note: Alternatively, the femoral vein can be used for venous access using the previously described procedure.

98.6 PERMANENT TRANSVENOUS PACEMAKER IMPLANTATION (JUGULAR VEIN)

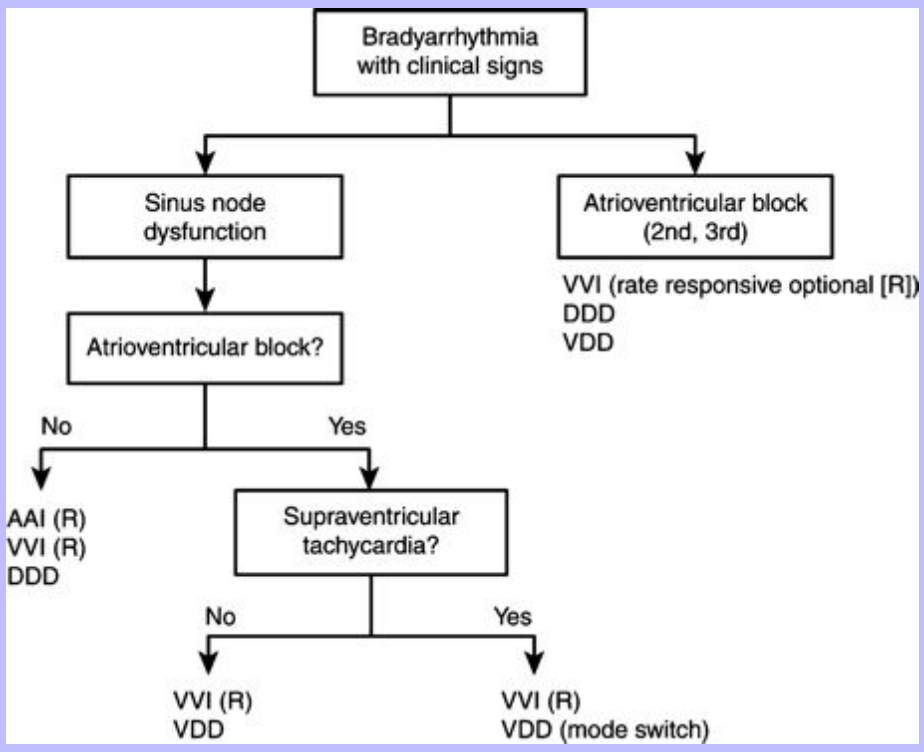
98.6.1 Ventricular Lead

When preparing a ventricular lead via the jugular vein, the clinician should do the following:

- Surgically prepare a large area over the right or left jugular vein, ipsilateral neck extending dorsally just to the contralateral side from the base of the skull to the midlevel of the scapula.
- Isolate a jugular vein segment via surgical cut-down and temporary encircling sutures or sterilized rubber bands.
- Perform a horizontal venotomy.
- Advance a straight or curved, appropriately sized stylet through the inner channel of the endocardial lead. 349
- Verify performance of extrusion-type active fixation leads by connecting the fixation tool to the connector pin and advance the corkscrew electrode by rotating the fixation tool clockwise. 350
- After extrusion, rotate the fixation tool counterclockwise to return the corkscrew into the lead. (The tool should not be overrotated counterclockwise or the mechanism may break.)
- Advance the endocardial lead through the venotomy site to the RA under fluoroscopic guidance. When using a curved stylet, the lead can often be directed into the apex of the RV. If using a straight stylet, withdraw some of the stylet to render the distal aspect of the lead more flexible and advance the distal tip to the apex of the RV.
- Advance a straight stylet to the end of the lead and gently advance the lead tip against the endocardial surface. With active fixation, connect the fixation tool to the connector pin and rotate clockwise to extrude the corkscrew under fluoroscopic guidance. Two radiopaque markers present at the lead tip touch when the corkscrew is fully extruded. With passive fixation, the lead is gently advanced to entangle the tines within the trabeculae of the RV.
- Ideally, at this time a PSA will be used to determine lead impedance and pacing thresholds. The lead can be placed at a different location within the ventricle if the pacing thresholds are determined to be inadequate for effective and safe pacing.
- Perform a “tug test” by gently pulling on the lead to verify that the endocardium is engaged.
- If a dual-chambered system is to be employed, insert the atrial lead prior to proceeding to the next step.

- Slide the suture sleeve on the lead distally and insert it into the distal aspect of the venotomy site. Place two to three circumferential nonabsorbable sutures around the jugular vein and the suture sleeve, taking care to advance enough lead to allow some slack for neck movement.
- Double ligate the proximal portion of the jugular vein.
- Make an incision over the dorsal neck. (Blunt dissection is used to create a pocket just large enough for the pulse generator.)
- Using a long, straight hemostat, tunnel to the venotomy site, grasp the proximal aspect of the lead, and pull until the lead enters the pulse generator pocket.
- Insert the connector pin into the ventricular lead channel of the pulse generator and tighten the screw or screws with a manufacturer-supplied wrench tool (overtightening should be avoided). If using a unipolar system, the pulse generator must be in contact with the tissues for pacing to occur. Temporary pacing should either be turned off or the rate dramatically slowed to not interfere with the permanent system.
- Place any excess lead underneath the generator, place a nonabsorbable suture through the suture sleeve on the generator, and anchor it to the deep fascia of the dorsal neck.
- Close incisions routinely, taking care to close as much dead space as possible to avoid possible seroma formation.

Figure 98-2 Bradyarrhythmia with clinical signs.



98.6.2 Atrial Lead

When placing an atrial lead via the jugular vein, the clinician should do the following:

- When used with a dual-chambered system, the ventricular lead is placed first. Care is taken when manipulating the atrial lead because dislodgement of the ventricular lead could result.
- If using a straight lead, insert a straight stylet into the lead and advance the lead tip under fluoroscopic guidance just until it enters the RA.
- Replace the straight stylet with a *J*-shaped stylet to direct the lead tip into the cranial-lateral aspect of the right auricle.
- If using a preformed *J*-shaped atrial lead, insert a straight stylet into the lead and advance the lead tip under fluoroscopic guidance just until it enters the RA.

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- Slowly retract the stylet while advancing the lead; this should allow the tip of the lead to move into the cranial-lateral aspect of the right auricle.
- *Note:* Proper placement of the lead tip is verified by dorsoventral movement or “wagging” in concert with the beating heart.
- Regardless of the lead used, a *J*-shaped stylet should then be advanced to the lead tip and fixation performed as with the ventricular lead.
- When removing the stylet, the clinician should advance some of the atrial lead while the stylet is removed to reduce the risk of dislodgement.
- Place circumferential sutures around the jugular vein and suture sleeve as with the ventricular lead.

98.7 PERMANENT TRANSVENOUS PACEMAKER IMPLANTATION (COSTOCERVICAL VEIN)

When implanting a permanent transvenous pacemaker via the costocervical vein, the clinician should do the following:

- Perform a thoracotomy at the right second intercostal space.
- Isolate the costocervical vein (CCV) and ligate it 2 to 3 cm distal to the cranial vena cava.
- Perform a venotomy and advance the lead into the RV as with the jugular technique.
- Create the generator pocket deep to the external abdominal oblique muscle by a vertical incision over the seventh rib.
- Tunnel the lead deep to the subcutaneous tissues and over the lateral thorax to enter the generator pocket.
- Close all incisions in routine fashion.

98.8 PERMANENT EPICARDIAL PACEMAKER IMPLANTATION

When implanting a permanent epicardial pacemaker, the clinician should do the following:

- Perform a ventral midline celiotomy extending from just caudal to the umbilicus to the xiphoid.
- Make a vertical incision in the diaphragm, left of midline, to expose the cardiac apex.
- Incise the pericardium and retract with tissue forceps to expose the apex of the LV.
- Implant an active fixation epicardial lead into the apex of the LV by using the manufacturer-supplied lead tool.
- Create the generator pocket between the transverse abdominis and internal abdominal oblique muscles along the lateral abdominal wall.

Note: The clinician should not suture the pericardium; instead, the diaphragm and abdominal incisions should be closed in routine fashion.

98.9 POSTOPERATIVE CARE AND MONITORING

Thoracic radiographs and electrocardiography are performed postoperatively to verify lead placement and record QRS morphology, respectively. The animal is generally placed in an intensive care unit (ICU) overnight with continuous ECG monitoring for possible arrhythmias and loss of capture. With endocardial systems placed via the jugular route, a padded bandage is placed around the neck to cover both the jugular and generator incisions to protect the incision sites and prevent excessive fluid accumulation. The bandage is changed every 2 to 3 days until the sutures are removed in 10 days. Antibiotics such as cephalexin (22 mg/kg q 12-8 hrs) or amoxicilin with clavulanic acid (13.75 mg/kg q 12 hrs) are continued orally for 7-10 days. Strict exercise restriction is required for the first month to reduce the risk of lead dislodgement. After 1 month, the lead is usually anchored firmly in place and the animal can resume normal activity.

The author follows a monitoring protocol of 1 month, 3 months, and 1 year after implantation with annual or biannual rechecks scheduled thereafter. Thoracic radiographs, surface ECG, and programmer interrogation by a PSA are performed to evaluate lead placement and function. Appropriate adjustments are made to the generator via the PSA as needed; end of battery life for the generator can also be identified.

99 CHAPTER • 99 Peritoneal Dialysis

Cathy Langston

Peritoneal dialysis is used to treat acute renal failure, occasionally poisoning by a dialyzable toxin (i.e., ethylene glycol, phenobarbital, ethanol), or chronic renal failure. Some peritoneal dialysis techniques can also be applied for peritoneal drainage (i.e., uroabdomen) or peritoneal lavage (i.e., pancreatitis, hypothermia, hyperthermia).

99.1 PERITONEAL DIALYSIS CATHETERS

Access to the peritoneal cavity is accomplished via a peritoneal catheter. The general design of percutaneously placed catheters includes multiple fenestrations at the tip of the catheter to allow fluid ingress and egress. A variety of catheters are available that are made specifically for this purpose (i.e., Peritoneal Lavage Catheter, Cook Veterinary Products, Spenser, Ind.; Pediatric Peritoneal Dialysis Catheter, Baxter Healthcare Corp., Deerfield, Ill.), or fenestrated chest tubes may be used. For percutaneous placement, local anesthesia in conscious animals or a short-acting injectable anesthetic may be used. The patient is placed in dorsal recumbency, and the abdomen is sterilely prepped and draped. A stab incision through the skin lateral to the midline at the level of the umbilicus allows introduction of a trocar threaded through the dialysis catheter. The trocar is tunneled under the skin for 1 to 2 cm before puncturing the abdominal musculature. The trocar should be directed toward the opposite hip. Having the abdomen slightly distended with fluid facilitates percutaneous placement. After the trocar has been introduced, the catheter is advanced off the trocar. The tip of the catheter should rest near the urinary bladder to facilitate fluid drainage. If a trocar is not provided with the catheter, the tip of the catheter can be grasped with curved hemostats, which can be used to tunnel the catheter under the skin and then puncture the abdomen.

The coaxial catheter (Cook Veterinary Products, Spenser, Ind.) and the fluted-T catheter (Ash Advantage Peritoneal Dialysis Catheter, Medigroup, Inc., Aurora, Ill.) are less likely to occlude with omentum. The fluted-T catheter has two limbs, each with channels extending the length of the catheter, to minimize the chance for complete occlusion. These catheters are placed surgically or via laparoscopy. Both have a Dacron cuff that allows attachment of fibroblasts in the subcutaneous portion to enhance stability and diminish leaks and infection. With surgical placement, the catheter is placed in the abdomen via a small caudal abdominal incision. The catheter should exit the ventral body wall through a separate stab incision (not through the abdominal incision), and tunnel under the skin lateral to the midline. The tip of the catheter should rest near the urinary bladder. A partial omentectomy is performed to diminish catheter occlusion. If omentectomy is not desired due to recent intestinal surgery, an omentopexy should be performed.

With both percutaneous and surgical placement, the catheter is secured to the skin at the exit site via a purse string suture. A sterile dry bandage is placed over the catheter. Ideally, the catheter would not be used for 24 hours after placement to allow formation of a fibrin seal, but the animal's condition rarely allows this. When the catheter must be used immediately, a small volume of dialysate (half of the standard volume) should be used for each exchange for the first 24 hours.

99.2 DIALYSATE SOLUTIONS

Dialysate is the fluid that is introduced into the abdomen. Uremic toxins (e.g., blood urea nitrogen [BUN], creatinine, potassium) diffuse from the area of high concentration (the patient's bloodstream) across the peritoneal membrane into the area of low concentration (dialysate). The dialysate is then drained and discarded and the process is repeated. Dialysate should be similar in content to plasma and should contain physiologic

concentrations of readily diffusible substances like sodium, chloride, calcium, and magnesium. It should also contain dextrose, which may be varied in concentration to create an osmotic gradient to either promote or retard fluid removal, based on the animal's needs. If no fluid removal is desired, a dextrose concentration of 1.5% is typically used. If the dog or cat is overhydrated, dextrose concentrations of 2.5% or 4.25% can be used to promote movement of water into the hypertonic dialysate in the abdomen—a process called *ultrafiltration*. Commercially prepared dialysate is available, or dialysate can be improvised from intravenous fluids. Dextrose is added to lactated Ringer's solution or saline to create the desired dextrose concentration (30 mL of 50% dextrose per liter for 1.5% solution, 50 mL per liter for 2.5% solution, or 85 mL per liter for 4.25% solution). Heparin (250 to 1000 U/L) should be added to the dialysate for the first few days after catheter placement to minimize fibrin clot formation. Magnesium should be added after the first several days of dialysis to achieve a concentration of 1.5 mEq/L. If saline is used, sodium bicarbonate should be added to achieve a concentration of 30 to 45 mEq/L. Each additive to the dialysate increases the risk of contamination and formulation error.

99.3 EXCHANGE PROCEDURE

Frequent dialysate exchanges are necessary in dogs or cats with acute oliguric or anuric renal failure, with hyperkalemia, or those that are overhydrated. Initially, exchanges may be as frequent as every 45 to 60 minutes. As the uremia improves (typically after 24 to 48 hours), the frequency of exchanges can be gradually decreased to four times a day, with the goal of maintaining the BUN concentration between 60 to 100 mg/dL. The volume of dialysate to instill is 40 mL/kg per exchange. With small volumes of dialysate, weighing the dialysate bag or using a burette is recommended to increase the accuracy of measurement. Dialysate should be warmed to 38°C to maintain body temperature and to improve peritoneal permeability. Dogs and cats need to be closely observed for signs of abdominal discomfort or respiratory compromise.

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Because peritonitis is a frequent complication of peritoneal dialysis, the catheter and all connections should be handled as aseptically as possible. The connection ports should be covered with antiseptic-soaked gauze and should be scrubbed prior to any connection or disconnection. Sterile gloves should be worn when handling the connections, and the frequency of connections and disconnections should be kept to a minimum. Most contamination occurs when connecting to the dialysate bags. A Y connector (or stopcock) can be placed on the catheter and connected to a multidose bag of fresh dialysate and to an empty bag to collect spent dialysate. A small amount of fresh dialysate is flushed into the drain bag with the catheter closed to the animal in an attempt to flush any contaminant that may have been introduced during the connection process into the drain bag and not into the abdomen. The dose of dialysate should then be instilled into the abdomen by gravity feed, usually taking less than 10 minutes. The fresh dialysate bag should then be clamped and the catheter closed to the dog or cat during the dwell time. After the appropriate dwell time, the catheter is opened to allow drainage of the abdominal fluid into the drain bag. It is important that the drain bag be positioned lower than the catheter to allow gravity drainage. Gentle ballottement of the abdomen and repositioning the animal can facilitate more complete drainage. After draining ceases (approximately 15 to 30 minutes), fresh dialysate is again instilled into the abdomen. If the entire volume of the fresh dialysate bag is infused per exchange, the empty bag should be clamped after infusion and left attached. After the dwell time, the clamp should be opened and the bag used as the drain bag.

The volume of dialysate instilled and the volume recovered should be monitored carefully, as should urine output and volume of administered fluids, medications, and feedings. When hypertonic dialysate is used (i.e., 4.25% dextrose), a larger volume of dialysate should be recovered than instilled, indicating net fluid removal from the animal. The dog or cat should be monitored for evidence of dehydration. If less dialysate is being recovered than is being instilled, the catheter tubing should be checked for kinks or occlusion and the animal repositioned. The catheter can be forcefully flushed with heparinized saline, or 15,000 U of urokinase can be instilled in the catheter for 2 to 3 hours to dislodge fibrin clots or omentum. If these measures do not restore flow, the catheter may need

to be repositioned or replaced. If the dog or cat is dehydrated, fluid may be reabsorbed from the peritoneal cavity, decreasing the volume of dialysate recovered.

In addition to meticulous attention to fluid balance, several other parameters should be monitored routinely. Blood glucose concentration should be monitored once or twice daily. If hyperglycemia is documented, low doses of insulin may need to be administered. Packed cell volume (PCV), total solids, and electrolytes should be monitored twice daily. Initially, BUN, creatinine, and albumin should be monitored once or twice daily. Cytology should be performed on the spent dialysate on a daily basis, and the dialysate should be cultured weekly or if it becomes cloudy.

99.4 COMPLICATIONS

Peritonitis is a major complication of peritoneal dialysis. Meticulous attention to aseptic technique is necessary to decrease this risk. Diagnosis is made by presence of clinical signs (e.g. abdominal pain, fever), cloudy dialysate, or greater than 100 inflammatory cells per mL of dialysate. Because *Staphylococcus* is the most common organism isolated, systemic cephalosporins are recommended pending culture results. Intraperitoneal administration of antibiotics may be helpful (i.e., 125 mg cephalothin per liter of dialysate). Although peritonitis may be successfully managed while continuing dialysis, removal of the peritoneal dialysis catheter may be required to allow resolution of unresponsive peritonitis.

Catheter occlusion is a common problem with peritoneal dialysis. The omentum has tremendous migratory capability and can rapidly encompass the catheter. Acute peritoneal dialysis catheters may occlude within 24 to 72 hours of placement. The fluted-T and coaxial catheters fare better, but occlusion can still occur with these. A partially occluded catheter drains more slowly and incompletely. Incomplete emptying of the dialysate decreases efficiency of toxin removal and risks overdistension of the abdomen, with concomitant problems (abdominal or respiratory distress). Flushing the catheter with saline in the first 24 hours after placement may help delay this problem. If the catheter occlusion cannot be dislodged with flushing or urokinase, the catheter may need to be replaced. Other catheter-related complications include dialysate leakage or exit site and subcutaneous tunnel infections.

Hypoalbuminemia is one of the most common complications of peritoneal dialysis and can be partially addressed by providing adequate nutrition either enterally or parenterally. Enteral feeding is frequently difficult, due to anorexia or vomiting. Gastrostomy or jejunostomy tubes are contraindicated in peritoneal dialysis due to exit site leaks and increased risk of infection. Dialysate containing amino acids may provide partial nutrition but should not be used unless adequate nonprotein calories are being provided.

99.5 DISCONTINUING DIALYSIS

Intermittent rest periods, in which no dialysate dwells in the abdomen, with close evaluation of the animal's clinical and biochemical status can be used to determine when dialysis can be discontinued. When the dog or cat can maintain homeo-stasis without dialysis, the catheter should be removed surgically. Unfortunately, survival with peritoneal dialysis has been low, with most reports around 30%.

100 CHAPTER • 100 Veterinary Nuclear Medicine

Brian A. Poteet

100.1 INTRODUCTION

Nuclear imaging (scintigraphy) has been used in veterinary medicine as a primary or secondary modality to aid in the diagnosis of disease processes and for therapy. The utility of nuclear medicine procedures lies in the fact that they enable the imaging of physiologic processes. Nuclear medicine is to physiology as radiographs are to anatomy. Table 100-1 lists six nuclear medicine studies and their primary indications for use. Although these studies and others have been used in animal patients, the thyroid scan, portal scan, bone scan, and glomerular filtration rate (GFR) scan are the most commonly performed scans in a clinical setting. The *Handbook of Veterinary Nuclear Medicine*[1] further describes these and other types of scans.

Nuclear imaging differs from radiographic imaging in that the instrumentation (a gamma camera) emits no radiation. Instead the patient emits gamma radiation after a dose of radiation has been intravenously administered. The most common radionuclide used for diagnostic purposes is ^{99m}Technetium (^{99m}Tc, Tc, Tech, or pertechnetate). ^{99m}Tc is eluted using sterile saline in liquid form from its parent isotope, ^{99}Molybdenum (^{99}Mo), in a lead-encased generator system (also known as the “cow”); the whole process commonly referred to as “milking the cow.” The eluate (^{99m}Tc suspended in saline) is then placed in a small lead-encased dosing bottle (known as the “pig”) and kept for use either alone (as a radionuclide) or it tagged to a pharmaceutical (to form a radiopharmaceutical). The amount of radioactivity obtained with each elution is variable and will depend on the size of the generator system, its age, and the timing of each elution. The most common unit of a dose of radioactivity is the Curie (Ci), with most fresh eluates being around 1 Ci in strength. Most patient doses are in the millicurie (MCi) range (1 Ci = 1000 MCi). An individual or institution must have a radioactive materials license (RML) from either the state in which they practice (an “agreement state”) or from the Nuclear Regulatory Commission (NRC). Qualifications and experience required to obtain an RML varies, but it generally requires proven experience and training in nuclear medicine procedures and radiation safety. The regulations concerning the use of radioactive materials in veterinary patients are often different from that of human patients. The major differences usually pertain to patient release criteria and safety requirements. For example, human patients are allowed to leave the hospital if they have been administered 30 MCi or less, as compared with animal patients that must typically be hospitalized for 24 hours until their exposure levels are below a specific level that the state has set (typically 0.5 mR/hour at 1 m. The overall dose of radiation that a patient is exposed to from a typical nuclear medicine procedure is minimal, and adverse side effects are rarely seen.

Table • 100-1 Commonly Performed Nuclear Medicine Studies in Veterinary Medicine

SCAN NAME	INDICATIONS FOR USE
Thyroid scan	Feline hyperthyroidism, occult hyperthyroidism
Portal scan	Macroscopic portosystemic shunt detection
Bone scan, three-phase bone scan	Occult lameness, differentiate septic arthritis or osteomyelitis vs. severe chronic degenerative joint disease (DJD), metastatic bone disease
Glomerular filtration rate (GFR) scan	Quantitative evaluation of differential renal function
Perfusion lung scan	Pulmonary thromboembolic disease
Multigated acquisition cardiac scan (MUGA)	Subjective and objective evaluation of cardiac performance

The site and method of tissue localization depends on several factors, the more important of which are blood flow, the type of radiopharmaceutical used, and individual species differences. When administered intravenously to a patient as a radionuclide (pertechnetate ion), localization will mimic that of halogenated compounds, such as iodine, and occurs in glandular tissues, such as the thyroid gland, choroid plexus, salivary glands, and mucosal glands that line the stomach. When administered as a radiopharmaceutical, the method and site of localization depend on the physical or chemical characteristics of the radiopharmaceutical itself. Table 100-2 lists commonly used radiopharmaceuticals, their various sites and methods of tissue localization, and their various uses.

Instrumentation required in a basic veterinary nuclear medicine lab will vary, but includes a gamma camera, an interfaced computer with acquisition and processing software, an exposure meter, safety equipment including a radioactive materials spill containment and clean-up kit, shielding material such as lead bricks, and a properly shielded and ventilated radiation isolation ward. New gamma cameras and computers are expensive, but good quality used and refurbished equipment is available.

Radiation safety is extremely important when performing nuclear medicine procedures. The word “nuclear” often conjures up thoughts of nuclear weapons, mushroom clouds, and genetic defects. In fact, many owners are surprised to find out that their animals will not “glow in the dark” after a scan. Four basic premises to radiation safety are considered universal: First, is the as low as reasonably achievable (ALARA) concept, which states that individuals should never allow themselves to be exposed to any more radiation than is absolutely required to do their jobs. The last three radiation safety guidelines that should be remembered are time, distance, and shielding. One should always minimize the time exposed to a radiation source, maximize the distance from it, and when possible place protective shielding (lead, cement walls) between him or herself and the radiation source when possible. For all nuclear medicine procedures performed in veterinary medicine, the users should always wear disposable exam gloves, a lab coat, and should always be monitored (properly wearing a radiation exposure detection device) with a film badge, thermoluminescent dosimeter (TLD) badge, or pocket dosimeter. For most institutions, employees working strictly with nuclear medicine patients will have about one tenth the dose of other employees who work in radiology sections.

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Table • 100-2 Commonly Used Radiopharmaceuticals

RADIOPHARMACEUTICAL OR RADIONUCLIDE	SITE OF LOCALIZATION	METHOD OF LOCALIZATION	TYPICAL USE
^{99m}Tc-Methylene diphosphate	Hydroxyapatite	Chemiadsorption	Bone scan
^{99m}Tc-Diethylene triamine pentaacetic acid	Glomerular filtrate	Active transport	GFR scan
^{99m}Tc-Macroasgregated albumin	Pulmonary capillary bed	Capillary blockade	Perfusion lung scan
^{99m}Tc-HIDA xxx	Hepatocytes and bile	Active transport	Hepatobiliary scan
^{99m}TcO4 xxx	Glandular tissue		Thyroid scan
^{67} Gallium xxx	Sarcoma tissue, abscess	Transferring analog	Sarcoma imaging, FUO
$^{123 \text{ or } 131}$MIBG xxx	Neuroendocrine cells	Active transport	Pheochromocytoma

100.2 THYROID SCINTIGRAPHY

100.2.1 Introduction and Basic Techniques

The thyroid scan is the most commonly performed diagnostic scan in veterinary nuclear medicine and is used to confirm and diagnose feline hyperthyroidism. The diagnostic thyroid scan is considered to be the "gold standard" means of diagnosing feline hyperthyroidism. Because technetium behaves as a halogen (iodine) when administered, it is actively trapped by thyroid cells. However, unlike iodine, technetium is only trapped and does not progress through the remaining steps of thyroid hormone synthesis (organification, coupling, storage, and release).[2,3] The trapping of technetium is competitive with iodine (recent administration of iodinated contrast material may hinder the uptake by the thyroid) and is also influenced by thyroid-stimulating hormone (TSH) levels.[4] Adenomatous hyperplasia of the feline thyroid results in a hyperfunctional gland in two ways. First, the gland synthesizes and releases too much thyroxine, resulting in an elevated T4 value and (more fundamentally) the gland has increased ability to trap iodine (and therefore technetium). This is not always true in the canine species as will be discussed later.

Although the thyroid scan can be performed with either ^{123}I or ^{99m}Tc, technetium has the advantages of being more economical, readily available, and it has a shorter half-life. If disparate imaging between the two radionuclides occurs, they are typically insignificant.[5] The dose of ^{99m}Tc used for a feline patient is typically 4 MCi (+/− 2 MCi) and is administered intravenously into a cephalic or medial saphenous vein. It has been shown that the maximal uptake by thyroid cells is at 45 to 60 minutes after injection[6]; although approximately 90% of cats will demonstrate positive scans in just seconds after injection. Normal salivary gland to thyroid gland ratios are 1:1.2 or less[7] and can be obtained by calculating the count density within a region of interest (ROI) encircling the respective glands. For practical purposes, however, the zygomatic salivary glands and thyroid gland should have very similar degree of uptake in normal cats. In hyperthyroid cats, a portion or all of one or both of the thyroid lobes will have significantly more uptake than that seen by the salivary glands.

100.2.2 Indications for Performing a Thyroid Scan

A thyroid scan should be performed for several reasons. The scan can be used to confirm suspect hyperthyroidism in feline patients that have elevated circulating thyroxine levels prior to administration of radioiodine. The majority of centers routinely perform thyroid scans on all patients prior to administration of radioiodine (^{131}I), thus preventing wrongful treatment of normal patients that have a false-positive elevated T4 or fT4 assays. Negative results of a thyroid scan will prevent an unnecessary surgery or inappropriate administration of radioiodine. The amount of uptake and size of the glands may also aid the clinician in determining the dose of radioiodine to be used, thus allowing some degree of individual tailoring of the dose of radioiodine. Lastly, by routinely performing a diagnostic thyroid scan on all patients, one may be able to exclude a patient whose scan suggests an aggressive thyroid carcinoma, the presence of which may change the owner's decision-making process.

Thyroid scanning may also diagnose patients with "occult" hyperthyroidism. In these cases a diagnostic thyroid scan can quickly diagnose hyperthyroidism in a patient that may otherwise be missed.

A thyroid scan can also be used before or after attempts at surgical resection of both or one lobe of the thyroid in clinically persistent hyperthyroid cats. In these cases, foci of ectopic thyroid tissue can be easily localized

within the cervical region (incomplete resection) or within the cranial mediastinum. Once located, the persistent hyperfunctional thyroid tissue can be removed or ablated with radioiodine.

100.2.3 Image Acquisition

A minimum of three views should be taken during acquisition of a routine feline thyroid scan (Figure 100-1). The first image should be a ventral view, which includes both lobes of the thyroid gland and the mandibular and zygomatic salivary glands. This view is used to confirm the diagnosis of hyperthyroidism because the amount of uptake by the thyroid glands can be easily compared with that of the salivary glands, either by drawing ROIs around the individual glands and comparing count density or by subjective comparison. The second ventral view should be a close up view of just the thyroid gland itself, taking care to include any area of uptake. This view is important in evaluation of the morphology of the thyroid itself. The last view that should be acquired is a lateral view (right or left), including the entire thorax. To ensure that the entire thorax is included, the thyroid should be seen on one side of the image and stomach uptake on the opposite side. This view is important in evaluating for possible uptake within the cranial mediastinal region and lung fields. If uptake is seen in these regions, a ventral view of the thorax and opposite lateral should also be obtained. All images should be acquired on a count basis (as opposed to a time acquisition) for approximately 200,000 counts using pinhole collimation. Each image acquisition should take approximately 3 minutes, giving a total scan time of about 10 minutes (assuming a ^{99m}Tc dose of 4 MCi).

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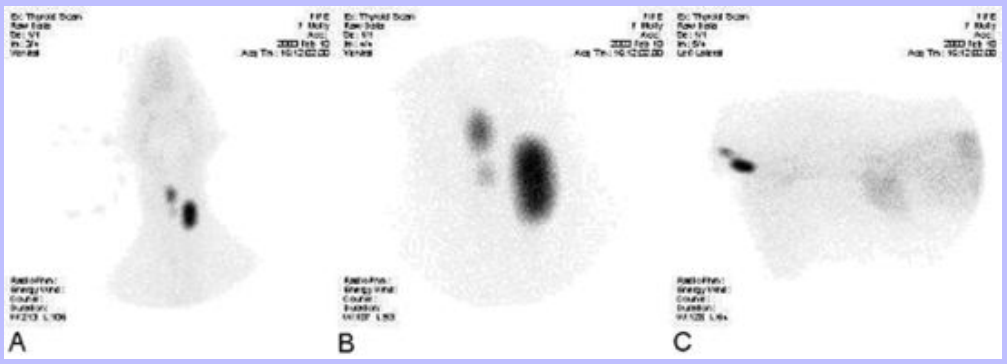
Figure 100-1 Thyroid Scan. Hyperfunctional thyroid adenoma, bilateral, in a fourteen-year-old domestic shorthair, male castrated technetium injected with 4 MCi of ^{99m}Tc. Images shown are 200,000-count static images with pinhole collimation. **A,** Ventral neck view. Focal intense activity is seen by both lobes of the thyroid glands, more so than that seen by the salivary glands. The right thyroid has a "hot" nodule in the cranial and caudal pole. **B,** Ventral thyroid view. Both glands exhibit benign scanning characteristics (intense center, homogeneous uptake, tapering margins, no evidence of regional tissue invasion). **C,** Left lateral thorax view. No abnormal areas of uptake in the thorax are seen.



100.2.4 Interpretation and Analysis

In normal cats (not hyperthyroid) the amount of uptake seen by the salivary glands and thyroid gland is very similar. Placement of ROIs around the salivary glands and thyroid tissue with comparison of the amount of uptake should yield a thyroid to salivary gland ratio of less than 1.2 in normal animals. In most cases the placement of ROIs is not needed to confirm the diagnosis of hyperthyroidism, and subjective evaluation of significantly more uptake within the thyroid tissue versus that of the salivary gland tissue is all that is needed (Figure 100-2).

False-positive ^{99m}Tc thyroid scans can be seen in hyperthyroid cats secondary to recent administration of methimazole because it may cause false increased uptake by the thyroid tissue due to stimulation by an elevated TSH concentration.[10] This same phenomenon has not been evaluated in normal euthyroid cats. False-negative thyroid scans are extremely rare but may be due to severe thyroiditis, recent intake of iodinated contrast material, or ingestion of excess dietary or administered iodine[11] overlying and attenuating soft tissues or malfunctioning nuclear medicine equipment.

Several classifications of feline hyperthyroidism exist based on the location of uptake. Unilateral uptake by one lobe with complete suppression of the contralateral lobe is reportedly seen in approximately one third of patients[3] (Figure 100-3, *A*). Bilateral uptake in both lobes is seen in the remaining two thirds[3] (Figure 100-3, *B*). Bilateral uptake is defined as uptake, regardless of the amount, seen in both thyroid lobes. It is common for one lobe to have more uptake, be larger than the contralateral lobe (incomplete suppression), or both; however, this is still considered to be bilateral because a normally functioning thyroid should demonstrate no evidence of autonomous function and be completely suppressed (thus not seen at all) (Figure 100-3, *C*).

Hyperfunctional ectopic tissue can occur anywhere from the base of the tongue to the base of the heart; the incidence is estimated to be as high as 10%[14] (Figure 100-4). The presence of ectopic hyperfunctional thyroid tissue does not imply malignancy. It is also very common to detect adenomas with intense focal uptake by very small (2 to 3 mm), nonpalpable, thyroid nodules (Figure 100-5).

A thyroid scan can also be used to help differentiate benign adenomatous hyperplasia versus a malignant thyroid carcinoma. Close examination of the morphologic scanning characteristics of each thyroid lobe may give clues that help distinguish nonaggressive disease versus an infiltrative carcinoma. Pinhole collimation is very helpful in evaluating the morphology of thyroid disease because it magnifies the appearance of the otherwise small lobes. Characteristics of a simple adenoma (benign) include round to oval shape, smooth or homogeneous uptake, margins that taper uniformly, and no evidence of regional tissue invasion. Malignant thyroid carcinomas often exhibit very abnormal shapes with poorly defined, irregular margins, heterogenic uptake, and evidence of invasion into surrounding tissue facial planes (Figure 100-6).

Figure 100-2 Normal feline thyroid scan. The amount of uptake by the thyroid gland is similar to that seen by the salivary glands.

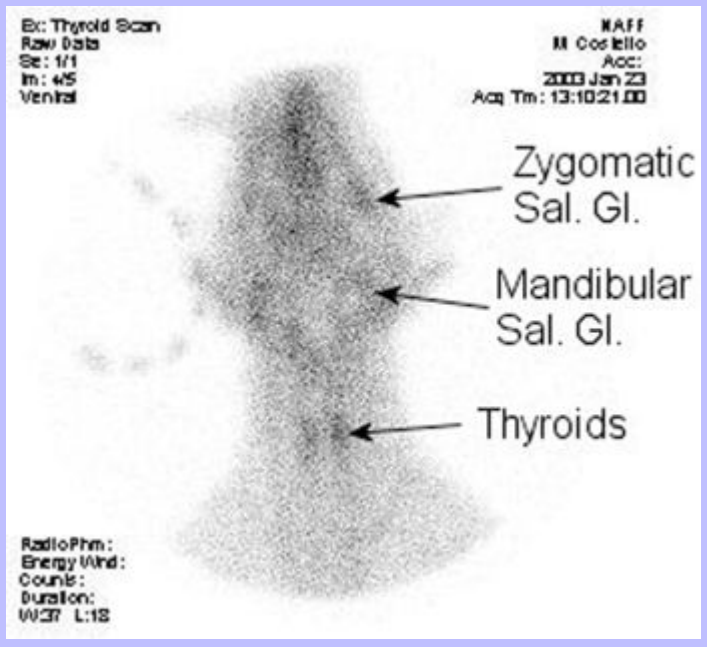
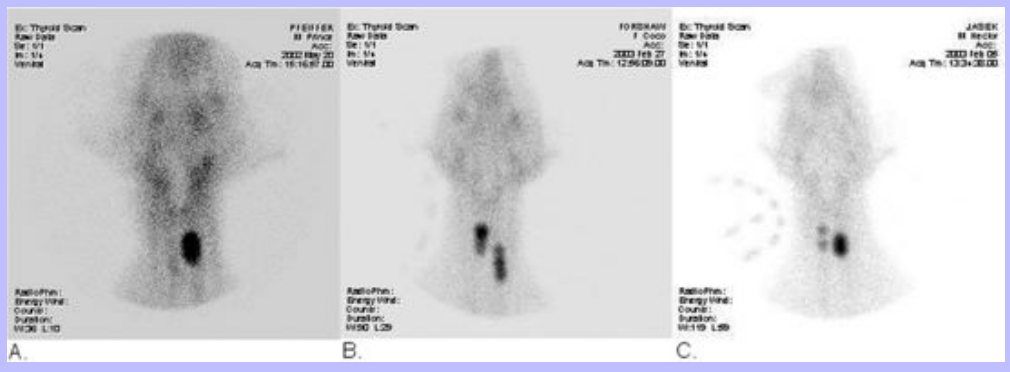


Figure 100-3 Variations of feline hyperthyroidism. Three commonly seen morphologic variations of feline hyperthyroidism exist. **A,** Unilateral with complete suppression of normal contralateral thyroid lobe. **B,** Bilateral hyperthyroidism. **C,** Bilateral hyperthyroidism with incomplete suppression of one thyroid lobe.

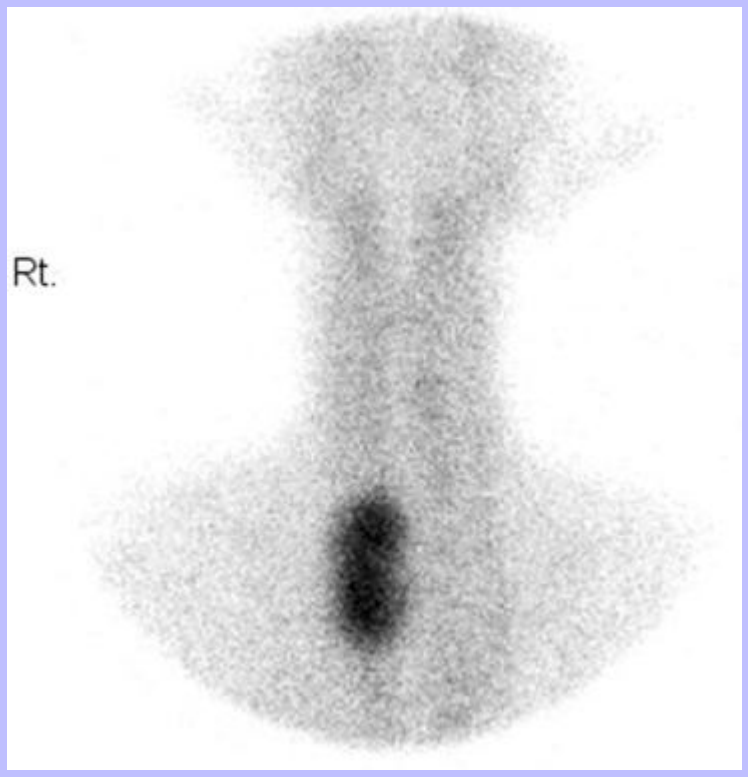


Common findings that occur in adenomas that can be confused with a carcinoma include nodular to multinodular uptake, photopenic areas caused by thyroiditis, follicular cyst or parathyroid adenoma, or ectopic

hyperfunctional tissue within the thoracic inlet or cranial mediastinum. In these cases it is important to examine each focal area of uptake individually for evidence of benignancy or malignancy. If the cat has undergone previous attempts at thyroidectomy, caution must be exercised because the surgical intervention can cause a very abnormal morphologic appearance of the persistent or recurrent thyroid tissue that can mimic a thyroid carcinoma (Figure 100-7).

In cats with suspected thyroid carcinoma, ultrasound is often the next step because it can often detect the reason for photopenic areas caused by follicular cysts or an enlarged parathyroid gland and evaluate if the thyroid appears to be well encapsulated. If none of the aforementioned are true, if the thyroid gland appears of mixed echogenicity, or if it appears invasive into surrounding tissues, surgical intervention usually follows.

Figure 100-4 Ectopic thyroid tissue. Ventral view shows focal intense uptake in functional thyroid tissue located within the cranial mediastinum on the right.



After a diagnostic thyroid scan using ^{99m}Tc, the feline patient must be housed in a radiation isolation ward until it clears the individual clinics release criteria, which is typically set by the issuer of the RML (the author's practice requires 0.5 mR/hour at 1 m). This is measured using an appropriate monitoring device such as a Geiger counter or “Cutie Pie” exposure meter. Once the animal returns home, the owner is instructed on how to care for the pet physically, told to minimize time holding the cat for the next week or so, and instructed how to handle the very small amount of radioiodine that will still be excreted in the cat's urine. (The specifics of these requests often vary from state to state.)

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Figure 100-5 Extremely small, nonpalpable thyroid tissue. Focal intense uptake is evidenced by a very small foci of thyroid tissue on the left side. This nodule was not palpable even in retrospect after the scan localized it.

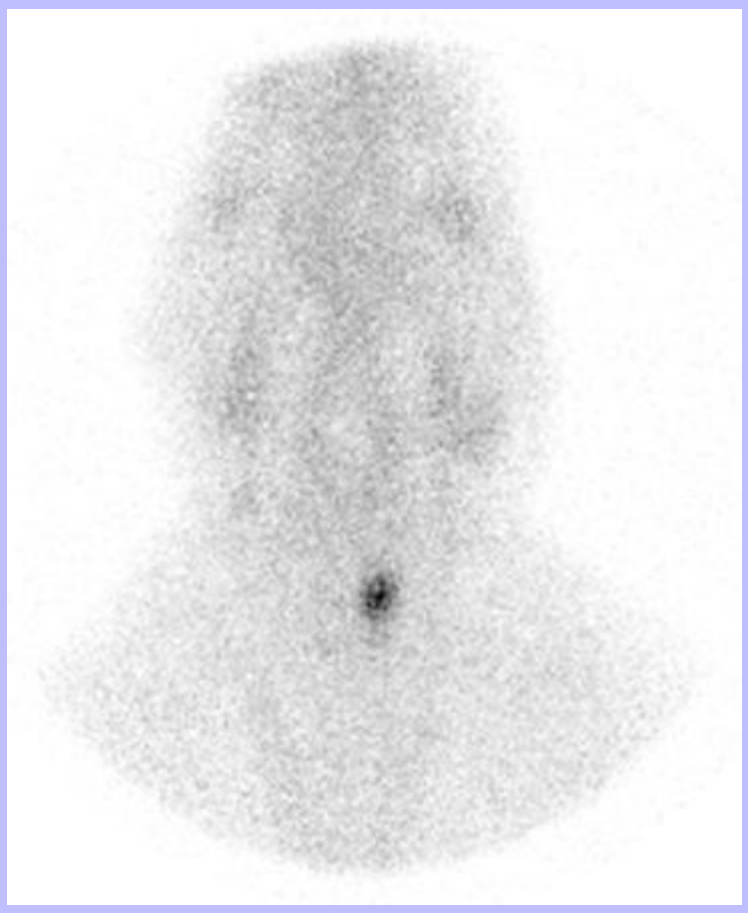
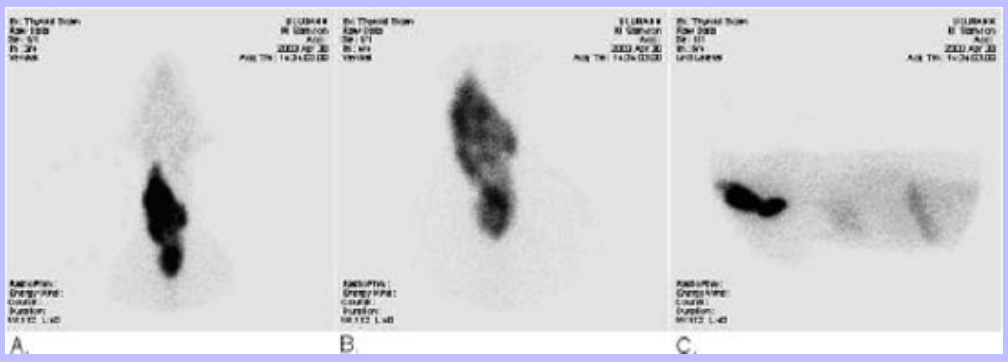


Figure 100-6 Feline thyroid adenocarcinoma. The right thyroid lobe shows very heterogeneous uptake with irregular margins. Extension of functional malignant tissue can be seen into fascial planes and into the cranial mediastinum. Numerous photopenic areas are present.



100.2.5 Radioiodine Therapy for Feline Hyperthyroidism

Three treatment options exist for feline hyperthyroidism: (1) medical therapy with methimazole, (2) surgical removal of the thyroid glands, and (3) radioiodine therapy. All methods have pros and cons, which will be discussed.

Radioiodine therapy using ^{131}I also has both advantages and disadvantages. Radioiodine therapy is extremely targeted in that once injected the iodine is preferentially trapped and organified by the hyperfunctional thyroid cells (little to know uptake is seen by normally suppressed thyroid cells) and once there, the high-energy beta particles that are emitted during the decay process cause irreparable damage to the cells. The distance of beta particle travel, and therefore the area of tissue damage, is confined to 1 to 2 mm; thus concurrent damage to adjacent parathyroid tissue is not seen. Administered radioiodine is taken up by all hyperfunctional thyroid tissue, regardless of its anatomic location. Because feline hyperthyroidism is not an autoimmune form of thyroid disease (human Grave's disease) and most closely resembles toxic nodular goiter (multinodular goiter), the great majority of cats that are diagnosed with hyperthyroidism retain some suppressed (but otherwise normal) thyroid cells. The advantage is that approximately 95% of cats treated with radioiodine will be euthyroid after treatment, requiring no supplementation. It is relatively common for cats to have subnormal total thyroid hormone levels immediately after radioiodine therapy, but it is extremely rare for any of these cats to demonstrate any signs of hypothyroidism. In these cats, a recheck of the thyroid hormone levels in 1 to 3 months after therapy will often demonstrate normal values.

Figure 100-7 Postsurgical thyroid. Fifteen-year-old domestic shorthair, female spayed. Patient is persistently hyperthyroid despite two attempts at bilateral subcapsular thyroidectomy. The left thyroid lobe is irregular in shape and bulbous in appearance secondary to previous surgical intervention (left-sided subcapsular thyroidectomy) and subsequent recurrence. The right thyroid lobe is incompletely suppressed.

Care must be taken regardless of the form of therapy chosen if the patient has concurrent renal compromise. Readers are encouraged to review the many studies that pertain to the correlation of the treatment of hyperthyroidism and renal disease.[15–17] In general, cats that have normal renal function based on normal serum blood urea nitrogen (BUN) and creatinine (CR) values should have few problems with any form of therapy for hyperthyroidism. In patients that are both hyperthyroid and show equivocal or definitive evidence of renal failure (azotemia and inability to concentrate urine), a 3-to 4-week trial period using methimazole is recommended. If at the end of this time the BUN and CR levels are not increased, the animal is not showing signs of renal failure, and the total T4 values have dropped to within the normal range, a more definitive form of therapy can be safely considered. In these patients a lower dose of radioiodine may be used in an effort to minimize any effects on the kidneys and, at the same time, control hyperthyroidism. Radioiodine itself is not toxic to the kidneys. The cause of the worsening of renal disease that can accompany any form of hyperthyroid therapy is unknown but may relate to changes in hemodynamics within the kidney and glomerular filtration. Supplementation of thyroid hormone in cats that experience manifestation of renal failure after definitive thyroid therapy may be of benefit; however, no such studies have been undertaken to prove this theory.

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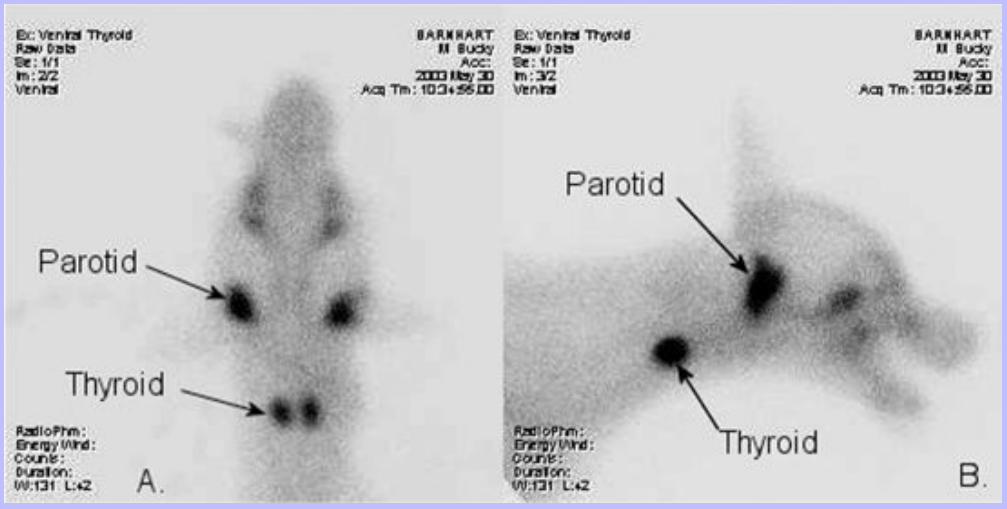
100.2.6 Thyroid Scan and Canine Thyroid Disease

The parotid salivary glands in dogs demonstrate much more uptake compared with those of cats; however, the amount of uptake by the salivary glands and thyroid should be very similar in individual animals of either species (Figure 100-8). The indications to perform thyroid scans in dogs are fewer than in cats but may include

presurgical evaluation of the degree of regional tissue invasion (which may aid the surgeon in evaluating the degree to which one rejects the cervical mass). A thyroid scan can also confirm that a cervical mass is indeed thyroid in origin and identify functional distant metastasis. Canine thyroid carcinoma is different from that seen in cats in that approximately one third of affected patients will demonstrate decreased or no uptake (inability to trap ^{99m}Tc), one third of patients will have relatively normal amounts of uptake (normal ability to trap ^{99m}Tc), with the last third demonstrating increased uptake (increased ability to trap ^{99m}Tc). Uptake by distant metastasis appears to have similar patterns. The same scanning characteristics of malignancy can be applied to the canine patient in that most carcinomas will demonstrate heterogeneous uptake, very irregular gland shapes, and often evidence of regional tissue invasion (Figure 100-9). Thoracic radiographs are more sensitive than a thyroid scan for the detection of pulmonary metastasis, and as such they should always be obtained whenever thyroid carcinoma is suspected.

Figure 100-8 Normal canine thyroid scan. Similar amounts of uptake of the radionuclide by the parotid salivary glands and the thyroid tissue occur. Both thyroid lobes are normal in size, shape, and location.



100.2.7 Radioiodine Therapy for Canine Thyroid Carcinoma

^{131}I has also been used as therapy for canine thyroid carcinoma.[18,19] Radioiodine therapy is best suited for therapy for micrometastatic disease in cases where the primary carcinoma is proven to retain the ability to trap iodine (technetium); as such a diagnostic thyroid scan using ^{99m}Tc or ^{123}I should be performed prior to surgical intervention. The thyroid-associated mass should be removed or debulked surgically followed by radioiodine therapy. Presurgical external beam radiation therapy may also be used in certain cases in an attempt to shrink the primary tumor prior to intervention. If the primary tumor exhibits no ability to concentrate iodine, then conventional chemotherapeutics may be preferential for potential or known micrometastatic disease in combination with external beam radiation therapy for any incompletely resected margins. The dose used for canine thyroid carcinoma varies widely but may range from 20 MCi to 100 MCi or more. The dose is usually administered intravenously through a preplaced catheter. After administration, the animal must be kept in a radiation isolation ward until it has cleared release criteria. Strict radiation safety practices must be instituted

during the entire stay, and it is not uncommon for these patients to contaminate their exterior surfaces with iodine. The typical hospital stay for these patients in the author's practice ranges from 10 to 21 days. Side effects seen with large-dose radioiodine therapy are rare but may include transient neutropenia that lasts only a few days.

100.3 PORTAL SCINTIGRAPHY

100.3.1 Background and Basic Techniques

Nuclear portography (portal scan) has been used as first introduced in the canine by Caride.[20] A portal scan greatly aids in the diagnosis of a macroscopic portosystemic shunt. The scan can rarely differentiate the types of portal shunts (it typically cannot differentiate if the shunt is intrahepatic versus extrahepatic or if a shunt is a single-vessel extrahepatic shunt or from a multivessel extrahepatic shunt). Hepatic microvascular dysplasia will result in a normal portal scan because the radioactive bolus is transported in normal fashion to the liver prior to the cardiac ROI.

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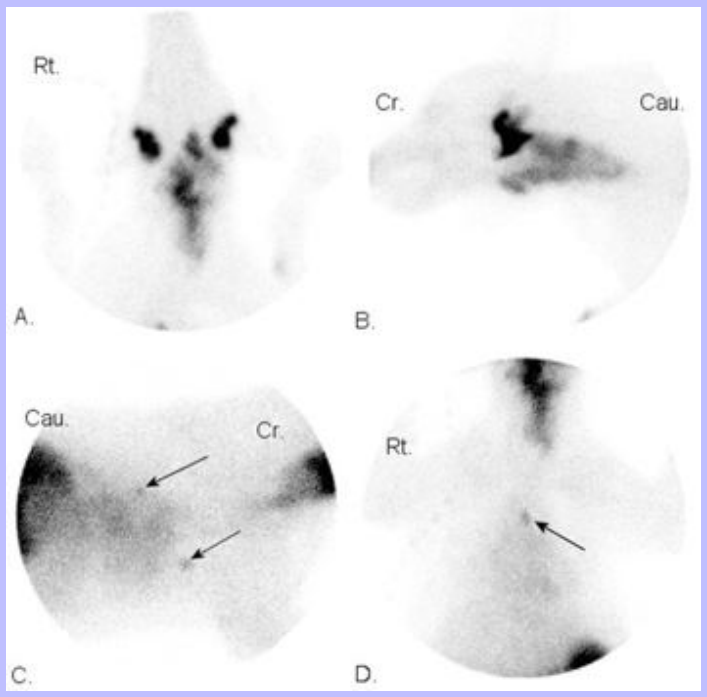
Figure 100-9 Canine thyroid adenocarcinoma. **A,** Ventral neck view shows heterogeneous, ill-defined uptake associated with the left thyroid lobe. Invasion into the caudal and cranial neck region and into fascial planes is seen. **B,** Lateral view of neck. **C,** Right lateral view of the thorax. The arrows are demonstrating two functional pulmonary metastatic lesions. **D,** Dorsal view of the thorax. The arrow points to a visible functional metastatic pulmonary nodule.



100.3.2 Indications for Performing a Portal Scan

The usefulness of a portal scan appears to be in patients that are suspected of having a portosystemic shunt based on clinical signs and high bile acid levels. The portal scan is performed to confirm the existence of a macroscopic shunt prior to surgical exploratory and subsequent ligation or coil placement.

100.3.3 Image Acquisition

A portal scan is performed on a tranquilized or (preferably) anesthetized animal in right lateral recumbency with the diaphragm centered over a gamma camera. The field of view (FOV) should include the entire heart and liver region. Although the scan can be performed without the aid of an interfaced nuclear medicine acquisition computer system, one is highly recommended and is necessary for any type of quantitative analysis and subsequent storage. To help localize the position of the heart and liver, an external source of activity (μCi point sources or the ends of a flexible cobalt ruler) are placed ventral to the animal, directly below the point of maximum intensity (heart) and level of the xiphoid (liver).

A red rubber catheter is placed into the descending colon and inserted to the level of the cranial most aspect of the ilial wings. Careful placement of the tip of the catheter along the ventral aspect of the colon is helpful in preventing a "fecal-o-gram." It is preferable to perform a portal scan with an empty colon and administration of a cleansing enema 2 to 3 hours prior to the scan is recommended by some[21]; however, it is not routinely required. A dose of approximately 3 to 8 MCi of ^{99m}Tc is used in a volume of 0.5 to 1.0 ml of saline. The higher the dose used, the more accurate the results will be owing to better counting statistics. A three-way stopcock is attached to the preplaced catheter, the dose syringe, and a 12-cc syringe filled with room air. A ⅛-inch thick piece of lead is placed between the camera top (imaging table) and the patient, directly under the tip of the catheter and caudal abdomen. Care must be taken to avoid placement of the lead under the liver region or too caudally so that it allows a "bloom" artifact from the radioactive bolus within the colon. The bolus of radiation is injected first, followed by a small amount (3 to 10 ml) of room air at a slow to moderate rate. A dynamic acquisition should be obtained, starting just prior to injection of the bolus of radiation, and continued at 4 seconds per frame for a total of about 3 minutes. Once the pertechnetate is placed within the colon, a small percentage (10% to 20%) is absorbed across the colonic mucosa and is taken up within the portal venous system.

100.3.4 Interpretation and Analysis

In normal patients, activity should be seen within the liver ROI prior to activity seen within the cardiac ROI (Figure 100-10). In animals with macroscopic shunts, the cardiac ROI is seen at the same time or preceding the liver ROI (Figure 100-11). With the aid of a computer and appropriate software, percent shunt fractions can also be obtained using the following formula:

$$\frac{(\sum \text{total heart counts over time i})}{[\sum (\text{total heart counts} + \text{total liver counts}) \text{over time i}]} \times 100$$

Normal animals will have a shunt fraction of less than 20%. A positive scan is considered to be one with a shunt fraction of greater than 50%. Values obtained between 20% and 50% are considered to be abnormal and may be caused by a less severe shunt. In these cases the scan should be repeated or the animal should be explored. A shunt fraction of 0% is not physiologic, owing to the hepatic arterial blood supply. Calculation of a shunt fraction is not necessary for the diagnosis of the existence of a shunt. False-negative scans may be caused by improper placement of the radionuclide bolus in the colon cranial to the level of the shunt, incomplete

absorption of the bolus across the colonic mucosa due to infiltrative disease of the colonic wall itself, or if the bolus is lodged in a ball of feces. Incorrect results (falsely elevated shunt fraction) may be seen if the bolus is administered too far cranially within the colon where a bloom artifact may overlie the liver ROI. This is commonly seen if the colon is filled with liquid, such as just after administration of an enema. The majority of the technetium is excreted in the feces (that which remains in the colon) and in the urine (that which was absorbed systemically) within the first 12 hours after the scan.

Portal streaming, as reported by Daniel,[22] is the phenomenon seen in a small portion of animals that causes only one or two lobes of the liver to scintillate. Portal streaming is caused by abnormal patterns of blood flow within the extrahepatic or initial portion of the intrahepatic vasculature that results in a “steering” of the radioactive bolus into only a section of the liver.

In the author's facility, animals with a positive portal scan accompanied by high pre-and postprandial bile acids are subsequently ultrasounded to help rule out the possibility of an intrahepatic shunt or multivessel extrahepatic shunt. If the ultrasound is negative for an intrahepatic shunt and no evidence of a multivessel extrahepatic shunt is seen, the patient proceeds to surgery for definitive localization and repair. Only in rare cases, intraoperative mesenteric portograms are required for definitive identification of the shunt vessel.

100.4 BONE SCINTIGRAPHY

100.4.1 Background and Basic Techniques

Bone scans are highly sensitive and equally highly nonspecific. Evaluation of the extent, pattern, and anatomic origin of an area of abnormal uptake, coupled with other factors such as the animal's age, sex, breed, history, physical examination, and radiographic findings can increase the specificity; in many cases a diagnosis can be made. Most images are acquired with the gamma camera head placed underneath a Plexiglas scanning table. Care should always be taken to ensure that the camera face is placed as close as possible to the underside of the imaging table and that the camera face is exactly parallel to the tabletop. By imaging from under the animal, positioning is easier and the patient feels less threatened than if the camera were placed above it. Dorsal and ventral dynamic or static images can be easily obtained on most, if not all, small animals. Using a large FOV gamma camera, a whole-body bone scan can be obtained on a large breed canine in approximately 30 to 45 minutes.

Figure 100-10 Normal portal scan. Dynamic image acquisition shows uptake within the liver region of interest (ROI) preceding that seen within the cardiac ROI.

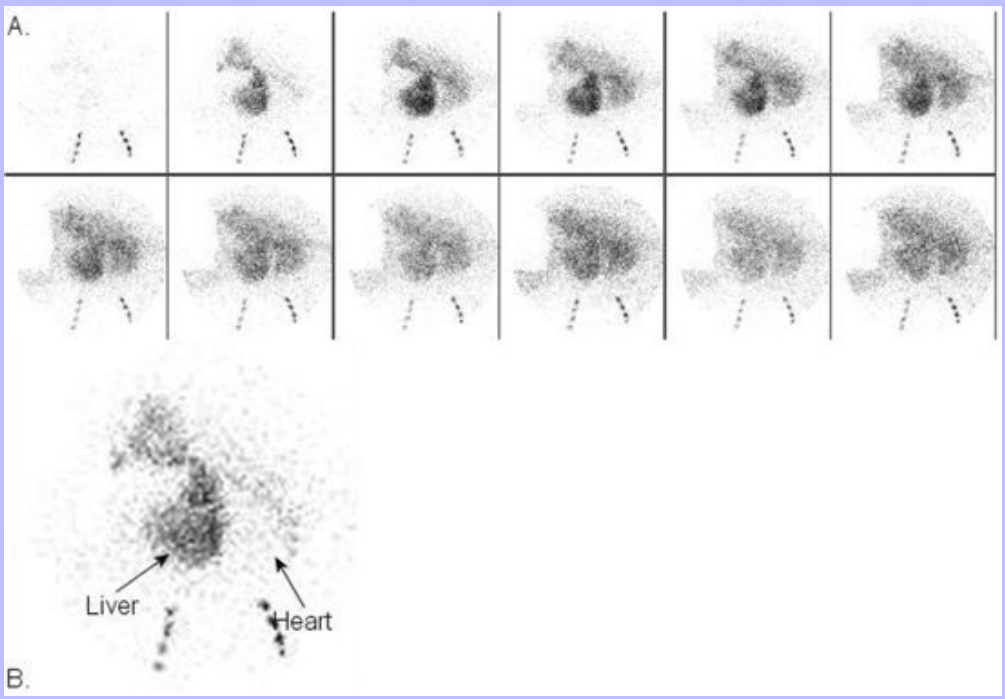
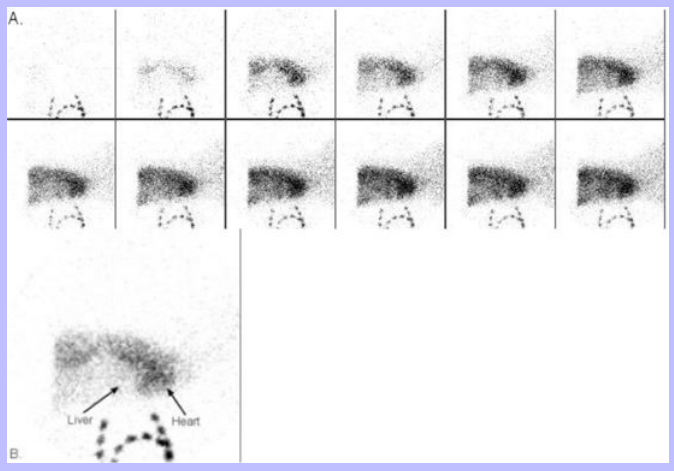


Figure 100-11 Abnormal portal scan. Dynamic image acquisition shows uptake within the cardiac region of interest (ROI) preceding that seen within the liver ROI.



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100.4.2 Indications for Performing a Bone Scan

Bone scintigraphy has multiple uses in small animals. These include evaluation for primary and metastatic disease, septic arthritis, osteomyelitis, prosthetic implant loosening or infection, soft tissue and bone viability, occult lameness, and fracture healing. Bone scanning can often times localize subtle lesions not seen radiographically until days or weeks later.

100.4.3 Image Acquisition

In small animals, all static images should be acquired on a count basis, as opposed to a timed acquisition. Timed acquisitions often result in images with low count densities and poor target-to-background ratios, which renders less than optimal image quality. The higher count density and high target-to-background ratio images that are obtained using count acquisition parameters are usually of much higher quality than those obtained on a time acquisition basis. The longer scan time needed per image (1 to 3 minutes) is only significant if the animal is not under general anesthesia and patient movement is likely.

Patient preparation prior to scanning is not needed. The radiopharmaceutical ^{99m}Tc-MDP is used commonly and results in high-quality images with good target-to-background ratios. Nonradioactive (“cold”) MDP is sold in a kit form and is easily made using a fresh eluate of reduced (Sn) $^{99m}TcO_4$, which allows the labeling (“tagging”) of the short chain polyphosphate. Because little binding of the radiopharmaceutical to plasma proteins takes place, urinary excretion is rapid, with 59% of the dose excreted within 24 hours.[23] Adequate blood flow is necessary for delivery of the radiopharmaceutical; however, once delivered, skeletal uptake is not a function of perfusion.[24] The exact mechanism of binding is not well understood, but it is known that the phosphate itself is merely the delivery vehicle for the ^{99m}Tc; once arriving at the hydroxyapatite surface, the ^{99m}Tc is released and then chemiadsorbs to the hydroxyapatite surface as ^{99m}Tc-oxide.[24,25] Uptake of the MDP is directly proportional to osteoblastic activity and can be affected by decreased perfusion and regional sympathetic tone.[26] Maximum bone uptake is at 65 minutes postinjection, with the maximum target-to-background ratio (highest activity in the bone and lowest activity in the soft tissues) occurring at 6 hours postinjection.[27]

Radiopharmaceutical dose ranges from approximately 5 MCi to 30 MCi, depending on the animal's size (Table 100-3).

Dosing of small animals for nuclear medicine procedures will vary; however, small breed canines (e.g., toy poodles) and cats are administered 5 MCi doses, medium-sized canines (e.g., Beagles) are given 10 to 15 MCi doses, large breed dogs (e.g., Labradors) are given 20 MCi doses, and giant breed dogs are given 30 MCi doses. As with all radiopharmaceuticals, intravenous routes of administration are used. If the dose is injected through a preplaced catheter, the catheter should be flushed well after the dose is given. Even a small amount of extravasated dose will result in an injection site hot spot on subsequent imaging. Because injection site hot spots occur, it is recommended to inject in a limb that is not in question for diagnosis or to inject into a rear limb if imaging a front limb, for example. For single-phase scans, bone phase images should be acquired no earlier than 3 hours after administration. During this incubation time, care should be taken to minimize external contamination of the animal by urine. When possible, the urinary bladder should be emptied just prior to scanning by passing a urinary catheter, manually evacuating the urine, and safely disposing of the radioactive waste when done. Emptying of the bladder should be done in a careful manner to minimize contamination in

the surrounding area. Clinicians should adhere to the ALARA concept in all cases; personnel that will handle the patient or urine should wear examination gloves to avoid exposure.

Table • 100-3 Small Animal Bone Scan Doses

ANIMAL SIZE	DOSE (MCi)
Toy breeds and cats	5
Medium breeds	10–15
Large breeds	20
Giant breeds	30

Routine bone scan images should be obtained using a general all-purpose (GAP), parallel hole collimator with a 20% window centered over the 140 keV gamma photo peak of ^{99m}Tc. Occasionally, a pinhole collimator is helpful in acquiring high-resolution images of small parts, such as the coxofemoral joints (Legg-Calve-Perthes Disease), elbows, carpi, and sesamoid bones associated with the extremities. If a pinhole collimator is used, the number of acquired counts will need to be decreased because the acquisition time becomes prohibitively long.

As with thyroid imaging, all static images should be acquired on a count basis. Generally speaking, the more counts that can be acquired, the higher quality the image will be. The following are suggestions regarding recommendations for static acquisitions for different body parts (Table 100-4).

During acquisition, the animal should not be allowed to move. Movement associated with respiration cannot be avoided; however, panting artifact can be minimized by manually holding the animal's muzzle closed.

Positioning of the animal for a particular body part to be imaged can be critical in obtaining a high-quality scan that is free of artifact. The following recommendations are an attempt to aid in positioning (Table 100-5).

Two methods for accurately comparing two similar ROIs (e.g., the elbows) are available. The easiest way is to place both limbs or ROIs in the middle of the camera in the same field of view. Care must be taken to ensure that both limbs are positioned exactly the same and not rotated. It is also very important to make sure that both limbs or ROIs are equally distant from the camera face, ideally in contact with the camera face. If one limb is further from the camera than the other, it will appear artifactually more intense. The second method for comparison of similar ROIs is to image the areas separately. This is accomplished by imaging one ROI for a preset number of counts and recording the time of acquisition. The contralateral ROI should then be imaged for the amount of time it took to acquire the first ROI image, then recording the total number of counts. For this method to be accurate it is very important to make sure that the two images used for comparison appear exactly the same on the field of view.

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Table • 100-4 Recommendations for Bone Scan Count Acquisitions

ANATOMIC SECTION	COUNTS TO ACQUIRE
Thorax	750,000 (750 k)
Pelvis*	500,000 (500 k)
Skull or C-spine	350,000 (350 k)
Lumbar spine*	350,000 (350 k)
Elbow or stifle	200,000 (200 k)
Distal extremity	100,000 (100 k)

* Assumes the urinary bladder is empty.

Table • 100-5 Positioning Recommendations

ANATOMIC SECTION	RECOMMENDATIONS
Dorsal or ventral skull, spine or pelvis	Animal is placed in radiolucent V trough, legs are extended out, and symmetrical placement is ensured
Lateral skull	Neck is extended, head is rotated axially so that eyes are perpendicular to tabletop, and forelimbs are pulled caudally
Lateral C-spine	Traction is applied to neck, head is rotated axially to straighten skull, and front limbs are pulled caudally
Lateral shoulder	Neck is extended, shoulder to be imaged is placed down with the ipsilateral front limb extended and pulled cranially, and contralateral limb is pulled caudally
Lateral thorax Lateral lumbar spine	Front limbs are pulled cranially
Lateral pelvis	Urinary bladder is evacuated (or shielded), rear limbs are pulled caudally, pelvis is rotated axially until ilia are superimposed
Lateral stifle	Urinary bladder is evacuated (or shielded), stifle to be imaged is placed down, rear limb is pulled caudally (placing stifle in center of the camera), and contralateral stifle is abducted out of field of view (FOV)
Distal limbs	Palmar/plantar view—both paws are placed side-by-side in same field of view, centered, and rotated until symmetrical Lateral view—limbs are extend, one limb is done for counts (note time of acquisition), contralateral limb is done for time of first acquisition (clinician should note total counts acquired and compare to contralateral limb)

100.4.4 Interpretation and Analysis

Without experience the normal bone scan in small animals can be difficult to interpret. Skeletally immature animals have very focal intense uptake in metaphyseal regions of long bones and at costochondral junctions (Figure 100-12). Normal areas of increased skeletal uptake in all (immature and mature) small animals include areas of thick bone (ends of long bones), temporomandibular joints (TMJs), occiput, the first cervical vertebrae (on the lateral image), sinuses, and costochondral junctions (Figure 100-13). Normal areas of soft tissue accumulation include kidney and urinary bladder. Activity in the kidneys can be minimal to marked. Activity in the bladder is marked, requiring evacuation prior to imaging or lead shielding.

Nonskeletal distribution of bone-seeking radiopharmaceuticals include calcinosis cutis, pulmonary mineralization, renal infarcts, acute rhabdomyolysis, lymph node uptake (after extravasation of the dose),[28] thyroid uptake of free pertechnetate, or dystrophic mineralization of soft tissues.[29] Tracer uptake has also been reported in lactating breast tissue of women[30–32] and the pregnant uterus.[33]

Several reasons exist for generalized poor skeletal uptake that results in poor image quality. These include decreased cardiac output, an increased overlying mass of soft tissue (edema formation), renal failure, or simple old age.

100.4.5 Neoplastic Disease

Bone scanning is the most common nuclear medicine procedure performed at many human hospitals, making up over nearly half of the nuclear medicine caseload. By far, the most common indication to order a bone scan

is for evaluation of possible or known metastatic bone disease.[34] Bone scanning has been shown to be a sensitive indicator for the detection of skeletal metastasis.[35,36] The majority of these patients have primary prostatic or breast cancer. In these patients, a whole-body bone scan is obtained using a moving gamma camera (or moving patient gantry) that acquires a static image of the entire human body in less than 30 minutes. If an abnormal area of uptake is seen, additional "spot" images can be obtained. In veterinary medicine, overall rate of occurrence of skeletal metastasis is not known but is considered low (<10%).[37] Tumors that have shown a propensity for bone metastasis include prostatic adenocarcinoma, transitional cell carcinomas, primary bone osteosarcoma, thyroid adenocarcinoma, and mammary carcinomas (Figure 100-14).[37,38] Bone scans have been shown to be 30% to 50% more sensitive for the detection of metastatic bone disease than radiographs.[39] Because of this, the bone scan may pick up metastatic disease before the animal shows skeletal pain.[38] In many cases, bone scans allow for earlier detection of metastatic bone disease, which can significantly alter the owner's decision to proceed with further therapy or change treatment options. Several patterns of metastatic bone disease have been described, the most common of which is variably sized, multiple, focal, intense hot spots, randomly distributed throughout skeleton.[40] The axial skeleton is most commonly affected (skull, vertebral bodies, ribs, and pelvis), followed by the femur and humerus.[41] In the skull the metastatic lesions are usually associated with suture lines. Rib uptake should be randomly distributed—uptake at the same level on adjacent ribs is most often due to previous trauma, not metastatic disease. If this is seen, a careful history should be obtained from the owner and radiographs of the ROI should be obtained. In the ribs the normal increased uptake of costochondral junctions should also be differentiated from metastatic bone disease. If the appendicular skeleton is involved, metastatic bone disease will typically spread to the diaphyseal portions of long bones, especially at the sites of nutrient foramen. False-negative bone scans are uncommon but can be due to the fact that up to 5% of bone metastasis are "cold," showing little to no uptake.[42] In most cases multiple myeloma or other purely lytic tumors are generally negative (although ^{99m}Tc-Sestamibi or ^{201}Tl may be positive), owing the fact that little osteoblastic activity takes place. Other benign lesions that may have similar focal intense uptake include sepsis, osteophytes, enthesiophytes, spondylosis deformans, and chronic healed fractures. These lesions can usually be differentiated based on the location of uptake (metaphyseal, diaphyseal, or within a joint space) and the history, signalment, and physical examination findings.

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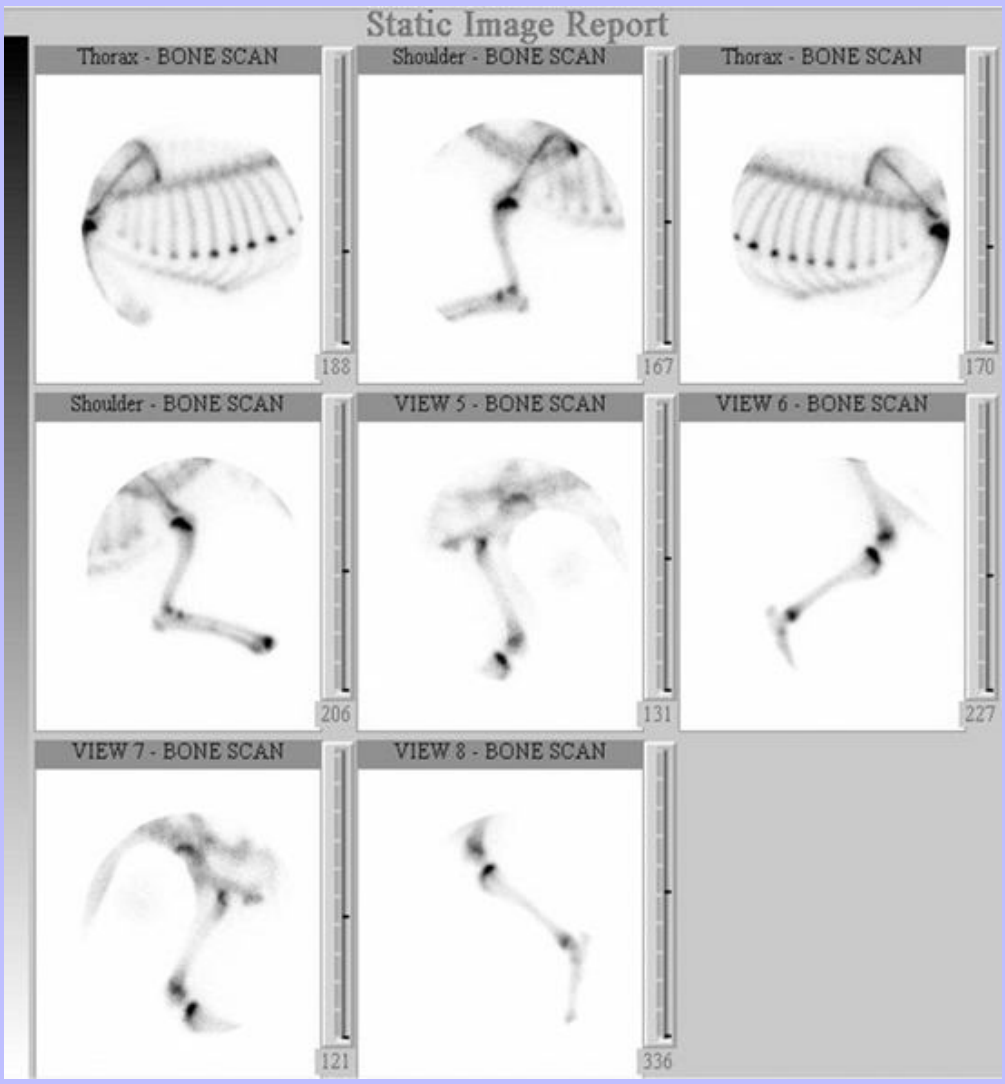
Figure 100-12 Normal bone phase images from skeletally immature canine. The reader should note the marked areas of normal uptake in the metaphyseal regions of long bones and the costochondral junctions.



A persistent problem in both human and veterinary medicine is that of a solitary focus of increased uptake in a patient known to have a primary tumor elsewhere. Although a similar study does not exist in veterinary medicine, Tumah and colleagues[43] reported only 10% of solitary rib lesions were due to metastatic disease in a group of patients with known breast cancer. In these cases radiographic correlation is essential, and demonstration of benign radiographic features can sometimes answer the question definitively. In some cases histological confirmation may be required.

Primary bone neoplasia such as osteosarcoma, chondrosarcoma, fibrosarcoma, or synovial cell sarcoma most commonly is seen first on radiographs. Scanning characteristics associated with primary bone tumors include metaphyseal location, extremely intense uptake, and extension toward the diaphyseal portion of the involved bone; many may have photopenic centers or heterogeneous uptake (Figure 100-15).[44,45] The usefulness of a bone scan in these patients is to rule out the presence of metastatic bone disease prior to costly amputation, chemotherapy, radiation therapy, or limb-sparring techniques. Magnetic resonance imaging (MRI) has proven to be superior to radiography, computed tomography (CT), and scintigraphy in evaluating the extent and degree of invasiveness of neoplastic bone tumors.[46–48] Bone scans tend to overestimate the extent of primary bone tumors due to the "bloom" effect (Figure 100-16).[44] Pulmonary metastasis may demonstrate a faint blush on bone scans, and areas of mineralized soft tissue (metastatic or dystrophic mineralization) will also be positive (Figure 100-17).

In rare cases a "super scan" is seen (Figure 100-18).[49,50] Although the exact mechanism is not clear, these scans are felt to be related to paraneoplastic hypercalcemia. Such scans will have marked, diffuse, symmetrical skeletal uptake; the kidneys are not seen; little-to-no soft tissue uptake occurs; and obvious bone activity is seen on soft tissue phase images. The significance of the "super scan" is not known, and it does not appear to be correlated to one particular tumor type.

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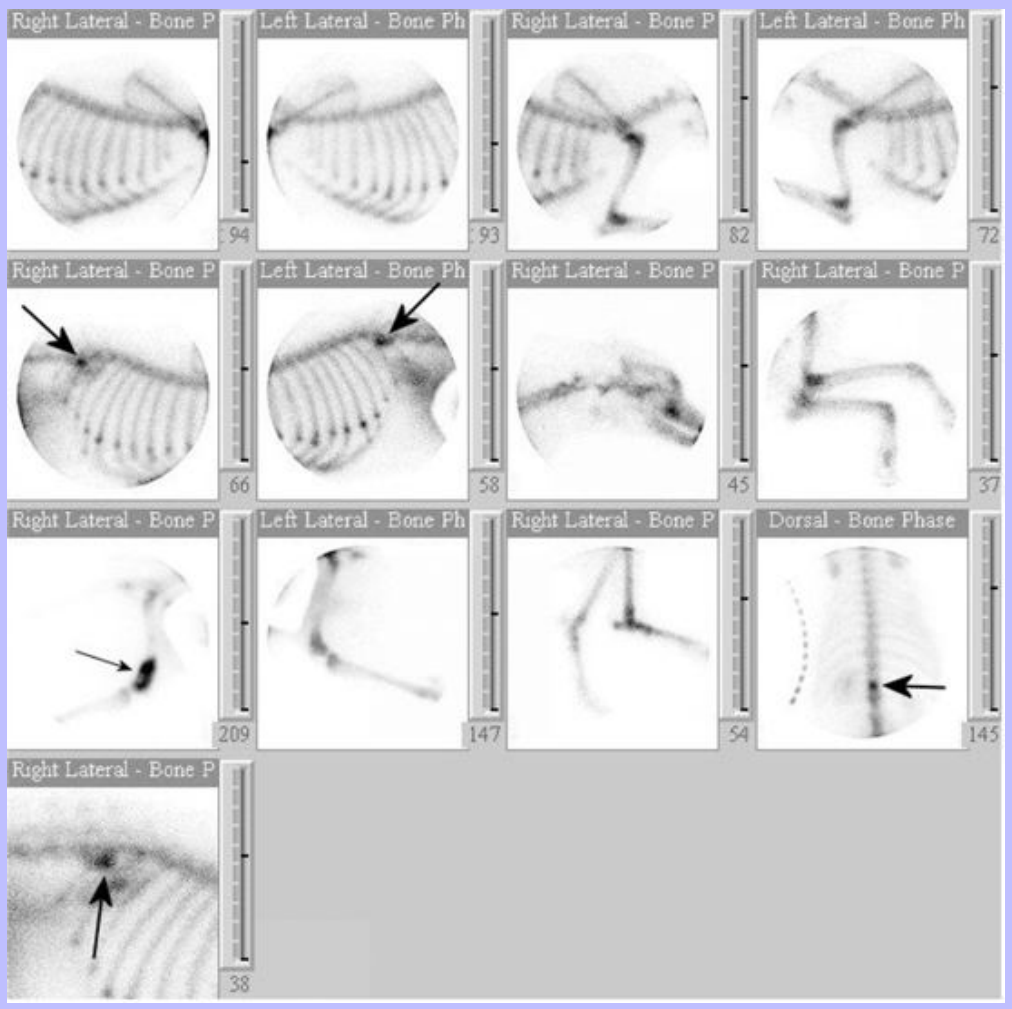
Figure 100-13 Normal bone scan in an adult canine. The reader should note the location of normal "hot spots" including C1 (end-on spinous processes), occiput, temporomandibular joints (TMJs), metaphyseal regions, and costochondral junctions. A primary bone tumor (osteosarcoma) is seen in the distal right humerus *(small-headed arrow)*. The hot spot on the ventral aspect of T13-L1 is spondylosis deformans *(large-headed arrow)* and should not be confused with a metastatic lesion.



100.4.6 Non-Neoplastic Disease

In small animals, acute hematogeneous osteomyelitis is relatively rare; however, septic arthritis, physitis, and discospondylitis are more common. Hematogeneous osteomyelitis will typically demonstrate intense linear cortical uptake within 24 to 48 hours[51] (radiographs are positive at 10 to 21 days).[52] The bone scan will often remain positive for weeks to months after the infection has resolved.[53] Because of this, bone scanning cannot confirm presence of *active* disease, but a negative scan excludes it. Septic arthritis (Figure 100-19), septic physitis, and discospondylitis will all demonstrate extremely focal intense uptake on bone phase images and in some cases may be positive prior to radiographs.[54,55]

Occult lameness can be defined as a persistent, often subtle, undiagnosed lameness that cannot be localized on physical or orthopedic examination. If anatomic localization is possible, radiographs are often normal or inconclusive. Causes for an occult lameness often include mild panosteitis, fragmented medial coronoid processes, partial tear of the cranial cruciate ligament, meniscal injury, stress fractures, fractures of the sesamoid bones, and small avulsion fractures (Figure 100-20). Both single-phase and three-phase bone scanning may be useful in definitively localizing these conditions.

Panosteitis appears on bone scans as intense linear uptake within the medullary cavity of the diaphysis on bone phase images, as well as having minimal-to-marked uptake on the soft tissue phase images (Figure 100-21). Bone scans can often diagnose panosteitis on animals with subtle, nonlocalizable lameness or may be helpful when radiographic findings are equivocal.

Although radiography is typically the primary imaging modality to assess abnormalities associated with the medial coronoid process, radiographs can often be inconclusive in the early stages of this developmental disease because many of the Roentgen signs include degenerative changes associated with the anconeal process and ulnar trochlear notch.[56–58] CT has also been shown to have excellent sensitivity in diagnosis of fragmented medial coronoid processes; however, the availability of CT may be limited.[57] Bone scan findings that suggest a fragmented medial coronoid process are dependent on the animal's age. In puppies the medial coronoid process overlies the proximal radial physis on the lateral view. Because this physis demonstrates typical physeal uptake, a focal intense “hot spot” in this region may be due to either a fragmented medial coronoid process or the proximal radial physis. In these dogs, however, comparison of the amount and pattern of uptake bilaterally can be helpful in diagnosing a unilateral fragmented medial coronoid process. Focal intense uptake associated with the proximal radial physis should be symmetrical. Asymmetrical uptake suggests a diagnosis of fragmented medial coronoid process. Because the diagnosis is dependent on asymmetrical activity in these young dogs, the scintigraphic diagnosis of bilateral fragmented medial coronoid processes may be insensitive using bone scan findings alone. Although rare, fragmented medial coronoid processes can occur in middle-aged to older dogs (Shetland Sheepdogs). In these animals the scintigraphic diagnosis is often easier because no focal increased uptake of the proximal radial physis occurs. In skeletally mature animals, the amount of uptake by the radial head and medial coronoid process region should be similar to that of the distal humeral condyles (in the lateral projection). Focal increased uptake by the region of the medial coronoid process that is significantly more than that seen by the distal humeral condyles is highly suggestive of a fragmented medial coronoid process (Figure 100-22).[59] In both young and older animals, anterior-posterior (AP) views or pinhole collimation (or both) may also be helpful in differentiating uptake by the radial head and the medial coronoid process.

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Figure 100-14 Metastatic bone disease. Focal intense uptake is seen that is associated with multiple ribs and proximal aspect of right scapula in an animal with a transitional cell carcinoma of the urinary bladder.

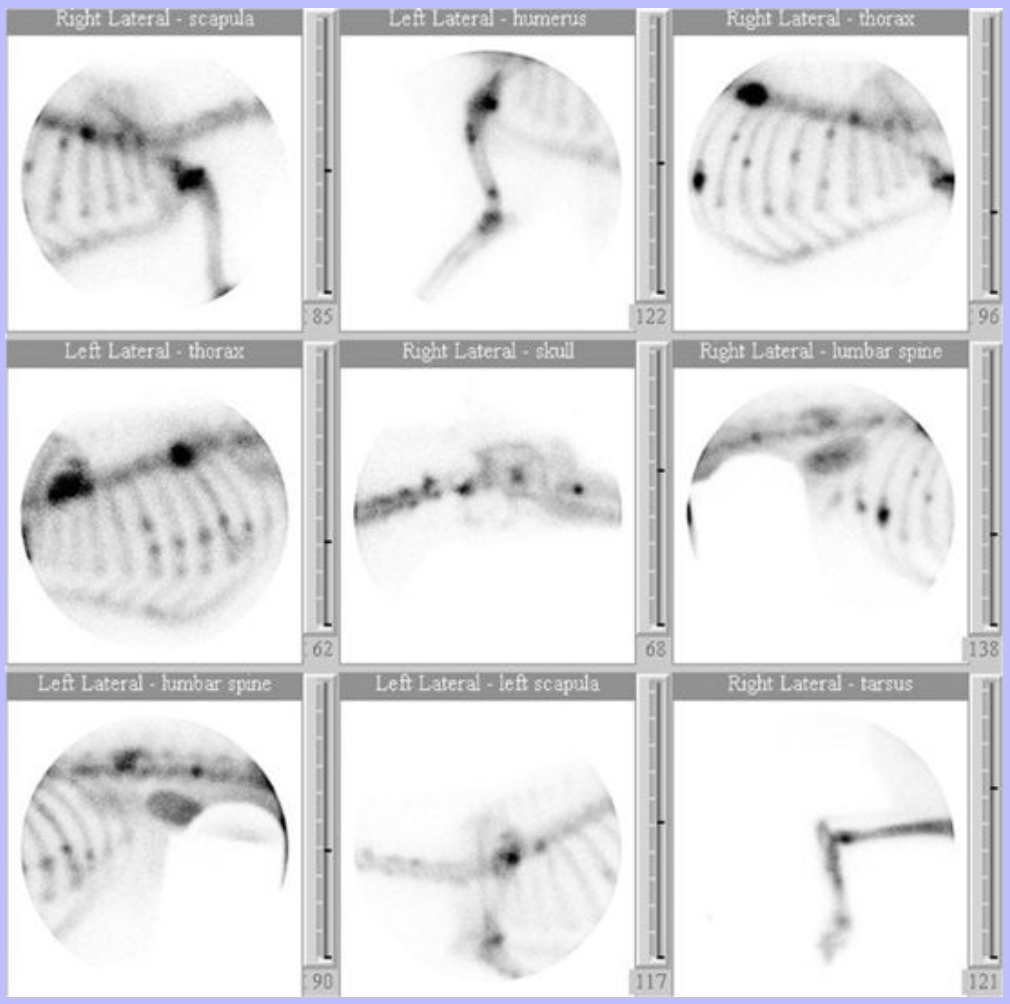


Figure 100-15 Primary osteosarcoma distal left tibia. An irregular area of focal intense heterogeneous uptake is seen in the distal metaphyseal region of the left tibia **(A).** With the intensity turned down, a photopenic center is visible, suggestive of a central area of necrosis **(B)**.

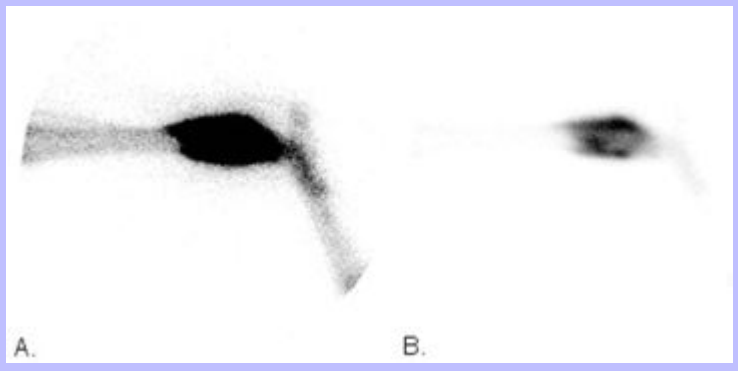


Figure 100-16 Primary osteosarcoma of the left humerus. A large, poorly defined area of intense uptake is seen in the proximal metaphyseal region of the left humerus. The reader should note that the lesion has marked heterogeneous uptake, does not appear to cross the scapulohumeral joint space, and appears to extend to the mid-diaphyseal region ("bloom" effect).

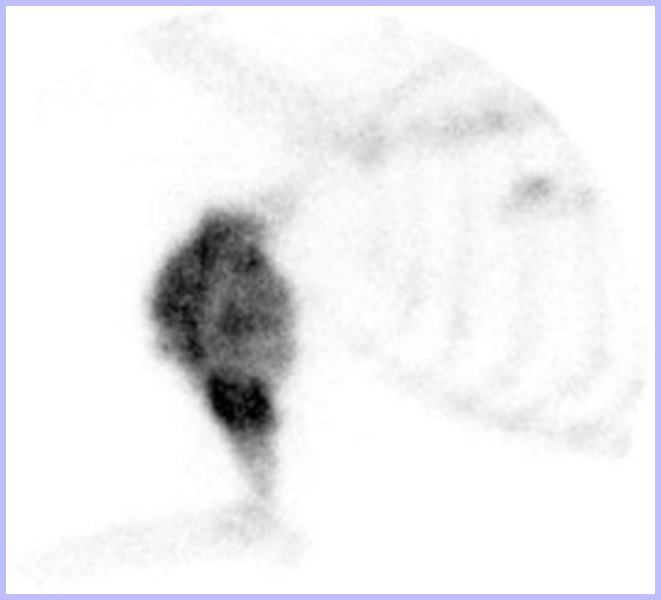


Figure 100-17 Pulmonary metastatic nodules seen on a bone scan. Areas of radiopharmaceutical uptake are seen between the ribs. The amount of uptake ranges from faint to marked. “Shine through” from rib lesions on the opposite side of the thorax should be differentiated from areas of uptake in the lung.

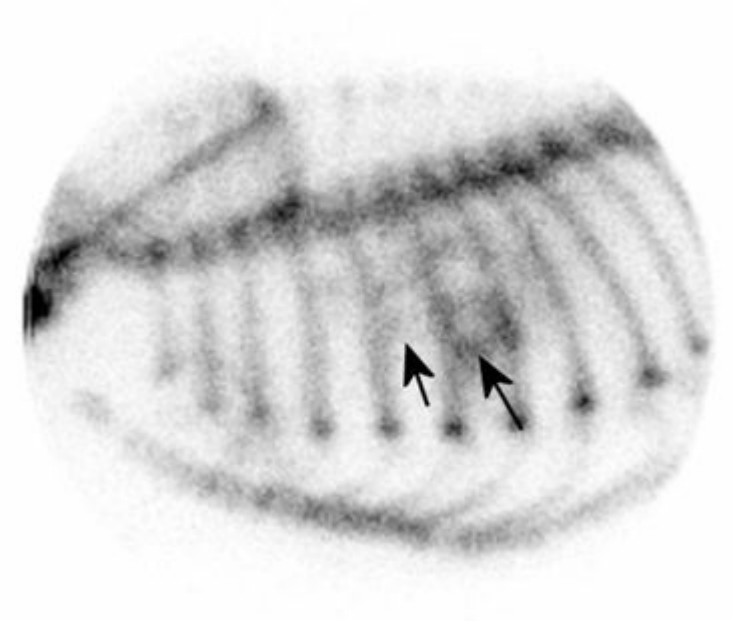


Figure 100-18 Super scan. The reader should note the “pretty bone scan” appearance with marked skeletal uptake within all portions of the skeleton and prominent kidney uptake.

Three-phase bone scans may also be helpful in diagnosing partial (incomplete) tears of the cranial cruciate ligament (Figure 100-23).[60] In these cases the soft tissue phases may be helpful in differentiating acute (active) synovitis from chronic (inactive) intracapsular soft tissue swelling. In the normal canine stifle, a distinct photopenic area is seen within the cranial aspect of the stifle joint that corresponds with the shape and location of the infrapatellar fat pad. In animals with active synovitis, this area demonstrates a faint uptake (blush). Comparison to the contralateral stifle is usually helpful. This same “blush” is not seen in animals with chronic effusion or joint capsule thickening. Bone phase images are not typically helpful in evaluating potential acute cruciate disease.

Stress fractures result from repetitive, prolonged muscular action on bone that is unaccustomed to such stress. Typical symptoms include mild to marked lameness, bone pain, minimal soft tissue swelling, and bone pain that are relieved by discontinuing the exercise. In dogs, stress fractures are seen in athletic and working species and most commonly occur within the diaphyseal portions of long bones, particularly the tibia (Figure 100-24). Bone scintigraphy has proven to be highly sensitive in the early detection of stress-related bone disease[61–63] and is often positive prior to radiographic abnormalities.

In human beings the incidence of bipartite sesamoid bones is approximately 10% to 33%. Although the incidence in small animals is unknown, breeds such as Rottweilers, Greyhounds, Dobermans, and Labradors may have higher incidence of sesamoid disease.[64,65] A bone scan can also differentiate bipartite sesamoid bones from fractured sesamoid bones. Bipartite sesamoids will have no abnormal uptake, whereas recently fractured sesamoid bones will have marked focal uptake (Figure 100-25).

Evaluation of fracture and fracture healing can also be performed using bone scanning. Bone phase images are very sensitive to fracture, and it can be difficult to differentiate acute pathologic conditions from healed previous fracture. It has been reported that bone scans (bone phase images) are 80% positive by 24 hours, 95% positive by 72 hours, 98% positive by 7 days.[66] It has also been shown that 90% of patients with previous fracture are negative on bone phase images at 2 years.[26] Bone scans may also be helpful in the evaluation of the nonunion fracture (lack of progressive healing at 6 months postfracture). Focal intense uptake at fracture ends indicates viable tissue and shorter time to union, whereas little uptake at fracture ends indicates nonunion is likely.[67]

Avascular necrosis of the femoral head (Legg-Calve-Perthes disease) has a unique appearance, depending on the maturation of the disease. Within 12 to 48 hours after injury, a focal photopenic area within femoral head is seen, which is then followed by a rim of moderately focal intense activity around a central photopenic core at 1 to 3 weeks. As the condition becomes chronic, the photopenic central core will fill in and have similar activity to the remainder of the femoral head.[68]

Figure 100-19 Osteomyelitis. Soft tissue phase and bone phase images of the right and left stifle joints obtained 3 months after bilateral cruciate surgery. On the soft tissue phase images, marked uptake is seen in the proximal metaphyseal and diaphyseal regions of the right tibia and within the cranial aspect of the stifle joint. The bone phase images show very intense uptake of the distal metaphyseal regions of the femurs and proximal metaphyseal regions of the tibias. *Staphylococcus aurous* was isolated from a joint fluid.

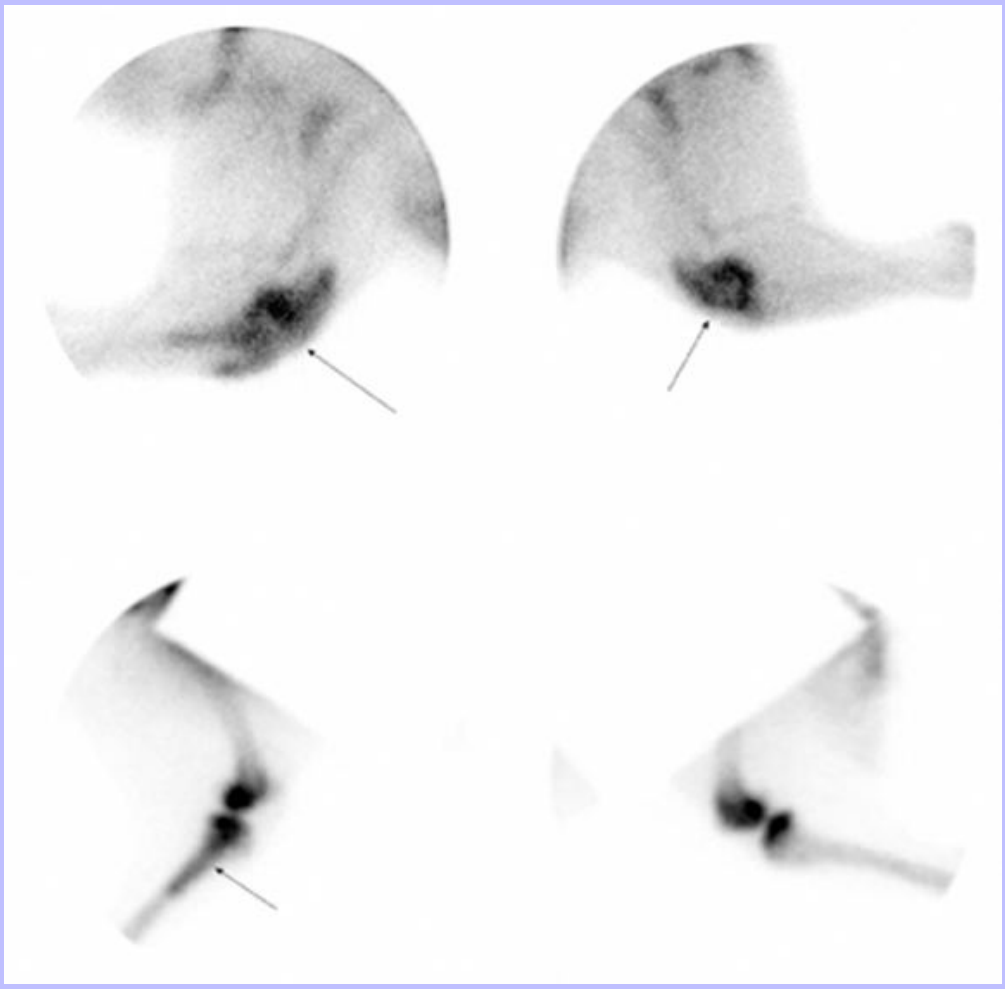
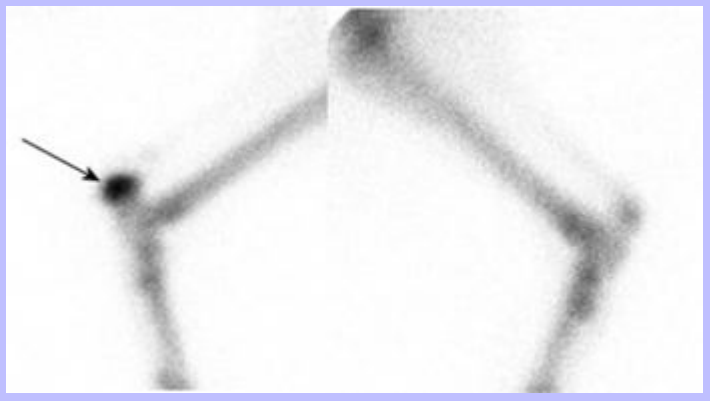


Figure 100-20 Enthesiopathy and syndesmitis of the insertion of the tendon of the gastrocnemius on the right tuber calcaneus. Bone phase images show marked focal uptake in the region of the right tuber calcaneus. The comparison view of the left tibial tarsal region is normal.



100.4.7 Three-Phase Bone Scanning

Multiphase bone scanning is extremely helpful in differentiating active septic from nonseptic conditions.[69] The three-phase bone scan (Table 100-6) consists of an initial "arterial phase" dynamic study (2 seconds/frame for 30 frames) of blood flow (Figure 100-26). The imaging sequence is started immediately upon injection of the radiopharmaceutical into a peripheral vein. The injection should be made as far away from the area of interest as possible to minimize any injection site hot spots that would interfere with interpretation. It is recommended that the dose be injected in bolus fashion (within 2 seconds) into a preplaced intravenous catheter followed by 12 ml of saline flush. The use of an extension set and three-way stopcock is preferred. Because of the dynamic acquisition, the arterial phase is limited to one ROI. Because of the number of images that are acquired over a short period of time, matrix sizes (in pixels) of 64 × 64 or 128 × 128 are used. Postprocessing of these images include viewing a cine loop and summing pertinent images together to render a high total count static image.

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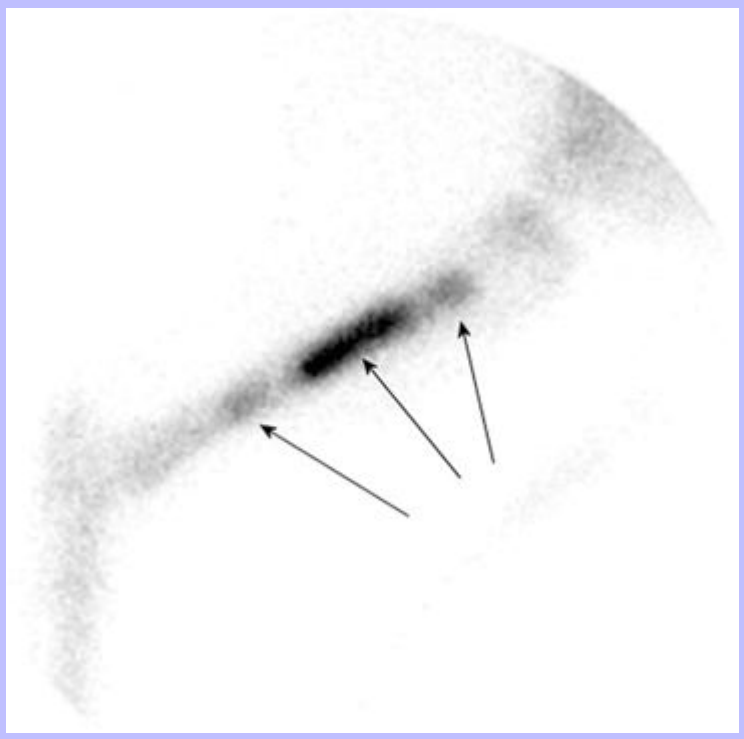
Figure 100-21 Canine panosteitis. Soft tissue and bone phase images of the right tibia demonstrate marked focal intense uptake in a linear pattern in the mid-diaphyseal region.



Phase two is termed the *blood pool phase* and is obtained by acquiring static images over the ROI at minutes postinjection (Figure 100-27). Blood pool (sometimes called *venous phase*) images include 1 to 2 static, 500 K images over the ROI and contralateral area for comparison.

Phase three represents the “bone phase” images. Static spot bone phase images of the ROI, comparison views of the contralateral side and remaining skeleton are obtained at 3 to 4 hours postadministration. A matrix size (in pixels) of 256 × 256 is recommended for both the blood pool phase and bone phase images.

The three-phase bone scan helps to differentiate noninflammatory versus inflammatory conditions. The technique can be helpful in differentiating a loosened versus a septic total hip prosthesis. The typical appearance of a loosened femoral component includes a normal vascular and blood pool phase with focal increased activity of moderate intensity seen at the level of the distal tip of the metallic stem, usually in the mid-diaphyseal region on the bone phase images (Figure 100-28). Loosening of the acetabular component is seen as curvilinear area of focal, moderately intense uptake in the acetabulum on bone phase images and normal soft tissue phase images. A septic prosthesis is suspect when moderate to marked uptake occurs on all three phases in and around the acetabular component or diffusely surrounding the femoral component (Figure 100-29).[70] When comparing with the contralateral limb on the same dorsal image, close attention to

symmetrical positioning should be made to ensure both acetabuli and femoral shafts are equidistant to the camera face and that no foreshortening of the limb occurs.

Figure 100-22 Fragmented medial coronoid process. Focal intense uptake is seen in the region of the right medial coronoid process *(long arrow)* greater than that seen by the adjacent humeral condyles. Comparison normal left elbow shows normal amount of uptake associated with the distal humeral condyles and less uptake seen by the normal medial coronoid process.

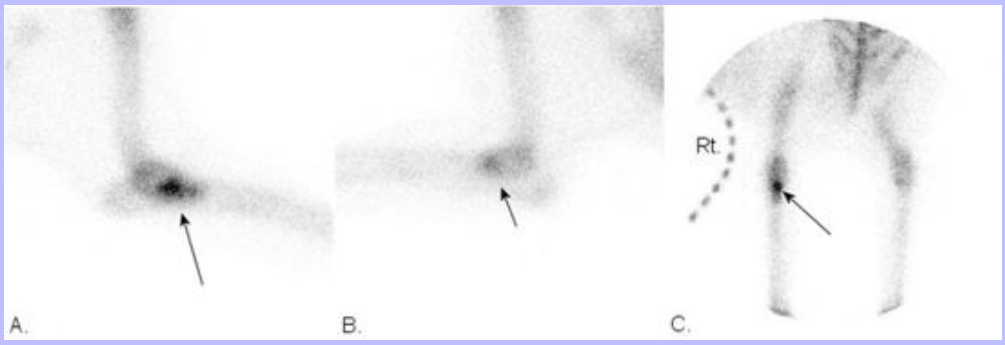


Table • 100-6 Three-Phase Bone Scan

	PHASE 1 (ARTERIAL)	PHASE 2 (POOL)	PHASE 3 (BONE)
Cellulitis	+	+/–	–
Septic arthritis	+	+	+
Osteomyelitis	+	+	+
Fracture	+/–	+/–	+
Chronic DJD	–	–	+

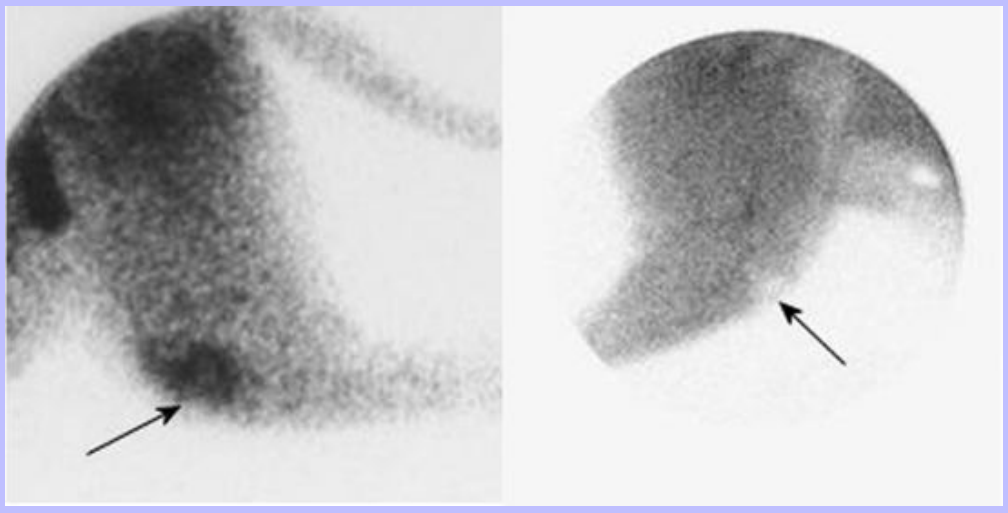
Three-phase bone scanning is also helpful in assessing tissue viability secondary to injury such as gunshot[71] and frostbite.[72] Decreased perfusion (soft tissue phase images) and uptake (bone phase images) indicate nonviable tissue, which usually necessitates amputation. Decreased perfusion but normal to slightly decreased uptake on bone phase images can often be successfully treated with débridement surgery and medical therapy.

100.5 QUANTITATIVE RENAL IMAGING (GFR SCANS)

100.5.1 Background and Basic Techniques

In contrast to radiographic intravenous pyelography that demonstrates well-defined morphology of the kidney and collecting system but little functional information, the GFR scan yields poor structural information but clinically important functional information. The importance of the GFR scan lies in the fact that individual renal function can be assessed and compared. The correlation between inulin clearance and a GFR scan using ^{99m}Tc-diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) has been reported to be 0.94 in dogs[73] and 0.81 in cats.[74]

Figure 100-23 Partial tear of the cranial cruciate ligament. Regional increased uptake is seen within the left stifle joint *(long arrow)* on soft tissue phase images. The normal right stifle shows the typical photopenic triangle that corresponds to infrapatellar fat pad *(short arrow)*.



The glomerulus acts similar to a sieve type of filter, only allowing particles of a certain very small size to pass into the ultrafiltrate. Renal function is commonly assessed with BUN and serum CR assays; however, it is known that up to 75% of the nephrons must be destroyed before these values may increase. Plasma clearance can be used to express the ability of the kidneys to remove a substance from the blood and is more accurate in assessing renal function. The plasma clearance of a substance can be calculated using the following equation:

$$\text{Clearance}_x = \frac{(U_x \text{mg/mL}) \times (V \text{mL/min})}{(P_x \text{mg/mL})}$$

Where Clearance_x = rate of clearance of substance_x per unit time (mL/min)

U_x = concentration of substance_x in urine (mg/mL)

V = volume of urine per minute (mL/min)

P_x = concentration of substance_x in plasma (mg/mL)

Figure 100-24 Stress fractures of the left tibia. Focal areas of intense uptake are seen in the mid-to distal diaphyseal region of the left tibia. Normal areas of focal uptake exist in the metaphyseal regions in this young animal.

For plasma clearance to be accurate, the substance must be (1) completely filtered at the glomerulus; (2) not synthesized, destroyed, reabsorbed, or secreted by the renal tubules; (3) physiologically inert; and (4) not significantly bound to plasma proteins. Classically, inulin clearance has been used to measure GFR; however, it is cumbersome and usually reserved for the research setting. CR clearance has also been used but is not as accurate, owing to the small amount of tubular secretion and its ability to only measure total GFR, not individual kidney GFR. Radionuclide techniques have been developed to measure both total GFR and differential GFR.

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Figure 100-25 Fracture of the ulnar carpal bone, left limb. A focal intense area of uptake is seen in the lateral aspect of the left carpus secondary to a small chip fracture of the ulnar carpal bone.

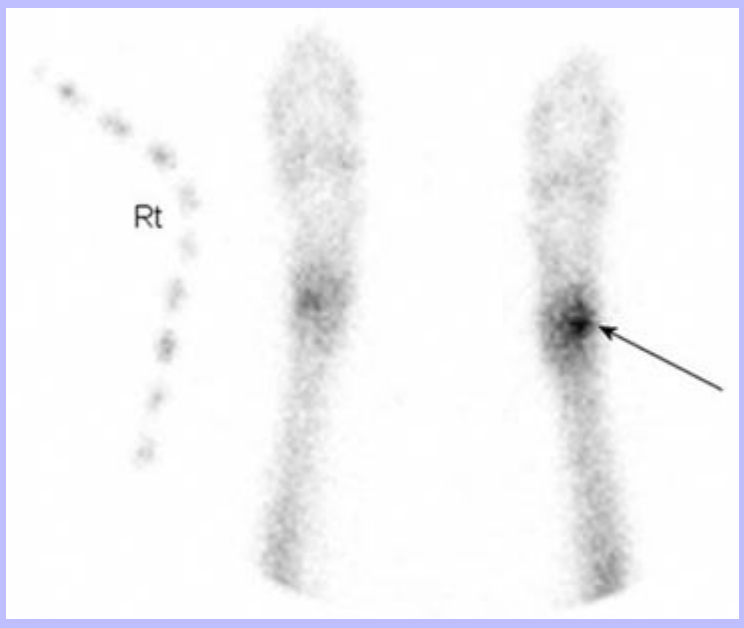
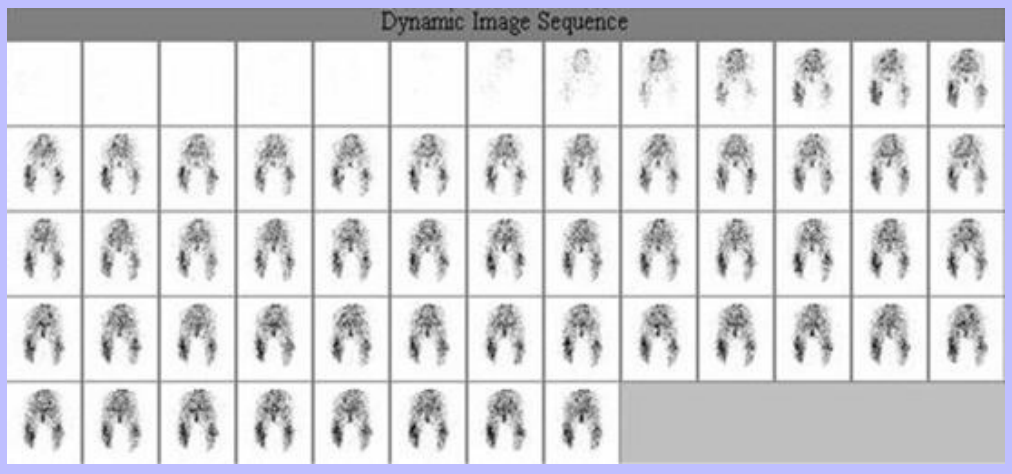


Figure 100-26 Dynamic ("arterial") phase images. Dorsal pelvic images obtained immediately after injection of a bolus of ^{99m}Tc-MDP. Images were obtained at 2 seconds per frame.



^{99m}Tc-DTPA is a radiopharmaceutical that diffuses evenly throughout and stays within the vascular space; it satisfies the requirements as a glomerular agent and can be used to accurately estimate total GFR (comparable to inulin clearance). By using a gamma camera, interfaced computer system, and proper software, both total and differential GFR (right kidney and left kidney) can be determined. Nuclear processing software uses the integral activity within ROIs placed over each kidney and separate ROIs for background subtraction during the 1-to 3-minute or 2-to 3-minute time period after the initial bolus of activity is seen within the kidney ROIs. Gates[75] first introduced this method that uses the following equation:

$$\mathrm{GFR} = \frac{\left\{\left[\left(\frac{\text{RKid ROI counts} - \text{bkgd}}{e^{-0.153 \times \text{kid depth in cm}}}\right)\right] + \left[\left(\frac{\text{LKid ROI counts} - \text{bkgd}}{e^{-0.153 \times \text{kid depth in cm}}}\right)\right]\right\}}{(\text{Preinjection counts} - \text{postinjection counts}) \times 100 \times 9.756 - 6.198 \text{ for CR clearance}}$$

Figure 100-27 Soft tissue ("blood pool") phase image. Static images of the bilateral rear limbs and pelvis obtained 3 to 5 minutes postinjection of ^{99m}Tc-MDP.

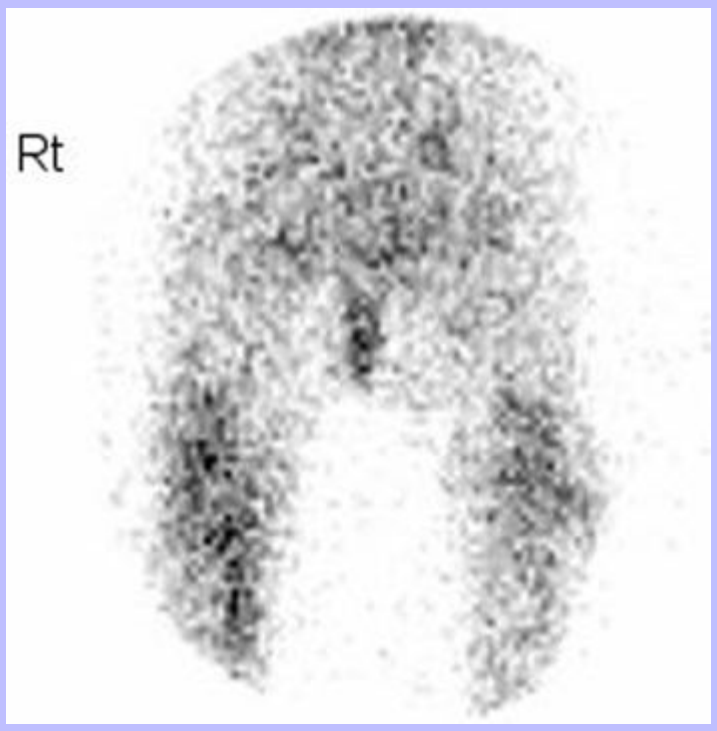


Figure 100-28 Loose acetabular and femoral components after total hip replacement. Focal areas of intense uptake of radiopharmaceutical are seen in the caudal cortex of the mid-diaphyseal region of the right femur *(short arrow)*, which corresponds to the level of the distal tip of the femoral stem, the caudal cortex of the proximal femur, and acetabular rim *(long arrow)*.

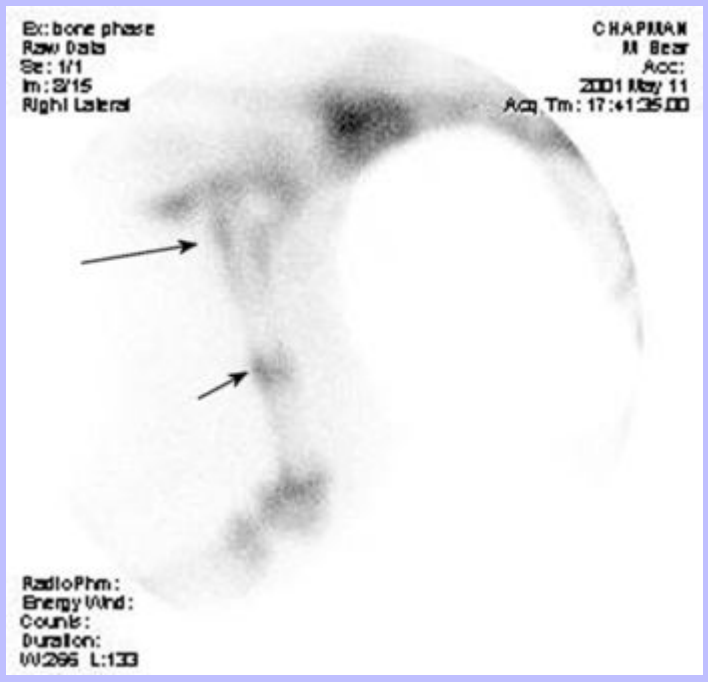
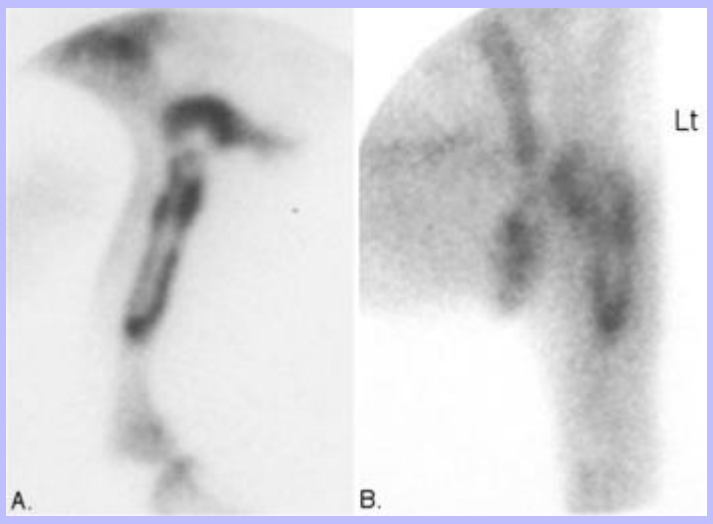


Figure 100-29 Septic total hip prosthesis. Left lateral bone phase image **(A)** and ventral soft tissue phase image **(B)** demonstrate marked uptake associated with the entire portion of the left femoral and acetabular prosthetic implants.



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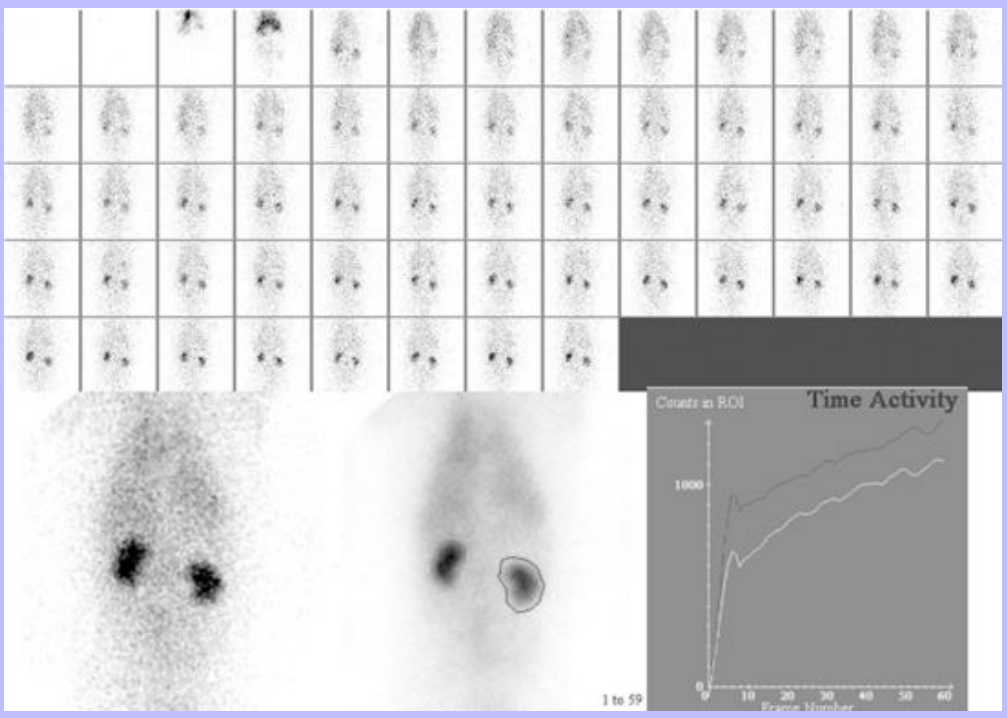
With minor modifications to the acquisition and processing, the same can be used for noninvasive estimates of renal function in dogs[73] and cats.[74] In human medicine, GFR results are reported in milliliters per minute and uses the assumption that all humans are approximately the same size (1.75 m^2). Due to the wide range of size differences in animals, it has become convention to normalize these values and report the GFR quantification as milliliters per minute per kilogram. Caution should be taken in that if nuclear medicine processing software designed for evaluation of human GFR scans is used in dogs and cats, the results will not be accurate for these species because the "r" value used to correct the mathematic formula used to calculate GFR is different for dogs and cats as compared with humans.

Figure 100-30 Normal glomerular filtration rate (GFR) scan. These dorsal images were obtained immediately after a bolus injection of ^{99m}Tc-DTPA at 6 seconds per frame. Dynamic, dorsal composite images with and without regions of interest (ROIs) drawn around the kidneys and time activity curves. Normal, intense, symmetrical uptake is seen within each kidney.



100.5.2 Indications for Performing a Glomerular Filtration Rate (GFR) Scan

Although the GFR scan will yield a total GFR that is more sensitive to abnormalities in the kidneys than elevated BUN or CR values, the primary indication for performing a GFR scan in small animals is to evaluate differential (individual) renal function in cases where a known abnormality exists that has altered the function of one kidney. The GFR scan is performed to correlate a suspected lack of function for the abnormal kidney and, at the same time, evaluate the opposite kidney for normal function. The scan is typically performed prior to scheduled unilateral nephrectomy of the diseased kidney to ensure that the nondiseased kidney has retained enough function to maintain life once the diseased kidney is removed. A GFR scan is not accurate in animals with significantly impaired renal function as demonstrated by severe azotemia because the kidneys may not be well visualized.

100.5.3 Image Acquisition

A dynamic acquisition is obtained at 6 seconds per frame for a total of 5 minutes (Figures 100-30 and 100-31). All images are made with the gamma camera centered over the dorsum of the patient's kidney region. The patient may be imaged while in right lateral recumbency (camera behind the patient) or in dorsal recumbency (camera underneath the patient). It is imperative that the patient not move during the 5-minute acquisition; therefore either a very cooperative patient (with skilled animal handlers) is needed, or mild sedation or general anesthesia is usually required. It is preferable not to administer tranquilizers or anesthetics because these agents will invariably affect the GFR quantification, rendering a less than optimal nonphysiologic measurement.

It is important that the radiopharmaceutical be administered in a bolus fashion, and it is preferable to inject through a preplaced patent catheter using a three-way stopcock apparatus and adequate sterile saline flush. To prevent the gamma camera from blushing with activity from the syringe and catheter itself during acquisition, a sterile intravenous extension tube can be used; however, care must be taken to ensure an adequate volume of fluid is available to flush the entire extension tubing. The bolus of activity should be injected as quickly as possible, preferably in less than 2 seconds. Immediately prior to injection, the acquisition should be started. By starting the acquisition computer just prior (4 to 6 seconds) to injection of the bolus, a “blank” frame will be obtained.

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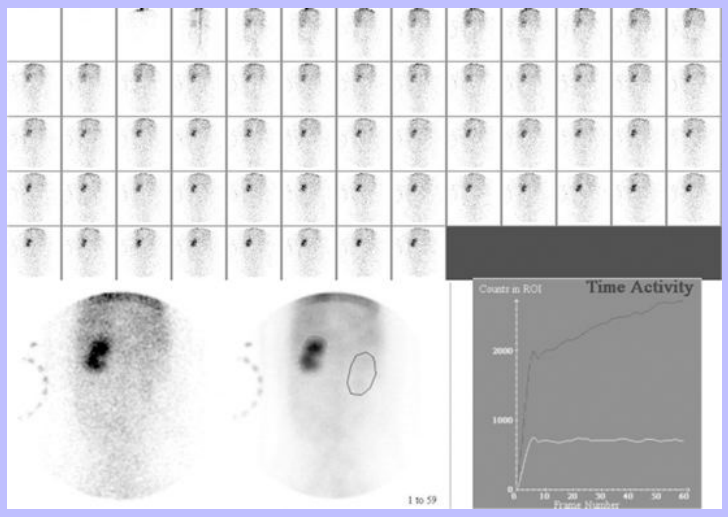
Figure 100-31 Glomerular filtration rate (GFR) scan with unilateral renal disease. Dynamic, dorsal composite images with and without regions of interest (ROIs) drawn around the kidneys and time activity curves show normal uptake in the right kidney and no uptake in the left kidney. The reader should note that the time activity curve of the left kidney and individual dynamic images show no evidence of normal excretion. This animal had severe left-sided hydronephrosis and mild hydronephrosis of the right kidney secondary to bilateral ureteroliths.



Within only seconds, activity will be seen first entering the right heart, lungs, left heart, and aorta; then a kidney blush will be seen. As the acquisition progresses, it is common to see activity within the urinary bladder. Ureters are rarely defined.

100.5.4 Interpretation and Analysis

At the end of the acquisition, a total of 50 individual images will be available for viewing, each representing a 6-second timed acquisition. These images should be examined subjectively and objectively using the computer's particular method of GFR analysis (visual inspection). The images can usually be run in a cine mode to create a movie appearance, which can be repeated over and over for evaluation.

Subjective analysis of the study should include rapid uptake of the radiopharmaceutical by both right and left kidneys. Cats will especially demonstrate rapid and intense uptake by the renal cortex. The kidneys should be inspected for size and shape, and the amount of uptake should be symmetrical. An initial intense blush is followed by further concentration of the Tc-DTPA within the kidneys until maximum concentration is seen (2 to 3 minutes), followed by gradual decrease in intensity as the kidneys excrete the activity into the ureters and bladder. During the scan, there will be a moderate amount of activity seen in the soft tissues, which should decrease to hardly noticeable amounts by the end of the scan. Activity within the urinary bladder is normal in the latter frames and should gradually increase over the time of the acquisition. Activity within a ureter is rarely seen; when present it often suggests hydroureter.

Calculation of GFR begins with summating all of the individual dynamic images into a single “composite” image. This image is then subjected to a spatial and temporal smoothing algorithm that helps define the boundaries of each kidney. Manual or automated ROIs for each kidney, as well as appropriate background ROIs for each kidney, are then placed. An ROI can also be drawn around the urinary bladder. Estimation of kidney depth performed with ultrasound or from an additional lateral view of the abdomen using the gamma camera can be used to correct for soft tissue attenuation of the technetium. Correction for kidney depth has been shown to increase the correlation between the calculated GFR and inulin clearance in the dog,[73,76] but not in the cat.[74] The amount of radiopharmaceutical within the summated kidney ROIs and background ROIs during a time period of 1 to 3 or 2 to 3 minutes postinjection is used to calculate the total GFR. Differential GFR is then determined by calculating the percent contribution of the total GFR by each kidney. Because most standard nuclear medicine software is designed for human use and the equation used to calculate GFR is different for dogs and cats, it is often necessary to export the appropriate numbers to another program, such as Microsoft Excel, for the results to be meaningful.

Besides the calculation of a total GFR and differential GFR, the time activity curves for each ROI should also be inspected. The normal kidney time activity curve should have a very sharp initial increase (which represents the initial arterial bolus of activity within each kidney), followed closely by a slight decrease in activity, then a longer “uptake” period (as the radiopharmaceutical is concentrated by the kidney), and finally a gradual and longer “washout” period (as the radiopharmaceutical is excreted from the kidney into the collecting system). In normal animals, kidney activity should peak at approximately 2.5 to 3.5 minutes postinjection. A delay in the time to peak (with a normal bolus peak) is consistent with glomerular disease. Animals undergoing diuresis may demonstrate a shorter time to peak activity. Each kidney's time activity curve should be similar in activity and may closely superimpose each other. A delayed onset or blunted initial “bolus” peak is consistent with a fragmented bolus injection, vascular abnormality, or significant renal disease. A lack of concentration by either kidney signifies renal insufficiency. A lack or delay of the excretory phase (washout) is suggestive of obstructive urinary disease. The time activity curves for each background area should be flat and not change

over time. If included, the urinary bladder ROI should start off at the *x*-axis and rise slowly during the entire acquisition.

For most animals the total GFR should be greater than 2.0 ml/minute/kg and be evenly distributed between each kidney (i.e., each kidney should have a differential GFR of 1.0 ml/minute/kg or greater). A total GFR value of 1.8 ml/minute/kg or greater is considered normal in older cats (values less than these imply some degree of renal insufficiency). Like most imaging procedures, an abnormal total GFR result is extremely nonspecific; in all but a few rare cases, the cause for the renal disease cannot be determined.

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101 CHAPTER • 101 Endoscopic and Cytologic Procedures for Evaluation of the Gastrointestinal Tract

Michael E. Matz

101.1 ENDOSCOPIC PROCEDURES

Gastrointestinal (GI) endoscopy is a minimally invasive, atraumatic technique that permits direct visualization of the mucosa of the esophagus, stomach, small bowel, and colon. GI endoscopy can provide valuable information when evaluating GI disorders. Diagnostically, it allows clinicians to obtain samples for cytologic and histologic examination with relative ease. Therapeutically, it can be used for the removal of foreign bodies, dilation of esophageal or colonic strictures, and placement of gastric or jejunal feeding tubes. These endoscopic procedures offer an alternative to surgical intervention. This section will focus on the technique involved in performing diagnostic upper GI endoscopy, proctoscopy (examination of the rectum), and colonoscopy.

101.2 ENDOSCOPIC EQUIPMENT

Both rigid and flexible endoscopes can be useful in GI endoscopy. Rigid endoscopes are available in several sizes. This type of endoscope is inexpensive and easy to use. Rigid endoscopes are most valuable for performing proctoscopy and colonoscopy. Poor visualization, limited maneuverability, and relatively short length compared with flexible endoscopes, limit the use of rigid endoscopes for other diagnostic procedures.

A number of flexible endoscopes of different makes, lengths, diameters, and functions are available for use in evaluating the GI tract. Fiberoptic endoscopes use fiber-optic bundles to deliver bright light to the tip of the endoscope and transmit the image to the eyepiece. The quality of the image is dependent on the number, size, and quality of the fibers. Numerous, small-diameter fibers produce a better image than larger, less numerous fibers. Video endoscopes replace the image fiber bundle with a computer chip camera that transmits an electronic signal to a processor where it is converted to a video image and displayed on a high-resolution monitor. Image quality is superior with video endoscopes.

Versatility is important because veterinary patients vary greatly. A flexible endoscope to be used for GI endoscopy in dogs and cats should possess the following characteristics: a working length of at least 100 cm (ideally 125 cm); an insertion tube diameter of less than 10 mm, optimally less than 8 mm; a minimum instrument channel diameter of 2.0 mm, with an ideal size being 2.8 mm; four-way distal tip deflection with at least 180 to 210 degrees in one direction and 90 to 100 degrees in the other three directions; automatic air-water insufflation; suction capabilities; a forward direction of view; an angle of view of 90 to 120 degrees; a depth of field of 3 to 100 mm; and comfortable handling. Light sources for the endoscope should be halogen or preferably xenon. An external vacuum source (portable or central) is necessary.

Additional instrumentation required for flexible diagnostic endoscopy include biopsy forceps and cytology brushes. The author prefers fenestrated ellipsoid biopsy forceps. For rigid endoscopes, alligator biopsy forceps (punchtype preferred) are necessary.

101.3 ENDOSCOPIC TECHNIQUE

101.3.1 Upper Gastrointestinal Endoscopy

Diagnostically, upper GI endoscopy is indicated for evaluation of dysphagia, persistent regurgitation, chronic vomiting, acute vomiting with hematemesis, melena, chronic small bowel diarrhea, and unexplained weight loss or anorexia.

It is essential for the animal to be fasted to prevent ingesta from interfering with the examination. In most cases an 8-to 12-hour fast is sufficient; however, a longer fast may be necessary if evidence of delayed gastric emptying exists. Upper GI endoscopy should not be performed within 24 hours of a barium contrast study. This allows for clearing of residual barium that often adheres to mucosal surfaces even though radiographically it may appear that the barium has been cleared from the GI tract. Appropriate preparation is essential for maximizing examination efficiency and for ensuring patient safety.

General anesthesia with placement of a cuffed endotracheal tube is necessary for upper GI endoscopy. The choice of anesthetic regimen should be made with respect to the animal's general condition and suspected disease processes. Narcotics (morphine, meperidine, butorphanol) increase antral motility and may increase pyloric tone, potentially interfering with the passage of the endoscope into the duodenum. The animal should be positioned in left lateral recumbency with a mouth speculum placed to protect the endoscope.

The insertion tube of the endoscope is passed initially over the endotracheal tube and through the oropharynx and upper esophageal sphincter. Once the endoscope is in the esophagus, air is insufflated until the esophagus is adequately distended to visualize the lumen. The endoscope is centralized in the esophageal lumen and then slowly advanced toward the gastroesophageal junction. *The endoscope should only be advanced when the lumen is clearly visible*. It is important to examine the esophagus completely during the insertion of the endoscope because it may become traumatized during passage of the endoscope. Normal esophageal mucosa is smooth, pale, and glistening. Submucosal vessels are not normally visualized in dogs, but are easily observed in cats. Little or no fluid is normally found in the esophageal lumen. In the proximal esophagus, an impression of the trachea can be seen. Pulsations of the heart and aorta are visualized in the thoracic esophagus. In the distal one-third of the esophagus of cats, concentric circular rings are observed because of the presence of smooth muscle. The gastroesophageal sphincter (GES) is usually closed in the normal animal. The bright pink to red color of the gastric mucosa may be visible at the GES, creating an irregular rosette appearance. At the GES, a slight directional change is necessary to align the tip of the endoscope with the center of the sphincter. Insufflation of air, while gently advancing the endoscope, should result in passage into the stomach. When properly directed there should be minimal resistance to advancing the endoscope into the stomach.

The large lumen of the stomach means the endoscopist must develop and maintain a systematic approach to gastroscopy so that completeness and reproducibility are ensured. During initial examination of the stomach it is important to obtain at least a cursory view of the mucosa as the endoscope is advanced to avoid misinterpreting endoscope-induced trauma as an abnormality during endoscope withdrawal. Normal gastric mucosa is smooth, glistening, and pink. Submucosal vessels are not normally observed, except in the cardia. The presence of ingesta or fluid, ease of distensibility of the gastric wall during insufflation, and the appearance of the rugal folds should also be evaluated.

Upon entry into the stomach, the endoscope will lie along the greater curvature. The stomach will be collapsed and prominent longitudinal rugal folds will be visible. Air should be insufflated into the stomach only until

spatial orientation is achieved. Care must be taken not to overinflate the stomach. Overdistension of the stomach can occur quickly in cats and small dogs because of their relatively small stomach size. The endoscope should continue to be advanced along the greater curvature until the junction between the antrum (characterized by the lack of rugal folds) and the body comes into view. A frontal view of this area is usually accomplished in dogs. In the cat, the antrum is often hidden behind the incisura angularis, a narrow shelf of tissue that separates the pyloric antrum from the lesser curvature of the gastric body. To enter the antrum the endoscope is advanced further along (dogs), or deflected off (cats), the greater curvature.

Once in the antrum, the endoscope can be slowly advanced toward the pylorus. The pylorus in most dogs and cats is readily visible. The appearance and location of the pylorus will vary. In general, the pylorus has clean margins and is not obscured by excessive folds. It may be closed or open. Passing the endoscope tip through the pylorus into the duodenum can be the most difficult part of upper GI endoscopy. It is most easily accomplished by gradually advancing the endoscope while keeping the pylorus aligned in the center of the field of view. Rapid and forceful advances of the endoscope should be avoided. If gastric distension is minimized the pylorus is usually in a more relaxed state, facilitating duodenal intubation. If the pylorus cannot be properly aligned, repositioning of the dog or cat (dorsal or right lateral recumbency) may help to improve alignment. Just past the pylorus the cranial duodenal flexure is encountered. To negotiate this sharp turn, the tip of the endoscope should be deflected downward and to the right while insufflating and gently advancing the endoscope. During this advancement the mucosa will be seen sliding by the viewing lens. Once the tip of the endoscope has successfully negotiated the flexure, centralization of the tip of the endoscope within the lumen will be possible. Normal intestinal mucosa is paler, more granular in texture, and more friable in nature than the gastric mucosa. The major duodenal papilla is observed on the medial wall of the duodenum in most dogs and in some cats. Careful examination may reveal the minor duodenal papilla in dogs. The papillae may be best visualized as the endoscope is slowly retracted back into the proximal duodenum because of their close proximity to the duodenal flexure. In dogs, Peyer's patches are often observed as shallow, pale craters on the lateral aspect of the nondistended descending duodenal wall. The endoscope should be advanced until it reaches its full working length, as long as only minimal resistance is encountered.

A more thorough evaluation of the duodenal and gastric mucosa is often best accomplished as the endoscope is withdrawn. Diagnostic procedures are also performed at this time. Once the endoscope has been retracted into the stomach, the pylorus, antrum, and incisura angularis are examined carefully. A frontal view of the angularis can usually be obtained while the endoscope is removed from the antrum. The endoscope is then withdrawn along the greater curvature and retroflexed 180 degrees to allow visualization of the lesser curvature, fundus, and cardia—the latter region being defined by the location of the entrance of the endoscope into the stomach and the presence of submucosal vessels. Torquing the endoscope at this point will provide complete (360 degrees) evaluation of this area. Once the proximal stomach has been thoroughly evaluated, the scope tip is straightened and the endoscope is slowly retracted. At this point, insufflation of the stomach should be sufficient to cause flattening of the rugal folds without causing overdistention, facilitating observation of the entire gastric mucosa. Before retraction of the endoscope into the esophagus, all air or residual fluid is suctioned from the gastric lumen. The esophagus should be carefully reexamined as the endoscope is removed.

101.3.2 Proctoscopy and Colonoscopy

Proctoscopy and colonoscopy are relatively easy to perform in dogs and cats because their large intestines are anatomically simple. For this reason, clinicians with an appreciation of normal and abnormal endoscopic anatomy can become proficient in performing proctoscopy and colonoscopy within a relatively short period of time.

Endoscopic examination of the rectum and colon can be accomplished with either a rigid or flexible endoscope. Rigid endoscopes limit visualization to the rectum and descending colon. Flexible endoscopes allow evaluation of the rectum, entire colon, cecum, and possibly the distal ileum.

Indications for proctoscopy and colonoscopy include chronic large bowel diarrhea, obstipation or tenesmus, dyschezia, or hematochezia that accompanies formed feces. Because most inflammatory diseases of the large intestine in the dog and cat are diffuse, their presence is usually detected in the descending colon, allowing rigid endoscopy to be a valuable procedure.

One of the keys to successful proctoscopy or colonoscopy is adequate patient preparation. Various protocols can be used depending on the extent of the examination to be performed, the availability of support staff to complete the necessary work, and the degree of patient cooperation. Proper preparation for colonoscopy requires complete evacuation of fecal material from the colon and production of a clear ileal effluent. Food should be withheld for a minimum of 24 to 36 hours before the procedure. If flexible endoscopy is to be used, use of an oral GI lavage solution is recommended, such as one containing polyethylene glycol as the main nonabsorbed solute (GOLYTELY®, NuLytely®, Colyte®). These are isosmotic solutions that result in a severe diarrhea with virtually no net absorption or secretion of electrolytes, bicarbonate, or water. This method has been shown to result in superior colonic preparation compared with multiple enemas in dogs. Disadvantages are that fairly large volumes of the colon electrolyte lavage solution need to be used, and administration via orogastric or nasoesophageal intubation is usually necessary. Although dose guidelines have not been firmly established for the dog and cat, two doses of a lavage solution are recommended at 30 mL/kg via orogastric (dog) or nasoesophageal (cat) tube 2 to 4 hours apart in the afternoon prior to the examination. In addition, a warm-water enema (20 mL/kg body weight) should be given after the first dose of lavage solution the morning before colonoscopy. The well-lubricated enema tube should be inserted a length equal to that from the anus to the last rib. Enemas should be avoided in animals with rectal pain.

For rigid endoscopy, patient preparation does not have to be as vigorous as the protocol outlined previously. Preparation may be limited to withholding food for an appropriate time (usually 36 to 48 hours) and administering multiple warm-water enemas 1 to 2 hours apart on the afternoon before the procedure. Enemas should be given until the water exiting the rectum is repeatedly clear. A final enema is given the next morning 2 to 4 hours before the procedure is begun.

These or similar protocols generally result in adequate rectal and colonic cleansing. It is essential that the rectum and colon be as clean as possible before endoscopy. Lesions may easily be missed if this is not accomplished.

General anesthesia is generally recommended for colonoscopy, although heavy sedation may be adequate for proctoscopy or rigid colonoscopy. Passage of a flexible endoscope into the transverse and ascending colon and cecum may cause painful stretching of mesenteric attachments.

Before performing endoscopy, a digital rectal examination should be done to rule out the possibility of anal and rectal lesions or perineal hernias. Insertion of a digit is also useful for straightening the rectal lumen, making it easier to insert the endoscope into the colon. Rigid endoscopy is usually performed with the animal in right lateral recumbency. Right lateral recumbency reduces gravitational flow of fluid and fecal material into the distal colon. The well-lubricated rigid endoscope is advanced into the rectum. Rigid endoscopes have a smooth obturator that facilitates advancement of the endoscope through the anal sphincter. The obturator is removed after entering the rectum and the hinged viewing lens is closed tightly over the end of the endoscope. Air is insufflated to distend the colon, and the endoscope is advanced under direct visualization until the entire length

of the endoscope has been inserted. With a rigid endoscope, air insufflation is done manually with a bulb-pumping device. The normal colon should have a pale pink, smooth, glistening mucosa with visible submucosal blood vessels. Lymphoid follicles, seen as 2 to 3 mm plaques (often with umbilicated surfaces) are normally observed in the descending colon and cecum.

Flexible endoscopy is performed with the animal in left lateral recumbency to prevent compression of the area of the ileocolic valve by abdomial viscera. After the endoscope is inserted into the rectum, air is insufflated. It is often necessary, especially when small-diameter flexible scopes are used, to have an assistant apply digital pressure around the anal orifice to prevent insufflated air from escaping from the colon. Insufflation distends the colon and flattens out mucosal folds, which are most prominent in the rectum and distal descending colon. The endoscope tip is then centralized and advanced slowly. *The endoscope should only be advanced if the lumen is clearly in view.* At the junction of the descending and transverse colon, a flexure (splenic) will be observed. The tip of the endoscope should be deflected around the flexure and advanced slowly along the mucosa. The mucosa should be seen sliding freely across the viewing lens. After passing the flexure, the tip of the endoscope can again be centralized within the lumen of transverse colon. The transverse colon is short in the dog and cat. Another flexure (hepatic) will be encountered at the junction of the transverse and ascending colon. This flexure can be passed in a manner similar to the splenic flexure. In the cat, distinct flexures delineating the boundaries between the sections of the colon are generally not observed as clearly as in the dog. Upon entering the ascending colon, the ileocolic junction is visualized. The ileocolic sphincter often protrudes into the lumen. If the ileum is to be entered, the tip of the endoscope should be centralized within the lumen of the sphincter and the endoscope advanced using gentle pressure combined with air insufflation. If the scope cannot be advanced into the ileum, blind biopsy specimens can be obtained by passing the biopsy forceps through the ileocolic sphincter. Using this blind biopsy technique does, however, increase the risk of perforation. The cecocolic junction may be partially open or, if closed, appear as a flat sphincter. The cecum usually can be entered. In the dog, the scope should be advanced into this spiral structure (8 to 30 cm in length) until the blind end is reached. The cecum of the cat is comma shaped and short (2 to 4 cm) in length.

A more thorough evaluation of the colon should be performed as the scope is withdrawn. Diagnostic procedures are performed at this time. The endoscope should be slowly retracted while making necessary directional adjustments to ensure that the entire circumference of the colon is carefully evaluated. As the rectum is approached in dogs greater than 15 kg, the flexible endoscope should be retroflexed 180 degrees to allow better visualization of the terminal rectum.

101.4 DESCRIPTIVE ENDOSCOPIC TERMINOLOGY

The esophageal, gastric, duodenal, jejunal, and colonic mucosa should be described using the following: hyperemia, friability, granularity, and erosion or ulceration, degree of luminal narrowing, stricture and visibility of submucosal vessels. The presence of an intraluminal mass or foreign body should be noted. Mucosal hyperemia should be carefully interpreted because it can be affected by a number of factors, including anesthesia, warm-water enema, and mild trauma from the endoscope. The amount of insufflation can alter the appearance of the mucosa and should be considered during evaluation. With experience, the endoscopist will learn to distinguish normal from abnormal GI mucosa. A description of the position and size of any lesions should be recorded. Size can be estimated by comparing the lesion to an open biopsy forceps.

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101.5 ENDOSCOPIC BIOPSY SAMPLES

Flexible endoscopic biopsy samples are small, 2 to 3 mm mucosal specimens obtained through the instrument channel of the endoscope. In view of the small size of these biopsy samples, multiple biopsies using sharp biopsy

forceps and good technique are essential to provide diagnostic material. To obtain a biopsy sample with the flexible scope, the tip of the endoscope should be placed in close proximity to the intended biopsy site. If possible, the tip should be directed at a 90-degree angle to the mucosal surface to be biopsied. Removing the majority of luminal air will facilitate attaining a perpendicular orientation of the tip in narrower tubular lumens such as the small intestine. A biopsy forceps is placed into the biopsy channel and advanced until it protrudes from the endoscope tip and is clearly visible. The endoscopic assistant opens the forceps, and the endoscopist advances the forceps towards the mucosa. The forceps should be advanced with gentle pressure until resistance is met. The assistant then closes the forceps, and the endoscopist pulls the biopsy instrument back into the biopsy channel. This tears the mucosa, capturing a small tissue sample.

As previously noted, biopsy specimens are obtained while the endoscope is gradually withdrawn from the area of the GI tract being investigated. In instances where a focal mucosal lesion is identified, multiple directed biopsy specimens should be taken. In instances where the abnormality is diffuse or where no gross abnormalities are visualized, multiple biopsy specimens should be obtained from various anatomic sites. For upper GI endoscopy, these sites include the duodenum jejunum (minimum of 8 to 10 biopsies), and antrum/angularis/lesser curvature, greater curvature, and cardia of the stomach. For colonoscopy, these sites include the cecum ascending colon transverse colon and proximal, middle, and distal descending colon.

To obtain biopsy specimens with a rigid endoscope, the tip of the endoscope should be placed 1 to 2 cm from the area to be sampled. The viewing lens is then opened, allowing the colon to collapse as air moves out. The area to be sampled should be visible in the tip of the endoscope. Alligator biopsy forceps are advanced through the endoscope, opened, and the area to be biopsied gently grasped. Before the tissue is pinched off, the biopsy forceps should be gently moved back and forth. If only mucosa or submucosa has been grasped, the tissue should be freely movable and the biopsy cups can be clamped down to obtain the sample. However, if the grasped tissue remains firmly attached to the colonic wall, this indicates that the forceps has gathered muscular tunics and colonic perforation is possible. In this event the forceps should be opened and a new site at least 1 cm away selected. A total of four to five samples should be obtained from the descending colon while the endoscope is progressively withdrawn.

Endoscopic biopsy specimens are delicate and easily damaged. Biopsy specimens should be handled gently and not allowed to dry. Placing the biopsy specimens on some form of support minimizes tissue contraction and preserves orientation. Transfer of the biopsy specimen directly from the biopsy forceps onto a moistened (normal saline) histopathology cassette sponge is recommended. Teasing the biopsy specimen from the biopsy forceps with a needle may damage the tissue. The sponge is placed in a labeled cassette and immersed in 10% formalin.

101.6 CONTRAINDICATIONS

Other than anesthetic considerations, GI endoscopy has no absolute contraindications. Endoscopic procedures are discouraged in inadequately prepared animals and in animals with bleeding disorders. Food within the stomach increases the risk of aspiration.

101.7 COMPLICATIONS

Complications of GI endoscopy include perforation of the GI wall, with resultant mediastinitis, pleuritis, or peritonitis. Perforation also can result from forceful insertion of the endoscope or biopsy forceps. *The endoscope should only be advanced if the lumen is visible*. Underlying disease in the bowel wall may predispose to perforation. Perforation usually results in the immediate development of air-filled body cavities (e.g., pneumoabdomen).

Overdistension of the stomach will cause cardiopulmonary compromise by impeding venous return, limiting tidal volume, and inducing vagal stimulation. Vagovagal reflexes can be induced by excessive traction on the mesentery. Significant hemorrhage can occur after biopsy procedures, but is rare. Enteropathogenic bacteria may be transmitted by poorly disinfected endoscopes. Gastric dilatation and volvulus can occur because of the inadequate removal of insufflated air.

101.8 CYTOLOGIC PROCEDURES

Cytologic samples can be used for the diagnosis of inflammatory, infectious, and neoplastic disorders of the GI tract of dogs and cats. Appropriate samples can be obtained manually (fecal smear, rectal scraping) or endoscopically.

The clinician prepares fecal smears by obtaining a fleck of mucus or a sample of feces from the surface of a stool and smearing the sample thinly on a microscope slide. To obtain a rectal scraping for cytologic evaluation, a gloved finger or small curette is inserted into the rectum and scraped along the mucosal surface. The sample collected should be thinly smeared on a microscope slide. After staining with new methylene blue or Wright's stain, the fecal smears and rectal scrapings can then be evaluated for the presence of inflammatory cells, pathologic organisms (e.g., *Histoplasma capsulatum*, *Prototheca* spp., *Campylobacter jejuni*, *Clostridium perfringens*), and neoplastic cells.

Cytologic examination of exfoliative specimens obtained endoscopically can be a useful adjunct to mucosal biopsy for the diagnosis of GI inflammation and malignancy in dogs and cats. It can also be useful for identification of *Helicobacter* in the gastric mucosa. Cytologic preparations can be obtained by brush or touch cytologic techniques (or both). The basic technique of brush cytology involves advancing a single-use guarded brush through the instrument channel, extending the brush beyond its protective sheath, and vigorously brushing the area of interest to exfoliate cells. The brush is then retracted into its sheath and removed from the endoscope. Finally, the brush is extended from its sheath and gently rolled across a glass slide. Theoretically, brush cytology offers the advantage of allowing for sampling of a larger surface area than biopsy. The touch cytology technique involves the transfer of an endoscopic mucosal biopsy to a glass slide. The clinician then makes multiple cytologic imprints by placing a second slide on top of, and at right angles to, the first slide and applying gentle pressure. Proper cytologic evaluation of samples obtained using these techniques requires an experienced GI cytopathologist.

102 CHAPTER • 102 Rhinoscopy, Nasal Flushing, and Biopsy

Mark J. Acierno

Mary Anna Labato

102.1 INDICATIONS

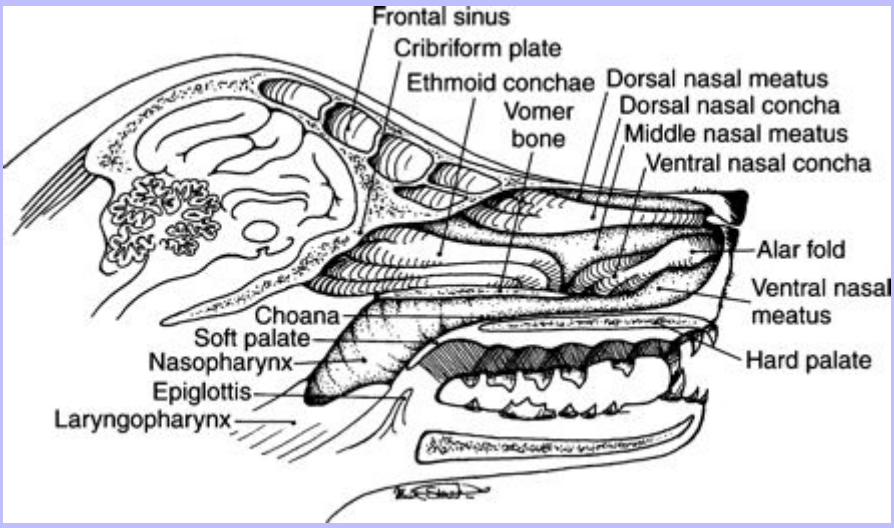
Clinical signs of acute and chronic nasal disorders vary but often include an obstruction of one or both nasal passages and a discharge that can be clear, mucoid, or hemorrhagic. Some dogs and cats respond to empirical therapy; others take a progressive and insidious course. These pets benefit from further diagnostics.

Nasal flushing and rhinoscopy are a part of the diagnostic workup for nasal diseases. Radiographic imaging should precede any invasive diagnostic procedure. Historical questions of interest include the onset and duration of the condition, whether one or both nostrils are involved, and the clinical progression of the disorder. The physical examination should include both the general physical and a detailed examination of muzzle, nasal planum, and nares. Looking at the condensation that forms on a glass slide placed in front of the nares is a convenient way to assess airflow. Diagnostic imaging is important not only because it may reveal a characteristic lesion but also because it may also provide information that can be used to direct the efforts of the nasal flush and rhinoscopy. Although computed tomography (CT) and magnetic resonance imaging (MRI) are significantly more sensitive in detecting and characterizing internasal lesions, skull radiographs taken under general anesthesia are often helpful. When used together, the history, physical examination, blood work, and diagnostic imaging provide an important foundation.

102.2 ANATOMY

A basic understanding of nasal anatomy is essential if consistently rewarding diagnostic procedures are to be performed (Figure 102-1). The left and right nasal cavities are separated by the bony nasal septum. The vestibule, located just within the nostril, contains the cartilaginous alar fold. The rostral aspect of each cavity is then divided into four airways (dorsal, middle, ventral, and common meatus) by the simple dorsal nasal concha and the more complex scroll-like ventral nasal concha. These conchae are primarily composed of cartilage rostrally and become increasingly calcified caudally. Nasal conchae are covered with a ciliated pseudocolumnar mucosal lining that serves to warm, humidify, and filter air as it travels through the meatus. The caudal aspect of the nasal cavities is filled with ethmoid conchae. These delicate, mucosa-covered scroll-like structures arise from the ethmoid bone; they extend to the cribriform plate and up to the sinuses. The cribriform plate, which also arises from the ethmoid bone, separates the nasal cavities from the cranial vault. Although dogs and cats have a complex arrangement of sinuses, these are rarely visualized during endoscopic procedures. All inspired air leaves the nasal cavity by passing from the ventral meatus to the nasopharynx via the choanae. The choanae is dorsal to the hard palate and funnels air from the two nasal sinuses into the common nasopharynx. The nasopharyngeal space, which is delineated ventrally by the soft palate and dorsally by the vomer bone, directs the flow of air into the oropharynx and eventually the trachea.

Figure 102-1 Nasal anatomy of canine. (Drawn by Mariah Steinwinter.)



102.3 NASAL FLUSH

The nasal flush is the least invasive method of obtaining diagnostic samples from the nasal cavity; however, this procedure has several limitations. Samples collected are obtained by infusing saline into the caudal aspect of the nasal cavity and collecting it as it leaves the nares. Therefore only cells and debris that are easily dislodged are collected. Many tumors will not exfoliate sufficient cells to permit diagnosis. In addition, no attempt is made to visualize the structures of the nasal cavity. This allows for gross abnormalities to escape detection. Lastly, although sterile saline is infused into the nasal cavity, it is collected as it flows out of the nares allowing for contamination by bacteria from outside the nasal cavity.

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The anesthetized patient is placed in sternal recumbency with its nose pointed toward the floor. A cuffed endotracheal tube should always be used to prevent possible aspiration. A mouth gag is placed and a soft catheter (red rubber) is inserted into the nasopharynx so that its tip is pointed rostrally and the end of the catheter exits via the mouth. Sterile saline is then forcibly injected into the end of the catheter and fluid is collected as it leaves the nares. Depending on the size of the patient, 5 mL to 60 mL of infused saline should be sufficient to obtain samples for bacterial culture, fungal culture, and cytologic study. The flush can be repeated several times to improve diagnostic yield.

102.4 MODIFIED NASAL FLUSH

A second technique for nasal flushing has been described. Briefly, the tip of a polypropylene urinary catheter is cut to form a jagged edge. The distance from the nares to the eyes is measured and then marked on the catheter. This line estimates the distance from the nares to the cribriform plate; the catheter should never be advanced beyond this distance. The patient is then positioned as described previously and the catheter is inserted into the nares and advanced into the nasal cavity. While using the syringe to both flush saline into the nasal cavity and then suction the fluid back out, the sharpened catheter tip is used to scrape the nasal mucosa. Although this procedure has the theoretic advantage of active exfoliation of cells and larger samples, it is still performed blindly and has

not been proven to provide greater diagnostic sensitivity. Some samples collected in this fashion may be suitable for histopathology.

102.5 RHINOSCOPY AND BIOPSY

A thorough examination of the upper respiratory tract requires direct visualization of each nasal cavity, nasopharynx, oropharynx, and larynx. The oropharynx and larynx can be examined in a sedated patient using only a laryngoscope, whereas visualization of the nasal cavities and nasopharynx requires general anesthesia and specialized equipment and techniques. Although no currently available endoscopic system will allow visualization of the entire nasal cavity and nasopharynx, the combined use of carefully selected rigid and flexible scopes will allow examination of most of the nasopharynx and nasal cavity.

Bacterial and fungal cultures should always be collected prior to rhinoscopy because the procedure is likely to introduce contamination. Once the patient is anesthetized, a nasal flush is performed and the sample submitted for culture. Alternatively, culture swabs are carefully inserted into the nasal cavity and then removed; contact with the external nares is avoided. Additional samples can also be retrieved during the rhinoscopy procedure if bacterial or fungal infection is suspected.

Examination of the nasopharynx is best achieved using a small flexible endoscope. Two commonly used instruments are the 5 mm bronchoscope and the 2.5 mm cystoscope. Although placement of the scope into the nasopharynx initially appears difficult, it is a skill that is easily mastered. The anesthetized patient is placed in sternal recumbency with the nose pointed slightly toward the floor. A cuffed endotracheal tube should always be used to prevent the aspiration of secretions, blood, or saline. In addition, a mouth gag is always used to prevent possible damage to the scope and facilitate proper scope placement. The scope is flexed to 180 degrees. Then, with the tip of the retroflexed scope parallel to the lower jaw, the scope is inserted into the oral cavity and advanced. Once past the caudal aspect of the soft palate, the scope is rotated so that the tip is pointing up and perpendicular to the lower jaw. By moving the scope slightly rostrally, the tip “hooks” the nasopharynx and proper placement of the scope is achieved.

Once inside the nasopharynx, a careful examination of the relevant structures can begin. It is important to remember that because the scope is flexed, the image will be inverted; therefore the soft palate will be viewed dorsally. The entire nasopharynx should be examined by moving the tip of the scope rostrally until the choanae can be clearly visualized. The nasopharynx and choanae should be assessed for texture, contour, and patency. The soft palate should be pink, smooth, and flexible, whereas the dorsal wall of the nasopharynx is smooth, dome shaped, and rigid. A cobblestone appearance to the mucosa may be evidence of lymphoid follicular hyperplasia (inflammation) or lymphoma. Fungal colonies will often appear as gray or yellow plaques. Large masses or polyps can protrude into the airway. Chronic inflammation, infectious diseases, or surgery all may result in scarring and stenosis of the nasopharynx, whereas a membranous obstruction of the choanae (atresia) can be caused by a congenital abnormality. Foreign material that has been vomited into the nasopharynx resulting in inflammation and obstruction may be visualized.

Any deviation from the normal anatomic structure should be investigated by biopsy and histopathology or culture. A biopsy instrument should not be passed through the scope's instrument channel when it is maximally flexed because the scope may sustain permanent damage. Therefore it is recommended that the scope be removed from the nasopharynx and straightened before the instrument is passed though the channel. The biopsy instrument should be positioned so that its forceps lie at the tip of the scope. Once in this position, the scope can be retroflexed and reinserted as described previously. This maneuver must be repeated for each biopsy sample.

Although the rostral most aspect of the nasal cavity can be examined by inserting a nasal speculum or flexible endoscope into the nares, a complete and through examination of the turbinates necessitates the use of a small-diameter rigid endoscope. One such instrument is the 2.7 mm universal telescope (Karl Storz Veterinary Endoscopy). When combined with a 4.0 × 5.5 mm oval cystoscopy cannula, this scope provides the user with a 16.5 cm working length and a 5 French (F) biopsy channel, which also allows for irrigation. The primary advantage of this system is that it allows direct visualization of a large portion of the nasal cavity and guided placement of biopsy forceps.

The anesthetized patient is placed in sternal recumbency with the nose pointed slightly toward the floor. The use of a cuffed endotracheal tube is essential to prevent aspiration. In addition, the placement of gauze sponges in the oropharynx may provide additional protection to the airway. Although the bleeding associated with rhinoscopy and biopsy can sometimes be a source of concern, instilling the nasal cavity with 0.25 to 0.5 mL of a dilute (1:10) mixture phenylepinephrine and lidocaine just prior to the procedures can be helpful in minimizing hemorrhage. The scope is inserted into the nasal cavity by lifting the flap of the nasal planum laterally and directing the scope over the alar fold. The scope can then be directed into the dorsal, middle, or ventral meatus. If the scope is equipped with a suitable channel, warm saline should be infused. This assists in visualizing the nasal structures by keeping the lenses free of blood, mucus, and debris. The scope is directed caudally to examine both the turbinates and air-filled meatus; however, the clinician should never advance the tip of the scope past the level of the eyes. The preliminary diagnostic workup may provide important information in regards to the location of a nasal lesion, yet a through examination of the entire nasal cavity is always recommended so as not to miss more subtle lesions.

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The turbinates should be examined for color, texture, and contour. They should be smooth, scroll-like, and covered with a shiny pink mucosa. Each meatus should be patent, free of debris, and contain minimal mucous. In addition, the air passages will gradually taper in the caudal aspect of the nasal cavity, and sudden widening or narrowing is evidence of a lytic or proliferative lesion. Abnormal endoscopic findings include increased mucus production, swelling of the turbinates, changes in the color or texture of the turbinates, foreign bodies, destruction or proliferation of the turbinates, fungal colonies, polyps, or tumors.

Increased mucus production, swelling of the turbinates, and changes in the appearance of the turbinates are nonspecific inflammatory findings that can be associated with allergic rhinitis, lymphoplasmacytic rhinitis, foreign bodies, bacterial infections, fungal infections, dental disease, and neoplasms. When a thorough endoscopic inspection fails to reveal a foreign body, mass, or fungal plaques, then biopsies of nasal mucosa should be submitted for histopathalogic examination and bacterial and fungal culture. It is important to remember that the source of the nonspecific inflammatory changes may be the result of dental disease. Therefore a thorough dental examination should always be performed while the patient is anesthetized.

Destruction of the turbinates is often associated with fungal rhinitis *(Aspergillus*, *Penicillium)*, bacterial rhinitis, viral rhinitis (cats), foreign bodies, and malignancies. Once again, if endoscopic examination does not reveal fungal colonies, a foreign body, or evidence of malignancy, then samples should be taken for histology and fungal and bacterial culture. As always, the teeth should be considered as a possible underlying cause of the turbinate destruction.

The appearance of masses in the nasal passage is variable but usually causes some degree of turbinate destruction, mucous production, and tissue proliferation, which obstructs the meatus. It is important to note that some fungal organisms, including *Rhinosporidium* and *Cryptococcosis*, can induce masslike formations rather than turbinate destruction. The appearance of any deviation in the normal appearance is sufficient reason to obtain a biopsy specimen and bacterial and fungal cultures.

103 CHAPTER • 103 Thoracic and Pericardial Taps and Drains

Lynette D'Urso

103.1 THORACOCENTESIS

Thoracic radiographs provide evidence that fluid or air exists within the pleural space. They show the location of the fluid and if pockets of fluid are present. If the patient is severely dyspneic and auscultation of the thorax indicates the presence of fluid or air, the clinician should proceed directly to thoracocentesis without taking radiographs. Care and good medical judgment are important factors in the decision to tap prior to radiography. For example, if a diaphragmatic hernia or solid mass was the origin of the pleural fluid then performance of thoracocentesis without initial diagnosis of the condition could lead to a puncture of an intestinal loop or the liver. Performing thoracic ultrasound prior to thoracocentesis is ideal due to the ease and rapidity at which it can be performed to identify fluid location.

Thoracocentesis is the technique used to remove air or fluid from the pleural space. Cytologic and chemical analysis of the pleural fluid assists in understanding the etiology and significance of abnormal fluid collection.

Materials required to perform thoracocentesis may include a butterfly catheter or 20-, 18-, 16-gauge needle or over-the-needle catheter, a three-way stopcock, an extension set, a large syringe (35 or 60 mL), tubes for fluid collection (EDTA and plain tubes), and slides for cytologic preparation.

The site for thoracocentesis varies with the individual patient and the amount and location of fluid or air. The seventh or eighth intercostal space is appropriate for a moderate to large quantity of fluid usually at the midthoracic level for fluid or more dorsally to remove air. In cats, an appropriate location is at the cranial right second to third or third to fourth intercostal space. The insertion site should avoid the caudal aspect of the ribs and therefore the intercostal vessels. If performance of thoracocentesis is ventral, the vessels along the sternum must be avoided. Similarly one must avoid the crura of the diaphragm and the liver, which lies just adjacent and caudal to the diaphragm.

A sterile three-way valve and 3-or 6-cc syringe are attached to the needle or tubing of the catheter. An extension set may also be used from the needle to the three-way valve to compensate for patient movement. The needle is advanced through the thoracic wall while gentle traction is maintained on the syringe. Once fluid is observed in the tubing, the needle is held in place or the needle angled so that it lies parallel to the chest wall. The first sample collected should be saved for analysis. Once a sample is collected a large (35-or 60-cc) syringe is attached and as much fluid as possible is drawn off. Holding the needle along the thoracic wall will decrease the chance of lung tissue laceration. The needle should be withdrawn if there is excessive patient movement or coughing to avoid a lung laceration. Fibrin clots may clog the end of the needle during the procedure. The needle may need to be moved to different locations or fluid occasionally injected into the pleural space through the needle to remove the clots.

An over-the-needle catheter may be used to avoid potential complications of lung laceration. Once inserted into the pleural space, the catheter is advanced and the needle removed. The extension set and stopcock are immediately attached. If repeated thoracocentesis is necessary, the catheter can be sutured in place; however, caution must be exercised. The patient must be properly restrained to avoid tampering with the catheter and the needle must be properly capped to avoid iatrogenic pneumothorax, as well as making sure it is very securely sutured in place. Too large an amount of fluid removal and/or removing fluid too quickly can lead to reexpansion lung injury. Removal of less fluid may be safer and will quickly help to stabilize the patient.

Following thoracocentesis, radiographs or ultrasound can be performed to assess the quantity of fluid remaining or to identify iatrogenic pneumothorax.

103.2 PERICARDIOCENTESIS

Pericardiocentesis confirms the suspicion of pericardial fluid and provides diagnostic and therapeutic benefit by relieving decreased cardiac function (cardiac tamponade).

Materials required for pericardiocentesis include 6-, 12-, 60-mL syringes; +/– three-way stopcock and IV fluid extension line; 16-gauge, 3¼-inch, or 5-inch over-the-needle Angiocath catheter; sterile gloves; lidocaine for local anesthesia; a scalpel blade; and tubes for collection and culture of fluid.

The most important consideration is a strong clinical suspicion of fluid collection in the pericardial sac. Physical examination findings include increased venous pressure, decreased heart sounds, and decreased peripheral blood pressure. Signs of right-sided heart failure may be observed (ascites and peripheral venous distension). Radiographs of the thorax aid in supporting the diagnosis if rounding of the entire cardiac silhouette is observed on both lateral and dorsoventral views. The heart appears globoid rather than elliptic in shape. The pericardial sac can become distended so that it contacts the thoracic wall. Ultrasound provides a definitive diagnosis of pericardial effusion and cardiac tamponade (see Chapter 205).

The suspicion of pericardial fluid is supported on ECG by a generalized decrease in electrical amplitude of the complexes or electrical alternans. If pericardial fluid has been confirmed by ultrasound there are no contraindications to the procedure except for a bleeding diathesis or ruptured left atrium leading to continual bleeding into the pericardial space.

Complications of pericardiocentesis could include puncture of the ventricular wall, which could induce an arrhythmia, puncture of a coronary blood vessel, or epicardial laceration.

Sedation can be used if necessary but acepromazine should be avoided to prevent exacerbation of preexisting hypotension. Most pericardiocenteses are performed without sedation and often with use of only lidocaine at the site of skin and thoracic wall puncture. The patient should be gently restrained either standing or in sternal or left lateral recumbency. ECG monitoring of the heart rate and rhythm during the procedure is recommended but not essential.

A wide area of the right ventral hemithorax is surgically prepared from the third to the eighth intercostal space (ICS) to avoid trauma to the lung by entering the pleural triangle where there is no lung tissue. One milliliter of lidocaine is infiltrated into the skin and down to the parietal pleura at the site of entry (costochondral junction over the fifth or sixth ICS). A stab incision is made through the skin to permit needle entry. A 6-or 12-cc syringe is attached to the end of an angiocatheter and it is advanced into the thorax through the incision cranial to the rib (the intercostal vessels caudal to each rib are avoided) while maintaining gentle traction on the syringe plunger. The needle and syringe are held perpendicular to the chest wall and directed medially and slightly dorsally (Figure 103-1). A small “pop” may be felt when passing through the pericardium. When fluid appears in the syringe, a small amount for evaluation is collected and the catheter is advanced into the thorax all the way to the hub while the stylet is held steady (Figures 103-2 and 103-3). The stylet is removed and a 60-cc syringe is attached to the angiocatheter. Negative pressure is not present within the pericardial sac and usually pericardial fluid continues to pulsate out of the catheter. If the catheter rubs on the myocardium, ventricular premature contractions (VPCs) may be observed; the needle should be withdrawn slightly.

Figure 103-1 Placement of the angiocatheter at the sixth intercostal space at an angle perpendicular to the chest wall to perform a pericardiocentesis. Gentle suction is applied to the end of the catheter with a 12-cc syringe while the needle is advanced into the thorax and pericardial sac.

If pericardial fluid is bloody it should be monitored for signs of clotting (Figure 103-4). If clotting is observed then acute bleeding from a ruptured vessel or the tapping of blood directly from within the heart is suspected and the catheter removed. Comparing clotting time and hematocrit of peripheral blood often assists in determination of the fluid type.

The amount of fluid removed should be recorded. Depending on severity and duration of the condition 1000 cc or more may be obtained from the pericardial sac of a large dog. The fluid sample should be submitted in a plain tube and a tube containing an anticoagulant for cytology and chemical analysis. A sample may be considered for culture.

Following the procedure a thoracic radiograph or ultrasound should be performed to determine if the fluid is re-accumulating or if total fluid withdrawal has been accomplished. When ultrasound availability is not present, a pneumopericardial study should be considered.

Figure 103-2 Pericardial fluid is first observed within the syringe. Advancing the needle is discontinued here.

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Figure 103-3 The catheter is advanced with one hand in one smooth motion while the other hand holds the stylet steady and prevents it from injuring the epicardium.

103.3 CHEST TUBE PLACEMENT

Temporary indwelling chest tubes are indicated for conditions requiring repeated thoracocentesis such as pneumothorax, tension pneumothorax, pyothorax, chylothorax, postoperative thoracotomy, or pleurodesis.

Appropriately sized tubes selected according to weight and tube size should comfortably fit in the intercostal space (Table 103-1). As a guide, the inside diameter of the chest tube should be the same size as the main stem bronchus

on radiographs if the fluid is viscous or contains clots. A smaller tube (12 French) can be used to evacuate a pneumothorax.

Types of tubes used include silicone rubber (does not easily occlude but difficult to place without a stylet), red rubber (irritating and non-radiopaque), and polyvinylchloride (commercially available).

Commercially available chest tubes have fenestrations (holes) preplaced. Additional holes can be made that encompass less than 30% of the tube circumference so as to not weaken it. To make such a hole the tube is prebent and a tiny amount at the angle of the tube is cut. The hole size will be approximately four times as large as the piece removed so the cut should be conservative. All holes must be within the portion of the tube placed within the thorax.

Figure 103-4 A 60-cc syringe is attached to the catheter and gentle traction is applied until all fluid has been removed. Appearance of the pericardial fluid is often bloody as seen here. This part of the procedure is no longer sterile.

Table • 103-1 Recommended Tube Sizes for Cats and Dogs

WEIGHT	TUBE SIZE (FRENCH)
<7 kg	14–16
dogs 7–15 kg	18–22
dogs 16–30 kg	22–28
dogs >30 kg	28–36

The clinical condition of the patient must be assessed prior to restraint or sedation for tube placement. The desired length of tube is premeasured from the tenth intercostal space (ICS) to the ipsilateral elbow.

Iatrogenic pneumothorax, laceration of a lung lobe or vessel, and tube migration within the thoracic cavity are potential complications to be considered with chest tube placement. Additional considerations include pain, lung or pleural irritation, and the presence of ventricular premature contractions with cardiac-induced pleural effusion.

The patient is gently restrained in lateral recumbency with the side for the tube placement facing up or is maintained sternally. Hair is clipped from shoulder to last rib and to the dorsal and ventral midline. Surgical preparation or cleaning of the skin follows. The tube is placed approximately mid-thorax at the seventh ICS. If air is suspected the tube is placed at the junction of upper third and lower two thirds of the chest wall. If fluid is to be removed, the tube is placed at the junction of the lower third and upper two thirds of the chest wall.

A local infiltrative block is performed directly at the site of tube placement or an intercostal or line block along the seventh ICS. There are two different techniques for incisions:

1. Incision is made using a blade over the tenth ICS (previously locally anesthetized). The tip of trocar is placed through skin incision and it is advanced subcutaneously cranially to the seventh ICS.

2. A gloved assistant pulls skin cranially starting just behind the elbow. A blade is used to incise the skin over the seventh ICS. The subcutaneous and intercostal muscles can be incised with the blade or dissected with Mayo scissors. The trocar is inserted through the full incision.

The trocar is placed in a vertical position perpendicular with the thoracic wall and the tip directed toward the opposite elbow. With one hand the trocar is held securely 2 to 3 cm above the skin to avoid penetration of the thoracic cavity too deeply. The palm of the other hand is placed on the head of the stylet and firm consistent pressure is applied to penetrate the trocar into the pleural space in a single motion. Once the pleura is penetrated, the trocar is angled so that it is parallel with the ribs and directed dorsally to remove air or ventrally for fluid. The stylet is pulled back very slightly and the tube and stylet advanced to the desired length. The tube is clamped with the handle portion of a hemostat as the stylet is removed to prevent pneumothorax. The skin is released and it will migrate caudally and form a tunnel to seal the hole just created. A tube adaptor and a 3-way stopcock with ports closed are attached to the tube.

A purse-string suture is used at the skin incision in addition to a Chinese finger trap or Roman sandal suture pattern to secure the tube to the chest wall. Alternatively, a “butterfly” is made out of 1-inch white tape around the tube just distal to the skin incision and suture the wings to the skin. 382 383

A thoracic radiograph confirms tube placement. Antibiotic ointment and sterile gauze are placed over the insertion site followed by a comfortable chest bandage. The bandage and skin incision should be checked at least several times daily. All connections must be secure with no leaks.

The tube can be removed when there is less than 2 mL/kg/day of fluid accumulation. One continuous rapid motion is used to remove the drain. Sedation is not necessary. Overwrap with a thoracic circumferential bandage for 1 to 2 days.

An E-collar or other method of preventing access to the tube must be utilized at ALL times. Initially the tube should be monitored and evacuated every 1 to 2 hours, more often if the patient becomes tachypneic or dyspneic. A large (35-or 60-cc) syringe can be used to provide intermittent suction in small dogs and cats, whereas continual suction may be required in large dogs. One additional consideration is that some patients may have a complete mediastinum due to pathology within the thorax. This may require chest tube placement on both sides of the thorax to completely remove fluid or air.

104 CHAPTER • 104 Transtracheal Wash and Bronchoscopy

Brian C. Norman

Transtracheal wash and bronchoscopy are diagnostic procedures used in the diagnosis of bronchopulmonary airway disease. The transtracheal wash is used to obtain tracheobronchial cells and secretions for cytology and microbiologic evaluation. The bronchoscope is a more specific procedure that allows visualization of the trachea and airways while obtaining samples. The choice of procedure should be based on stability of the patient, diffuseness of disease, and operator skill level.

104.1 TRANSTRACHEAL WASH

A transtracheal wash can be performed in animals with a diffuse disease that cannot undergo prolonged sed ation. The ventral portion of the patient's neck is clipped and aseptically prepared. The patient is then placed in sternal recumbency with an assistant holding the head and pointing the nose up. Sedation with Propofol (Diprivan) or a short-acting barbiturate anesthetic is preferred. In dogs, a 16-gauge through-the-needle jugular catheter is inserted between proximal tracheal rings or the cricothyroid membrane and advanced down the airway. In cats, an open-end polypropylene urinary catheter or 5 F red rubber catheter can be placed through a sterile endotracheal tube. The catheter is slowly advanced down the trachea. Warm sterile saline is infused through the catheter: 5 mL is infused for cats and small dogs up to a maximum of 20 mL in large dogs. After 5 to 10 seconds, the operator attempts to retrieve the sample by applying gentle negative pressure several times with the syringe. Generally, 50% of the original volume will be retrieved. Several drops of the sample should be placed on a culture swab for culture and sensitivity, and the remainder should be placed in a sterile tube or container for cytology.

Pneumomediastinum and subcutaneous emphysema are complications of this procedure that may need to be addressed.

104.2 BRONCHOSCOPY

Bronchoscopy is best performed with a flexible fiber-optic bronchoscope. The patient is anesthetized with Propofol® and maintained on a drip or gaseous anesthesia. In larger animals, an endotracheal tube may be placed and the bronchoscope can go through the tube. In smaller animals, the bronchoscope is too large and the animals cannot be intubated during the procedure. After the animal is lightly anesthetized, the bronchoscope is inserted through the arytenoids and into the trachea. Inspection of the trachea should include the appearance of the mucosa, the amount of secretions, and any evidence of collapse. The carina should then be identified, and each lung lobe should be systematically examined. (Figures 104-1 and 104-2). The operator must note the presence of mucus plugs, foreign bodies, dynamic collapse of airways, masses or nodules, and parasites.

The bronchoscope offers several options to sample the airways. The first method uses a bronchoscope brush. The brush is covered by plastic that can be pulled back once the brush is in its desired location. With the bronchoscope in the desired location, a small sampling brush is passed through the sampling channel. When the brush is visualized, the brush is extended and gently scraped against the airway. The brush is then pulled back into its casing and removed from the scope. The brush can be cultured and then gently rubbed on a glass slide for cytology.

The second sampling method uses a biopsy instrument. In a similar method, the bronchoscope is placed in the desired location and then the biopsy instrument is inserted into the sampling port. The bronchoscope is then used

to guide the instrument to the desired location and the biopsy is taken. The sample can be submitted for culture and histopathology.

The third sampling method is bronchial or bronchoalveolar lavage. This is performed after all lobes have been inspected. The bronchoscope is directed into the desired lung and then advanced until it is wedged or is occluding the airway. The clinician should instill 10 to 30 mL of warm sterile saline into the sampling port, and (5 to 10 seconds later) aspirate the sample using a syringe. Approximately 40% to 50% of the sample should be retrieved. It is helpful if the patient is not heavily sedated. The lightly sedated animal will cough, producing a better sample. This procedure can be repeated several times. Several drops of the sample should be cultured, and the rest should be placed in sterile tubes for cytologic evaluation.

Figure 104-1 Diagram of normal bronchoscopic image of the division of the carina, demonstrating the position of the right and left main stem bronchi.

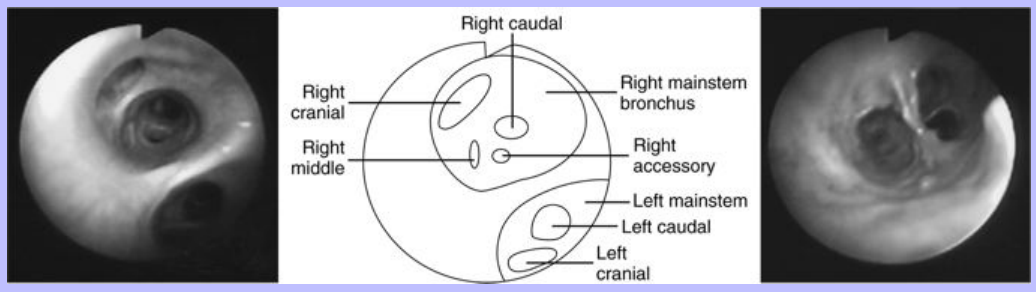
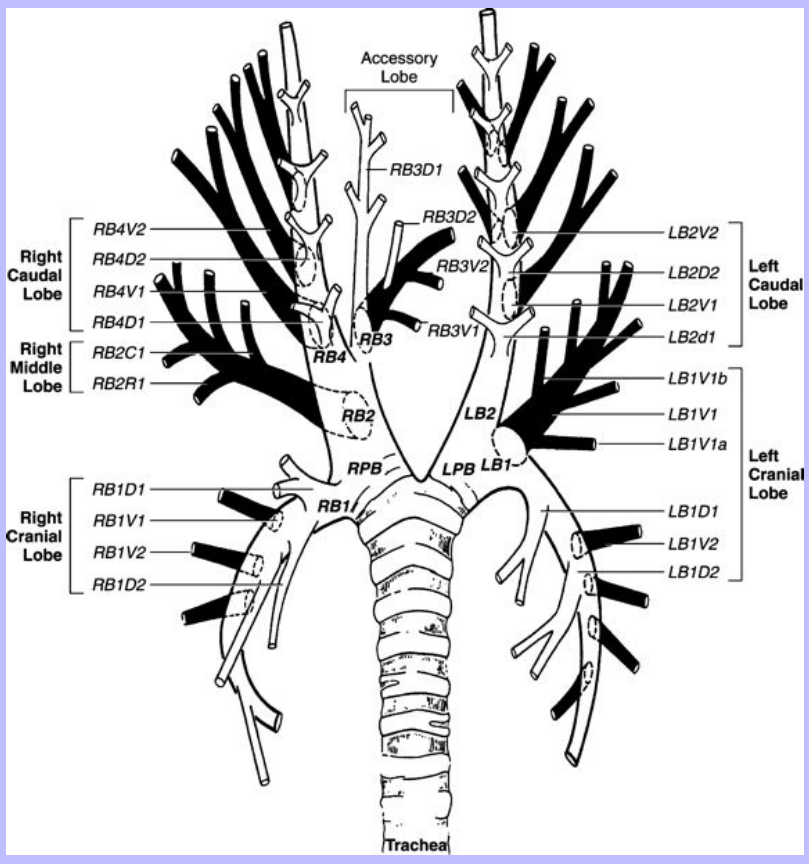


Figure 104-2 Diagram of normal bronchial anatomy in dogs. Each lobar bronchus is subdivided into segmental bronchi: *V1,* first ventral segmental bronchus; *V2,* second ventral segmental bronchus; *D1,* first dorsal segmental bronchus; *D2,* second dorsal segmental bronchus; *C1,* first caudal segmental bronchus; and *R1,* first rostral segmental bronchus. Segmental bronchi are subdivided into subsegmental bronchi: *V1a,* first subsegmental bronchus; *V1b,* second subsegmental bronchus. *LB1,* Lobar bronchus of left cranial lung lobe; *LB2,* lobar bronchus of left caudal lung lobe; *LPB,* left main stem bronchus; *RB1,* lobar bronchus of right cranial lung lobe; *RB2,* lobar bronchus of right middle lung lobe; *RB3,* lobar bronchus of accessory lobe; *RB4,* lobar bronchus of right caudal lung lobe; *RPB,* right main stem bronchus. (From Amis TC, McKiernan BC: Systematic identification of endobronchial anatomy during bronchoscopy in the dog, *Am J Vet Res* 47:2649, 1986.)



105 CHAPTER • 105 Unblocking the Urethra of the Male Cat

Mary H. Bowles

The male cat may have an obstructed urethra due to inflammation, spasms, trauma, congenital defects, urethral or periurethral masses, foreign bodies, uroliths, and urethral plugs. The length and narrow diameter of the urethra predisposes these cats to obstruction. The urethral plug is the most frequent cause of obstruction.

Cats with feline lower urinary tract disease often display similar clinical signs regardless of the cause or the presence or absence of obstruction. Dysuria, hematuria, and frequent attempts to urinate are common but not exclusive signs of urethral obstruction. However, when these signs are combined with vocalization, licking the prepuce or penis, or systemic evidence of illness (e.g., depression, loss of appetite), it is likely that the animal has a urethral obstruction. Palpation of a distended bladder that is difficult to express is a key feature of urethral obstruction.

When urethral obstruction is suspected, a thorough assessment of the cat's physical condition is indicated prior to catheterization, especially if the cat is systemically ill. In addition to establishing further evidence of urethral obstruction by bladder palpation and inspection of the distal penis, special attention should be paid to the cardiac status because hyperkalemia-related arrhythmias may be present that affect the treatment plan. Quick assessment tests (QUATS) (e.g., blood urea nitrogen [BUN], glucose, packed cell volume [PCV]) are indicated in any cat prior to catheterization to evaluate both anesthetic risk and overall condition. Appropriate blood samples should be saved for subsequent complete blood count (CBC) and biochemistry profile evaluation, especially in systemically ill cats. Bladder decompression by cystocentesis provides optimum samples for urinalysis and culture, alleviates distress, and may facilitate flushing obstructive material back into the bladder when necessary. Urethral catheterization usually requires general anesthesia unless the cat is moribund. Anesthetic agents requiring renal excretion should be used with caution.

105.1 UNBLOCKING TECHNIQUE AND INDWELLING CATHETER PLACEMENT

The cat should be placed in lateral recumbency. The clinician should then clip the hair in the perineal area and surgically scrub the prepuce and tip of the penis, taking care to avoid undue trauma to the penis. The tail and hindlimbs should be drawn forward toward the head to provide better exposure of the preputial area. Using sterile technique, the prepuce should be pushed back toward the body, exposing the distal end of the penis. Because urethral plugs often lodge near the external urethral orifice, the exposed distal penis should be gently massaged to loosen any obstructing material present and extrude it from the urethra. The lubricated tip of an open-ended tomcat catheter (3.5 F polypropylene, 4.5 to 5.5 inches in length) or a Minnesota olive-tipped feline urethral catheter (22 G × ½-to 1½-inch E-JAY International, Inc., Glendora, Calif.) is then inserted into the external urethral orifice, extending the penis caudally and dorsally until it is parallel to the spine to facilitate advancement of the catheter (Figure 105-1). Once the obstruction has been reached, the clinician should attach a syringe (ε20 mL) filled with saline or lactated Ringer's solution to the catheter either directly or by an intravenous extension set. A liberal amount of flushing solution is then injected into the urethral lumen, allowing fluid to run back out of the urethral orifice. The clinician should periodically attempt to cautiously advance the catheter toward the bladder, noting evidence of relief of obstruction, such as debris emerging from the orifice or a decrease in reflux of flushing solution. Applying moderate pressure to the bladder wall and occasionally repeating gentle massage of the extruded penis between flushings may facilitate dislodgement of a urethral plug or urolith.

If the previously described technique does not result in relief of obstruction, the clinician should continue to flush while manually occluding the urethra around the catheter tip, attempting to dilate the urethral lumen and force the

obstructive material back into the bladder. As pressure builds up in the obstructed urethra, the clinician should try to carefully advance the catheter toward the bladder. To prevent iatrogenic damage to the urethra, excessive force should be avoided when advancing the catheter and when injecting flushing solution from the syringe into the manually occluded urethra.

If the urethra is successfully unblocked, a catheter should be inserted into the bladder lumen and the majority of urine aspirated from the bladder, saving a portion for urinalysis +/– culture if not obtained previously by cystocentesis. The bladder should be flushed repeatedly with saline or lactated Ringer's solution until aspiration of the flushing solution appears relatively free of blood and particulate material. If a urethral plug or urolith was obtained during the unblocking procedure, it should be saved for analysis. Urethral plugs can be examined cytologically, and uroliths can be submitted for quantitative analysis +/– culture.

Figure 105-1 Proper positioning of the feline penis for urethral catheterization with a 3.5 F polypropylene catheter. The penis is extended caudally and dorsally while the tail and hind limbs are drawn forward toward the head.

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If the unblocking techniques previously described are unsuccessful, the bladder can be serially decompressed by cystocentesis or a cystostomy tube can be placed for temporary urine diversion. These procedures provide relief while the cat receives supportive therapy and has diagnostic imaging performed to further define the source and location of obstruction; they also allow for alternative treatment plans to be developed.

Monitor urination for at least 24 hours after relief of obstruction. Express the bladder manually at least three times daily if the cat is not voiding regularly or a large amount of urine is retained in the bladder after voiding. Place an indwelling catheter immediately after the unblocking procedure if a strong urine stream is not present on expression, the cat is systemically ill, excessive hematuria exists, or relief of obstruction was difficult. An indwelling catheter may be placed up to several hours later if the patient reobstructs or has difficulty urinating due to an atonic bladder. Ideally, a 5 French (F) (the 3.5 F. size may be used but becomes obstructed more easily) red-rubber (polyvinyl) or Foley catheter should be used because these catheters are more pliable than the polypropylene variety and less likely to cause injury to the urethral and bladder mucosa. Placement may require the use of a wire guide due to the increased pliability. The application of a generous amount of lubricant is often required to facilitate passage, especially for the balloon portion of the Foley catheter. To minimize bacterial contamination after insertion into the bladder lumen, the clinician should attach the indwelling catheter to a sterile, closed urine collection system available as a commercial product (Cook Urological, Spence, Ind.) or constructed from a recently emptied intravenous (IV) fluid bag attached to a sterile IV administration set. The clinician can

reduce tension placed on the indwelling catheter by the collection system by using elastic wrap and suture to attach the apparatus to the cat (Figure 105-2). Indwelling catheters should be removed as soon as possible, generally within 1 to 3 days after placement. Although indwelling catheters predispose the cat to urinary tract infection, antibiotic therapy is not recommended unless evidence of urinary tract or systemic infection exists.

Figure 105-2 Indwelling 5 F. Foley urethral catheter attached to a sterile, closed urine collection system. Elastic wrap attaches the urine collection system to the tail, and an elastic wrap flange is loosely sutured in the preputial area to reduce the tension on the urethral catheter and help keep it in place.

106 CHAPTER • 106 Venous and Arterial Puncture

Harold Davis

106.1 VENIPUNCTURE

The most commonly used veins for venipuncture are the cephalic (dog and cat), lateral saphenous (dog), medial saphenous (cat), and jugular (dog and cat). The ear veins (dog and cat), sublingual veins (dog and cat), and abdominal veins (dogs) have also been used. Any visible vein is an option for venipuncture.

The most important aspects of any venipuncture technique are the proper restraint of the animal and proper distention and immobilization of the vessel. These objectives are most easily accomplished when the procedure is done as a two-person project. The phlebotomist should only attempt the venipuncture when the vessel can be clearly delineated. Blind venipuncture attempts, in the hopes of accidentally "skewering" the vein, are doomed to failure and create unnecessary patient discomfort. If the phlebotomist is unable to locate the vessel (by visual inspection or digital palpation), the manner in which the vessel is distended and immobilized must be changed.

Awake animals need to be restrained for any of these procedures, but excessive restraint should be avoided because it may incite more resistance from the animal than the venipuncture procedure itself. All venipunctures (and arterial punctures) must be done aseptically. The hair should be clipped and the skin prepared with antiseptic solutions as if for surgery.

106.2 CEPHALIC VEIN VENIPUNCTURE

The dog or cat may be positioned in sternal or lateral recumbency. The restrainer leans over the top of the animal and grasps the leg of interest at the elbow. The other hand or arm can be used to restrain the animal's head if the animal is awake, to prevent an aggressive response to the skin puncture. If the animal is in sternal recumbency, the restrainer should lean on his or her elbow to help prevent the animal from withdrawing its leg at some critical time during the procedure. The thumb or forefinger is wrapped around the leg at the level of the elbow. Pressure at this point occludes the cephalic vein. The skin is then rotated outward to roll the vein to the top (anterior) of the leg.

The phlebotomist grasps the leg with one hand at the level of the metacarpus and further extends the leg. In loose-skinned animals, it may be necessary to flex the carpus. The objective is to tether the vein between the two points of traction (at the elbow and at the carpus) so that the vein is both distended and does not roll from side to side. It should not be necessary for the phlebotomist to use his or her thumb to help immobilize the vein; this may only serve to collapse the vein, making venipuncture more difficult.

The needle is directed, as much as possible, along the longitudinal axis of the vein. The needle is inserted through the skin with the bevel facing up. It is not necessary to achieve both skin and vein puncture in the first movement. The skin puncture is the painful part, and animals will often move in response to it. Once the animal has settled down, the needle can be directed into the vein. If blood does not spontaneously flow into the hub of the needle, the phlebotomist should gently aspirate to determine if the needle is or is not in the vein. If it is not in the vein, the needle should be advanced a bit further and the process repeated. The needle can be advanced to its full length. If at this point the venipuncture has not been successful, the needle will have to be withdrawn to its subcutaneous position (it should not be removed entirely, because another skin puncture will then be necessary). It is most important to withdraw the needle slowly, while gently aspirating. The deep wall of the vein may have been inadvertently penetrated, and the lumen will thereby be found as the needle is withdrawn.

Figure 106-1 The various positions used for dog and cat venipuncture. **A,** Dog positioned for venipuncture of the lateral saphenous vein. **B,** Cat positioned for venipuncture of the medial saphenous vein. **C,** Dog positioned for venipuncture of the jugular vein. **D,** Cat positioned for venipuncture of the jugular vein.

Once the blood sample is taken or the drug is administered, the needle is withdrawn from the vein and digital pressure applied over the venipuncture site for at least 30 seconds. The site should be monitored for bleeding or hematoma formation for an additional several minutes.

106.2.1 Lateral Saphenous Venipuncture

Dogs are usually positioned in lateral recumbency for this procedure (Figure 106-1, *A*). The restrainer grasps the upper leg at the stifle. The other hand or arm can be used to restrain the animal's forelegs and head if the animal is awake. Circumferential pressure is applied at the stifle to occlude and distend the vein. The phlebotomist grasps the leg with one hand at the level of the metatarsus. In loose-skinned animals it may be necessary to extend the leg and flex the tarsus to better tether and immobilize the vein. It should not be necessary for the phlebotomist to use his or her thumb to help immobilize the vein. The venipuncture is performed as described previously.

106.2.2 Medial Saphenous Venipuncture

Cats are usually positioned in lateral recumbency for this procedure. The restrainer grasps the lower leg at the stifle while reflecting the upper leg caudally with the forearm. The other hand or arm can be used to restrain the animal's forelegs and head if the animal is awake. Circumferential pressure is applied at the stifle to occlude and distend the vein. Alternatively, in the cat, the phlebotomist should grasp it by the scruff of the neck and place in lateral recumbency (Fig 106-1, *B*). The upper hind leg is abducted and flexed to expose the medial surface of the bottom leg. Applying pressure with the edge of the hand that abducts and extends the upper leg distends the vein. The phlebotomist grasps the leg with one hand at the level of the metatarsus. In loose-skinned animals it may be necessary to extend the leg and flex the tarsus to better tether and immobilize the vein. It should not be necessary for the phlebotomist to use his or her thumb to help immobilize the vein. The venipuncture is performed as described previously.

106.2.3 Jugular Venipuncture

Dogs and cats may be positioned in sternal or lateral recumbency for this procedure. In sternal positioning, one convenient technique includes backing the animal into a corner, between the legs of the holder (Fig 106-1, *C*). Alternatively, the dog or cat can be restrained on a table in sternal recumbency (Fig. 106-1, *D*). One hand grasps the legs at the carpel joint and stretches the legs over the edge of the table. In any position the head will need to be extended. Either the restrainer or the phlebotomist occludes the vein by applying occlusive pressure at the thoracic inlet. Care must be taken not to compress the trachea or impair breathing. Vein distention and immobilization can be maximized by pressing into the thoracic inlet in a caudal direction and by further extending the head. Extensive longitudinal traction, however, can collapse the vein. With optimal positioning, the vein is easy to palpate (or visualize) and does not roll much from side to side. In sternal positioning, the venipuncture is usually done in a cephalad direction; in lateral positioning the venipuncture is generally done is a caudal direction. The venipuncture is performed as described previously.

106.2.4 Arterial Puncture

The dorsal metatarsal (pedal) and femoral arteries are most commonly used for arterial blood sampling. The dorsal metatarsal is smaller but the interstitial connective tissues around it are tight (compared with the femoral artery), which facilitates vessel positioning and minimizes postpuncture hematoma formation. The radial, brachial, aural, and sublingual arteries have also been used.

Arterial puncture is usually done with the animal in lateral recumbency; however, it can be accomplished when the animal is standing if it resents the lateral recumbent positioning. The pulse is palpated with one or two fingers of one hand. The needle is inserted through the skin but not into the artery. Once the animal settles down from the skin puncture, the needle is aligned with the longitudinal axis of the artery (bevel up). The tip of the needle and the artery are simultaneously palpated with the one finger, and the needle inserted into the artery. Blood should spontaneously flow into the hub of the needle in an animal with normal blood pressure; however, gentle aspiration on the plunger may be required in animals with low blood pressure or when small needles are used. If the arterial puncture is unsuccessful, the needle can be inserted a bit further. As for venipuncture, when the needle is withdrawn, it should be done slowly and with gentle aspiration applied to the plunger in case the deep wall of the artery was inadvertently punctured during needle introduction. The needle is withdrawn to its subcutaneous position and the arterial puncture is reattempted.

Once the sample collection is complete, the clinicians should withdraw the needle and apply digital pressure over the puncture site for at least 1 minute; then the animal should be monitored for bleeding or hematoma formation for another 4 minutes. If blood gas measurements cannot be done immediately, the sample should be stored in ice water to minimize in vitro metabolic changes in the measured parameters.

107 CHAPTER • 107 Skin Scrapings and Skin Biopsies

Sonya V. Bettenay

Ralf S. Mueller

107.1 GETTING THE MOST FROM SKIN SCRAPINGS

Skin scrapings in veterinary dermatology are used to identify ectoparasites or to evaluate cells and organisms from the skin surface cytologically. The focus of this chapter is obtaining skin scrapings to diagnose cutaneous ectoparasites.

107.1.1 Superficial Skin Scrapings

107.1.1.1 Indication

Superficial skin scrapings are taken to detect mites living on the skin surface, such as *Cheyletiella* spp. or *Otodectes cynotis*, or to identify mites burrowing in the stratum corneum, such as *Sarcoptes scabiei* or *Notoedres cati*. All these mites can cause pruritus (which is seen least commonly in cheyletiellosis). Particularly in any severely pruritic small animal, where itching began suddenly or where other animals or humans in the household are affected (or both occur), scabies should be suspected. The preferred anatomic sites vary with the ectoparasite. Scabies most commonly affects the elbows, ear margins, hocks, and ventrum. *Notoedres cati* in cats most commonly affects the face. In both dog and cat, the dorsum is most commonly affected with *Cheyletiella* mites, which typically cause scaling. Superficial skin scrapings should thus be performed in any scaly or pruritic dog or cat.

107.1.1.2 Procedure

Mineral oil or pyrethrin eardrops should be put on the scalpel blade *and* affected skin. The authors select nonexcoriated sites, preferably in scaly or papular areas. It is important to scrape a large area. In hairy dogs with suspected scabies, it is recommended to clip the hair first. It is important not to remove the surface scale or crust that may be present, should such clipping be necessary. *Sarcoptes* mites are located superficially within the epidermis and may be dislodged with such cleansing. Clipping is contraindicated in animals with possible cheyletiellosis. Mineral oil is applied to the affected skin, gently scraped off the surface, and translocated onto a microscope glass slide. Scrapings are done in the direction of hair growth. The oil on the skin will facilitate gathering of debris and increase the chance of positive results. When evaluating a sample microscopically for ectoparasites, a cover slip is applied to distribute debris evenly. This minimizes the chance of missing mites covered by debris and enables a rapid yet thorough scanning at low magnification without the need for continuous adjustment of focus. The condenser of the microscope should be lowered for easy identification of parasites.

107.1.1.3 Interpretation

For scabies or cheyletiellosis, one mite or egg is diagnostic and adequate for initiating miticidal therapy. In canine scabies, 50% of affected dogs may be negative on several scrapings and trial therapy may be needed. Occasionally, a short-bodied *Demodex* mite may be found on superficial skin scrapings. These short-bodied

mites are supposed to live in the epidermis rather than the follicles, and their detection should trigger deep skin scrapings because they may occur in combination with a proliferation of follicular *Demodex* mites.

107.1.2 Deep Skin Scrapings

107.1.2.1 Indication

Deep skin scrapings are performed to detect *Demodex* mites. In the dog, *Demodex canis* lives in the hair follicle; a longer-bodied *Demodex* mite is suspected to live in the sebaceous glands. Papules, pustules, and crusts characterize canine demodicosis. Comedones, scales, and alopecia also may be seen. Demodicosis is on the list of differential diagnoses in almost any dog presented with skin disease. A deep skin scraping is one of the most common diagnostic procedures performed in veterinary dermatology. Demodicosis in the cat is less common, usually affects the head, and typically occurs secondary to systemic disease.

107.1.2.2 Procedure

A small area of affected skin (1 to 2 cm^2) is scraped in the direction of hair growth until capillary bleeding is observed. A blade covered with mineral oil should be used. Follicular papules or pustules are particularly suited for scraping. Because *Demodex* mites live in the hair follicles, it is useful to squeeze the skin prior to and during the scraping in an attempt to push the mites out from the depths of the follicles. A survey conducted by summer dermatology students revealed a 50% higher mite count when the skin was squeezed prior to scraping. Paws and faces are difficult to scrape, and skin biopsies may be needed in some of these dogs to confirm the diagnosis. Old English sheepdogs, Scottish terriers, and especially Shar Peis with demodicosis are anecdotally reported to be negative on scrapings and may have to be biopsied for diagnosis. Although not documented, it is thought that these breeds have more tortuous and deep hair follicles. Trichograms (hair plucks) provide an alternative test in these situations. Hairs are plucked with a hemostat and placed in mineral oil on a glass slide for examination. Approximately half of all dogs with demodicosis will show positive trichograms; a negative result does not rule out the disease, and the clinician must initiate further testing.

107.1.2.3 Interpretation

Although *Demodex canis* is a normal part of cutaneous fauna (and thus an occasional mite can be found on skin scrapings of normal dogs), one should never see more than one *Demodex* mite on a dog not affected by demodicosis. If only one mite is found, further scrapings or a biopsy are recommended. When evaluating deep skin scrapings, it is important to assess and to note in the record the site of scraping and the relative numbers of adults, larvae, nymphs, and eggs per low-power field (LPF). In subsequent visits, assessment of response to therapy relies on the comparison of such numbers. It is recommended that repeat scrapes at the same sites take place monthly when monitoring.

107.2 GETTING THE MOST FROM A SKIN BIOPSY

Skin biopsies are recommended as useful in textbooks and by dermatologists, yet the results are often “inconclusive.” The manner in which a biopsy sample is obtained can significantly influence the end results.

Lesions have “lives,” disease is a dynamic process, and the biopsy section is like a single frame taken from a roll of movie film. If clinicians set the “film” on a developing lesion, it would display many different appearances

throughout its evolution. Because a single biopsy reveals only one "snapshot," the clues as to the cause of the disease may simply not be present at that point in time. *Taking multiple samples* from well-chosen clinical sites exhibiting a variety of lesions will potentially help to avoid inconclusive results. In a pustular disease, erythematous macules develop into papules, then pustules, and finally crusts and erosions. Sampling every single one of these stages and then several of the most exciting lesions, the pustules, will give the pathologist the widest range of lesion development and hence the best chance to come up with some helpful comments.

107.2.1 Selection of the Site

Site selection requires careful examination of the entire animal for the most representative range of lesions. With the exception of a solitary nodule, multiple tissue samples are taken. Pustules or vesicles are fragile lesions, that have to be handled with great care to prevent rupture.

Depigmenting lesions should be biopsied *in an area of active depigmentation* (i.e., gray color) rather than the final stage (i.e., white). Once the pigment has been lost from the epidermis, active disease is probably absent; a biopsy of a depigmented area should be expected to reveal loss of melanocytes and pigment but not necessarily the reason for the depigmentation.

Alopecia should be biopsied *in the center of the most alopecic area*, as well as in junctional and normal areas. The clinician should remember that the glabrous (nonhaired) areas of the body normally contain fewer hair follicle units and smaller sebaceous glands; therefore if possible, these areas should be avoided if diseases with follicular pathology are on the list of differential diagnoses.

Ulcerated areas should also be avoided, unless they are sampled *in addition* to other areas or unless one is looking for a deep dermal, vascular, or pannicular pathologic disease.

Adjacent normal skin should be sampled where possible. In a bacterial folliculitis and furunculosis with a possible underlying allergy or endocrinopathy, the presence of a lymphocytic infiltrate consistent with hypersensitivity or follicular atrophy seen with hormonal diseases can be completely obliterated by the inflammation of a severe secondary pyoderma so that only a diagnosis of deep infection can be made. Clues in regard to the primary diagnosis may be present only in adjacent skin.

107.2.2 Preparation of the Site

Surgical preparation of the site should not be performed at all. Crusts should be left on the skin. If they are accidentally dislodged, they should still be placed in the formalin. It may be helpful to wrap them inside a piece of lens-cleaning tissue paper prior to placement in the formalin container to prevent accidental loss. Crusts may contain microorganisms, inflammatory or acantholytic cells (epidermal cells that have become detached from their neighbors and "rounded up"), which will help establish a diagnosis. Infection as a result of this lack of surgical preparation is almost never seen.

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107.2.3 Helping the Laboratory Technician to Orient the Sample

After formalin fixation, it is impossible even for the most experienced technician to recognize most lesions because the sample appears as gray amorphous tissue. Drawing a line in direction of the hair growth on the skin prior to biopsy using a waterproof pen will help the technician to orient the tissue appropriately (Figure 107-1).

107.2.4 Surgical Technique

The overlying hair should be clipped and gently removed. If crusts are present, scissors may be less traumatic to use than electric clippers. No aseptic preparation is performed (except when excising solitary nodules). If manual restraint or sedation is planned, then the subcutaneous injection of 1 or 2 mL of Xylocaine without adrenaline will usually provide adequate local anesthesia. The needle entry point should be kept outside the proposed biopsy area to avoid disruption to the tissue in the biopsy. The clinician should draw a line in the direction from nose to tail to enable easy relocation of the site and to aid laboratory orientation. General anesthesia is indicated for facial or paw biopsies.

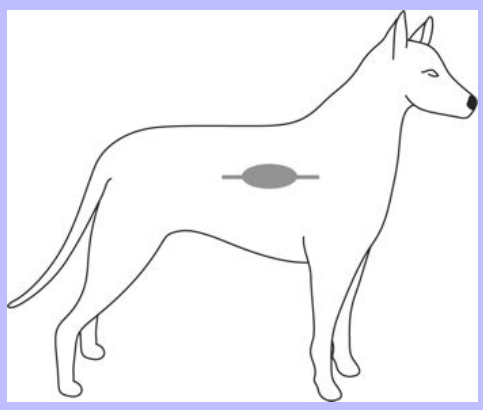
107.2.5 Wedge versus Punch Biopsy

The punch biopsy is quick, relatively atraumatic, and usually used with suspected infectious, inflammatory, and endocrine dermatoses. Disposable biopsy punches are readily available in 4, 6, and 8 mm diameter sizes (8 mm punches are routinely used). However, in small dogs and cats, 6 mm punches may be used (4 mm punches are reserved for biopsies of footpads, nasal planum, mucocutaneous junctions, or eyelids).

107.2.5.1 Punch Biopsy Sampling

The clinician should hold the punch at a vertical angle to the surface of the skin, firmly brace the surrounding skin, and rotate the punch in one direction with continuous pressure. When the skin no longer tries to “turn” with the rotation of the punch, a sufficient depth has been reached to free the dermis from its underlying attachment. The punch is then removed, and any blood is carefully blotted. The tissue is gently grasped at the base—which should be the panniculus—and the subcutaneous attachments severed. Fine instruments (e.g., iris scissors, forceps) should be used. Under no circumstances should the dermis or epidermis be grasped with forceps because this leads to “crush artifact.” Crushed tissue may be misinterpreted as scarring at best; at worst it renders the sample worthless. The specimen should be placed in formalin immediately.

Figure 107-1 Draw a line from nose to tail to help orient the laboratory technician. This technique has revolutionized the interpretation of follicular pathology. The clinician should not draw over fragile lesions like pustules, which may rupture with pressure.



Note: The punch technique is not suitable for biopsy of the skin when lesions of the panniculus or deep dermis are suspected.

The wedge biopsy is used as an excisional technique when removing solitary nodules and fragile lesions such as vesicles or as an incisional technique when complete excision is not possible or desirable. Biopsies of deeper tissues such as in suspected cases of panniculitis cannot be adequately taken using a punch and must be taken with a wedge technique. Finally, when an area of skin exhibits a range of changes radiating from the center to the edge of a lesion, a wedge may be preferable—a punch should not be used in the margin of a lesion (Figure 107-2). Ulcers are best sampled with a wedge biopsy extending from the center of the ulcer to adjacent normal tissue.

107.2.5.2 Excisional and Incisional Sampling

Tissue is surgically excised and closed routinely. The tissue is rolled on gauze to gently blot the blood from its surface. The clinician should use a minimum volume of formalin of (approximately) ten times the volume of the sample. Nodules should be sectioned into 1 cm thick pieces to allow adequate penetration of the formalin into the center of the lesion. They should not be sectioned through completely but should be left attached at the base (fat tissue side), so they are held together in the original piece. Cytology from the impression of the freshly excised surface is a valuable adjunctive test.

107.2.6 When Should a Skin Biopsy Be Performed?

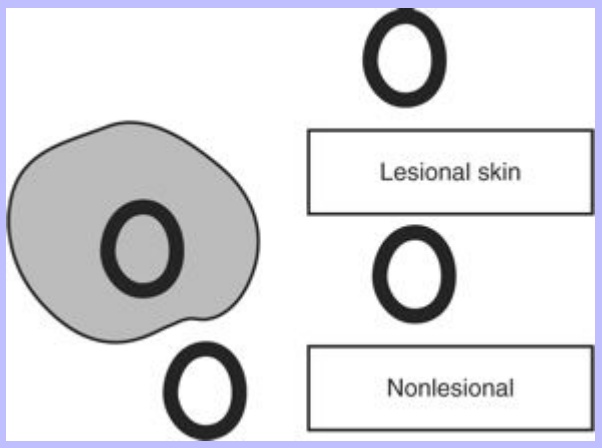
A skin biopsy should be performed for the following reasons:

- When lesions appear unusual to the clinician
- When lesions fail to respond to empiric therapy
- When nodular lesions are present
- When neoplasia is a differential diagnosis

107.2.7 Interpretation—Brief Comments

One of the major reasons to perform a skin biopsy is to rule out other diagnoses. “I think this is an allergy but…” In this situation the biopsy report of “chronic hyperplastic dermatitis with mononuclear perivascular infiltrate,” although not confirming allergy, has at least ruled out the common infectious agents and unusual dermatoses. A supportive pathologic diagnosis interpreted in conjunction with the clinical impressions may be just as useful as a confirmatory diagnosis.

Figure 107-2 Rule of thumb: The clinician should include 100% lesional or nonlesional skin when sampling with a punch biopsy.



The skin has only a limited number of ways to react to the infections, parasites, and allergens. Therefore many conditions share the same microscopic changes. Most dermatoses are diagnosed using a combination of the signalment, clinical presentation (distribution, type of lesions), history (in particular previous response to therapy), and *supportive* histopathologic changes.

107.2.8 Differential Diagnosis List and Submission of Biopsy Samples

A differential diagnosis list is important to any clinical case, but it is essential in dermatology. If the list of clinical differentials fails to correlate with the histopathology, a further review of the sections is undertaken. If the submission clearly states that a deep infectious process is suspected, then special stains may be done to rule out infectious organisms. If an immune-mediated dermatosis is the major differential diagnosis and convincing supportive evidence is not seen on the first section, then recuts may reveal this. When the pathologist is supplied with sufficient clinical information, he or she will likely initiate further examinations (rather than waiting until prompted by a phone call).

To obtain a better skin biopsy result, the clinician should:

1. Not prepare the skin surface.
2. Thoroughly look for a representative range of lesions.
3. Select multiple samples (six is a good rule of thumb) that represent the range of lesions from normal to most severely affected.
4. If possible, include a normal sample collected from haired skin of the dorsum or flank, not the ventrum.
5. Draw an orientation line in the direction from the nose to the tail tip.
6. Use 6 to 8 mm punches or an excisional biopsy except on noses and paws.

7. Handle the biopsy specimen carefully; treat it like tissue paper even when excising.

8. Give the pathologist a complete history, signalment, and physical-findings report, with a list of at least 4 differential diagnoses.

9. Choose a pathologist with an active interest in dermatopathology or a dermatologist with advanced dermatopathology training.

108 CHAPTER • 108 Inhalation Therapy for Airway Disease

Patricia M. Dowling

The latest approach to the management of inflammatory airway disease is inhalation therapy using metered dose inhalers (MDIs). With inhalation therapy, high drug concentrations are delivered directly to the lungs and systemic side effects are avoided or minimized. The onset of action for inhaled bronchodilators and anti-inflammatory drugs is substantially shorter than for oral or parenteral formulations. Nebulizers have been used for a long time in veterinary patients, but the overall efficiency of drug delivery is low, and the equipment is cumbersome and inconvenient for owners. Administration of medications with an MDI is now commonplace in the treatment of human asthma and appears beneficial in the management of veterinary patients as well.

Human MDIs are designed for actuation during a slow, deep inhalation for optimal lung delivery. This is obviously impossible to control in infants and animals. The addition of a spacer enables the MDI to be used in young children and small animals. Spacers decrease the amount of drug deposited in the oropharynx (up to 80% of the actuated dose with the MDI alone), thereby substantially reducing systemic drug absorption and other potential side effects, such as yeast overgrowth (thrush), coughing, and dysphonia.

The drugs currently available in MDI formulations include beta$_2$ agonists, glucocorticoids, ipratropium bromide, cromolyn sodium, and nedocromil. Each product delivers a set amount of drug per actuation (puff). In the United States, MDIs are labeled according to the amount of drug delivered at the mouthpiece, whereas in Canada and the European Union, they are labeled according to the amount of drug delivered from the valve. The U.S. system is used in this chapter.

For client convenience, MDIs are color coded to aid identification. (For a pictorial guide to MDIs, see the website www.peds.arizona.edu/allergyimmunology/southwest/devices/inhalers-asthma/mdikeyhtml.htm.) Even in human medicine, the relative potencies, risks of adverse effects, and optimal dose of the different inhaled asthma medications are still unclear. The results of clinical use in asthmatic cats and dogs with chronic bronchitis have been promising but anecdotal, and clinical trials are needed to determine the most efficacious therapies.

108.1 BETA$_2$ AGONISTS

108.1.1 Albuterol

Albuterol is available in the United States under the trade names Ventolin (GlaxoSmithKline, Research Triangle Park, North Carolina) and Proventil (Schering Corp., Kenilworth, New Jersey). It is marketed as salbutamol in Canada and the European Union. Albuterol is a short-acting beta$_2$ agonist that is the medication of choice for treating acute exacerbations of bronchoconstriction. It relaxes smooth muscle and increases airflow within 5 minutes of administration. Albuterol's effects last 3 to 6 hours. Although effective for symptomatic relief of bronchoconstriction, albuterol does not control inflammation. Monotherapy may exacerbate airway disease and increases morbidity and mortality in human asthmatics. Tolerance may develop with chronic therapy from down-regulation of beta$_2$ receptors. The Proventil MDI is dark blue, and the Proventil MDI is light orange. Each actuation delivers 90 µg of albuterol.

108.1.2 Salmeterol

Salmeterol (Serevent [GlaxoSmithKline]) is a long-acting $beta_2$ agonist. Its onset of action is slow (15 to 30 minutes), but its duration of action is long (over 12 hours). It is not recommended for use in acute bronchoconstriction, but it improves symptom control when used daily in addition to glucocorticoids, more than would simply increasing the glucocorticoid dose. The salmeterol MDI is green, and each actuation delivers 21 µg.

108.1.3 Glucocorticoids

Inhaled glucocorticoids are the most potent inhaled anti-inflammatory drugs currently available. In human beings, early intervention with inhaled glucocorticoids improves asthma control and normalizes lung function and may prevent irreversible airway damage. Improvement after inhaled administration of glucocorticoids can occur within 24 hours of beginning treatment, although maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment. When glucocorticoids are discontinued, asthma stability may persist for several days or longer. The potential risk of adverse side effects of glucocorticoids is well balanced by their efficacy in chronic management of inflammation. Oral candidiasis (thrush), dysphonia, and reflex cough and bronchospasm are the most common adverse effects in humans; all of these effects are reduced by the use of a spacer. The risks of systemic side effects, such as suppression of the hypothalamic-pituitary axis, are less than with oral prednisone or prednisolone therapy. Inhaled glucocorticoid formulations include fluticasone (Flovent [GlaxoSmithKline]); beclomethasone (Beclovent [GlaxoSmithKline] and Vanceril [Schering Corp.]); budesonide (Pulmicort [AstraZeneca, Wilmington, Delaware]); and Proventil [Schering Corp.]); and triamcinolone (Azmacort [Aventis Pharmaceuticals, Bridgewater, New Jersey]). Currently, fluticasone is considered the most potent glucocorticoid formulation with the longest duration of action. Because of its large molecular size, systemic absorption is minimal. Fluticasone MDIs are orange. Fluticasone is available in three sizes; each actuation delivers 44, 110, or 220 µg.

108.2 ANTICHOLINERGIC DRUGS

Ipratropium bromide (Atrovent [Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut]) is a quaternary derivative of atropine that lacks its adverse side effects. In asthmatic humans, ipratropium bromide is used as an additional reliever medication to reverse bronchoconstriction when inhaled short-acting $beta_2$ agonists do not give enough relief. Its anticholinergic action also decreases mucous secretions. In an experimental model of feline asthma, long-term antigen sensitization caused an augmented muscarinic receptor response to acetylcholine. Modulation of muscarinic receptors with anticholinergic drugs may be useful for treatment of asthmatic cats. Currently, there are no published reports of the use of ipratropium in the cat; however the drug has shown efficacy in horses. It is not well absorbed after inhalation and therefore does not cause systemic cholinergic effects. The Atrovent MDI is encased in a clear holder with a white mouthpiece and green cap; it delivers 18 µg per actuation.

108.3 MAST CELL STABILIZERS

Cromolyn sodium (Intal [Aventis Pharmaceuticals]) and nedocromil sodium (Tilade [Aventis Pharmaceuticals]) are chloride channel blockers that modulate mast cell mediator release and eosinophil recruitment. Cromolyn and nedocromil both have strong human safety profiles, but nedocromil has a broader spectrum of efficacy. In human beings, the clinical response to either of these drugs is less predictable than the response to glucocorticoids, therefore cromolyn and nedocromil are usually used as adjunctive therapy to treatment with bronchodilators and

glucocorticoids. Currently, there are no published reports of the use of cromolyn or nedocromil in asthmatic cats or dogs with bronchitis; however, pretreatment with nedocromil aerosols attenuated viral-induced airway inflammation in beagle puppies. Because of the sensitivity of the cat to serotonin released from degranulating mast cells, these drugs should be further investigated in asthmatic cats. The cromolyn MDI is white and delivers 800 μg per actuation. The nedocromil MDI is also white and delivers 1.75 mg per actuation.

108.4 SPACERS

Human MDIs (OptiChamber [Respironics HealthScan Asthma and Allergy Products, Cedar Grove, New Jersey] and Aerochamber [Forest Pharmaceuticals]) may be modified for use in dogs and cats. Also, recently a small animal–specific spacer has become available (AeroKat [Trudell Medical International, London, Ontario, Canada]). The OptiChamber must be modified with a suitable face mask, such as the type used to "mask" cats for anesthesia. The Aerochamber is available with a variety of face masks intended for infants, children, and adults that will conform to a variety of veterinary patients. The Aerochamber is color coded according to the type of face mask (orange for infants, yellow for children, blue for adults). Both the OptiChamber and the Aerochamber are equipped with one-way valve leaflets that allow the owner to actuate the inhaler away from the cat or dog and then apply the spacer. The AeroKat spacer is valveless, therefore actuation must occur with the mask applied. The device fits cats and most small dogs. Human spacers can be purchased at most pharmacies.

108.5 TECHNIQUE FOR USING MDIS AND SPACERS IN DOGS AND CATS

The steps for using the MDI are as follows:

1. Prime the MDI prior to first use or if it has not been used recently, because the initial actuation contains higher drug concentrations than subsequent actuations.

2. Immediately before each use, shake the inhaler.

3. Remove the cap from the mouthpiece and insert the mouthpiece into the spacer.

4. Keep track of the number of actuations administered. Some manufacturers include a "check off" list in the patient directions. For daily maintenance medications, divide the number of actuations per canister (printed on the canister) by the number of puffs to be taken each day to calculate how many days the device will last and when the MDI should be replaced. The widely used method of immersing the inhaler in water to see if it floats is inaccurate. Discard the canister after the labeled number of actuations.

5. If using the AeroKat spacer, position the inhaler over the animal's face prior to actuation. If using a valved MDI, the device can be actuated before placing the mask on the animal's face (Figure 108-1).

6. Press down firmly and fully on the top of the metal canister with the index finger. Hold the mask in place over the animal's face for 5 to 10 seconds. Wait 30 to 60 seconds and then shake the inhaler again. Repeat these steps for each inhalation as prescribed by the veterinarian.

Figure 108-1 Albuterol MDI can be actuated into the Aerochamber prior to placing the mask over a cat's nose and mouth.

NOTE: When a beta$_2$ agonist is used in conjunction with a glucocorticoid or anticholinergic drug, it should be administered 5 minutes before the glucocorticoid or anticholinergic drug. The resulting bronchodilation results in increased deposition of the glucocorticoid or anticholinergic drug in the smaller airways.

7. Replace the mouthpiece cap after each use and make sure to clean the inhaler thoroughly and frequently. Remove the metal canister and clean the plastic case and cap by rinsing thoroughly in warm, running water at least once a day. (Do not immerse metal canisters containing cromolyn or nedocromil.) After thoroughly drying the plastic case and cap, gently replace the canister in the case with a twisting motion and replace the cap.

8. The manufacturer's recommendations for care of the spacer should be followed. Typically, the spacer only needs to be soaked weekly in a diluted dishwashing solution and air dried. It is not necessary to rinse the device, because the soap helps disperse aerosol particles that come in contact with the spacer's surface.

108.6 SUGGESTED TREATMENT REGIMENS

108.6.1 Dyspnea

For emergency management of dyspnea, two to four puffs of albuterol should be given every 20 minutes until clinical signs resolve. Additional therapy may include oxygen administration and an intravenous dose of a rapid-acting glucocorticoid.

108.6.2 Feline Asthma and Chronic Canine Bronchitis

The current recommended chronic therapy for feline asthma and chronic canine bronchitis is salmeterol, the long-acting bronchodilator, at a dosage of one puff (21 µg) twice a day and 220 µg of fluticasone twice a day. For initial therapy of moderately affected animals, a 5-day course of oral prednisone (1 mg/kg) may be helpful.

Severely affected animals may require 1 mg/kg of prednisone every other day. Adjunctive therapy with ipratropium or nedocromil or cromolyn may be useful in some patients. Therapy must be individualized for the patient.

109 CHAPTER • 109 Acid-Base, Oximetry, and Blood Gas Emergencies

Marie E. Kerl

Acid-base and oxygenation disorders occur commonly in emergency and critical care medicine as a response to respiratory or metabolic abnormality from trauma, intoxication, or naturally occurring disease. Technologic advances in point of care testing have made laboratory assessment of these disorders accurate, practical, and affordable in the veterinary emergency setting. A working knowledge of acid-base and respiratory physiology and pathophysiology, as well as appropriate therapies, is imperative for achieving successful patient outcomes.

Testing of blood gas samples may be performed with arterial or venous blood. Arterial blood must be used to assess oxygenation. Acid-base parameters other than partial pressure of oxygen (PO_2) may be evaluated using either arterial or mixed venous samples. In most emergent patients, venous blood is easier to obtain. Samples should be drawn into syringes that are coated with 1:1000 heparin to prevent clot formation. Immediately after sample acquisition, the syringe should be made airtight to prevent contamination with room air, which could alter gas measurements. The sample should be analyzed within 15 minutes or placed on ice.

109.1 BASIC ACID-BASE PHYSIOLOGY

The following is a brief description of traditional acid-base physiology; in-depth discussion is beyond the scope of this publication. For further information, the reader is referred to the Suggested Readings.

An *acid* is a hydrogen ion (H^+) (i.e., proton) donor, and a *base* is a proton acceptor. Acids typically are represented by the notation HA, which signifies a hydrogen ion and any negatively charged particle. When placed in solution, HA dissociates into H^+ (acid) and A^- (base). Hydrogen ions are nonvolatile or fixed acids produced by normal metabolism of proteins and phospholipids and are renally excreted. A base combines with an acid to lower the amount of acid in solution, or to buffer the solution.

Carbon dioxide (CO_2) is a volatile acid, or fat-soluble gas, that can combine with water in the presence of carbonic anhydrase to form carbonic acid (H_2CO_3). Carbon dioxide is formed during normal carbohydrate and fat metabolism and is excreted via the respiratory system. These two sources of acid (H^+ and CO_2) are interrelated, as is shown in the carbonic acid equation:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$$

This equation can go either direction, depending on the availability of substrate on either side of the formula. The enzyme carbonic anhydrase catalyzes this reaction, and any cell containing carbonic anhydrase is capable of this reaction.

By definition, *pH* is the negative log of the hydrogen ion concentration. A gain of H^+, or acid gain, results in a decrease in blood pH (acidemia), whereas a loss of H^+ results in an increased pH (alkalemia). Acid can be gained systemically from abnormal renal elimination of a naturally occurring compound or from ingestion of an exogenous acid source. Changes in CO_2 influence the H^+ concentration, as evidenced by the carbonic acid equation. As CO_2 is eliminated by increasing alveolar ventilation, carbonic acid dissociates to form more CO_2,

and H+and bicarbonate (HCO_3-) combine in turn to form carbonic acid. This effectively lowers the H^+ concentration and increases pH. Conversely, as CO_2 increases from ventilation impairment, pH decreases.

Buffers act to bind H^+ to prevent large fluctuations in pH. A variety of buffer systems exist in the body, including nonbicarbonate buffers (proteins and phosphates), which are primarily intracellular, and HCO_3-, which is the primary extracellular buffer. Bicarbonate is an effective buffer system because it exists in relatively large concentrations compared with other buffers, and it participates in the carbonic acid formula to produce CO_2 gas, which can be eliminated through ventilation. The HCO_3-buffer system, therefore, is considered an *open system,* which can continue to buffer as long as the respiratory system is functional. When $HCO_3-$is lost excessively from the urinary or gastrointestinal system, CO_2 and H_2O combine to form carbonic acid, which dissociates to increase H^+ and cause acidemia.

109.2 ACID-BASE DISORDERS

According to the Henderson-Hasselbalch equation, which is

$$pH = 6.1 + \log \{HCO_3^-/0.03PCO_2\}$$

pH can be characterized by changes in $HCO_3-$and partial pressure of carbon dioxide (PCO_2). Because a predictable change in HCO_3- occurs with gain or loss of H^+ ions, HCO_3-can be used to correctly identify acid base abnormalities arising from metabolic disorders. Acidemia or alkalemia resulting from a respiratory disorder should show an increase or a decrease in PCO_2. Respiratory acidosis results in an increase in PCO_2, and respiratory alkalosis causes a decrease in PCO_2. In metabolic acidosis, an H^+ increase shifts the carbonic acid equation to; and in metabolic alkalosis, an H^+ cause a decrease in HCO_3-decrease has the opposite effect on HCO_3-. Blood gas analyzers typically measure pH and PCO_2 and calculate HCO_3-.

This equation can also be used to predict how compensatory mechanisms engage to reduce the degree of change in the pH. When metabolic acidosis develops, the respiratory system is stimulated to increase the respiratory rate to eliminate CO_2 from the lungs and create respiratory alkalosis. Likewise, with a primary respiratory disorder, the opposite metabolic disorder is generated. The respiratory system provides rapid compensation, changing within minutes of onset of a metabolic disorder. Metabolic compensation occurs more slowly, becoming maximally effective in days. With either system, compensatory mechanisms should slow down as the pH improves, and compensation should never completely normalize the pH.

Base excess, which is expressed in milliequivalents per liter (mEq/L), is a value in which the amount of base above or below the normal buffer base is calculated, taking into account the expected change in HCO_3-secondary to acute changes in PCO_2. The general rule of thumb is that the HCO_3-concentration rises about 1 to 2 mEq/L for each acute 10 mm Hg increase in $PaCO_2$ above 40 to a maximum increase of 4 mEq/L, and that the HCO_3-concentration falls 1 to 2 mEq for each acute 10 mm Hg decrease in $PaCO_2$ below 40, to a maximum decrease of 6 mEq/L. Some authors refer to a negative base excess as a base deficit.

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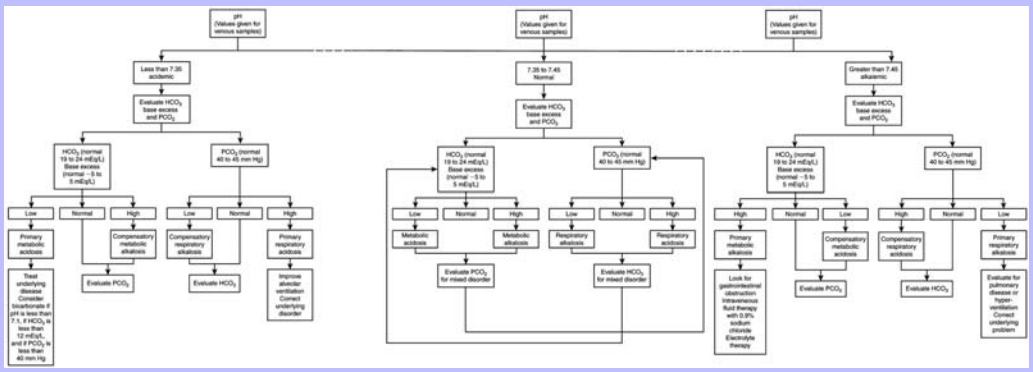
Figure 109-1 Algorithm for interpretation of blood gas values.



By convention, a simple acid-base disorder is limited to the primary disorder and the appropriate compensatory response. A mixed disorder is one in which at least two separate abnormalities occur simultaneously. Normal values at sea level for venous blood gas interpretation are pH, 7.35 to 7.45; PCO_2, 40 to 45 mm Hg; and HCO_3−, 19 to 24 mEq/L. Base excess normally should be −5 to 5 mEq/L.

Respiratory acidosis results from an increase of CO_2 in the blood (hypercapnia). Hypercapnia can be caused by anything that prevents normal gas exchange in the lungs, including impaired pulmonary circulation, reduced respiratory rate, circulation of blood to nonventilated portions of the lung, or impairment of gas diffusion. Diffusion impairment is the least likely cause of hypercapnia, because CO_2 is approximately 20 times more diffusible than oxygen. Disorders in which respiratory acidosis occurs include circulatory failure from cardiopulmonary arrest, central nervous system disease, respiratory muscle failure, physical impairment of ventilation (e.g., pleural space disease, pain, thoracic wall disease, external constriction), or primary pulmonary disease (e.g., alveolar flooding, interstitial disease, pulmonary thromboembolism). Iatrogenic respiratory acidosis results from inadequate ventilatory monitoring and assistance under general anesthesia. Clinical signs of hypercapnia are consistent with the underlying disorder. Situations that might cause respiratory acidosis must be anticipated and diagnosed with appropriate monitoring.

Treatment for respiratory acidosis involves correcting the underlying disorder by increasing alveolar ventilation. Chronic respiratory acidosis should be corrected slowly. Sodium bicarbonate should not be administered, because this drug exacerbates hypercapnia. Increasing the inspired oxygen concentration may be lifesaving; however, with severe hypercapnia, stimulation for respiration becomes driven by hypoxia. Resolution of the hypoxia may result in decreased voluntary respiration. The hypoxic drive for respiration remains adequate below a dissolved oxygen content of arterial blood (PaO_2) of 60 mm Hg.

Respiratory alkalosis results from an increase in the ventilatory rate, resulting in elimination of more CO_2 than is produced by normal metabolic function. Hypocapnia develops, and alkalemia ensues. Causes of respiratory alkalosis include hypoxemia caused by pulmonary or circulatory abnormalities, primary pulmonary diseases that stimulate ventilation independent of hypercarbia, central nervous system disorders, and iatrogenic tachypnea with assisted ventilation. Most disorders of respiratory alkalosis result in hyperventilation. Chronic respiratory alkalosis is usually well compensated

Treatment for respiratory alkalosis should be directed at normalizing the underlying disorder. Clinical signs are minimal, and no other therapy should be needed if the first treatment goal can be achieved.

Metabolic acidosis results most commonly from a gain of H^+ through ingestion of an acid into the body, increased production of an endogenous acid, or failure of elimination of an acid load at the renal tubular cells. Metabolic acidosis can also be caused by a loss of HCO_3^- buffering ability. Differentiating these two types of metabolic acidosis can assist diagnosis of the underlying cause.

When acid accumulates in the circulation, H^+ combines with HCO_3^- to buffer the acid load. When the acid dissociates, the anion remains in solution. Because electroneutrality must be maintained, another anion in circulation must decrease correspondingly. Anion gap (AG) is a formula that was created to classify disorders that cause metabolic acidosis. Anion gap, which is calculated from four common cations and anions from a serum chemistry profile, states:

$$AG = [Na^+ + K^+] - [Cl^- + HCO_3^-]$$

In normal animals, AG is 16 ± 4. Elevated anion gap metabolic acidosis is caused by a gain of acid, whereas normal anion gap metabolic acidosis (hyperchloremic metabolic acidosis) is caused by loss of bicarbonate buffers or a failure to excrete H^+ ions, with a corresponding increase in chloride to maintain electroneutrality. Causes of anion gap metabolic acidosis include ethylene glycol intoxication, uremia, tissue hypoxia, diabetic ketoacidosis, salicylate intoxication, and other unusual intoxications (e.g., drugs, alcohol). Hyperchloremic metabolic acidosis is less common and is caused by renal tubular acidosis (failure of the renal bicarbonate buffer system) or by severe diarrhea and loss of intestinal bicarbonate, or it occurs iatrogenically after administration of an alkali-free chloride containing solution for intravenous volume replacement.

Clinical signs associated with metabolic acidosis include lethargy, decreased cardiac output, decreased blood pressure, and decreased hepatic and renal blood flow. These signs may be referable to the acidemia or to the underlying cause of the acid-base disorder. Compensatory mechanisms would cause an increase in the respiratory rate to eliminate CO_2 generated by carbonic acid formation.

Treatment should be aimed at correcting the underlying disorder by improving tissue perfusion with intravenous fluid therapy; eliminating ingested toxin; and correcting metabolic, renal, or gastrointestinal disease. With severe metabolic acidosis (pH of 7.1 and HCO_3^- <12 mEq/L), sodium bicarbonate may be administered judiciously according to the following formula:

$$\text{Bicarbonate dose} = (0.3)(\text{Body weight [kg]})(\text{Base deficit})$$

Half of this dose should be administered slowly intravenously over 6 hours, and the acid-base status should be re-evaluated prior to continuation of therapy. Chronic metabolic acidosis should be corrected slowly to avoid undesired side effects, including hyperosmolality, hypernatremia, hypokalemia, hypocalcemic tetany from a shift of calcium from the ionized to the protein-bound form, and iatrogenic metabolic alkalosis.

Metabolic alkalosis is generated by loss of chloride in excess of extracellular fluid volume, which occurs as a result of upper gastrointestinal (GI) fluid loss or sequestration or of administration of a thiazide diuretic, causing chloride wasting. Rarely, metabolic alkalosis may be caused by overzealous administration of sodium bicarbonate or another organic anion or by hyperaldosteronism, causing sodium retention in excess of chloride. The most commonly associated clinical disease in small animal practice is gastric obstruction, with loss of

chloride-containing gastric fluid. Renal compensation prevents an acid-base disorder until hypovolemia causes aldosterone release. Aldosterone increases renal uptake of sodium. During normal renal function, sodium is reabsorbed with bicarbonate or chloride or is exchanged for potassium. Gastric fluid has high chloride and potassium concentrations, and when these are depleted, sodium can be reabsorbed only with bicarbonate.

Clinical signs associated with metabolic alkalosis depend on the predisposing disorder. Muscle twitching and seizures have been reported. Signs associated with concurrent potassium depletion may include weakness, cardiac arrhythmias, renal dysfunction, and gastrointestinal motility disturbances.

Treatment of metabolic alkalosis is directed at resolving the predisposing disorder. Intravenous 0.9% sodium chloride (0.9% NaCl) should be initiated to restore intravenous volume. Fluids should not contain buffer. If vomiting is the underlying cause, use of drug therapy to minimize gastric hydrochloric acid (HCl) excretion may be warranted. Intravenous potassium therapy should be used to treat the hypokalemia frequently encountered with metabolic alkalosis.

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109.3 OXYGENATION

Hypoxemia may be seen as a result of a low concentration of inspired oxygen, hypoventilation, diffusion impairment, dead space ventilation, or pulmonary shunting. Two methods are available to assess oxygenation in the emergency setting: measurement of PaO_2 and measurement of peripheral oxygen saturation (SpO_2) by pulse oximetry. A pulse oximeter is a noninvasive device that calculates hemoglobin oxygen saturation by measuring differences in absorption of two wavelengths of light (red and infrared) by oxygenated and deoxygenated hemoglobin. The measured light absorption values are applied to a preset nomogram, and a value for SpO_2 is determined. If tissue perfusion is adequate, SpO_2 approximates arterial hemoglobin saturation (SaO_2).

The advantage of oximetry as a monitoring tool is that it provides continuous, noninvasive determination of hemoglobin oxygen saturation. Technical aspects that help ensure accuracy include placing the probe on nonpigmented, moist skin with adequate perfusion (usually the tongue, the buccal, vaginal, or preputial mucosa, or the ear pinna), avoiding probe movement and light pollution, and monitoring the pulse rate to ensure accurate pulse signal transmittance. In poorly perfused tissues, the SpO_2 may be falsely low compared with the SaO_2. If inaccuracy of oximetry is suspected, the arterial blood gas PaO_2 may be obtained to evaluate oxygenation. In patients with alterations of hemoglobin concentration causing increased carboxyhemoglobin or methemoglobin, oximetry may be normal despite severe patient abnormality. Oximetry does not evaluate the PCO_2 and cannot be used to determine appropriate ventilation.

The hemoglobin saturation of oxygen and PaO_2 both contribute to arterial oxygen content (CaO_2) according to the following formula:

$$CaO_2\ (\text{mL } O_2/\text{dL}) = \{SaO_2\ (\%) \times \text{Hemoglobin (g/dL)} \times 1.34\ (\text{mL } O_2/\text{g})\} + \{PaO_2\ (\text{mm Hg}) \times 0.003\ (\text{mL } O_2/\text{dL/mm Hg})\}$$

Increasing the PaO_2 by increasing the inspired oxygen concentration has a minimal effect, whereas increasing the SaO_2 has a greater potential effect. In an anemic patient, increasing the arterial oxygen content would best be accomplished by increasing hemoglobin.

By the oxyhemoglobin dissociation curve, an SaO_2 of 90% corresponds to a PaO_2 of 60 mm Hg. This value is clinically important in that precipitous declines occur below these values, and small decreases in either parameter

may have tremendous clinical consequences. The goal of treatment for hypoxemia is to maintain the SpO_2 above 90% through supplemental oxygen therapy. Methods of increasing the inspired oxygen content include use of an oxygen chamber, tent or mask administration, placement of an indwelling nasal oxygen catheter, or mechanical ventilation with an increased fraction of inspired oxygen.

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110 CHAPTER • 110 Acute Abdomen

Dez Hughes

The term *acute abdomen* is often used to refer to animals that have a rapid onset of abdominal pain; however, not all life-threatening intra-abdominal problems are painful. Furthermore, depressed mentation, including chemical sedation, may reduce response to painful stimuli. A more encompassing definition for the acute abdomen is any situation involving an acute onset of clinical signs referable to intra-abdominal pathology. Because this is a potentially life-threatening clinical syndrome rather than a definitive diagnosis, the underlying cause must be rapidly identified. Many causes (Box 110-1) require emergency surgery, and these animals must be promptly iden-tified to allow definitive treatment to optimize the chances of survival. Because acute abdomen has so many potential causes, it is important to prioritize the list of diagnostic differentials based on pertinent findings from the history, physical examination, and initial diagnostic testing. Diagnosis and successful treatment of the dog or cat with an acute abdomen is one of the greatest challenges in emergency and critical care.

110.1 SIGNALMENT AND HISTORY

A full history should be obtained for all animals suspected of having an acute abdomen; however, with critically ill patients, this may have to be delayed to allow initial evaluation and stabilization. The history may occasionally be extremely suggestive of the underlying cause; for example, bitches with dystocia, witnessed ingestion of a foreign body, or protracted dysuria and pollakiuria with urethral obstruction. More commonly, however, the owner reports vague, nonspecific signs such depression, anorexia, lethargy, vomiting, and diarrhea. The only premonitory sign in some severe cases is acute collapse. Most dogs with a complete intestinal obstruction or pancreatitis exhibit profuse and frequent vomiting; however, diarrhea may or may not be present, and the severity of clinical signs can vary. Any sick, intact female should be evaluated for pyometra, regardless of whether the classic signs of anorexia, lethargy, vomiting, polyuria, polydipsia, and vaginal discharge are present. Any older intact male with hypoperfusion or caudal abdominal pain could have prostate gland disease. Dogs with prostatic disease may also exhibit hindlimb stiffness or an abnormal hindlimb gait, in addition to hematuria, pollakiuria, or dyschezia. A history of trauma raises the possibility of hemoabdomen or rupture of the urinary or biliary tracts. Any prior medical therapy by a veterinarian or by the owner should also be determined. For example, an old dog receiving nonsteroidal anti-inflammatory agents may be at risk of developing gastric ulceration, hemorrhage, or perforation.

110.1.1 Box • 110-1 Causes of Acute Abdomen

110.1.1.1 Gastrointestinal Tract

Necrosis/rupture/ulceration/perforation

Surgical wound dehiscence

Intestinal obstruction/intussusception

Gastric dilatation ± volvulus

Gastroenteritis (parvoviral; bacterial, toxic, hemorrhagic gastroenteritis [HGE] origin)

Mesenteric torsion

Duodenocolic ligament entrapment

Pancreatitis

Mesenteric thrombosis/embolism

Obstipation

Portal venous thrombosis

Colitis

110.1.1.2 Urogenital Tract

Pyometra/uterine rupture

Prostatitis/prostatic abscess

Dystocia

Cystic calculi

Urethral obstruction or rupture

Uroabdomen

Pyelonephritis

Renal abscess

Vaginal rupture

Testicular torsion

110.1.1.3 Hepatobiliary System

Necrotizing cholecystitis

Liver lobe torsion

Hepatic abscess

Bile peritonitis

Acute hepatitis/cholangiohepatitis

Biliary obstruction

110.1.1.4 Other Causes

Hemoabdomen (usually parenchymatous organ rupture)

Retroperitoneal hemorrhage

Neoplasia

Penetrating wounds/crush injury

Evisceration

Surgical contamination

Strangulated hernia

Splenic torsion

Splenic abscess

Pansteatitis

110.1.1.5 Conditions That May Mimic Acute Abdomen

Spinal disease with pain

Lead poisoning

Hypoadrenocorticism

Some extra-abdominal conditions may mimic signs of an acute abdomen, the most common being thoracolumbar intervertebral disk disease. Owners occasionally incorrectly assume that their animal has abdominal pain because the pet vocalizes when picked up beneath the abdomen. The clinician must always maintain a high index of suspicion that an acute onset of pain, especially in a chondrodystrophoid breed, may be spinal in origin. Even on physical examination, it can sometimes be difficult to differentiate between spinal and abdominal pain. The veterinarian must take care, especially with smaller animals, to avoid placing the thumbs along the spine when palpating the abdomen.

110.2 MAJOR BODY SYSTEM EVALUATION

Major body system evaluation initially is performed to identify and prioritize life-threatening problems of the cardiovascular, respiratory, and neurologic systems. Life-threatening problems should be addressed without delay while performing the initial examination. Hypovolemia may be mild, moderate, or severe. Animals with an inflammatory process and adequate circulating blood volume may demonstrate the classic signs of hyperdynamic systemic inflammatory response syndrome (SIRS), such as injected mucous membranes, strong pulses of short duration, fast capillary refill time (CRT), moderate tachycardia, and pyrexia. With severe hypovolemia, tachycardia is often severe (170 to 200 beats per minute in a dog), femoral pulses are weak, and the CRT is prolonged. Despite severe hypovolemia, dogs with peritonitis can have injected rather than pale mucous membranes, and this discrepancy in clinical perfusion parameters should prompt a search for an underlying cause of SIRS. Although a dog with an acute abdomen may exhibit tachypnea due to pain, animals that have been vomiting should always be evaluated for aspiration pneumonia.

When tympanic gaseous abdominal distension is present in a large breed dog, gastric dilatation and volvulus is the most likely diagnosis. Although pneumoperitoneum can occasionally cause abdominal distension, it is usually not tympanic. Dogs with a large volume of abdominal effusion may have an abdominal fluid "wave." However, smaller amounts of effusion may not be palpable, especially if the dog is recumbent. A fluid wave may also be detectable due to intra-abdominal fat, hepatomegaly, or fluid contained within a tubular viscus. Abdominal distension is not always noticeable in an animal with intra-abdominal fluid. For example, a dog with acute hemoabdomen after being hit by a car would likely be in severe hypovolemic shock before the slightest hint of abdominal distension would be noticed.

Bacterial peritonitis and pancreatitis almost always cause abdominal pain or discomfort in dogs, even in animals with severe hypoperfusion. When an animal in hypovolemic shock is rousable only by abdominal palpation, a diagnosis of peritonitis should be aggressively pursued.

Pyometra is not usually painful, and abdominal pain in conjunction with pyometra raises the likelihood of septic peritonitis. Pain appears to be an inconsistent finding with uroabdomen (acute uroabdomen tends to be more painful than chronic uroabdomen). Significant pain associated with a uroabdomen should prompt evaluation for septic peritonitis.

Occasionally dogs with cranial abdominal pain adopt the "prayer position"; however, this is the exception, not the rule. As a generalization, focal pain other than in the right cranial quadrant, or focal pain associated with the intestines, is often associated with a surgical lesion. The majority of animals with bile peritonitis are icteric unless the biliary tract rupture is recent.

A rectal examination should be performed in all animals with acute abdomen, but especially in older intact male dogs. When prostatomegaly has caused the prostate gland to descend over the pelvic brim, simultaneous abdominal and rectal palpation may be necessary to achieve a complete prostatic examination.

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110.3 STABILIZATION

In a hemodynamically unstable patient, aggressive intravenous fluid therapy is often necessary. In many animals with peritonitis, especially septic peritonitis, hypoperfusion is due both to maldistribution (abnormally dilated arterioles) and to hypovolemia. Crystalloid infusion rates of 60 to 90 mL/kg/hour in the dog and 40 to 60 mL/kg/hour in the cat are often necessary. It is best to place two intravenous catheters to achieve this rate and to provide an alternative in case one catheter becomes dislodged or blood products are required. Fluid resuscitation with blood products or synthetic colloids (e.g., hydroxyethyl starch or dextran 70) may be more effective in animals with systemic and intra-abdominal vasculitis. Major body systems and perfusion parameters (mucous membrane color, CRT, pulse rate and quality, heart rate, and urine output) should be continually assessed during fluid resuscitation to ensure an appropriate response. Failure to respond adequately to intravenous fluids usually indicates the presence of sepsis or ongoing hemorrhage. In severely affected animals with sepsis, continuous-rate infusions of catecholamines may be required to maintain adequate blood pressure.

Broad-spectrum, bactericidal, intravenous antibiotics should be started as soon as a diagnosis suggests the possibility of leakage or translocation of gastrointestinal bacteria. Antibiotics with activity against gram-positive and gram-negative aerobes and anaerobes should be used. In septic peritonitis, intravenous administration has shown a trend toward improved survival compared with intramuscular or intraperitoneal routes. The most frequent isolates from cases of bacterial peritonitis are *Escherichia coli,* clostridia, and enterococci. Appropriate antibiotic combinations for these bacteria include ampicillin combined with cefoxitin, enrofloxacin, or amikacin; however,

the use of amikacin often is contraindicated in animals with hypovolemia, dehydration, and pyrexia. Metronidazole may be added for additional anaerobic coverage.

Corticosteroids have long been advocated in the treatment of sepsis, but because of equivocal clinical evidence, their use appears to be declining. They are potent inhibitors of transcription of interleukin-1 and interleukin-6 and tumor necrosis factor alpha; however, much of the evidence demonstrating a benefit from corticosteroids involves administration prior to the infectious insult.

Interestingly, improved survival has been shown in experimental studies of septic peritonitis when dogs are treated with heparin, ostensibly due to improved bacterial clearance from the abdomen or to reduction of disseminated intravascular coagulation.

Novel therapies include prophylactic use of recombinant human granulocyte colony-stimulating factor, which has a protective effect in bacterial peritonitis and results in better survival than antibiotics alone. Encapsulation of antibiotics in liposomes may prolong the drug's half-life and improve reticuloendothelial targeting, and better survival has been demonstrated in fecal peritonitis models compared with conventional methods of antibiotic delivery.

Most animals with hemoabdomen have suffered abdominal trauma or rupture of an intra-abdominal mass. To minimize ongoing hemorrhage, an abdominal pressure bandage should be applied prior to aggressive fluid resuscitation. As the majority of intra-abdominal hemorrhage is due to venous rather than arterial bleeding, the abdominal wrap need provide pressure only in excess of venous blood pressure (0 to 5 mm Hg), which can be achieved by a firm but not excessively tight bandage. In general, padding beneath the wrap should be avoided because it allows the bandage to move caudally rather than provide compression in the cranial abdomen, where it is most effective.

110.4 DIAGNOSTIC EVALUATION

Blood should be obtained for analysis when the intravenous catheter is placed. As a minimum, packed cell volume (PCV), refractometric total solids, glucose, and serum electrolytes should be evaluated. Parameters must be re-evaluated frequently in animals receiving aggressive intravenous fluid support. A low total solids concentration with a normal PCV should prompt a search for hemorrhage or severe vasculitis. Animals with septic peritonitis often have panhypoproteinemia, presumably due to exudation of protein into the peritoneal cavity. In the absence of hemorrhage or liver or kidney disease, an abnormally low serum total solids concentration in a dehydrated and hypoperfused animal should raise the possibility of severe vasculitis, most commonly bacterial peritonitis. Hypoglycemia should prompt a search for sepsis and pancreatic or hepatic neoplasia.

If in-house hematology and blood chemistry analysis are available, a complete blood count, serum biochemical analysis, urine analysis, and coagulation screen should also be obtained prior to fluid resuscitation. Depending on the severity and chronicity of the underlying condition, the neutrophil count may be increased, normal, or low, and a left shift may or may not be present. Most puppies with parvoviral enteritis have severe neutropenia. Serum chemistry changes can provide helpful information. For example, bile peritonitis often results in increased serum alkaline phosphatase, alanine transaminase, and total bilirubin concentrations. Unless it is peracute or the animal is still voiding urine, uroperitoneum is usually associated with an increase in blood urea nitrogen, creatinine, and potassium.

The main aim of the initial diagnostic evaluation of the animal with an acute abdomen is rapid identification of the patient that needs immediate surgery. If available, immediate abdominal ultrasound to detect abdominal effusion, followed by cytologic fluid analysis, is the fastest way to diagnose septic peritonitis. In early cases of peritonitis,

even with bowel rupture, little or no abdominal effusion may be present; in other words, the absence of abdominal effusion does not rule out peritonitis. Nevertheless, most animals with peritonitis have an abdominal effusion.

Abdominal ultrasonography may also identify the cause of the acute abdomen. Abscesses in parenchymal organs, pyometra, pancreatitis, abdominal masses, and abnormalities of organ blood flow, such as in splenic torsion, can all be detected by trained personnel. The accuracy of ultrasonography in detecting or ruling out gastrointestinal obstruction can vary, and caution should be exercised in the interpretation of ultrasound findings.

If ultrasound is not available, abdominal radiographs should be obtained as soon as the animal has been stabilized. Abdominal radiographs are superior to abdominal ultrasound in detecting intestinal obstruction or foreign material in the gastrointestinal tract. Abdominal radiographs may also demonstrate free gas and/or loss of intra-abdominal detail suggestive of fluid or increased soft tissue in the peritoneal cavity. Free gas may result from rupture of a hollow viscus, gas-forming bacteria, abdominocentesis, recent abdominal surgery, or penetrating injuries; however, many animals with penetrating abdominal injuries do not have free gas in the abdomen. Pneumoperitoneum can complicate radiographic and ultrasonographic evaluation of the postoperative abdomen. After experimental injection of air, radiographic evidence of intraperitoneal gas may persist for up to 18 days in dogs.

Abdominocentesis, with or without ultrasound guidance, is a quick, easy, and safe method for detecting and retrieving abdominal fluid. Contraindications to abdominocentesis are few but include coagulopathy, organomegaly, and distension of an abdominal viscus. If these conditions are a possibility, abdominal radiographs should be obtained prior to abdominocentesis or the tap should be performed with ultrasound guidance. Penetration of the gastrointestinal tract during abdominocentesis is unusual unless the viscus is dilated or adherent to the abdominal wall. Abdominocentesis may be performed by means of a single centesis, a four-quadrant approach, or diagnostic peritoneal lavage (DPL).

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Prior to abdominocentesis, the site is clipped and prepared using standard aseptic technique. Closed needle abdominocentesis is performed using a 20-or 22-gauge hypodermic needle attached to a syringe. Initially, the ventral aspect of the right cranial quadrant is used (where fluid pools by gravity and diaphragmatic movement) to minimize the chance of splenic puncture. If blood is aspirated, the needle should be withdrawn and the blood observed to see if it clots. Blood from a vessel or organ clots, whereas blood from the abdominal cavity does not in all but the most peracute cases of hemoabdomen. Free air is not usually seen on radiographs after a closed abdominocentesis.

Diagnostic peritoneal lavage may be sensitive in detecting intra-abdominal pathology. The conventional method of DPL usually requires sedation and uses a peritoneal dialysis catheter with the animal in either lateral or dorsal recumbency. However, an over-the-needle catheter can be placed into the abdomen just caudal to the umbilicus and 10 to 20 mL/kg of isotonic crystalloid solution infused. This procedure should not require sedation. The catheter is then removed, and the abdomen is gently palpated. Thirty minutes later, a single or four-quadrant abdominocentesis is performed. Because DPL introduces free fluid into the abdomen and because it is not uncommon to retrieve only a small portion of the infused fluid, abdominal radiographs and ultrasound scans should be obtained prior to lavage.

Biochemical, cytologic, and microbiologic analysis of abdominal fluid is extremely useful in the diagnosis of the underlying cause. Initially the appearance of the fluid should be noted, followed by determination of the PCV, refractometric total solids concentration, and cytologic results to classify the fluid as a transudate, modified transudate, or exudate. Toxic degenerate neutrophils with intracellular and extracellular bacteria are indicative of bacterial peritonitis and warrant surgical exploration once the animal is hemodynamically stable. Rupture of the gastrointestinal tract is more likely if multiple bacterial species are seen and very likely if plant fibers are present.

Occasionally bacteria are not seen with bacterial peritonitis, and in these dogs and cats, differentiation from severe pancreatitis can be difficult. Both are associated with high numbers of degenerate neutrophils in the effusion.

The abdominal fluid amylase and lipase concentrations may be helpful in detecting pancreatitis; however, it is vital to appreciate that more than half the cases of septic peritonitis may have concurrent pancreatitis, therefore a diagnosis of pancreatitis does not preclude the presence of bacterial peritonitis. An abdominal effusion glucose concentration of less than 50 mg/dL is often indicative of bacterial peritonitis.

With uroabdomen, abdominal fluid almost always shows higher blood urea nitrogen (BUN), creatinine, and potassium concentrations than does serum; however, the difference can be relatively minor. Creatinine equilibrates more slowly with the intravascular space and can therefore more be more useful. To enable comparison of serum and abdominal fluid, samples must be obtained within minutes of each other. If a bolus of intravenous fluids is administered after the abdominal fluid sample is obtained, the serum levels can be diluted, and ascites of another cause may be misdiagnosed as uroabdomen.

When uroperitoneum is suspected, retrograde contrast urethrocystography and/or excretory urography should be performed to confirm the site of leakage. The most common causes of bile peritonitis are rupture of the biliary tract secondary to trauma or necrotizing cholecystitis. A green abdominal effusion is usually present, which sometimes contains dark green, brown, or black particulate matter. The bilirubin concentration should be higher in the effusion than in serum.

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111 CHAPTER • 111 Cardiac Emergencies

Kirstie A. Barrett

The management of cardiac emergencies can be very rewarding if a prompt diagnosis is made and if the proper treatment is instituted without delay. Sometimes patients are not stable enough to handle extensive diagnostics, and treatment decisions must be made quickly. In such cases, an insightful history and physical examination are critically important, because the choice of further diagnostics may be limited.

Cardiac emergencies commonly seen in veterinary patients are arrhythmias, acute congestive heart failure, pericardial effusion, and arterial thromboembolism. Other cardiac emergencies or potential cardiac emergencies, described elsewhere in detail, include cardiopulmonary resuscitation (CPR), shock, syncope, hypertension, and hypotension.

111.1 ARRHYTHMIAS

Arrhythmias, which occur in a high percentage of critical patients, represent a disturbance in the rate, regularity, or site of cardiac electrical impulse formation. Their clinical significance is a result of a heart rate that is either too slow or too rapid, depressing cardiac output and potentially leading to heart failure or circulatory collapse. Cardiac arrhythmias are particularly ominous if they have the potential to deteriorate into an electrically unstable form, causing or exacerbating circulatory failure or cardiac arrest.

A correct electrocardiographic (ECG) diagnosis is essential to appropriate management and therapy and should always be interpreted in the context of the patient's history and current clinical status. Identification and correction of precipitating factors (e.g., cardiopulmonary disease, metabolic derangements, acid-base and electrolyte imbalances, current drug therapy) are equally essential to successful management of cardiac arrhythmias and to the clinician's decision on whether to initiate antiarrhythmic therapy.

Arrhythmias that cause clinical signs generally warrant therapy. Clinical signs that reflect decreased cardiac output may be acute or progressive and include weakness, exercise intolerance, syncope, collapse, ataxia, pulse abnormalities, congestive heart failure, and sudden death.

Arrhythmias present during cardiopulmonary arrest (CPA) include asystole (complete absence of QRS-T complexes), ventricular fibrillation (chaotic depolarization of the ventricles characterized by a lack of QRS-T complexes with unorganized fibrillation waves), and electromechanical dissociation (little or no myocardial contractile activity with a normal ECG tracing). All these arrhythmias require immediate intervention using standard CPR recommendations. Other potentially lethal arrhythmias include continuous (sustained) or intermittent (paroxysmal) ventricular tachycardia, ventricular flutter, paroxysmal or sustained supraventricular tachycardia, sick sinus syndrome (SSS), complete or high-grade second-degree atrioventricular block, and sinus standstill. Sinus bradycardia frequently precedes CPA in critically ill patients. Antiarrhythmic therapy should be initiated if treatment of the underlying disorder does not improve the arrhythmia; if hemodynamic impairment is identified; or if the risk of sudden death exists. Identification of the above arrhythmias and treatment options are discussed in detail elsewhere (see Chapter 202).

111.2 HEART FAILURE

Heart failure is a clinical syndrome caused by cardiac disease that results in systolic or diastolic cardiac dysfunction or both. Systolic failure describes decreased myocardial performance and diastolic failure results from abnormal filling of the ventricles during diastole.

Decompensated heart failure manifests either as congestion/edema (backward heart failure) or circulatory failure (low-output, forward heart failure). Right-sided congestive heart failure results in systemic venous congestion and may manifest as jugular distention, subcutaneous edema, hepatic congestion, ascites, and/or pleural effusion. Left-sided congestive heart failure presents as pulmonary edema.

Because the clinical signs of left-sided congestive heart failure can mimic those of pulmonary disease, it is important to determine accurately which condition is truly present. The signalment, history, and response to treatment can be helpful in making this distinction. The single most useful test for confirming congestive heart failure is a thoracic radiograph. However, the potential stress of any diagnostics must be seriously considered, because the anxiety associated with even minimal handling of a severely dyspneic animal can be life-threatening.

The goal of medical therapy in congestive heart failure is to improve cardiac output by increasing contractility, decreasing afterload, or normalizing a cardiac dysrhythmia. It is equally important to relieve clinical signs by reducing abnormal fluid accumulation. Furosemide is the diuretic of choice for relieving acute pulmonary edema and normalizing cardiac filling pressures. High doses of furosemide (up to 4 mg/kg given intravenously or intramuscularly every 2 hours) may be used initially to induce diuresis. Intravenous furosemide acts within 5 minutes, peaks within 30 minutes, and dissipates after 2 to 3 hours. Use of the intravenous route is preferred, but this must be weighed against the potential stress of administration.

Intramuscular administration of furosemide is an alternative. The dose is highly variable and depends on the response desired. The dose and frequency should be reduced as a clinical response (diuresis, respiratory rate reduction, and respiratory character improvement) is achieved. Cats tend to be more sensitive to furosemide than dogs and respond to lower doses (2 mg/kg).

In addition to the diuretic, a low dose of morphine (0.05 to 0.1 mg/kg given subcutaneously or intramuscularly) can reduce the anxiety associated with pulmonary edema and provide mild venodilatation.* The dose is repeated up to four times a day, as necessary, to achieve the desired effect. The primary adverse consequence of using morphine is respiratory depression, therefore it must be used with caution in hypoxic animals. Acepromazine (0.05 to 0.1 mg/kg given subcutaneously) is an anxiolytic that does not depress respiration. Acepromazine is an alpha-adrenergic blocker that decreases peripheral vascular resistance, which may also be beneficial.

Nitroglycerin, a venodilator, may further reduce congestion, although information in the veterinary literature is merely anecdotal. Nitroglycerin paste can be applied to the inner surface of the pinna of the ear (¼ to 1 inch every 6 hours in the dog; ⅛ to ¼ inch every 6 hours in the cat). Nitroglycerin is typically used for only 48 hours due to the drug tolerance that develops.

Hydralazine, a potent arteriolar dilator, can be used in the emergency management of a normotensive congestive heart failure patient (0.5 to 2.0 mg/kg given orally). Nitroprusside is both a potent venodilator and a potent arteriolar dilator for use in severe, refractory congestive heart failure (1 to 2 μg/kg/minute given intravenously initially). Continual blood pressure monitoring is essential with nitroprusside. Dobutamine (2.5 to 10 μg/kg/minute, intravenously), which is primarily a $beta_1$ agonist, is used to improve cardiac output by increasing

contractility in hypotensive patients with refractory congestive heart failure. Digoxin is especially beneficial in the emergency treatment of congestive heart failure when supraventricular tachycardia or atrial fibrillation is present.

Strict cage rest and prevention of stress are critically important to the management of a congestive heart failure patient. Additional measures that may benefit the patient are thoracocentesis and oxygen therapy. Cats with congestive heart failure often present with both pulmonary edema and pleural effusion. When congestive heart failure results in pleural effusion of significant quantity and the animal is dyspneic, thoracocentesis often results in prompt and dramatic improvement (the technique is described elsewhere in this text).

Dogs and cats with severe pulmonary edema are hypoxic due to the decreased ability of oxygen to diffuse from the alveoli into the pulmonary capillaries. Supplemental oxygen increases this pressure gradient, resulting in an increase in arterial oxygen tension. Therefore it is of critical importance that patients with severe edema have supplemental oxygen. This can be achieved using an oxygen cage (40% oxygen) adjusted to maintain a normal temperature (20°to 22°C [68°to 72°F]) and appropriate humidity (45% to 55%). Oxygen cages are generally better tolerated and less stressful than other means of administration. In a larger dog, oxygen can be administered through a nasal cannula. An oxygen mask is an alternative but should not be used if the animal is struggling against the mask.

Endotracheal intubation may be required in animals with extreme respiratory distress and fulminant pulmonary edema to provide controlled ventilation and 100% oxygen administration. In addition, copious amounts of pulmonary edema may be removed physically by suction or postural drainage. Intravenous fluids are rarely indicated in the treatment of acute, cardiogenic pulmonary edema because they often exacerbate the edema. 405 406

* Notably, morphine can cause agitation and aggression in cats.

111.3 PERICARDIAL EFFUSION

Pericardial effusion is an abnormal accumulation of fluid in the pericardial sac. The hemodynamic effects of pericardial effusion depend on the rate and volume of the fluid accumulation and the compliance of the pericardium itself. If the effusion develops slowly, the pericardium will expand and the intracardiac pressure will not increase enough to compromise cardiac filling. In contrast, acute cardiac tamponade is characterized by rapid accumulation of fluid in the pericardial space, leading to a rise in intrapericardial pressure. The results are restriction of ventricular filling, decreased cardiac output, and arterial hypotension. Clinical signs of right-sided congestive heart failure or reduced cardiac output predominate and include anorexia, lethargy, syncope, dyspnea, weakness, exercise intolerance, and abdominal distention (hepatomegaly, ascites). Common physical examination findings are muffled heart sounds, jugular venous distension, sinus tachycardia, and weak femoral pulses. Pulsus paradoxus (an exaggerated decline greater than 10 mm Hg in systemic arterial pressure during inspiration) is a valuable clinical sign that may also be appreciated in cardiac tamponade.

Although thoracic radiography typically demonstrates an enlarged, globoid cardiac silhouette, echocardiography is the most sensitive and specific noninvasive means of diagnosing pericardial effusion. The therapeutic goal for patients with pericardial effusion is to reduce the intrapericardial pressure quickly. Pericardiocentesis is the treatment of choice for initial stabilization of dogs and cats with pericardial effusion and cardiac tamponade (the technique is described in Chapter 205). Attempts to lower venous pressures with medical therapy (i.e., diuretics) should be avoided because the patient's cardiac preload depends on these elevated pressures. The result can be a significantly reduced cardiac output, manifested as hypotension or syncope or both.

111.4 ARTERIAL THROMBOEMBOLISM

Arterial thromboembolism is a common sequela to all types of feline myocardial disease (hypertrophic cardiomyopathy, dilated cardiomyopathy, and restrictive cardiomyopathy); it is uncommon in the setting of a structurally normal or mildly abnormal heart. Arterial thromboembolism results in significant morbidity and mortality. Systemic thromboembolism is rarely reported in the dog and is usually associated with neoplasia, sepsis, Cushing's disease, protein-losing nephropathy, or other hypercoagulable states. Distal aortic embolization (saddle thrombus at the distal aortic trifurcation) occurs in more than 90% of feline cases. Corresponding clinical signs may occur with embolization of other organs, such as the lungs (respiratory distress), kidneys (acute renal failure), brain (central nervous system signs), gastrointestinal tract (bowel ischemia), and right (more commonly than left) brachial artery (pain and paresis).

A distal aortic embolism presents as peracute paresis or paralysis with vocalization due to intense pain. The clinical consequences depend on the site, extent, and duration of the embolization, as well as the degree of functional collateral circulation. The *four Ps* characterize the clinical signs of changes observed in the extremities: paralysis, pain, pulselessness (lack of palpable femoral pulses), and pallor (cold, pale distal extremities and pads). Absence of bleeding from a cut nail on the affected limb may also be seen. Ten to 12 hours after the embolization, the anterior tibial and gastrocnemius muscles often become firm as a result of ischemic myopathy. In most cases these muscles become softer after 24 to 72 hours. Respiratory distress is commonly associated with systemic thromboembolism in cats because most have concurrent congestive heart failure. Acute aortic blockade by the thromboembolus increases afterload to the left ventricle. The clinician must differentiate the respiratory changes seen with congestive heart failure from those seen with pain.

A variety of therapeutic measures can be used to offset the consequences of a thromboembolism. These range from attempts to limit thrombus growth or formation and pain control to supportive care and treatment of accompanying congestive heart failure.

Although heparin has no effect on established thrombi, it is commonly administered in hopes of limiting thrombus growth.* Heparin can be administered at an initial dose of 220 U/kg given intravenously, followed by a maintenance dose of 70 to 200 U/kg given subcutaneously every 6 hours. Thrombolytic agents such as streptokinase, urokinase, and tissue plasminogen activator (t-PA) are used extensively in humans and infrequently in cats. These agents are expensive, have not been studied extensively, and are associated with high mortality and poor outcomes. Risks of bleeding complications, death from reperfusion syndrome (hyperkalemia, metabolic acidosis), and rethrombosis are common.

During the initial stages of the disease, most cats experience intense pain. The pain subsides as sensory nervous function is lost. Common choices for pain control include oxymorphone (0.05 to 0.15 mg/kg given intramuscularly or intravenously every 6 hours), butorphanol (0.1 mg/kg given intravenously or 0.02 to 0.4 mg/kg given intramuscularly or subcutaneously every 4 hours), and/or acepromazine (0.05 to 0.1 mg/kg given intravenously). Euthanasia should be considered as an option when severe, unrelenting pain is present.

General supportive care consists of maintaining hydration and normal electrolyte status, massaging firm muscles, expressing the bladder as necessary, and preventing self-mutilation. Management of concomitant congestive heart failure is discussed above.

* Heparin has never been proven to limit thrombus growth.

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112 CHAPTER • 112 Cardiopulmonary Arrest and Resuscitation

Nishi Dhupa

***C**ardiopulmonary arrest* is defined as the cessation of effective ventilation and circulation. Resuscitative efforts should be aimed at patients with potentially reversible disease. The ultimate goals of cardiopulmonary resuscitation (CPR) are to maintain adequate tissue oxygenation and thereby preserve organ viability during the low-flow "arrest" state, to rapidly restore a spontaneous and effective cardiac rhythm, and to protect cardiovascular and neurologic function following resuscitation in order to improve the chances of survival as well as the return of acceptable cerebral and motor functions.

CPR may be divided into three phases. Basic life support (BLS) is the provision of artificial ventilation, oxygenation, and circulation in order to maintain vital organ perfusion. Advanced life support (ALS) involves the recognition and treatment of the arrest rhythm and other modalities to resuscitate the patient. Prolonged life support (PLS) covers post-resuscitative care. Guidelines for veterinary CPR are extrapolated from human medicine. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation has recently reviewed and updated its guidelines on CPR.[1] Methods that improve coronary perfusion pressure are being prioritized in an effort to improve resuscitation rates and outcomes.

112.1 RECOGNITION OF CARDIOPULMONARY ARREST

Incipient cardiopulmonary arrest (CPA) may be recognized by bradycardia or other cardiac arrhythmias, slow or irregular respirations, mental obtundation, hypotension, and hypothermia. In dogs and cats, the most common "arrest rhythms" are asystole and pulseless electrical activity (PEA) (otherwise known as electromechanical dissociation); a lower percentage display ventricular fibrillation (VF). CPR must begin immediately in the unresponsive, breathless, and pulseless patient. The chances of recovery from CPA are increased in cases of respiratory arrest alone, anesthetic overdose, upper airway obstruction, trauma or hemorrhage, vagally mediated arrest, electrolyte abnormalities, or upper airway obstruction. Patients with terminal or multisystemic disease will have a poorer prognosis.

112.2 BASIC LIFE SUPPORT

BLS should be initiated as rapidly as possible after the recognition of CPA. Traditionally BLS has been carried out according to the "ABC" mnemonic (airway, breathing, circulation). The first step is to secure the airway through endotracheal intubation. If pulmonary edema fluid discharges through the endotracheal tube, postural drainage, with the head hanging below the body, and suction will aid in clearing of the airway. Once intubated, positive pressure ventilation should be initiated at 15 to 25 breaths per minute using a rebreathing (AMBU) bag attached to high flow oxygen. The chest should be observed and ausculted to verify appropriate ventilation.

The goal of circulatory support during CPR is to maximize cerebral and myocardial oxygenation in order to achieve a rapid return of spontaneous circulation (ROSC) and long-term neurologic recovery. Ventilation with 100% oxygen ensures maximal saturation of hemoglobin and improves arterial oxygen content. Cerebral perfusion depends on cardiac output and cerebral vascular resistance; perfusion pressure is determined by the difference between mean arterial pressure and intracranial pressure. Myocardial perfusion is determined by the difference between aortic diastolic and right atrial pressure. Various compressive and therapeutic strategies are used to maximize these perfusion pressures.

First, during closed-chest CPR, rapid chest compressions are initiated at a rate of 80 to 100 per minute. In smaller patients, compressions are performed directly over the heart, with the patient in lateral recumbency, in order to maximize forward blood flow. In larger patients, greater increases in intrathoracic pressure can be achieved by performing chest compressions over the point of the sternum, with the patient in dorsal recumbency. The optimal compression: relaxation ratio of 50:50 allows for diastolic filling of the heart and maximizes myocardial perfusion.

Alternating abdominal compressions may be used to improve cardiac preload and cardiac output. Greater intrathoracic pressure changes can also be achieved during simultaneous compression-ventilation. In hypovolemic patients, aggressive fluid therapy is essential to restore circulating blood volume. The effectiveness of chest compressions and adjunctive strategies must be evaluated through palpation of femoral pulses, detection of orbital vessel blood flow through Doppler ultrasound applied to the cornea, and end-tidal carbon dioxide measurement (a higher value following chest compression is indicative of improved pulmonary perfusion and gas exchange).

Open chest CPR, with direct cardiac massage, is indicated in patients with conditions that interfere with the generation of intrathoracic pressure, which is necessary for forward blood flow. These include pneumothorax, diaphragmatic hernia, flail chest, severe obesity, pericardial effusion, very large animals, and severe hypotension. Although this modality is superior in terms of generation of blood flow, it is an invasive procedure, associated with increased morbidity and intensive after-care.

Recently, the “CAB” mnemonic has been suggested as an alternative to “ABC.” This has some application in human patients in whom primary cardiac arrest is more common. In veterinary patients, in whom respiratory and vagally mediated arrests are common and hypoxia, hypercarbia and acidosis often precede cardiac arrest, the “ABC” approach, with its emphasis on early oxygenation, is still valid.

112.3 ADVANCED LIFE SUPPORT

ALS is initiated once effective artificial ventilation and circulation have been established. ALS consists of techniques to augment artificial circulation and encourage ROSC through arrhythmia recognition (using electrocardiography) and treatment with drugs and defibrillation. First, any anesthetic, analgesic, or sedative agents must be discontinued or reversed to minimize cardiorespiratory depression (Table 112-1). The most common arrest rhythms are treated as follows: asystole is treated with atropine and epinephrine; pulseless electrical activity with atropine and epinephrine; and ventricular fibrillation with electrical defibrillation (see Table 112-1). Emergency drugs are administered through either the central venous (preferred), endotracheal, or intraosseous route (see Table 112-1). Intratracheal administration is achieved by a doubling of the intravenous dose, dilution to 5 to 6 mL in saline, and administration at the level of the carina via a 5-to 8-French red rubber tube.

Atropine is a vagolytic agent that is indicated in the treatment of sinus bradycardia, asystole, or PEA (all seen in up to 70% of small animal CPA) due to the role of the parasympathetic nervous system in these arrhythmias (see Table 112-1).

Epinephrine is an adrenergic vasopressor that is the current drug of choice for asystole, PEA, and refractory VF. Its alpha-adrenergic activity results in increased aortic diastolic pressure and improved myocardial perfusion, thus encouraging ROSC. The beta effects (inotropy, chronotropy) may increase myocardial work and oxygen demand, with the potential for tachyarrythmias and myocardial dysfunction following ROSC.

Several newer drugs are undergoing extensive study and may have value in CPR protocols. Vasopressin (Pitressin, Monarch Pharmaceuticals, Bristol, TN) is a potent nonadrenergic vasopressor, acting through direct stimulation of

vasopressin (V1) receptors in vascular smooth muscle. Its advantages over epinephrine include the fact that the vaso-constrictive effects are not blunted in the presence of acidosis and, following ROSC, there is no increase in myocardial oxygen demand. In human CPA protocols, vasopressin is now being considered an alternative to epinephrine in refractory VF; it has also been used in asystole and PEA.[1] The single use of vasopressin, at a dose of 0.8 µ/kg IV, has been proposed for similar arrhythmias in veterinary CPR.[2] However, there is little data to support a strong recommendation at this time.

Table • 112-1 Drugs Used in Cardiopulmonary Resuscitation

DRUG	DOSAGE AND ROUTE	INDICATIONS
Amiodarone	5–10 mg/kg IV	Refractory VF
Atipamezole	0.1–0.2 mg/kg IV	α_2 adrenergic reversal
Atropine	0.04 mg/kg IV, IT, IO	Bradycardia, asystole
Calcium gluconate	50 mg/kg IV, IO	Hypocalcemia, hyperkalemia
Diltiazem	0.05–2 mg/kg IV 1–10 µg/kg/min IV	Supraventricular arrhythmia after ROSC
Dobutamine	5–10 µg/kg/min IV	Reduced cardiac output after ROSC
Dopamine	5–10 µg/kg/min IV	Hypotension after ROSC
Epinephrine	0.02–0.2 mg/kg IV, IT, IO;	Asystole. Repeat q 3-5 min
Flumazenil	0.02 mg/kg IV, IT, IO	Benzodiazepine reversal
Lidocaine	2–4 mg/kg (dogs), 0.5 mg/kg (cats), IV, IT, IO followed by 50 µg/kg/min IV	Hemodynamically unstable ventricular arrhythmias after ROSC
Magnesium sulfate	30 mg/kg IV, IO	Hypomagnesemic patients; polymorphous ventricular tachycardia
Mannitol	0.25–1 g/kg IV, IO	Cerebral edema
Naloxone	0.01–0.04 mg/kg IV, IT, IO	Opioid reversal
Sodium bicarbonate	0.5–1 mEq/kg IV, IO (NOT IT)	10 minutes into CPA; earlier if pre-existing acidosis; hyperkalemia
Vasopressin	0.8 µ/kg IV, IO	Asystole, refractory VF

IV, Intravenous; *IT*, intratracheal; *IO*, intraosseous; *VF*, ventricular fibrillation; *ROSC*, return of spontaneous circulation.

Aminophylline is an adenosine antagonist that has recently been used in human CPR in an effort to counteract the negative chronotropic effect, inhibition of catecholamine receptors, and vasodilation caused by endogenous vasodilators such as adenosine during CPA. Aminophylline can decrease defibrillation threshold and may be useful in refractory VF. More extensive studies into the use of this drug are underway.

Amiodarone is a newer antiarrhythmic agent that has been included in human CPR guidelines for use in ventricular arrhythmias refractory to lidocaine or procainamide, as well as for treatment of refractory VF.[1] To date, there is no data on its use in small animal CPR.

Aggressive fluid therapy during CPR can increase preload and interfere with cerebral and myocardial perfusion. However, as CPA progresses, increasing fluid volumes are required in order to maintain an effective circulating blood volume in the presence of systemic vasodilation. Fluid choice is dependant on volume status; colloids may augment isotonic crystalloid administration in hypovolemic patients.

Electrical defibrillation is the treatment of choice for VF, with the goal of conversion to asystole (with subsequent epinephrine administration) or a perfusing rhythm. In known VF, defibrillation may be carried out prior to the ABCs. Electrical countershocks are applied across the chest wall using hand-held defibrillator paddles coated with electrode gel, with the animal in dorsal recumbency. The initial electrical shock should be in the range of 3 to 5 J/kg. Two or three shocks are delivered in rapid succession, with increasing energy (5 to 10 J/kg) being applied if

necessary. For internal defibrillation, during open chest CPR, an initial dose of 0.5 to 1 J/kg is used. The ECG is evaluated and countershocks are discontinued when VF converts.

112.4 PROLONGED LIFE SUPPORT

Successful resuscitation is characterized by the return of a perfusing rhythm and effective respirations. A large percentage of successfully resuscitated patients will suffer a second arrest within a few hours. This is due to multiorgan failure secondary to hypoxic damage during low-flow CPA and CPR.

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Aggressive monitoring and supportive care is required to optimize cardiac output, blood pressure, and vital organ function. Cardiovascular support is provided through appropriate fluid therapy, vasopressor or inotropic support, and the control of hemodynamically unstable arrhythmias (see Table 112-1). Stable and perfusing ventricular escape rhythms should not be suppressed with drug therapy. Ventilatory support may be essential for some hours following resuscitation, in order to maximize oxygenation and to prevent hypercarbia (and associated cerebral vasodilation). Neurologic recovery is also maximized by maintainance of mean arterial pressure (and therefore cerebral perfusion pressure) as well as by treatment for hypoxia-induced cerebral edema with Mannitol (see Table 112-1). Hyperglycemia has been associated with worse neurologic outcomes; for this reason, corticosteroids are not currently used in post-arrest protocols.

Good prognostic signs include the rapid recovery of upper airway function (coughing) and ocular reflexes, and rapid return of consciousness following cardiac arrest. The presence of prolonged unconsciousness, the absence of the oculocephalic (doll's eye) reflex, or any deterioration in neurologic status, following ROSC, suggests progressive cerebral ischemia and indicates a poor outcome. Blindness is a common but often reversible sequela to CPA.

112.5 REFERENCES

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113 CHAPTER • 113 Traumatic Brain Injury

Rebecca S. Syring

Traumatic brain injury (TBI) is an important cause of morbidity and mortality in veterinary medicine. The severity of brain injury after head trauma can be quite variable, with neurologic signs ranging from relatively minor deficits to life-threatening impairments. An understanding of the pathophysiologic changes that occur after TBI and the appropriate diagnostic and therapeutic interventions for the animal with head injury can help the clinician optimize the outcome.

113.1 PATHOPHYSIOLOGY OF BRAIN INJURY

TBI can be caused by blunt or penetrating trauma. Blunt force to the head is the most common category of TBI. With blunt trauma, the kinetic energy from the impact is diffusely dissipated across the surface of the body. Head injury may be overtly obvious in these dogs and cats or may be overshadowed by more severe injuries elsewhere in the body. Although less common, penetrating injuries to the head, such as gunshot, stab, or bite wounds, are more likely to result in isolated trauma to the brain, because the kinetic energy from the trauma is focally dissipated along the penetrating tract.

113.1.1 Primary versus Secondary Injury

Two phases have been described as following TBI: primary and secondary injury. *Primary injury* refers to pathologic changes that take place when the injury is sustained. Examples of primary injury include direct axonal damage, such as compression or laceration from forces applied to the skull during impact or displaced skull fractures, and vascular disruption, including focal hematomas or diffuse parenchymal hemorrhage. Primary injury is complete at the time of trauma and, with the exception of surgical evacuation for focal hematomas or decompression of depressed fractures, little can be done to alter its course.

Secondary injury refers to a variety of pathologic processes that occur after the primary insult and that result in progressive neuronal damage not only at the initial site of trauma but extending to the brain globally. Because the brain has high metabolic requirements, decreased cerebral oxygen delivery or hypoglycemia can rapidly result in adenosine triphosphate (ATP) depletion, cell membrane pump failure, and loss of ion homeostasis. This can lead to excitotoxicity, oxidative stress, cytotoxic and vasogenic cerebral edema, inflammatory mediator release, activation of the coagulation cascade, vasospasm, and cell death. With anaerobic metabolism, hyperglycemia has been documented to exacerbate neurologic damage by increasing lactic acid accumulation in the brain, resulting in neuronal and glial cell death. These are just a few examples of types of secondary injury that occur after TBI. Because secondary injury occurs after the initial insult and is progressive in nature, medical intervention should focus on preventing the development or limiting the side effects of this type of injury. Two factors that have a significant impact on the perpetuation of secondary injury are systemic hypoxia and hypotension, both of which can be easily recognized and treated clinically.

113.1.2 Intracranial Pressure and Cerebral Perfusion Pressure

In the healthy brain, pressure autoregulation ensures that cerebral blood flow (CBF) is maintained within an acceptable range over a wide spectrum of systemic mean arterial blood pressures (50 to 150 mm Hg). In response to changes in blood pressure, parallel changes in cerebral vascular resistance occur to maintain blood flow to the brain. Above and below these values, cerebral blood flow is directly proportional to systemic blood

pressure. This protective mechanism is often impaired (either globally or regionally) in animals with TBI, at which time cerebral blood flow becomes linearly dependent on systemic blood pressure.

Intracranial pressure (ICP) is defined as the pressure exerted between the skull and its intracranial contents. The components of ICP are the volume of blood, brain tissue, and cerebral spinal fluid (CSF) within the cranial vault. In dogs and cats with TBI, brain volume increases with hemorrhage or edema. The body attempts to maintain ICP with a compensatory decrease in the production of CSF or shunting of CSF into the cisterna magna or by arterial vasoconstriction to lower the blood volume. ICP increases when intracranial volume exceeds the system's capability for compensatory decreases in the other components. The normal ICP for cats and dogs is 5 to 10 mm Hg.

Cerebral perfusion pressure (CPP) is considered the primary determinant of cerebral blood flow in animals with TBI. With intracranial hypertension, CPP is equal to the systemic mean arterial blood pressure (MAP) less intracranial pressure:

$$CPP = MAP - ICP$$

Maintaining CPP above a minimum value of 70 mm Hg is recommended in order to optimize oxygen and nutrient delivery to the brain. CPP is a measure of global blood flow and does not necessarily reflect blood flow on a regional level. Because ICP is infrequently measured in veterinary medicine, determination of CPP is not always possible. However, this equation stresses the importance of optimizing blood pressure in head trauma patients. Relatively small increases in ICP (e.g., 15 mm Hg) can result in inadequate CPP with a normal MAP of 80 mm Hg. Additionally, with normal ICP, if pressure autoregulation is no longer intact, minor decreases in MAP result in inadequate CPP.

113.2 ASSESSMENT

In the evaluation of animals with TBI, it is imperative that the examiner assess all body systems, rather than focus solely on the brain, because head trauma often occurs coincident with traumatic injuries to other body systems. It has been reported that 50% to 65% of dogs with TBI have sustained blunt vehicular trauma, a common cause of multisystemic injury. Common injuries seen after blunt trauma, such as pulmonary contusions, pneumothorax, and hemoabdomen, can impair systemic oxygenation and perfusion and perpetuate secondary injury if not rapidly addressed. Developing a systematic approach to the traumatized pet that focuses on evaluation of the major body systems, cardiovascular and respiratory stabilization, followed by a secondary assessment and definitive medical therapy, can help the clinician prioritize treatment goals and can improve the outcome (see Chapter 117). A full neurologic examination is not necessary and may not be in the animal's best interest during the initial assessment. Instead, an abbreviated neurologic assessment that focuses on three main categories—level of consciousness, brain stem reflexes, and motor activity/posture—should provide ample information for initial assessment and stabilization.

An altered level of consciousness indicates abnormalities in the cerebral cortex or brain stem (reticular activating system). Level of consciousness can be divided into four main categories: alert, depressed/obtunded, stuporous, or comatose. Depressed to obtunded animals are aware of but less responsive to their environment. An obtunded animal should still respond to noise or touch. Stupor indicates a severely impaired level of consciousness, with response only to noxious stimuli. A truly comatose dog or cat exhibits no response to any type of manipulation, including repeated noxious stimuli. The use of these standardized categories to describe level of consciousness allows for uniform comparison of neurologic function over time in individual animals. In the assessment of pets with altered levels of consciousness, it is important to remember that shock (decreased tissue oxygen delivery) can cause moderate alterations in consciousness, which should improve with treatment that improves tissue perfusion.

Brain stem reflex assessment should focus on pupils (size, symmetry, and position), pupillary light responses, and physiologic nystagmus. Miotic pupils indicate a lesion above the brain stem leaving the oculomotor nerve, a pupillary constrictor, intact and unopposed from higher centers. Mydriatic pupils are seen in animals with brain stem lesions affecting the oculomotor nerve on the side of the injury. Anisocoria may indicate a neurologic lesion affecting one side exclusively or simply one side more than the other. In the absence of other underlying ophthalmologic disorders, lack of a pupillary light response, unilaterally or bilaterally, indicates disruption or compression of the oculomotor nerve tracts ipsilateral to the injury. Ventrolateral strabismus may also be seen with oculo-motor nerve damage. Physiologic nystagmus, a reflex that tests cranial nerves III and VIII, is intact when the normal tracking movements of the eye are seen in response to turning of the head from side to side. Absence of this reflex indicates injury to the central region of the brain stem, as may be seen with brain stem hemorrhage or compression caused by swelling or herniation.

Abnormalities in any of these brain stem reflexes can aid in the localization of neurologic lesions and in the grading of the severity of injury. Additionally, serial evaluation of these reflexes assists in the monitoring of progression or improvement of neurologic function. It is important to remember that pupils of normal size that are not responsive to light represent significant brain stem dysfunction and are only one step less severe than a fixed and dilated pupil. For example, if midrange or mydriatic pupils without a pupillary light reflex are present on initial examination and no progression is noted, brain stem hemorrhage may be suspected. These signs, in conjunction with a comatose state and loss of physiologic nystagmus, are associated with a grave prognosis. Alternatively, a gradual progression of pupils toward mydriasis or loss of pupillary light response may indicate the development of intracranial hypertension, as occurs with edema formation, which may potentially respond to therapy directed toward lowering ICP.

The animal's motor activity and posture may aid in the localization of neurologic lesions (e.g., focal subdural hematomas). Following TBI, ataxia, hemiparesis, or tetraparesis may be the result of a lesion in the cerebral cortex or brain stem. The presence of other cranial nerve abnormalities can help in the differentiation of intracranial from cervical neck lesions. Decerebrate rigidity (extension of all four limbs and opisthotonus) indicates a rostral brain stem lesion and is often associated with brain stem compression secondary to marked intracranial hypertension and/or herniation. Decerebellate rigidity (extension of the front legs with hindlimb flexion) indicates a cerebellar lesion, as may be seen with cerebellar herniation. Animals with decerebrate posturing have a markedly altered level of consciousness, whereas those with decerebellate posturing usually are alert and aware of their surroundings.

The Cushing (or CNS ischemic) response is a compensatory mechanism that can be seen with markedly elevated ICP. Intracranial hypertension results in decreased CBF, which is sensed in the vasomotor center of the brain. In response to local carbon dioxide (CO_2) accumulation from decreased blood flow, the vasomotor center emits a massive sympathetic discharge, resulting in peripheral vasoconstriction, which results in an elevation in MAP to maintain CPP. The increased blood pressure is sensed at baroreceptors, resulting in a reflex bradycardia. The combination of hypertension and bradycardia in an animal with a decreased level of consciousness should alert the clinician to the possibility of increased ICP and should prompt aggressive treatment.

113.3 THERAPEUTICS AND CARE

113.3.1 Extracranial Stabilization

It is essential that extracranial organ systems be assessed and stabilizing medical therapy be instituted before therapy directed at lowering intracranial pressure is begun. The goals of extracranial stabilization should be to

optimize systemic oxygenation, ventilation, and tissue perfusion. Abnormalities in these three areas are common, given the propensity for multisystemic injuries with blunt trauma and the possibility of direct damage to the respiratory center in the brain. Early stabilization of the extracranial system minimizes secondary neurologic injury.

Hypoxemia should be avoided at all costs. Episodes of desaturation have been shown to worsen the outcome in humans with head trauma. Oxygen supplementation should be provided to maintain a hemoglobin saturation above 97% or a partial pressure of arterial oxygen (PaO_2) greater than 90 mm Hg. When in doubt, especially when oxygenation cannot be measured, the clinician should provide supplemental oxygen to avoid any potential adverse consequences from hypoxemia. Oxygen can be supplemented by many routes, including oxygen cages, flow-by masks, and hoods. Intranasal and intratracheal routes should be avoided when possible, because they can cause sneezing or coughing, both of which transiently increase ICP. Insufficient oxygenation despite an inspired oxygen concentration up to 60% necessitates intubation and positive pressure ventilation.

Hypoventilation, resulting in an elevated partial pressure of arterial carbon dioxide ($PaCO_2$), can occur. Reasons for hypoventilation include direct damage to the respiratory center, sedatives, thoracic trauma that causes pain or pleural space disease, and head or neck trauma that causes mechanical airway obstruction. Acute hypercarbia results in a respiratory acidosis that is sensed at the central chemoreceptors. In response to this acidosis, vasodilatation of the cerebral vasculature occurs, thus increasing CBF and potentially exacerbating elevations in ICP. $PaCO_2$ should be maintained below 40 mm Hg in patients with TBI. If $PaCO_2$ concentrations cannot be maintained within a normal range, intubation alone or in combination with mechanical ventilation is required.

The primary goal of fluid therapy in the pet with TBI is rapid restoration of tissue perfusion and blood pressure such that CPP is maintained above 70 mm Hg. Restriction of fluids should be avoided, because only minimal decreases in ICP are achieved and the animal is placed at greater risk for hypovolemia, which detrimentally affects CPP and exacerbates cerebral ischemia. Fluid therapy should be directed toward restoration of euvolemia, provision of maintenance requirements, and replacement of ongoing losses while avoiding overhydration.

A variety of fluid types are available for intravascular volume replacement in veterinary head trauma animals, including isotonic crystalloids, hypertonic saline, artificial colloids, and blood products (see Chapter 114). No one fluid type is optimal for every situation. Hypotonic solutions (5% dextrose in water, 0.45% sodium chloride) should be avoided for resuscitation, because these types of fluids preferentially expand the intracellular space and may exacerbate cerebral edema. Hypertonic saline (7.5%) is considered by many to be a superior fluid for resuscitation because of its ability to rapidly restore euvolemia due to its hyperosmolarity, which allows small volumes (3 to 5 mL/kg given over 10 to 15 minutes) to be used for resuscitation. Additional attractive properties of hypertonic saline are its ability to lower ICP by means of an osmotic effect and its ability to minimize vasospasm, excitotoxicity, and the inflammatory response in the brain.

113.3.2 Intracranial Stabilization

Once the cardiovascular and respiratory systems have been addressed, steps may be taken to stabilize the brain. The goals of intracranial stabilization are to limit intracranial hypertension by decreasing cerebral edema and optimizing intracranial blood volume and to minimize elevation of the cerebral metabolic rate.

Cerebral edema is a common problem in TBI. It can cause a progressive increase of ICP. Mannitol has traditionally been the drug of choice to help decrease cerebral edema. In addition to its osmotic properties,

mannitol may scavenge free radicals involved in oxidative stress and improve microvascular flow within the injured brain. The concern that mannitol may exacerbate intracranial hemorrhage is unfounded, and the global beneficial effects of its use far outweigh this potential risk. Mannitol should not be administered unless euvolemia has been restored, because the osmotic diuresis resulting from its use will further intravascular volume contraction and potentially worsen CPP. With hypovolemia, hypertonic saline (7.5%) may be a better choice, because this fluid will both restore intravascular volume and exert osmotic effects on the brain.

The use of corticosteroids to decrease cerebral edema has fallen out of favor, because multiple prospective clinical trials in human head trauma patients have shown no benefit. This, in combination with the many adverse effects of corticosteroids (hyperglycemia, immunosuppression, gastric ulceration, delayed wound healing, and exacerbation of a catabolic state), precludes its recommendation for use in animals with TBI.

Another mechanism by which ICP can be lowered is optimization of intracranial blood volume. Elevating the head and neck uniformly 15 to 30 degrees above the rest of the body facilitates venous drainage from the brain. Angles higher than 30 degrees and kinking of the neck such that the jugular veins become occluded should be avoided because arterial inflow and venous outflow can be compromised. Hyperventilation can be used as a short-term method of decreasing intracranial blood volume, because cerebral vasoconstriction occurs in response to alkalosis. Care should be taken to avoid excessive hyperventilation ($PaCO_2$ no lower than 30 mm Hg), because this can worsen cerebral ischemia.

Although less common in veterinary medicine than in humans, space-occupying masses, such as subdural hematomas, may require surgical evacuation in the face of static or worsening neurologic status. Computed tomography (CT), rather than magnetic resonance imaging (MRI), is the diagnostic tool of choice for dogs and cats with TBI, because it provides good detail for bone, cerebral edema, and acute hemorrhage; it is more readily available; and it allows for greater access to the animal during the scan.

Minimizing elevations in the cerebral metabolic rate is another important concern for animals with TBI. Seizures should be controlled with anticonvulsants. Hyperthermia, which can be a result of direct trauma to the thermoregulatory center or of excitement, paddling, iatrogenic causes (heating pads), or pain, should be avoided.

113.3.3 Ancillary Therapeutics and Monitoring

Analgesia and nutrition are two important treatment concerns. Adequate analgesia is essential, using drugs that minimize cardiovascular and respiratory depression (e.g., butorphanol or hydromorphone). Barbiturates, propofol, and etomidate are acceptable anesthetic agents because they do not adversely affect cerebral blood flow or the cerebral metabolic rate. Ketamine, acepromazine, and xylazine do affect these functions and should be avoided. Immediately after head injury, a hypermetabolic state develops that persists for many days. Early institution of nutritional support is crucial in order to minimize protein catabolism and supplement important antioxidants needed to limit oxidative injury.

Careful monitoring and diligent nursing care are vital to successful management. Physical examination parameters that characterize tissue perfusion (i.e., mucous membrane color, capillary refill time, heart rate, respiratory rate, and pulse quality) should be assessed frequently. Oxygenation and blood pressure should be monitored continuously or as often as feasible in the early phase of treatment, with the goals of maintaining oxygen saturation above 97% (PaO_2 greater than 90 mm Hg) and mean arterial blood pressure above 80 mm Hg. Likewise, $PaCO_2$ should be monitored to assess for adequate ventilation. The blood glucose, hematocrit, and total protein concentrations should be checked at least twice daily to ensure adequate fuel, oxygen-carrying capacity, and oncotic pressure. Sampling from the jugular vein should be avoided, because even temporary

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occlusion of this vessel can result in a rapid elevation in ICP. Given the propensity for excessive free water loss through the kidney with mannitol therapy, at minimum, electrolytes (particularly sodium) should be measured daily and urine output should be quantified. An effort should be made to adjust fluid input to account for ongoing losses.

Nursing care should focus on provision of adequate bedding, frequent turning, and passive range of motion physical therapy on the limbs to prevent pressure sores and limb contraction. The eyes should be lubricated frequently if the palpebral reflex is absent. Also, if an indwelling urinary catheter is not in place, the bladder should be manually expressed in animals that do not urinate voluntarily. Colonic enemas may be required.

Initially the neurologic status should be evaluated and recorded hourly to assess the response to treatment. The Small Animal Coma Scale, a modification of the Glasgow Coma Scale used in human medicine, has been developed for veterinary medicine to allow quantitative scoring of the severity of neurologic injury. This scale recently was validated retrospectively in dogs with head trauma and was shown to correlate with the 48-hour outcome. Serial evaluation of scores can be used to objectively evaluate improvement or deterioration over time.

Successful management of the dog or cat with severe TBI can be a rewarding experience. When neurologic signs have improved or reached a static level and the pet is able to maintain hydration and nutritional requirements (voluntarily or with a feeding tube), it can be sent home. Neurologic recovery may be completed over a period of time, or residual deficits may persist. Owners need to be dedicated and educated to the fact that substantial caretaking may be required of them once their pet has been sent home.

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114 CHAPTER • 114 Crystalloid and Colloid Fluid Therapy

Rebecca Kirby

Elke Rudloff

The goal of fluid resuscitation and maintenance is to restore perfusion and hydration while preventing volume overload and its complications of pulmonary, peripheral, and brain edema. The choice of the type and amount of crystalloid or colloid fluid to use begins with determination of where the fluid deficit is located. Capillary dynamics and the composition of the fluids administered govern how those fluids are distributed. The challenge is to deliver the right fluid, in the right amount, at the right time.

114.1 FLUID COMPARTMENT AND CAPILLARY DYNAMICS

Fluids and solutes are dispersed among the intracellular, interstitial, and intravascular compartments. The rate and volume of distribution within these spaces depends on membrane permeability, capillary dynamics (Starling's forces), and osmotic forces (Figures 114-1 and 114-2). Intracellular compartments are surrounded by membranes permeable to water but not to most charged particles (e.g., sodium). The space between blood vessels and cells is the interstitial compartment. Filtering and exchange of interstitial fluid are critical for cellular metabolism and survival. The arteries, veins, and capillaries contain the fluid of the intravascular compartment. Starling's forces affect the volume of fluid exchanged between the intravascular and interstitial compartments.

114.2 FLUID CHARACTERISTICS

The number, charge, and size of the particles in water, together with capillary dynamics, determine the movement of that fluid throughout the different fluid compartments. The dynamics of the various fluid compartments change during critical illness and shock. Inflammatory mediator action at the postcapillary venule causes endothelial cells to contract, resulting in large interendothelial gaps. Intravascular albumin (69,000 daltons) and other similar-sized molecules pass across the capillary membrane into the interstitium. The characteristics of a particular fluid affect the distribution of that fluid between the fluid compartments.

By osmosis, water passes through the membrane toward the side with the greater concentration of solutes. *Osmolality,* the osmotic pressure generated by a solution (in milliosmoles per kilogram of H_2O), opposes movement of water across a membrane. Sodium is the most significant osmotic ion in the extra-cellular space. The ability of a solution to move water across the cellular membrane depends on the osmolality of the solution compared to the intracellular osmolality; this is called *tonicity*. The tonicity of the administered fluid determines the resultant fluid shifts between the body compartments (Figure 114-3).

Proteins are the only dissolved substances in the plasma and interstitial fluid that do not readily cross the capillary membrane. Proteins are responsible for the osmotic pressure at the capillary membrane, called the *colloid osmotic pressure (COP)* or *oncotic pressure*. A serum protein concentration of 5.2 to 5.4 g/dL creates a COP of 17 mm Hg. When the serum protein falls below this range, the intravascular COP may be reduced. The type of fluid selected for therapy depends on the fluid's osmotic and colloidal properties and on the compartment requiring fluid.

Figure 114-1 Cross section of a capillary. Lipid-soluble molecules, such as oxygen and carbon dioxide, diffuse through the interstitial and intravascular space. Non-lipid-soluble particles, to include water, must pass through intercellular clefts between endothelial cells. Colloid molecules that are too large to pass through the membrane cleft are retained in the capillary.

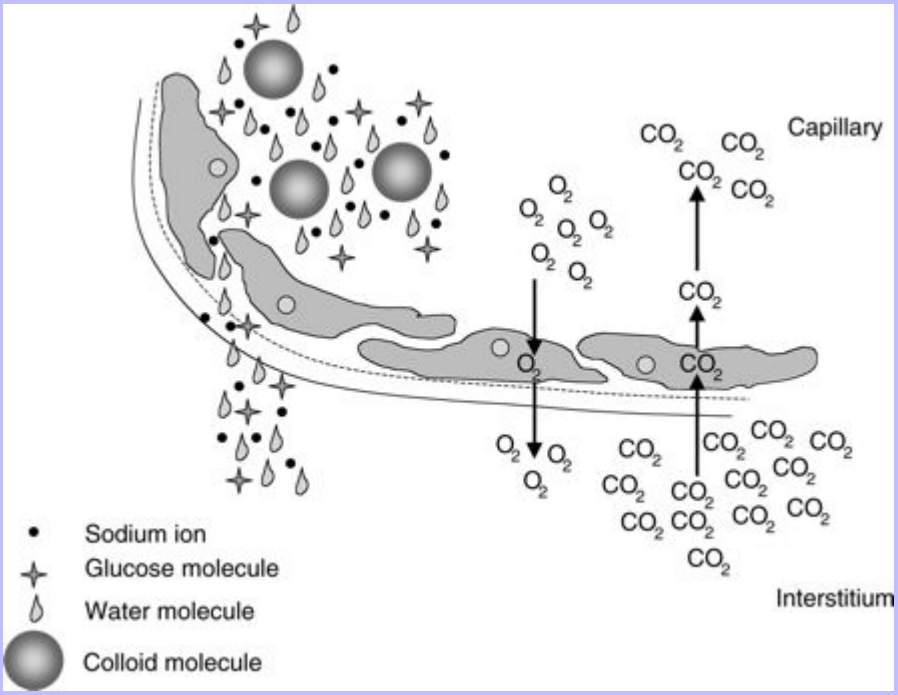


Figure 114-2 Illustration of Starling's forces between the intravascular and interstitial compartments. The intravascular and interstitial fluid compartments are separated by a semipermeable membrane. In solution in the intravascular compartment are large molecular weight molecules, called colloids, that cannot easily cross the membrane because of the minute size of the membrane pore. The force exerted on the membrane from the osmotic gradient created by these colloids is the colloid osmotic pressure (COP). The smallest and most numerous of the protein particles in plasma that create COP is albumin (~69,000 daltons). The overall negative charge of albumin increases its osmotic capability by 50% (called the Gibbs-Donnan effect). Whether fluid remains in the intravascular space or moves into the interstitium is the result of the cumulative effects of Starling's equation. The volume of fluid *(v)* that filters between the capillary *(c)* and interstitium *(i)* across the capillary wall depends on the interendothelial pore size *(sigma),* the pore's reflection coefficient *(kf),* and transcapillary forces of hydrostatic pressure *(P)* and COP, which oppose lymph removal *(Q)* of fluid. Intravascular fluid moves into the interstitial space when (1) Pc (capillary hydrostatic pressure) is increased over COPc (capillary colloid osmotic pressure); (2) capillary membrane pore size increases; or (3) COPc drops below COPi (capillary hydrostatic pressure).

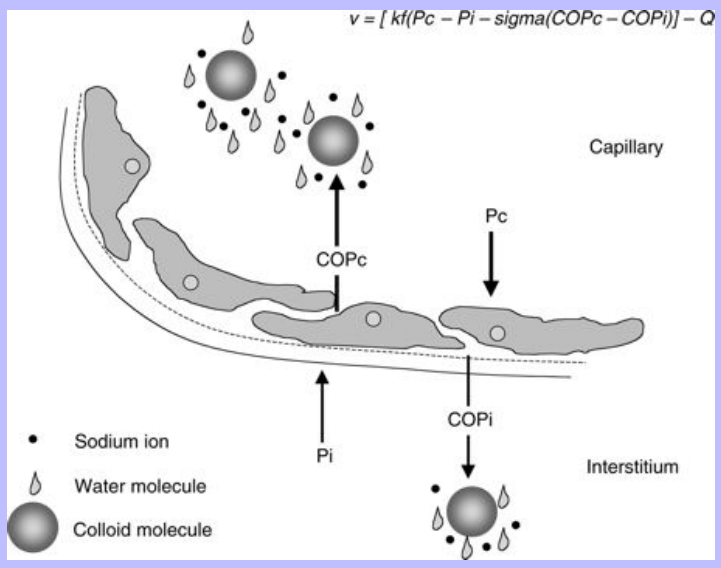
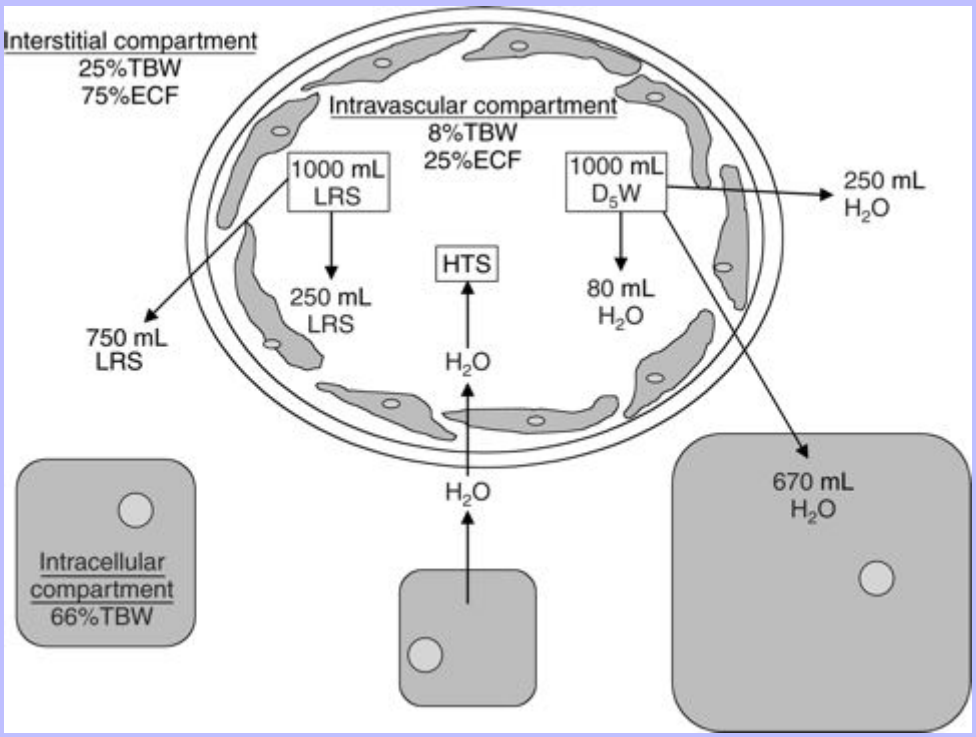


Figure 114-3



Tonicity and the distribution of various crystalloid fluids between body fluid compartments. Sixty percent of body weight is water. Of this water (total body water [TBW]), 66% is intracellular and 33% is extracellular fluid (ECF). Of the TBW that is extracellular, 25% is intravascular and 75% is interstitial. The membrane separating the intravascular and interstitial compartments is freely permeable to water and small ions, whereas the membrane surrounding the intracellular space is permeable only to water.

When solute-free water (e.g., D_5W), which has no osmotically active particles, is infused, it is distributed according to each body water compartment's percentage of TBW. Infusion of 1 L of solute-free water results in a net intravascular expansion of only 80 mL after 30 minutes of equilibration time.

When a hypertonic solution (HTS) is infused (e.g., 7% hypertonic saline or mannitol), the high concentration of osmotically active solutes draws water from the interstitial space into the intravascular space. The resulting increase in interstitial osmolality forces intracellular water to flow out into the interstitial space.

When a solution isotonic with plasma (e.g., LRS, Plasmalyte-A, Normosol-R) is infused, no alteration occurs in extracellular osmolality, and water remains in the extracellular space. Therefore, after infusion of 1 L of an isotonic solution, 250 mL remains in the intravascular space and 750 mL flows into the interstitial space after 45 minutes of equilibration time.

114.3 FLUID SELECTION

The two major types of fluid administered are crystalloids and colloids. A *crystalloid* fluid is a water-based solution with small molecules that are permeable to the capillary membrane. A *colloid* fluid is a crystalloid solution that contains large molecules that are not readily permeable at the capillary membrane. The most commonly used crystalloids, colloids, and hemoglobin-based oxygen carriers (HBOCs) and their specific characteristics are listed in Table 114-1.

114.3.1 Crystalloids

Crystalloid fluids replace and maintain extracellular volume. Because 75% to 80% of the isotonic crystalloids administered intravenously move to the extravascular space within 1 hour in a normal animal, crystalloids are necessary for interstitial rehydration (see Figure 114-3). The needs of the patient are weighed against the specific electrolyte concentration, osmolality, and pH of the fluid selected.

The sodium and glucose concentrations of crystalloids determine the osmolality and tonicity of the fluid and therefore the distribution between the fluid compartments. In most critical situations, an isotonic, balanced electrolyte *replacement* crystalloid solution, such as lactated Ringer's solution (LRS), Plasmalyte-A, or Normosol-R, is used to replace electrolytes and buffers in concentrations typical of the extracellular fluid. Normal saline (0.9% sodium chloride solution) is also an isotonic replacement fluid but is not “balanced” with electrolytes or buffers.

Hypotonic solutions, such as 5% dextrose in water (D_5W), contain water in excess of solutes. Once the dextrose has been rapidly metabolized, the remaining water is distributed among all fluid compartments (see Figure 114-3). The use of hypotonic fluids should be restricted to slow infusion to replace calculated free water deficits; slow administration of constant-rate infusion drugs; or combination with replacement fluids to create half strength *maintenance* fluids.

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Crystalloid solutions are made hypertonic by the addition of sodium or glucose. Hypertonic crystalloids comprise 3%, 7%, and 7.5% saline and 5% glucose in replacement solutions. The concentrated solutes produce an osmotic gradient, drawing water into the vascular space after intravenous administration (see Figure 114-3 for more information). If ongoing loss of plasma water is a factor or if the interstitium is dehydrated, these fluids should be avoided. Hypertonic saline is often combined with colloids to prolong intravascular volume retention.

The basal need for solute-free water by the cells directs the sodium concentration in *maintenance* fluids to be approximately 50% of the plasma concentration. Potassium requirements for maintenance are up to three times the replacement fluid concentrations. Maintenance crystalloid solutions are made isotonic by the addition of glucose to make a 2.5% concentration.

114.3.2 Colloids

Colloid solutions are primarily intravascular volume-replacing fluids (see Table 114-1). Whole blood, plasma products, and concentrated albumin contain natural colloids in the form of proteins, primarily albumin. Dextran 70 and hydroxyethyl starches (hetastarch and pentastarch) are synthetically derived colloids. It is the difference in their macromolecular structure and weight that dictates their colloid osmotic effect, method of excretion, and solution half-life. The greater the number of small molecules per unit volume, the greater the initial colloid

osmotic effect and plasma volume expansion. Colloid solutions, in order of greatest plasma volume expansion, are 25% albumin, dextran 70, Oxyglobin, pentastarch, hetastarch, whole blood, and plasma. Often a combination of colloid solutions is the best therapeutic approach.

114.3.2.1 Natural Colloids

Natural colloid solutions are selected when the animal requires a colloid (albumin) as well as red blood cells, coagulation proteins, and/or antithrombin. A concentrated 25% albumin solution is available for rapid, low-volume resuscitation. In humans, 25% albumin is administered to the edematous patient who requires intravascular volume resuscitation. Although concentrated canine and feline albumin is not readily available, the human form has been used therapeutically in hypoalbuminemic dogs.

Dogs and cats receiving red blood cells in any solution should be blood typed and cross-matched. If time is a limiting factor, a dog erthrocyte antigen (DEA) 1.1-negative transfusion is preferred for the dog. Blood products should be warmed to normal body temperature prior to infusion and administered within 6 hours via an 18-μmicropore filter. The serum calcium should be monitored during multiple transfusions. Administration of large volumes of blood products can also cause a dilutional coagulopathy.

114.3.2.2 Synthetic Colloids

Synthetic colloid solutions were developed to provide timely and convenient fluid resuscitation while increasing the COP beyond that attainable with natural colloid solutions. They can be used in conjunction with whole blood or plasma but are not considered a substitute for blood products when albumin, red blood cells, antithrombin, or coagulation proteins are needed. Dextrans and hydroxyethyl starches (HES) are synthetic colloids, each with a pharmacology, specific qualities, and potential side effects that make it unique (see Table 114-1). The selection of a specific synthetic colloid is based on these individual characteristics.

114.3.3 Hemoglobin-Based Oxygen Carriers

Stroma-free hemoglobin solutions (e.g., Oxyglobin) are hemoglobin-based oxygen carriers (HBOCs) made of polymerized bovine hemoglobin suspended in LRS. These solutions have colloidal properties similar to those of heta-starch and exert a vasopressor effect. Administration of HBOCs improves oxygen saturation in the pulmonary capillary, with oxygen release at the tissue capillary at oxygen pressures of 40 mm Hg. Dosages up to 30 mL/kg/day have been approved for use in anemic dogs, with the rate of infusion equal to or less than 10 mL/kg/hour. When a HBOC is used in an animal with normal blood volume, slow administration and careful monitoring are necessary to prevent volume overload.

114.4 FLUID THERAPY PLAN

The fluid therapy plan must be adequate to replace fluid deficits in a timely manner, to replace continuing losses, and to meet the patient's ongoing requirements. Normal kidney and cardiovascular systems can correct most fluid therapy miscalculations, but these functions may be compromised in a critically ill animal. Often the clinician is challenged to promote organ perfusion while avoiding life-threatening interstitial edema. A fluid therapy plan should be formulated in a logical sequence, using end-point resuscitation techniques.

114.5 RESUSCITATION

During resuscitation, fluid therapy rapidly replaces a fluid deficit that is causing or has the potential to cause life-threatening organ compromise. A fluid deficit in the intravascular space manifests primarily as a *perfusion* problem. With a fluid deficit in the interstitial or intracellular space, the physical signs reflect a *hydration* problem.

114.5.1 Perfusion

Perfusion problems are manifested as changes in the heart rate, pulse intensity, mucous membrane color, capillary refill time, and rectal temperature. Resuscitation of perfusion deficits associated with hypovolemia requires rapid intravascular volume expansion by intravenous or intraosseous routes of administration. Fluid selection and doses are in part based on the animal's cardiovascular status and emergency data base (packed cell volume; total protein; serum glucose; sodium, calcium, potassium, and blood gas values; Table 114-2 and Box 114-1).

Crystalloids can be administered without colloids; however, perfusion end-points (Table 114-3) may be more difficult to reach without complications of edema. Large volumes of crystalloids rapidly administered intravenously cause an immediate increase in intravascular hydrostatic pressure and a reduction in COP, leading to extravasation into the interstitium. Extreme care must be taken when crystalloids alone are administered during resuscitation of animals with pathology of the brain, lungs, kidneys, or heart. The total amount of fluid required for resuscitation may be less or more than the estimated plasma volume (50 to 60 mL/kg in the dog; 40 to 50 mL/kg in the cat), requiring titration of volumes to effect.

Resuscitation using both colloids and crystalloids requires less volume and achieves faster resuscitation times. When colloid is added, crystalloid infusion rates can be reduced by 40% to 60% of that required if crystalloids were used alone. Synthetic colloids increase the COP effect, resulting in an increase in intravascular volume greater than the volume infused. Resuscitation of conditions with increased capillary permeability necessitates selection of a solution containing colloids larger than the pore size of the capillaries. This makes hetastarch, pentastarch, or stroma-free hemoglobin the preferred colloids. When the animal requires red blood cells, clotting factors, antithrombin, or albumin, natural colloids are the administered products. With natural colloids, the blood volume is increased by an amount equal to the amount infused. A combination of crystalloid, synthetic colloid, and natural colloids often is required to meet the patient's needs.

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Table • 114-1 Characteristics of Crystalloids and Colloids

NAME	FLUID COMPARTMENT	OSMOLARITY (mOsm/L)	pH	Na^+ (mEq/L)	Cl^- (mEq/L)	K^+ (mEq/L)	Mg^{++} (mEq/L)	Ca^{++} (mEq/L)	DEXTROSE (g/L)	BUFFER	COP (mm Hg)	ADDITIONAL CHARACTERISTICS
CRYSTALLOID												
Replacement												
0.9% Saline	Extracellular	308 (isotonic)	5.0	154	154	0	0	0	0	None	0	Fluid of choice for treating hyperkalemia or hypochloremia associated with alkalosis.
Lactated Ringer's solution	Extracellular	275 (isotonic)	6.5	130	109	4	0	3	0	Lactate	0	Should not be administered in the same lines with citrate-containing transfusions.
Plasmalyte-A (pH 7.4)	Extracellular	294 (isotonic)	7.4	140	98	5	3	0	0	Acetate, gluconate	0	
Normosol-R	Extracellular	295 (isotonic)	5.5–7	140	98	5	3	0	0	Acetate, gluconate	0	
7% Saline	Extracellular	2396 (hypertonic)		1197	1197	0	0	0	0	None	0	Should not be used in a dehydrated patient or during hyperosmolar disease states.
5% Dextrose in water	Intracellular	252 (hypotonic)	4.0	0	0	0	0	0	50	None	0	Primarily used as a carrier for constant rate infusion drugs.
Maintenance												
2.5% Dextrose in ½ strength lactated Ringer's solution	Extracellular	264 (isotonic)	4.5–7.5	65.5	55	2	0	1.5	25	Lactate	0	
ProcalAmine	Extracellular	735 (hypertonic)	6–7	35	41	24	5	0	30	Acetate, phosphate	0	Contains 3% amino acid solution + 3% dextrose; beneficial during partial anorectic states.
3% FreAmine III	Extracellular	405 (hypertonic)	6–7	35	41	24	5	0	0	Acetate, phosphate	0	Contains 3% amino acid solution; beneficial during partial anorectic states.
COLLOID												
Natural												

Fresh whole blood	Intravascular	300 (isotonic)	Variable	140	100	4	0	0	0–4	None	20	Contains red blood cells, albumin, fibrinogen, globulins, alpha macroglobulins, coagulation proteins, and antithrombin. Factors V and VIII and platelets are absent in stored whole blood.
Stored whole blood												
Fresh frozen plasma, frozen plasma	Intravascular	300 (isotonic)	Variable	140	110	4	0	0	0–4	None	20	Contains albumin, fibrinogen, globulins, alpha macroglobulins, coagulation proteins, and antithrombin. Factors V and VIII are absent in frozen plasma.
25% Albumin	Intravascular	300 (isotonic)	Variable	130–160	0	1	0	0	0	None	100	Used during resuscitation of hypovolemic, edematous states. Slow infusion is used during hypoalbuminemic states.
Synthetic												
6% Hetastarch	Intravascular	310 (isotonic)	5.5	154	154	0	0	0	0	None	30	Molecular weight range is 10,000–3,400,000 daltons. Half-life is 25 hours. May increase plasma amylase and coagulation times.
10% Pentastarch	Intravascular	326 (isotonic)	5.0	154	154	0	0	0	0	None	25	Molecular weight range is 10,000–1,000,000 daltons. Half-life is 2.5 hours. May increase plasma amylase and coagulation times.

Dextran 70	Intravascular	310 (isotonic)	3–7	154	154	0	0	0	0	None	60	Molecular weight range is 15,000–160,000 daltons. Half-life is 25 hours. May increase coagulation times.
Hemoglobin-Based Oxygen Carriers												
Stroma-free hemoglobin (e.g., Oxyglobin)	Intravascular	300 (isotonic)	7.8	150	118	4	0	4	0	Lactate	40	Molecular weight range is 65,000–500,000 daltons. Half-life is 30–40 hours. Higher doses may result in darkening of plasma color, which may affect serum and urinalysis results.

Na^+, Sodium; Cl^-, Chloride; K^+, potassium; Mg^{++}, magnesium; Ca^{++}, calcium.

Table • 114-2 Emergency Data Base Information That Guides Formulation of a Fluid Therapy Plan

TEST	VALUE	COMMENTS
PCV (%)	≤20 or declining trend	Administer RBCs or HBOCs.
	>60	Causes hyperviscosity. Need rapid and aggressive hemodilution with crystalloids (+/– colloids).
Total protein (g/dL)	<5.0	Administer hetastarch during resuscitation and maintenance.
	>9.0	Need rapid and aggressive hemodilution with crystalloids (+/– colloids).
Glucose (mg/dL)	<60	May require 0.5 g/kg IV dextrose bolus.
	>400	Use slow rehydration to avoid rapid drop in plasma osmolality and cerebral edema. May require insulin therapy after resuscitation.
Sodium (mEq/L)	≥175 or ≤130 mEq/L	Give small volume resuscitation with 0.9% saline.
Potassium (mEq/L)	≥8.0	Use 0.9% saline if oliguric.
	≤2.0	Supplement resuscitation fluids if respiratory muscle fatigue is present.
	2.0–5.5	Supplement maintenance fluids.
Total calcium (mg/dL) (corrected value)	≥13.0	Use 0.9% saline for calciuresis.
pH and bicarbonate	Metabolic alkalosis	Use 0.9% saline if patient is hypochloremic.
	Metabolic acidosis	Aggressive fluid resuscitation usually corrects acidemia; recheck values after resuscitation.

RBC, Red blood cells; *HBOC*, hemoglobin based oxygen carrier; *PCV*, packed cell volume.

114.5.1.1

Box • 114-1 Steps for Formulating a Fluid Therapy Plan

1. Determine whether a fluid deficit exists based on the physical examination findings.

a. Poor perfusion (intravascular loss): Consider colloid and isotonic replacement crystalloid combination.

b. Dehydration (interstitial loss): Use isotonic replacement crystalloid.

2. Determine the resuscitation technique and end-points to be used.

a. Small volume resuscitation is used in the cat (Figure 114-5).

b. Most causes of hypovolemic shock in the dog warrant rapid intravascular resuscitation (Figure 114-4).

c. Complications such as heart disease, hemorrhage, lung or brain pathology, hyperglycemia, or hypernatremia warrant small volume resuscitation (Figure 114-4).

3. Assess the emergency data base (Table 114-2).

4. Determine which crystalloid to administer.

a. Each fluid therapy plan incorporates crystalloids.

b. A balanced isotonic crystalloid (e.g., Plasmalyte-A, Normosol-R, LRS) is usually selected for initial resuscitation.

c. 0.9% saline is used if hypernatremia, hyponatremia, hypercalcemia, hypochloremic metabolic alkalosis, or oliguric renal failure is a factor.

5. Determine which colloid to administer if poor perfusion is the result of hypovolemia.

a. Hetastarch is the colloid of choice if systemic inflammatory response syndrome is anticipated or if the patient is hypoalbuminemic.

b. Dextran 70 can be used for initial resuscitation if systemic inflammatory response syndrome is not suspected.

c. Anemia (PCV ≤20% or rapidly declining) may require administration of whole blood, packed red cells with a colloid, or stroma-free hemoglobin.

6. Evaluate for vascular leakage, vasodilatation, and third spacing of body fluids, which may require larger volumes of fluid to reach end-points of resuscitation.

7. If unable to reach or maintain end-points of resuscitation:

a. Evaluate for causes of nonresponsive shock (e.g., inadequate volume replacement, ongoing hemorrhage, ongoing fluid loss, heart failure, brain failure, hypoglycemia, hypoxia, hypokalemia, excessive vasodilatation/vasoconstriction).

b. Consider administering Oxyglobin in 5 mL/kg increments (dogs) for vasopressor and COP effects if not used previously.

c. Consider administering dopamine (5 to 15 µg/kg/min) as a constant-rate infusion.

8. After perfusion has been restored (Table 114-5), estimate the percentage of dehydration and calculate the fluid deficit.

    a. % Dehydration × Body weight (kg) = Fluid deficit (L)

    Example: 30 kg dog that is 10% dehydrated:

    0.10 × 30 = 3.0 L fluid deficit

9. Rehydration therapy may require a crystalloid different from that used to resuscitate the perfusion deficit.

114.5.1.1.1 Maintenance Fluid Plan

1. Estimate ongoing losses caused by vomiting, diarrhea, third spacing of body fluids, and polyuria.

    a. Use isotonic balanced replacement crystalloid fluids (e.g., Plasmalyte-A, Normosol-R, or LRS).

    b. Use 0.9% saline if hypernatremia, hyponatremia, hypercalcemia, hypochloremic metabolic alkalosis, or oliguric renal failure is a factor.

    c. Add crystalloid (2 mL/kg/h; see steps 2a and 2b below) to the volume of the estimated ongoing losses.

    d. Supplement potassium in fluids:

Serum Potassium (mEq/L)	Potassium Supplementation
4.0–5.5	5 mEq/250 ml fluids
3.0–3.9	7 mEq/250 ml fluids
2.5–2.9	8 mEq/250 ml fluids
≤2.5	10 mEq/250 ml fluids

2. Maintenance crystalloid fluids (see Table 114-1) are selected when no ongoing losses are present.

    a. Administer 2 mL/kg/h to replace free water and electrolytes consumed during metabolism and insensible losses.

    b. Dosage increases 1–2 mL/kg/h if fever or hyperpnea is present.

3. During anesthesia, replacement crystalloids (5–8 mL/kg/h) are used for maintenance.

    a. Adjust potassium supplementation according to the fluid rate; potassium-supplemented fluids are not used for rapid volume replacement.

    b. Keep warm bags of replacement crystalloids that do not contain potassium supplementation within easy reach, in the event rapid, large-volume boluses are required for resuscitation during the period of anesthesia.

4. For hypernatremia (Na^+ ≥170 mEq/L) with normal perfusion and hydration: Replace solute free water using maintenance crystalloids.
    a. [(Measured Na^+ – 140)/140] × Body weight (kg) × 0.3 = Free water deficit (L).
    b. Replace free water deficit over 24 to 48 hours: Lower 1 mOsm/kg/h.
    c. Add volume for metabolism and insensible losses (see steps 2a and 2b, above).

114.5.2 Rapid Intravascular Volume Resuscitation for Dogs

Dogs experiencing shock due to hypovolemia or maldistribution of blood flow from nontraumatic causes can benefit from rapid intravascular resuscitation techniques (Table 114-4). Whole blood products can be administered rapidly in catastrophic hemorrhagic situations, with input at least matching ongoing losses. Additional colloids can be administered using small volume intravascular resuscitation techniques if perfusion has not improved to the desired end-point after the initial bolus (see Figure 114-5). Rapid intravascular volume resuscitation techniques are not recommended in the cat in shock.

114.5.3 Small Volume Intravascular Resuscitation

Hypovolemic dogs with closed cavity hemorrhage, head trauma, pulmonary contusions, cardiogenic shock, oliguric renal failure, hypernatremia, or hyperglycemia can benefit from careful resuscitation using small volume intravascular resuscitation techniques (Figure 114-4). This also applies to all hypotensive cats (Figure 114-5). Hypothermia, especially in the cat, can significantly blunt cardiovascular responses to fluid resuscitation. Active external warming should occur once fluid resuscitation has been initiated. The goal is to reach a rectal temperature above 98°F within 30 minutes to maximize cat-echolamine receptor response. If no heart disease is present, small volume resuscitation efforts with crystalloids and synthetic colloid infusion is continued until the desired endpoints are obtained.

When the dose of hetastarch and dextran 70 exceeds 40 mL/kg/day in the dog and 20 mL/kg/day in the cat, plasma transfusions may be necessary to maintain adequate coagulation times. Stroma-free hemoglobin can be used in the dog, the total not exceeding 30 mL/kg/day. If the arterial blood pressure remains below 70 mm Hg after the maximum recommended doses have been administered, an investigation into causes of nonresponsive shock (e.g., severe vasodilatation/vasoconstriction, cardiac dysfunction) should be started, and administration of dopamine (5 to 15 µg/kg/min in a constant-rate infusion [CRI]) or stroma-free hemoglobin (if not yet used) should be considered for vasopressor effects.

114.5.4 Rehydration

Fluid deficit in the extravascular space (interstitial and intracellular) causes *dehydration*. Severe dehydration can lead to impaired perfusion due to fluid movement from the intravascular space to the dehydrated interstitium. To replenish the interstitial space, crystalloid fluids isotonic to plasma that contain specific electrolytes based on the patient's needs should be administered (see Table 114-1). The amount of crystalloid is determined by using physical parameters to estimate the percent dehydration (see Box 114-1 and Table 114-5). Intravenous or intraosseous administration of the fluid is preferred, although subcutaneous routes can be used.

The rate of administration should be determined by the urgency of the situation. Acute loss warrants acute replacement over 1 to 4 hours. Chronic losses or dysfunction of the lungs, heart, or brain usually require slower resuscitation rates, over 4 to 12 hours. The total amount given and the rate of administration should be determined by monitoring for specific endpoint parameters (see Table 114-3).

Table • 114-3 End-Point Parameters Monitored During Resuscitation

PARAMETER	NORMAL	COMPENSATORY STAGE	EARLY DECOMPENSATORY STAGE	LATE DECOMPENSATORY STAGE	RESUSCITATION END-POINT	TECHNICAL NOTES
Mentation	Alert	Excited and alert	Normal to decreased	Decreased to comatose	Alert	
Heart rate (beats/minute)	Dog: 60–120	Dog: >140	Dog: >140	Dog: <140	Dog: 80–140	Ensure pain relief.
	Cat: 170–200	Cat: Variable	Cat: Variable	Cat: <160	Cat: 180–220	Examine ECG with abnormal rate/rhythm and correct arrhythmia if contributing to perfusion deficit.
Mucous membrane color	Pink	Brick red	Pale	Grey/blue	Pink	Yellow color may also suggest icterus.
Capillary refill time (sec)	1–2	<1	>2	>2	1–2	Can be determined by examining gums, conjunctiva, vulvar/preputial membrane.
Mean arterial blood pressure (mm Hg)	80–100	>80	Variable	<80	80–100*	Renal blood flow is affected at MAP
					60–80**	<60 mm Hg; cerebral and coronary perfusion pressures are affected at MAP <70 mm Hg.
						Acute hypertension can occur with compensatory stages of shock.
Central venous pressure (cm H_2O)	0–2	Variable	<5	Variable	5–10*	Tip of catheter should be in the superior vena cava at the level of the right atrium.
					2–8**	Unexpected elevations can occur with right heart failure, loss of venous compliance, and increased intrathoracic pressure.
Urine output (mL/kg/h)	>1.67	Variable	<0.27	<0.08	>1	With decreased urine output, check for urine obstruction first (patent urine collection). MAP >60 mm Hg is required for adequate renal blood flow.

SpO_2	>97%	>97%	Falsely low levels can be caused by poor peripheral perfusion, dark pigmentation, bilirubinemia, and severe anemia. Falsely increased levels can be caused by carboxyhemoglobinemia or methemoglobinemia.
Packed cell volume	Dog: 40%–55% Cat: 30%–45%	25%–30%	Transfusion products containing red blood cells (whole blood, packed red cells) or a HBOC (in the dog) should be used; HBOCs do not change the PCV, therefore the hemoglobin level must be monitored. Ongoing hemorrhage must be controlled.
Hemoglobin (g/dL)	13.8–21.4	7–10	HBOC can be administered when the hemoglobin is <7 g/dL.
Albumin (g/dL)	2.6–3.9	>2.0	Plasma or albumin transfusion is required when the serum albumin is <2.0 g/dL.
Colloid osmotic pressure (mm Hg)	Dog: 21–25 Cat: 23–25	14–20	
Rectal temperature (°F)	100–102.5	98–102	

ECG, Electrocardiogram; *MAP*, mean arterial pressure; *SPO_2*, pulseoximeter hemoglobin saturation of oxygen; *HBOC*, hemoglobin based oxygen carrier; *PCV*, packed cell volume.

* Supranormal.

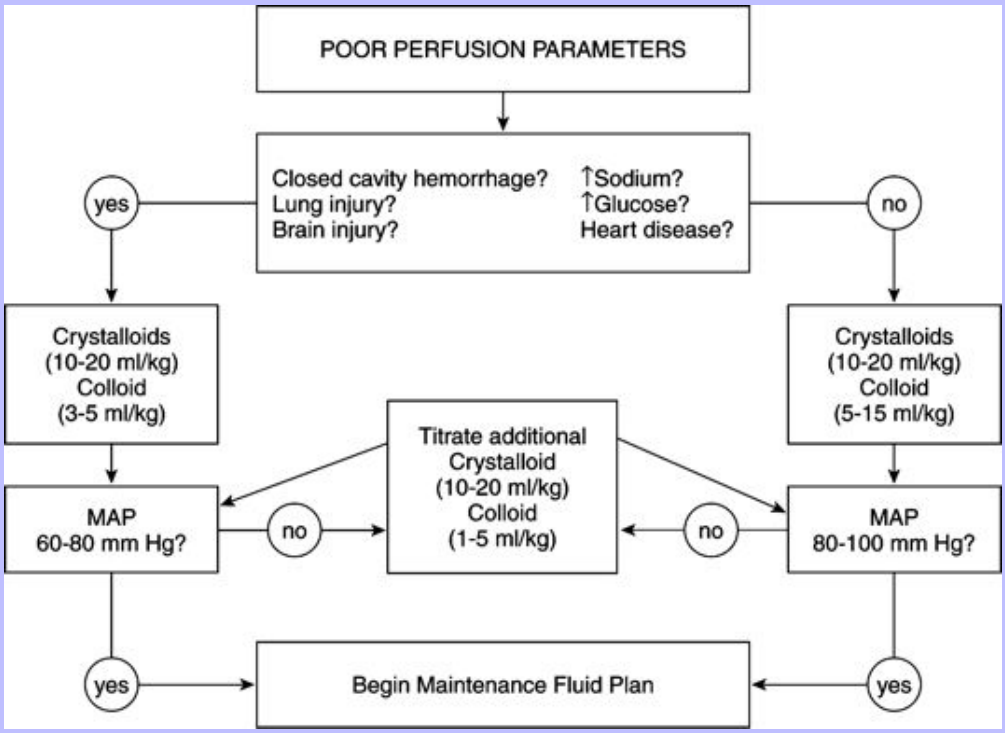
** Hypotensive.

Table • 114-4 Options for Fluid Types and Doses During Resuscitation

CARDIOVASCULAR STATUS	FLUID TYPE	COMMENTS
Compensatory shock	Isotonic crystalloid	If EP is not reached with several boluses, consider adding synthetic colloid.
	or	Treat for pain.
	Isotonic crystalloid + synthetic colloid	Not a condition typically seen in the hypovolemic cat.
Early decompensatory shock	Isotonic crystalloid	Rapidly correct hypothermia.
		Treat for pain.
	or	If EP is not reached with several boluses, consider adding synthetic colloid.
	Isotonic crystalloid + synthetic colloid	Rapidly correct hypothermia.
		Treat for pain.
		If EP is difficult to maintain, place patient on HES CRI, 0.8 mL/kg/h.
		Do not administer HTS to a dehydrated animal or one with pulmonary injury or cardiac disease.
Late decompensatory shock	Isotonic crystalloid + synthetic colloid	Rapidly correct hypothermia.
		Treat for pain.
	or	If EP is not reached with multiple boluses, consider administering vasopressors or oxyglobin boluses (5 mL/kg), up to 30 mL/kg/day (dog).
	Isotonic crystalloid + 7% HTS + synthetic colloid	If EP is difficult to maintain, place patient on HES CRI, 0.8 mL/kg/h.
	or	
Acute hemorrhage (PCV <25%; Hg <8 g/dL)	Whole blood	May require active hemostasis.
		Crossmatch and typing are preferred, time permitting.
	or	
	Packed red blood cells and/or	Can be reconstituted with isotonic saline, plasma, HES, or DEX.
	Oxyglobin	May require additional red cell transfusion.
Hypovolemia with pulmonary injury, head injury, or cardiac insufficiency	Isotonic crystalloid + HES	If EP is difficult to maintain, place patient on HES CRI, 0.8 mL/kg/h.
Low plasma albumin (<2.0 g/dL)	Plasma	Repeat as needed to increase albumin >2.0 g/dL and/or to normalize clotting times.
		Use fresh frozen plasma if factor V or VIII deficiency is present.
Coagulopathy (prolonged PT/PTT)		Consider heparin if DIC is suspected.
Low antithrombin		

HES, hydroxyethyl starch; *DEX,* dextran-70; *HTS,* hypertonic saline; *EP,* end-point; *CRI,* constant rate of infusion; *PCV,* packed cell volume; *Hg,* hemoglobin; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *DTC,* disseminated intravascular coagulation.

Figure 114-4 Resuscitation technique for the dog with poor perfusion. Low-volume resuscitation (left arm of algorithm) is used when the consequences of fluid overload are life-threatening (e.g., lung, brain, or heart disease; closed cavity hemorrhage; or hyperosmolar condition). Low-volume bolus doses of crystalloid and colloid fluids are administered until the mean arterial pressure (MAP) is in the low-normal range. When the risk of fluid overload is not as likely, resuscitation fluid volumes are maximized (right arm of algorithm) to establish a high-normal MAP using larger volume boluses of crystalloid and colloid fluids. When the dose of colloid has reached 40 mL/kg without response, an investigation for causes of nonresponsive shock is begun, and use of vasopressors may be required.

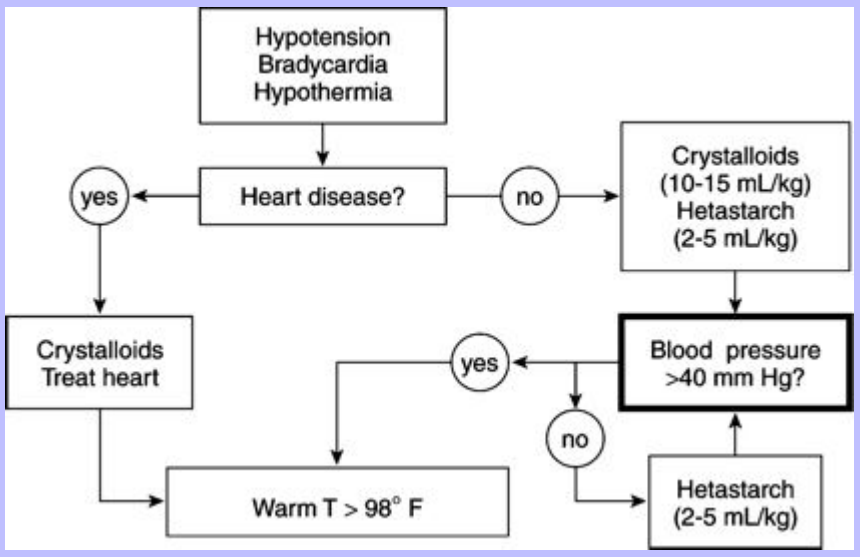


114.5.5 End-Point Resuscitation

Successful resuscitation therapy depends on the administration of quantities of fluids sufficient to reach specified endpoints. This process is termed *end-point resuscitation*. Prior to resuscitation, the clinician should determine the end-point values that will indicate successful resuscitation. Physical, hemodynamic, and blood

chemistry parameters are the mainstays of end-point monitoring (see Table 114-3). The inciting cause of the fluid deficit, as well as vital organ function, dictate the end-points selected and the end-point resuscitation techniques used.

Figure 114-5 Resuscitation technique for the cat with poor perfusion. When heart disease is suspected (auscultation of a murmur, arrhythmia, moist lung sounds, pleural effusion), isotonic replacement crystalloid fluids are administered at a maintenance rate; treatment of heart disease is instituted; and active external warming is provided. When poor perfusion is not attributed to heart disease, low volumes of crystalloid and colloid fluids are administered in bolus doses until the blood pressure registers above 40 mm Hg, and the cat is actively warmed. When the dose of colloid has reached 20 mL/kg without response, an investigation for causes of nonresponsive shock is begun, and use of vasopressors may be required.



For hypovolemic shock and systemic inflammatory response syndrome (SIRS), if brain or lung compromise is not a factor, resuscitation of perfusion to supranormal values to increase oxygen delivery is recommended. Restoration of physical perfusion parameters (lower heart rate, stronger pulses, normal capillary refill time, and pink mucous membranes) is used in conjunction with hemodynamic parameters (e.g., packed cell volume [PCV], COP, arterial blood pressure, urine output, and central venous pressure) as a measure of therapeutic success.

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Table • 114-5 Parameters Used to Estimate Interstitial Fluid Deficit

ESTIMATED % DEHYDRATION	CLINICAL PARAMETERS
4–6	Sticky mucous membranes
	History of vomiting, diarrhea, lack of water intake
6–8	Loss of skin moisture
	Dry mucous membranes
8–10	Loss of skin moisture
	Dry mucous membranes
	Sunken eyes
>12	Loss of skin moisture
	Dry mucous membranes
	Dull mentation
	Dull corneas
	Perfusion deficit present

Traumatic shock with closed cavity hemorrhage and/or brain hemorrhage warrants hypotensive resuscitation. The animal is resuscitated to end-points of improved physical perfusion parameters, but the target blood pressure is in the low-normal range (see Figure 114-4). This method is used to avoid dislodging clots that may be providing life-saving hemostasis.

114.5.6 Maintenance

Crystalloids are the mainstay of fluid therapy, and the type of fluid chosen is based on the needs of the animal (see Table 114-2 and Box 114-1). Maintenance fluids can provide electrolytes, COP support, proteins, coagulation factors, glucose, or nutrients, depending on the fluid selected and the way it is supplemented (see Table 114-1). Increased capillary permeability and hypoproteinemic states can require ongoing maintenance of COP by a constant-rate infusion of hetastarch combined with maintenance crystalloid.

Normal maintenance fluid rates account for insensible, obligatory (urinary and fecal), and metabolic losses of water and electrolytes. The standard crystalloid fluid maintenance requirement is estimated to be 40 to 60 mL/kg/day. Ongoing losses through diuresis, fever, vomiting, diarrhea, or extravasation of fluid into third body spaces should be estimated and replaced with isotonic replacement crystalloids. This estimated volume is added to the total daily “maintenance” volume requirement, and oral intake volumes should be subtracted. The maintenance fluid therapy plan must be reassessed for the duration of therapy, with adjustments made accordingly.

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115 CHAPTER • 115 Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Syndrome

Michael Schaer

Dogs and cats afflicted with either diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar syndrome (HHS) can become acutely ill and benefit from prompt diagnosis and treatment. These disorders usually occur in middle-aged to old pets, often after a variable period of time characterized by polydipsia, polyuria, and weight loss. Alternatively, they can occur as acute metabolic complications of other conditions, such as acute pancreatitis or sepsis. The primary pathophysiology, clinical signs, and medical management of these interesting and challenging disorders are discussed in this chapter. Certain clinical findings shared by the two syndromes are discussed in the section on ketoacidosis.

115.1 PATHOPHYSIOLOGY OF KETOACIDOSIS

Hyperglycemia and accelerated ketogenesis occur when there is an absolute or relative deficiency of insulin and a relative excess of glucagon and other "counter regulatory hormones" such as cortisol, growth hormone, and epinephrine. Consequently, glucose and ketoacids are both overproduced and underutilized. Because the pathophysiologic details of DKA are discussed elsewhere in this text and throughout the medical literature, only those germane to the care of the critically ill patient are mentioned in this section.

The nitroprusside reaction is used to detect and semiquantitate plasma, serum, and urinary ketones. The test detects acetone and acetoacetate but does not react with beta hydroxybutyrate. This characteristic has clinical importance in situations in which shocklike states promote the production of beta hydroxybutyrate, thereby disabling clinical detection of ketoacidosis with the nitroprusside test.

After institution of insulin treatment, the beta hydroxybutyrate to acetoacetate (B:A) ratio decreases as a result of the metabolism of beta hydroxybutyrate to acetoacetate. Although acetoacetate concentrations eventually decrease, the shifting B:A ratio explains the clinical paradox occasionally encountered in which test results initially are negative for ketones but, with the same test given on the second and third days of treatment, are positive despite clinical improvement. A lingering ketonuria can also occur as a dog or cat improves because of the delayed clearance of acetone. Therefore it is not uncommon for ketones to persist well into the third or fourth hospital day while the pet shows signs of improvement.

115.2 DIAGNOSIS

115.2.1 History and Physical Examination

The history for either DKA or HHS often indicates that anorexia, depression, weakness, and vomiting have been observed for only 1 to 3 days. A complete physical examination is essential to detect any concurrent disorders that can significantly affect the outcome. It has been suggested that both conditions are invariably associated with concurrent disorders. The term *diabetic coma* is frequently used to describe the mental effects of the ketoacidotic and hyperosmolar conditions, but only a small percentage of dogs or cats actually have profound decreases in consciousness.

115.3 DIAGNOSTIC EVALUATION

Medical evaluation of a sick diabetic dog or cat should be thorough and should include thoracic radiographs, abdominal ultrasound scans, hematology, serum chemistry, and urinalysis. The acquired information creates an important data base for subsequent medical and sometimes surgical management.

Because hepatic production of glucose is increased in diabetic dogs or cats, the degree of hyperglycemia is determined by the severity of plasma volume depletion. Therefore extreme levels of hyperglycemia tend to occur only when extracellular fluid volume and blood pressure have decreased so much that urine flow is impaired. This is most obvious in dogs or cats that have extreme increases in blood glucose concentrations with minimal glucosuria. Marked hyperglycemia may also signify oliguria.

Metabolic acidosis is mainly attributed to ketoacid buildup, but acidosis can be enhanced by coexisting disease, such as renal failure and lactic acid production. The metabolic acidosis often is accompanied by a large anion gap (AG) (greater than 30 mEq/L) that can be calculated using the following formula:

$$AG = (Na^+ + K) - (HCO_3^- + Cl^-)$$

Hyponatremia in both syndromes can be factitious (attributable to hypertriglyceridemia) or real (due to urinary or gastrointestinal loss of sodium ions). Spurious hyponatremia can also occur when increases in the plasma glucose concentration draw water into the extracellular space, thereby diluting plasma constituents.

The serum potassium concentration in DKA and HHS can range from low to normal to increased. Hyperkalemia can result from a shift of potassium from the intracellular to the extracellular space as a consequence of acidemia, insulin deficiency, and plasma hyperosmolarity. It may also be associated with oliguric or anuric acute renal failure.

Hypokalemia is the most common and most serious electrolyte disturbance. This is usually a reflection of a substantial reduction in total body potassium stores. Even patients with normokalemia may have a considerable deficit of total body potassium; because 98% of total body potassium is intracellular, these concentrations are not easily assessed. Potassium losses occur with vomiting and osmotic diuresis and can be further complicated by therapy. Serum dilution from rehydration, continued urinary losses, correction of acidosis, and increased cellular uptake can “unmask” hypokalemia.

Phosphorus is an integral component of lean body mass. The enhanced catabolism of muscle and fat that invariably occurs in diabetes mellitus results in increased urinary phosphorus excretion and phosphorus wasting.

Increased serum liver transaminase (ALT) and alkaline phosphatase (SAP) activity is commonly attributable to the hepatic lipidosis that occurs in patients with DKA. Hypovolemia-induced central lobular necrosis can also increase liver enzyme values. These hepatic changes are completely reversible, and serum liver enzyme activity moves toward normal after successful treatment. Because diabetic dogs and cats almost always have abnormal liver enzyme values, it is not common for these test results to completely “normalize.”

Azotemia can be either prerenal or renal in origin. Extensive primary renal dysfunction is characterized by isosthenuria (fixed urine specific gravity of 1.008 to 1.012) in a dehydrated patient and an accompanying azotemia that does not readily resolve with rehydration. It should be remembered, however, that both glycosuria and hyperosmolarity can raise a urine specific gravity that remains “isosthenuric” (a specific gravity of 1.020 when the serum osmolality is 400 does not indicate good renal function). Urine sediment should be screened for any signs of infection such as pyuria and bacteriuria. Urine output should be monitored to detect oliguria or anuria.

A leukocytosis with a mature neutrophilia in the 20×10^3 range can be due to the stress associated with both disorders. Detection of bands and toxic cell changes should prompt a search for an inflammatory focus, which may or may not be accompanied by an infection.

115.4 TREATMENT

115.4.1 Fluid and Electrolytes

Disturbances in hydration and electrolyte balance are of great importance in DKA and HHS and require expedient correction (Figure 115-1). The calculated fluid requirements include the patient's dehydration deficits, the 24-hour maintenance needs, and extra losses that result from vomiting or diarrhea. The dehydration status is approximated on a scale ranging from mild (5%) to extreme (12%). The needed isotonic crystalloid fluid replacement volume can be calculated using either of the following equations:

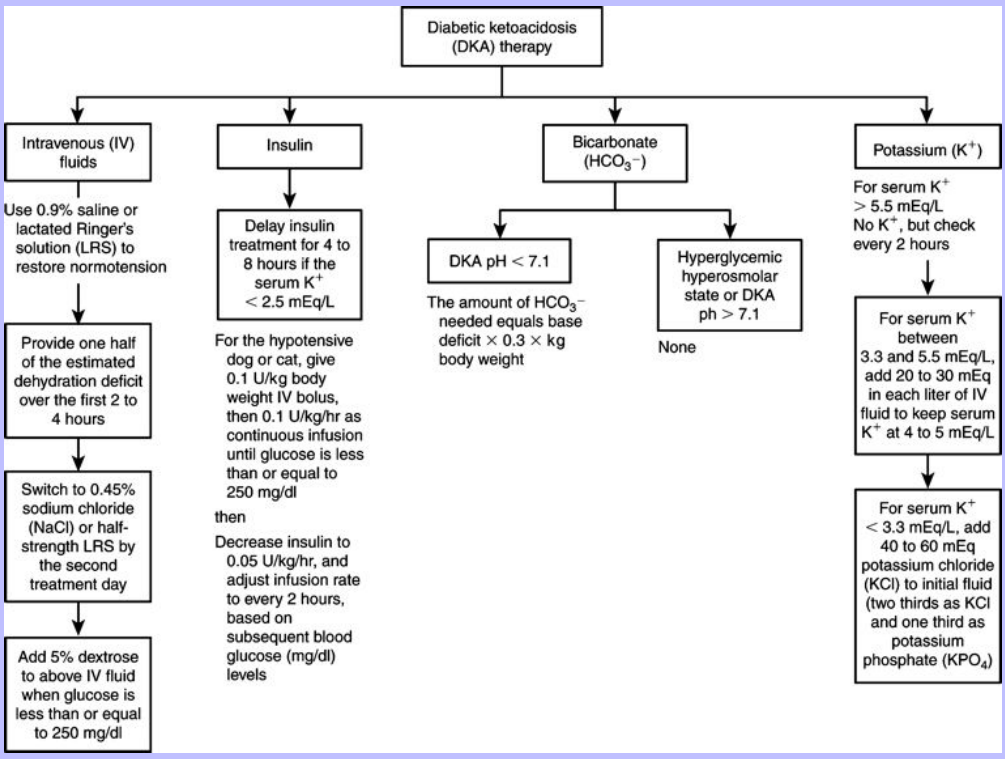
- Dehydration volume deficit (mL) = Dehydration (%) × Body weight (kg) × 1000
- Dehydration (%) × Body weight (lb) × 500

The 24-hour maintenance volume is roughly estimated (assuming adequate urine output) at 66 mL/kg (30 mL/lb). Therefore the first 24-hour total fluid volume is the sum of the dehydration and the maintenance volumes plus any ongoing losses from vomiting or diarrhea.

If the animal is 8% to 12% dehydrated, half of the estimated dehydration deficit should be administered intravenously over the first 2 to 4 hours of hospitalization; the remaining replacement and maintenance volumes, given over the following 20 to 22 hours, should be accompanied by any adjustments necessitated by changes in urine volume.

Hydration alone can substantially decrease the blood glucose level and hyperosmolarity. Hypovolemia in DKA and HHS is corrected with isotonic solutions, such as lactated Ringer's solution or 0.9% saline. Recommended maintenance solutions include 0.45% saline or half-strength lactated Ringer's solution. Dextrose solutions (2.5% to 5%) are used when the patient's blood glucose declines to 250 mg/dL or less in the setting of continued insulin administration.

Figure 115-1 Algorithm for the management of the critically ill dog and cat with diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome. (Modified from Umpierrez GE et al: Hyperglycemic crises in urban blacks. Arch Intern Med 157:669, 1997.)



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Hyponatremia for both disorders is corrected with intravenous 0.9% saline solution to avoid any plasma hypo-osmolality that might occur when the hyperglycemia is reduced with insulin treatment. Plasma hypo-osmolality can cause a reversal of osmotic gradients and overexpansion of the intracellular compartment with resultant cerebral edema.

Potassium supplementation is best provided by adding potassium chloride solution to the parenteral fluids. If concurrent hypophosphatemia is present, one third of the potassium supplement can be in the form of potassium phosphate. Potassium supplementation is best begun after the first 2-hour period of fluid replacement, when hydration, blood pressure, and urine output are improved. If the patient is initially hypokalemic, potassium chloride (KCl) can be added to the hydrating solution; however, the infusion should be slowed so that half the dehydration replacement volume is delivered over an additional 1 to 3 hours. Although most texts list the maximum rate of potassium ion administration as 0.5 mEq per kilogram of body weight (BW) per hour, the author's experience has shown that this rate can be safely doubled when the patient is severely hypokalemic (serum potassium level less than 2.5 mEq/L) as long as electrocardiographic and urine output monitoring is done. The recommended amount of potassium that can be added to the parenteral fluids *over a 24-hour period* is shown, using two different but equally effective methods.

- *Mild hypokalemia* (serum K^+ of 3.0 to 3.5 mEq/L): administer 2 to 3 mEq/kg *or* add 20 to 30 mEq KCl per liter of replacement fluid
- *Moderate hypokalemia* (serum K^+ of 2.5 to 3.0 mEq/L): administer 3 to 5 mEq KCl/kg *or* add 40 to 60 mEq KCl per liter of replacement fluid
- *Severe hypokalemia* (serum K^+ below 2.5 mEq/L): administer 5 to 10 mEq KCl/kg *or* add 60 to 80 mEq KCl per liter of replacement fluid.

Daily serum electrolyte determinations and the necessary treatment adjustments are made until normal values are obtained. Intravenous fluids are discontinued when serum biochemistry values are normal, hydration is normal, and the patient is able to eat and drink without vomiting.

Any needed phosphate replacement can be given as potassium phosphate solution at the recommended dose of 0.01 to 0.03 mmol/kg BW/hour, with repeat serum phosphorus determinations every 6 hours. Attention should be given to avoiding iatrogenic hyperphosphatemia and hypocalcemia.

Hypomagnesemia has been shown to cause specific problems, especially cardiac arrhythmias, in diabetic humans; however, its association with any particular dysfunction in diabetic dogs and cats has not yet been demonstrated. The ionic and total bound forms of magnesium can be measured.

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Sodium bicarbonate treatment for DKA is controversial. Advocates of this treatment cite concern that severe acidosis (blood pH less than 7.0) can adversely affect cardiovascular function; opponents base their concern on the treatment's causal relationship with paradoxical cerebrospinal fluid acidosis, hypokalemia, and worsened intracellular acidosis with overshoot alkalosis.

The use of sodium bicarbonate should be restricted to dogs or cats with a blood pH below 7.1 or those with a serum total carbon dioxide (CO_2) concentration less than 10 to 12 mEq/L. During most treatment courses, metabolic acidosis reverses without bicarbonate treatment because of the cessation of ketogenesis, the metabolic conversion of ketones to bicarbonate after initiation of insulin treatment, improved renal function, and conversion of the lactate in lactated Ringer's solution to bicarbonate. In severe cases of metabolic acidosis (i.e., an anion gap greater than 30 mEq/L and an arterial pH less than 7.1), sodium bicarbonate ($NaHCO_3$) can be given according to the following equation:

$$NaHCO_3\ (mEq) = \text{Base deficit (mEq)} \times 0.3 \times \text{Body weight (kg)}$$

Subsequent alkali treatment depends on the results of repeat plasma pH measurements; it should be discontinued when the blood pH has been restored to 7.2 or higher or until the serum total CO_2 concentration is greater than 10 to 12 mEq/L.

115.4.2 Insulin

The cornerstone of management of a sick DKA or HHS dog or cat is insulin administration. Regular crystalline insulin is used when the pet has signs of depression, dehydration, anorexia, and vomiting. Regular insulin has several advantages, including its various routes of administration (intravenous, intramuscular, and subcutaneous), rapid onset of action, and short duration of action. These properties allow adequate insulin titration throughout the day according to the animal's needs. The clinician must remember that the blood

glucose concentration declines much earlier than ketones, allowing for the persistence of ketonuria for the first 48 to 96 hours.

Regular insulin given intravenously by slow constant-rate infusion (CRI) is the preferred method of treatment for the critically ill hypotensive pet. The pet's hypovolemia should be partially corrected over the first 2 hours, before the insulin is administered.

A separate intravenous cannula is usually necessary for the insulin infusion. The CRI insulin solution is prepared by adding 5 U of regular insulin to a 500 mL bottle of 0.9% saline or lactated Ringer's solution to make up a solution that provides 0.01 U of insulin per milliliter. The infusion is delivered by an automatic injection syringe, an intravenous infusion pump, or a pediatric intravenous infusion set to deliver a therapeutic insulin dose of 0.1 U/kg BW/hour. To prevent binding of insulin to the intravenous lines, some clinicians prefer to run some of the diluted insulin infusion through the line before attaching it to the patient. Before this slow infusion is begun, the patient can receive an initial intravenous insulin bolus at a dosage of 0.1 U/kg. To avoid any complicating osmotic disequilibrium effects on the brain, the rate of decline in the blood glucose level should not exceed 75 to 100 mg/dL/hour. When the blood glucose level has declined to 250 mg/dL, after several hours of the CRI insulin infusion, the rate should be decreased to half the initial amount (i.e., 0.05 U/kg/hour), and dextrose should be added to the intravenous fluid to achieve a 2.5% to 5% dextrose concentration. The blood glucose level subsequently should be determined every 2 hours, using glucose oxidase reagent strips or a reflectance meter. Thereafter the rate of insulin infusion should be adjusted to maintain a blood glucose range of 150 to 250 mg/dL to avert hypoglycemia.

The disadvantages of the CRI insulin administration technique are the frequent need for a separate intravenous cannula, intensive care monitoring, and frequent monitoring of the blood glucose and serum potassium concentrations. If the patient initially is hypokalemic, the clinician can begin treatment with isotonic fluids containing added potassium chloride and delay insulin treatment for the first 4 to 8 hours.

Low doses of regular insulin also can be given intramuscularly. Initially, 2 U are injected into the thigh muscles of cats and dogs weighing less than 10 kg. For dogs weighing more than 10 kg, the initial dose is 0.25 U/kg BW. Subsequent hourly injections of 1 U for cats and small dogs and 0.1 U/kg BW for larger dogs are given until the blood glucose level is less than 250 mg/dL, at which time the subcutaneous route can be used to administer the insulin every 6 hours or as needed. The low doses used in this technique can be accurately measured with a special low-dose calibrated syringe.

Subcutaneous administration of regular insulin is a suitable alternative to the intravenous and intramuscular methods when intensive care monitoring is unavailable and when the patient is alert and normotensive. The initial dose is 0.5 U/kg BW, with subsequent doses given every 6 to 10 hours, depending on the need.

The patient is regarded as stable when normal hydration has been restored, blood glucose levels are below 250 mg/dL, serum and urine ketones are minimal to absent, and eating resumes. Subsequent insulin treatment can be changed to the intermediate-acting or the ultra-long-acting type.

115.5 COMPLICATIONS

The main complications of insulin treatment include hypo-glycemia, hypokalemia, cerebral edema, metabolic alkalosis, and paradoxical cerebrospinal fluid acidosis. Most of these problems are avoidable with meticulous medical management geared toward avoiding overtreatment of the patient.

115.6 HYPERGLYCEMIC HYPEROSMOLAR SYNDROME

The hyperglycemic hyperosmolar syndrome (HHS) is characterized by extreme dehydration, renal dysfunction, abnormal brain function, marked hyperglycemia, and the lack of significant ketoacidosis. The incidence of this disorder in the dog and cat has not been reported; however, isolated case reports can be found in the veterinary literature spanning the past 25 to 30 years. Underlying renal disease and a precipitating condition, such as an infection or pancreatitis, can often be found.

115.7 PATHOPHYSIOLOGY

Only the main pathophysiologic mechanisms are covered in this section. The development of HHS is attributed to three main factors: (1) decreased insulin utilization and glucose transport, (2) increased hepatic gluconeogenesis and glycogenolysis, and (3) impaired renal excretion of glucose.

Two concepts have been advanced to reasonably explain the pathophysiology of HHS. The first suggests that an insulinized liver (reflecting residual beta cell secretory activity) coexists with a diabetic periphery, resulting in inactivation of intrahepatic oxidation of incoming free fatty acids, which are directed largely along nonketogenic metabolic pathways, such as triglyceride synthesis. This could account for the absence of hyperketonemia. The second proposal suggests that enhanced gluconeogenesis occurs in the liver due to the prevailing elevated portal vein ratio of glucagon to insulin. This effect, accompanied by severe dehydration (greater than 8%), is mainly responsible for the development of marked hyperglycemia.

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The decrease in consciousness and the onset of the associated neurologic abnormalities that characterize HHS result from the direct effects of hyperosmolarity-induced dehydration on the brain parenchyma.

115.8 DIAGNOSTIC EVALUATION

Several clinicopathologic abnormalities characterize the HHS. The blood glucose levels are often elevated above 800 mg/dL. Serum osmolality is elevated (normal serum osmolality is 290 to 310 mOsm/kg body water) and can be determined by the freezing point depression method with an osmometer, or it can be calculated using the following formula:

$$sOsm = 2\left(Na^{+} + K^{+}\right) + \frac{Glu}{18} + \frac{BUN}{2.8}$$

where Na^{+} is serum sodium, K^{+} is serum potassium, Glu is serum glucose, and BUN is blood urea nitrogen.

Most patients are azotemic, a condition that may be renal or prerenal in origin. The disturbances in serum electrolyte concentrations were described in the DKA section, above. It should be noted that an elevated serum sodium level during severe hyperglycemia can be explained only by significant plasma volume contraction caused by large water losses associated with hypotonic urine excretion.

115.9 TREATMENT

The main treatment objectives with HHS include reestablishment of normal hydration and adequate urine output; judicious use of insulin to avoid a precipitous decline in blood glucose levels; and ample potassium supplementation to make up the total body potassium deficit. Treatment techniques were described in the previous

section. The regular insulin dosage requirements for the hyperglycemic hyperosmolar diabetic are oftentimes less than those needed to treat diabetic ketoacidosis, but the technique for delivery is the same.

The diabetic ketoacidotic and hyperglycemic hyperosmolar syndromes pose noteworthy challenges to the practicing clinician. A sound understanding of the underlying pathophysiology, along with logical and timely therapeutic intervention, can usually lead to a remarkably optimistic outcome.

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116 CHAPTER • 116 Gastrointestinal Emergencies

Elke Rudloff

Rebecca Kirby

Shock, dehydration, collapse, acute pain, electrolyte imbalances, respiratory distress, and cardiac arrhythmias are potential life-threatening consequences of gastrointestinal (GI) emergencies. The history, physical examination findings, and clinical signs attributed to the GI tract (e.g., vomiting, diarrhea, abdominal pain or distention) direct the investigation for either primary GI disease or pathology in other organs that manifests with GI signs.

Primary pathology involving the GI tract (i.e., the esophagus, stomach, small intestines, large intestines, cecum, rectum, and/or anus) can be a result of distention, inflammation, obstruction, hypoxia, and/or ischemia of affected GI tissues (Table 116-1).

Inflammatory mediators are released locally, causing local arteriolar and venous dilatation and increased capillary permeability. Severe inflammation results in loss of blood, fluids, electrolytes, and proteins from the capillaries into the GI tract (third body fluid spacing). Distension or inflammation of the GI tract can cause peripheral receptor stimulation of the vomiting center in the brain stem (Figure 116-1). Alterations in GI motility, secretory function, or permeability can result in diarrhea. Further increased vagal tone, aspiration pneumonia, bacterial translocation, and malnutrition are life-threatening consequences of vomiting and diarrhea.

Gastrointestinal signs can occur secondary to disease of other organs or to systemic diseases (see Table 116-1). Stimulation of receptors associated with the vomiting center and chemoreceptor trigger zone, as well as stimulation of peripheral GI receptors, can be caused by other organ inflammation or distention, circulating and ingested drugs or toxins, and central nervous system pathology (see Figure 116-1). Alterations in nerve conduction and smooth muscle action as a result of toxins and electrolyte or acid-base imbalances may also affect GI function.

The systemic consequences of vomiting and diarrhea are similar whether the cause is a primary or a secondary GI emergency. The animal must be rapidly assessed for life-threatening complications (primary survey) and rapidly resuscitated. Once the patient has been stabilized, diagnostic tests are performed to determine the underlying cause. One of the key immediate diagnostic goals is to determine whether the underlying pathology requires emergency surgical intervention. Careful monitoring is required during treatment and recovery.

116.1 PRIMARY SURVEY

The primary survey is a rapid evaluation of the patient's history and physical parameters to detect life-threatening complications that require immediate attention. The history may reveal evidence of vomiting, diarrhea, abdominal pain or distension, collapse, or respiratory distress. Airway, breathing, and circulation are rapidly assessed. Upper airway obstruction from aspiration of gastric contents can manifest with labored, loud breathing, heard without the aid of a stethoscope, and cyanosis. When aspiration pneumonia causes lung parenchymal pathology, physical evidence of a labored, synchronous breathing pattern with moist or harsh lung sounds may be heard on lung auscultation.

Figure 116-1 Vomiting Reflex and Antiemetics. Receptors located in the vomiting center and chemoreceptor-trigger zone (CRTZ) in the brain stem can be triggered by sensory and chemical input from multiple sources. Targeting the different neurotransmitters is the basis of anti-emetic therapy. Specific anti-emetic therapy should be selected based on the most likely mechanism initiating the stimulus to vomit. a-D_2 Dopaminergic antagonist Metoclopromide (0.2-0.4 mg/kg SQ q6-8h or followed by a 1.0-2.0 mg/kg/day IV by constant rate infusion) b-5-HT_3 Serotoninergic antagonists Ondansetron (0.1-0.2 SQ q8h, or 0.5 mg IV load then 0.5 mg/kg/hr constant rate infusion) Anzemet (0.6 mg/kg q8-12h) Metoclopramide (0.2-0.4 mg/kg SQ q6-8h or followed by a 1.0-2.0 mg/kg/day IV by constant rate infusion) c-M_1 muscarinic cholinergic antagonists Chlorpromazine (0.01-0.025 mg/kg IV (cats) q4-6h in cardiovascularly stable) Ranitidine (2 mg/kg IV q12h) d-H1/2 Histaminergic antagonist Meclizine (25 mg/kg q24h) e-Opioids Butorphanol (0.2-0.4 mg/kg IV load then 0.05-0.1 mg/kg/h by constant rate infusion) f-α_2-adrenergic antagonists Chlorpromazine (0.05 mg/kg IV (dogs) and 0.01-0.025 mg/kg IV (cats) q4-6h in cardiovascularly stable) Prochlorperazine (0.05-0.25 IV mg/kg q6-8h) g-5-HT_{1A} Serotoninergic antagonist Ondansetron (0.1-0.2 SQ q8h, or 0.5 mg IV load then 0.5 mg/kg/hr constant rate infusion) Anzemet (0.6 mg/kg q8-212h) Metoclopramide (0.2-0.4 mg/kg SQ q6-8h or followed by a 1.0-2.0 mg/kg/day IV by constant rate infusion) h-Gastrointestinal motility enhancers: 5-HT_4 serotoninergic agonists Metoclopramide (0.2-0.4 mg/kg SQ q6-8h or followed by a 1.0-2.0 mg/kg/day IV by constant rate infusion) Cisapride (0.1-0.5 mg/kg PO q8-12h (dog) 0.5-1 mg/kg PO q8h (cat)) i-Motilin agonists Erythromycin (0.5-1 mg/kg PO/IV q8h (dog)) j-Nasogastric or gastrostomy tube suctioning

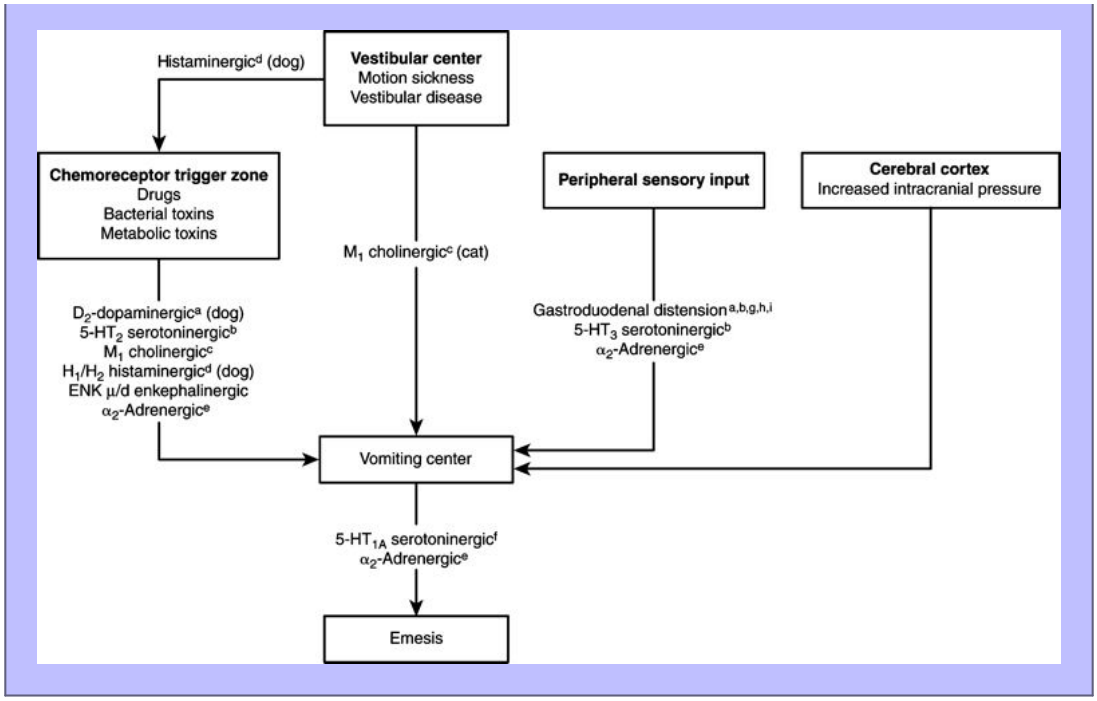

Table • 116-1 Causes of Gastrointestinal Emergencies

PRIMARY	SECONDARY
Gastrointestinal Obstruction	Organ dysfunction
Foreign body*	Pancreatic disease
Neoplasia*	Urinary tract disease
Pyloric hypertrophy	Hepatobiliary disease
Intestinal stricture*	Pyometra/metritis
Functional ileus	Adrenocortical insufficiency
Gastrointestinal inflammation	Diabetic ketoacidosis
Infection (bacterial, fungal, viral, protozoal)	Central nervous system disorder
Trauma	Increased intracranial pressure
Diffuse neoplasia	Meningoencephalitis
Adverse reaction to food	Vestibular disease
Inflammatory bowel disease	
Hemorrhagic gastroenteritis	**Systemic Disorders**
Drugs/toxins	Electrolyte disorders
Ulcerative disease*	Acid-base disorders
Lymphangiectasia	Peritonitis
	Toxemia/sepsis
Gastrointestinal Hypoxia/Ischemia	
Gastric dilatation-volvulus*	**Toxin/Drug Reaction**
Mesenteric torsion*	
Intestinal volvulus*	
Intussusception*	
Mesenteric thromboembolic disease*	

* May require requires emergency surgical intervention for correction.

Poor perfusion can result from rapid fluid loss, organ hypoxia, and endotoxemia; it is evidenced by pale mucous membranes, a prolonged capillary refill time, poor pulse quality, and tachycardia (in the dog). Dehydration is detected by dry mucous membranes, increased skin tenting and, when severe, dry corneas. An altered level of consciousness or the presence of an arrhythmia can suggest electrolyte and/or acid-base imbalances, hypoglycemia, circulating toxins, or hypoxia. Bradycardia may be a result of excessive vagal stimulation or late-stage decompensatory shock. Abdominal pain or distension or a fluid wave alerts the clinician to shock, dehydration, and serious primary GI pathology.

116.2 RESUSCITATION

Life-threatening problems are immediately resuscitated prior to further diagnostics. Any breathing abnormalities warrant flow-by oxygen administration. An intravenous catheter is placed, and analgesia is provided if pain is present. If upper airway obstruction is evident, the oropharynx is suctioned, an airway is established and oxygenation and ventilation are provided. Poor perfusion and dehydration are treated with fluid therapy, specifically crystalloid (balanced isotonic type, 10 to 20 mL/kg given intravenously) and colloid (hetastarch, 5 mL/kg given intravenously) in increments to effect. If a gastric dilatation-volvulus is suspected, careful percutaneous decompression of the stomach is recommended during fluid resuscitation to relieve pain and reduce pressure on the diaphragm and vena cava. Depressed consciousness due to hypoglycemia is treated with dextrose (0.5 g/kg given intravenously). Life-threatening bradycardia is treated with atropine (0.02 mg/kg given intravenously) and warrants rapid assessment of the serum potassium level.

116.3 SECONDARY SURVEY

Once the patient's condition has been stabilized, information is obtained from a more thorough history and physical examination to determine the origin of the GI signs. Historical information should be obtained regarding the vaccination and internal parasite history, recent or chronic administration of medications (e.g., nonsteroidal or steroidal anti-inflammatory agents); changes in appetite; sudden changes or excessive fat content in the diet; access to garbage, bones, or moldy food; and the availability of string, foreign bodies, toys and balls, corncobs, socks, and other small items or toxins. Vomiting is differentiated from regurgitation. Nonproductive vomiting or retching may indicate the presence of a gastric dilatation-volvulus. Vomiting and/or diarrhea should be characterized with respect to color, consistency, and frequency (Table 116-2).

The rectal temperature can reveal fever associated with inflammation or hypothermia from poor perfusion. Digital examination demonstrates the consistency of the stool. Careful abdominal palpation can detect abdominal pathology associated with organ distension, thickening, masses, foreign body (FB), free fluid, or fluid in the bowel. Physical signs that increase the possibility of emergency surgical intervention include: gas distention of the stomach or bowel; nonresponsive shock with evidence of intra-abdominal pathology; progressive abdominal distension; palpation of intestinal plication or a painful mass or FB; and persistent, severe vomiting unresponsive to therapeutic intervention.

116.4 TESTS

Blood, urine, and fecal samples are collected and evaluated. An immediate data base (packed cell volume, total protein, blood glucose, electrolyte panel, acid-base panel, blood urea nitrogen, platelet estimate, and activated clotting time) may be useful in detecting the presence of hemorrhage, a coagulopathy, protein depletion, hypoglycemia (supporting sepsis), hypoxemia, or a gastric outflow obstruction (hypochloremia with a metabolic alkalosis). In addition, a complete blood count, serum biochemistry profile (including amylase and lipase),

microscopic fecal examination, parvoviral fecal antigen test (when indicated), fecal cultures, urinalysis, and coagulation profile may aid in the determination of the underlying cause and whether secondary complications or additional organ dysfunction exists. Hyperphosphatemia is not unexpected with intestinal ischemia or severe inflammation. Specific diagnostic tests to identify secondary GI disease are performed as indicated (e.g., adrenocorticotropic hormone [ACTH] stimulation, preprandial and postprandial bile acids).

Two-view abdominal radiography (Table 116-3), as well as abdominal ultrasonography, may help identify the cause of the GI signs. A lateral thoracic radiograph may show a gas-dilated esophagus indicative of megaesophagus. When the pathology is likely intra-abdominal and the definitive cause cannot be determined by radiographs or ultrasound, abdominal paracentesis and/or diagnostic peritoneal lavage are indicated (see Chapter 72). Emergency surgical intervention becomes part of the diagnostic and therapeutic plan when primary GI pathology is suspected to be associated with ischemia, severe ongoing hemorrhage, or sepsis or when a diagnosis is lacking in a dog or cat whose condition is deteriorating.

116.5 MEDICAL INTERVENTION

Fluid therapy is adjusted to meet ongoing fluid, electrolyte, and acid-base abnormalities. Definitive treatment of the underlying pathology is initiated as soon as possible. When GI integrity is compromised, injectable antibiotics are administered against gram-positive, gram-negative, and anaerobic bacteria that translocate from the bowel into the bloodstream. Cefazolin (20 mg/kg given intravenously [IV] every 8 hours), in addition to metronidazole (10 mg/kg given via slow IV every 8 hours), can provide broad-spectrum coverage. Signs of pain are treated with opioid drugs (for mild pain: butorphanol, 0.4 mg/kg given intravenously, followed by a constantrate infusion of 0.1 mg/kg/hour; for moderate pain: hydromorphone, 0.1 to 0.2 mg/kg given intravenously every 4 to 6 hours). Analgesia can be augmented with concurrent administration of antianxiolytic and sedative medication (e.g., diazepam, 0.5 mg/kg given intravenously).

The selection of antiemetic agents is based on the likely mechanisms of vomiting (see Figure 116-1). Motility inhibitors (e.g., centrine) are not used as antiemetics/antidiarrheals because they reduce GI motility, which allows toxins to accumulate, and they affect nutrient delivery and absorption. A nasogastric tube allows for continued gastric decompression, cold water lavage for severe intragastric hemorrhage, and trickle flow feeding of the gastric mucosa. Promotility agents are administered only after GI obstruction has been ruled out.

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When esophageal or gastric ulceration is suspected, H_2-blockers (cimetidine, 4 mg/kg given intravenously every 6 to 8 hours, or ranitidine, 2 to 2.5 mg/kg given every 12 hours IV) or H-pump inhibitors (omeprazole, 0.7 mg/kg up to 20 mg given orally every 24 hours) are administered to reduce acid secretion and reflux and promote mucosal healing. Liquid sucralfate (0.5 to 1 g given orally every 4 to 8 hours) is administered to protect the area of ulceration once vomiting has been controlled.

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Table • 116-2 Character and Origin of Vomiting and Diarrhea

CHARACTER OF VOMIT OR VOMITING EPISODE	LESION	DIFFERENTIAL CAUSES
Occurs shortly after eating	Gastric inflammation	Gastric ulceration
	Gastric obstruction	Foreign body (FB)
		Toxin ingestion
		Infection
Large amounts of undigested food up to 6 hours postprandial	True vomiting: Pyloric outflow obstruction	Pyloric hypertrophy
		Pyloric mass
	Gastric atony	Foreign body
		Electrolyte imbalance
		Megaesophagus
	Regurgitation: Esophageal outflow obstruction	Esophagitis
		Esophageal FB/mass/stricture
		Persistent right aortic arch
		Hiatal hernia
Projectile vomiting	Pyloric or upper duodenal outflow obstruction	Pyloric hypertrophy
	Upper duodenal ileus	Mass
		Foreign body
		Pancreatitis
		Infiltrative bowel disease
Blood in vomit in the absence of nasal or oral disease	Esophageal hemorrhage	Ulceration
	Gastric hemorrhage	Coagulopathy
Streaks of blood	Duodenal hemorrhage	Severe inflammation
	Gastric mucosal damage	Persistent vomiting
White or mucoid fluid	Gastric fluid	Gastritis
	Swallowed saliva from true regurgitation	Megaesophagus
		Esophagitis
		Gastric dilatation-volvulus
		Gastric outflow obstruction
Yellow	Gastric fluid	Gastritis
		Foreign body
Green	Upper duodenum	Duodenal ileus/obstruction
Fetid brown fluid	Lower duodenum	Pancreatitis
	Jejunum	Intestinal obstruction
CHARACTER OF DIARRHEA	**LESIONS**	**DIFFERENTIAL CAUSES**
Watery	Small bowel inflammation	Infectious disease
		Partial small intestinal obstruction
		Pancreatitis
		Toxin/drug reaction
Mucoid	Large bowel inflammation	Infectious disease
		Partial large intestinal obstruction
		Toxin/drug reaction
Presence of digested blood (black stool) in the absence of nasal or oral disease	Esophageal hemorrhage	Ulceration
	Gastric hemorrhage	Coagulopathy
	Small bowel hemorrhage	Severe inflammation
		Ischemia

Presence of frank (bright red) blood	Large bowel hemorrhage	Ulceration Coagulopathy Severe inflammation Ischemia

Table • 116-3 Radiographic Changes Noted During Gastrointestinal Emergencies

RADIOGRAPHIC CHANGE	INDICATION	CAUSE
Generalized loss of radiographic detail	Intra-abdominal fluid	Ascites Peritonitis Hemorrhage
Diffuse gas dilatation of the small and large intestines	Ileus	Enteritis Mesenteric volvulus
Severe segmental gas dilatation of the small intestine	Obstruction	Foreign body Mass Mesenteric volvulus
Intestinal bunching, plication, “string of pearls”		Intussusception Linear foreign body
Severe segmental gas dilatation of the large intestine +/−colonic displacement	Colonic obstruction	Colonic torsion
Severe gas dilatation of the stomach without pyloric displacement	Gastric outflow obstruction	Foreign body Pyloric mass Pyloric hypertrophy Motility disorder
with pyloric displacement		Gastric dilatation-volvulus
Free intra-abdominal gas	Gastrointestinal (GI) rupture	Rupture of GI tract
	Infection	Growth of gas-forming bacteria Abdominal wall perforation
Radio-opacities involving the GI tract	Foreign body Mass lesion	Foreign body Neoplasia
Duodenal loop sign or loss of contrast in right upper abdominal quadrant	Duodenal ileus Focal inflammation	Pancreatitis

116.6 SURGICAL INTERVENTION

When emergency surgery is indicated, rapid stabilization of perfusion and hydration is optimal prior to anesthetic induction. However, stabilization may be difficult to achieve with significant ongoing large-volume fluid loss, organ ischemia (gastric or intestinal volvulus/torsion, intussusception, necrosis), or uncontrollable hemorrhage. Rapid induction of anesthesia using injectable anesthetics is recommended, because ventilation capabilities may be impaired with significant abdominal distension, aspiration pneumonia, or analgesic medication. Oropharyngeal and esophageal suctioning may be required if gastric fluid has refluxed.

Surgical intervention for acute GI emergencies may require the use of specific equipment and access to a GI stapling device to reduce the surgical time. Clinicians are referred to surgical texts for detailed surgical techniques for specific GI problems.

Gastric dilatation-volvulus requires decompression, derotation, and gastropexy. Gastric necrosis requires resection of compromised tissue. If a gastric FB is palpated or gastric ulcers are present, a gastrotomy is performed.

Ulcerative mucosal lesions are resected and submitted for histopathologic evaluation. When a GI foreign body is present, an attempt can be made to gently pull it from the intestines and out through the gastrotomy site. If resistance is felt, the FB is transected at the level of the pylorus and an attempt is made to massage the remaining FB through the intestines to the distal colon, where it can be removed by means of a digital rectal examination. When a linear FB is present, the gastric portion is cut and the remaining portion is sutured to a red rubber feeding tube, which can be massaged out through the colon. If the FB cannot be milked through the intestines into the distal colon, one or more enterotomies may be required to remove the object.

Ischemic or perforated bowel requires debridement or resection prior to closure. The most difficult regions requiring resection are the descending duodenal flexure (where the duodenum is fixed to the parietal peritoneum) and the ileocecal region (where various vascular supplies feed the region). When multiple ischemic sites in proximity are discovered, en bloc resection may prove more efficient and pose less risk of complications. Either simple interrupted or continuous closure can be performed, provided there is good apposition and minimal restriction of blood flow. GI stapling can also be used for rapid anastomosis.

Placement of a nasogastric, nasoesophageal, esophagostomy, gastric, or jejunal feeding tube is considered if injury to the GI tract is significant or if a prolonged time to voluntary oral nutrition (longer than 2 days) is expected. A gastrostomy tube can help maintain gastric decompression when motility disorders are present. When gastric or proximal intestinal tract dysfunction or procedures are a factor (e.g., pancreatitis, peritonitis, Billroth procedures), placement of a jejunostomy tube allows immediate initiation of enteral feeding. The intra-abdominal tubes are placed prior to closure. 432 433

When bowel or peritoneal perforation has occurred, a decision must be made regarding open abdominal drainage or the placement of drains. If the peritoneal wall and serosal surfaces appear only mildly hyperemic and the repair is considered curative, copious saline lavage and suctioning may be all that is required. If inflammation of the peritoneal wall or serosal surfaces is localized to the surgical site, placement of an abdominal suction drain in the affected area may be of benefit. Open abdominal drainage is indicated with generalized abdominal contamination or inflammation or when re-examination of the surgical sites is desired.

If there is no nonresectable pathology of any organ, multiple biopsies are obtained. Tissue samples should be obtained from the liver, stomach, duodenum, jejunum, and mesenteric lymph nodes. Fluid from the duodenum is evaluated for *Giardia* organisms. Samples of the spleen, pancreas, and kidney, as well as fluid from the gallbladder and urinary bladder, are taken for histopathologic evaluation and are cultured at the discretion of the surgeon. Intensive care and monitoring are required during medical and postoperative treatment of GI emergencies.

116.7 RECOVERY

An organized, systemic approach is required during the recovery phase of the GI emergency. The *Rule of 20* provides a check list of critical parameters that must be monitored and treated for an optimal outcome (Box 116-1).

116.7.1 Box • 116-1 Rule of 20

Monitoring and treatment of the following critical parameters help ensure the best outcome for the recovery phase of a gastrointestinal emergency.

Fluid balance

Colloid osmotic pressure

Serum albumin

Blood pressure

Heart rate and rhythm

Electrolytes and acid/base balance

Oxygenation and ventilation

White blood cell count, immunity and antibiotic therapy

Red blood cell and hemoglobin concentration

Mentation

Drug dosages and interactions

Liver function and drug metabolism

GI motility and integrity

Nutrition

Renal function

Coagulation

Wound care

Nursing care

Body temperature

Pain control

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117 CHAPTER • 117 Global Approach to the Trauma Patient

Kenneth J. Drobatz

***T**rauma* is defined as a "wound or injury" caused by numerous "accidents." The severity may range from mild to fatal. Trauma may affect only one organ system or multiple organ systems, either directly or indirectly. Therefore a global and thorough approach is required to improve survival and decrease morbidity in traumatized dogs and cats. The initial approach to the critically ill trauma patient often makes the difference in the eventual outcome. The veterinary staff should be well versed in the evaluation and therapy of a traumatized pet. The initial trauma assessment involves a primary survey that includes assessment of tissue oxygen delivery (respiratory and cardiovascular systems), the central nervous system, and the urinary system. The primary survey is followed by a secondary survey that involves a complete examination of all other systems.

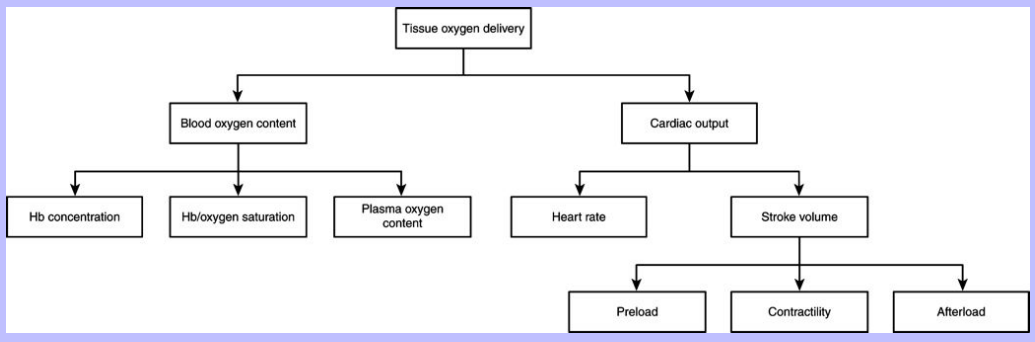
117.1 PRIMARY SURVEY

The first goal with a critically injured trauma patient is to optimize oxygen delivery to the tissues. All assessments and therapeutics are oriented toward this goal in the initial approach and resuscitation. Emphasis on early detection and aggressive reversal of impaired tissue perfusion or oxygen delivery improves survival and minimizes multiorgan dysfunction. Oxygen delivery depends on the blood oxygen content and tissue perfusion (Figure 117-1).

117.2 BLOOD OXYGEN CONTENT

Maintaining oxygen saturation of hemoglobin through assessment and treatment of respiratory abnormalities is one of the first goals of the critical care team in maintaining oxygen delivery. Pale, cyanotic, or gray mucous membranes; signs of respiratory distress, such as increased respiratory rate and effort, extended head and neck, and open mouth breathing; and loud upper airway sounds and abnormal or diminished breath sounds on auscultation are all potential indicators of inadequate oxygen saturation of hemoglobin. More objective assessments of the oxygenation of blood include pulse oximetry and arterial blood gas analysis. Initially, supplemental oxygen should be provided to any critically ill traumatized animal until it is proved that oxygen supplementation is not necessary.

Figure 117-1 Determinants of tissue oxygen delivery.

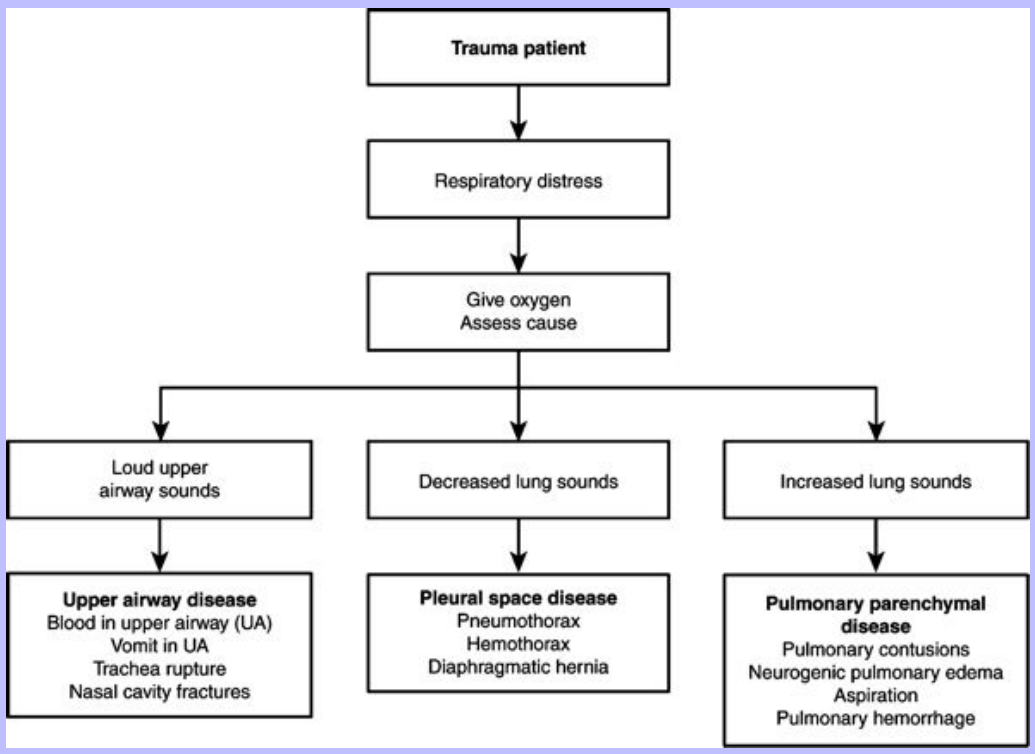


A variety of conditions associated with trauma can result in respiratory distress and decreased oxygenation of hemoglobin (Figure 117-2; also see Thoracic Trauma; Chapter 126), but the most common are pneumothorax and pulmonary contusions. In animals suspected of having pleural space disease (decreased lung sounds with signs of respiratory distress), thoracocentesis should be performed even before thoracic radiographs are taken. If done correctly, the benefits far outweigh the risks (see Thoracic and Pericardial Taps and Drains). Tension pneumothorax is rare but is an acute, life-threatening pleural space abnormality. It is characterized by extreme respiratory distress, poor tissue perfusion and, rarely, a "barrel chest" appearance. Rapid thoracocentesis is immediately indicated. A small incision in the intercostal space may release the air more quickly in animals in whom death or collapse is imminent.

Increased bronchovesicular sounds in a traumatized animal are commonly a result of pulmonary contusions. Pulmonary contusions often worsen before they improve. Intravenous fluid therapy for other conditions should be given with caution in these dogs and cats. There is no specific therapy for pulmonary contusions. Supportive care, with oxygen supplementation and pain relief, is the mainstay of treatment. Most dogs and cats with pulmonary contusions begin to improve 24 to 36 hours after the initial insult (see Thoracic Trauma; Chapter 126).

Other respiratory conditions include open chest wounds, flail chest, and rib fractures. The open chest wound should be covered and sealed as soon as possible. Once that has been done, the closed pneumothorax should be resolved by thoracocentesis. Treatment of an animal with a flail chest or rib fractures primarily involves oxygen supplementation and pain management. Surgical repair is rarely necessary.

Figure 117-2 Causes of respiratory distress in a trauma patient.



Neurogenic pulmonary edema occurs rarely but is most often associated with severe head trauma. The pulmonary edema can range from mild to severe enough to require mechanical ventilation. Most of these cases are managed successfully with supportive care, such as oxygen supplementation and judicious diuretic therapy. Generally, respiratory problems in animals with neurogenic pulmonary edema caused by head trauma improve substantially within 48 hours, or the animal dies of severe respiratory compromise.

An adequate amount of hemoglobin in the vascular space is essential to maintenance of tissue oxygen delivery. A decreased hemoglobin content severely limits the oxygen-carrying capacity of the blood and can contribute to decreased tissue oxygen delivery. The packed cell volume (PCV) provides the most rapid estimate of the hemoglobin concentration in a traumatized dog or cat, but it should be interpreted in conjunction with assessment of the vascular volume status (see Tissue Perfusion, below) to get a complete assessment of the total hemoglobin content of the vascular space. Acute blood loss often is not reflected by the initial PCV measurement because of splenic contraction in the dog and the length of time it takes for interstitial fluid to shift into the vascular space to dilute the PCV. Initial total solids (TS) and serial measurements of the PCV and TS as intravenous fluid is administered are more sensitive indicators of acute blood loss. There is no specific PCV at or below which transfusion is required. Transfusion therapy should be based on whether the animal is affected by the decreased hemoglobin content, which is indicated by clinical signs such as pale mucous membranes, tachycardia, tachypnea, bounding or weak pulses, depressed mentation, or cardiac arrhythmias. As with any animal in critical condition, it is best to anticipate and treat problems before they cause physiologic compromise. For example, if the PCV is dropping rapidly, it is best to start a blood transfusion or administer hemoglobin solutions before the hemoglobin content drops to a life-threatening level.

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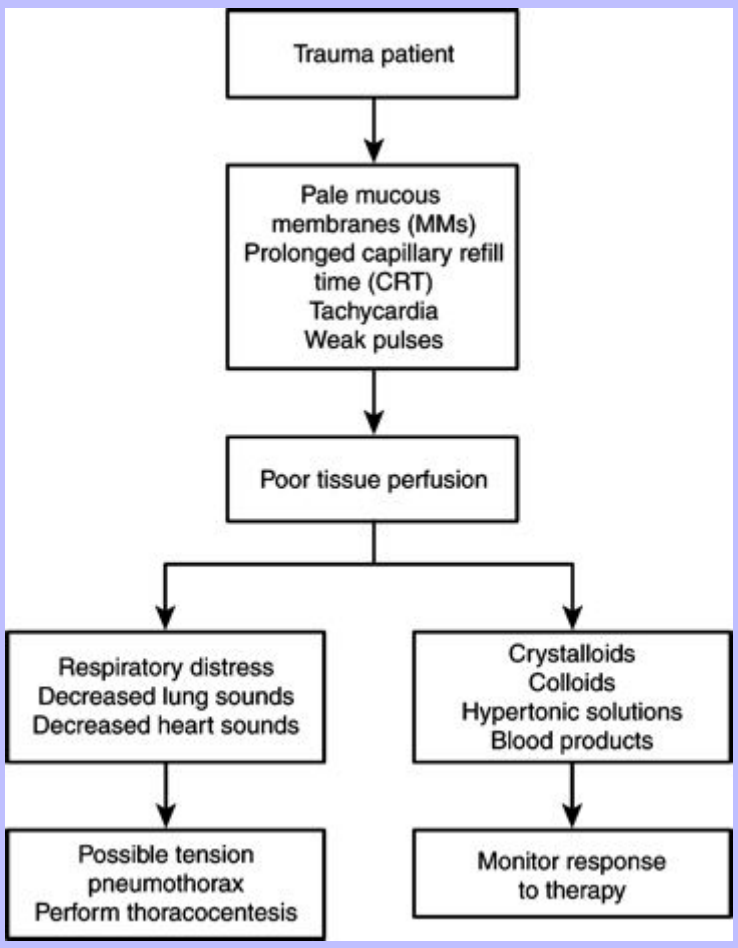
117.3 TISSUE PERFUSION

Physical assessments of tissue perfusion on the first examination include mucous membrane color, capillary refill time, and pulse rate and quality (Figure 117-3). The arterial blood pressure should be measured directly or indirectly by Doppler or oscillometric techniques when possible. The most common clinical signs indicative of poor tissue perfusion are pale or gray mucous membranes, a prolonged capillary refill time, a rapid heart rate, and weak pulses. The most common cause of poor tissue perfusion after a traumatic event is hypovolemia secondary to hemorrhage.

Administration of a balanced electrolyte solution at a rate of 90 mL/kg body weight/hour in the dog (40 to 60 mL/kg body weight/hour in the cat) is indicated with physical evidence of poor tissue perfusion. Two separate, large-bore, intravenous catheters may be required in large dogs (i.e., body weight exceeding 20 to 30 kg). Mucous membrane color, capillary refill time, pulse quality, heart rate, and blood pressure (if available) should be assessed continuously and the intravenous fluid rate adjusted as perfusion parameters improve or worsen. In most uncomplicated situations, improvement in tissue perfusion often is seen by the time one half of a vascular volume of fluid (45 mL/kg in the dog, 20 to 30 mL/kg in the cat) has been administered.

If clinical perfusion parameters or the blood pressure has not significantly improved after this volume of fluid has been administered, an investigation into causes of nonresponsive cardiovascular shock should be pursued. Such causes include ongoing intravascular volume loss (most commonly due to ongoing hemorrhage) or, less commonly, cardiogenic causes, such as arrhythmias, pericardial effusion, myocardial depression or failure, electrolyte abnormalities, decreased venous return (e.g., tension pneumothorax), or ischemic organs. The most common location of substantial hemorrhage that can lead to hypovolemia is the peritoneal space. Less common locations are the pleural space and retroperitoneal space, external hemorrhage, and hemorrhage into the muscles surrounding the femur.

Figure 117-3 Assessment of tissue perfusion.



Abdominal binding may help control ongoing intra-abdominal hemorrhage (see Abdominal Trauma). However, this is no substitute for adequate intravascular volume supplementation. In human beings, some physicians advocate delayed resuscitation (see Abdominal Trauma). In animals with severe hemorrhage, the fluid of choice is whole blood, packed red blood cells and plasma, hemoglobin substitutes (e.g., Oxyglobin), and/or colloid supplementation, such as hydroxyethyl starch or dextran 70 (see Crystalloid and Colloid Therapy; Chapter 114). Hypertonic solutions can be considered after head trauma if the dog or cat is hypovolemic (see Traumatic Brain Injury; Chapter 113) or if the animal is in severe hypovolemic shock and may die before an adequate amount of balanced electrolyte solution can be administered (see Chapter 124).

Traumatized animals are physiologically dynamic and should be continuously monitored until physiologic parameters are stable. Close monitoring of cardiovascular and respiratory trends allows early detection of problems, before they become life-threatening.

117.4 CENTRAL NERVOUS SYSTEM AND URINARY TRACT

The central nervous system (CNS) (brain and spinal cord) and the renal system are two other organ systems that should be assessed and supported as priorities. Compromise of either of these systems can result in irreversible damage. After the initial assessment and treatment of the cardiovascular and respiratory systems, it is important that the clinician do a thorough neurologic examination, including assessment of mentation and of cranial nerve and spinal cord function, to establish a baseline for further monitoring and potential therapy. Brain dysfunction may be a result of poor oxygen delivery to the brain, direct brain tissue damage, intracranial hemorrhage, cerebral edema, ischemia, and/or increased intracranial pressure. Therapeutic considerations with head trauma and brain dysfunction include optimization of tissue perfusion, administration of mannitol (0.5 g/kg given intravenously), mild elevation of the head (avoiding flexion of the neck and occlusion of the jugular veins), hyperventilation, and maintenance of oxygenation (see Traumatic Brain Injury; Chapter 113).

Spinal cord assessment should include thorough palpation of the spine and assessment of spinal function, including voluntary motor movement, conscious proprioception, ambulation, spinal reflexes, and pain sensation.

Assessment of neurologic function should always be evaluated in light of how well the central nervous system is perfused. In most animals, head trauma is obvious. However, those with severely compromised perfusion may have severely depressed mentation, as well as diminished pain sensation. The mentation and sensation abnormalities may normalize with correction of the poor tissue perfusion.

Manifestations of urinary tract injury or dysfunction may not be immediately evident and may not be detected until after several hours of continuous monitoring. Potential renal system abnormalities include direct kidney damage (e.g., contusions, hematomas, avulsion), ureteral rupture, bladder rupture, and urethral trauma. Any animal that has been traumatized may have experienced renal system trauma. Therefore serial assessment of the blood urea nitrogen, creatinine, and serum potassium levels, as well as of urine output, should be considered. It should be remembered that animals with a ruptured urinary bladder might still urinate. Ureteral rupture may result in urine accumulation in the retroperitoneal space, a situation in which abdominocentesis fails to obtain fluid. Abdominal radiographs, abdominal ultrasound scans, and intravenous contrast studies may be necessary to diagnose ureteral rupture. If free abdominal fluid is present, it should be analyzed for the creatinine and potassium concentrations, which should be compared to the concentrations in peripheral blood. If the fluid is urine, the creatinine and potassium concentrations are higher.

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117.5 SECONDARY SURVEY

After assessment of tissue oxygen delivery, CNS function, and renal function, a full physical examination should be performed. Limb function should be evaluated and should include palpation of the entire appendicular and axial skeletal system. The eyes and oropharyngeal area should be examined for evidence of trauma. The mouth should be manually opened and closed to assess for malocclusion, pain, or crepitus. A rectal examination should be performed, and attention should be paid to palpation of the pelvic canal for fractures or instability and evidence of blood in the rectum. The skin should be thoroughly examined for lacerations, abrasions, and bruising.

117.6 MONITORING

After the initial assessment, all the above systems should be monitored for at least 24 to 48 hours, despite how well the animal looks when first examined. In general, if problems are going to occur, they usually occur within this time frame. The intensity and duration of the monitoring should be proportional to the degree of compromise.

The owner should also be warned that rarely, complications may arise several days later. For example, clinical signs of a ruptured gallbladder are not often manifested until several days after the traumatic injury.

In summary, assessment of tissue oxygen delivery should be performed at presentation and treated appropriately. Assessment should also include the CNS and renal systems, as well as the musculoskeletal, cutaneous, and peripheral nervous systems. A global approach, with emphasis on the most life-threatening conditions first, optimizes the outcome.

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CHAPTER • 118 Heatstroke

Roger Gfeller

Heatstroke is a syndrome of cellular damage caused by a marked increase in body temperature with loss of thermoregulatory control. This potentially fatal syndrome occurs when heat production (high ambient temperature, metabolism) overwhelms normal heat dissipation mechanisms (conduction, convection, evaporation, and radiation). Heatstroke can result in damage to nearly every body system. The degree of injury is determined by the magnitude and duration of core temperature elevation. Direct thermal injury occurs at approximately 109°F (42.8°C), resulting in enzymatic alterations and denaturation of proteins. Systemic damage has been reported in patients with *sustained* temperatures as low as 105°F (40.6°C). On the other hand, literature reports at least one case of full recovery in a patient that had a core temperature of 115.7°F (46.5°C).

Most cases of heatstroke are reported during the time of year when ambient temperatures are high and pets are not acclimated. Predisposition to heatstroke may arise from environmental factors (high temperature, high humidity, lack of water, poor ventilation), medical factors (obesity, laryngeal paralysis, upper airway obstruction, concurrent heart disease, concurrent central nervous system disease, hyperthyroidism, seizures, lack of conditioning), and variable other factors (previous episodes of heatstroke, toxins, drugs, exertion). The most common cause of heatstroke in dogs is confinement in a closed automobile, in which ambient temperatures can reach dangerously high levels in minutes. Cats are commonly affected when they get trapped in clothes dryers.

Heatstroke affects almost all systems of the body. Acute renal failure is common; it can manifest as oliguric or polyuric renal failure and can be fatal. Oliguric renal failure causes acidemia, hypokalemia, inactivation of heparin, and possibly cerebral edema. These patients are prone to volume overload and electrolyte imbalances. Polyuric renal failure causes fluid and electrolyte loss. Protein loss accompanies polyuric renal failure if the glomerulus is damaged.

Disseminated intravascular coagulation (DIC) is very common in heatstroke and may appear early or late. Activation of coagulation and fibrinolysis occurs early and is profound and sustained in heatstroke. Liver dysfunction related to heatstroke results in loss of production of active coagulation proteins.

The cardiovascular system may be in a compensatory or hyperdynamic state (high cardiac output, low systemic vascular resistance) early in the course of heatstroke. With continued hyperthermia this state progresses to the hypodynamic state, in which signs of hypotension, hypoxemia, hypoperfusion, and hypovolemic shock are manifest. Cardiac myocyte necrosis rarely causes overt heart failure, but rather initiates arrhythmias up to 36 hours after the initial insult.

Central nervous system (CNS) injury can occur as a result of: direct thermal injury, respiratory alkalosis, thrombosis, or hypoperfusion from shock. DIC and hyperthermia lead to intraparenchymal hemorrhage that can result in seizures, thus sustaining hyperthermia. Complications of CNS injury include seizures, hypoventilation, coma, respiratory arrest, and cardiac arrest. CNS dysfunction and future episodes of heat stroke may be sequelae.

The gastrointestinal tract (GIT) is exquisitely sensitive to heatstroke. Direct thermal injury damages the gastrointestinal barrier. Hypoperfusion and hypoxemia result in necrosis, death, and sloughing of the mucosa, leading to bacterial translocation. Bacterial translocation can cause sepsis and systemic inflammatory response syndrome (SIRS). Mucosal ulceration and loss of the gastrointestinal barrier leads to hemorrhage into the GIT, fluid and protein losses, and electrolyte imbalances.

Direct thermal injury and hypoxemia from hypoperfusion also damage the liver. Liver dysfunction results in loss of protein synthesis, including albumin and several coagulation factors. Complications associated with liver failure can include hypoalbuminemia, hyperammonemia, coagulopathies, icterus, and hypoglycemia. Persistent hypoglycemia or hypoalbuminemia is associated with increased mortality. Damage to the monocyte-macrophage system of the liver may result in endotoxemia and sepsis, leading to SIRS.

Heatstroke damages the muscles of the body, especially if it is the result of excessive exertion (seizures, excessive exercise without adequate training). Widespread necrosis of muscle cells results in hyperkalemia, hypocalcemia, lactic acidosis, and rhabdomyolysis. Rhabdomyolysis results in systemic release of myoglobin, which is toxic to kidney cells. Fibrinolysis is initiated by release of thromboplastin from injured myocytes. Conditions associated with muscle damage include acute renal failure, cardiac arrhythmias, DIC, pain, and hypocalcemic tetany.

Acid-base and electrolyte balances are affected by heat-stroke. Initially animals pant, which does not increase alveolar ventilation and does not affect the acid-base balance. As the core temperature increases, panting gives way to hyperventilation, resulting in respiratory alkalemia. Respiratory alkalemia is associated with hypokalemia and hypophosphatemia. Later, respiratory alkalemia gives way to metabolic acidemia as shock induces lactic acidosis. Metabolic acidemia is associated with hyperkalemia, heparin inactivation, cardiac arrhythmias, loss of peripheral vascular tone and ongoing hypotension, and decreased myocardial contractility.

Clinical signs of heatstroke are related to the systems affected and the degree of injury to those systems. Early signs include panting, hypersalivation, tachycardia, hyperemic mucous membranes with shortened capillary refill time (CRT), bounding pulses, and increased blood pressure. The patient is often excited and hyperactive. The rectal temperature is often elevated.

Signs of shock become more pronounced as the syndrome progresses. The rectal temperature may be high, normal, or low. Tachycardia is common. The mucous membranes are pale and have a prolonged CRT. Blood pressure is often low. Tachypnea and hyperventilation are noted. Dehydration (often severe) is common. Hematemesis, hematochezia, and melena accompany injury to the GIT. The pupils are commonly dilated but may be miotic if the syndrome has caused CNS damage. Altered mentation and cortical blindness have been reported. Respiratory distress with or without cyanosis may be noted later in the syndrome. Generalized petechiation, evidence of thromboembolism, and/or hemorrhage can be seen as DIC progresses. Muscle tremors, seizures, collapse, and coma often precede cardiopulmonary arrest.

Laboratory findings are also variable and, again, depend on the systems affected and the severity of injury. The packed cell volume (PCV) is often high due to dehydration, but it may be low if significant blood loss through the GIT has occurred. Total solids are often high as a result of the acute dehydration but also may be low due to renal and/or gastrointestinal protein losses or fluid shifts due to increased vascular permeability. Leukocytosis is common, but severely affected patients can be leukopenic. Thrombocytopenia is common. Nucleated red cells are often seen in blood smears as a result of thermal damage to bone marrow.

Azotemia (elevated blood urea nitrogen and creatinine levels) is a common finding and may be prerenal or renal in origin. These values can increase over 24 to 48 hours as renal failure progresses. Hypoglycemia is common early in the syndrome. Persistent hypoglycemia is associated with a poor prognosis. Liver enzymes are elevated due to direct thermal damage and hypoperfusion of the liver. Cholestasis is common. Hyperbilirubinemia is associated with a poor prognosis. Rhabdomyolysis results in increased levels of serum creatine kinase and myoglobinemia.

Blood gas and electrolyte values are variable. Respiratory alkalosis as a result of hyperventilation and metabolic acidosis as a result of shock and lactic acid production are commonly found in a mixed acid-base disorder. Sodium

and potassium levels are normal, high, or low, depending on the degree of dehydration, the severity of muscle damage, and whether vomiting and/or diarrhea is present. The onset of renal failure also affects electrolyte levels.

Urinalysis may reveal tubular cell casts, proteinuria, glucosuria in the absence of hyperglycemia, and increased urine gamma glutyl transferase (GGT), all of which indicate renal damage. Myoglobinuria indicates muscle damage and rhabdomyolysis and can exacerbate tubular necrosis.

Coagulation tests often reveal prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT). Thrombocytopenia is common. Hypofibrinogenemia and elevated levels of fibrin degradation products (FDPs) are common. Test values for D-dimer are often increased, whereas antithrombin 3 levels are decreased.

Early, aggressive treatment of heat-related signs and proactive treatment protocols directed at the complications of heatstroke reduce patient morbidity and mortality (see Figure 118-1). The most important aspect of treatment is to lower the core temperature. The pet owner should be instructed to initiate cooling measures before and during transportation. Effective cooling measures include wetting the patient with cool or tepid water and enhancing evaporation by providing air movement around the patient. It is important to note that ice water or cold water results in cutaneous vasoconstriction and loss of heat dissipation. It is also uncomfortable for the patient and can initiate the shivering reflex, resulting in heat production. More aggressive cooling techniques, such as cold water (or saline) enemas or gastric (or peritoneal) lavage with cool fluids, have not been shown to be any more effective than cool water baths and provision of air movement. Application of isopropyl alcohol has been recommended, but cutaneous vasodilatation may lead to absorption and intoxication. This measure is no longer recommended.

Cooling measures should continue upon arrival at the hospital if the core temperature is greater than 104°F (40°C). If the core temperature is 104°F (40°C) or lower, cooling measures must be discontinued and the patient protected from hypothermia, which increases morbidity and mortality. The patient should be given supplemental oxygen by mask, flow-by, oxygen hood, or nasal catheter.

Intravenous fluids are often required in the treatment of heatstroke, but their use must be determined on a case by case basis. Early in heatstroke or in cases of hyperthermia related to seizures, tremors, or ineffective panting, fluid imbalances are minimal, and aggressive fluid therapy can lead to volume overload. In more advanced cases of heatstroke, the patient has relative and absolute fluid losses that result in hypovolemia and perfusion deficits. These patients need aggressive fluid therapy.

Depending on the aggressiveness of fluid therapy needed, one or two catheters are implanted. In the least severe cases, crystalloid fluids (lactated Ringer's solution, Normosol-R, Plasmalyte, normal saline) are administered rapidly until perfusion parameters improve. The fluids should be room temperature. The clinician must administer “enough” fluid but not “too much.” “Enough” improves mucous membrane color, capillary refill time, blood pressure, heart rate, pulse quality, and urine production. “Too much” causes dilutional anemia, hypoproteinemia, and edema formation, particularly pulmonary edema.

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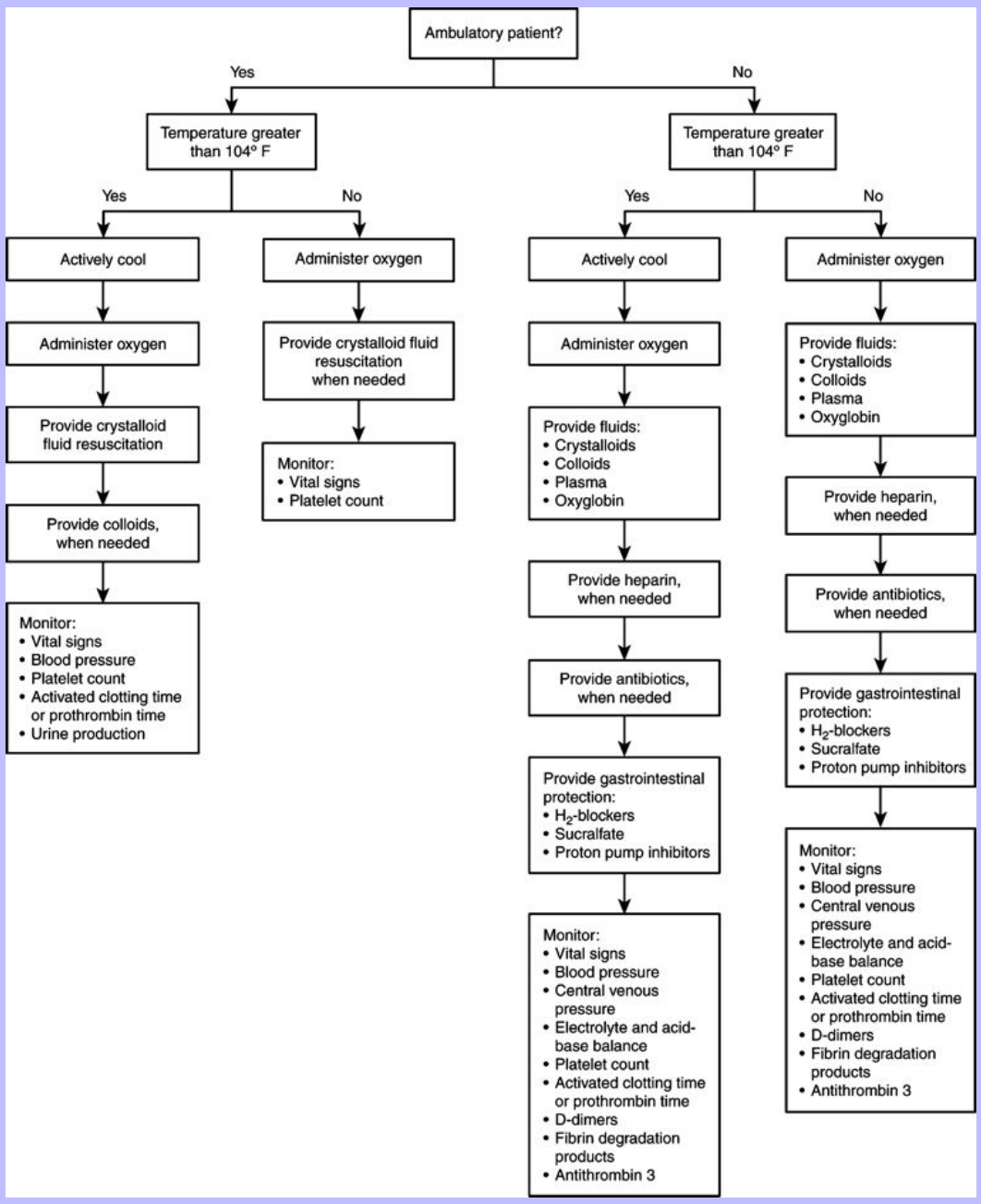
Figure 118-1 Treatment of heatstroke.



In more severe cases of heatstroke, a combination of crystalloid and colloid fluids (dextrans, hetastarch, pentastarch) is recommended. Again, fluids are administered rapidly to achieve targeted end-points. When colloids are used, the volume of crystalloid can be reduced by as much as 40% to 60%. Colloids expand the intravascular volume more

effectively than crystalloids and minimize fluid loss from the increased vascular permeability that often accompanies heatstroke.

Although not approved by the U.S. Food and Drug Administration for use in heatstroke, Oxyglobin (BioPure Corp., Cambridge, Massachusetts) has been reported to be of benefit. Oxyglobin is a potent colloid that carries oxygen and is effective in improving oxygen delivery. Because many heat-stroke patients suffer decreased oxygen delivery, Oxyglobin would seem to be an effective treatment modality. The manufacturer's recommended dosage is 10 to 30 mL/kg; however, it is likely more appropriate to administer it “as needed” to achieve specific hemodynamic end-points. Anecdotal reports indicate that the dosage is often not as high as the manufacturer's recommendations.

Vasculitis, increased capillary permeability, and DIC are common in heatstroke. These conditions require the use of fresh, fresh frozen, or frozen plasma. Because early diagnosis of these conditions is difficult, experts often recommend administration of plasma and advocate a proactive treatment protocol rather than a reactive one. The author's rule of thumb is: if the patient had to be carried into the hospital, plasma should be given. The dose of plasma is variable; 10 to 20 mL/kg can be used as a guideline.

Although controversial, heparin should be considered (50 to 250 U/kg given subcutaneously every 6 to 8 hours) when plasma is administered.

Use of corticosteroids (CCS) in heatstroke is controversial. When swelling and inflammation play a role (e.g., brachycephalic syndrome), use of these drugs likely is appropriate. Although CCS are said to stabilize membranes, suppress inflammation and cytokine production, and decrease the severity of endotoxemia, as well as have antipyretic properties, they are also known to worsen gastrointestinal ulceration and ischemic damage to the kidneys. Studies of the use of CCS have shown mixed results. The use of CCS is not routinely recommended, nor is it contraindicated if other appropriate therapy has been initiated. Nonsteroidal anti-inflammatory drugs are contraindicated.

Broad-spectrum antibiotic therapy is recommended. Combinations of ampicillin, amoxicillin, cefazolin, and enrofloxacin are acceptable in most cases. Aminoglycosides may be used only after renal function has been evaluated.

Sedatives (e.g., diazepam) are given to control seizures but must be used with caution. The use of sedatives often results in hypothermia. Intravenous dextrose is necessary in hypoglycemic patients. Gastrointestinal protectant drugs, such as sucralfate, famotidine or other H_2-blockers, and/or omeprazole, are recommended if signs of GIT inflammation or ulceration are present. Intense nursing care and vigilant monitoring are essential for successful treatment of heatstroke.

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119 CHAPTER • 119 Hepatic and Splenic Emergencies

David E. Holt

119.1 HEPATIC AND SPLENIC EMERGENCIES ASSOCIATED WITH HEMOPERITONEUM

Traumatic injury to the liver or spleen or rupture of splenic or hepatic masses can cause life-threatening intraperitoneal hemorrhage. Trauma to the liver and spleen is often associated with motor vehicle accidents, falls, and accidental or malicious blunt abdominal injuries, such as kicks. The most common nontraumatic cause of hemoperitoneum in dogs is rupture of splenic hemangiosarcomas. Hemorrhage from other vascular, intra-abdominal masses, including splenic hematomas and hepatic tumors, can also occur in dogs but is less common. Hemorrhage from hepatic and splenic neoplasms accounts for approximately half of feline nontraumatic hemoperitoneum cases.

Traumatized animals have often sustained severe injuries to several organs. A rapid initial examination that focuses on life-threatening injuries to the central nervous, respiratory, and cardiovascular systems should be performed. Common clinical findings in animals with traumatic hemoperitoneum include depressed mentation, pale mucous membranes, delayed capillary refill time, a rapid heart rate, and poor peripheral pulse quality. The abdomen may or may not be visibly distended. Animals with nontraumatic, bleeding splenic or hepatic masses show either acute collapse or more chronic problems, including lethargy, anorexia, weight loss, or vomiting that has acutely worsened. The physical examination findings associated with poor tissue perfusion are similar to those in animals with traumatic hemoperitoneum; however, a mass is often detected on abdominal palpation.

Intravenous (IV) access is mandatory in animals with either traumatic or nontraumatic hemoperitoneum. The veterinarian may consider placing two large-bore IV catheters. Blood samples are obtained for a minimum data base, and resuscitation can commence. The rate and type of IV fluid resuscitation is based on the assessment of the animal's perfusion deficits and the presence of concurrent injuries. Full shock doses of crystalloids (60 to 90 mL/kg/hour in the dog; 45 to 60 mL/kg/hour in the cat) or hypertonic saline and dextran (5 to 7 mL/kg given over 5 minutes) followed by crystalloids may be necessary. Fluid resuscitation should be limited in animals suspected of having pulmonary contusions (10 to 20 mL/kg given intravenously for the first hour). Temporary application of a tight abdominal bandage (abdominal counterpressure) can slow or arrest bleeding by raising intra-abdominal pressure. However, increasing intra-abdominal pressure for prolonged periods can adversely affect renal and hepatic blood flow.

The response to therapy and ongoing requirements for crystalloid or colloid fluids should be continually assessed from repeated clinical, laboratory, and monitoring (urine output, EKG, blood pressure, pulse oximeter) evaluations. Blood component therapy is often required to maintain the animal's packed cell volume (PCV) above 25%. Autotransfusion can be a lifesaving source of red blood cells in dogs or cats when fresh whole or stored blood is not available. Intra-abdominal sepsis or neoplasia is a contraindication to autotransfusion; hence, animals with no history of trauma should not be autotransfused. Peritoneal fluid is evaluated cytologically before auto-transfusion.

Hemoperitoneum may be suspected from the history and physical examination findings. A focal or generalized loss of serosal detail on abdominal radiographs indicates free peritoneal fluid. The diagnosis of hemoperitoneum should be confirmed by peritoneal fluid evaluation. A sample is obtained by abdominocentesis with or without ultrasound guidance. In animals with hemoperitoneum, the peritoneal fluid sample should not clot unless the spleen has been inadvertently aspirated. The PCV of abdominal fluid usually is greater than or equal to that of the

peripheral blood. Unfortunately, peritoneal fluid cytology is rarely helpful in diagnosing neoplastic causes of hemoperitoneum. In animals with either a palpable abdominal mass or no history of trauma, splenic neoplasia is a distinct possibility. Obvious pulmonary metastatic disease should be ruled out by evaluation of opposite lateral and dorsoventral thoracic radiographs. Abdominal ultrasonography may be useful for defining an intra-abdominal mass and for evaluation of other abdominal organs for evidence of metastatic disease.

Definitive treatment varies, depending on the underlying cause of the hemoperitoneum and the response to medical stabilization. Some dogs and cats with traumatic splenic or hepatic hemorrhage stabilize with fluid resuscitation, blood transfusion, and abdominal counterpressure. Surgery is indicated in animals with traumatic hemoperitoneum that continue to hemorrhage despite appropriate medical treatment. In humans, such circumstances would initially be investigated with interventional radiologic techniques, and obvious bleeding arteries would be embolized. These techniques are currently investigational at several veterinary schools. In animals with hemoperitoneum secondary to a bleeding splenic or hepatic mass, the aims of surgery are to stop ongoing hemorrhage, remove the mass, obtain a histopathologic diagnosis, and perform a complete exploratory to rule out gross metastatic disease. The prognosis for these animals depends on the tumor type. The two most common splenic masses in dogs are hemangiosarcoma and hematoma. Dogs have an excellent prognosis after hematoma removal; dogs with splenic hemangiosarcoma have a very guarded long-term prognosis even with chemotherapy.

119.1.1 Splenic and Liver Lobe Torsion

Although uncommon, splenic torsion should be considered in any dog with either chronic gastrointestinal (GI) signs or signs of acute abdominal disease. The pathogenesis of splenic torsion and the predisposing factors for this condition are not completely understood, but Great Danes and German shepherds are at increased risk. In many dogs, the history includes chronic signs of abdominal discomfort and GI disease, such as depression, anorexia, vomiting, and weight loss. However, some dogs with splenic torsion are initially examined as true emergency cases with signs of acute, worsening abdominal disease. The physical examination findings depend on the degree of cardiovascular instability and may include pale mucous membrane color, poor capillary refill time, and poor peripheral pulse quality. Splenomegaly may be detected on abdominal palpation in most cases and should increase the clinician's suspicion for splenic disease.

The differential diagnosis for such animals should include gastric dilatation-volvulus syndrome, GI foreign body obstruction, mesenteric torsion, peritonitis, and other causes of splenomegaly, including neoplasia. A complete blood count, serum biochemical screening, and abdominal imaging are indicated to further define the underlying disease. Radiographs show splenomegaly in all affected dogs; some can also have a loss of abdominal detail associated with peritoneal effusion or hemorrhage. Abdominal ultrasound findings of a hypoechoic pattern in the splenic parenchyma and decreased flow through the splenic veins strongly support a diagnosis of splenic torsion.

Animals should be stabilized with IV fluid resuscitation prior to induction of anesthesia. Some animals with moderate to severe anemia may require preoperative or intraoperative transfusions. Because many dogs with splenic torsion have evidence of abnormal coagulation, a coagulation screen and blood type and crossmatch are indicated prior to surgery. A protocol of balanced anesthesia with minimal cardiovascular depression should be used. Ventricular arrhythmias commonly develop intraoperatively or postoperatively, therefore electrocardiographic and blood pressure monitoring is vital. At surgery, the spleen should be removed without untwisting the splenic pedicle. Many surgeons also recommend concurrent gastropexy to prevent subsequent gastric volvulus. The prognosis is good for dogs with splenic torsion when appropriate emergency resuscitation and critical care management are combined with prompt diagnosis and surgical treatment.

Liver lobe torsion occurs rarely in dogs and cats. Clinical signs and laboratory data are nonspecific. A distended abdomen or a palpable abdominal mass can sometimes be detected on physical examination. The diagnosis is confirmed at exploratory laparotomy. The affected liver lobe should be resected either manually or with stapling equipment and submitted for histopathology.

119.1.2 Hepatic and Splenic Abscesses

Hepatic and splenic abscesses are both uncommon clinical entities in dogs but may present as true emergencies. The clinical signs and physical examination findings in dogs with these conditions are not specific. Dogs most commonly have a history of anorexia and lethargy that may be accompanied by vomiting and diarrhea. They are often febrile and have pain and hepatomegaly or splenomegaly on abdominal palpation. Occasionally, dogs with hepatic abscessation have evidence of epistaxis, ecchymosis, or hematochezia, indicating abnormal blood clotting function.

A complete blood count, serum biochemical profile, coagulation screen, and abdominal imaging studies are logical diagnostic steps in animals with these physical examination findings. Historically, all dogs with hepatic abscessation have had increased serum alkaline phosphatase (ALP) and alanine aminotransferase (ALT) activity, and the majority have a leukocytosis, thrombocytopenia, and hypoalbuminemia. The results of abdominal radiography may not be diagnostic; in one study of dogs with hepatic abscesses, most had hepatomegaly, one third had splenomegaly, and one third had a loss of abdominal detail. Abdominal ultrasound is useful in these cases and shows either hypoechoic or anechoic changes in one or more liver lobes. Samples can be obtained from affected lobes for cytology and aerobic and anaerobic culture and sensitivity testing using ultrasound guidance. If ultrasonography is not available, peritoneal lavage or exploratory laparotomy may be required to make a definitive diagnosis.

The etiology of hepatic and splenic abscesses is the subject of debate and probably is multifactorial. However, given that hematogenous bacterial spread is a potential cause, once a diagnosis has been established, possible reservoirs of bacterial infection, such as the urinary tract and heart valves, should be investigated. The animal can also then be evaluated for concurrent conditions associated with hepatic and splenic abscessation, such as biliary tract disease, diabetes mellitus, pancreatitis, neoplasia, and endogenous or exogenous glucocorticoid excess. Thoracic radiographs are indicated to rule out pneumonia; in one study, radiographic evidence of alveolar infiltrates consistent with pneumonia were found in nearly half the cases examined.

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Initial stabilization in affected animals involves cardiovascular support with IV fluids and administration of broad-spectrum bactericidal antibiotics with gram-positive, gram-negative, and anaerobic coverage pending the results of culture and sensitivity tests. Bacteria cultured from canine hepatic abscesses have included *Escherichia coli, Klebsiella pneumoniae*, *Staphylococcus epidermidis*, enterococci, and clostridia. Treatment involves surgical resection of the abscessed liver lobe or lobes. In cases with diffuse hepatic involvement, percutaneous, ultrasound-guided drainage of abscesses may be appropriate. All affected animals should be treated with long-term antibiotic therapy (6 to 8 weeks). Follow-up ultrasound evaluations are recommended to monitor the response to treatment.

119.1.3 Rupture of the Biliary System

Rupture of the biliary system has been more commonly seen in dogs than cats and is usually caused by abdominal trauma or is associated with severe cholecystitis and rupture of the gallbladder. In animals with trauma-associated biliary leakage, there is usually a lag time of days to weeks between the initiating trauma and

the development of clinical signs associated with bile peritonitis. Animals with underlying cholecystitis may have chronic or intermittent clinical signs associated with the hepatic and GI systems. Once the biliary tract begins to leak substantially, clinical signs of peritonitis develop, prompting owners to seek veterinary attention.

Clinical signs vary in severity, depending on the extent of the peritonitis (local or general) and whether secondary bacterial infection of the bile and peritoneal fluid is a factor. Clinical signs may include lethargy, anorexia, vomiting, and diarrhea. On physical examination, the mucous membranes may be icteric; parameters indicating perfusion, such as the capillary refill time, heart rate, and pulse quality, are variably altered, depending on the severity of the peritonitis. The abdomen is often distended and painful. Plain abdominal radiographs show a local or generalized loss of abdominal detail. In cases of necrotic cholecystitis, choleliths and/or free gas may be visible in the cranial abdominal quadrant. Blood work often shows a leukocytosis and an increase in the serum bilirubin concentration and ALP and ALT activity. A diagnosis of bile leakage potentially can be made from analysis of peritoneal fluid samples. The finding of free bile crystals on cytology or a peritoneal fluid bilirubin level higher than that of serum should prompt exploratory surgery.

Prior to surgery, the animal is rapidly and aggressively stabilized with IV crystalloids and possibly colloids. Broad-spectrum bactericidal antibiotics are administered, because bile peritonitis often involves gram-negative bacterial contamination. A preoperative coagulation screen is mandatory in these cases, because the absence of bile salts in the duodenum and jejunum precludes absorption of fat and fat-soluble vitamins such as vitamin K. Fresh frozen plasma is required to prevent excessive surgical hemorrhage secondary to lack of coagulation factors. Vitamin K supplementation should be given immediately (1 to 2 mg/kg subcutaneously). In cases of traumatic biliary leakage, the biliary system is directly repaired or bile is diverted by means of a cholecystoenterostomy. In cases of gallbladder rupture secondary to cholecystitis, a cholecystectomy is performed. Samples are taken from the liver and peritoneal cavity for bacterial culture and sensitivity testing. The liver is biopsied. The peritoneal cavity is copiously lavaged with sterile isotonic fluid and either closed or left open. (Chapter 43 presents a more detailed description of the management of peritonitis.)

119.1.4 Acute Hepatic Failure

Peracute hepatic failure has many potential causes in small animals, including chemical agents; biotoxins; anesthetics and other drugs; viral, bacterial, and other infectious agents; neoplasia; copper storage disease; and hepatic lipidosis in cats. Hepatic failure is diagnosed in humans that have hepatic encephalopathy (HE) and a concurrent coagulopathy. Hepatic encephalopathy is a complex syndrome of neurologic alterations seen in association with moderate to severe liver disease. The cause of the neurologic signs seen in HE is multi-factorial; elevations in serum and central nervous system (CNS) ammonia levels alter the glutamate, gamma amino butyric acid, and serotonin neurotransmitter systems. Changes in the central and peripheral benzodiazepine receptor systems also occur. Small animals often have clinical signs of weakness, depression, collapse, anorexia, vomiting, and diarrhea. Physical examination findings are rarely specific; signs of spontaneous hemorrhage, including ecchymosis, icterus, and cranial organomegaly, increase suspicion for liver disease but do not differentiate between an acute hemolytic crisis and extrahepatic biliary obstruction. Owners should be questioned carefully about possible drug or toxin exposures.

A diagnosis may be suspected from the history and physical examination findings and the results of serum biochemical and liver function tests, including a coagulation profile. Abdominal ultrasonography may be helpful for visualizing the liver and obtaining either aspirates or biopsy specimens for cytology, culture, and histopathology. Treatment is largely supportive and involves cardiovascular support with crystalloid and colloid fluids, correction of electrolyte and acid-base imbalances, reduction of serum ammonia levels, and treatment of any seizurelike activity. The clinician should pay particular attention to hypokalemia and alkalosis, because both of these conditions increase ammonia uptake to the CNS. Serum ammonia is lowered by administering

lactulose, a nondigestible disaccharide that acidifies the colon, decreasing ammonia production and converting ammonia into nonabsorbable ammonium ions. In comatose animals, lactulose is administered as an enema (10 to 80 mL). In some instances administration of flumazenil, a benzodiazepine receptor antagonist (0.02 mg/kg given intravenously), is helpful. In animals with HE and seizure-like activity, propofol is administered as a bolus (0.5 1 mg/kg given intravenously) and then as an infusion (0.05 to 0.1 mg/kg/minute given intravenously).

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120 CHAPTER • 120 Pulmonary Emergencies

Fred A. Mann

Exacerbation of any pulmonary disease can result in life-threatening hypoxia requiring emergency treatment. Pulmonary emergencies that occur as a direct result of acute injury or disease in previously normal lungs include pulmonary edema, pulmonary contusion, aspiration pneumonia/pneumonitis, smoke inhalation, near-drowning, pulmonary thromboembolism, and acute lung injury/acute respiratory distress syndrome.

120.1 PULMONARY EDEMA

Pulmonary edema is the accumulation of fluid in the pulmonary interstitium and alveoli due to imbalance among the six interstitial fluid control factors: (1) capillary hydrostatic pressure, (2) capillary oncotic pressure, (3) interstitial hydrostatic pressure, (4) interstitial oncotic pressure, (5) capillary wall integrity, and (6) pulmonary lymphatic function (Figure 120-1).

Cardiogenic pulmonary edema is due to increased capillary hydrostatic pressure induced by congestive heart failure. Noncardiogenic pulmonary edema may result from alterations in any one or more of the interstitial fluid control factors, including capillary hydrostatic pressure. Examples of conditions that can cause noncardiogenic pulmonary edema include head injury, seizures, and electrical shock, all of which have unknown mechanisms but seem to involve both increased capillary hydrostatic pressure and increased capillary permeability; smoke inhalation, near-drowning, aspiration pneumonia/pneumonitis, acute lung injury/acute respiratory distress syndrome, uremia, pancreatitis, and toxins, all of which are thought to involve altered capillary permeability; liver disease, protein-losing enteropathy, protein-losing nephropathy, and burns, all of which are characterized by hypoproteinemia and decreased capillary oncotic pressure but may involve other interstitial fluid control factors; infiltrative pulmonary neoplasia, which may result in pulmonary edema due to lymphatic obstruction; postobstruction pulmonary edema; and re-expansion pulmonary edema. Postobstruction pulmonary edema occurs when correction of airway obstruction results in loss of intrinsic positive end-expiratory pressure (PEEP). Exhalation against an obstruction creates a PEEP that is suddenly gone when the obstruction is relieved, resulting in interstitial and alveolar flooding. Re-expansion pulmonary edema occurs when atelectatic lungs are rapidly re-inflated through (manual or mechanical) positive pressure ventilation. The rapidity of reinflation, not the chronicity of the atelectasis, is the cause. Re-expansion pulmonary edema is thought to be a form of increased-permeability pulmonary edema arising from hypoxic injury to capillary and alveolar membranes followed by a rapid increase in capillary hydrostatic pressure during re-expansion.

Pulmonary edema is life-threatening because it impairs pulmonary compliance, vital capacity, and pulmonary gas exchange. Treatment is directed at the underlying cause but also includes oxygen administration and the use of bronchodilators and diuretics. Failure of oxygen and medical therapy to resolve hypoxemia necessitates ventilation therapy and PEEP. Monitoring of pulmonary edema involves thoracic radiography; however, clinical signs may precede, and pulmonary recovery may lag behind, the radiographic appearance.

120.2 PULMONARY CONTUSION

Pulmonary contusion, the accumulation of hemorrhage in lung parenchyma as a result of traumatic injury, can cause fatal pulmonary impairment. Fortunately, most pulmonary contusions are self-limiting and respond to supportive treatment with oxygen administration, rest, and judicious fluid therapy. Fluid overload is a concern because many pulmonary contusion patients are in shock and require intravascular volume expansion. Overzealous

fluid administration for resuscitation may be avoided by using hypertonic saline (4 to 5 mL/kg given intravenously) followed by isotonic crystalloids to achieve targeted perfusion parameters. Diuretic therapy may be required to treat fluid overload. Antibiotics are not indicated for treatment of pulmonary contusions. If the patient remains hypoxic on supportive treatment, ventilation therapy with PEEP is required.

Because pulmonary contusions can worsen over 48 to 72 hours, they require close monitoring, and in some cases, therapeutic interventions for concurrent injuries must be postponed. Thoracic radiographs are used to monitor the progression and resolution of pulmonary contusions, but the radiographic appearance may not correlate with the clinical signs and the ability of the injured lungs to accommodate another insult, such as anesthesia. Radiographic resolution may precede full recovery of pulmonary function.

120.3 ASPIRATION PNEUMONIA AND PNEUMONITIS

Pneumonia and *pneumonitis* are characterized by the accumulation of inflammatory fluid in the pulmonary interstitium and alveoli (Figure 120-2). Emergent onset of pneumonia or pneumonitis occurs as a result of aspiration. If an infectious substance, such as oropharyngeal bacteria, is aspirated, the inflammatory condition is referred to as *aspiration pneumonia*. If acidic stomach contents are aspirated, a noninfectious, chemical-induced inflammation, referred to as *aspiration pneumonitis,* may occur. It is important to distinguish between pneumonia and pneumonitis because of important differences in therapy. Antibiotic therapy is not indicated, at least initially, with aspiration pneumonitis because the antibiotic may select for resistant organisms. Conversely, antibiotics should be promptly administered in cases of aspiration pneumonia after a transtracheal wash sample has been obtained for culture and susceptibility testing. Lungs with aspiration pneumonitis experience oxygen toxicity at typically safe levels of oxygen administration and therefore can be harmed by excessive oxygen, whereas lungs with aspiration pneumonia may benefit from standard oxygen therapy. If pneumonitis is suspected, the lowest inspired oxygen concentration that maintains normal hemoglobin saturation is used.

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Figure 120-1 Causes of pulmonary edema.

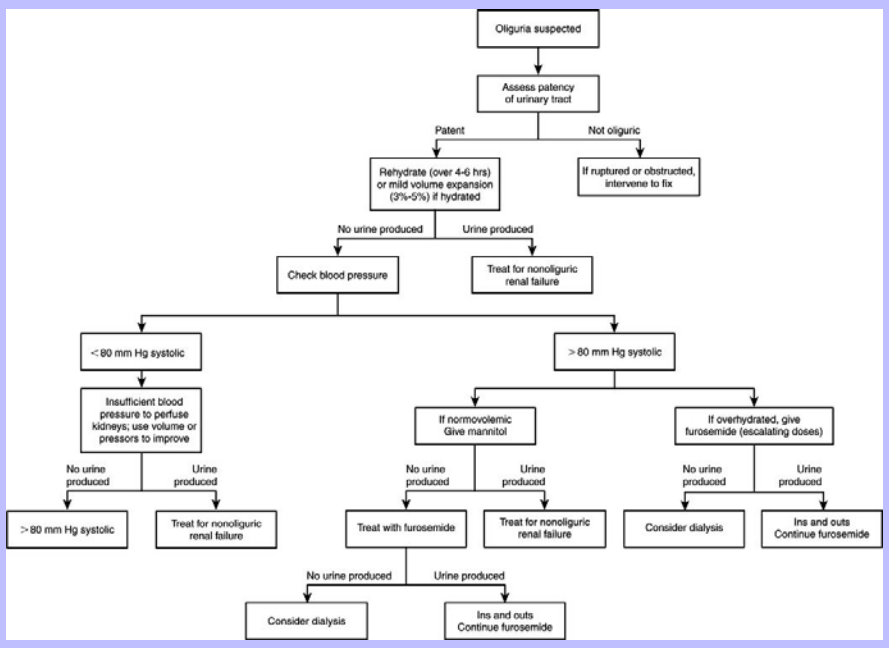
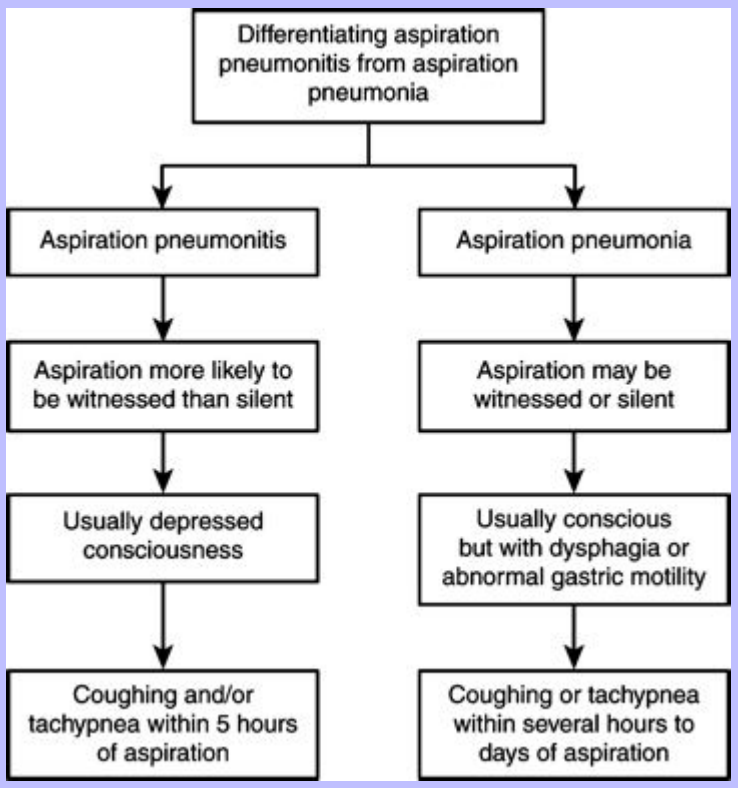


Figure 120-2 Differentiation of aspiration pneumonia and pneumonitis. *Note:* Because of the difficulty in clinical differentation, treatment strategy is based on whether the aspiration event is witnessed.



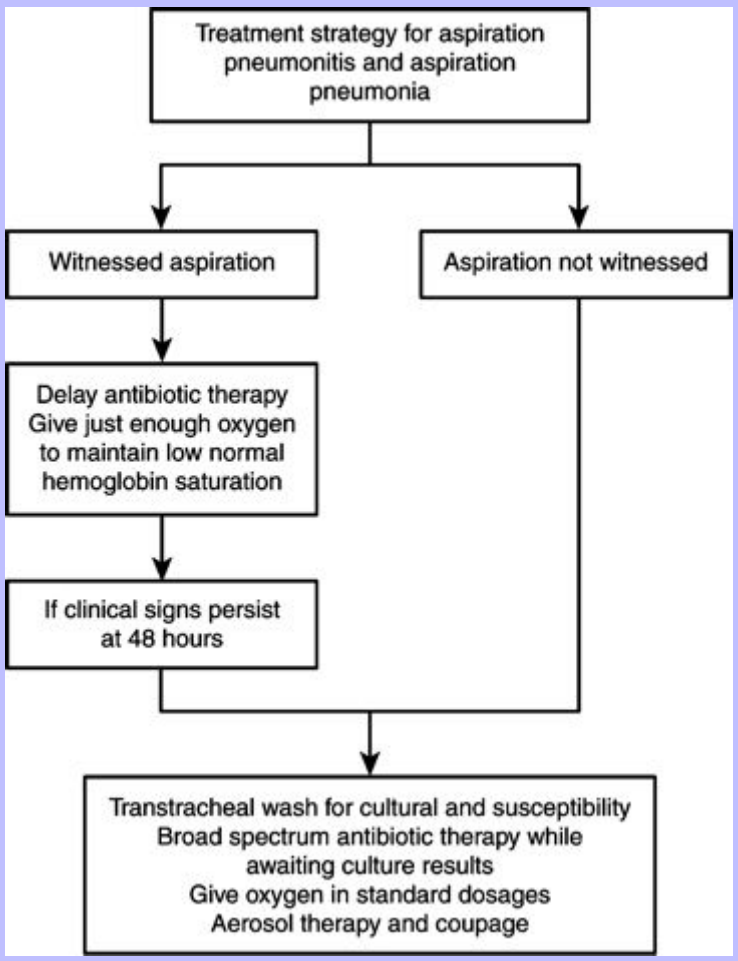
Unfortunately, the differentiation between pneumonitis and pneumonia is not straightforward. Both types of aspiration may be witnessed or silent, but aspiration pneumonitis is more likely if the aspiration event is witnessed. Pneumonitis is more common in patients with depressed consciousness, whereas pneumonia is more common in patients with dysphagia and/or gastric motility disorders. Clinical signs may be absent in both, but when they occur, the onset may differ. Coughing and/or tachypnea typically occur within 5 hours of aspiration in pneumonitis, but they occur later (several hours to days) in pneumonia, depending on how long it takes the aspirated bacteria to reach pathogenic numbers.

Because of the difficulty in differentiation, the following therapeutic approach is recommended (Figure 120-3):

- *If the aspiration event is witnessed:* Antibiotic therapy is delayed, and just enough oxygen is administered to maintain normal oxygen saturation of hemoglobin. Antioxidant therapy, such as administration of vitamin E, may also be beneficial. If clinical signs fail to resolve within 48 hours, broad-spectrum antibiotic therapy is begun, preferably after transtracheal wash samples have been obtained.
- *If the aspiration event is not witnessed:* A transtracheal wash is performed, and broad-spectrum antibiotic therapy is pursued until culture and susceptibility results become available. Standard doses of oxygen are

administered to maintain normal oxygen saturation of hemoglobin. With pneumonia, aerosol therapy and coupage may be used to facilitate both delivery of antibiotics to the respiratory tree and elimination of excessive respiratory secretions.

Figure 120-3 Treatment strategy for aspiration pneumonitis and pneumonia.



120.4 SMOKE INHALATION

Thermal injury from inhaled smoke is typically limited to the airways, but carbon monoxide and other toxic substances in smoke may cause pulmonary injury and dysfunction. Carbon monoxide binds with great affinity to hemoglobin, and the resultant carboxyhemoglobin is unable to carry oxygen. Administration of 100% oxygen shortens the half-life of carboxyhemoglobin from 4 hours to 30 minutes. As such, the most important treatment for smoke inhalation is early, preferably at the scene, oxygen therapy. Toxic substances may injure the lungs to the point of pulmonary edema, necessitating diuretics, careful fluid therapy, continued oxygen, and supportive care. Fluid therapy cannot be avoided, particularly if concurrent burns are a factor, but fluid rates must be monitored closely, preferably incorporating central venous pressure monitoring, to avoid fluid overload. The prognosis for

smoke inhalation injury is good if no signs of pulmonary impairment are present on the day of admission. The prognosis is also good for patients with signs of respiratory dysfunction upon admission if the signs do not worsen the day after admission.

120.5 NEAR-DROWNING

The ultimate concern in near-drowning is hypoxic brain injury. In the lungs, abnormalities of gas exchange may occur as a result of (1) fluid aspiration and destruction of surfactant, (2) disruption of alveoli and capillaries, and/or (3) pulmonary hypertension, all of which contribute to the development of pulmonary edema. The most successful near-drowning cases are those in which immediate reversal of hypoxia is achieved, before permanent neurologic impairment ensues. Immediate resuscitation provides the best possible outcome; however, first-responder cardiopulmonary-cerebral resuscitation at the scene is not widely available in veterinary medicine. Once the resuscitated near-drowning victim reaches the hospital, priorities are given to maintaining normoxemia, treating pulmonary edema, assessing neurologic function, and providing neurologic support therapies.

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120.6 PULMONARY THROMBOEMBOLISM

Pulmonary thromboembolism (PTE) is rarely diagnosed ante mortem and is probably responsible for many acute unexpected deaths. Clinical diagnosis of PTE is based on unexplainable dyspnea concurrent with normal thoracic radiographs or thoracic radiographs with hypovascular lung regions or alveolar infiltrates that do not correlate with the degree of respiratory distress. The diagnosis is supported by known risk factors, such as dirofilariasis, nephrotic syndrome, immune-mediated hemolytic anemia, hyperadrenocorticism, pancreatitis, sepsis, neoplasia, and any condition that sets the stage for Virchow's triad: (1) hypercoagulable state, (2) vascular stasis, and (3) disruption of vascular endothelium.

Treatment for pulmonary thromboembolism includes symptomatic respiratory support and anticoagulant therapy. Rarely is thrombolytic therapy used. Most commonly, the patient is heparinized. A baseline activated partial thromboplastin time (aPTT), prothrombin time (PT), and activated clotting time (ACT) are obtained, and an initial intravenous dose of heparin (200 U/kg) is given, followed by 100 to 200 U/kg given subcutaneously or intravenously every 6 hours. The actual repeat doses are often even lower and are based on maintenance of the aPTT at one and one half to two times normal. The ACT can be used to adjust doses such that it is prolonged to 15 to 20 seconds over baseline; however, the aPTT should be monitored at least once daily. Heparin therapy may be slowly discontinued if the inciting cause is reversed. If prolonged anticoagulant therapy is needed, Warfarin may be given per os at a dosage of 0.2 mg/kg once, followed by 0.05 to 0.1 mg/kg to achieve a PT of one and one half to two times normal. Warfarin must be started before heparin is discontinued because Warfarin may be thrombogenic initially.

120.7 ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are severe conditions that result from direct lung insult, such as pulmonary contusion, pneumonia, smoke inhalation, near-drowning, and oxygen toxicity, or from indirect lung injury associated with sepsis, systemic inflammatory response syndrome, shock, pancreatitis, parvoviral enteritis, organ torsion, and some toxicities. Differentiation of ALI from ARDS is based on the severity of hypoxemia; the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FIO_2) in ALI is 200 to 300, whereas the ratio for ARDS is less than 200. All ARDS cases result from progression of ALI, but not all ALI cases lead to ARDS. The hallmark of ALI/ARDS is hypoxemia refractory to increasing amounts of oxygen.

In ALI/ARDS, direct or indirect injury to pulmonary vascular endothelium and/or alveolar epithelium results in local inflammation that for unknown reasons spreads to the entire pulmonary system. Edema worsens. Flooded alveoli are perfused but cannot be ventilated; therefore, refractory hypoxemia results. Edema leads to decreased functional residual capacity, airway closure, atelectasis, decreased compliance, and increased work of breathing. Clinical signs, which are usually seen within 24 hours of the inciting cause, include dyspnea (which may be the only sign in early stages), tachypnea, increased abdominal effort, crackles, and harsh lung sounds. Hypotension and fever may also be present. The most common radiographic finding is diffuse alveolar infiltrates with normal cardiac silhouette and pulmonary vasculature. The diagnosis is supported by the presence of hypoxemia and alveolar infiltrates in the absence of congestive heart failure.

Treatment of ALI/ARDS consists of identification and treatment of the underlying cause and maintenance of adequate oxygen delivery to tissues. Tissue oxygenation is promoted by treatment or avoidance of edema, hypotension, volume overload, infection, and oxygen toxicity. Supplemental oxygen is given to maintain the arterial hemoglobin saturation above 90% and the PaO_2 above 60 mm Hg, to decrease the work of breathing, and to decrease the myocardial workload. Oxygen supplementation at an FIO_2 of less than 0.5 is administered to avoid oxygen toxicity. If a higher FIO_2 is necessary after 8 hours of supplementation, ventilation therapy with PEEP is warranted. Strict fluid balance, usually with a combination of crystalloids and colloids, is necessary to ensure tissue perfusion while avoiding fluid overload, because most deaths are the result of secondary organ failure rather than the pulmonary disease. Likewise, supportive management should include monitoring of blood pressure, coagulation, hemoglobin content, renal function, and nutrition, and appropriate therapeutic intervention when needed.

121 CHAPTER • 121 Renal Emergencies

Cathy E. Langston

Immediate care is required for a dog or cat that is not excreting an adequate amount of urine (i.e., 1 to 2 mL/kg/hour). The patency of the urinary tract should be evaluated for obstruction or rupture. To restore adequate urine flow, the structural problem must be alleviated or bypassed (Figure 121-1).

Insufficient blood flow to the kidney from prerenal causes can substantially decrease the glomerular filtration rate (GFR). Long-standing ischemia may also lead to intrinsic renal failure. A wide variety of factors can cause acute intrinsic renal failure (ARF), which may exist as oligoanuria (less than 0.25 mL/kg/hour), nonoliguria (0.25 to 2 mL/kg/hour), or polyuria (greater than 2 mL/kg/hour). Dogs and cats with chronic renal failure may have a decompensated uremic crisis, which initially should be managed as nonoliguric acute renal failure.

The pet may have a known history of potential renal insult (e.g., ingestion of a nephrotoxic drug or antifreeze, a recent ischemic event), or it may have signs suggestive of ARF (recent onset of polyuria and polydipsia, vomiting, and anorexia). The physical examination may reveal renomegaly, pain, uremic ulcers, or halitosis.

In the initial stages of ethylene glycol intoxication (30 minutes to 12 hours after ingestion), clinical signs may include central nervous system (CNS) depression, incoordination, ataxia, somnolence, seizures, and coma. Hypothermia and vomiting are also common. Marked polydipsia occurs in dogs, and both dogs and cats initially become polyuric. These signs may resolve, to be followed by signs of ARF after 24 to 72 hours in dogs and as early as 12 hours in cats.

With leptospirosis, clinical signs commonly encountered include fever, musculoskeletal pain, severe and persistent vomiting and diarrhea, oculonasal discharge, hemorrhagic diathesis, peripheral lymphadenopathy, and dyspnea. The presence of icterus in an animal with ARF is suggestive of leptospirosis, although not all serovars are associated with hepatic involvement. Leptospirosis is a zoonotic disease, and appropriate precautions should be taken when handling any dog suspected of having the disease.

Test results consistent with ARF include an increased anion gap, metabolic acidosis, hypocalcemia, or hyperkalemia. Ethylene glycol toxicity may cause hyperglycemia. In addition to isosthenuria, urinalysis may reveal proteinuria, glucosuria, hematuria, pyuria, or cylindruria. Oxalate crystals may be present with ethylene glycol toxicity.

Abdominal radiographs typically show either normal or enlarged kidneys; the contours should be smooth with ARF. With ethylene glycol toxicity, the kidneys may appear more radiopaque than surrounding soft tissue structures. Abdominal ultrasonography usually shows normal to enlarged kidneys with normal architecture. Ethylene glycol toxicity frequently results in hyperechoic cortices compared with the liver. Thoracic radiographs may show an interstitial pattern with leptospirosis or an interstitial to alveolar pattern if volume overload has led to pulmonary edema.

A serum chemistry panel documents azotemia and hyperphosphatemia. Liver enzyme activity may be increased in leptospirosis, with peak liver involvement occurring about 6 to 8 days after the onset of renal involvement. Changes in the complete blood count are usually nonspecific. Dogs with leptospirosis may have a mild, nonregenerative anemia, leukocytosis, or thrombocytopenia. Urine culture may demonstrate bacterial growth in animals with bacterial pyelonephritis.

Specific tests available for ARF include an ethylene glycol test to confirm exposure. However, because of the limits of detection of the test, cats can have nephrotoxic ethylene glycol concentrations and yet produce a negative test

result. The test result may be negative in both dogs and cats 12 hours after ingestion as a result of metabolism of ethylene glycol. Leptospirosis serology is not available on an emergency basis.

Fluid therapy is one of the first considerations for treatment of renal emergencies. Rehydration should take place over 4 to 24 hours, depending on the animal's cardiovascular status. Most ARF patients should be rehydrated over a short time (4 to 6 hours). If the animal is hydrated, a fluid volume equal to 3% to 5% of body weight should be administered to account for clinically undetectable dehydration. Urine output should be assessed after rehydration, and fluid therapy should be tailored to fluid output (ins-and-outs). Administered fluid should be at a base rate equaling insensible loss (22 mL/kg/day) plus the volume of sensible loss (urine production) over the previous time period. If vomiting is profuse, an estimate of this volume is added to measurements of urine output. This method is appropriate both for oliguric/anuric animals, to avoid overhydration, and for polyuric dogs and cats, in which the volume of urine frequently exceeds the clinician's estimate. Plasma or colloids (e.g., hetastarch, dextran) may be indicated.

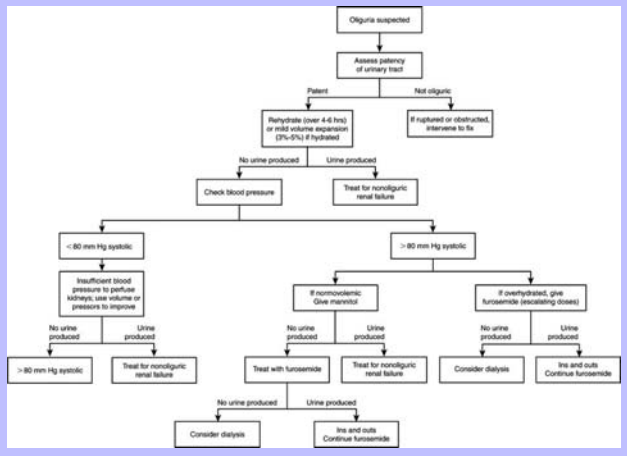
If urine output remains low (less than 0.25 mL/kg/hour) in a hydrated animal with a blood pressure adequate to perfuse the kidneys (mean arterial pressure [MAP] greater than 80 mm Hg), diuretics are indicated. Mannitol (0.5 g/kg given intravenously over 20 minutes) is an osmotic diuretic but is contraindicated in dehydrated or overhydrated animals. Furosemide, a loop diuretic, may induce urine flow within 20 to 30 minutes after an initial intravenous bolus of 2.2 mg/kg. If this does not occur, the dose can be doubled, up to 10 mg/kg. Higher doses may lead to ototoxicity. Furosemide and mannitol can be given together. Use of dopamine as a diuretic is controversial, although it is useful at higher doses as a pressor agent for hypotensive patients.

Treatment of metabolic acidosis is recommended when the serum pH is below 7.2 or the serum bicarbonate concentration is less then 16 mEq/L. Sodium bicarbonate should be dosed according to the following formula:

$$\text{Body weight (kg)} \times 0.3 \times (20 - \text{Patient's bicarbonate concentration})$$

One quarter to one third of the dose is administered over 10 to 20 minutes, and an additional $1_{/4}$ to $1_{/3}$ of the dose is administered over the next 4 to 8 hours. Rapid administration, excessive dosing, or administration to an animal with impaired respiratory function can lead to paradoxical CNS acidosis.

Figure 121-1 Algorithm for the management of a dog or cat suspected of having oliguric or anuric acute renal failure.



Hyperkalemia may cause cardiac or ECG abnormalities, characterized by bradycardia; wide, flattened, or absent P waves; peaked T waves; wide QRS complexes; atrial standstill; idioventricular rhythm; ventricular fibrillation; or asystole. Regular insulin (0.1 to 0.25 U/kg given intravenously) with dextrose to prevent hypoglycemia (1 to 2 g/unit of insulin as an intravenous bolus, followed by 1 to 2 g/unit over the next 4 to 8 hours) or bicarbonate (0.5 to 2 mEq/kg given intravenously) temporarily shifts potassium intracellularly, with an effect occurring within about 20 to 30 minutes. If a more immediate effect is needed, 10% calcium gluconate (0.5 to 1.0 mL/kg) can be administered as a slow intravenous bolus for its cardioprotective effect, although it does not decrease plasma potassium concentrations. These emergency treatments must be followed by procedures that remove potassium from the body (i.e., induction of urine flow or dialysis).

Uremia may induce gastritis or gastric ulceration. Histamine (H_2 receptor) blockers are commonly used to treat gastritis. They include famotidine (0.5 to 1 mg/kg given intravenously every 24 hours), ranitidine (2.2 mg/kg given intravenously every 24 hours), or cimetidine (2.5 to 5 mg/kg given intravenously every 12 hours). Because renal excretion of ranitidine and cimetidine is significant, this is a reduced dose. Sucralfate (0.25 to 1 g given orally every 6 to 8 hours) aids healing of uremic ulcers. It should be given at least 30 to 60 minutes before oral antacids. Uremic toxins can induce nausea by stimulating the chemoreceptor trigger zone. Metoclopramide (0.2 to 0.5 mg/kg given intravenously or intramuscularly every 6 to 8 hours, or 0.25 to 0.5 mg/kg/day given intravenously as a constant-rate infusion) is a centrally acting antiemetic. It is also a dopamine receptor antagonist and should not be administered concurrently with dopamine. Other antiemetics, such as chlorpromazine, can cause hypotension if the animal is not adequately hydrated. Little information is available on the use of 5-HT_3 serotonin receptor antagonists (e.g., ondansetron or dolasetron) in the treatment of vomiting associated with renal failure in animals.

Hyperphosphatemia is common in both acute and chronic renal failure as a result of decreased renal excretion. An acute increase in the phosphate concentration causes a compensatory decrease in the calcium concentration. Because the ionized calcium concentration is usually maintained within normal limits, signs of hypocalcemia tetany are infrequently observed. Oral phosphate binders (e.g., aluminum hydroxide) should be used once vomiting has been controlled and the animal is being fed enterally.

Respiratory compromise from pleural effusion caused by volume overload may require thoracocentesis. No effective method of addressing pulmonary edema exists in anuric animals other than ultrafiltration by means of dialysis. Careful attention to fluid therapy and urine output is crucial to avoid this complication.

Hypertension may accompany either acute or chronic renal failure, and excessive volume expansion (particularly in the face of oliguria or anuria) can exacerbate the condition. Therapy may not be necessary if the hypertension is mild and renal failure is resolving rapidly. However, in more severe cases emergency therapy may be necessary to prevent catastrophic effects.

Anorexia is common with acute renal failure. Because of the highly catabolic state associated with ARF, nutritional support should be started early in the course of the illness. If vomiting can be adequately controlled pharmacologically, enteral feeding with a feeding tube should be started. If enteral feeding is not possible, partial or total parenteral nutrition should be instituted. Calories should be predominantly carbohydrates, with restricted protein content. Ideally, protein should be supplied as essential amino acids.

Uremia induces a thrombocytopathy, and the risk of bleeding should be considered when invasive procedures are planned (e.g., renal biopsy, feeding tube placement). Because coagulation parameters and platelet numbers may be normal, a buccal mucosal bleeding time is the preferred method of assessment.

For ethylene glycol toxicity, specific antidotes are indicated. Four-methylpyrazole (4-MP (fomipezole); Antizol-Vet, Orphan Medical, Minnetonka, Minnesota) is effective in dogs if given within 8 hours of ingestion. Standard doses are not effective in cats. Dosing for dogs is 20 mg/kg initially, given intravenously, then 15 mg/kg at 12 and 24 hours, and 5 mg/kg at 36 hours. If 4-MP is not available, 20% ethanol can be used to competitively inhibit alcohol dehydrogenase. A dose of 5.5 mL/kg every 4 hours for five treatments, then every 6 hours for four treatments, can be given as an intermittent intravenous bolus but is better administered as a constant-rate infusion. In cats, 20% ethanol can be dosed at 5 mL/kg every 6 hours for five treatments, then every 8 hours for four treatments. Drinking alcohol (50% ethanol [100 proof]) can be diluted with saline. Respiratory depression can be profound with alcohol. Neither 4-MP nor alcohol is effective if started more than 8 hours after toxic ingestion.

Antibiotics should be administered if leptospirosis or pyelonephritis is suspected or documented. High doses of penicillin are effective at clearing leptospiremia. Doxycycline (2.5 mg/kg PO or IV every 12 hours) is effective at clearing leptospiremia and possibly leptospiuria. The most common cause of bacterial pyelonephritis is *Escherichia coli* infection. Empirically used antibiotics should have a good gram-negative spectrum and should not be nephrotoxic.

Adequate monitoring of animals with acute renal failure is essential. They are acutely and severely ill. Their status can change rapidly and dramatically. Urine output should be monitored in all animals with renal failure. This is most accurately accomplished with an indwelling urinary catheter with a closed collection system. Changes in body weight over the course of hospitalization primarily reflect changes in body water content and hydration. Other parameters (e.g., blood pressure, central venous pressure, packed cell volume) should be monitored as needed.

If conventional medical management fails to induce diuresis in an oliguric or anuric dog or cat, if life-threatening complications are present (i.e., hyperkalemia, volume overload), or if azotemia fails to improve after 24 hours of therapy, dialytic therapy (either hemodialysis or peritoneal dialysis) should be considered. (see Figure 121-1.)

The outcome of acute renal failure is poor. Approximately 60% of dogs and cats die or must be euthanized. Renal trauma may require emergency surgery to control massive hemorrhage.

121.1 SUGGESTED READINGS

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122 CHAPTER • 122 Gynecologic Emergencies

Saralyn Smith-Carr

Most gynecologic emergencies occur during the periparturient, diestrus, or postestrus periods. It is the responsibility of the veterinarian to act quickly to ensure preservation of the life of the bitch, the neonate and future reproductive potential of the bitch (in that order). The reasons owners seek veterinary assistance for reproductive emergencies are listed in Table 122-1. A complete breeding history should always be obtained along with a thorough physical examination. Details of each reproductive disorder have been reviewed elsewhere.

122.1 DYSTOCIA

Dystocia is the inability of the female to expel the fetus through the birth canal at parturition. The bitch's body temperature drops below normal (<100°F), 8 to 24 hours before the onset of labor, due to serum progesterone, decreasing to less than 2 ng/dl. There are three stages of labor. During the first stage, the bitch may become anxious, restless, or seek seclusion. There are no obvious uterine contractions but cervical dilation occurs and clear vaginal fluid discharge may be seen, which indicate chorioallantois membrane rupture. During stage II labor there are noticeable abdominal contractions, fetal membranes are visualized at the vulva, and the puppy or kitten is immediately expelled. Delivery of the first newborn usually occurs within 20 to 30 minutes of the onset of stage II labor. Stage III labor is a resting period, during which the placental membranes are passed and the bitch cares for the neonate. Causes of dystocia may be maternal or fetal in origin. Specific details on maternal and fetal causes of dystocia have been reviewed elsewhere.

Table • 122-1 Reasons for Seeking Veterinary Assistance for Reproductive Disorders

PRESENTING COMPLAINT	DISORDER(S)
No signs of labor at >24 hours after temperature decrease to <100°F More than 1 week overdue Fetal membranes in vulva >15 minutes Strong contractions >30 minutes without delivery	Normal or dystocia
No fetus produced after 4–6 hours of onset of stage II labor	Dystocia
More than 3 hours between fetal delivery	Dystocia in canine
Vaginal discharge	Dystocia, metritis, pyometra
Temperature >103.5°F in the bitch Profuse vomiting, diarrhea and toxemia in bitch Incessant crying of offspring	Dystocia, metritis, pyometra, uterine torsion, mastitis
Anorexia, lethargy, depression >24 hours postpartum	Metritis, mastitis
Hot, painful, swollen mammary glands	Mastitis
Extreme restlessness, panting, tremors, and stiff gait	Eclampsia

Regardless of the origin of dystocia, maternal or fetal, either primary or secondary uterine inertia occurs and the owner seeks veterinary assistance. After taking a history, a general physical examination should be performed to determine the degree of maternal compromise. Next, detailed examination of the reproductive tract should be performed beginning with visual inspection of the vulva for presence of discharge, fetal membranes, or fetal parts. Mucoid or greenish black (lochia) vaginal discharge are normal findings but may indicate obstruction if present for more than 2 hours without delivery. Sanguineous or bloody vaginal discharge may indicate vaginal trauma or uterine torsion. Reddish brown fetid discharge indicates fetal death and subsequent metritis.

Presence of fetal membranes or fetal parts should prompt digital examination of the vagina and/or rectum to palpate for any obstruction. Abdominal palpation should be performed to ascertain fetal presence and discern fetal movement. Auscultation of the abdomen for fetal heartbeats should be performed although absence may not indicate fetal death. Fetal heart rates below 200 bpm may indicate fetal compromise and dictates need for immediate treatment. If obstruction of the birth canal is suspected, surgery rather than medical therapy should be chosen. Therefore, abdominal radiographs are recommended to evaluate fetal size and position related to the birth canal of the dam. Abdominal ultrasound should be performed to determine fetal viability and presence of uterine or abdominal fluid that may indicate infection or peritonitis, respectively.

In a periparturient bitch that demonstrates signs of compromise, a CBC and serum chemistry should be performed to aid in evaluating for sepsis, hypoglycemia, hypocalcemia, and her general health. Parenteral oxytocin administration, with or wit hout calcium and glucose, may be all that is needed. Often, however, dogs and cats with dystocia usually require C-section. It is important to consider the effects of anesthesia on the bitch and fetus. Anesthetic protocols should be chosen to minimize respiratory depression of either fetus or the bitch. Surgical preparation of the bitch needs to be performed prior to anesthesia induction, which decreases exposure of bitch and fetus to cardiac and respiratory depression caused by general anesthetics. The physiologic changes of the pregnant bitch should also be taken into consideration and appropriate measures taken to treat respiratory and cardiovascular compromise due to increases in intra-abdominal pressure. Supplemental oxygen during anesthesia induction, along with intravenous fluid administration and tilting the surgery table toward the surgeon during surgery, are recommended.

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Fluid therapy may be needed to correct dehydration due to vomiting or hypovolemia due to shock. Pregnant bitches may be prone to vomiting. Therefore antiemetics may be needed. Care should be taken to resuscitate neonates. Therefore trained staff should be available to remove fetal membranes, stimulate respiration, remove fluid from their nares using gentle suction, and to ensure proper clamping and cutting of umbilical cords. Proper care of neonates has been reviewed elsewhere.

122.2 ECLAMPSIA

Hypocalcemia usually occurs in the second or third weeks of lactation. Less commonly, hypocalcemia occurs in the first or fourth weeks of lactation. Rarely, it is diagnosed in the final 1 or 2 weeks of gestation. Hypocalcemia is due to a loss of calcium into the milk more rapidly than it can be absorbed from bone and because some of these dogs fail to eat properly. Predisposing factors are high-calcium diet during pregnancy, calcium supplementation during pregnancy, and heavy lactation demands postpartum. Clinical signs include nervousness, panting, salivation, stiff gait, ataxia, and clonic-tonic muscle contractions that may progress to seizures. If not treated, death may result. Diagnosis is usually based on history and clinical signs. Laboratory finding of hypocalcemia is not usually necessary. If assessed, total serum calcium concentrations are usually below 7 mg/dL in bitches and less than 8 mg/dL in queens. Serum ionized calcium concentrations provide more direct information on biologically available calcium. However, treatment should be instituted before serum calcium results are available, if blood is taken.

Calcium should be administered intravenously slowly at 5 to 10 mL increments. The heart should be monitored for bradycardia and arrhythmias during calcium administration via auscultation and ECG. A 10% to 20% calcium gluconate solution is usually given; however, other calcium preparations have been used. Once acute signs have resolved, subcutaneous calcium may be given at 8-hour intervals. Caution is advised in the choice of calcium supplements since calcium concentration differs and some are irritating when given IM or SQ. Dogs and cats should then be placed on oral calcium supplementation for the remainder of their lactation period with close monitoring for return of clinical signs. If signs return, puppies or kittens should be weaned or bottle-fed.

122.3 METRITIS

Metritis may occur during the postpartum period due to obstetric manipulations, retained fetal remains, or retained placenta. Clinical signs may include reddish brown fetid vaginal discharge, fever, anorexia, lethargy, or lack of interest in the neonate. Physical examination may reveal an enlarged uterus and clinical signs of sepsis. Abdominal radiographs and ultrasound should confirm the presence of an enlarged, fluid-filled uterus. The CBC typically reveals a leukocytosis, neutrophilia, and a left shift. Serum chemistry profiles reflect degree of dehydration and may demonstrate hypoglycemia in some septic animals. Increases in liver enzyme activities may occur due to endotoxemia. Abdominal ultrasound may be used to determine the thickness of the uterine wall. If there is evidence of a thin uterine wall or medical therapy is unsuccessful, ovariohysterectomy is recommended. Medical therapy consists of oxytocin or prostaglandin therapy for emptying the uterus. Broad-spectrum antibiotics should be administered also chosen with consideration of the nursing neonate.

122.4 MASTITIS

Mastitis is bacterial infection of the mammary gland. Clinical signs can occur during the postpartum period alone or accompanying metritis or in pseudopregnancy. Clinical signs may include fever, anorexia, lethargy, and lack of interest in the neonate. Physical examination may reveal fever, hardened, painful mammary glands, and in some cases gangrenous mammary glands. Infection of the mammary gland is considered ascending but could be due to hematogenous spread. Diagnosis is based on history, clinical signs, and physical examination findings. Cytology and culture of mastitic milk often reveals degenerating neutrophils and, typically, pure colonies of staphylococci, streptococci, or *Escherichia coli*. Treatment consists of broad-spectrum antibiotics while culture results are obtained. The dog or cat should be switched to an appropriate antibiotic after culture results are obtained. Choice of antibiotic should consider the nursing neonate. Puppies or kittens should be allowed to nurse (actually encouraged) except if the glands are abscessed or gangrenous. Abscessed and/or gangrenous glands should be surgically treated.

122.5 UTERINE TORSION

Uterine torsion refers to rotation of one or both uterine horns. The condition is uncommon and can occur in the gravid or non-gravid uterus. Uterine torsion occurs more often during pregnancy and is more common in the queen than the bitch. Clinical signs are abdominal pain and shock. Acute abdominal enlargement may be seen in the non-pregnant female and signs of dystocia in the pregnant female. A high degree of suspicion of uterine torsion is made in the bitch or queen experiencing abdominal pain, enlarged uterus, and radiographic signs of uterine gas or acute distention of the abdomen. Definitive diagnosis is made by exploratory laparotomy. An immediate ovariohysterectomy is required. Appropriate fluid therapy should be administered to combat shock and broad-spectrum antibiotic should be administered for infection. Saving the life of the queen or bitch is more important than preservation of their reproductive potential.

122.6 PYOMETRA

Pyometra and cystic endometrial hyperplasia are common illnesses in older nulliparous bitches and queens. During diestrus, the endometrial glands of the uterus are stimulated, which causes hyperplasia and hypersecretion leading to cystic endometrial hyperplasia. Pyometra is uterine inflammation and bacterial infection that leads to an accumulation of pus in the uterine lumen. Most bitches with pyometra are seen during diestrus, whereas queens

are brought to veterinarians post estrus. The pathophysiology is not completely understood but is considered due to multiple exposure of the uterus to progesterone. Pathophysiology has been reviewed elsewhere.

The disease has been further divided into open and closed cervix distinctions based on the degree of cervical patency. Usually the bitch has a history of predisposing factors such as multiple estrous cycles, use of exogenous estrogen, or use of progestins. Clinical signs, often more severe in animals with closed cervix pyometra, include anorexia, fever, vomiting, polyuria, and polydipsia. Animals with "open-cervix" pyometra have a purulent vaginal discharge. Sepsis, endotoxemia, and renal failure can occur in some bitches with pyometra. Vaginal discharge with systemic signs and history of estrus 1 to 12 weeks prior to development of clinical signs leads to the suspicions of pyometra. Blood work abnormalities consist of a neutrophilia with a left shift and non-regenerative anemia. Azotemia, the raised serum protein concentrations (both albumin and globulin) and elevated liver enzymes are seen. These changes are caused by dehydration and endotoxemia. Urinalysis reveals normal to low urine specific gravity and sometimes proteinuria. Urinary tract infection occurs in some cases. The most common bacteria associated with pyometra are *E. coli,* although streptococci, staphylococci, and *Proteus* and *Klebsiella* spp. have also been reported. Diagnosis, based on history and clinical signs, is usually confirmed by radiography and/or ultrasound. Lateral radiographic views of the abdomen are most helpful. An enlarged sacculated uterus can be seen, especially in animals with closed-cervix pyometra. This cannot be distinguished from a pregnant uterus less than 42 days into gestation. Abdominal ultrasound is valuable for the diagnosis of pyometra. A fluid filled uterus can be visualized and differentiated from fetal sacs. Medical and surgical treatment options exist but surgery is usually recommended. Dehydration and sepsis is addressed first with fluid therapy and broad-spectrum antibiotics. Medical treatment with prostaglandin can be used if the cervix is open. Treatment protocols with natural prostaglandin have been reviewed elsewhere. Surgical treatment consists of ovariohysterectomy. Stabilization of the dog or cat with fluids and antibiotics is required before any treatment medical or surgical. Antibiotic therapy should be continued for 1 month.

In summary gynecologic emergencies may be challenging. Knowledge of clinical signs and reproductive history is critical to diagnosis. A complete physical examination and laboratory workup is necessary to determine complications associated with each emergency.

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123 CHAPTER • 123 Sepsis and the Systemic Inflammatory Response Syndrome

Linda Barton

Stedman's Medical Dictionary defines sepsis as “the presence of various pus-forming and other pathogenic organisms, or their toxins, in the blood or tissues.” However, increased understanding of the pathogenesis of sepsis has shifted the focus from the microorganisms causing infection to the host's response to that infection. The clinical syndrome of sepsis represents the body's systemic response to infection, characterized by signs of inflammation, particularly when that response becomes deleterious to the host.

The human and veterinary medical literature has used a variety of terms interchangeably to describe patients with adverse systemic manifestations of infection. In an attempt to standardize the literature and to identify homogeneous patient populations for clinical trials, a consensus conference was sponsored in 1991 by the American College of Chest Physicians and the Society of Critical Care Medicine. The consensus conference agreed on definitions for the terms *bacteremia, sepsis, severe sepsis, septic shock,* and *multiple organ dysfunction syndrome* (MODS) (Box 123-1). Conference attendees recognized the clinical course of sepsis as a continuum. *Sepsis* is the term used to describe patients with infection-induced systemic inflammation. The occurrence of organ dysfunction secondary to sepsis is defined as *severe sepsis*. The development of hypotension, not responsive to IV fluid administration, is defined as *septic shock.*

Recognizing that severe insults other than infection can produce a generalized systemic reaction, organ dysfunction, and shock indistinguishable from those induced by sepsis, conference attendees created the term *systemic inflammatory response syndrome* (SIRS). SIRS can be used to describe evidence of systemic inflammation due to either an infectious or noninfectious process. Only when SIRS is associated with infection is it defined as sepsis. The SIRS criteria have been modified for the cat and dog (Table 123-1). Noninfectious processes associated with SIRS in animals include pancreatitis, tissue trauma, heat stroke, ischemia, burns, and pansystemic neoplasia.

123.1 PATHOGENESIS

Infection or tissue injury triggers a local immune response. Toxic effects from infecting organisms, components of infecting organisms (such as endotoxin, the lipopolysaccharide associated with the membrane of gram-negative bacteria), exotoxins, or aminophospholipids from damaged cell membranes stimulate the release of a variety of pro-inflammatory and anti-inflammatory mediators into the local environment. This local immune response is a desired host defense. In some individuals, inflammatory mediators spill over into the systemic circulation, which triggers a more generalized reaction. A systemic inflammatory reaction is more likely to develop with a severe insult or when a patient receives sequential insults. The “second-hit” theory proposes that patients with a controlled inflammatory process may develop SIRS if they sustain a second infectious or inflammatory insult.

The clinical manifestation of this generalized reaction depends on the balance between pro-inflammatory and anti-inflammatory mediators. In a controlled response, pro-inflammatory and anti-inflammatory cascades are balanced and homeostasis is restored. An imbalance in favor of anti-inflammatory cytokines results in relative immunosuppression. SIRS/sepsis and the progression to severe sepsis and septic shock result from an imbalance in favor of the pro-inflammatory mediators.

123.1.1 Box • 123-1 1991 ACCP/SCCM Consensus Conference Definitions

Bacteremia: The presence of viable bacteria in the blood.

Systemic Inflammatory Response Syndrome (SIRS): The systemic inflammatory response to a variety of infectious or non-infectious insults. The response is manifested by two or more of the following criteria:

Temperature >38°C or <36°C

Heart rate >90 beats/minute

Respiratory rate >20 breaths/minute or $PaCO_2$ <32 torr

WBC >12,000 cells/mm^3, <4000 cells/mm^3, or >10% immature (band) forms Sepsis: The systemic response to infection. SIRS as a result of infection.

Severe sepsis: Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Clinical manifestations include lactic acidosis, oliguria and altered mentation.

Septic shock: Sepsis with hypotension, despite adequate fluid resuscitation.

Multiple Organ Dysfunction Syndrome (MODS): The presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

The clinical signs of SIRS, organ dysfunction, and septic shock are produced by the pathophysiologic effects of inflammatory mediators. The effects on the cardiovascular system are characterized by peripheral vasodilation, which results in decreased systemic vascular resistance and myocardial dysfunction manifest as ventricular dilation, a decreased ejection fraction, impaired contractile response to volume loading, and decreased left ventricular compliance. Vascular endothelial injury occurs secondary to enhanced neutrophil activation and adhesion, which leads to increased vascular permeability.

Interactions between inflammatory and coagulation cascades during sepsis have become increasingly apparent. Large quantities of tissue factor (TF), the important trigger of the extrinsic coagulation cascade, are expressed by injured endothelial cells, and cytokine-stimulated neutrophils and macrophages. The procoagulatory state created by increased TF is further amplified by consumption of naturally occurring anticoagulants such as activated protein C, tissue factor pathway inhibitor, and antithrombin. Enhanced thrombin formation leads to deposition of fibrin in the microvasculature, which obstructs blood flow and exacerbates tissue hypoxia. This condition may progress to fulminant disseminated intravascular coagulation (DIC).

Table • 123-1 Criteria for Systemic Inflammatory Response Syndrome

CLINICAL PARAMETERS	DOGS	CATS
Heart rate	>120 bpm	<140 bpm or >225 bpm
Respiratory rate	>40 bpm or $Paco_2$ <30 mm Hg	>40 bpm
Temperature	<100.4° F or >104.0° F	<100.0° F or >104.0° F
Leukogram	>18,000 or <5000 WBC/µL	>19,000 or <5000 WBC/µL

From Otto CM: Sepsis. In Wingfield WE, editor: *The Veterinary ICU Book*, Jackson Teton NewMedia, 2002, p 694.

123.2 CLINICAL PRESENTATION AND DIAGNOSIS

Recognizing SIRS/sepsis and its sequelae as a continuum, clinical signs vary from animals with mild abnormalities to those with signs of organ dysfunction and septic shock. No single set of clinical, laboratory, and hemodynamic parameters can describe all situations. In addition to the SIRS-related changes in body temperature, heart rate, respiratory rate, and white blood cell count, affected animals may have decreased mentation, hypotension, bounding or hypodynamic peripheral pulses, thrombocytopenia, hypoalbuminemia, hypoglycemia, prolonged clotting times, increased fibrin split products, increased D-dimer, decreased antithrombin, increased bilirubin, increased liver enzymes, increased BUN/creatinine, oliguria, lactic acidosis, and/or hypoxemia.

The animal may have signs related to the underlying infection (i.e., coughing and dyspnea associated with bacterial pneumonia). Alternatively, the systemic inflammatory response may manifest before signs of the infection and should alert the clinician to search for an infectious cause. When animals have unexplained shock (no history or physical exam findings consistent with trauma, blood or fluid loss, or cardiac disease) sepsis should be suspected as the underlying cause.

Suspicion of sepsis demands an “infection hunt.” Common causes of sepsis in dogs and cats include peritonitis, pyometra, prostatitis, prostatic abscess, pyelonephritis, pneumonia, pyothorax, and endocarditis. In hospitalized animals, nosocomial infections should be considered. IV catheters, urinary catheters, and other invasive devices should be carefully inspected and removed, as required. Translocation of bacteria from a diseased or unused GI tract is another possible source of infection. Signalment, history, and physical exam are useful in localizing the nidus of infection. Samples should be collected for CBC, serum biochemical profile, and urinalysis to assist in the localization of infection and to detect evidence of organ dysfunction. Additional information may be provided by evaluation of an arterial blood gas or coagulation profile. Radiographs and ultrasound of the thorax and abdomen may also be indicated.

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123.3 TREATMENT

Therapy of sepsis has three major components: first to identify and eradicate the infection, second is supportive care to maintain adequate tissue perfusion and minimize organ dysfunction, and finally therapy to alter the pathologic inflammatory cascade. The prognosis declines as SIRS/sepsis progresses to septic shock and MODS, which emphasizes the importance of early recognition and treatment.

Rapid institution of appropriate antibiotic therapy has been shown to improve survival in humans with sepsis. Empiric parenteral broad-spectrum antibiotic therapy should be initiated following collection of appropriate culture specimens (bronchoalveolar fluid, urine, blood, wound drainage, loculated fluid, or IV catheter tip) and can be modified when results of culture and sensitivity are available. In animals with an unknown infection source, blood and urine cultures should be obtained. The agent chosen depends on the host status and the suspected causative organism. Important factors to consider include the suspected source of infection, nature of the pathogen most likely responsible (community-acquired or nosocomial), local resistance patterns, and underlying immune status. Sepsis in dogs and cats is most often associated with gram-negative enteric bacteria. Prevalence of common bacterial isolates based on site of infection in dogs and cats has been reported. In addition to antibiotic therapy, surgical drainage of abscesses, and debridement of infected or devitalized tissue may be necessary to remove the nidus of infection/inflammation.

As the infection/inflammation resolves, animals must be aggressively monitored and supported to ensure adequate organ and tissue perfusion. Hypoperfusion can be detected by changes in physical exam parameters (decreased

mentation, tachycardia [or bradycardia in cats], prolonged CRT, decreased pulse quality, decreased extremity temperature), decreased arterial blood pressure, oliguria, or development of hyperlactemia. Most affected animals have decreased preload caused by fluid leakage secondary to increased vascular permeability. Vasodilation of peripheral vessels and maldistribution of blood flow cause a relative hypovolemia. Therefore volume resuscitation is the best initial therapy for hypoperfusion. Aggressive volume administration is best guided by measurement of central venous pressure (CVP) or ideally pulmonary capillary wedge pressure (PCWP). IV fluid boluses (15 to 20 mL/kg isotonic crystalloid, or 5 mL/kg colloid) should be administered until normal perfusion has been restored or until risk of volume overload and pulmonary edema are evident (CVP >8 cm H_2O or PCWP >18 mm Hg). Use of colloids is thought to prevent the development of interstitial edema in patients with increased vascular permeability, although there is no proven advantage of colloid over crystalloid fluid therapy. The type of fluid administered is probably less important than the rapidity with which resuscitation is achieved and the use of physiologic end points to evaluate the response to therapy.

If fluid therapy alone fails to restore adequate blood pressure and perfusion, vasopressor agents should be added. Dopamine (5 to 20 μg/kg/min) increases systemic blood pressure through both improved cardiac performance (β-agonist effect) and increased systemic vascular resistance (α-agonist effect). The vasopressor effect predominates at the higher end of the dose range. Therefore to prevent excessive vasoconstriction of peripheral and splanchnic vessels, dopamine should be started at 5 μg/kg/min and the dose titrated to effect. Evidence in human patients suggests that norepinephrine (0.25 to 2.0 μg/kg/min) is superior to dopamine in the treatment of hypotension associated with septic shock.

Oxygen delivery to tissues depends not only on the volume of blood delivered but also on the oxygen content of the arterial blood. To ensure normal oxygen delivery, factors that affect blood oxygen content should be monitored. Hemoglobin concentration should be maintained at at least 8 g/dL (PCV ≥24%) and hemoglobin saturation at at least 90%. Transfusions of pRBCs, Oxyglobin, supplemental oxygen, and/or mechanical ventilation should be used as needed to optimize oxygen delivery to the tissues.

Serial monitoring of key organ systems (the cardiovascular, pulmonary, coagulation renal gastrointestinal and central nervous systems are commonly affected in sepsis) is necessary to detect early derangements in function. Electrolytes and blood glucose should be monitored and supplemented as needed. Enteral nutrition is important to support host defenses and bowel integrity.

The final goal of therapy is to control or inhibit the actions of the inflammatory cascade. Clinical trials of a number of specific anti-inflammatory therapies, including antibody to endotoxin, IL-1 receptor antibody, antibradykinin, antiplatelet activacting factor, anti-TNF, and high-dose glucocorticoids, have been conducted in humans, and with the exception of activated protein C (APC) have not demonstrated a significant reduction in mortality. Drotrecogin alfa (activated), a human recombinant APC with antithrombotic, profibrinolytic, and anti-inflammatory properties, demonstrated a significant reduction in mortality in humans with severe sepsis and received FDA approval in 2001. The cost of the drug (approximately $6,800/person) will prohibit its use in veterinary medicine.

Until cost-effective specific anti-inflammatory therapies become available, optimal management of the septic veterinary patient will depend on rapid recognition, eradication of the source of infection/inflammation, and meticulous supportive care directed at restoring normal oxygen delivery to tissues.

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124 CHAPTER • 124 Shock

Cynthia M. Otto

Shock is not a disease but a complex physiologic state. Historically, shock was described as the effect of generalized circulatory abnormalities that led to inadequate tissue perfusion. Although this classic description still holds important clinical relevance, the complexity of shock states result not from the initial insult per se, but the systemic response to that insult. This is most clearly demonstrated in septic shock, in which the cascade of events that leads to irreversible cardiovascular collapse is the systemic inflammatory response initiated by products of infectious agents. This systemic inflammatory response syndrome (SIRS) can also be triggered by noninfectious insults including tissue hypoxia, tissue acidosis, pancreatitis, trauma, and major surgery. Similarly, although hypovolemia can be reversed, reperfusion of ischemic tissues leads to inflammation, and production and release of mediators. These complex cascades confound the treatment of shock; reversing the perfusion abnormalities may not stop the progression once the inflammatory cascade has been initiated. Treatment directed at the downstream cellular mediators of shock has not proven beneficial either. Whether the cause is infection, blood loss, or tissue hypoxia, one of the most successful approaches to the treatment of shock is early recognition and correction of the inciting cause before the cascade of inflammation is triggered.

Shock is a dynamic state and the clinical condition can change in a matter of minutes, hours, or even days. Early stages of shock may not be clinically obvious, as the compensatory mechanisms are recruited to maintain cardiac output and tissue perfusion. In late stages of shock, compensatory mechanisms fail; systemic inflammation leads to multiple organ dysfunction and death. In these late stages of shock, successful clinical intervention is uncommon. This chapter focuses on the clinical presentations associated with the three major types of shock in the early and intermediate stages of shock. Shock is classically divided into three main categories based on the mechanisms of impaired perfusion: cardiogenic, hypovolemic, and distributive.

124.1 TYPES OF SHOCK

Cardiogenic shock results predominantly from failure of adequate forward flow. The dysfunction can occur in either the diastolic or systolic phase or can result from an obstruction of flow. Systolic or forward flow failure results from overt heart failure or severe tachyarrhythmias. Diastolic or filling failure can result from pericardial tamponade, tension pneumothorax, or hypertrophic cardiomyopathy. Obstructive shock can be the result of thromboembolic disease, tumors, or distended organs (e.g., gastric dilatation and volvulus; GDV) occluding either forward flow or venous return. The location, degree of obstruction, and resulting compromise to systemic perfusion are important determinants of whether flow occlusion will lead to shock.

Hypovolemic shock leads to inadequate delivery of oxygen and nutrients to tissues and accumulation of byproducts of cellular metabolism due to insufficient circulating blood volume. Intravascular volume depletion can result from acute or chronic fluid loss or sequestration of fluids into third spaces.

Distributive shock is a condition in which the effective circulating volume is inadequate to provide tissue perfusion. The classic example of distributive shock is septic shock. However, other vasodilatory states can also lead to distributive shock such as heat stroke, anaphylaxis, neurogenic shock, and SIRS. The common defect in distributive shock is inappropriate vasodilation, which leads to a relative hypovolemia. Sepsis and heat stroke are both complicated by a vigorous systemic inflammatory response and further compromised tissue oxygenation due to maldistribution of blood flow and mitochondrial dysfunction.

The types of shock vary in their etiology, clinical signs, and treatment. The categories of shock are not mutually exclusive and many animals with distributive shock will also have some degree of hypovolemia, particularly as SIRS leads to increased vascular permeability and fluid loss. Mediators of SIRS and ischemia reperfusion injury include substances that contribute to cardiac dysfunction. Thus progression of both distributive and hypovolemic shock can lead to cardiogenic shock. Cardiac patients are frequently volume-depleted. Any animal with inadequate intestinal perfusion may develop bacterial translocation and sepsis. Unrecognized, untreated shock initiates a cascade of doom. Therefore early recognition based on index of suspicion, aggressive monitoring in patients at risk, and appropriate interventions are essential in the successful treatment of shock states.

124.2 CLINICAL SIGNS OF SHOCK

The normal physiologic response to poor tissue perfusion is to increase sympathetic tone, which results in increased heart rate, respiratory rate, and vasoconstriction. In the early (sometimes called *compensated*) stages, tachycardia may be the only clinical sign. With time and progression to the intermediate stages (also referred to as *early decompensated*), profound vasoconstriction results from the attempt to increase venous return and maintain stroke volume. In the intermediate stages, additional compensatory mechanisms trigger an increase in salt and water retention (angiotensin-aldosterone and ADH) and release of vasoconstrictors (e.g., vasopressin), that contribute to an increase in stroke volume. Clinically these compensatory mechanisms result in signs typically seen in cardiogenic and hypovolemic shock, including pale to white mucous membranes, a prolonged capillary refill time (>2 sec), cool extremities, a normal to decreased rectal temperature, decreased mentation, tachypnea, and hypotension. Although the overall compensatory response is consistent regardless of the etiology, the hallmark of distributive shock is the failure of effective vasoconstriction. The circulating mediators released in response to sepsis or SIRS result in vasodilation that leads to an effective hypovolemia. The clinical signs associated with distributive shock include red mucous membranes, rapid capillary refill time (<1 sec), and normal or increased rectal temperature. Distributive shock also leads to dysregulation of the normal stress response, and although hyperglycemia may be seen early, classically it is hypoglycemia that is associated with distributive (septic) shock. One other unique feature of distributive shock is that cats frequently become bradycardic rather than tachycardic.

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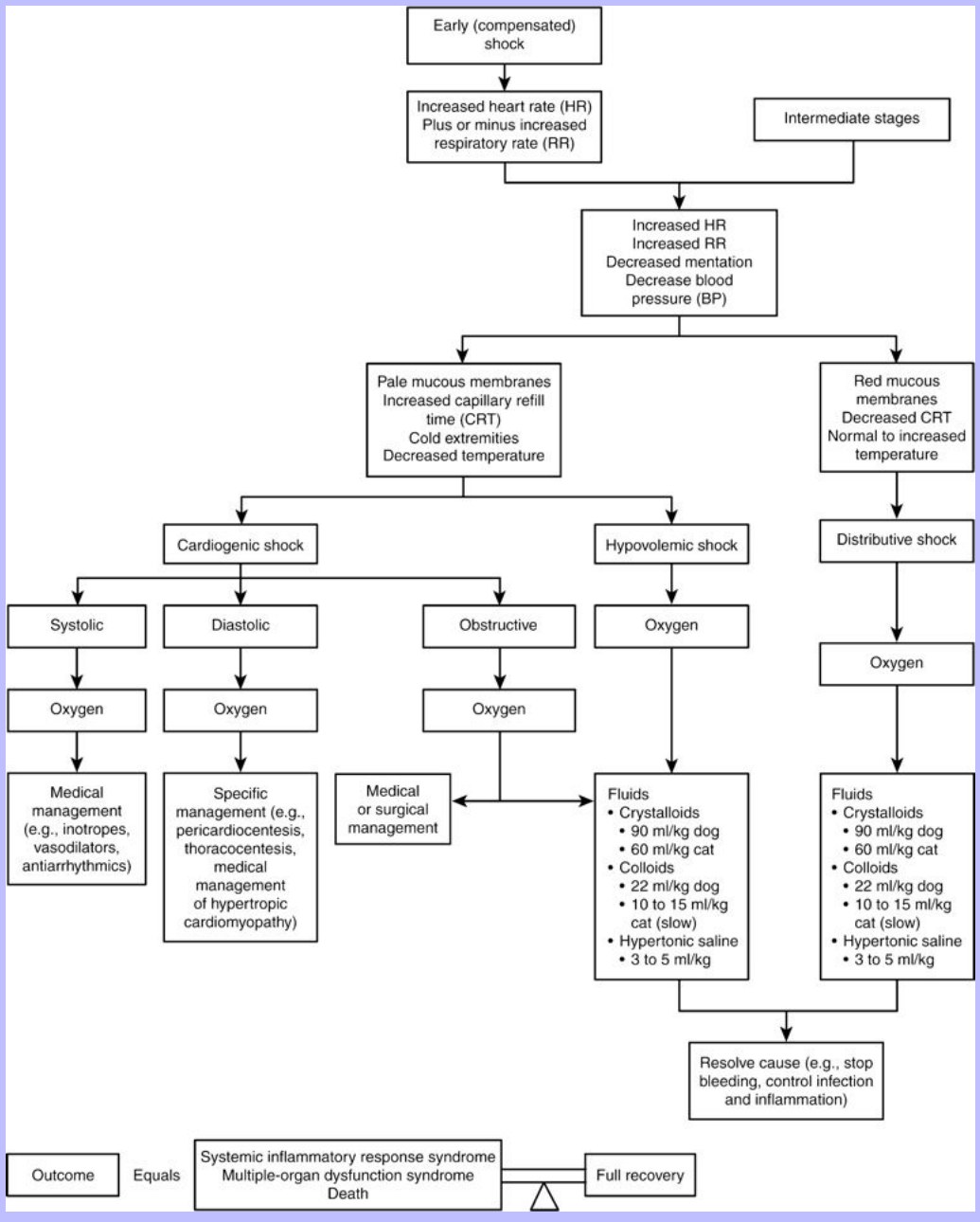
Figure 124-1 Algorithm for assessment and treatment of shock. *HR*, Heart rate; *RR,* respiratory rate; *mm,* mucous membranes; *CRT,* capillary refill time; *T*, rectal temperature; *BP*, blood pressure; *mgt,* management; *HCM,* hypertrophic cardiomyopathy; *SIRS,* systemic inflammatory response syndrome; *MODS,* multiple organ dysfunction syndrome.



In order to differentiate cardiogenic shock from hypovolemic shock, a thorough cardiac evaluation and complete history are beneficial. Unfortunately, animals in shock are frequently not stable enough to obtain extensive diagnostic tests and therapy needs to be initiated based on physical examination and historical findings. Distributive shock that is complicated by concurrent fluid loss (due to changes in vascular permeability and fluid compartment shifts or the underlying etiology) may initially demonstrate clinical signs more typical of hypovolemic shock, but upon resuscitation, develop clinical signs of distributive shock.

124.3 TREATMENT OF SHOCK

The goal of treatment in early shock is to restore effective tissue perfusion and oxygenation (Figure 124-1). In later stages of shock, restoration of perfusion alone is usually insufficient to halt the progression of the inflammatory cascade. Aggressive support of organ function and prevention of additional pro-inflammatory complications (including hypotension, hypoxia, and infection) are critical. At all stages, correction of the inciting cause is necessary.

Oxygen is universally administered in patients regardless of the type of shock. Additional therapy depends on the etiology of the shock. For both hypovolemic and distributive shock, fluid therapy is essential (see Chapter 114). The goal is to increase the effective circulating volume. The choice of fluids depends on the cause of shock; however, initial treatment is typically provided by crystalloids (balanced electrolyte solutions) at volumes of approximately 90 mL/kg in the dog and 60 mL/kg in the cat. The fluid rate and the actual volume given should be tailored to each individual animal. Typically, one fourth of the bolus is provided within the first 5 to 15 minutes, with repeated evaluation of the cardiovascular response (e.g., heart rate, mucous membrane color, pulse quality, and capillary refill time). Colloids can be used for shock resuscitation (22 mL/kg bolus in dogs, and 10 to 15 mL/kg infusion in cats) of hypoproteinemic animals and in conjunction with (reducing the volumes of both fluid types) or instead of crystalloids. Due to potential anticoagulant effects, colloid administration generally should not exceed 22 mL/kg per day. (For a more extensive discussion of fluid therapy see Chapter 114). The resuscitative fluid of choice for hemorrhagic hypovolemic shock is blood. Typical recommendations limit blood transfusions to 22 mL/kg; however, massive transfusions (greater than one blood volume) may be required in some cases (see Chapter 127). Hypertonic saline (HTS) is typically mixed with a colloid (to a final concentration of 7% saline) and may be considered for resuscitation at 3 to 5 mL/kg over 5 to 20 minutes. The small volumes required may be particularly beneficial in larger animals in which volumes of crystalloid are rate limiting. The hypertonic nature may also be beneficial in animals with shock and concurrent head injury. It has been demonstrated, however, that HTS, and other therapies that rapidly increase blood pressure may predispose to excessive bleeding in uncontrolled hemorrhage.

In cardiogenic shock, aggressive fluid therapy may be fatal. Treatment of cardiogenic shock relies on correction of the underlying cause. For systolic dysfunction, treatment of arrhythmias, diuretics, vasodilators, or inotropes may be required (see Chapter 199). Pericardiocentesis is necessary for treatment of tamponade and thoracocentesis/chest tube placement for tension pneumothorax. Diastolic dysfunction resulting from cardiac hypertrophy can be a challenge to treat (see Chapter 204). Resolution of obstruction to flow may require surgical intervention (e.g., tumors, GDV) or medical management (e.g., thromboembolic disease). Prior to surgery, adequate circulatory volume and optimal perfusion should be established.

Specific therapy should be directed at the cause of shock, such as in hemorrhagic hypovolemia, bleeding must be controlled and in septic shock the source of infection must be eliminated. Vasopressors may be required in distributive shock when hypotension persists despite adequate volume repletion. Detailed discussion of sepsis can be found in Chapters 123 and 124. Despite over 30 years of investigation, specific anti-inflammatory therapies have generally failed in clinical trials of shock and sepsis (see sepsis chapter). Although long touted for beneficial

effects in shock, there is no clinical evidence to support pharmacologic doses of glucocorticoids in the treatment of any form of shock.

Monitoring is critical during the resuscitation of shock. In addition to routine cardiovascular parameters (e.g., heart rate, mucous membrane color, pulse quality, and capillary refill time), respiratory rate, temperature, mentation, blood pressure monitoring (see Chapter 124), hematocrit, electrolytes, blood gases, base excess and lactate may help direct therapy. Central venous pressure monitoring is invaluable in shock to aid in determination of volume status and guide fluid resuscitation. More advanced monitoring that may be beneficial in managing the shock patient include cardiac output, oxygen delivery, oxygen extraction, and pulmonary capillary wedge pressure.

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125 CHAPTER • 125 Systemic Anaphylaxis

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Systemic anaphylaxis is an acute, life-threatening allergic reaction resulting from massive, generalized release of mast cell mediators, including histamine. Anaphylaxis can be triggered by venoms from insects and reptiles; medications, including hormones, antibiotics, nonsteroidal anti-inflammatory drugs, anesthetics, and sedatives; parasiticides; and other miscellaneous drugs and foods (Box 125-1). Immediate recognition and treatment of the veterinary patient with anaphylaxis is essential for a successful outcome.

125.1 Box • 125-1 Causes of Anaphylaxis

125.1.1 Venoms

Insects of the Hymenoptera order—bees, wasps, ants

Spiders—black widow, brown recluse

Lizards—Gila monster, Mexican beaded lizard

Snakes—pit vipers (rattlesnakes, copperheads, water moccasins), coral snakes

125.1.2 Hormones

Insulin

Corticotropin

Vasopressin

Parathyroid hormone

Betamethasone

Triamcinolone

125.1.3 Antibiotics

Penicillins—amoxicillin, ampicillin, procaine penicillin

Chloramphenicol

Lincomycin

Gentamicin

Tetracycline

Sulfonamides

Cephalosporins

Polymixin B

Doxorubicin hydrochloride

125.1.4 Nonsteroidal Anti-Inflammatory Drugs

Aspirin

Ibuprofen

125.1.5 Anesthetics and Sedatives

Acepromazine maleate

Ketamine hydrochloride

Barbituates

Lidocaine and other local anesthetics

Narcotics

Diazepam

125.1.6 Parasiticides

Dicholophen

Levamisole hydrochloride

Piperazine

Dichlorvos

Diethylcarbamazine

Thiacetarsamide

125.1.7 Miscellaneous

Blood products

Aminophylline

Asparaginase

Calcium disodium edetate

Iodinated contrast media

Neostigmine

Amphotericin B

Vaccines

Allergen extracts—pollens, molds, foods

Enzymes—chymotrypsin and trypsin

Vitamins—vitamin K, thiamine, and folic acid

Dextrans and gelatins

125.1.8 Foods

Milk

Egg

white

Shellfish

Legumes

Fruits—citrus

Chocolate

Grains

125.1.9 Physical Factors

Cold

Heat

Exercise

125.2 PATHOGENESIS

Anaphylaxis can be caused by either an anaphylactic or anaphylactoid reaction. Anaphylactic reactions are mediated by an interaction of antigen and IgE antibody on the surface of sensitized mast cells, which causes the release of histamine and other inflammatory mediators. This is defined as a type I, IgE mediated, hypersensitivity reaction. Sensitization requires previous exposure to an antigen or hapten, which can range in size from a protein to a small, low molecular weight drug. Proteins act directly as an antigen, while the smaller drugs will bind to cells and act as haptens. IgE is produced by and bound on the surface of mast cells and basophils by high-affinity receptors (FcεRI) for the Fc portion of the immunoglobulin. When an antigen causes cross-linkage of two surface IgE molecules, the mast cell is activated and primary and secondary mediators are released (Box 125-2). The

cross-linking of the FcεRI receptors activates tyrosine kinases, which cause activation of phospholipase C, leading to production of diacylglycerol and inositiol triphosphate. These mediators increase intracellular calcium concentrations and activate multiple protein kinases. Phosphorylation of myosin, found in intracellular filaments, causes granules to move to the cell surface, fuse, and release the primary mediators of anaphylaxis: histamine, heparin, tryptase, kallikreins, proteases, proteoglycans, eosinophilic chemotactic factor of anaphylaxis (ECF-A), and neutrophil chemotactic factor of anaphylaxis (NCF-A). Cross-linking of the FcεRI receptors also activates phospholipase A_2, which produces arachadonic acid from membrane phospolipids, which results in release of the secondary mediators: leukotrienes, prostaglandins, thromboxanes, and platelet-activating factor. The protein kinases also change gene expression, which results in synthesis and secretion of other cytokines (IL-4, IL-5, IL-6, IL-13, TNF-α, MIP-1α), which are responsible for the late-phase inflammatory response. Release of the inflammatory mediators is rapid: granule exocytosis occurs within seconds to minutes, activation of the arachadonic acid cascade in minutes, and cytokine synthesis and secretion within 2 to 24 hours.

Anaphylactoid reactions cause anaphylaxis without IgE, either through directly activating mast cells to release histamine, or more commonly, by activating the complement pathway. They do not require previous exposure and sensitization. Activation of complement results in production of C3a and C5a, the anaphylotoxins, which cause degranulation of mast cells and release of histamine and other primary mediators, activation of the arachidonic acid cascade, and gene expression and synthesis of the inflammatory mediators. Anaphylactoid and anaphylactic reactions have exactly the same clinical appearance and are treated identically.

125.2.1 Box • 125-2 Mediators of Inflammation in Anaphylaxis

Mediators	*Effects*
Primary	
Histamine	Increased vascular permeability, vasodilation, constriction of smooth muscle of bronchi and GI tract, increased mucus production
Proteases	Kinin production, activation of complement, initiation of disseminated intravascular coagulation
Heparin	Anticoagulation, urticaria, immune modulation
ECF-A	Eosinophil chemotaxis
NCF-A	Neutrophil chemotaxis
Secondary	
Prostaglandin E_2	Vasodilation, increased vascular permeability
Prostaglandin D_2	Bronchoconstriction, increased vascular permeability, pulmonary vasconstriction, peripheral vasodilation
Prostacyclin	Vasodilation, inhibition of platelet aggregation
Leukotrienes	Bronchoconstriction, increased vascular permeability, vasodilation, increased WBC chemotaxis
Thromboxane A_2	Increased platelet aggregation, smooth muscle contraction
Platelet activating factor	Platelet aggregation, platelet sequestration, increased platelet thromboxane production, increased vascular permeability, vasoconstriction, and bronchoconstriction

125.3 CLINICAL MANIFESTATIONS

Anaphylaxis can result in hypotension, bronchospasm, urticaria, erythema, pruritis, pharyngeal and laryngeal edema, arrhythmias, vomiting, and hyperperistalsis. Clinical signs are dependent on species and method of exposure. In dogs, the liver is considered the shock organ, and clinical signs result from hepatic vein congestion and portal hypertension. Initial signs may include excitement, vomiting, defecation (often diarrhea), then progress to respiratory distress, collapse secondary to hypovolemic shock, and death within one hour if not treated. A dog

with anaphylaxis may have generalized wheals, angioedema (particularly of the face), pruritis, pale mucous membranes, poor capillary refill time, tachycardia, poor pulse quality, and appear depressed or even collapsed. Severe cases may result in respiratory distress secondary to upper airway obstruction from laryngeal and pharyngeal edema.

In cats, the lungs are considered the shock organ, and respiratory distress is the first sign in cats with systemic anaphylaxis. Respiratory distress results from airway obstruction secondary to laryngeal edema, bronchoconstriction, and increased mucus production. Other signs in cats include severe pruritis, vomiting, diarrhea, depression, and death. A cat with anaphylaxis usually has severe respiratory distress, some wheezes on auscultation, pale mucous membranes, poor capillary refill time, and poor pulse quality.

The most severe anaphylactic reactions are generally seen if the antigen is given by parental injection. Oral ingestion often causes vomiting, diarrhea, urticaria, and angioedema. Inhalation can result in rhinitis and bronchospasm. Topical administrations can cause conjunctivitis and urticaria with or without systemic signs. *459*

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125.4 DIAGNOSIS

Diagnosis of systemic anaphylaxis is based on the history of exposure and peracute onset of clinical signs. Clinical signs often occur within seconds to minutes of exposure. Oral exposure can cause a delay of up to 30 minutes or longer before clinical signs appear.

125.5 TREATMENT

Initial treatment of a dog or cat presenting with anaphylaxis consists of the basics of emergency medicine. These include ensuring that the patient has a patent airway, is effectively breathing/ventilating, addressing cardiovascular dysfunction, and drugs and fluids as indicated. Dogs or cats having an anaphylactic reaction may have respiratory distress resulting from upper airway obstruction. The clinician should be prepared to intubate with an endotracheal tube or perform a tracheostomy if intubation is not possible. If respiratory distress without airway obstruction is present, oxygen should be administered by mask or flow-by during initial assessment and stabilization, and then by nasal catheter or oxygen cage. Vascular access is essential for treatment of these patients, both for fluid therapy and medications. Hypovolemic shock is a significant contributor to morbidity and mortality in anaphylaxis. Hypovolemia occurs secondary to increased vascular permeability and venous pooling. Fluid therapy, often starting with a shock bolus of crystalloids at a rate of 90 mL/kg/hr in dogs and 60 mL/kg/hr in cats, is indicated. Ongoing crystalloid therapy will be necessary at rates higher than maintenance to keep up with ongoing losses and will need to be tailored to the individual patient. Additional fluid therapy may include synthetic colloids, such as dextran or hetatstarch, given in small incremental boluses of 10 mL/kg/hr in dogs and 6 mL/kg/hr in cats. A constant rate infusion of synthetic colloids of 1 mL/kg/hr may also be used once the patient has been resuscitated. If a coagulopathy is present, blood products, especially fresh frozen plasma, may be necessary. This should be given at a dose of 10 to 20 mL/kg over several hours (or faster if needed for volume resuscitation). Fluid therapy is guided by clinical parameters inlcuding heart rate, pulse quality, mucous membrane color, capillary refill time, respiratory rate and effort, and packed cell volume and total solids.

Epinephrine is essential therapy for treatment of systemic anaphylaxis and should be administered immediately. A dose of 0.01mg/kg of the 1:10,000 solution given slowly IV is most effective, although 0.02 mg/kg can be given into the trachea if the patient is intubated and IV access cannot be obtained. Epinephrine can also be administered SQ or IM at a dose of 0.01 mg/kg in less severe cases. Epinephrine is useful because of its inotropic and chronotropic effects on the heart, bronchodilation, and increased intracellular concentrations of cyclic adenosine monophasphate, which decreases synthesis and release of inflammatory mediators of anaphylaxis. Heart rate,

rhythm, and blood pressure should be monitored when giving epinephrine, especially when given intravenously because of its ability to cause arrhythmias and hypertension (at high doses). Epinephrine and fluid therapy should begin to improve clinical signs within minutes. Dogs and cats ideally will be fully stabilized within an hour.

Other medications that may be useful in the treatment of systemic anaphylaxis include pressors, glucocorticoids, antihistamines, aminophylline, and atropine. Dopamine at a dose of 4 to 10 mcg/kg/min or other pressors may be used if refractory hypotension is present. Aminophylline may be used if bronchoconstriction is refractory to epinephrine. It will cause bronchodilation, increase respiratory drive, and increase contractility of the muscles of respiration. A dose of 10 mg/kg IV for dogs and 5 mg/kg IV for cats is recommended. Atropine at a dose of 0.02 to 0.04 IV or IM should be used if bradycardia is present despite epinephrine administration. Glucocorticoids are useful in blocking the arachadonic acid cascade and reducing the severity of the late-phase anaphylactic reactions. Doses of 1 to 2 mg/kg IV for dexamethasone have been recommended. It is essential that glucocorticoids not be used in place of epinephrine in the emergency situation as they have little effect on the immediate stages of anaphylaxis. Antihistamines competitively bind at the histamine receptors and block its effects. Diphenhydramine, a H_1 blocker, should be administered at 0.5 to 1.0 mg/kg slow IV or IM to reduce pruritis and angioedema. The H_2 blockers, cimetidine, ranitidine, and famotidine, can be used to decrease gastric acid secretion stimulated by histamine. Dose varies with each of the H_2 blockers. Antihistamines are also not very useful in the acute, life-threatening stage of anaphylaxis, but may be helpful after the patient has been stabilized.

Intense monitoring of the patient for at least 12 to 24 hours after the anaphylactic episode is essential. This should include respiratory rate and effort, heart rate and rhythm, blood pressure, pulse oximetry and/or arterial blood gases, coagulation parameters, renal and hepatic function, and PCV, total solids, and glucose. Other supportive care, such as ventilatory support, should be provided as needed. Avoidance of the trigger for anaphylaxis is prudent in the future. Careful questioning of the owner about recent exposure to insects, reptiles, foods, topical therapies, and medications is essential. Prognosis for a patient presenting with systemic anaphylaxis is variable. The earlier the patient receives appropriate therapy, the better the prognosis. This is especially important since death can ensue in 1 hour or less from time of exposure.

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126 CHAPTER • 126 Thoracic Trauma

Matthew W. Beal

Trauma to the thorax can be classified as blunt or penetrating. Blunt thoracic trauma commonly occurs after motor vehicle accidents, falls from a height, human-animal interactions, and dog bites. Dog bites are also a commonly recognized cause of penetrating thoracic trauma along with gunshot wounds and impalement injuries. Independent of the cause of the trauma, it is critical for veterinarians to recognize that trauma is most commonly a multisystemic problem (polytrauma). This necessitates attention to the entire animal. Similarly, injuries to the thorax are rarely isolated and more commonly are identified in combination (e.g., pneumothorax and pulmonary contusion). Keys to maximizing the likelihood of a positive outcome in dogs and cats with thoracic trauma include thorough physical examinations, anticipation of common injuries, understanding the pathophysiology of those injuries, and a proactive method to their identification and treatment.

126.1 TRAUMA-ASSOCIATED PLEURAL SPACE PATHOLOGY

Trauma associated pleural space pathology includes pneumothorax, hemothorax, and diaphragmatic hernia. As a group, these injuries are most likely to manifest with varying degrees of dyspnea accompanied by muffled lung and heart sounds on auscultation of the thorax. Differentiating these injuries will be largely based on a thorough physical examination and aided by thoracocentesis and diagnostic imaging techniques.

126.1.1 Pneumothorax

Pneumothorax is the accumulation of air in the pleural space between the parietal and visceral pleurae and is one of the two most commonly recognized results of traumatic injury to the thorax. Traumatic pneumothorax is classified as “closed” or “open.” Closed pneumothorax may result from rapid compression of the thorax (and lungs) against a closed glottis, which causes alveolar disruption, laceration of the lung by a broken rib, rupture of bullae or blebs, or from pneumomediastinum. Air enters the pleural space from an injury to the thoracic wall in cases of open pneumothorax. Tension pneumothorax occurs due to a one-way-valve effect, in which air enters the pleural space during inspiration and cannot be evacuated during expiration. The resultant increase in intrapleural pressure results in hypoventilation and decreased venous return, manifesting with signs of severe respiratory and cardiovascular compromise.

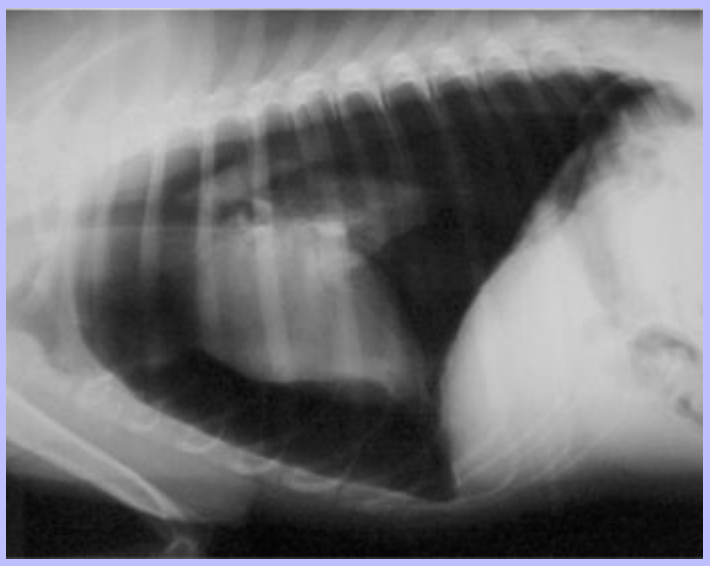
Appropriate management of the traumatized small animal patient necessitates the assumption that *pneumothorax is present until proven otherwise*. That assumption will remind the veterinarian to pay particular attention to those physical examination findings that will identify the problem. *Clinically significant pneumothorax is a physical examination diagnosis*. Most animals with pneumothorax prefer to stand or to position themselves in sternal recumbency. In this position, on auscultation, decreased lung sounds are most likely to be noted dorsally and most often are noted in both hemithoraces. Temporary relief and definitive diagnosis of pneumothorax is based on oxygen administration and bilateral thoracocentesis (see Chapter 103). Radiography for the diagnosis of clinically significant pneumothorax may jeopardize the stability of a dog or cat and should be avoided. When pneumothorax is noted on radiographs of a dog or cat that is not in distress after trauma, findings will include retraction of the lung from the chest wall (loss of vascular markings in this space), consolidation of lung lobes, and on lateral radiographs, the appearance of the heart “floating” on a cushion of air (Figure 126-1). The latter radiographic finding is due to collapse of the heart to the side of the atelectatic lung lobe. Often, a single thoracocentesis is sufficient treatment for traumatic closed pneumothorax. However, if pneumothorax recurs (sometimes rapidly), thoracostomy tube placement and continuous pleural

space drainage are recommended. Closed traumatic pneumothorax is rarely a condition that requires surgical correction. Open pneumothorax warrants immediate covering of the wound with an occlusive dressing and evacuation of the thorax by thoracocentesis or thoracostomy tube placement. Once stability has been achieved, open pneumothorax is *always* managed surgically (see Penetrating Thoracic Injury).

126.1.2 Hemothorax

Hemothorax is the accumulation of blood in the pleural space. Hemothorax results from disruption of pulmonary, thoracic wall, or mediastinal blood vessels. Hemothorax can also be seen in dogs and cats with diaphragmatic hernia and concurrent hemoabdomen. *Clinically significant hemothorax (although uncommon) is a physical examination diagnosis*. Hemothorax results in decreased lung and heart sounds ventrally to diffusely 461
and concurrent signs of hypovolemic shock (pale mucous membranes, slow CRT, high heart rate, weak pulses) 462
and dyspnea. The volume of blood loss necessary to cause signs of hypovolemia is less than the volume that causes signs of dyspnea in dogs and cats with hemothorax. Diagnosis of a clinically significant hemothorax, much like pneumothorax, is based on thoracocentesis. Oxygen support and vigorous volume expansion techniques are always indicated as part of the initial treatment strategy for dogs and cats with hemothorax. Thoracostomy tube placement and continuous pleural drainage is indicated when greater than 5 mL/kg of blood is retrieved from the pleural space. Continuous drainage allows quantification of ongoing blood loss, prevention of atelectasis, and autotransfusion of shed blood.

Figure 126-1 Pneumothorax. Note retraction of the lung from the chest wall, consolidation of lung lobes, and the appearance of the heart falling to the side of the atelectatic lobes.



126.1.3 Diaphragmatic Hernia

Diaphragmatic hernia is most common after blunt thoracic trauma and is thought to result from rapid compression of the abdomen with the majority of the force directed cranially against an open glottis.

Penetrating thoracic and abdominal injuries can also cause diaphragmatic hernia. The dog or cat with diaphragmatic hernia may not show clinical signs or may have dyspnea, decreased lungs sounds ventrally to diffusely, borborygmi on auscultation of the thorax, an "empty" abdominal palpation, or a combination thereof. Diaphragmatic hernia is commonly associated with pleural effusion. Some dogs and cats may develop clinical signs of diaphragmatic hernia months to years after the initial trauma. Oxygen support will be beneficial in the initial stabilization of animals with diaphragmatic hernia. In addition, positioning the pet with the chest slightly higher than the abdomen may promote movement of mobile abdominal viscera back into the abdomen. Diaphragmatic hernia may be suspected on physical examination but is confirmed through diagnostic imaging techniques (survey radiographs, positional radiographs, positive contrast peritoneography, upper gastrointestinal contrast study, ultrasound, or computed tomography). Diaphragmatic hernia is a surgical problem that necessitates elective repair as soon as the respiratory and cardiovascular systems have been stabilized. Indications for immediate surgical intervention include fever, small bowel obstruction, biliary obstruction, protracted vomiting or a distended stomach within the pleural space. In the latter clinical syndrome, transthoracic gastrocentesis or orogastric intubation are indicated prior to anesthesia to relieve signs of dyspnea. Prognosis for survival of dogs and cats with diaphragmatic hernia ranges from 50% to 90%.

126.2 TRAUMA-ASSOCIATED PULMONARY INJURIES

126.2.1 Pulmonary Contusion

Pulmonary contusion (PC) refers to lung lesions that occur after a compression-decompression injury. Subsequent hemorrhage and edema lead to alveolar collapse and lung consolidation. Hypoxemia results from ventilation: perfusion mismatch, shunt, diffusion impairment, and in severe cases, hypoventilation. Much like pneumothorax, pulmonary contusion is common after trauma. *All dogs that have sustained trauma have PC until proven otherwise*. If the veterinarian makes this assumption, they are more likely to identify important physical examination findings and make treatment decisions that will improve outcome. *The presence of clinically significant PC (severe enough to cause clinical signs) is a physical examination diagnosis*. On auscultation of the thorax, increased lung sounds distributed unevenly between the hemithoraces is most commonly recognized. However, exceptions include the presence of concurrent pleural space disease and complete lobar consolidation, both of which may result in decreased lung sounds. Coughing and hemoptysis may be seen in dogs with moderate to severe PC. Small animals with rib fractures or flail chest often have concurrent PC. Radiographic evidence of PC includes interstitial to alveolar infiltrates and lobar consolidation. Initial therapy for PC is oxygen support to maintain oxygen saturation >92%. Severity of PC can be quantified through arterial blood gas analysis and calculation of alveolar-arterial oxygen gradient and the PaO_2:FiO_2.

Treatment of PC is largely supportive. The cornerstones of therapy include oxygen delivery by cage, hood, or nasal cannulae to maintain SpO_2 greater than 92% on FiO_2<0.60 with-out severe increases in respiratory effort. Often overlooked is the importance of frequent changes in position of the animal. Standing and short walks may prevent and combat atelectasis. Positive pressure ventilation (PPV) is indicated if oxygenation or ventilation requirements cannot be met or if they can only be met with severe increases in respiration efforts. Fluid therapy in the animal with PC is challenging. Basic guidelines include maintainance of euvolemia in light of concurrent injuries, maintainance of hydration, and efforts to avoid fluid overload. Despite numerous opinions, there is no clear answer to the question of whether crystalloid or colloid therapy is most appropriate for dogs with PC. In a 1999 study by Powell et al, corticosteroids were not shown to decrease duration of hospitalization or need for oxygen support. Because PC is associated with increased vascular permeability, furosemide is unlikely to be of benefit unless iatrogenic fluid overload has taken place. Bronchodilators are unlikely to be of benefit because PC is not a reactive small airway disease, and antibiotics are not indicated because of the exceedingly low

incidence of bacterial pneumonia in dogs with PC. Prognosis for dogs with PC is based on severity of pulmonary injury but is generally good. Dogs that require positive pressure ventilation to maintain oxygenation and adequate ventilation have a more guarded prognosis.

126.3 TRAUMA-ASSOCIATED THORACIC WALL INJURIES

Thoracic wall trauma is most often associated with a host of concurrent thoracic injuries such as pneumothorax and pulmonary contusion.

126.3.1 Penetrating Thoracic Injury

Wounds to the thorax should be immediately covered with an occlusive sterile dressing. Following stabilization and management of concurrent injuries (pneumothorax) and radiography, the dog or cat should be placed under general anesthesia and the wounds explored. Simple probing is *not* adequate to determine whether or not wounds have penetrated the pleural space. Penetrating thoracic wounds should be explored, debrided, lavaged, cultured, and reconstructed with use of appropriate drainage techniques. Broad-spectrum antibiotic therapy is indicated to combat bacterial infection. Antibiotic therapy should be empirical based on likely contaminants while culture is pending. The external wound in animals with penetrating thoracic injury is often the "tip of the iceberg" and necessitates an aggressive, proactive approach to maximize the likelihood of a favorable outcome.

126.3.2 Rib Fractures and Flail Chest

Rib fractures happen with variable frequency after trauma and are diagnosed based on physical examination and/or thoracic radiography. Pain is the primary problem induced by rib fractures; however, penetration of the visceral pleura by a broken rib could result in pneumothorax and/or hemothorax. The chest wall is a resilient structure that requires significant force to cause a fracture. When such forces are applied across the thorax, intrathoracic injury is common. *Rib fractures are commonly associated with pulmonary contusion*. Pain associated with rib fractures can be controlled with regional anesthesia (narcotic epidural), systemic analgesics, or local intercostal blockade with bupivicaine (dogs: 0.75% solution diluted to 0.25% infiltrated as a small bleb caudal to the rib and dorsal and ventral to rib fractures; block single nerves cranial and caudal to the injured rib or segment; total dose should not exceed 1.5 mg/kg and extreme caution should be exercised so as not to compromise ventilation by blocking too many intercostal nerves). Flail chest refers to the fracture of multiple adjacent ribs in multiple locations, which creates a floating thoracic segment that moves paradoxically to the remainder of the chest wall. Flail chest is a diagnosis based on physical examination. The combination of pendulous airflow, underlying pulmonary trauma, concurrent pleural space injuries, and pain predispose to hypoxemia and hypoventilation. Treatment of flail chest should initially be directed towards pain control and management of concurrent thoracic injury (e.g., pulmonary contusion, pneumothorax, etc.). Surgical fixation of flail chest is frequently unnecessary. When needed, it should be performed after the animal is stable.

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126.4 TRAUMA-ASSOCIATED MYOCARDIAL INJURY

126.4.1 Arrhythmias

Cardiac arrhythmias, most commonly of ventricular origin, are often diagnosed 12–36 hours after trauma. These arrhythmias, often referred to as "traumatic myocarditis" and "myocardial contusion," may result from direct injury to the heart but are more likely a result of transient decreased myocardial oxygen delivery resulting from shock, with subsequent ischemia and later reperfusion injury. Physical examination may reveal pulse

deficits, high pulse rate, and/or weak pulses. Severe arrhythmias may cause signs of shock. Common arrhythmias include isolated premature ventricular contractions, accelerated idioventricular rhythms, and ventricular tachycardia. Much debate exists as to when or if trauma associated ventricular arrhythmias need to be treated. Definite indications for treatment of ventricular arrhythmias include heart rate greater than 180 bpm, R on T phenomena, and any arrhythmia that is causing signs of decreased tissue perfusion. It is recommended that treatment be based on heart rates greater than 140 bpm, to decrease myocardial (and thus whole body) oxygen consumption. Prior to use of antiarrhythmic agents, blood pressure should be normalized (if possible), SpO_2 should be greater than 93%, and electrolyte and acid base status should be normalized. Subsequent treatment with lidocaine (2 to 4 mg/kg bolus followed by 50 to 80 μg/kg/min CRI in dogs) will abolish most ventricular arrhythmias. Refractory arrhythmias causing clinical signs of decreased perfusion of the tissues may be treated with procainamide. Most trauma-associated arrhythmias will resolve over 2 to 4 days.

126.4.2 Pericardial Effusion

Pericardial effusion is a rare complication of trauma in the dog and cat; however, it should be considered as a differential diagnosis in animals with clinical signs of shock. Clinically significant pericardial effusion should be suspected from physical examination findings and confirmed through echocardiographic assessment. Physical examination findings consistent with pericardial effusion include pale mucous membranes, slow capillary refill time, and muffled heart sounds, pulsus paradoxus (waxing and waning pulse pressure with respiratory cycle), and distended jugular veins. In the trauma situation, however, these physical examination findings may be complicated by concurrent injuries and hypovolemia. In this situation echocardiography is the most appropriate diagnostic test. Thoracic radiography may be helpful, but in acute pericardial effusion, the cardiac silhouette may not appear significantly enlarged although it may be more round than normal. Pericardial effusion should be relieved by pericardiocentesis.

126.5 TRAUMA-ASSOCIATED MEDIASTINAL INJURY

126.5.1 Pneumomediastinum

Pneumomediastinum is defined as an accumulation of air within the mediastinal space and, like rib fractures, should serve as a “flag” for concurrent injuries. Pneumomediastinum may result from injury to the large airways (see below), esophagus, alveoli (with subsequent tracking of air back into the mediastinum), and the cervical region. In the cervical region, air can track along the trachea and vascular structures of the neck into the mediastinum. Pneumomediastinum is rarely of clinical consequence but may be suspected in animals with subcutaneous emphysema in the cervical region. Pneumomediastinum can be definitively diagnosed on thoracic radiographs. An effort should be made to identify and definitively treat concurrent injuries.

126.5.2 Tracheal Avulsion

Tracheal avulsion is thought to occur due to a rapid and extreme hyperextension injury to the head or neck and is more common in cats than in dogs. Tracheal avulsion may affect the intrathoracic or extrathoracic trachea. Both intrathoracic and extrathoracic tracheal avulsion can be associated with subcutaneous emphysema, signs of respiratory distress, and airway obstruction on initial physical examination. Radiographic examination will illustrate pneumomediastinum and may or may not reveal discontinuity of the tracheal silhouette. Frequently, clinical signs will abate as the airway is maintained by a thin mediastinal reflection. However, within the following 1 to 2 weeks, dyspnea usually develops secondary to fixed airway obstruction as the ends of the

avulsed trachea begin to stenose. Subsequent radiographic evaluation will better illustrate lack of continuity of the tracheal silhouette. Treatment is surgical repair and reconstruction of the trachea.

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127 CHAPTER • 127 Blood Transfusions, Component Therapy, and Oxygen-Carrying Solutions

Ann E. Hohenhaus

Important advances have occurred in veterinary transfusion medicine over the past 10 years due to an increased knowledge and expertise. The major innovation has been the advent of component therapy. Component therapy is considered the optimal method of transfusion since it allows specific transfusion therapy: red blood cells for anemia and plasma to provide deficient coagulation factors. The use of whole blood in anemic patients wastes the plasma, which could be used to control hemorrhage in a dog with anticoagulant rodenticide toxicity. A dog with anemia secondary to chronic renal failure does not require coagulation factor replacement and needs only a red blood cell transfusion. The plasma from this unit of blood can be used for a different dog with a bleeding disorder. By transfusing only the component required to treat the disorder, the risk of adverse reaction is decreased while efficacy is maintained.

Blood for the production of components is collected as whole blood in an anticoagulant preservative solution. The collection bag is sterilely manufactured and comprises multiple bags interconnected via sterile tubing. The whole blood collected into this system is processed through one or more centrifugation steps to produce the various blood components. Each component has a specific composition, storage requirement, and clinical use (Table 127-1). Blood components are the products typically available from veterinary blood banks (Table 127-2).

Table • 127-1 Blood Products Available from Veterinary Blood Banks

PRODUCT	CONTAINS	USES	DOSAGE*	REACTIONS
Whole blood	RBCs, WBCs, plasma, platelets, anticoagulant	Feline transfusions	10–20 mL/kg	Fever, acute hemolytic
		Hypovolemic anemia Pediatric transfusions		Volume overload
Packed red blood cells	RBCs	Clinically symptomatic anemia	6–10 mL/kg	Acute hemolytic, fever
Fresh frozen plasma	Plasma, anticoagulant	Coagulation factor deficiency	6–10 mL/kg	Volume overload, allergic, fever
	All clotting factors, immunoglobulins	Failure of passive transfer		
Frozen plasma	Plasma, anticoagulant	Failure of passive transfer	6–10 mL/kg	Volume overload, allergic, fever
	Low levels of clotting factors, immunoglobulins			
Cryoprecipitate	Factors VIII, XIII, vWF, fibrinogen	Deficiency of factors VIII, XIII, vWF, fibrinogen	1 unit/10 kg	Allergic, fever
Cryo-poor plasma	Factors II, IV, IX, X	Rodenticide intoxication	6–10 mL/kg	Allergic, fever
Platelet rich plasma	Platelets, plasma	Decreased platelet production	1 unit/10 kg	Allergic, fever
Frozen platelets	1×10^{11} platelets	Undefined	1 unit/10 kg	Bradycardia
	DMSO, plasma	ITP?		

* The dosage of any blood product is simply a guideline for the initial transfusion. All transfusions are given "to effect," which means that until the RBC count is high enough to adequately improve the recipient's oxygenation or adequate coagulation factors have been transfused to cor-rect the hemorrhagic process. *NA,* Not applicable.

To improve the ability of veterinarians to use blood components effectively, this chapter discusses the various components available for use in veterinary patients regarding their composition, clinical use, dosage, and most common adverse reactions. Although there have been many advances in veterinary transfusion medicine, there is currently not a consensus regarding the size of a "unit" of blood. For the purposes of this chapter, a unit of canine whole blood will be defined as the American Association of Blood Banks defines a unit of human blood (see Table 127-2). A unit of whole blood will be the blood (450 mL +/−45 mL) plus the anticoagulant (63 mL) collected from one dog into a standard blood bag. A "unit" of a component is the volume of product, for example, packed red blood cells or fresh frozen plasma obtained from 1 unit of whole blood. This information will not apply to blood from all blood banks, and the reader is referred to the specific product inserts for information regarding a particular blood bank's products. Because feline blood is collected in such a small volume (40 to 50 mL of whole blood per cat) and there is a lack of appropriate sized multi-bag systems, feline blood is not routinely processed into components, but it is possible to do so and feline components can be purchased from some veterinary blood banks.

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Table • 127-2 Volume in Various Units of Canine Blood Products

COMPONENT	VOLUME OF BLOOD OR PLASMA	VOLUME OF ANTICOAGULANT	TOTAL VOLUME IN ONE UNIT
Whole blood in standard anticoagulant	405–495 mL	63 mL	468–558 mL
Packed red blood cells in additive solution	200–240 mL	100-mL additive solution	300–350 mL
Packed red blood cells	200–240 mL	NA	200–240 mL
Fresh frozen plasma	200–240 mL	NA	200–240 mL
Cryoprecipitate	60–70 mL	NA	60–70 mL
Cryo-poor plasma	~100 mL	NA	~100 mL
Platelet rich plasma	200–240 mL	NA	200–240 mL

When deciding to transfuse a patient with either a red blood cell product or a plasma product, the veterinarian must have in mind the goal of administering the transfusion. The veterinarian must recognize that transfusions do not cure any disease but merely supplements an absent or deficient component of blood on a temporary basis while the underlying disease is treated and the deficiency resolves. The decision to transfuse should always weigh the expected benefit to the patient against the risk of adverse effects of the therapy. To ensure safe administration of a transfusion, each patient who receives a transfusion will require pretransfusion testing, and monitoring during and after administration to prevent or recognize the side effects of that particular blood component.

127.1 RED BLOOD CELL PRODUCTS

Blood products that contain red blood cells include whole blood, packed red blood cells (pRBCs), pRBCs in additive solution, and leukoreduced pRBCs. The only indication for transfusion of a red blood cell containing component is a clinically symptomatic anemia (Table 127-3). Packed red blood cells, pRBC in additive solution, and leukoreduced pRBCs are appropriate products to treat anemia caused by blood loss, hemolysis, or bone marrow failure (see Table 127-3). Patients who are assymptomatic for their anemia do not need to be transfused, but an exact hemoglobin concentration or hematocrit level at which a red blood cell transfusion should be given has not been determined. Clinical signs of anemia that indicate red blood cell transfusion should be considered are tachycardia, weakness, tachypnea, and collapse. However, these clinical signs can also be attributed to many underlying diseases associated with anemia. The ability for physiologic mechanisms to compensate for a lack of red blood cells and the body's ability to produce red blood cells should be considered in the decision to transfuse. Because full compensation for anemia requires several days, a rapid onset of anemia from traumatic hemorrhage will require transfusion at a higher hemoglobin concentration or hematocrit than an anemia with a slow onset, such as pure red cell aplasia. Dogs or cats with pulmonary disease may require a transfusion at a higher hematocrit than

those without, since the compromise of the respiratory system will decrease oxygenation of hemoglobin. Concurrent cardiac disease may limit the compensatory increase in cardiac output in response to anemia and dogs and cats with significant cardiac disease may require a transfusion at a higher hemoglobin or hematocrit than those without cardiac disease. When the hemoglobin reaches 3 g/dL or the hematocrit 12%, the major organs have reached the limit in their ability to compensate for a lack of red blood cells and the need for red blood cell transfusion is urgent. Above that level of hemoglobin concentration or hematocrit, the requirement for transfusion becomes less urgent and the clinical status of the patient, the rapidity of decline of red blood cells and the ability of the bone marrow to replace the red blood cells must be weighed against the likelihood of adverse effects from transfusion.

Table • 127-3 Suggested Blood Components for Treatment of Various Anemias

TYPE OF ANEMIA	OPTIMAL COMPONENT	ALTERNATE COMPONENT	ALTERNATE COMPONENT
Blood loss anemia (hypovolemic)	Packed red blood cells and crystalloid or colloid solutions	HBOC	Whole blood
Blood loss anemia (normovolemic)	Packed red blood cells	HBOC	Whole blood
Anemia of chronic renal failure	Packed red blood cells	Whole blood	
Anemia of bone marrow failure	Packed red blood cells	Whole blood	HBOC
Hemolytic anemia	Packed red blood cells	HBOC	Whole blood

HBOC, Hemoglobin based oxygen carrier.

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Pretransfusion testing prior to transfusion of a red blood cell containing component should include a blood type in every cat receiving a red blood cell transfusion. If a cat has not previously been transfused, a blood type is sufficient pretransfusion testing. Blood typing or cross matching a dog prior to the first transfusion is not necessary. In subsequent transfusions in both, dogs and cats, a cross match should be performed to determine compatibility of the red blood cells to be transfused.

The most serious adverse effect of administration of any red blood cell containing component is acute hemolytic transfusion reaction due to recipient antibodies against the donor red blood cells. The most common reaction, fever, is believed to be due to cytokines contained in the transfused blood or from antibodies against RBC, WBC, or platelets. As with any transfusion, there is a risk of volume overload, Type I hypersensitivity reactions causing facial edema, allergic reactions, vomiting, and fever.

Whole blood (WB) is blood collected from the donor, plus the anticoagulant. A standard blood bag contains 63 mL of anticoagulant. It is probably the most commonly used product in veterinary practice since it can be produced without any expensive equipment. Whole blood is typically used to transfuse cats. Feline units of blood are usually 40 to 50 mL of blood plus 5 to 9 mL of anticoagulant preservative solution. Ideally, WB should rarely be used in the dog since component therapy conserves blood and allows more dogs to be transfused from one unit of donated blood. WB would be most appropriate in pediatric transfusions when it would waste an entire unit of blood to open it for 10 or 20 mL to transfuse a small puppy. Whole blood would also be appropriate for exchange transfusions, in which the patient's blood is removed and replaced. In addition to supplying red blood cells, whole blood would replace clotting factors and albumin, which are removed in the exchange process. Whole blood could be used for patients who are experiencing hypovolemic anemia from hemorrhage, but packed red blood cells and crystalloid or colloid solutions will achieve the same effect.

Whole blood should not be used in normovolemic anemia because of the risk of volume overload from the additional volume plasma adds to the transfusion.

The initial dosage of WB is 10 to 20 mL/kg.

Packed red blood cells are the cells and a small amount of plasma remaining after the plasma and anticoagulant is removed. The PCV is approximately 80%, which makes pRBC very viscous. Normal (0.9%) saline is the only solution that should be added to any blood product and can be done with pRBC to improve flow.

The initial dosage of packed red blood cells is 6 to 10 mL/kg. Packed red blood cells in additive solution are processed similarly to pRBCs, but after the red blood cells are separated from the plasma, 100 mL of an additive solution are added to the red blood cells. PCV is 55% to 60%. Additive solution contains dextrose, adenine, mannitol, and sodium chloride preserving the red blood cell function longer than the traditional anticoagulants ACD or CPDA (35 to 37 versus 21 days). It eliminates the need to add saline to the pRBC to decrease viscosity and improve flow. The fresh frozen plasma obtained from this process is identical to FFP produced from standard anticoagulant bags. This blood product is administered exactly the same as pRBCs.

The initial dosage of pRBCs in additive solutions would be 10 to 15 mL/kg.

Leukocyte-reduced packed red blood cells are produced from whole blood via centrifugation in the same manner as standard packed red blood cells, but an additional processing step is used to remove the white blood cells. Removal of 99.9% of white blood cells is accomplished by passing the blood between the collection bag and an accessory bag via an integral filter. Filtration can be performed at the time of blood collection or immediately prior to transfusion. White blood cells are removed because they have been implicated as a cause of certain types of transfusion reactions. Filters are designed to remove white blood cells without decreasing red blood cell biochemical characteristics, viability, storage time, or PCV.

The major reaction to leukocyte reduced pRBCs is an acute hemolytic transfusion reaction. The risks of non-hemolytic fever, transfusion transmitted infections, immunosuppression, and alloimmunization should be decreased with leukocyte reduction. This blood product is administered exactly the same as pRBC.

The initial dosage of leukocyte reduced pRBC would be 15 mL/kg.

127.2 PLASMA COMPONENTS

Fresh frozen plasma (FFP) is the plasma obtained from WB, which has been centrifuged, and the red cells removed within 6 hours of collection (Table 127-4). The anticoagulant remains in the plasma fraction during processing. When it is frozen at −20°C, the clotting factors maintain activity for 1 year. FFP is an excellent source of clotting factors and can be used to treat a wide variety of hemorrhagic disorders, including hemophilia, von Willebrand's disease, rodenticide intoxication, and disseminated intravascular coagulation. It is not a good source of albumin or nutrition, and calculations indicate 45 mL/kg would be required to increase the serum albumin concentration by 1 g/dL. FFP may be used in puppies or kittens with failure of passive transfer. Plasma transfusions may cause volume overload or allergic reactions. Blood typing before administration of a plasma transfusion is required in cats because antibodies contained in the plasma will cause a transfusion reaction if plasma incompatible with the recipient's red blood cells is administered.

The initial dosage of FFP is 6 to 10 mL/kg one to three times daily. The dosage depends on the condition being treated. In kittens with failure of passive transfer, a dose of 150 mL/kg of serum SC or IP has raised serum IgG to normal levels. A dose of 22 to 40 mL/kg of serum has been recommended in puppies with passive transfer, but normalization of IgG levels was not attained. Plasma can be used in place of serum.

Frozen plasma (FP) is plasma that has not been processed and frozen within 6 hours of collection or fresh frozen plasma stored at−20°C for more than 1 year. Both contain reduced levels of labile coagulation factors V and VIII. It may also be produced from WB stored more than 6 hours. Frozen plasma may be used in puppies or kittens with failure of passive transfer. Albumin is preserved at that temperature for 5 years and frozen plasma may be used as a source of albumin.

The initial dosage of FP is 6 to 10 mL/kg one to three times daily depending on the condition being treated.

Cryoprecipitate is a concentrated source of von Willebrand's factor, fibrinogen (factor I), and factor VIII prepared from 1 unit of FFP. Fresh frozen plasma is thawed at 4°C. During thawing, a white precipitate (cryoprecipitate) forms in the plasma and this precipitate contains vWf, factors VIII and I. The cryoprecipitate is separated from the liquid plasma by centrifugation. The liquid plasma is termed cryo-poor plasma. Cryoprecipitate is used to treat von Willebrand's disease, hemophilia A, and fibrinogen deficiency. Storage and handling of cryoprecipitate is similar to fresh frozen plasma. It can be stored at−20°C for 1 year. Like any plasma component, cryo-precipitate may cause allergic reactions. One unit of cryoprecipitate is the amount produced from 1 unit of FFP.

The initial dosage of cryoprecipitate is 1 unit per 10 kg of body weight.

Cryo-poor plasma is the plasma that remains after the cryo-precipitate is removed. Cryo-poor plasma contains factors II, VII, IX, and X, which make it useful for the treatment of rodenticide intoxication. Storage and handling of cryo-poor plasma is similar to fresh frozen plasma. Like any plasma component, cryo-poor plasma may cause allergic reactions.

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Table • 127-4 Suggested Blood Components for Treatment of Various Coagulopathies

TYPE OF COAGULOPATHY	OPTIMAL COMPONENT	ALTERNATE COMPONENT
Anticoagulant rodenticide intoxication	Fresh frozen plasma	Cryo-poor plasma
Disseminated intravascular coagulation	Fresh frozen plasma	
Von Willebrand's disease	Cryoprecipitate	Fresh frozen plasma
Hemophilia A Factor VIII deficiency	Cryoprecipitate	Fresh frozen plasma
Hemophilia B Factor IX deficiency	Fresh frozen plasma	
Liver disease coagulapathy	Fresh frozen plasma	

The initial dosage of cryo-poor plasma is 1 unit per 10 kg of body weight.

Platelet-rich plasma (PRP) is prepared from fresh whole blood by centrifugation at a slower centrifuge rate than for production of pRBC and plasma. The platelets are suspended in plasma to facilitate transfusion and transfused within hours of collection. PRP should not be refrigerated as it inactivates platelet function. Allogeneic platelet transfusions should be most useful in cases of decreased platelet production rather than cases of increased consumption or destruction of platelets. Unfortunately, increased destruction of platelets is the most common cause of thrombocytopenia in the dog. Platelet transfusions may cause allergic reactions or fever. Multiple platelet transfusions may result in alloimmunization and refractory thrombocytopenia.

The dosage is 1 unit of platelets via PRP per 10 kg of body weight.

127.2.1 Other Blood Components

Frozen platelets are collected through plateletpheresis. Platelets are preserved by DMSO and also contain a small amount of fresh frozen plasma. Efficacy data on this product has not been published, but immune-mediated thrombocytopenia is the recommended target disease for this product. Because the product contains DMSO, it must be infused slowly or bradycardia will result. The dosage is 1 unit of platelets per 10 kg of body weight. The product insert indicates this dose should increase the platelet count 20,000/μL when measured 1 to 2 hours post transfusion.

Human immunoglobulin is a concentrated source of immunoglobulin produced from the plasma of more than 1000 human donors via ethanol cold fractionation technique. In a limited number of cases, it has been used to treat acute canine immune-mediated hemolytic anemia (IMHA). Human immunoglobulin has also been used to treat immune-mediated thrombocytopenia in humans and cutaneous drug reactions in a dog and a cat. It is believed that providing the large number of immunoglobulin molecules overwhelms the reticuloendothelial system and prevents it from destroying additional red blood cells. Immunoglobulin may also neutralize or modulate pathogenic autoantibodies and modulate activation and cytokine production. Immunoglobulin therapy of dogs with IMHA has been associated with thrombosis and thrombocytopenia, but these abnormalities may be a result of the primary disease not the immunoglobulin infusion. Theoretically, repeat administration could cause severe anaphylactic shock, but no reports of a second infusion have been published. The recommended dosage is 0.5 to 1 g/kg and the reconstituted product is infused over 6 to 8 hours.

127.3 OXYGEN-CARRYING SOLUTIONS

The term *blood substitute* is a poor description of intravenous solutions designed to deliver oxygen to the tissues as an alternative to homologous red blood cells. These solutions substitute for only one function of blood, the ability to carry oxygen; therefore they are used to treat patients with anemia from blood loss, hemolysis, or bone marrow failure. They do not contain coagulation factors, platelets, or white blood cells and consequently cannot perform the functions associated with those elements of blood. There are 2 major types of oxygen-carrying solutions: perflurocarbon emulsion-based carriers, and hemoglobin-based oxygen carriers (HBOC). Currently, the majority of the products are under clinical investigation in humans and the only product approved for use in veterinary patients is an HBOC.

HBOC-201 (Oxyglobin, Biopure Corporation, Cambridge, MA) differs from red blood cells in several ways. It is an acellular hemoglobin clear, dark purple solution with a pH of 7.8, produced from purified bovine hemoglobin. Oxyglobin contains 13 g/dL polymerized hemoglobin in a modified lactated Ringer's solution. It has an osmolality of 300 mOsm/kg.

Because Oxyglobin contains no red blood cells, the hemoglobin polymers transport oxygen in the plasma. Oxyglobin increases oxygen carrying capacity without increasing red blood cells; consequently, the PCV does not rise in patients who receive Oxyglobin and patient monitoring must include a measurement of total (RBC +plasma) hemoglobin to fully assess oxygen carrying capacity. Not all hematology analyzers measure hemoglobin concentration and only those that measure hemoglobin should be used to assess the effect of Oxyglobin. Hemoglobin can readily be measured using a hemoglobin meter, HemoCue, (HemoCue, Inc., Mission Viejo, CA), which has been validated in veterinary patients and uses a modified azide methemoglobin reaction to measure hemoglobin. The Hemavet multispecies analyzer (CDC Technologies, Oxford, CT), impedance analyzers and flow cytometric analyzers measure hemoglobin. I-Stat (Sensor Devices, Inc., Waukesha, WI) and IRMA Blood

Analysis System (Diametrics Medical, Saint Paul, MN) calculate hemoglobin and should not be used to measure the effect of Oxyglobin.

Although polymerization of hemoglobin molecules prolongs the half-life in the plasma over that of native hemoglobin ($t_{1/2}$ =18 to 43 hr, at a dose of 10 to 30 mL/kg), the half-life of Oxyglobin is shorter than that of transfused allogeneic red blood cells, (days to weeks). Oxyglobin is labeled to increase oxygen-carrying capacity when compatible canine blood is not available due to inadequate supply or serologic incompatibility. It has a 36-month shelf life without refrigeration, and there is no requirement for preinfusion blood typing or crossmatching since antigenic red blood cell membranes are removed during ultrapurification.

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Adverse effects differ from red blood cell–containing components. The intense purple color of the solution temporarily imparts an abnormal color to mucous membranes and urine. Fortunately, the discoloration does not affect oxygen saturation monitoring via pulse oximetry. The presence of Oxyglobin in plasma also limits laboratory testing, especially when colorimetric methodology is used. Tests most commonly affected are bilirubin, liver enzymes, creatinine, glucose, urine dipstick measurements, but the effect varies with the equipment used and the concentration of Oxyglobin in the plasma or urine. Oxyglobin is currently labeled as a single dose product, because there are concerns about the antigenicity of bovine hemoglobin in non-bovine species, but to date, antibodies do not appear to result in anaphylactic or anaphylactoid reactions in dogs administered multiple doses of the product. The large polymers of hemoglobin exert an oncotic effect in the plasma, which results in volume expansion. Parameters such as central venous pressure, respiratory rate, and respiratory sounds should be monitored during and following an Oxyglobin infusion to prevent volume overload, pulmonary edema, and pleural effusion.

The manufacturer's recommended dosage is 10 to 30 mL/kg administered as a continuous intravenous solution in dogs. Typically, the low end of the dose range is used for the initial infusion. If required, the remaining dose can be infused. Oxyglobin has not been approved for use in cats and the optimal dose and rate of infusion have not been determined in cats, although Oxyglobin has been administered safely to cats.

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128 CHAPTER • 128 Blood Pressure Assessment

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Routine assessment of blood pressure (BP) in clinical veterinary patients is a relatively recent development, and the volume of published literature regarding what is normal and abnormal in pet dogs and cats is growing rapidly. In contrast to human hypertension (HT), hypertension in veterinary patients most often is associated with a causative underlying disease[1–4] (Table 128-1). BP values obtained during diagnostic evaluation are assessed in conjunction with other clinical findings (e.g., evidence of retinal detachment, a history of polyuria and polydipsia), because these associated findings may point to the cause of the HT or indicate HT-associated end-organ damage. A single high BP value should never be used to diagnose systemic HT in the absence of other clinical information.

BP measurements that exceed published normal ranges are not always indicative of disease. Patient distress[5] or physical manipulations, such as fluid administration, may elevate BP acutely. The degree of clinical concern associated with elevated BP is proportional to the degree of elevation in combination with the clinical signs and clinical condition of the patient.

128.1 DEFINITION OF NORMAL

Normal ranges for BP in dogs[6–9] and cats[4,10–12] are often expressed as a mean value for a normal population ±2 standard deviations; animals with BP values outside this range are considered abnormal. The drawbacks to this approach to diagnosis of HT include inadvertent inclusion of normal animals with a BP value outside the "95% range" (leading to unnecessary diagnostic testing or therapy) or exclusion of HT as a diagnosis in an affected animal with mild or moderately elevated values (increasing the risk of end-organ damage). In addition, a dichotomous "normal" versus "too high" diagnostic result cannot take into account the differing risk of end-organ damage with increasing BP values.

Table • 128-1 Diseases/Clinical Findings Commonly Associated with Systemic Hypertension in Dogs and Cats*

DOGS	CATS
Ocular findings consistent with hypertensive choroidopathy, hypertensive retinopathy or intraocular hemorrhage	Ocular findings consistent with hypertensive choroidopathy, hypertensive retinopathy or intraocular hemorrhage
Chronic or acute renal failure	Chronic or acute renal failure
Hyperadrenocorticism	Hyperthyroidism
Diabetes mellitus	Diabetes mellitus
Neurologic signs unexplained by other causes	Any neurologic signs
Pheochromocytoma	Age ≥10 years
Unexplained left ventricular hypertrophy	Murmurs gallop rhythm
	NOTE: Idiopathic hypertrophic cardiomyopathy cannot be diagnosed without excluding hypertension.

* A complete funduscopic examination and BP measurement are indicated in animals known to have or suspected of having these disease conditions. Conditions that are rare in the species (e.g., hyperthyroidism in dogs) are not included. BP measurement is often included in routine cardiac evaluations.

Another approach to the diagnosis of HT is based on establishing diagnostic "cutoff" values at the level usually associated with clinically detectable disease. Clinical information regarding the BP typically associated with ophthalmologic[13] and renal[2,4,11] abnormalities in spontaneous canine and feline HT is available, but there is no information about threshold BP values for end-organ damage in this group of patients. Furthermore, the "trigger point" at which elevated BP results in clinical signs likely differs from patient to patient and may be affected by the rapidity with which the HT develops.[14]

Previous definitions of the high end of normal for dogs varied between 160 and 180 mm Hg and between 160 and 200 mm Hg in cats, but progression of renal damage in dogs is already enhanced with systolic BP (SBP) values in this range,[15] and clinical studies have documented end-organ damage at SBP values as low as 170 mm Hg.[13] Accordingly, current recommendations consider a SBP greater than or equal to 160 mm Hg (as measured by oscillometric or Doppler ultrasonographic methods) worthy of further diagnostic concern in both dogs[16] and cats,[17] although the use of antihypertensive medications may not be warranted (Table 128-2). The prevalence and importance of diastolic HT in dogs and cats are not well defined, therefore most recommendations for BP assessment relate to systolic BP measurement.

Table • 128-2 Recommended Approach to Assessment of Abnormal Blood Pressure Values

PATIENT STATUS	BLOOD PRESSURE (mm Hg)	RISK OF END-ORGAN DAMAGE	RECOMMENDED ACTION*
Clinical signs of hypertension (HT): Known underlying disease	≥180/120	High	Begin anti-HT medication prior to full evaluation of underlying disease conditions. Treat underlying disease.
	160–179/100–120	Moderate	Begin anti-HT medication prior to full evaluation of underlying disease conditions. Treat underlying disease.
	150–159/95–100	Low	Begin anti-HT medication prior to full evaluation of underlying disease conditions. Treat underlying disease.
	<150/95	Minimal	Treat underlying disease. Search for other causes of clinical signs (e.g., coagulopathy). If no other cause of signs is found, monitor BP over time.
Clinical signs of HT present No known underlying disease present	≥180/120	High	Begin anti-HT medication prior to full evaluation of underlying disease conditions. Perform diagnostic evaluation for underlying disease.
	160–179/100–120	Moderate	Begin anti-HT medication prior to full evaluation of underlying disease conditions. Perform diagnostic evaluation for underlying disease.
	150–159/95–100	Low	Consider anti-HT medication prior to full evaluation of underlying disease conditions. Perform diagnostic evaluation for underlying disease. Search for other causes of clinical signs (e.g., coagulopathy).
	<150/95	Minimal	Search for other causes of clinical signs (e.g., coagulopathy), If no other cause of signs is found, monitor BP over time.
No clinical signs of HT present	≥180/120	High	Treat underlying disease. Begin anti-HT medication.
At risk due to concurrent disease	160–179/100–120	Moderate	Treat underlying disease. Consider anti-HT medication if rapid resolution of underlying disease is not anticipated.
	150–159/95–100	Low	Treat underlying disease.

			Monitor BP every 3–6 months for progression.
	<150/95	Minimal	Treat underlying disease. Monitor BP every 3–6 months for progression.
Clinically healthy	≥180/120	High	Confirm BP value by repeated testing. If values are consistent, consider therapeutic trial of anti-HT medication.†
	160–179/100–120	Moderate	Confirm BP value by repeated testing. If values are consistent, monitor BP every 3–6 months for progression or development of clinical signs or compatible disease.
	150–159/95–100	Low	Confirm BP value by repeated testing. If values are consistent, monitor BP every 3–6 months for progression.
	<150/95	Minimal	Normal No further testing is indicated.

* The clinical course of action should be tailored to the individual patient's circumstances. Recommendations may change as more clinical information becomes available.

† The normal BP range for healthy sight hounds may be higher than for other breeds.[20]

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128.2 APPROACH TO PATIENT GROUPS

The goals of detection of HT in cats and dogs are to alleviate clinical signs and to prevent future clinical signs or subclinical deterioration of organ function. Veterinary clinicians are at a disadvantage in the early detection of clinical signs of HT. In humans, stage 1 and stage 2 HT (BP values of 140–179/90–109 mm Hg) are frequently asymptomatic. When symptoms are reported, they often include patient perceptions that would be difficult to assess in veterinary patients, including morning headaches, a sense of fullness in the head, or "general unease"[18]. Similar BP, however, values have been associated with progression of renal damage in dogs with renal failure.[15] Because the first clinical sign of HT in dogs and cats may be catastrophic (e.g., retinal detachment), detection of BP elevations below the level likely to produce clinical signs is preferable. Therefore, except for in patient with overt clinical signs, detection of HT is a preventive measure. BP values are obtained using accurate and repeatable methodology (see Diagnostic Blood Pressure Measurement, Chapter 76). Persistent elevation of BP is a clinical finding that leads to further clinical investigation and to consideration of therapy.

128.3 PATIENTS WITH CLINICAL SIGNS OF HYPERTENSION

Hypertension has been documented in association with clinical abnormalities of the ocular, neurologic, cardiovascular, and renal systems,[13,19,20] and effective therapy of HT in these circumstances typically eases, if not resolves, clinical signs.[13] Animals with clinical signs of HT and elevated BP should receive immediate antihypertensive therapy to decrease BP and thereby alleviate clinical signs. A detailed evaluation for known causes of HT in the species in question follows acute antihypertensive therapy. In some cases, gaining control of

the underlying disease (e.g., pheochromocytoma, hyperadrenocorticism) may result in lowering or normalization of BP.

128.4 PATIENTS AT RISK FOR HYPERTENSION

Patients considered at risk for HT are those with no clinical signs of HT that have a disease condition or clinical signs of a disease known to be associated with HT in that species. Even though little reliable information is available on the effect of the duration of BP elevation and the extent of end-organ damage in spontaneous canine and feline HT, it is likely that with the exception of acute, extreme BP elevations, chronic BP elevations are more damaging to end-organ vascular beds than short-term elevations. Therefore early detection of elevated BP in dogs and cats at risk is aimed at detecting and managing any treatable underlying conditions and at attempting to maintain BP within a range less likely to lead to end-organ damage (see Table 128-2).

128.5 APPARENTLY HEALTHY PATIENTS

The prevalence of HT in apparently healthy dogs is low,[21] and oscillometric and Doppler ultrasonographic test methods are moderately sensitive and specific at a diagnostic SBP cutoff value of 160 mm Hg.[16] These test characteristics result in a low positive predictive value for abnormal test results in healthy dogs. Therefore, based on current information, routine screening of BP in this population is not recommended. The prevalence of HT in the healthy feline population is also low,[10] but the prevalence of renal disease and hyperthyroidism (both diseases commonly associated with feline HT) in older cats is high enough to prompt consideration of routine screening of cats over the age of 10 years.[13,17]

BP assessment is a diagnostic test indicated in patients likely to have HT and as part of preventive medical care in patients at risk. Aspects of BP assessment that may change over time include the degree of BP elevation leading to clinical concern and possibly intervention, the importance placed on systolic versus diastolic HT, and the selection of patient groups to be included in screening procedures.

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129 CHAPTER • 129 Pathophysiology of Systemic Hypertension

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Systemic arterial blood pressure (BP) is the product of cardiac output and total peripheral resistance. Cardiac output may be further factored as the product of heart rate and stroke volume, yielding the following relationship:

$$\text{BP} = (\text{Heart rate} \times \text{Stroke volume}) \times \text{Total peripheral vascular resistance}$$

Thus any factor or process that persistently elevates one or more of these three determinants of BP can cause systemic hypertension. Similarly, to be effective, antihypertensive therapy must target one of the three determinants of BP.

Systemic hypertension can be simply defined as persistently elevated BP. Systemic hypertension is often defined on the basis of BP measurements in human beings as a systolic BP (SBP) greater than 140 mm Hg and/or a diastolic BP (DBP) greater than 90 mm Hg. In dogs and cats the definition of systemic hypertension is controversial, although one definition that applies to cats and most breeds of dogs is a SBP greater than 160 mm Hg and/or a DBP greater than 100 mm Hg in repeated, reliable measurements of BP in a calm animal.

The term *isolated systolic* (and *diastolic*) *hypertension* refers to a condition in which only the SBP (or DBP) persistently exceeds the corresponding normal range. In the past physicians were more concerned about elevation of the DBP, but recent studies suggest that end-organ damage, particularly renal, is better correlated with the degree of SBP elevation. Isolated systolic hypertension is common in elderly people as the result of a loss of arterial compliance, which develops as arterial walls stiffen with age. Although isolated systolic and diastolic hypertension is observed in dogs and cats, the prevalence and importance of these findings have yet to be well studied in veterinary medicine.

129.1 CLASSIFICATION SYSTEM

Systemic hypertension is often classified on the basis of causation as either primary (essential) or secondary. *Essential hypertension* exists when BP is persistently elevated even though a careful diagnostic evaluation fails to identify a cause of the hypertension. *Secondary hypertension* occurs when there is a known cause, generally a disease process that alters renal or neurohormonal functions. A clinical definition of essential hypertension is persistent elevation of BP in an animal with no clinical or biochemical evidence of a renal or endocrinologic abnormality that could cause hypertension (e.g., hypercorticism, hyperthyroidism, pheochromocytoma, hyperaldosteronism, or diabetes mellitus). Because of the broad normal ranges for creatinine and blood urea nitrogen (BUN) levels, the absence of azotemia is a necessary, but not sufficient, condition to eliminate renal disease as a cause of secondary hypertension in a dog or cat. Only a normal urinalysis, normal glomerular filtration rate (GFR), and normal renal biopsy can achieve this purpose. Essential hypertension accounts for 95% of cases of hypertension in human beings but has rarely been identified in dogs and has not been conclusively reported in cats.

Although used for decades in human beings, this primary (essential) versus secondary terminology is overly simplistic and misleading. As noted above, the BP cannot be elevated unless stroke volume, heart rate, and/or peripheral vascular resistance are increased (i.e., something must be abnormal). More important, the normal long-term renal response to systemic hypertension is natriuresis and diuresis, which should normalize the BP by reducing extracellular fluid volume and cardiac output. Therefore BP cannot remain persistently elevated without

an abnormality in renal sodium handling. Indeed, the kidney must play a causal or permissive role in any animal with systemic hypertension. At the very least, a functional kidney "disease" exists in every chronically hypertensive animal, regardless of whether the animal has essential or secondary hypertension. Nonetheless, it is important in the clinical evaluation of every hypertensive animal that an exhaustive search be made for an inciting cause of the increase in BP. This distinction between primary (essential) and secondary hypertension suggests and facilitates that search; for this reason, this terminology remains useful for clinical purposes.

129.2 GENESIS OF HIGH BLOOD PRESSURE

Because essential hypertension is rare in veterinary medicine, yet accounts for 95% of cases of identified hypertension in human beings, it might be expected that systemic hypertension is uncommon in veterinary medicine. To the contrary, diseases associated with secondary hypertension are quite common in certain veterinary species. In particular, chronic renal disease is frequently observed in geriatric cats and dogs, with the prevalence reaching nearly one in three cats in select populations. Because kidney disease is often associated with disturbances of neuroendocrine factors and body fluid balance, it is not surprising that most, although not all, surveys have identified systemic hypertension in a significant proportion of cats and dogs affected with kidney disease. Other examples of conditions associated with the development of secondary hypertension in dogs and cats include diabetes mellitus, hyperadrenocorticism, pheochromocytoma, and hyperthyroidism.

Systemic hypertension can arise from an excess of circulating glucocorticoids, caused by adrenocortical overproduction or exogenous administration. These compounds have a variety of effects, including a mineralocorticoid type, which stimulates renal retention of salt and water and resultant increases in blood volume and cardiac output. These animals also may suffer from overproduction of renin, which elevates peripheral vascular resistance, contributing further to the development of hypertension. Animals with diabetes mellitus similarly may develop systemic hypertension as a result of overproduction of renin and blood volume expansion associated with hyperglycemia.

Hyperthyroidism is relatively common in geriatric cats and is associated with increases in BP. Thyroid hormone enhances cardiac function and sensitivity of the myocardium to catecholamines. The result is tachycardia and increased stroke volume, resulting in systemic hypertension. It remains unclear whether hyperthyroid cats with systemic hypertension often, or always, have kidney disease as a contributing factor to the high BP.

Pheochromocytomas are rare tumors of the neuroendocrine cells of the adrenal medulla in which overproduction of epinephrine and norepinephrine leads to peripheral vasoconstriction, tachycardia, and an increase in stroke volume. Often the release of hormones is episodic, causing periodic "attacks" of tachycardia and hypertension.

A variety of medications may also produce secondary hypertension. Examples include corticosteroids (as noted above), cyclosporin A (vasoconstriction leading to increased peripheral vascular resistance), phenylpropanolamine (increased peripheral vascular resistance from alpha adrenergic effects), and erythropoietin (increased blood viscosity, which enhances peripheral vascular resistance).

The role of dietary factors in the causation of secondary hypertension is unclear in veterinary medicine. A segment of the human population and certain strains of rats exhibit sensitivity of BP to changes in dietary salt intake. However, most studies indicate that the BP of dogs and cats is salt insensitive unless the salt intake is massive or there is a pre-existing cause of secondary hypertension. However, sodium chloride (NaCl)-rich therapeutic agents can raise BP, particularly intravenous fluid and electrolyte solutions. Maintenance fluid administration with isotonic electrolyte solutions generally provides 250 to 500 mg NaCl/kg body weight/day, compared with a typical dietary intake of 25 to 50 mg NaCl/kg body weight/day. Overzealous fluid therapy, therefore, can contribute to or

cause systemic hypertension in susceptible patients. Any animal with systemic hypertension or a condition known as a possible secondary cause of hypertension (e.g., renal disease) should be considered potentially salt sensitive.

Ingestion of dietary omega-3 polyunsaturated fatty acids appears to be antihypertensive in human beings, but this may not be the case in dogs, in which these fatty acids' vascular effects appear to be intrarenal rather than systemic. Little is known about the vascular or intrarenal effects of dietary omega-3 polyunsaturated fatty acids in cats.

129.3 CONSEQUENCES OF SYSTEMIC HYPERTENSION

Unfortunately, systemic hypertension is usually asymptomatic initially and may go unrecognized for months or years until irreversible tissue damage becomes evident as organ failure ensues. Systemic hypertension in human beings is associated with complications in the cardiovascular system (e.g., myocardial infarctions, “strokes”), central nervous system (e.g., hypertensive encephalopathy, “strokes”), urinary system (e.g., progressive renal damage) and eyes (e.g., retinal and choroidal injury). In veterinary medicine, hypertension is recognized with increasing frequency in cats and dogs, where it has been linked to damage in these same tissues. Although this remains somewhat speculative, and some breeds of dogs (especially sight hounds) have unusually high normal ranges for BP, data are accumulating that suggest that cats and most breeds of dogs with systemic hypertension (systolic BP equal to or greater than 160 mm Hg) are at risk for adverse effects (Figure 129-1). The most commonly identified adverse effects of marked systemic hypertension occur when the systolic BP exceeds 180 mm Hg, especially if an acute rise in the SBP of 30 mm Hg or more occurs within 48 hours; these complications include hypertensive retinopathy (intraocular hemorrhage, retinal edema, and/or retinal detachment in cats and dogs), hypertensive encephalopathy (progressive stupor, coma, and seizures associated with intracranial edema), and central nervous system (CNS) “stroke” (uncommon in dogs and cats). At a somewhat lower BP (SBP of 160 to 180 mm Hg), chronic changes induced by hypertensive damage to the kidney, eye, and cardiovascular system are also recognized in dogs and cats; the threshold for this injury is not certain but lies at approximately 160 mm Hg in cats and most breeds of dogs.

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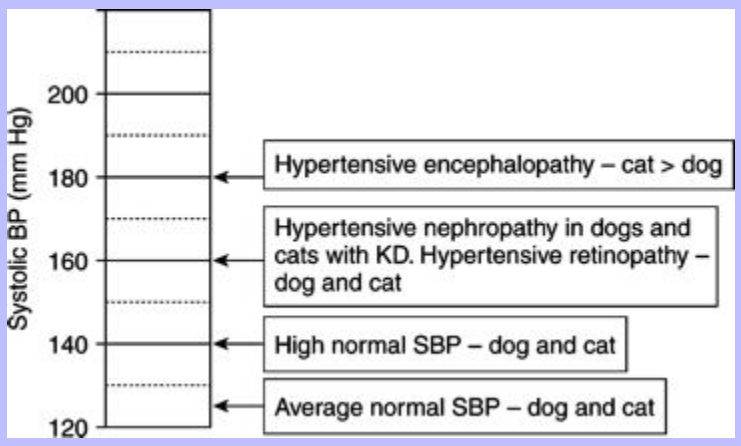
Figure 129-1 Proposed thresholds for end-organ damage in dogs and cats with systemic hypertension (see text for details).



129.4 CARDIOVASCULAR EFFECTS OF HYPERTENSION

The most commonly observed effect of hypertension in the cardiovascular system is left ventricular hypertrophy. Cardiac muscle responds to chronically increased afterload by concentric hypertrophy (increased wall thickness without dilatation). Although left ventricular stiffness and reduced diastolic filling can elevate left ventricular diastolic pressure, leading to pulmonary congestion, this is uncommon. Functional failure (congestive heart failure) is also uncommon as a sequela of hypertension in dogs and cats unless a pre-existing or additional cardiovascular abnormality is present. Left ventricular hypertrophy may be documented clinically by thoracic radiography or cardiac ultrasonography. Effective antihypertensive therapy may reverse some of these changes.

A variety of vascular changes are observed in people with chronic hypertension. High pressures in small arteries and arterioles leads to extravasation of plasma into the vessel wall, producing a thickening referred to as *hyaline arteriosclerosis*. Chronic hypertension also induces vascular smooth muscle hypertrophy. Elderly human beings develop arteriosclerosis with a loss of large artery compliance and elasticity with aging. However, these vascular changes are seemingly absent or mild in dogs and cats, because they are seldom documented in these species.

129.4.1 Central Nervous System Effects of Hypertension

Circulation to the brain is generally well regulated locally, resulting in the property of *autoregulation*. This autoregulatory control of blood flow across a range of BP is mediated primarily by arteriolar smooth muscle, which constricts in response to a rise in BP (Figure 129-2). This protects the central nervous system from many of the adverse effects of systemic hypertension across a broad range of BP. However, there is a limit to the ability of these arterioles to prevent the transmission of elevated BP to the local microcirculation (i.e., arterioles, capillaries, and venules). Further rises in BP above this autoregulatory limit lead to increases in pressure and flow within the microcirculation, which alters Starling forces across the capillary wall. The subsequent rise in intracapillary hydrostatic pressure, in particular, tends to increase transcapillary fluid filtration, promoting the development of interstitial edema within the brain parenchyma. Because the brain is "compartmentalized" within the bony cranium, this increase in interstitial volume can lead to a rise in intracranial pressure, causing neurologic dysfunction referred to as *hypertensive encephalopathy*. Clinical signs caused by brain edema may include disorientation, head pressing, ataxia, stupor, coma, and seizures. If severe, edema-induced increases in intracranial pressure can lead to cerebral herniation under the tentorium or cerebellar herniation through the foramen magnum. Brain herniation is generally a fatal complication of hypertensive encephalopathy. Although this condition occurs in both species, for poorly understood reasons, cats are particularly susceptible to the development of hypertensive encephalopathy.

Hypertension may also lead to small artery rupture and resultant localized ischemia ("stroke" or cerebrovascular accident [CVA]), but this is uncommon in veterinary species, perhaps because medium and large vessel disease (atherosclerosis and arteriosclerosis, respectively) are relatively uncommon. A CVA can occur as a result of small artery rupture within the cerebral vasculature (hemorrhagic CVA) or from vessel thrombosis (thrombotic CVA). In both cases, affected portions of the brain suffer infarction, and the animal may exhibit clinical signs such as ataxia, disorientation, seizure, stupor, or coma. These occur in hypertensive patients in veterinary medicine but seem to be less common than hypertensive encephalopathy, particularly in cats.

129.5 OCULAR EFFECTS OF HYPERTENSION

Perhaps because routine screening of animals for hypertension by BP measurement is uncommon, sudden onset of blindness from hypertensive retinopathy is one of the most common presenting complaints for animals with systemic hypertension. As with other microvascular beds (see Figure 129-2), once the upper limit of autoregulation has been reached, any subsequent rise in choroidal arteriolar and capillary flows and pressures leads to plasma leakage with associated abnormalities, including edema, hemorrhage, and detachment of the retina.

129.6 RENAL EFFECTS OF HYPERTENSION

Hypertension and kidney disease are integrally linked in human beings, with hypertension serving as a leading cause of renal failure and renal failure frequently contributing to the genesis and maintenance of systemic hypertension. This applies to any type of kidney disease, be it acute or chronic; vascular, tubulointerstitial, or glomerular; or mild, moderate, or severe. It has been argued that high BP and kidney disease are a complex cause-effect dilemma (i.e., a "chicken and egg" issue), but this is probably not the case in dogs and cats. There is no evidence that a persistent elevation of BP in the absence of a pre-existing primary renal disease can produce structural renal damage in dogs and cats. Indeed, there is evidence to the contrary. The more common scenario is the initial presence of a kidney disease, with activation of the renin-angiotensin system and/or interference with renal sodium handling, which produces systemic hypertension, which then is capable of damaging the diseased kidney.

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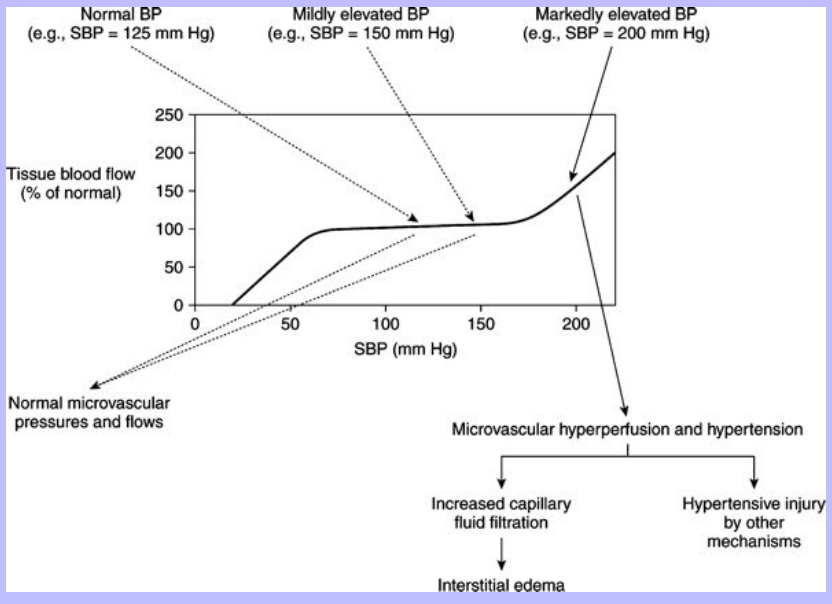
Figure 129-2 The relationship between systolic blood pressure (SBP) and tissue blood flow demonstrates a range of pressures wherein tissue blood flow is maintained constant (autoregulated) by the local vasculature. When SBP exceeds this range, tissue hyperperfusion and hypertension, and subsequent injury, ensue (see text for details).



Systemic hypertension can contribute to renal injury in dogs with kidney disease, and the same is likely to be the case in cats. The renal microcirculation is unique in that the glomerular capillary bed is both preceded and followed by an arteriole. In kidney disease of any type, patchy areas of ischemia may result in overproduction of renin, with resultant increases in circulating and/or local concentrations of angiotensin II (Figure 129-3). Systemic generation of angiotensin II raises cardiac output and peripheral vascular resistance, exacerbating systemic hypertension. Critically, if kidney disease is present, the afferent arteriole is dilated. This site-specific dilatation represents an adaptive (perhaps maladaptive) response to the presence of a kidney disease. Constriction of the efferent arteriole by angiotensin II, coupled with this afferent dilatation, dramatically raises glomerular capillary pressure. The affected glomerular capillary bed and its associated nephron and interstitium are susceptible to hypertensive injury. Chronically sustained, hypertension in a dog or cat with kidney disease and a SBP greater than 160 mm Hg can lead to nephron destruction and can contribute to progressive renal failure.

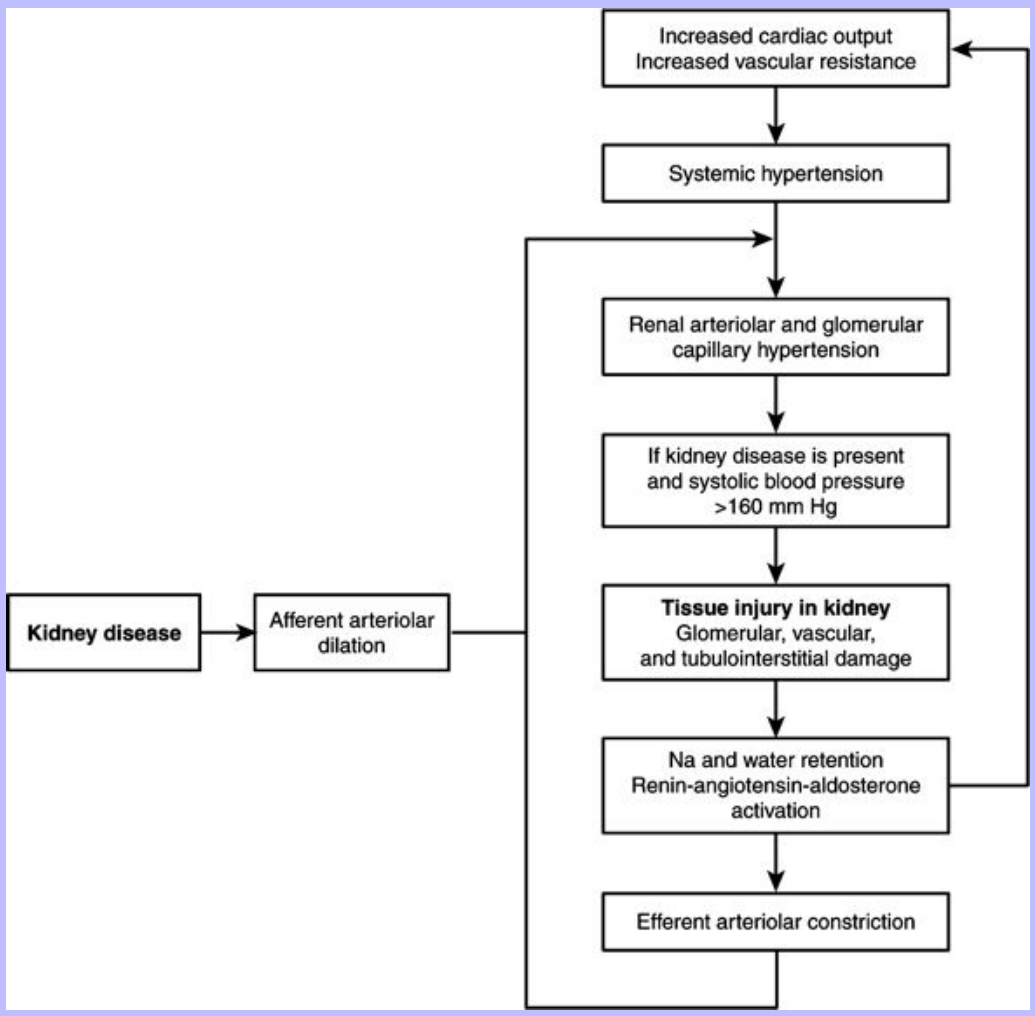
129.7 RENOPROTECTIVE ROLE OF ANTIHYPERTENSIVE AGENTS

Kidney function (i.e., GFR and microvascular pressures and flows) is generally preserved during variations in BP as a result of the intrinsic property of renal vasculature referred to as autoregulation (see Figure 129-2). The normal kidney autoregulates, or maintains stability of, its own blood flow and GFR and is capable of achieving this effect despite variations in mean BP from 60 to 160 mm Hg. Unfortunately, studies have shown that animals with acute and chronic renal insufficiency lose the ability to autoregulate renal blood flow and GFR, making them more susceptible to renal damage from increases in BP.

In animals with systemic hypertension and chronic kidney disease, the most frequently recommended antihypertensive agents are vasodilators because they tend to produce renal vasodilatation, preserving GFR. Two classes of vasodilatory agents have proved to have renoprotective effects in rodents and human beings; these are the angiotensin-converting enzyme inhibitors (ACEIs) and the calcium channel antagonists (CCAs). As noted above, glomerular capillary pressure, the largest driving force for GFR and a site for the initiation of the deleterious effects of hypertension in the kidney, depends on afferent and efferent arteriolar tone. Dilatation of the afferent arterioles or constriction of the efferent arterioles increases glomerular capillary pressure (undesirable) and GFR (desirable).

An antihypertensive with a vasodilating effect at the efferent arteriole, such as an ACEI (e.g., benazepril, enalapril, ramipril, or spirapril), lowers BP by producing systemic vasodilatation and may have other beneficial effects in hypertensive dogs with kidney disease. In cats, the role of the renin-angiotensin system in the maintenance of systemic hypertension has been questioned. However, these agents may prove efficacious, because they lower intraglomerular pressure, presumably through inhibition of intrarenal formation of angiotensin II. Alternative methods of interfering with the renin-angiotensin-aldosterone system have not been fully evaluated in veterinary medicine (e.g., aldosterone and angiotensin receptor antagonists).

Figure 129-3 Kidney disease and systemic hypertension are closely linked in a series of complex processes that are self-perpetuating (see text for details).



Some drugs classified as CCAs reduce total peripheral vascular resistance, leading to a decrease in BP. Amlodipine besylate is a long-acting dihydropyridine calcium antagonist that has been used effectively in hypertensive cats. The CCAs preferentially dilate the afferent arteriole. Vasodilatation at this site tends to raise intraglomerular pressure and could promote renal injury and/or proteinuria. However, these agents are most frequently used in cats, in which they are quite effective at lowering BP. The overall effect on intraglomerular pressure of reducing BP coupled with afferent arteriolar vasodilatation is hard to predict. Furthermore, the calcium channel antagonists have nonhemodynamic effects that may offer renoprotection. In dogs, in which CCAs seem less effective at lowering BP, use of these drugs as sole agents could predispose the animal to renal damage by allowing the high BP to be transmitted unimpeded through a dilated afferent arteriole to the susceptible glomerular capillary tuft.

Currently, co-administration of a CCA and an ACEI is advocated for hypertensive human beings with chronic kidney disease, because this therapy may reduce BP while equally dilating both the afferent and efferent arterioles, producing a balanced effect on the GFR and glomerular capillary pressure.

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130 CHAPTER • 130 Management of Hypertension

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Once a diagnosis of hypertension has been made, the decision to treat and the choice of antihypertensive medication depend on numerous factors, including the presumed cause of the hypertension, the presence of target organ damage, and the severity of the blood pressure elevation. The goals of antihypertensive therapy should be to reduce blood pressure and slow the progression of target organ damage caused by long-standing hypertension.

If an underlying cause of the hypertension can be identified, this condition should be addressed in the overall treatment plan for the hypertension. However, even if the presumed cause of the hypertension is controlled, antihypertensive treatment is usually continued indefinitely. If target organ damage is present, treatment of hypertension is usually initiated at systolic blood pressures greater than 160 mm Hg (Table 130-1). If target organ damage is not observed, documentation of a systolic blood pressure greater than 180 mm Hg on three separate occasions is considered sufficient evidence to begin treatment to lower blood pressure. There is less agreement among clinical researchers regarding treatment decisions based on diastolic blood pressure measurements.

Hypertensive animals that show neurologic signs are seen infrequently; however, if neurologic signs are observed, immediate intervention is necessary, using an antihypertensive agent that exerts gradual but effective blood pressure control. The more typical presentation is the pet with severe hypertension without life-threatening signs; these animals often exhibit such signs as blindness due to retinal hemorrhage or detachment. Because the stress of hospitalization could contribute further to elevations in blood pressure, most hypertensive animals are not hospitalized unless neurologic signs are seen. However, animals with severe hypertension deserve close monitoring, which may necessitate frequent visits for evaluation and blood pressure measurement until the hypertension improves.

Table • 130-1 Drugs Used to Treat Hypertension in Cats and Dogs

	DOSAGE	
DRUG	**CATS**	**DOGS**
Furosemide (Lasix, generic)	1–4 mg/kg PO, IV q12-48h	2–4 mg/kg PO, IV q8-24h
Atenolol (Tenormin, generic)	2 mg/kg PO q12-24h	0.25–1 mg/kg PO q12-24h
Propranolol (Inderal, generic)	2.5–5 mg total dose PO q8-12h	0.2–1.0 mg/kg PO q8-12h
Enalapril (Enacard, Vasotec, generic)	0.25–0.5 mg/kg PO q12-24h	0.5 mg/kg PO q12-24h
Benazepril (Lotensin, Fortekor)	0.25–0.5 mg/kg PO q24h	0.25–1.0 mg/kg PO q24h
Ramipril (Altace, Vasotop)	None Available	0.125–0.25 mg/kg q24h
Nitroprusside (Nitropress)	None Available	2–10 µg/kg/min IV CRI
Phenoxybenzamine (Dibenzyline)	0.25–0.5 mg/kg PO q12h	0.25–1.5 mg/kg PO q8-12h
Prazosin (Minipress, generic)	None	0.5–2 mg total dose PO q8-12h
Amlodipine (Norvasc, Istin)	0.18–0.3 mg/kg PO q24h	0.2–0.4 mg/kg PO q24h
Acepromazine (Promace, generic)	0.05–0.1 mg/kg SC, IV	0.05–0.1 mg/kg SC, IV
Hydralazine (Apresoline, generic)	2.5–5 mg total dose PO q12-24h	0.5–3 mg/kg PO q12h

130.1 DIET

Salt restriction has been the foundation of antihypertensive therapy in human beings. The goal of sodium restriction is to decrease total body sodium and extracellular fluid volume. Unfortunately, with the exception of a small population of dogs with essential hypertension, sodium restriction alone has not been shown to ameliorate hypertension in naturally hypertensive dogs and cats. Although one recent study showed that feeding a food with a moderately increased sodium level (1.0% sodium) to normotensive cats did not cause an elevation in systolic blood pressure, it should be noted that these were young cats with normal blood pressure. It is currently recommended that diets high in sodium (1.3% or higher) be discontinued if possible.

Although an obesity-induced hypertension dog model exists, and overweight dogs have slightly higher blood pressures than dogs with normal body weights, the feeding of calorie-restricted diets has not been shown to lower blood pressure in obese, spontaneously hypertensive dogs and cats.

130.2 DIURETICS

By contracting the extracellular fluid volume, diuretics decrease blood pressure. Although still commonly used in hypertensive humans, diuretics in general have not been of benefit in spontaneously hypertensive dogs or cats; however, some clinical researchers suggest that furosemide may be useful on an acute basis when used in conjunction with other antihypertensive agents. Diuretics should not be used in dehydrated, hypertensive patients or those with metabolic imbalances such as hypokalemia.

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130.3 ADRENERGIC BLOCKING AGENTS

Beta-adrenergic receptor blockers are thought to decrease blood pressure by reducing the heart rate and cardiac contractility, thereby decreasing cardiac output (an important component of blood pressure). No difference is apparent in the antihypertensive effects of the cardioselective beta blocker atenolol and the nonselective beta blocker propranolol. The advantages of atenolol are that less frequent dosing is required, and fewer $beta_2$-blocking effects (e.g., bronchoconstriction) are seen. Propranolol, when used as a single antihypertensive agent, has not been effective in hypertensive cats. Even when it is combined with enalapril and phenoxybenzamine, few cats show substantial improvement in blood pressure. Recently, propranolol and atenolol have been used in conjunction with the calcium channel blocker amlodipine in cats with refractory hypertension.

Beta blockers are considered the treatment of choice in hypertensive, hyperthyroid cats, because excess thyroid hormone causes an exaggerated response to catecholamines. If the hypertension fails to respond to beta blocker therapy, amlodipine can also be used in hyperthyroid cats. There is limited experience with the antihypertensive effects of beta blockers in hypertensive dogs. Beta blockers should not be used as an antihypertensive agent in dogs suspected of having hypertension due to a pheochromocytoma.

Blocking of postsynaptic $alpha_1$-receptors in blood vessels results in vasodilatation. Phenoxybenzamine, an alpha-adrenergic blocking agent, has been used with mixed results alone and in combination with ACEIs or amlodipine in hypertensive cats. Phenoxybenzamine is considered the antihypertensive drug of choice in dogs with pheochromocytomas. Another alpha-adrenergic blocker, prazosin, has been reportedly used in hypertensive dogs.

Labetalol, a beta-and alpha-receptor blocker, has received attention in human medicine as an antihypertensive agent for which the primary antihypertensive effect is vasodilatation by alpha-receptor blockade. Because of its

fast onset of action, it may be useful in emergency settings; however, experience with the drug in veterinary medicine currently is limited.

130.4 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme inhibitors (ACEIs) control blood pressure by blocking the conversion of angiotensin I to angiotensin II, thereby reducing circulating angiotensin II, a potent vasoconstrictor. Reducing angiotensin II concentrations also decreases the secretion of antidiuretic hormone and aldosterone, which promote sodium secretion and therefore water excretion, effectively decreasing extracellular fluid volume and lowering blood pressure. Plasma renin activity and angiotensin I concentrations were not elevated but aldosterone concentrations were increased in hypertensive cats with chronic renal failure, compared with normotensive control cats. However, in a study of 16 hypertensive cats, plasma aldosterone did not change significantly with the administration of the ACEI benazepril or enalapril, and hypertension remained uncontrolled in 14 of 16 cats. In contrast, Brown and others showed that benazepril decreased both glomerular capillary pressure and systemic arterial blood pressure in an experimental feline model of chronic renal insufficiency.[1]

No one has compared the antihypertensive effects of the various ACEIs currently available in hypertensive dogs or cats, and most veterinary experience with ACEIs stems from their use in animals with congestive heart failure. The ACEI dosage used to treat hypertension appears to be similar to that used for congestive heart failure, although for hypertension some clinicians have used slightly higher doses if the animal did not have renal compromise and was not receiving concomitant diuretic therapy.

The number of dogs that require antihypertensive therapy is small compared to the number of cats that are hypertensive, and our experience in treating hypertensive dogs is considerably less, therefore minimal information is available on effective antihypertensive agents in dogs. Currently, the first-line therapy option for dogs with systemic hypertension is either an ACEI or a calcium channel blocker, usually amlodipine. When enalapril was given to dogs with idiopathic glomerulopathy, blood pressure decreased significantly (even in animals that were not hypertensive).

Even if control of hypertension is not optimal with an ACEI, the drug may have other beneficial actions, such as renoprotection. In refractory hypertension, ACEIs have been combined with other classes of antihypertensive agents, such as beta blockers and calcium channel blockers, to improve blood pressure control.

130.5 CALCIUM CHANNEL BLOCKERS

The calcium channel blockers decrease blood pressure by promoting vasodilatation and preventing an increase in the cytosolic calcium in vascular endothelial cells that is necessary for vasoconstriction.

Amlodipine besylate, a member of the dihydropyridine class of calcium channel blockers, is the treatment of choice in cats with systemic hypertension. Its long duration of action allows for once daily dosing, and it is safe to use in animals with renal compromise, a common finding in cats with hypertension.

Amlodipine is the only antihypertensive agent proven to be effective in a placebo-controlled clinical trial of naturally occurring systemic hypertension in cats. In this study, systolic blood pressure declined significantly after 1 week of therapy (pretreatment value, 212 mm Hg; post-treatment value, 160 mm Hg) and remained controlled when the cats were re-examined 4 months later.[2] Amlodipine was also effective in controlling hypertension in cats with surgically induced renal insufficiency and hypertension. Most recently, amlodipine was shown to lower systolic blood pressure from a mean of 202.5 mm Hg to 153 mm Hg in 20 hypertensive cats. In hypertensive cats

with secondary ventricular hypertrophy, amlodipine administration resulted in resolution of the hypertrophy in 50% of the cats. Although amlodipine has been used safely in cats with renal dysfunction, there have been scattered reports of worsening azotemia in a small percentage of cats given the drug. For this reason, re-evaluation of a serum biochemistry panel is advised 1 to 2 weeks after initiation of amlodipine therapy.

Although there is less reported experience with amlodipine in hypertensive dogs, it is often prescribed as a first-line therapy for hypertension. If the drug is not effective at controlling hypertension in dogs, an ACEI can be combined with or substituted for the amlodipine.

130.6 COMBINATION THERAPY

Several clinical investigators have used ACEIs with beta blockers, or amlodipine combined with either beta blockers or ACEIs, in attempts to control blood pressure in cats with particularly resistant hypertension. Unfortunately, because no clinical reports are available on large numbers of cats or dogs effectively treated with combination therapy, information is lacking regarding preferred combinations or efficacy.

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130.7 OTHER THERAPIES

The phenothiazine derivative acepromazine maleate is a vasodilating agent commonly used in most veterinary practices. Its blood pressure–lowering effects are believed to be associated with alpha-adrenergic blocking effects. In the acute setting, when immediate blood pressure control is needed and other antihypertensive agents are not available, acepromazine can be administered. The vasodilator hydralazine has been used in cats receiving renal allograft that showed clinical signs of systemic hypertension. Administration of hydralazine reduced systolic blood pressure to the normal range within 15 minutes.

Sodium nitroprusside releases nitric oxide in vascular smooth muscle and causes vasodilatation (both arterial and venous). Its primary use has been in dogs with fulminant congestive heart failure. Nitroprusside should be administered as an intravenous constant-rate infusion, with an infusion pump used to improve the accuracy of dosing. However, it should be noted that because of vascular adaptations to long-standing, elevated blood pressure, abrupt decreases in blood pressure in chronically hypertensive animals can compromise cerebral perfusion and may not be in the patient's best interest.

130.8 ADDITIONAL TREATMENT RECOMMENDATIONS

Pet owners should be closely questioned about other drugs the hypertensive animal may be receiving that could affect blood pressure. The administration of corticosteroids, phenylpropanolamine, subcutaneous fluids, and even topical preparations such as ocular phenylephrine could make blood pressure control more difficult in some hypertensive patients. If possible, these drugs should be discontinued, or the lowest possible dose should be used.

Re-evaluation of the hypertensive patient should include appropriate biochemical evaluation (serum biochemistry panel, thyroid testing), funduscopic examination, and indirect blood pressure measurement. The frequency of the re-evaluations depends on the patient's clinical signs, the type and severity of end-organ damage, and the degree of blood pressure elevation. Re-examination may also be dictated by any potential underlying medical problems that could contribute to or cause the blood pressure elevation. Goals for successful control of hypertension are still being debated; however, a general guideline is a systolic blood pressure under 160 mm Hg in an awake, unstressed animal.

When hypertension is diagnosed, our initial response is a desire to lower blood pressure immediately to protect organs from further damage. In most of our patients, hypertension has been a long-standing condition when the diagnosis is made. Long-standing hypertension leads to adaptations in the cerebral vasculature such that a rapid drop in blood pressure may compromise cerebral perfusion. Rapid decreases in blood pressure are most often associated with administration of parenteral drug therapy, therefore these drugs should be reserved for cases in which the benefits of parenteral therapy outweigh the risk posed by the hypertension.

Because antihypertensive therapy is likely to be lifelong, administration of a single agent with a long duration of action (preferably an agent administered once daily) is ideal for improving owner compliance. If adverse effects are observed, another drug, usually from a different class, should be substituted. If the response to the initial agent is inadequate, the dose may be increased (if possible) or another agent, usually from another class, can be combined with the initial agent. If blood pressure control is still not achieved, monitoring of the blood pressure throughout the day to observe trends before and after drug administration may be useful. Owner and patient noncompliance and inadequate management of the underlying cause of the hypertension should also be considered if control of hypertension is difficult. A final consideration for inadequate control of hypertension is the concomitant use of other drugs that could contribute to the increased blood pressure.

130.8.1 Adverse Effects

Lowering of the blood pressure below normal is a potential complication of any antihypertensive agent and, as mentioned earlier, rapid lowering of blood pressure can lead to cerebral ischemia. These are less likely to occur with the commonly used oral antihypertensive therapies. Anorexia, vomiting, and diarrhea are the most common side effects seen with the antihypertensive agents, but the development of azotemia or worsening azotemia may also be seen once an antihypertensive agent is initiated. Monitoring of renal parameters on serial biochemistry panels is advised for any animal receiving chronic drug administration, including animals on long-term antihypertensive therapy.

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131 CHAPTER • 131 Hypotension

Lori S. Waddell

H*ypotension* is defined as a systolic arterial blood pressure of less than 80 mm Hg and/or a mean pressure of less than 60 mm Hg in either dogs or cats. Causes of hypotension include decreased preload to the heart, decreased vascular tone, and cardiac dysfunction. Untreated hypotension can lead to *shock,* which is defined as inadequate tissue perfusion and oxygen delivery to the tissues. Treatment of hypotension should always be aimed at correcting the underlying problem. Recognition and treatment of hypotension are essential to prevent the development of refractory shock, organ failure, and death (Figure 131-1).

Blood pressure provides a measurement of tissue perfusion. The two are not equivalent, but blood pressure monitoring is the simplest means of obtaining an objective parameter. Subjective measures of tissue perfusion are obtained by physical examination; they include pulse quality, mucous membrane color, capillary refill time, and heart rate and rhythm. Combined with blood pressure monitoring, these parameters provide the basis for a more accurate assessment of tissue perfusion. A normal blood pressure does not necessarily mean that the tissues are adequately perfused, as blood pressure may be maintained with severe peripheral vasoconstriction.

131.1 CLINICAL MANIFESTATIONS

The clinical signs associated with hypotension depend on the severity and cause of the condition. In dogs, hypotension is usually associated with tachycardia, bounding to weak pulses, pale mucous membranes, slow capillary refill time, mental dullness, and weakness. If the underlying cause is sepsis, the mucous membranes may be injected or red with a rapid capillary refill time. Cardiac causes of hypotension can also change the clinical picture, with arrhythmias; weak, irregular pulses; and even severe bradycardia possible. Hypotensive cats also usually have tachycardia, poor pulse quality, pale mucous membranes, slow capillary refill time, mental dullness, and weakness. However, unlike dogs, cats with sepsis or systemic inflammatory response syndrome (SIRS) often have bradycardia rather than tachycardia and rarely have injected mucous membranes. In both species, hypotension is often associated with decreased urine output, hyperventilation, hypothermia, and cold extremities.

Inability to palpate pulses peripherally can be useful in assessing blood pressure. When metatarsal pulses are palpable, the systolic blood pressure is above 70 to 80 mm Hg. Although measurement of blood pressure can confirm the presence of hypotension, the diagnosis can certainly be made on physical examination findings alone.

131.2 PATHOGENESIS

Blood pressure is dependent on cardiac output and peripheral vascular resistance. Cardiac output is determined by heart rate, contractility, preload, and afterload. The three main causes of hypotension are decreased preload, decreased cardiac function, and decreased vascular tone (Box 131-1). These may occur individually or in combination.

Multiple compensatory mechanisms are activated by hypotension. The baroreceptors in the carotid sinuses and aortic body sense a lack of stretch, resulting in increased sympathetic nervous system activation, increased release of antidiuretic hormone (ADH) and adrenocorticotropic hormone (ACTH) from the pituitary, and increased release of catecholamines and cortisol from the adrenal glands. These changes result in an increased heart rate, increased vasoconstriction, and increased water retention by the kidneys. Simultaneously, the macula densa in the glomeruli are affected, and the renin-angiotensin-aldosterone system is activated, resulting in sodium retention by the

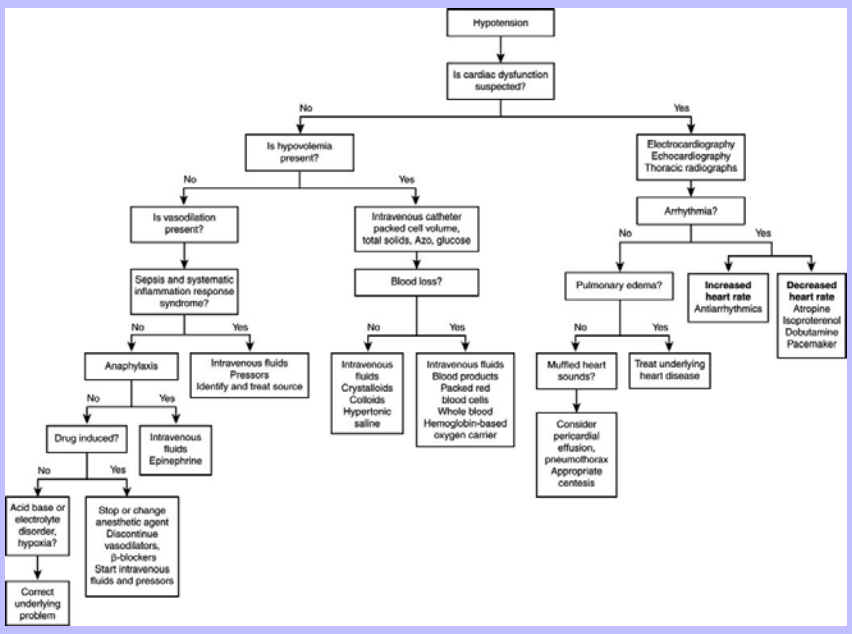
kidneys and further vasoconstriction. These mechanisms serve to increase blood volume by means of sodium and water retention and to preferentially perfuse the brain and heart while decreasing perfusion to the skin, muscles, and abdominal organs, including the kidneys. Recognition and treatment of hypotension are essential to prevent the development of refractory shock and organ failure. Acute renal failure is one of the most common consequences of hypotension, but others include decreased coronary artery perfusion due to the increased heart rate, increased risk of bacterial translocation from the gastrointestinal tract, impaired hepatic function, and activation of the coagulation cascade.

Hypovolemia results in decreased cardiac output secondary to decreased venous return to the heart, which results in decreased preload. Moderate to severe hypovolemia must be present to affect blood pressure due to the normal compensatory actions that occur, including increased heart rate to maintain cardiac output and increased peripheral vascular resistance secondary to vasoconstriction. The compensatory mechanisms maintain adequate blood pressure until more than 20% to 25% of the intravascular volume has been depleted. Hypovolemia can occur with blood loss or increased fluid losses secondary to vomiting, diarrhea, polyuria, or third spacing of fluid.

Restriction of filling of the heart also results in decreased preload, decreased cardiac output, and hypotension. Pericardial effusion with tamponade and restrictive pericarditis can result in hypotension by this mechanism. Severe pneumothorax and positive pressure ventilation can also reduce venous return to the heart. Hypertrophic cardiomyopathy in cats reduces left ventricular volume, thereby reducing preload and cardiac output.

Bradyarrhythmias can affect blood pressure by reducing cardiac output, especially when the heart rate is extremely slow. Although the pulses may be strong when the bradyarrhythmias occur, overall cardiac output can be drastically reduced by the infrequency of systole. The resulting low cardiac output may be severe enough to cause syncopal episodes secondary to hypotension and decreased perfusion of the brain. Tachyarrhythmias can result in hypotension by reducing preload to the heart. At very rapid heart rates, filling of the heart is limited by the relatively short time of diastole. This results in reduced cardiac output despite an increased heart rate. 480 482

Figure 131-1 Algorithm for differential diagnoses and treatment of hypotension.



131.2.1 Box • 131-1 Causes of Hypotension

131.2.1.1 Decreased Preload

Hypovolemia

Hemorrhage

Trauma

Gastrointestinal losses

Polyuria

Hypoadrenocorticism

Effusions or third spacing of fluid

Burns

Heatstroke

131.2.1.2 Decreased venous return

Pericardial tamponade

Restrictive pericarditis

Severe pneumothorax

Positive pressure ventilation

Gastric dilatation and volvulus

Heartworm disease (caval syndrome)

131.2.1.3 Decreased Cardiac Function

Cardiomyopathy

Valvular disease

Bradyarrhythmias

Tachyarrhythmias

Electrolyte abnormalities

Acid-base disturbances

Severe hypoxia

131.2.1.4 Decreased Vascular Tone

Sepsis/systemic inflammatory response syndrome (SIRS)

Anaphylaxis

Neurogenic

Drug induced (anesthetic agent, vasodilators [e.g., beta blockers, calcium channel blockers])

Electrolyte abnormalities

Acid-base disturbances

Severe hypoxia

Decreased cardiac output can also occur due to primary cardiac disorders. Dilated cardiomyopathy is characterized by reduced stroke volume and reduced cardiac output caused by decreased contractility. Valvular incompetence, resulting in regurgitant flow, also causes decreased stroke volume. Other causes of decreased cardiac contractility include myocarditis, myocardial infarction, myocardial depression secondary to sepsis, SIRS, anesthetic drugs, beta blockers and calcium channel blockers, and acid-base and electrolyte abnormalities.

Decreased peripheral systemic resistance can also cause hypotension. Common causes of vasodilatation are sepsis/SIRS; anaphylaxis; anesthesia; use of vasodilators, including beta blockers and calcium channel blockers; electrolyte abnormalities; and acid-base disturbances. Many of these mechanisms also affect cardiac contractility, resulting in hypotension mediated by decreased cardiac output and vasodilatation simultaneously.

131.3 MEASUREMENT OF BLOOD PRESSURE

Blood pressure monitoring can be divided into two main types, noninvasive and invasive methods. The noninvasive methods are most commonly used, and in dogs and cats usually consist of either an oscillometric system (Cardell Monitor, Sharn Veterinary, Tampa, Florida or Dinamap, Critikon, Tampa, Florida) or Doppler methods (Parks Electronics, Aloha, Oregon). Invasive blood pressure monitoring is performed by direct arterial pressure measurement and is the most accurate method available.

131.4 TREATMENT

It is essential that the treatment of hypotension always be aimed at correction of the underlying physiologic problem: decreased preload, cardiac dysfunction, or peripheral vasodilatation. Differentiation of cardiac and noncardiac causes of hypotension is a critical first step (Figure 131-1). If the animal is hypovolemic, intravenous fluids should be administered until euvolemia has been attained. If hypovolemia is severe enough to cause hypotension, a shock bolus should be given. The standard doses of isotonic crystalloids are 60 to 90 mL/kg/hour for dogs and 45 to 60 mL/kg/hour for cats. If colloids are indicated in place of crystalloids, approximately one fourth of the crystalloid dose should be given. Hypertonic saline is a rapid intravascular volume expander and can be used when immediate resuscitation is needed. The dose for hypertonic saline is 5 mL/kg given over 5 to 10 minutes for dogs and 3 to 4 mL/kg given over the same time period for cats. After administration of hypertonic

saline, it is essential to follow with one third to one half of a shock bolus of isotonic crystalloids to provide continued intravascular volume expansion and to replenish the interstitial space. If hypovolemia occurs secondary to blood loss, blood products, such as whole blood or packed red blood cells, or a hemoglobin-based oxygen-carrying solution should be administered to provide adequate oxygen-carrying capacity.

If the volume status is unknown or if there are concerns about overloading the animal with intravenous fluids, a central venous catheter can be placed for central venous pressure (CVP) monitoring. A low CVP (less than 0 cm H_2O) indicates hypovolemia due to fluid loss or vasodilatation secondary to decreased peripheral resistance. A high CVP (greater than 10 cm H_2O) indicates volume overload, right-sided heart failure, or increased pulmonary vascular resistance (afterload). If the significance of a CVP reading is questionable, a small test bolus of fluids can be given. A rapid bolus of 10 to 15 mL/kg of crystalloid or 3 to 5 mL/kg of colloid is used. The vascular bed is a compliant system, able to accommodate changes in volume with minimal changes in pressure. If the animal has a low CVP due to hypovolemia, the CVP will show either no change or a transient rise toward normal followed by a rapid decrease. The mean arterial pressure may also increase transiently. A bolus given to a dog or cat that is euvolemic usually causes a small increase in the CVP of 2 to 4 cm H_2O with a return to baseline within 15 minutes. A large increase (greater than 4 cm H_2O) and slow return to baseline (longer than 30 minutes) are seen with hypervolemia or reduced cardiac compliance.

If the animal remains hypotensive once euvolemia has been achieved, the use of pressors should be considered. Commonly used pressors include dopamine, epinephrine, and phenylephrine administered as constant-rate infusions. These drugs need to be titrated to effect, requiring frequent blood pressure monitoring. They should never be used in place of adequate volume expansion, because most dogs and cats with hypovolemia already have compensatory vasoconstriction.

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Cardiac causes of hypotension must be addressed on a case by case basis. If tachyarrhythmias are the cause, antiarrhythmic therapy should be administered. Bradyarrhythmias may respond to medical therapy or may require placement of a pacemaker. Obstruction of cardiac filling by pericardial effusion or severe pneumothorax should be addressed by appropriate centesis. Positive inotropes should be administered when decreased cardiac contractility is suspected.

131.5 DIAGNOSTIC PLAN

Diagnosis of the underlying cause of the hypotension must often wait until after therapy has been initiated due to the critical nature of hypotension. History and physical examination abnormalities can often help in the determination of a tentative diagnosis, allowing therapy to be started. Initial diagnostics in an unstable hypotensive dog or cat should include packed cell volume, total solids, and glucose values and an estimate of the blood urea nitrogen level (Azostix, Bayer corporation, Elk-hart, IN). Electrolytes and acid-base status can also be helpful. Depending on the clinical signs, an electrocardiogram (ECG), abdominal and thoracic radiographs, abdominal ultrasonography, echocardiography, CVP and pulse oximetry determinations, and arterial blood gas analysis can be useful. A complete blood count, serum chemistry profile, and urinalysis should also be performed. If indicated, an ACTH stimulation test should be considered. If sepsis is suspected, blood and urine cultures should be done unless the source of sepsis can be directly cultured.

132 CHAPTER • 132 Clueing in Customers*

Leonard L. Berry

Neeli Bendapudi

Nobody likes going to the hospital. The experience is at best unnerving, often frightening, and, for most of us, a potent symbol of mortality. What's more, it's very hard for the average patient to judge the quality of the "product" based on direct evidence. You can't try it on, you can't return it if you don't like it, and you need an advanced degree to understand it—yet it's vitally important. Therefore when we're considering a doctor or a medical facility, most of us unconsciously turn detective, looking for evidence of competence, caring, and integrity—processing what we can see and understand to decipher what we cannot.

The Mayo Clinic doesn't leave the nature of that evidence to chance. By carefully managing a set of visual and experiential clues, Mayo tells a consistent and compelling story about its service to customers: At Mayo Clinic, the patient comes first. From the way it hires and trains employees, to the way it designs its facilities, to the way it approaches care, Mayo offers patients and their families concrete and convincing evidence of its strengths and values. The results are exceptionally positive word of mouth and abiding customer loyalty, which have allowed Mayo Clinic to build what is arguably the most powerful brand in health care—with very little advertising—in an industry where few institutions have any brand recognition beyond their local markets.

It's called "evidence management": an organized, explicit approach to presenting customers with coherent, honest evidence of your abilities. Evidence management is a lot like advertising, except that it turns a company into a living, breathing advertisement for itself. Other organizations manage evidence well, too. Ritz Carlton, for example, very effectively communicates outstanding personal service: Employees at all levels take note of customer preferences and are empowered to solve problems on the spot, continually tailoring the experience to each person. Mayo Clinic does not have all the answers; health care is a highly inventive industry, and many institutions could serve as fine examples to business. However, during our extensive study of the Mayo organization over a five-month period, we saw evidence— management practices that rival or surpass anything we've seen in the corporate sector, practices that are applicable outside of health care. As part of our research design, we interviewed approximately 1000 Mayo employees and patients, observed hundreds of doctor-patient visits at two of Mayo's three major campuses (Scottsdale, Arizona, and Rochester, Minnesota; the third is in Jacksonville, Florida), and stayed in the hospitals overnight as patients. In almost every experience and interaction, in subtle and not-so-subtle ways, we got the message that at Mayo Clinic, the patient comes first (Box 132-1).

Many businesses sell products that are intangible or technically complex—financial and legal services, software, and auto repair are just a few—and their customers naturally look for clues that can help explain what they don't understand or see. In fact, in just about any organization, the clues emitted by people and things (humanics and mechanics, respectively, as introduced to the management literature by Lewis Carbone and Stephan Haeckel) tell a story to customers or potential customers. The question for managers is whether the clues tell the intended story. Mayo Clinic's effectiveness at designing and managing evidence offers a lesson other service organizations would do well to heed: Understand the story you want to tell, and then make sure your people and your facilities provide evidence of that story to customers, day in and day out.

132.1 CLUES IN PEOPLE

When we interviewed Mayo patients, we were struck by how consistently they described their care as being organized around their needs rather than the doctors' schedules, the hospital's processes, or any other factor related to Mayo's internal operations. The actions of Mayo staff members, according to what we were told, clearly signal the patient-first focus. Here are representative remarks: “My doctor calls me at home to check on how I am doing. She wants to work with what is best for my schedule.” “When I had a colonoscopy, [my doctor] waited to tell me personally that I had a polyp because he remembered that my husband died from small bowel cancer, and he knew that I would be worried I may have the same thing.” “My oncologist is…the kindest man I have ever met. He related some of his personal life to me. I was more than my problem to him. He related to me as a person.”

Such glowing praise isn't limited just to the doctors and nurses. One patient, for example, was “amazed” at how well the people at the registration desk handle requests: “People who come up to the desk are nervous, or angry, or abusive. These ladies at the registration desk just keep their cool. I wish they could train the customer service reps in department stores.”

It's no accident that employees communicate a strong, consistent message to patients. Mayo explicitly and systematically hires people who genuinely embrace the organization's values. The clinic emphasizes the importance of those values through training and ongoing reinforcement in the workplace, a practice that began in the very early part of the twentieth century, when Drs. William and Charles Mayo started the organization. Indeed, William Mayo's credo—“The best interest of the patient is the only interest to be considered”—guides hiring decisions to this day.

It's difficult to get a job at Mayo Clinic because of intellect or technical skill alone. Demonstrated task competence is essential, of course, but the hiring managers are also trained in behavioral interview techniques, and they are expected to use them to elicit an applicant's values. A candidate may be asked, for instance, to discuss a time when he set a development goal for himself and how he met that goal or to describe the proudest moment in his career or even the moment he found most frustrating. Interviewers avoid discussing hypothetical situations that allow candidates to figure out the “right” answer and instead probe for specific details that reflect true experiences and perspectives. For example, a candidate who identifies making a difference in a patient's life as his or her proudest moment may be more attuned to Mayo's values than one who mentions achieving a career milestone.

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132.1.1 Box • 132-1 The Research

Mayo Clinic has three major campuses (Rochester, MN; Scottsdale, AZ; and Jacksonville, FL); primary care clinics in more than 60 communities; 21 owned or managed hospitals; more than 2800 staff physicians; medical technology, medical publishing, laboratory, and health care benefits-administration businesses; and revenue in excess of $4 billion. It serves more than 500,000 individual patients annually.

For this article, we conducted the largest service study ever done at Mayo Clinic. During a 5-month period, we interviewed approximately 1000 Mayo patients, physicians, nurses, allied health staff, and managers at the original Rochester campus and the Scottsdale campus. We also collected data as participant observers, checking into the hospitals as patients, observing surgeries in the operating room and more than 250 doctor-patient interactions in the examination room, making hospital rounds, and flying on the Mayo One emergency rescue helicopter service. We formally studied service delivery in 14 medical specialties selected to provide a cross-section of the practice: cardiac surgery, cardiology, dermatology, emergency medicine, endocrinology, family medicine, gastroenterology, medical and

radiation oncology, neurology, orthopedic surgery, preventive medicine, thoracic surgery, transplant surgery, and urology. Mayo Clinic gave us complete access to study its service culture and processes, and the Mayo Clinic Institutional Review Board approved our study.

The people who make the cut—indeed, the people who are drawn to Mayo in the first place—are those who take pride in having the freedom to put patients first. We heard many doctors and nurses say that they appreciate being allowed to practice medicine as they feel it should be practiced. Those feelings of pride and the alignment of employees' attitudes with Mayo's values contribute to lower staff turnover across the board. Annual turnover among hospital nurses is only 4% at Mayo versus 20% for the industry as a whole—continuity that, in turn, helps boost the quality of care.

Once hired, all new employees go through an orientation process specifically designed to reinforce the patient-first mentality. The program for nonphysician employees—whether janitors, accountants, or nurses—is designed to help all staff people understand how their jobs affect patients' care and well-being. If housekeeping fails to maintain sanitary conditions, for instance, a patient's health may be compromised no matter how excellent the medical care received. Storytelling figures heavily in these programs, with the emphasis on how employees have used Mayo values to make difficult decisions on patients' behalf.

Storytelling continues in the workplace because, once people are away from the classroom, the idea of putting the patient first can seem distant and sometimes even unrealistic, given the stress and unpredictability of day-to-day work. Consider, for instance, one story featured at several orientation sessions and widely disseminated throughout the organization. A critically ill patient was admitted to the Scottsdale hospital shortly before her daughter was to be married, and she was unlikely to live to see the wedding. The bride told the hospital chaplain how much she wanted her mother to participate in the ceremony, and he conveyed this to the critical care manager. Within hours, the hospital atrium was transformed for the wedding service, complete with flowers, balloons, and confetti. Staff members provided a cake, and nurses arranged the patient's hair and makeup, dressed her, and wheeled her bed to the atrium. A volunteer played the piano and the chaplain performed the service. On every floor, hospital staff and visiting family and friends ringed the atrium balconies, “like angels from above,” to quote the bride. The wedding scene provided not only evidence of caring to the patient and her family but also a strong reminder to the staff that the patient's needs come first. They got the message: We heard the story multiple times in our interviews with employees.

Another story was initially told at a leadership development program for rising Mayo administrators. In one session, Mayo staff members shared experiences that showed how the service philosophy affects care. An emergency room physician told of a patient who walked into the ER with severe shortness of breath. When told she had a bacterial infection requiring immediate surgery, the woman expressed concern about her sick dog, which was in her illegally parked truck. The attending nurse assured her that he would move the truck and take care of the dog, but when he walked outside, what he saw was not a pickup but a semi, which he wasn't licensed to drive. He was about to have it towed—for $700—when he stopped to consider ways he might save the patient the expense. In the end, the nurse took it upon himself to obtain permission to park the truck at a nearby shopping center for a few days and find a fellow nurse—a former trucker—to drive the truck there. He took the dog to a veterinarian and then cared for it in his own home while the patient recovered. When asked what prompted him to do this, the nurse replied, “At Mayo Clinic, the patient's needs come first.”

Various events celebrating exceptional service on behalf of patients further reinforce employees' commitments. The Rochester campus hosts an annual Heritage Week, celebrating the clinic's history and values and reinforcing their relevance to Mayo's work today through historical presentations and displays, lectures, ecumenical and liturgical services, concerts, and social events. Employees, retirees, volunteers, patients, visitors, and members of the community are invited. Mayo Rochester also recognizes exceptional service with its quarterly campus-wide

Karis Award (Karis is Greek for caring). All staff members are eligible and can be nominated by a coworker, patient, or family member; the identity of the nominator is not disclosed, which removes political considerations from the process. One 1999 winner, a world-renowned colorectal surgeon with numerous scientific recognitions, told his tablemates at the award luncheon that he cherished the Karis more than any other award he's received, calling it, “The only award I have for just being a really good doctor.”

* Used by permission from *Harvard Business Review*, Feb 2003.

132.2 CLUES IN COLLABORATION

In 1910, William Mayo said, “In order that the sick may have the benefit of advancing knowledge, union of forces is necessary… It has become necessary to develop medicine as a cooperative science.” Dr. Mayo's vision profoundly influences the organization's approach to care. Patients experience the Mayo Clinic as a team of experts who are focused on patients' needs above all else. They perceive an integrated, coordinated response to their medical conditions and, often, to related psychological, social, spiritual, and financial needs. Elsewhere, doctors may be reluctant to admit to any gaps in their knowledge. Not so at Mayo. Mayo Clinic assembles the expertise and resources needed to solve the patient's problem. If a Mayo doctor can't answer a question and needs to bring someone else onto a team, she freely admits it to the patient. The doctors meet with one another and with the patient— visible evidence that they are collaborating to solve the patient's problem rather than passing it from one doctor to another. One patient we interviewed expressed a common sentiment when he said, “I have a lot of problems, and I like that I can go to Mayo and be seen by a team of specialists who work together to see the big picture.” Collaboration is particularly important because the institution's reputation has become so well known that patients often come in looking for a miracle. Many have consulted several other doctors and consider Mayo the last resort, so the physicians there regularly see patients with complex problems and high expectations, a situation that puts the doctors under extra pressure to make the right diagnoses and treatment decisions and not miss often subtle medical distinctions.

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Mayo Clinic encourages this type of collaboration through various organizational incentives. All physicians are salaried, so they don't lose income by referring patients to colleagues, and the organization explicitly shuns the star system, downplaying individual accomplishments in favor of organizational achievements. In the words of one cardiovascular surgeon, “By not having our economics tied to our cases, we are free to do what comes naturally… to help one another.” Doctors who are focused on maximizing their incomes or who want to be the star of the show don't work for Mayo Clinic. A surgeon specializing in the liver explained, “The kind of people who are attracted to work for Mayo Clinic have a value system that places the care of those in need over personal issues such as salary, prestige, and power. There is little room for turf battles. It is never a problem to add [a new case] on to the workload of the day. It's simply the best thing to do for the patient.”

Mayo also supports teamwork with its use of technology. Staff members partner via a combination of face-to-face and remote collaboration using a sophisticated internal paging, telephone, and videoconferencing system that connects people quickly and easily. Remote teamwork through voice or virtual interaction is just as common as in-person teamwork at hallway or bedside consults. One physician told us, “I never feel I am in a room by myself, even when I am.” Recently, for example, a Mayo ENT specialist in Scottsdale called together 20 doctors from all three campuses to discuss a difficult case—a patient with skin cancer at risk for metastasis and, owing to the necessary surgery, nerve injury and disfigurement. The team, assembled in a day, met by videoconference for an hour and a half and reached a consensus for a course of treatment, including specific recommendations on how aggressively to sample the patient's lymph nodes and how best to reconstruct the surgical wound.

Mayo's electronic medical record (EMR) improves the clinic's ability to present a seamless, collaborative organization and manage the evidence that patients see. The EMR provides an up-to-date narrative of the patient's

symptoms, diagnoses, test results, treatment plans, procedures, and other related data, connecting in-and outpatient information and communicating across disciplines in outpatient practices. This connection is critical to patient-first decisions in ways that patients don't necessarily see. One emergency room physician said it had prevented her from intubating a patient who had asked not to be resuscitated, for instance, and others told of the importance of the EMR in managing patient medications to avoid allergic reactions or dangerous drug interactions. However, patients also notice and appreciate the single source of information, as we heard repeatedly in our research. One patient told us, “On my last visit, the doctor pulled up all my test scores from the past five years on a computer and showed me the trends, and we discussed what to do. I thought that was excellent.” In short, patients told us in numerous interviews that Mayo's team service gave them a sense that the organization was coordinating its resources to provide the best possible care, with the patients' needs foremost in employees' minds.

132.3 CLUES IN TANGIBLES

In health care, the visual clues about an institution's core values and the quality of care are particularly difficult to separate from the actual service because people spend significant time in the facility—some stay for days or even weeks. The physical environment is also connected to medical outcomes: The potential of design to promote healing through stress reduction has been documented in dozens of studies. For these reasons, more medical institutions are making an effort to create open, welcoming spaces with soft, natural light. Mayo Clinic goes further with its design philosophy, which is perhaps as well honed and articulated as that of any major service provider in America, and pays strict attention to how every detail affects the patient's experience.

From public spaces to exam rooms to laboratories, Mayo facilities have been designed explicitly to relieve stress, offer a place of refuge, create positive distractions, convey caring and respect, symbolize competence, minimize the impression of crowding, facilitate way finding, and accommodate families. In the words of the architect who designed Mayo Rochester's new 20-story Gonda Building, “I would like the patients to feel a little better before they see their doctors.” A well-designed physical environment has a positive impact on employees as well, reducing physical and emotional stress—which is of value not only to employees but also to patients because visible employee stress sends negative signals. In our interviews, patients commented on the lack of apparent stress; one said, “It did not seem like a doctor's office when we went to Mayo. There was no tension.”

The Gonda Building has spectacular wide-open spaces, a marble stairwell and floor, glasswork sculpture suspended above, and a multistory wall of windows looking onto a garden. The building's soaring lobby houses a cancer education center because, as one administrator put it, “The more visible the center, the more you remove the stigma of having cancer.” The lobby of Mayo Clinic Hospital in Scottsdale is also visually stunning, with its atrium, indoor waterfall, stonework, and wall of windows overlooking a mountain range.

Mayo doesn't limit its facilities' clue management to public spaces. After all, the scary stuff in a medical facility happens elsewhere—in the catheterization lab, in diagnostic imaging, in the hospital room. At Mayo hospitals, staff members write the names of attending doctors and nurses on a white board in every patient's room, which helps stressed-out patients and families keep track of multiple caregivers and serves as a visible clue that there's a real person they can talk with about any concerns. In-hospital showers, microwave ovens, and chairs that convert to beds are available for family members because, as one staff member explained, “People don't come to the hospital alone.” The pediatric section of Mayo's St. Mary's Hospital in Rochester transformed artwork by local schoolchildren into a colorful array of wall and ceiling tiles. The resuscitation equipment in pediatric examination rooms is hidden behind a large picture (which slides out of the way when the equipment is needed). While the hospital was under construction at the Scottsdale campus, officials arranged to have an automobile lifted into the building so physical rehabilitation patients would be able to practice getting in and out of a car in the privacy of a hospital.

Environmental clues in the outpatient setting are orchestrated just as carefully. Mayo Clinic buildings include quiet, darkened private areas where patients can rest between appointments. Public spaces are purposely made softer with natural light, color, artwork, piano music, and the sights and sounds of fountains. In examination rooms, the physician's desk is adjacent to a sofa large enough for the patient and family members, a design that removes the desk as a barrier between doctors and their patients.

Mayo also understands that the way employees present themselves sends a signal to patients. Patients don't encounter doctors in casual attire or white coats. Instead, the more than 2800 staff physicians wear business attire, unless they are in surgical scrubs, to convey professionalism and expertise. It's a dress code that some outside Mayo have called “pretentious”; yet we'd argue that it's no more pretentious than, say, the dress code for airline pilots. Airline passengers don't want to see their pilot in a polo shirt, and patients feel the same way about doctors. In effect, Mayo Clinic doctors—just like service workers in many other industries—work in a uniform; it is a visible clue that communicates respect to patients and their families.

Such attention to visual clues extends to the minutest detail. Mayo Rochester employee Mary Ann Morris, the administrator of General Service and the Office of Patient Affairs, often tells a story about her early days with the organization. She was working in a laboratory—a job that required her to wear a white uniform and white shoes—and after a hectic morning getting her two small children to school, she arrived at work to find her supervisor staring at her shoes. The supervisor had noticed that the laces were dirty where they threaded through the eyelets of Morris's shoes and asked Morris to clean them. Offended, Morris said that she worked in a laboratory, not with patients, so why should it matter? Her boss replied that Morris had contact with patients in ways she didn't realize—going out on the street wearing her Mayo name tag, for instance, or passing patients and their families as she walked through the halls—and that she couldn't represent Mayo Clinic with dirty shoelaces. “Though I was initially offended, I realized over time [that] everything I do, down to my shoelaces, represents my commitment to our patients and visitors,” Morris told us. “Twenty-eight years later, I still use the dirty shoelace story to set the standard for the service level I aspire to for myself and my coworkers.”

A dirty shoelace might seem minor, given the important work of caring for the ill; but a shoelace is something a customer can see, whereas medical expertise and technical ability are not. It's a piece of evidence—a small but integral part of the story Mayo tells to its customers. We aren't arguing that “patients first” is the only story a medical institution might choose to tell patients. A hospital might instead choose to signal, “We hire the smartest doctors,” and manage the evidence with prominent displays of academic credentials and awards, a lecture series, and heavy publicity about new research. What Mayo Clinic has done better than just about any organization we can think of, however, is clearly identify a simple, consistent message and then manage the evidence—the buildings, the approach to care, and yes, even the shoelaces—to support that message, day in and day out.

133 CHAPTER • 133 Rational Use of Diagnostic Tests

Andrew S. Peregrine

Diagnostic tests are used routinely in veterinary practice for screening animals and for identification of a specific target disorder in a diseased animal. However, very few diagnostic tests are accurate all the time. Thus not all animals that test positive necessarily have the target disorder under investigation. To correctly interpret diagnostic data, information is required on (1) a diagnostic test's *sensitivity*, the proportion of animals with the target disorder that test positive; (2) the test's *specificity,* the proportion of animals without the target disorder that test negative; and (3) the prevalence of the target disorder in animals similar to the one you are testing, or the probability that the animal has the target disorder before the test is run. Without this information, interpretation of diagnostic data is not possible.

Because diagnostic tests for heartworm *(Dirofilaria immitis)* infection in dogs are used commonly by veterinary practitioners, the following text describes how sensitivity, specificity, and prevalence estimates should be used to interpret data generated by these tests. The principles described apply to all diagnostic tests, including the clinical history and physical examination.

Heartworm antigen tests are the most common type of diagnostic method used to examine dogs for heartworm infection and typically have a sensitivity and specificity of approximately 80% and 98%, respectively.[1,2] Table 133-1 summarizes data from 1000 dogs when examined with such a test. Since the prevalence of heartworm infection in this population of animals is 30%, the total number of dogs infected with heartworm is 300. Because the antigen test's sensitivity is 80%, 240 (0.80 × 300) of the 300 infected dogs will test positive (cell *a*). The remaining 60 (300–240) infected dogs will test negative (cell *c*). Animals in cell *a* are therefore *true-positives,* whereas those in cell *c* are *false-negatives*. In light of the test's specificity of 98%, 686 (0.98 × 700) of the 700 uninfected dogs will test negative (cell *d*). The remaining 14 dogs (700-686) will erroneously test positive (cell *b*). Dogs in cell *d* are therefore *true-negatives,* whereas those in cell *b* are *false-positives*. In summary, the test has classified correctly dogs in cells *a* and *d* (*true-positives* and *true-negatives*) but has classified incorrectly dogs in cells *b* and *c* (*false-positives* and *false-negatives*).[3,4]

A sensitivity of 100% for the heartworm antigen test would rule out heartworm infection in all dogs that test negative. Likewise, if the test had a specificity of 100% all dogs that test positive could be diagnosed with heartworm.[3] However, because both parameters are less than 100%, some animals will be misclassified. *Predictive values* therefore need to be calculated. These indicate the likelihood that a test result has correctly classified the heartworm status of an animal. The *positive-predictive value* indicates the proportion of all animals that test positive for heartworm (cells *a* + *b*) that are truly infected with heartworm (cell *a*) and in Table 133-1 is 94.5%. Thus when one of the described dogs tests positive for heartworm antigen, the likelihood that the animal is truly infected with heartworm is 94.5%. Similarly, the *negative-predictive value* indicates the proportion of all animals that test negative for heartworm antigen (cells *c* + *d*) that are truly not infected with heartworm (cell *d*). In Table 133-1 this value is 92.0%. In other words, if a negative test result is obtained, it is 92% certain that the dog is not infected with heartworm.

Table • 133-1 Performance of a Heartworm Antigen Test* When Applied to a Dog Population with a Prevalence of Heartworm Infection of 30%

		Heartworm infection			
		Present	**Absent**	**Total**	
Heartworm antigen test	Positive	*a* 240	*b* 14	*a+b* 254	Positive-predictive value $=\frac{a}{a+b}=\frac{240}{254}=94.5\%$
	Negative	*c* 60	*d* 686	*c+d* 746	Negative-predictive value $=\frac{d}{c+d}=\frac{686}{746}=92.0\%$
	Total	*a +c* 300	*b +d* 700	*a+b+c+d* 1000	
		Sensitivity $=\frac{a}{a+c}$ $=\frac{240}{300}=80\%$	Specificity $=\frac{d}{b+d}$ $=\frac{686}{700}=98\%$		Prevalence $=\frac{a+c}{a+b+c+d}=\frac{300}{1000}=30\%$

* Sensitivity = 80%, specificity = 98%.

Unlike sensitivity and specificity, *predictive values* are strongly influenced by the true prevalence of the target disorder and therefore are not stable characteristics for a test.[4,5] To illustrate this point, Table 133-2 describes the performance of the aforementioned heartworm antigen test when applied to a population of dogs with a prevalence of heartworm infection of 0.5%. Although the sensitivity and specificity of the test are unaltered, the *positive-predictive value* has dropped to 16.7%. Thus only one in approximately every five positive test results is a *true-positive*. Therefore in this situation, heartworm infection should not be diagnosed solely on the basis of one positive antigen test (unlike the situation in Table 133-1). Additional diagnostic information is required to determine whether the positive result is a *true-* or *false-positive*. In contrast to the *positive-predictive value*, the antigen test's *negative-predictive value* of 99.9% (see Table 133-2) is higher than the situation described in Table 133-1. A negative antigen test result can therefore be used to rule out heartworm infection with a high level of certainty when applied to dogs with a prevalence of heartworm infection of 0.5%.

An understanding of the impact of prevalence on predictive values is of fundamental importance in interpretation of diagnostic data. Table 133-3 indicates how the *positive-* and *negative-predictive values* for the heartworm antigen test alter as the prevalence of heartworm infection increases from 0.02% to 50%. The sensitivity and specificity remain unaltered. Over this range the *positive-predictive value* increases from 0.8% to 97.6%, whereas the *negative-predictive value* decreases from 100% to 83.1%. Thus as the prevalence increases, the *positive-predictive value* increases. By contrast, the *negative-predictive value* decreases.[3] At a prevalence of infection of 10% or less the *positive-predictive value* is less than 90%. An additional diagnostic test(s) should therefore be used to confirm or refute a positive test result when obtained from such populations of dogs. Finally, in light of the effect of prevalence on predictive values (particularly *positive-predictive values*)[3,5], it is important to appreciate that the prevalence of heartworm infection is dependent on both the geographic location of an animal and on whether or not an animal has been on heartworm-preventive medication. Thus in every veterinary practice, routine screening of healthy dogs with heartworm antigen tests is actually carried out on two distinct populations of animals: those that were not on preventive medication the previous year and those that were. Although the prevalence of heartworm infection in the former dogs may be as high as 45%, the prevalence in the latter is typically less than 1%, even in high-prevalence

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areas. Interpretation of an antigen test result is therefore dependent on which dog population is being examined. Both estimates can be obtained from dogs examined at a practice over the previous 1 to 2 years.

Table • 133-2 Performance of the Heartworm Antigen Test* Described in Table 133-1 When Applied to a Dog Population With a Prevalence of Heartworm Infection of 0.5%

		Heartworm infection			
		Present	Absent	Total	
Heartworm antigen test	Positive	*a*	*b*	*a+b*	Positive — predictive value
		4	20	24	$=\frac{4}{24}=16.7\%$
	Negative	*c*	*d*	*c+d*	Negative- predictive value
		1	975	976	$=\frac{975}{976}=99.9\%$
	Total	*a+c*	*b +d*	*a+b+c+d*	Prevalence
		5	995	1000	$=\frac{5}{1000}=0.5\%$

* Sensitivity =80%, specificity =98%.

Table • 133-3 Predictive Values for a Typical Heartworm Antigen Test* When Applied to Dog Populations With Various Prevalences of Heartworm Infection

REVALENCE OF INFECTION††	POSITIVE-PREDICTIVE VALUE‡‡	NEGATIVE-PREDICTIVE VALUE	1-(NEGATIVE-PREDICTIVE VALUE)§§
0.02%	0.8%	100%	0%
0.2%	7.4%	100%	0%
0.5%	16.7%	99.9%	0.1%
1.0%	28.8%	99.8%	0.2%
2.0%	44.9%	99.6%	0.4%
5.0%	67.8%	98.9%	1.1%
10.0%	81.6%	97.8%	2.2%
30.0%	94.5%	92.0%	8.0%
50.0%	97.6%	83.1%	16.9%

* Sensitivity =80%, specificity =98%.

† Pre-test probability of infection.

‡ Probability of infection following a positive test.

§ Probability of infection following a negative test.

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If a diagnostic test is to be useful, it must have the potential to have a major effect on diagnosis, prognosis, or therapeutic decisions.[6] Thus, if the probability that an animal has a target disorder after application of a test is not significantly different from the probability prior to using the test (*the pre-test probability*), the diagnostic method does not have clinical utility. The *pre-test probability of the target disorder* is the proportion of animals with the

target disorder among all animals tested and is the same as the true prevalence. In the case of the heartworm scenario described at a prevalence of 30% (see Tables 133-1 and 133-3) the *pre-test probability* of heartworm infection is 30%. Since the *probability of infection following a positive test* is indicated by the *positive-predictive value*, the probability of infection at this prevalence for a test-positive animal is 94.5%. The positive result has therefore increased the certainty of infection by 64.5%. To what extent does a negative test rule out heartworm infection? The *probability of infection following a negative test* indicates the proportion of animals testing negative that are infected with heartworm and is calculated as 1-(*negative-predictive value*). At a prevalence of heartworm infection of 30% a negative antigen test decreases the probability of infection to 8% (see Table 133-3). Thus when the *pre-test probability of infection* is 30%, both positive and negative tests provide useful diagnostic information. In contrast, when the *pre-test probability of heartworm infection* is 0.5%, the probability of infection following a positive antigen test is 16.7%, whereas the probability of infection following a negative test is 0.1% (see Table 133-3). A positive test has therefore increased the probability of infection by 16.2% (from 0.5% to 16.7%), whereas a negative test has decreased the probability of infection by 0.4% (from 0.5% to 0.1%). Very little information has therefore been learned from both positive and negative test results in this situation.[3]

133.1 REFERENCES

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134 CHAPTER • 134 Principles of Drug Therapy

Dawn M. Boothe

134.1 DOSE-RESPONSE RELATIONSHIP

The intent of drug therapy is to induce a desired pharmacologic response for a sufficiently long period of time and avoid adverse drug events. Adverse events fall into two categories. Type A ("augmented"; Type I) generally are dose or duration dependent and result from plasma drug concentrations (PDC) that either are below (therapeutic failure) or exceed the maximum therapeutic range. As such, Type A events are largely predictable and potentially unavoidable if the clinician is sufficiently familiar with the drug and the patient.

134.2 DETERMINANTS OF DRUG DISPOSITION

134.2.1 Drug Movement

After administration of a fixed dose of a drug, several dynamic drug movements, largely dependent on passive diffusion, act in concert to determine PDC across time (Figure 134-1). The major movements include absorption from the site of administration to systemic circulation, defined as the major vessels and well-perfused organs; distribution of the drug from systemic circulation to tissues (target and non-target) and back again; and elimination of the drug from the body, accomplished by metabolism and excretion.

134.2.1.1 Plasma Drug Concentration Versus Time Curve: Clinical Pharmacokinetics

Pharmacokinetics scientifically (mathematically) describe the relationship of drug concentrations in a tissue across time such that dosing regimens and drug response can be predicted in animals. Because tissue samples cannot be collected easily, drug is most often measured in plasma. The four dynamic drug movements that affect PDC time most commonly follow first order, that is, a constant fraction rather than a constant amount of drug moves per unit time. As such, log drug concentrations are plotted across time (Figure 134-2, *A* and *B*). When the data is fit to the best line (based on sum of residuals), an equation is generated that allows prediction of drug behavior in a patient (or sample population). If the data can be accurately described by a single slope (as can occur only with intravenous [IV] administration [see Figure 134-2, *A*]), one drug movement (irreversible elimination) causes the change in PDC and the drug is described as following a one compartment (i.e., one component) open (i.e., the drug leaves the system) model. The slope of the PDC versus time curve describes the rate of elimination (k_{el}) of the drug and determines the time for 50% of the drug to be irreversibly eliminated from the body or the *elimination half-life*. The amount of tissue to which a drug is distributed is estimated by the volume of distribution (V_d), a theoretical and mathematically derived parameter that directly and inversely influences PDC after administration of a specific dose (see Figure 134-2). Calculation of V_d considers that concentrations of the drug occur throughout the body at the same concentration as that measured in the plasma. Clearance (volume/time) describes the fraction of the V_d from which drug is irreversibly eliminated and is calculated from V_d and k_{el}:

$$Cl = V_d \times k_{el}$$

Few drugs behave as a one compartment open model. If multiple drug movements influence the PDC (as occurs with any drug undergoing absorption from the site of administration; see Figure 134-2, *B*), two or more slopes may be necessary to describe the data, with each slope being influenced by one or more drug movements. Generally, computer-assisted linear regression "strips" each slope from the curve before the data is best fit to the multiple components. For multicompartment open models, each component is described by a slope or rate (ki) and y intercept PDC (e.g., A, B) (see Figure 134-2, Plot B). The first component of the curve is generally considered to represent drug distribution (slope = α) and the terminal (in this case, second) component elimination (e.g., k_{el}, or β, γ, depending on the number of components that describe the curve). The distribution *half-life,* calculated from α, is the time necessary for 50% of drug to be distributed. The elimination half-life is determined from the terminal component of the curve. Two V_d can be calculated, which represent either the central or peripheral compartments, respectively (see Figure 134-2, Plot B). Oral administration results in at least a two component model, with input generally also following first order input (see Figure 134-2, Plot C). The *absorption half-life* derived from the slope of the upswing of the oral PDC curve (K_a) is the time necessary for 50% of a drug to be absorbed.

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Figure 134-1 The determinants of plasma drug concentration act in concert following administration of a fixed dosing regimen. Each determinant can be influenced by patient (e.g., species, age, gender), pharmacologic (i.e., drug interactions), or disease factors.

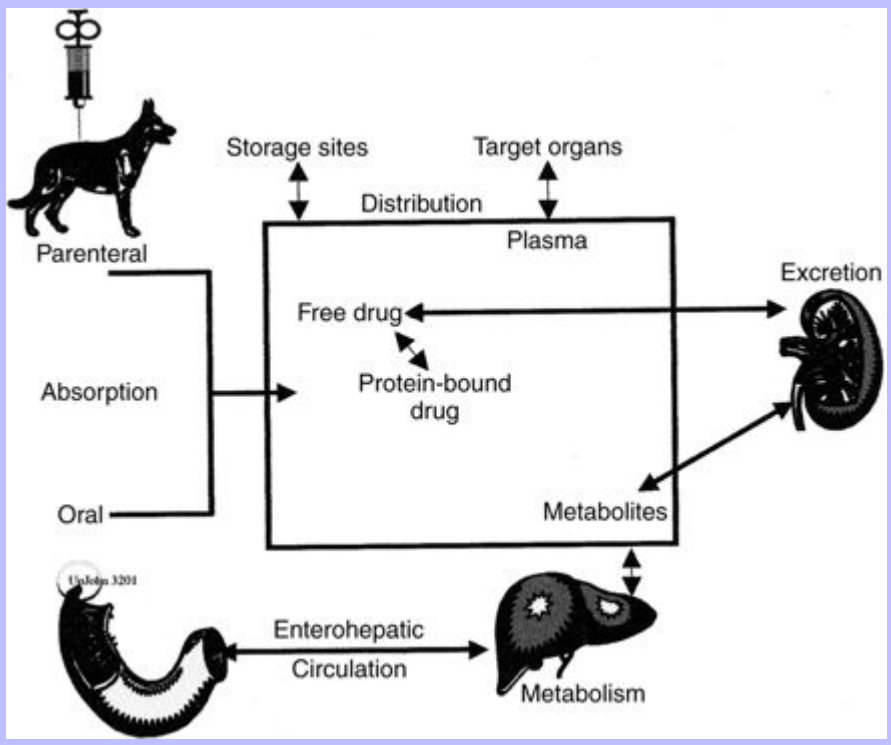
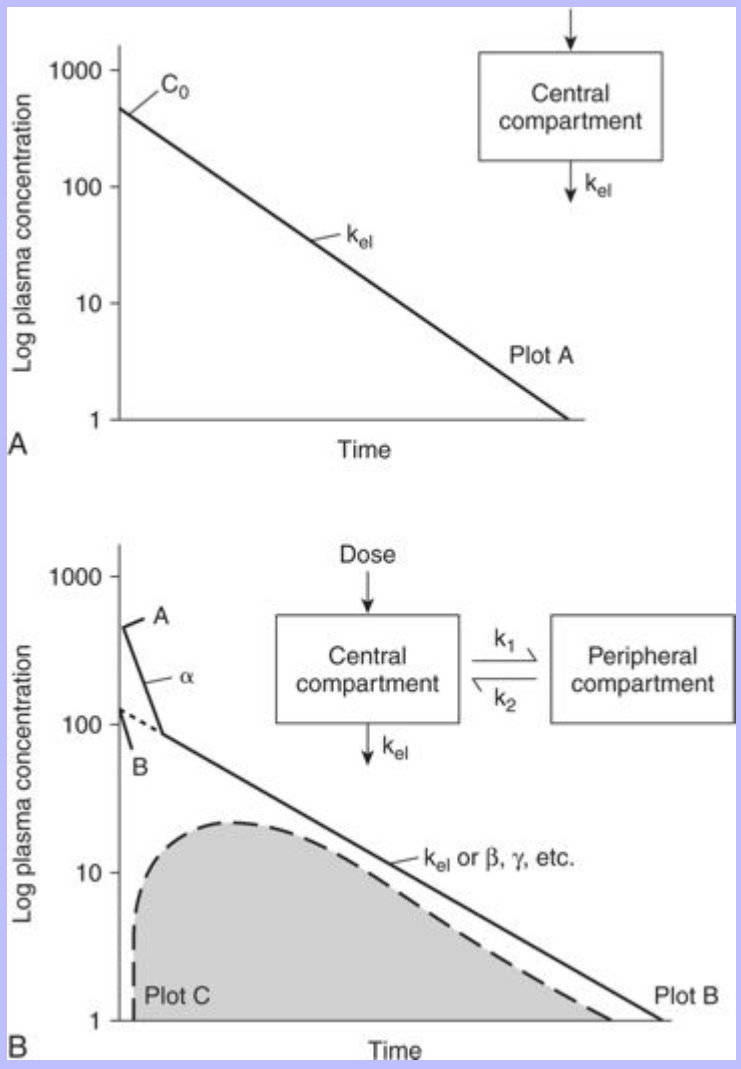


Figure 134-2 Log plasma drug concentration (PDC) versus time curves is subjected to linear regression. Following intravenous (IV) administration, a drug that fits a one-compartment open model will plot as a straight line. The equation y = mx + b when plotted semilogarithmically becomes $C = C_o e^{-kt}$ where *C* is the predicted drug concentration (mass/volume) at any time, *t*, following drug administration, C_o is the concentration of drug at time *0*, which is extrapolated back from the first data point, and *k* is the elimination rate constant ($time^{-1}$). The rate also can be calculated from two data points (i.e., peak and trough samples collected as part of therapeutic drug monitoring (*inset*, Plot B). Distribution for A is either instantaneous or does not occur. The V_d (volume/mass) is calculated: $V_d = Dose/C_o$. For drugs distributed into peripheral tissues, at least two components are present (Plot B). PDC decline in the first phase due to both distribution into tissues and elimination. Once a distribution equilibrium has been reached, PDC decline only due to elimination (second component). Linear regression yields the equation for a two compartment open model: $\mathbf{C} = Ae^{-\alpha t} + Be^{-\beta t}$. The slope (α) is the distribution rate constant whereas the slope of the second (terminal) component is the elimination rate constant (β or k_{el}). The V_d of the central compartment for such a drug is calculated from PDC extrapolated to the y intercept from the first component prior to distribution (A) and the V_d of the peripheral compartment from the y intercept of the second component (B, after distribution equilibrium is reached). For oral administration (Plot C), absorption generally also follows first order, and the general equation becomes $C = Be^{-\alpha t} - Ae^{-kat}$ (the absorption component is subtracted from the remainder of the curve). The absorption rate constant (k_a) can be derived from the upswing of the curve, but only after the elimination component of the curve is stripped. Generally, the distribution phase of non-IV doses is masked by the absorptive phase. Bioavailability *(F)* of the drug would be determined from the ratio of area under the curve measured from data collected

after administration of the extravascular dose *(dotted line)* and the IV dose. The AUC for each route must be adjusted for any dose differences: $F = AUC_{oral} \times Dose_{oral}/AUC_{IV} \times Dose_{IV}$.



The dose of drugs not administered IV is based on the *bioavailability,* or the percent of administered drug that reaches systemic circulation *(F)*. Bioavailability is calculated by comparison of the area under the PDC versus time curve *(AUC)* generated from data collected following administration both IV (defined as 100% bioavailable) and the alternative route being studied (Figure 134-2, *C*). If the AUC for both curves are equal following adjustment for dose differences, bioavailability is 100% (F = 1.0). However, the pharmacologic response to a drug may vary even if bioavailabilities are equal. A drug whose rate of absorption is slower than another may be completely absorbed (i.e., bioavailability is 100%), but PDC may not reach the same magnitude or peak when in a different preparation.

Subjecting PDC across time may force the data to fit a model that is not appropriate. Non-compartmental (model independent) analysis describes drug behavior based on statistical moments, area under the time versus concentration curve (AUC), and area under the moment curve, which are generated from computer analysis. Elimination half-life is based on the slope of the terminal component of the curve. However, a comparable parameter, mean residence time (MRT), which describes the time needed for 63% of an IV dose to be eliminated, is more physiologically relevant.

134.2.1.2 Mechanisms of Drug Movement

Each drug movement is affected by a number of physiologic factors, the most important being the rate and extent of passive diffusion. Lipid solubility, molecular weight, and drug pK_a are major determinants of passive diffusion that reflect the chemical structure of the drug and thus cannot be modified. The concentration gradient of diffusible drug across the site of drug movement is the single most important determinant of passive drug diffusion; thus passive drug movement is most simply increased by increasing drug dose. However, the amount of diffusible drug can be influenced by many factors, particularly dissolution and ionization. In its ionized form, a drug cannot traverse lipid membranes and may be "trapped" in the environment. A weakly acidic drug is generally ionized when surrounded by an environmental pH that is greater than its pK_a (i.e., a basic environment) or, if a weak base, less than its pK_a (i.e., an acidic environment). Thus orally administered aminoglycosides (pk_a 9 to 10) are ionized and trapped in the acidic environment of the gastrointestinal tract, whereas as weak acids, such as the betalactam antibiotics (e.g., amoxicillin or cephalothin) will be predominantly unionized and more likely to be well absorbed (if not destroyed by gastric acidity). Likewise, aminoglycosides are less effective in an acidic urine compared with an alkaline urine, although they will be more rapidly eliminated. Beta lactams, however, will be unionized in an acidic urine, and as such, they not only will penetrate bacteria more easily but they are more likely to be passively reabsorbed from the renal tubular lumen and hence "recycled" before being eliminated in the urine. Other host determinants of passive diffusion include thickness of the membrane to be traversed (i.e., edematous compared with normal tissues); surface area (e.g., small intestine versus stomach); and temperature.

134.2.1.3 Determinants of Drug Disposition

134.2.1.3.1 Absorption

Both rate and extent of absorption from the gastrointestinal tract are influenced by a number of host factors, most of which affect passive diffusion. These include gastrointestinal pH, which favors absorption of weak acids; surface area, which favors absorption in the small intestine instead of the stomach; motility, which mixes the drug, thus increases the concentration of diffusible drug at the site of movement; permeability and thickness of the mucosal epithelium, which can be negatively or positively impacted by disease; and, less commonly, intestinal blood flow, which maintains the concentration gradient across the mucosal epithelium. The latter factor is important only for drugs capable of rapid transfer across the epithelium. Other factors such as the impact of acidity on product stability or the presence of p-glycoprotein in intestinal epithelial cells (e.g., for cyclosporine) can also affect gastrointestinal drug absorption. Bioavailability of an orally administered drug also is decreased if the drug is metabolized by intestinal epithelial cells (e.g., again cyclosporine) or microbes, or the liver. Hepatic metabolism can profoundly affect systemic delivery of an orally administered drug because absorption into the portal vein exposes the drug to the liver prior to systemic circulation. Drugs

characterized by a high hepatic extraction ratio (>70%) are almost completely removed from the blood by hepatocytes during the first passage of blood through the liver (first-pass metabolism). Oral doses of such drugs must be increased despite good to excellent oral absorption if PDC are to be therapeutic. The effects of first-pass metabolism may be reduced if drug metabolites are also pharmacologically active (i.e., propranolol and diazepam).

Novel routes of drug administration may overcome the detrimental effects of first pass metabolism of some drugs. Examples include transdermal delivery such as patches, ointments, or gels; buccal patches and iontophoresis; aerosolization; and rectal administration. However, before a novel route is accepted as an effective method of drug delivery by the medical community, it must be scientifically established for the drug, as is exemplified by the use of transdermal gels for systemic delivery of drugs in cats, which have been proven effective following single-dose administration of several days.

134.2.1.3.2

Distribution

Once a drug reaches systemic circulation, it must be distributed from the central (blood) compartment to the site of drug action in peripheral tissues and then back into the central compartment to be eliminated (see Figure 134-2). Because C_{max} (Figure 134-3) is not achieved in tissues until distribution has reached equilibrium, peak drug monitoring samples should not be collected immediately after dosing. The major factors that determine drug distribution include lipid solubility of the drug (its ability to penetrate cell membranes); concentration of diffusible drug (thus not bound to proteins or other tissue components), and regional (organ) blood flow. The lipid solubility of the drug influences the extent of protein binding as well as the extent of drug distribution, and thus V_d and dose. Although V_d is useful for determination of doses and extent of distribution, it cannot confirm where the drug has been distributed. However, lipid soluble drugs distribute to total body water. As such, they are characterized by a V_d ε 0.6/kg. A V_d of this magnitude suggests that the drug is distributed to total body water because it can penetrate cell membranes, which might be an important consideration in selection of some drugs (e.g., antibiotics, drugs active in the central nervous system). In contrast, the distribution of water-soluble drugs is limited to extracellular fluid (ECF) and V_d for such drugs generally is 0.3 L/kg or less. If the V_d of a drug changes due to disease (or varies among species), the dose of drug necessary to get the same PDC must similarly change. For lipid soluble drugs. as weight increases, the V_d of the drug will proportionately change with weight and dosing on a mg/kg basis is appropriate. However, predicting the effect on water-soluble drug is more difficult. Pediatric patients are characterized by an ECF compartment that is proportionately greater than that in adults. Thus doses of water-soluble drugs should be higher for them compared with adults. Diseases associated with fluid retention (ascites, edema) or intensive fluid therapy are likely to increase V_d of many water-soluble drugs (and thus decrease PDC), whereas obesity, dehydration, or weight loss is likely to decrease V_d and thus increase PDC of a water-soluble drug. Dosing based on body surface area (i.e., mg/m^2) may also avoid increased risk of adverse events that occur in some patients due to differences in body size. This method of dosing also takes into account differences in excretion. However, this method may increase the risk of toxicity in very small animals (<10 kg).

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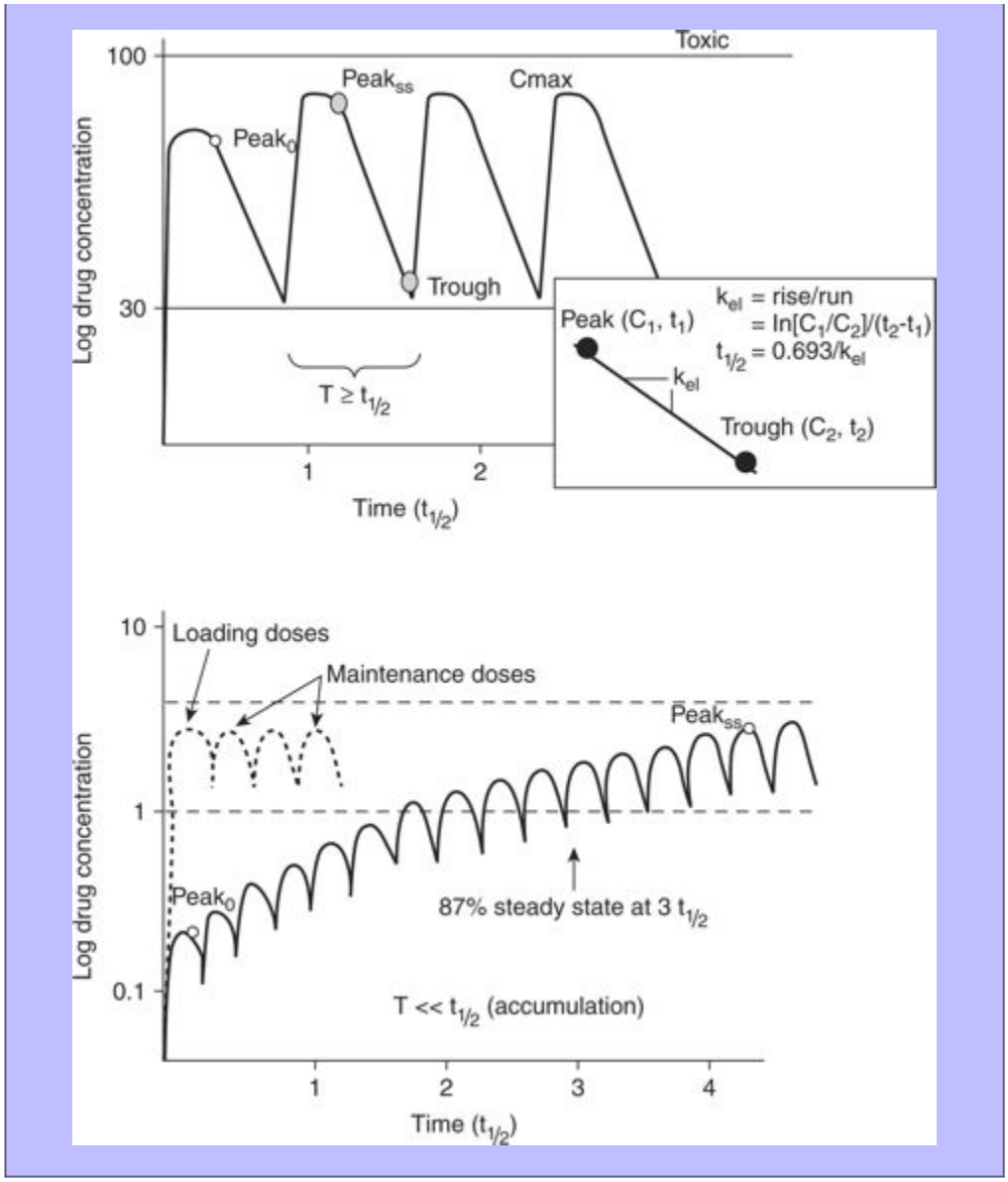
Figure 134-3 The goal of a fixed dosing regimen is to maintain PDC in the therapeutic range after multiple extravascular dosing. The therapeutic range of a drug is defined by a peak or maximum concentration (C_{max}) above which toxicity is more likely, and a trough or minimum concentration (C_{min}) below which therapeutic failure is more likely. A drug whose dosing interval is longer than its half-life *(A)* will be largely eliminated before the next dose is given. The fluctuation in PDC can be unacceptably large for such drugs. In contrast, a drug administered at an interval shorter than its half-life *(B)* will accumulate since most of the drug is still in the body by the next dose. At steady-state, which occurs at 3 to 5 drug half-lives, the fluctuation in drug concentrations during the dosing interval is small. For any drug, half-life can be determined from peak (C_{max}) and trough (C_{min}) P (*inset*, **B**). Since the PDC is plotted logarithmically, the equation for slope (rise over run) becomes: ln $[C_1/C_2]/t_2$-t_1. For example, if gentamicin samples collected at 2 hours and 12 hours after an IV dose were 10.5 and 2.0 µg/ml, the k_{el} for gentamicin in this animal would be 0.17 hr^{-1}, where C_{max} and C_{min} are the desired peak and trough concentrations, respectively. Since C1/C2=2 at one $t_{1/2}$ (where t_2-t_1= $t_{1/2}$), $t_{1/2}$= 0.693/k (0.693-natural log [Ln] of 2). For gentamicin in this example, the elimination half-life would be $0.693/0.17^{-1}$hr or 4.2 hr. If a dosing interval is deemed inappropriate, a more appropriate interval (T_{max}) can be calculated: T_{max}= ln$[C_{max}/C_{min}]k_{el}$.



Drug binding to proteins affects distribution. Plasma protein-binding renders a drug more water soluble, which facilitates movement in circulation. Weakly acidic, lipid-soluble drugs tend to bind to albumin, whereas basic drugs tend to bind to α_1 glycoproteins. Drugs also may bind to tissue proteins. However, the protein-bound drug cannot be distributed between plasma and tissues. Protein-bound drug is not pharmacologically active, cannot be renally excreted, and for many drugs, does not distribute into hepatocytes responsible for hepatic metabolism. Highly protein-bound (>80%) drugs are more likely to be involved in adverse drug events because displacement of only a small proportion of drug from the protein (i.e., due to competition with other protein-bound drugs, or hypoalbuminemia) can significantly increase the proportion of free, active drugs. For example, displacement of only 1% of a drug that is *99%* protein-bound (e.g., nonsteroidal antiinflammatories) such that it becomes 98% bound doubles the

concentration of pharmacologically active drug. However, increased renal and hepatic clearance of the unbound drug will increase such that PDC eventually return to normal as a new equilibrium is reached. Highly protein-bound drugs are characterized by a V_d of less than 5%, the volume of the plasma or blood central compartment. However, displacement from plasma proteins increases the V_d of the drug as free drug enters tissues. Protein-binding of drugs complicates extrapolation of dosing regimens among species because the proportion of bound drug often is not determined. Fortunately. the majority of drugs are not highly protein-bound. Distribution of drugs into tissues also may be influenced by proteins that pump drugs out. For example, β-glycoprotein effectively removes many drugs from the CNS; deficiencies in collies and related dogs have been correlated with CNS drug toxicities.

134.2.1.3.3

Metabolism

Irreversible drug elimination from the body is the final determinant of PDC. Most drugs are eliminated by hepatic metabolism and/or renal excretion. Lipid soluble drugs often require conversion to a water soluble form to facilitate renal elimination. Metabolism most commonly occurs in the liver in one or two phases. Phase I induces a chemical change that increases water solubility and renders the drug more susceptible to phase II metabolism. Reactions include oxidation, hydrolysis, or reduction and are mediated most commonly by cytochrome P450 (microsomal) enzymes. Phase I metabolites are often inactive (e.g., phenobarbital), but can be equally, more (i.e., a pro-drug, such as enalapril), or less active (e.g., diazepam) than the parent compound. Often, the drug becomes more toxic (e.g., acetaminophen). Multiple superfamilies of P450 enzymes exist and deficiencies or increases (e.g., drug induced, genetic) in one or more P450 enzymes are increasingly recognized for their role in selected adverse drug events. Phase II is also referred to as *conjugation* because a large, water-soluble molecule is added to either the parent drug or phase I metabolite. Glucuronidation, a reaction in which the cat is deficient, is the most common phase II reaction. Addition of glutathione to a reactive metabolite is an important mechanism by which reactive metabolites can be scavenged before tissue damage occurs. Sulfonation and acetylation, the latter being a reaction in which the dog is deficient, are less common phase II reactions. With the exception of some acetylation reactions (e.g., procainamide), phase II metabolites are inactive. Metabolites are generally eliminated in the urine, or less commonly, in the bile. Drug metabolism also occurs in other tissues, including the kidney, lungs, skin, and intestines. Drug-induced toxicity in these organs may reflect their metabolic capacity.

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Factors that can affect hepatic drug metabolism include the amount and activity of drug metabolizing enzymes, and if the drug is characterized by a high extraction ratio (>70%; “flow-limited” drug), hepatic blood flow. Changes in protein-binding of highly bound drugs can also affect the rate of hepatic metabolism of drugs characterized by a low (<70%: “capacity-limited” drug) extraction ratio. The rate of elimination of capacity-limited drugs is inversely proportional to their degree of protein binding. Disease, drug interactions, and species differences can have a profound impact on drug metabolism and thus duration of drug elimination. For example, drugs that induce (phenobarbital, rifampin) metabolism increase the clearance of other drugs metabolized by the liver and can cause therapeutic failure, or possibly increased toxicity (due to metabolite formation) with the other drug. Induction generally requires multiple days of therapy and reflects an increase in the synthesis of enzymes. In contrast, inhibition can occur immediately, often due to competition for the same enzymes. Inhibitors (e.g., chloramphenicol, cimetidine, ketoconazole) will prolong the half-life of other drugs and may result in drug toxicity. Inhibitors can be used therapeutically as is exemplified by the use of cimetidine to decrease the toxicity of acetaminophen or ketaconazole to prolong the half-life of cyclosporine.

134.2.1.3.4 Renal and Biliary Excretion

Renal excretion is the most important route of drug elimination for both parent drugs and their metabolites. Host factors that determine renal excretion include glomerular blood flow, active tubular secretion, and tubular resorption, each of which is directly influenced by renal blood flow. The kidney is also capable of metabolizing some drugs, although this capacity is only occasionally of clinical importance.

Glomerular filtration is a passive process. Drugs enter the glomerulus by bulk flow, being excluded if too large (>60,000 MW), such as occurs if the drug is protein-bound. In contrast, active transport of drugs in the proximal tubules is very efficient, rapid, and independent of protein-binding. Separate transport proteins exist for acidic, basic, and neutral drugs. Transport is susceptible to competition among drugs, although drug interactions as a result of competition are not frequent and seldom clinically relevant. The prototypic example of competition is the use of probenecid to compete with and thus inhibit the renal excretion of expensive beta-lactam. Resorption of drugs from renal tubules into peritubular capillaries slows renal excretion and prolongs drug half-life. The extent to which a drug is reabsorbed depends upon its lipid solubility and its ionization. Weakly acidic drugs are more likely to be resorbed in acidic urine but are more likely to be trapped and excreted in alkaline urine. Changes in urinary pH (especially acidification) might be therapeutically altered to modify the rate of renal drug excretion. Because renally excreted drugs are concentrated in the kidney (urine), selection of antibiotics for treatment of bacterial cystitis (but not other urinary tract infections) based on minimum inhibitory concentrations (MIC) may markedly underestimate the efficacy of the drug because MIC generally are based on plasma, rather than urine, drug concentrations.

In contrast to renal excretion, biliary excretion is very slow and is much less clinically important. Drugs are eliminated in the bile by at least three active transport systems: one each for organic acids, bases, or neutral compounds. Characteristics that determine biliary excretion of drugs include chemical structure, polarity, and molecular weight (generally >600 MW); the latter is one of the major determinants. Drugs excreted in the bile are in greater contact with the intestine and its flora compared with other drugs and are thus more likely to cause adverse reactions in the gastrointestinal tract. Whereas a conjugated drug will not be resorbed from the intestinal tract, intestinal microbes can unconjugate drugs so that they are reabsorbed *(enterohepatic recirculation)*. The half-life and exposure of the drug to the intestinal tract is subsequently prolonged.

134.2.1.3.5 Elimination

The combined effects of renal and biliary excretion, as well as other routes of elimination (i.e., pulmonary, sweat) irreversibly remove drug from the body. The elimination half-life of a drug is the time necessary for half the drug to be eliminated from the body and is derived from the terminal component of the PDC versus time curve. It is one of the most useful parameters for determining an appropriate dosing interval. At one drug elimination half-life, 50% of the dose has been eliminated; by 3 to 5 drug half-lives, 87 to 99% of the drug has been eliminated. Thus for a drug with a 4-hour half-life, approximately 12 to 20 hours must elapse before most of the drug has been eliminated. For drug intoxication, 1 to 2 elimination half-lives is generally sufficient for PDC to drop below the toxic range unless a massive overdose has occurred. An exception occurs if hepatic drug (or other) metabolizing enzymes become saturated. In such cases, elimination becomes zero order and half life is no longer an applicable parameter.

Plasma clearance (CI) is the volume of plasma irreversibly cleared of the drug per unit time and represents the sum total of organ clearance. Unlike elimination (a rate), clearance is a volume per unit time. The volume of blood cleared per unit time by an organ is independent of PDC. The same volume of blood will be irreversibly cleared of drug by an organ regardless of how much drug is in the blood. If the drug is cleared exclusively by one organ (e.g., renal clearance of aminoglycosides or hepatic clearance of caffeine), then plasma clearance also represents clearance of the specific organ and can be used to evaluate the function of the organ. Although clearance is the physiologic activity responsible for drug elimination, it generally is not directly measured, but rather, is calculated from other parameters (see Figure 134-2). However, it can be determined only after IV administration. The impact of changes in clearance tends to be estimated by changes in elimination half-life. However, although half-life is the clinically useful estimate of how long a drug stays in the body, it is a "hybrid" parameter in that it is influenced by both distribution and clearance. The greater the volume of drug cleared per unit time, the shorter the drug half-life. However, the larger the V_d, the longer the half-life because the distributed drug cannot access the organs of clearance. Thus drug elimination half-life changes directly (and proportionately) with the volume of distribution of a drug but inversely (and proportionately) with the clearance of the drug. The clinical significance of these relationships might be exemplified in a patient that has become dehydrated as a result of uncompensated chronic renal disease. As tissue volume contracts with dehydration, the V_d decreases. Although PDC (and the risk of drug toxicity) increases, because the volume cleared per unit time does not change, and because more drug is in each milliliter of blood, the drug is actually eliminated more rapidly. If all else remains normal, drug half-life will decrease. In the patient that is not dehydrated but suffers from significantly comprised renal function, renal clearance decreases and drug half-life thus also decreases. In the patient with both volume contraction due to dehydration and compromised renal function, the effects of the changes in clearance and volume of distribution balance one another. Drug elimination half-life may not change, even though renal function may be impaired. With successful volume replacement, half-life may increase unless renal function also improves.

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134.3 FIXED DOSING REGIMENS

134.3.1 Dose

A fixed dosing regimen is comprised of a dose and interval. The dose necessary to achieve a specified target PDC (e.g., C_{max}) depends on the V_d:

$$\text{Dose} = [C_{max}][V_d]$$

The dose of drug must be increased or decreased proportionately with changes in V_d to achieve the same target PDC. The V_d of a drug is the sole determinant of PDC achieved after an IV dose is administered for drugs that do not accumulate (i.e., the dosing interval is sufficiently long that each dose is essentially eliminated before the next dose; see below). For drugs that do accumulate, the initial dose of the drug must also take into account the magnitude of accumulation, which is in turn dependent upon the elimination half-life of the drug in relation to the dosing interval.

134.3.2 Interval

The frequency of dosing or the dosing *interval* is determined by the time (T_{max}) it takes for maximum PDC (C_{max}) to drop to a point below which the desired response no longer occurs, C_{min} (Figure 134-3, *A*). Thus T_{max} depends on the amount of fluctuation in PDC desired during the dosing interval and the elimination rate constant (k_{el}). If C_{min} for a drug is close to half of C_{max}, then approximately 1 drug half-life (i.e., $T_{max} = t½$) can elapse before the next dose must be administered. A more appropriate interval can be calculated using k_{el} if C_{min} does not approximate half of C_{max}. The longer the elimination half-life of a drug, the longer the interval (or T_{max}) can be between doses.

Decreasing a dosing interval is of no benefit for drugs whose half-life is long. For example, an 8-hour dosing interval for phenobarbital (drug half-life 50 to 100 hours average 72 hours) offers no advantage to a 12-hour interval since very little drug will be eliminated during the 12-hour period between doses. An exception is made if induction of drug metabolizing enzymes by phenobarbital has decreased drug half-life to less than 24 hours. In contrast, prolonging a dosing interval for convenience may be dangerous for drugs with a short half-life (e.g., many antibiotics). For example, if the drug half-life is two hours, a 4-hour increase in the dosing interval will result in a *75%* decrease in C_{min} since 2 half-lives will elapse between the dosing interval. For drugs with a short half life, often adding an additional dose (i.e., shortening the dosing interval) is more effective (and cheaper) than doubling the dose. An example might be a time dependent (betalactam) antibiotic or cyclosporine. Some drugs remain effective despite dosing intervals that are longer than the elimination half-life of the drug. Examples include antimicrobials that exhibit a post antibiotic effect (e.g., aminoglycosides); drugs that accumulate in tissues (e.g., omeprazole); drugs whose metabolites are active (particularly if the metabolite half-life is longer than the parent compound [e.g., tepoxalin]); and drugs that destroy targets that must be resynthesized before the effect resolves (e.g., selected antiprostaglandins).

Drug half-lives can be as short as 2 minutes or less (e.g., epinephrine and dobutamine) or as long as several weeks (e.g., potassium bromide). Drugs with half-lives that are too short for convenient dosing are either given as constant IV infusion (e.g., lidocaine) or may be prepared as slow-release preparations (e.g., benzathine penicillin). Although the elimination half-life of the drug does not vary for slow release preparations compared with other preparations of the drug, the absorption of the drug is much slower. The intent, although not always successful, is to maintain constant therapeutic concentrations by ensuring continuous addition of drug into plasma. Note, however, that absorption may be so slow that therapeutic concentrations are never reached. Many oral drugs are prepared as slow-or continuous-release preparations (e.g., quinidine or theophylline). However, these preparations have been formulated for humans and the release kinetics may vary substantially in animals. Use of these preparations should be reserved for drugs that have been studied in animals. Alternatively, therapeutic drug monitoring for some drugs can be used to ensure that drug concentrations fall within the therapeutic range.

134.3.3 Accumulation

For drugs with very long half-lives, the dosing intervals can be correspondingly prolonged to allow for convenience. However, a dosing interval that is too long is also often inconvenient (e.g., phenobarbital and 3 days). In addition, for drugs with a narrow therapeutic range, fluctuation of PDC during the dosing interval must be minimized. In both situations, the recommended dosing interval (e.g., every 12 hours for phenobarbital) may be shorter than the drug elimination half-life. With each subsequent dose of drug administered at an interval *(T)* that is shorter than drug half-life, drug from the previous dose will remain in the

body. The amount of drug remaining depends upon how much shorter the dosing interval is compared with the half-life. In such situations, the drug begins to accumulate with multiple doses (see Figure 134-3, *B*). Eventually, a steady-state is reached for the drugs such that the amount of drug administered with each dose equals the amount eliminated during the dosing interval. As with drug elimination, approximately 3 to 5 drug half-lives must elapse following a fixed dosing regimen before steady-state is reached. Steady-state is a relevant issue only for drugs that accumulate. The amount that a drug will accumulate as steady-state is reached depends on the difference between drug elimination half-life and the dosing interval. The greater the difference (the larger half-life is compared with the interval), the more the accumulation. For example, bromide (half-life 21 days) will accumulate more than phenobarbital (half-life 3 days) when both are administered twice daily. The amount of accumulation can be approximated. If the elimination half-life is equal to dosing interval, drug will accumulate twofold; if the elimination half-life is twice the interval, concentrations at steady state will accumulate fourfold. The relationship between elimination half-life and dosing interval also determines the amount that PDC may fluctuate during a dosing interval. The larger the elimination half-life compared to the dosing interval, the smaller the fluctuation in PDC during a dosing interval. For drugs administered at an interval equal to the elimination half-life, PDC will fluctuate twofold between doses. The relationship between drug half-life and dosing interval also influences the number of samples collected for therapeutic drug monitoring. For drugs with a long half-life (compared to the closing interval), a single sample (often trough) may be sufficient (e.g., bromide, often phenobarbital), whereas both peak and trough samples are indicated for drugs with a short half-life (e.g., digoxin) that allows fluctuation during the dosing interval.

Drugs that accumulate protect the patient in that PDC are stable (i.e., do not fluctuate during a dosing interval). 497
However, drugs that accumulate also present problems that are not encountered with drugs administered at an 498
interval that precludes accumulation. Maximum therapeutic efficacy will not be realized until steady-state concentrations have been reached, which may be an unacceptable time for some patients (i.e., epileptics receiving potassium bromide which has a 21 to 24 day half-life in dogs). In such situations, a loading dose can be administered. This single dose, based on bioavailability and V_d of the drug and target concentrations (usually between C_{max} and C_{min}),

$$\text{Dose} = C^{*}V_d/F,$$

is intended to achieve therapeutic concentrations with the first dose. A disadvantage to loading dose is that the body cannot gradually adapt to the drug. Additionally, the maintenance dose may not maintain PDC reached by loading. In such cases, PDC may gradually decrease below C_{min} *or* increase above C_{max} and the change may not be evident until a new steady-state has been reached 3 to 5 drug half-lives later. For bromide, monitoring immediately after a loading dose and at one month (1 half-life) allows proactive evaluation of the maintenance dose. If the two concentrations are not similar, the maintenance dose can be appropriately modified. For drugs that accumulate, the addition of a single maintenance dose of the drug to the total amount of drug in the patient's body at steady state can be considerably small, and multiple doses (i.e., a small loading dose) must be given to immediately influence PDC. Alternatively, the maintenance dose will need to be increased and a new steady state reached 3 to 5 drug half-lives later.

134.3.4 Therapeutic Range

The therapeutic range provides a target for the dosing regimen and is designed to generate therapeutic but not toxic concentration at the tissue site. Fixed dosing regimens comprise a dose (e.g., mg/kg) and an interval (e.g., every 8 hours) that should result in PDC in the therapeutic range throughout most of the dosing interval. The therapeutic range generally consists of a minimum effective PDC (trough or C_{min}), below which therapeutic failure is likely to occur; and a maximum effective PDC (peak or C_{max}), above which a type A adverse reaction

is more likely (see Figure 134-1). However, a therapeutic range is a population statistic and targets concentrations between which a large proportion (e.g., 95% of the population) will respond. A small percentage of animals will respond above or below the therapeutic range whereas others will exhibit clinical signs of toxicity below the maximum therapeutic range. When possible, therapeutic drug monitoring should establish the therapeutic range for the individual patient. The most appropriate therapeutic range for a drug as a target is complicated the class and intent of the drug. For example, therapeutic ranges for antimicrobials are based on the microorganism (e.g., immune-inhibited) and whether or not the antimicrobial is a time (e.g., beta-lactamase) versus concentration (e.g., aminoglycosides) dependent drug. The therapeutic range for digoxin is greater if improved contractivity is the target as opposed to decreased heart rate.

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135 CHAPTER • 135 Antimicrobial Drug Therapy

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The administration of antimicrobials to animals is among the most common treatments in veterinary medicine. The development of new drugs, revised approaches to dosing, and the emergence of resistant bacteria have modified this approach to therapy. The intent of this chapter is to discuss the important factors that guide and affect antimicrobial drug therapy in animals. Although "antimicrobial therapy" encompasses other aspects of therapy, such as antifungal, antiparasitic, and antiviral therapy, this chapter focuses on antibacterial therapy.

135.1 STRATEGIES FOR SELECTION OF AN APPROPRIATE ANTIBIOTIC

135.1.1 Empirical Drug Selection

Initial bacterial therapy can be instituted for many infections based on the presumptive activity of drugs against the bacteria and the historical performance (or in some instances anecdotal performance) of available drugs. Prescribing empirically is more reliable when resources provide guidelines on the susceptibility of bacteria, or clinical trials predict efficacy. Several surveys have been published and drug manufacturers have provided susceptibility information on their package inserts that is helpful. Based on this information, some general guidelines are possible:

If the bacteria is suspected to be a streptococci (but not *Enterococcus* spp.), β-streptococci, or *Bacillus*, *Actinomyces,* or *Pasteurella* spp., successful therapy can be achieved by administration of a penicillin such as ampicillin, or amoxicillin, amoxicillin + clavulanate (e.g., Clavamox), a tetracycline, or trimethoprim-sulfonamide. Other drugs also may be effective, but the more expensive, newer drugs or injectable agents might be considered overkill for such susceptible bacteria.

Staphylococcal infections in small animals are usually caused by *Staphylococcus intermedius*. Susceptibility can be expected to first-generation cephalosporins (e.g., cephalexin, cefadroxil, or cefazolin), amoxicillin-clavulanate (Clavamox), clindamycin, or one of the fluoroquinolones (e.g., enrofloxacin, difloxacin, marbofloxacin, or orbifloxacin). All of these drugs have been effective in clinical trials.

Gram-negative bacteria are more likely to develop resistance. Gram-negative bacilli of the Enterobacteriaceae (e.g., *Escherichia coli, Klebsiella pneumoniae*, and *Enterobacter* spp.) are resistant to many of the commonly used first-line drugs such as amoxicillin, ampicillin, tetracyclines, and first-generation cephalosporins (e.g., cephalexin, cefadroxil). Published studies have shown that the proportion of these bacteria resistant to these drugs can exceed 50%.[1–3]

Other problem bacteria include indole-positive *Proteus* spp., such as *Proteus vulgaris,* and *Pseudomonas aeruginosa*. Of the gram-positive bacteria, the problem bacteria include the enterococci, such as *Enterococcus faecium* or *Enterococcus faecalis. Staphylococcus* spp. (especially *S. aureus*) may acquire a resistance gene and become unaffected by β-lactam antibiotics, including cephalosporins. Fortunately, the prevalence of resistant staphylococci is still low in veterinary medicine.

P. aeruginosa is inherently resistant to many drugs because it lacks high-permeability porin proteins by which antibiotics gain access to bacteria. It also may produce beta-lactamase. A wild strain of *P. aeruginosa* has inherent resistance to most common drugs but should be susceptible to amikacin, gentamicin, or tobramycin, extended-spectrum penicillins (ticarcillin, piperacillin), some selected third-generation cephalosporins (e.g., ceftazidime), carbapenems (e.g., meropenem or imipenem), and perhaps a fluoroquinolone. Of the fluoroquinolones, ciprofloxacin, a human-registered drug, is the most active.

In clinical cases in which a resistant strain or bacteria with unpredictable sensitivity is suspected, a susceptibility test is advised to confirm the drug selection. But before results are available, initial therapy to treat infections caused by gram-negative enteric bacteria can be initiated with a fluoroquinolone (e.g., enrofloxacin, ciprofloxacin, difloxacin, marbofloxacin, or orbifloxacin), a cephalosporin, amoxicillin-clavulanate (e.g., Clavamox), or an aminoglycoside (e.g., gentamicin or amikacin).

If the bacteria is anaerobic, the gram-positive species such as *Clostridium* or *Actinomyces* species are susceptible to penicillins (e.g., penicillin G, ampicillin, amoxicillin), metronidazole, or clindamycin. The gram-negative anaerobes are usually susceptible to the same group of drugs except that bacteria of the *Bacteroides fragilis* group may be β-lactamase producers. In these cases, one should consider amoxicillin-clavulanate, metronidazole, clindamycin, or a second-generation cephalosporin (e.g., cefoxitin or cefotetan). Chloramphenicol also is active against anaerobic bacteria, but this drug is not as available as in previous years. The activity of first-generation cephalosporins and trimethoprim-sulfonamide combinations may be unpredictable for anaerobic infections.[4]

135.2 BACTERIAL SUSCEPTIBILITY TESTING

Bacterial susceptibility testing is recommended for cases that are not responding to antibiotic treatment, or in cases in which the suspected bacteria is known to possess a pat-tern of resistance that makes empirical drug selection unreliable. Although not perfect, susceptibility tests help refine the antibiotic selection process. If an organism tests resistant to a particular antimicrobial, the likelihood of successful therapy with that drug is diminished. On the other hand, a test that indicates susceptibility is no guarantee of clinical success.

135.2.1 Agar-Disk Diffusion Test

The most familiar test for measuring bacterial susceptibility to antimicrobials has been the Agar-Disk-Diffusion (ADD) test, also known as the Kirby-Bauer Test. Details for performing this test have been previously described.[5,6] The ADD test measures the inhibition of bacterial growth against the antimicrobial concentration from a paper disk placed on the agar. The zone size is roughly correlated to the minimum inhibitory concentration (MIC). The larger the zone size, the lower the MIC, and vice versa. Since each antibiotic diffuses at different rates throughout the agar, use published standards for interpreting the sensitivity.[6]

135.2.2 Dilution Test for MIC Determination

The dilution test directly measures the MIC. This test is now available in many veterinary microbiology laboratories. It is a more quantitative measurement of susceptibility, and the test better correlates with clinical efficacy. The interpretation of the MIC test relies on knowing the breakpoints for each drug. Some selected MIC breakpoints[6] for bacteria are shown in Table 135-1.

135.2.2.1 Interpretation of Susceptibility Information

The interpretation uses the "SIR" system, which is sensitive, intermediate, and resistant. If the MIC is below the suscepti-ble breakpoint, the organism is sensitive and a cure can be expected using standard doses. If the MIC is above the resistant breakpoint, the organism is resistant and drug therapy with that drug is not recommended. MIC values between resistant and sensitive categories fall in an "intermediate" zone. (This also has been called "moderately susceptible.") If the MIC is intermediate, the organism should ordinarily be considered resistant. However, successful therapy can be achieved when the drug concentrates at high levels as it does when treating a lower urinary tract infection, or when topical therapy is used. In extreme cases, high doses have been used to achieve drug levels for organisms with susceptibility in the intermediate range, but this should not be considered unless the drug has a high therapeutic index (e.g., with the β-lactam antibiotics). For some fluoroquinolones, the intermediate interpretation was called the "flexible dose" zone, for which high doses can be considered, but the flexible dose category was recently abandoned by the NCCLS.

135.2.3 Limitations of Bacterial Sensitivity Testing

There are important limitations to consider when assessing the clinical relevance of *in vitro* antibacterial susceptibility tests. Sensitivity tests assume equal plasma and tissue concentrations and will overestimate the antimicrobial activity in tissues that may be difficult to penetrate, such as the central nervous system, prostatic fluid, and mammary gland. Sensitivity tests will underestimate activity of topical treatments, local infusions, and antibacterials that concentrate in the urine. Susceptibility tests also may underestimate activity at drug concentrations below the MIC (sub MIC effects). Sensitivity tests do not detect potentially synergistic antibiotic combinations (except for trimethoprim-sulfonamides and amoxicillin-clavulanate). An example of a synergism is the combination of a β-lactam antibiotic and an aminoglycoside. Bacteria may be resistant to either drug alone but sensitive when administered in combination. Finally, sensitivity tests cannot consider the local factors that may affect antimicrobial activity such as pus, necrotic tissue, low oxygen tension, and poor blood perfusion. For example, an aminoglycoside may not be effective *in vivo* if the infection is in necrotic tissue or an abscess, despite an *in vitro* test that indicates susceptibility. Likewise, the activity of fluoroquinolones is decreased in an acid environment, or one in which there are cations present (e.g., Mg^{++}, Ca^{++}), such as urine. In these instances, even when the MIC is in the "susceptible" range, the organism may be resistant *in vivo*.

Table • 135-1 Minimum Inhibitory Concentrations (MIC) Breakpoints

ANTIMICROBIAL	SUSCEPTIBLE (µg/mL)*	RESISTANT (µg/mL)
Amikacin	≤16	≥64
Ampicillin	≤8†	≥32
Ampicillin/clavulanic acid	≤8/4†	≥32/16
Cefazolin	≤8	≥32
Cefotaxime	≤8	≥64
Ceftazidime	≤8	≥32
Cephalothin‡	≤8	≥32
Cefoxitin	≤8	≥32
Chloramphenicol	≤8	≥32
Ciprofloxacin	≤1	≥4
Clindamycin	≤0.5	≥4
Difloxacin	≤0.5	≥4
Enrofloxacin	≤0.5‖	≥4
Erythromycin	≤0.5	≥8
Gentamicin	≤2	≥8
Imipenem (and meropenem)	≤4	≥16
Marbofloxacin	≤1	≥4
Orbifloxacin	≤1‖	≥8
Oxacillin¶	≤2	≥4
Rifampin	≤1	≥4
Tetracycline	≤4	≥16
Ticarcillin	≤64†	≥128
Trimethoprim/sulfa	≤2/38	≥4/76
Vancomycin	≤4	≥32

For ampicillin, susceptibility for staphylococci and streptococci is ≤0.25 µg/mL;
For amoxicillin/clavulanate, susceptibility for staphylococci is ≤4/2 µg/mL;
For ticarcillin, susceptibility for *Pseudomonas* spp.is ≤64 g/mL for, *Pseudomonas* spp., and ≤16 g/mL for enteric gram-negatives;
For erythromycin, susceptibility for streptococci is ≤0.25 g/mL.

* Values between the susceptible and resistant range are interpreted as "intermediate."

† There are exceptions for interpreting some pathogens.(See NCCLS, 2002 for details.)

‡ Cephalothin is used as a marker to test for susceptibility to cephalexin and cefadroxil.

‖ For enrofloxacin and orbifloxacin, the "intermediate" category may require higher doses.

¶ If organisms are resistant to oxacillin, they should be considered resistant to other β-lactam antibiotics also.

135.3 DESIGNING OPTIMAL DOSING REGIMENS

Pharmacodynamics refers to the action of the drug on the bacteria (i.e., if it is bactericidal, bacteriostatic, time-dependent killing, concentration-dependent killing). *Pharmacokinetics* describes the disposition of drug in the body and forms the profile of the drug concentration versus time in the body. The pharmacokinetic-pharmacodynamic (PK-PD) relationships are used to define optimal dosing guidelines for antibiotics in animals. To accomplish this, the pharmacokinetic profile is defined according to its relationship to the MIC.

PK-PD relationships have been correlated to certain variables such as the peak plasma concentration (C_{MAX}), the area of the plasma concentration versus time curve (AUC), and the length of time that the plasma concentration is above the MIC (T>MIC) during a 24-hour interval. These relationships are shown graphically in Figure 135-1. Antibacterial drugs have been described as either bacteriostatic or bactericidal. Bacteriostatic drugs inhibit bacteria, but growth may resume when the drug concentration falls below the MIC. Bactericidal drugs kill the bacteria if the drug concentration is high enough above the MIC, or if the MIC is exceeded for a long enough time. Bactericidal drugs may be either time-dependent in their killing or concentration-dependent. The optimal dosage regimens for classes of drugs can be devised by consideration of these relationships.

135.3.1 Bacteriostatic Drugs

Drugs considered bacteriostatic include tetracyclines, macrolides (erythromycin), azithromycin, sulfonamides, and clindamycin. Under most conditions, chloramphenicol also is bacteriostatic. For these drugs, optimum therapy is achieved by using dosage regimens that maximize the drug concentration above the MIC throughout the dosing interval. Therefore, all bacteriostatic drugs are considered time-dependent (T>MIC). For drugs in this group, if they do not have long half-lives, they must be administered frequently to achieve this goal. Some of the macrolide antibiotics, such as azithromycin, achieve this goal because the drug concentrations persist in tissues much longer than in the plasma after dosing.

135.3.2 Bactericidal Drugs

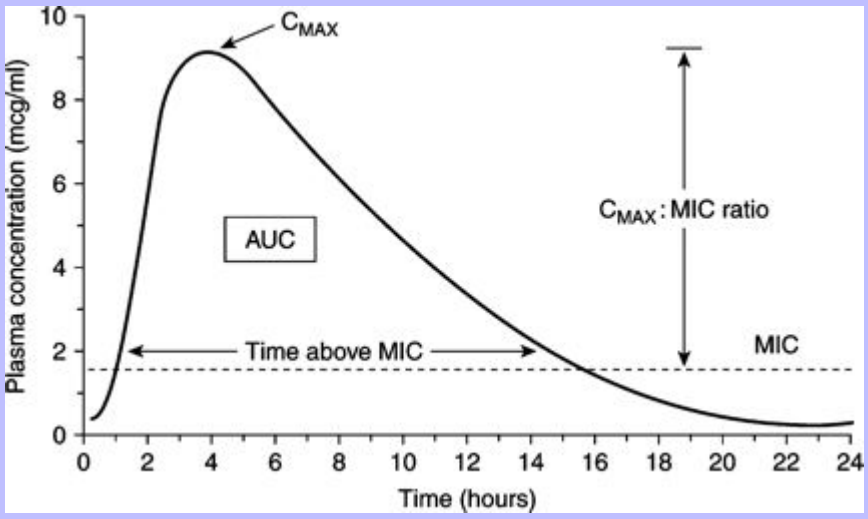
For the *time-dependent* bactericidal drugs, clinical efficacy is achieved when the time of drug concentration above MIC is maximized (T>MIC). The time-dependent drugs include the β-lactam antibiotics such as penicillins, potentiated-aminopenicillins (e.g., amoxicillin-clavulanate), and cephalosporins. There is a threshold of four to five times the MIC, above which increased bacterial killing is not observed. Therefore the most effective treatment is expected with these drugs when they are administered at more frequent intervals, rather than by increasing the dose. A constant rate infusion, although impractical in many veterinary settings, would be the most optimal. For intermittent dosing, the optimum duration of time above the MIC has not been determined for all bacteria, but in general, the T>MIC should be at least 50% of the dose interval in the non-neutropenic patient. Since most penicillins and cephalosporins in small animals have elimination half-lives of only 1 to 2 hours, dosage regimens should consider these pharmacokinetic-pharmacodynamic relationships. When a gram-negative infection is treated, especially a serious one, penicillin derivatives and cephalosporins are administered at least three to four times per day for optimum results.

A few exceptions exist to these guidelines: For the specialized group of β-lactams, the carbapenems (e.g., imipenem and meropen), the T>MIC may be less than 50% because these drugs are more bactericidal. For example, meropenem can be administered twice daily for infections in small animals.[7] Secondly, since the MICs of β-lactam antibiotics are lower for some gram-positive bacteria (e.g., *Staphylococcus* spp.), and antibacterial effects occur at concentrations below the MIC, longer dose intervals may be possible compared with regimens used for other bacteria. For example, cephalexin is effective for treating infections caused by *Staphylococcus* spp. when administered only once or twice a day in dogs[8], despite a half-life of only a few hours.

For *concentration-dependent drugs,* either the peak concentration (C_{MAX}) or the area-under-the-curve (AUC) is the best predictor of clinical efficacy. Aminoglycoside antibiotics such as gentamicin or amikacin are more bactericidal when the peak plasma concentrations are 8 to 10 times above the MIC. After attaining this peak,

plasma concentrations can fall below the MIC for several hours and still achieve a cure. Current dosage regimens for these drugs are designed to produce a C_{MAX}: MIC ratio of 8 to 10 when administered only once daily. Because nephrotoxicosis associated with aminoglycosides is increased by the duration of exposure, not the peak, the once-daily regimens for these drugs are as effective, and less nephrotoxic than lower doses administered more frequently.[9]

Figure 135-1 The variables of minimum inhibitory concentration (MIC), maximum (peak) plasma concentration (C_{MAX}), area-under-the-curve (AUC) for the plasma concentration versus time profile, are used to derive the time above MIC (T >MIC), C_{MAX}: MIC ratio, and AUC: MIC ratio.



The fluoroquinolone antimicrobials (e.g., difloxacin, enrofloxacin, ciprofloxacin, marbofloxacin, and orbifloxacin) also are concentration-dependent. Although, the peak concentration (C_{MAX}: MIC ratio), has been correlated with *in vitro* bactericidal activity, the AUC: MIC ratio for a 24-hour period is probably a better predictor of clinical efficacy. Optimum therapy is achieved when this ratio is above 125, but a ratio of 50 in an immunocompetent animal is also sufficient for a clinical cure for many bacterial pathogens, especially when treating gram-positive bacteria.[10]

The AUC is proportional to the dose administered. Therefore to achieve appropriate AUC: MIC ratios, fluoroquinolones can be administered to treat highly susceptible organisms with the lowest registered dose, once daily. Susceptible bacteria of the Enterobacteriaceae usually have low MIC values in this range. For bacteria that are more resistant (i.e., the MIC values are higher, even though they are still considered susceptible), a higher dose is needed. For example, to achieve the necessary peak concentration for treating infections caused by *Pseudomonas aeruginosa,* which often has an MIC of 0.5µg/ml or higher, doses at or near the highest registered dose, once daily, may be needed.

135.4 TISSUE DISTRIBUTION OF ANTIBIOTICS

If the drug cannot reach the site of action (the tissue), even the most active drugs will be ineffective. With adequate perfusion, there is no barrier to impede diffusion of antibiotics from the vascular compartment to extracellular fluid of most tissues. Antibiotic drug concentrations in the serum or plasma will predict the drug concentration at the site of infection in the extracellular space (interstitial fluid). Pores and fenestrations in the endothelium of capillaries are large enough to allow drug molecules to pass through, unless the drug is highly protein bound in the blood. Therefore most soft tissues and bone do not present a barrier to drug diffusion as long as there is adequate blood perfusion. Only a few drugs are so highly bound that protein binding will impair their tissue penetration. Doxycycline is one of the few examples of a highly protein bound antibiotic used in small animals.

Because protein binding, rather than lipophilicity, is the most important factor for drug tissue penetration, there is no evidence for differences in efficacy among antibiotic drugs that can be attributed to differences in drug's lipid solubility. But drug diffusion can be limited when a lipid membrane (such as tight junctions on capillaries) presents a barrier to drug diffusion. These tissues include sequestered sites such as the central nervous system and eye, the epithelial lining fluid of the lung, and glandular tissues such as the prostate and mammary gland. To treat infections in tissues for which there is a permeability barrier, a drug must be sufficiently lipid soluble to diffuse through the lipid barrier or penetrate via carrier-mediated transport.

An example of a sequestered site is the central nervous system (CNS), which generally restricts poorly-lipid soluble and polar antibiotics. Most cephalosporins (except those classified as third generation), penicillins, and aminoglycosides do not attain adequate antibacterial concentrations in the central nervous system when administered systemically. Antibiotics with better penetrating ability include metro-nidazole, chloramphenicol, trimethoprim, and the third-generation cephalosporins such as cefotaxime. If more polar, less lipophilic drugs are used for treating CNS infections, high doses must be given to attain effective antibacterial concentrations.

135.5 TREATMENT OF SPECIFIC INFECTIONS

135.5.1 Skin and Soft-Tissue Infections

The most important skin pathogen in dogs is *Staphylococcus intermedius*. Other bacteria identified usually are opportunistic. Other staphylococci have been identified (e.g., *Staphylococcus aureus*) that are often more resistant. Wound infections or skin-fold infections may be caused by *Pseudomonas aeruginosa* or bacteria of the Enterobacteriaceae (*Escherichia coli, Klebsiella* spp., and *Proteus* spp.). Anaerobic bacteria, including *Actinomyces* spp., have been isolated from deep infections. Bacteria causing skin or other soft-tissue infection in cats induced by a bite wound can be *Pasteurella* spp., streptococci, or other inhabitants of the oral cavity, including anaerobes.

Since most skin and soft-tissue infections are extracellular, the most important feature of drug delivery is to ensure there are sufficient antibiotic drug concentrations in the extracellular fluid. As discussed previously, adequate concentrations in plasma usually ensure effective concentrations in these tissues. When purulent infections are treated, drug activity can be diminished by wound or tissue components. For example, pus may bind and inactivate certain drugs and a necrotic environment with cellular debris may inhibit activity of aminoglycosides and trimethoprim-sulfonamides. This issue may be important when treating an infection associated with an abscess or when treating otitis.

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For treating infections caused by *Staphylococcus* species, the *in vitro* incidence of resistance is lowest for first-generation cephalosporins (e.g., cefadroxil, cephalexin), β-lactamase inhibitor combinations (e.g., amoxicillin-clavulanate), and fluoroquinolones (e.g., enrofloxacin, difloxacin, marbofloxacin, orbifloxacin). Other drugs that have a somewhat higher incidence of resistance but have been used successfully include erythromycin, lincomycin, clindamycin, and trimethoprim-sulfonamide or ormetoprim-sulfonamide combinations. After treatment with these drugs, resistance can be acquired, especially in cases of recurrent pyoderma.

135.5.2 Urinary Tract Infections

The most common bacteria in dogs and cats causing urinary tract infections (UTIs) are gram-negative bacilli such as *E. coli, Klebsiella,* and *Enterobacter* species. *Proteus mirabilis* and *P. aeruginosa* also may be isolated. Of the gram-positive bacteria causing infections, *Staphylococcus* spp. and streptococci are the most common. Occasionally enterococci cause infection of the urinary tract in dogs and cats, although this is usually an opportunistic pathogen of low virulence.

Treatment considerations include the antibiotics that are excreted via renal mechanisms and concentrate in the urine. These drugs include any of the penicillins and cephalosporins, tetracyclines (except doxycycline), fluoroquinolones, aminoglycosides, and trimethoprim-sulfonamides. These drugs are concentrated 10-to 100-fold in the urine compared with the plasma. Therefore it is possible to attain high drug concentrations in urine and good treatment success unless the infection is complicated by an underlying problem. Dose rates administered usually can be at the lower end of a dose range because of the concentrating effect of antibiotic in the urine. Empirical selection of antibiotics is acceptable for urinary tract infections because the antimicrobial susceptibility tests can underestimate the true activity of the drugs *in vivo*.

If the animal is an intact male, infection of the prostate gland is possible. Drug penetration into the prostate is limited because of a barrier between prostatic glandular cells and the serum or plasma.[11] Drugs that are poorly lipophilic at the pH of plasma (e.g., penicillins, cephalosporins, and aminoglycosides) do not diffuse well into prostate. Drugs that are lipophilic at the pH of plasma, such as macrolides (e.g., erythromycin), lincosamides (e.g., clindamycin), trimethoprim, or fluoroquinolones diffuse more easily into the prostate and can achieve concentrations in the prostate that exceed plasma concentrations. However, the macrolides and clindamycin usually do not have the gram-negative spectrum needed for a prostate infection. Therefore the most effective drugs for prostatic infections are the fluoroquinolones, and trimethoprim (usually administered as the combination of trimethoprim-sulfonamide). Chloramphenicol and tetracycline concentrations in prostate fluid of dogs are low after systemic administration.

135.5.3 Respiratory Tract Infections

Treatment of infections in the respiratory tract is challenging because these usually occur in small animals that are compromised by another primary problem, such as megaesophagus or immunosuppression. Antibiotics distribute into the parenchyma of lung tissue and achieve therapeutic drug concentrations in most cases because there are no barriers to diffusion as long as there are not consolidated lung lobes. Drugs administered to animals with pneumonia will achieve concentrations in the extracellular fluid of the lungs that are equal to, or exceed, plasma concentrations. However, the bronchial secretions present a barrier owing to the blood-bronchus barrier, and non-fenestrated capillaries of the alveoli. In these cases there may be insufficient drug concentrations in the epithelial lining fluid of the respiratory tract to treat infections associated with bronchitis.[12]

Drugs with poor lipid solubility such as penicillins and aminoglycosides produce low concentrations in bronchial secretions after systemic administration, but this barrier may be diminished when it is inflamed. Drugs that are able to achieve effective concentrations in bronchial secretions are macrolide antibiotics, tetracyclines (but not necessarily doxycycline), chloramphenicol, and fluoroquinolones. (However, the availability of chloramphenicol has diminished recently.)

When the infection is in the chest cavity (e.g., pyothorax) drug diffusion into the pleural cavity is not compromised. However, when fluid is present, or the condition has caused pus and fibrin to accumulate, this may compromise diffusion of antibiotic concentrations in the chest cavity high enough to achieve a cure. In these cases, effective drainage or surgical intervention is necessary to assist drug penetration.

The bacteria causing respiratory infections in small animals can cover the full spectrum of gram-positive, gram-negative, and anaerobes and may include *Bordetella bronchiseptica, Streptococcus zooepidemicus, E. coli, P. aeruginosa, K. pneumoniae, Staphylococcus* spp., alpha-and beta-streptococci, and *Pasteurella multocida*. A culture and sensitivity test obtained from a bronchoalveolar lavage (BAL) or transtracheal wash (TTW) is usually used for drug selection. However, the results of a TTW or BAL may not always represent the bacterial pathogen causing disease deeper in the lung, nor are cultures from nasal secretions likely to represent the cause of an infection deeper in the airways.

In the case where a gram-positive cocci is identified, or a gram-positive anaerobe, a penicillin, cephalosporin, or a penicillin-β-lactamase inhibitor combination (e.g., amoxicillin-clavulanate or ampicillin-sulbactam), is a good choice. When the organism is a gram-negative bacilli, a fluoroquinolone, aminoglcoside (e.g., amikacin, tobramycin, or gentamicin), or an extended-spectrum cephalosporin (e.g., cefoxitin, cefotaxime) are needed. Combinations of these drugs are rational in cases of mixed infections.

The role of *Mycoplasma* spp. in respiratory infections has been a source of debate. Although *Mycoplasma* spp. can be isolated from a high percentage of animals with respiratory signs, it is unclear whether or not this organism plays a role in the disease. It also is possible that the *Mycoplasma* spp. are simply inducing inflammation that has allowed other organisms to colonize the respiratory tract. Most *Mycoplasma*-positive dogs have co-infection with other organisms, and selection of drugs active against *Mycoplasma* is usually not an important factor in achieving a cure.

Bordetella bronchiseptica presents a special case. *Bordetella* spp. are a gram-positive aerobic coccobacilli. Among its important virulence factors is the ability to adhere to the bronchial epithelium (ciliated epithelial cells) and produce exotoxins that inhibit neutrophil migration to the infection site. Infections are often mild and self-limiting that require no specific antibiotic treatment. But in cases where antibiotics are indicated, one should select a drug that achieves concentrations in bronchial secretions, such as: tetracyclines, chloramphenicol, or macrolides (e.g., erythromycin, azithromycin). Aminoglycosides, cephalosporins, and penicillins may not achieve drug concentrations at the infection site and quinolones are not consistently active against this organism. Another treatment route that is considered is aerosolization of antibiotics (e.g., tobramycin).

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135.5.4 Treatment of Infections in Bones and Joints

Staphylococci, *E. coli, Pseudomonas, Proteus,* and anaerobes have been causes of joint and bone infections in small animals. Often these may be mixed infections. Staphylococci can be particularly troublesome because they adhere to bone by expression of receptors for components of bone matrix. It also may be internalized by osteoblasts and survive intracellular. Infections in bone, especially those associated with surgical sites that

contain metal implants, are difficulty to treat because of the presence of a biofilm that can render bacteria resistant to antibiotics.[13]

Aggressive treatment is necessary because the consequences of treatment failure is often loss of a limb or long-term morbidity. Drug selection should be made on the basis of a reliable susceptibility test taken from a culture deep within the wound. Drug safety also is an important consideration since treatment is required for a long duration, usually a minimum of 6 weeks. Bone and joints do not present a barrier for drug diffusion; therefore one drug group is not preferred over another because of superiority of better penetration. However, the presence of pus, necrotic tissue, devitalized bone, or foreign body may delay antibiotic diffusion. Surgery to remove or reduce this material is recommended.

β-lactam antibiotics active against staphylococci can be administered orally for long periods. These first-line drugs include first-generation cephalosporins (e.g., cefadroxil, cephalexin), and amoxicillin-clavulanate. Other drugs effective for small animals are the fluoroquinolones, and clindamycin. Bacterial infections caused by *Pseudomonas* spp., *E. coli,* or *Enterobacter* spp. may be resistant to the drugs listed above and a susceptibility test is needed to accurately select the most appropriate drug. In some instances, aggressive treatment with injectable drugs may be necessary.

135.5.5 Treatment of Nonspecific Fever

Often the only sign of a potential infection is fever. If there also is evidence that the patient is immunosuppressed, antibiotic therapy is justified. Evidence of immunosuppression may include documented neutropenia, corticosteroid administration, Cushing's disease, or anticancer treatment. In patients treated for cancer, granulocyte counts less than 1000 cells/μL accompanied by fever should immediately warrant antibiotic administration. Blood cultures are recommended but may be unrewarding. Since results of blood culture may not be available for 48 to 72 hours, empirical antibiotic treatment should be instituted.

Select a drug protocol that gives maximum coverage with minimal risk of adverse effect. For patients that can be treated with oral drugs, a combination of a fluoroquinolone (e.g., enrofloxacin, difloxacin, marbofloxacin, or orbifloxacin) plus a potentiated amoxicillin (e.g., Clavamox) or an oral cephalosporin (e.g., cephalexin or cefadroxil) is a rational combination with a high safety index. If the patient is more critically ill, or if the infection becomes more life-threatening, injectable drugs should be considered. In these cases, the combination of an aminoglycoside (gentamicin or amikacin) plus a cephalosporin or potentiated ampicillin (e.g., Unasyn) is a rational combination. Alternatively, injectable enrofloxacin plus a cephalosporin (e.g., cefazolin), or potentiated ampicillin (e.g., ampicillin-sulbactam combination: unasyn) covers the spectrum of bacteria that may be causing the problem. If the organism has been refractory to therapy and resistance is possible due to infection caused by *E. coli, Klebsiella* spp., or another gram-negative bacilli. In these situations, the administration of drugs with greatest activity should be considered, such as cefotaxime, amikacin, or possibly a carbapenem (e.g., imipenem-cilastatin, or meropenem).

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136 CHAPTER • 136 Glucocorticoid Therapy

Leah A. Cohn

Glucocorticoid agents are among the most commonly used veterinary drugs. They exert myriad effects on nearly every tissue in the body and result in desired and undesired actions. These effects vary with potency and preparation of the glucocorticoid product, dose and route of administration, duration of glucocorticoid exposure, and individual patient factors. Most often, the desired action of therapeutically administered glucocorticoids is suppression of inflammation or of a damaging immunologic response. Other properties of glucocorticoids are exploited for the treatment of hormonal deficiency states, neoplasia, and shock, among other miscellaneous uses.

Unfortunately, even for disease states in which glucocorticoid therapy is proven to be beneficial, there is little scientific evidence of what constitutes an optimum treatment protocol. Instead, veterinarians rely largely on anecdote and experience to design glucocorticoid treatment regimens. Because effects vary with dose and potency, the veterinarian must be familiar with the equivalent dose range of various drug preparations required to produce physiologic, anti-inflammatory, immunosuppressive, or other effects. As a general rule, glucocorticoids should be used "to effect" rather than at an arbitrary dose and therefore minimize exposure and adverse effects.

136.1 PHYSIOLOGY OF GLUCOCORTICOIDS

Glucocorticoid drug preparations are derivatives of the endogenously produced adrenal hormone cortisol (hydrocortisone). Most glucocorticoid actions result from altered cellular gene transcription.[1] Glucocorticoids move passively into cells and then bind intracytoplasmic receptors; receptor numbers vary with tissue and cell type. Bound receptors translocate to the nucleus, where they modify gene transcription. Proteins are either up-or down-regulated by the actions of glucocorticoids, which leads to specific cellular actions. Together, these actions affect the function of nearly every tissue type and result in a tremendous variety of effects (Box 136-1). Metabolic, anti-inflammatory, and immunosuppressive effects of glucocorticoids are particularly relevant to their therapeutic use.[2] Metabolic effects are primarily catabolic and include insulin antagonism, increased glycogen formation, and increased gluconeogenesis. Glucocorticoids inhibit liberation of arachidonic acid to diminish production of eicosanoid proinflammatory mediators, and they increase production of anti-inflammatory proteins.[3]

Many anti-inflammatory effects of glucocorticoids overlap with immunosuppressive effects. The glucocorticoid stress leukogram (mature neutrophilia, lymphopenia and eosinopenia, and variable monocytosis) results from altered membrane expression of cellular adhesion molecules. The most pronounced immunologic effects of glucocorticoids are diminished mononuclear phagocytic function and altered cytokine production.[3] Although glucocorticoids affect cell-mediated immunity directly and profoundly, the effect on humoral immunity is largely indirect and not as pronounced.[3] Although dog and cat lymphocytes are resistant to glucocorticoid-induced lysis, neoplastic and activated lymphocytes are susceptible to glucocorticoid-induced apoptosis.[3]

136.1.1 Box • 136-1 Selected Physiologic Effects of Glucocorticoids

136.1.1.1 Metabolic Effects

Increase gluconeogenesis

Increase protein catabolism

Antagonize insulin

Mobilize free fatty acids

Redistribute adipose tissue

136.1.1.2 Dermal Effects

Thinning or atrophic skin

Atrophic hair follicles

136.1.1.3 Cardiovascular Effects

Optimize catecholamine receptor numbers

Positive inotropic effects

Vasoconstriction

136.1.1.4 Gastrointestinal and Hepatic Effects

Induce alkaline phosphatase enzyme (dogs only)

Decrease calcium and iron absorption

Promote hepatic fat and glycogen deposition

Alter mucin structure

Increase secretion of digestive hormones

136.1.1.5 Renal Effects

Increase glomerular filtration rate

Inhibit renal tubules response to antidiuretic hormone

Promote water, sodium, and chloride retention

Promote potassium and calcium excretion

136.1.1.6 Neurologic and Muscular Effects

Euphoria or behavioral change

Increase numbers or sensitivity of adrenergic receptors

Muscular atrophy

Muscular weakness

136.1.1.7 Endocrine Effects

Decreased ACTH production

Suppressed thyroid stimulating hormone and T3/T4 concentrations

136.1.1.8 Hematopoietic Effects

Increase circulating mature neutrophils

Decrease circulating lymphocytes, lymphocyte sequestration, lymphoid tissue involution

Apoptosis of activated and neoplastic lymphocytes

Decrease circulating eosinophils

Increase circulating monocytes

Increase circulating red blood cells

Increase circulating platelets

136.1.1.9 Inflammatory and Immunologic Effects

Decreased eicosanoid (prostaglandin and leukotriene) formation

Inhibit mononuclear phagocytosis and chemotaxis

Decrease or increase cytokine production

Depress cell-mediated immunity

Diminish humoral immunity (secondary effect)

136.1.1.10 Miscellaneous Effects

Stimulate appetite

Inhibit fibroblast proliferation and collagen synthesis

Accelerate bone reabsorption

Stabilize lysosomal membranes

Antioxidant

The release of endogenous glucocorticoids is controlled by an endocrine-feedback axis consisting of the hypothalamus, the pituitary gland, and the adrenal gland (HPA axis).[2] The hypothalamus produces

corticotropin-releasing hormone (CRH), which stimulates production of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. In turn, ACTH causes production and release of cortisol from the zona fasciculata and zona reticularis of the adrenal cortex. Cortisol then inhibits release of CRH and ACTH and dampens further glucocorticoid production. Pharmacologic derivatives of cortisol exert a similar negative feedback, but suppression varies with glucocorticoid potency.

136.2 PHARMACOLOGY OF GLUCOCORTICOIDS

Numerous modifications of the 17-carbon atom steroid nucleus have been developed to enhance or diminish particular glucocorticoid drug properties (e.g., mineralocorticoid or glucocorticoid potency, receptor binding strength).[4] Other modifications have been made through esterification of the glucocorticoid drug product to change solubility and duration of action.[4] Although affinity of the particular product varies, the majority of glucocorticoid in plasma is bound to proteins. Corticosteroid binding globulin (transcortin), and to a lesser extent other proteins including albumin, hold glucocorticoid unavailable for diffusion into the cell.[4] Only glucocorticoid in excess of this binding capacity enters the cell and exerts a biologic effect.

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Modifications of the basic glucocorticoid hormones have resulted in the development of numerous drug products available for either systemic or topical administration. The potency of these products is expressed as it relates to cortisol (Table 136-1). Importantly, the same metabolic effect can be attained by any of these glucocorticoid products when administered in a metabolically active form at equipotent dosages. The biologic half-life of systemically administered glucocorticoids is disparate from the plasma half-life. Because the biologic effects are largely due to alterations in genetic regulation of protein production, biologic effects are delayed and prolonged in comparison with plasma drug concentration. Glucocorticoid drugs are often divided into three groups based on duration of HPA suppression. Short-acting glucocorticoids typically suppress the HPA less than 12 hours; long-acting glucocorticoids more than 48 hours; and intermediate-acting products fall somewhere between.[5]

Many glucocorticoid products are combined with esters that affect water solubility of the compound and therefore affect rate of absorption of injectable preparations.[4] Sodium phosphate, hemisuccinate, and sodium succinate esters are the most water soluble and allow for rapid absorption and action. The duration of action of these esterified compounds is equivalent to that of the base glucocorticoid. Acetate and diacetate esters are poorly water soluble, whereas pivalate, diproprionate, hexacetate, and acetonide are least soluble. Slow absorption from the site of injection prolongs the duration of action of any glucocorticoid base with which these esters are combined.[4,5] For example, although the biologic duration of methylprednisolone is 12 to 36 hours, the duration of the repositol formulation methylprednisolone acetate is 3 to 6 weeks.

Certain synthetic glucocorticoid compounds require conversion to an active metabolite.[6] An example is prednisone, which requires hepatic conversion to prednisolone for activity; prednisone would therefore not be suitable for topical application. The two drugs are used interchangeably via systemic administration, however, because hepatic conversion is rapid and nearly complete.

Table • 136-1 Comparison of Various Glucocorticoids

	RELATIVE ANTI-INFLAMMATORY POTENCY	EQUIVALENT PHARMACOLOGIC DOSE (mg)	RELATIVE MINERALO-CORTICOID POTENCY	PLASMA HALF-LIFE DOGS/PEOPLE (HOURS)	BIOLOGIC HALF-LIFE IN PEOPLE (HOURS)
Short-Acting Glucocorticoids					
Hydrocortisone	1	20	2	1/1.5	8–12
Cortisone	0.8	25	2	?/1.5	8–12
Intermediate-Acting Glucocorticoids					
Prednisone	4	5	1	?/1	12–36
Prednisolone	4	5	1	1–3/2–3	12–36
Methyl-prednisolone	5	4	0	1.5/3	12–36
Triamcinolone	5	4	0	?/4 or more	24–48
Long-Acting Glucocorticoids					
Dexamethasone	30	0.75	0	2/5 or more	35–54
Betamethasone	30	0.6	0	?/5 or more	>48

An anecdotally supported belief by some veterinarians holds that a proportion of normal cats inadequately convert prednisone to prednisolone, so prednisolone is often preferred in this species. Cats have fewer, less sensitive, cellular glucocorticoid receptors than dogs.[7] Therefore cats often require twice the glucocorticoid dosage to achieve equivalent biologic effects, and side effects of glucocorticoid use in cats are less pronounced than those in dogs.

136.3 CLINICAL UTILITY OF GLUCOCORTICOIDS

Glucocorticoids are used to treat a variety of disease processes and often suppress the consequences of disease rather than curing disease. Evidence supporting these usages varies from irrefutable (e.g., hypoadrenocorticism) to unsubstantiated (e.g., septic shock). Even when good evidence exists to support the use of glucocorticoids in a particular disease process, there are few “right” or “wrong” treatment regimens.

Equipotent amounts of any metabolically active glucocorticoid exert similar effects, which means that a higher dose of a less potent glucocorticoid can achieve the same effect as a lower dose of a more potent product. Physiologic actions of glucocorticoids occur at a much lower dose of an equipotent glucocorticoid than do anti-inflammatory effects, which in turn occur at a lower dose than do immunosuppressive effects.[8] When choosing an initial treatment protocol, the veterinarian must begin by recognizing a goal of glucocorticoid therapy (physiologic replacement, suppression of inflammation, suppression of immunity, or some other action). Additional variables relate to the patient (e.g., species, concurrent disease), the disease process (e.g., chronic or acute, localized or systemic), and available glucocorticoid products (e.g., solubility, duration of action, route of administration). Ideally, when glucocorticoid therapy is required in only a localized area (e.g., ocular inflammation), treatment can be administered topically, thus minimizing effects of glucocorticoids on other tissues. Systemic therapy using parenteral or oral products is best suited to situations in which several body systems and/or tissues are targeted for therapy (e.g., anaphylaxis, systemic lupus erythematosus). Realistically, glucocorticoids are often administered systemically even when only a single tissue is targeted.

136.3.1 Physiologic Replacement Therapy

Hypoadrenocorticism is the failure of the adrenal gland to produce enough corticosteroid hormones. Commonly, both mineralocorticoid and glucocorticoid deficiency exists, but isolated glucocorticoid deficiency can occur. Administration of prednisone or methylprednisolone, which are detected along with endogenous cortisol during assay, should be avoided prior to completion of diagnostic ACTH stimulation testing. If a substantial delay in testing is unavoidable, dexamethasone may be administered (0.1 to 0.2 mg/kg) without altering diagnostic test results. Life-long hormonal replacement is the basis of therapy.[9]

Although some corticosteroid drugs possess glucocorticoid and mineralocorticoid activity, separate replacement of each is often required. The glucocorticoid of choice for replacement should be administered systemically at a physiologic dose and should have a biologic duration of approximately 24 hours. Predniso(lo)ne 0.2 to 0.3 mg/kg once daily meets these requirements. During times of stress (e.g., boarding, illness) the amount of glucocorticoid administered should be temporarily increased (typically doubled) to meet increased physiologic demands.[9]

136.3.2 Anti-Inflammatory Therapy

Glucocorticoids are used most often for their excellent anti-inflammatory properties. Prior to initiating glucocorticoid therapy, attempts should be made to identify and eliminate the underlying cause of inflammation. Frequently, an underlying cause either cannot be found or cannot be entirely eliminated. Anti-inflammatory therapy can be of benefit in such cases, and glucocorticoids are often the most effective such therapy.

It is particularly important to rule out infectious causes of inflammation, especially fungal infection, prior to beginning glucocorticoid therapy. Because inflammation is intimately tied to innate defense mechanisms, and because of the additional suppressive effects of glucocorticoids on specific immunity, these drugs are relatively contraindicated in infection. Glucocorticoids often lead to a temporary improvement in animals with inflammation secondary to infection, but failure to control infection can lead to worsening of disease or even death. Because glucocorticoids reduce fever, stimulate appetite, and can induce feelings of euphoria and suppress clinical evidence of inflammation, it can be difficult to detect worsened infection until it is too late. There are exceptions to every rule, and glucocorticoids are actually indicated for the treatment of some infectious diseases.[10] Typically, they are combined with antimicrobial therapy to reduce inflammatory (e.g., *Pseudomonas* otitis)[11] or immunologic (e.g., red cell destruction due to *Mycoplasma hemofelis*) consequences of infection.[12]

Specific treatment decisions regarding anti-inflammatory therapy with glucocorticoids are based on a number of factors, including desired rapidity of action and expected duration of therapy. Rarely, a rapid onset of action is required, such as when respiratory inflammation compromises the animal's ability to breathe; injectable phosphate or succinate preparations are most useful in these situations. In most cases, anti-inflammatory therapy will be required for days, weeks, or months. Intermediate acting steroid preparations allow dosage to be titrated to effect and thereby minimized for chronic administration. The most often used anti-inflammatory glucocorticoid is predniso(lo)ne at an initial dosage of 0.5 to 1.0 mg/kg/day for dogs or 1 to 2 mg/kg/day for cats. Because the biologic half-life is 24 to 36 hours, there is little obvious advantage to division of the daily dosage. Once initial inflammation is suppressed, steroid dose is reduced to the lowest necessary level. Treatment with repositol products (e.g., methylprednisolone acetate) is not advisable in dogs even when

long-term therapy is anticipated. Repositol therapy severely suppresses the HPA axis, prevents accurate dose titration or early drug withdrawal, and is associated with more pronounced side effects. Additionally, such therapy can interfere with accurate diagnostic testing (e.g., allergen skin testing, endocrine testing) for long periods of time.[13] There are limited indications for the use of repositol therapy in steroid-resistant cats. Repositol therapy may be used to treat feline eosinophilic granuloma or allergic and inflammatory skin conditions when the owners are unwilling or unable to administer oral medications, but iatrogenic hyperadrenocorticism and its consequences (i.e., insulin resistance) may result.[14]

Regional inhibition of inflammation can often be accomplished via local application of glucocorticoids. Glucocorticoid products are available in a variety of formulations designed specifically for local application, and injectable preparations can be used to achieve a local effect. Because the intended actions are local rather than systemic, the products should include only metabolically active glucocorticoids (e.g., prednisolone rather than prednisone). Although local application minimizes unwanted effects, absorption does occur and can lead to systemic effects and suppression of the HPA axis.[15,16]

The eyes, skin, respiratory and gastrointestinal tracts, and joints are the sites most often treated via local glucocorticoid application. Topical suspensions (e.g., 1.0% prednisolone acetate), solutions (e.g., 0.1% dexamethasone phosphate), or ointments (e.g., 0.05% dexamethasone phosphate) are indicated for inflammatory disease of external ocular structures or the anterior segment, such as non-infectious conjunctivitis or uveitis. Therapy is typically titrated to effect by adjusting frequency of application (every 1 to 8 hours). Contraindications to ocular glucocorticoid use include corneal ulceration or ocular infection. Ulcers can be exacerbated by glucocorticoids, and in the presence of infection stromal melting may occur.[17] Because of its frequent association with infection, feline conjunctivitis is a relative contraindication to ophthalmic glucocorticoid use.[18]

Dermatologic inflammation is often treated via systemic glucocorticoid administration, but topical products can augment or replace systemic glucocorticoids. Glucocorticoids should not be used to treat dermatologic disorders until serious attempts are made to diagnose the cause of dermatopathy. They should only be used after efforts are exerted to eliminate or control precipitating and predisposing factors. Even then, steroids should be used sparingly; topical therapy may spare excessive tissue exposure. Glucocorticoids in the form of 1% hydrocortisone (the metabolically active form of cortisone) are available in shampoos, conditioners, lotions, creams, ointments, and otic medications. These products are particularly useful in reduction of pruritus associated with atopy when used in conjunction with other therapies such as antihistamine medications. Stronger glucocorticoid preparations, including triamcinolone acetonide (e.g., Panalog®), betamethasone valerate (e.g., Gentocin Spray®, Otomax®) and fluocinolone acetonide (e.g., Synotic®), are effective in reducing erythema, swelling, and pruritus. However, systemic absorption makes these products inappropriate for extended daily use, particularly when dermal barriers are no longer intact.

Glucocorticoids are frequently used to treat chronic inflammation of the respiratory and gastrointestinal tracts. Methods of local application have been developed for use in people to minimize the adverse effects associated with long-term systemic administration. Metered dose inhalers (MDI), nasal sprays or drops, glucocorticoid retention enemas, rectal foams, and suppositories can be used in small animals. Although systemic steroid administration remains the mainstay of treatment for cats with reactive airway disease, bronchodilators and glucocorticoids (e.g., fluticasone propionate) can be applied to the airway lumen directly via MDI delivery.

Delivery systems for MDI use in cats can either be obtained commercially or made by simple modification of readily available, inexpensive equipment.[8] Although unproven, the method has met with good anecdotal success. Some dogs and cats with allergic or idiopathic rhinitis respond well to intranasal glucocorticoids; such

therapy should not be attempted until neoplastic and infectious diseases have been ruled out. Nasal sprays are available, but two drops of ophthalmic 1% prednisolone acetate instilled in each nostril two to three times daily can be used successfully. Topical therapy of gastrointestinal disease is limited to the mouth, rectum, and colon. Dogs with refractory colitis have been successfully treated with glucocorticoid suppositories and rectal foams, whereas successful intralesional injection of oral eosinophilic granuloma with glucocorticoids has been described in cats.[8,13]

Orthopedic pain and inflammation may be relieved by local injection of glucocorticoids, although such injections are never considered curative. Although injections can bring about a rapid return to function, they are also associated with potentially devastating complications (e.g., cartilage damage and impaired healing of osteochondral defects, accelerated osteoarthritis, and joint sepsis).[19,20] Intra-articular glucocorticoids injections are used less often in small animals than in either horses or people.[19,21] Perhaps the best use of local glucocorticoid therapy in small animal orthopedic medicine is in the treatment of bicipital tenosynovitis in dogs. Typically, 1 mg/kg of repositol methylprednisolone acetate is injected directly into the tendon and tendon sheath.[22] Injection is followed with several weeks' strict rest prior to slow return to activity.

136.3.3 Immunosuppressive Therapy

Suppression of damaging immunologic responses in dogs and cats is most often achieved by the administration of systemic glucocorticoids at a dosage higher than that required to suppress inflammation. The beneficial role of glucocorticoids in the treatment of autoimmune disease is well documented. Additionally, glucocorticoids are used to suppress harmful immunologic reactions associated with diseases like feline infectious peritonitis or rejection of transplanted organs.[23,24] Oral administration of intermediate-acting preparations is the most common choice for chronic immunosuppression. The initial dose of predniso(lo)ne required for immune suppression is usually 2 to 4 mg/kg/day for dogs or 2 to 8 mg/kg/day for cats. Despite predniso(lo)ne's biologic half-life of 24 to 36 hours, dividing this high dose and administering the drug twice daily may lessen GI irritation.

Some clinicians recommend initiating immunosuppressive therapy with dexamethasone rather than prednisone,[25] but evidence for an advantage of one drug over the other at equipotent dosages is lacking. Dexamethasone injection should be chosen when oral drug administration is difficult (e.g., due to vomiting or inability to swallow). Ideally, once disease is controlled, the use of glucocorticoids can be slowly tapered until it is discontinued altogether.

Immune-mediated disease refractory to glucocorticoids alone may be controlled by the addition of a different immunosuppressive agent (e.g., azathioprine). Such combination therapy may have a steroid sparing effect, which allows control of disease using a lower total glucocorticoid dose. This type of combination therapy is particularly useful in animals with unacceptable adverse effects from glucocorticoid therapy.

136.3.4 Anti-Neoplastic Therapy

Glucocorticoids have proven useful in the treatment of several neoplastic and paraneoplastic conditions. Benefits can be attributed to direct tumorcidal effects, anti-inflammatory and/or immunosuppressive properties, and to metabolic properties of glucocorticoids. Commonly, glucocorticoids are used in conjunction with other chemotherapeutic agents in the treatment of lymphoma.[26] Although glucocorticoids sometimes induce remission of lymphoma when used alone (predniso[lo]ne 2 mg/kg/day), rapid development of multi-drug resistance leads to brief remission and decreases the chance that other, more aggressive chemotherapy protocols

will be successful.[26] Because glucocorticoids induce apoptosis of neoplastic lymphocytes, the use of these drugs prior to diagnosis may interfere with the ability to cytologically or histopathologically confirm lymphoma. Other cancer types that may respond directly to glucocorticoids include multiple myeloma, certain leukemias, and mast cell tumors.[26–28]

Some paraneoplastic syndromes and some complica-tions from neoplasia may respond to glucocorticoid therapy even when glucocorticoids are not directly tumorcidal.[8] Glucocorticoids are antagonistic to insulin and are therefore used to increase plasma glucose concentrations in animals with insulinoma (predniso[lo]ne 0.5 mg/kg/day). Hypercalcemia resulting from lymphoma or a variety of other neoplastic conditions may respond to systemic glucocorticoid therapy as well (predniso[lo]one 1 to 2 mg/kg/day). In addition to direct effects on lymphoid neoplasia, they inhibit bone resorption, inhibit intestinal calcium absorption, and promote caluresis. Edema and inflammation associated with many types of neoplasia are frequently treated with systemic glucocorticoid therapy on either a short (e.g., during perioperative period surrounding tumor manipulation) or long-term basis (e.g., as palliative therapy for brain tumor).

136.3.5 High Dose, Short-Term Therapy

In certain disease processes, glucocorticoids are used for short periods (often a single dose) in dosages much higher than those required to initiate immunosuppressive therapy. At such dosages glucocorticoids exert actions in addition to those mediated by gene transcription; these actions are somewhat nebulous but include antioxidant properties, membrane stabilization, and hemodynamic effects. Examples of processes treated in this way include central nervous system trauma and various shock states.[29–31] Because a rapid onset of action is required, injectable succinate and phosphate esters are most appropriate. Animals with recent spinal cord injuries (<8 hours from time of insult) benefit from treatment with methylprednisolone sodium succinate (15 to 40 mg/kg IV), although a similar benefit has not been demonstrated for animals with brain injury.[29,32,33] Repeated boluses of 15 mg/kg may be administered 2 and 6 hours later, followed by either boluses of 7.5 mg/kg every 6 hours for 24 hours or by a 24 hour continuous rate infusion of 2.5 mg/kg/hr.

High-dose glucocorticoid treatment for shock has fallen repeatedly in and out of favor. Anaphylactic shock is the only type for which routine treatment still involves the administration of high-dose glucocorticoids.[34] Decades ago, high-dose glucocorticoids were used to treat hemorrhagic shock because of their ability to increase blood pressure. Steroids have fallen out of favor for this use, and treatment should focus on volume, colloid, and hemoglobin replacement. The role of glucocorticoid therapy in septic shock is more controversial. Experimental literature of the 1970s seemed to support claims that high doses of short-acting glucocorticoids (30 mg/kg methylprednisolone) decreased morbidity from septic shock. However, clinical trials in people failed to support these claims, and high-dose steroid therapy in sepsis was discouraged.[35] Recently, glucocorticoids have regained favor in the treatment of sepsis and septic shock, but at much lower dosages designed to counter occult adrenal insufficiency.[36] Thus far, occult adrenal insufficiency has not been documented in critically ill dogs,[37] which leaves the role of low-dose steroids for septic animals in doubt.

Many veterinarians utilize short-term high dose glucocorticoid therapy for treatment of conditions in which massive cytokine release is anticipated (e.g., gastric-dilatation volvulus, snake bite envenomation). A beneficial role for glucocorticoids in most such situations has been neither confirmed nor denied. Serious complications from intensive short-term glucocorticoid treatment are rare, but they do occur.[38] Therefore it is difficult to recommend high-dose glucocorticoids therapy in the absence of proven benefit for these types of conditions.

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136.4 ADVERSE EFFECTS OF GLUCOCORTICOIDS

Adverse reactions associated with glucocorticoids are numerous and range from the merely bothersome to the life threatening (Box 136-2). Conditions exacerbated by glucocorticoid effects (e.g., infection, diabetes mellitus, pancreatitis) are relative contraindications to their use. Generally speaking, the more potent the product, higher the dosage, and more prolonged the administration, the more serious are the adverse effects. The most common side effects of glucocorticoid use are polyuria, polydipsia, and polyphagia. Iatrogenic hyper-adrenocorticism, distinguishable from pituitary or adrenal dependent hyperadrenocorticism only through clinical history and suppression of response to exogenous ACTH, can occur during prolonged corticosteroid administration.[39] Rapid withdrawal of exogenous glucocorticoids in an animal with suppression of the HPA axis can leave the adrenal gland unable to produce requisite levels of glucocorticoids, creating a state of adrenocortical insufficiency that can have life-threatening consequences. More commonly, rapid cessation of chronic (>2 weeks) therapy results in a constellation of clinical signs including depression, decreased appetite, and vomiting.

136.4.1 Box • 136-2 Adverse Effects of Glucocorticoid Administration

Abortion

Alopecia

Calcinosis cutis

Colonic perforation

Comedones

Delayed wound healing

Diabetes mellitus

Gastrointestinal ulceration

Growth suppression

Hypercoagulable state

Hyperlipidemia

Iatrogenic hyperadrenocorticism

Immunosuppression (secondary infection, worsened infection, recrudescence of latent infection)

Insomnia, agitation, behavioral changes

Insulin resistance

Ligament and tendon rupture

Muscle atrophy

Muscle wasting

Myotonia/myopathy

Osteoporosis

Panting

Polyphagia

Polyuria/polydipsia

Proteinuria

Psychosis/behavioral change

Seizure threshold lowered

Skin thinning

Vacuolar hepatopathy

Glucocorticoid administration can impact therapy with other pharmaceutical agents. For example, animals receiving immunosuppressive dosages of glucocorticoids should not be given modified live vaccines due to the risk of vaccine-induced disease.[40] Certain pharmaceuticals alter metabolism or clearance of the glucocorticoids,

which results in either increased or decreased biologic glucocorticoid effects at a given steroid dose. Additionally, glucocorticoids can impact the effectiveness or toxicity of co-administered pharmaceuticals.[41]

136.5 GLUCOCORTICOID REDUCTION PROTOCOLS

Ideally, glucocorticoids should be used at the lowest dose possible to achieve the desired effect. When administered for more than 2 weeks, the dosage should be reduced slowly. This principle fits nicely with the ideal of adjusting the glucocorticoid dose "to effect," particularly in those cases requiring prolonged therapy (e.g., autoimmune disease).

Once clinical evidence suggests that the condition being addressed is controlled (e.g., red cell count normalized when treating immune mediated hemolytic anemia [IMHA], diarrhea resolved when treating inflammatory bowel disease), the dosage of glucocorticoids should be tapered. There is no single ideal way to conduct this tapering, but certain principles apply. First, the clinical condition should be monitored closely. Worsening soon after a dose reduction suggests that the taper is too rapid. Second, the severity of the condition holds implications as to the rapidity of the taper. Glucocorticoids used to treat life-threatening disease (e.g., IMHA) should be tapered more slowly than glucocorticoids used to treat other conditions. Third, consolidated dosing with prolonged dosing intervals might spare HPA suppression while maintaining much of the desirable biologic drug effect. For example, if administering 5 mg prednisone twice daily, it may be better to first switch to 10 mg once a day rather than simply decreasing the twice daily dose. The daily dose can then be decreased incrementally. Dose interval is then changed to an every-other-day (EOD) basis, usually when the daily dose nears a minimal anti-inflammatory range (0.5 mg/kg for dogs). Often, veterinarians choose to increase to dose given on the treatment day so that the total 2-day dose remains unchanged or only slightly decreased initially. Eventually, the glucocorticoid dose is lowered until it is discontinued altogether. Theoretically, EOD (or even every third day) dosing allows the HPA axis to recover from suppression during the "off steroid" day.[42,43] This type of EOD dosing scheme depends on the biologic duration of the steroid preparation and is thus only serviceable using intermediate acting glucocorticoids.

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CHAPTER • 137 Over-the-Counter Human Medications

Etienne Côté

Using human nonprescription (over-the-counter, or OTC) drugs in veterinary medical therapy is an attractive option because these drugs usually are inexpensive and widely available. Veterinarians deal with OTC drugs either when they advocate their use for medical treatment or when they manage OTC drug intoxications.

A dizzying variety of brand names and products exists on the OTC pharmaceuticals market. Products with similar names often have very different components. Therefore the veterinarian needs to specify the active ingredients of the drug in question to avoid confusion. For example, many products containing acetylsalicylic acid (ASA) can safely be used for treating dogs and cats, yet varieties of these same products are available in nearly identical packaging and are labeled “aspirin-free,” “pain-relief,” “cold,” “flu,” or “sinus.” These versions often contain acetaminophen as the active ingredient instead of ASA and therefore have a completely different, and potentially adverse, pharmacologic profile.

A brand name alone (e.g., Anacin, Benadryl) often is inadequate and could be disastrously misleading. Manufacturers may change the contents of a product without changing the brand name. For example, the active ingredient in Kaopectate was formerly kaolin-pectin; now, the active ingredient is either attapulgite or bismuth subsalicylate, but the name of the product remains the same. When the veterinarian advocates the use of a product, confusion can be minimized by giving the client the names of the desired active ingredients and the name of active ingredients to avoid, in writing, and urging the client to seek pharmacist confirmation at the time of purchase (Box 137-1).

Human drugs approved for OTC sale in the United States must be proved to be safe and efficacious in humans, but not in ill dogs or cats. The absorption characteristics of OTC human preparations, particularly time-release or entericcoated formulations, are designed for the human gastrointestinal (GI) tract but not for that of dogs or cats. Clinical trials assessing the effectiveness of any human OTC-formulated drug against placebo in the veterinary setting remain rare. Therefore when a prescription veterinary drug is available, it may often be safer and more reliable to prescribe it rather than to advocate a human OTC equivalent.

137.1

Box • 137-1 Equivalence of Units Commonly Used in Over-the-Counter Human Medications

1 teaspoon (tsp) = 5 ml

1 tablespoon (tbsp) = 15 ml

1 fluid ounce (oz) = 28 ml

1 cup = 237 ml

1 grain = 65 mg

1 pound (lb) = 0.454 kg

None of the drugs described in this chapter has Food and Drug Administration approval for non-prescription use in dogs or cats in the United States. Advocating the use of these drugs in an extralabel manner signifies that the veterinarian and client understand the risk inherent in using medications not specifically designed for use in animals.

137.2 ANALGESICS

Aspirin, plain (e.g., Norwich, St. Joseph, Bayer, Anacin, ASA) or buffered (e.g., Bufferin, Ascriptin, Ecotrin), has traditionally been a common treatment for musculoskeletal pain in dogs and cats. The widespread availability of prescription anti-inflammatory drugs that cause fewer adverse GI effects (e.g., carprofen, etodolac, meloxicam) has made aspirin a second choice for therapy. A recommended therapeutic dose of aspirin in dogs is 5 to 12 mg/lb (10 to 25 mg/kg) by mouth two to three times a day, and dogs may require 10 to 39 mg/lb (23 to 86 mg/kg) twice a day to control signs of osteoarthritis. Substantial overlap between therapeutic and toxic doses exists; in dogs, doses of 12 mg/lb (25 mg/kg) by mouth three times a day for 14 days systematically produced adverse GI effects, and doses of 45 to 50 mg/lb (100 to 110 mg/kg) once a day for 1 to 4 weeks were lethal. Concurrent treatment with misoprostol or omeprazole can reduce GI toxicity, but treatment with the H_2-receptor blocking drug cimetidine does not.

Parenteral administration of the salicylates also produces GI toxicity; therefore administering aspirin in pulverized form and/or with a full meal may reduce topical irritation in the stomach, but not all adverse GI effects can be eliminated this way. One regular aspirin tablet, plain or buffered, typically contains 325 mg ASA; “baby” or “low-dose” tablets, 81 mg; and “extra strength” tablets, 500 mg.

Aspirin is indicated for anticoagulation in dogs and cats at doses much lower (dogs: 0.22 mg/lb [0.5 mg/kg] orally every 12 hours; cats: 81 mg/*cat* orally every 72 hours) than the anti-inflammatory dose. Few adverse GI effects can be expected at these doses, but efficacy in animals in a hypercoagulable state, particularly cats with heart disease that are susceptible to arterial thromboembolism, is questionable.

Acetaminophen (Excedrin, Feverall, Liquiprin, Midol, Panadol, Pamprin, Percogesic, Tempra, Tylenol, Bromo-Selzer, paracetamol, and many others, including most “aspirin-free” formulations) is an analgesic drug sometimes used in dogs (7 to 13 mg/lb [15 to 28 mg/kg] by mouth every 8 hours for up to 4 days). It is strictly contraindicated in cats because it induces methemoglobinemia and hemolytic anemia. Hematologic and hepatic adverse effects occur in dogs ingesting large doses (usually >45 mg/lb [>100 mg/kg], but as little as 9 mg/lb [20 mg/kg] in one case). Acetylcysteine (65 mg/lb [140 mg/kg] by mouth or slowly intravenously once, then 32 mg/lb [70 mg/kg] by mouth or slowly intravenously every 4 hours for three to seven treatments) is an antidote.

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Other OTC nonsteroidal anti-inflammatory drugs are not currently recommended for veterinary use. Naproxen (e.g., Aleve, Naprosyn) and ibuprofen (e.g., Advil, Motrin, Nuprin) are associated with severe GI ulcerations and perforations in dogs. Ketoprofen (e.g., Actron, Orudis) is approved for use in horses as an injectable, Ketofen, and may eventually be approved for use in dogs and cats in the United States given its common use in small animal medicine in other countries. The current OTC human formulation, like other enteric-coated preparations, may have variable absorption characteristics in small animals.

137.3 ANTIDIARRHEALS

Such adsorbents as attapulgite (e.g., Kaopectate, Donnagel) are considered generally harmless but of questionable clinical efficacy. Bismuth subsalicylate (e.g., Pepto-Bismol, 8.7 mg salicylate/ml; Pepto-Bismol Maximum Strength, 15.7 mg salicylate/ml; Pepto-Bismol Caplets, 102 mg salicylate/caplet) has been shown to have a beneficial effect on the morbidity of acute diarrhea in humans. The liquid is given at a dose of 0.125 ml/lb (0.25 ml/kg, or approximately half of a 5 ml teaspoon for a 25 lb [11 kg] patient) by mouth every 4 to 6 hours in dogs and cats. Doses of up to 0.9 ml/lb (2 ml/kg) every 6 to 8 hours has been advocated for dogs only. Cats reportedly are more sensitive to salicylates than are dogs and probably should not receive frequent or high doses of bismuth subsalicylate because some of the salicylate is absorbed systemically.

Loperamide (e.g., Imodium A-D) is an effective opiate antidiarrheal medication. The recommended dose for dogs, 0.04 mg/lb (0.08 mg/kg) by mouth three to four times a day, may be difficult to achieve in smaller animals receiving the tablet form (2 mg loperamide/tablet). The oral liquid preparation (0.2 mg loperamide/ml) may allow a more accurate dosage in smaller patients (e.g., half of a 5-ml teaspoon for a 14 lb [6 kg] dog). Intoxication, manifesting with central nervous system (CNS) signs and vomiting, has been reported in dogs (especially collies) and cats. Naloxone (0.001 to 0.01 mg/lb [0.002–0.02 mg/kg] intravenously or intramuscularly) is an antidote.

137.4 ANTIEMETICS

The efficacy of OTC human antiemetics in small animal medicine remains unproved. Such drugs as dimenhydrinate (e.g., Gravol, Dramamine [50 mg/tablet]; dose: 2 to 4 mg/lb [4 to 8 mg/kg] by mouth up to every 8 hours), meclizine (e.g., Bonine, Dramamine II; dose: 0.6 mg/lb (1.25 mg/kg) by mouth once daily; maximum single dose: 25 mg), and cyclizine (e.g., Marezine) are sometimes given for the short-term prophylaxis of motion sickness in dogs and cats. Adverse effects appear to be uncommon, but CNS depression and lethargy have been reported anecdotally in dogs receiving 4 to 9 mg/lb [10 to 20 mg/kg] dimenhydrinate, and similar, mild signs have occurred with dogs that ingest meclizine 2.2 to 4.5 mg/lb (5 to 10 mg/kg).

137.5 CHRONIC RENAL FAILURE DRUGS

Such phosphate binders as aluminum hydroxide (e.g., Amphojel, 64 mg $Al(OH)_3$/ml; AlternaGEL, 120 mg $Al(OH)_3$/ml) are advocated for use in the treatment of hyperphosphatemia at an initial dose of 4.5 to 14 mg/lb (10 to 30 mg/kg) by mouth every 8 to 12 hours. Exact titration of the dose depends on effect (subsequent serum phosphorus levels). Constipation and loss of appetite are possible side effects. Other phosphate binders include calcium carbonate (e.g., Titralac, Tums [500 mg $CaCO_3$/tablet]; dose: 4.5 to 14 mg/lb [10 to 30 mg/kg] by mouth every 8 to 12 hours and adjusted based on degree of control of phosphorus levels), although less effective phosphate binding and hypercalcemia are possible drawbacks. The use of magnesium-containing phosphate binders (e.g., Maalox, Mylanta) is discouraged because of the commonly impaired ability to excrete magnesium in cases of renal failure, potentially leading to hypermagnesemia.

137.6 COUGH SYRUPS

Most OTC cough syrups contain one or more of the following five active ingredients: acetaminophen, chlorpheniramine, pseudoephedrine, guaifenesin, and dextromethorphan. Acetaminophen and pseudoephedrine are described elsewhere in this chapter. Guaifenesin is considered to be of minimal therapeutic value in the treatment of coughs; it has been thought to attenuate the cough reflex and to make respiratory secretions thinner, but clinical

trials have shown that it does neither. Antihistamines are considered minimally useful in the treatment of nonallergic causes of cough. Of these five active ingredients, dextromethorphan has been used successfully (though empirically) in the treatment of coughing dogs and cats at a dose of 0.22 to 0.9 mg/lb (0.5 to 2 mg/kg) by mouth every 6 to 8 hours. Although seemingly less effective than opioid antitussives, it is an effective cough suppressant and therefore is contraindicated when cough is beneficial, such as in the expectoration of pus in cases of pneumonia. Most cough syrups contain multiple active ingredients, and currently only a few, such as Vicks Formula 44 (not 44D, 44E, or 44M) and Robitussin Maximum Strength Cough contain only dextromethorphan (2 mg/ml and 3 mg/ml, respectively). Unwanted and potentially dangerous active ingredients are present in many preparations. For instance, NyQuil liquid contains dextromethorphan as a cough suppressant, but it also contains pseudoephedrine and more than 150 mg acetaminophen/5 ml teaspoon.

137.7 DERMATOLOGIC DRUGS

Several antihistamines are used in veterinary dermatology. Chlorpheniramine (e.g., Chlor-Trimeton; dose: 2 mg/*cat* by mouth every 12 hours; 2 to 8 mg/*dog* by mouth every 12 hours, not to exceed 0.22 mg/lb [0.5 mg/kg] every 12 hours), effectively controls 70% of seasonally pruritic cats and is of some value for the same problem in dogs. Clemastine fumarate (e.g., Tavist Allergy; dose: 0.022 to 0.045 mg/lb [0.05 to 0.1 mg/kg] by mouth every 12 hours) and diphenhydramine (e.g., Benadryl Allergy; dose: 1 to 2 mg/lb [2 to 4 mg/kg] by mouth every 8 hours) also control pruritus of allergic origin in some dogs.

Such topical antibacterials as bacitracin (e.g., Bacitracin Plus) and triple antibiotic combinations (e.g., Neosporin) are probably minimally effective but also minimally harmful. Such antifungals as clotrimazole (e.g., Lotrimin, Cruex) and miconazole (e.g., Micatin) are effective against several types of fungi, including *Malassezia* yeasts, dermatophytes, and saprophytes such as *Aspergillus* spp. The reader is referred to additional sources for exact protocols for the use of these drugs.

Zinc oxide creams (e.g., Desitin) frequently are applied to burned or irritated skin. The usefulness of zinc oxide in treating such conditions, and as a sunscreen, must be weighed against the potential for toxicity, which can manifest as vomiting and lethargy after animals lick the product off the skin.

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Benzocaine is present in some dermatologic “soothing” preparations. It can cause hemolytic anemia in cats and dogs that ingest it. In these species, such preparations should be used cautiously if at all.

137.8 EMETICS

For those situations in which emesis is to be induced, oral administration of syrup of ipecac is effective and safe (2 to 6 ml by mouth). Only one additional dose is recommended if vomiting has not occurred within 15 minutes. Orally administered 3% hydrogen peroxide (dose: 0.11–0.22 ml/lb [0.25–0.5 ml/kg] by mouth; the dose can be repeated once after 5 to 15 minutes if vomiting has not occurred) also effectively induces emesis in many dogs and cats. Both of these products are widely available as generics. Large doses of table salt, although sometimes emetic, are not recommended because of the potentially serious consequences of hypernatremia if no vomiting occurs.

137.9 GASTRIC ACID–REDUCING DRUGS

The phosphate binders described earlier are also antacids. They are rarely used in canine and feline medicine because of the frequent dosing needed to maintain a high gastric pH. The H_2-receptor blocking drugs cimetidine (e.g., Tagamet HB 200; dose: 4.5 mg/lb [10 mg/kg] by mouth every 8 hours), ranitidine (e.g., Zantac; dose: 0.9 mg/lb [2 mg/kg] by mouth every 8 to 12 hours), famotidine (e.g., Pepcid AC; dose: 0.22 mg/lb [0.5 mg/kg] by

mouth every 12 to 24 hours), and nizatidine (e.g., Axid AR; dose: 1.1 to 2.2 mg/lb [2.5 to 5 mg/kg] by mouth every 24 hours) all decrease gastric acid secretion. Some (ranitidine, nizatidine) also have GI prokinetic activity. Famotidine and nizatidine do not affect hepatic p450 enzymes. The H_2-blockers have a wide margin of safety; for example, no deaths were recorded in dogs acutely given famotidine 900 mg/lb (2000 mg/kg) by mouth or nizatidine 360 mg/lb (800 mg/kg) by mouth, nor were there overt adverse effects in dogs given cimetidine 65 mg/lb (144 mg/kg) by mouth once daily for 7 years.

137.10 LAXATIVES AND ENEMAS

A variety of OTC preparations is available to effectively manage constipation. Such stimulant laxatives as bisacodyl (e.g., Dulcolax, Correctol, Ex-Lax Ultra; dose: 5 mg/*cat* by mouth once daily; 5 to 20 mg/*dog* by mouth once daily) increase myenteric nervous activity and peristalsis. They are advocated for short-term use only. Emollient laxatives (docusate [Colace, Surfak]; dose: 1 mg/lb [2 mg/kg] by mouth once daily in dogs; 25 mg/*cat* by mouth once daily) soften the stool and are said to be more effective in acute rather than chronic constipation. Hard capsule formulations make the dosage of this type of laxative challenging in small patients. Constipation prevention may be achieved using such soluble fiber products as psyllium mucilloid (e.g., Metamucil; dose: 1 tsp/11 to 22 lbs [5 to 10 kg] body weight, added to the food), with the exact dose titrated to result in soft, formed feces. Newer laxatives containing anthraquinone derivatives like senna have yet to be used in a widespread fashion in veterinary medicine and some aspects of their effects remain controversial in human gastroenterology.

Phosphate enemas (e.g., Fleet) are contraindicated in cats, and possibly small dogs, because of the severe hyperphosphatemia they induce. Instead, pediatric emollient enemas (e.g., docusate sodium) have been used successfully and safely.

137.11 OPHTHALMIC DRUGS

Irrigating solutions (e.g., Dacriose, Collyrium for Fresh Eyes) are used for cleaning debris and pus from the eyes on a short-to long-term basis. Artificial tears (e.g., Adsorbotear, Tears Naturale) are used for tear replacement; solutions that contain polyvinyl alcohol may be irritating, however. Ophthalmic decongestants (e.g., Visine, OcuClear) are of essentially no therapeutic worth; they obscure the diagnosis and may cause chronic conjunctivitis.

137.12 URINARY INCONTINENCE DRUGS

In 2000, phenylpropanolamine was completely withdrawn from the U.S. market due to its association with hemorrhagic stroke in humans. Although no such link has been noted in veterinary medicine, the lack of OTC phenylpropanolamine has increased interest in pseudoephedrine (e.g., Sudafed 30 mg or 120 mg tablets; also in many cold/flu products [see cough syrups, above]) as an alternative drug for controlling urinary incontinence at a starting dose of 0.1 to 0.2 mg/lb (0.2 to 0.4 mg/kg) by mouth every 8 to 12 hours. Clinical evaluation of pseudoephedrine for urinary incontinence in dogs is limited; higher doses of 15 or 30 mg by mouth every 8 hours to dogs weighing less than or more than 55 lbs (25 kg), respectively, have effectively controlled signs of incontinence with no recorded side-effects. However, a narrow margin appears to exist between therapeutic and toxic doses of pseudoephedrine in some dogs, with clinical signs occurring with single-dose ingestions of 2.2 to 2.8 mg/lb (5 to 6 mg/kg) and deaths with ingestions of 4.5 to 5.4 mg/lb (10 to 12 mg/kg). The high concentration of drug in tablets can make exact dosage more difficult in small dogs; choosing other medications, or meticulous preparation of exact doses, may be preferable for these patients. Advocation of the use of pseudoephedrine should be cautious, and with an understanding of the possible, common adverse reactions (e.g., restlessness, excitement, and tachycardia), which could be detrimental, particularly in patients with cardiac or neurologic diseases.

Over-the-counter drugs may be useful in specific therapeutic situations in which convenience, lack of an effective veterinary equivalent, or cost play an important role in drug selection. These advantages need to be weighed against the drawbacks of drug formulations meant for humans, frequent lack of proven efficacy, absence of veterinary labeling for these products, and the potential for selection of the wrong product by the client.

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138 CHAPTER • 138 Compounding Drugs

Ron Johnson

For drug therapy to be considered rational, practitioners must ensure that administration of the drug is safe and efficacious for its intended use. Veterinary medicine does not have a plethora of U.S. Food and Drug Administration (FDA)–approved animal drugs and dosage forms. Added to this dilemma is the need to treat several species of different sizes and biologic make-ups. Compounded drugs can alleviate some of the drug-related issues that face veterinary medicine, provided compounding is approached in a rational manner. The Animal Medical Drug Use Clarification Act (AMDUCA) of 1994 legitimizes compounding from approved animal and human drug dosage forms provided certain criteria are met.[1,2] In this context, compounding is defined by the FDA as any manipulation of the product to produce a drug dosage form other than that manipulation provided for in the directions for use on the labeling of the approved drug product.[2] This form of compounding results in extra-label use of the approved drug product. Compounding from unapproved drug products and bulk products (active ingredient in the unfinished form) are also possible. To encompass these situations, a more general definition of compounding is needed. This includes the preparation of therapeutic compounds that utilize active ingredients and vehicles obtained within the law.

138.1 PHARMACOLOGY CONSIDERATIONS WHEN COMPOUNDING IN COMPANION ANIMALS

Veterinarians need to understand the pharmacologic issues associated with the use of compounded drugs in their patients. Although the decision to compound can be necessary and acceptable under certain conditions, it should not be driven by convenience or economics. Rather, rational therapy based on scientific justification should prevail. The mixing or combining of drugs or the addition of diluents (e.g., lactated Ringer's solution), vehicles (e.g., propylene glycol, dimethylsulfoxide), or flavoring agents to a drug may produce a chemical or physical interaction that renders the product inactive and yields therapeutic failure or may produce a potentially toxic compound. These forms of drug interactions are pharmaceutical interactions or incompatibilities and are demonstrable *in vitro*, that is, outside the body. Manipulations of the dosage form can also result in contamination of a sterile product meant for injection or affect drug bioavailability through alterations in drug release rates.

Compounding by medical professionals and pharmacists is not equivalent to the formulation of commercially manufactured products by reputable pharmaceutical firms. Drug formulation requires an immense understanding of the physical and chemical characteristics of the active ingredient, along with the other agents (e.g., vehicles, excipients) used to produce the administered drug's effectiveness and safety profile. To this end, a compounded drug must possess adequate potency and purity and demonstrate stability (shelf-life) to maintain acceptable bioavailability (extent of systemic drug absorption) of the active ingredient but not produce toxicity or adverse effects. However, for most drugs compounded by veterinarians or pharmacists, there is a lack of adequate pharmaceutical testing and clinical testing to ensure drug quality. Because safety, efficacy, and drug pharmacokinetics have not been determined for most compounded products, and likely not to be, it is important for the veterinarian to establish objective parameters, which indicate whether the compounded product is efficacious, subtherapeutic, or toxic.[3] Objective parameters can include hematologic or clinical chemistry changes, serum drug levels when drug monitoring is available, clinical signs, and clinical end-points.

138.2 COMPOUNDING BY THE VETERINARIAN VERSUS PHARMACIST

Compounded products for use in veterinary medicine must be prepared either by the veterinarian in conjunction with a valid Veterinarian-Client-Patient Relationship (V-C-P-R) or by a licensed pharmacist under the order of the veterinarian. Some of the reasons for employment of compounded drugs in animals include the lack of FDA-approved animal product at an appropriate concentration, drug formulated in a usable dosage form, or available in the required combination.

Requests to pharmacists from veterinarians for compounded prescriptions often surround reformulation of human-labeled drugs for use in companion animals, particularly tablets and capsules.[4] Requests for the mixing of multiple drugs in a single product and formulation of novel systems for drug delivery such as transdermal gels are also increasing. Palatability concerns with various oral preparations have seen the use of flavoring agents to enhance preparation acceptability. Most pharmacists will compound drugs for veterinarians; however, care must be exercised with the selection of a compounding pharmacist. With the need for compounding on the rise, many pharmacists have become members of societies dedicated to reputable compounding, such as the International Academy of Compounding Pharmacists or the Professional Compounding Center of America. Pharmacists with advanced training in compounding can provide valuable expertise and should be sought when the decision to use a compounded drug is made by a veterinarian. Veterinary organizations such as the American Veterinary Medical Association, the American College of Veterinary Clinical Pharmacology, and the American Academy of Pharmacology and Therapeutics along with published literature in reputable journals also represent valuable sources of information on compounding for animals.

The FDA Center for Drug Evaluation and Research has made available a concept paper that evaluates drug products for human use that demonstrate difficulty when compounded because of reasons of safety or effectiveness.[5] The goal of the paper is to identify drugs that are demonstrably difficult to compound based on several evaluating factors, which are also pertinent to compounding for veterinary use. Among these evaluating factors training, facilities and equipment, testing, and quality assurance provide the clearest argument for separating compounding by the pharmacist versus the veterinarian, when other than minor manipulations to the product are required.[4,5] Product categories found notoriously difficult to compound that should be avoided include sterile products, sustained release products, and most transdermal delivery systems.[5] In contrast, candidates most suited for compounding can include drugs with a wide therapeutic index, and drugs for which therapeutic drug monitoring or quantitative end-point measurement is possible and clinical data regarding their use in the intended species and condition is available.

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138.3 DOSAGE FORMULATION AND STABILITY OF COMPOUNDED PRODUCTS

Compounded preparations must possess acceptable potency, purity, and quality with appropriate labeling and packaging to ensure effectiveness, proper use and safety.* Compounding should be conducted in accordance with good pharmacy practices and relevant scientific literature. Pharmacy facilities used for compounding should have adequate room and equipment and be maintained in a clean and sanitary condition to be effective and prevent contamination and errors. Areas used for preparation of sterile products such as sterile injectables or ophthalmic solutions should be separate from nonsterile compounding areas (Box 138-1).

The stability of a compounded preparation is critical to the determination of an expiry or beyond-use date, after which the compounded product should not be used. When a manufactured product is used as the active ingredient source for compounding nonsterile preparations, the manufactured product expiration date cannot be used to

directly extrapolate a beyond-use date for the compounded product. Whenever possible, drug-specific and general stability data and literature should be consulted prior to compounding. In the absence of stability data applicable to a particular drug and specific compounded preparation, the conservative maximum beyond-use or expiry dates recommendations listed in Box 138-2 may serve as suggested general guidelines for nonsterile compounded drug products, which are packaged in tight, light-resistant containers and usually stored at room temperature.

138.3.1 Transdermal Delivery of Drugs with Organogels

The skin offers an ideal alternative to systemic delivery of drugs in veterinary patients; however, significant interspecies differences in skin structure and function represent potential challenges to this route of drug delivery. Delivery of drugs that use transdermal gels is among the newest drug delivery system being utilized in veterinary medicine. Transdermal gels can be utilized effectively and safely in veterinary medicine and can enhance patient compliance. Absorption of drug via the transdermal route is primarily passive. As such, ideal drug molecules for this route of delivery are low molecular weight (<400 Daltons), lipophilic in nature, and soluble in both water and oil.[7]

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The growing list of drugs available in transdermal gel formulation from compounding pharmacists includes antimicrobials, anticonvulsants, hormones, antineoplastics, prokinetic drugs, analgesics, and anti-inflammatory agents. The vast majority of these compounded products are prepared in a pluronic lecithin organogel (PLO) vehicle. Lecithin is an emulsifying agent that forms a viscous gel when combined with water. Pluronic is a surfactant that enhances the formation of drug-containing micelles in a gel matrix. Together, these carriers can dissolve and deliver either hydrophilic or lipophilic molecules, which makes them convenient for delivery of a variety of chemical agents. The transdermal route of drug delivery provides for several advantages, including owner compliance, patient tolerance, ease of administration, and most importantly, the ability to by-pass first pass metabolism by the liver.[7,8] As such, it is possible to deliver agents with low oral bioavailability. Transdermal gels offer an exciting new mode of drug delivery for the veterinary patient. Although investigations with transdermal delivery of drugs are currently underway, most agents compounded with organogels have had little to no clinical data generated with their use. Therefore the clinician must assess both benefits and risks with this mode of drug delivery.

138.3.1.1 Box • 138-1 Aspects of Dosage Formulation Applicable to Drugs Compounded for Companion Animal Use

1. When formulations require the use of water for compounding nonsterile preparations, purified water must be used.
2. Water used for preparation of a sterile product must be either: (a) water for injection, (b) sterile water for injection, or (c) bacteriostatic water for injection.
3. When compounding any formulation starting with a solid material or component, the particles should be reduced to the smallest reasonable size before mixing.
4. When compounding emulsions, solutions, or suspension dosage forms, or semisolid dosage forms such as creams, ointments, topical gels and pastes, an excess amount of the total formulation should be prepared to ensure the prescribed amount can be accurately dispensed.
5. Solutions should contain no visible undissolved materials when dispensed to the client.

6. Emulsions and suspensions should contain instructions to “shake well before using” to ensure uniform dispersion of the active ingredient.

7. Creams, topical gels, ointments, and pastes should not be prepared with ingredients that are irritating or caustic to the skin, and appropriate vehicles or bases should be employed to achieve the desired local or systemic therapeutic effects.

8. The uniformity of dispersion of the compounded gel, cream, ointment, or paste should be assessed by spreading a thin film of finished product on a flat transparent surface, e.g., clear glass.

138.3.1.2

Box • 138-2 Guidelines for Maximum Expiry Dates for Nonsterile Compounded Drug Products

1. For solid dosage formulations and nonaqueous liquids where the manufactured drug product is the active ingredient source, the beyond-use date should not exceed 25% of the time remaining until the manufactured products expiration (or 6 months, whichever is earlier).

2. For water-containing formulations prepared from active ingredients in solid form such as bulk drug (active ingredient in the unfinished form), capsules or tablets, the beyond-use date should not exceed 14 days from preparation when the compounded product is cold-stored.

3. For other formulations, the beyond-use date should not exceed the duration of therapy (or 30 days, whichever is earlier), unless supportive stability date for the compounded preparation exists.

* Information presented in this section, including recommendations and precautions regarding dosage formulation and expiry dates of compounded drugs listed in Boxes 138-1 and 138-2, respectively, can be found in the United States Pharmacopeia and National Formulary.[6]

138.4 REGULATION OF COMPOUNDING FOR VETERINARY MEDICINE

The FDA Center for Veterinary Medicine (CVM) provides regulatory surveillance and enforcement of drug compounding for veterinary medicine under the authority of the Food and Drug Cosmetic Act. The circumstances whereby compounding from approved drugs (animal and human) for animal use by veterinarians is legal can be found in the contents of AMDUCA.[1,9] The FDA-CVM does recognize the need, in limited situations, to compound products from unapproved drugs and occasionally from bulk drugs, provided certain conditions are met. Compliance Policy Guideline 7125.40 was written by the agency to outline guidelines for compounding from approved animal and human dosage form drugs, and unapproved drugs and bulk drugs that ordinarily will not merit regulatory action even though they are technically in violation of AMDUCA.[1] The latter is termed *regulatory discretion*.

Recent FDA concerns regarding compounding have focused on pharmacies that generate large amounts of unapproved drugs for animal use that are largely copies of FDA-approved drugs. These practices constitute attempts to by-pass the drug approval process and can be construed as illegal manufacturing disguised as compounding. The purpose of compounding by a veterinarian or pharmacist under the order of a licensed practitioner is to prepare an individualized drug treatment and not manufacture products for resale.[3,4] Summary recommendations for compounding drugs for use in companion animals are found in Box 138-3.

138.4.1 Box • 138-3 Recommendations for Compounding Drugs for Companion Animal Use

1. The use of compounded drugs should be based on rational therapy originating from a veterinarian and not a pharmacist.
2. Compounding drugs to provide appropriate medical therapy may be necessary when (a) a legitimate medical need exists such as suffering or death resulting from a lack of treating the affected animal, (b) an appropriate dosage regimen does not exist for the species, size, age, or medical problem of the intended animal, or (c) there is no marketed approved animal or human drug available to treat the condition or there is reason to believe the approved drugs will not be efficacious or safe in the intended animal.
3. Compounding must be conducted within the limits of a legitimate pharmacy or veterinary practice.

   Legitimate Pharmacist: A person dispensing pharmaceuticals based on a valid prescription while holding a valid license and conforming to state laws.

   Legitimate Veterinarian: A person prescribing or dispensing pharmaceuticals based on a valid Veterinarian-Client-Patient Relationship while holding a valid license and conforming to state laws.
4. The advice or assistance of pharmacists dedicated to reputable compounding should be sought.
5. Compounded drugs dispensed by a veterinarian (or pharmacist) should contain adequate labeling information to ensure safe and acceptable product use and patient records must be kept.
6. Compounded products should be sold to the individual client and not to other veterinarians or pharmacists for resale.

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139 CHAPTER • 139 Nutraceuticals

John E. Bauer

Development of complete and balanced formulated pet foods has been the foundation for dietary recommendations in small animal practice. Modern veterinary nutrition and food manufacturing techniques have culminated in consistent and reliable “functional food” products. Their use is not likely to be abandoned and improvements continue to be made. Nonetheless, many individuals who are interested in dietary supplements, functional foods, and beverages (e.g., nutraceuticals) are also pet owners who wish to provide an extra margin of nutritional benefit for their companion animals. Thus it is no surprise that functional ingredients, treats, supplements, and even beverages have begun to appear that are specifically designed for dogs and cats. These owners see maintaining companion animal health and seeking optimal nutrition for dogs, cats, and other companion animals as an important component of responsible pet ownership. With the myriad products and supplements currently available, veterinary health professionals are often asked to comment on the use of these materials and may find themselves recommending some of them for pet health management. Thus it is important to obtain a better understanding of nutraceuticals, supplements, and functional food ingredients.

139.1 REGULATORY ASPECTS

Legal definitions for the term *nutraceutical* do not exist, although the word was originally coined to refer to any substance that can be administered orally (as are foods) to promote good health and that is not a drug.[1] The Food and Drug Administration (FDA) defines a food as a substance that provides nutrition, taste, or aroma.[2] By comparison a drug is a substance that is either a food or non-food substance used to treat, cure, mitigate, or prevent disease.[2] Drugs, by law, must undergo an approval process that substantiate their safety and efficacy. Therefore an important distinction between a food and a drug exists. In the midst of these definitions, nutraceuticals have found a place for themselves somewhere between foods and drugs. One of the well-known examples of such a substance is fish oil, available in gel capsules from several manufacturers. These and other such substances are in use today in veterinary practice.

The Dietary Supplement Health and Education Act (DSHEA) was passed by the U.S. Congress in 1994. This act facilitated the availability of various nutritional products and supplements for human beings because it considered dietary supplements as a separate food category. It also opened the possibility of certain types of claims (i.e., structure/function claims) to be made without having any scientific evidence submitted to the FDA prior to marketing. However, DSHEA applies only to human foods. Discussion of animal dietary supplements was left out of the deliberations.

With respect to animal foods, responsibility for enforcing all aspects of the Food, Drug and Cosmetic Act that may apply to foods and drugs for animal use rests with The Center for Veterinary Medicine (CVM) of the FDA. This group is involved in reviewing food and feed additives. For reasons beyond the scope of this chapter, the CVM has essentially assigned “low regulatory significance” to most nutraceuticals. As a result, individual states were left to rule on market access to these substances.[3]

139.2 CLINICAL USE

It is helpful to know that, although the DSHEA governs human dietary supplements, this act is generally interpreted by the FDA's CVM office to not apply to animals.[4] However, pet owners often purchase nutraceuticals

and other supplements labeled for human use and administer them to their pets. What, then, should be the basis for veterinary recommendation of a specific substance?

139.3 GENERAL GUIDELINES

In the absence of a science-based regulatory consensus, the best advice is to proceed cautiously and seek out new information as it becomes available. Scientific data about certain substances is often unknown or incomplete, although they may be promoted as if conclusive evidence exists.

Four important types of information should be borne in mind during consideration of the use of a particular dietary supplement in companion animals. This type of information ideally should be known prior to recommendation of any widespread or long-term nutraceutical usage. The more gaps that are found in a particular substance's information profile, the more cautiously one should proceed regarding dosage, indications, and patient monitoring. These four categories of information can be easily recalled using the acronym *PETS* (Product Quality, Efficacy, Tolerance, and Safety) and can be used to assist discussions with clients about a particular supplement.

139.3.1 Product Quality (P)

The product quality of a substance should be documented and available. Independent of any scientific proof of efficacy or safety (discussed below) if a product is making a structure/function claim, it must first contain an amount within a realistic concentration range of potential efficacy and safety. Some manufacturers reportedly place a small amount of a popular ingredient in a product, which then allows what is termed "label dressing."[5] This practice is not highly regarded among reliable manufacturers. Also, manufacturers should be knowledgeable about their product, its formulation, and ingredient sources.

For the most part, nutritional supplements should be considered chemicals rather than commodities such as grains or protein meals. Each batch the manufacturer receives should have specifications as to its purity. Some preparations may contain less of the "active" material, which is all right as long as the product is formulated to provide enough of the ingredient and as long as there are no harmful or interfering materials present. To some extent, the cost of a substance may reflect its quality but not always. Individual distributors should be consulted for further information regarding the manufacturer. The manufacturer then may be contacted for answers to any questions regarding product quality. The answers should include information on specifications and what other substances may be present in the product formulation. The manufacturer should readily supply quality control and other supporting information when requested. This latter point may be an important part of any decision to use a particular product. Any reluctance on the part of the manufacturer or distributor to provide information should warrant finding another source of that particular substance.

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139.3.2 Efficacy (E)

Efficacy of any therapy is established by scientific testing. Demonstrating efficacy of a nutraceutical substance requires rigorous and often expensive testing, depending on the extent to which claims for a product are being made and the regulatory environment surrounding that substance. Manufacturers should be asked to supply supportive documentation of efficacy. This information may be proprietary, but reprints of articles and other information should be available upon request. If supporting information is not offered, another product should be selected and the process begun again. Any materials sent should be reviewed with the following questions in mind: What is the active ingredient? Are there several active ingredients acting together? Have any efficacy studies been performed in the species of interest (target species) and, if not, in other species? Were the studies

controlled and published under peer-review? Was the same dose used in the studies as is now being recommended for the product?

139.3.3 Tolerance (T)

Tolerance for any nutraceutical must exist for it to be effective. It must be acceptable by the animal and to the pet owner. For example, administering fish oil capsules to dogs is a simple task because most dogs will readily accept them as treats. However, some animals may smell “fishy” and owners may object. Administering fish oil capsules to cats is more difficult, especially if a cat happens to bite into a capsule and develop a taste aversion. In some cases, the inert ingredients that often serve as dispersants or diluents may cause an adverse reaction. An example is the flatulence that may occur due to inclusion of a fermentable fiber. The net effect may result in erroneously shifting blame on the pet food rather than the supplement. Alternatively, product intolerance may cause an owner unnecessary expense in searching for some medical reason for the problem. Milk sugars, such as lactose, may cause gastrointestinal upset, diarrhea, or vomiting. Eliminating the supplement or changing to another product to eliminate these inert materials may be all that is required. However, veterinary personnel must remember to think of these possibilities when owners' insist on using supplements. Also, it must be identified what other medications that animal is receiving. An interaction with the nutraceutical may be occurring, which would render traditional therapies useless.

139.3.4 Safety (S)

Safety is paramount and must be known before using a dietary supplement, as expressed in the dictum, “Above all else, do no harm”? Historical data on usage of certain substances may provide practical information regarding safety. Using a particular supplement in the absence of any published safety data in the target species is particularly risky and caution is advised. Also, lack of reports in the literature of any adverse effects should not be interpreted to indicate safety. The cost and expense to conduct safety studies may be more than some supplement marketers may wish to incur. Even for those substances for which such data is provided, caution is warranted: as the actual concentrations and purities of a particular substance can vary from source to source.

Many pet owners will be administering nutraceuticals to their pets regardless of veterinary advice or supervision. Labels of any products used should list the ingredients along with their amounts and purity in decreasing order of concentration based on weight. Directions for use and other requisite guarantees should be included on the label depending on state feed regulations for specific, more traditional components, such as crude protein, crude fat, fiber, ash, and moisture. Herbal type products should be especially evaluated with caution due to potential toxicities and product quality concerns.

With increased interest in human supplement usage, the opportunity for accidental ingestion of nutraceuticals by companion animals also exists. A recent report summarized 47 dogs suspected of caffeine and ephedrine toxicosis that had access to herbal preparations that contained guarana and ma huang.[6] Clinical signs included the full gamut of those associated with the gastrointestinal tract, CNS, and cardiopulmonary system. Amounts of guarana (caffeine) and ma huang (ephedrine) ingested by these dogs ranged from 80 to 3600 mg of guarana and 24 to 1080 of ma huang.[6]

The ready availability of supplements in retail outlets, by mail order, and the Internet along with supporting brochures may be all that many pet owners need to conclude that a particular product is safe. Clients must be made aware of health concerns with use of an unproven substance against the veterinarian's best judgment. Any dietary histories taken must include the use of any nutraceutical type substances.

139.4 NUTRACEUTICALS OF CURRENT INTEREST

Although scientific data in target species remains limited for many types of nutraceuticals, some usage categories of pet dietary supplements and ingredients presently are receiving closer attention by the pet industry and veterinarians. Two of these categories include joint soundness and skin health. Antioxidants are also gaining becoming more popular and these are covered in a separate chapter.

139.4.1 Joint Health

Improvements in pet food quality and feeding practices combined with better veterinary care has resulted in increased longevity of companion animals. However, as with human beings, increased life expectancy has increased the risks for the development of chronic, progressive disease such as osteoarthritis, obesity, renal failure and their complications. With increased age, the genetically influenced degenerative diseases such as intervertebral disk disease, hip dysplasia, cognitive disorders, and familial disorders may also become exacerbated. In addition to specialty foods containing substances with purported benefits, a number of supplement products have been developed in response to improving joint and bone health. Some of these substances are glucosamine, chondroitin sulfate, green-lipped mussel, methylsulfonyl methane, and trace minerals such as zinc, copper, and manganese. Many products use combinations of some but not all of these materials. Although it is often difficult to scientifically prove that one particular substance is efficacious when combined with others, there is growing evidence that some of these products have a beneficial effect on joint health. Some mention will be made of combination products that are available. However, to the extent possible, the discussion focuses on effects of single agents such as glucosamine and other compounds.

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Glucosamine is an amino sugar that is naturally produced in the body. It is a component of glycosaminoglycans (GAGs) present in joints, tendons, ligaments, skin, and blood vessels. The GAGs are long chain molecules that can hold water and allow the joint capsule to adapt to changes in pressure and therefore absorb shock induced by mechanical stress. Destruction of cartilage is characterized by destruction of the GAGs and loss of this property of the joint capsule. Theoretically it is expected that provision of supplemental glucosamine to joint issues will stimulate new GAG production. Data demonstrates that glucosamine can be absorbed via the gastrointestional tract in dogs after oral ingestion and is taken up by articular cartilage.[7]

A biochemical basis for the use of glucosamine in treatment of chronic inflammatory disease has also been shown in the rat model of lipopolysaccharide-induced inflammation. Here it was found that glucosamine inhibits inducible nitric oxide synthesis. Excess nitric oxide mediates the pathogenesis of osteoarthritis.[8] Recently, in human osteoarthritis patients, the long-term effects of glucosamine sulphate have been evaluated using a randomized, placebo-contolled clinical trial (1500 mg orally).[9] Symptom-modifying and structure-modifying effects were found, which suggests the compound could mitigate osteoarthritis. Regarding the safety of this compound, no significant differences in adverse events compared with placebo were found.[9]

Long-term safety studies of the chondroprotective agents in dogs or cats have not been reported. However, one caveat regarding the widespread use of glucosamine should be noted. Glucosamine infusions in ducks and dogs have been reported to cause hyperglycemia due to the release of glucagon immunoreactivity and possible insulin suppression.[9,10] Similarly in human beings, glucosamine infusions produced acute insulin resistance[11] and glucosamine may also induce or exacerbate insulin resistance.[12]

Thus, in cases of diabetes or possibly even obese animals prone to type II diabetes, the use of glucosamine may be contraindicated. An anecdotal report using a high oral dose of glucosamine (1000 mg/day, duration unspecified) in an 11 year-old Labrador retriever noted urinary incontinence, polyuria, and polydipsia, which abruptly returned to normal when the dosage was reduced to 500 mg/day.[13] However, serum glucose concentration tested using a midday, nonfasted sample was normal and follow-up tests were not conducted in this dog. By contrast, one study in rats was unable to demonstrate adverse effects of glucosamine or chondroitin sulfate on glucose metabolism.[14] Until more usage data is obtained, caution is advised and patients should be carefully monitored, especially if higher dosages are being used or considered.

With respect to other chondoprotective agents, data exist that support an interactive, or synergistic, effect between glucosamine and chondroitin sulfate in helping maintain joint health. Combinations of glucosamine with other products that contain mucopolysaccharides or other substances may help alleviate joint problems or rebuild degenerating cartilage. One proprietary product in particular, which combines glucosamine with chondroitin sulfate and manganese ascorbate, has been subjected to several cell culture and animal studies in dogs and other target species.[15–18] Survey data of practicing veterinarians have provided information that pain relief as well as mobilility was good to excellent with this type of combination product.[16]

Other substances that may benefit joint health include methylsulfonylmethane (MSM) and green-lipped mussel extracts. Purported benefits of MSM relate to it as a bioavailable source of sulfur, which is a component of several structural compounds found in joints.[19] The use of MSM in dogs or cats remains to be evaluated. Studies using green-lipped mussel extract, a mixture of glucosaminoglycans and omega-3 fatty acids and possibly other compounds, have been inconsistent in dogs exhibiting chronic lameness.[20,21] Additional proprietary combinations have also been evaluated.[22,23] In these cases, potential benefits of glucosamine may be further enhanced by the addition of other known collagen-matrix components or even anti-inflammatory agents.

As additional findings of both proprietary mixtures and single substances are reported, further confidence in the safe and efficacious use of chondroprotective materials, in certain clinical cases, will develop. However, at present, caution is advised with these agents in dogs and cats, especially the use of glucosamine compounds in animals at risk for diabetes.

139.4.2 Skin Health

When animals have skin problems, a full dermatologic work-up should be conducted rather than simply using diet or dietary supplements in the hopes of improvement. Shampooing, brushing, and use of moisturizers are significant components of skin care. Ensuring that the animal is fed a well-formulated diet is also important. Supplementation with therapeutic amounts of fatty acids or diet change is generally considered where animals are pruritic due to hypersensitivity reactions, exhibit dry, flaky skin, or have suspected abnormalities of fatty acid metabolism.

Omega-6 fatty acids (e.g., linoleic acid) are used preferentially for select functions. These include incorporation into the lipid ceramide layer of the epidermis, which imparts its water-barrier character or their provision of precursors for physiologically important eicosanoid synthesis to help maintain cell membrane integrity.[24,25] The omega-3 fatty acids, especially long chain types from marine oils (>18 carbon chain length), are noted for their preferential role in neurologic development and potential for reduced inflammatory response.[25,26] The plant-derived 18 carbon omega-3 fatty acid, alpha-linolenic, may also play a supportive role in the

inflammatory response. However, their limited conversion to active long-chain derivatives and favored use as substrate for energy requires substantially greater dietary amounts to achieve such an effect compared with supplying the already-formed long chain active fatty acids.[27,28] The 18 carbon omega-3 fatty acids are not as potent a source for the above desired effects as are the 20/22 carbon types. Products that contain both 18 and 20/22 carbons omega-3 acids should have their labels carefully scrutinized as to the source, types, and amounts of the various fatty acids. The dosage needed will be different, depending on the intended use of the product.

Should a therapeutic supplement of dietary omega-3 fatty acids be desired (i.e., as an adjunct to atopy treatment or inflammatory condition), an oil supplement containing 100% fish or other marine oil should be used. Conversely, if redness and inflammation is not present, selection of a proprietary blend that contains both omega-6 and omega-3 fatty acids, or simply 1 teaspoon per 10 lb body weight of a liquid vegetable oil daily should be sufficient in most instances. Although the clinical efficacy of fatty acid supplements is considered only modestly effective[29], a recent study has shown significant short-term improvements in skin and hair coat scores of clinically normal dogs when fed either linoleic (omega-6) or alpha-linoleic (omega-3) acid supplements.[30] Another study found a synergistic effect using linoleic acid, zinc, and biotin noting a reduction in hair coat scaliness scores.[31] Finally the safety of dietary fatty acid supplements in the amounts recommended above and in the literature appear to be well tolerated. However, it should be noted that extra calories are present in fatty acid or vegetable oil supplements (approx. 9 kcal/g) so caution is advised especially in small companion animals prone to obesity.

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140 CHAPTER • 140 Nonsteroidal Anti-Inflammatory Analgesics

Karol A. Mathews

Nonsteroidal anti-inflammatory analgesics (NSAIAs) are a group of pharmaceutical agents that possess analgesic and anti-inflammatory properties. The NSAIAs are frequently used in human and veterinary medicine to relieve mild, moderate, and severe pain. The efficacy of many recent NSAIAs can compare to the pure mu agonist opioids (morphine, oxymorphine, hydromorphine) in managing soft tissue and orthopedic post-operative pain[1,2]. When used in combination with opioids, NSAIAs appear to confer synergism and may require reduced dosing of the opioid. The NSAIAs concentrate in inflamed joints and tissues, which likely contribute to duration of effect, which varies between 12 and 24 hours.[3] The duration and efficacy of the NSAIAs makes them ideal for treating acute and chronic pain in veterinary patients; however, due to their potential for harmful adverse effects, animal and NSAIA selection must be considered prior to administration (Table 140-1).

140.1 PHARMACOLOGY

A significant part of the NSAIAs' antinociceptive effects is exerted at the spinal cord and supraspinal levels.[4] This action, in addition to pain relief, may account for the observed overall well-being and improved appetite of animals that receive injectable NSAIAs for relief of acute pain. Nonsteroidal anti-inflammatory analgesics are, with varying differences, inhibitors of cyclooxygenase enzyme-1 (COX-1), COX-2 or both, which result in reduced prostaglandin synthesis. Cyclooxygenase-1 is increased approximately two-or three-fold in tissue injury and therefore is involved in pain transmission but to a lesser degree than COX-2. With respect to pain, COX-2 is inducible and synthesized by macrophages and inflammatory cells, potentially increasing by 20-fold over baseline, in the presence of tissue injury and inflammation.[4] Increased cyclooxygenase levels increase prostanoid production, where these compounds mediate inflammation and amplify of nociceptive input and transmission in both the peripheral and central nervous systems.[4] By this mechanism, COX-2 is responsible for most of the pain and hyperalgesia experienced after tissue injury.

Based on these findings emphasis is placed on COX-1 versus COX-2 activity of NSAIAs, with respect to safety and efficacy. However, both have important constitutive functions and the notion of “good versus bad COX” is not an “all-or-none” event. COX-1 is a constitutive enzyme, present in tissues, that ultimately converts arachidonic acid into prostanoids (thromboxanes, prostacycline, and prostaglandins [PG]E_2, PGF_2 and PGD_2).[5] The most common, and clinically apparent, potential adverse effects of a COX-1 preferential NSAIA is the reduction in activity of these prostanoids and consequently affect primary plug formation of platelets, modulation of vascular tone at the level of the kidney, and inhibition of cytoprotective functions on the gastric mucosa.[5] These actions are frequently noted with respect to prostaglandin activity.

However, prostaglandins are ubiquitous throughout the body and regulate many other functions. For example, these functions include thermoregulation and vascular and bronchial smooth muscle tone. Prostaglandins exert a negative feedback effect on cyclic adenosine monophosphate (c-AMP) with potential perturbations in many physiologic functions. As an example, renal water reabsorption depends on the action of antidiuretic hormone (ADH), which is mediated by c-AMP; inhibition of PG (prostaglandin) synthesis may lead to increased levels of c-AMP with a potential for enhanced ADH activity. Urine volume may be decreased through this mechanism but without renal injury.[5,6] Cyclooxygenase-2 has some important constitutive functions; there may be a protective role for COX-2 in maintenance of gastrointestinal integrity, ulcer healing, and experimental colitis in rats. In

addition, there is constitutive activity associated with nerve, brain, ovarian and uterine function, and bone metabolism.[6] Most importantly, COX-2 has constitutive functions in the kidney, which differ from those of COX-1. The COX-2 is important in nephron maturation.[7] The canine kidney is not fully mature until 3 weeks after birth; continual administration of a NSAIA during this time, or to the bitch prior to birth, may cause a permanent nephropathy. On the other hand, COX metabolites have been favorably implicated in functional and structural alterations in glomerular and tubulointerstitial inflammatory disease.

Administration of COX-2 selective inhibitors decreased proteinuria and inhibited development of glomerular sclerosis in rats with reduced functioning renal mass.[7] Because COX-2 expression is also increased in glomerulonephritides such as lupus nephritis, it is possible that COX-2 inhibitors may also alter the natural history of glomerular inflammatory lesions.[7] The COX-2 derived metabolite production is regulated and localized to the structures in the kidney that plays an essential role in renal blood flow associated with renin activity and fluid-electrolyte homeostasis.[2] Cyclooxygenase-2 is glucocorticoid sensitive, in that it is reduced after administration of glucocorticoids, which may partially explain the anti-inflammatory and analgesic effects of this class of medications. Of interest, in addition to the COX-2 role in inflammation, aberrantly upregulated COX-2 expression is increasingly implicated in the pathogenesis of Alzheimer's disease and possibly other neurologic conditions and a number of epithelial cell carcinomas, including colon, esophagus, breast, and skin.[8,9] The COX-2 inhibitors are being researched as potential anticarcinogenic agents. Associated with the use of NSAIAs is the risk of purturbation of the constitutive functions of COX-1 and COX-2, resulting in potential organ dysfunction. However, “not all NSAIAs are created equal” in this regard. Some NSAIAs have both COX-1 and COX-2 inhibitory effects (aspirin, ketoprofen, ketorolac), whereas others preferentially inhibit COX-2 or are COX-1 sparing to varying degrees (meloxicam, carprofen, etodolac, tolfenamic acid).

As the COX-2 appears to play a significant role in nociceptive transmission, medications that prevent COX-2 activity and spare COX-1 should be effective, with potentially less adverse effects, in the management of pain. The COX-2 specific inhibitors (rofecoxib, celecoxib), currently available in human medicine, appear to have less 518
gastrointestinal adverse effects than other NSAIAs. However, long-term use in some people has resulted in similar 519
gastrointestinal problems as those experienced with commonly used NSAIAs; therefore it cannot be assumed that these NSAIAs will be a safe treatment for all cats and dogs with chronic administration. The COX-2 specific NSAIAs are currently being investigated in veterinary medicine. At the time of publication, deracoxib has recently been approved for control of postoperative pain and inflammation associated with orthopedic surgery in dogs. The incidence of vomiting and diarrhea were similar in dogs receiving deracoxib compared with dogs that received placebo in a perioperative field trial; however, overall the drug was well tolerated and effective. A good review of “the Coxibs” is available.[8]

Table • 140-1 Nonsteroidal Analgesic Dosing Regimen Per Body Weight*

DRUG	INDICATION	SPECIES, DOSE, ROUTE	FREQUENCY
Ketoprofen	Surgical pain	Dogs: ≤2.0 mg/kg, IV, SC, IM, PO	Once postoperative
		Cats: ≤2.0 mg/kg, SC	Once postoperative
		Dogs and cats: ≤1.0 mg/kg	Repeat q24h
	Chronic pain	Dogs and cats: ≤2.0 mg/kg, PO	Once
		≤1.0 mg/kg	Repeat q24h
Meloxicam	Surgical pain	Dogs: ≤0.2 mg/kg IV, SC	Once
		≤0.1 mg/kg IV, SC, PO	Repeat q24h
	Chronic pain	Dogs: ≤0.2 mg/kg PO	Once
		≤0.1mg/kg PO	Repeat q24h
	Surgical pain	Cats: ≤0.2 mg/kg SC, PO	Once
		≤0.1mg/kg SC, PO lean weight	Daily for 2 to 3 days
	Chronic pain	Cats: ≤0.2 mg/kg SC, PO	Once
		≤0.1 mg/kg PO lean weight	2 to 3 days
		0.025 mg/kg PO lean weight (~0.1 mg/CAT max)	3 to 5 times weekly
Carprofen	Surgical pain	Dogs: ≤4.0 mg/kg, IV, SC ≤2.2 mg/kg PO	Once upon induction
			Repeat q12h-24h PRN
		Cats: ≤2.0 mg/kg SC lean weight	Once upon induction
	Chronic pain	Dogs: ≤2.2 mg/kg PO	q12h-24h
Etodolac	Chronic pain	Dogs: ≤10–15 mg/kg PO	Once daily
Deracoxib	Peri-operative pain	Dogs: 3.0 mg/kg PO	Once daily for 7 days
	Chronic pain	Dogs: 1–2 mg/kg PO	
Tepoxalin	Chronic pain	Dogs: 10 mg/kg PO	Once daily
Tolfenamic acid	Acute and chronic pain	Cats and dogs: ≤4 mg/kg SC, PO	Once daily for 3 days. 4 days off. Repeat the cycle
Flunixin	Pyrexia	Dogs and cats: 0.25 mg/kg SC	Once
Meglumine	Ophthalmologic procedures	Dogs and cats: 0.25–1.0 mg/kg SC	q12h-24h PRN for 1 or 2 treatments
Ketorolac	Surgical pain	Dogs: 0.3–0.5 mg/kg IV, IM	q8h-q12h for 1 to 2 treatments
		Cats: 0.25 mg/kg IM	q12h for 1 to 2 treatments
	Panosteitis	Dogs: 10 mg/DOG ≥30 kg, PO	Once daily for 2 to 3 days
		5 mg/DOG >20 kg <30 kg, PO	
Piroxicam	Inflammation of the lower urinary tract	Dogs: 0.3 mg/kg, PO	q24h for 2 treatments, then
			q48h
Acetaminophen	Acute or chronic pain	Dogs only: 15 mg/kg PO	q8h
Aspirin	Acute or chronic pain	Dogs: 10 mg/kg PO	q12h

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PRN, As required.
Modified with permission.

* See text for details on the contraindications for use.

Recently reported cloning and expression of canine COX-1 and COX-2 reveal these enzymes to be highly homologous to their human counterparts. Assays developed to assess the potency of inhibition of the canine cyclooxygenases by various NSAIAs indicated no difference from their potency on human enzymes, maintaining the same rank order of potency. The researchers concluded that any differences that may occur *in vivo* between

canine and human inhibition of COX-1 and COX-2 can be attributed to factors other than inhibition of these enzymes.

Most NSAIAs that inhibit COX have been shown to result in diversion of arachidonate to the 5-lipooxygenase pathway. This results in an excessive production of leukotrienes, which have been implicated in the creation of NSAIA-induced ulcers.[5] Tepoxalin, a dual COX/lipooxygenase inhibitor, has recently been approved for management of osteoarthritic pain in dogs. *In vitro,* tepoxalin inhibited COX-1 with at least a thirty-fold higher potency than for COX-2. The potencies for tepoxalin as a lipooxygenase and COX inhibitor, seemed to be in the same range; however, *in vivo* studies showed less potency against lipooxygenase than against COX and efficacy comparable with meloxicam or carprofen and safety comparable to placebo.

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140.2 GENERAL CONSIDERATIONS

The general health of the animal must be considered prior to prescribing NSAIAs. Cats and dogs are more susceptible than people to the adverse effects of NSAIAs. Therefore the reported safety of any drug approved for humans should not be assumed to be safe in dogs or cats. Most NSAIAs require accurate dosing to avoid potential adverse effects, especially when used long term. Anecdotal reports of single, accidental, large overdoses have been reported with no adverse effects; however short-term prophylactic gastric and renal protection may be advised with extremely high overdose.

NSAIAs should be restricted to animals older than 6 weeks of age (may be older depending on the NSAIA) that are well-hydrated and normotensive and have normal renal and hepatic function. Although these are general guidelines, COX-1 sparing NSAIAs may prove safe in animals with non–clinically significant elevations in creatinine and liver enzymes where the benefit outweighs the risk. Some animals may be receiving other medications and NSAIA interaction must be considered.[3]

Plasma levels of NSAIAs are effectively reached within 1 hour after oral administration.[3] When given per os, NSAIAs must be given with food to protect the gastric mucosa from high localized concentrations of the drug increasing the potential for gastric erosion. However, potential for gastric erosion exists with all NSAIAs regardless of route of administration. To reduce this, NSAIAs should be decreased to the lowest possible dose that will confer analgesia. If evidence of gastric erosions/ulcers exists, drug withdrawal and gastroprotective therapy is advised. NSAIA induced renal insufficiency is usually temporary, if identified early, and reversible with drug withdrawal; administration of IV fluids may be required. An increase in serum alanine aminotransferase (ALT) activity can occur with most NSAIAs, is reversible with NSAIA withdrawal, and appears to be of little clinical significance. Rare, acute hepatotoxicity after carprofen administration has been reported in dogs (Labrador retrievers highly represented) in North America[1] but has not been reported in Europe.

140.3 INDICATIONS FOR NSAIA ADMINISTRATION

The indications proposed here assume no contraindications (below) to their use.

1. **Postoperative pain:** Orthopedic[1,2] and selected soft tissue surgical procedures[1,2] may warrant NSAIA administration, especially where extensive inflammation or soft tissue trauma is present. Opioid administration is beneficial immediately after most surgical procedures, due to the sedative and synergistic analgesic effects, to ensure a smooth recovery. Injectable NSAIAs can be co-administered with an opioid initially and subsequently used alone as the repeat analgesic after orthopedic and selected soft tissue surgery. The initial dose of NSAIAs depends on the expected severity of pain. Assuming a difficult fracture

repair would require the recommended loading dose, then a laparotomy without complications, could be successfully treated with half this dose. The administration of NSAIAs prior to surgical procedures is controversial due to their potential for harm. Various studies investigating pre-operative administration of NSAIAs in animals did not specifically screen for adverse reactions.[1] Studies that specifically assess efficacy and safety of NSAIAs given preoperatively, where intraoperative fluid therapy was administered and patient monitoring conducted, noted rare adverse reactions with some of the NSAIAs[1].

A recent study conducted at the Ontario Veterinary College demonstrated no ill effects with the administration of meloxicam or carprofen prior to orthopedic or soft tissue surgery in both cats (meloxicam) and dogs (meloxicam and carprofen) (unpublished data). In these studies, in which intraoperative fluids were administered, the NSAIA did provide very good to excellent analgesia, for longer than 24 hours, in approximately 70% of animals that underwent orthopedic procedures. The remaining animals required a much lower dose of opioid than expected to manage moderate to severe postoperative pain. The benefit of preoperative use of NSAIAs is the potential for a pre-emptive effect and the presence of analgesia upon recovery. Analgesia during the recovery period is essential. The recently released deracoxib is also approved for pre-and post-operative use at 2 mg/kg once daily for 7 days. Where NSAIAs are administered postoperatively, opioids should be administered concurrently because 45 minutes are required for therapeutic effect of the NSAIA. Another potential approach could be to administer the NSAIA upon completion of the surgical procedure at least 45 minutes prior to extubation.

Ketoprofen is an excellent analgesic but is an inhibitor of both COX-1 and COX-2. Therefore unwanted side effects are a potential problem requiring careful patient selection. Ketoprofen should be reserved for postoperative use to reduce the potential for hemorrhage. Flunixin meglumine is used as an antiinflammatory agent in selected ophthalmologic surgical procedures; however, the potential for side effects is of major concern[1] and potentially safer NSAIAs are as effective.

2. **Inflammatory conditions:** NSAIAs appear to be more efficacious than opioids for relief of pain due to meningitis, soft tissue inflammation, polyarthritis, cystitis, otitis, severe inflammatory dermatologic diseases, or injury (i.e., degloving, animal bites). Because many of these animals may be more prone to NSAIA toxicity, careful patient selection and management is advised. Combination opioids and low dose NSAIAs are also effective in these conditions. An exception is necrotizing fasciitis where NSAIAs are reported to increase morbidity and mortality.[1]

3. **Miscellaneous conditions:** Other indications for the use of NSAIAs are panosteitis, hypertrophic osteodystrophy (HOD), cancer pain (especially of bone), radiation-induced stomatitis in cats and dental pain[1]. Non–COX-1–sparing NSAIAs should be used with caution after dental extractions where bleeding is, or may be, of concern. Ketoprofen or ketorolac is suggested for the management of refractory pain associated with hypertrophic osteodystrophy and panosteitis. The HOD of Weimeraners is poorly responsive to NSAIA therapy and is better treated with high dose, short-term corticosteroids, provided infectious disease has been ruled out and clinical signs are consistent with HOD alone.[1]

4. **Osteoarthritis:** Long-term studies of the adverse effects of NSAIAs (carprofen, meloxicam, etodolac) for osteoarthritis, appear to be minimal and are predominantly associated with the gastrointestinal tract.[10] As many animals with osteoarthritis are geriatric a rapid reduction of the dose, to affect a comfortable state, is advised to reduce potential toxicity. For example, alternating to every third day therapy of meloxicam, with half the label recommended dose, proved efficacious in some dogs during a 12-month period.[1] As the long-term dosing of carprofen in Europe is 2.2 mg/kg once daily, potentially reduced dosing for dogs in

North America may also be beneficial. If a particular NSAIA appears ineffective in managing pain, prescription of a different NSAIA may be effective due to individual variation in response to the different analgesics. In situations in which the adverse effects of an NSAIA are a concern, reduction of the dose and addition of an opioid may be equally as effective for chronic severe pain.

However, for many geriatric animals with renal insufficiency and increased serum ALT activity, NSAIAs may be the only effective class of analgesic. For these animals the quality of life is of major importance. In this situation, a COX-1 sparing/COX-2 preferential NSAIA, at the lowest dose possible, may be suggested for both cats and dogs. Anecdotal reports indicate that worsening of renal function may not be a problem in some animals. Client understanding of potential worsening of renal or hepatic function is necessary prior to treatment. Water must be available at all times. Dietary indiscretions and stressful situations must be avoided. During NSAIA therapy all dogs and cats should be monitored for hematochezia or melena, vomiting, increased water consumption, and a nonspecific change in demeanor. If this occurs, the owner should be instructed to stop the medication and consult the veterinarian. Intermittent monitoring of creatinine and ALT is recommended when NSAIAs are prescribed chronically.

140.4 PYREXIA

Most veterinary-approved NSAIAs, aspirin and acetaminophen, are effective antipyretics. The antipyretic effect is obtained with a lower than analgesic dose. Dipyrone is an excellent antipyretic and is available as tablets and solution for injection. Dipyrone should be given intravenously to avoid the irritation when given intramuscularly. The analgesia produced is not adequate for moderate to severe postoperative pain. Gastric ulceration or nephrotoxicity is not a concern in the short term even in critically ill patients.

140.5 CONTRAINDICATIONS FOR THE USE OF NSAIAS

Nonsteroidal antiinflammatory analgesics should not be administered to animals with acute renal insufficiency, hepatic insufficiency, dehydration, hypotension, conditions associated with low “effective circulating volume” (i.e., congestive heart failure, ascites), coagulopathies (i.e., factor deficiencies, thrombocytopenia, von Willebrand's disease), concurrent use of any other NSAIAs or corticosteroids, evidence of gastric erosion (vomiting with or without the presence of “coffee ground material,” melena), or spinal injury (including herniated intervertebral disc) as most of these patients receive corticosteroid with medical or surgical management. NSAIAs should never be administered to animals in shock or those that have been recently traumatized. NSAIAs should not be given if hemorrhage is evident (i.e., epistaxis, hemangiosarcoma, head trauma). Animals with severe or poorly controlled asthma, or other moderate to severe pulmonary disease, may deteriorate with COX-1 inhibiting NSAIAs. The administration of NSAIAs in head trauma, pulmonary diseases, or thrombocytopenia may prove to be safe with further study of the COX-2 preferential/COX-1 sparing NSAIAs. NSAIAs may have adverse effects on the reproductive tract and fetus as they may block prostaglandin activity resulting in cessation of labour, premature closure of the ductus arteriosus in the fetus, and disruption of fetal circulation.[6] As COX-2 induction is necessary for ovulation and subsequent implantation of the embryo,[6] NSAIAs should be avoided in breeding females during this stage of the reproductive cycle.

Topically applied nonsteroidal anti-inflammatory analgesics were significantly more effective than placebo in many human clinical trials involving acute and chronic painful conditions.[1] Topical NSAIAs were not associated with the gastrointestinal adverse effects seen with the same drugs taken orally.[1] At the time of writing this chapter, there are no published studies investigating the use of topical NSAIAs in the veterinary literature.

140.6 NSAIAS NOT APPROVED FOR USE IN VETERINARY PATIENTS (OFF LABEL USE)

Ketorolac parenteral formulation and tablets are comparable to oxymorphone in efficacy and to ketoprofen in duration and efficacy in managing post-laparotomy and orthopedic pain in dogs.[1] Only one to two doses should be administered. Ketorolac is included for the benefit of those working in the human research setting, where the availability of ketorolac is more likely than other NSAIAs. Ketorolac has been used successfully for treatment of severe panosteitis in dogs in which all other therapies had failed. Ketorolac given with food for 2 to 3 days in hydrated dogs resolved signs in approximately 99% of those treated. In the other 1%, signs recurred within a few days to months (unpublished observations). Misoprostol should be coadministered.

Aspirin is available in tablet form. It is most commonly used as an analgesic for osteoarthritic pain in dogs. It is formulated in combination with opioids, aspirin and codeine, or aspirin and oxycodone, for a synergistic effect for the treatment of moderate pain. It is also used as an antipyretic and anticoagulant in dogs and cats.

Acetaminophen is available in tablet form. It may be used as an antipyretic or as an analgesic. It is formulated in combination with opioids, acetaminophen and codeine, or acetaminophen and oxycodone.

Over several years, many studies have reported the safety and efficacy of the commonly used NSAIAs in various clinical settings[1]; similar studies that investigate the use of the recently approved COX-2 specific and dual cyclooxygenase/lipooxygenase inhibitors, with well-designed prospective clinical trials and laboratory studies, should determine the safety and efficacy of these NSAIAs in both the acute and chronic pain management settings.

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141 CHAPTER • 141 Antioxidants in Health and Disease

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Free radicals are molecular fragments that have at least one unpaired electron. This characteristic makes them highly reactive in biologic systems. Their activity can be beneficial because they participate in oxidative burst reactions and other mechanisms that characterize neutrophil and other inflammatory cell function that serve to phagocytose and kill bacterial invaders. However, when free radicals are present in excess, oxidative metabolic damage, and destruction of normal cell membranes, or destruction of cell content may occur. To help keep these mechanisms in check, biologically active scavengers of free radicals help interrupt further cell damage. These scavengers, the antioxidants and related mechanisms, thus normalize the effects of an overabundant and destructive cell process.

Evidence supports the concept that humans who include appropriate amounts of fruits and vegetables in their diet, which are high in antioxidants, appear to lower risk of cardiovascular disease and cancer risk.[1] Specific dietary factors responsible for these benefits are not known. Plant and plant products contain numerous phytochemicals that may play some role. There is a need for carefully conducted studies to determine whether extracted plant or other antioxidant material, when ingested as a single nutrient, would help prevent any specific disease. To date, however, no direct connection has been made between antioxidant consumption and prevention of chronic disease. In some cases overconsumption may even prove harmful.

141.1 ANTIOXIDANTS AND FREE RADICAL DAMAGE

Free radical reactions are ubiquitous *in vivo*. They are associated with oxidation-reduction reactions, energy metabolism, biosynthesis, cell signaling, body defense, and detoxification mechanisms. Because of potential adverse effects of oxygen and related oxygen products, cell systems utilize numerous defensive mechanisms. These systems include direct interaction with reducing agents (e.g., vitamin C, glutathione); free radical scavenging (vitamin E, vitamin C, carotenoids, superoxide dismutase); reduction of hydroperoxides (e.g., glutathione peroxidase, catalase); removal of transition metals by protein binding (e.g., ferritin, ceruloplasmin, and other chelators); preventing reactive oxygen from reaching specific sites; and even repair of oxidative damage.[2]

There is considerable interest in the function and metabolism of antioxidants and their ability to scavenge free radicals. The generation of free radicals and its related oxidative damage appears to be a consequence of stress, various diseases, aging, trauma, environmental factors such as cigarette smoke or air pollution, infectious organisms, and other factors. As a by-product of oxidative metabolism, the generation of free radicals can probably not be halted entirely but only moderated. Consequently there is a need for biologically active antioxidants and associated scavenger mechanisms. Because free radicals arising from metabolism or environmental sources interact continuously in biologic systems, the oxidants and antioxidants are in a continual “utilization and replenishment” cycle that must be balanced to minimize cellular and tissue damage.

One of the most well-studied systems of biologic oxidative processes has been the effect of free radicals on lipid peroxidation in both cell free and biologic systems. The mechanism of lipid peroxidation consists of three stages: initiation, progression, and termination (Figure 141-1).[3,4] Initiation of lipid peroxidation occurs by abstracting a hydrogen atom from a methylene group, such as exists on an unsaturated fatty acid, by a free radical species. The resulting molecule is now a free radical, which can react rapidly with molecular oxygen to form a peroxy radical. The peroxy radical then abstracts another hydrogen atom from another unsaturated fatty acid to form another free radical species. Because a new free radical is formed, a chain reaction is created resulting in many free radicals being formed from one event. This chain reaction can be terminated when the chain-propagating species reacts

with an antioxidant molecule to form non–free radical products. In the meantime, left to propagate, many highly reactive free radical species are formed. Evidence of this process exists in the numerous molecular markers of tissue destruction that form, such as lipofuscin pigments, iosprostanes, carbonyl and nitrotyrosine protein derivatives, and DNA fragments. Antioxidants thus have the potential to terminate these chain reactions prior to their generating a large degree of cellular damage and hence provide cells the opportunity to complete their individual life cycles.

There are a number of biologic and dietary types of antioxidants. These include various tocopherols (vitamin E), vitamin C, beta-carotene, and the enzyme superoxide disumutase. Among these free radical scavengers, vitamin E is often promoted as a diet supplement or food ingredient. Vitamin E is a fat-soluble vitamin and is absorbed from the intestine into the lymph system on lipoproteins. It is then transported to the liver for utilization or storage. Compared with other fat-soluble vitamins (A, D, and K), vitamin E is not efficiently stored.

141.1.1 Vitamin E

Vitamin E is the major lipid-soluble antioxidant present in plasma, erythrocytes, and tissues. The term *vitamin E* actually refers to a group of fat-soluble compounds known as the tocopherols. α-tocopherol is generally regarded as having the greatest antioxidant activity. Its function as a scavenger of free radicals serves to prevent free radical or oxidative damage to polyunsaturated fatty acids in membranes, thiol-rich proteins of membranes, and nucleic acids. Support for an antioxidant role of vitamin E *in vivo* also comes from observations that synthetic antioxidants can either prevent or alleviate certain clinical signs of vitamin E deficiency. Numerous studies have established vitamin E as an essential nutrient.[5,6] Vitamin E has beneficial effects on the canine immune system and a prolonged dietary deficiency of vitamin E will cause oxidative damage and degeneration of the retina of the eye, and lead to reduced visual acuity.[7–13]

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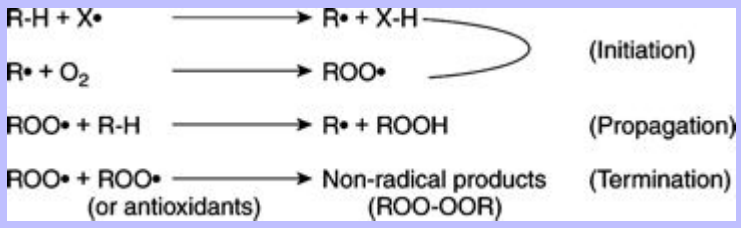
Figure 141-1 Model of fatty acid oxidation by a free-radical mechanism. R-H represents a fatty acid; XX, a free radical capable of abstracting a hydrogen from R-H; RX, a free radical of the fatty acid; ROOX, the peroxy radical; ROOH, a lipid hydroperoxide.



141.1.2 Antioxidant Combination

Vitamin E and other supplementary antioxidants are readily available as commercially manufactured over-the-counter products. Their use as individual dietary supplements is not widespread in veterinary practice. Instead, antioxidant combinations are often incorporated into pet food or supplements are formulated to contain one of more of these substances. One such combination included vitamin E, vitamin C, α-lipoic acid, L-carnitine, and fruit and vegetable-based ingredients that contain flavonoids and carotenoids in a pet food. A study utilizing this food noted that some age-dependent cognitive deficits of dogs were improved.[14] Another

report of using combinations of vitamin E, C and beta-carotene resulted in increased serum vitamin E concentrations and suppressed serum biomarkers of lipid peroxidation (i.e., total serum alkenyls) in dogs and cats. Diet supplementation of sled dogs with beta-carotene, lutein, and vitamin E "normalized" adverse effects of exercise on immune status.[16]

One bioflavonoid blend was fed to cats before administration of acetaminophen and was found to provide some protection against Heinz body formation. Methemoglobinemia formation was not prevented[17]. When cats were pretreated with vitamin E, vitamin C, or N-acetylcysteine, no beneficial effect on Heinz body formation induced with onion powder was seen. However, admininstration of N-acetylcysteine was associated with higher relative amounts of reduced glutathione concentrations in whole blood[18]. When propylene glycol was used to induce Heinz body formation, again only N-acetylcysteine showed a significant effect.

141.1.3 Antioxidants and High-Fat Diets

Is there need for additional dietary antioxidants when higher amounts of polyunsaturated fatty acids are present in the diet? The prevailing opinion is that more vitamin E, particularly α-tocopherol, should be consumed. In humans, when the dietary polyunsaturated fatty acid is linoleic acid, a ratio of 0.4 mg α-tocopherol to 1.0 g polyunsaturated fatty acid is considered appropriate.[19] However, studies to support the need for increased intakes of vitamin E when diets are enriched with longer chain omega-3 fatty acids are equivocal.[20] However, in dogs, when diet intake of vitamin E is high, plasma content on a volume basis was lower in a fish oil supplemented group but it was equivalent when expressed on a plasma lipid basis.[21] In humans plasma tocopherol concentrations either increased (volume basis) or did not change.[20] Thus the results appear to depend upon how the data are expressed, the measures of peroxidation used or the tissues studied. Based on this single study using dogs, it would appear that dietary vitamin E content should be increased when diets high in polyunsaturated fat are employed.

141.1.4 Other Antioxidants

141.1.4.1 Trace Minerals (a Supporting Role)

Trace minerals may be incorporated into antioxidant enzyme proteins. Their adequate provision should help ensure synthesis and activity of these enzyme-based antioxidant systems. These include selenium in glutathione peroxidase, iron in catalase and copper, zinc, or manganese dependent superoxide dismutases. Other antioxidants, such as ceruloplasmin and ferritin, are nonenzymatic antioxidants containing copper and iron, respectively. Assuming that ample dietary quantities of these minerals are present, direct supplementation of these compounds is not required.

141.1.4.2 Vitamin C

Vitamin C can be synthesized by both dogs and cats, and hence is not considered a dietary essential. Nonetheless in response to stress, dietary supplementation may be beneficial.[22,23] Vitamin C may also help prevent oxidative damage induced by onion powder or propylene glycol ingestion in cats.[24] Studies in other species have shown beneficial effects to immune function.

141.1.4.3 Carotenoids

Beta-carotene and other plant-derived substances (lycopene) may provide antioxidant activities in dogs and cats. In dogs, beta-carotene is a precursor of vitamin A, but this pathway is nonfunctional in cats. These materials may also have antioxidant properties, although beta-carotene has been shown to act as a pro-oxidant if large quantities are consumed. Several clinical trials in humans have been terminated because of negative side effects associated with supplementation. These results call for their cautious use in dogs and cats until their safety and efficacy has been established.

141.1.4.4 S-adenosyl-methionine (SAMe)

This compound is synthesized in animals derived from methione in conjunction with adenosine tripohosphate. It is involved in various biochemical and cellular reactions and is a precursor to glutathione via the so-called *transsulfuration pathway*. This pathway is important not only for detoxification reactions but also helps protect against cellular oxidation. In the absence of SAMe, oxidative damage and toxin retention occurs, which presumably contributes to cell injury and disease progression. It has been studied to some extent in dogs and cats and has shown promise in support of liver function in dogs with vacuolar hepatopathy.[24] It has also been evaluated in normal adult cats and appears to be safe at the dosages employed.[24] Its use in clinical cases of liver insult or injury in cats and dogs appears to be increasing although further controlled case studies are warranted.

141.1.4.5 α-Lipoic Acid

This compound is also involved in modifcation of the relative distribution of reduced versus oxidized glutathione and, as such, provides a protective effect against oxidative injury. α-lipoic acid is similar in structure to octanoic acid (an 8-carbon medium chain fatty acid) and can participate in oxidation-reduction reactions, which are fundamental to numerous antioxidant mechanisms. Administration of α-lipoic acid to dogs over a 6-month period was found to increase the reduced versus oxidized glutathione ratios.[25] A dose-dependent response was not observed because the lowest supplement group resulted in the most significant increase. This finding suggests that a narrow dosage range may exist to achieve the desired effect. Also cats reportedly have a decreased capacity to metabolize α-lipoic acid compared with dogs[26] for which some caution is advised regarding its use in this species.

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142 CHAPTER • 142 Herbal Medicine

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Until the twentieth century, most remedies were botanicals found by trial and error at a great human cost. Some remedies were harmful and some even deadly. With advancements in pharmacologic methods of isolation and purification, active ingredients were identified, characterized, quantified, and sold as prescription or over-the-counter drugs. More recently, the use of botanical medications has become increasingly popular (approximately $5 billion per year industry in the United States). The use of herbal medicine by veterinarians has been increasing for the last 30 to 40 years.

The growing use of herbal remedies in the United States has far exceeded the available information on their benefits, adverse effects, and drug interactions. A coherent, easily accessible database (human or animal) on such remedies is still nonexistent. FDA's Center for Veterinary Medicine is concerned about these products because they lack scientific data showing safety, efficacy, or even standard good manufacturing practices.[1–3]

These animal herbal products are believed by many to be sold under the Dietary Supplement Health and Education Act (DSHEA) passed by Congress in 1994 because they contain human dietary ingredients. Under DSHEA, FDA regulation is not required and hence most of these products do not have pre-market approval. However, the FDA contends that DSHEA does not apply to animals, and this position has been upheld in at least one court case. Therefore most of the herbal products currently on the market would be considered *unapproved* animal drugs or food additives for animals. Although these products are technically in violation of the law, they are of low enforcement priority except when there are public or animal health concerns.[4]

There are published case reports of people suffering from lead poisoning, renal failure, CNS disorders, and digitalis toxicity linked directly to their herbal medications. Some people have exclusively embraced alternative therapies while refusing known effective conventional therapies.[1,5] Analogous cases are most likely occurring within the field of the veterinary medicine when owners choose to diagnose and treat their pet's medical condition concurrent with or without a veterinarian. Clearly it has been a “buyer beware” market under DSHEA. Late in 2002, the FDA announced a new initiative encouraging companies to make accurate product health claims and to prevent companies from making bogus claims. Dietary supplement companies will have to show “the weight of scientific evidence” supports their product health claims; however, this initiative did not address the issue of product safety.

“It is time for the scientific community to stop giving alternative medicine a free ride. There cannot be two kinds of medicine: a medicine that works and one that may or may not work.” This statement appeared in the *New England Journal of Medicine* in 1998.[5] It would appear that, although herbal medicine has been in use for centuries, the time has come for such remedies to be tested by scientific method. The scientific method is the process by which scientists, collectively, over time, construct an accurate, reliable, consistent, and nonarbitrary representation of the world (Box 142-1). Recognizing that personal and cultural beliefs influence perceptions and interpretations of natural phenomena, through the use of standardized procedures and criteria to minimize those influences, theories are developed. There are pseudo-scientific theories that wrap themselves in a mantle of apparent “experimental” evidence but, when examined closely, they are found to be statements of faith, hearsay, testimonial, or worse, fraud.[6]

The scientific method distinguishes science from other forms of explanation because it requires systematic experimentation. Where there is active study and open communication, the biases of individuals or groups will cancel

out because different groups, with different biases and sources of systematic error, repeat similar experiments. A consensus and theory will develop based upon those experimental results that have stood the test of time. Why has the herbal industry not yet chosen to demonstrate product safety and efficacy using the scientific method?

142.1 HERBAL POLYPHARMACY

The term *drug* comes from the ancient word for "root." Until the 1930s plant drugs were the primary source of medicines.[7] Plants may contain thousands of chemical constituents. Phytochemicals are nonnutritive plant constituents that contain protective, disease-preventing compounds, and more than 900 have been identified as components of food. Some constituents are pharmacologically unique and have been isolated by the drug industry, but other constituents have important activity as well.

Investigating the efficacy of herbal therapies is complicated by these mixtures of compounds, some of which exist in varied forms. Constituents isolated from herbs and tested may have important pharmacologic activity, but data from an isolate may under-or overstate actions of the parent herb. The other "minor" constituents may modify the activity of the primary active constituent, either synergistically or antagonistically. For instance, foxglove is less toxic than its active ingredient digoxin because other plant constituents, some of which antagonize, modulate the actions of digoxin.

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142.1.1 Box • 142-1 The Scientific Method—a Simple Version[6]

1. Observe some aspect of the universe.
2. Invent a tentative description—hypothesize.
3. Use the hypothesis to make predictions.
4. Test those predictions by experiments or further observations and modify the hypothesis in the light of your results.

Repeat steps 3 and 4 until there are no discrepancies between hypothesis and the experiment results and/or observation. When consistency is obtained, the hypothesis becomes a theory and provides a coherent set of propositions that explain a class of phenomena. A theory is then a framework within which observations are explained and predictions are made.

Quality control problems in the production of herbal medicine exist on several levels. First, plant constituents vary naturally according to climate, culture conditions, and time of year. William Withering, in his famous Account of Foxglove, noted that some patients got minimal results with what he considered to be an overdose and discovered that the only time to gather foxglove leaves for consistent clinical results was while the plant was in early flower.[8]

Manufacturing practices lend a second level of variability to the product. This is due to (1) the use of different (sub-) species and proper identification of the plant; (2) the use of different parts of the plant (herb, roots, leaves, or combination); (3) different methods of extraction (pressed juice, alcoholic extraction); and (4) the variable presence or absence of other plant constituents. An herbal product may contain highly variable amounts of a variety of bioactive ingredients depending on these factors. Herbalists use products usually from one or two manufacturers and continue to do so after becoming comfortable with the potency of those particular products. Some practitioners have found standardized extracts helpful. For a particular medicinal plant, one active

constituent is chosen for standardization and that constituent is concentrated to a predetermined level. A "standardized extract" product ensures that the product has one active constituent at a certain known concentration. However, standardized extracts rely on an admittedly incomplete knowledge of the remaining constituents extracted from that plant.

It has been said that herbal remedies cannot be patented and manufacturers do not expect to recoup the estimated $350 million to confirm FDA safety and efficacy studies.[9] Without patent protection, pharmaceutical companies have not provided financial support for herbal medicine research. The National Institutes of Health since 1992 have only been able to offer limited funding. The lack of regulation on quality control and product standardization for active ingredients that may vary 200-fold between different manufacturers, and batches make it difficult to establish safe or reasonable starting dosages in clinical research protocols.

It would appear that the greatest advantage of herbal medicine, polypharmacy, is at this time its greatest downfall to progress. Polypharmacy, use of multiple drugs with similar, synergistic, or complementary actions, in some respects is discouraged in veterinary medicine. The "shotgun" approach may alleviate clinical signs in the short term but does not increase general medical knowledge, and inadvertently, there may be adverse effects long term. In reality, many practitioners find the use of multiple drugs necessary most commonly in geriatric patients or those with complicated medical problems. At other times, animals are treated with use of multiple drug combinations as in antibiotics, antiparasitic control, vaccines, and anesthesia. Similarly, an herbal formula may contain an astringent (blackberry leaf), soluble fiber (slippery elm), and an antimicrobial (barberry) for treating diarrhea, and the adverse effects of each may be mitigated while addressing several therapeutic principles. Herbal polypharmacy offers the same advantages of efficacy while using lower dosages of the individual active ingredients.

In herbal medicine, polypharmacy is befitting. There are two basic functions performed with herbal medicines: (1) elimination and detoxification and (2) health building and management. The individualized polypharmaceutical approach of herbal medicine is intuitively sensible when encountering a complex, chronic, and often recalcitrant inflammatory process, in which it is advantageous to attack several aspects of the disease process simultaneously. Herbal practitioners create many different formulas for different types of applications. The formulation is contingent on the circumstances, condition being treated, type or part of the plant used, and the characteristics of the patient. For example, in treating lupus erythematosus, one patient may be prescribed a formula designed to relieve joint inflammation and glomerulonephritis, whereas herbs against pleuritis and polyarthropathy are prescribed for another. Herbalists attempt to anticipate and manage associated problems and possible side effects of treatments proactively. The treatment concept is not simply to suppress a symptom but optimize function in a variety of systems while symptoms are resolved.

142.2 EVIDENCE-BASED APPROACH TO HERBAL MEDICINE

There are appropriately designed clinical studies that assess herbal medicinals in reputable human medical journals, which serve well as examples for veterinary researchers.[10–12] There are substantive veterinary studies in the current scientific literature to help elucidate the effects of herbal constituents mostly in dogs, rarely cats:

- A triple antibiotic ointment and an aloe vera extract gel were evaluated as to their effects on open wound healing of pad wounds in dogs. The primary difference between the two medications was noticed at 7 days when the aloe vera extract gel–treated wounds had a smaller unhealed wound area than did control wounds and wounds treated with triple antibiotic ointment (author abstract).[13]

- The effects of garlic (*Allium sativum* L., Liliaceae) dialysate were studied on arrhythmias induced in anesthetized dogs. Garlic dialysate suppressed premature ventricular contractions and ventricular tachycardia in ouabain-intoxicated dogs (abbrev author abstract).[14]

- Effect of [3] ginger (*Zingiber officinale* Roscoe, Zingiberaceae) extracts (acetone, 50% ethanolic and aqueous) was investigated for antiemetic activity induced by 3 mg/kg cisplatin in healthy mongrel dogs. The acetone and 50% ethanolic extract at the doses of 25, 50, 100, and 200 mg/kg per os exhibited significant protection, whereas aqueous extract at these doses was ineffective against cisplatin-induced emesis (abbrev author abstract).[15]

- To determine the effect of a fraction of licorice extract, FM100, on the endogenous release of secretin and exocrine pancreatic secretion, five dogs were prepared with chronic pancreatic fistulas and gastric cannulas. Intraduodenal administration of licorice extract in three different doses (0.5, 1.0, and 2.0 g) resulted in significant increases of both plasma secretin concentrations and pancreatic bicarbonate secretion in a dose-related manner (abbrev author abstract).[16]

- A single oral dose of the lyophilized deathcap fungus *Amanita phalloides* (85 mg/kg BW) caused gastrointestinal signs of diarrhea, retching, vomiting, and death in beagles. Silibinin (milk thistle) administration (50 mg/kg) 5 and 24 hours after intoxication suppressed the serum biochemical changes and markedly reduced the hemorrhagic hepatic necrosis. All silibinin-treated dogs survived (abbrev author abstract).[17]

- Groups of greyhounds and domestic cats infested with *Ctenocephalides felis* were sprayed once with azadirachtin (neem seed extract) with or without diethyltoluamide (Deet) and/or citronella. The results show that methanolic extracts with 200, 1000, or 2400 ppm azadirachtin reduced fleas in a dose-dependent manner in fleacontaminated environments (abbrev author abstract).[18]

- Treatment with an extract of Saw Palmetto (*Serenoa repens*) for 91 days did not significantly affect the prostate gland of asymptomatic dogs, and no adverse effects were evident. Although products containing extracts of S repens are widely advertised for men with prostatic hyperplasia, beneficial or harmful effects of this plant extract were not found in dogs with prostatic hyperplasia (author conclusion).[19]

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- In an open multi-center study, the efficacy and safety of a standardized 10% tea tree oil cream (Bogaskin) applied thinly and twice daily for 4 weeks was tested in 53 dogs with chronic dermatitis, particularly nonspecific eczema, allergic dermatitis, interdigital pyoderma, acral lick dermatitis, and skinfold pyoderma. Efficacy assessed by investigating veterinarians showed a positive response ($p = 0.05$) to treatment in 82% of the dogs (abbrev author abstract).[20]

142.3 HERB TOXICITY

There are reports of medicinal herb toxicity in dogs and cats, although traditional herbal medicine is usually presented with the assumption that humans are the target species (Box 142-2). It is well to remember that herbal drugs should be given the same considerations as when using conventional human pharmaceuticals in dogs and cats. Tea tree oil should only be used topically and never as an oral medication. Comfrey, garlic, and ma huang (ephedra) have documented toxicities and should be used orally only with care and diligent monitoring.[21,22]

Cats present a particularly difficult problem with use of compounds that have not been well studied in felines. Cats have anomalous receptor responses to a number of drugs (e.g., narcotics), are particularly susceptible to phenols, have decreased UDP-glucuronyl transferase activity and increased transaminase and deaminase activities, which makes dosing even more tenuous than in dogs, and hemoglobin that is particularly susceptible to oxidation. Cats have known sensitivities to coumarins, salicylates, and essential oils (aromatherapy included). Herbs of concern in cats may include white willow, birch, garlic, chamomile, and essential oils such as tea tree, pennyroyal, thyme, and eucalyptus.

Dogs are generally more tolerant of xenobiotics but there are documented toxicities to d-limonene, hops, and pennyroyal.[23,24] These should not be used unless under the guidance of an experienced veterinary herbalist, if at all. Onions and garlic (*Allium* sp.) can cause intravascular hemolysis with Heinz bodies, hemoglobinemia, hemoglobinuria, anisocytosis, poikilocytosis, reticulocytosis, and anemia.[25–27] The most common cause of Heinz body hemolysis in dogs is related to ingestion of onions (raw, cooked, or dehydrated). The hemolytic episode may be difficult to correlate with onion ingestion because it occurs several days later.[28]

142.3.1 142.3.1 Box • 142-2 Known Herb Toxicities in Dogs and Cats[24]

Ma Huang	Dogs: CNS and CV sympathetic signs
Guarana	Dogs: caffeine signs
5-HTP (Griffonia)	Dogs: GI and CNS—serotonin syndrome
Echinacea	Dogs: GI, lethargy
Valerian	Dogs and cats: lethargy
Chamomile	Cats: GI, lethargy, epistaxis
St. John's wort	Dogs: GI, depression
Garlic	Dogs and cats: Heinz body anemia, GI
Essential oils	Dogs and cats: CNS, contact dermatitis, liver
Hops	Dogs: malignant hyperthermia

142.4 HERB-DRUG INTERACTIONS

In clinical practice, polypharmacy is not uncommon, particularly if the owner uses the services from several veterinary practices. Many medicinal herbs and conventional drugs are therapeutic at one dose and toxic at another. Interactions between herbs and drugs may increase or decrease the pharmacologic or toxicologic effects of other.[29] Underreporting of drug interactions in conventional medicine is a major problem that may be more so for herb-drug or herb-herb interactions as herbs are considered “natural and therefore harmless” by the general public. However, in several large hospital studies completed in Taiwan, Philippines, Hong Kong, United Kingdom, and by the World Health Organization Collaborating Center for International Drug Monitoring, herb-drug interactions were documented in 0.2% to 25% of cases, depending on survey design.[30]

Anesthesiologists have reported significant changes in heart rate or blood pressure in human patients taking herbal medications such as St. John's wort, gingko biloba, and ginseng. Research is ongoing to determine how certain herbals interact with certain anesthetics and in general, the findings thus far indicate that certain herbal medicines do prolong the effects of anesthesia and increase the risks of bleeding or raise blood pressure.[7] Herbal medicines significantly affect the cardiovascular system and many herbal preparations have multiple cardiovascular effects, which can be additive. In general, the dilution of active components in herbal medicines results in fewer adverse and toxic effects as compared with the active components in pharmaceuticals; however, these interactions should not be overlooked for the overall well-being of the patient.[31]

One of the best overall reviews completed to date discusses herbal-drug interactions from both the herbal and conventional medicinal perspectives using *in vivo, in vitro,* case reports, and clinical (animal and human) studies citing dosages and statistically significance when available.[32,33] Herb and drug interactions should also be researched.[34,35] The German Ministry of Health established the Commission E, a committee of doctors, pharmacists, scientists, and herbalists to evaluate the safety, quality, and efficacy of herbs. The monographs contain recommendations on dose, indications, contraindications, interactions, and mechanisms of action.[36] The chemical composition, pharmacologic action, toxicity, and therapeutic value of more than 400 herbs with correlations between Western pharmacology and the teachings of traditional Chinese medicine for pharmacologists, physicians, and toxicologists can be found in Huang.[37]

In summary, the individualized polypharmaceutical approach of herbal medicine would appear appropriate and not particularly out of the ordinary for veterinary medicine. Although, this approach does make scientific analysis more challenging, the time has come for such analysis; it will be necessary for herbs to gain greater acceptance and widespread use. A systematic analysis and clinical testing of herbal remedies is feasible. Food may serve as a worthy example. Like herbal remedies, foods are not made up of just one nutrient, and their chemical composition is highly variable for the same reasons as herbs. Foods and nutritional supplements also cannot be patented as single ingredients, but specific unique combinations thereof can be reliably produced, researched, and marketed (e.g., Cosequin).[*†] Veterinary herbalists would do well to proactively develop a standard for some therapeutic herbs, consistently produce and document reliable efficacy, and then participate in the scientific method by publishing their case results.

* NutraMax Laboratories, Inc., Edgewood, MD.

† The Veterinary Botanical Medicine Association (http://www.vbma.org) has begun this work.

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143 CHAPTER • 143 Adverse Drug Reactions

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Any harmful and undesirable phenomenon that occurs during treatment of a patient is termed an *adverse event* (AE). When drug treatment is associated with an adverse event, it is termed an *adverse drug reaction* (ADR). Although no universally accepted definition exists, most medical and veterinary authorities concur that an ADR is a reaction that is harmful and unintended and occurs at doses normally used for prophylaxis, diagnosis, or treatment of disease or the modification of physiologic function.

All drugs have the potential to result in an ADR. However, because it is frequently difficult to substantiate the cause of an adverse event, it is common to refer to an ADR as a *suspected ADR* (sADR) until a clearer picture of etiology emerges. ADRs present a continuum of clinical significance, but of greatest concern are serious ADRs described as adverse drug reactions that are fatal, life threatening, disabling, or incapacitating or which result in permanent or prolonged adverse clinical signs. Figure 143-1 provides an overview of the rational approach to investigating AEs and ADRs.

If not prevented, ADRs can result in additional treatment costs, ongoing disability, mortality, and the client's loss of trust in and diminished satisfaction with the veterinarian. To maintain the highest standards of care and to ensure that ADRs are not needlessly replicated, it is critical that sADRs be fully investigated. Reports of sADRs to manufacturers, regulatory authorities, and the profession are valuable. They help build a risk profile of the implicated drug and its class, improve the knowledge and therapeutic skills of clinicians, provide pivotal information for pharmacoepidemiologic studies, and assist in clarification of the cause.

143.1 CLASSIFICATION OF ADVERSE DRUG REACTIONS

An alphabetic approach to ADRs has been recommended.[1]

Type A (augmented) ADRs are expected but exaggerated pharmacologic or toxic responses to a drug. They may be an exaggeration of the intended response to the drug, a secondary response affecting an organ other than the target organ but predictable based on the pharmacology of the drug, or at the extreme, a toxic response.

Most ADRs of this type are attributable to differences in drug disposition that result in higher plasma and tissue drug concentrations, which arise from dysfunction of organs of metabolism and excretion, or inappropriate dosage (e.g., the administration of a non-lipid soluble drug to an obese dog with no dose adjustment). Type A ADRs are usually dose-dependent and avoidable if sufficient drug and animal information is available and considered.

Type B (bizarre) reactions are unexpected or aberrant responses that are unrelated to the drug's pharmacologic effect, are not dose dependent, and are unpredictable (idiosyncratic). Type B ADRs include allergic and pseudoallergic (nonimmunologic) reactions, direct toxic effects on organs that are associated with actions unrelated to any desired therapeutic effect (the mechanisms for which may be complex and obscure), and aberrant responses in different species.

Type C (chronic) ADRs occur during prolonged treatment programs. For example, iatrogenic Cushing's syndrome with chronic use of prednisolone.

Type D (delayed) ADRs are experienced remote from the time of treatment and therefore may be difficult to diagnose in the absence of an astute clinician and an excellent history. Second cancers developing in patients treated with alkylating agents are classical examples, as is human phocomelia after thalidomide administration.

Type E (end of treatment) ADRs occur in specific situations when drug treatment is terminated suddenly; for example, withdrawal seizures manifested on termination anticonvulsant therapy, or adrenocortical insufficiency subsequent to interruption of chronic glucorticoid treatment.

Type F (failure) ADRs occur when the expected response to treatment is not achieved. Although there are myriad examples of clinical failure, critical analysis reveals primary drug failure to be an infrequent principal cause.

Type G (gaffes) ADRs result from human error, either delayed or inaccurate diagnosis, withholding treatment, prescription of an inappropriate drug, administration of an incorrect dosage regimen, or failure to monitor the response to treatment.

143.2 INCIDENCE OF ADVERSE DRUG REACTIONS

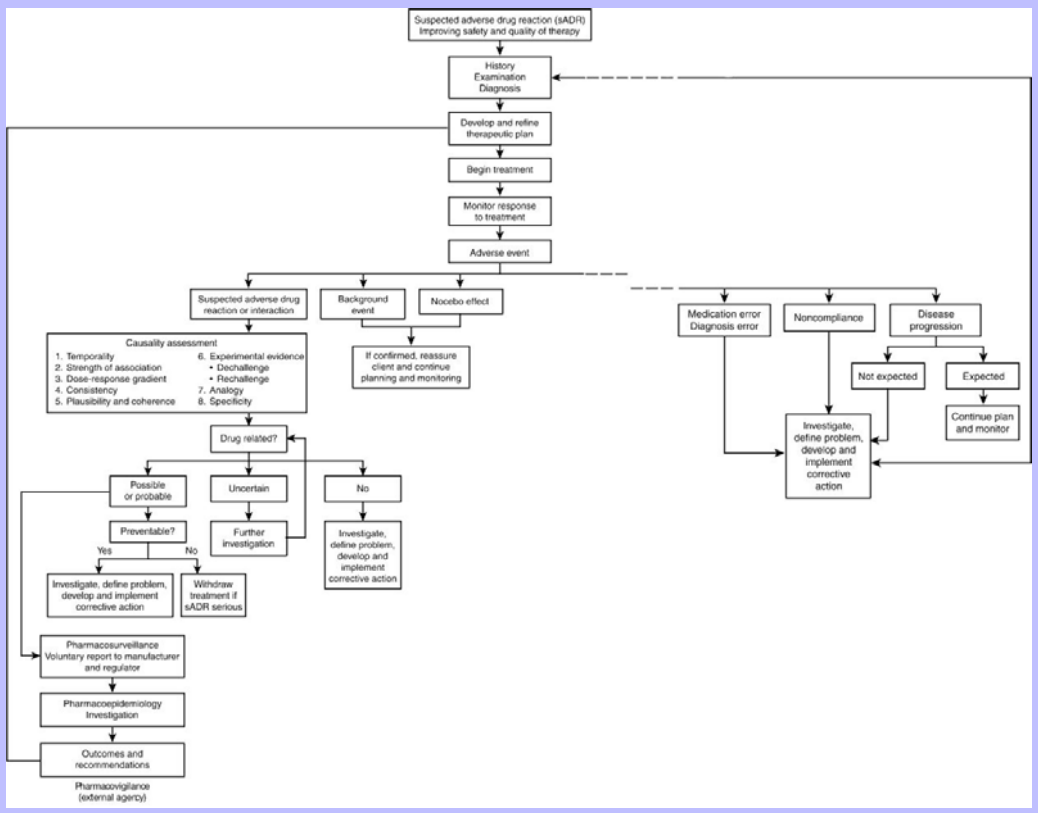
The incidence of ADRs in veterinary medicine is not well known. Studies of human ADRs provide a variety of estimates from 1.5% to 35% of patients developing an ADR while hospitalized.[2] It has been estimated that 1% of the veterinary hospital population treated with drugs experience ADRs but there are divergent opinions between clinicians about the frequency and importance of ADRs.[3] It is certain that ADR reporting rates are low within the medial community and likely substantially lower in veterinary practice.

Furthermore, the occurrence of ADRs is not homogenous throughout any population. Animals with genetic, physiologic, or pathologic predispositions have a higher likelihood of an ADR than those without. Although complacency in reporting is widespread, an examination of those factors associated with an increased rate of reporting reveals that the likelihood of reporting is related to the novelty of the reaction, severity of the reaction, limited time of suspected drug on the market, media coverage, and the litigiousness of the owner.

143.3 DIFFICULTIES IN DIAGNOSIS OF ADVERSE DRUG REACTIONS

One problem in determination of the incidence of ADRs is difficulty in diagnosis. Appropriate ADR diagnosis is heavily dependent on the expertise of the clinician and the quality of the information available. Even experienced clinicians have difficulty in determining causality, and experts disagree more than 50% of the time when assigning causality to an ADR.

Figure 143-1 Algorithm for adverse drug reactions.



The clinical signs of an ADR are almost always nonspecific and rarely pathognomonic. In humans, the most common symptoms of ADRs (e.g., nausea/vomiting, diarrhea, abdominal pain, rash, pruritis, drowsiness, headache) are also reported in 80% of healthy patients who receive no medication.[2] Placebo administration increases the percentage of patients with symptoms and the number of symptoms per patient.[2] Adverse reactions occurring in response to administration of a placebo are termed *nocebo effects* (from the Latin root that gives rise to noxious and nociception, and which translates as "I will harm").[4] During the clinical field study to substantiate the benefits of carprofen[5] and etodolac,[6] a variety of adverse reactions were reported in dogs that received the placebo formulation, including inappetence (1.6% of dogs), vomiting (2.4%), regurgitation (2.6%), lethargy (2.6%), and diarrhea/soft stools (2.4%). Of the full complement of ADRs that occurred in response to active treatment, a fraction were due to the nocebo phenomenon, and another fraction reflected the background frequency of adverse signs in the untreated population. As veterinarians are reliant on the observations of owners who are potentially subject to various conscious and subconscious influences associated with expectation, suggestion, and prior conditioning, nocebo effects are likely to contribute to reports of ADRs. Complicating ADR identification further is the possible impact of the nocebo phenomenon that influences client compliance.

Other factors that hinder the diagnosis of a true ADR include multiple medications, underlying pathology, and the assumption that the active principle of a medication is responsible for the ADR. Reactions may be due to excipients or may arise in response to degradation products formed during product storage.

143.4 IDENTIFICATION OF ADVERSE DRUG REACTIONS

The likelihood, frequency, and severity of ADRs are dependent on the interaction of drug, animal, disease, and client factors. Table 143-1 provides information that should allow the risk of ADRs to be reduced in animals with compromised renal or hepatic function. Table 143-2 identifies drugs not recommended for use in cats. Justification for selection of any drug includes the favorable ratio of anticipated benefits versus potential risks. In life-threatening situations, use of a drug with a narrow therapeutic ratio may be warranted, whereas the use of a drug with a narrow therapeutic ratio to treat trivial problems has little merit.

Accurate identification of an ADR may go undetected if the clinical signs are indistinguishable from those shared with common disease syndromes, including the disease being treated. Clinicians must always be alert to the possibility that abnormalities developed during the course of an illness may be due to the treatment rather than to the disease process itself.

Assessment of causality of an ADR can also pose a significant challenge. Figure 143-1 summarizes eight major steps in the process of attribution of cause. These steps are explained in greater detail by Maddison and Page[7] and in clinical epidemiology texts.[8,9] By application of a systematic approach, a critical, objective, and transparent conclusion can be reached, which avoids undue influence of intuition, preconception, and suggestion.

In many situations, it is not possible to judge an individual case and further information and cases must be sought. 530
The potential value of post-marketing pharmacovigilance programs conducted by many national regulatory agencies can be realized only if clinicians submit details of sADR. Important benefits include identification of preventable ADRs, discovery of trends and clusters of significant ADRs, assessment of the safety of drug regimens, measurement of ADR incidence (only if information on drug use is available), and identification of patient risk factors. Clinician-driven ADR reports potentially signal need for further investigations. 531

Table • 143-1 Examples of Drugs That Should Be Avoided or Used with Caution in Animals with Hepatic or Renal Disease

DRUG CLASS	SPECIAL CONSIDERATION IN PATIENTS WITH LIVER DISEASE	SPECIAL CONSIDERATION IN PATIENTS WITH RENAL DISEASE
Antimicrobial drugs	Chloramphenicol	Aminoglycosides*‡
	Chlortetracycline*	Amphotericin*‡
	Erythromycin estolate*	Fluoroquinolones
	Flucytosine	Lincomycin
	Griseofulvin	Naficillin
	Ketoconazole	Nalidixic acid
	Lincosamides	Nitrofurantoin
	Macrolides	Polymyxins
	Metronidazole	Sulphonamide-trimethroprim
	Sulphonamide-trimethoprim*†	Sulphonamides
	Sulphonamides	Tetracyclines (except doxycycline)
	Tetracyclines	
Anesthetics/sedatives/anticonvulsants	Anticonvulsants	Acepromazine
	Barbiturates*‡	Chlorpromazine
	Chlorpromazine	Ketamine
	Diazepam‡	Methoxyflurane*‡
	Halogenated anesthetics	Procainamide
	Ketamine	
	Lignocaine	
	Propofol	
Cardiac drugs	Beta blockers	Angiotensin-converting enzyme inhibitors
	Lignocaine	
	Quinidine	
		Cardiac glycosides
		Procainamide
Diuretics		Spironolactone
		Thiazides
Anti-inflammato-ries and analgesics	Butorphanol	Nonsteroidal anti-inflammatorydrugs*‡
	Corticosteroids	Meperidine(pethidine)
	Meclofenamic acid	Polysulfatedglycosamino-glycan
	Phenylbutazone	
	Polysulfated glycosamino-glycan	
Cytotoxic drugs	Doxorubicin	Cisplatin*
		Doxorubicin*‡
		Fluorouracil

		Methotrexate*‡
Miscellaneous	Doxapram	Allopurinol
	Heparin	Doxapram
	Suxamethonium	Gallamine
		Piperazine

* Avoid.

† Hepatoxic or hepatotoxic.

‡ Nephrotoxic.

Table • 143-2 Drugs Not Recommended for Use in Cats

DRUG	EFFECT
Acetominophen (paracetamol)	Methemoglobinemia and Heinz body anemia
Apomorphine	Significant CNS depression
Azathioprine	Bone marrow suppression
Benzocaine	Methemoglobinemia
	Laryngeal edema
Cisplatin	Fatal, acute pulmonary edema
Hexachlorophene (found in surgical scrubs, enemas)	Vomiting
	Depression
	Ataxia
	Paralysis
Permethrin	Seizures
	Hyperesthesia
	Tremor and muscle fasciculation
Primidone	Efficacy as anticonvulsant due to poor conversion to pheno-barbitone questionable and high incidence of toxicity
Propylthiouracil	Lethargy
	Weakness
	Anorexia
	Bleeding diathesis
Phenytoin	Sedation
	Ataxia
	Anorexia
	Dermal atrophy
Scopolamine	Tendency to cause behavioral changes
Sodium phosphate enemas	Depression
	Ataxia
	Vomiting
	Bloody diarrhea
Thiacetarsamide	Drug fever
	Respiratory distress
	Fulminant pulmonary edema

Greatest clinical benefit arises from focus on those signals meeting the **SNIP** criteria[10]: **S**trength of the signal (number of reports and their plausibility); **N**ew and unexpected ADRs; **I**mportance of the ADR clinically as judged by severity and seriousness; and **P**reventative potential of various interventions. At the time a new drug is first introduced, only an incomplete description of its adverse reaction profile is available due to the limited numbers of animals included in clinical studies, the short duration of most studies, and the relatively narrow population base studied. Only when used in large numbers in a heterogenous population can infrequent adverse

reactions be identified and risk factors characterized, highlighting the clinical importance of continued pharmacovigilance.

143.5 FACTORS THAT INFLUENCE TYPE A ADVERSE DRUG REACTIONS

It is important to understand the factors that modify the effects of drugs and their dosage to anticipate when a patient may be at increased risk of a Type A ADR. The potential for a Type A ADR is higher in animals with organ dysfunction (see Table 143-1), particularly renal, hepatic, or cardiac dysfunction; in very young or very old animals; in animals to whom a number of drugs are administered concurrently (potentially including all non-prescribed medications); in species for which safe use of the drug or class of drugs has not been established (see Tables 143-2 and 143-3 in relation to cats) and in obese or cachectic patients. In general, type A ADRs should be avoidable if the above factors are considered and dosage regimens are altered appropriately. The reader is referred to other sources for a more complete discussion of these factors.[3,7,11]

143.6 TYPE B ADVERSE DRUG REACTIONS (HYPERSENSITIVITY)

Type B ADRs are unrelated to dose, hard to predict, and difficult to avoid. The major example of these idiosyncratic ADRs are allergic or hypersensitivity reactions. Drug hypersensitivity reactions are more common in patients with a prior history of allergic reactions to the drug or atopic patients. However, they can occur in any individual.

Allergic drug reactions may occur as a result of a number of different immunologic mechanisms, including immediate hypersensitivity (Type I), cytotoxic hypersensitivity (Type II), immune complex formation (Type III), and delayed hypersensitivity (Type IV). However, the pathophysiology of many drug reactions eludes precise characterization and some immune reactions are a result of a combination of mechanisms.

Relatively few drugs are responsible for inducing allergic drug reactions as most drugs are not capable of covalently bonding with proteins, a requisite step to render a molecule immunogenic. The drug/drug metabolite-protein complex must have multiple antigenic combining sites to stimulate a drug-specific immune response and to elicit an allergic reaction. For those drugs that are capable of inducing an immunologic response, it is generally the metabolites of the drug that are chemically reactive and easily form covalent bonds with macromolecules.

Drug hypersensitivity may manifest in different ways. Acute anaphylaxis is associated with IgE and mast cell degranulation. It is characterized by one or all of the following clinical signs: hypotension, bronchospasm, angioedema, urticaria, erythema, pruritis, pharyngeal and/or laryngeal edema, vomiting, and colic. The main shock or target organ for anaphylactic reactions varies between species (e.g., hepatic veins are the main target in dogs and the bronchi, bronchioles, and pulmonary vein in cats).

A systemic allergic reaction may also occur associated with drug use related to deposition of immune complexes in tissues and activation of complement. Drug hypersensitivity should be considered in the differential diagnosis of any apparent immune-mediated disease, for example polyarthropathy, hemolytic anemia, and vesicular/ulcerative dermatitis.

Table • 143-3 Therapeutically Useful Drugs in Cats with Different Dose Recommendations or Side Effect Profiles Compared with Dogs

DRUG	EFFECT IN CATS COMPARED WITH DOGS
Aminoglycosides	Cats more sensitive to nephrotoxic and ototoxic effects
Amphotericin	Cats more sensitive to adverse effects including anaphylaxis
Bethanecol	Administer orally only; parenteral administration associated with life-threatening adverse reactions
Carprofen	Chronic use not safe due to long half-life Single use only
Chloramphenicol	Much lower dose than dogs; 50 mg/cat bid versus 50 mg/kg bid in dogs
Digoxin	Cats more sensitive to toxicity; reduce dose and frequency 30 g every other day for cats that weigh less than 3 kg, 30 µg every day for cats that weigh more than 6 kg
Doxorubicin	Renal failure may occur; use lower dose (25 mg/m^2)
Enrofloxacin	Acute blindness reported with (usually but not always) high dose use
Furosemide	More susceptible to dehydration and hypokalemia; use lower end of dose range
Griseofulvin	Bone marrow dyscrasia risk increased in FIV-positive cats
Ketoconazole	Anorexia and GI side effects more common
Lignocaine	Cats more commonly develop seizures with lignocaine and must be used cautiously
Megestrol acetate	Mammary hypertrophy and neoplasia Cystic endometritis and pyometra Diabetes mellitus
Naloxone	Reversal of opioids is unpredictable
Opioids	Inconsistent sedation
Morphine	Increased risk of excitation Use one tenth of dose in dogs Meperidine (pethidine), butorphanol, and buprenorphine are more predictable
Potassium bromide	Shorter half-life than in dogs (mean of 1.56 versus 5.3 weeks) Adverse effects more common in cats than dogs Coughing is common side effect
Salicylates	Aspirin has a longer half-life; dose every 72 hours Use sulphasalazine (reduce dosing frequency) and bismuth salicylate (avoid repeated use) with caution
Tetracyclines	Drug fever

Prior exposure to the drug is not essential, because hypersensitivity may develop within the course of repeated drug administration. For example, in humans, drug hypersensitivity can develop within as little as 5 to 7 days in a patient previously unexposed to the drug.

Allergic drug reactions should be managed by withdrawal from the drug and treatment with corticosteroids if needed. Adrenaline and fluid therapy may be needed to successfully manage acute anaphylactic reactions.

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144 CHAPTER • 144 Therapeutic Use of Acupuncture for Pain Control

James S. Gaynor

144.1 INTRODUCTION TO ACUPUNCTURE

Acupuncture is the stimulating of specific anatomic points in the body to produce therapeutic or analgesic effects. Clinicians most frequently perform acupuncture by using a fine-gauge needle to puncture the skin, although heat and pressure may also be used. In the last several decades, acupuncture has received increasing attention in the United States and Western Europe, resulting in training programs for physicians and veterinarians. In addition, increased research funding has allowed investigators to formulate and test hypotheses of physiologic explanations of acupuncture's actions. The results have been promising enough for the National Institutes of Health (NIH) to develop a specific office to organize funding, national research, and workshops centering on acupuncture and other complementary therapies. A recent report from NIH listed several indications for acupuncture, of which pain management was one.[1,2]

144.2 WHAT IS ACUPUNCTURE?

Acupuncture is an ancient form of diagnosing, treating, and preventing disease that recognizes and encourages the body's own healing potential. It involves the insertion of needles, or other forms of stimulation, into acupuncture points that are precisely defined loci just beneath the surface of the body. An acupuncture point can be stimulated in many ways, including dry needling, injection of fluid into the point, low-intensity or “cold” laser stimulation, and manual pressure on the point (acupressure). The effects of stimulating these points may be intensified, or the duration lengthened, by heating or electrically stimulating the needles. The effects of acupuncture may be prolonged by injection of fluid (e.g., physiologic saline or vitamin B_{12}) or implantation of gold beads into the point. Several hundred acupuncture points are recognized; most are located along acupuncture meridians, or channels, each of which have specific locations and functions. In practice, however, an acupuncturist's repertoire of points may only include a fraction of these. Characteristics of acupuncture points and of the tissues between them allow for body-wide transmission and integration of bioelectric, humoral, and nervous information.

144.3 TRADITIONAL CHINESE MEDICAL BASIS OF ACUPUNCTURE

The commonly accepted explanation for the methods of acupuncture can be traced back over 3000 years, when acupuncture became an important part of traditional Chinese medicine (TCM). With limited knowledge of anatomy or physiology, early explanations were metaphysical in nature and based upon numerology and the philosophy of Taoism. Acupuncture served to increase or decrease the flow of energy (Qi) in hypothesized lines or channels called *meridians*. Although meridians have never been demonstrated to exist, meridian theory is widely enunciated as an explanation for many of the practices of TCM.

From a TCM perspective, pain can be a result of an excess condition leading to the obstruction of the circulation of Qi and blood. Pain can also be caused by deficiency conditions, such as deficiency of Qi and blood and consumption of body fluids from *yin* deficiency. These conditions cause malnourishment of the channels and hence pain. Stagnation of Qi causes distension, with distending pain and no fixed location.[3]

The principles behind acupuncture therapy are to restore a balance in the body. Acupuncture needles placed in appropriate locations can help resolve the underlying causes. This ultimately restores Qi and blood circulation to

normal. With no obstruction, no pain is felt.[3] Although some medical professionals may find the concepts of TCM untenable, the physiologic and clinical evidence for acupuncture's usefulness makes it a viable treatment option and prevents it from being cast aside as witchcraft or voodoo.

144.4 PHYSIOLOGIC BASIS FOR THE USE OF ACUPUNCTURE

The effects of acupuncture on the central nervous system (CNS) and peripheral nervous system (PNS) include an activation of the body's endogenous multilevel pain modulatory systems, causing a release of serotonin, opioid substances, and other neurotransmitters, thereby serving to alter nociceptive processing and perception.[4,5] Although in the West, acupuncture is most widely recognized for its analgesic and musculoskeletal effects, signals generated from stimulation of acupuncture points can also affect the viscera, the immune system, and more. How these signals enter the nervous system as a result of acupuncture is well researched, with several proposed mechanisms. It is likely that a combination of all of them is responsible for what is observed clinically.

In 1976, shortly after opiate receptors were discovered in the periaqueductal gray matter, the limbic system, and the periventricular gray matter of the CNS, it was demonstrated that acupuncture analgesia could be reversed by naloxone, a pure antagonist at all known opioid receptors.[4] This led to the first awareness that acupuncture analgesia was likely mediated through a system of endogenous opioids.

Nociceptive information is transmitted in the CNS by neurotransmitters. Changes in cerebrospinal fluid (CSF) concentrations of neurotransmitters such as serotonin and biogenic amines have been shown with acupuncture.[6] Although several neurotransmitters are involved in the transmission, inhibition, and perception of nociceptive information, the opioid peptides (met-enkephalin, leu-enkephalin, beta-endorphin, and dynorphin) have been the most thoroughly studied with respect to the observed systemic and analgesic effects of acupuncture.

These opioid peptides are involved in activation of descending tracts that inhibit transmission of nociceptive information in the spinal cord.[6] In addition, no inhibition of ascending tracts that transmit nociceptive information occurs. When large unmyelinated A delta fibers, which transmit touch and pressure sensation, are stimulated by the insertion of an acupuncture needle, impulses from small unmyelinated C fibers, which transmit ascending nociceptive information, are blocked by a “gate” of inhibitory interneurons in the substantia gelatinosa of the spinal cord, which release neurotransmitters such as gamma-aminobutyric acid (GABA) and enkephalins.[6] This results in inhibition of transmission of pain impulses to the brain for conscious perception. In addition, a regional effect is seen when the A delta fibers transmit both cranially and caudally in the dorsolateral funiculus before entering the substantia gelatinosa to stimulate inhibitory interneurons.[6]

Several different lines of basic research show that some of the effects of acupuncture are at least partially mediated by substances with opiate-like activity. Substances known to block opioid biosynthesis (e.g., cyclohexamide) or action (e.g., naloxone) reduce acupuncture analgesia, whereas peptidase inhibitors such as D-amino acids (e.g., D-phenylalanine) can potentiate and prolong acupuncture analgesia, presumably by inhibiting degradation of the analgesic opioid peptides.[7] Mice deficient in opioid receptors and rats deficient in opioids show poor acupuncture analgesia.[8] Opioid levels rise in the blood and CSF and fall in specific brain regions during acupuncture analgesia.[9] In sum, part of the analgesia obtained from acupuncture involves the activation of a neurohumoral system resulting in the release of endogenous substances with opioid analgesic activity.[10] Naloxone administration does not lower baseline thresholds for pain, indicating that the analgesic effects observed are from acupuncture alone. A differential release of beta-endorphin, met-enkephalin, and dynorphin occurs in response to low-and high-frequency electroacupuncture.[11] Electroacupuncture involves the application of electricity to the needles

during stimulation of a point. Different opioid receptors mediate the analgesia produced by low-and high-frequency acupuncture. The clinical significance of this differential release is that low-frequency 533
electroacupuncture (2 to 15 Hz), which causes the release of beta-endorphin and met-enkephalin in the brain and dynorphin in the spinal cord, seems to alleviate deep and chronic pain more effectively than does higher-frequency stimulation (100 Hz), which causes release of dynorphin. In addition, the effects of acupuncture in the periaqueductal gray matter may be predominantly mediated by the enkephalins and beta-endorphin, whereas spinal cord effects are predominantly dependant upon enkephalins and dynorphin.[12] Overall it is likely that the three types of opioids act synergistically because they preferentially bind their receptors; beta-endorphin and met-enkephalin bind both mu and delta receptors, whereas dynorphin is a relatively specific kappa agonist. Because acupuncture analgesia can be largely blocked by antagonists of any of these receptors, or with the removal or blockage of any of these opioids, it is likely that they have a synergistic relationship with respect to conferring analgesia when they are simultaneously stimulated by acupuncture. The lack of decrease in observed analgesia with vascular occlusion is further evidence indicating that a nonhumoral mechanism (i.e., opioid neurotransmitter activity) is responsible for the analgesic effects of acupuncture. The mechanism may involve a change in the body's bioelectric environment leading to modulation of the endogenous pain inhibitory system via the CNS. It is now accepted that acupuncture analgesia is not just the result of the actions of endogenous opioids, even though much of the research has focused on this aspect. 534

144.5 USES FOR ACUPUNCTURE

Acupuncture has traditionally been used for virtually all of the same medical conditions for which conventional medicine has been used. These areas include (but are not limited to) pain, as well as musculoskeletal, neurologic, dermatologic, cardiovascular, respiratory, gastrointestinal (GI), urogenital, and reproductive disorders. Many of the claims of efficacy are related to anecdotal evidence and are not based on good clinical or laboratory research. There is strong evidence to support the positive effects of acupuncture on a number of problems (e.g., its ability to alleviate pain in humans and animals).

144.6 SPECIFIC TECHNIQUE FOR PROVIDING ACUPUNCTURE ANALGESIA

Multiple principles exist for choosing points to provide analgesia. One principle indicates choosing points in the affected area. Relative to limb pain, other principles describe using an opposite or contralateral limb. This may be especially useful for limbs that have been traumatized and are not accessible due to bandaging or casting. This is also important for patients with cancer-related pain. Acupuncture may be contraindicated at the sight of a tumor because needle placement may increase blood flow to the area. Another concept is to use empiric points that have been demonstrated to provide analgesia in one or more areas. An evolving principle is to use points proximal and distal to the painful area. All of these treatment principles have been combined for the protocols in Table 144-1. Low-frequency (2 to 5 Hz) electrical stimulation (EAP) is recommended when paired points are listed. For most protocols, points are paired on the same meridian, although exceptions exist. For good analgesia, electrical stimulation should last a minimum of 18 to 20 minutes. It is common for an anesthetized patient's heart rate to drop during this time, a probable indication of central endorphin release.

The acupuncture protocols in Table 144-1 are useful for multiple types of pain. Initially, patients with chronic pain will benefit from frequent treatments. For example, a patient with chronic hip dysplasia will typically be treated three times the first week, two times the second week, once the third week, and then intermittently over weeks to months to maintain comfort. Longer duration chronic pain often requires more frequent treatments early on; it is important for the client to understand that multiple treatments may be required before a significant effect is produced. It is usually recommended that clients commit to six to eight acupuncture treatments before making an assessment of its efficacy for chronic pain.

Table • 144-1 Commonly Used Points for Orthopedic Pain

AREA OF PAIN	POINTS TO BE USED
Hip pain	BL 54-BL 40: EAP
	GB 29-GB 30: EAP
	GB 34
	BL 11 bilaterally
Femoral pain	BL 54-BL 40: EAP
	GB 30-GB 34: EAP
	BL 11 bilaterally
Stifle pain	GB 33-GB 34: EAP
	LIV 8-SP 9: EAP
	Xiyan: EAP
Tibia/fibula pain	BL 40-BL 60: EAP
	ST 35-ST 41: EAP
	GB 34-GB 39: EAP
	SP 6-SP 9: EAP
	BL 11 bilaterally
Tarsal pain	BL 40-BL 62: EAP
	SP 3-SP 6: EAP
	ST 41-ST 44: EAP
	BL 60
	KI 3 (may be needled with BL 60)
	BL 11 bilaterally
Shoulder pain	TH 14-LI 15: EAP
	SI 9-SI 11: EAP
	GB 20
	GB 34
Humeral pain	TH 14-TH 5: EAP
	SI 9-SI 3: EAP
	BL 11 bilaterally
Elbow pain	TH 14-TH 3: EAP
	SI 3-SI 8: EAP
	LI 4-LI 15: EAP
	HT 3
	PC 3
	LU 5
	BL 11 bilaterally
Radius/ulna pain	SI 3-SI 9: EAP
	LI 4-LI 15: EAP
	PC 6-PC 3: EAP
	BL 11 bilaterally
Carpal pain	TH 14-TH 3: EAP
	SI 3-SI 8: EAP
	PC 8-PC 6: EAP
	LI 4-LU 7: EAP
	BL 11 bilaterally

EAP, Electrical stimulation:2–5 Hz, alternating current, continuous stimulation for 20 minutes.

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Acupuncture can be used anytime in the perioperative period for cases involving surgical procedures. Protocols may be useful as preemptive analgesia prior to surgery to help decrease the amount of anesthetics necessary and to aid in keeping the patient more comfortable upon awakening. When used postoperatively, it is ideal to provide the acupuncture while the patient is still asleep. This makes needle placement and electrical stimulation very easy without the constraints of a patient who may wake up immediately painful or in anesthetic emergence delirium.

Although electrical stimulation is not necessary, it helps enhance and ensure adequate analgesia that may last hours to days, depending upon the individual and the procedure.

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145 CHAPTER • 145 Meeting the Needs of Patient and Client Through Compassionate Care

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Cancer, diabetes, inflammatory bowel disease, osteoarthritis, cognitive dysfunction disorder; these words can be frightening to many pet owners. To our clients and to some crucial members of our veterinary health care teams, these and other terms are as dark and empty as the diseases they represent. Each day we enter our practices to diagnose, treat, and support our patients, but we often forget the emotion and feelings that surround each patient and client. These diagnoses often bring with them feelings of overwhelming fear, a spiraling sense of loss of control, and most devastating of all, the loss of hope. This loss of hope can be paralyzing for clients, for veterinary staff, and for veterinarians. This evaporation of hope and control occurs regardless of whether the patient is a human family member or a precious pet. When clients face many diseases in a beloved pet, it is sometimes even more difficult than if they themselves had these diseases. Clinicians and their clients often feel responsible for making important and life-changing decisions for animals that rely on them for their well-being. These animals not only share our homes, our lives, and our experiences but also our hearts. These "family members" extend unconditional love and attention, and they deserve proper decisions to enhance their quality and dignity of life. Our goal becomes to share as many moments as possible within this wonderful relationship that some term *the human-animal bond*, *the family-pet-veterinary bond*, or just *the bond*.

The purpose of this chapter is to reignite within the reader the very reason why most of us came to this profession: to care for our animal patients not only using our knowledge and skills but also our hearts. The information is not necessarily new, but it is often lost after days and years of busy practice life. These principals reside within every member of the veterinary health care team and are the very reason why the veterinary profession has been revered as one of compassion and caring.

145.1 DISPELLING THE MYTH (STEP 1)

It is important for veterinarians to dispel the myths[1,2] and misperceptions that surround many diseases and their treatments with honest, realistic, balanced information that translates into knowledge. Knowledge of a disease, options for care, and the likely course of the malady displaces fear, restores control, and allows for a more objective decision-making process. Indeed, in most situations, clients should be comforted that after they have considered all the information and options, there may still be no ideal decision for their pets; however, the best decision will be one that works at the particular time with the client's finances, philosophy, and goals for quality of life. The reader should note that dispelling the myths does not suggest "sugar coating" information, but it does suggest providing honest, accurate, realistic, measured, honest hope.

The most obvious example of a disease that is shrouded in myths and misperceptions is the diagnosis of cancer. Most people have an irrational fear of cancer. However, cancer is the most curable of all chronic diseases. Unjustified, ingrained fears about unrealistic cost, toxicity, and the lack of efficacy associated with care blocks many of us from even considering options for the diagnosis and treatment of cancer. Dispelling the myths associated with cancer can empower the medical team and the client to make clear rational decisions considering all the options.

145.1.1 Examples of Action Steps for Dispelling Myths

To dispel myths, clinicians can do the following:

- Lend the client a recording of an actual discussion of disease and treatment.
- Write out “bullet points” of the discussion.
- Provide preprinted information on the most common disorders and treatments.
- Give the client phone numbers of past clients who are willing to discuss the realities of care and disease.
- Provide web site information on diseases.
- Tour the hospital and introduce the staff.
- Include the client in as much patient care as law and ethics will allow.
- Ask the client to summarize information.
- Follow up treatment with a phone call.

145.2 BUILDING THE TEAM (STEP 2)

The second step in providing excellent veterinary care is to build a team[1–3] of dedicated, caring, and knowledgeable individuals who are compatible in their vision, energy, compassion, and philosophy. Every member of the staff, from the practice manager, office personnel, technicians, nurses, and other staff, should understand that they each play a role in meeting the medical needs of the animal and the nonmedical needs of the client (Figure 145-1). This “team” extends beyond the clinic or hospital to incorporate pathologists, specialists, pharmacists, social workers, and others who should be included whenever possible to maximize quality care. The veterinary health care team should strive to include the client through education and the ability to provide ongoing day-to-day care and assessment. Without input from the client, care of the pet, regardless of the underlying disease, will not be optimal.

Figure 145-1 Each member of the veterinary health care team, especially veterinary nurses, should be incorporated in the care of patients and clients. When the entire team delivers care, it is more efficient, rewarding, and complete.

Forming a team is not easy. It requires careful selection of people who have similar goals and ideals and using their unique abilities and knowledge. Selecting, rewarding, and allowing people to support each other (as well as the pet and client) are important. Building a team also requires constant education and restructuring to meet the dynamic needs and growth of the team. Finally, it requires willingness to listen, to grow, and to allow the team to improve, evolve, and excel in serving the needs of the client and the patient.

145.2.1 Examples of Action Steps for Building the Team

To build the team, clinicians can do the following:

- Hire, pay, and promote only the best, most compassionate members.
- Frequently review and revise the mission statement and goals written by the team.
- Ensure the team interviews and participates in decisions involving the hiring of new members.

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- Share and celebrate when clients or others recognize the work of the team.
- Meet at least weekly to listen to team members; value their input, feelings, and thoughts.
- Introduce nurses and receptionists to the client at the first visit. “Team” the case, and ensure each member of the team is aware of changes in the case.

145.3 DELIVER THE CARE (STEP 3)

Once the myths and misperceptions have been dissolved and a caring team is forged, the delivery of *compassionate care* can begin.[1–3] Compassionate care focuses not only on the pet in health and disease but also on the client (caregiver or “owner”) who has sought out veterinary care for the pet. Compassionate care is the outward manifestation of caring with both science and sincerity. This type of care should be operational in health and wellness, as well as in sickness and disease. Compassionate caring begins from the first moment of contact, through the process of making a diagnosis, to understanding the pathogenesis of the disease in the pet, to treatment of the condition, and finally to supporting the pet and client. After a diagnosis is made, then the real and perceived concerns should be addressed.

Delivering care can be done in several steps that can be divided into two main phases. The first phase involves providing caring support of the animal by anticipating or responding to the pet's medical needs and the client's nonmedical concerns. During this phase, the clinician should remember several things:

- Pain control is an extremely important medical priority. The use of analgesics, especially to prevent pain, will reassure the caregiver that quality of life is important. This can be in the form of oral medications (morphine, codeine, feldene, carprofen, or others), transdermal delivery systems for fentanyl, and intravenous delivery systems.
- Preventing or treating nausea, vomiting, and diarrhea is important for the pet and client. With the availability of new drugs and knowledge of the ways therapies can be administered with few adverse effects, nausea and vomiting as a result of chemotherapy can be minimized. Other chapters in this book provide details on specific medications for these problems.

- The veterinarian, client, and other members of the team often accurately perceive appetite and adequate nutritional intake as integral with quality and quantity of life. Nutrients and specific dietary profiles have been shown to be helpful for cardiac disease, diabetes, gastrointestinal (GI) disorders, renal disease, and even cancer. Basic nursing care is valuable (warming food, providing aromatic foods and comfortable environments). These animals may benefit from medicinal appetite stimulants and, when needed, assisted-feeding techniques such as esophagostomy, gastrostomy, or jejunostomy tube placement.

The second phase of delivering care involves providing direct therapy for the underlying disease. Each phase of the process of compassionate care is interdependent on the others. In addition, each client has his or her own goals for quality and length of life, as well as personal limits regarding adverse effects and cost of care.

145.3.1 Examples of Action Steps for Delivering the Care

To deliver care, clinicians can do the following:

- Avoid prejudging client desires and capabilities (review all options, regardless of cost or outcome).
- Discuss team philosophy for patient care with the client.
- Outline the steps to prevent toxicity or illness.
- Outline the procedure to follow if problems occur, including plans for weekends, nights, and holidays.
- Provide the client with information about the particular disease and its treatment (the goal should be to have clients know as much as possible).
- Anticipate and listen to client's needs, goals, and concerns.

145.4 SETTING THE GOALS FOR CURE, CONTROL, OR SUPPORT

As mentioned previously, all options should be given for each pet, regardless of the disease, from the very highest level of curative treatment, to palliative therapy, to supportive and hospice care, and finally to euthanasia. Each client should be allowed to make the choice and set goals for cure, control, or support[1–3] that are appropriate for them; clients should be made to feel that their decisions will be honored and supported by the entire team. The following are a few of the options that may be considered for each dog or cat:

- Definitive, curative intent: Cure is the goal of every client and veterinary health care team, it is often mistaken as the only goal. The success rate of curative intent is improved by determining what disease exists and by planning to achieve these curative goals while maintaining quality of life.
- Palliative care: Palliative care is treatment of a dog or cat to improve quality of life but not necessarily the length of life. For example, course fraction radiation to a site of bony metastasis is primarily designed to alleviate pain but will not cure the animal of its cancer. This is commonly done in many non-neoplastic, chronic diseases such as osteoarthritis and chronic renal failure.
- Supportive care: Little difference exists between palliative and supportive care. Both are defined as treatment to improve quality of life without necessarily lengthening life. Supportive care often implies minimizing clinical signs rather than direct treatment of a disease. Supportive care is often used in

combination with all forms of care, including palliative care. The clinician provides supportive care by administering such drugs as analgesics, antiemetics, appetite stimulants, as well as treatments for anemia and leukopenia.

- Hospice care: Hospice care is a type of supportive care; however it is usually defined as comfort or supportive care at the end of life. Hospice care, or care to maintain quality of life, especially comfort in the terminal phases of a disease, is a defined specialty in human medical care. This type of care is developing in veterinary medicine. Dignity and comfort until death, whether due to euthanasia or a natural death, may be important to many clients and veterinarians. As with palliative and supportive care, hospice care requires careful client communication. The client and the veterinary health care team need to define goals and realistic expectations. Boundaries and limits have to be set by both sides, with the intent of providing compassionate care for the patient.

- When philosophic differences exist between the veterinary health care team and the client, referral to another center may be necessary. If support groups or counselors with specific training in pet loss and bereavement exist, their expertise should be used when appropriate (usually before a moment of crisis). In addition, creating a plan for a natural death or euthanasia is important, preferably at a time when objectivity is possible.

- Euthanasia and bereavement: It is essential that the entire team handle this portion of life through adequate client preparation. An ongoing dialogue between the entire veterinary health care team and the caregivers should exist prior to (and at the time of) death and euthanasia.

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145.4.1 Examples of Action Steps for Establishing Goals

To establish goals, clinicians can do the following:

- Review all the possibilities for cure, palliation, support, terminal care, and euthanasia (include cost, time requirements, potential toxicity, and probability of success of care).

- Educate the client that care is often a cascade from palliation and support to hospice care and finally to euthanasia.

- Set milestones of time to review goals using medical information in combination with emotional support.

145.5 COST OF CARING: COMPASSION FATIGUE

Providing compassionate care requires the ability to express empathy. When we fail to express empathy, then we separate compassion from caring. It is in the action of this empathetic response that can lead to “compassion fatigue.”[4] Simply put, compassion fatigue is the depletion of resources from within as we care for others. This development is not a reflection of the character, professionalism, or even professional skill, but rather the strength and willingness to be emotionally engaged with another being that is hurting. This condition is often “diagnosed” by well-meaning individuals as another entity known as *burn out;* however, compassion fatigue is a distinct entity with unique symptoms, outcome, and treatment.

Symptoms of compassion fatigue are often nonspecific but include psychological, emotional, behavioral, work-related, and interpersonal symptoms. Mild symptoms can include lowered frustration tolerance, loss of confidence, dread of working with certain clients, subtle manipulation of clients to avoid painful or traumatic

situations, and loss of enjoyment of one's career. The more severe symptoms can result in reduced functioning in and out one's job situation.

Prevention and therapy are actually quite straightforward. The first step is to acknowledge that as caring professionals we are at risk for this condition. Compassion fatigue has struck and will strike us all. By recognizing the condition openly within each clinic and team, and by providing support and encouragement for each other, the symptoms can be more mild and recovery quicker. When we fail to recognize the condition and to support each other, compassion fatigue builds up until individuals become emotionally overwhelmed. One must take proactive steps to develop a balance between personal and professional life, as well as to establish and maintain boundaries.

145.5.1 Examples of Action Steps to Reduce or Treat Compassion Fatigue

To reduce or treat compassion fatigue, the clinician can do the following:

- Educate the entire veterinary health care team about compassion fatigue.
- Establish weekly debriefing sessions for the entire staff to discuss needs, concerns, and cases that weigh upon them.
- Form teams of professionals that look out for each other in the workplace and that identify high-risk moments for compassion fatigue.
- Identify professionals within the community who understand compassion fatigue, and notify team members regarding how to obtain access to these people.
- Establish a library for team members, with books and resources on compassion fatigue.
- Identify a sanctuary or “comfort room” where team members can be alone, meditate, relax, and debrief.
- Ensure team members are fully informed about each case and are allowed to have adequate closure at the end of any patient's life.
- Whenever possible, work out sabbatical or continuing education opportunities for reward and growth. The break from caring can be very rewarding in the long run.
- Teach all staff members the correct limits and boundaries.
- Use humor whenever appropriate.

145.6 CONCLUSION

Compassionate care is nothing new, but rather one name of a brand of caring that defines veterinary medicine. This type of care springs from our hearts and minds and is innate. Compassionate care often begins most effectively by dispelling the myths associated with each condition, disease, and treatment. Replacing myths and misperceptions with facts and reality frees the team and client to ensure the care is unfettered. Clinicians can build a “team” by hiring those who have a similar vision and goals. This includes the receptionist, the nurses, the veterinarian, and all other members of the clinic or hospital. Compassionate care is delivered by the team but is not without risk if it is truly done from the heart. Indeed, compassion fatigue is the enemy of compassionate care.

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146 CHAPTER • 146 Gene Therapy

Marilyn E. Dunn

***G**ene therapy* is defined as the introduction of new genetic and synthetic material into a living cell or organism for therapeutic purposes. In contrast to traditional therapeutics, in which a medication is administered to a patient to achieve a therapeutic response, gene therapy allows patients to "manufacture" their own treatment. Traditionally, gene therapy has been thought of as a method to treat monogenic (single gene) diseases, such as hemophilia; however, its scope has expanded to include the treatment of polygenic disorders of infectious, vascular, and neoplastic origin. New deoxyribonucleic acid (DNA) technology has been used to study the role of different genes and their products in disease. This technology has facilitated the diagnosis and treatment of these diseases by producing genetically engineered therapeutic proteins. The production of such proteins has been the basis of a number of clinical trials in both human and veterinary medicine. Although the majority of clinical trials performed to date have focused on human diseases, a growing number of trials are now being performed in veterinary medicine. Domestic animals increasingly are being recognized as ideal models for a number of human diseases.

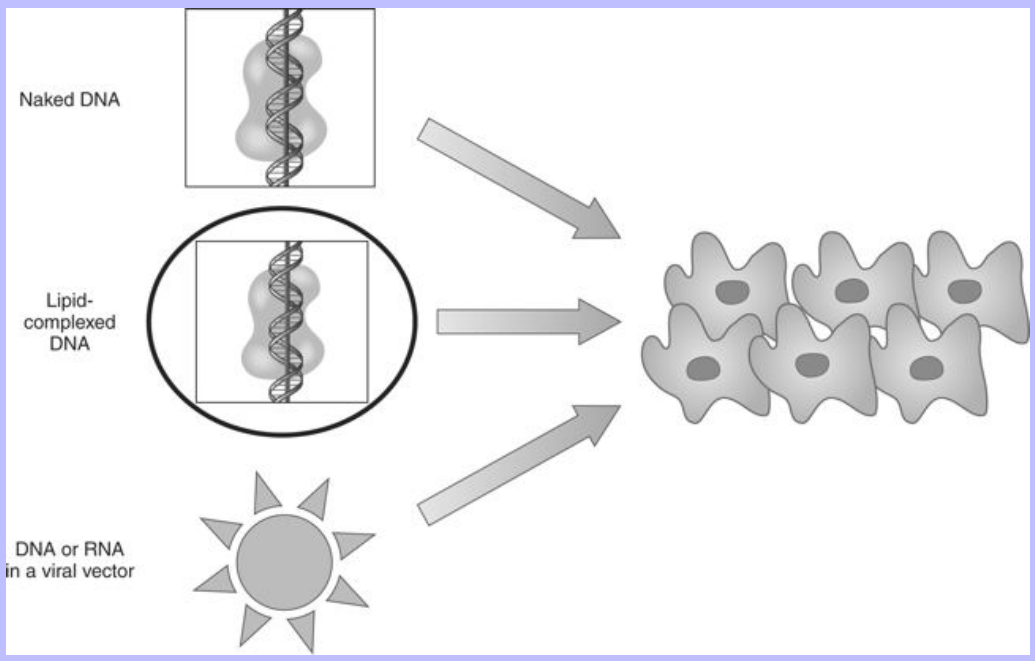
146.1 HISTORICAL BACKROUND

The term *genetic engineering* was first used in 1932 at the Sixth International Congress of Genetics and was taken to mean the application of genetic principles to plant and animal breeding. The term *gene therapy* was coined to distinguish this modality from genetic engineering. During the 1960s, the basics of molecular genetics and gene transfer in bacteria were established. In the late 1970s, recombinant DNA technology, the discovery of viral genomes, and the basics of gene transfer were established. In the early 1980s, the discovery of retroviruses led to more efficient gene transfer.[1]

In 1990 the first two approved *ex vivo* gene therapy trials in humans were performed in the United States. The first trial involved the use of gene therapy to correct for the enzymatic deficiency responsible for severe combined immunodeficiency syndrome (SCID), and the second trial involved the use of tumor necrosis factor (TNF) -transduced lymphocytes from tumors as immunotherapy for melanoma.[2] Both of these trials were unsuccessful, but they opened the door to a decade of intense research and clinical trials in the area of gene therapy.

In 1999, gene therapy suffered a major setback with the death of a young patient enrolled in a trial for a hepatic enzyme deficiency. This first death of a human patient enrolled in a gene therapy trial raised a number of ethical issues, which are still being actively debated. In 2000 the first two successful gene therapy clinical trials were reported. The first involved the successful treatment of two children suffering from SCID, also known as bubble-boy syndrome, using a retroviral vector for gene delivery.[3] The other reported the successful treatment of three hemophilia B patients using an adeno-associated viral vector for gene delivery.[4]

Figure 146-1 Methods of introducing genes into cells.



Over the past decade, research in human gene therapy has increased from two clinical trials in 1990 to 636 approved trials in 2002 involving over 4000 patients. The majority of these trials (64%) have focused on cancer research, 12% have focused on monogenic diseases, 8% on vascular diseases, and 6% on infectious diseases (primarily acquired immunodeficiency syndrome). Only 1% of the trials have thus far reached phase III.[5]

In veterinary medicine, three successful gene therapy trials have been reported: the correction of hemophilia B using an adeno-associated virus for gene delivery in five dogs; restoration of vision in three dogs afflicted with briard hereditary retinal dystrophy using an adeno-associated virus for gene delivery; and disease regression and prolonged survival in 12 dogs with malignant melanoma using cationic liposomes for gene delivery.[6]

146.2 SUCCESS FACTORS FOR GENE THERAPY

For gene therapy to be effective, the therapeutic gene must be transferred to the target cell and expressed at an appropriate level for a sufficient length of time to achieve the desired effect. The transfer and expression of the introduced gene must be safe for the cell and the animal being treated.

146.3 METHODS OF GENE TRANSFER

A gene may be transferred either by introducing it directly into a patient's cells *in vivo* (injection into a tumor) or by removing cells from the patient (e.g., bone marrow stromal cells), introducing the gene, and returning the cells to the patient (Figure 146-1). For gene transfer to occur, a vector or vehicle is required.[7]

146.3.1 Viral Systems

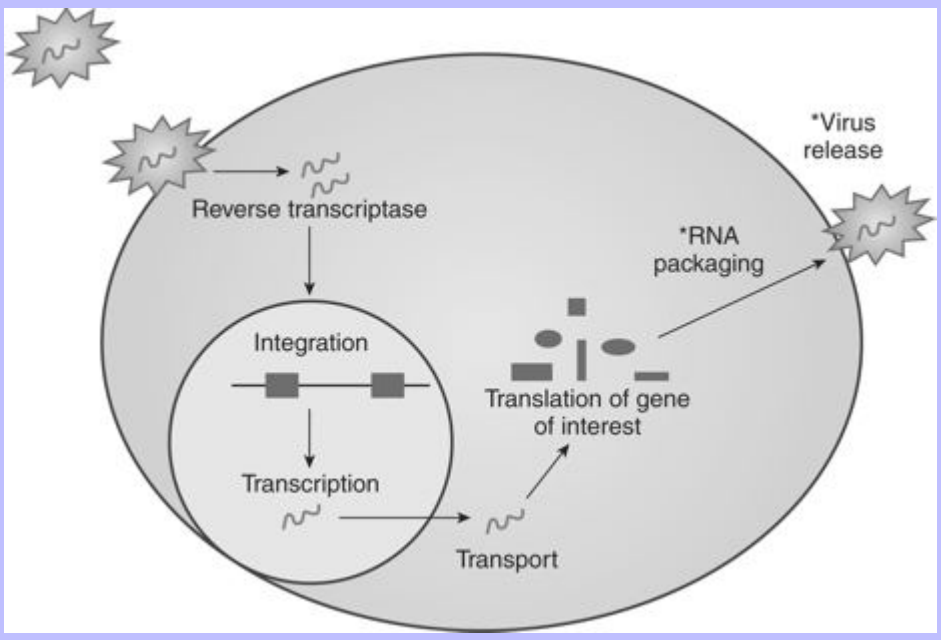
To date, the majority of gene therapy clinical trials have used viral vectors for gene transfer. Viruses have acquired biologic mechanisms over millions of years that make them ideal vectors. Viruses effectively recognize and enter cells, travel through the cytosol to the nucleus, translocate into the nucleus, and express their genes in the host cell.[8] Despite these many advantages, viruses also have a drawback: the ability to replicate within the host cell, resulting in the liberation of infectious viral particles. Because this is undesirable, viral vectors must be rendered *replication deficient* before they can be used for gene transfer. This is accomplished using molecular techniques that replace the viral gene's coding for replication with the therapeutic gene or genes of interest.[7]

146.3.1.1 Retroviral Vectors

Retroviruses are ribonucleic acid (RNA) viruses containing two copies of a single-strand RNA genome capable of integrating DNA within a host cell. Using a specific receptor, the retrovirus attaches itself to and enters a host cell. Viral RNA is then transcribed to DNA by viral reverse transcriptases and transported to the nucleus, where it integrates into the host genome. The *provirus,* or integrated viral DNA, is transcribed and translated to produce viral proteins. Some of the proteins are packaged, via a packaging signal, into viral capsids that bud from the host cell, releasing mature viruses (Figure 146-2). Retroviral vectors have been modified by substituting the gene of interest in place of certain viral protein coding regions (e.g., *gag, pol, env* regions). This substitution renders the vector replication deficient.[9]

Retroviral vectors are the most common vectors used in human gene therapy clinical trials. Their advantages include the ability to stably integrate themselves into a host, the lack of expression of viral proteins, and the ability to carry large amounts of DNA (8 kb). Their disadvantages include low titers, resulting in low levels of gene transfer; an inability to infect nondividing cells; and the risk of insertional mutagenesis.[8,10] The use of new envelopes or pseudotypes has conferred greater physical stability on retroviral vectors, allowing ultracentrifugation and the production of higher titers. Although the inability to infect nondividing cells can be perceived as a disadvantage, in cancer gene therapy, it can be quite useful. Retroviral vectors can be used to target dividing cancer cells specifically without affecting nondividing surrounding tissue. An example is the use of a retroviral vector in the treatment of brain cancer. The vector can integrate itself into the cancer cells without affecting surrounding nondividing nerve tissue.[11]

Figure 146-2 Retrovirus replication cycle. The asterisk (*) indicates elements that are absent in a retroviral vector.



146.3.1.2 Adenoviral Vectors

Adenoviruses are double-strand DNA viruses with a tropism for epithelial cells. Unlike retroviruses, which insert themselves into the host's genome, adenoviruses remain episomal or extrachromosomal. Adenoviral vectors are made replication deficient by the removal of genes in the E region. Genes of interest can then be inserted into the adenoviral vector.[9]

The advantages of adenoviral vectors are that they can infect both dividing and nondividing cells; they can be produced in high titers; and they can carry large amounts of DNA (10 kb). However, given their episomal expression, adenoviral vectors do not lead to stable integration of the host genome, which results in transient gene expression. This short-lived effect often requires multiple treatments with an adenoviral vector to maintain therapeutic gene expression. Adenoviral vectors are highly immunogenic and lead to a marked immune response, which may interfere with repeated applications. Given their tropism for epithelial cells, adenoviral vectors have been used extensively in gene therapy research for cystic fibrosis.[12] Although their short-lived effect and ability to provoke an intense immune response may be perceived as disadvantages, these characteristics may be useful in cancer gene therapy in which short-term protein expression accompanied by a marked inflammatory response is desirable.[9,10]

146.3.1.3 Adeno-Associated Viral Vectors

Adeno-associated viruses (AAVs) are small, single-strand DNA viruses that replicate only in the presence of a helper virus, such as an adenovirus or a herpes simplex virus. In the absence of a helper virus, an AAV cannot replicate but can integrate itself into the host genome. Therefore, compared with adenoviral vectors, an AAV results in more stable, prolonged gene expression. Although the process is technically difficult, AAVs can be produced in high titers; however, a major limitation to their use is their small size, which restricts their DNA carrying capacity to 4 kb.[10,13] Unlike adenoviruses, AAVs do not contain viral coding sequences and thus do not lead to immune or inflammatory responses. To produce an AAV, a helper virus is required. Contamination of the AAV preparation by a pathogenic helper virus (adenovirus or herpes simplex virus) is a concern.[13]

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146.3.2 Nonviral Systems

Nonviral methods of gene transfer are generally less efficient, resulting in low gene transfer rates. These vectors do not integrate into the host genome, and consequently the majority of DNA molecules entering the cell are rapidly degraded, resulting in only transient gene expression. These methods are best used when long-term gene expression is unnecessary, such as in cancer gene therapy in which transient immune modulation is beneficial or in vaccination with naked DNA.[7]

Nonviral vectors are desirable, because they can be produced under controlled conditions, eliminating the risk of viral contamination.

146.3.2.1 Naked DNA

Nucleic acid injected directly into a cell is taken up and expressed by the cell and thus can serve as a method of gene delivery. Short-term gene expression makes this method potentially useful for the development of nucleic acid–based vaccines in both human and veterinary medicine.[9]

146.3.2.2 DNA in Cationic Liposomes

Positively charged cationic liposomes attach to DNA, forming a lipid-DNA complex. The complex binds to the cell membrane and increases the efficiency of gene transfer. These complexes have been used to deliver genes to the lungs by aerosol[14] and by intratumoral injection.[15] Currently, receptors are being incorporated into the lipid-DNA complex to target specific tissues.

146.3.2.3 Particle-Mediated Gene Transfer

Nucleic acid is adsorbed onto gold beads, which are then shot under pressure by a “gene gun.” The DNA-coated gold beads are propelled into cells, resulting in transient gene expression. This method of gene transfer has been used *in vivo* to transfect epithelial cells, giving it a potential role in veterinary DNA vaccination.[7]

146.3.2.4 Cell-Based Delivery of Therapeutic Genes

Therapeutic genes can be delivered by *ex vivo* manipulation of cells, which are then reintroduced into a patient. Hematopoietic stem cells, mesenchymal stem cells, neuronal stem cells, and embryonic stem cells are preferred for this type of delivery because of their pluripotential capacity or ability to give rise to various cell lineages. Currently, much stem cell research is under way to select vectors that will provide efficient stem cell gene transduction, control of gene expression during lineage progression, and control of stem cell growth and differentiation *in vivo*.[8]

Stem cell research has caused considerable controversy and raised a number of ethical issues that currently are being debated.

146.4 CLINICAL APPLICATIONS OF GENE THERAPY IN VETERINARY MEDICINE

Gene therapy has been an area of intense research in human and veterinary medicine over the past 15 years. Gene therapy can be used to treat diseases as varied as monogenic diseases, cardiovascular disease, and cancer. Advancements in gene therapy have been made in a number of areas, although no U.S. Food and Drug Administration (FDA)–approved gene therapy products are commercially available.

146.4.1 Monogenic Diseases

As mentioned previously, gene therapy initially was thought of as a way to correct single-gene defects, such as are present in monogenic diseases. The first human gene therapy clinical trial was performed on a patient suffering from SCID, which is the result of an adenosine deaminase deficiency that causes the loss of T lymphocytes. In human medicine, hemophilia, cystic fibrosis, thalassemia, and hereditary retinal dystrophy (Leber amaurosis) have been investigated as targets for gene therapy. In veterinary medicine, gene therapy has been successful in the correction of briard retinopathy and hemophilia B in the dog.

Briard retinopathy and its human counterpart, Leber congenital amaurosis, both result in retinal dystrophy secondary to a single-gene mutation in the retinal pigment epithelium. This mutation causes the accumulation of toxic metabolites in the retina, leading to progressive degeneration and complete blindness. In the study, an AAV carrying the gene of interest was injected subretinally in three dogs suffering from briard retinopathy. All three dogs in this study, which were blind initially, had complete restauration of vision. Unfortunately, it was not stated in the study whether the improvement was sustained.[16]

Two canine studies have successfully shown long-term phenotypic correction of hemophilia B. The first study demonstrated partial phenotypic correction of hemophilia B in five dogs using an AAV administered by percutaneous intramuscular injection into the tibialis anterior and vastus lateralis muscles. All dogs had a marked rise in factor IX, which prevented spontaneous bleeding episodes; however, coagulation profiles were prolonged, and the dogs still bled with moderate trauma. Thirteen months after AAV administration, factor IX plasma levels were maintained.[17]

The second study demonstrated almost complete phenotypic correction of hemophilia B in three dogs after a liver-directed AAV was administered through a mesenteric vein. All dogs had resolution of bleeding episodes and correction of coagulation profiles. Seventeen months after AAV administration, factor IX plasma levels were maintained.[18]

The question is, despite these apparent successes, why are only 12% of the clinical trials being performed in human medicine focusing on monogenic diseases? One reason is the fact that monogenic disorders are less common than other diseases, such as cardiovascular disease and cancer, therefore the benefits would be felt by a smaller clinical population. Also, current vectors are more suited to cancer therapy, given the difficulty of achieving long-term gene expression.

Monogenic disease is managed differently in veterinary medicine than in human medicine in that breeding programs designed to eliminate the disease can often be accomplished. However, animals suffering from these diseases can serve as models for their human counterparts.

146.4.2 Cancer

The most popular disease target in gene therapy is cancer. Despite great advances in human and veterinary oncology, cancer remains a disease with high morbidity and mortality. This reality has fueled the search for alternative treatments, such as gene therapy.

Cancer gene therapy has six major approaches, which involve introduction of (1) a suicide gene, (2) a cytokine gene, (3) a tumor suppressor gene, (4) an antisense oncogene, or (5) a multiple drug resistance gene, and also (6) inhibition of angiogenesis (Figure 146-3).

146.4.2.1 Suicide Gene

A suicide gene is one that codes for a specific enzyme that is capable of metabolizing a substance into a toxic metabolite. In one study, a retrovirus containing a thymidine kinase gene was injected intratumorally into human patients with brain tumors. Gancyclovir, which is metabolized to a toxic metabolite by thymidine kinase, was then administered systemically. Small tumors showed partial regression, but larger tumors did not respond. Because retroviruses can infect only dividing cells, surrounding nervous tissue was unaffected.[19] It is believed that a *bystander effect* is partly responsible for some of the successes achieved with suicide gene therapy. The bystander effect is thought to be mediated by the transfer of toxic metabolites from one transduced cell to surrounding cells. The immune reaction secondary to cell death also plays a role in the bystander effect. Currently, suicide gene therapy is being investigated for the treatment of malignant melanoma in the dog.[7] One of the hurdles that must be overcome in suicide gene therapy is low tumor transduction, which often results in poor or partial responses to therapy.

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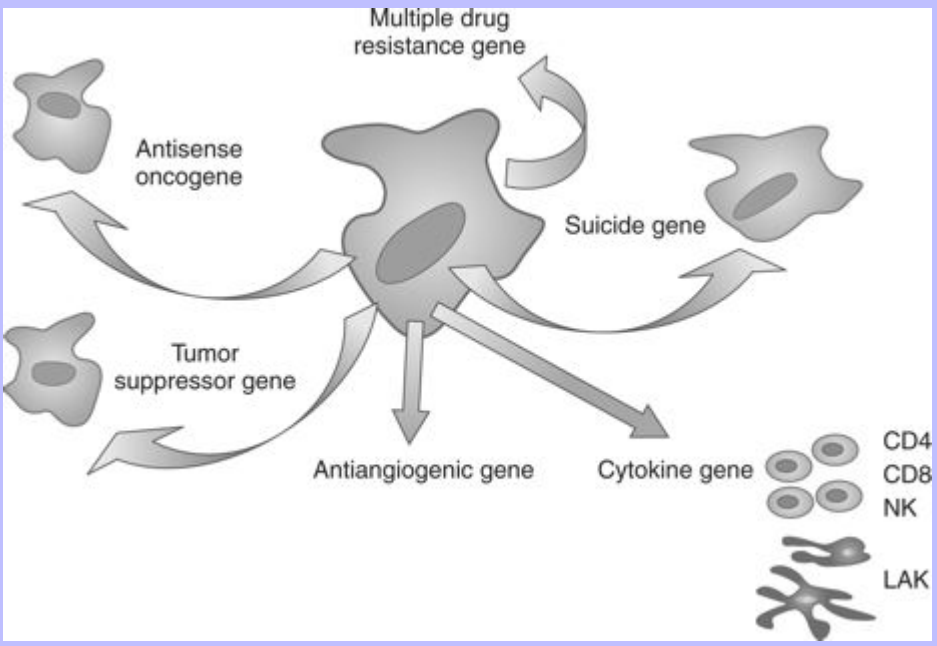
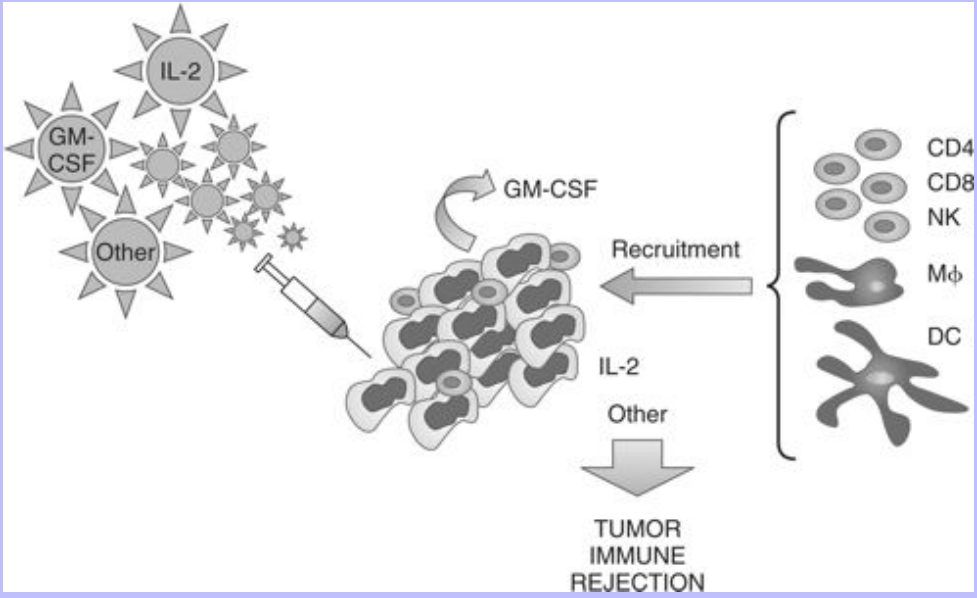
Figure 146-3 Potential targets of cancer gene therapy. *NK,* Natural killer cells; *LAK,* lymphokineactivated killer cells.



146.4.2.2 Cytokine Gene

Cytokine genes can be inserted directly into tumor cells, allowing recognition of the tumor cell and distant metastases by the immune system (Figure 146-4). This process has been referred to as *tumor vaccine*. The term *autologous tumor vaccine* refers to *ex vivo* transduction of autologous tumor cells, which are then reintroduced into the patient.[20] In one study, histoincompatible cells expressing interleukin-2 (IL-2) were introduced into animals with spontaneous canine malignant melanoma and feline fibrosarcoma. The outcome of this study was favorable in that treated animals showed improved survival compared with controls.[21] Another study evaluated the effect of intratumoral injection of lipid-complexed DNA encoding for a bacterial superantigen and either IL-2 or granulocyte-macrophage colony stimulating factor (GM-CSF) in 26 dogs with malignant melanoma. This therapy was capable of inducing both local and systemic tumor regression, with an overall response rate of 46%.[22] Another study evaluated the usefulness of an autologous tumor vaccine transfected with GM-CSF in 16 tumor-bearing dogs. Evidence of an antitumor response was seen in three dogs.[23] Despite these encouraging results, a number of other clinical trials have showed marked variability in tumor response to cytokine therapy.

Figure 146-4 Retroviral vectors coding for interleukin-2 (IL-2), granulocyte-macrophage colony stimulating hormone (GM-CSF) or other cytokines can be introduced directly into tumor cells. These tumor cells produce cytokines, resulting in recruitment of inflammatory cells that leads to immune tumor rejection. *M,* Macrophage; *DC,* dendritic cell.



146.4.2.3 Tumor Suppressor Gene

Cancer can result from mutations or deletions in the tumor suppressor gene, resulting in uncontrolled cell growth. The introduction of a tumor suppressor gene (e.g., p53 gene) into a tumor cell can prevent the cell from entering into the cell cycle, thereby leading to *apoptosis* (programmed cell death). In a human clinical trial, 28 patients with lung cancer were treated by intratumoral injection of an adenovirus containing the p53 gene. Eight percent of the patients showed a partial response, but the treatment had no effect on distant metastases.[24] The lack of vectors capable of efficient systemic gene delivery thus far has limited the usefulness of this approach.

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146.4.2.4 Antisense Oncogene

Oncogenes are genes that, when mutated or overexpressed, result in uncontrolled cell growth. Antisense oligodeoxynucleotides are short sequences of RNA that are complementary to the messenger RNA (mRNA) of an oncogene. The antisense oncogene blocks tumor RNA transcription, blocking tumor protein synthesis and thereby leading to tumor cell apoptosis. Human clinical trials, using antisense oncogenes, have demonstrated partial responses in a small number of patients. A major limitation to this approach is the inability to deliver antisense oncogenes efficiently to tumor cells.[9]

146.4.2.5 Multiple Drug Resistance Gene

Expression of the multiple drug resistance (MDR) gene decreases toxicity from certain chemotherapeutic drugs such as doxorubicin, vincristine, and actinomycine D by encoding for a transmembrane pump. Expression of the MDR gene by tumor cells is associated with resistance to chemotherapy. Human clinical trials have used this approach primarily in the treatment of leukemic patients. Healthy bone marrow hematopoietic cells are withdrawn from the patient, transduced with the MDR gene, and reinfused. The goal of this approach is to decrease hematopoietic toxicity from chemotherapy by rendering the healthy hematopoietic cells chemoresistant. Some of the difficulties encountered with this approach are poor hematopoietic cell transduction and the occurrence of nonhematopoietic toxicities with the use of high-dose chemotherapy protocols.[8]

146.4.2.6 Inhibition of Angiogenesis

In 1970, Folkman discovered that tumors produce substances that stimulate the growth of their vasculature.[25] These substances have since been identified as proangiogenic cytokines. Angiogenesis can be inhibited by blocking the production of proangiogenic cytokines. For example, the VHL gene has been shown to downregulate vascular endothelial growth factor in human renal cancer cells.[9] Angiostatin, endostatin, and interleukin-12 are known to be endogenous inhibitors of angiogenesis. Transduction of tumor cells resulting in expression of these inhibitors, has been shown to decrease tumor angiogenesis in murine models.[26]

In the future, combined approaches to cancer gene therapy may prove to be most beneficial. For example, introduction of both a suicide and a cytokine gene into tumor cells may result in a local tumor effect and a systemic immune response directed at distant metastases.

146.4.3 Other Potential Veterinary Applications

Inflammatory, infectious, and cardiovascular diseases are areas in which much gene therapy research currently is under way. Inflammatory conditions such as osteoarthritis and rheumatoid arthritis, which are influenced by the aberrant expression of certain inflammatory cytokines, have been targets of such research.[27] Gene therapy approaches have also been applied to certain infectious diseases, in particular that caused by the human immunodeficiency virus (HIV). One such approach is the transfer of antiviral genes to hematopoietic stem cells to ensure a renewable source of HIV-protected cells to the patient.[28] If successful, these approaches could be used in the treatment of cats infected with feline immunodeficiency virus (FIV).

The usefulness of gene therapy in the treatment of cardiovascular disease in humans has recently been investigated. Attempts are being made to develop vectors that can efficiently deliver genes into the myocardium to treat myocardial infarction and into the vasculature to treat atherosclerosis. These therapies could be used in veterinary medicine to treat patients with myocardial disease.[8]

146.5 CONCLUSION

Gene therapy is a relatively new area of research that has yielded a multitude of research protocols but thus far has resulted in few clinically applicable treatments. Gene therapy success has been limited by difficulties in delivering genes safely and efficiently to target cells. In the future, advances in vector design may help overcome some of the

hurdles currently encountered. Other issues, such as the risk of insertional mutagenesis and the production of replication-competent viruses, as well as ethical concerns, also need to be addressed.

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147 CHAPTER • 147 Constant Rate Infusions

Nishi Dhupa

A constant rate infusion (CRI) is a precisely calculated amount of drug added to a specific volume and type of diluent fluid, delivered as a continual IV infusion for the duration of the treatment period. The intent of drug therapy is to produce the desired pharmacologic response while avoiding adverse drug reactions. Drugs with very short half-lives, such as dobutamine or epinephrine (less than 2 minutes) and nitroprusside (0.4 minutes), must be administered by CRI to maintain steady-state serum concentrations and achieve desired pharmacologic effects. Other drugs such as furosemide may be delivered by CRI to increase efficacy and to reduce total daily dose.

147.1 PHARMACOKINETICS

The drug half-life is defined as the time it takes for the blood concentration of the drug to diminish by 50% and is a function of both clearance and volume of distribution. The half-life predicts how long it takes for a drug-dosing regimen to achieve steady-state serum concentrations. With initiation of therapy, if a loading dose is not administered to provide “instantly” a desired serum drug concentration, four to five half-lives will elapse before the patient reaches steady-state drug concentrations. For drugs with very short half-lives (less than 2 minutes), loading doses may not be required. Many cardiac and vasoactive drugs fall into this category. When delivered by CRI, immediate hemodynamic improvement can be achieved and the dose can be titrated to achieve desired effects.

147.2 PHARMACEUTICAL DRUG INTERACTIONS

The safe use of parenteral drugs depends on the drug's pharmaceutical integrity, including stability and compatibility. Pharmaceutical drug interactions occur before a drug is administered to the patient *(in vitro)*. These interactions occur primarily because of a drug's physical incompatibility with another drug or fluid solution (acid-base interactions or affinity to charged particles in another solution) or the drug's container (including intravenous tubing). Drug solutions are formulated to ensure their chemical stability; mixing drugs with different preservatives, vehicles, and buffers compromises this stability. These concerns apply most to the veterinary critical care environment, where multiple drug administration is common. Drug incompatibilities can change the chemical or physical nature of the drug and can influence efficacy and toxicity. Although many unstable solutions do not show obvious changes, any change in solution color (or the development of cloudy precipitates) should halt administration and elicit inquiry. Some color changes, such as a pink discoloration of dobutamine solutions, may not affect potency if used within 24 hours; conversely a violet or pink dopamine solution indicates inactivation.

The stability of a drug in fluids is related to an optimal pH and therefore diluent solutions must be chosen carefully. Saline solutions have a pH of 5 to 6, and 5% dextrose solutions have a pH of 5. These may be used as diluents for drugs that are weak bases (formulated as salts of hydrochloric acid) and must be kept in acidic state to maintain their stability in aqueous solution. Examples of these drugs include dopamine, dobutamine, epinephrine, and isoproterenol; they are incompatible in alkaline solutions. Questions regarding the stability of drugs and interactions between drugs in solution can be answered by reading the package insert of each drug and various excellent publications.[1]

The adsorption of drugs to plastic or glass surfaces may result in variable dose delivery. Highly lipid-soluble drugs such as diazepam will lose a significant amount of potency when administered through plastic infusion tubing at slow flow rates. Regular insulin (used as a CRI for treatment of diabetic ketoacidosis) binds to glassware and

many plastics. This binding process can be saturated, and the flushing of intravenous lines with a sufficient volume (50 mL) of the drug in solution prior to administration will result in more accurate dosing. Drugs such as nitroprusside, which manufacturers package in brown containers, may be sensitive to light. Care should be taken to provide protection from ultraviolet (UV) light during infusion.

147.2.1 Specific Drugs

A list of drugs administered as CRI in small animal veterinary medicine is presented in Table 147-1. The most common CRI drugs are positive inotropes (dobutamine, dopamine), pressor agents (epinephrine, norepinephrine), vasodilators (nitroprusside), and antiarrhythmics (lidocaine, procainamide).

147.2.2 Dose Calculation and Constant Rate Infusion Preparation

CRI doses must be calculated carefully. In general, doses for most CRI drugs are expressed as *micrograms per kilogram of body weight per minute*, but the drugs themselves are available in concentrations of *milligrams per milliliter*. Therefore dose calculations must convert from micrograms (μg) to milligrams (mg) to ascertain the volume of drug required. The objective is to determine how much drug to add to a specific volume of diluent fluid to achieve the required dose: *μg × kg × min = μg of drug to be added to a known volume of diluent fluid.* In this formula, the microgram (μg) dose and the body weight (kg) of the patient is known; the number of minutes that each bag of intravenous fluid will last is calculated by dividing the volume in the fluid bag by the fluid administration rate per hour; then multiplying this by 60 to determine the number of minutes. The formula can then be solved to provide the total number of micrograms required for addition to the fluid bag; this can be divided by 1000 to convert the dose to milligrams. With a known concentration of drug (mg/mL), the required volume can be added to the diluent intravenous fluid bag. For precise dosing, the equivalent volume of diluent fluid should be discarded prior to addition of drug to the diluent solution.

Note: For infusions lasting exactly 1000 minutes (e.g., 250 mL fluid bag infused at 15 mL/hour or 500 mL infused at 30 mL/hour), a simpler formula may be used: *μg × kg = mg of drug required.* 544 545

Example 1: The clinician must calculate a dobutamine CRI in 0.9% saline at 10 μg/kg/minute for a 20 kg dog in septic shock. Using the previous formula (μg × kg = mg of drug required) the clinician would add 200 mg of dobutamine to 250 mL of saline, to infuse at 15 mL/hour. The concentration of dobutamine is 12.5 mg/mL; therefore 16 mL of dobutamine will be added to 234 mL of saline (16 mL removed prior to addition of the drug).

Table • 147-1 Drugs Administered Via Constant Rate Infusions*

DRUG NAME AND FORMULATION	ACTIONS AND INDICATIONS	CONSTANT RATE INFUSION (CRI) DOSE	RECOMMENDED DILUENT (D) AND INCOMPATIBILITIES (I)	COMMENTS
Atracurium besylate 10 mg/mL	Competitive neuromuscular blockade; induction of respiratory muscle paralysis during mechanical ventilation	LD: 0.2–0.5 mg/kg IV (dog and cat) CRI: 3–9 µg/kg/min (dog) 0.37 µg/kg/min (cat)	D: 5% Dextrose, 0.9% NaCl I: should not be mixed with other Drugs	Infusion started 5 min. after loading dose; respiratory and cardiovascular monitoring should be provided
Butorphanol 10 mg/mL	Synthetic opiate; analgesia +/−sedation	LD: 0.2 mg/kg CRI: 0.1 mg/kg/hr	D: Any IV fluid I: Diazepam, pentobarbital	Partial agonist
Calcium gluconate 100 mg/mL	Treatment of hypocalcemia, hyperkalemic dysrhythmias, hypermagnesemia	CRI: 10 mg/kg/hr	D: Any IV fluid I: Dobutamine, sodium bicar-bonate, potassium phosphate	ECG should be monitored; CRI should be discontinued if bradycardia develops
Cimetidine 300 mg/2 mL	H_2 receptor antagonist; used in treatment of gastric ulceration, metabolic alkalosis	LD: 2.5 mg/kg CRI: 0.5 mg/kg/hr	D: Any IV fluid I: Pentobarbital, atropine	Too rapid an infusion or use of a central vein may cause hypotension and arrhythmias
Cisplatin 1 mg/mL	Cell cycle nonspecific antineoplastic agent; used for various neoplasms	CRI: 60–70 mg/m^2 over 2–6 hours	D: 0.9% NaCl I: Metoclopramide	Should not be used in cats; saline diuresis should be provided to avoid nephrotoxicity
Diazepam 5 mg/mL	Enhances effects of GABA in the brain; anticonvulsant, sedative, and skeletal muscle relaxant effects (tetanus)	LD: 5–10 mg CRI: 0.1–0.5 mg/kg/hr; increase to effect	D: 5% Dextrose, 0.9% NaCl I: Many drugs†; cloudiness in admixture indicates precipitation and reduced potency	Adsorbs to plastic IV tubing resulting in unreliable dosing; does not adsorb to plastic syringes; should be protected from light; new infusion should be started every 4 hours
Diltiazem 5 mg/mL	Calcium channel blocker, negative inotropic and chronotropic effect; used in hypertrophic cardiomyopathy and supraventricular tachycardias	LD: 0.2–0.4 mg/kg CRI: 0.2–0.5 mg/kg/hr or 5–20 µg/kg/min consulted) to effect	D: Any IV fluid I: None listed (drug insert should be	Loading dose is not always used
Dobutamine 12.5 mg/mL (250 mg/20 mL vial)	Synthetic catecholamines; positive inotrope via beta effect; useful in cardiogenic or septic shock to treat decreased cardiac contractility	2–20 µg/kg/min (dog) 1–15 µg/kg/min (cat)	D: 5% Dextrose or 0.9% NaCl I: Alkaline solutions, sodium bicarbonate; mixing with other drugs should be avoided†	Pink discoloration occurs with slight oxidation, but no loss of potency if used within 24 hours; may cause focal facial seizures in cats

Dopamine 40 mg/mL (200 mg/5 mL)	Low dose: Dopaminergic at low dose; improves renal blood flow; may play a role in treatment of oliguric renal failure	2–5 µg/kg/min	5% Dextrose or 0.9% NaCl I: Sodium bicarbonate or alkalinizing solutions	Do not use if solution has a pink or violet color; stable in fluids for 24–48 hours; extravasation may cause necrosis; should be treated locally with 5–10 mg phentolamine in 10–15 mL saline
	Moderate dose: Beta agonist and positive inotrope at moderate dose	5–10 µg/kg/min		
	High dose: Pressor agent at high dose; increases blood pressure	7–20 µg/kg/min		
Epinephrine 1:1000 (1 mg/mL)	Alpha and beta agonist, positive inotrope and chronotrope; used in cardiac arrest, hypotension, severe asthma, and anaphylaxis	0.1–1.5 µg/kg/min to effect	D: 5% Dextrose or 0.9% NaCl I: Alkaline solutions; calcium-containing solutions	Solution should be protected from light
Esmolol 10 mg/mL	Short-acting beta-1 (cardioselective) blocker; used in tachycardia or hypertension	LD: 500 µg/kg (over 1 min) CRI: 25–200 µg/kg/min	D: 5% Dextrose, 0.9% NaCl I: Sodium bicarbonate	Concurrent use of calcium channel blockers should be avoided
Ethanol 100% (1000 mg/mL)	Treatment of ethylene glycol toxicity	LD: 0.6 g/kg CRI: 100 mg/kg/hr	D: 0.9% NaCl to a 7% solution I: None listed	7% solution is prepared by adding 7 mL 100% ethanol to 93 mL NaCl
Fentanyl citrate 0.05 mg/mL (50 µg/mL)	Narcotic analgesic; synthetic opioid; used for analgesia and sedation; may be used to facilitate mechanical ventilation	LD: 10–20 µg/kg IV (dog) CRI: 0.3–0.7 µg/kg/min (dog) LD: 2 µg/kg (cat) CRI: 0.1–0.3 µg/kg/min (cat)	D: 5% Dextrose I: Mixing with other drugs should be avoided	Alternative dose: 1–5 µg/kg/hr
Furosemide 50 mg/mL	Loop diuretic; promotes diuresis in oliguric renal failure, treats pulmonary edema in CHF, promotes calciuria in hypercalcemia	3–8 µg/kg/min or 0.1–1 mg/kg/hr to effect	D: Any IV fluid I: Acidic solutions; precipitates when combined with many drugs[†]	Should be protected from light
Heparin 1000 U/mL	Activates antithrombin III, prevents thrombin and fibrin formation; used in DIC and throm-boembolic disease	LD: 100–300 U/kg CRI: 10–50 U/kg/hr (dog) 5–10 U/kg/hr (cat)	D: Any IV fluid I: Any drugs that are unstable in an acidic environment[†]	Adjust dose based on activated partial thromboplastin time; clinician should aim for increase of 1.5–2.5 times original rate

Hetastarch 6 g/100 mL	Synthetic colloid; used for its oncotic properties and as a volume expander	1–2 mL/kg/hr	Available as a 6% solution in 0.9% NaCl	Should not be used if brown in color or precipitate present
Hydrocortisone sodium phosphate 100, 250, or 500 mg vials	Treatment of addisonian crisis and of adrenal insufficiency induced after adrenalectomy	0.625 mg/kg/hr	D: Any IV fluid; should be diluted to 0.1–1.0 mg/mL I: Mixing with other drugs should be avoided†	Proper dilution volume should be used to avoid precipitation; should not be administered if discolored
Insulin (regular) 100 U/mL	Lowers blood glucose, used in diabetic ketoaci-dotic patients and for adjunctive treatment of hyperkalemia	1.1–2.2 U/kg/day (use lower doses for cats)	D: 0.9% NaCl I: Sodium bicarbonate; mixing with other drugs should be avoided†	Binds to IV tubing; tubing should be flushed with insulin solution prior to IV infusion
Isoproterenol 0.2 mg/mL (1 mg/5 mL)	Beta-adrenergic agonist, causes positive inotropy and chronotropy; also vasodilator and bronchodilator; used in advanced heart block	0.02–0.1 µg/kg/min	D: 5% Dextrose or 0.9% NaCl; dilute to 1 mg in 500 mL (1:500,000 solution) I: Sodium bicarbonate	Causes peripheral vasodilation
Ketamine 100 mg/mL	Neuroleptanalgesia; may be used as an adjunct to opioid therapy to ease severe pain	1–3 µg/kg/min; clinician should prepare a 1–2 mg/mL solution (500 mg added to 500 mL)	D: 5% Dextrose or 0.9% NaCl I: Diazepam, barbiturates	Should be used with opioid or tranquilizers
Lidocaine 20 mg/mL (2%)	Class IB ventricular antiarrhythmic	LD: 2–4 mg/kg (dog) CRI: 50–100 µg/kg/min (dog) LD: 0.25–0.75 mg/kg (cat) CRI: 10–20 µg/kg/min (cat)	D: 5% Dextrose; 0.9% saline less preferred I: Alkaline solutions; mixing with other drugs should be avoided†	Adsorption to polyvinyl chloride bags; stable in IV fluids for 24 hours; cats are very sensitive to the drug (may seizure)
Magnesium sulfate (parenteral) 4.06 mEq/mL 50% (500 mg/mL)	Used as a source of magnesium in hypomagnesemia and refractory hypokalemia	Up to 1 mEq/kg/day	D: 5% Dextrose diluted to <20% I: Many drugs,† including those containing calcium, vitamin B complex, sodium bicarbonate	Use with caution with impaired renal function; overdose causes bradycardia, muscle weakness; treat with calcium
Mannitol 25% (250 mg/mL)	Osmotic diuretic; free radical scavenger; has a role in treatment of oliguric renal failure, glaucoma, cerebral edema	0.5–1 g/kg/hr for 2–6 hr	D: 5% Dextrose to 8% -10% solution I: Blood, strongly acidic or alkaline solutions; mixing with other drugs should be avoided	Clinician should warm to remove crystallization of high (25%) concentrations; easier in glass containers than plastic

Methylprednisolone sodium succinate 40 mg/mL	Treatment of head/spinal cord trauma	LD: 30 mg/kg followed by 15 mg/kg at 2 and 4 hrs CRI: 2.5 mg/kg/hr for 42 hours reducing dose gradually	D: 5% Dextrose or 0.9% NaCl I: Normosol-R, Normosol-M, selected drugs†	Precipitation may occur if dilution is too small; reconstituted solution should be used within 48 hours
Metoclopramide 5 mg/mL	Antiemetic; gastrointestinal (GI) stimulant	1–2 mg/kg/day or 0.7–1.4 µg/kg/min or 0.01–0.02 mg/kg/hr (dog) and 0.01 mg/kg/hr (cat)	D: Any IV fluid without calcium I: Sodium bicarbonate; mixing with other drugs should be avoided†	Should be protected from light
Midazolam 5 mg/mL	Anticonvulsant, sedative; similar to diazepam	LD: 0.1 mg/kg (dog) CRI: 0.35 µg/kg/min (dog)	D: 5% Dextrose, 0.9% NaCl I: Mixing with other drugs should be avoided	Does not adsorb to plastics and therefore can be dosed more reliably than diazepam
Morphine 15 mg/mL	Opiate agonist; used in treatment of acute pain	LD: 1–10 mg/hr CRI: 0.01–0.1 mg/kg/hr	D: 5% Dextrose; should be diluted to 0.1–1 mg/mL I: Mixing with other drugs should be avoided†	Lower dose should be used in cats; cats may show CNS excitability
Norepinephrine 1 mg/mL	Potent adrenergic vasopressor; used for short-term blood pressure support	0.05–1.0 µg/kg/min to effect	D: 5% Dextrose or 0.9% NaCl I: Mixing with other drugs should be avoided	Initial systolic pressure should not be raised by >40 mm Hg; extravasation should be treated with phentolamine
Nitroprusside 200 µg/mL	Venous and arterial vasodilator; used in acute, congestive heart failure to treat fulminant pulmonary edema or systemic hypertension	0.5–10 µg/kg/min (dog) 0.1–0.3 µg/kg/min (cat); clinician should start low and increase slowly; BP should be monitored	D: 5% Dextrose; must use with infusion pump only I: Mixing with other drugs should be avoided†	Should be used with extreme caution; over-dose results in cyanide toxicity; should not be used in oliguric patients; solution must be shielded from light
Oxytocin 20 U/mL	Used for enhancement of uterine contractions at parturition	5–10 U over 30 min (dog) 2–5 U over 30 min (cat)	D: 5% Dextrose or 0.9% NaCl I: Mixing with other drugs should be avoided†	Should be used when cervix is open; normal glucose and calcium levels should be ensured first
Pancuronium 1 mg/mL	Neuromuscular blockade as an adjunct to anesthesia or mechanical ventilation	LD: 0.04–0.1 mg/kg CRI: 0.06–0.1 mg/kg/hr	D: 5% Dextrose or 0.9% NaCl, by syringe pump I: Drug insert should be consulted	Cardiovascular and respiratory monitoring must be used
Pentobarbitol 65 mg/mL	GABA-mimetic; used as an anticonvulsant and for chemical restraint during mechanical ventilation	LD: 3–30 mg/kg to effect CRI: 0.2–1 mg/kg/hr	D: 5% Dextrose or 0.9% NaCl I: Mixing with other drugs should be avoided†	Respiratory activity should be monitored; ventilatory support may be required

Phenylephrine 100 mg/mL	Causes vaso-constriction via alpha-adrenergic effects; used to treat hypotension under anesthesia	1–3 µg/kg/min	D: 5% Dextrose or 0.9% NaCl I: Sodium bicarbonate	Extravasation injuries must be treated with phentolamine locally
Potassium chloride 2 mEq/mL	Used to treat serum potassium deficits	In IV fluids: 28–80 mEq/L	D: Any IV fluid I: Diazepam	IV administration should not exceed 0.5 mEq/kg/hr
Potassium phosphate 3 mM/mL phosphorous, 4.4 mEq/mL potassium	Used in correction of hypophosphatemia	0.01–0.03 mM/kg/hr for 6 hr or 0.03–0.12 mM/kg/hr for DKA patients	D: 0.9% NaCl I: Dobutamine, lactated Ringer's solution	50%-75% of potassium supplied using KCl, the rest as KPO4; phospho-rous levels checked every 12 hours in DKA patients, until >2.5 mg/dl
Procainamide 100 or 500 mg/mL	Class IA antiarrhythmics; used in treatment of ventricular arrhythmias	LD: 2–20 mg/kg over 5 min (dog) CRI: 20–50 µg/kg/min LD: 1–2 mg/kg (cat) CRI: 10–20 µg/kg/min (cat)	D: 0.9% NaCl I: Decomposes if admixed with dextrose	Light yellow (but not amber) discoloration does not affect potency; should not be used if dark yellow; stable in fluids for 24 hours
Propofol 10 mg/mL	Short-acting hypnotic	0.05–0.2 mg/kg/min	D: 5% Dextrose I: Should not be mixed with other drugs	Propofol supports bacterial growth; should be used as strict asepsis
Sodium bicarbonate 1 mEq/mL	An alkalinizing agent; used to treat metabolic acidosis; adjunctive therapy in hyperkalemic crises	50% of calculated dose (based on deficit) IV over 4–6 hours	D: 5% Dextrose or 0.9% NaCl I: Mixing with other drugs should be avoided†	Deficit calculation: 0.3 × kg body weight × base deficit
Verapamil 2.5 mg/mL	Calcium channel blocker; used for supraventricular tachyarrhythmias	LD: 0.05–0.15 mg/kg CRI: 2–10 µg/kg/min	D: 5% Dextrose or 0.9% NaCl I: Mixing with other drugs should be avoided	Loading dose not always used
Vitamin B complex (injectable)	Provides B complex supplementation	2–4 mL/L at maintenance fluid rate	D: Any IV fluid I: Sodium bicarbonate	Compatible with IV fluid and TPN solutions

IV, Intravenous; *LD*, loading dose; *CRI*, constant rate infusion; *TPN*, total parenteral nutrition; *GABA*, gamma aminobutyric acid; *CHF*, congestive heart failure; *DIC*, disseminated intravascular coagulation; *BP*, blood pressure; *mM*, millimoles.

* Data compiled from references listed.

† See package insert for details.

Example 2: The clinician must calculate a lidocaine CRI at 60 µg/kg/minute for a 40 kg dog with ventricular tachycardia. The lidocaine will be added to the maintenance fluids, Normosol R in 500 mL bags, running at a rate of 100 mL/hour. To solve this, the clinician would use this formula: µg × kg × minute = µg of drug to be added to a known volume of diluent fluid.

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To calculate number of minutes each bag will last:

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500 mL at 100 mL/hour = 5 hours
5 hours × 60 minutes/hour = 300 minutes

To solve the equation:

60 µg (required dose) × 40 kg × 300 minutes = 720,000 µg

To convert µg to mg:

720,000 µg/1000 = 720 mg

To calculate the amount of drug needed per 1000 mL bag, the clinician should divide the amount of drug needed by the concentration of drug being used (in this case, 2% lidocaine or 20 mg/mL):

720 mg/20 mg/mL = 36 mL of lidocaine

Note: 36 mL of Normosol R should be removed from the 1000 mL bag prior to the addition of 36 mL of 2% lidocaine.

Drug manufacturers provide specific diluent recommendations based on drug trials providing stability information. Drugs should be added to small volumes of diluent (usually 60, 100, or 250 mL) and administered separately from the patient's maintenance needs to allow for dose titration, through changes in CRI volume, without affecting the patient's other fluid dose. CRI solutions should always be labeled with the amount of drug added, the date, and the volume of diluent. Solutions should be changed every 24 hours. Drug admixtures should be avoided; when necessary, specific package insert and other recommendations should be consulted.

147.2.3 Drug Delivery Systems

The accurate delivery of parenteral drugs is dependent on the use of sophisticated infusion device technology. The traditional gravity delivery systems (using in-line drip chambers) have been shown to have wide variations in the accuracy of delivery due to factors such as length and diameter of infusion set tubing, distance from the patient, and resistance to flow. These devices are acceptable for intravenous fluid therapy but are not advised for the provision of minute doses of vasoactive drugs. Mechanical devices such as *volumetric infusion pumps* generate positive pressure to achieve the delivery of small and precise volumes. Those that deliver fluid by continuous flow are preferred because the intermittent delivery of vasoactive drugs, particularly when at high concentrations with low flow rates, can cause adverse pharmacodynamic effects. As an example, variable delivery of epinephrine can result in blood pressure variations, whereas variable delivery of nitroprusside may cause toxicity.

Infusion pumps may be classified, according to mechanism of operation, into peristaltic systems, cassette systems, and syringe pump systems. Peristaltic systems (linear or rotary) use a motor-driven mechanism to squeeze the tubing and move fluid toward the patient (Baxter Flo-Gard 6200, Travenol Flo-Gard 6200, Sigma 6000). These systems tend to be less expensive but slightly less accurate than the cassette systems. Cassette systems (Travenol 8000 series, IMED pumps) use an administration set that contains an in-line chamber of a measured volume. Syringe pumps (Baxter 150XL, IVAC 700, Medfusion 3010A) may use motoror nonmotor-driven mechanisms to move the syringe plunger and cause fluid delivery in eithera continuous or intermittent fashion. When an infusion or syringe pump is not available, CRIs may be delivered through a burette type of administration set. This allows the infusion to be limited to a small volume (100 mL). Inherent

inaccuracies exist with this system; for drugs with narrow therapeutic-to-toxic ratios, such as nitroprusside, infusion pump use is essential.

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148 CHAPTER • 148 Hyperbaric Medicine

Jennifer J. Devey

Hyperbaric medicine is performed under conditions of greater than 1 atmosphere absolute (ATA) of pressure (Figure 148-1). A specially designed chamber is used, and variable pressures and concentrations of oxygen are delivered based on the condition being treated. In hyperbaric therapy, concentrations of oxygen greater than 21% typically are delivered. However, a recent study examined the use of pressurized air versus pressurized oxygen. Outcomes were similar between the treatment groups, suggesting that pressure, not just oxygen, may be an important factor in hyperbaric oxygen therapy.

148.1 PHYSIOLOGIC EFFECTS

The primary effect of hyperbaric oxygen is to increase the amount of oxygen dissolved in plasma. At 2 ATA and 100% oxygen concentration, the amount of dissolved oxygen in the blood is increased by up to 15 times.

In normoxic tissues, except the heart and lungs, hyperoxic conditions cause vasoconstriction, which helps reduce edema. This in turn improves oxygen delivery to tissues by reducing the barrier to gas diffusion. The decrease in cerebral blood flow also helps reduce intracranial pressure. Decreases in cerebral blood flow have not been noted to be a problem clinically until pressure is greater than 3 ATA. If the tissues are hypoxic, vasoconstriction does not occur.

In neurologic tissue, the increase in oxygen delivery also helps reduce the ischemic penumbra seen in traumatic brain injury and transient ischemic attacks. In traumatic spinal injuries, hyperbaric oxygen has been shown to decrease ischemia, edema, and lactic acidosis and to directly reverse damage associated with bruising.

Hyperbaric oxygen enhances wound healing by promoting the growth of new capillaries, enhancing fibroblast proliferation, increasing collagen formation, and increasing the rate of epithelialization.

Figure 148-1 Pressure conversion table.

1 Bar = 15 psi = 100 kPa = 0.99 atm

psi – pounds per square inch, kPa – kilopascals, atm – atmospheres

Hyperbaric oxygen has been shown to improve immune function, which is impaired in the presence of tissue hypoxia. However, above 2.5 ATA, the immune system is inhibited. Oxygen has a direct bacteriostatic and bactericidal effect that is equivalent to some antibiotics. It is effective against gram-positive and gram-negative bacteria, mycobacteria, and fungi but is most effective in treating anaerobic infections.

Free radicals are produced; phagocytosis is stimulated; and the number of lymphocytes is increased. The levels of immunoglobulin G (IgG) and immunoglobulin E (IgE) decrease, which may be of benefit in the treatment of allergic reactions.

The elasticity of red blood cells is improved and platelet aggregation is reduced, which improves rheology. Hemoglobin synthesis is upregulated after acute blood loss. Hyperbaric oxygen has been used for 25 years as a treatment when blood transfusions have not been readily available.

Hyperbaric oxygen increases the affinity of endorphins for receptor sites, improving analgesia. By improving the microcirculation and decreasing edema, it may help reduce the degree of pain the patient experiences.

Hyperbaric oxygen has been shown to enhance the sensitivity of neoplastic cells to radiation therapy as long as the tumor cells are hypoxic. It does not seem to be effective as an adjunct to radiation therapy if metastases are present. Currently there is no proof that hyperbaric oxygen therapy increases the likelihood of recurrence of the cancer.

148.1.1 **Box • 148-1 Partial List of Conditions Approved for Medicare Reimbursement That Apply to Veterinary Medicine**

Actinomycosis

Birth asphyxiation

Brown recluse spider bite

Cyanide poisoning

Carbon monoxide poisoning

Cerebral edema

Compromised skin graft flaps

Crush injury/compartment syndrome

Diabetic wounds/ulcers

Hypoxic nonhealing wounds

Exceptional blood loss anemia

Frostbite

Gas embolism

Gas gangrene

Near-drowning

Near-hanging

Necrotizing soft tissue infections

Peripheral ischemia

Radiation necrosis

Refractory osteomyelitis

Refractory mycoses

Stroke (transient ischemic attack)

Thermal burns

Traumatic brain injury

148.2 INDICATIONS IN HUMAN MEDICINE

A number of conditions have been approved for U.S. Medicare reimbursement of hyperbaric oxygen therapy. Box 148-1 presents a partial list of these conditions, those that are relevant to veterinary medicine. Based on clinical experience, research findings, and anecdotal reports in human medicine, some other conditions also may respond to hyperbaric oxygen therapy (Box 148-2).

148.3 CONTRAINDICATIONS

The only absolute contraindication for hyperbaric oxygen therapy is untreated tension pneumothorax. Veterinary patients with evidence of any kind of pneumothorax are not placed in the hyperbaric chamber unless a chest tube attached to a relief valve (i.e., Heimlich valve) has been inserted.

Some relative contraindications in human medicine are upper respiratory infections; the presence of pulmonary lesions, even if they are not symptomatic; heart failure; a history of ear or thoracic surgery; and uncontrolled high fever. High fever is a contraindication because of the increased likelihood of seizures; however, this does not appear to be a concern in veterinary medicine. In fact, febrile veterinary patients often experience a reduction in temperature in 100% hyperbaric oxygen environments as long as they are not anxious (see above). Pregnant patients should not receive hyperbaric oxygen because experimental evidence suggests an increased incidence of congenital defects. Epilepsy is not considered a contraindication, but pressure should be kept below 2 ATA.

148.3.1 Box • 148-2 Conditions That May Benefit from Hyperbaric Oxygen Therapy

Cardiac surgery postoperatively

Cranial nerve lesions

Post cardiopulmonary resuscitation

Degenerative myelopathy

Gastrointestinal ulcers

Geriatric vestibular disease

Glaucoma

Head trauma

Hepatotoxins that cause damage after oxidative transformation

Ileus

Methemoglobinemia

Myocardial contusions

Organophosphate toxicity

Osteomyelitis

Pancreatitis

Perianal fistulas

Peripheral neuropathies

Snakebite

Spinal cord injuries or ischemia

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148.4 COMPLICATIONS IN HUMAN MEDICINE

Complications primarily relate to oxygen toxicity; however, pressure-related problems, such as sinus pain, middle ear barotrauma, and pulmonary barotrauma, have been reported in human medicine. Complications related to oxygen toxicity are rare, especially if pressure does not exceed 1.5 ATA.

Oxygen-induced seizures can occur in the dog if the pressure exceeds 2.2 to 2.5 ATA. The mechanism is unknown but may relate to the presence of oxygen free radicals, inactivation of nitric oxide, alterations in gamma-aminobutyric acid (GABA), and changes in the levels of biologically active peptides. Seizures normally cease as soon as the oxygen levels drop and/or the pressure decreases. Oxygen-induced seizures are not a contraindication for further treatment; however, the pressure and time of exposure to hyperbaric oxygen should be decreased.

Oxygen-induced lung injury should not be a problem if the lung tissue has sufficient time to recover between episodes. Pulmonary dysfunction has not been noted in humans exposed to prolonged hyperbaric oxygen therapy.

148.5 COMPLICATIONS IN VETERINARY MEDICINE

The complications listed above presumably can occur in all species; however, in more than 5000 hyperbaric treatments, none of them have been observed in clinical veterinary medicine. In veterinary medicine the most common complications are hypothermia in small, sedated, or depressed patients and anxiety, sometimes accompanied by hyperthermia.

148.6 HYPERBARIC CHAMBERS

Chambers can be multiplace or monoplace. High-pressure chambers deliver oxygen concentrations of 100% and pressures up to 6 ATA. The oxygen concentration in lower pressure chambers typically is approximately 30%, and pressures reach a maximum of 1.25 ATA.

Spontaneous combustion, although rare, can occur in hyperbaric chambers that deliver 100% oxygen under pressure. Certain precautions should be taken when using 100% oxygen; electrical devices should not be permitted in the chamber; no nylon should be allowed in the chamber; and the patient must not have an oil-based product on its skin.

Portable hyperbaric chambers compress entrained room air. As a result, the temperature of the room air and the air in the hyperbaric chamber are the same. If the room air is hot, it should be cooled by running the air hose through an ice bath before it reaches the chamber. This prevents overheating of the patient.

Variable levels of oxygen can be provided to patients being treated in lower pressure hyperbaric chambers. When an oxygen source is attached to the chamber, an inspired oxygen concentration of approximately 30% is provided. Alternatively, an oxygen hood can be placed on the patient, in which case the inspired oxygen concentration may be as high as 80%.

148.7 TREATMENT PROTOCOL

Currently no consensus exists on the best regimen for hyperbaric oxygen therapy, although administration within 4 hours of injury appears to be critical in the treatment of neurologic disease. Research indicates that the effects of a single treatment last at least 6 hours.

Current human recommendations are to treat patients for 1 hour at 1.5 to 2 ATA, consisting of 10 minutes of compression, 45 minutes of treatment at the designated pressure, and 5 minutes of decompression time. The time in the chamber is doubled if infections are present.

The author's clinical experience with dogs and cats suggests that pressures of up to 1.25 ATA generally are well tolerated and appear to provide beneficial effects. Treatments last 1 hour and are performed twice daily in the acute stages of the injury or illness and then once daily after the first 3 to 5 days. The twice daily treatments are continued if the patient appears to respond better to treatments at 12-hour rather than 24-hour intervals. With chronic conditions, owners are encouraged to continue treatments two or three times weekly on an outpatient basis if clinical improvement still is noted or if there is concern that relapse will occur if treatment is discontinued.

The vast majority of patients do not object to hyperbaric oxygen therapy, as evidenced by dogs' willingness to walk voluntarily into the chambers repeatedly and by the lack of any outward signs of distress in cats. Anxious patients are provided with anxiolytics. Depending on the patient, this may include narcotics, benzodiazepines, or acepromazine. If any concern arises that the patient is not tolerating the hyperbaric oxygen, the session is discontinued.

Hyperbaric oxygen therapy should not replace approved treatments; however, cats and dogs are affected by a number of disease conditions that appear to benefit from adjunctive therapy with hyperbaric oxygen.

149 # CHAPTER • 149 Nutritional Assessment

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The purpose of nutritionally assessing a patient is to allow the clinician to answer the question, “Is intervention for this patient necessary?” and to aid the clinician in selecting the most appropriate nutritional intervention for that patient. The process involves evaluating both subjective and objective information regarding the patient and its dietary practices. In addition to aiding in the selection of a suitable diet and feeding management for the patient, it will also help the clinician to anticipate potential problems or complications and to devise strategies to avoid or monitor such developments.

149.1 ## TAKING A DIET HISTORY

The more information that is available about the patient's diet and feeding management, the better the clinician will be able to assess the adequacy of nutrient intake, the suitability of feeding practices, and the urgency for nutritional intervention. At the core of a dietary history is the careful gathering of information that will give an accurate picture of the foods that the patient consumes. Ideally the person who is most responsible for feeding the patient should be questioned; however, it is important to find out who else resides in the household or has regular contact with the patient, including other pets. The patient's caregiver should be questioned about all foods that the patient receives (Box 149-1) and asked whether the information reflects what is typical for this pet, whether changes have occurred, and if so when they happened.

In addition to particulars about the patient's diet, the history should also include information regarding appetite, documented or perceived changes in body weight or condition, level of physical activity, and occurrence of any gastrointestinal (GI) signs. Again, the patient's caregiver should be queried as to whether the information reflects what is typical for this pet or whether (and if so when) changes have occurred. Although it is often the case that a pet owner cannot precisely recount an exact weight change, he or she may have an impression of the period of time over which the change occurred. Rapid weight loss and deterioration in body condition, particularly if associated with muscle wasting, suggests a greater degree of metabolic derangement or reduction in food intake (or both) and greater potential for significant malnutrition than a more gradual loss of weight.

149.1.1 ### Box • 149-1 Information To Be Included In A Diet History

- Commercial pet foods (brand and daily portion; dry foods should be weighed or measured with an 8 oz measuring cup; canned foods should be measured by can size and portion used)
- Commercial treats (brand, size, and frequency of use)
- Table foods or scraps (detailed information about type of food, portion size, and frequency of use)
- Treats for chewing (e.g., rawhide, pig's ears; size and frequency of use)
- Dietary supplements (brand and daily portion)
- Foods used for medication of the patient (type of food, portion size, and frequency of use)
- Pet's access to garbage

- Pet's ability to scavenge or roam

149.2 PATIENT ASSESSMENT

Evaluation of body condition is the chief consideration in the assessment of the animal. Although some sophisticated techniques are currently being used in human patients or in a research setting (e.g., multiple-frequency bioelectrical impedance, dual-energy radiographic absorptiometry (DEXA), neutron activation), they have either not been sufficiently validated in companion animals or do not lend themselves to a clinical setting because of logistic considerations or expense. Body condition scoring, although subjective, is simple to learn, requires no special equipment, and has been shown to be repeatable and consistent among multiple observers.[1] The body condition scoring systems that have been published for companion animals are principally based on characterization of body silhouette and palpation of body fat. These systems are useful, particularly for identification of patients that have an overweight body condition; however, they may misclassify some malnourished patients. It is important to recognize that catabolism of lean body tissue can occur very rapidly and may account for a disproportionate amount of the body mass lost in sick patients. Although the purpose of adipose tissue is to serve as an energy reserve, no analogous reserve of endogenous protein exists. Because all endogenous protein is serving some function, the result of continuous catabolism will eventually have deleterious consequences for the patient. Therefore the process of body condition assessment should include not only the standard evaluation of body silhouette and evaluation of adipose tissue as assessment of energy reserves but also a separate evaluation of muscle mass as a subjective means of assessing lean tissue status. This can be accomplished by palpation of skeletal muscle over the axial skeleton and other bony prominences.

Other aspects of the physical examination of a patient that should be taken into consideration include haircoat quality and skin condition, evidence of peripheral edema or ascites (which may indicate hypoproteinemia), and clinical signs that may indicate specific micronutrient deficiencies such as neck ventroflexion or tetany.

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149.3 SPECIAL CONSIDERATIONS REGARDING ASSISTED FEEDING

No definitive tests are available for establishing a patient's nutritional status. However, based on the information gathered from the patient's medical and dietary history and physical examination (as described previously), the clinician should be able to classify broadly the patient as being well nourished, mildly malnourished, or severely malnourished. The decision whether or not to intervene with some form of nutritional support for a patient has to balance the anticipated benefits with the potential risks and costs of the proposed intervention. Therefore the intent of nutritional assessment should not simply be to diagnose inadequate food intake or malnutrition, but rather to identify patients that are at risk of a poor outcome as a result of their compromised nutritional status. Investigations of human patients have found increased risk of morbidity and mortality associated with various objective markers of nutritional status including hypoalbuminemia, lymphopenia, and attenuated delayed hypersensitivity reactivity. Other investigators have found that clinical assessment of patients based on a carefully performed history and physical examination, as described previously, has predictive value similar to that of objective markers of nutritional status such as serum albumin concentration.[2] Furthermore, investigations of the effect of nutritional support on improving clinical outcome suggest that it is the most significantly malnourished patients that are likely to show benefit from nutritional support.[3]

There has been only limited investigation of the prognostic value of nutritional assessment in veterinary patients. Admission serum albumin concentration has been shown to correlate with risk of poor clinical outcome in critically ill dogs, and elevation of serum creatine kinase activity has been found to be associated with anorexia in

feline patients.[4,5] To date there have not been any investigations of the prognostic value of subjective nutritional assessment or the impact of nutritional support on clinical outcome in companion animals; however, it is not unreasonable to expect results similar to those found in human patients. Therefore it is recommended that patients assessed to be significantly malnourished on presentation or that are at risk of becoming significantly malnourished in the course of their illness due to decreased food intake, malassimilation of diet, or metabolic derangement, should be considered candidates for assisted feeding.

149.4 MONITORING NUTRITIONAL INTERVENTIONS

Once a dietary recommendation has been made, the patient should be reassessed after an appropriate interval of time. The actual timing of reassessment depends on the severity of the patient's illness and the type of nutritional intervention it has received. One should determine whether the prescribed recommendations are being followed if problems with diet acceptance or tolerance are seen, if the desired outcomes have been achieved, or if any adverse events associated with the diet or feeding management have occurred. A thorough nutritional assessment at the outset will often identify potential problems or complications and thereby determine what parameters should be monitored in the patient. At the least, body weight and condition should be reassessed regularly to ascertain that the patient is maintaining, gaining, or losing weight appropriately.

149.5 REFERENCES

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150 CHAPTER • 150 Nutrition of Healthy Dogs and Cats in Various Stages of Adult Life

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Although both dogs and cats are classified as carnivores, their nutrient requirements are not identical. The metabolism and nutritional needs of dogs approach those of omnivores, whereas the metabolism of cats is consistent with that of a strict meat-eating mammal. [1–3]

Dogs have the capability to use plant sources for synthesizing taurine, arachidonic acid, and vitamin A from their metabolic precursors, cysteine, linoleic acid, and beta-carotene, respectively. Cats, by contrast, either have diminished enzyme activities for synthesizing these nutrients (taurine and arachidonic acid) from their metabolic precursors, or they do not possess the enzyme (vitamin A). Cats must therefore obtain these nutrients from their diet. Both dogs and cats possess some similar metabolic characteristics such as an obligation to conjugate bile acids with taurine and an inability to synthesize vitamin D. However, the cat digests uncooked starch somewhat better than the dog, so not all evidence is fully consistent with the cat being a strict carnivore and the dog simply being an omnivore.

150.1 FOOD INTAKE AND PALATABILITY

The diet of feral cats is based largely on small mammals, birds, lizards, and insects. When domesticated cats are fed free choice, they eat 10 to 20 meals per day (12 mice per day provide the energy requirement of a normal cat) about equally divided between the light and dark period. Significant breed differences are seen in the feeding behavior of dogs: beagles have feeding patterns similar to cats, whereas basenjis and poodles eat only during the daylight hours. The number of meals can vary widely from 5 to 20. Adult dogs adapt to one meal a day, and cats at maintenance can adapt to a similar regimen. During gestation and lactation, however, performance is enhanced by feeding several times a day or by feeding free choice. During the latter part of gestation and lactation, bitches should be offered food at least twice a day and preferably fed free choice. Both cats and dogs prefer meat-based canned products rather than dry expanded diets, in part owing to the higher moisture content of canned products and in part because blood and fluids contain positive palatability factors. Texture is important; cats and dogs both prefer soft, moist foods to dry, powdery foods. Dogs respond positively to protein, peptides, certain free amino acids, sugar, and mononucleotides, together with certain electrolytes. The response of cats is neutral to protein and sugar, positive to peptides and certain free amino acids, and negative to mononucleotides. Good-quality animal fats enhance palatability for both cats and dogs. Medium chain triglycerides are strongly aversive to cats but not to dogs. Both dogs and cats respond positively to fresh meat extracts, whereas cats but not dogs generally show strong negative palatability to oxidized or rancid fats and breakdown products of trinucleotides or mononucleotides. In summary, cats are more sensitive to adulteration, oxidation, and rancidity in foods than are dogs. Uncooked or cooked meat extracts (broth) are the most palatable natural ingredients to use to enhance the palatability of unpalatable foods for both dogs and cats.

Food intake of cats and dogs fed diets of low or high palatability is quite well controlled. The level at which the animal controls its weight is complex and depends on factors such as genetics (breed and strain), life stage, physical activity, food availability, food palatability, and whether or not the animal is neutered. Both dogs and cats maintain their weight and stay healthy if their diet is complete and balanced, even if the diet has poor palatability. Highly palatable high-fat diets increase the risk for obesity. Nevertheless, dogs and cats control their food intake,

albeit at a higher level of body weight, even when fed highly palatable high-fat diets. It is always easier to prevent obesity by selecting or manipulating the aforementioned factors before obesity occurs rather than to try to limit food intake to affect weight loss. In herbivores and omnivores, food intake is depressed, and strong avoidance of a particular diet is exhibited when animals are fed diets with various nutrient deficiencies or excesses (e.g., deficiencies of thiamine, sodium, phosphate, protein, specific essential amino acids). In most species, including cats and dogs, emetics (e.g., lithium chloride, apomorphine) induce an aversion to the taste of the food just previously eaten. This behavior is called a *learned taste aversion*. In cats there appears to be a neural disassociation between the neural response to the nutrient deficiency and feeding behavior. For those deficiencies and excesses that have been examined (protein deficiency and excess, individual essential amino acid deficiency and excess, sodium deficiency), no learned taste aversions have been demonstrated, despite the fact that food intake may have been depressed.[3,4] Thus palatability may override nutrient metabolic effects in cats, whereas nutrient metabolic effects (caused by nutrient deficiencies and excesses) override palatability effects in herbivores and omnivores (Figure 150-1). It is notable that even though cats do not appear to develop learned aversions to simple nutrient deficiencies or excesses, it has been shown that cats do avoid diets that cause hyperammonemia[5] or metabolic acidosis.[6]

150.2 GENERAL FEEDING RECOMMENDATIONS

Practitioners should advise clients to choose a commercial diet that has passed an Association of American Feed Control Officials (AAFCO) animal protocol test for the particular life stage of the cat or dog. This ensures that the diet has undergone an animal feeding test. An AAFCO nutrient profile label means only that a diet meets a calculated nutrient profile. In most cases it is safest to feed a diet that has passed an AAFCO all-stages protocol. The exception would be if a particular dog or cat has a medical problem; then a specific therapeutic diet should be fed. In selecting an appropriate therapeutic diet, one should always select a diet that has been tested for the intended purpose. If no particular diet has been tested clinically for the particular medical condition, a clinical nutritionist should be consulted for advice or to formulate a balanced homemade diet that is appropriate. It is prudent to check whether a commercial diet (regular or therapeutic) has been properly tested in animals for the intended purpose. No reason exists not to feed a diet that has large built-in safety factors in nutritional requirements, but likewise no reason exists to pay for extra nutrients if they have not been shown to be of extra benefit to the cat or dog. When a diet is complete, balanced, and tested and has been shown to be fully adequate in animals, no reason exists to feed a diet containing even more of one or more essential nutrients. Nevertheless, a paucity of information is available on specific nutrient requirements in adult life stages, including maintenance. There has been considerable research on the nutrient requirements for dogs and cats for growth, because it is the easiest life stage for which to determine requirements. Therefore requirements for growth have been used to formulate requirements during pregnancy. Additional information from epidemiologic evidence and from other species has been used to formulate requirements for maintenance.

150.3 MEETING ENERGY NEEDS

About 80% of the food eaten by mature cats and dogs is used to provide their energy needs. The requirements for protein, minerals, and vitamins can be met in the remaining dry matter. Therefore meeting energy needs is the first consideration in feeding cats and dogs. Energy, unlike individual amino acids, vitamins, and minerals, is not supplied by any single nutrient but is provided by the oxidation of substrates, primarily fats, carbohydrates, and proteins. The energy needs of dogs or cats may be supplied by diets with varying ratios of these three nutrients. The only avenue an animal has for disposal of excess energy is by oxidation to produce adenosine triphosphate or to store the excess energy in the form of adipose tissue. Mature dogs and cats that are in energy balance convert all

the available or metabolizable energy (ME) from food into heat. To calculate the amount of food required by dogs or cats, the ME value of the food should be known.

The energy requirements of mature, nonpregnant cats and dogs are not constant but decrease on a unit-body-weight basis with age, which is related to the reduction in general activity with age. As indicated, many individual cats and dogs adjust their energy intake from food to balance their energy needs. However, in some adults, this balance is not maintained, leading either to body weight loss, resulting in catabolism of body energy stores, or to obesity and body weight gain owing to excessive energy intake.

The maintenance energy requirements of adult cats and dogs may be estimated from formulas relating ME requirements to body weight. Because mature dogs have about a fiftyfold range in body weight, and because ME requirements per unit of body weight decrease with body weight, formulas generally include some power function of body weight (e.g., body weight raised to three-fourths power). A common linear formula used for dogs is ME = 30 W + 70, and an exponent formula is ME = 132 $W^{3/4}$, where W is body weight in kilograms and ME is kilocalories per day. The first equation approximates the relationship for small dogs such as beagles but overpredicts energy requirements for large breeds. Because the body-weight range of adult cats is much less than that of adult dogs, a power function is not used with cats. The formula ME = 80 W has been used for active cats and ME = 70 W for inactive cats.

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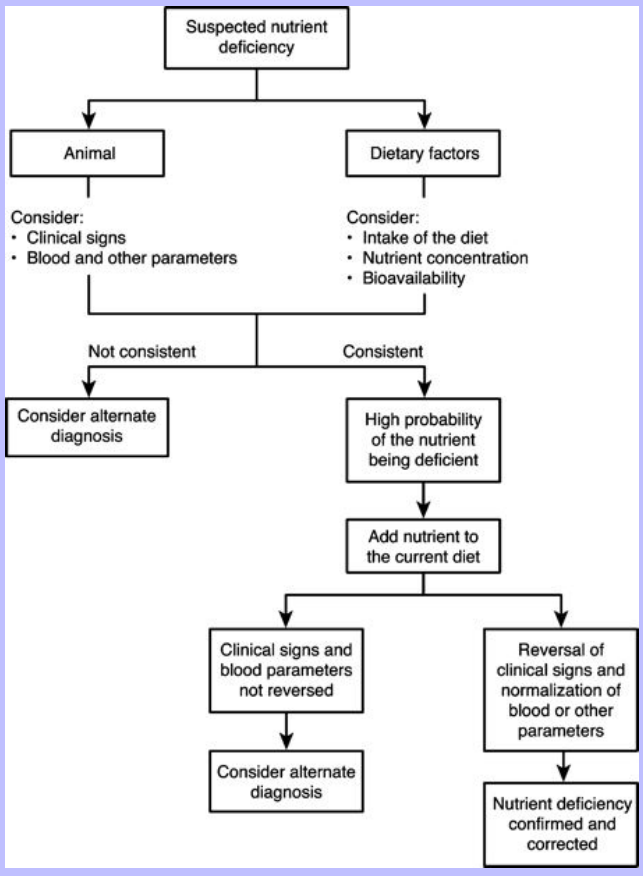
Figure 150-1 Algorithm for solving a nutrient deficiency in an adult dog or cat.



Although these formulas are useful starting points, they are not absolute requirements because considerable individual animal variation exists. It has been shown that a large variation exists in the prediction interval of maintenance energy requirement.[8] However, when enteral or parenteral nutritional support is necessary, a requirement estimate must be made. Similarly, when a weight reduction program is undertaken, an estimate of maintenance energy requirements is desirable. All adult cats and dogs that are voluntarily consuming food should be fed relative to their body condition and not by a formula. If an adult dog or cat is fed free choice and becomes obese, either the amount of food offered or the energy density (available caloric density) of the food should be reduced. When an adult cat or dog is not maintaining body weight, either more food or a more palatable food should be fed to increase intake or a diet of a higher caloric density should be fed (or both should be done).

Pregnancy causes a demand for energy greater than normal adult maintenance requirements. Different responses to pregnancy occur in the ingestive behavior of bitches versus queens, even though the length of gestation is similar. Queens increase food intake soon after conception and have an almost linear increase in body energy stores with duration of gestation. In contrast, bitches normally do not increase food and energy intake until the latter stages of pregnancy. Queens and bitches in normal body condition may be given food free choice during pregnancy to allow for the increase in body tissue that will be mobilized during lactation and by fetal energy demands. Whereas the latter stages of pregnancy increase energy requirements by about a third, lactation places a huge demand on the bitch and queen and can result in energy intakes three to four times above maintenance. Depending on the number of kittens or pups, queens or bitches sustain a loss of body weight during lactation. This tissue loss should be largely the tissue gained during the prepartum period; with a good diet and normal litter size the weaning body weight of the mother should not be less than the body weight at conception.

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150.4 PROTEINS AND AMINO ACIDS

Proteins are added to diets to provide essential amino acids and nitrogen. Nitrogen requirements are usually expressed as the crude protein requirement, because crude protein is defined as the quantity of nitrogen times 6.25. Nitrogen is used for the biosynthesis of dispensable amino acids, heme, purines, pyrimidines, and so forth. Both essential and dispensable amino acids are necessary at the cellular level for protein synthesis. Several amino acids are precursors for hormones and neurotransmitters. If the amino acid and crude protein requirements are known for each life stage, the clinical nutritionist can formulate a diet using amino acid composition tables for particular proteins and ensure that both essential amino acid and nitrogen requirements are met. However, a weakness of diet formulation using nutrient composition tables is that the bioavailabilities of amino acids and nitrogen from food sources are usually not known, or the effect of processing on the particular food (or food combinations) is not known. The most accurate way to tell if the diet is adequate in protein is to evaluate plasma amino acid concentrations during the absorptive state after feeding a particular diet. Amino acid patterns can be used not only to verify that essential amino acid requirements have been met but also to diagnose various nutritional problems (e.g., protein-energy malnutrition, essential amino acid deficiency) and metabolic problems (e.g., liver or kidney disease).

Carnivores have no problem meeting their protein or amino acid requirements if they eat other animals, because the body composition of various animals is quite similar and is high in good-quality protein. Nutritional problems arise only if a client attempts to feed a carnivore a vegetarian diet or a diet that has poor-quality ingredients (e.g., by-products that are high in collagen, such as skin and bone) or products that have been excessively processed. Quality control of ingredients in pet foods is a problem in the pet food industry, because large quantities of animal by-products do not always have a constant composition; thus these by-products may have variable digestibilities and bioavailabilities for nitrogen and amino acids. Specific amino acid deficiencies or excesses can cause a variety of problems, such as cataracts, dermatitis, hair loss or reddening of black hair or both, irritability, neurologic

deficits, hyperammonemia, fatty liver, low glutathione, and emesis. After reviewing the literature and using our experience in feeding dogs and cats, we have developed an estimate of dietary nutrient allowances (Table 150-1). These allowances include an approximate 25% to 50% in excess of the minimal requirement to allow variation in bioavailability. Our estimate of minimal requirement is undoubtedly high for several of the amino acids, because so many data are missing, especially for the adult life stages. Nevertheless, these values may be used as guidelines until more refined data are available. It is possible, using diet composition tables, that these recommendations may be too low owing to poor-quality ingredients with low digestibility coefficients. Most cat and dog foods are formulated to meet or exceed these recommendations. Major pet food companies have competent nutritionists who take digestibility and bioavailability values into account in formulating diets, and most of the major diets have been tested. Therefore veterinarians should be confident in recommending any pet food that has passed the AAFCO feeding protocol for the life stage in question. The bottom line is simple for adult dogs and cats: feed a commercial diet for the appropriate life stage from a reputable company. The only other safe course is consultation with a small animal nutritionist to attempt to evaluate a diet or to formulate a homemade diet. The latter is not recommended because of the difficulty in predicting bioavailability of ingredient nutrients and the difficulty in getting good compliance in making and feeding such a diet.

Table • 150-1 Suggested Nutrient Allowances* for Adult Dogs and Cats at Maintenance (Nutrient Per 1000 kcal of Dietary Metabolizable Energy)

NUTRIENT	UNIT	ADULT DOG	ADULT CAT
Protein†	g	37.5	75.0
Arginine	g	1.43	3.13
Histidine	g	0.54	0.90
Isoleucine	g	1.05	1.75
Leucine	g	1.80	3.75
Lysine	g	2.25	3.00
Methionine +cysteine	g	1.50	2.75
Methionine	g	0.75	1.50
Phenylalanine +tyrosine	g	2.10	2.50
Phenylalanine	g	1.05	1.25
Threonine	g	1.20	2.00
Tryptophan	g	0.35	0.50
Valine	g	1.28	1.75
Calcium	g	1.6	1.2
Phosphorus	g	1.2	1.2
Potassium	g	1.2	1.25
Sodium	g	0.40	0.40
Chloride	g	0.20	0.20
Magnesium	g	0.11	0.08
Iron	mg	20.0	20.0
Copper	mg	0.8	1.1
Manganese	mg	1.4	1.1
Zinc	mg	9.7	11.0
Iodine	mg	0.16	0.07
Selenium	mg	0.03	0.02
Vitamin A (retinol)	mg	0.3	0.21
Vitamin D (cholecalciferol)	g	2.75	2.6
Vitamin E (alpha-tocopherol)	mg	6.1	7.0
Vitamin K	g	—	2 1.0
Thiamine	mg	0.3	1.1
Riboflavin	mg	0.7	0.9
Pyridoxine	mg	0.3	0.9
Niacin	mg	3.0	10.0
Pantothenic acid	mg	2.7	1.0
Folic acid	mg	0.54	0.17
Vitamin B_{12}	µg	7.0	4.0
Biotin	µg	—	15.0
Choline	mg	340.00	500.00

* These values are not minimal nutrient requirements, but nutrient allowances. Requirements have been increased to accommodate variation in digestibility and bioavailability of nutrients in natural foods and individual animal variation.

† For a protein of good quality. The requirement for protein and amino acids needs to be increased for proteins of lower quality or lower digestibility.

150.5 MINERALS AND VITAMINS

Adult cats and dogs require the same minerals and vitamins that are essential to growing kittens and puppies. Although the requirements for growing kittens and puppies are fairly well defined, those for adults are not known with the same precision. The dietary concentration for growth satisfies adult requirements, even though the food intake of adults on a unit-body-weight basis is less than that during growth. The function and clinical role of vitamins have been reviewed.[8]

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150.5.1 Minerals

Mineral requirements for adult cats and dogs for maintenance (expressed per 1000 kcal dietary ME) are given in Table 150-1. These requirements are based on published values[9,10] with updated information. Expression on an equivalent energy basis shows that the requirements of adult cats and dogs are similar. The requirements given in Table 150-1 are for minerals with a high bioavailability, such as from mixtures of the salts of these minerals or from bone. Applying these values to practical diets requires bioavailability values to be taken into account. Although these have not been determined in cats and dogs, values originating in other simple-stomached species give useful approximations. The bioavailability of calcium, phosphorus, and magnesium from plant sources is considerably less than that from mineral salts or bone and should be discounted by 50%. In contrast, sodium, potassium, and chloride are readily exchangeable, and no adjustments are necessary concerning their source.

Bioavailability of trace elements, especially as they pertain to cats and dogs, is not known, but observations indicate that the availability of zinc and copper in diets containing high proportions of plant products is compromised. Zinc deficiency has not been uncommon in dogs fed some of the lower-quality dry diets containing a high proportion of plant products. Clinical signs of copper deficiency have been reported in newborn kittens from queens given diets containing copper oxide as a supplementary source of copper. Reproductive performance of the queens was also reduced. The requirements for many of the major minerals (e.g., calcium, potassium, sodium) increase greatly in lactation. However, because food intake is also increased about twofold, the percentage in the diet need not change.

Diagnosis of mineral deficiencies should be based on specific clinical signs, blood, plasma, or tissue concentrations for the species, as well as on reversal of clinical signs after supplementation with the specific mineral while the cat or dog is maintained on the same diet.

150.5.2 Vitamins

Vitamin requirements of adult cats and dogs expressed based on 1000 kcal of ME are given in Table 150-1. The values are based on published data[9,10] that have been modified when newer information was available. For the fat-soluble vitamins A, D, and E, the requirements are similar for adult cats and dogs. Cats, unlike dogs, are unable to use beta-carotene as a precursor for retinol, so they depend on preformed vitamin A in the diet. The values for vitamin A and D are in excess of minimal requirements, and further supplementation in normal animals is unwarranted. Neither cats nor dogs are capable of synthesizing vitamin D from ultraviolet (UV) light.[11] Although vitamins A and D are regarded as the most toxic of all the vitamins when given in excess, adult cats can tolerate large excesses (50 times requirement) of these two vitamins with no discernible deleterious effects. In normal cats and dogs, in contrast to most other animals, large concentrations of retinyl esters occur in plasma. Requirements for vitamin E are a function of the total polyunsaturated fatty acids

(PUFAs) in the diet. Because cats frequently consume diets high in PUFAs, the requirement to prevent steatitis in cats is higher than that for dogs that are subjected to lower dietary inputs of PUFAs. Both cats and dogs require an exogenous source of vitamin K, but intestinal synthesis appears to be adequate to supply this need in dogs. When cats are fed some high-fish diets, they have a prolongation of clotting time and require supplemental vitamin K.

In contrast to the fat-soluble vitamins, the requirements for the water-soluble vitamins for cats versus dogs are different. Cats have a higher requirement than dogs for thiamine (vitamin B_1) and are exposed to dietary ingredients that often contain both thiaminases (e.g., fish) and to canned diets that have sustained extensive processing, causing loss of thiamine. As thiamine stores are rapidly exhausted, thiamine deficiency can readily occur in cats given deficient diets. Cats, unlike dogs, are unable to use tryptophan as a precursor for niacin synthesis, so niacin is an absolute essential dietary nutrient for cats. Niacin is normally obtained from foods by hydrolysis of nicotinamide adenosyl dinucleotide (NAD) and nicotinamide phosphodinucleotide (NAPD) in the gut. Meats contain high levels of these nucleotides and thus are a principal source of this vitamin.

The published vitamin requirements[9,10] for growing kittens and puppies appear to satisfy the requirements of mature cats and dogs. However, in applying these values, it is necessary to take into consideration the bioavailability of the vitamin and its stability in the product. The bioavailability of the fat-soluble vitamins is high in the absence of most fat malabsorption syndromes, whereas the bioavailability of most of the B vitamins in natural products is variable and can be quite low.

150.6 TAURINE

Taurine, a beta-sulfur amino acid, occurs in all animal cells and is virtually the sole conjugate of the bile acids in cats and dogs. Taurine is synthesized de novo by dogs and cats from the sulfur amino acids cysteine and methionine. Although cat diets contain a higher level of sulfur amino acids than do dog diets, the rate of taurine synthesis by cats is low; cats given a low-taurine diet are readily depleted of this amino acid. This very low rate of taurine synthesis in cats is a consequence of low activities of two enzymes in the pathway of synthesis. Taurine depletion is associated with a wide range of clinical conditions, including feline central retinal degeneration, reversible dilated cardiomyopathy, reproductive failure in queens, and developmental defects and growth retardation in kittens. The amount of dietary taurine required for cats to maintain adequate blood concentrations varies twofold with the type of diet. For expanded (dry) diets, 1250 mg taurine/kg dry matter is adequate. Canned diets, which promote higher intestinal degradation of taurine exposed in the enterohepatic circulation, require 2500 mg/kg dry matter to maintain blood concentrations in the normal range.

Until recently, diet-associated taurine deficiency in dogs has not been recognized. However, low blood taurine concentrations and dilated cardiomyopathy (DCM) has recently been identified in dogs that do not have a genetic predilection to this disease. A common finding among the cases was the consumption of commercial dry diets containing lamb meal, rice, or both as the primary ingredients. Cardiac parameters and blood taurine concentrations improved with treatment and taurine supplementation. Dogs that survived longer than 1 year were able to be removed from all cardiac mediations except taurine, suggesting that these were not typical cases of DCM. Suggested mechanisms for taurine deficiency in these dogs were considered to be (1) insufficient synthesis of taurine, (2) extraordinary loss of taurine or its precursors in urine, (3) extraordinary gastrointestinal (GI) loss of taurine in bile acid conjugates (as found in cats), or (4) a reduction in protein digestibility. Based on clinical findings, blood taurine concentrations, and common diet histories, it appears that the consumption of diets with inadequate or unavailable sulfur amino acid taurine precursors, plus rice bran increasing GI loss, results in taurine deficiency and low blood taurine concentrations in these dogs. The low plasma taurine concentrations can lead to the development of abnormal cardiac function and DCM.

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150.7 ESSENTIAL FATTY ACIDS

The diets of healthy dogs and cats, like those of other animals, must contain polyunsaturated fatty acids (PUFAs). Because these fatty acids cannot be synthesized de novo by animals, they are designated as essential fatty acids (EFAs). Dogs require two EFAs in the diet: linoleic acid C18:2 n-6 and linolenic acid C18:3n-3. The letter followed by the number (e.g., n-6 or ω-6, n-3 or ω-3) refers to the location of the first double bond in the fatty acid from the methyl (or omega) end of the fatty acid. Animals cannot insert double bonds further than 9 carbons from the carboxyl end of a fatty acid. In addition to linoleic and linolenic acids, cats under certain conditions may require arachidonic acid, a member of the n-6 family of fatty acids in the diet. The activity of the hepatic delta-6-desaturase enzyme required in one of the pathways for the synthesis of arachidonic acid from linoleic acid is low in cats. This limited activity appears to be sufficient for growth and reproduction in male cats (where the testis also has delta- 6-desaturate activity) but may be inadequate for sustained reproduction in queens. Other fatty acids, particularly those of the n-3 series, may also limit reproduction in queens.

Fatty acids function as precursors of eicosanoids, which include prostaglandin, leukotrienes, and thromboxanes. These extremely active biologic compounds have both paracrine and endocrine activity. As a group the eicosanoids of the n-6 series tend to be involved in a more proinflammatory role, whereas those of the n-3 have an anti-inflammatory or only a mildly inflammatory role.

Of the EFAs, the quantitative requirement of cats and dogs is greatest for linoleic acid. A deficiency of linoleic acid results in hyperkeratosis of skin, fatty degeneration of the liver, and degeneration of the testis. In addition, increased water loss through the skin occurs. Cats and dogs require about 1% to 2% of the calories as linoleic acid to prevent clinical signs of deficiency, though higher levels of total fat in the diet may result in better coat condition. The n-3 fatty acid, linolenic acid, occurs in high concentration in some plant oils such as linseed (flaxseed) oil, and higher homologues of this fatty acid occur in animal fats, particularly marine oils such as herring and tuna. In cats, the production of these higher n-3 homologues also appears to be limited, which may contribute to the poor reproductive performance of queens given some vegetable fat diets.

Clinical signs of arachidonate deficiency in cats are associated with eicosanoid dysfunction and include defective reproduction in queens and changes in blood platelet aggregation. The requirement of cats for arachidonic acid has not been defined but appears to be of the order of 200 mg/kg dry matter. Arachidonate in natural diets comes from animal tissue membranes. Recently a fungal source of arachidonate has become commercially available, so it is possible to add this fatty acid to diets for cats without the inclusion of animal fat.

150.8 OTHER NUTRIENTS AND NUTRACEUTICALS

Choline is often included among the “essential” vitamins because it supplies labile methyl groups. Methionine and betaine can also supply methyl groups. A lack of total methyl groups in the diet leads to fatty liver because of an inability to mobilize hepatic fat.

Ascorbate, or vitamin C, is synthesized de novo by dogs and cats from glucose, and no substantiated evidence exists (except anecdotal reports in liver disease) to indicate that dogs or cats benefit from the addition of ascorbate to the diet. In contrast, some breeds of dogs have a limited capacity to synthesize adequate carnitine and benefit from its supplementation. Synthetic antioxidants are frequently added to human and animal diets to prevent lipid peroxidation during storage. Substantial evidence contraindicates the consumption of lipid peroxides. It is debatable whether these synthetic antioxidants are deleterious when used at the recommended concentrations in the diet. Natural antioxidants such as alpha-tocopherol, though less effective than the synthetic antioxidants, can

also be used. A number of human foods such as onions and chocolate cause adverse effects in cats and dogs, respectively; thus some human foods should not be fed to cats and dogs indiscriminately. Food faddism in human nutrition has resulted in malnutrition, toxicities, and deficiencies.[12] These same practices occur in dog and cat nutrition and should be avoided.

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151 CHAPTER • 151 Neonatal and Pediatric Nutrition

Johnny D. Hoskins

The nutritional requirements, feeding, and care of puppies and kittens from birth to early adulthood are substantially different during their different stages of growth. The growth phase is a critical time in the life of a puppy or kitten; some will fail to grow to the size determined by their hereditary factors unless they consume appropriate food of adequate quality.

151.1 FEEDING THE PUPPY

Healthy puppies, during the first 2 to 3 weeks of life, should only eat and sleep. Nursing should be vigorous and active, with each puppy receiving sufficient milk from its mother. If the mother is healthy and well nourished, the puppy's nutritional needs for its first 3 to 4 weeks of life should be provided completely by her. Indications that the puppy is not receiving sufficient milk are constant crying, extreme inactivity, or failure to achieve weight gains in accordance with thegeneral guidelines that a puppy should gain 1 to 2 g/day/lb (2 to 4 g/day/kg) of anticipated adult weight (or at least 10% gain per day).[1] For example, if the adult dog is expected to weigh 30 lb, as a puppy it should gain 30 to 60 g/day during its first 5 months of life.

The transition from mother's milk to solid food should be a gradual process beginning at about 3 weeks of age (4 weeks of age for toy breeds); however, if necessary, supplemental feeding may be started as soon as the puppy fails to showsufficient weight gain. During the changeover to solid food, the puppy can be offered a thick, gruel-like mixture of good-quality puppy food designed for growth and water (one part dry food blended with three parts water, or two parts canned food blended with one part water). To get the puppy eating, the gruel is placed in a shallow food dish, the puppy is encouraged to lap the gruel by touching its lips to the food, or the feeder can put a finger in the gruel and then into the puppy's mouth. It can also be force-fed using a commercial dosing syringe. Once the puppy accepts the gruel, the amount of water is gradually reduced until it is omitted.

By 6 weeks of age, the puppy should be receiving at least 25% of its requirements from the weaning diet. The puppy may be permanently separated from the mother as soon asit learns to eat readily and drink satisfactorily. Most puppies are completely weaned at 7 to 8 weeks of age, depending somewhat on size and breed. Early weaning and separation from littermates, prior to 6 weeks of age, however, can cause malnutrition or numerous behavioral problems later in life. Because of this, complete weaning should not be attempted until puppies are at least 6 weeks old and close humancontact has been established.

Feeding the weaned puppy should always be directed to attaining the appropriate growth rate for the breed.[1] Instead of making food available to the puppy at all times (free-choice feeding), time-limited meal feeding is recommended. At each feeding, the puppy should be given 15 to 20 minutes to eat all that it wants; then the remaining food should be removed. From the time of weaning to 4 to 6 months of age (9 months for giant breeds), puppies are best fed at least three timesa day at regular intervals. Thereafter, puppies should be fed twice a day on a regular schedule.

Some large and giant breeds of dogs (those over 30 kg body weight at maturity) have the genetic capacity to grow rapidly and will do so if provided with a food that meets or exceeds their nutrient and energy needs. However, a rapid growth rate is not compatible with normal skeletal growth and may result in certain types of developmental bone disease.[2,3] Beginning at weaning and continuing until they reach maturity, large and giant breeds of dogs should be fed for a moderate growth rate. This can be accomplished by limiting food intake or, even better, by

feeding a growth-formulated puppy food for large and giant breeds. If osteochondrosis or hypertrophic osteodystrophy occurs, nutritional management should be aimed at reducing caloric intake by decreasing the amount of food that is fed or feeding a growth-formulated puppy food for large and giant breeds.

151.2 FEEDING THE KITTEN

Healthy kittens, during their first 4 weeks of life, should nurse vigorously and actively. If the mother is healthy and well nourished, the nutritional needs of the kittens during this time should be filled completely by her. Each kitten should receive sufficient milk from its mother. Kittens not receiving sufficient milk cry constantly, are restless or extremely inactive, or fail to achieve the expected weight gain of 10 to 15 g/day.[1]

Kittens should be encouraged to begin eating solid food at 4 weeks of age. At this time, the kitten can be offered a thick, gruel-like mixture of good-quality kitten food designed for growth and milk or water (one part dry food blended with three parts milk, or two parts canned food blended with one part milk). The gruel is fed to kittens from a shallow bowl or force-fed by using a commercial dosing syringe. The feeder can encourage the kitten to eat the gruel by smearing some of the gruel on the kitten's lips, being careful not to get any in the nose, or placing a finger in the gruel and then into the kitten's mouth. This usually encourages the kitten to eat from a bowl at an early age. Once the kitten is eating the gruel well, the amount of milk or water in the gruel is gradually reduced until the kitten is consuming only solid food. The kitten may be permanently separated from the mother as soon as it learns to eat readily and drink satisfactorily. Most kittens are completely weaned at 6 to 8 weeks of age. Early weaning andseparation from littermates before 6 weeks of age can resultin behavioral problems such as slowness to learn and more suspicious, cautious, and aggressive actions.[4]

Food given to weaned kittens should be one specifically formulated for growth. Feeding between 3 to 3.5 oz of dry food per day or 8 to 10 oz of canned food per day usually meets the growth requirements of most kittens. Becausethe kitten's eating habits are still in the formative stage after weaning, it is important that easily digested, high-quality, calorically dense food is provided. Cow's or goat's milk is often fed to kittens after weaning and is a good food, provided that it does not cause diarrhea. Milk should never be given in place of fresh water.

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Kittens should be fed all the food they will consume. Excessive caloric intake and excessively rapid growth rate are seldom problems in growing kittens. Most kittens are not voracious. When food is always available, they nibble at it frequently. Kittens fed unlimited amounts of food (free-choice feeding), regardless of the form of food (dry or canned), eat every few hours. Free-choice feeding, or at least three-times-a-day feeding, is preferred during growth.

At 12 weeks of age the kitten's energy needs are three times greater than those of an adult cat, or more than 200 kcal/kg of body weight. As kittens mature past 6 months of age, their growth rate slows and their food needs decrease. Their energy needs are still greater than adult cats, or approximately90 kcal/kg of body weight.

151.3 REARING NURSING PUPPIES AND KITTENS

Newborn puppies and kittens are unable to effectively control their body temperature.[5] During their first 4 weeks of life, they gradually progress from being largely poikilothermic to being homeothermic. That is, for the first week of life their body temperature is directly related to the environmental temperature, and a steady ambient temperature of 30° to 32° C (86° to 90° F) is needed. Over the next 3 weeks, the ambient temperature can be gradually lowered to 24° C (75° F). Humidity should be maintained at 55% to 60%. It is equally important that sudden changes of environmental conditions be avoided.

The most obvious alternative to a mother rearing her own young is for another nursing mother to act as a foster mother. If a foster mother is not available, it is necessary to hand-feed the puppies or kittens a replacement food that is a prototype of nutritive substance formulated to meet the optimum requirements of the puppy or kitten. Mother's milk is the ideal food. Various modifications of homemade and commercially prepared formulas simulating mother's milk have been used with good success. [5–7] Commercially prepared formulas are preferred, because they closely compare to mother's milk. These formulas generally provide 1 to 1.24 kcal of metabolizable energy per milliliter of formula. The caloric needs for most nursing-age puppies and kittens are 22 to 26 kcal per 100 gof body weight. Therefore the average puppy or kitten should daily receive approximately 13 mL of formula per 100 g of body weight during the first week of life, 17 mL of formula per 100 g of body weight during the second week, 20 mL of formulaper 100 g of body weight during the third week, and 22 mL of formula per 100 g of body weight during the fourth week. These amounts of formula should be given in equal portions three or four times daily. For the first 3 weeks of life, theformula should be warmed before each feeding to about100° F (37.8° C) or to a temperature near the animal's body temperature.

After each feeding, the abdomen should be enlargedbut not overdistended. When a formula is used, less thanthe prescribed amount should be given per feeding for the first feedings. The amount should then be gradually increased to the recommended feeding amount by the second or third day. The amount of formula should then be increased accordingly as the puppy or kitten gains weight and a favorable response to feeding occurs. Puppies should gain 1 to 2 g/day/lb (2 to 4 g/day/kg) of anticipated adult weight for the first5 months of their lives. At birth the kitten should weigh 80 to 140 g (most weighing around 100 to 120 g) and gain 50 to 100 g weekly.[1]

When preparing formula the clinician should always follow the manufacturer's directions for its proper preparation and keep all feeding equipment scrupulously clean. A good way of handling prepared formula is to prepare onlya 48-hour supply at a time and divide this into portions required for each feeding. Once formula is prepared, it is best stored in the refrigerator at 4° C.

The easiest and safest way of feeding prepared formulato nursing-age puppies and kittens is by nipple bottle, dosing syringe, or by tube.[1] Nipple bottles made especially for feeding orphan puppies or kittens or bottles equipped with preemie infant nipples are preferred. When feeding with a nipple bottle, the clinician or other staff member should hold it so that the puppy or kitten does not ingest air. The hole in the nipple should be such that when the bottle is inverted, milk slowly oozes from the nipple. It may be necessary to enlarge the nipple hole with a hot needle to get milk to ooze from the bottle when inverted. When feeding, a drop of milk should be squeezed onto the tip of the nipple and the nipple shouldbe inserted into the animal's mouth. Milk should never be squeezed out of the bottle while the nipple is in the animal's mouth; doing so may result in laryngotracheal aspiration of the milk into the lungs. In addition, prepared formula should never be fed to a puppy or kitten that is chilled or that does not have a strong sucking reflex. Only when the sucking reflex is present should feeding with nipple bottle be attempted.

Tube feeding is the fastest way to feed orphaned puppies or kittens. Most owners can do it easily with a little training. The following may be used: a No. 5 French (F) infant feeding tube for puppies or kittens weighing less than 300 g, a No. 8 to 10 F infant feeding tube for puppies or kittens weighing over 300 g, or an appropriately sized, soft, male urethral catheter. Once weekly, the feeding tube should be clearly marked to indicate the depth of insertion to ensure gastric delivery (that is, the distance from the last rib to the tip of the nose can be measured and marked off on the feeding tube as a guide). The animal should never be fed into the distal esophagus. When feeding, a syringe should be filled with warm, preparedformula and fit it to the feeding tube. The clinician or staff member should be sure to expel any air in the tube or syringe. The animal's mouth should be opened slightly and, with the animal's head held in the normal nursing position, the feeding tube should be gently passed to the marked

area. If an obstruction is felt, or coughing occurs, before reaching the mark, the tube should be assumed to be in the trachea. If this does not happen, the prepared formula should be slowly administered over a 2-minute period to allow sufficient time for slow filling of the stomach. Regurgitation of formula rarely occurs; but if it does, the feeding tube should be withdrawn and feeding interrupted until the next scheduled meal.

A vital aspect of tending orphaned puppies and kittensis to simulate after feeding, the mother's tongue action onthe anogenital area, which provokes reflex micturition and defecation. Application of this stimulus has to be taken over by the person tending the puppies or kittens. The clinician can achieve the necessary result by swabbing the anogenital area with moistened cotton or dry, soft tissue paper to manually stimulate the reflex elimination. It is sometimes possible to effect the same response simply by running a forefinger along the abdominal wall. This stimulation should be regularly provided after each feeding using nipple bottle or tube. After they reach about 3 weeks of age, puppies and kittens are usually able to relieve themselves without simulated stimulation.

Most puppies and kittens benefit from gentle handling before feeding to allow for some exercise and to promote muscular and circulatory development. In addition, at least once a week the orphaned puppy or kitten should be washed gently with a soft moistened cloth for general cleansing of the skin, simulating the cleansing licks of the mother's tongue.

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152 CHAPTER • 152 Nutrition-Related Skeletal Disorders

Herman A.W. Hazewinkel

152.1 INTRODUCTION

Some skeletal diseases can be linked to unbalanced nutrition (alimentary hyperparathyroidism, rickets). The incidence of many hereditary, developmental skeletal diseases (hip dysplasia [HD], osteochondrosis) may be enhanced by inappropriate nutrition. More than 99% of body calcium (Ca) is stored in the skeleton, giving it rigidity. The extracellular Ca concentration ($[Ca^{2+}]$) is also of paramount importance for different cellular, contractive, and enzymatic processes. Plasma $[Ca^{2+}]$ is maintained in a relatively narrow range with the aid of physiochemical processes: increase in $[Ca^{2+}]$ causes Ca transport to cell organelles, storage of Ca in the labile Ca-pool of bone, and increased glomerular Ca excretion with fine tuning by a variety of regulators, including the calciotropic hormones parathyroid hormone (PTH), calcitonin (CT), and vitamin D (vitD). These hormones have direct or indirect actions (or both) on the skeleton, kidneys, and gut[1] (Figure 152-1). The skeleton includes both bone and cartilage cells and their matrix. Appositional growth of bones occurs by osteoblasts originating from the periosteum; growth in length takes place via endochondral ossification, whereas bone remodeling is controlled by osteoclasts.

152.2 ALIMENTARY HYPERPARATHYROIDISM

Chronic insufficient Ca intake or absorption results in increased PTH synthesis and secretion. PTH, in turn, increases osteoclast activity (deliberate Ca and phosphorous [P] from the skeleton), increases calcitriol synthesis in the kidney (thus increasing intestinal Ca and P absorption), and decreases P reabsorption from renal tubuli (thus causing hyperphosphaturia)[2,3] (see Figure 152-1). Consequently, hyperparathyroidism will normalize the extracellular $[Ca^{2+}]$. When the increase in Ca absorption in the intestine is not covering the daily requirements, the skeleton is the only remaining source of Ca. Ca will be resorbed at the endosteal surface of the diaphyses and in the areas of cancellous bone. Mineralization of osteoid and cartilage will be undisturbed.[4,5]

152.2.1 Clinical and Radiologic Examination

The most commonly affected dogs and cats are young and raised on foods that are extremely low in Ca content. Usually this includes meat or by-products. Therefore this metabolic bone disease is sometimes referred to as “all-meat syndrome.” However, food of low quality binding Ca to phytate may also cause chronic Ca deficiency, especially in young dogs of large breeds. Affected dogs and cats are reluctant to stand and walk and can even be paralyzed due to spinal compression by pathologic fractured vertebrae. Blood investigation will not reveal hypocalcemia, although elevated PTH and calcitriol ($1,25[OH]_2$vitD) levels can be detected [3,5] (see Figure 152-1). Radiographs may reveal thin cortices, wide medullary cavities, folding (green stick) fractures, normal height of growth plates with relatively white metaphyseal borders, as well as compression fractures of cancellous bone of epiphyses and vertebrae.[4,5]

152.2.2 Differential Diagnosis

Ca deficiency can be complicated with vitD deficiency when solely lean meat (which is low in Ca and vitD) is fed. Bone disease due to an inborn error may resemble alimentary hyperparathyroidism, including osteogenesis imperfecta, mucopolysaccharidosis, and other rare diseases.

152.2.3 Therapy

It is extremely important to prevent more pathologic fractures (especially of the vertebrae). The skeleton is too fragile for bandages, splints, or implants. Analgesics will facilitate early mobility, which is not desirable. Changing to a balanced diet with a Ca content up to 1.1% on a dry-matter basis will allow the skeleton to mineralize within 3 to 4 weeks, because almost 100% of the ingested Ca will be resorbed due to the hyperparathyroid-induced high calcitriol levels.[3] Extra Ca as Ca-carbonate or Ca-lactate (and not Ca-phosphate or bone meal) at 50 mg Ca/kg body weight might even accelerate osteoid mineralization. Corrective osteotomies can be planned, when necessary, after the skeleton is normally mineralized. Even pets with compression fractures of the spinal cord may have a full recovery.

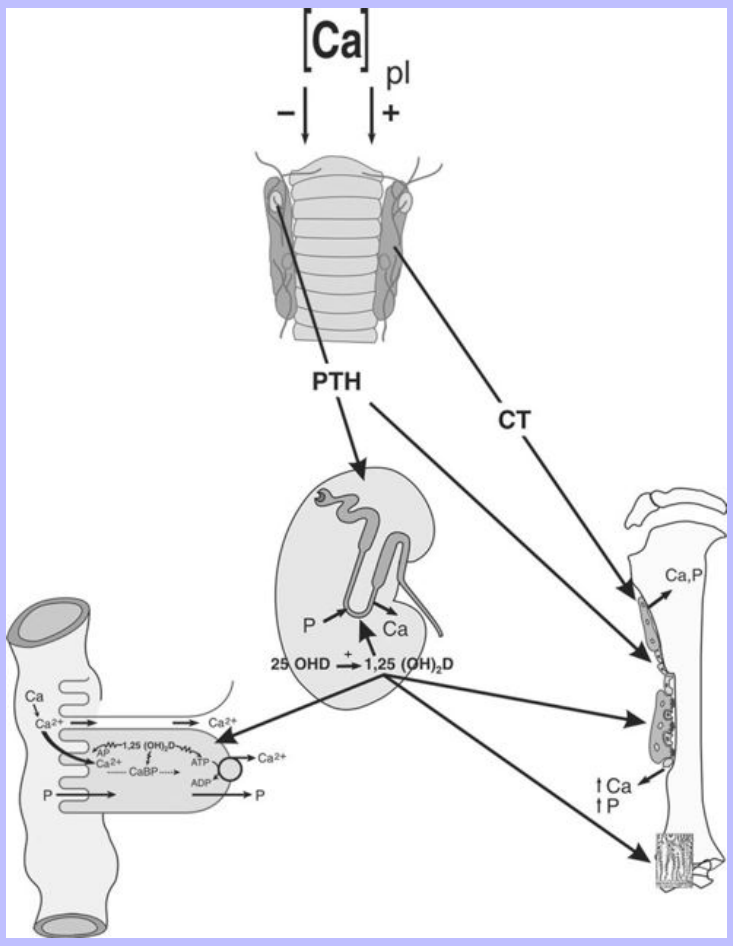
152.3 RICKETS

Hypovitaminosis D in young animals is known as *rickets*, whereas in adults it is called *osteomalacia*. Dietary vitD is absorbed by the intestine and transported to the liver where it is hydroxylated into 25-OHvitD.[1] Dogs and cats are not able to synthesize vitD in their skin under the influence of sunlight, unlike many other species.[1,4] A second hydroxylation takes place in the kidney, either to 24,25$(OH)_2$vitD or to 1,25$(OH)_2$vitD (calcitriol).[1] Calcitriol is the active metabolite that stimulates active absorption of Ca and P in intestine and renal tubular cells. Both metabolites are necessary for osteoid and cartilage mineralization.[1] Rickets is characterized by poor mineralization of newly formed osteoid and cartilage and a thickening of metaphyseal areas of bone.[4] Hypovitaminosis D in adult animals may be more common than the condition in young dogs and cats, but it does not cause obvious clinical signs. It might play a role in chronic renal insufficiency due to decreased capacity of hydroxylation of 25-OHvitD, despite renal secondary hyperparathyroidism. Normal vitD intake together with high Ca intake starting at an early age (3 weeks of life) may cause hypercalcemia, secondary hypoparathyroidism and tertiary decreased calcitriol formation. Rickets is the result.[5,6]

152.3.1 Clinical and Radiologic Examination

An unbalanced diet (either low in animal fat or enriched with calcium salts) fed from an early age onward is the most common problem. Thus a diet history is quite important.

Figure 152-1 Calcium homeostasis regulated by calciotropic hormones. An increase (+) of plasma calcium concentration $[Ca]_{pl}$ stimulates secretion of calcitonin (CT) from the thyroid glands with consequently retraction of the ruffle boarder of osteoclasts (OCL) with—in case of long duration—disturbance of skeletal remodeling and endochondral ossification. A decrease (–) of $[Ca]_{pl}$ stimulates parathyroid hormone (PTH) secretion from the parathyroid glands causing (1) shrinkage of osteoblasts, allowing OCL to resorb bone, and (2) increased reabsorption of Ca and excretion of P and increased formation of $1,25(OH)_2$vitD in the kidney. As a result of the latter, active absorption of Ca and P is increased, renal Ca and P reabsorption is increased, and mineralization of newly formed osteoid and cartilage is stimulated.



Radiographs demonstrate thin long bone cortices and extremely thickened growth plates. Plasma [Ca^{2+}] can be normal or low-normal due to hyperparathyroidism, also causing hypophoshatemia together with hyperphosphaturia (see Alimentary Hyperparathyroidism).[1,6] Determination of circulating vitD concentrations will reveal decreased levels of 25-OHvitD, whereas normal 25-OHvitD but low $1,25(OH)_2$vitD indicates alimentary induced hypoparathyroidism or renal disease.[1]

152.3.2 Treatment

First the diet has to be changed to a major commercial dog or cat food. These foods are known to contain sufficient vitD to resolve and prevent rickets.[1,4] Mineralization of bone cortices, callus, and growth plates will occur within 3 weeks. If the dog or cat fails to respond to a balanced diet, vitD therapy can be recommended.

152.4 HIP DYSPLASIA

Environment, including nutrition, plays a role in the expression of HD. Dogs raised on a diet with high Ca content instead of the recommended level of 1.1% Ca on dry-matter base, have retarded secondary ossification centers.[7] Delayed ossification of the skeleton at a given age, weight, and activity might allow for skeletal deformation when compared with dogs with a more advanced stage of skeletal development. In addition, excessive Ca intake will induce hypercalcitoninism, which may cause decreased skeletal modeling (see Figure 152-1). Changes in femoral neck angle during growth may result from osteoclast activity and can thus be hampered in animals with excess Ca intake.[8] Osteoclast activity can also be influenced by a change in base excess.[9] It has been suggested, but not proven, that an excess of cations (Na, K, Ca, Mg) and the expected compensatory alkalosis lowers bone cell activity and thus skeletal modeling.[9] Hypervitaminosis C can also cause hypercalcemia-induced hypercalcitoninism, contributing to the development of HD.[9,10] Excessive energy intake–induced excess in body weight has negative influences on hip joint development in dogs prone to HD.[9–11] Subluxation of the femoral head together with excess body weight causes the acetabular rim to deform as is seen in young dogs with severe HD. In addition, subluxation causes a corresponding increase in pressure on joint cartilage, which might cause irreversible cartilage damage and thus osteoarthrosis.[9] Excessive dietary protein per se has not proven to influence hip joint development.[3] High calorie intake may result in more rapid rate of growth of young dogs, both in length and in weight, and thus increase the risk of HD to develop.[9,12]

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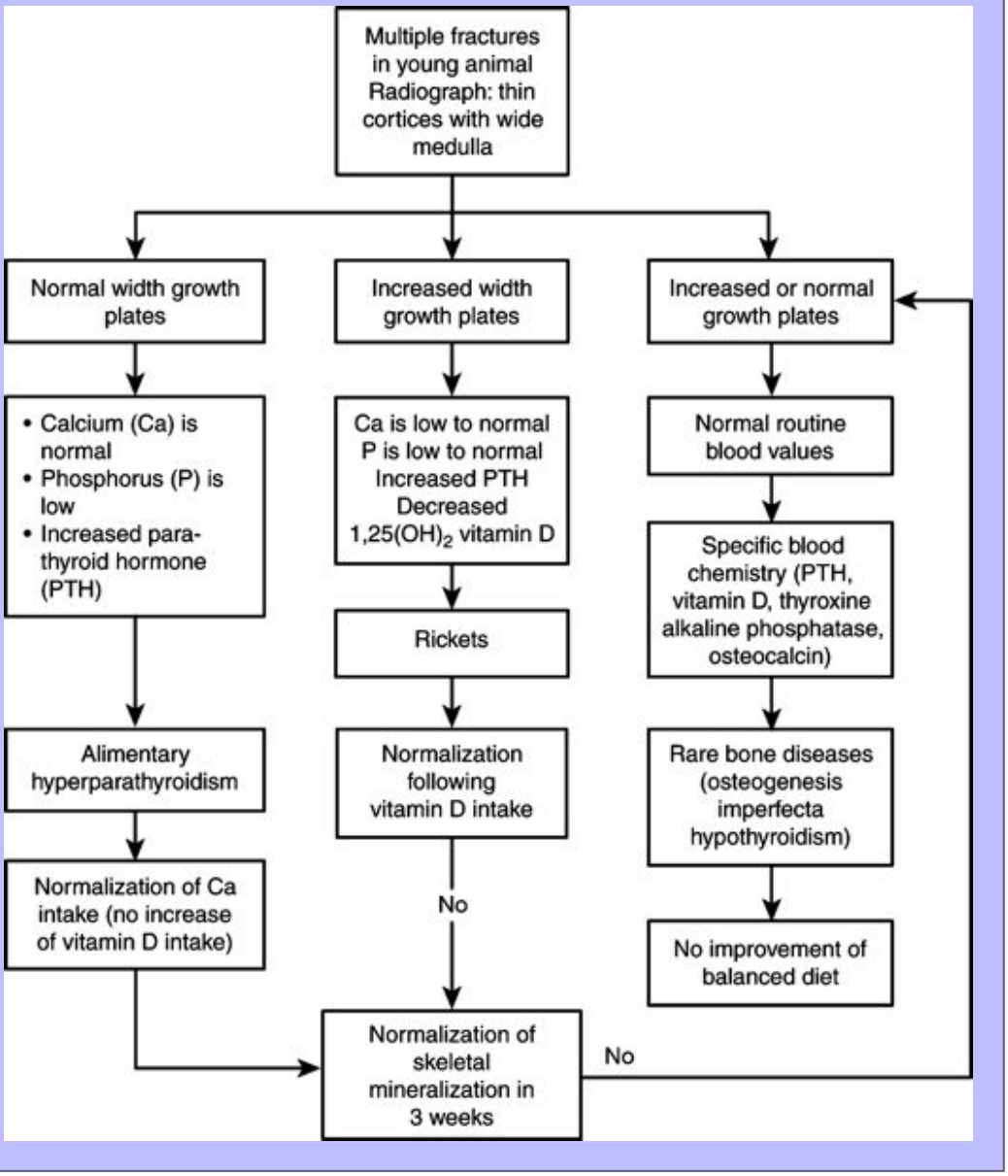
152.4.1 Treatment

Proper nutrition can help prevent HD. Proper nutrition in adult dogs can also serve as a conservative treatment of the osteoarthrosis due to HD. It is advocated to raise young dogs on a balanced diet with appropriate calories but without mineral excess. Nutritional treatment of osteoarthrosis should focus on weight reduction. Omega-3 fatty acids originating from fish may stimulate the synthesis of noninflammatory leukotrienes-5 (LTB_5) rather than the proinflammatory LTB_4. Combinations of chondroitin sulfate and glucosamine may be of benefit for treatment of osteoarthrosis when chronically administered at a dose of sufficient magnitude. In those cases where conservative treatment (activity reduction, appropriate diet and analgesics) is not sufficient in treating osteoarthrosis, surgery may be indicated. Diets restricted in calories (30% to 50% of the current quantity) might be used to assist in weight loss. However, these “light diets” should only be fed to overweight adult dogs and

not to growing young dogs, because the danger exists that such low-energy but complete dog foods fed to a young dog may cause excessive mineral uptake.[9,12]

Figure 152-2 An algorithm for multiple pathological fractures in young dogs and cats.



152.5 OSTEOCHONDROSIS

Growing cartilage is present in the growth plates and around the bony ends. Growth and closure of growth plates depends on age, breed, location, as well as on humoral and nutritional factors.[7] Overnutrition diets with excess Ca, diets with limited energy, and balanced foods with excessive vitD content[13] have all been proven to be important factors in the development of osteochondrosis (OC).[2–4,6,8,13] OC is a disturbance in the process of endochondral ossification of growth plates and joint cartilage. Ossification of cartilage will become clinically evident whenever fissure lines cause a cartilage flap (i.e., osteochondritis dissecans [OCD]). Not relative, but absolute amounts of mineral consumed per kilogram of body weight (or per kilogram of metabolic body weight) have to be taken into account.[6] Dietary Ca diffuses passively through the intestinal wall of the growing dog when dietary Ca content is larger than 1.0% on dry matter basis (dmb); therefore the absolute amount of ingested Ca determines the daily Ca absorption.[14] Ca excess causes hypercalcitoninism with decreased osteoclast activity, decreased skeletal remodeling, and (in large breed dogs) disturbed endochondral ossification.[2,3,8]

152.5.1 Clinical and Radiologic Examination

OC is considered to be a hereditary disease, seen most often in large breed males and rapidly growing females during their developmental growth phase. In case of retained cartilage cones, inspection of the front and rear legs may demonstrate bilateral valgus deformation.[4] In dogs with OCD, palpation and extension of shoulder, elbow, stifle, and tibiotarsal joints may demonstrate overfilling, pain reactions, or both. Measurement of circulating concentrations of Ca, P, calcitonin, and calcitriol may not provide insight into the dietary content or absorption rates of these elements.[5,6,13] Radiographs of growth plates or affected joints may reveal an abnormality in the alignment, whereas other imaging techniques, including arthroscopy, may support the diagnosis.[4,6]

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152.5.2 Treatment

Young dogs of large breeds should be raised with limited amounts of food, preferably a food of good quality and containing ingredients according to the requirements of growing dogs.[9] Overfeeding and oversupplementation must be avoided. The increased level of protein in puppy food will not cause these skeletal disturbances![2,3] Surgery is indicated in case of malalignment or OCD.

152.6 PANOSTEITIS (= ENOSTOSIS = EOSINOPHILIC PANOSTEITIS)

Intake of food, and especially of Ca, causes the release of gastrointestinal (GI) hormones, some of which will cause calcitonin release from the thyroid glands. Increased plasma calcitonin concentrations prevent Ca release from the skeleton by influencing osteoclasts (see Figure 152-1). High Ca intake in young dogs leads to hyperplasia of calcitonin-producing cells with reduced osteoclastic activity, even months after an episode of high Ca intake.[2,6,8] In immature dogs, a large blood supply to the metaphyseal area (bordering the growth plates) exists. This network of arteriolae receives blood from branches of the periosteal side (i.e., the epiphyseometaphyseal arcade) and the medullary arteries. The latter enter the bone mainly in the foramen nutritium. The direction of efferent blood flow is through the diaphyseal cortex, centrifugal from medulla to periosteum, and runs through rigid bone canals including Volkmann's canals.[15] When, during growth, widening of the bony canals lags behind

the growing vessels, vessel occlusion will result in edema formation inside the medullary cavity. Ultimately, new bone formation will take place on the fibrous tissue formed. Increased pressure and finally new bone formation is first seen near the foramen nutritium. Edema may also accumulate underneath the periosteum and thus make the periosteum painful in response to pressure or muscle activity, causing extra lamellar bone formation.[5] So far, no causes other than high food[8] and Ca[6] intake have been demonstrated.

152.6.1 Clinical and Radiologic Investigation

Panosteitis is mainly seen in medium and large-breed dogs (especially German shepherd dogs), starting at 6 months of age with a sudden onset of shifting lameness showing pain reaction upon deep palpation at several long bones. An increased body temperature may be present. Blood investigation or culture of blood or bone is negative, although electrophoresis of plasma proteins may reveal abnormalities.[16] Radiographs demonstrate a blurring of the trabecular pattern and well-defined subperiosteal cortical thickening can be noticed.

152.6.2 Therapy

Because the disease is self-limiting and is not diagnosed in dogs over 22 months of age, treatment is limited to analgesics and nursing of the dogs. Analgesics can relieve pain. Dietary corrections include a decrease in the amount of Ca to the minimal requirements for dogs. The role of dietary proteins is suggested by some[16] and rebutted by others.[2,3]

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153 CHAPTER • 153 Adverse Reactions to Foods: Allergies versus Intolerance

Philip Roudebush

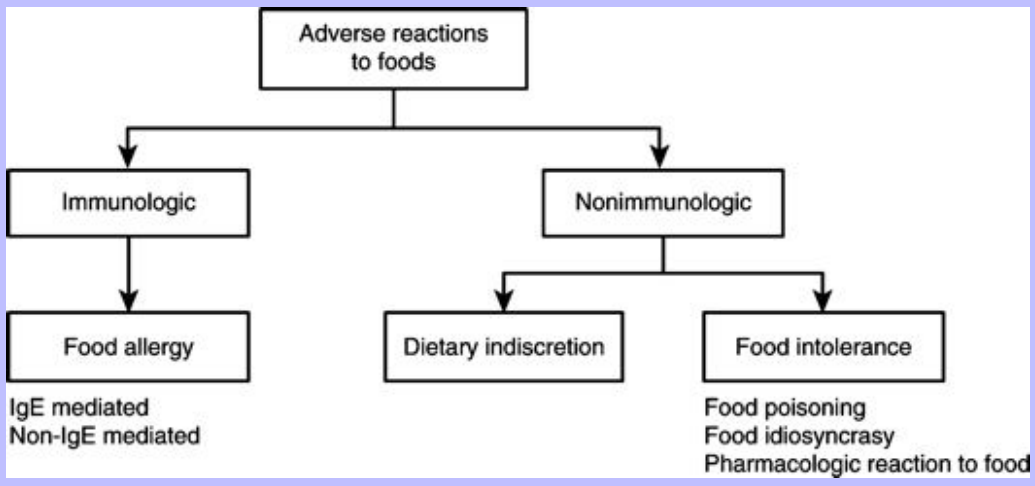
An adverse reaction to food is a clinically abnormal response to an ingested food or food additive. In general, the pathogenic mechanisms that cause adverse food reactions include ingestion of the inciting agent followed by interaction of the agent with a biologic amplification system that leads to inflammation and clinical signs.

In view of the number of diverse foods that are routinely ingested by animals, it is not surprising that adverse reactions develop to dietary substances. The fact that food-related reactions appear relatively infrequently is testimony to the effectiveness of the intestinal mucosal barrier and oral tolerance. Adverse reactions to food have been blamed for a variety of clinical syndromes in cats and dogs, usually involving the skin and gastrointestinal tract.

153.1 TERMINOLOGY

Adverse reactions to food comprise a variety of subclassifications based on pathomechanisms. The following terms and definitions are recommended by the American Academy of Allergy and Immunology (Figure 153-1).[1,2] *Food allergy (food hypersensitivity)* is an adverse reaction to a food or food additive with a proven immunologic basis. *Food anaphylaxis* is an acute food allergy with systemic consequences, such as respiratory distress, vascular collapse, and urticaria. *Food intolerance* is a nonimmunologic, abnormal physiologic response to a food or food additive. Food intolerance can be further classified as food idiosyncrasy, food poisoning, and pharmacologic reactions to food. *Food idiosyncrasy* is an abnormal response that resembles food allergy but that does not involve immune mechanisms. A direct nonimmunologic action on the host of food or a toxin in food is termed *food poisoning*. Adverse reactions due to a druglike or pharmacologic effect of a food substance on the host are called *pharmacologic reactions to food*. When adverse reactions result from such behaviors as gluttony, pica, or ingestion of indigestible materials, the term *dietary indiscretion* is used. Traditionally, the term *food allergy* has been used to describe all adverse reactions to food in dogs and cats, including reactions that were actually food intolerance.

Figure 153-1 Classification of adverse reactions to food.



153.2 FOOD ALLERGENS

The specific food allergens that cause problems in animals have been poorly documented. In general, the major food allergens that have been identified in human beings are water-soluble glycoproteins that have molecular weights ranging from 10,000 to 70,000 daltons and that are stable when treated with heat, acid, or proteases.[3,4] Other physiochemical properties that account for their unique allergenicity are poorly understood.

Twelve different studies, representing a total of 265 dogs, have described cutaneous lesions associated with adverse reactions to specific foods or ingredients.[5] These studies reported findings from a wide geographic area, including the United States, United Kingdom, France, Australia, and Japan. Adverse reactions to beef, dairy products, and wheat accounted for two thirds of reported cases in dogs. Adverse reactions to chicken, chicken eggs, lamb, or soy accounted for approximately 25% of reported canine cases. Adverse reactions to corn, pork, rice, or fish ingredients are rarely reported in dogs.

In cats, 10 different studies, representing a total of 56 animals, have described cutaneous lesions or gastroenteric signs associated with adverse reactions to specific foods or ingredients.[5] These studies have also reported findings from a wide geographic area, including the United States, United Kingdom, France, New Zealand, and Japan. Adverse reactions to beef, dairy products, and fish accounted for more than 80% of reported cases.

Human allergy reference books often have phylogenetic tables of animal and vegetable foods so that food-allergic individuals can avoid other closely related foods. Cross-reactivity among food allergens has been only briefly investigated in pet animals.[6]

153.3 FOOD INTOLERANCE

Nonimmunologic, abnormal physiologic reactions to food include food intolerance and dietary indiscretion (see Figure 153-1). Like the term *food allergy,* the term *food intolerance* has been applied inappropriately to any and all adverse reactions to food. Food intolerance mimics food allergy except that it can occur with the first exposure to a food or food additive, because nonimmunologic mechanisms are involved. The incidence of food intolerance versus food allergy in animals is unknown.

Idiosyncratic adverse reactions to food additives often occur in human beings. Although food additives are frequently cited as the cause of problems in dogs and cats, few data confirm this perception. Propylene glycol and onion ingredients have been documented to cause hematologic abnormalities in cats.[7,8]

Another cause of food intolerance is pharmacologic reactions to substances found in food. Vasoactive or biogenic amines such as histamine cause clinical signs when present in excessive levels in food. Adverse reactions to histamine in scombroid fish (e.g., mackerel, tuna) have been observed in cats and dogs.[9] Vasoactive or biogenic amines may not be present in levels high enough to cause clinical signs, but they may lower the threshold levels for allergens in individual dogs and cats.

The diarrhea, bloating, and abdominal discomfort that occur when animals with lactose intolerance ingest milk are relatively common metabolic adverse reactions in dogs and cats. Osmotic diarrhea often occurs when excessive levels of lactose are consumed. Puppies, kittens, or adult animals may develop diarrhea when given cow's or goat's milk because these milk sources contain more lactose than either bitch's or queen's milk.

Intolerance to disaccharides commonly occurs secondary to enteritis or rapid food changes. Loss of intestinal brush border disaccharidase activity contributes to the diarrhea associated with enteritis. Inadequate intestinal disaccharidase activity is another factor responsible for diarrhea subsequent to rapid food changes. Several days are required for intestinal disaccharidase enzyme activity to adapt to changes in food carbohydrate sources.

153.4 CLINICAL FEATURES IN DOGS AND CATS

153.4.1 Dermatologic Responses in Dogs

Reports of adverse food reactions in dogs with cutaneous disease did not document a gender predisposition, and ages ranged from 4 months to 14 years. However, up to one third of canine cases may occur in dogs less than 1 year old. Because many adverse food reactions occur in young dogs, the index of suspicion for food allergy may rise above that for atopic dermatitis when intense pruritus occurs in dogs less than 6 months old. Most investigators have not found a breed predilection, whereas others have found that cocker spaniels, springer spaniels, Labrador retrievers, collies, miniature schnauzers, Chinese Shar Pei, West Highland white terriers, wheaten terriers, boxers, dachshunds, Dalmatians, Lhasa apsos, German shepherds, and golden retrievers are at increased risk.

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Adverse food reactions in dogs typically occur as nonseasonal pruritic dermatitis, occasionally accompanied by gastrointestinal (GI) signs. The pruritus varies in severity. Lesion distribution is often indistinguishable from that seen with atopic dermatitis; the feet, face, axillae, perineal region, inguinal region, rump, and ears are often affected. Many dogs with adverse food reactions have lesions only in the region of the ears. This finding suggests that adverse food reactions should always be suspected in dogs with pruritic, bilateral otitis externa, even if it is accompanied by secondary bacterial or yeast infections.

Adverse food reactions often mimic other common canine skin disorders, including pyoderma, pruritic seborrheic dermatoses, folliculitis, and ectoparasitism. Twenty percent to 30% or more of dogs with suspected adverse food reactions may have concurrent allergic disease, such as flea-allergy or atopic dermatitis.

Food anaphylaxis is an acute reaction to food or food additives with systemic consequences. The most common clinical manifestation in dogs occurs in localized form and is referred to as *angioedema* or *facioconjunctival edema*. Angioedema is typically manifested by large, edematous swellings of the lips, face, eyelids, ears, conjunctivae, and/or tongue, with or without pruritus. Most veterinary practitioners attribute angioedema solely to insect envenomation (biting or stinging insects); however, a number of other common causes are food, drugs, vaccines, infections, atopy, and blood transfusions. Urticarial reactions (hives) are characterized by localized or generalized wheals, which may or may not be pruritic. They usually occur within minutes of allergen exposure and generally subside after 1 to 2 hours.

153.4.2 Dermatologic Responses in Cats

Gender predisposition has not been documented in adverse food reactions in cats, and ages have ranged from 6 months to 12 years. Siamese and Siamese-cross cats may be at increased risk, because they have accounted for nearly one third of cases.

Dermatologic signs include several different clinical reaction patterns, such as (1) severe, generalized pruritus without lesions; (2) miliary dermatitis; (3) pruritus with self-trauma centered around the head, neck, and ears; (4) traumatic alopecia; (5) moist dermatitis; and (6) scaling dermatoses. Angioedema, urticaria, and

conjunctivitis occur commonly in cats with adverse food reactions. Adverse reactions to food may also cause self-inflicted alopecia (psychogenic alopecia, or neurodermatitis), eosinophilic plaques, and indolent ulcers of the lips in some cats. Concurrent flea-allergy or atopic dermatitis may occur in up to one third of cats with suspected adverse food reactions.

Moderate to marked peripheral lymphadomegaly and absolute eosinophilia are commonly found in cats with dermatologic manifestations of food allergy.

153.4.3 Gastrointestinal Responses in Dogs and Cats

Gender predilections have not been established for GI disease resulting from adverse reactions to foods. Similarly, there are no well-documented breed predispositions to GI food allergy, but Chinese Shar Peis and German shepherds are commonly affected. Gluten-sensitive enteropathy has been well documented in Irish setters. A wide age range of patients can be affected, including dogs and cats as young as weaning age.

Every level of the GI tract can be damaged by food allergies. In cats and dogs, clinical signs usually relate to gastric and small bowel dysfunction, but colitis can also occur. Vomiting and diarrhea are prominent features. The diarrhea can be profuse and watery, mucoid or hemorrhagic. Intermittent abdominal pain is occasionally observed. Concurrent cutaneous signs may be seen. GI disturbances occur in up to 50% of dogs and cats with cutaneous manifestations of food sensitivity. These GI disturbances may be relatively mild such as soft feces, intermittent diarrhea, flatus, and increased frequency of defecation. Adverse reactions to food should always be considered likely in dogs and cats with concurrent cutaneous and GI signs.

The role of food allergy in canine and feline inflammatory bowel disease is unknown. Hypersensitivity to food is probably involved in the pathogenesis of this syndrome; at least some affected animals could be more appropriately diagnosed as suffering from food protein-induced enterocolitis.[2]

Irritable bowel syndrome is a disease of dogs characterized by chronic recurrent abdominal pain and large bowel diarrhea. Feeding changes often alleviate the signs of irritable bowel disease, implying that food allergy or food intolerance plays a role in this syndrome.

153.5 DIAGNOSIS

Dietary elimination trials are the main diagnostic method used in dogs and cats with suspected adverse food reactions. At the present time, intradermal skin testing, radioallergosorbent tests (RASTs), and enzyme-linked immunosorbent assays (ELISAs) for food allergy are considered unreliable in animals.[10,11]

The ideal elimination food should (1) include a protein hydrolysate or reduced number of novel, highly digestible protein sources; (2) avoid protein excesses; (3) avoid additives and vasoactive amines; and (4) be nutritionally adequate for the animal's life stage and condition.[12] Excess protein levels should be avoided so as to reduce the amount of potential allergens to which the dermatologic patient is exposed. However, a higher protein level may be necessary to counteract protein losses from the GI tract or impaired absorption in patients with hypoproteinemia and weight loss associated with severe GI disease. Although elimination trials are performed only for several weeks to months, the food used in the trial should be nutritionally complete and balanced for the intended species, age and lifestyle of the animal. Elimination trials are often performed with young animals, in which nutritionally inadequate foods are more likely to result in nutritional disease.

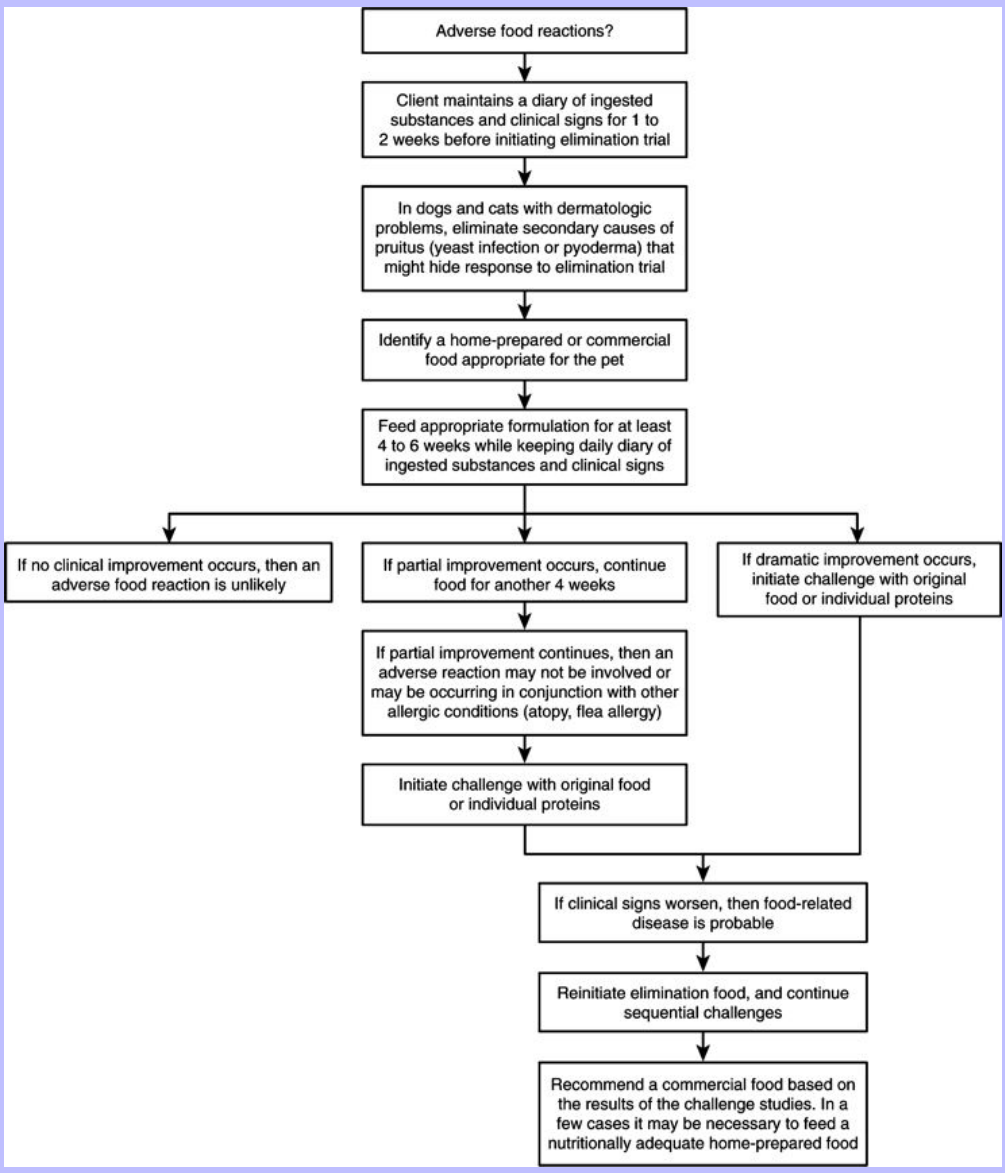
153.5.1 Homemade Elimination Foods

Homemade foods are often recommended as the initial test food for dogs and cats with suspected food allergy. Homemade test foods usually include a single protein source or a combination of a single protein source and a single carbohydrate source. However, many homemade foods fail to meet nutritional requirements because they are made from a minimum of ingredients.[12] In general, homemade foods lack a source of calcium, essential fatty acids, certain vitamins, and other micronutrients and contain excessive levels of protein, which are contraindicated in animals with food allergy. Feeding nutritionally inadequate homemade foods for more than 3 weeks may result in nutritional disease, especially in young animals.

153.5.2 Commercial Elimination Foods

A variety of foods with limited and different protein sources are manufactured by several companies. These commercial products are attractive because they are convenient and nutritionally complete and balanced for either cats or dogs. The newest concept for managing animals with suspected adverse food reactions is use of commercial foods containing hydrolyzed protein ingredients. Veterinary therapeutic foods containing protein hydrolysates offer several hypothetical advantages over traditional commercial or homemade elimination foods. Protein hydrolysates of appropriate molecular weight (less than 10,000 daltons) do not elicit an immunologically mediated response and may be regarded as truly “hypoallergenic” ingredients. Novel or unique protein sources are less important with protein hydrolysates. Protein hydrolysates have been used for many years in human infant formulas and for human patients with various gastrointestinal diseases.

Figure 153-2 Protocol for elimination-challenge trials for the diagnosis of adverse reactions to food. (From Hand MS, Thatcher CD, Remillard RL, et al [eds]: Small Animal Clinical Nutrition, 4th ed. Topeka, Kansas, Mark Morris Institute, 2000.)



Few commercial foods have been adequately tested in dogs and cats with known adverse food reactions; only a few commercial foods have undergone the scrutiny of clinical trials using patients with dermatologic or GI disease. In published clinical trials, two thirds to three fourths of patients with suspected adverse food reactions showed significant improvement in clinical signs when fed commercial foods.

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153.5.3 Performing an Elimination Trial in Patients with Dermatologic Disease

Before an elimination trial is initiated, the client should feed the animal its usual food for several days. During this time, the client should record the type and amount of food ingested, any other ingested food items (e.g., table scraps, treats, and snacks), and the occurrence and character of adverse reactions. The patient is then fed a controlled elimination food for 4 to 12 weeks. During the elimination trial, no other substances should be ingested, including treats, flavored vitamin supplements, chewable medications, fatty acid supplements, or chew toys. The client should document daily the type and amount of food ingested and the occurrence and character of adverse reactions. A daily food diary helps document progression of clinical signs during the elimination trial and whether a strict elimination trial was performed in the home environment. Examples of food diaries can be found in other publications.[12]

A tentative diagnosis of an adverse food reaction in dermatologic patients is made if the level of pruritus markedly decreases. This improvement may be gradual and may take 4 to 12 weeks to become evident.

A diagnosis of an adverse food reaction is confirmed if clinical signs reappear 10 to 14 days after the animal's former food and other ingested substances are offered as a challenge.

Elimination trials are often difficult to interpret because of concurrent allergic skin disease. Patients with other allergic diseases may only partially respond to an elimination trial. Flea-allergy and atopic dermatitis are the most common canine and feline allergies and should be eliminated through other diagnostic testing.

153.5.4 Performing an Elimination Trial in Patients with Gastrointestinal Disease

Elimination-challenge trial designs for patients with GI food disease are similar to those for patients with dermatologic problems (Figure 153-2). However, shorter elimination periods (2 to 4 weeks) are usually satisfactory. In chronic relapsing conditions, the elimination period chosen must be greater than the usual symptom-free period of the patient to allow reliable assessment of how food sensitivity contributes to the patient's signs.

As with skin disease, the degree of clinical improvement during the elimination trial will be 100% only if food allergy or food intolerance is the sole cause of the patient's problems. For instance, resolution of allergies acquired as a result of GI disease will not eliminate the clinical signs due to the primary GI disease process. Recrudescence of GI signs after challenge of a food-sensitive patient with the responsible allergen usually occurs within the first 3 days but may take as long as 7 days, particularly if the responsible allergen was removed from the food for longer than 1 month.

153.6 TREATMENT

For most food allergies, avoiding the offending foods is the most effective treatment. How selective or meticulous an avoidance diet must be depends on the individual animal's sensitivity. Some dogs and cats may suffer adverse reactions to even trace amounts of an offending food, whereas others may have a higher tolerance level. Concurrent allergies influence the threshold level of clinical signs in some animals. Symptomatic therapy in pruritic animals can also include corticosteroids and antihistamines. Corticosteroids, along with dietary change, are often used in cats with inflammatory bowel disease.

Both homemade and commercial foods can be used for long-term maintenance of patients with suspected food allergy. It is very important that any homemade recipe for long-term maintenance ensures a nutritionally adequate ration. An attempt should always be made to find an acceptable commercial food that will increase owner compliance with the dietary change and ensure a nutritionally adequate ration.

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154 CHAPTER • 154 Nutritional Management of Gastrointestinal Conditions

Debra L. Zoran

The gastrointestinal (GI) tract is a complex systemprimarily responsible for acquiring and digesting food, absorbing nutrients and water, and expelling wastes from the body in the form of feces. A proper diet andnormally functioning GI tract are integral to the deliveryof nutrients, the prevention of nutrient deficiencies andmalnutrition, the repair of damaged intestinal epithelium, the restoration of normal luminal bacterial populations, the promotion of normal GI motility, and the maintenanceof normal immune functions (e.g., both tolerance of andprotection from pathogens).[1] Dietary characteristics, suchas the amount of food, its form, the frequency of feeding, and the composition of the diet, also have important effects on GI function and may be used to help ameliorate signsof disease. Both nutrients and non-nutritional componentsof a diet support normal GI functions, but they also maycause or influence the development of GI pathology (e.g., antibiotic-responsive diarrhea [ARD], inflammatory bowel disease [IBD], and dietary intolerance or sensitivity/allergy). In chronic or severe GI disturbances, diet may have a profound effect on intestinal recovery and successful management of the disease.

154.1 ROLE OF CONSISTENCY, FREQUENCY, AND MEAL SIZE

For many acute, non-life-threatening GI disturbances, treatment customarily includes the withholding of food and water for24 to 72 hours, along with correction of fluid and electrolyte deficits. This approach often is an effective treatment forvomiting or diarrhea due to dietary indiscretion or for mild forms of infectious or toxin-induced gastroenteritis.[2] After this short fasting period, the dog or cat should be fed a highly digestible diet (i.e., minimal fat and easily digested proteinand carbohydrate [CHO] sources). This should be followed by gradual reintroduction of the original diet. In previously healthy animals, fasting would not be expected to be harmful nutritionally, systemically, or to the GI tract. However, the traditional approach of “resting” the GI tract (i.e., extended fasting) may be harmful or may prolong recovery, especially in injured or sick animals fasted longer than 3 to 4 days or in any nutritionally compromised animal. Deficiency of protein and calories leads to immune system dysfunction, reduced availability of antioxidants and free radical scavengers, reduced energy for vital cellular functions, lack of precursors for repair of injured or diseased tissue and, ultimately, loss of lean body mass.[3] Prolonged fasting also deprives the GI epithelium of its primary metabolic fuel source, the glutamine present in chyme.[4] This metabolic fuel is necessary not only for replacement of theGI mucosal cells lost in normal turnover (every 3 to 5 days), but also for repair of mucosal injury.[4]

One alternative is to provide an oral rehydration solution containing CHO, peptides, and electrolytes to “feed through the diarrhea” in animals that are not vomiting or severely dehydrated (including glutamine).[5] However, if the animal is vomiting or the gut is not functional, the animal's protein (including glutamine) and calorie needs, can and should be met through parenteral nutritional support.[6] Whatever route is chosen, feeding should be instituted as soon as possible. A good rule of thumb for induction of nutritional support is the 3-5-7 day rule: On day 3 of anorexia, planning should begin for implementation of nutritional support, and the plan should be implemented by day 5; otherwise, by day 7 protein and calorie malnutrition will occur, requiring an immediate response.

A major consideration in choosing a diet to feed an animal with GI disease is nutrient digestibility. Typical maintenance pet foods have protein and CHO digestibilities ranging from 70% to 85% on a dry matter (DM) basis.[7] Pet foods formulated for dietary therapy of GI disease have CHO and protein digestibilities of 90% DM or

higher.[7] Therapeutic dietsalso have low levels of fat (less than 15% DM in cats and less than 10% to 15% DM in dogs), are lactose free, and have reduced amounts of dietary fiber and other poorly digestible CHO. Many different, highly digestible, therapeutic diets areavailable. Each formula is unique and therefore can elicit adifferent individual response. For example, these diets have different protein or CHO sources and varying levels and types of fat (e.g., some add omega 3 fatty acids), and some areformulated with ingredients designed to enhance GI health, such as fructooligosaccharides (FOS). Although the benefits of these individual additives have not been proven in large clinical trials, feeding highly digestible diets to pets with both acute and chronic GI diseases is widely accepted as beneficial.

The amount of a diet fed should be calculated based onthe energy needs of the individual animal. Although there is ongoing discussion among nutritionists regarding the best equation for determining the energy requirements of sick animals, at the very least, the resting (or basal) energy requirements (RER) should be met.[8] One generally accepted equation for determining resting energy requirements in dogs and cats is 70 $(BW_{kg})^{0.75}$. Once energy requirements have been determined, meal size, frequency, and consistency are considered. Generally, small meals (e.g., less than one third of stomach capacity) are fed several times per day (three to six meals). The feline stomach has a smaller capacity (approximately 60 mL/kg) and is less distensible than the stomach of a dog (nearly 80 to 90 mL/kg), which is designed for greater storage.[9] Feeding small meals reduces gastric distension, decreases gastric acid secretion, and may reduce nausea, vomiting, and gastroesophageal reflux.[1,7] Furthermore, the larger the volume of food ingested, the less that can be effectively assimilated. In general, liquid diets empty faster from the stomach than canned foods, and canned foods empty faster than dry.[7] Therefore if liquid diets are fed too quickly or in large volumes, diarrhea may occur. In veterinary medicine, liquid diets are primarily used in specialized circumstances (e.g., for nasoesophageal or jejunostomy tube feeding) or with certain GI conditions (e.g., esophageal stricture, selected cases of megaesophagus, or gastric outflow disturbances) because they may reduce regurgitation or vomiting.

154.2 NUTRIENT COMPOSITION

A variety of nutritional and non-nutritional diseases affect the GI tract; however, treatment of most GI disease is enhanced by appropriate diet selection. Numerous therapeutic diets are available for treatment of GI disease, including highly digestible diets, novel antigen or so-called hypoallergenic diets, hydrolyzed protein diets, and diets with increased dietary fiber. Each of these diets may be used in the management of various GI disturbances; however, selection of the most appropriate diet requires an understanding of the differences in the nutrient composition of these formulations. Furthermore, under some circumstances, specific diets (e.g., homemade or novel) are required for successful dietary management of severe GI disease.

154.3 PROTEIN

The effects of protein on the GI tract are subtle and oftenless clinically obvious than those of fat or CHO, but they are no less important. Protein in the GI tract increases lower esophageal sphincter pressure; is a potent stimulus for the secretion of hormones, including gastrin and pancreatichormones; and increases both gastric emptying and intestinal transit.[1,7] Despite this, protein malassimilation is not a major stimulus for diarrhea; for example, dogs with protein-losing enteropathies (PLE) often do not have diarrhea unless they have concurrent fat malabsorption. However, intact protein reaching the distal small intestine and colon increases bacterial ammonia production, alters bacterial numbers and species, and may contribute to colitis or colonic hypersensitivity.[10] Furthermore, protein antigens in food are responsible for the development of most food hypersensitivity reactions in dogs and cats (see Chapter on food hypersensitivity). In animals with severe mucosal disruption (e.g., IBD, lymphoma),

intact proteins cross the mucosa, exposing the mucosal immune cells of the lamina propria to these antigens. This results in the development of hypersensitivity to that protein and perpetuation of the aberrant immune response. For this reason, feeding a “sacrificial” diet during the initial stages of therapy of severe GI disease, until the inflammation is under control, has been recommended.[11] Once the inflammatory disease has been suppressed, a new, highly digestible or novel antigen diet can be introduced for long-term therapy. Feeding hydrolyzed diets (e.g., peptides of less than 15,000 daltons) in this situation may be beneficial as there is no intact protein to stimulate animal response. However, epitopes may still exist on these peptides that can be recognized as foreign, and thus may not eliminate the possibility of immune stimulation, nonetheless, anecdotal evidence suggests many dogs and cats benefit from this dietary approach.

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Protein-losing enteropathies are a group of severe intestinal diseases that occur as primary enteropathies (e.g., lymphangiectasia) or familial enteropathies (e.g., soft-coated wheaten terriers, basenjis, Irish setters[12]). Alternatively, they occur secondary to infectious, neoplastic, or inflammatorydiseases that infiltrate the GI mucosa and result in loss of mucosal function, including malassimilation of nutrients, motility disturbances, and loss of normal gut functions.[12] Protein loss may also occur from a lack of available or functional enzymes, such as exocrine pancreatic insufficiency (EPI). Regardless of the cause, nutritional therapy is anessential aspect of successful management of PLE. Inmild forms of PLE, feeding a highly digestible, low-fat diet, in addition to specific therapy for the primary disease, maybe sufficient. However, when severe intestinal disease results in significant loss of serum proteins (serum albumin lessthan 1.5 g/dL), subsequent development GI mucosal edema causes further nutrient malassimilation. In these animals, hydrolyzed diets or elemental diets (e.g., diets containing no intact nutrient sources) may be required. In animals with severe PLE, a combination of parenteral and enteral nutrition may also be needed to replace lost oncotic proteins, resolvegut edema, and correct protein-calorie malnutrition. Once serum albumin concentrations are more stable (greater than 1.75 g/dL) highly digestible, low-fat diets containing intact protein may be tolerated. However, some dogs with PLE may require feeding of ultra-low-fat homemade diets (e.g., nonfat cottage cheese, egg whites, rice, cooked potatoes) or combinations of hydrolyzed, ultra-low-fat (less than 10% fat DM), or elemental diets indefinitely.[11]

154.4 FATS AND FATTY ACIDS

Generally, the higher the density of nutrients, the slower the food empties from the stomach. This is primarily because most nutrient-dense foods are higher in fat, which slowsgastric emptying in both dogs and humans but not in cats.[1,7] In contrast to the effects of protein, increased levels of dietary fat decrease the tone of the lower esophageal sphincterand may lead to an increased risk of gastroesophageal refluxor vomiting.[13] Because digestion and absorption of fat isa complex process, malassimilation of fat in animals withGI disease is common. Fat or fatty acids reaching the distal ileum or colon increase the fermentation of bacteria (especially nonbeneficial species), result in the formation of proinflammatory and prosecretory hydroxy fatty acids, andcan cause osmotic diarrhea.[10,13] Nevertheless, the complete absence of fat from the diet is also undesirable and maylead to a deficiency of essential fatty acids. Essential fattyacids must be supplied to provide the phospholipid and cholesterol building blocks for cellular growth and repair and for synthesis of prostaglandins, leukotrienes, and thromboxanes.[13] Dietary fat is also important because it enhances the palatability and acceptance of food, and it is an essential energy source for sick or injured animals that cannot effectively utilize CHO.

Recently, attention has been focussed on the addition of anti-inflammatory omega 3 fatty acids (fish oils) to dietsused for therapy of GI disease. In humans with ulcerativecolitis, the addition of fish oils to the diet resulted in a reduction in inflammatory mediators, improved mucosal function and fluidity, and reduced the use of anti-inflammatorydrugs to maintain control of the disease.[14] The clinical benefit of fish oils in the treatment of

inflammatory skin disease in dogs is well recognized; however, studies specifically assessinga reduction of intestinal inflammation in dogs and catsfed omega 3 fatty acids are lacking. Nevertheless, sometherapeutic diets have omega 3 fatty acids added to theirformulations.

154.5 CARBOHYDRATES

There are no requirements for CHO in the diet of dogs or cats. The CHO present in pet foods are primarily plant starches, such as rice, potato, corn, wheat, and barley.[13] Another typeof CHO present in some diets are the beta-linked polysaccharides (i.e., those not readily broken down by mammalian amylases), which include the dietary fibers.[13] CHO digestibility is determined by its origin and the degree of cooking;for example, rice and wheat are generally highly digestible, whereas uncooked maize or potato starch is less digestible.[13] CHO malassimilation results in the development of osmotic diarrhea, the production of increased intestinal gas (flatus), loss of water and electrolytes, increased fermentation ofbacteria in both the small intestine and the colon, overgrowth of pathogenic bacteria, and acidification of the colonic luminal environment, promoting the formation of hydroxy fatty acids and other potentially toxic intermediates.[7,13] White rice is the CHO of choice for most dogs (and is the most commonly used CHO in therapeutic diets), because it is gluten free (some dogs, especially Irish setters and soft-coated wheaten terriers, are sensitive to gluten or may develop sensitivity to gluten, which is present in wheat, oats, and barley), highly digestible, and nonantigenic.[1,2,7,12] Other gluten-free CHO sources include potato, corn, and tapioca, but potato and tapioca are less digestible, and corn may be antigenic to animals prone to develop food sensitivity.

Dietary fibers are a large, complex group of CHO that include starch and nonstarch polysaccharides found in plants; they are readily digested by bacterial enzymes but less well digested by mammalian enyzmes.[13] Traditionally, fibers were classified as *soluble* (highly fermentable) or *insoluble* (poorly fermented or nonfermentable) based on their digestion by amylase; however, a physiologically relevant classification, based on their activity in the GI tract, is currently recommended. Fibers are soluble if they form gels in solution (thus attracting water), delay gastric emptying and slow intestinal transit, inhibit the absorption of cholesterol and some other nutrients, are poor bulking agents, are highly fermentablein the colon (i.e., increase the numbers of bacteria and increase short chain fatty acids, especially butyrate, an essential colonic fuel source), acidify the lumen, and stimulate colonic cellular proliferation.[1,15] Examples of soluble fibers include FOS, pectins, psyllium, oats, barley, guar gum, fruits, and some legumes.[13] Insoluble fibers do not form gels, haveno effect on gastric emptying, increase or “normalize” intestinal transit, have no effect on nutrient absorption, are good bulking agents (i.e., dilute colonic content and thus bindnoxious agents in the colon), are fermented less and therefore produce fewer short chain fatty acids, and increase fecal weight.[1,15] Typical examples of insoluble fibers are cellulose, wheat and rye fibers (most cereal fibers), and the woody parts of plants (e.g., lignins).[13]

FOS are kestose or nystose sugars present in a varietyof fruits, vegetables, and grains that behave in the GI tractlike soluble fibers. These sugars have generated considerable interest in both human and veterinary medicine, because they are preferentially fermented by beneficial bacterial species(e.g., *Lactobacillus* and *Bifidobacteria* spp.) and prevent the growth of pathogenic species.[16] In studies of humans with IBD or colitis, adding FOS to the diet greatly improved the response to therapy, clinical disease was reduced, and relapses were fewer.[17] Only a few studies in dogs (and even fewer in cats) have evaluated the role of FOS in the dietary therapy of GIdisease. However, preliminary evidence supports the finding in humans that FOS increases the numbers of beneficial bacteria in the colon of both dogs and cats[18,19] and may prove beneficial in controlling bacterial overgrowth, ARD, or other inflammatory diseases believed to have a bacterial origin (e.g., IBD).

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Table • 154-1 Vitamin Deficiencies Caused by Severe Intestinal Disease

VITAMIN	SIGNS OF DEFICIENCY	COMMENTS
A	Impaired growth, loss of epithelial integrity	Stored in liver; deficiency is rare
D	Osteomalacia, nutritional secondary hyperparathyroidism	Stored in liver; cats more likely to be deficient
E	Dermatoses, pansteatitis	Caused by malabsorption
K	Hemorrhage, increased PT	Caused by fat malabsorption
Thiamin (B_1)	CNS dysfunction, anorexia, muscle weakness	Cats more likely to be deficient; thiaminase
Riboflavin (B_2)	CNS dysfunction, dermatitis	Important cofactor in energy metabolism
Niacin (B_3)	Oral/mucosal disease	Cannot be synthesized by cats, which have a greater requirement for B_3
Pyridoxine (B_6)	Microcytic, hypochromic anemia	Greater requirement for B_6 in cats
Pantothenic acid	Anorexia, weight loss	Part of coenzyme A; deficiency is rare
Biotin	Dermatitis	Eggs a rich source
Choline	Neurologic dysfunction, fatty liver	Methyl donor; synthesized in the body
Cobalamin (B_{12})	Anemia (cofactor for energy metabolism)	GI disease may cause deficiency; some of the vitamin is stored.
Folic acid	Anemia, leukopenia	DNA synthesis, bacteria can synthesize
C		Not required

154.6 NUTRITIONAL DEFICIENCIES RESULTING FROM GASTROINTESTINAL DISEASE

Nutritional deficiencies commonly occur as a consequenceof GI disease.[20] Protein and calorie malnutrition is the most common nutritional deficiency in severe or chronic GI disease. Not surprisingly, deficiencies of electrolytes (e.g., sodium, potassium, chloride, and bicarbonate) and divalent cations (e.g., magnesium, zinc, and calcium) are also common and shouldbe corrected.[20] A variety of vitamin deficiencies may occur as a result of severe intestinal disease (Table 154-1). Deficiencies of B vitamins, especially cobalamin, and of some of the fat-soluble vitamins (E and K) are the most common and clinically important micronutrient deficiencies recognized in dogs and cats.[1,7,20] Little is known about deficiencies of microminerals; however, it is reasonable to assume that levels of copper, selenium, zinc, and others may be affected and deficiencies thus corrected by nutritional support.

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155 CHAPTER • 155 Nutritional Management of Hepatic Conditions

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The objectives of nutritional therapy in dogs and cats with liver disease are to provide optimal conditions for hepatic repair and regeneration and to prevent or manage complications of hepatic failure, such as hepatic encephalopathy. Hepatic healing and maintenance require a positive caloric balance and nitrogen intake with some consideration given to particular nutrients in certain types of hepatic disease.

155.1 CALORIES AND FEEDING FREQUENCY

The major consequences of malnutrition in any animal are decreased immunocompetence, decreased tissue synthesis and repair, and altered intermediary drug metabolism.[1] The foundation of adequate nutritional management of a dog or cat with hepatic disease is the provision of adequate calories. It is prudent first to provide for the total caloric need and then to consider the protein requirement. When sufficient calories are supplied as fat or carbohydrate, less endogenous or dietary protein is catabolized for energy, resulting in a decrease in the demand to metabolize nitrogen to urea. Enteral nutritional support is preferred to parenteral nutrient administration because it provides antigenic stimulation to the gut-associated lymphoid tissue (GALT) and stimulates secretion of IgA, which helps maintain an intact gut barrier to prevent bacterial translocation into the portal circulation. The method and quantity of food fed must be adjusted according to the animal's ability to handle metabolites. Small, frequent meals (three to six per day) help optimize blood flow through the liver, manage fasting blood glucose, and minimize episodes of hepatic encephalopathy. In the dog, blood glucose concentrations are maintained through glycogenolysis, which begins within 4 to 5 hours of the last meal. The liver exports glucose in order to maintain blood glucose concentrations. In a normal liver, blood glucose concentrations can be maintained through glycogenolysis for another 12 to 28 hours without food. A diseased liver with fewer functioning cells cannot store normal amounts of glycogen and adequately maintain blood glucose concentrations between meals. In the cat, blood glucose concentrations are maintained through gluconeogenesis from fat and protein stores because hepatic glycogen stores are normally minimal. Hepatic glycogen storage in cats is relatively small compared with dogs due to lower glycogen synthase and glucokinase activities. Nonprotein calories should come from highly digestible carbohydrate and fat sources. Most dogs and cats with liver disease can adequately digest and absorb dietary long chain fats; hence, fats should not be routinely restricted unless there is clinical evidence of steatorrhea.

155.2 PROTEIN QUANTITY AND QUALITY AND AMINO ACID PROFILE

Body protein content is not static, but rather is always in a flux between anabolism and catabolism. Protein degradation involves deamination of amino acids. The resulting carbon skeleton is oxidized for energy, and the amino group enters the urea cycle. Under normal metabolic circumstances, about 15% of the daily energy expenditure occurs through the oxidation of amino acids.[2] Protein intake should be balanced with calories consumed. Sufficient calories must be available from fat or glucose before amino acids are used for tissue synthesis and repair. Hence, every effort should be made to minimize protein catabolism in any animal with hepatic disease. Excessive protein feeding requires energy expenditure to rid the body of excess nitrogen, which may not be handled well by the liver and kidneys. Feeding excess nitrogen can result in azotemia or hyperammonemia and accompanying clinical signs of encephalopathy. Conversely, insufficient protein intake has been linked to a low serum albumin concentration, poor immune response, poor healing, and increased risk of

dehiscence and muscle wasting. Hospitalized animals with hepatic disease receiving parenteral nutrition do well clinically with 3 to 5 g of protein per 100 kcal at resting energy requirements (RER). Therapeutic diets well tolerated by dogs contain 3 to 4 g/100 kcal, but feline diets should contain 6 to 7 g/100 kcal. Protein recommendations per 100 kcal of energy are not the same as per kilogram of body weight (BW). Administration of 5 to 6 g of protein on a BW basis delivers 40% more than on a per calorie basis and has resulted in encephalopathic signs in sensitive animals. The protein intake for a particular dog or cat should be adjusted according to the animal's ability to handle these initial protein recommendations.

155.3 VITAMINS, CARNITINE, AND CHOLINE

Water-soluble vitamins are coenzymes that are vital to optimal hepatic metabolism. Folic acid, thiamine, riboflavin, niacin, pantothenic acid, pyridoxine, and B_{12} are essential for hepatic metabolism of glucose, fat, and protein. They are essential coenzymes in the Krebs cycle and for adenosine triphosphate (ATP) production and red blood cell metabolism. They are required in small amounts relative to other nutrients but are required daily and are not optional if tissue energy metabolism is to operate efficiently. These vitamins are easily and inexpensively replaced and should be included in all forms of nutritional support. Few dogs or cats require fat-soluble vitamin supplementation unless there is a history of prolonged weight loss, inappetence, and decreased fat absorption. Animals with long-standing liver disease may benefit from fat-soluble vitamin supplementation because vitamins A, D, and K are primarily stored in the liver. In these cases, it is much simpler and more cost-effective to administer 1 mL of a vitamin A, D, and E product* intramuscularly every 3 to 4 months. Intramuscular or subcutaneous administration of vitamin K_1 (1 to 5 mg/kg body weight/day) may be required for several days.

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Carnitine is an essential cofactor in mitochondrial transport of fatty acids and in subsequent long chain fatty acid beta-oxidation in all cells. Carnitine, residing in the mitochondrial intermembranous space, binds and transports fatty acyl-CoA into the mitochondrial matrix, where beta-oxidation takes place. Carnitine requirements are met by de novo hepatic synthesis using lysine and methionine, but carnitine is viewed as a conditionally essential nutrient when de novo synthesis is inadequate. There is no stated minimum carnitine concentration for pet foods. Beginning in 2002, carnitine supplementation of cat foods was allowed under the regulations of the Association of American Feed Control Officials (AAFCO) at levels not to exceed 1000 ppm on a dry matter basis (DMB).

Choline is an important methyl donor that is required for de novo synthesis of phosphatidyl choline, which is essential in the packaging of very low density lipoprotein (VLDL) in the liver and, therefore, hepatic exportation of triglycerides. A choline deficiency with concurrent lipolysis may slow VLDL export and promote hepatic lipid accumulation. In humans and rats, choline deficiency has been shown to result in tri-acylglyceride (TG) accumulation, depress VLDL synthesis, and cause liver dysfunction.[3] There is clearly a relationship between carnitine and choline. Tissue levels of carnitine are decreased in choline-deficient rats; conversely, adding choline to a choline-deficient diet has been shown to increase hepatic carnitine levels. Although there is evidence and a rationale for the importance of carnitine and choline as separate cofactors in hepatic lipid metabolism, a synergistic relationship may actually be the key. All complete and balanced cat foods should contain at least 60 mg choline/100 kcal, according to AAFCO regulations. Hepatic recovery diets should contain choline and carnitine, although the efficacy levels are not known.

* Vital E-A+D, containing 100 kIU vitamin A, 10 kIU vitamin D, and 300 IU alpha tocopherol per milliliter (Schering-Plough Animal Health Corp., Kenilworth, New Jersey).

155.4 ANTIOXIDANT SUPPLEMENTATION

There is evidence of free radical damage in certain types of liver disease. Two endogenous antioxidant systems exist to scavenge free radicals, a cytosolic system and a membrane-bound system, but they often require a nutritional cofactor. Adding antioxidants to the diet, although the exact effective dose is truly unknown, appears to be reasonable. These “antioxidant” nutrients are known to be part of the body's antioxidant system (directly and indirectly) and may ultimately help minimize the tissue damage. Antioxidant nutrients—vitamin A as beta carotene (5000 IU), vitamin C (250 to 1000 mg), vitamin E as alpha tocopherol (200 to 500 IU), zinc (7.5 mg), selenium (15 µg), copper (1 mg), and manganese (1.5 mg)—are reasonable daily dosages per os with food for a 10 to 30 lb dog or cat. Supplements carrying a United States Pharmacopeia (USP) label are recommended, and the product must be stored at refrigerator temperatures in a container protected from light.

A plethora of herbal remedies have been touted for hepatic patients; however, only two are currently worth consideration: S-adenosyl-L-methionine (SAMe) and milk thistle. Herbal remedies are not nutritional supplements. Taken orally, they should be viewed as compounds with pharmacologic properties.

155.5 NUTRITIONAL CONCERNS IN SPECIFIC HEPATIC CONDITIONS

155.5.1 Feline Hepatic Lipidosis

Hepatic lipidosis (HL), a well-recognized syndrome that occurs in several companion animal species, is characterized by the accumulation of triacylglycerides, which causes hepatic dysfunction and cholestasis. HL historically has been associated with anorectic, obese cats; however, cats with a normal or thin body condition also can be afflicted. Prolonged inappetence is the common denominator, often resulting from a stressful event or occurring secondary to another disease (e.g., diabetes, pancreatitis, cholangiohepatitis). The changes in liver metabolism that occur during HL are similar to those that occur during food deprivation. In the adaptation from the fed to the starved state, fuel usage by the animal shifts from primarily a mixture of fuels to one in which the primary fuel is fatty acids. In cats, lipolysis delivers fatty acids as triglycerides to the liver within hours of fasting because glycogen stores are normally small. The exact metabolic or biochemical aberration or aberrations responsible for the accumulation of fat in the liver during HL are not known. Protein deficiency, lipid oxidation abnormalities, and decreased VLDL exportation are under consideration.

Regardless of the biochemical derangement, it is clear from clinical responses that in feline hepatic lipidosis, adequate caloric and protein intake is the key to recovery. The provision of calories and protein in a complete and balanced formulation, delivered as small, frequent meals or as a continuous rate infusion (CRI), is the only known treatment. Overfeeding must be avoided. Hence, a balanced formulation sufficient to meet the cat's RER (20 kcal/lb BW) at its current weight is a safe starting food dose. However, grossly obese cats with a body condition score of 8/9 or 9/9 may be carrying 35% or more fat; these cats should not be fed at their current body weight, but rather at a lower, estimated optimal weight. If clinical signs of hepatic encephalopathy should begin with feeding, the food dose should be reduced by 50% until signs resolve. Serum phosphorus and potassium levels should be monitored daily during the first few days of refeeding to avoid a clinically relevant decrease caused by the intercellular electrolyte shift that occurs with refeeding. If electrolyte abnormalities occur, the feeding dose should be reduced by 50% and corrective fluid therapy must be instituted. If electrolyte abnormalities persist or become difficult to correct, measurement of and supplementation with magnesium should be considered.

Cats with HL appear to metabolize both enterally and parenterally administered lipids in the form of chylomicrons without exacerbation of clinical signs. The key to the hepatic derangement may lie in the differences between how various types of fat are metabolized in cats. When enteral feeding is not possible due to vomiting or encephalopathy, parenteral nutrition (PN) administration using fat, dextrose, and amino acids (4 g/100 kcal) is possible and should be instituted until a feeding tube can be placed. Fewer (1 g/100 kcal) or no amino acids may be required with hepatic encephalopathy (HE). Administration of a 20% lipid product* at RER through a peripheral catheter for 24 to 48 hours has worked well, as evidenced by improved hepatic serum profiles, when no better feeding alternative is possible. When a feeding tube of any type has been successfully placed, cats with small bowel atrophy due to prolonged anorexia (longer than 5 days) should be fed a monomeric diet with glutamine at RER for the first 24 to 48 hours.† Bolus feeding often can begin as three to six (30 ml) meals per day in a 4.5 kg cat. Initially, feeding via CRI (5 to 10 mL/hour) using a pump or gravity and a liquid product works very well for cats intolerant of bolus feedings and does not cause refeeding diarrhea.‡ 575

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In cats with HL, the plasma, liver, and skeletal muscle concentrations of carnitine are increased relative to normal cats.[4] Despite this generalized increase in synthesis, the overall carnitine levels attained are still inadequate to meet the body's demands when dietary intake is poor or nonexistent. When a cat is fed enterally, carnitine-supplemented cat foods should be fed to aid the animal's recovery. Choline, like carnitine, may become deficient in anorectic cats; however, the roles of dietary choline and carnitine in feline HL have not been investigated.

* LipoSyn II (Abbott Laboratories, Abbott Park, Illinois); IntraLipid (Baxter Healthcare Corp., Deerfield, Illinois).

† Perative (Ross Products, a division of Abbott Laboratories); Peptamen (Baxter Healthcare Corp.).

‡ Feline CliniCare (Ross Products).

155.5.2 Cholangitis, Cholangiohepatitis, Hepatitis, and Cirrhosis

Nutritional strategies are intended to control the complications of hepatic failure. This goal is met by (1) reducing ammonia and ascites formation; (2) compensating for altered dietary lipid, essential fatty acid, and fat-soluble vitamin absorption; and (3) reversing hypoalbuminemia if present.[5] In the refeeding of an anorectic, catabolic animal, provision of calories above the resting energy expenditure, particularly as glucose, may result in metabolic and septic complications.[6] The liver plays a central role in blood glucose homeostasis through the processes of glycogenolysis and gluconeogenesis. Insulin resistance with subsequent glucose intolerance, as evidenced by hyperglycemia, hyperglucagonemia, and hyperinsulinemia, may develop in dogs or cats with liver disease.[7] Liver and, in some cases, muscle glycogen stores are depleted in chronic liver disease, leaving body fat as the main source of energy between meals. In comparison to a dog with normal liver function, glycogen stores may provide substrate only for 10 to 12 hours in a dog with cirrhosis. As a result of impaired glycogen stores, protein catabolism is accelerated.

There is no consensus regarding the level and sources of carbohydrate or fat calories appropriate for patients with compromised liver function. In theory, an adequate supply of highly digestible carbohydrate would reduce muscle and dietary protein catabolism for energy. Provision of at least 30% to 50% of dietary calories as highly digestible grain (cooked starch) is consistent with these metabolic changes. Dextrose should comprise 20% to 40% of the caloric admixture when a dog or cat is supported with PN. Animals with hepatobiliary disease may benefit from fermentable fiber sources. Dietary fiber enables nitrogen fixation by enteric bacteria, reduces the nitrogenous waste substances available for absorption, binds endotoxins and bile salts, and alters the colonic

pH. Dietary soluble fiber can be incorporated into commercial diets using psyllium husk fiber (1 teaspoon per 5 to 10 kg of body weight).[8]

Dietary fats supply a dense form of calories, provide essential fatty acids, and aid in fat-soluble vitamin absorption. Fat is also a palatability enhancer to help inappetent animals. Appropriate dietary fat levels for most animals with hepatic disease range from 15% to 30% DMB. Complications of cholestasis can be associated with reduced excretion of bile salts, resulting in fat malabsorption and steatorrhea.[9] In these cases, dietary fat levels should be lowered. If necessary, an alternate fat source, such as medium chain triglycerides (MCT), could be considered. MCT is reported to be useful for malnourished people with cirrhosis and advanced cholestatic hepatic disease, but reports of clinical trials in animals are not yet available. Therapeutic diets containing MCT can be slowly worked into the diet, which is preferable to adding the oil to food directly. MCT oil alters the palatability of any diet, may result in food refusal, and does not contain essential fatty acids; hence MCT should not exceed 25% of the daily caloric requirement. The inflammatory component of hepatic disease, particularly that associated with hepatitis, may be attenuated by omega 3 (n-3) fatty acid supplementation. Although a specific dosage and the optimal ratio of omega 6 (n-6) to omega 3 fatty acids is not known, n-3 fatty acids have been shown to moderate various aspects of immune cell function. Several therapeutic veterinary diets formulated for the management of liver disease are n-3 enhanced.[10] When parenteral nutrition is necessary, lipid should comprise 60% to 80% of the calories in an admixture.

The liver processes both endogenous and exogenous amino acids; therefore altered protein metabolism may be the most clinically significant metabolic disturbance in an animal with hepatic disease. Increased protein catabolism occurs in early cirrhosis, and protein deficiency generally worsens with progression of liver disease. Addressing the protein needs of an animal with liver disease is a challenge, especially if the pet is critically ill or if signs of HE are apparent. In the absence of HE, protein should not be restricted because many animals with chronic hepatitis or advanced cirrhosis are catabolic and hypoalbuminemic, and most can tolerate standard enteral protein formulas.[11] Protein restriction and an increased branched chain to aromatic amino acid ratio should be limited to HE patients and those clinically unable to tolerate standard formulations.

Most therapeutic diets formulated for the management of dogs and cats with liver disease have a lower protein content (14% to 18% DMB) than the maintenance level (20% to 34% DMB). Recommendations on specific dietary protein concentrations have significant limitations. As the biologic value of a protein increases, less total protein is required to meet the amino acid requirements of the patient. In non-HE patients, a starting range for dietary protein would be 18% to 30% DMB. A more restricted protein level (8% to 15%, DMB) may be required for dogs exhibiting signs of HE postprandially. In all cases, protein ingredients of high biologic value (HBV) should be used so that the total nitrogen consumed may be minimized. Supplementation of the diet with HBV protein sources (e.g., cooked egg whites) provides essential amino acids while minimizing nitrogenous metabolites. It has been recommended that the proportion of branched chain amino acids (BCAA) to aromatic amino acids (AAA) be high in those diets. As liver disease progresses, the plasma concentration of BCAA decreases and AAA increases, because peripheral organs use BCAAs as a source of energy. There is increased cerebral uptake of AAAs, which may promote encephalopathy via synthesis of false neurotransmitters. To date, no data exist to suggest that BCAA formulations are superior to standard AAA formulations for animals with liver disease except when HE is present. Although dogs normally can synthesize sufficient amounts of taurine, in the case of severely compromised liver function, supplementation (250 to 500 mg/day) may be beneficial to choleresis. Additionally, taurine has some antioxidant action, which can help ameliorate the damage associated with excessive oxidative stress in liver disease.

Vitamin deficiency is common in chronic liver disease. The water-soluble B vitamins can be lost through vomiting or urinary losses or can become deficient as a result of anorexia, intestinal malabsorption, or

decreased hepatic metabolism. High daily B vitamin intakes are recommended for patients with chronic forms of hepatic disease because excesses are excreted in the urine.* Nutrient malabsorption and the increased amounts of unconjugated bile salts associated with cirrhosis primarily alter absorption of fat-soluble vitamins, because absorption of vitamins A, D, E, and K depends on the availability of bile salts.

Gastrointestinal ulceration and hemorrhage associated with chronic hepatitis may result in iron (Fe) deficiency. 576
This deficiency can be addressed by altering dietary Fe concentrations or with oral supplementation or 577
injectable Fe solutions. Supplementation should be approached with caution, because hemosiderosis is observed when liver disease has an inflammatory component; the hepatic Fe concentration should be assessed prior to supplementation. Diets supplying 80 to 140 ppm DMB of Fe should be adequate to meet daily Fe requirements. A zinc (Zn) deficiency results in abnormal ammonia metabolism, but diets containing more than 200 ppm DMB of Zn should be adequate. Diets can be supplemented with Zn gluconate (3 mg/kg body weight/day) or Zn sulfate (2 mg/kg body weight/day) divided into three doses. In cases of advanced hepatocellular damage with hypoalbuminemia and ascites, sodium restriction (0.01% to 0.25% DMB), with chloride at 1.5 times sodium, is recommended to help manage fluid balance and portal hypertension.

* B-Vitamin Complex, containing 50 mg thiamine, 2 mg riboflavin, 100 mg niacin, 2 mg pyridoxine, 10 mg pantothenic acid, and 0.4 ppm B_{12} per milliliter (Butler Co., Columbus, Ohio).

155.6 COPPER-ASSOCIATED HEPATOTOXICOSIS

Copper (Cu) storage disease impairs biliary excretion of Cu, resulting in signs of Cu toxicosis. The condition has been identified in the Bedlington terrier breed and is considered the canine counterpart of Wilson's disease in humans. These homozygous recessive individuals accumulate excessive amounts of Cu in the hepatocytes. If the condition is left untreated, the life expectancy is only 3 to 7 years.[12] With DNA technology, affected dogs can be identified and dietary changes can be initiated early in the disease process. The predominant feature is the progressive accumulation of Cu in hepatocytes, with hepatotoxicosis occurring at 2000 µg/g DMB. The time course can be as short as 8 to 12 weeks after birth, or Cu may accumulate for up to 1 year before clinical signs of toxicity become evident. Definitive diagnosis of Cu-associated hepatotoxicosis requires histochemical staining and quantitative assay of Cu in a liver biopsy sample.[13] Non-Bedlington terriers, cocker spaniels, and Doberman pinschers also can accumulate excess Cu in hepatocytes. Whether elevated hepatic Cu is the cause or consequence of the documented hepatitis and cirrhosis reported in these patients is not yet clear.

Copper-associated hepatotoxicosis is managed by feeding a low Cu diet and use of Cu-chelating agents. The AAFCO recommends 7.3 to 250 ppm DMB of Cu in both growth and maintenance canine foods. Therapeutic veterinary diets designed for liver patients contain 3 to 5 ppm DMB copper. Vitamin C and zinc supplementation are often used with copper hepatotoxicosis. Ascorbic acid augments urinary excretion of Cu and Zn and induces synthesis of intestinal metallothionein, which, because it has a much greater affinity for Cu than for Zn, binds excess dietary Cu. Elemental Zn can be supplemented in the acetate, sulfate, gluconate, or methionine forms. The recommended loading dose is 100 mg of elemental Zn per os given biweekly for 3 weeks, followed by a maintenance dose of 50 mg per os twice daily. Zn supplementation should be given between meals in a small amount of food to decrease the nausea and vomiting side effects.

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156 CHAPTER • 156 Nutritional Management of Endocrine Diseases

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With the exception of diabetes mellitus, the role of diet in the management of endocrine disorders of dogs and cats is largely uninvestigated. When abnormalities related to nutrient metabolism are seen, treatment of the primary endocrinopathy usually resolves the problem. Most of this chapter deals with the use of diet as a means of enhancing glycemic control in diabetics. A brief mention is made of dietary considerations in the management of endocrinopathy-associated hyperlipidemia and insulinomas.

156.1 DIABETES MELLITUS

With few exceptions, dietary management of diabetes mellitus in dogs and cats is done in conjunction with insulin or other pharmacologic treatment. Therefore it is important to stress that although appropriate dietary therapy can improve glycemic control, emphasis should be placed on adjustment of the insulin (or oral hypoglycemic) dosage and schedule and control of concurrent diseases. The objectives of dietary management of these animals are establishing and maintaining an optimal body weight, integrating feeding and insulin injection schedules, and optimizing glycemic control through diet composition. Beyond these goals, it is important to recognize that no single diet or dietary regimen fits all or even the majority of cases. To arrive at an appropriate dietary regimen, the practitioner must evaluate each dog or cat based on its body condition, on insulin therapy, and on whether coexisting diseases are a factor. Once a regimen is in place, it is critical that it be adhered to it as closely as possible, because alterations affect the efficacy of insulin therapy.

156.1.1 Body Condition

Obese dogs and cats can show insulin resistance that may resolve with weight loss.[1,2] In some cats with diabetes, the condition resolves naturally once loss of excess weight has been achieved. Many diabetic animals first have some form of medical crisis. Often, they have excess body fat but at the same time have also had some degree of muscle wasting. It is important that these animals be stabilized before any kind of caloric restriction for weight reduction is instituted. Many diabetic animals are underweight when first examined; after they have been stabilized, they should be fed a modest increase in calories to promote repletion.

156.1.2 Meal Timing and Diet Composition

The timing of meals is necessarily linked to the insulin dosage schedule. Ideally, the feeding timetable and the diet composition promote slow, steady absorption of nutrients from the gastrointestinal tract at times of peak insulin activity. Complex carbohydrates are generally absorbed in this fashion and should provide 50% to 60% of the calories in diets for canine diabetics. Soft, moist pet foods should be avoided, because they contain a high proportion of simple sugars.

Cats have evolved eating relatively little dietary carbohydrate. There are two major factors in which cats differ from more omnivorous species in their response to a carbohydrate-containing meal. The first is the lack of inhibition of hepatic gluconeogenesis. The activity of key gluconeogenic enzymes does not alter in the fed or fasted state, so that glucose will be synthesized from precursors, such as amino acids and glycerol, regardless of the extent of dietary carbohydrate intake. The second feature unique to feline carbohydrate metabolism is the lack of the enzyme glucokinase in both hepatic tissues and pancreatic islet cells. The maximal rate of this

enzyme occurs when glucose concentrations are elevated; this facilitates the uptake and metabolism of glucose postprandially, both by serving as the "glucosensor" of the pancreatic beta cell for the release of insulin and by initiating the metabolism of glucose in the liver.

Some preliminary clinical trials have investigated the use of low-carbohydrate diets in diabetic cats.[3] The results have been encouraging, with the majority of cats responding with improved clinical signs, decreased insulin requirements (with some cats no longer requiring any insulin therapy at all), and improved serum glucose curves and fructosamine concentrations. One problem with interpreting the results of these investigations is the difficulty encountered in differentiating cats with insulin-dependent diabetes and those with transient disease. It may be that this type of dietary therapy is more or less indicated in a given cat, depending on the form of diabetes mellitus the animal has.

Increased dietary fiber has been recommended as an adjunct therapy for managing diabetes mellitus in dogs and cats. This recommendation was based largely on clinical studies involving humans, in whom fiber seems to aid in glycemic control by modulating glucose absorption from the gastrointestinal tract. There is a limited amount of experimental and clinical research involving dogs and one clinical trial in cats that suggest that high-fiber diets may aid in glycemic control in these species as well. Most of the data in human studies pointed to soluble fibers as being the effective fiber type for modulating glucose absorption. However, there is evidence that insoluble fibers are also effective in improving glycemic control in dogs with naturally occurring diabetes mellitus.[4] One published clinical trial investigating diabetic cats showed some benefits from feeding a diet that contained insoluble fiber over a low-fiber diet.[5] The diets also differed somewhat in protein and carbohydrate content (the fiber-containing diet was higher in protein and lower in carbohydrates). It is not entirely clear whether the improved glycemic control when cats consumed the fiber-containing diet was attributable to the fiber, the macronutrient makeup of the diet, or a combination of the two. Therefore currently there is no proven rationale for placing a nonobese diabetic cat on a commercial high-fiber diet.

It must be stressed that uniform caloric intake and normalization of body condition take precedence over the use of fiber-containing diets in the management of this disease. Many of the fiber-containing diets on the market today have been formulated as calorically restricted for the purpose of weight control and therefore would be contraindicated in an underweight or debilitated patient. In addition, "fiber" is a generic term, and one cannot simply expect any diet with additional fiber or even a specific category of fiber (e.g., insoluble, fermentable) to have the same physiologic effects a particular diet had in an investigation. Furthermore, increasing the amount of fiber in a diet generally decreases the digestibility and absorption of most nutrients. Many high-fiber diets are fortified with minerals and protein, but beyond the results of basic maintenance feeding trials conducted by the Association of American Feed Control Officials, data are lacking on the effects of these diets on nutrient availability. Caution should be used when supplementing a diet with fiber. If the diet contains marginal amounts of nutrients with respect to the nutritional requirements of the pet eating the diet, the addition of fiber may lead to deficiency of one or more nutrient.

156.1.3 Role of Ultra-Trace Elements

A brief mention should be made of the role of the ultra-trace elements chromium and vanadium in the management of canine and feline diabetes mellitus. Chromium appears to be involved in the maintenance of glucose tolerance. True dietary chromium deficiency has not been documented in companion animals. To date, clinical trials investigating whether pharmacologic amounts of chromium might improve glycemic control in diabetic dogs and cats are inconclusive.[6] Vanadium, when dosed in pharmacologic amounts, has insulin-like effects. Again, clinical trials in dogs and cats are lacking; however, vanadium has been documented to cause

gastrointestinal side effects when administered orally, and chronic excessive intake may have toxic effects.[6] This element therefore should be used with caution.

156.2 HYPERLIPIDEMIA

A number of endocrinopathies can be associated with hyperlipidemia, including diabetes mellitus, hypothyroidism, and hyperadrenocorticism. Depending on the primary condition, hypertriglyceridemia, hypercholesterolemia, or both may be present. In general, therapy should be directed toward managing the underlying disease. Successful treatment often results in resolution of this condition. In some instances, dietary management can be used as an adjunctive therapy. The current diet should be evaluated, and if greater than 30% of the calories come from fat, a trial with a lower fat food should be considered.

156.3 INSULINOMA

Dietary therapy may aid in the management of the clinical signs that accompany an insulinoma. The goal is to minimize hypoglycemia by providing a highly digestible diet that contains low to moderate amounts of complex carbohydrates (as opposed to simple sugars and highly digestible starches) and to divide the daily feeding portion into three to six meals administered throughout the day. If signs of hypoglycemia do occur, the pet should be fed immediately and, if possible, foods or solutions containing simple carbohydrates should be avoided, because these may overstimulate the tumor and lead to another episode of hypoglycemia a short time later.

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157 CHAPTER • 157 Nutritional Modulation of Heart Disease

Lisa M. Freeman

John E. Rush

The goal of nutrition is no longer just to prevent deficiencies. It is now known that modification of diet can be an important part of medical therapy for heart disease. In the 1960s, the main nutritional recommendations for dogs with congestive heart failure (CHF) were to feed a low-sodium diet (for all stages of heart disease), to feed a restricted protein diet, and to provide supplemental B vitamins.[1] Few changes to these recommendations were made until the 1980s, when the question of how early to institute sodium restriction was raised and one of the first mentions of cardiac cachexia appeared in veterinary medicine.[2] It was also in the late 1980s that the discovery of the relationship between taurine deficiency and feline dilated cardiomyopathy (DCM) was published.[3] Now, research is beginning to show that nutrition may be able to modulate heart disease, either by slowing the progression, minimizing the number of medications required, improving quality of life or, in rare cases, actually curing the disease. There is potential for the use of diet as an important adjunct to medical therapy for animals with heart disease.

The main goals of diet therapy for heart disease are to maintain optimal body weight, to avoid nutritional deficiencies and excesses, and to take advantage of the potential benefits of pharmacologic doses of certain nutrients.

157.1 OPTIMAL WEIGHT MAINTENANCE

A key goal for the optimal management of heart disease is to maintain optimal body weight, because both obesity and weight loss can adversely affect health.

157.1.1 Obesity

Some patients with heart disease are overweight (i.e., over ideal body weight) or obese (i.e., more than 20% over ideal body weight). Endocrine disease, such as hypothyroidism and Cushing's disease, can be risk a factor for obesity and should be ruled out as an underlying cause; however, most obese animals simply suffer from overeating. Obesity has adverse effects on cardiac output, pulmonary function, neurohumoral activation, blood pressure, and heart rate in people and in experimental animal models, therefore it is likely to be similarly deleterious for companion animals with heart disease.[4] Owners often find that severely obese dogs and cats with cardiac disease that successfully lose weight appear less dyspneic and more active.

Successful weight reduction is a difficult and often unsuccessful endeavor. A careful dietary history is necessary to determine and control all sources of caloric intake as part of a successful weight loss program. Typically, the pet food is only one source of calories for the pet, and as many or more calories may be coming from treats and table food.[5] Additional sources of calories can be food intended for other household pets or food given by other people in the house, neighbors, or people delivering mail or packages. Because diets that are marketed as being reduced calorie vary tremendously in their caloric density, it is important to recommend a specific pet food and amount based on caloric requirements for weight loss, rather than making the general recommendation to switch to a “reduced calorie” pet food. Also, veterinarians should recommend a specific type and number of treats that can be fed to avoid overindulgence. Nonstarchy vegetables (fresh, frozen, or canned forms labeled “no salt added”) are excellent, low-calorie treats for dogs that are obese and have heart disease. The practitioner should recheck the animal's body weight after 2 weeks on the diet, and if the animal is

not losing weight, the owner should be questioned to find other potential sources of calories. If compliance appears to be good, the amount of food should be reduced further. The animal should be weighed every 2 weeks until consistent weight loss is achieved (1% to 2% per week) and then once monthly until the goal weight is achieved.

157.1.2 Cachexia

Cardiac cachexia is the muscle wasting commonly seen in patients with CHF. In one study of dogs with DCM, more than 50% of patients had some degree of cachexia.[6] The weight loss that occurs in animals with CHF is unlike that seen in a healthy dog or cat that loses weight. In a healthy animal receiving insufficient calories to meet requirements, metabolic adaptations allow fat to be used as the primary fuel source, thus preserving lean body mass. Conversely, the primary fuel source in animals with an acute or chronic disease, including heart disease, is amino acids from muscle, therefore these animals quickly catabolize muscle and lean body mass. Thus the distinguishing feature of cachexia is a loss of lean body mass, which has direct and deleterious effects on strength, immune function, and survival.[7] Cachexia is often mistakenly viewed as an end-stage syndrome manifested by an emaciated dog or cat. In fact, cachexia is a slowly progressive process of muscle loss that can be very subtle initially and can even occur in an obese animal. Recognizing the process of cachexia at an early stage may provide better opportunities to manage it effectively.

The loss of lean body mass in cardiac cachexia is a multifactorial process caused by anorexia, increased energy requirements, and metabolic alterations.[7] The anorexia may be secondary to fatigue or dyspnea or may be due to medication toxicity or feeding of an unpalatable diet.[7] Anorexia is present in 34% to 75% of dogs with heart disease.[5,8] However, increased production of inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), is the primary mediator of cachexia.[7] These inflammatory cytokines are known to directly cause anorexia, to increase energy requirements, and to increase the catabolism of lean body mass. Of particular pertinence to heart disease, TNF and IL-1 also cause cardiac myocyte hypertrophy and fibrosis and have negative inotropic effects.

Cardiac cachexia is typically recognized only after CHF has developed. It is more common in dogs than in cats and is most often seen in DCM or right-sided heart failure. Loss of lean body mass is most readily evident in the epaxial, gluteal, scapular, or temporal muscles. Nutritional considerations for cardiac cachexia should include management of anorexia, if present. Nutritional modulation of cytokine production also may be helpful. One method of decreasing the production and effects of cytokines is omega 3 (n-3) polyunsaturated fatty acid supplementation (see below). Supplementation of fish oil, which is high in n-3 fatty acids, can decrease cytokine production in dogs with CHF and improve cachexia.[6] In some but not all dogs with CHF-induced anorexia, fish oil supplementation can improve food intake.[6] In addition, reduction of cytokines has been correlated with survival in dogs with CHF.[6]

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157.2 MODULATION OF SPECIFIC NUTRIENTS

Nutritional deficiencies once were a common cause of cardiac disease in people and probably animals. In cats, taurine deficiency was a common cause of heart disease until as recently as the late 1980s. Identifiable nutritional deficiencies are now uncommon in dogs and cats but still could play a role in the etiology of some heart diseases. Nutritional deficiencies also may develop secondary to the disease or its treatment. A new area of nutritional research is that of nutritional pharmacology, the concept that supplementation of certain nutrients may provide benefits above and beyond their known nutritional effects. Therefore modulation of various nutrients by reducing

or increasing their intake (either a small amount or to pharmacologic levels) may be recommended for animals with heart disease.

157.2.1 Protein and Taurine

157.2.1.1 Protein

In the 1960s authors recommended a restricted protein intake for dogs with CHF to prevent "metabolic stress" on the kidneys and liver.[1] There is no evidence that protein restriction is necessary for dogs and cats with CHF and, in fact, it probably is deleterious, because these patients are predisposed to loss of lean body mass. Many of the diets designed for dogs with cardiac disease are low in protein (3.6 to 4.2 g/100 kcal), and protein-restricted diets designed for renal disease are often recommended for animals with heart disease. Unless severe renal dysfunction is present (i.e., serum creatinine >3.0 g/dL), high-quality protein should be fed to meet canine (5.1 g/100 kcal) and feline (6.5 g/100 kcal) minimum levels according to Association of American Feed Control Officials (AAFCO).[9]

157.2.1.2 Taurine

Taurine is an amino acid found in high levels in the myocardium. Despite our knowledge of the role of taurine deficiency in feline DCM, a small number of cats still develop DCM.[3] Most current cases of feline DCM do not involve taurine deficiency, but it should be suspected in all cases of this disorder. A dietary history should be elicited from owners to determine whether the cat has been fed a poor quality, homemade, vegetarian, or otherwise unbalanced diet. Plasma and whole blood taurine levels should be measured, and treatment with taurine (125 to 250 mg given orally twice a day) should begin concurrently with medical therapy. If the taurine concentration is found to be normal, taurine supplementation can be discontinued.

Unlike cats, dogs are able to synthesize adequate amounts of taurine, which is not considered a requirement for canine diets. Most dogs with DCM do not have taurine deficiency, but low taurine concentrations have been found in some dogs with the disorder, particularly breeds in which DCM is not a common disease.[10] The most common breeds in which DCM has been reported to be associated with taurine deficiency are the American cocker spaniel, golden retriever, Labrador retriever, Newfoundland, Dalmatian, and English bulldog.[10–12] In one small study, cocker spaniels supplemented with taurine and carnitine showed clinical and echocardiographic improvement.[13] It is not known whether the response would be similar with either taurine or carnitine alone.

Taurine deficiency in dogs may be related to dietary factors, because it is thought to be more common in dogs eating high-fiber or certain lamb meal and rice-based diets. Taurine deficiency also may be the result of increased renal or fecal loss of taurine or other metabolic defects present in certain breeds. In a study of Portuguese water dog puppies, plasma taurine was low in all puppies tested, and DCM was diagnosed in eight of nine puppies.[14] Taurine supplementation was instituted in six of the puppies, and this significantly increased both circulating taurine concentrations and cardiac function.[14] A recent study showed that a low-taurine, very low protein diet fed to beagles for 48 months caused decreased whole blood taurine concentrations, and DCM developed in one of 16 dogs.[15]

In the authors' experience, although some dogs of atypical breeds with DCM have low circulating taurine concentrations, not all of them respond to taurine supplementation. In one small retrospective study, dogs

that were taurine deficient and supplemented with taurine (with or without carnitine) did not show a significantly different response from that of dogs with DCM that were not taurine deficient and were not supplemented with taurine.[11] Dogs with DCM and taurine deficiency that respond to taurine supplementation generally do not have as dramatic a response as do taurine-deficient cats with DCM. Nonetheless, measurement of plasma and whole blood taurine concentrations is warranted in cocker spaniels and some other breeds of dogs with DCM. Supplementation with taurine (500 mg give orally two or three times a day), with or without carnitine (1 g given orally two or three times a day), is recommended in dogs with documented taurine deficiency. Some of the potential benefits of taurine in dogs with DCM may be due to the amino acid's positive inotropic effects or to its role in calcium regulation in the myocardium.

The AAFCO minimum for taurine for adult cats is 25 mg/100 kcal for dry food and 50 mg/100 kcal for canned foods.[9] Because taurine is a nonessential nutrient in dogs (i.e., it is not thought to be required in the diet), no minimum level has been established for commercial dog foods. The dietary taurine content of commercial dog foods, based on manufacturers' information, varies widely (less than 5 to over 50 mg taurine/100 kcal). To achieve a dose of 500 mg every 12 hours for a 40 kg dog (although this has not been determined to be the *optimal* dose of taurine for a dog with DCM), a diet would have to contain approximately 50 mg/100 kcal of taurine.

157.2.2 Fat

Fat provides calories and increases the palatability of pet foods, but it also can significantly affect immunologic, inflammatory, and hemodynamic parameters. The n-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are long chain fatty acids in which the first double bond is at the position of the third carbon from the methyl end (in the omega 6 [n-6] polyunsaturated fatty acids [i.e., linoleic, gamma linolenic, and arachidonic acids], the first double bond is at the sixth carbon). This minor chemical difference gives a different structure and characteristics to the fatty acid. Plasma membranes normally contain very low concentrations of n-3 fatty acids, but levels can be increased by a food or supplement enriched with n-3 fatty acids. Dogs with CHF have been shown to have plasma fatty acid abnormalities, including decreased concentrations of EPA and DHA, compared to normal dogs.[6,16] In one study of dogs with DCM and CHF, fish oil supplementation normalized these plasma fatty acid abnormalities.[6]

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Another potential benefit of n-3 fatty acid supplementation is that breakdown products of the n-3 fatty acids (series 3 and 5 eicosanoids) are generally less potent inflammatory mediators than eicosanoids derived from n-6 fatty acids (series 2 and 4 eicosanoids). This decreases the production of cytokines and other inflammatory mediators, which may reduce cachexia.[6] The authors currently recommend a dosage of 40 mg/kg EPA and 25 mg/kg DHA for dogs and cats with anorexia or cachexia. With the exception of a few specially designed therapeutic diets, commercial diets do not achieve this level of n-3 fatty acids, therefore supplementation is usually necessary. Because the amount of EPA and DHA in individual fish oil supplements varies widely, it is important to know the exact amount in the brand of supplement recommended. The most common formulation of fish oil, however, is 1 gram capsules that contain approximately 180 mg EPA and 120 mg DHA; these can be purchased over the counter at most human pharmacies or health food stores. At this concentration, fish oil can be administered at a dose of 1 capsule per 10 pounds of body weight to achieve the authors' recommended EPA and DHA dosage. Fish oil with higher concentrations of EPA and DHA can be obtained from medical supply catalogs and may be more feasible for large dogs. Fish oil supplements should always contain vitamin E as an antioxidant, but other nutrients should not be included to avoid toxicities. Cod liver oil and flax seed oil should not be used as sources of n-3 fatty acids.

157.2.3 Minerals

157.2.3.1 Sodium

Even before clinical signs become apparent in cardiac disease, the renin-angiotensin-aldosterone (RAA) system is activated and sodium excretion is reduced. Based on this knowledge, authors in the 1960s and 1970s recommended changing to a severely sodium-restricted diet when a heart murmur was first detected, even before clinical signs were present. However, dietary sodium restriction can further activate the RAA system, therefore it is not clear whether sodium restriction in early heart disease is beneficial or harmful.[17] A study of low-sodium diets in dogs with CHF showed that measures of cardiac size decreased significantly on a low-sodium diet compared with a moderate-sodium diet, especially in dogs with chronic valvular disease, but the effect of low-sodium diets on survival was not studied.[16]

The optimal time to institute sodium restriction and the degree of sodium restriction is not known, but severe sodium restriction (i.e., near the AAFCO minimum of 20 mg/100 kcal for dogs and 50 mg/100 kcal for cats) is not currently recommended for early heart disease. For an animal with heart disease without CHF (e.g., a dog with chronic valvular disease with no clinical signs or an asymptomatic cat with hypertrophic cardiomyopathy), the authors recommend that the animal be fed a mildly sodium-restricted diet (i.e., sodium content less than 100 mg/100 kcal) and that the owner be instructed to avoid giving the pet high-sodium treats or table food. Most owners are unaware of the sodium content of pet foods and human foods and need very specific instructions regarding appropriate foods and acceptable low-salt treats (Table 157-1). When CHF first arises, additional sodium restriction is recommended (i.e., less than 80 mg sodium/100 kcal). This can be achieved with a therapeutic diet designed for animals with early heart disease or with some diets designed for use in older dogs.

If a diet designed for senior dogs is used, the characteristics of the individual product must be examined. There is no legal definition for a senior diet, therefore the levels of calories, protein, sodium, and other nutrients can vary dramatically. Diets designed for animals with renal disease are not recommended for most cardiac patients because of the protein restriction (unless severe renal dysfunction is present). As CHF becomes more severe, more sodium restriction may allow lower dosages of diuretics to be used to control clinical signs. To achieve severe sodium restriction, it is usually necessary to feed a commercial therapeutic diet designed for cardiac patients. Typically, these diets are severely restricted in both sodium and chloride; levels of other nutrients vary with the individual product.

Table • 157-1 Examples of Low-Sodium Treats*

PRODUCT	kcal/Sodium (treat)/ (mg/treat)
Dog Treats	
Science Diet Senior Treats (medium)	20/13
Milk-Bone Super Premium Chicken Meal & Rice Flavored Biscuits	10/10
Iams Original Formula Biscuits (small)	22/10
Hill's Prescription Diet Canine Treats	13/5
Stewart Fiber Formula Dog Biscuits (medium)	25/5
Baby carrots	4/4
Alpo Healthy Snacks Variety Snaps with Real Meat	13/6
Apple (raw, 1 slice) or orange (1 section)	10/0
Cat Treats	
Essentials Brand Overall Health for Cats	2/3
Purina Whisker Lickin's Crunchy Cat	2/2
Treats—Tartar Control (all flavors) Stewart Fiber Formula Cat Treats	1/1
Treats to Avoid	
Baby food; pickled foods; bread; pizza; condiments (e.g., ketchup, soy sauce); lunch meats and cold cuts (e.g., ham, corned beef, salami, sausages, bacon, hot dogs); most cheeses, including "squirtable" cheeses (unless specifically labeled as low sodium); processed foods (e.g., potato mixes, rice mixes, macaroni and cheese); canned vegetables (unless labeled as no salt added); snack foods (e.g., potato chips, packaged popcorn, crackers); soups (unless homemade without salt); and most other pet treats.	

* Even low-sodium treats, if fed in large quantities, can provide a large dose of sodium (this especially can be a problem in cats or small dogs).

157.2.3.2 Potassium

Hypokalemia causes muscle weakness, predisposes patients to digitalis toxicity, and potentiates arrhythmogenesis. In addition, Class I antiarrhythmic drugs (e.g., procainamide, quinidine) are relatively ineffective in the face of hypokalemia. Hypokalemia can be precipitated by the use of loop diuretics (e.g., furosemide), thiazide diuretics (e.g., hydrochlorothiazide), or by inadequate dietary intake (often associated with anorexia). In the past, when the mainstays of therapy were diuretics and digoxin, hypokalemia was recognized as a significant problem in people and dogs with CHF.

Angiotensin-converting enzyme (ACE) inhibitor therapy has gained widespread use in the management of dogs with CHF, and this class of drug results in renal potassium sparing. ACE inhibitors cause an increase in serum potassium, and some animals develop hyperkalemia. Spironolactone, now used in some dogs and cats with heart disease, is an aldosterone antagonist and a potassium-sparing diuretic. Animals receiving ACE inhibitors and/or spironolactone can develop hyperkalemia, particularly if they eat a diet that contains high levels of potassium. Because some commercial cardiac diets contain higher potassium concentrations to counteract the theoretical potassium loss due to diuretics, these diets can contribute to hyperkalemia.

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Commercial diets vary widely in potassium concentrations. Commercial reduced-sodium diets for dogs can have 143 to 381 mg potassium/100 kcal (the AAFCO minimum is 170 mg/100 kcal).[9] Commercial feline reduced-sodium diets can have 152 to 362 mg potassium/100 kcal (AAFCO minimum of 150 mg/100 kcal).[9] If hyperkalemia is present in a dog or cat with heart disease, a diet with a lower potassium content should be selected. Conversely, if an animal is hypokalemic, a diet higher in potassium may be indicated, or oral potassium supplementation may be instituted.

157.2.3.3 Magnesium

Magnesium plays an important role in normal cardiac function. Alterations in magnesium homeostasis can occur in people and dogs and can have deleterious effects in a variety of cardiovascular conditions, including hypertension, coronary artery disease, congestive heart failure, and cardiac arrhythmias. Some cardiac drugs, including digoxin and loop diuretics, are associated with magnesium depletion. Therefore animals with heart failure receiving these medications have the potential to develop hypomagnesemia. Hypomagnesemia can increase the risk of arrhythmias, decrease cardiac contractility, cause muscle weakness, and contribute to renal potassium loss and can potentiate the adverse effects of certain cardiac medications. Hypomagnesemia has not been a consistent finding in studies of animals with heart disease, but this may be because serum magnesium concentrations are a poor indicator of total body stores.[16,18,19] Therefore a normal serum magnesium level does not necessarily mean there are adequate total body stores. We currently recommend routine measurements of serum magnesium, especially in animals with arrhythmias or those on large doses of diuretics.

As with potassium, magnesium concentrations vary widely in commercial pet foods. Commercial reduced-sodium diets for dogs can have 9 to 40 mg magnesium/100 kcal (AAFCO minimum of 10 mg/100 kcal).[9] Commercial feline reduced-sodium diets can have 8 to 69 mg magnesium/100 kcal (AAFCO minimum of 10 mg/100 kcal).[9] A diet high in magnesium would be indicated for an animal with a low serum magnesium concentration. In some animals with low serum magnesium concentrations, diet adjustment alone does not correct the problem, and oral supplementation is required.

157.2.4 Vitamins

157.2.4.1 B Vitamins

Thiamine deficiency is known to be a cause of cardiomyopathy in humans, but there has been little investigation into the role of B vitamin deficiency as a cause of heart disease in dogs and cats. Anorexia and urinary loss of water-soluble vitamins can contribute to low B vitamin concentrations in patients with heart failure. Thiamine has been the B vitamin studied in greatest detail. In one study, more than 90% of people with CHF had low thiamine concentrations.[20] As with other nutrients, such as potassium, B vitamin deficiencies may have been much more common when furosemide was the primary means of therapy for patients with CHF. Recent research has shown that vitamin B_{12}, but not vitamin B_6 or folate, was significantly lower in cats with cardiomyopathy than in healthy controls, an effect that was unrelated to diet or furosemide use.[21] Based on information from other species, however, animals with cardiac disease (at least those receiving diuretics) may have higher B vitamin requirements. Most commercial cardiac diets have increased amounts of water-soluble vitamins to offset urinary losses, therefore supplementation usually is not required.

157.2.5 Other Nutrients

157.2.5.1 Carnitine

L-carnitine is concentrated in skeletal and cardiac muscle and is critical for fatty acid metabolism and energy production. Carnitine deficiency has been associated with primary myocardial disease in a number of species, including a family of boxer dogs.[22] Anecdotal reports exist regarding the efficacy of carnitine in canine DCM, but no blinded prospective studies have been done, therefore a causative role has not been established. Even if carnitine deficiency is not the inciting cause of DCM, carnitine supplementation could be beneficial by improving myocardial energy production. In human DCM patients, most studies of carnitine have not been well controlled. However, one randomized, double-blind, placebo-controlled study showed improved 3-year survival in human DCM patients receiving 2 g/day of carnitine.[23] It is not yet clear whether the carnitine deficiency seen in some dogs with DCM is the cause of the disease or occurs secondary to the development of CHF. A study of rapid pacing–induced heart failure in dogs showed that myocardial concentrations decreased in normal dogs after the onset of CHF.[24] Carnitine supplementation has few side effects, but the high cost is a deterrent for some owners. We currently offer the option of carnitine supplementation (50 to 100 mg/kg given orally every 8 hours) to owners of dogs with DCM.

157.2.5.2 Antioxidants

Much attention has been given to antioxidants for their potential role in the prevention and treatment of human cardiac diseases. Reactive oxygen species are a by-product of oxygen metabolism, for which the body normally compensates through the production of endogenous antioxidants. An imbalance between oxidant production and antioxidant protection, however, could increase the risk of heart disease. Antioxidants are produced endogenously but also can be supplied exogenously. The major antioxidants include enzymatic antioxidants (e.g., superoxide dismutase, catalase, glutathione peroxidase) and oxidant quenchers (e.g., vitamin C, vitamin E, glutathione, and beta carotene). Most of the research in human cardiology has been done on coronary artery disease; however, in dogs with DCM and CHF, oxidative stress increases and vitamin E concentrations decrease with more severe disease.[25] Additional research is required, but antioxidant supplementation may hold promise as a component of therapy for animals with heart disease.

157.2.5.3 Coenzyme Q10

Coenzyme Q10, like carnitine, is a cofactor in a number of reactions required for energy production; however, it also is an antioxidant. Although coenzyme Q10 supplementation has anecdotally been reported to be beneficial, controlled prospective studies are necessary to judge the efficacy of this product accurately. Most human studies of coenzyme Q10 supplementation have not been well controlled, and the results are conflicting. One study of experimentally induced CHF in dogs showed that serum coenzyme Q10 levels were not reduced in dogs with CHF.[26] Coenzyme Q10 supplementation increased serum, but not myocardial, concentrations in one canine study.[26] The current recommended dose in dogs is 30 mg given orally twice a day, although a dose of up to 90 mg given orally twice a day has been recommended for large dogs. Possible reasons for the purported benefits of supplementation include correction of a deficiency, improved myocardial metabolic efficiency, or increased antioxidant protection.

157.3 PRACTICAL ASPECTS OF FEEDING THE PATIENT WITH HEART DISEASE

There is no single “best” diet for managing heart disease. It is important to match the nutritional needs of an individual patient to the diet or diets that best suit those needs. Patients with heart disease vary in terms of clinical signs, laboratory parameters, and food preferences, all of which affect diet selection. For example, animals with asymptomatic heart disease require less severe sodium restriction than animals with CHF. Dogs with cardiac cachexia require a calorically dense diet, whereas an overweight dog should be fed a calorically restricted diet. Concurrent diseases also influence diet choice and, in one study, were present in approximately two thirds of dogs with heart disease.[5] For example, a cat with hypertrophic cardiomyopathy and a history of struvite urolithiasis would need a diet that is both sodium restricted and also nutritionally modified to reduce the risk of struvite urolith formation. Laboratory results, such as the presence of hypokalemia or hyperkalemia, also can alter diet selection.

Based on these and other patient parameters, diets can be matched to the individual patient. A number of commercial veterinary diets are specifically designed for animals with cardiac disease. The specific characteristics of these foods vary, but they are moderately to severely sodium restricted and generally have increased levels of B vitamins. Some cardiac diets may also have increased levels of taurine, carnitine, antioxidants, or n-3 fatty acids. Above all, the diet must be palatable enough that the animal eats it willingly. The authors typically determine several diets that would be appropriate for an individual animal, and these diets then are offered as choices for the owner and the pet. Having dietary choices is particularly beneficial for owners of more severely affected patients, because a cyclic or selective loss of appetite is common in these pets. All diet recommendations should include a discussion of treats, table food, and foods used for medication administration.

As mentioned earlier, anorexia is a common problem in animals with heart disease and can contribute to the syndrome of cachexia. Another important problem with anorexia is that it may affect survival by influencing an owner's decision to euthanize the pet. In one study of owners of dogs euthanized for CHF, anorexia was one of the most common contributing factors to the euthanasia decision.[8] Anorexia becomes more common as the heart disease becomes more advanced. Recommendations for managing anorexia are listed in Box 157-1.

A note of caution: For animals with an acute episode of CHF, the diet should not be changed until the patient's condition has been stabilized. Once the animal is home and has been stabilized on medications, a gradual change to a new diet can be made. Forced dietary changes when the animal is sick or starting new medications may induce food aversions.

In many cases, the desired nutrient modifications can be achieved through diet alone. However, supplementation of certain nutrients may be warranted if these nutrients are not included in a particular diet or if they are not present at high enough levels to achieve the desired effect. It is important to be aware that dietary supplements do not require proof of safety, efficacy, or quality control to be marketed. Therefore careful selection of type, dose, and brand is important to avoid toxicities or complete lack of efficacy. Recently, the United States Pharmacopeia (USP) established the Dietary Supplement Verification Program (DSVP) for human dietary supplements. Supplements with the DSVP certification mark on the label have been tested and verified by the USP for their ingredients, the finished product, and the manufacturing process. This voluntary program helps ensure the safety and quality of dietary supplements, but it does not test the overall safety of use of the product or of health claims made for it. Much additional information is needed to define the role of dietary supplements in heart disease, when they should be used, when they should not be used, and optimal dosages.

157.3.1 **Box • 157-1 Keys to Managing Anorexia in Patients with Cardiac Disease**

- Assess the patient for optimal medical control of heart failure.
- Assess the patient for side effects of medications (e.g., digoxin toxicity or azotemia).
- Feed more frequent but smaller meals.
- Warm the food to body temperature.
- Gradually introduce a more palatable diet (e.g., switch from a dry food to a canned food, change to a different brand, or have a nutritionist formulate a balanced homemade diet).
- Use flavor enhancers, such as cooked meat or fish or low-sodium tuna juice for cats, and cooked meat or sweeteners (e.g., yogurt, maple syrup, or honey) for dogs.
- Administer fish oil supplements if the diet does not contain high concentrations of omega-3 fatty acids.

In addition to finding a diet that has the desired nutritional properties and palatability, the practitioner must construct an overall dietary plan that meets the owner's expectations. This involves finding a diet that the owner perceives the pet to enjoy, providing information about acceptable treats, and devising a satisfactory method of administering medications. In one study, more than 90% of dogs with heart disease received treats, and these are often high in sodium.[5] In addition, the majority of people who administer medications to their dogs use food as a means of achieving this (Box 157-2). To ensure success with nutritional modification, it is important to include information on how best to use food for this purpose in the overall diet plan.

157.3.2 **Box • 157-2 Methods for Administering Medication to Dogs and Cats**

1. Teach the owner to pill the animal without using foods.
2. Use a Pet Piller or Pet Pill Gun (Jorgensen Laboratories, Loveland, CO).
3. Use a compounded, flavored liquid medication instead of a pill (remember that compounding may alter the pharmacokinetics of a drug).

   Caution: Always determine the sodium content of a compounded product.
4. Insert medications into appropriate foods, such as the following:
   - Fruit (e.g., grapes, banana, orange, melon)
   - Low-sodium cheese
   - Low-sodium canned pet food
   - Peanut butter (labeled as “no salt added”)
   - Home-cooked meat (without salt); not lunch meats

5. Insert medication into a Canine Veterinary Tab Pocket (Waltham, Vernon, CA)

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158 CHAPTER • 158 Nutritional Management of Urinary Tract Conditions

India F. Lane

Dietary modifications can be used in managing urinary tract disease to influence excretory needs, acid-base status, fluid and electrolyte balance, and urine composition. Nutritional principles are described for acute and chronic renal failure, proteinuric renal disease, urolithiasis, and idiopathic feline lower urinary tract disease.

158.1 CHRONIC RENAL FAILURE

Chronic renal failure (CRF) is characterized by a progressive decline in renal function from renal insufficiency to azotemic renal failure to uremia to death or euthanasia.[1,2] Because diet can affect many consequences of renal failure, nutritional modification is a cornerstone of management. The most common derangements that occur with CRF include decreased ability to excrete nitrogenous wastes, phosphorus, and sodium; increased loss of potassium, and development of metabolic acidosis. Secondary hyperparathyroidism, systemic hypertension, and nonregenerative anemia are additional consequences of CRF. Dietary manipulation is designed to minimize protein precursors for urea and to minimize hyperphosphatemia and acid by-products; to provide an alkalinizing effect; and to supply adequate potassium while providing adequate calories to prevent further catabolism or malnutrition[1–3] (Table 158-1 and Chapter 260). The addition of soluble fiber to these diets has been recommended in an effort to provide fermentable substrate for bacteria in the large intestine. This may enhance both urea delivery and incorporation of ammonia generated into bacterial protein excreted in feces (nitrogen trapping).[4]

Dietary strategies also may help modulate progressive renal injury. In models of induced renal failure in dogs[5] and cats,[6] phosphorus intake has been linked to mortality, with increased mortality in animals consuming diets high in phosphorus. Phosphorus restriction appears to slow renal tubulointerstitial lesions, minimize secondary hyperparathyroidism and renal mineralization, and reduce development of hyperlipidemia.[1]

The influence of protein restriction is less clear, because an increased protein intake has not consistently hastened progression of renal failure in dogs or cats with induced renal dysfunction.[7] However, protein restriction decreases the nitrogenous solutes, phosphorus, and acid by-products that failing kidneys must handle. Protein restriction, therefore, is a feature of low-phosphorus diets designed for animals with moderate renal failure.

Modulation of dietary lipids may also be beneficial in slowing progressive renal failure. In dogs with induced renal insufficiency, supplementation of menhaden fish oil, which is high in omega 3 polyunsaturated fatty acids, resulted in reduced intraglomerular pressure, reduced proteinuria, and a slightly improved glomerular filtration rate (GFR) over a 20-week period. Dogs supplemented with safflower oil, which is high in omega 6 fatty acids, had progressive loss of renal function.[8] In another group of dogs with naturally ocurring chronic renal failure, however, the measured GFR *increased* during a 6-week period in those dogs fed safflower oil.[9]

Table • 158-1 Dietary Modifications Recommended in the Treatment of Urinary Diseases in Dogs and Cats

DISORDER	DIETARY RECOMMENDATIONS
Chronic renal failure	Reduced phosphorus
	Reduced protein
	Nonacidifying
	Potassium replete
	Reduced sodium
	Omega 3 fatty acid supplemented (dogs) +/– Increased soluble fiber
Proteinuric renal disease	Reduced protein
	Reduced sodium
	Omega 3 fatty acid supplemented (Additional modifications as above if animal is azotemic/uremic)
Struvite urolithiasis	Acidifying
	Increased moisture content (or induced diuresis)
	Reduced magnesium
	Reduced phosphorus
	Reduced protein
Calcium oxalate urolithiasis	Nonacidifying
	Reduced protein
	Adequate magnesium
	Adequate phosphorus
	Increased moisture content (or induced diuresis)
	Increased fiber (hypercalcemic cats)
Urate urolithiasis	Reduced protein (purines)
	Alkalinizing
Cystine urolithiasis	Reduced protein
	Reduced sodium
	Alkalinizing
Idiopathic lower urinary tract disease	Increased moisture
	Modifications as for struvite urolithiasis (if associated with struvite crystalluria)

Modified from Brown SA et al: Dietary considerations for urinary diseases. *In* Ettinger SJ, Feldman E (eds): *Textbook of Veterinary Internal Medicine*, 5th ed. Philadelphia, WB Saunders, p 269.

Dietary strategies may also be directed at other factors that may contribute to the progression of renal failure, including systemic hypertension, hyperparathyroidism, and renal ammoniagenesis (exacerbated by metabolic acidosis).

Studies of specific dietary components fed to dogs and cats with experimentally induced renal insufficiency have demonstrated the potential benefits of dietary modification. Recently, the overall benefit of "renal diets" has been investigated in cats and dogs with naturally occurring renal failure.[10–12] In a prospective study of cats with stable, azotemic chronic renal failure, feeding a canned renal failure diet resulted in significant reductions in plasma urea and phosphorus while prolonging survival times (median, 633 days) compared with cats that ate other diets (median, 264 days).[10] Unfortunately, diet groups were not randomized because they were determined by cat and owner preference. Consequently, cats with more advanced or complicated disease (potentially more selective about food) may have been more heavily represented in the non-renal failure diet group. Despite this limitation, the dramatic difference in survival times between the two groups supports the hypothesis regarding influence of diet on longevity.[10]

In a similar study, cats that ate low-protein/low-phosphorus diets had lower serum phosphorus concentrations and parathyroid hormone measurements than cats that ate other diets.[11] In a prospective, double-blind study of dogs with chronic renal failure, those fed a renal failure diet had delayed development of uremic crisis and a decrease in renal-related deaths as compared with dogs fed a diet formulated to mimic commercial adult maintenance diets.[12] In this study, other treatments were allowed as clinically necessary, such as phosphate-binding agents, potassium supplementation, and antihypertensive agents. Modification of the diet is recommended as soon as renal failure is detected.

158.2 ACUTE RENAL FAILURE

In acute renal failure (ARF), decline in renal function takes place over just a few days, limiting adaptability to loss of excretory function. In addition, insulin resistance, severe acidosis, release of stress hormones, and other metabolic derangements lead to a marked hypercatabolic state.[13] Optimal nutritional support in animals with ARF may minimize additional catabolism and azotemia, maximize chances for renal tissue repair, increase immunity against infectious complications, and improve survival.[13,14] Initial strategies (i.e., in the first 24 to 48 hours) are directed at managing fluid and electrolyte needs while avoiding large amounts of potentially damaging nutrients, such as amino acids or glucose. In maintenance and recovery phases after ARF, nutritional support should be provided as simple carbohydrates, fats, and protein, depending on the degree of uremia or malnutrition. Some authors recommend more protein for cats than dogs. Water-soluble vitamin supplementation is also recommended. Enteral or parenteral feeding often is required for animals with anorexia or vomiting. Aggressive, early use of antiemetics and gastrointestinal protectants is necessary to alleviate gastrointestinal erosion, hyperacidity, and reflux.[13,14]

158.3 PROTEINURIC RENAL FAILURE

A mildly to moderately reduced protein diet is recommended to limit protein loss in dogs with significant protein-losing nephropathy and normal albumin levels. If the serum albumin concentrations decrease below reference limits, protein supplementation may be necessary to improve hepatic albumin synthesis and to counter protein loss. Sodium restriction is also recommended because of the high incidence of hypertension associated with glomerular disease. In addition, omega 3 fatty acid supplementation may help modulate glomerular

inflammation and decrease systemic hypertension, as well as hyperlipidemia, hypercholesterolemia, and platelet aggregation.[15]

158.4 MINIMIZING ANOREXIA ASSOCIATED WITH RENAL DISEASE

With worsening uremia, anorexia often complicates management of renal failure and compromises quality of life.[16] First, management of uremic gastroenteritis and other metabolic consequences of renal failure alleviates uremic anorexia. Dietary changes should be made gradually in the home environment, with food introduced that has a similar texture and flavor as the historical diet. Warming food, adding water or flavored (low sodium) broths or flavoring agents (butter, cottage cheese, clam juice, and garlic), and feeding small, frequent meals may increase palatability. It is important to avoid mixing unpalatable drugs with food, force feeding, or combining feeding with stressful, unpleasant, or painful procedures, such as injections or sample collection.[16]

Originally considered for preconditioning renal transplant patients, feeding by *percutaneous* or *surgically placed gastrostomy tubes* is a valuable tool in the management of some animals with renal failure.[3,17,18] Tube access also facilitates fluid intake and administration of medications. In 56 dogs with renal failure, gastrostomy tubes were used for a mean of about 2 months, and tubes in seven dogs were used for longer than 6 months. In these 56 dogs, increased gastric bleeding (transient), peristomal infection, and inadvertent tube removal were among the reported complications.[7] Preoperative gastrostomy tube feeding support is recommended for renal transplant candidates that have lost ≥10% of their body weight.[18]

158.5 UROLITHIASIS

Dietary strategies for the prevention or dissolution of uroliths are based on the principle of urine saturation.[19,20] Crystal precipitation occurs when urine becomes *oversaturated*. The amount, concentration, and types of ions and mineral present, as well as the urine pH, determine the overall solubility of a substance. When urine is *undersaturated* with such substances in a favorable pH, crystals do not precipitate or aggregate. In fact, some crystals or uroliths dissolve in such an environment. Dietary and other management strategies for urolithiasis, therefore, are designed to create a state of undersaturation for calculogenic minerals. Undersaturation is accomplished by (1) reducing the amount of dietary urolith precursors; (2) decreasing concentration of minerals by increasing urine volume; (3) modifying the urine pH to enhance solubility; and (4) providing optimal concentrations of crystallization inhibitors.[19,20] Using these principles, diets have been formulated to aid in the dissolution of magnesium ammonium phosphate (struvite), urate, and cystine uroliths and to minimize recurrence of other urolith types (see Table 158-1 and Chapters 266 and 267).

158.6 IDIOPATHIC FELINE LOWER URINARY TRACT DISEASE (OR IDIOPATHIC CYSTITIS)

Episodic or recurrent lower urinary tract signs related to a noninfectious inflammatory disorder of unknown etiology is still a common clinical disorder of cats. Because the obstructive form of the disease was frequently associated with struvite crystalluria (and struvite crystals are still the predominant crystal found in urethral plugs), diets formulated for prevention or dissolution of struvite urolithiasis have traditionally been recommended.[21] However, many cats do not exhibit significant crystalluria along with the sterile hemorrhagic inflammation, therefore other dietary factors may be important. Dry cat food diets and decreased fluid intake appear to be significant risk factors for the development of both obstructive and nonobstructive disease, which may be reduced by maximizing moisture intake. In a prospective study of affected cats fed either a dry or canned formulation of

mineral-controlled, acidifying diet for up to 12 months, fewer recurrences and significantly reduced urine specific gravities were seen in the cats that ate the canned preparation.[22]

Cats accustomed to dry food may not accept an exclusive canned food diet. Therefore other methods of increasing water intake must be considered, such as adding water to existing food; placing fresh, full water bowls near food; adding broths or juices to food or water; offering distilled or bottled water; leaving a faucet dripping slowly, or using pet water "fountains." Constancy of diet (i.e., limiting diet changes) also has been proposed as a protective measure in the management of idiopathic cystitis in cats.[23]

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159 CHAPTER • 159 Parenteral Nutritional Support

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Metabolic responses to illness or injury place critically ill animals at high risk for malnutrition and its deleterious effects. These problems include alterations in energy metabolism, compromised immune function, decreased wound healing, and, probably a negative impact on overall survival.[1–3] Whereas healthy animals lose primarily fat when they do not receive adequate calories (simple starvation), sick or traumatized patients catabolize lean body mass when they are not provided with sufficient calories (stressed starvation). Inadequate calorie intake is a common problem in critically ill animals due to anorexia, an inability to eat or tolerate feedings (e.g., vomiting), or decreased absorptive capabilities.[1,4]

Because malnutrition may occur quickly in these animals, it is important to provide nutritional support by either enteral or parenteral means if oral intake is not adequate. The goals of nutritional support are to prevent development of malnutrition and to treat malnutrition when present. Although unproven in dogs and cats, treatment or prevention of malnutrition is thought to decrease morbidity and mortality.[1,2,5–7] Whenever possible, nutritional support via the enteral route should be used because it is the safest, most convenient, most physiologically sound, and least expensive method. Although enteral nutrition is preferred in critically ill animals, parenteral nutrition (PN) is an established method of providing nutritional support to dogs and cats whose gastrointestinal tracts cannot tolerate enteral feedings.[3,5–6,8–9]

Although the use of parenteral nutritional support has certainly increased in recent years, there sometimes is a perception that this technique is technically difficult, associated with many complications, and limited to university hospitals and referral centers. In reality, parenteral nutritional support can be adopted in many practices and complications can be significantly reduced with proper management techniques. The goals of this chapter are to outline identification of dogs and cats most likely to benefit from PN; to review the process of formulating, implementing, and monitoring parenteral nutritional support; and to discuss how PN can be incorporated into various practice situations.

159.1 NUTRITIONAL ASSESSMENT

The first step in consideration of nutritional support is appropriate assessment. Assessing nutritional status via objective measurements of body composition (e.g., anthropometry, bioelectrical impedance, dual energy X-ray absorptiometry, or serum indicators of malnutrition) is rarely employed in clinical veterinary medicine. Therefore subjective clinical assessment remains paramount in identification of malnourished animals that require nutritional support as well as those in which nutritional support will help prevent malnutrition. Indicators of malnutrition include weight loss, poor hair coat, muscle wasting, signs of inadequate wound healing, hypoalbuminemia, lymphopenia, and coagulopathy. However, these abnormalities are not specific to malnutrition and do not occur early in the process. In addition, fluid shifts may mask weight loss in critically ill animals. Given these limitations, it is crucial to identify early risk factors that may predispose patients to malnutrition, such as anorexia of greater than 3 days' duration, serious underlying disease (e.g., trauma, sepsis, peritonitis, pancreatitis, gastrointestinal surgery), or significant protein loss (e.g., protracted vomiting, diarrhea, protein-losing nephropathies, draining wounds, or burns).

Nutritional assessment also identifies factors that can affect the nutritional plan, such as the identification of specific electrolyte abnormalities; hyperglycemia, hypertriglyceridemia, or hyperammonemia; or comorbid

illnesses, such as renal or hepatic disease. Such findings require adjustments to be made to the formulation of PN and in some cases prompt changing the nutritional plan. Appropriate laboratory analyses (e.g., serum biochemical profile, serum ammonia, urinalysis) should be performed in all dogs and cats to assess these parameters.

159.2 GOALS OF NUTRITIONAL SUPPORT

The goals of nutritional support are to provide for the animal's ongoing nutritional needs, prevent or correct nutritional deficiencies and imbalances, minimize metabolic derangements, and prevent further catabolism of lean body tissues. Restoration of optimal body condition is not necessarily the goal of nutritional support in the acute stages of disease. In severely malnourished dogs and cats, nutritional support should be directed to preservation of lean body tissue and organ function, rather than complete reversal of malnutrition, which is accomplished only when the animal becomes convalescent. The necessity for instituting nutritional support is dictated by individual needs and not by the specific disease. The ultimate goal of nutritional support is to provide the necessary nutrients and calories until the dog or cat voluntarily consumes an adequate amount of food in its own environment.

159.3 NUTRITIONAL PLAN

The key to successful nutritional management of a critically ill animal lies in proper diagnosis and treatment of underlying disease. Another crucial factor is selection of the appropriate route for nutritional support. Providing nutrition via a functional digestive system is the preferred route of feeding and so particular care should be taken to determine whether enteral feedings would be tolerated. Even if only small amounts of enteral nutrition would be tolerated, this route of feeding should be pursued and supplemented with PN as necessary to meet nutritional needs. On the basis of the nutritional assessment, the anticipated duration of nutritional support, and appropriate route of delivery (i.e., enteral or parenteral) a nutritional plan is formulated to meet each dog's or cat's nutritional needs.

The first steps in instituting nutritional support include re-establishing proper hydration status, correction of electrolyte or acid-base disturbances, and achieving hemodynamic stability. Commencing nutritional support before these abnormalities are addressed can increase risk of complications and, in some cases, further compromise the animal. Implementation of the nutritional plan should be gradual, with the goal of reaching target level of nutrient delivery in 48 to 72 hours.

159.4 CALCULATION OF NUTRITIONAL REQUIREMENTS

Ideally, the provision of nutritional support should provide ample substrates for gluconeogenesis, protein synthesis, and energy necessary to maintain homeostasis. The clinician must ensure that enough calories are being provided to sustain critical physiologic processes, such as immune function, wound repair, and cell division and growth. Therefore calculating the pet's total energy expenditure is necessary. However, as direct measurements of energy expenditure in clinical dogs and cats are still in the developmental phases, the use of mathematical formulas remains the only practical means of estimating energy requirement. The resting energy requirement (RER) is defined as the number of calories required for maintaining homeostasis at rest in a thermoneutral environment while the animal is in a postabsorptive state.[10] Although there are several formulas proposed to calculate the RER, a widely used allometric formula can be applied to both dogs and cats of all weights. For animals that weigh between 2 and 30 kg, there is also a linear formula that provides reasonable estimation of the RER.

$$\text{RER} = 70 \times (\text{current body weight in kg})^{0.75}$$

or for animals weighing between 2 and 30 kg:

$$\text{RER} = (30 \times \text{current body weight in kg}) + 70$$

Despite the convention of multiplying the RER by an illness factor between 1.0 to 1.5 to account for increases in metabolism associated with different diseases and injuries, less emphasis is now being placed on such subjective and extrapolated factors.[4] The current recommendation is to use more conservative energy estimates, that is, to start with the animal's RER, to avoid overfeeding. Overfeeding can result in metabolic and gastrointestinal complications, hepatic dysfunction, and increased carbon dioxide production.[9]

As the preservation of lean body mass is a primary goal of nutritional support, close monitoring of body weight, fluid distribution, response or tolerance to feedings, and changes in the underlying condition should dictate whether to increase the number of calories provided in the nutritional plan. Typically, if an animal continues to lose weight on nutritional support, the number of calories provided should be increased by 25% and the plan should be reassessed in a few days. Additional adjustments to the nutritional plan might also include the addition or restriction of electrolytes such as magnesium and potassium as dictated by serial biochemical profiles.

159.5 NUTRITIONAL SUPPORT

A major advantage of enteral nutrition is superior maintenance of intestinal structure and function, as the presence of nutrients within the intestinal lumen elicits trophic effects that mediate mucosal cell proliferation. It has also been proposed that a lack of enteral nutrition contributes to the impairment of mucosal barrier function, which allows for the translocation of intestinal bacteria or endotoxins leading to sepsis and a systemic inflammatory response.

However, in patients that are unable to tolerate enteral feedings, such as those that are vomiting, regurgitating, or unable to protect their airway, parenteral nutrition should be considered. Inability to tolerate enteral feeding is, in fact, the only major indication for parenteral nutritional support. Although obtaining enteral access in critically ill animals can be difficult, every effort must be made to ensure that a functional gastrointestinal tract is not bypassed. A more extensive review of enteral nutrition is provided elsewhere (see Nasoesophageal, Esophagostomy, and Gastrostomy Tube Placement Techniques).

159.6 PARENTERAL NUTRITION

Parenteral nutrition has sometimes been characterized as a technique fraught with complications. In reality, many of the complications attributed to PN in the past might have had more to do with overfeeding or "hyperalimentation," rather than with the route of feeding itself. Although metabolic complications can be associated with PN, these complications are generally mild, have minimal consequences, and rarely require discontinuation of nutritional support. Septic complications associated with PN can be dramatically minimized with careful attention to aseptic technique in the compounding of PN, placement of dedicated PN catheters, and monitoring of the catheter site.

159.7 TYPES OF PARENTERAL NUTRITION

Given that the different types of PN can be defined in a number of ways, it may be simpler to categorize the different types of parenteral nutrition in terms of calories provided, that is, when parenteral nutrition is formulated to meet 100% of an animal's energy requirements, it is referred to as *total parenteral nutrition* (TPN). Parenteral

nutrition formulated to provide only a portion of the energy requirements, typically 40% to 70%, is termed *partial parenteral nutrition* (PPN). The lower osmolarity of PPN solutions, as compared with TPN solutions, is achieved by diluting the solution (ideally to less than 800 mOsm/L), which decreases the caloric and protein density but makes it suitable for administration via peripheral veins. For this reason, PPN may also be referred to as *peripheral parenteral nutrition.* The lower osmolarity is achieved in part, by utilizing 5% dextrose instead of 50% dextrose in the preparation of PPN and sometimes by the addition of isotonic and sometimes hypotonic crystalloids. As such, PPN is intended for short-term use (less than 5 days) and should be limited to dogs and cats that are not debilitated. Partial parenteral nutrition is also sometimes used as interim nutritional support until TPN can be formulated or it is used when specific contraindications exist to placement of jugular catheters, such as increased intracranial pressure or coagulopathies.

159.8 PARENTERAL NUTRITION COMPONENTS

Parenteral nutrition is formulated as a mixture of a carbohydrate source (dextrose), amino acids, and, usually, a fat source (lipid). Carbohydrates in the form of dextrose (typically 5% or 50%), may have benefits beyond acting as a fuel substrate. These potential benefits include stimulation of insulin secretion, reduction of muscle protein catabolism, and inhibition of hepatic glucose output, which may spare muscle proteins from being catabolized for gluconeogenesis. However, the sole administration of dextrose or supplementation of maintenance fluids with dextrose, in most cases, does not amount to adequate nutritional support and should therefore be discouraged. For example, a 5% dextrose infusion provides only 170 kcal per liter of solution and would provide less than 25% of the RER, at maintenance fluid rates. Dextrose infusions are more appropriate for the treatment of hypoglycemia rather than nutritional support.

Crystalline amino acids solutions are an essential component of PN. The importance of supplying amino acids relates to the maintenance of positive nitrogen balance and repletion of lean body tissue, which may be vital in the recovery of critically ill dogs and cats. Supplementation of amino acids may support protein synthesis and spare tissue proteins from being catabolized via gluconeogenesis.[9] The most commonly used amino acid solutions (Travasol, Clintec Nutrition, Deerfield, IL) contain most of the essential amino acids for dogs and cats, with the exception of taurine. However, as PN is typically not used beyond 10 days, the lack of taurine does not become a problem in most circumstances. Amino acid solutions are available in different concentrations from 4% to 10%, but the most commonly used concentration is 8.5%. Amino acid solutions are also available with and without electrolytes. Animals with normal serum electrolytes typically receive amino acid solutions with electrolytes, whereas those with electrolyte disturbances may benefit from amino acid solutions without electrolytes. Special formulations of amino acid solutions containing higher concentrations of the branched-chain amino acids are available at a much greater expense. Although these solutions were originally thought to be useful in management of highly catabolic metabolic diseases or when hepatic encephalopathy was present, studies have not confirmed a clear benefit in overall survival.[12]

Lipid emulsions are the calorically dense component of PN and a source of essential fatty acids. Lipid emulsions are isotonic and are available in 10% to 20% solutions (Intralipid, Clintec Nutrition, Deerfield, IL). These commercially available lipid emulsions are made primarily of soybean and safflower oil and provide predominantly long-chain polyunsaturated fatty acids, including linoleic, oleic, palmitic, and stearic acids. These solutions are emulsified with egg yolk phospholipids and their tonicity is adjusted with glycerol. The emulsified fat particles are comparable in size to chylomicrons and are removed from the circulation via the action of peripheral lipoprotein lipase. A common misconception exists in regard to the use of lipids in cases of pancreatitis. Although hypertriglyceridemia may be risk factor for pancreatitis, infusions of lipids have not been shown to increase pancreatic secretion or worsen pancreatitis and are therefore considered safe.[13] One exception, however, could be when serum triglycerides are increased, which indicates a clear failure of triglyceride clearance.

According to the most recent guidelines provided by the American Society of Parenteral and Enteral Nutrition, humans with serum triglycerides exceeding 400 mg/dL should have the lipid proportion in PN markedly reduced or eliminated altogether.[13] Although specific data regarding the maximal safe level of lipid administration in dogs and cats is not available, it would seem prudent to maintain normal serum triglyceride concentrations.

Another concern surrounding the use of lipids in PN are purported immunosuppressive effects via impairment of the reticuloendothelial system, particularly in PN solutions containing a high percentage of lipid.[9] Despite *in vitro* evidence supporting the notion that lipid infusions can also suppress neutrophil and lymphocyte function, studies have not yet correlated lipid use and increased rates of infectious complications.

Daily vitamin recommendations for dogs and cats that receive PN are extrapolated from established oral nutritional requirements.[9] Multivitamin preparations intended for intravenous administration provide a convenient and practical means for vitamin supplementation. It is recommended to add 0.2 ml/kg of a multivitamin preparation (M.V.I.-12 NeoSan Pharmaceuticals Inc., Wilmington, NC) to each PN bag at the time of compounding, up to 10 mL/day. This provides most of the water-and fat-soluble vitamins, except for vitamin K. In certain situations (e.g., longstanding malnutrition, malabsorptive disorders), 0.5 mg/kg of vitamin K can be administered subcutaneously, once weekly. Trace metals (4 Trace Elements, Abbott Laboratories, North Chicago, IL) can also be added to the PN solution at a dose of 0.1 mL/kg (up to 5 mL/day) to provide zinc, manganese, copper, and chromium. Although vitamins are commonly added to PN solutions, trace metals are usually only added when PN is to be administered for greater than 5 days or when food has not been consumed for a prolonged period.

The addition of other parenteral medications to the PN admixture is possible; however, their compatibility must first be verified. Drugs that are known to be compatible and sometimes added to PN include heparin, insulin, potassium chloride, and metoclopramide. Although the addition of insulin to PN is often required in people receiving PN, the hyperglycemia seen in dogs and cats receiving PN does not usually require insulin administration; however, diabetic patients will require adjustments to their insulin regimen. Although there is a described veterinary protocol for the addition of insulin directly to PN, it is often easiest to manage diabetics on PN with subcutaneous injections of insulin.[9] The addition of metoclopramide to PN solutions is often useful in the management of vomiting and ileus, which are commonly encountered in critically ill animals.

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159.9 PARENTERAL NUTRITION COMPOUNDING

Based on the nutritional assessment and plan, PN can be formulated according to the worksheets found in Boxes 159-1 and 159-2. For TPN (see Table 159-1), the first step is the calculation of the animal's RER. Protein requirements (grams of protein required per day) are then calculated, taking into consideration factors such as excessive protein losses or severe hepatic or renal disease. Although some recommendations provide all energy requirements with only dextrose and lipids, the protocol listed accounts for the energy provided from amino acids in the calculation and subtract it from the daily RER to estimate the total non-protein calories required. The non-protein calories are then usually provided as a 50:50 mixture of lipids and dextrose; however, this ratio can be adjusted in cases of persistent hyperglycemia or hypertriglyceridemia (e.g., a higher proportion of calories would be given from lipid in an animal with hyperglycemia). The calories provided from each component (amino acids, lipids, and dextrose) are then divided by their respective caloric densities and the exact amounts of each component are added to the PN bags in an aseptic fashion. The amount of TPN delivered will often provide less than the daily fluid requirement. Additional fluids can either be added to the PN bag at the time of compounding or be provided as a separate infusion.

159.9.1 Box • 159-1 Total Parenteral Nutrition (TPN) Calculations

1. Calculate resting energy requirement (RER)

RER =70 × (current body weight in kg)$^{0.75}$ or for animals weighing between 2 and 30 kg:

RER = (30 × current body weight in kg) +70 — RER =___kcal/day

2. Protein requirements

	Canine (gm/100 kcal)	Feline (gm/100 kcal)
*Standard	4	6
*Reduced (hepatic/renal disease)	2-3	3-4
*Increased (excessive protein losses)	6	6

$(RER \div 100) \times \underset{\text{protein req}}{____} \text{ gm/100 kcal} = ____ \text{ gm protein required/day}$

3. Volume of nutrient solutions required

a. 8.5% amino acid solution = 0.085 gm protein/ml

___g protein required/day ÷ 0.085 gm/ml — =___ ml/day of amino acids

b. Non-protein calories:

The calories supplied by protein (4 kcal/gram) are subtracted from the RER to get total non-protein calories needed.

___g protein req/day × 4 kcal/gram — =___kcals provided by protein

RER – kcals provided by protein — =___total non-protein kcal/day required

c. Non-protein calories are usually provided as a 50:50 mixture of lipid and dextrose

*20% lipid solution = 2 kcal/ml

To supply 50% of non-protein calories

___lipid kcal required ÷ 2 kcal/ml — =___mls of lipid

*50% of dextrose solution = 1.7 kcal/ml

To supply 50% of non-protein calories

___dextrose kcal required ÷ 1.7 kcal/ml — =___mls of dextrose

4. Total daily requirements

___mls of 8.5% amino acid solution

___mls of 20% lipid

___mls of 50% dextrose

___total mls of TPN solution to be administered over 24 hr

Note: Using a common 8.5% amino acid solution containing potassium (i.e., Travasol), TPN made according to this worksheet will provide potassium at higher than maintenance levels. Therefore you may not need to supplement potassium in any other fluids your patient is receiving. TPN for animals that are hyperkalemic should be formulated using amino acid solutions without electrolytes. Rates of other IV fluids being concurrently administered should be adjusted accordingly.

For formulation of PPN, Box 159-2 provides a step-by-step protocol in which animals of various sizes can be given 70% of their RER and approximately meet their daily maintenance fluid requirement. In very small animals (≤3 kg), the amount of PPN will exceed the maintenance fluid requirement and increase the risk for fluid overload, so adjustments in volume are necessary. Also, in animals requiring conservative fluid administration (e.g., congestive heart failure), these calculations for PPN may provide more fluid then would be safe. This formulation has been designed so that the proportion of each PN component is dependent on animal weight such that a smaller animal (between 3 and 5 kg) will receive proportionally more calories from lipids, compared to a large dog (greater than 30 kg), which would receive more calories in the form of carbohydrates. This allows the resulting formulation to approximate the daily fluid requirement.

Ideally, compounding of parenteral nutrition should be done aseptically under a laminar flow hood using a semi-automated, closed-system, parenteral nutrition compounder (e.g., Automix compounder, Clintec Nutrition, Deerfield, IL). If an automated compounder is not available, manual compounding can be done in a clean, low-traffic area with strict adherence to aseptic technique using a 3-in-1 bag (All-In-One EVA container, Clintec Nutrition, Deerfield, IL). Given these ideal conditions, it is often easier and more cost effective to have a local human hospital or a human home healthcare company compound parenteral nutrition solutions. Alternatively, commercial ready-to-use preparations of glucose or glycerol and amino acids are available for intravenous (peripheral) use (Table 159-1). Although these ready-to-use preparations are convenient, they provide only 30% to 50% of caloric requirements when administered at maintenance fluid rates and as a result should only be used for interim nutritional support or to supplement low-dose enteral feedings.

159.9.2

Box • 159-2 Partial Parenteral Nutrition (PPN) Calculations

1. Calculate resting energy requirement (RER)

RER =____ kcal/day

RER = 70 × (current body weight in kg)$^{0.75}$ or for animals weighing between 2 and 30 kg:

RER = (30 × current body weight in kg) + 70

2. Calculate the partial energy requirement (PER):

Plan to supply 70% of the animal's RER with PPN: PER = RER × 0.70 =____ kcal/day

3. Proportion of nutrient requirements according to body weight:

(Note for animals ≤3 kg, the formulation will exceed maintenance fluid requirements)

a. Cats and dogs 3 to 5 kg:

PER × 0.20 =____ kcals/day carbohydrate required

PER × 0.20 =____ kcals/day protein required

PER × 0.60 =____ kcals/day lipid required

b. Cats and dogs 6 to 10 kg:

PER × 0.25 =____ kcals/day carbohydrate required

PER × 0.25 =____ kcals/day protein required

PER × 0.50 =____ kcals/day lipid required

c. Dogs 11 to 30 kg:

PER × 0.33 =____ kcals/day carbohydrate required

PER × 0.33 =____ kcals/day protein required

PER × 0.33 =____ kcals/day lipids required

d. Dogs >30 kg:

PER × 0.50 =____ kcals/day carbohydrate required

PER × 0.25 =____ kcals/day protein required

PER × 0.25 =____ kcals/day lipid required

4. Volumes of nutrient solutions required:

a. 5% dextrose solution = 0.17 kcals/ml =____ ml/day dextrose

____kcals carbohydrate required/day ÷ 0.17 kcals/ml

b. 8.5% amino acid solution = 0.34 kcals/ml

=____ ml/day amino acids

____kcals protein required/day ÷ 0.34 kcals/ml

c. 20% lipid solution = 2 kcal/ml

=____ ml/day lipid

____kcals lipid required/day ÷ 2 kcals/ml

=____ total ml of PPN to be administered over 24 hrs

Note: This formulation provides approximately a maintenance fluid rate. Commonly used 8.5% amino acid solutions (i.e., Travasol) with electrolytes contain potassium. For animals ≤35 kg, the PPN solution made according to this worksheet will provide approximately maintenance levels of potassium. For animals >35 kg, the potassium contained in the PPN solution will be lower than maintenance levels. Rates of other IV fluids being concurrently administered should be adjusted accordingly.

159.10 PARENTERAL NUTRITION ADMINISTRATION

The administration of any PN requires a dedicated catheter used solely for PN administration and that is placed using aseptic technique. In most cases, this will require placement of additional catheters because PN should not be administered through existing catheters that were placed for reasons other than PN. Long catheters composed of silicone, polyurethane, or tetrafluroethylene are recommended for use with any type of PN to reduce the risk of thrombophlebitis. [3–4] Multilumen catheters are often recommended for TPN because they can remain in place for long periods and can also be used for blood sampling and administration of additional fluids and intravenous medications without the need for separate catheters placed at other sites. [5,11]

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Table • 159-1 Commercially Available Alternatives for Partial Parenteral Nutrition (PPN)

PRODUCT NAME	FEATURES	MANUFACTURER
Clinimix	2.75% amino acid 5% dextrose	Clintec Nutrition, Deerfield, IL
Quickmix	2.75% amino acid 5% dextrose	Clintec Nutrition, Deerfield, IL
ProcalAmine	3% amino acids 3% glycerol	McGraw Inc., Irvine, CA

Note: These solutions only provide 30% to 50% of resting energy requirements when administered at maintenance fluid rates. Therefore these should only be used as an interim form of nutritional support or to supplement low-dose enteral nutrition.

Although placement of multi-lumen catheters does require more technical skills than conventional jugular catheters, they can be valuable in treatment of any critically ill pet. The high osmolarity of TPN solutions (often 1200 mOsm/L) require its administration through a central venous (jugular) catheter, whereas PPN solutions can be administered through either a jugular catheter or catheters placed in peripheral veins. The concern with administering fluids high in osmolarity is that it may increase the incidence of thrombophlebitis, although this has not been consistently demonstrated in veterinary medicine.

Because of the various metabolic derangements associated with critical illness, TPN should be instituted gradually over 48 hours. At the hospital where the author practices, TPN is started typically at 50% of the RER on the first day and then increased to the targeted amount by the second day. In most cases, PPN can be started without gradual increase. It is also important to adjust the rates of other fluids being concurrently administered. For both TPN and PPN, the animal's catheter and infusion lines must be handled aseptically at all times to reduce the risk of PN-related infections.

Parenteral nutrition should be administered as continuous rate infusions over 24 hours via fluid infusion pumps. Inadvertent delivery of massive amounts of PN can result if administration is not properly regulated. Cyclic administration of PN (i.e., alternating PN with other parenteral fluids every 12 hr) has also been described. However, this practice is not recommended as it circumvents maintenance of a closed-system for PN

administration and can increase the rate of complications. Once a bag of PN is set up for administration, it should not be disconnected even for walks or diagnostic procedures. The drip regulator is decreased to a slow drip and accompanies the pet throughout the hospital. Administration of PN through an in-line filter (Air eliminating filter, Clintec Nutrition Division, Deerfield, IL) is also recommended and is attached at the time of set up. This set-up process is performed daily with each new bag of PN. Each bag should only hold one day's worth of PN and the accompanying fluid administration sets and in-line filter are changed at the same time using aseptic technique. Discontinuation of PN should be done when the animal resumes consuming an adequate amount of calories of at least 50% of RER. Whereas TPN should be gradually discontinued over a 6-to 12-hour period, PPN can be discontinued abruptly.

159.11 COMPLICATIONS

As with any therapy for critically ill animals, complications can occur. Complications associated with PN can include mechanical complications of the catheter and lines, thrombophlebitis, metabolic abnormalities, and sepsis. Mechanical complications such as inadvertent catheter removal, catheter occlusion, and line disconnection or breakage are probably not inherently related to PN and are likely no more common than in any dog or cat with an intravenous catheter. Metabolic complications are much more likely to be related to PN and include hyperglycemia, hypertriglyceridemia, hyperbilirbinemia, increased alkaline phosphatase activity, azotemia, electrolyte shifts, and hyperammonemia.[2,5,11] The more commonly encountered complications, namely hyperglycemia and hypertriglyceridemia, are for the most part transient and can be effectively managed without serious consequences. Decreasing the rate of infusion for 12 to 24 hours is often effective; although in some instances, re-formulation of PN is required. Animals with biochemical changes subsequent to initiation of PN should have more frequent evaluation of laboratory parameters.

Septic complications, including cathetersite infections with and without systemic sepsis have also been reported in dogs and cats receiving PN but are uncommon and range from 3% to 12% in dogs and cats that receive PN.[5,11] Septic complications can be minimized by strict adherence to established protocols and careful attention to early signs of problems relating to catheter care. Any catheter suspected of causing fever, white cell count elevations, or other sign compatible with infection should be removed and cultured.

One of the proposed advantages of PPN over TPN is lower risk of complications. This is supported by a recent study that documents lower rates of complications in dogs and cats receiving PPN, compared with previously reported complication rates associated with TPN in dogs.[5,11] Although direct comparisons between the two patient populations cannot be made, there were approximately 0.17 complications per day of PPN administration versus 0.53 complications per day reported with TPN administration in dogs.[5,11] Reasons for these differences could be attributed to differences in severity of illness between these animal populations, although there is a potential that hypocaloric nutritional support may actually confer some benefits in certain populations, including lower complication rates.[15]

159.12 MONITORING

Given the potential for complications, monitoring of dogs and cats receiving PN is a vital part of nutritional support. This monitoring is similar to that already in place for critically ill pets. Careful monitoring of the catheter site is recommended to detect problems early (e.g., signs of inflammation or malposition) and should be done on a daily basis. The catheter should be evaluated for patency and the bandage should be changed daily. At a minimum, body weight, body temperature, respiratory rate, catheter site, and serum glucose should be evaluated daily. All blood tubes should be inspected for visible lipemia. Monitoring of other parameters (e.g., electrolytes, complete

blood count, biochemical profile) may also be indicated. Persistent hyperglycemia, hypertriglyceridemia, or signs of encephalopathy should prompt re-evaluation and may necessitate decreasing rate of infusion or re-formulation of parenteral nutrition and serial evaluation of blood work.

159.13 SUMMARY

With the growing recognition that nutritional support is an integral part of the therapeutic regimen for many critically ill pets, it is becoming increasingly important for veterinarians to be able to incorporate parenteral nutritional support in their practice or to refer these pets to facilities capable of providing such therapy when necessary. Proper identification of dogs and cats most likely to benefit from PN and the ability to formulate, administer, and monitor PN are key factors in ensuring successful incorporation of parenteral nutritional support in their care.

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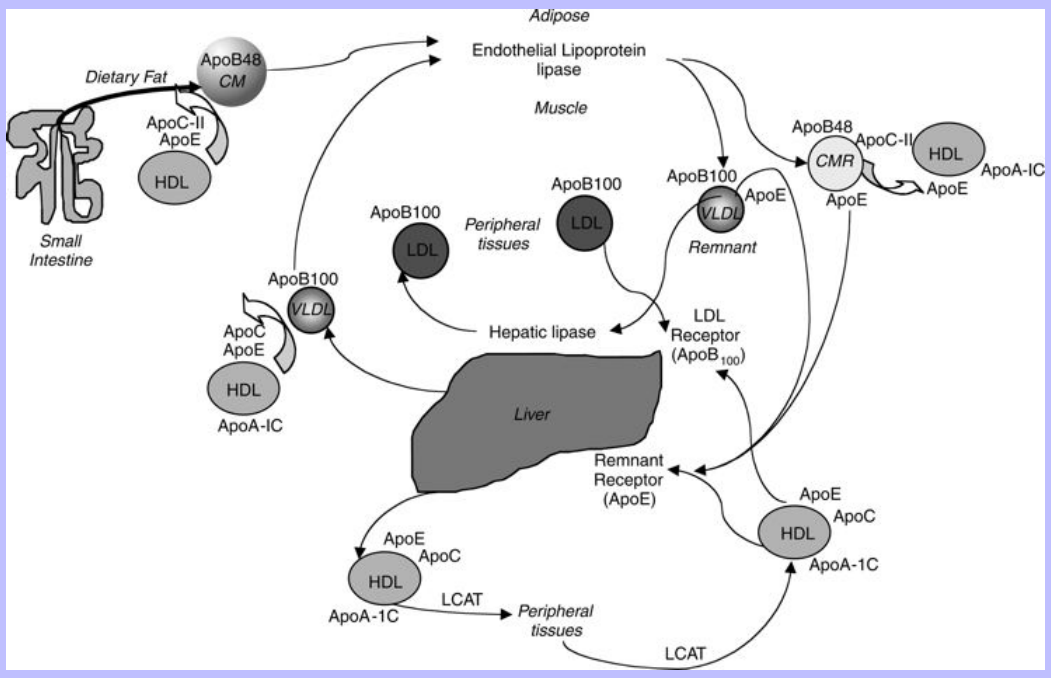
160 CHAPTER • 160 Dietary and Medical Considerations in Hyperlipidemia

Denise A. Elliott

Hyperlipidemia is a consequence of elevated plasma concentrations of triglyceride and/or cholesterol and is due to a disturbance in plasma lipoprotein metabolism.[1] In the fasted state hyperlipidemia is an abnormal finding that represents either accelerated production or delayed degradation of lipoproteins. The lipoproteins function to transport insoluble triglyceride and cholesterol through the blood. Lipoproteins consist of a triglyceride and cholesteryl ester core surrounded by a surface layer of cholesterol, phospholipid, and apolipoproteins. The apolipoproteins (A, B, C, E) are responsible for the structure of the lipoprotein particle, for binding of the particle to cell surface receptors, and activation of enzymes.[1] There are four major classes of lipoproteins that differ in their lipid and apoprotein content and their physicochemical characteristics. These variabilities include size, density, and electrophoretic mobility.

Lipoproteins are categorized according to their buoyant density upon ultracentrifugation into the chylomicron, very–low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and the high-density lipoprotein (HDL). The classification system is arbitrary and it should be appreciated that there is significant structural and functional heterogeneity within each category. In addition, the system is dynamic; one class produces another during its metabolism (Figure 160-1). The chylomicron and VLDL are involved primarily in triglyceride metabolism, whereas HDL and LDL are involved primarily in cholesterol metabolism.

Figure 160-1 Schematic representation of lipid metabolism. *CM,* Chylomicron; *CMR,* chylomicron remnant; *VLDL,* very low-density lipoprotein; *LDL,* low-density lipoprotein; *HDL,* high-density lipoprotein; *LCAT,* lecithin: cholesterol acyl transferase.



160.1 PATHOPHYSIOLOGY

After digestion and absorption, cholesterol and triglyceride are packaged into chylomicron particles by enterocytes. Chylomicrons are secreted into mesenteric lymph, through which they ultimately reach the systemic circulation. Here they receive Apo E and Apo C-II from HDL. In adipose and muscle tissues, endothelial lipoprotein lipase is activated by apoprotein C-II and hydrolyzes the triglyceride core of the chylomicron to free fatty acids and glycerol. The free fatty acids diffuse into adjacent tissues and are either resynthesized into triglyceride and stored (adipocyte) or used for energy (myocyte). Lipoprotein lipase activity is influenced by factors such as heparin, insulin, glucagon, and thyroid hormone. Depletion of the triglyceride component of the chylomicron alters the surface so that the chylomicron is converted into a chylomicron remnant. The remnant particle transfers phospholipid and Apo C-II back to the HDL particle, prior to being recognized and removed from the circulation by specific Apo-E hepatic remnant receptors. Within the hepatocyte, the contents of the chylomicron remnant are degraded and utilized. Chylomicrons are present in plasma 30 minutes to 2 hours after a fat-containing meal and hydrolysis is normally complete within 6 to 10 hours after a meal.

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Intrahepatic free fatty acids may originate from residual dietary triglyceride present in chylomicron remnant particles, from endogenous production secondary to surplus dietary carbohydrate, and from excessive endogenous mobilization. Intracellular hormone sensitive lipase is responsible for hydrolysis of stored adipocyte triglyceride to release free fatty acids and glycerol. Hormone sensitive lipase can be activated by epinephrine, norepinephrine, ACTH, corticosteroids, growth hormone, thyroid hormone, and insulin deficiency. Excess free fatty acids that are not directly oxidized for energy are transformed by the hepatocyte into triglyceride, packaged into VLDL particles, and secreted into blood. Analogous to chylomicron metabolism, the VLDL particle acquires ApoC-II and ApoE from the VLDL particle. Endothelial lipoprotein lipase then removes and hydrolyzes the triglyceride portion of the VLDL into free fatty acids and glycerol. In addition, an endothelial hepatic lipase will also hydrolyze the triglyceride portion of the VLDL. Removal of the triglyceride core converts the VLDL to a LDL particle. The LDL particle is a cholesterol-and phospholipid-rich entity that functions to transport cholesterol to tissues where it may be used for membrane synthesis or steroid hormone production. Ultimately, the LDL particle binds to the LDL receptor that recognizes $ApoB_{100}$, and is removed by the liver.

The liver also secretes nascent HDL particles into the circulation. These particles consist of a phospholipid bilayer, unesterified cholesterol, Apo C, Apo E, and Apo-A-I. The HDL acts as a reservoir of Apo C and Apo E and transfers these apolipoproteins to chylomicron and VLDL particles. Plasma lecithin: cholesterol acyl transferase (LCAT), activated by Apo-A-I, esterifies cholesterol to hydophobic cholesteryl ester, which moves from the surface to the inner core of the HDL. A concentration gradient is thus produced such that excess tissue cholesterol is transferred to the HDL particle. HDLs scavenge excess unesterified cholesterol from cells and other lipoproteins and return it to the liver for excretion into bile. This process is often referred to as *reverse cholesterol transport*. In humans, a second enzyme (cholesteryl ester transfer protein; CETP) can function to transfer HDL cholesteryl esters to chylomicrons, VLDL and LDL particles, in exchange for triglyceride. However, dogs do not appear to have CETP. Rather, the HDL particles are removed by the liver via Apo E binding LDL and remnant-receptors.[2] It is not yet apparent if the cat has CETP.

Hypertriglyceridemia can develop secondary to increased chylomicron production (excessive dietary intake of lipid), ineffective clearance of the chylomicron particle, increased VLDL production (excessive dietary intake of lipids and/or carbohydrate, excessive endogenous production, or mobilization of lipids), and ineffective clearance of the VLDL particle. Likewise, hypercholesterolemia can arise from increased production of the LDL precursor (VLDL), or reduced clearance of the LDL or HDL particle.

160.2 CLASSIFICATION

Post-prandial hyperlipidemia is the most common cause of hyperlipidemia in the dog and cat. This is a normal physiologic manifestation caused by the production of triglyceride-rich chylomicrons and usually resolves within 2 to 10 hours. Pathologic abnormalities in plasma lipids and lipoproteins may be of genetic or familial origin (primary) or arise as a consequence of disease (secondary). Primary hypertriglyceridemias include idiopathic hyperlipidemias of miniature Schnauzers and hyperchylomicronemia of cats. Idiopathic hyperlipidemia of miniature Schnauzers is characterized by excessive VLDL particles with or without concurrent chylomicronemia, and mild hypercholesterolemia.[3] The exact mechanism and genetics have not been fully elucidated. Feline familial hyperlipidemia is characterized as a fasting chylomicronemia with a slight increase in VLDL and is due to production of an inactive lipoprotein lipase.[4] Idiopathic hyperchylomicronemia has also been observed in dogs and is characterized by hypertriglyceridemia, hyperchylomicronemia, and normal serum cholesterol concentrations. Idiopathic hypercholesterolemia due to an increase in LDL has been reported in Doberman Pinschers and Rottweilers.

Diseases associated with secondary hyperlipidemia include endocrine disorders (hypothyroidism, diabetes mellitus, hyperadrenocorticism), nephrotic syndrome, cholestasis, and drug-induced (glucocorticoids, megastrol acetate).[5] Hypothyroidism is the most common cause of hypercholesterolemia in the dog. It is attributed to both a decrease in lipid synthesis and degradation (lipid degradation is more severely affected). Decreased lipoprotein lipase activity contributes to the impaired removal of triglyceride-rich lipoproteins. In addition, thyroid hormone deficiency reduces the biliary excretion of cholesterol. The resultant increase in intrahepatic cholesterol down-regulates the hepatic LDL receptor, increasing the level of circulating LDL and HDL. Insulin deficiency reduces the production of lipoprotein lipase, with subsequent decreased clearance of triglyceride-rich lipoproteins. Furthermore, hormone sensitive lipase is activated, which causes the release of large quantities of free fatty acids into the blood, which are ultimately converted by the liver into triglycerides, packaged into VLDL particles, and secreted back into the circulation. Therefore hypertriglyceridemia seen with diabetes mellitus is attributed to both a reduction of lipoprotein lipase and increased production and decreased clearance of VLDL particles. Insulin deficiency increases the synthesis of cholesterol in the liver. The increased intrahepatic cholesterol concentration down-regulates the hepatocyte LDL receptor and consequently reduces the clearance of circulating LDL and HDL particles. The mechanism of hypertriglyceridemia associated with hyperadrenocorticism is probably due to stimulation of hormone-sensitive lipase with release of free fatty acids into the circulation. Similarly to diabetes mellitus, excess free fatty acids are converted into VLDL particles. In addition, glucocorticoids inhibit lipoprotein lipase activity, thereby reducing the clearance of triglyceride-rich lipoproteins.

160.3 CLINICAL FEATURES

Waxing and waning vomiting, diarrhea and/or abdominal discomfort are the most common clinical presentations associated with hypertriglyceridemia.[6] Severe hypertriglyceridemia (>1000 mg/dL) has been associated with pancreatitis, lipemia retinalis, seizures, cutaneous xanthomas, peripheral nerve paralysis, and behavioral changes. Cutaneous xanthomas, which represent lipid-laden macrophages and foam cells, are the most common manifestation of hypertriglyceridemia in the cat. Severe hypercholesterolemia has been associated arcus lipoides corneae, lipemia retinalis, and atherosclerosis.

160.4 DIAGNOSIS

Lipemic serum suggests that the animal has hypertriglyceridemia. Lactescence refers to increases of triglyceride sufficient (typically >1000 mg/dL) to cause serum or plasma samples to become milk-like in appearance and opaque. Conversely, patients with pure hypercholesterolemia do not exhibit lipemic or lactescent serum as LDL and HDL particles are too small to refract light. Blood samples to confirm hypertriglyceridemia should be obtained after a 12-to 18-hour fast. A serum sample rather than whole blood or plasma should be submitted for assessment. The sample can be refrigerated or frozen for several days without affecting the test. During assessment of the sample for hypertriglyceridemia, the laboratory should not clear the sample prior to determination of the triglyceride concentration. Clearing lipemic samples by centrifugation removes chylomicrons, which will artificially lower the triglyceride concentration.

The chylomicron test, which requires refrigeration of a sample for 12 hours, can be helpful to delineate if the lipemia is predominantly a chylomicron or VLDL defect.[6] The chylomicrons are least dense and will float to form an opaque cream layer over a clear infranatant of serum. If the hypertriglyceridemia is due to excess VLDLs, the plasma sample will remain turbid. Formation of a cream layer over a cloudy serum layer suggests both excess chylomicrons and VLDL particles.

Lipoprotein electrophoresis can be utilized to distinguish the lipoproteins and ultracentrifugation can provide a quantitative measurement of each lipoprotein class.[7] However, both of these procedures are time consuming and not routinely available. The activity of lipoprotein lipase can be assessed by the heparin release test. Serum samples for the determination of triglyceride (and if possible, lipoprotein) concentrations are obtained prior to and 15 minutes after the intravenous administration of heparin (90 IU/kg BW dog; 40 IU/kg BW cat). Heparin causes the release of lipoprotein lipase from the endothelium and stimulates the hydrolysis of triglycerides. A defect in lipoprotein lipase is suspected if there is no difference between the pre-and post-serum triglyceride concentrations.

160.5 MANAGEMENT

Prior to recommending therapy, every attempt should be taken to determine if the hyperlipidemia is primary or secondary, as lipemia secondary to an underlying disorder will typically resolve or improve with correction of the metabolic disturbance. Therefore each dog or cat requires a full history, physical examination, complete blood count, serum biochemistry panel, serum lipase, serum thyroxine concentration, and urinalysis. Additional diagnostic tests such as bile acids, abdominal ultrasound, and evaluation of the adrenocorticotropic hormone axis may be required. A recommendation to treat hyperlipidemia involves a life-long commitment by the owner and must therefore not be undertaken lightly. In general, severe hypertriglyceridemia (>500 mg/dL) mandates treatment. In this circumstance catabolic mechanisms can be assumed to be overwhelmed and the triglyceride level is sensitive to small increases from the intestine or liver. The triglyceride levels must be decreased to prevent complications including pancreatitis. In other situations, the recommendations will be influenced by additional variables, including the underlying disease process. A realistic goal of therapy is to reduce the triglyceride concentrations to less than 400 mg/dL.

Chylomicrons are produced from dietary fat, hence restriction of dietary fat is the cornerstone of therapy for hypertriglyceridemia. The dietary history should be reviewed and the diet altered to one that contains less than 20% fat on a metabolic energy basis for dogs, and less than 25% fat on a ME basis for cats (Table 160-1). Treats should be restricted to 5% of the daily caloric intake and changed to low-fat commercial varieties. Carrots or brown rice crackers are useful alternatives. In addition to providing a low-fat diet, the absolute caloric intake should be evaluated. If the pet is overweight, caloric restriction is indicated and beneficial as it decreases the

production of VLDL from excess dietary energy. The triglyceride concentration should be reevaluated after 4 weeks of feeding a low-fat diet. If the reduction in triglyceride concentration is less than ideal, the history should be reevaluated to ensure that there are no extra fat calories from treats, no access to other pet foods, and no additional family members or neighbors who are inadvertently providing the patient with fat. Unfortunately, inappropriate initial dietary selection is the most likely reason for failure to respond to nutritional therapy. A commercial diet should not be selected because the manufacturer recommends the diet for the management of hyperlipidemia. Rather, the diet should be selected because the dietary fat content is less than 20% on a metabolic energy basis. In addition, care should be given to the form of the diet as the fat content of canned and dry version of the diet may differ significantly (see Table 160-1). The medical record should also be reviewed to ensure the exclusion of underlying disorders. If commercial products are not able to control hypertriglyceridemia, then a complete and balanced ultra–low-fat (10% to 12% ME), home-prepared diet can be specifically formulated by a veterinary clinical nutritionist.

Diets rich in omega-3 fatty acids have been suggested to improve hypertriglyceridemia in humans by decreasing the production of VLDL particles. In addition, fish oils are poor substrates for triglyceride synthesizing enzymes and lead to the formation of triglyceride poor VLDL particles. Menhaden fish oil (200 mg/kg BW, dog) has been recommended for use in dogs.[6]

Treatment with drugs, all of which have toxicity, should be undertaken with particular care. In general, drugs should not be used when the serum triglyceride concentration is less than 500 mg/dL. Several classes of drugs are available for humans[8]; however, there are few reports of their use in cats and dogs. Until further studies evaluate the dose, effect, and toxicity, drug therapy is indicated only in those animals that have clinical signs associated with severe elevations in triglyceride that cannot be ameliorated by dietary therapy.

Niacin (100 mg/day, dog) reduces serum triglyceride concentrations by reduction of free fatty acid release from adipocytes and by reduction of the production of VLDL particles. Adverse effects are frequent and include vomiting, diarrhea, erythema, pruritus, and abnormalities in liver function tests. Fibric acid derivatives (clofibrate, bezafibrate, gemfibrozil, ciprofibrate, fenofibrate) lower triglyceride concentrations by stimulating lipoprotein lipase activity, in addition to reducing the free fatty acid concentration, which decreases the substrate for VLDL synthesis. In humans, the fibrates generally lower serum triglyceride concentrations by 20% to 40%. Gemfibrizol has been used in the dog (200 mg/day) and cat (10 mg/kg BW q12hr). Reported adverse effects include abdominal pain, vomiting, diarrhea, and abnormal liver function tests. The statins (lovastatin, simvastatin, pravastatin, fluvastatin, cerivastatin, atorvastatin) are HMG-CoA reductase inhibitors that primarily suppress cholesterol metabolism. As a consequence of lower intracellular cholesterol concentrations, the hepatic LDL receptor is up-regulated to increase the removal and clearance of LDL (VLDL remnant particles) from the circulation. In addition, the statins decrease hepatic production of VLDL. In humans, the statins can lower triglyceride by 10% to 15%. Adverse effects include lethargy, diarrhea, muscle pain, and hepatotoxicity.

Table • 160-1 Key Nutrients* in Diets Recommended by Selected Manufacturers for Hypertriglyceridemia

CANINE	TYPE	FAT g/1000 kcal (%ME)	PROTEIN g/1000 kcal (%ME)	ME kcal
WALTHAM Canine Veterinary Diet Low Fat	Dry	21 (18%)	66 (24%)	274/8 oz
WALTHAM Canine Veterinary Diet Low Fat	Can	20 (16%)	93 (31%)	377/13.6 oz
Purina Veterinary Diets EN GASTROENTERIC	Dry	28 (26%)	62 (23%)	397/8 oz
Purina Veterinary Diets EN GASTROENTERIC	Can	34 (31%)	76 (25%)	424/12.5 oz
Purina Veterinary Diets OM OVERWEIGHT MANAGEMENT	Dry	22 (16%)	104 (37%)	276/8 oz
Purina Veterinary Diets OM OVERWEIGHT MANAGEMENT	Can	34 (28%)	178 (55%)	189/12.5 oz
Purina Veterinary Diets HA HYPOALLERGENIC	Dry	26 (24%)	53 (19%)	302/8 oz
Hill's Prescription Diet Canine w/d	Dry	27 (24%)	58 (21%)	226/8 oz
Hill's Prescription Diet Canine w/d	Can	38 (31%)	53 (18%)	372/14.75 oz
Hill's Prescription Diet Canine r/d	Dry	29 (25%)	84 (30%)	205/8 oz
Hill's Prescription Diet Canine r/d	Can	28 (24%)	85 (30%)	292/14.25 oz
Eukanuba Veterinary Diets Nutritional Weight Loss Formula Restricted-Calorie	Dry	17 (15%)	63 (18%)	238/8 oz
FELINE				
WALTHAM Feline Veterinary Diet Calorie Control	Dry	28 (18%)	128 (50%)	208/8 oz
WALTHAM Feline Veterinary Diet Selected Protein with Rice and Duck	Dry	38 (25%)	99 (38%)	258/8 oz
Purina Veterinary Diets OM Overweight Management	Dry	25 (20%)	112 (42%)	326/8 oz
Purina Veterinary Diets OM Overweight Management	Can	37 (22%)	113 (45%)	150/5.5 oz
Hills Prescription Diet Feline w/d	Dry	28 (24%)	110 (39%)	281/8 oz
Hills Prescription Diet Feline w/d	Can	44 (38%)	110 (40%)	148/5.5 oz
Hills Prescription Diet Feline r/d	Dry	29 (25%)	114 (41%)	263/8 oz
Hills Prescription Diet Feline r/d	Can	28 (24%)	114 (40%)	116/5.5 oz
Eukanuba Veterinary Diets Nutritional Weight Loss Formula Restricted-Calorie	Dry	26 (23%)	92 (34%)	271/8 oz

* Information obtained from manufacturers' published information.

Unlike in humans, hypercholesterolemia rarely poses a health risk to dogs or cats. Specific therapy is only indicated if a prolonged marked increase in the serum cholesterol (>800 mg/dL) is documented because it may be associated with the development of atherosclerosis. Nutritional therapy with low fat diets is the initial treatment of choice for severe hypercholesterolemia (see Table 160-1). The addition of soluble fiber to the diet may also help to reduce cholesterol by as much as 10%. Soluble fiber interferes with the enteric reabsorption of bile acids. Consequently, the liver uses cholesterol to increase the synthesis of bile acids.

Pharmacologic agents that can be considered for the management of severe hypercholesterolemia include bile acid sequestrates, HMG-CoA reductase inhibitors, and Probucol. Bile acid sequestrates are ion exchange resins that interrupt the enterohepatic circulation of bile acids. Decreased reabsorption of bile acids stimulates the liver to synthesize bile acids and therefore uses intrahepatic cholesterol. Depletion of intrahepatic cholesterol stores stimulates the hepatic LDL receptor to increase the removal of LDL and HDL particles from the circulation. Cholestyramine (1 to 2 g PO BID) is effective at lowering cholesterol. However, its use has been associated with constipation, it interferes with the absorption of several oral medications, and it may increase hepatic VLDL synthesis with an increase triglyceride concentration. HMG-CoA reductase is the rate-limiting enzyme for cholesterol synthesis. The HMG-CoA reductase inhibitors are the most potent cholesterol lowering agents and, in humans, may reduce cholesterol concentrations by 20% to 40%. Lovastatin, 10 to 20 mg PO every 24 hours, may

be tried in dogs with persistent severe idiopathic hypercholesterolemia that does not respond to diet alone. Potential adverse effects include lethargy, diarrhea, muscle pain, and hepatotoxicity. Lovastatin should not be administered to dogs with hepatic disease. Probucol is a cholesterol-lowering agent whose mechanism of action is not completely clear. Probucol is not widely recommended for the management of hypercholesterolemia as its effect on lowering cholesterol concentration is variable and it has been associated with the development of arrhythmias.

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161 CHAPTER • 161 The Principles and Implementation of Enteral Nutrition

Stanley L. Marks

The documented benefits of enteral nutritional support of hospitalized human patients and experimental animal models include maintenance of intestinal structure and function, decreased mucosal permeability to bacteria and endotoxins, and preservation of secretory immunoglobulin A concentrations in biliary tract secretions.[1,2] Despite these benefits, veterinarians may fail to respond to the nutritional needs of sick animals, perhaps because the translation of research findings into practical applications is difficult. In addition, the nutritional needs of sick animals may be neglected due to the intense focus on life-threatening medical and surgical problems. The goal of nutritional support is to provide a formula of fuels and nutrients in proportions that can be utilized by animals with maximal efficiency. Choosing the proper enteral access technique requires knowledge of the limitations and benefits of the techniques available for obtaining enteral access. The reader is encouraged to read the section on Nasoesophageal, Esophagostomy, and Gastrostomy Tube Placement Techniques for a thorough review of the techniques and complications associated with placement of these devices.

161.1 RATIONALE FOR ENTERAL NUTRITIONAL SUPPORT

Enteral feeding is indicated for animals unable to ingest adequate amounts of calories but that have sufficient gastrointestinal function to allow digestion and absorption of feeding solutions delivered into the gastrointestinal tract via an enteral feeding device. The rationale for prescribing enteral nutrition rather than parenteral nutrition (PN) is based on the superior maintenance of intestinal structure and function, safety of administration, and reduced cost of enteral alimentation. The average daily cost of TPN for maintaining the caloric requirements of a 20-kg dog at the University of California, Davis, Veterinary Medical Teaching Hospital, is approximately seven times greater (excluding catheter costs) than the cost of a commercial liquid enteral formula and a commercial canned diet. The most important stimulus for mucosal cell proliferation is the direct presence of nutrients in the intestinal lumen. Bowel rest due to starvation or administration of TPN leads to villous atrophy[3], increased intestinal permeability, and a reduction in intestinal disaccharidase activities.[4] Prolonged fasting in the stressed, critically ill animal can lead to intestinal barrier failure and increased permeability to bacteria and endotoxins.

161.2 PATIENT SELECTION FOR NUTRITIONAL SUPPORT

Efforts to assess nutritional status and attempts to decide whether nutritional support is required on the basis of a single biochemical measurement or body weight determination are simplistic and of limited value. Objective methods of assessing nutritional status such as body composition measurement (anthropometry, impedance measurements, dual energy X-ray absorptiometry) are still in their infancy in veterinary medicine, with the result that a subjective global assessment of an animals nutritional status needs to be performed. This technique is based on easily collected historical information (changes in oral intake, degree of weight loss, presence of vomiting or diarrhea) and changes found on physical examination (muscle wasting, body condition, and presence of edema or ascites).

Although body weight is routinely determined in sick animals, it is important to appreciate its limitations. The appearance of the animal cannot be equated with its state of nourishment because body weight does not differentiate between fat, lean tissue, and extracellular water. The animal's serum albumin concentration and total lymphocyte count are insensitive determinants of nutritional status because of the large number of disease processes that influence these parameters unrelated to the effects of malnutrition. Nutritional support should be

considered for animals that demonstrate recent weight loss that exceeds 10% of optimal body weight or for those whose oral intake has been or will be interrupted for more than 5 days. Animals with increased nutrient losses from chronic diarrhea or vomiting, wounds, renal disease, or burns should also be considered for nutritional support.

161.3 CALCULATION OF NUTRITIONAL REQUIREMENTS

Nutritional support provides substrates for gluconeogenesis and protein synthesis and provides the energy needed to meet the additional demands of host defense, wound repair, and cell division and growth. An estimate of an animal's nutrient requirements is needed to determine the minimum amount of food necessary to sustain critical physiologic processes (Box 161-1). The resting energy requirement (RER) is the animal's energy requirement at rest in a thermoneutral environment and in a postabsorptive state. A linear formula can be applied to determine the RER of dogs and cats weighing at least 2 kg, but no more than 15 kg. Alternatively, an allometric formula can be applied to dogs and cats of all weights.

$$\text{Linear formula: RER (kcal/day)} = (30 \times BW_{kg}) + 70$$
$$\text{Allometric formula: RER (kcal/day)} = 70\ (BW_{kg}^{0.75})$$

Accurate, direct measurements of energy expenditure in sick dogs and cats are not available. Despite the paucity of data on energy requirements of sick animals, veterinary nutritionists have recognized that the caloric requirements of critically ill animals are less than normal maintenance amounts (MER), but greater than RER. Hospitalized animals should be fed at their calculated RER initially, although their actual energy requirement is likely to change over the course of the disease process through recovery. Use of “fudge factors” extrapolated from the human literature to calculate the energy requirements of critically ill animals is discouraged, particularly in the early phase of nutritional support. Close observation of changes in body weight, physical examination findings (decreased subcutaneous fat stores, muscle wasting, and presence of edema or ascites), and ongoing losses (diarrhea, vomiting, exudative wounds) will help determine whether to increase or decrease the patients caloric intake towards the illness energy requirement (IER) or RER, respectively. The term *illness energy requirement* (IER) is used to determine caloric requirements of critically ill animals and can be determined from these formulas:

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$$\text{Canine IER (kcal/day)} = 1.2 - 1.4 \times \text{RER}$$
$$\text{Feline IER (kcal/day)} = 1.1\text{–}1.2 \times \text{RER}$$

161.3.1 Box • 161-1 Enteral Feeding Worksheet for Dogs and Cats

1. Calculate resting energy requirement (RER):

   Body weight 2 to 45 kg: RER (kcal) = 30 Wt_{kg} + 70

   Body weight <2 or >45 kg: RER = 70 ($Wt_{kg}^{0.75}$)

   Body weight =___ kg

   RER =___ kcal

2. Calculate illness energy requirement (IER)*

   Illness factor = 1.2 to 1.4 for dogs

Illness factor = 1.1 to 1.2 for cats

IER = RER × illness factor

IER =___ kcal

3. Calculate amount of diet to feed:

   Daily volume to feed: IER ÷ energy density (kcal/mL)

   Daily volume =___ mL

4. Evaluate responses and modify as needed:

   Weight changes often reflect fluid dynamics in the early period after injury. Caloric requirement may need to be increased or decreased depending on animal's metabolic rate and response to nutritional support.

Modified from Marks SL: The principles and practical application of enteral nutrition, *Vet Clin North Am Small Anim Pract* 28:677, 1998.

* Animals should be fed their RER initially, and have their body weights, physical examination findings, and ongoing losses carefully evaluated before gradually increasing their caloric intake based on the IER formula.

161.4 DIET SELECTION

The type of formula to feed the patient depends on the selected route of feeding, the functional status of the gastrointestinal tract, and the animal's nutrient requirements. Other factors, such as cost, availability, and ease of use may also be important. Animals fed via nasoesophageal or jejunostomy feeding tubes are limited to receiving liquid enteral formulas that have a caloric density of approximately 1 kcal per ml. When selecting a liquid formula for feeding, veterinary professionals should pay particular attention to the amount of protein in the formula, the type of protein (intact proteins, peptides, and amino acids), and the quality of the protein. Whole egg has the highest biologic value, followed by cow milk, lactalbumin, beef, soy, and casein. Most human liquid formulas contain less than 20% protein calories, precluding their use for the long-term (longer than 2 weeks) feeding of cats. The lower-protein formulas should be supplemented with protein modules such as Promod (Ross Laboratories, Columbus, OH), Casec (Mead-Johnson, Evansville, IN) or Promagic (Animal Nutrition Laboratories, Burlington, NJ) at 15 to 30 g casein or whey powder per 8 fl oz can. Almost all human liquid enteral formulas lack taurine, an essential amino acid in cats, which necessitates its supplementation (250 mg taurine per 8 fl oz can) in this species. High-protein commercial human liquid formulations contain between 21% to 30% protein calories and include Impact (Sandoz Nutrition, Minneapolis, MN), Immun-Aid (McGaw, Inc., Irvine, CA), Alitraq (Ross Laboratories, Columbus, OH), Promote (Ross Laboratories, Columbus, OH), and Traumacal (Mead-Johnson, Evansville, IN).

Polymeric solutions contain macronutrients in the form of isolates of intact protein (casein, lactalbumin, whey, egg white), triglycerides, and carbohydrate polymers. The carbohydrates are usually glucose polymers in the form of starch and its hydrolysates and the fats are of vegetable origin. The osmolality varies between 300 and 450 mOsm/kg in solutions with a caloric density of 1 kcal/ml; however, the osmolality may reach 650 mOsm/kg in solutions with a greater caloric density. Monomeric solutions contain protein as peptides or amino acids, fat as long-chain triglycerides (LCT), or a mixture of LCT and medium-chain triglycerides (MCT), and carbohydrates as

partially hydrolyzed starch maltodextrins and glucose oligosaccharides. These solutions require less digestion and their absorption is more efficient than regular foods or polymeric solutions; however, the partially digested macronutrients contribute to the higher osmolality, which is between 400 and 700 mOsm/kg.

Commercial blenderized pet food diets are recommended for feeding via pharyngostomy, esophagostomy, or gastrostomy tubes. In select cases, the feeding of a liquid enteral formulation may be indicated (nasoesophageal or jejunostomy tube feeding). There are a number of complete and balanced veterinary enteral formulations (Table 161-1) that contain adequate amounts of protein, taurine, and micronutrients, which precludes the need for supplementation in most situations. Feeding should be delayed for 24 hours after placement of a gastrostomy tube, to allow return of gastric motility and allow formation of a fibrin seal. In contrast, feeding can be instituted immediately after esophagostomy tube placement, once the animal has fully recovered from anesthesia. Diet can be administered as bolus feedings or continuous infusion when a gastrostomy tube is used for feeding. Improved weight gain and decreased gastroesophageal reflux have been reported in human patients given continuous feedings[5], although similar studies are lacking in the veterinary literature. If continuous feeding is employed, it should be interrupted every 8 hours to determine the residual volume by application of suction to the feeding tube. If the residual volume is more than twice the volume infused in 1 hour, feeding should be discontinued for 2 hours, and the rate of infusion decreased by 25% to prevent vomiting. Treatment with metoclopramide (1 to 2 mg/kg/24 hour as a continuous infusion) may be used to enhance gastric emptying and prevent vomiting.[6]

With bolus feeding, the required daily volume of food should be divided into four to six feeds. Dogs and cats are usually fed approximately 25% of their caloric requirement on the first day of feeding, with a gradual increase of 25% of the caloric requirement per day. Most animals are able to reach their energy requirement by the fourth or fifth day of feeding. The food should be warmed to room temperature and fed slowly through the tube to prevent vomiting. Flushing of the tube with 15 to 20 mL of lukewarm water helps prevent clogging. Before each feeding, aspirate the tube with an empty syringe to check for residual food left in the stomach from the previous feeding. If more than half of the last feeding is removed from the stomach, the feeding should be skipped and residual volume rechecked at the next feeding.

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Table • 161-1 Macronutrient Composition of Selected Veterinary Liquid Enteral Formulations

			NUTRIENTS (% OF TOTAL kcal)			
PRODUCT	PROTEIN TYPE	CALORIC DENSITY (kcal/ml)	PROTEIN	FAT	CARBOHYDRATE	FORMULA CHARACTERISTICS
Prescription diet Canine & Feline a/d (Hill's)	Liver Chicken Corn flour Casein	1.3	34	55	4	Isotonic, lactose free, fiber 1.3% DM, adequate taurine, fatty acid ratio (n6:n3 = 2.2:1)
Eukanuba Maximum-Calorie Canine & Feline (Iams)	Chicken Chicken by-product meal	2.1	29	66	5	Isotonic, lactose free, fiber 1.6% DM, adequate taurine, fatty acid ratio (n6:n3 = 8.3:11)
CliniCare Canine (Abbott)	80% casein 20% whey	1.0	20	55	25	Isotonic (230 mOsm/kg), lactose free, fiber free, fatty acid ratio (n6:n3 = 6.4:1)
Clinicare Feline (Abbott)	60% casein 40% whey	1.0	30	45	25	Isotonic (235 mOsm/kg), lactose free, fiber free, adequate taurine, fatty acid ratio (n6:n3 = 6.4:1)
Clinicare RF Specialized Feline (Abbott)	80% casein 20% whey	1.0	22	57	21	Isotonic (165 mOsm/kg), lactose free, fiber free, adequate taurine, fatty acid ratio (n6:n3 = 6.4:1)

Modified from Marks SL: The principles and practical application of enteral nutrition, *Vet Clin North Am Small Anim Pract* 28:677, 1998.

Jejunal feeding can be started within 6 hours of tube placement if peristalsis is present. Continuous feeding should be used with jejunostomy feeding to avoid abdominal cramping and diarrhea associated with bolus feeding via this route. Continuous infusion is recommended at an initial flow rate of 1 ml/kg/hr and increased gradually over 48 hours until the total daily volume can be given over a 12-to 18-hour period.[7]

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162 CHAPTER • 162 Serology

Michael R. Lappin

***S**erology* is the study of antigen-antibody reactions in vitro. Immunoassays for use with serum, blood, or plasma can be developed to detect antigens, antibodies, or antigen-antibody complexes; some assays are only qualitative, and others are quantitative. Some assays have been adapted to detect antigen-antibody reactions in other body fluids as well. This chapter discusses the use of immunoassays in the diagnosis of infectious diseases. Commonly used terms and their definitions are listed in Table 162-1. A discussion of serologic tests used in the diagnosis of immune-mediated diseases is presented in Chapters 277 and 278.

Complement fixation, hemagglutination inhibition, serum neutralization, agglutination assays, agar gel immunodiffusion, indirect fluorescent antibody assay (IFA), enzyme-linked immunosorbent assay (ELISA), and Western blot immunoassay are commonly used methodologies. It is beyond the scope of this chapter to discuss the intricacies of each assay; the reader is directed to other chapters and publications for further information on the development, validation, and techniques for the different assays.[1–5] It is impossible to make generic statements concerning the sensitivity, specificity, predictive values, and precision of different immunoassays in general or to compare the results of one type of assay with those of another. When new immunoassays are made available, the veterinary health care worker should critically evaluate the published results of the assay prior to use.

In serologic test results, the *analytic sensitivity* defines the minimum detectable amount of the substance in question that can accurately be measured; the *analytic specificity* defines whether the substance detected cross-reacts with other substances. The *diagnostic sensitivity* is the proportion of positive test results from known infected animals; the *diagnostic specificity* is the proportion of negative test results from known uninfected animals. The *predictive value of a positive test* is the probability that a test-positive animal is diseased; the *predictive value of a negative test* is the probability that a test-negative animal is normal. The lower the prevalence of disease, the lower the predictive value of a positive test result. Disease prevalence has little effect on negative predictive values.

The following is a brief discussion of the interpretation of test results for antibody and antigen assays used with blood, serum, plasma, or other body fluids by small animal veterinary health care workers.

162.1 ANTIBODY DETECTION

Once exposed to foreign antigens, the immune system generates serum antibodies (humoral immune response). Complement fixation, hemagglutination inhibition, serum neutralization, agglutination assays, agar gel immunodiffusion, IFA, ELISA, and Western blot immunoassay are commonly used to detect serum antibodies against infectious agents. Complement fixation, hemagglutination inhibition, serum neutralization, and agglutination assays generally detect all antibody classes in a serum sample. Specific antibodies for which assays are most commonly performed include immunoglobulin M (IgM), immunoglobulin G (IgG), immunoglobulin A (IgA), and immunoglobulin E (IgE). ELISA, Western blot immunoassay, and IFA are the assay types that are usually adapted to detect specific IgM, IgG, or IgA responses. Western blot immunoassays have the potential advantage of allowing the determination of the different antigens recognized by the humoral immune responses (Figure 162-1). Comparison of IgM, IgA, and IgG antibody responses against an infectious agent can be used to attempt to prove recent or active infection. In general, immunoglobulin M (IgM) is the first antibody produced after antigenic exposure.[6] Antibody class shift to IgG occurs in days to weeks. Serum IgA responses often mirror those of IgG (Figure 162-2).

The timing of antibody testing is important. In general, serum antibody tests in puppies and kittens cannot be interpreted as specific responses until at least 8 to 12 weeks of age because of the presence of antibodies from the dam, which are passed to the puppy or kitten in colostrum. Most infectious agents can induce disease within 3 to 10 days of initial exposure; with many assays, serum IgG antibodies usually are not detected until at least 2 to 3 weeks after initial exposure. Examples include *Ehrlichia canis,*[7] feline immunodeficiency virus,[8] and *Rickettsia rickettsii*.[9] For these reasons, falsely negative serum antibody test results during acute disease are probably common in small animal practice. If specific serum antibody testing is negative initially in an animal with acute disease, repeat antibody testing should be performed in 2 to 3 weeks to assess for seroconversion. Documentation of increasing antibody titers is consistent with recent or active infection. Because of a slight potential for interassay variation, it is preferable to assess both the acute and convalescent sera in the same assay on the same day.

Many of the infectious agents encountered in small animal practice infect a large percentage of the population, resulting in serum antibody production, but they induce disease only in a small number of animals in the infected group. Notable examples include coronaviruses, *Bartonella henselae, Toxoplasma gondii,* and *Borrelia burgdorferi*.[6,8,10,11] For these examples, even though assays with good sensitivity and specificity for the detection of serum antibodies are available, the predictive value of a positive test result for the presence of disease is extremely low because antibodies are commonly detected in nondiseased animals. The diagnostic utility of some serologic tests is also limited by the presence of antibodies induced by vaccination. Examples include feline coronaviruses, some *B. burgdorferi* assays, feline herpesvirus-1 (FHV-1), feline immunodeficiency virus, parvoviruses, calicivirus, and canine distemper virus.

Positive results in serum antibody tests should always be interpreted only as evidence of present or prior infection by the agent in question. Recent or active infection is suggested by the presence of IgM, an increasing antibody titer over 2 to 3 weeks, or seroconversion (negative antibody result on the first test, positive antibody result on convalescent testing). Documentation of increasing antibody titers may suggest recent exposure to an antigen. However, the interval between the first positive result and maximal antibody titers can be very short. For example, some cats experimentally inoculated with *T. gondii* progress from the first detectable titer to the maximal titer within 1 to 2 weeks.[6]

Table • 162-1 Terms Commonly Used in Serologic Tests

TERM	DEFINITION
Affinity	The intrinsic attractiveness of one substance for another (e.g., antibody for antigen)
AGID	Agar gel immunodiffusion; an immunoassay in which the immunochemical reaction between antigen and antibody occurs in agar
Analyte	The antigen or antibody to be measured
Antibody binding site	The site of the variable region of antibodies that binds to the antigen epitope
Antigen	A substance specifically recognized by the immune system (e.g., antibody in immunoassays)
Antiglobulin	An antibody that detects another antibody
Avidity	The property of a molecular dissociation that inhibits disassociation; usually the combination of affinity and the interaction of reagents with the solid phase
Blocking	A protein or detergent used to block nonspecific reactions between reagents of an enzyme-linked immunosorbent assay (ELISA) or between reagents and the solid phase
Capture antibody	An immobilized antibody used to capture the antigen of interest from the sample
Competitive ELISA	An ELISA in which detection of the analyte is based on its ability to quantitatively inhibit the binding of a known amount of a standard analyte to a limiting amount of antibody
Conjugate	A covalent complex of two biomolecules; in ELISA, the conjugate is an antibody or antigen bound to enzyme
Direct ELISA	An ELISA in which the primary antigen-antibody interaction is measured directly because the enzyme is directly labeled to one or the other
Epitope	The portion of a biomolecule (antigen) that is specifically recognized by the antibody binding site; also called an antigenic determinant
HI	Hemagglutination inhibition
IFA	Immunofluorescent antibody assay; an immunoassay in which the primary antigen-antibody reaction is detected by a fluorescein-labeled secondary antibody
Immunoblot	An immunoassay in which the immunochemical reaction between antigen and antibody occurs on a blotting membrane
Indirect ELISA	An ELISA in which the primary antigen-antibody reaction is detected using an enzyme-labeled antiglobulin
LA	Latex agglutination
Nitrocellulose	The membrane most commonly used for immunoblot
Nonspecific binding	Binding of the conjugate in a nonimmune/nonspecific fashion, possibly resulting in a high signal and false-positive reactions
Precision	Agreement of replicate measurements within an assay or between assays; a measure of reproducibility
Reporter substance	A biomolecule that generates a signal as an indication of its presence; in ELISA, the substrate often is the reporter substance
Sandwich ELISA	A type of ELISA in which the analyte is captured by one antibody and detected by another, enzyme-linked antibody
SN	Serum neutralization
Titer	The reciprocal of the highest dilution of sample giving a predefined positive reaction in an immunoassay
Western blot (immunoassay)	A method by which molecules are electrophoretically separated on a gel, transferred to a blotting membrane, and then detected by antibodies or special stains

Detection of recent infection based on antibody testing does not always prove disease caused by the agent in question. This is especially true in affected animals with a subclinical infection. *B. burgdorferi, T. gondii,* and *B. henselae* are common examples of this. Conversely, failure to document recent or active infection based on serologic testing does not exclude a diagnosis of clinical disease. For example, many dogs with ehrlichiosis and dogs or cats with systemic fungal infections develop clinical signs of disease after serum antibody titers have reached their plateau.

Individual animals vary in the humoral responses against specific antigens. Some animals are high responders and produce large concentrations of specific antibody, whereas others do not. Thus the magnitude of an antibody titer does not definitely document that an antigenic exposure was recent, active, or associated with clinical disease. This is particularly true for the IgG class of antibody and for agents resulting in persistent infections. For example, many healthy cats experimentally inoculated with *T. gondii* have had IgG antibody titers greater than 1:10,000 even 6 years after the last inoculation.[6] Because no antibody test by itself can prove the presence of disease, clinical diagnosis of an infectious disease usually includes the following factors:

- Clinical signs referable to the agent
- Serologic evidence of exposure to the agent
- Exclusion of other causes of the clinical syndrome
- Demonstration of the agent or of response to treatment

Figure 162-1 Example of a Western blot immunoassay. The bands that have developed in the suspect serum lanes are consistent with an antigen-antibody reaction. Comparison to the molecular mass standards allows determination of the approximate size of the antigen inducing the immune response.

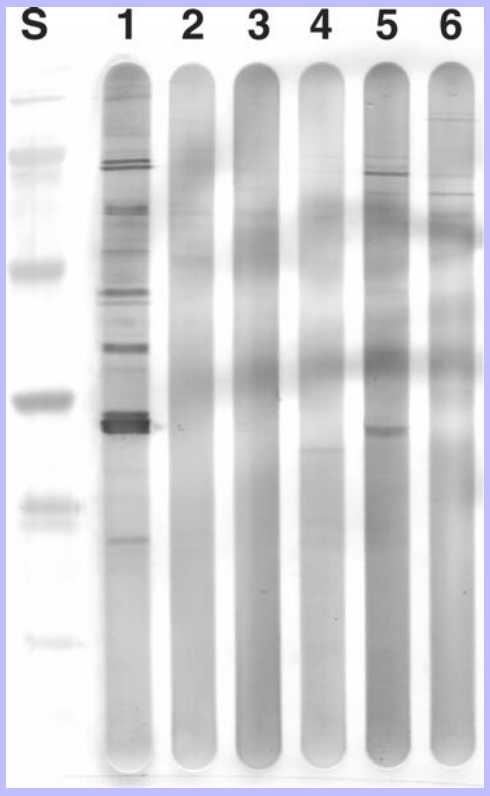
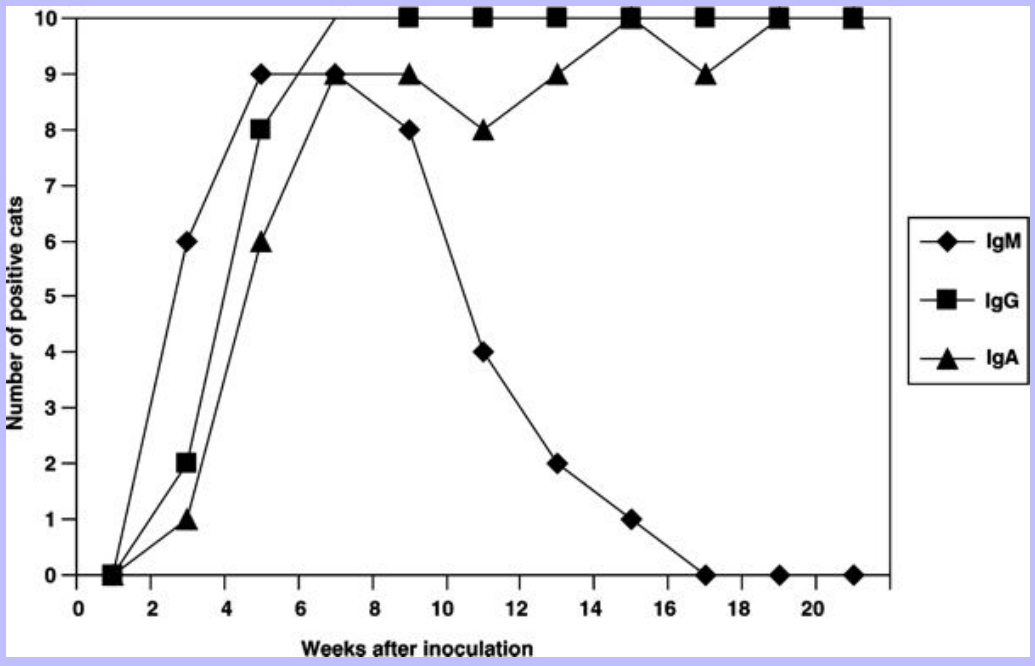


Figure 162-2 Graphic representation of IgM, IgG, and IgA immune responses characteristic for cats after antigenic exposure in week 0.



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162.2 ANTIGEN DETECTION

Immunoassays can be used to measure any substance against which an antibody can be generated. Examples include antigens of infectious agents, cell-associated antigens (including tumors), receptors, hormones, and drugs. Positive results in immunoassays that detect the presence of antigens of an infectious disease agent document that the animal is currently infected. The presence of antibodies denotes current or previous infection.

Immunoassays are commercially available for the detection of *Dirofilaria immitis,*[12] feline leukemia virus (FeLV),[13] and *Cryptococcus neoformans*[14] antigens in serum, plasma, or blood. The performance of specific assays may vary with the different fluids; in general, serum gives the most consistent results. For the most part, the sensitivities and specificities of the infectious disease antigen assays are good. *D. immitis* antigen test results can be negative in some animals with low worm burdens or single sex infections; this is particularly true for cats.[12] Feline leukemia virus antigen test results can be negative in cats with localized or sequestered infection (latent). Serum-or plasma-based feline leukemia virus antigen tests can also yield transiently positive results in cats that are limiting infection; the results for healthy, ELISA-positive cats should always be confirmed by repeat ELISA testing or by IFA testing.[14] Because clinically normal animals can be antigen positive by ELISA, the positive predictive value for disease is not 100%, particularly if the prevalence of disease is low. Positive feline leukemia antigen test results also do not prove immunodeficiency. In dogs and cats with localized cryptococcosis, serum antigen test results can be negative.

162.2.1 Body Fluids

Some infectious agents induce disease of the eyes and central nervous system (CNS). Documentation of agent-specific antibodies in aqueous humor, vitreous humor, or cerebrospinal fluid (CSF) can be used to prove the involvement of these tissues. Quantification of ocular and CSF antibodies is difficult to interpret if serum antibodies and inflammatory disease are present, because serum antibodies leak into ocular fluids and CSF in the presence of inflammation. Detection of local production of antibodies in the eye or CNS has been used to aid the diagnosis of canine distemper virus infection (see Chapter 169) and feline toxoplasmosis (see Chapter 169). The following ratio is a method of proving local antibody production by the eye or CNS:

$$\frac{\text{Aqueous humor or CSF specific antibody}}{\text{Serum specific antibody}} \times \frac{\text{Serum total antibody}}{\text{Aqueous humor or CSF total antibody}}$$

A ratio greater than 1 suggests that the antibody in the aqueous humor or CSF was produced locally. This formula has been used extensively in the evaluation of cats with uveitis. Approximately 60% of cats with uveitis in the United States have *T. gondii*–specific IgM, IgA, or IgG values greater than 1.[6,15] This technique also was used to help prove that FHV-1[16] and *B. henselae*[17] are causes of uveitis in cats.

Feline leukemia virus antigen can be detected in saliva, tears, and cells from the bone marrow or direct blood smear.[13] The sensitivity and specificity of FeLV tests using tears and saliva are less than for those using serum. Detection of FeLV antigen in cells by fluorescent antibody testing generally denotes persistent infection. *T. gondii* antigens have been detected in aqueous humor and CSF, but their presence does not correlate with the presence of disease.[6] The *C. neoformans* latex agglutination procedure for detection of antigen can also be performed on aqueous humor, vitreous humor, and cerebrospinal fluid.

Immunoassays are available for the detection of parvovirus, *Cryptosporidium parvum,* and *Giardia spp*. in feces. The commercially available parvovirus assay was titrated for use with canine feces and canine parvovirus, but generally it can detect panleukopenia antigen in the feces of infected cats as well. Sensitivity appears to be good with parvovirus fecal antigen tests, but positive test results are not specific for natural exposure because modified live parvovirus vaccines are shed into feces, giving transiently positive results (see Chapter 169). The currently available assays for the detection of *C. parvum* and *Giardia spp*. in feces were titrated for human isolates and feces. Minimal sensitivity and specificity results are available for these assays when they are used with feces from small animals (see Chapter 168). If these assays are used, the results should be interpreted with results from fecal examination techniques for oocysts *(Cryptosporidium)* or cysts *(Giardia)*.

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163 CHAPTER • 163 Canine Vaccination

Richard B. Ford

The recent publication of the *2003 Canine Vaccine Guidelines and Recommendations*[1] is the first such effort intended to provide a unified consensus reference on canine vaccination for the veterinary profession.

As published, the *Guidelines* address 15 types of canine vaccine licensed for use in the United States and provide critical information pertinent to the development and implementation of vaccination protocols for dogs. The *Guidelines* are *not* intended to represent vaccination *standards* for dogs nor do they define a uniform vaccination protocol for use in clinical practice. As new information is gained and as new vaccines are licensed for use in dogs, these *Guidelines* will be updated.

The context of the *2005 Canine Vaccine Guidelines* centers on vaccine selection and frequency of use. Additional supportive information includes an overview of immunology as it pertains to vaccination, the role of serologic testing in determination of the need to administer booster vaccines to individual patients, vaccine adverse events, and pertinent legal and liability issues related to administering vaccines. The Canine Vaccine Guidelines outlined by the Task Force are summarized in Table 163-1. The reader is encouraged to consult the full text of the Guidelines for further information on individual vaccine types and supporting literature.[2]

163.1 VACCINE SELECTION

Vaccination guidelines published for cats as well as dogs have endorsed terms (*core* and *noncore*) that categorize vaccine types (not individual products) using criteria such as health risk associated with infection, disease incidence and severity, and vaccine efficacy. *Core* vaccines are generally defined as those vaccines that should be administered to *every* dog (and every cat) that is 6 months of age or younger or is not known to have received prior vaccination. These vaccines are deemed particularly important because the infections they prevent are associated with significant morbidity and mortality, are widely distributed, or are zoonotic. The Canine Vaccine Task Force has designated vaccines against canine distemper, canine parvovirus, canine adenovirus-2, and rabies virus as *core*.

Vaccines defined as *noncore* (or “optional”) are those that should be administered only after consideration of the risk an individual dog has for exposure to a defined infectious agent. Factors such as geographic distribution of the disease (e.g., Lyme borreliosis), age of the patient (puppy versus adult), and lifestyle (strict indoor versus free-roaming) are considered in the decision to administer, or not administer, noncore vaccines. Vaccines placed in this category are recommended when it is the objective to protect individual dogs against less common, or less severe, infections that are either self-limiting or amenable to treatment. The Canine Vaccine Task Force has designated vaccines against measles (distemper-measles), canine parainfluenza, *Leptospirosis* spp., *Bordetella bronchiseptica*, and *Borrelia burgdorferi* as *noncore*.

Additionally, the Task Force has designated vaccines against *Giardia* spp., canine coronavirus, and canine adenovirus-1 (canine hepatitis) as “not generally recommended.” The basis for such designation is based on information discussed in detail within the context of the *Guidelines*. Reasons for placing a particular vaccine in this category have been based on one or more of the following: the disease a vaccine is intended to prevent is either of little or no clinical significance (e.g., coronavirus), the vaccine is known to be associated with potentially serious adverse events (e.g., adenovirus-1), or the vaccine does not prevent infection (e.g., *Giardia* spp.).

The Canine Vaccine Task Force acknowledges the fact that all veterinarians may not agree with which vaccines belong in which category. For that reason, the *Canine Guidelines* have been written to support individual clinicians and practices in designation of which vaccines should be given to all dogs presented to the practice and which vaccines are administered only on the basis of a defined health risk assessment. Veterinarians are therefore encouraged to designate, for the individual practice, which vaccines should be *core* and which *noncore*. The decision to administer, or *not* to administer, a vaccine categorized as *noncore* rests with the individual clinician after interviewing the pet owner and assessing reasonable risk for exposure. For example, the Canine Vaccine Task Force designated canine adenovirus-2 vaccine as *core* and the canine parainfluenza vaccine as *noncore*. However, the majority of parainfluenza vaccine products on the market today are combined with canine adenovirus-2. It is therefore quite reasonable for an individual practice to designate *both* canine adenovirus-2 and parainfluenza vaccines as *core* when developing a vaccine protocol.

163.2 FREQUENCY OF VACCINE USE

Among the most significant recommendations made by the Canine Vaccine Task Force is that, despite traditional recommendations, certain vaccines, when administered to adult dogs as a booster vaccination, may be administered at intervals of 3 years without degradation of protection or increased risk if exposed to the virulent agent. In fact, limited studies involving most core vaccines support a minimum duration of immunity (DOI) of 5 to 7 years. Recommendations pertaining to *initial* vaccination intervals for puppies and adult dogs (not previously vaccinated) remain unchanged.

Current information on DOI, as presented in the full text of the *Guidelines,* supports the recommendation for 3-year booster vaccination intervals for the following vaccines: canine distemper (modified-live and recombinant), parvovirus (modified-live), canine adenovirus-2 (modified-live), and parainfluenza virus.

Obviously the actual DOI for any vaccine is influenced by such factors as the vaccine manufacturing process, route of administration, concentration of antigen in the product, product handing, health status of the patient at time of vaccination, and genetic variances in an individual animal's ability to response to a vaccine.

Table • 163-1 Canine Vaccine Recommendations—2005

VACCINE	PRIMARY VACCINATION (PUPPY) ≤16 WEEKS	PRIMARY VACCINATION (ADULT) >16 WEEKS	REVACCINATION (BOOSTER) RECOMMENDATIONS	COMMENTS
Canine Distemper Virus (MLV)	Administer one dose at 6–8 weeks, then 9–11 weeks, then 12–14 weeks of age	1 dose is protective	First booster is administered 1 year following the last dose of the initial (puppy) series. **Additional boosters are administered every 3 years thereafter.**	***Highly Recommended:***Despite manufacturer's annual booster recommendations, studies have shown that adult dogs challenged 7 years (Rockborn Strain) and 5 years (Onderstepoort Strain) following MLV vaccination were protected. A booster vaccination interval of every 3 years among adult dogs in protective.
CORE				
rCanine Distemper Virus (**r**CDV) (recombinant vaccine)	Administer one dose at 6–8 weeks, then 9–11 weeks, then 12–14 weeks of age	2 doses, 2–4 weeks apart	Booster annually-or- **Booster may be administered (see comments section) every 3 years.**	***Recommended:***May be used interchangeably or as an alternative to the MLV-CDV vaccine. Does not provide “sterile” immunity and may take longer to protect immunologically naïve dogs. Minimum demonstrated. Duration of Immunity (DOI) for **r**CDV is >2 years. Does not routinely provide sterile immunity and may take longer to protect immunologically naïve dogs. The vaccine is not recommended where the threat of exposure to CDV may be significant (e.g., shelters; pet stores). NOTE: A vaccination program that includes MLV-CDV vaccine for the initial vaccination followed by booster vaccination with **r**CDV would provide excellent protection; revaccination with **r**CDV every 3 years would then be reasonable.
CORE VACCINE (alternative to MLV CDV)				

Distemper-Measles Virus (MLV) **Administer by the INTRA-MUSCULAR route only**	One dose between 4 and 12 weeks of age⋯ **only**. (Follow with one dose of MLV-CDV-or- 2 doses of **r**CDV vaccine after 12 weeks of age)	Not recommended for use in dogs over 12 weeks of age	Booster vaccination is **NOT** recommended.	**Optional.** ***Not Recommended for Routine Use.*** Intended to provide *temporary* protection in young dogs only. Indicated for use in households/kennels where distemper is a recognized problem. **Do not administer to female dogs over 12 weeks of age.** **Not recommended for use in ANY dog over 12 weeks of age.** NOTE: If used in adults, the vaccine may result in maternal measles virus antibody that would be passed to offspring. This maternal antibody would interfere with subsequent vaccination against distemper. This vaccine will not immunize dogs if given by the subcutaneous route.
NONCORE				
Canine Parvovirus (MLV)	Administer one dose at 6–8 weeks, then 9–11 weeks, then 12–14 weeks of age	1 dose (however, recommend-ing 2 doses, 3–4 weeks apart is acceptable)	First booster is administered 1 year following the last dose of the initial (puppy) series. **Additional boosters are administered every 3 years thereafter.**	***Highly Recommended:*** Although annual boosters are recommended by vaccine manufacturers, studies have shown protection against challenge up to 7 years post-vaccination with MLV vaccine.
CORE				

Canine Parvovirus (killed)	Administer one dose at 2, 3 and 4 months of age	2 doses, 3–4 weeks apart	Annual NOTE: Studies are not currently available demonstrating an extended DOI for killed CPV products. NOTE: Puppies completing the initial series with an MLV CPV vaccine and revaccinated 1 year later with an MLV CPV vaccine could be vaccinated every 3 year thereafter with the KILLED virus vaccine.	***Recommended:***A suitable to the MLV alternative canine parvovirus vaccine in a LOW-risk environment, ALTHOUGH most practices routinely use the MLV vaccine. NOTE: Killed parvovirus products are susceptible to maternal antibody interference in puppies as old as 16 to 18 weeks of age. NOTE: Studies have shown protection against challenge 16 months post-vaccination in dogs only vaccinated with killed vaccine.
NON-COREan alternative to the MLV vaccine				
Canine Adenovirus-1 (CAV-1) (MLV and killed)	Administer one dose at 6–8 weeks, then 9–11 weeks, then 12–14 weeks of age	2 doses, 2–4 weeks apart (Killed vaccine) 1 dose (MLV vaccine)	Annual (manufacturer recommendation)	***Not Recommended.***Infectious Canine Hepatitis is uncommon in the U.S. Considering the low (to absent) prevalence, the risk of “hepatitis Blue-Eye” reactions, and the fact that CAV-2 will cross-protect against CAV-1, use of vaccines containing CAV-1 are notrecommended.
NOT RECOM-MENDED				***Caution:*** **At least 9 OTC vaccines Caution: At least 9 OTC vaccines (available to pet owners without a prescription) are currently on the market. Three of those vaccines contain a combination of BOTH CAV-1 and CAV-2!**

Canine Adenovirus-2 (CAV-2) (MLV-parenteral or topical) (Killed)	Administer one dose at 6–8 weeks, then 9–11 weeks, then 12–14 weeks of age	2 doses, 2–4 weeks apart (Killed vaccine) 1 dose (MLV vaccine)	First booster is administered 1 year following the last dose of the initial (puppy) series. **Additional boosters are administered every 3 years thereafter.**	***Highly Recommended.*** Demonstrated cross protection against canine hepatitis (CAV-1) and CAV-2, one of the agents known to be associated with infectious tracheobronchitis (ITB). Usually combined with CDV and CAV vaccine. *Currently this product is not available as a monovalent vaccine.* Adult dogs challenged 7 years following CAV-2 MLV vaccination were found to be protected against the more virulent CAV-1.
CORE				
Parainfluenza Virus (CpiV) (MLV-parenteral or topical)	Administer one dose at 6–8 weeks, then 9–11 weeks, then 12–14 weeks of age	1 dose is adequate (However, recommend-ing 2 doses, 3–4 weeks apart is acceptable.)	*Parenteral:* First booster is administered 1 year following the last dose of the initial (puppy) series. **Additional boosters are administered every 3 years thereafter.** *Intranasal:* Available only in combination with those *Bordetella bronchiseptica* indicated for intranasal administration. **Unpublished data suggests the DOI may persist beyond 1 year.**	***Recommended.***Usually combined with CDV and CAV vaccine. Currently this product is not available as a monovalent vaccine. Parenterally administered vaccine is less effective than topically (intranasal) administered vaccine. DOI by challenge has been shown to be at least 1 year (unpublished) for topical vaccine. Parenteral CPiV vaccine is available in combination with CDV, CPV, and CAV-2 vaccines. Intranasal CPiV vaccine is available In combination with *B. bronchiseptica* and CAV-2 vaccines.
NONCORE				

Bordetella bronchiseptica (killed bacterin)-Parenteral	Administer one dose at 6–8 weeks, then 10–12 weeks of age	2 doses, 2–4 weeks apart	Annual	***Optional.***Recent studies suggest the parenteral *B. bronchiseptica* vaccine may be more efficacious than the topical vaccine when administering boosters to adult dogs. The DOI is believed to be less than 1 year. There is no clear advantage in administration of the parenteral and the topical *B. bronchiseptica* simultaneously.
NONCORE *Bordetella dogs bronchiseptica* (live avirulent bacterin) + Parainfluenza Virus (MLV) **TOPICAL (intranasal) USE ONLY**	Administer a single dose as early as a 3 WEEKS OF AGE. (See product literature for age recommendations.) If topical vaccine is administered prior to 5–6 weeks of age, it should be administered again after 6 weeks of age and at least 2 weeks following the last dose.	Not stipulated, although a single dose is recommended.	Annual ⋯ if notvaccinated within the last 6 months, a booster is recommended 1 wk prior to known exposure (e.g., boarding, showing)	***Optional-Recommended***for housed in kennels, shelters, pounds; prior to boarding in kennels. Transient (3–10 days) coughing, sneezing, or nasal discharge occurs in a small percentage of vaccinates. Antimicrobial therapy may be indicated (Rx Doxycycline, 5–7 days) to manage post-vaccination upper respiratory signs (persistent cough and nasal discharge). DOI is believed to be approx. 10 months for *B.bronchiseptica*. NOTE: Topically administered vaccines for canine infectious tracheobronchitis may provide a superior local immune response compared to parenterally administered vaccines.
NONCORE *Bordetella bronchiseptica* (live avirulent bacterin) + Parainfluenza Virus (MLV) + Canine Adenovirus-2 (MLV) **TOPICAL (intranasal) USE ONLY OPTIONAL**	Administer a single dose at ≥8 weeks of age. Some manufacturers may recommend administration as early as 3 to 4 weeks of age. This is recommended only when extremely high risk of exposure is likely.	A single dose is recommended.	Annual ⋯ if notvaccinated within the last 6 months, a booster is recommended 1 wk prior to known exposure (e.g., boarding, showing)	***Recommended***for dogs considered to be at risk of exposure to any of the pathogens listed. NOTE: Topically administered vaccines for canine infectious tracheobronchitis may provide a superior local immune response compared to parenterally administered vaccines. DOI as noted above for individual vaccines.

Borrelia burgdorferi; **r**Lyme borreliosis (recombinant) Outer Surface Protein A (OspA) **NONCORE**	Initial dose may be given at 9 weeks of age and a required second dose 2–4 weeks later. Optimal age for the initial dose is ≥3 months with a second dose 2–4 weeks later.	2 doses, 2–4 weeks apart	Annual (The Task Force has recommended that, depending on geographic location, the vaccine be administered prior to the start of the tick season.)	***Optimal. NOTE:*** Lyme disease has limited regional prevalence; therefore recommendation for use is limited to dogs known to have a high risk of exposure. The minimum DOI for the recombinant vaccine is 1 year based on challenge.
Borrelia burgdorferi; Lyme borreliosis (killed whole bacterin) **NONCORE**	Initial dose may be given at 9 weeks of age and a required second dose 2–4 weeks later. Optimal age for the initial dose is ≥3 months with a second dose 2–4 weeks later.	2 doses, 2–4 weeks apart	Annual (The Task Force has recommended that, depending on geographic location, the vaccine be administered prior to the start of the tick season.)	***Optional.*** Lyme disease has limited regional prevalence. Recommendation for use is limited to dogs with a known high risk of exposure, preferably dogs living in the Northeastern U.S. and the upper Midwest (Wisconsin, Michigan) or perhaps those traveling to endemic areas when the risk of tick exposure is considered to be high. Minimum DOI based on challenge studies is 1 year.

	Canine coronavirus (killed and MLV)	Administer one dose every 2–4 weeks of age until 12 weeks of age (MLV and killed). The *killed* vaccine may be administered as early as 6 weeks of age followed by an additional dose every 2–3 weeks with the final dose at 12 weeks of age.	1 dose (if using MLV) 2 doses, 2–3 wks apart (if using killed) (The Task Force does not recommend the use of CCV vaccine in adult dogs since neither need nor benefit has been demonstrated in challenge studies.)	Annual (manufacturer recommendation) Neither product is recommended until clinical benefit demonstrated over combined vaccines (e.g., CPV and CDV only) that do not contain CCV antigen.	Prevalence of clinical cases of confirmed canine coronavirus infection does not justify routine inoculation of all dogs. Clinical infections are most likely to occur in puppies less than 6 weeks of age. Clinical signs are mild or not apparent and typically resolve spontaneously. It is recommended that animal shelters NOT utilize CCV vaccine in routine vaccination programs due to additional costs incurred by doing so and the lack of defined benefit. Experience has shown no additional increase in infectious enteritis among adults or puppies subsequent to discontinuing CCV vaccine. The DOI for CCV vaccine can not be determined since control dogs that are challenged do not become ill. Neither the MLV CCV vaccine nor the killed CCV vaccine has been shown to significantly reduce disease caused by a CCV + CPV challenge.
	NOT GENERALLY RECOMMENDED				

	Leptospira interrogans (L. canicola combined with *L. icterohaem-orrhagiae)* (killed bacterin) (Also available with serovars *grippotyphosa and pomona*)	Administer 1 dose at 12 weeks and a second at 16 weeks of age. NOTE: For optimal response, do not administer to dogs less than 12 weeks of age.	2 doses, 2–4 weeks apart	Annual Some authors recommend a booster every 6 months in dogs known to be at *significant* risk of exposure, i.e., documentation of infections in the practice population or area. Arbitrary administration of leptospirosis vaccines every 6 months is NOT recommended.	***Optional.***NOTE: Disease prevalence is likely to vary for each serovar. Vaccine recommendations are therefore difficult to make due the lack of information on prevalence of specific serovar infections among dogs living in various geographic regions of the U.S. Anecdotal reports from veterinarians and breeders suggest that the incidence of post-vaccination reactions (acute anaphylaxis) in puppies (less than 12 weeks of age) and small breed dogs is high. Reactions are most severe in young (<9 weeks of age) puppies. Routine use of the vaccine should be delayed until dogs are ≥12 weeks of age. Minimum DOI based on challenge studies has been shown to be approximately 12 months for serovars *L. canicolaand L. icterohaemorrhagiae*. Efficacy, however, is <75%. (Data is not available on theDOI for *L. grippotyphosa and L.pomona*)
NONCORE					

Giardia lamblia (killed)	An initial dose may be given at 8 weeks of age; a second dose should be given 2–3 weeks later.	2 doses, 2–4 weeks apart	Annual (manufacturer's recommendation) The Task Force recommends that boosters are NOT necessary in dogs ≥1 year of age.	***Not Recommended***. The vaccine may prevent oocyst shedding but does not prevent infection. Infection in puppies (and kittens) is often subclinical. Although giardiasis is the most common intestinal parasite among people in the U.S. the source of human infection is contaminated water. Infections in dogs and cats are not considered to be zoonotic. The vaccine does NOT prevent infection, therefore a minimum DOI based on challenge is not reported.
NOT GENERALLY RECOM-MENDED				
Rabies **1-year** (killed) ROUTE OF ADMINISTRA-TION MAY NOTBE OPTIONAL–see product literature for details.	Administer 1 dose as early as 3 months of age.	Administer a single dose.	Annual. State, provincial, and/or local laws apply. The **1-year** rabies vaccine may be used as a booster vaccine when dogs are required, in accordance with local statutes, to be vaccinated annually against rabies.	***Required.*** MLV vaccines are no longer available for administration in the U.S. State and local statutes govern the frequency of administration for products labeled as "1-Year Rabies." NOTE: The Rabies (1-year) vaccine is generally administered as the initial dose followed, 1 year later, by administration of the Rabies (3-year) Vaccine. State and local statutes may dictate otherwise.
CORE				

Rabies **3-year** (killed) ROUTE OF ADMINISTRA-TION MAY NOTBE OPTIONAL—see product literature for details.	Administer 1 dose as early as 3 months of age. NOTE: The 3-year rabies vaccine may be used as an alternative to the 1-year rabies vaccine for initial and subsequent doses. Local statutes apply.	Administer a single dose. NOTE: The 3-year rabies vaccine may be used as an alternative to the 1-year rabies vaccine for initial and subsequent doses. Local statutes apply.	The **second** rabies vaccination is recommended 1-year following administration of the initial dose regardless of the animal's age at the time the first dose is administered. Depending on local statutes, booster vaccines should be administered annually or every 3 years thereafter.	**Required.** State and local statutes govern the frequency of administration for products labeled as Rabies (3-year) ⋯ these statutes vary throughout the U.S. and Canada. NOTE: The Rabies (1-year) vaccine is generally administered as the initial dose followed, 1 year later, by administration of the Rabies (3-year) Vaccine. State and local statutes may dictate otherwise. The Task Force recommends that every effort should be made to change laws that require vaccination with the 3-year rabies vaccine at any interval less than 3 years. Doing so does not increase efficacy and may actually be associated with adverse events.
CORE				
NOTE: Letter designation "**r**" preceding the name of the antigen indicates a recombinant vaccine. *NOTE: Route of administration is SQ or IM unless otherwise noted by the manufacturer.*				

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163.3 CONCLUSION

In the absence of specific and reliable tests for immunity to infectious disease, each veterinarian must accept the responsibility of developing a rational vaccination protocol that, based on health risk profiling and vaccine(s) available, will best protect the individual patient at the most appropriate stages of life. The *Canine Vaccine Guidelines* have been specifically written to support safe, effective, and rational vaccination decisions.

163.4 REFERENCES

1. Report of the American Animal Hospital Association (AAHA) Canine Vaccine Task Force: executive summary and 2003 canine vaccine guidelines and recommendations. *J Am Anim Hosp Assoc*. **39**, 2003, 119.

2. The complete Task Force Report (which includes supporting literature and additional references) is currently available on-line to members of the American Animal Hospital Association:.

164 CHAPTER • 164 Feline Vaccinations

James R. Richards

The overall objectives of feline vaccination are to vaccinate the largest possible number of cats in the population at risk, vaccinate each cat no more frequently than necessary, and vaccinate only against infectious agents to which the cat has a realistic risk of exposure and subsequent development of disease. Kittens less than 4 months of age are usually more susceptible to infection and disease than are adult cats, and they are the principle targets for vaccination.[1]

164.1 VACCINATION EFFICACY

The success of vaccination against an infectious agent rests upon the ability of the immune system to protect against the disease in question.[2] Vaccines against agents that do not establish persistent infections (e.g., feline panleukopenia virus) are the most successful. Vaccines against agents characterized by persistent infections (e.g., feline herpesvirus [FHV], feline calicivirus), that evade host defense mechanisms (e.g., feline leukemia virus [FeLV], feline immunodeficiency virus [FIV]), that mutate as they replicate within the host (e.g., FIV, feline calicivirus, feline coronavirus), or that use normal host defenses to cause disease (e.g., feline coronavirus) are generally less successful.

Vaccines do not induce the same degree of protection in all animals, nor do most vaccines induce complete protection from either infection or disease. Factors that negatively affect an animal's ability to respond to vaccination include maternal antibody interference, congenital or acquired immunodeficiencies, concurrent disease, inadequate sanitation, immunosuppressive medication, and stress due to overcrowding.[3] An optimal response to vaccination cannot be obtained until the influence of these factors is reduced.

Table • 164-1 Guidelines for Administration of Feline Vaccines

ANTIGEN	VACCINE TYPES[a]	PRIMARY VACCINATION		BOOSTER VACCINATION	COMMENTS
		Cats <12 Weeks Old	Cats ≥12 Weeks Old		
Feline parvovirus[b]	MLV vaccine for parenteral administration MLV vaccine for topical administration Adjuvanted inactivated-virus vaccine for parenteral administration	If ≥6 weeks old, clinician should vaccinate at initial visit and every 3 to 4 weeks until ≥12 weeks old[c]	2 doses, 3 to 4 weeks apart	1 year after primary vaccination, then no more frequently than every 3 years	*Highly recommended for all cats;* in most cats, protection derived after administration of booster vaccination 1 year after primary vaccination is sustained for at least 3 years and probably 5 to 6 years or more; MLV vaccines should *not* be administered to pregnant queens or kittens <4 weeks old
Feline herpesvirus-1 (FHV-1) and feline calicivirus	Combined MLV vaccine for parenteral administration Combined adjuvanted inactivated-virus vaccine for parenteral administration	If ≥6 weeks old, clinician should vaccinate at initial visit and every 3 to 4 weeks until ≥12 weeks old[c]	2 doses, 3 to 4 weeks apart	1 year after primary vaccination, then every 3 years	*Highly recommended for all cats;* MLV vaccine should *not* be administered to pregnant queens
FHV-1 and feline calicivirus	Combined MLV vaccine for topical administration	If ≥6 weeks old, clinician should vaccinate at initial visit and every 3 to 4 weeks until ≥12 weeks old[d]	1 dose	1 year after primary vaccination, then every 3 years	*Highly recommended for all cats;* may be used as an alternative to the parenteral product; may be preferable to parenterally administered vaccines in cats reared in or entering environments in which viral upper respiratory tract disease is endemic (e.g., some catteries, boarding facilities, shelters); MLV vaccine should *not* be administered to pregnant queens

Rabies	Adjuvanted inactivated-virus vaccine for parenteral administration every year[e f]	Not eligible for vaccination	1 dose	1 year after primary vaccination, then every year[e]	*Highly recommended for all cats*; rabies vaccination of cats is required by law in some regions of the country, and veterinarians should comply with state and local statutes regarding type of vaccine to be used and vaccination interval
Rabies	Adjuvanted inactivated virus vaccine for parenteral administration every 3 years[e]	Not eligible for vaccination	1 dose	1 year after primary vaccination, then every 3 years[e]	*Highly recommended for all cats*; rabies vaccination of cats is required by law in some regions of the country, and veterinarians should comply with state and local statutes regarding type of vaccine to be used and vaccination interval
Rabies	Canarypox virus–vectored recombinant vaccine for parenteral administration	1 dose to cats as young as 8 weeks old	1 dose	1 year after primary vaccination, then every year	The *recombinant* rabies virus vaccine can be used as an alternative to other products approved for annual use; this product does not contain an adjuvant, and postvaccination inflammation at the vaccine site appears minimal; however, whether use of this product will be associated with a decreased likelihood of vaccine-associated sarcoma formation is not presently known
Feline leukemia virus (FeLV)	Adjuvanted and nonadjuvanted inactivated-virus vaccines for parenteral administration	2 doses, 3 to 4 weeks apart to cats as young as 8 weeks old[f]	2 doses, 3 to 4 weeks apartf	Annually	Recommended for cats that are notrestricted to a closed, indoor, FeLV-negative environment; most important for cats <16 weeks old;[d] not recommended for cats ≥16 weeks old with minimal to no risk of exposure to FeLV-infected cats

Chlamy-dophila felis	MLV vaccine for parenteral administration Adjuvanted inactivated vaccine for parenteral administration	2 doses, 3 to 4 weeks apart to cats as young as 9 weeks old	2 doses, 3 to 4 weeks apart	Annually	Not recommended for routine use; can be considered for use in cats in multiple-cat environments where *C. sittaci* infections associated with clinical disease have been documented
Feline infectious peritonitis (FIP) virus	MLV vaccine for topical administration	Not approved for cats <16 weeks old	2 doses, 3 to 4 weeks apart to cats ≥16 weeks old	Annually	Not recommended; at this time, insufficient evidence exists to support the conclusion that the vaccine induces clinically relevant protection
Microsporum canis	Adjuvanted inactivated vaccine for parenteral administration	Not approved for cats <16 weeks old	First dose administered SC to cats ≥16 weeks old; second dose administered SC 12 to 16 days after the first dose; third dose administered SC 26 to 30 days after the second dose	Not stipulated	Not recommended for routine use; vaccination may be considered as one component of a comprehensive control program in multiple-cat environments in which *M. canis* infection is endemic or as adjunctive treatment to hasten resolution of clinical signs in individual cats
Bordetella bronchi-septica	MLV vaccine for topical administration	1 dose (0.2 mL) intranasally to cats ≥4 weeks old	1 dose (0.2 mL) intranasally	Not stipulated	Not recommended for routine use; vaccination may be considered for cats entering or residing in multiple-cat environments where *B. bronchiseptica* infections associated with clinical disease have been documented[g]
Giardia lamblia	Adjuvanted inactivated vaccine for parenteral administration	2 doses, 3 to 4 weeks apart to cats as young as 8 weeks old	2 doses, 3 to 4 weeks apart	Annually	Not recommended for routine use; vaccination may be considered as one component of a comprehensive control program in multiple-cat environments in which *G. lamblia* infections associated with clinical disease have been documented
Feline immuno-deficiency virus (FIV)	Adjuvanted inactivated whole virus vaccine for parenteral administration[h]	3 doses, 2 to 3 weeks apart to cats as young as 8 weeks old	3 doses, 2 to 3 weeks apart	Annually	Not recommended for routine use; vaccination may be considered for cats not restricted to a closed, FIV-negative environment.[i]

MLV, Modified-live virus; *SC,* subcutaneously.

Adapted from the American Association of Feline Practitioners and Academy of Feline Medicine Advisory Panel on Feline Vaccines. Used by permission.

a. Parenteral vaccines containing antigens limited to feline panleukopenia virus, FHV, and feline calicivirus (with or without *Chlamydophila felis*) should be administered as distally as possible on the lateral right forelimb. Monovalent parenteral FIV vaccines should be administered as distally as possible over the left forelimb. Vaccines containing rabies virus antigen (plus any other antigen) should be administered as distally as possible on the lateral right hindlimb. Vaccines containing FeLV antigen (plus any other antigen except rabies virus) should be administered as distally as possible on the lateral left hindlimb.

b. Cause of feline panleukopenia.

c. For kittens that are orphaned or at high risk of exposure, vaccination when as young as 4 weeks old may be indicated.

d. For kittens that are orphaned or at high risk of exposure, vaccination when as young as 2 weeks old may be indicated.

e. A specific route of administration may be required; see product information for details. Most often, the product approved for use annually is given for initial vaccination, followed 1 year later and every 3 years after that by administration of the product approved for use every 3 years; however, vaccination interval must comply with local and state statutes.

f. FeLV testing is recommended before vaccination; infected cats do not derive any benefit from vaccination.

g. This product is *not* the same as the *B. bronchiseptica* vaccine approved for use in dogs; the product approved for use in dogs should not be used in cats.

h. This formulation of FIV vaccine is the only one available at the time of this writing.

i. Some FIV vaccines induce antibodies indistinguishable by current tests from those induced by natural infection, and may confound attempts to diagnose infection. Cats should test negative for infection before such vaccines are initially administered.

The United States Department of Agriculture (USDA), under the authority granted by the Virus, Serum, Toxin Act of 1913, requires that vaccines produced for interstate sale be pure, potent, safe, and efficacious. Efficacy, as defined by the USDA, is an in vivo determination of a vaccine's ability to induce an immune response and is usually determined by either direct challenge exposure of test animals (usually 20 to 30 vaccinates and a smaller number of nonvaccinated controls) or by measurement of serologic response. Although such tests are necessary, they provide little information regarding whether the immune response induced by vaccination is clinically relevant. Several reasons exist for these shortcomings: the test animals tend to be of uniform age and lineage, the number used is usually small, the route and dose of challenge agent may not mimic natural exposure, and the virulence and genetic-antigenic diversity of field isolates may be highly variable and differ from the challenge agent. Studies that involve larger numbers of animals of diverse ages, health status, lineage, as well as those that are exposed under natural settings provide additional information, but they are expensive, difficult to control, and uncommonly performed.

164.2 VACCINATION SITES

Standardizing and recording parenteral vaccine sites in the patient's permanent record is important for monitoring local reactions and management of vaccine-associated sarcomas. Parenteral vaccines should not be administered in

the dorsal spinal region or body wall. Limiting administration to the distal limbs provides the best opportunity for control of vaccine-associated sarcomas[4] (Table 164-1).

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164.3 INDIVIDUALIZING VACCINATION PROTOCOLS

The benefits of vaccination are well documented, but harmful effects can result in some individuals. As with any medical procedure, the benefits of vaccine administration should far outweigh any vaccine-associated risks. In deciding whether a particular vaccine antigen should be administered to a particular cat, it is necessary to estimate several patient and vaccine variables. Patients should be evaluated based on their risk of exposure (which requires an understanding of the means of infectious agent transmission) and the expected response to exposure (likelihood of infection if exposed, likelihood and severity of disease if infected). Vaccine variables include the proportion of vaccinates expected to benefit from vaccination, the expected immune response to vaccination (sufficient to prevent infection, sufficient to reduce the severity of disease if infection occurs), and the likelihood and severity of vaccine-associated adverse events. The suggested vaccination protocol outlined in Table 164-1 takes these variables into consideration.

164.4 References

1. JR Richards, I Rodan: Feline vaccination guidelines. *Vet Clin N Am*. **31**, 2001, 455.

2. IR Tizard: Vaccination and vaccines. In IR Tizard (Ed.): *Veterinary immunology: an introduction*. ed 6, 2000, WB Saunders Co, Philadelphia, 235.

3. CE Greene: Immunoprophylaxis and immunotherapy. In CE Greene (Ed.): *Infectious diseases of the dog and cat*. ed 2, 1998, WB Saunders Co, Philadelphia, 717.

4. AE Hershey, et al.: Prognosis for presumed feline vaccine-associated sarcoma after excision: 61 cases. *JAVMA*. **216**, 2000, 58.

165 CHAPTER • 165 Diseases Caused by Systemic Bacterial Infections

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Craig E. Greene

165.1 LEPTOSPIROSIS

165.1.1 Etiology

Leptospirosis, a zoonotic disease of worldwide significance in many animals and humans, is caused by infection with antigenically distinct serovars of the motile spirochetal bacterium *Leptospira interrogans sensu lato*. The bacterium can persist in wildlife reservoirs, contaminating the environment.[1] *Leptospira* organisms are thin, flexible, filamentous bacteria made up of fine spirals with hook-shaped ends. They are motile through writhing and flexing movements while rotating along their long axis.[2] Confusion may arise about the classification of leptospires because serogrouping used in the past overlaps with newer classifications based on genetic methodologies.

In all surveys of domestic animals, antibody prevalence is greater than clinical illness, suggesting that subclinical infections occur commonly. However, these spirochetes also can cause severe, sometimes fatal, disease. More than 200 different serovars have been identified in the *Leptospira interrogans* complex,[3] although the pathogenic importance of individual isolates is unknown.[4–6] Each serovar has a primary host that maintains the organism and contributes to its dissemination in the environment. Although all mammals are susceptible to infection, clinical signs are most severe with non-host-adapted serovars.[7] Leptospirosis is common in dogs, and its importance in veterinary practice may be underestimated. Reports of leptospirosis in cats are rare.

Canine leptospirosis was first described in 1899. Prior to 1960, serovars *icterohaemorrhagiae* and *canicola* were believed to be responsible for most clinical cases of canine leptospirosis. The disease, caused by acute or subacute hepatic and renal failure, typically was characterized by acute hemorrhagic diathesis, icterus, or uremia.[8] After a bivalent, serovar-specific vaccine against *canicola* and *icterohaemorrhagiae* came into widespread use, the incidence of “classic” leptospirosis in dogs appeared to have decreased.[9] However, these vaccines did not induce immunity against other serovars, leading to a relative increase in the incidence of disease attributed to serovars of other serogroups.

Awareness of leptospirosis has expanded as the range of tested serovars has increased. The serovar *grippotyphosa,* first discovered in kenneled hunting dogs in the southeastern United States, has been identified as a predominant serovar in dogs east of the Mississippi River. In the northeastern states, *pomona* has predominated; on the western coast, *bratislava* and *pomona*. Serogroup *Australis* has been incriminated in an outbreak in Canada and has been documented as the cause of chronic hepatitis in dogs in France. In Germany, the predominant serovars are *grippotyphosa, bratislava, saxkoebing,* and *sejroe;* a recent survey in Italy identified *bratislava* and *grippotyphosa*.[8–16]

165.1.2 Pathogenesis

Leptospires can be transmitted directly between hosts in close contact through urine, venereal routes, placental transfer, bites, or ingestion of infected tissues as the organism penetrates mucosa or broken skin. Shedding by infected animals occurs, usually via urine. The exact duration of shedding and potential spread to other dogs or humans is uncertain and may depend on the serovar. Recovered dogs can excrete organisms in urine intermittently for months to 4 years after infection.[17] Indirect transmission, which happens more often, occurs through exposure of susceptible animals to a contaminated environment (e.g., soil, food, or bedding). Water contact is the most common means of spread, and habitats with stagnant or slow-moving warm water favor organism survival. Leptospires in contaminated water invade the host through skin wounds or through intact mucous membranes. Because optimum survival conditions include a neutral or slightly alkaline pH, the organism survives only transiently in undiluted acidic urine (pH 5.0 to 5.5), whereas dilute urine provides a suitable habitat. Ambient temperatures between 0° and 25° C favor survival and replication, whereas freezing markedly decreases survival. Temperature and pH requirements explain the apparent increased incidence of canine leptospirosis in late summer and early fall, in the southern, semitropical belt of the United States, and in similar climatic regions worldwide. Clustering of cases depends on environmental factors. Seasonality is clearly associated with rainfall,[18–20] and disease outbreaks often occur during or immediately after periods of flooding.

Once in a susceptible host, leptospires begin to multiply as early as 1 day after entering the blood vascular space.[21] They invade many organs, including the kidneys, liver, spleen, central nervous system (CNS), eyes, and genital tract. Leptospires damage organs by replicating and causing inflammation. Initial replication mainly damages the kidneys and liver. The extent of damage to internal organs varies, depending on the virulence of the organism and host susceptibility.[22]

Recovery from infection depends on the production of specific antibodies. As serum antibodies increase, the organism is cleared from most tissues, except for the kidneys. Renal colonization occurs in most infected animals, and the organism usually persists in renal tubular epithelial cells, causing shedding from the kidneys for months to years after clinical recovery. The prognosis is highly dependent on conservation of renal function.

165.1.3 Clinical Signs

Signs of hepatic and renal dysfunction and of coagulation defects usually predominate in dogs with leptospirosis. The severity of clinical signs depends on the age and immunocompetence of the host, the environmental factors affecting the organisms, the serovar involved, and the virulence and quantity of the acquired bacteria. Younger dogs (less than 6 months) are more severely affected and develop more signs of hepatic dysfunction in any disease outbreak.

A majority of leptospiral infections in dogs are subclinical. Peracute leptospiral infections are characterized by massive leptospiremia, causing shock and often death with few premonitory signs. Less severe infections are characterized by fever, anorexia, vomiting, dehydration, increased thirst, and reluctance to move. 616 617

Leptospiral infection can lead to similar clinical signs independent of the etiologic serovar, and reports on different clinical appearances may be more related to geographic distribution. Renal colonization occurs in most infected animals because the organism replicates and persists in renal tubular epithelial cells, even in the presence of neutralizing antibodies. Acute impairment of renal function may result from decreased glomerular filtration caused by swelling that impairs renal perfusion. Progressive deterioration in renal function results in

oliguria or anuria. Renal function in some dogs that survive acute infections may return to normal within several weeks, or chronic compensated polyuric renal failure may develop.

The liver is another major parenchymatous organ damaged during leptospiremia. Profound hepatic dysfunction may occur without major histologic changes because of subcellular damage. The degree of icterus in both canine and human leptospirosis usually corresponds to the severity of hepatic necrosis. In contrast, the icterus, hemoglobinemia, and hemoglobinuria that develop in cattle with leptospirosis result from a specific hemolytic toxin produced by serovar *pomona*. In dogs, icterus is less likely a result of hemolysis because even decreased osmotic fragility has been detected in canine leptospirosis. Chronic active hepatitis and hepatic fibrosis have occasionally been demonstrated as sequelae to serovar *grippotyphosa* infection in dogs. Presumably, the initial hepatocellular injury and the persistence of the organism in the liver result in altered hepatic circulation and immunologic disturbances that perpetuate the chronic inflammatory response. This process may cause extensive hepatic fibrosis, cirrhosis, and failure.

Tissue edema and disseminated intravascular coagulation (DIC) may occur rapidly and result in acute endothelial injury and hemorrhagic manifestations. *Leptospira* lipopolysaccharides stimulate neutrophil adherence and platelet activation, which may be involved in inflammatory and coagulatory abnormalities.

Other body systems may also be damaged during the acute phase of infection. A benign meningitis is produced when leptospires invade the CNS; however, it is not as common as in humans. Uveitis occasionally is present in naturally occurring and experimentally induced canine leptospirosis. Abortion and infertility resulting from transplacental transmission of leptospires associated with serovar *bataviae* infection have been described. Pulmonary manifestations include labored respiration and coughing. Interstitial pneumonia has been documented as the cause in humans, whereas lung changes in dogs with leptospirosis are associated with pulmonary hemorrhage, most likely due to endothelial damage and vasculitis.[23]

Laboratory abnormalities usually include leukocytosis, thrombocytopenia, increased serum urea and creatinine, electrolyte disturbances, bilirubinemia, and increased serum hepatic enzyme activities. Coagulation parameters may be altered in severely affected animals. Urinalysis abnormalities include bilirubinuria, sometimes glucosuria, proteinuria, and increased numbers of granular casts, leukocytes, and erythrocytes in the sediment.

165.1.4 Diagnosis

Establishment of a diagnosis is important, because animals can serve as reservoirs and pose potential zoonotic risks. The diagnosis of leptospirosis can be accomplished by several techniques. Detection of antibodies using the microscopic agglutination test (MAT) is the most common diagnostic method[4,7,24,25]; however, other methods to detect antibodies, such as immunofluorescent assays or enzyme-linked immunosorbent assay (ELISA), have been used. The problem in interpretation of antibody test results is the high prevalence of subclinical infections and the persistence of antibodies. In addition, leptospiral vaccines induce antibodies, therefore the presence of antibodies in itself does not necessarily reflect disease. However, a high MAT titer to a nonvaccinal serovar and no (or only low) titers against vaccinal serovars, accompanied by clinical signs of leptospirosis, must be considered highly suggestive of active infection.[2,4,9] In some cases, cross-reactive results may make identification of the infecting serovar difficult. High titers to a specific serovar may not definitely identify the causative serovar, because shared epitopes among organisms of related serovars frequently induce production of cross-reactive antibodies.[25] Laboratory variation and differences in host-specific humoral immune responses sometime make correct assignment of antibody tests even more difficult.

Another diagnostic criterion is a fourfold increase in MAT titers. Because antibody test results are often negative in the first week of illness, especially in young dogs (less than 6 months of age), a second serum sample should be obtained within l to 2 weeks. Negative initial antibody tests can be explained by the 7 to 9 day period required before MAT antibodies are detected. MAT titers become positive after about l week, peak at 3 to 4 weeks, and remain positive for months after both natural infection and vaccination.[2] Therefore, to confirm current infection versus previous infection or vaccination, a rising titer should be demonstrated. Antimicrobial therapy early in the course of the disease may decrease the magnitude of the titer rise. Lower levels of antibodies to leptospiral antigens used in the MAT may also indicate exposure to infection with nonleptospiral spirochetes (e.g., oral spirochetal infections). However, dogs exposed to ticks harboring *Borrelia burgdorferi* that developed high titers to that organism did not show significant increases in anti-leptospira titers on the MAT. In contrast, leptospiral infections can affect antibody results for borreliosis. An advantage of the MAT is its serovar specificity; however, it cannot distinguish between IgM and IgG antibodies.

Besides the widely used MAT, a combined IgM/IgG ELISA[26–28] or immunofluorescent assay (IFA)[29] can be used to measure leptospiral antibodies. IgM antibodies increase within the first week of infection (before the MAT titer); the maximum IgM titer develops within 14 days and decreases thereafter. IgG antibody tests turn positive 2 to 3 weeks after infection and persist for months, with a maximum titer after l month.[2] A combined IgM/IgG test from a single sample is better suited to distinguishing natural infection from vaccine-induced immunity than is the MAT, because dogs that have been vaccinated and have received booster shots demonstrate a high IgG titer but low or negative IgM antibodies. However, these combined tests cannot distinguish between different serovars.

The organisms can be identified directly by means of several techniques, including visualization in fresh urine by dark-field microscopy or in tissue sections or on air-dried smears by light microscopy as well as by culturing the organism or by detection of deoxyribonucleic acid (DNA) by polymerase chain reaction (PCR). However, all direct methods are reliable only with positive results. A negative result never excludes the presence of the infectious agent. Identification of leptospires in urine by dark-field microscopy[9,24,30] is frequently unrewarding, and both positive and negative results should be followed by culture or antibody testing. Leptospires sometimes can be seen by light microscopy in tissue sections or on air-dried smears with Giemsa stain or silver impregnation. Immunofluorescence and immunohistochemical staining techniques have been adapted to identify *Leptospira* organisms in tissues imprints of liver and kidney and in body fluids such as blood or urine, and these techniques potentially can be used to identify animals shedding organisms in urine when culture is impossible or too time-consuming.[31]

Although culture of the organism from blood, urine,[25] or cerebrospinal fluid[32] would be the ideal method, leptospires are difficult to culture and may take weeks to months to grow. They are fastidious, and sampling should always precede institution of antimicrobial therapy. Dogs are leptospiremic during the first week of infection, but the number of circulating organisms subsequently decreases as serum antibodies increase. Urine (sampled by cystocentesis to avoid overgrowth by normal flora) is the best fluid for culture. If animals are adequately hydrated, administration of a low dose of a diuretic such as furosemide (0.5 mg/kg) just before urine collection may facilitate recovery of organisms. Urine should be alkalinized to pH 8.0 or greater during transport. Special liquid, semisolid, or solid culture media should be used. Definitive differentiation of the etiologic serovar can also be accomplished using culture (if culture is successful).

PCR has been used to detect leptospires in blood, cerebrospinal fluid (CSF), aqueous humor, and urine. Because the concentration of leptospires is highest in urine, urine testing is recommended. PCR techniques for identifying the organisms in urine has been experimentally shown to be sensitive and specific and can help

establish a diagnosis at an early stage of infection. In two studies comparing PCR, culture, and antibody testing in healthy and diseased animals, PCR was significantly more sensitive than the other methods in identifying shedders and diagnosing the disease.[33–35] Because culturing of urine is time-consuming and insensitive, the PCR approach may be most useful for direct detection of the organism. Unfortunately, PCR is not yet widely available. Recent advances in PCR techniques have allowed not only diagnosis of leptospirosis but also identification of specific *Leptospira* serovars.[36]

165.1.5 Treatment

Supportive therapy for animals with leptospirosis depends on the severity of the clinical signs, whether renal or hepatic dysfunction is present, and other complicating factors. Antimicrobial therapy is essential to terminate bacteremia. Treatment is divided into two stages. The goal of the first stage is to immediately inhibit multiplication of the organism and rapidly reduce fatal complications of infection, such as hepatic and renal failure. Penicillin and its derivatives are the antibiotics of choice for terminating leptospiremia. Initially, ampicillin (22 mg/kg given intravenously every 8 hours) or, preferentially, amoxicillin, if available for intravenous (IV) use (22 mg/kg given every 12 hours), can be administered parenterally to a vomiting, uremic, or hepatically compromised animal. These drugs prevent shedding and transmission of the organism within 24 hours of therapy. They do not, however, clear renal infections or eliminate the carrier state and chronic shedding. The goal of the second stage, therefore, is to eliminate the carrier state through administration of drugs such as tetracyclines, aminoglycosides, or the newer erythromycin derivatives. Doxycycline (5 mg/kg given orally every 12 hours for 3 weeks) is the drug of choice. Doxycycline treatment should start as soon as oral therapy is possible and liver function is uncompromised. Doxycycline is usually given orally because IV administration can cause shock and vomiting, and subcutaneous injection leads to abscessation. Oral administration, however, can cause gastrointestinal side effects. Doxycycline can be given regardless of the degree of renal dysfunction, whereas aminoglycosides must be strictly avoided if any degree of renal dysfunction is present. The doxycycline dose does not need to be adjusted in animals with renal failure because it is predominantly excreted in the feces. However, doxycycline can lead to liver toxicity. It should be started only after the animal stops vomiting and liver enzyme values have returned to the reference range. In animals with only mild clinical signs, doxycycline can be used for both initial and elimination therapy.

The extent of renal damage after treatment determines the overall prognosis for affected dogs. Some dogs have an apparent clinical recovery after treatment, whereas others develop persistent azotemia.

165.1.6 Prevention

Inactivated bacterins against *icterohaemorrhagiae* and *canicola* infection have been widely used, and this strategy has reduced the prevalence of highly virulent forms of illness. However, these vaccines are not cross-protective against the serovars responsible for most of the current infections in dogs. A recently developed bacterin vaccine that contains *grippotyphosa* and *pomona* strains, either as bivalent or quadrivalent products with the other two strains (Duramune LGP or Duramune LCI-GP, respectively; Fort Dodge Animal Health, Fort Dodge Iowa), is now on the market in the United States. The use of multistrain vaccines likely will reduce disease prevalence.[37] Because the highest titers are produced by multiple injections, yearly (and eventually biannual) vaccinations should be given to dogs in endemic areas, and all dogs should receive at least three injections in the primary vaccination series. IgG titers, which are primarily responsible for protection in dogs, are produced for at least l year after the third vaccination.

Debate has arisen over the necessity of routine vaccination in dogs. As inactivated bacterins, leptospiral vaccines have caused allergenic reactions, especially when combined with other adjuvanted agents. However, many manufacturers have improved and purified their leptospiral vaccines, producing safer multicomponent products. A number of these newer vaccines have been shown to protect against challenge for at least 1 year and to prevent the development of a carrier state in many vaccinated animals.[2] *Icterohaemorrhagiae* and *canicola* infections continue to occur in unvaccinated animals, which indicates that these agents have not been eradicated.

Doxycycline has been given at a low dose (200 mg once weekly) to humans in endemic areas for prophylaxis when vaccination with appropriate serovar bacterins is unavailable. Such therapy may result in the development of bacterial resistance and is not recommended for dogs (or humans).

Wild animal reservoirs and subclinically affected domestic animals continue to harbor and shed organisms. Therefore control of rodents in kennels, maintenance of environmental conditions to discourage bacterial survival, and isolation of infected animals are important steps in preventing the spread of disease. Control of shedding by wild animal reservoirs is impossible. For these reasons, vaccination of dogs is essential.

165.1.7 Leptospirosis in Cats

The prevalence of clinical illness is low in cats, despite the presence of leptospiral antibodies in the feline population and the exposure of cats to leptospires excreted by wildlife. Serovars *canicola, grippotyphosa*, and *pomona* have been isolated from cats. Outdoor cats have the highest antibody prevalence, and transmission from rodents is suspected. Cats may also be exposed to the urine of cohabiting dogs. Although cats develop antibodies after exposure, they appear to be less susceptible than dogs to both spontaneous and experimental infection. Clinical signs are usually mild or not apparent in feline leptospirosis, despite the presence of leptospiremia and leptospiuria and histologic evidence of renal and hepatic inflammation. The lack of clinical cases may be related partly to cats' aversion to water and partly to natural resistance to infection.

165.1.8 Public Health Considerations

The majority of leptospiral infections in humans are identified among those involved in water-related activities, either through work or leisure activities. In some outbreaks, simultaneous exposure of humans and dogs occurs. 618
Urine from infected dogs can cause disease in humans when it comes in contact with mucosal surfaces or a 619
break in the epidermal barrier. Latex gloves are necessary when urine or urine-contaminated items are handled, and face masks and goggles should be worn when contaminated kennel areas are hosed down.
Urine-contaminated areas should be cleaned with dry paper first (to avoid dilution of urine), then washed with detergent and treated with iodophor disinfectants, to which the organism is susceptible. All dogs known to be or suspected of shedding should be treated with doxycycline.

165.2 BORRELIOSIS

165.2.1 Etiology

Tick-borne spirochetoses are a group of diseases that affect humans and animals worldwide. They can be divided into the Lyme disease group (Lyme borreliosis), which is transmitted by *Ixodes* ticks, and the relapsing fever group, which is transmitted by soft ticks. The Lyme disease group was recognized more recently and is

now the most commonly diagnosed vector-borne disease in humans.[1] Borreliosis has been known in Europe since the early 1900s; Alan Steere of Yale University first described the disease and the connection to tick bites after a 1975 outbreak in Lyme, Connecticut (which led to the name *Lyme disease*). However, evidence suggests that this infection in indigenous wildlife and their tick vectors is much older. Studies have demonstrated that ear skin samples from museum specimens of white-footed mice collected near Dennis, Massachusetts, in 1894 contained *Borrelia* DNA.[38] *Borrelia* organisms also were detected in British ticks from 1897.[39] Lyme disease now has been reported in North America, Europe, and Asia, with unconfirmed cases in Australia, South America, and Africa. Experimentally induced and naturally occurring Lyme borreliosis has been described in dogs, cats, and other domestic animals.[40] Antibody prevalence in dogs in endemic areas correlates with living in forested and urban areas and time spent outdoors.[41] In some endemic areas (e.g., Southern Germany), about 30% of ticks are infected,[42,43] and approximately 95% of dogs have antibodies indicating exposure.

Lyme disease is caused by *Borrelia burgdorferi sensu lato,* which comprises several species that affect humans and dogs worldwide. Like most spirochetes, *Borrelia* organisms are small, corkscrew-shaped, motile, microaerophilic bacteria of the order Spirochaetales that can move in connective tissue using their flagella. At least six species have been found in dogs and humans. *B. burgdorferi sensu stricto* predominates in humans and dogs in the United States. It also is found in Europe but only in about 10% of isolates. *B. garinii* and *B. afzelii* are the most common species in Europe. *B. japonica* has been isolated from ticks on humans and dogs in Japan. Recently, two new species (*B. lusitaniae* and *B. valaisiana*) have been detected. In cats, the natural disease is poorly documented, although cats can be infected experimentally. Cats seem to be less susceptible to clinical signs than dogs, and dogs less susceptible than humans.

The presence of disease and its clinical features depend on the isolate in a given geographic region. Genetic variability of isolates also occurs within each continent. In humans, different species are clearly associated with different tissue tropism and clinical problems; this is also likely in dogs. In humans, *B. burgdorferi sensu stricto* infection is associated with annular skin lesions, polyarthritis, and meningitis. Meningopolyneuritis (Bannwarth's syndrome) is the primary clinical sign in humans with *B. garinii* infection in Europe, whereas *B. afzelii* infection has been associated with chronic arthritis and dermatitis *(erythema chronicum migrans)*.[44]

165.2.2 Pathogenesis

Unlike *Leptospira* spp., *Borrelia* organisms do not survive free living in the environment. They are host associated and are transmitted between vertebrate reservoir hosts and hematophagous arthropod vectors. The principal vectors of *B. burgdorferi sensu lato* are various species of hard ticks of the *Ixodes* complex. *I. ricinus* and *I. persulcatus* are the primary vectors in Europe and Asia, respectively. In the United States, the closely related black-legged ticks *I. scapularis* (Northeast, Midwest, and Southeast) and *I. pacificus* (West) are the main vectors. These small *Ixodes* ticks (less than 3 mm) generally feed on more than one host during their life cycle. *I. scapularis* is a three-host tick with a 2-year life cycle. Infected nymphs overwinter, and in the spring they transmit infection to reservoir hosts, which in turn infect feeding larvae. Larvae and nymphs feed primarily on rodents and small mammals (northern *I. scapularis*) and reptiles (southern *I. scapularis*), whereas adult ticks feed on deer or larger mammals. Humans and pets are usually infected by nymphs or adult ticks. Because reptiles are not competent reservoir hosts, the infection rate of southern *I. scapularis* ticks is much lower than that of northern *I. scapularis* ticks. Furthermore, because the southern *I. scapularis* ticks do not always feed on mammals, the prevalence of *Borrelia* infection is relatively low in the southern regions.[40] Other ticks and insect vectors have been found to harbor *Borrelia* organisms but do not seem to maintain infection or to be important for transmission. Direct transmission of *Borrelia* spirochetes between reservoir hosts is unlikely, as is transovarial transmission in ticks. Canine urine is also an unlikely source of spread. In a natural infection

model, control dogs in direct contact with infected dogs for up to l year did not develop antibodies, and organisms could not be isolated from the urine of infected dogs. These studies also did not document any evidence of *in utero* spread.[45] However, *Borrelia* organisms can survive freezing and storage, which makes artificial insemination a potential source of infection.[46] Blood transfusions offer another potential source of infection.

Natural spirochete transmission requires 48 hours of tick attachment, during which time organisms multiply and cross gut epithelium into the hemolymph, disseminate to the salivary glands, and infect the host through tick saliva.[47] Once in the body, *Borrelia* spirochetes usually cause persistent infection. Experimental evidence suggests that *Borrelia* organisms exist extracellularly and, in an undetermined way, can evade immune clearance. Organisms can persist and proliferate for extended periods (probably lifelong in most animals) in intercellular spaces in the skin at the site of the tick bite. Most infected animals never develop clinical signs. In dogs that do not develop clinical signs, it is likely that *Borrelia* organisms persist but do not invade connective tissues and therefore do not cause clinical signs but do cause persistent antibody response. In very few animals, *Borrelia* organisms proliferate and migrate from the skin at the site of the tick bite through connective tissues, including joints, beginning in close proximity to the tick bite. Clinical illness in these dogs results from the host's inflammatory response to their presence and migration. Despite treatment for months or years, *Borrelia* spirochetes can persist in the skin, connective tissues, joints, and nervous system and be detected by PCR or sometimes by culture of blood, cerebrospinal fluid, or urine.

It is still not known why a specific animal or human being develops clinical signs. Pathogenicity depends on the *Borrelia* species, and *B. burgdorferi sensu stricto* seems to be more pathogenic in dogs than the species mainly found in Europe. Evidence suggests that about 5% to 10% of dogs with antibodies in endemic areas in the United States develop clinical disease within 2 to 5 months of infection[48]; the percentage is much lower in endemic areas in northern Europe. Experimental studies have shown that the number of infected ticks that feed is critical. The age and immune status of the animal also seem to be important. Treatment with high doses of glucocorticoids at the time of infection has been shown to increase the likelihood of clinical signs. The development of immune complications, such as arthritis, is probably related to host immunodeficiency. Humans with certain haplotypes of the major histocompatibility complex are prone to more severe clinical manifestations of the disease.[49]

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165.2.3 Clinical Signs

All experimental infections in dogs have used *B. burgdorferi sensu stricto* strains, therefore the clinical condition caused by this organism is relatively well described. In experimentally infected dogs, clinical illness begins 2 to 5 months after tick exposure. Clinical signs include fever, inappetence, lethargy, lymphadenopathy, and episodic shifting limb lameness related to polyarthritis. Arthritis starts first in the joint that is closest to the tick bite. It has been shown that the release of proinflammatory cytokines and especially interleukin-8 (IL-8) plays an important role in the pathogenesis of acute arthritis.[50,51] Despite the transient nature of the arthritis, pathologic changes in the joints are progressive. Chronic nonerosive polyarthritis is the primary condition after prolonged infection, and it may persist despite antimicrobial therapy.

The clinical signs that develop in natural infection or in infections caused by other *Borrelia* species have been less definitively characterized. Glomerulonephritis and protein-losing glomerulopathy progressing to renal failure have been described in naturally infected dogs.[52,53] An acute, progressive renal failure associated with azotemia, uremia, proteinuria, peripheral edema, and body cavity effusions has been described in 49 dogs with positive antibody test results from *Borrelia*-endemic areas. Labradors and golden retrievers were commonly

affected.[54] In Europe, glomerulonephritis is often found in Bernese Mountain dogs with high antibody titers to *Borrelia* organisms. *Borrelia* organisms are likely involved, but not yet proven, in this rapidly progressing glomerular disease. A dermatologic lesion of expanding erythema around the site of the tick bite has not been well documented in affected dogs. A small, reddened lesion, not as dramatic as the erythema migrans seen in humans, can be seen but disappears within the first week. However, the organism can be isolated from the skin area for an extended period. Neurologic manifestations caused by meningitis or encephalitis have not been well documented in either experimental or natural canine infection. Another nonarthritic syndrome that has been reported is cardiac arrhythmia from myocarditis, similar to that reported in humans.

No specific hematologic or biochemical changes are associated with Lyme disease. In contrast to leptospirosis, leukocytosis is not seen, probably because *Borrelia* organisms rarely spread hematogenously, but rather through connective tissue. Dogs with renal manifestation may have proteinuria due to glomerulonephritis sometimes secondary azotemia, hematuria, pyuria, and tubular casts. Synovial fluid analysis findings are typical for a suppurative polyarthritis, with leukocyte counts ranging from 2000 to 100,000 nucleated cells per microliter.

165.2.4 Diagnosis

Lyme borreliosis is likely overdiagnosed in human and veterinary medicine because it has become a “trendy” illness. Overestimation results from antibody cross-reactivity to other infectious agents, from the inaccuracies of antibody tests, and from the predominance of asymptomatic infections. The presence of antibodies to *Borrelia* organisms signifies exposure to a spirochete but does not prove that current clinical illness is caused by *Borrelia*. In endemic areas, most animals in the population have antibodies without ever developing clinical signs.

Various problems have been noted with antibody testing. First, no standardization exists for antigen preparations, techniques, and interpretation by different laboratories. Matched sera sent to 10 commercial laboratories for antibody testing found only 53% agreement.[55] Antibody screening procedures available for animals are ELISA and IFA techniques, usually using whole cells that contain many cross-reactive proteins to other bacteria, especially other spirochetes. In humans it has been shown that other inflammatory conditions, such as autoimmune diseases, rheumatoid arthritis, syphilis, and periodontal disease, can produce positive results.[2] *Leptospira*-positive canine sera also can have low levels of reactivity to *B. burgdorferi* in ELISA and IFA. In Great Britain, dogs with periodontal disease and presumed oral spirochetosis showed a higher level of antibodies against *B. burgdorferi* than healthy dogs from the same hospital population.[56] Some of the reports of human and animal Lyme disease in the western United States may actually be related to relapsing fever and the nonspecificity of whole-cell ELISA or IFA. Dogs vaccinated against borreliosis show antibodies in whole-cell ELISA and IFA for months to years after vaccination.

Paired titers are not helpful in the diagnosis of Lyme disease because high antibody titers usually persist for a long period. Simultaneous measurement of IgG and IgM in a single specimen theoretically would provide more information in other diseases. However, in naturally *Borrelia*-infected dogs and humans, IgM persists for many months, therefore a positive IgM titer does not help to confirm recent exposure or infection.[57,58]

False-negative antibody test results are rare. Early antibody tests are usually negative because the immune response to *B. burgdorferi* develops gradually. Experimentally infected dogs have ELISA-positive results by 4 to 6 weeks after exposure. Titers were at their highest levels by 3 months after exposure. Titer increases almost always precede clinical lameness and fever in experimentally infected dogs,[45] therefore a negative titer in an animal with clinical signs rules out Lyme disease with a high probability.

Because the routine antibody tests (ELISA and IFA) are nonspecific and because neither testing of paired samples nor IgM/IgG differentiation is useful, other confirmatory tests must be performed, such as the Western blot assay or the new C6 ELISA. These tests, which have higher specificity and sensitivity than whole-cell ELISA or IFA, can be used to detect antibodies that specifically indicate infection with *B. burgdorferi* and to exclude vaccination or contact with other bacteria. Western blot assays detect a spectrum of antibodies, and the pattern of antibody reactivity after natural infection differs from that produced after vaccination. After natural exposure to *B. burgdorferi,* antibodies develop to several proteins, including outer surface proteins. One of these outer surface proteins, OspC, appears to be expressed by *Borrelia* organisms in the host at warmer temperatures but is lost at lower temperatures in the tick or with *in vitro* cultivation. However, OspC is a prominent protein response to infection, and high amounts of anti-OspC antibodies are produced after natural infection. In contrast, the protein OspA is mainly expressed by *Borrelia* during the arthropod state (or if cultured *in vitro*). Therefore reactivity to OspA but not OspC occurs in vaccinated dogs (because the vaccine strains are cultured *in vitro*) but is lacking in naturally infected dogs. This effect is even more prominent if recombinant vaccines containing OspA are used rather than whole *Borrelia*. Thus the Western blot antibody pattern expressed by vaccinated dogs differs from that of naturally infected dogs.[59,60]

Newer ELISA tests that incorporate OspC also help differentiate between natural infection and vaccination.[61] Recently the antigenic properties of a 26 amino acid–long invariable region located within the central domain of the VlsE molecule, the variable surface of *B. burgdorferi,* were investigated. This region, named *IR* (invariable region) *6,* was determined to be antigenetically conserved among strains of the *B. burgdorferi sensu lato* complex and to be immunodominant in both human and canine hosts.[62] A new, in-house ELISA (C6 ELISA), designed using the IR6 sequence as a peptide (C6) biotinylated at the N-terminus, recently became available in the United States (SNAP 3Dx; IDEXX, Portland, Maine). The anti-C6 antibody response is highly specific for *B. burgdorferi* and is more sensitive than whole-cell tests in early infection, detecting antibodies as early as 3 weeks post exposure.[63] It also is more sensitive in detecting *Borrelia* infection in Europe than other commercial ELISA kits.[64] Dogs with leptospirosis, Rocky Mountain spotted fever, babesiosis, ehrlichiosis, and heartworm disease do not have antibodies to C6. Furthermore, C6 is not affected by the currently available Lyme vaccines.[65] C6 antibody levels also seem to correlate to *Borrelia* loads, dropping rapidly after treatment with antibiotics,[66] whereas conventional ELISA results stay at medium levels for a long time even after successful treatment.[67] Although already used in veterinary practice in endemic areas,[68] the C6 ELISA has not been validated in controlled studies. It must be considered that both the Western blot assay and the C6 ELISA, although more specific, only indicate natural exposure to *B. burgdorferi* and do not predict clinical disease.

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In humans, CSF antibody titers have been compared with serum antibody titers in an attempt to diagnose neuroborreliosis. Intrathecal production of specific antibodies to *B. burgdorferi* can be demonstrated if the ratio of CSF to serum *B. burgdorferi* antibodies is greater than the CSF to serum concentration of albumin, total IgG, or specific IgG against another infectious agent. An increased intrathecal antibody concentration was demonstrated in dogs with neurologic dysfunction. The results of such reports are difficult to assess because the dogs were from endemic areas, and no supporting histopathology or culture findings were supplied.[40]

Culture of spirochetes from specimens of a diseased patient is the most definitive means of diagnosis but in most cases is difficult due to the low number of organisms present and the insensitivity of isolation methods. Special media (e.g., modified Barbour-Stoenner-Kelley medium) are required, but even then culturing is insensitive.[69] Skin appears to be the most consistent tissue for premortem or postmortem culture when specimens are taken at or near the site of tick attachment.[67] Xenodiagnosis, in which uninfected ticks become

infected after feeding on suspect infected hosts, has proved reliable in a research laboratory setting but is too time-consuming and is not useful for routine clinical diagnosis.

PCR is highly specific. The best materials for diagnosis are skin samples, which should be taken at a location closest to the tick bite. If the tick bite location is unknown, a sample should be taken close to the joint in which the first lameness or swelling was observed. If no arthritis is or was present, the sample should be taken from an area that is generally most exposed to ticks (usually the front part of the dog). PCR can also be performed using urine,[70] which is slightly less sensitive. Blood is not useful, because *Borrelia* organisms rarely spread hematogenously. Joint fluid,[71] synovia samples, or CSF samples are excellent PCR material if clinical signs are present. PCR cannot distinguish between live and dead organisms. Research has shown that small DNA fragments of *Borrelia* may persist in synovial membranes after treatment,[67,72] and these fragments may induce positive PCR results. However, experimentally injected *Borrelia* DNA (without replicating *Borrelia*) was destroyed and was not detectable after 3 weeks. The sensitivity of PCR is high, but the sample must contain *B. burgdorferi* DNA. A negative PCR result, therefore, never excludes the presence of the organism elsewhere in the body.

165.2.5 Treatment

Because of the difficulty involved in obtaining an accurate diagnosis, antibiotics often are given empirically in an attempt to make a therapeutic diagnosis. Many reports exist of successful recovery after institution of antimicrobial therapy in dogs "diagnosed" with Lyme arthritis. However, clinical improvement after any therapeutic intervention should be viewed with caution, because acute limb and joint dysfunction is intermittent and often resolves after several days to weeks, regardless of whether antibiotics are given.[73] Doxycycline, the drug of choice, by itself has been shown to be chondroprotective in noninfectious arthritis in dogs[74] and thus leads to improvement also in arthritis not related to Lyme disease.

The antibiotics that are most effective for treating *Borrelia* infection are the tetracyclines, ampicillin or amoxicillin, some third-generation intravenous cephalosporins, and erythromycin and its derivatives. Doxycycline (10 mg/kg given orally every 12 hours for 30 days) is the first choice because it is a lipid-soluble tetracycline of relatively low cost. The other drugs are usually reserved for refractory or chronic infections. Improvement often occurs within 24 to 48 hours of initiation of antimicrobial therapy. The greatest success is achieved in the initial phases of clinical illness.

Research suggests that the organism is difficult to eliminate from animals with established infection and that relapses occur despite seemingly adequate treatment regimens.[73,75] Most treatment is instituted for a minimum of 30 days. However, on the basis of research studies, clearance of the organism after 30 days of treatment is questionable. Relapse can occur and PCR results can become positive after discontinuation of antimicrobials.[76,77] Also, inflammatory changes that occur in various tissues, such as the joints, may become self-perpetuating. Intra-articular persistence of *Borrelia* organisms may stimulate chronic immune and inflammatory processes. Animals with more chronic borreliosis are less likely to show improvement or to have relapses, even if treatment is continued for weeks to months. The current recommendations for treating chronic borreliosis are to repeat the 30-day anti-biotic treatment four or five times in 3-month intervals. The *Borrelia* organisms may possibly be eliminated after years of such therapy.[77]

Nonsteroidal anti-inflammatory drugs may be helpful for pain relief during episodes of recurrent arthritis. Immunosuppressive doses of glucocorticoids definitely should be avoided, because immunosuppression may

potentiate infection exacerbation.[76] Tick-exposed dogs that had recovered from clinical signs of Lyme disease and that were treated with oral prednisolone for a 2-week period 16 months after original exposure again demonstrated lameness and polyarthritis.[78]

165.2.6 Prevention

In United States, whole-cell bacterins and recombinant protein OspA vaccines for dogs are commercially available. Whole-cell bacterin vaccines should be avoided, because it is generally undesirable to have multiple components in a vaccine that are not involved in protection from infection and that have the potential to induce a delayed adverse response. Hamsters immunized with whole-cell bacterins and challenged by infected ticks developed arthritis several weeks to months later.[79] This concern has precluded development of a whole-cell bacterin from consideration as a human vaccine. All human vaccines that had been sold in the United States were based on recombinant DNA production of Osp products, but even they have been removed from the market. In Europe and other geographic areas, only whole-cell bacterins are available for dogs (and no vaccines are available for humans) because the multiplicity of infecting strains makes the development of a recombinant product that would protect against the different *Borrelia* species difficult. Multiplicity of infecting strains also makes questionable the protection induced by whole-cell vaccines (which are now on the market in Europe containing *B. burgdorferi sensu stricto* stains), because cross-protectivity between *B. burgdorferi* species could not be demonstrated.

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The advantage of recombinant protein OspA vaccines is that they induce antibodies only to OspA, the protein that is expressed in the tick and not in the dog. Vertebrate hosts infected by *Borrelia* organisms through tick bites rarely develop antibodies to OspA. OspA is expressed by *Borrelia* in unfed ticks but is changed to OspC during transmission from the vector due to the warm conditions during feeding on the vertebrate host. During feeding, antibodies against OspA that are present in the vertebrate's blood due to vaccination enter the tick and neutralize *Borrelia* before the organism enters the host. Antibodies to OspA from the host cause an arrest of growth and salivary gland invasion in the ticks.[80] Spirochetes either are killed instantly by antibody-induced complement lysis or their mobility is reduced such that they cannot continue their migration to the salivary glands of the ticks.[81] In the vaccinated host, only OspA antibodies are present, and these cannot bind to *Borrelia* organisms expressing OspC. Thus the risk of the development of immune complex diseases is reduced compared with whole-cell *Borrelia* vaccines.

The disadvantage of vaccination in general is that the induced antibodies cause positive results on routine antibody testing for months to years. Western blot or C6 ELISA testing must be performed to distinguish vaccine induced from natural exposure antibodies. An additional disadvantage of the vaccine is the possibility that a hypersensitivity reaction may occur if the vaccine is given to a dog harboring the organism.[82] Vaccination of an already infected animal does not clear infection or prevent clinical illness. Local and systemic allergic reactions have been noted with whole-cell vaccines.[83] Vaccines might also be subject to breaks in protection in the future because *Borrelia* organisms are known to change their genotypic and phenotypic makeup, allowing survival despite organism-specific antibodies.

Vector control using residual insecticides or growth regulators is a supportive measure that can help reduce the prevalence of infection in humans and pets. Amitraz-impregnated collars may reduce transmission of *Borrelia* spirochetes in dogs.[84]

165.2.7 Borreliosis in Cats

Cats have been found to be antibody positive for *Borrelia*, and experimental infection has been produced, but naturally acquired disease has not been documented. Approximately 13% of cats tested in the United States had antibodies; however, there was no difference in positive results from cats with or without lameness.[40] In the United Kingdom, 4% of tested cats had antibodies.[85] Cats may be more resistant than dogs to the development of clinical signs. However, when cats were inoculated experimentally with organisms directly from arthropods, they developed multiple limb lameness and had joint, pulmonary, lymphoid, and CNS inflammation at necropsy. Arthritis and meningitis predominated.

165.2.8 Public Health Considerations

There is no evidence that infected pet dogs or cats pose a direct risk to humans except by introducing unfed tick stages into a household. The ticks do not survive long indoors and, if fed, tick stages do not reattach without moulting. However, partly fed ticks can refeed and can pose a greater risk of infection because of the shorter required period of attachment. Direct horizontal spread from dogs and cats to humans is unlikely. It has been speculated that urine from infected dogs could be a source of human infection. *Borrelia* organisms, however, deteriorate quickly in urine, and there is no evidence that human infections have occurred after contact with infected dogs.[86] In addition, in a recent study in the Netherlands, no positive correlation was observed between antibody prevalence in hunters compared with their dogs.[87] Although Lyme disease is classified as a zoonosis, dogs, cats, and humans are incidental hosts for a sylvan cycle that exists in nature. Lyme borreliosis in humans is usually associated with outdoor activities that result in exposure to tick vectors.

165.3 MYCOBACTERIOSIS

165.3.1 Etiology and Pathogenesis

Mycobacteriosis is caused by bacteria belonging to the genus *Mycobacterium,* family Mycobacteriaceae, order Actinomycetales.[40] Mycobacterioses are becoming increasingly important in dogs and cats (partly due to the increase in mycobacterial infections in humans and partly due to improved diagnostic methods), and their importance in veterinary medicine is probably underestimated. These diseases are more common in cats than dogs. In dogs and cats, mycobacteriosis can be divided into three groups, classic tuberculosis (tuberculous form),[88] opportunistic mycobacteriosis (opportunistic form),[89] and feline leprosy (lepromatous form).[90] All three groups can cause cutaneous signs (typically skin nodules with draining tracts and/or ulceration), but mycobacteria of the classic tuberculosis complex can also cause systemic disease. Classic tuberculosis can be caused by *Mycobacterium tuberculosis, M. bovis, M. avium, M. microti, M. microti*-like, and *M. simiae*. Opportunistic mycobacteria recognized as causes of disease in dogs and cats include *M. fortuitum, M. chelonae, M. smegmatis, M. phlei, M. thermosresistibile, M. terrae, M. genavense,* and *M. xenopi*. Feline leprosy is caused by *M. lepraemurium*.

Mycobacterium is a genus comprising morphologically similar, aerobic, environmentally resistant, non-spore-forming, acid-fast, gram-positive bacteria. Mycobacteria have the distinctive property of retaining hot carbolfuchsin and other stains after subsequent treatment with acid or alcohol, a property that facilitates diagnosis. This acid-alcohol fastness is due to the high lipid content of mycolic acid in the cell wall. Mycobacteria are more resistant to heat, pH change, and routine disinfection than other non-spore-forming

bacteria. Most mycobacteria are found in habitats such as water or soil; however, a few can act as pathogens in animals and humans. They have a wide host affinity and pathogenic potential, and with their structural properties and ability to survive intracellularly, they produce granulomatous inflammation.

Classic tuberculosis has become increasingly important[89] in immunosuppressed individuals since the detection of the human immunodeficiency virus (HIV), and it has been caused by more resistant forms of mycobacteria. *M. tuberculosis, M. bovis, M. africanum,* and *M. microti* can cause the disease in humans. Currently, tuberculosis is the leading infectious cause of death in humans, and one third of the world's population is thought to be infected. However, only 10% of immunocompetent individuals develop active disease in their lifetime; the other 90% neither become ill nor transmit the organism. *M. tuberculosis* is the major cause of tuberculosis in humans, and humans are the only reservoir hosts. The inter-related factors of homelessness, illicit drug use, and HIV infection have resulted in an increased prevalence. Multiple-drug-resistant *M. tuberculosis* has emerged in these populations because of irregular compliance with drug therapy.

In dogs and cats, classic tuberculosis can be caused *M. tuberculosis, M. bovis, M. avium, M. microti, M. microti*-like, and *M. simiae*. Although *M. tuberculosis* can cause tuberculosis in dogs and cats,[91,92] it more commonly infects dogs. Dogs and cats are usually infected through direct contact with infected humans, and a canine or feline infection is considered an inverse zoonosis.[93] *M. tuberculosis* has an affinity for tissues with high oxygen content, which explains its common localization in the lungs. Animals with tuberculous pneumonitis discharge organisms in the sputum, as do infected humans, and aerosolized droplets are the primary means of transmission of this disease. To be maintained in nature, *M. tuberculosis* requires infection of reservoir mammalian hosts, because environmental survival is limited to a maximum of l to 2 weeks. Although pets acquire the infection from humans and spread from dogs or cats to humans has not been reported, infected animals are a potential risk to humans, and euthanasia should be considered.

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M. bovis is closely related to *M. tuberculosis* and difficult to distinguish except by biochemical tests and nucleic acid probes. Like *M. tuberculosis, M. bovis* does not exist long in the environment (4 days in summer, less than 28 days in winter), and reservoir hosts are essential for survival of the organism. *M. bovis* is the pathogen of classic “feline tuberculosis.”[94] Cats are more commonly infected with *M. bovis* than dogs, and on an experimental basis, cats appear to be more susceptible to *M. bovis* than to *M. tuberculosis*. Dogs and cats are usually infected by means of unpasteurized milk, uncooked meat, or offal from infected cattle. Clinical disease, therefore, commonly involves the intestines. In areas in which bovine tuberculosis is well controlled, *M. bovis* infections have become extremely rare. In countries such as New Zealand, however, where *M. bovis* has become established in the wildlife population, domestic animals continue to become infected. Dogs and cats may be involved in the maintenance of *M. bovis* on farms, where it is enzootic, and may be responsible for transmission of *M. bovis* to humans. Orally infected dogs and cats usually excrete the organism through feces.

M. avium is a saprophytic organism that has been recognized in recent years as causing infection, especially in cats.[95–101] Poultry and swine are primarily susceptible to *M. avium* infection after contact with infected food or water. Dogs and cats seem to have innate resistance, but exposure is much greater than to *M. tuberculosis* and *M. bovis* because *M. avium* is ubiquitous in the environment. Certain breeds (e.g., Siamese cats[96] and basset hounds) seem to be more susceptible. Immunosuppression seems to play a role, and one case in a cat after renal transplantation has been described.[101] *M. avium* organisms are present in acidic conditions (pH 5.0 to 5.5) and in soils high in organic matter (e.g., acidic swamp areas, coastal plains, and brackish coastal waters). Unlike *M. tuberculosis* and *M. bovis*, *M. avium* organisms remain viable for at least 2 years in the environment. The feces of infected birds contain large numbers of *M. avium,* and infection of dogs and cats occurs from ingestion of infected meat or contact with infected soil contaminated by poultry carcasses or feces. There is no evidence of

spread of *M. avium* between or within animals and humans. *M. avium* can cause disease in immunocompromised humans, but infection usually occurs through exposure to contaminated soil.

M. microti is a rodent pathogen that in earlier literature was reported to infect cats. A few cases in the Netherlands have been described in which hunting cats became infected.[102–104] *M. microti*-like is a new variant that has been identified as a common cause of tuberculosis in cats in Great Britain. It was predominantly found in rural cats with avid hunting behavior. and the source of infection is thought to be a prey species.[105,106]

M. simiae was recently found in an 8-year-old domestic short-hair cat with disseminated mycobacterial disease involving the skin, lungs, lymph nodes, and one eye. *M. simiae* is known to cause pulmonary, cutaneous, or disseminated infection in humans infection with HIV but has not been encountered as a pathogen in companion animals.[107]

Opportunistic mycobacteria that cause disease in companion animals include *M. fortuitum, M. chelonae, M. smegmatis, M. phlei, M. thermosresistibile, M. terrae, M. genavense*, and *M. xenopi*.[108–121] These saprophytic, nontuberculous, nonlepromatous, opportunistic species, also called *atypical mycobacteria,* are ubiquitous in nature, especially in water and wet soil, and are not pathogenic for animals under normal circumstances. Opportunistic mycobacteriosis appears to be more common in tropical and subtropical areas of the world; however, difficulties associated with diagnosis may underestimate the true prevalence. Cats are more often affected than dogs, and adult cats with a hunting or fishing lifestyle are more likely to be affected. Animal-to-animal transmission does not generally occur, and there is little zoonotic risk. Most opportunistic mycobacteria that infect dogs and cats are acquired from the environment after trauma to the skin or soft tissues (puncture or fight wounds) and cause localized tissue reactions in the skin (granulomas and abscesses) or deeper tissues. These organisms are particularly pathogenic if directly inoculated into adipose tissue. Entry through either the gastrointestinal or respiratory tracts is extremely rare. Although systemic immunosuppression has not always been apparent, *M. genavense* infection in a cat infected with the feline immunodeficiency virus (FIV) has been reported.[119]

Opportunistic mycobacteria can be characterized as slow-growing or fast-growing species. Fast-growing *M. fortuitum, M. chelonae, M. smegmatis, M. phlei,* and *M. thermosresistibile* are the species commonly isolated from cats and sometimes dogs with cutaneous lesions in the United States and Australia. Although the slow-growing opportunistic mycobacteria are responsible for several well-characterized cutaneous diseases in humans, they are less commonly isolated from dogs and cats, possibly because of the lengthy time needed for culture. However, the slow-growing species *M. terrae, M. genavense,* and *M. xenopi* have now been described in cats.

Feline leprosy, a disease seen only in cats and not in dogs or humans, is caused by *M. lepraemurium,* the agent of rat leprosy, and is usually introduced via bite wounds from rodents (possibly as soil contaminant) or contact with infected rats. There is no zoonotic risk. The disease is seen most in areas with a temperate maritime climate. Occurrence in cats has been confined to seaport cities of the western United States, New Zealand, Great Britain, Australia, and the Netherlands, with a greater incidence in winter. The organism cannot be cultivated by routine mycobacterial culture methods and requires special media. Feline leprosy is mainly a cutaneous syndrome; regional lymphadenopathy may be present, but systemic disease is rare. FIV or feline leukemia virus (FeLV) infection may play a role in the pathogenesis and predispose to septemic disease. Although the disease is more common in young cats, a clinical syndrome has been described in older cats in which disease progression was prolonged, typically taking months to years, and skin nodules did not ulcerate. This clinical picture was attributed to a *Mycobacterium* species closely related but slightly genetically different from *M. lepraemurium*.[122] In contrast to tuberculous and opportunistic mycobacterial infections, the prognosis

in feline leprosy is good after surgical removal of the cutaneous lesion. Spontaneous resolution of lesions does occur.

165.3.2 Clinical Signs

Infection with tuberculosis-causing mycobacteria in dogs and cats is often asymptomatic or insidious. It is unclear what factors contribute to the host's resistance. Cell-mediated immunity typically is associated with protection against facultative intracellular pathogens such as mycobacteria and seems to be associated with enhanced capacity of activated macrophages to kill mycobacteria or to inhibit their intracellular multiplication. When clinical signs occur, they reflect the site of granuloma formation. Skin lesions (found on the face, neck, forepaws and, less frequently, ventral thorax and tail base) include dermal nodules or nonhealing wounds with draining sinus tracts, often accompanied by enlarged regional lymph nodes. In pulmonary disease that occurs mainly in *M. tuberculosis* infection, bronchopneumonia, pulmonary nodule formation, and hilar lymphadenopathy are seen, causing fever, weight loss, anorexia, and harsh, nonproductive coughing. Intestinal localization, more common in *M. bovis* infection, can cause weight loss, anemia, vomiting, and diarrhea as signs of intestinal malabsorption. Mesenteric lymph nodes may be palpably enlarged, and abdominal effusion is present in some cases. Oropharyngeal lesions can cause dysphagia, retching, hypersalivation, and tonsillar enlargement. Tuberculous choroiditis and retinal detachments, granulomatous uveitis, and CNS signs occasionally occur. A granulomatous myelitis has been described in a dog with *M. avium* infection.[123] Lameness and fractures may be observed with bone localization.

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Clinical laboratory findings in tuberculosis are frequently nonspecific, although leukocytosis and hyperglobulinemia may be present. Radiographically visible masses and tracheobronchial lymphadenopathy may be apparent in the thoracic cavity. Abdominal radiography and ultrasonography may reveal enlargement of parenchymatous organs such as liver and spleen or solitary abdominal masses. Fluid may be present in the abdominal cavity, and calcified mesenteric lymph nodes may be noted. Osteoproliferative lesions may be found in the axial or appendicular skeleton.

Opportunistic mycobacteriosis in cats most commonly occurs as skin lesions with multiple fistulous draining tracts associated with purulent drainage into the caudal abdominal, inguinal, and lumbar subcutaneous tissues. Most cats, even those with extensive cutaneous involvement, remain active and normal except for the draining tracts. Fever occasionally occurs, but anorexia, weight loss, and other features of chronic infection are usually absent. Dogs with opportunistic mycobacteriosis usually have a history of fight wounds or trauma followed by granulomatous proliferation of cutaneous tissues with serous or seropurulent drainage. Clinical laboratory findings are usually unremarkable in opportunistic mycobacteriosis, although hypercalcemia occurred in one cat with granulomatous skin masses.[124]

Feline leprosy is characterized by soft, fleshy, focal nodules in the skin and subcutis of the head and extremities. The lesions develop rapidly and are usually freely movable and painless. They may be haired or superficially ulcerated, and regional lymph nodes may be enlarged. Clinical laboratory findings are unremarkable.

165.3.3 Diagnosis

The diagnosis of classic tuberculosis can be established by demonstrating acid-fast organisms within a lesion by means of biopsy and histologic examination or by direct smears of exudates or fluids. The acid-fast staining method is ideal for aspirates of tissue and granulomas and for identifying organisms in bacterial cultures. Mycobacteria can be stained with carbolfuchsin or fluorescent dyes. Fluorochrome stains are more sensitive and

technically less difficult to examine than conventional carbolfuchsin stains. Although often present in low numbers, intracellular mycobacteria are recognized by their clubbed shape and beaded appearance. In *M. avium* infection, higher numbers usually can be seen. Granulomatous lesions consist of areas of focal necrosis surrounded by infiltrations of plasma cells and macrophages and an outer connective tissue capsule. Calcification of granulomas may occur.

Intradermal skin testing is used as an aid in the diagnosis of human mycobacterial infections and to evaluate delayed-type hypersensitivity in animals. Intradermal skin testing is generally useful in diseases in which the cellular immune response should be tested because humoral immunity does not play a role. Although useful in humans, intradermal tuberculin testing is inconsistent and unreliable in dogs, and is not useful in cats.[125,126] If dogs are tested, the highest concentration of the tuberculin solution used for testing humans is needed, and the inner surface of the ear pinna should be injected.[88]

Testing of antimycobacterial antibodies is unreliable in dogs and cats because antibodies are produced inconsistently. Antibody tests include hemagglutination and complement fixation but should be critically interpreted due to their inaccuracies.

Culture is the definitive means of diagnosing tuberculosis and of identifying the specific mycobacteria species involved. Mycobacteria of the tuberculosis complex are slow growing, often requiring 4 to 6 weeks to establish visible colonies. The different species can be identified by colony growth and biochemical characteristics. Culture and identification of the specific organism is helpful for definitive diagnosis, long-term management, and prognosis and for calculating the zoonotic risk.

PCR testing has been developed for species relevant in human medicine, and animal specimens can also be evaluated.[127] Commercial kits (e.g., AccuProbe; Gen-Probe, San Diego, California) simplify the identification. Although final identification in culture takes up to 6 weeks, PCR followed by restriction analysis and nucleic acid hybridization can shorten this time to a few days. Unfortunately, PCR does not exist for all species that are relevant in dogs and cats.

Confirmation of opportunistic mycobacteriosis is not always easy because a diligent search for organisms in impression smears from exudates or tissue biopsy is usually required. Histology is characterized by extensive granulomatous to pyogranulomatous inflammation of the dermis and associated panniculitis. Application of acid-fast stains may reveal a few organisms within extracellular lipid vacuoles surrounded by neutrophils and macrophages. Bacterial culture of deep tissue (especially the panniculus) biopsy specimens and identification of the organism are essential for definitive diagnosis, but cultures from multiple tissue samples may be necessary. Fast-growing mycobacteria grow within 3 to 5 days, whereas the slow-growing types require 4 to 6 weeks. A 16S rRNA PCR and partial sequencing has been used to identify *M. genavense* infection in a cat.[119]

Diagnosis of feline leprosy is made by finding large numbers of acid-fast mycobacteria on histologic or cytologic samples or impression smears. A diffuse, granulomatous inflammatory infiltrate composed of vacuolated macrophages is present on histologic examination, and numerous mycobacteria are noted within macrophages or extracellularly within dermal vacuoles. Culture results are routinely negative with standard mycobacterial media, and specific media are needed (e.g., 1% Ogawa egg yolk medium). Animal inoculation using guinea pigs, rabbits, mice, or hamsters has been performed historically to identify *M. lepraemurium,* but this technique is obsolete. A PCR amplifying a sequence of the 16S rRNA gene has been developed to detect *M. lepraemurium,*[122,128] but its availability is limited.

165.3.4 Treatment

The decision to treat a dog or cat with classic tuberculosis is controversial. The zoonotic risk of pets that may harbor *M. tuberculosis* or *M. bovis* must be considered. Species differentiation by culture or PCR is recommended, especially if the animal has generalized disease, respiratory tract involvement, or extensive draining cutaneous lesions. If treatment is opted, the owner must know that it is long term and difficult to maintain (especially in cats). The inherent toxicity of some drugs and the financial costs must be explained. In some cases, the drugs may at best suppress the disease and indefinite treatment may be required. Surgical excision of small cutaneous lesions may be considered but is successful in only a few cases, and systemic therapy should accompany the surgical procedure. Debulking of larger lesions risks wound dehiscence and local recurrence of infection.

Pending a definitive diagnosis, interim therapy with fluoroquinolones is recommended. If signs of regional spread or systemic involvement are present, double or triple therapy should be initiated immediately. Ideally, treatment should consist of an initial and a continuation phase. The initial phase usually requires at least three drugs and should last 2 months; the continuation phase requires two drugs and lasts at least an additional 4 months, depending on the type and extent of disease. Some animals require lifelong treatment. If triple therapy is not feasible (e.g., in difficult cats), treatment should at least involve two drugs, which should be given for a minimum of 9 months.

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Traditionally, a combination of rifampin, isoniazid, and ethambutol (a common combination for humans) has been considered the most effective regimen for treatment of tuberculosis in animals. These drugs are relatively hepatotoxic for dogs and cats. The results of recent studies suggest less toxic combinations that are equally effective. The current treatment recommendation is an initial phase of 2 months involving a combination of rifampin (10 mg/kg given orally every 12 hours), enrofloxacin (5 mg/kg given orally every 24 hours), and azithromycin (10 mg/kg given orally every 12 hours), followed by a continuation phase of rifampin *plus* either enrofloxacin or azithromycin in these dosages. When resistance develops, a combination of rifampin, isoniazid, and ethambutol may be considered. If necessary, pyrazinamide or dihydrostreptomycin (if available) can be substituted for ethambutol. If *M. bovis* infection has been confirmed, however, pyrazinamide is not recommended due to the organism's natural resistance. Rifampin and isoniazid are more effective and less toxic than ethambutol and dihydrostreptomycin and consequently more appropriate choices if only two drugs are given. The prognosis depends on the extent and severity of infection but is generally guarded, especially when systemic disease is present. Uncomplicated cutaneous cases carry the best prognosis.[129]

In opportunistic mycobacteria infection, species identification should be performed and antibiotic susceptibility testing should be requested. A fluoroquinolone should be used pending diagnosis. Treatment after diagnosis should be tailored to the individual case. *M. fortuitum* and *M. smegmatis* are usually sensitive to high dosages of fluoroquinolones (ciprofloxacin, enrofloxacin, and ofloxacin), whereas *M. chelonae* is not. In contrast, *M. chelonae* is usually sensitive to clarithromycin. Double or triple therapy should be considered, as for tuberculosis, and antibiotic therapy should be continued for at least 2 months. In some cases clinical cure was achieved only after 6 to 8 months of therapy; other patients have required lifelong treatment. Surgical resection or debulking of large granulomatous masses has been more beneficial in dogs. Cats may improve with surgical resection of small lesions, but dehiscence, proliferation of the wound margins, and further progression of lesions are common sequelae. Surgical intervention should be radical and planned as for removing a locally invasive neoplasm. Antibiotic therapy is always necessary in combination with surgery. The prognosis is poor to guarded and is worse if previous attempts at surgery have failed. Dogs apparently have a better prognosis for

remission. Despite expensive, long-term therapy, an infected pet that has continual serous drainage occasionally must be euthanized.

In feline leprosy, surgical removal of lepromatous granulomas is the desired treatment. Complete surgical excision of all nodules has proved beneficial in many cats. A fluorquinolone should be used pending the diagnosis. When surgery is not feasible or when removal is incomplete, treatment with clofazimine (8 mg/kg given orally every 24 hours), rifampin (15 mg/kg given orally every 24 hours), or clarithromycin (5 mg/kg given orally every 12 hours) has proved successful.[122,129] Clofazimine appears to have minimal toxicity in cats. Dapsone may be another alternative to surgery but is considered relatively toxic in cats. In contrast to other mycobacterial infections, the prognosis is good, and spontaneous resolution without treatment may occur.[130]

165.3.5 Prevention and Public Health Considerations

Mycobacterial infections are a major public health problem. Humans are susceptible to all mycobacteria that cause classic tuberculosis in dogs and cats. Identification of cases of *M. tuberculosis* infection in humans and outbreaks of *M. bovis* infection in cattle should be followed by evaluation of pet contacts. However, diagnosis of exposure in a healthy animal is difficult, because intradermal skin tests and antibody tests are not reliable. Euthanasia of animals infected with *M. tuberculosis* or *M. bovis* is generally recommended due to the public risk. *M. avium, M. microti, M. microti*-like, and *M. simiae* are just as likely to be acquired from environmental sources by humans as by pets, therefore treatment can be considered. However, to avoid any potential concern, families with members who are immunocompromised generally should be advised not to keep mycobacteria-infected pets. Vaccines are available to protect humans against infection with *M. tuberculosis,* but their efficacy is questionable. The attempt to control tuberculosis in dogs with modified live vaccines has had moderate success in that some dogs have shown resistance to infection; however, the immunity was only partial, therefore vaccination has not been generally recommended.

Opportunistic mycobacteria are free-living saprophytes, and there is little risk of transmission of these infections from animal to animal or animal to human. However, wound disinfection and contact precautions are usually advised, especially if immunosuppressed individuals are present in the same environment. Subcutaneous inoculation of *M. chelonae* organisms into a person reportedly occurred through penetration of dog hair into the owner's Achilles tendon by means of prolonged, vigorous rubbing of the person's ankle. Human hospital–acquired infections have also occurred.

There is no zoonotic risk in feline leprosy. Because the disease is acquired from rodents, prevention of exposure to rodents likely minimizes the possibility of disease in cats.

165.4 BRUCELLOSIS

165.4.1 Etiology

Canine brucellosis is caused by *Brucella canis,* a small, gram-negative, aerobic, coccobacillary bacterium that naturally infects dogs, causing an insidious bacteremia and reproductive disturbances.[1] *B. canis* has a limited host range; only dogs and wild Canidae have been found to be susceptible in nature. A survey testing free-ranging coyotes in Yellowstone National Park in Wyoming did not find antibodies to *B. canis*.[132] Cats can be infected experimentally with *B. canis* but are relatively resistant. Rabbits and nonhuman primates (but no other animal species) can also be experimentally infected. Human cases have been reported as a result of laboratory accidents or contact with infected dogs, but people are relatively resistant to *B. canis*. Dogs also are

susceptible to infection with *Brucella abortus* and *Brucella suis,* which they can acquire naturally through ingestion of contaminated placentas and aborted fetuses from livestock.[133]

165.4.2 Pathogenesis

A relatively low prevalence of *B. canis* infections has been reported in the United States and Japan (1% to 18%), with a higher rate seen in the southern United States (approximately 8%). The prevalence is higher in Central and South America, with rates as high as 28%, as well as in Asia and North Africa. *B. canis* infections are extremely rare in northern Europe, but cases have been reported in southern and eastern European countries, (e.g., Spain and Czechoslovakia). The prevalence of infection varies according to a number of factors, including the age of the investigated population, housing condition, breed, and geographic location. Pet dogs in urban environments have a lower prevalence compared with stray dogs in economically depressed areas, which may reflect increased population density and uncontrolled breeding of dogs.

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B. canis is most commonly transmitted venereally; the organism penetrates the mucous membranes and enters the lymphoreticular system. The infection rate is high during breeding or after abortion. The highest number of organisms is found in aborted material. Shedding of *B. canis* may occur for up to 6 weeks after an abortion. The milk of infected bitches contains lower concentrations of organisms and appears to be less important in the transmission of infection to surviving pups, most of which having already been infected *in utero*. Although only low numbers of organisms are seen in semen and urine, seminal fluid and urine have been incriminated as sources of infection in male dogs that harbor the organisms in the prostate and epididymides. Alternative means of transmission occur less frequently under natural circumstances. Transmission via fomites has been reported after vaginoscopy, blood transfusion, artificial insemination, and use of contaminated syringes. *B. canis* is short lived outside the dog and is easily inactivated by common disinfectants.

After invading the mucous membranes, the bacteria enter phagocytic cells (and persist intracellularly in mononuclear phagocytes) and are transported to lymphatic and genital tract tissues. A leukocyte-associated bacteremia occurs beginning l to 4 weeks after infection and can last 6 to 64 months. *B. canis* may also spread to nonreproductive tissues, such as the intervertebral disks, eyes, and kidneys. The greatest numbers of *B. canis* organisms are found in the lymph nodes, spleen, and tissues of gonadal steroid dependency. As with other intracellular pathogens, cell-mediated immunity is probably the most important defense mechanism against *B. canis*. Persistent, nonprotective antibodies are characteristic of such infections; they appear to have little influence on the level of bacteremia or the number of organisms in tissues but characteristically cause hyperglobulinemia.

Spontaneous recovery from infection may occur within l to more than 5 years after infection. Some dogs may have persistent bacteremia throughout this time, whereas others can harbor bacteria in tissues for several months after bacteremia ceases. Dogs that recover naturally have low or negative antibodies and yet are immune to reinfection, which also suggests that protective immunity is cell mediated.

165.4.3 Clinical Signs

Despite generalized systemic infection with *B. canis,* adult dogs rarely are seriously ill. Fever is uncommon, and lymph node or spleen enlargement may rarely be noted. Except in males that commonly have epididymitis, most infections are not diagnosed through intact history or a routine physical examination. Dry, lusterless coats, loss of vigor, and decreased exercise tolerance are occasionally reported by owners of working dogs. Nongravid females mostly show no signs of illness.

The primary problems in intact male dogs are epididymitis, scrotal enlargement, and scrotal dermatitis. Inflammation of the epididymides and testes in males causes sperm leakage, which provokes the immune system to produce a complex of antisperm agglutinating antibodies and delayed-type hypersensitivity reactions against sperm that are unrelated to the antibodies against *B. canis*. The immune responses produced against spermatozoa contribute to the epididymitis, infertility, and eventual spermatogenic arrest seen in most infected male dogs.[133]

Bitches in late gestation (40 to 60 days) usually abort dead puppies but show no other clinical signs. Puppies are usually partly autolyzed. Some puppies are stillborn or weak. Conception failures also occur, but infection with *B. canis* does not interfere with normal estrous cycles. A high proportion of bitches that abort may subsequently have normal litters. However, some infected bitches show intermittent reproductive failures.

Less often, *B. canis* may localize in nonreproductive tissues such as the end-arterial circulation of the intervertebral disk, causing diskospondylitis.[134] Other tissues that filter blood-borne organisms or immune complexes also may become involved, including eyes (uveitis), kidneys (glomerulonephritis), and meninges (meningoencephalitis). Dogs with diskospondylitis initially experience spinal pain and later paresis and ataxia if spinal cord compression develops. Osteomyelitis of the appendicular skeleton causes lameness of the affected limb. Meningoencephalitis has been reported after experimental and natural infections; however, neurobrucellosis in dogs, as in humans, is uncommon.[135] Chronic multifocal pyogranulomatous dermatitis that resembled lick granuloma lesions also has been reported, but a direct causal relationship was not established. Recurrent anterior uveitis with corneal edema has been detected in infected dogs, either alone or in combination with other signs.[133]

Hematologic and biochemical values are either unaltered or nonspecific in canine brucellosis. Hyperglobulinemia with concomitant hypoalbuminemia has been the most consistent finding in chronically infected dogs. Some dogs have a positive Coombs' test in the absence of hemolytic anemia. CSF analysis may reveal pleocytosis, primarily consisting of neutrophils, and an increased protein concentration with meningoencephalitis, but it is unremarkable when diskospondylitis alone is present. Urinalysis is usually normal despite the variable presence of bacteriuria unless glomerulonephritis is present. Semen abnormalities include immature sperm, deformed acrosomes, swollen midpieces, detached tails, and head-to-head agglutination of sperm, often accompanied by neutrophilic and mononuclear inflammation.

165.4.4 Diagnosis

Antibody testing is the most frequently used diagnostic method for detecting canine brucellosis. Antibody tests available to veterinarians, however, pose a particular dilemma because several tests currently in use by diagnostic laboratories have not been evaluated critically and may provide false-positive results.[136] These tests are subject to considerable interpretive error because lipopolysaccharide antigens of several bacterial species cross-react with *B. canis*. False-negative results are rare, but antibody tests are usually negative during the first 4 weeks after infection despite the presence of bacteremia by 2 weeks after infection. Antibiotic therapy may suppress bacteremia and the associated antibody response, contributing to negative antibody tests and failure to isolate the organism in infected dogs.

ELISA and IFA for antibody detection exist, but they have not been well standardized or widely evaluated. Some newer ELISAs have been developed,[137–139] but no comparison studies involving large numbers of canine sera samples are available to assess the usefulness of these tests. The 2-mercaptoethanol rapid slide

agglutination test (ME-RSAT) (D-Tec CB; Synbiotics, San Diego, California) is preferred as an in-office screening procedure because it is inexpensive, rapid, and sensitive and it detects antibodies early. There is a high correlation between a negative test and lack of infection. However, false-positive test results are possible. *B. canis* cross-reacts with other *Brucella* species and other bacterial species, such as *Pseudomonas, Bordetella bronchiseptica, Actinobacillus equilli* and, possibly, others. Some breeds (e.g., Irish wolfhounds and Old English sheepdogs) have an exceptionally high false-positive rate, for unknown reasons. The tube agglutination test (TAT) is used by some laboratories after a positive ME-RSAT result to obtain confirmation and quantitative titers. Unfortunately, it suffers from the same nonspecific results and has not been well standardized among laboratories. Nevertheless, results of the ME-RSAT correlate well with the ME-TAT, both of which should be considered as screening tests. The agar gel immuno-diffusion (AGID) test is a sensitive procedure for antibody detection. Two antigens, either from the cell wall or cytoplasm (Cp), have been used in this test. The better CpAg-AGID uses cytoplasmic antigens and is highly specific for *Brucella* infection in dogs.[140] This test is performed by certain commercial laboratories and should be used as a confirmatory antibody testing procedure.

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Culture, if positive, is the only definitive way to diagnose brucellosis. Isolation of *B. canis* is time-consuming but not difficult, because the organism grows well aerobically on conventional media used for all *Brucella* species. Negative results, however, may occur in chronically infected dogs with intermittent bacteremia. Blood is the best source for isolating the organism. Whole blood should be cultured, because the organisms are associated with the leukocyte fraction. Bacteremia is detected 2 to 4 weeks after oronasal infection and, if left untreated, can persist for as long as 5 years.[133] Culture of the organism from urine or semen is less reliable. However, urine culture can be positive in some dogs, especially males, when blood cultures are negative; only cystocentesis urine should be used to avoid overgrowth of other bacteria. Collection of semen by ejaculation is valuable for culture during the first 3 months of infection, when the concentration of organisms is greatest. *B. canis* can also be isolated at necropsy from several tissues.

A PCR has been developed for humans that identifies all *Brucella* species relevant for human medicine; the test uses genus-specific primers that bind to a conserved region of the 16S rRNA gene. With carbohydrate profiling, *B. canis* can be differentiated from the other species.[141,142] This PCR could be used in dogs.

165.4.5 Treatment

Treatment of *B. canis* infection is difficult because of the intracellular persistence of the organism. Relapses are common after antimicrobial therapy stops. Bacteremia often recurs days to months after treatment is discontinued, making follow-up evaluation essential because animals still can harbor infection in certain tissues. For these reasons and because of the zoonotic risk, client education is critical, and euthanasia may be considered. If treatment is an option, infected pets should be neutered and given a strict regimen of antibiotic therapy to reduce the chance of family members becoming infected through genital secretions. The organism can persist in the tissues of neutered animals, but shedding is believed less likely. Treatment of intact breeding dogs should be considered only under exceptional circumstances. Infected male dogs rarely, if ever, recover; they usually become sterile. Infected female dogs have recovered in some instances and have been returned to breeding programs. Aborting females may subsequently produce normal litters, but even in those cases the success of therapy is uncertain. Thus breeding of such animals should be done only when it is considered essential (e.g., loss of a valuable blood line) and after the risk has been explained to the owner.

Various antimicrobial agents have been considered for treatment. Repeated courses of antibiotic therapy are recommended on the basis of follow-up antibody testing and blood cultures. Cure of brucellosis must not be assumed, because bacteremia may recur weeks or months after antibiotics are discontinued, and reports of

successful cures should be viewed with caution unless subsequent cultures and antibody tests have been performed for at least 6 months. Infected dogs respond poorly or not at all to drugs when they are given alone or for a single course of therapy. *In vitro,* synergy has been noted among tetracyclines and fluoroquinolones and aminoglycosides and sulfonamides,[143] and combination therapy, usually performed with tetracyclines and aminoglycosides, offers the best chance of eliminating infection. Unfortunately, the best known regimen (minocycline *plus* dihydrostreptomycin) is unobtainable in many countries because of the restricted availability of dihydrostreptomycin. Gentamicin has been substituted for dihydrostreptomycin, but the efficacy is less than with dihydrostreptomycin.[133] The recommended treatment regimen is gentamicin (5 mg/kg subcutaneously every 24 hours for 7 days) administered twice in the first and fourth week, in combination with high-dose oral minocycline (25 mg/kg orally every 24 hours) for 4 weeks. Eventually, generic doxycycline can be substituted for minocycline at the same dosage at lower cost. Renal function must be closely monitored during gentamicin treatment phases. Lower dosages of this combination or other antibiotics alone or in combination are not as effective. Infected animals may have to be treated with two or more courses of this antimicrobial treatment regimen. Sequential antibody tests at 3-to 6-month intervals are recommended to monitor treatment efficacy.

165.4.6 Prevention

There is no vaccine for brucellosis, and the results of experimental vaccination studies have been unsatisfactory. The desirability of a vaccine is questionable, especially with the available diagnostic testing, because an effective vaccine would be required to provide serviceable immunity but not confound the antibody tests.

Control of canine brucellosis in a kennel with confirmed cases is a difficult, time-consuming, and agonizing experience both for dog owners and veterinarians. A kennel should be quarantined as soon as the diagnosis of *B. canis* infection is ascertained, and infected animals should be promptly eliminated. Appropriate disinfection procedures should be implemented to arrest the spread of infection via fomites. All dogs and discharges or secretions in an infected kennel should be handled with gloves until antibody testing can be done to determine the extent of the infection. Animals should not be admitted to or released from the kennel until the disease is eradicated. Movement of dogs within a colony also should be restricted to removal of proven and suspect cases to isolation quarters. New additions are at high risk for infection, especially if dogs are not individually penned, which also increases the number of animals requiring repeated testing during the eradication process. Animals must not be released for sale or any other purpose. All dogs in an infected kennel should be antibody tested for at least 3 months after a negative status is achieved, especially before each breeding, even by artificial insemination. If animals are retained as pets or working dogs or if treatment is contemplated, the animals should be neutered and moved to separate housing. Prevention is accomplished by quarantine of all new acquisitions until two antibody test results at l-month intervals are negative. Animals used for breeding should be tested 3 to 4 weeks before each mating to allow time for test results to be reported. Brood bitches should not be mated unless both male and female have been tested and certified negative. If dogs leave a colony, they should be tested before readmission.[133]

165.4.7 Brucellosis in Cats

Cats can be infected experimentally and develop bacteremia but are relatively resistant and do not develop clinical signs. The relevance of *B. canis* infection in cats in the field is unknown.

165.4.8 Public Health Considerations

Pathogenic *Brucella* species in humans include *B. melitensis, B. abortus, B. suis,* and *B. canis*. Human brucellosis caused by other *Brucella* species is still prevalent in many southern countries, especially in the Mediterranean basin, and ingestion of raw milk and milk products is the most common mode of transmission.[142,144–146] Humans are relatively resistant to infection with *B. canis,* and the disease is relatively mild compared with infections caused by other *Brucella* species. However, more than 40 cases of human infection caused by *B. canis* exist in the literature. Natural and laboratory-acquired infections have been reported in several countries; however, the actual number of cases is unknown because human infections are often undiagnosed. Contact with aborting bitches was the source of infection for the majority of infected pet owners. A proportion of cases are asymptomatic and can be detected only by testing for antibodies. Fever, chills, fatigue, malaise, lymphadenomegaly, and weight loss have been seen in symptomatic patients. Rare complications include endocarditis,[147] meningitis, arthritis, hepatitis, and visceral abscesses. Two infected adolescent boys had pleural effusion and pulmonary nodules.[148] Human infections are readily and effectively treated with tetracyclines.

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Clients should always be informed about the potential health hazard in keeping *B. canis*–infected pets. Laboratory workers should use caution in handling or pipetting samples submitted for diagnostic testing. Veterinarians should practice good hygiene when examining suspected dogs, especially aborting bitches.

165.5 TETANUS

165.5.1 Etiology

Tetanus is caused by the action of a potent neurotoxin formed in the animal or human body by *Clostridium tetani,* a motile, gram-positive, nonencapsulated, anaerobic, spore-forming bacterium.[1] Although strain differences of *C. tetani* exist throughout the world, the toxin produced by all strains is antigenically homogeneous. Resistant spores of the organism can be found in the environment, especially in rich soil. Spores can survive adverse weather conditions in the absence of direct sunlight for months to years and can be found readily in dust and debris in indoor environments. Organisms can be isolated from the feces of many domestic animals, including dogs and cats, and humans without pathogenetic significance.[149] The prevalence of the disease in dogs and cats is relatively low[150] compared with that in other domestic animals (e.g., horses) and humans. However, a number of cases in dogs[151–160] and cats[161–167] are reported in the literature. The low prevalence in dogs and cats is mainly related to the natural resistance of dogs and cats to the toxin. It could be shown that this resistance is caused by the inability of the toxin to penetrate and bind to nervous tissue, because direct CNS injection of toxin produce equivalent signs in all species.[168]

165.5.2 Pathogenesis

Tetanus develops when spores are introduced into wounds or penetrating injuries. Most cases develop after penetrating skin wounds, but tetanus has also been described in female dogs after parturition[169] or ovariohysterectomy.[170,171] The spores vegetate in response to anaerobic conditions at the site of the injury. Two toxins have been identified from *C. tetani*. Tetanolepsin causes hemolysis of erythrocytes *in vitro* but is not considered clinically significant. In contrast, tetanospasmin enters the body from the wound site and has

marked effects on neurologic function. It is not absorbed from the gastrointestinal tract, where it is usually destroyed by digestive enzymes. Its high molecular weight (176,000) precludes its entry into the placenta.

Tetanospasmin enters the axons of the nearest motor nerves at the neuromuscular endplate and migrates by retrograde transport within motor axons to the neuronal cell body in the spinal cord or brain stem. It can spread in the CNS in this fashion. Alternatively, it can be transported in the bloodstream from the area of the wound to nerves at distant sites. Thus the condition can cause localized, progressive illness or a more generalized syndrome. Tetanospasmin blocks inhibitory transmission to motor neurons. It has additional effects on the neuromuscular junction and autonomic ganglia that can cause further visceral and motor neuron disturbances.

165.5.3 Clinical Signs

Clinical signs of tetanus usually occur within 5 to 10 days of injury, but because of the higher resistance of dogs and cats, the onset may be delayed up to 3 weeks. This may account for the absence of a detectable wound by the time dogs show clinical signs. Because cats have an even more pronounced innate resistance, their wounds are usually so extensive that they are still obvious at presentation. Wounds nearer the head are associated with more rapid onset and generalized tetanus than are injuries to distant extremities.

The clinical signs of tetanus can be explained by the pathophysiologic effects of tetanospasmin on the nervous system. The toxin inhibits release of glycine and gamma-aminobutyric acid (GABA) neurotransmitters of inhibitory neurons of the brain and spinal cord. It has an affinity for gangliosides in the gray matter of the CNS, which may explain the cerebral signs that appear in some cases without obvious spinal cord involvement. Tetanospasmin also has an affinity for binding at the neuromuscular junction, which can induce direct neuromuscular facilitation before the migration of toxin to the CNS. The toxin may affect sympathetic preganglionic neurons in a manner similar to that in the lower motor neurons in the spinal cord and cause signs of autonomic dysfunction.[168]

Localized tetanus is more common in cats than in dogs and more common in dogs than in other domestic animals or humans because of the relative resistance of carnivores to the toxin. This condition is characterized by increased stiffness of a muscle or an entire limb, first noted in close proximity to the wound site. The stiffness usually spreads gradually and eventually may involve the entire nervous system.

Animals affected with generalized tetanus generally have a stiff gait and an outstretched or dorsally curved tail. They have difficulty standing or lying down in comfortable positions because of their extreme muscle rigidity. The rectal temperature is usually elevated due to excessive muscular activity. The ears are held erect, the lips are drawn back, and the forehead is often wrinkled as a result of facial muscle spasm. The animal characteristically appears to be continuously smiling *(risus sardonicus)*. Protrusion of the third eyelid and enophthalmus result from retraction of the globe from hypertonus of extraocular muscles. Trismus (lockjaw) is caused by contraction of masticatory muscles. Increases in salivation and the respiratory rate, as well as laryngeal spasm and dysphagia, can result from involvement of parasympathetic and somatic cranial nerve nuclei. Regurgitation and gastroesophageal reflux may result from esophageal hiatal hernia and megaesophagus,[172] potentially leading to aspiration pneumonia, a major complication in many animals with tetanus. Animals become apprehensive and react strongly to tactile or auditory stimulation. Dogs and cats usually remain conscious until they develop convulsions. The signs may proceed to periodic generalized tonic contraction of all muscles with opisthotonus or grand mal convulsions.

Bradycardia associated with tetanus probably results from vagal-parasympathetic hyperactivity. Tetanospasmin also blocks neurotransmitters in the parasympathetic cardiac inhibitory center of the nucleus ambiguous,

resulting in increased vagal tone and pronounced bradyarrhythmias. Increased catecholamine release associated with adrenergic stimulation can cause episodes of hypertension or tachycardia.[173]

Hematologic abnormalities, including leukocytosis with neutrophilia and left shift, are the result of large wounds or aspiration pneumonia that may be present. Serum biochemistry and CSF values are unaffected, except for increased muscle enzyme activities (creatine kinase, aspartate aminotransferase). 628 629

The progression of clinical signs culminates in death, which is usually caused by respiratory compromise as a result of rigidity of the respiratory musculature, reflex spasms of the larynx, increased airway secretions, and central respiratory arrest from medullary tetanospasmin effects or anoxia. Dogs and cats not as severely affected may recover. The binding of tetanospasmin to presynaptic sites of inhibitory neurons is irreversible; recovery depends on sprouting of new axon terminals.

165.5.4 Diagnosis

Tetanus is one of the few infectious diseases that can be diagnosed by "classic" clinical signs. Measurement of serum antibody titers to tetanospasmin has been used to substantiate the diagnosis. Values must be compared with those of control animals. Antibody measurements might be helpful in a clinical setting to confirm the cause of undiagnosed muscle stiffness. Isolation of *C. tetani* from wounds is usually unrewarding. The organisms are only present in low concentrations, and although Gram-stained smears may demonstrate gram-positive rods and dark-staining spherical endospores, the morphology is similar to that of many other anaerobic bacteria. If culture is attempted, it should be done under strict anaerobic conditions at 37° C for at least 2 weeks.

165.5.5 Treatment

Treatment of severely affected animals is costly and time-consuming, and owners must be advised of the possibility of complications and lengthy hospitalization. Mildly diseased animals recover from the neurologic dysfunction with wound management alone. More severe cases, if left untreated, can prove fatal. These animals are suffering, therefore euthanasia must be the alternative to treatment.

The immediate concern in treating tetanus is administration of antitoxin to neutralize any toxin that is unbound to the CNS or has yet to be formed. The timing and route of antitoxin administration are important in determining effectiveness. Use of antitoxin should be a routine measure; however, elimination of bound toxin by the affected animal occurs gradually, and administration of antitoxin does little to hasten the process. Therefore recovery in most cases is slow and progressive. Intravenous administration of antitoxin is superior to intramuscular or subcutaneous administration for producing a rapid and marked increase of circulating antitoxin. The equine antitoxin (2.5 to 25 IU/kg) should be given slowly intravenously over 5 to 10 minutes. Larger animals should receive a proportionally lower dose on the basis of body weight. Intravenous administration of antitoxin is commonly associated with anaphylaxis, warranting appropriate precautions. An initial test dose (0.1 to 0.2 mL) of antitoxin should be given intradermally 15 minutes before IV administration. Epinephrine, glucocorticoids, and antihistamines should be readily available in case of an adverse reaction, or the latter two may be given before the intravenous injection, depending on the intradermal test outcome. A therapeutic blood level of antitoxin persists in dogs for 14 days after injection; repeated administration is usually unnecessary and increases the chance of an anaphylactic reaction. Local intramuscular injection of a small dose of antitoxin (1000 IU) around and proximal to the wound site has been shown to be beneficial in experimental studies. Intrathecal injection of antitoxin in laboratory animals has been shown to be beneficial; however, use in affected humans has not proven to be effective.

Local and parenteral antibiotic therapy should be instituted in an attempt to kill any vegetative *C. tetani* organisms present in the wound. Although antibiotics by themselves do not neutralize circulating toxin, they significantly reduce the amount of antitoxin released in experimental tetanus. Penicillin G is the drug of choice and should be given intravenously (as potassium or sodium salt) at a high dose (20,000 to 50,000 IU/kg every 6 hours for 10 days). A portion of the dose can be injected intramuscularly (as procaine salt) in close proximity to an identified wound site. Penicillin derivatives, such as ampicillin, are not as effective against the organism, and their use may cause little or no response. Metronidazole (10 mg/kg orally every 8 hours for 10 days) may be more active than penicillin G because it is bactericidal against most anaerobes and achieves effective therapeutic concentrations even in anaerobic tissues. Some treatment regimens recommend a combination of penicillin G and metronidazole; however, metronidazole toxicity has to be considered, and only low dosages should be used (not more than 250 mg total every 12 hours in cats). Clindamycin (5 mg/kg intravenously every 8 hours for 10 days) also has been used in some cases.

Surgery may be required if tissue necrosis or abscess formation is extensive. Antitoxin should be administered before surgery because of the release of toxin in the circulation during tissue manipulation. General anesthesia is usually required to debride wounds and remove necrotic tissue. The prognosis for recovery is always greater if the wound site is located and can be debrided.

Supportive measures are imperative in the successful management of an animal with tetanus. Sedation is usually needed for an excitable animal, and phenothiazines appear to be highly effective, even though they are contraindicated in most seizure disorders. Fluids are needed for hydration. Tracheostomy may be required if laryngeal spasm is severe. Esophagostomy or gastrostomy tubes may be needed if trismus prevents eating.

In mildly affected animals, normal function usually returns within 3 weeks of the initiation of treatment. The prognosis for severely affected animals is extremely guarded, and many die as a result of complications associated with respiratory or cardiovascular dysfunction or uncontrollable muscle spasms.

165.5.6 Prevention

Active immunoprophylaxis with tetanus toxoid is not recommended for dogs and cats; it is used in more susceptible species such as humans and horses. Appropriate care of infected wounds and rational antibiotic therapy should minimize the occurrence of tetanus.

165.5.7 Tetanus in Cats

Cats are even more resistant to tetanus toxin than dogs and more commonly develop only localized tetanus.[161–167]

165.5.8 Public Health Considerations

There is no risk of transmission from dogs or cats to humans.

165.6 BOTULISM

165.6.1 Etiology

Clostridium botulinum is a gram-positive, spore-forming, saprophytic, anaerobic rod that is distributed in soil worldwide. Botulism is an intoxication caused by a neurotoxin produced by the organism that causes neuromuscular paralysis.[1] In humans, outbreaks of botulism are commonly described in the literature; the contaminated food sources are variable and have included canned beef stew,[174] home-canned mushrooms,[175] and restaurant potato salad.[176] Sources of recent outbreaks include a commercial canned cheese sauce in the United States,[177] a mascarpone cream cheese dessert in Italy,[178] and a locally produced cheese in Iran.[179]

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To cause disease, either the organism or its spores must contaminate a food source. Most cases in animals are caused by ingestion of the preformed toxin in food. Naturally occurring botulism in dogs has been mainly attributed to the eating of carrion or raw meat. The disease in cats is similar to that in dogs under experimental conditions, although there are no reports of naturally occurring disease.

Seven subtypes of *C. botulinum* (A, B, C, D, E, F, and G) have been identified on the basis of their antigenically distinct neurotoxins. All have similar structure and the same neurotoxic effect. Subtypes A, B, E, and F are associated with human disease. Most cases in animals are caused by subtypes C and D, which are closely related immunologically. All canine cases to date have been caused by subtype C toxin[180–186] with the exception of two cases of subtype D reported from Senegal.[187,188]

Clostridial spores are resistant to heat, light, drying, and radiation, and specific conditions are necessary for germination. The organism grows best in anaerobic and warm conditions (15° to 45° C). All types of botulinal toxin are inactive when initially released by bacterial lysis, and bacterial or tissue proteases are necessary to cleave them to generate the active dichain neurotoxin.

165.6.2 Pathogenesis

Botulism is usually caused by ingestion of the preformed toxin, although a variant of the disease in humans, infant botulism, is induced by ingestion of spores, mostly present in honey. Adults are usually resistant to intestinal coloniza-tion with *C. botulinum,* mainly thanks to the intestinal microflora.

Once ingested, the toxin is absorbed from the stomach and upper small bowel and enters the lymphatic system. It circulates by unknown transport mechanisms to the neuromuscular junction of cholinergic nerves, where it exerts its effects. A metalloproteinase similar to tetanus toxin, the botulinal toxin, prevents the presynaptic release of acetylcholine at the neuromuscular junction; both the spontaneous release of acetylcholine and its release caused by a nerve action potential are inhibited. Binding of the toxin occurs very quickly and is irreversible, unaffected by temperature and independent of neural activity. The cell membrane receptors for the toxin have a very high affinity for it because very small quantities (less than 10 mol) are sufficient to cause death, making it the most potent toxin known.[189] Variations in receptor affinity for different types of toxin explain the different sensitivities of animal species to the different botulinal toxins.

165.6.3 Clinical Signs

The incubation period after ingestion of contaminated food in dogs ranges from hours to 6 days. The earlier the signs appear, the more serious the disease. The duration of illness in dogs that have recovered ranged from 14 to 24 days. The severity of signs varies with the amount of toxin ingested and the individual susceptibility.

The blockage of acetylcholine release results in generalized lower motor neuron and parasympathetic dysfunction. Clinical signs are characterized by a symmetric, ascending weakness from the rear to the forelimbs that can result in quadriplegia. Limb reflexes are depressed, and cranial nerve motor responses are affected, causing mydriasis, decreased jaw tone, decreased gag reflexes, and excess salivation. Megaesophagus may be present. Pain perception is intact; muscle atrophy and hyperesthesia do not develop. Death may result from respiratory paralysis.

Hematologic and biochemical parameters are unaffected. Electromyography shows conduction defects primarily in the neuromuscular junction and less in the peripheral nerve.

Blockage of neurotransmission can cause death of the affected animal from inability to breathe. If recovery occurs, it is complete. Botulinal neurotoxin does not cause death of the affected neuron; it only causes paralysis and degeneration of the intoxicated synapse. If the animal survives, recovery occurs by development of new terminal axons with functional neuromuscular junctions. Cranial nerve, neck, and forelimb functions tend to return first during recovery. Thus the effect of botulinal neurotoxin always has the potential for a complete reversal.

165.6.4 Diagnosis

Botulism is usually suspected from the history and clinical signs. Confirmatory diagnosis is based on finding the toxin in serum, feces, vomitus, or samples of the food ingested. Serum should be collected as early in the disease course as possible and when clinical signs are maximal. About 10 mL of serum or 50 g of feces, vomitus, or food are needed. The preferred method for identifying the toxin still is the neutralization test in mice. Serum or an extract of contaminated material is injected alone and in combination with type-specific antitoxin into the peritoneal cavity of mice. The mice are then observed for signs of botulism. Survival of one group protected with one type of antitoxin and death of the other groups with signs consistent with botulism confirm the presence of botulinal toxin. Newer *in vitro* tests, including radioimmune assay (RIA), passive hemagglutination, ELISA,[190] and PCR, have been developed to identify botulinal toxin but have not replaced the mouse test to date due to lack of accuracy.

165.6.5 Treatment

Antitoxin is not effective after the toxin has penetrated the nerve endings, which occurs rapidly after the toxin enters the bloodstream. However, antitoxin may prevent further toxin binding if intestinal absorption and circulation are still occurring. Most cases in dogs are type C; thus type C antitoxin should be given. The recommended dose for treating dogs is the same as that for treating human adults (10,000 to 150,000 IU/dog IV or IM, two doses 4 hours apart). Because the antitoxin remains in circulation for 40 days after administration, there is no need for further administration. Anaphylaxis is a potential risk. Intradermal skin testing can be performed with 0.1 mL 20 minutes before intravenous injection. Any immediate reaction at the test site is a warning that an allergic response may occur, and glucocorticoids and antihistamines should be applied *before* application of the antitoxin in these cases.

The use of antibiotics in botulism is the subject of debate. Penicillin and metronidazole have been administered in dogs and humans in an attempt to reduce any potential intestinal growth of *C. botulinum*. The efficacy of these drugs is doubted because the disease occurs usually due to ingestion of preformed toxin and because neither drug is certain to eradicate *C. botulinum* from the intestine. The possibility that these drugs could make the disease worse by releasing more toxin through bacterial lysis is discussed. Even in infant botulism, which may involve intestinal colonization with *C. botulinum,* penicillin has no effect on recovery. Antibiotics also can alter the intestinal microflora, which might allow *C. botulinum* to grow. Therefore antibiotics should only be given if secondary infection (e.g., aspiration pneumonia) develops. Aminoglycosides should be avoided because they also have the potential to block neuromuscular function.

Supportive treatment, which can be time-consuming and expensive, is the most important intervention in the therapy of animals with botulism. Spontaneous and complete recovery occurs in moderately affected animals if respiratory and urinary tract infections can be avoided. Affected animals should be padded when recumbent and assisted to eat and drink. Several drugs, including guanidine hydrochloride, 4-aminopyridine, and 3,4-diaminopyridine, have been used as neuromuscular potentiators but without demonstrable efficiency in clinical cases in humans or animals.

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165.6.6 Prevention

Preventing access to carrion and thorough cooking of any food fed to dogs and cats prevents the disease. Botulinal toxin is destroyed by heating food to 80° C for 30 minutes or to 100° C for 10 minutes. Vaccination with a toxoid has been successful in cattle and in exposed laboratory workers but has not been used in dogs or cats is not recommended because of the low prevalence of the disease.

165.6.7 Botulism in Cats

Although botulism has been experimentally produced in cats, no natural cases of botulism have been reported. A cat that ate contaminated yogurt did not become ill, even though two humans eating the same yogurt did. Botulism has been reported in lions, but jaguars and coatis eating the same food as the lions were not affected.[191] Produced under experimental conditions, the disease in cats is similar to that occurring in dogs because botulinal neurotoxins cause similar signs in all species. Although there are no reports of natural disease in cats, cats can be the source of outbreaks in cattle. In one case, 427 Holstein cattle that had been fed a rotten bale of oat hay contaminated with a dead cat died from botulism, and the presence of botulinum toxin type C was identified.[192]

165.6.8 Public Health Considerations

The disease is not transmitted from animals to humans.

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166 CHAPTER • 166 Obligate Intracellular Bacterial Pathogens

Edward B. Breitschwerdt

166.1 GENERAL CONSIDERATIONS

From an evolutionary and clinical perspective, several groups of bacteria have developed an obligate intracellular life style that facilitates their existence within an insect vector or within one or more animal hosts. Due to the persistent nature of many of these intracellular infections, the factors that ultimately predispose to the development of pathology in many animal hosts are as yet incompletely understood. Recent genetic analyses of 16S rRNA genes, heat shock, and surface protein genes have resulted in a substantial reclassification of the genera *Anaplasma*, *Ehrlichia*, *Cowdria*, *Neorickettsia*, and *Wolbachia*.[1] As a result, the genus *Ehrlichia* is now comprised of: *E. canis*, *E. chaffeensis*, *E. ewingii*, *E. muris*, and *E. ruminantium*. The genus *Anaplasma* is now comprised of: *A. phagocytophilum*, (previously *E. equi*, *E. phagocytophila*, or the human granulocytic ehrlichia [i.e., the HGE agent]), *A. bovis*, and *A. platys. E. risticii* has been transferred to the genus *Neorickettsia,* which includes: *N. sennetsu*, *N. helminthoeca, N. risticii*, and the salmon fever agent. Organisms within the genus *Wolbachia* are currently recognized as arthropod pathogens or symbiotes but appear to be of emerging importance as vertebrate pathogens. Within the genera *Rickettsia*, *Ehrlichia*, *Anaplasma*, and *Neorickettsia*, numerous species can be pathogenic for animals, including man. Many of these organisms are found throughout the world and can be transmitted by ticks, fleas, chiggers, or the ingestion of insects or flukes. These organisms can induce disease manifestations that range in severity from subclinical to life threatening.

Because of this reclassification, clinicians will have to reorganize the nomenclature that involves pathophysiology, diagnosis, treatment, and preventive strategies related to these organisms.[1,2] Although a currently cumbersome task, the recent reclassification should result in enhanced clarity when considering similarities and differences among organisms in the same or different genera. The terms *rickettsioses*, *ehrlichioses*, *anaplasmoses*, and *neorickettsial infections* have taken on new clinical meaning as a result of advances in microbial genetics and clinical medicine. A more detailed description of Rocky Mountain spotted fever (RMSF), typhus group rickettsiae, canine ehrlichiosis, salmon-poisoning disease, and *Coxiella burnetii* infection is provided in the fifth edition of this text (see Chapter 86, The Rickettsioses).

166.2 RICKETTSIOSES: THE SPOTTED FEVER GROUP RICKETTSIAE

Spotted fever group (SFG) rickettsiae have been described from all continents. The group includes nine species: *Rickettsia rickettsii* (the type species), *R. africae*, *R. akari, R. australis*, *R. conorii*, *R. montana*, *R. parkeri*, *R. rhipicephali*, *R. sibirica*, and *R. felis*, although many other SFG rickettsiae have been described. *Dermacentor, Rhipicephalus, Haemaphysalis,* and *Amblyomma* species ticks transmit SFG rickettsiae. Rickettsia-induced endothelial cell damage results in vasculitis, altered vascular permeability, edema, and necrosis. *R. felis*, which is transmitted by fleas, is recognized as a cause of human febrile illness in the United States and Central and South America. The pathogenicity of *R. felis* in cats or dogs has not been established. As the most pathogenic of the SFG rickettsiae, *R. rickettsii* will be considered in detail.

166.3 ROCKY MOUNTAIN SPOTTED FEVER

RMSF is a tick-transmitted rickettsial disease of dogs, people, and other vertebrate species. The causative agent is *Rickettsia rickettsii*. Veterinarians should anticipate a spectrum of illness after naturally occurring infection with

R. rickettsii in endemic regions. Clinical abnormalities associated with RMSF include fever, anorexia, depression, mucopurulent ocular discharge, scleral injection, tachypnea, coughing, vomiting, diarrhea, muscle pain, neutrophilic polyarthritis, and a diverse group of neurologic signs including hyperesthesia, ataxia, vestibular signs, stupor, seizures, and coma. In some dogs, weight loss is very severe, considering the short duration of illness. Poorly localizing joint, muscle, or neurologic pain that is suggestive of polyarthritis, polymyositis, or meningitis may represent the only or most prominent clinical finding. Retinal hemorrhages are a consistent finding but may be absent early in the course of the disease. Epistaxis, melena, hematuria, and petechial-to-ecchymotic hemorrhages occur in some dogs but may not develop unless diagnosis and treatment are delayed for 5 or more days after the onset of clinical signs. Scrotal edema, hyperemia, hemorrhage, and epididymal pain are frequently observed in male dogs. Signs associated with cardiovascular collapse, oliguric renal failure, or brain death can develop in the terminal stages of the disease.[3,4] Gangrene affecting the distal extremities, scrotum, mammary glands, nose, or lips is associated with severe vascular obstruction and can induce substantial tissue loss, necessitating reconstructive surgery.

166.3.1 Diagnosis

Seasonal occurrence, history of tick infestation, fever, and combinations of the previously described clinical findings should suggest the possibility of RMSF. Due to marked variation in clinical presentation, confirmation of the diagnosis of RMSF is important for the clinician to gain familiarity with the disease. In addition, confirmation of RMSF in household pets warrants owner education as to the enhanced risk associated with tick exposure in that environment. Thrombocytopenia, generally mild in degree, is the most consistent hematologic finding.

Leukopenia generally occurs during the early stages of infection (first 24 to 48 hours), followed by progressive leukocytosis, which increases in proportion to the severity of vascular injury. Toxic granulation of neutrophils, metamyelocytes, eosinopenia, lymphopenia, and monocytosis may accompany the more typical changes in platelet and neutrophil number. A mild anemia may occur. Severe anemia, leukopenia, and thrombocytopenia can accompany fulminant canine RMSF.[4] Biochemical abnormalities reflect the effects of generalized vascular damage and vary with the severity and duration of infection. Hypoproteinemia, hypoalbuminemia, azotemia, hyponatremia, hypocalcemia, and increased liver enzymes (serum alkaline phosphatase, alanine aminotransferase) may occur in dogs with RMSF. Bilirubinuria and bilirubinemia also occur in dogs with RMSF. Synovial or cerebrospinal fluid (CSF) analysis will generally reflect a mild increase in protein and cells, which, in the early disease process, are composed of a high percentage of neutrophils and later, mononuclear cells.

Confirmation of a diagnosis requires either direct immunofluorescent testing for *R. rickettsii* antigen in tissue biopsy or necropsy specimens, serologic testing, or polymerase chain reaction (PCR) amplification of rickettsial DNA. Using the indirect fluorescent antibody (IFA) test, documentation of a fourfold or greater increase in antibody titer between acute and convalescent sera confirms a diagnosis of RMSF. To facilitate the accurate interpretation of serologic results, it is important to obtain the acute-phase sample as early in the disease course as possible and the convalescent sample 2 to 3 weeks thereafter. If acute-phase sera are obtained several days after the onset of clinical signs, a high antibody titer may be found. Although early initiation of antirickettsial antibiotic therapy will slightly decrease the intensity of the humoral immune response to *R. rickettsii* antigen, experimental studies indicate that collection of appropriately timed serum samples should still facilitate an accurate diagnosis of RMSF in dogs.[5] Direct immunofluorescent testing or PCR amplification of *Rickettsia* DNA provides the opportunity for rapid diagnosis by demonstrating *R. rickettsii* in skin biopsies or by detecting

DNA in blood or tissue samples.[6] Prior initiation of antibiotic therapy can cause a false-negative test results with both direct immunofluorescent testing and PCR.

166.3.2 Treatment

Tetracycline (22 mg/kg three times a day for 14 days) or doxycycline (5 mg/kg twice a day for 14 days) is effective for treatment of SFG rickettsiae infection. Fluoroquinolones, such as enrofloxacin, appear to be equally effective for treating RMSF but not ehrlichiosis. After initiation of treatment, a rapid clinical response occurs in dogs without severe vascular damage or neurologic sequela. Defervescence should be anticipated within 24 hours after the initiation of antibiotics. Delay in diagnosis or the use of antibiotics such as penicillin, cephalosporin derivatives, or aminoglycosides that lack anti-rickettsial spectrums, may result in increased morbidity or mortality. Due to severe vascular damage, fluid therapy should be used with extreme caution. Prednisolone administered at anti-inflammatory or immunosuppressive doses in conjunction with doxycycline does not potentiate the severity of *R. rickettsii* infection in experimentally infected dogs.[5]

166.3.3 Prevention

Immunity after natural infection is probably permanent. It is possible that undiagnosed mild or asymptomatic *R. rickettsii* infections, or repeated exposure to nonpathogenic SFG rickettsiae, can also contribute to the prevention of severe RMSF in dogs with heavy tick exposure in endemic regions. Minimizing tick exposure, using acaracidal preparations, and routinely removing ticks from dogs represent the most effective means of prevention. After infection with *R. rickettsii*, the duration of rickettsemia is brief, approximately 5 to 14 days.[5,6] Therefore infected dogs do not play an important reservoir role and pose a minimal zoonotic threat to humans. In contrast, if RMSF is diagnosed in a household pet, the dog serves as a valuable environmental sentinel for potential human exposure to infected ticks. Care should be exercised in removing ticks, so as not to contaminate one's hands with infective hemolymph from ticks. Although the risk of inadvertent transmission is small, contact with rickettsemic blood during intravenous catheter placement, blood collection procedures, or laboratory sample analysis should be avoided. Zoonotic warning labels are recommended for blood samples obtained from dogs in which a differential diagnosis of RMSF is being considered. The role of typhus group rickettsiae as canine pathogens is yet to be established.[7]

166.4 CANINE EHRLICHIOSIS

Canine ehrlichiosis is an infectious disease of dogs, caused by *E. canis*, *E. chaffeensis*, *E. ewingii*, and potentially *E. ruminantium*.[2,8] Although the clinicopathologic course of disease can vary depending upon the infecting *Ehrlichia* species, illness is typically characterized by an acute reduction in cellular blood elements, most often thrombocytopenia. Investigators from South Africa have obtained molecular evidence (16S rDNA sequencing) that supports infection of dogs and people with an organism that is identical or closely related to *E. ruminantium* (previously *Cowdria ruminantium*). The implications of this recent finding could prove to be of great importance, if *E. ruminantium*, the organism that causes heartwater in cattle in Africa, could be introduced into the United States by way of dog transport.

Historically, *Ehrlichia* species were designated by their cellular tropism (i.e., monocytes, granulocytes, platelets). 632
With the advent of species-specific molecular diagnostic testing, defining an infection in an animal based solely 633
upon the putative cell tropism is of minimal scientific or medical utility for several reasons. As an example, granulocytic morulae can be found on stained blood smears from dogs infected with *E. ewingii* or *A.*

phagocytophilum. Based upon current nomenclature, one dog has ehrlichiosis and the other anaplasmosis. In addition, detection of morulae is a highly insensitive means of diagnosis, which further limits the clinical utility of a cell tropism–based classification.

The distribution of canine ehrlichiosis is related to the distribution of the vector ticks, *Rhipicephalus sanguineous*, the brown dog tick and vector for *E. canis* throughout the world, as well as *Amblyomma americanum*, the lone star tick and primary vector for *E. chaffeensis* and *E. ewingii* in the United States. It is probable that other tick species transmit known and yet to be characterized *Ehrlichia* spp. to wild and domestic animals in Europe, Asia, Africa, and South America. Although ehrlichiosis is diagnosed most frequently in dogs living in the Southeastern and Southwestern United States, the disease has been reported from nearly every state. Because of chronic, subclinical infection,[9] a dog can be transported from an endemic to a nonendemic region and subsequently develop disease manifestations years after the initial infection.

E. canis and *E. chaffeensis* are small, pleomorphic bacteria that most frequently infect circulating mononuclear cells. *E. canis* infections have been reported in dogs that have a concurrent infection with *Anaplasma platys, Babesia canis* or *Hepatozoon canis*, *Bartonella vinsonii (berkhoffii)* or in conjunction with *E. chaffeensis* or *E. ewingii*. In some instances simultaneous transmission of organisms from vector ticks occurs, whereas in other instances coinfection reflects frequent tick exposure and multiple independently obtained chronic infections. Concurrent infection with phaeohyphomycosis or cryptococcosis may represent coincidental infections, or it may represent secondary opportunistic infection associated with chronic ehrlichiosis.

Clinical signs during the acute phase of disease will vary from depression, anorexia, and fever to severe loss of stamina, weight loss, ocular and nasal discharges, dyspnea, lymphadenopathy, and edema of the limbs or scrotum. Acute-phase clinical signs are transient and usually resolve in 1 to 2 weeks without treatment. Thrombocytopenia and leukopenia generally occur 10 to 20 days after infection. Despite moderate to severe thrombocytopenia, hemorrhages are rarely observed. A variety of ocular and central nervous system (CNS) signs, including hyperesthesia, muscle twitching, and cranial nerve deficits, may occur due to inflammation or bleeding into the eye or meninges respectively.[9,10] Clinical findings in the acute phase of ehrlichiosis can be identical to canine RMSF. Clinical signs associated with the chronic phase of the disease would be characterized as mild to asymptomatic in some dogs and severe in other dogs. A combination of bleeding tendencies, pallor due to anemia, severe weight loss, debilitation, abdominal tenderness, anterior uveitis, retinal hemorrhages, and neurologic signs consistent with meningoencephalitis, typify dogs that develop disease manifestations during chronic infection with *E. canis*, *E. chaffeensis,* or *E. ewingii*. Concurrent bacterial infections may be documented, particularly in neutropenic dogs. Numerous patterns of hemorrhage may occur in dogs with ehrlichiosis. Epistaxis, once considered a hallmark of the disease, is reported infrequently in more recent case series.

In addition to hematologic abnormalities that would be consistent with *E. canis* (anemia, neutropenia, thrombocytopenia, lymphocytosis, monocytosis, and eosinophilia) infection with *E. ewingii* causes neurologic dysfunction and lameness involving one or more limbs, muscular stiffness, a stilted gait, reluctance to rise, an arched back posture, and joint swelling and pain.[11,12] Polyarthritis or meningoencephalitis, characterized by a predominantly neutrophilic inflammatory response and generally accompanied by fever, is frequently reported. Morulae can be found in joint or CSF and have been observed most frequently in peripheral blood neutrophils from dogs receiving glucocorticoid or cancer chemotherapeutic drugs. Although the importance of this clinical observation is unclear, it may suggest that chronically infected dogs develop ehrlichiemia if immunosuppressed or that immunosuppression potentiates morulae development during an acute infection. Asymptomatic infections with *E. ewingii* have been documented with PCR testing.[11,12]

In addition to clinical signs that may be suggestive of ehrlichiosis, severe laboratory abnormalities can contribute to the index of suspicion for the disease.[13,14] Hematologic abnormalities including pancytopenia, aplastic anemia, neutropenia, or thrombocytopenia, would be consistent with canine ehrlichiosis. Thrombocytopenia is the most consistent hematologic abnormality in both the acute and chronic stages of ehrlichiosis.[14,15] However, after experimental infection, platelet numbers are frequently in the low laboratory reference range. Pancytopenia is documented in less than 25% of dogs in retrospective clinical studies. Profound lymphocytosis, accompanied by atypical or reactive lymphocytes, has been associated with ehrlichiosis. Because *E. canis* causes defective platelet function, bleeding can be detected in dogs with normal, increased, or mildly suppressed platelet counts. Moncytic morula in peripheral blood smears or buffy coat smears is consistent with a diagnosis of *E. canis* or *E. chaffeensis,* whereas neutrophilic morulae are consistent with a diagnosis of *E. ewingii*, which has been most frequently described in dogs in Missouri, Oklahoma, Tennessee, North Carolina, and Virginia. Anemia, if present, will vary in degree of severity among affected dogs. Positive Coombs' tests suggest that immune damage, due to circulating erythrocyte antibodies, can contribute to an acute hemolytic crisis in some dogs with ehrlichiosis. In this situation, a regenerative anemia may be encountered; however, a nonregenerative anemia is most frequently documented in chronically infected dogs. Although highly variable, bone marrow examination usually reveals a hypocellular marrow with varying degrees of suppression of the erythroid, myeloid, and megakaryocytic series. Hyperplasia of the bone marrow, especially megakaryocytic hyperplasia, occurs during the acute phase of the disease. Although encountered in other chronic inflammatory diseases, plasmacytosis is a frequently reported bone marrow finding in ehrlichiosis.

Serum proteins are increased above expected values in approximately 50% to 75% of *E. canis* seropositive dogs.[13] Hyperglobulinemia is characterized by increased beta or gamma globulins (or both). Serum protein electrophoresis may reveal a polyclonal or monoclonal gammopathy. A monoclonal gammopathy, in association with severe bone marrow plasmacytosis, could be easily misdiagnosed as a plasma cell myeloma or, when found in association with lymphocytosis, misdiagnosed as lymphocytic leukemia. Hypoalbuminemia occurs in association with protein-losing nephropathy (PLN) or a reciprocal decrease in albumin associated with hyperglobulinemia. Experimentally, a transient, spontaneously reversible PLN associated with ultrastructural glomerular damage occurs 2 to 5 weeks postinoculation. In the chronic disease phase, *E. canis* can induce a severe PLN most likely related to immune complex glomerulonephritis. Less frequently encountered laboratory abnormalities include azotemia, and increased serum alanine aminotransferase and alkaline phosphatase activities, and increased total bilirubin.

Diagnosis of ehrlichiosis requires visualization of morulae, detection of *E. canis* antibodies, or PCR amplification of *E. canis*, *E. chaffeensis*, or *E. ewingii* DNA.[16–19] The IFA technique, dot enzyme-linked immunosorbent assay (ELISA) test, or recombinant ELISA test is available for detection of *Ehrlichia* species antibodies.[16–18] Due to cross-reactivity to immunoreactive proteins, most dogs infected with *E. canis* or *E. chaffeensis* will have positive IFA or ELISA test results, whereas less than half of the dogs infected with *E. ewingii* will have measurable cross-reacting antibodies.[12] Although interlaboratory variation in serologic results occurs due to interpretation error, the IFA test for *E. canis* is highly sensitive. Serologic cross-reaction has not been reported in association with *R. rickettsii, B. canis*, *A. platys*, or *A. phagocytophilum*. A positive titer is considered indicative of infection, because most experimentally infected dogs become seronegative within 6 to 9 months after effective treatment, whereas untreated dogs remain seropositive. Infection with *E. canis* does not infer protective immunity; therefore subsequent exposure to infected ticks after treatment will result in disease recurrence, generally of decreased severity. After antibiotic treatment some dogs become asymptomatic but maintain high *E. canis* antibody titers for years.[20] Clinically, dogs are assumed to have eliminated the infection with an *Ehrlichia* spp. if hyperglobulinemia resolves progressively after treatment or if *Ehrlichia* spp. DNA cannot be amplified from EDTA blood samples.

Infrequently, a dog maintains a high antibody titer or a hematologic abnormality such as thrombocytopenia persists for years after antibiotic therapy.[21] Although it is unclear whether these dogs are chronically infected with *E. canis*, infected with other pathogens, or if the persistent hematologic abnormalities are mediated through altered immunoregulation induced by the organism, little evidence exists to support antimicrobial resistance among *Ehrlichia* spp. that leads to persistent infection. Increasingly, PCR is becoming an important clinical diagnostic tool to differentiate the infecting *Ehrlichia* spp. and to determine if treatment has effectively eliminated the infection.[17,19] In dogs with persistently high *E. canis* antibody titers, PCR testing is indicated, preferably when antibiotics are not being administered.

Tetracycline (22 mg/kg three times a day for 21 days) or doxycycline (5 mg/kg twice a day for 21 days) are currently recommended for treatment of canine ehrlichiosis.[21,22] Experimentally, enrofloxacin will suppress the infection and may result in clinical and hematologic improvement but does not eliminate the infection.[23] Although imidocarb dipropionate has gained clinical acceptance in some endemic regions for treating severe, chronic, or presumed refractory cases of ehrlichiosis, lack of efficacy has been demonstrated in treating some dogs with ehrlichiosis.[22] Clinical improvement may be observed with penicillin or sulfonamides, but the response is variable and infection generally persists.

The short-term prognosis for canine ehrlichiosis is generally good. Dramatic clinical improvement usually occurs within 24 to 48 hours after initiation of tetracycline or doxycycline in dogs with acute-phase or mild chronic-phase disease. Following treatment, rapid clinical improvement is frequently noted in chronically infected dogs; however, periods up to a year may be necessary for complete hematologic recovery. The long-term prognosis is variable, potentially related to failure to diagnose concurrent infections.[24] Continuous or long-term administration of antibiotics, such as tetracycline, has apparently contributed to delayed hematologic recovery in dogs with obvious clinical improvement. Hemorrhage or concurrent infection may contribute to death of chronically infected dogs, despite the initiation of tetracycline therapy. The duration of doxycycline treatment for chronically affected dogs or those with severe pancytopenia or aplastic anemia remains controversial. Supportive therapy, including fluids, blood transfusion, vitamins, and anabolic steroids is required in some dogs. Long-term tetracycline prophylaxis (6.6 mg/kg once daily), repositol oxytetracycline (200 mg intramuscularly [IM] twice weekly), and topically applied acaracides have been used in military working dogs to prevent *E. canis* infection in highly endemic regions. This approach may be appropriate for recurrent infections in kennels if tick control measures are of limited effectiveness. Because of extensive dog transport and chronic asymptomatic *E. canis* infection, the establishment of new endemic foci in previously naive regions is possible. Tick control measures are very important but may not always provide an effective means to prevent infection with an *Ehrlichia* spp.[25] No vaccine is currently available.

It appears that most *Ehrlichia* spp. are capable of infecting people; however, for various reasons dogs play a seemingly minor role in the acquisition of human infections. Early reports suggested that nonhuman primates could be infected with *E. canis* and, more recently, an organism genetically related to *E. canis* was isolated from a veterinarian in Venezuela.[26] Both *E. chaffeensis* and *E. ewingii* can cause serious disease manifestations in people, including meningoencephalitis, acute renal failure, and acute respiratory failure.[27,28]

166.5 CANINE ANAPLASMOSIS

In endemic regions, *Ixodes scapularis*, *I. pacificus*, or *I. ricinus* (Europe) transmit *Anaplasma phagocytophilum* to cats, dogs, sheep, horses and human beings.[29] Numerous species of small rodents, including *Peromyscus leucopus*, the white-footed mouse, serve as reservoirs for the organism in nature.[30] Infection has also been documented in

numerous species of wild and domestic animals. California, Minnesota, Wisconsin, and several New England states (areas endemic for *I. scapularis* or *I. pacificus*) report a particularly high prevalence of infection, generally in dogs, horses, and human beings. Fever, lethargy, and a reluctance to move, accompanied by lymphopenia, thrombocytopenia, elevated serum alkaline phosphatase and amylase activities, and hypoalbuminemia are the most common clinical abnormalities reported in dogs. In the Northeast and North Central United States, acute disease occurs most frequently in the fall months during the period that adult *I. scapularis* ticks are active. Granulocytic morulae can be found within neutrophils and acute and convalescent serology is recommended to document seroconversion to *A. phagocytophilum* antigens in acutely ill dogs, cats, or horses. Infection with *A. phagocytophilum* can also be confirmed by PCR. Both ELISA and IFA tests using *E. canis* antigens will in most instances not detect cross-reacting antibodies in dogs with anaplasmosis. Therapeutically, tetracycline hydrochloride or doxycycline elicit rapid improvement in clinical status. The extent to which *A. phagocytophilum* induces chronic infection in dogs in North America is unclear; however, in Sweden, chronic infection with *A. phagocytophila* has been documented in experimentally infected dogs for up to 6 months after infection.[31] Administration of corticosteroids facilitated the detection of neutrophilic inclusions.

166.6 CANINE CYCLIC THROMBOCYTOPENIA

Canine cyclic thrombocytopenia is caused by *A. platys*, a bacterial organism that replicates only in platelets.[32,33] The mode of *A. platys* transmission is presumed to be by tick vector, but experimentally, *Rhipicephalus sanguineous*, the vector for *E. canis*, did not transmit *A. platys* infection. In the United States, *A. platys* is generally considered to be minimally pathogenic, and is usually recognized as an incidental observation during blood smear examination. The distribution of *A. platys* infection in the United States has not been established; however, most reports have originated from the South and Southeast, with occasional reports from the North and North Central portion of the country. With the exception of a single case report of uveitis, naturally occurring and experimental infections have not been associated with clinical signs. Similar to anaplasmosis in cattle, *A. platys* causes cyclic bacteremia, accompanied by thrombocytopenia, at approximately 10 to 14 day intervals. At its nadir, thrombocytopenia can be severe (20,000 to 50,000 platelets/µl), and platelets are hypoaggregatable. A mild normocytic, normochromic, nonregenerative anemia, leukopenia, hypoalbuminemia, and hyperglobulinemia, has been reported in association with experimental *A. platys* infection. On Giemsa-stained blood smears, *A. platys* appears as single or less frequently multiple basophilic inclusions within platelets. The duration of infection in untreated dogs has not been clearly established.

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Diagnosis of *A. platys* requires visualization of platelet inclusions, detection of serum antibodies by indirect immunofluorescence, or PCR amplification. Sera from *A. platys*–infected dogs does not cross-react serologically with *E. canis, A. phagocytophilum*, or *N. risticii* antigens. Antibodies appear in the serum 2 to 3 weeks after experimental infection and are usually detectable during the initial thrombocytopenic episode. In a study of thrombocytopenic and healthy kennel dogs in Louisiana, seroprevalence to *A. platys* was 40.7% in the thrombocytopenic group and 54.2% in healthy kennel dogs. *Anaplasma platys* morulae were detected in only one of the thrombocytopenic dogs. These results suggest that exposure to *A. platys* in southern states is extensive, and that premunition most probably develops after several cycles of thrombocytopenia. Coinfection with *E. canis* and *A. platys* is common, and it has been theorized that *A. platys* infection might intensify the clinical course of canine ehrlichiosis.

Treatment with oral tetracycline (22 mg/kg every 8 hours for 14 days), or presumably doxycycline (5 mg/kg every 12 hours for 14 days), should eliminate the organism. Because experimental studies have not identified abnormal clinical signs associated with *A. platys* infection, caution should be exercised in ascribing clinical illness to *A. platys*. In such cases, other infectious and noninfectious causes of thrombocytopenia should be pursued diagnostically.

166.7 NEORICKETTSIA RISTICII

In 1994, Kakoma and colleagues reported serologic evidence of over 100 cases of "atypical canine ehrlichiosis" with 3 fatalities.[34] These dogs were not seroreactive to *E. canis* antigens by IFA but were reactive to *N. risticii* antigens at generally low antibody titers. *Neorickettsia risticii* is the cause of Potomac horse fever.[35] Serum samples in this study were derived from California, Texas, Arizona, Illinois, Washington, Florida, and Michigan. Isolates obtained from 3 dogs were morphologically and genetically (based on partial 16S rRNA gene sequence) indistinguishable from *N. risticii*.[34] Successful experimental transmission of a dog isolate has not been reported. Clinical abnormalities, described for 6 dogs, included lethargy, vague signs of abdominal discomfort with intermittent vomiting, persistent bleeding or petechial hemorrhages, polyarthritis, dependent edema, and posterior paralysis. Hematologic abnormalities were variably present and included anemia, thrombocytopenia, prolongation of prothrombin time (PT), and hypercalcemia. Therapy with tetracycline also appears to be variably efficacious for treatment of this infection, with substantial improvement in some dogs and a complete lack of response in other dogs. The authors propose that pending additional research, the canine isolate be referred to as *N. risticii* subsp. *atypicalis*. The definitive pathophysiologic characterization of this organism as a cause of disease in dogs awaits additional study.

166.8 FELINE EHRLICHIOSIS, ANAPLASMOSIS, AND NEORICKETTSIOES

Morulae-like inclusion bodies have been observed in monocytes, lymphocytes, or granulocytes of cats living in Kenya, France, Sweden, and the Northeastern, Midwestern and Western United States.[36–38] Antibody reactivity to *E. canis* or *N. risticii* antigens has also been reported.[38] Although the precise clinical significance of these observations awaits the results of future studies, it seems probable that cats can be infected by one or more members of the genus *Ehrlichia*, *Anaplasma*, and *Neorickettsia*. Experimentally, inoculation of cats with *A. phagocytophilum* resulted in asymptomatic infection, or mild fever and depression, and the development of neutrophilic and eosinophilic morulae. Recently, several laboratories have amplified *A. phagocytophila* DNA from the blood of acutely ill cats with fever, lethargy, inappetence, and thrombocytopenia.[37,39] These feline cases have been identified in geographic regions that are endemic for canine, equine, or human anaplasmosis.

Anorexia, loss of body condition, fever, splenomegaly, lymphadenopathy, normocytic normochromic anemia, radiographic evidence of interstitial lung disease, and mononuclear intracytoplasmic inclusions typical of the genus *Ehrlichia* were described in three cats from Kenya. Neutropenia and hyperglobulinemia were each reported in one cat. These cats were infested with *Haemaphysalis laechi* ticks. Resolution of disease signs was reported after treatment with either tetracycline hydrochloride or imidocarb dipropionate. Intracytoplasmic inclusions resembling morulae have been observed during cytologic evaluation of a lymph node aspirate from a cyclically febrile, anorexic cat from Colorado. Laboratory abnormalities included a normocytic normochromic nonregenerative anemia, hyperglobulinemia, and pyogranulomatous lymphadenitis. Serum immunoglobulin G (IgG) antibodies to *E. canis* antigen were detected, and the cat responded rapidly to doxycycline despite a previous lack of response to several other antibiotics. Serologic evidence of ehrlichiosis was reported in 12 sick cats with clinical and laboratory abnormalities including fever, malaise, weight loss, anorexia lymphadenopathy, nonseptic suppurative polyarthritis, anemia, thrombocytopenia, neutropenia, and polyclonal or monoclonal gammopathy.[36,38] Each of these cats responded favorably to doxycycline. Based upon PCR amplification and DNA sequencing, *E. canis*-like infection has been reported in cats from the United States, Canada, and France.[40,41] Consistent with previous reports, these cats had polyarthritis or bone marrow suppression accompanied by anemia, thrombocytopenia or pancytopenia. However, despite chronic illness and the detection of

antinuclear antibodies (ANAs), IFA testing using *E. canis* antigens was negative. Antibody reactivity (IFA and Western immunoblot) to *N. risticii* antigens was described in five cats from California.[38] Hematologic abnormalities included leukopenia, anemia, and thrombocytopenia. All attempts to isolate, transmit, or detect *E. risticii* by PCR were unsuccessful. Additional studies are needed to isolate and genetically characterize feline *Ehrlichia*, *Anaplasma*, and *Neorickettsia* organisms to clarify further the pathogenic importance of these organisms in cats.

166.9 COINFECTION WITH MULTIPLE TICK-TRANSMITTED PATHOGENS

Recent serologic and PCR evidence indicates that coinfection with *Ehrlichia, Babesia, Rickettsia,* and *Bartonella* spp. occurs more frequently in dogs than previously realized.[42–45] The extent to which infection with multiple organisms complicates the clinical, diagnostic, and therapeutic features that would be anticipated if a dog were infected with only one organism is not clear. In general, coinfection should be considered in dogs with unusually severe clinical presentations. For example, infection with *Bartonella* in dogs concurrently infected with *Ehrlichia canis* may contribute to the tendency to develop epistaxis. Recent observations also illustrate the difficulty in attributing causation to a single organism in dogs or people coinfected with multiple tick-transmitted pathogens.[45] As certain *Borrelia*, *Ehrlichia*, *Babesia*, and *Bartonella* spp. can cause chronic, insidious infection in dogs, the relative role of each organism to the pathogenesis of specific disease manifestations in a sick, naturally infected dog will remain difficult to establish. From an evolutionary perspective, it is obvious that vectors, vector-borne intracellular organisms, and animal and human hosts have developed a highly adapted form of interaction. In general, vectors need blood for nutrition; the bacterial, rickettsial, and protozoal organisms need an intracellular environment to survive; immunologically, most hosts appear to be able to support chronic infection with many vector-borne organisms for months to years without obvious deleterious effects. Certainly more recent evidence indicates that clinicians should screen for a panel of intracellular pathogens when dealing with sick dogs with a history of tick and flea exposure. This same evidence emphasizes the importance of strategies to control ticks and fleas on dogs and cats.

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166.10 References

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167 CHAPTER • 167 Canine Bartonellosis

Edward B. Breitschwerdt

B*artonella* species are fastidious gram-negative bacteria that are highly adapted to a mammalian reservoir host and within which the bacteria usually cause a long-lasting intraerythrocytic bacteremia.[1,2] In the natural host, chronic bacteremia with a *Bartonella* species can frequently be detected by culture or PCR in seemingly healthy individuals. Until recently, mechanisms that facilitate persistent *Bartonella* bacteremia in mammals were not well understood. Recent studies, have identified an intraerythrocytic localization for these bacteria, which is a unique strategy for bacterial persistence.[1–6] Nonhemolytic intracellular colonization of erythrocytes would preserve the organisms for efficient vector transmission, protect *Bartonella* from the host immune response, and potentially contribute to decreased antimicrobial efficacy.[3] *Bartonella* spp. are an important cause of bacillary angiomatosis, peliosis hepatis, fever of unknown origin, endocarditis, granulomatous hepatitis, and a rapidly expanding spectrum of less frequently diagnosed medical conditions in people.[7–9]

Bartonella vinsonii (*berkhoffii*) was isolated from a dog with endocarditis in 1993.[10,11] Retrospectively, long-term administration of immunosuppressive doses of corticosteroids for a presumptive diagnosis of systemic lupus erythematosus (SLE) may have facilitated the isolation of *B. vinsonii (berkhoffii)* from this dog. Subsequent attempts to isolate *B. vinsonii* from immunocompetent dogs with serologic or molecular evidence of *Bartonella* infection have not been successful in most instances. When using the currently recommended microbiologic techniques, there appears to be considerable variation in the degree of difficulty associated with the isolation of different *Bartonella* spp. from the blood of different animal species. *Bartonella vinsonii (berkhoffii)* is difficult to isolate, as compared with the relative ease of isolating *B. henselae* from the blood of infected cats. For this reason, sensitive molecular-based detection methods are proving to be diagnostically useful.

167.1 SEROPREVALENCE

Due to the relatively recent recognition that dogs can be infected with *B. vinsonii (berkhoffii)* and potentially other *Bartonella* spp., seroprevalence data is limited.[12–15] Seroprevalence was determined in 1920 sick dogs from North Carolina or surrounding states that were evaluated at a veterinary teaching hospital.[12] Using a reciprocal titer of greater than 64, 3.6% of the dogs had antibodies to *B. vinsonii (berkhoffii)*. Risk factors that could be associated with seroreactivity included heavy tick exposure (odds ratio, 14.2), cattle exposure (odds ratio, 9.3), rural versus urban environment (odds ratio, 7.1), and heavy flea exposure (odds ratio, 5.6). These data were interpreted to support the possibility that exposure to *B. vinsonii (berkhoffii)* was more likely in dogs in rural environments that were allowed to roam and were likely to have a history of heavy tick infestation. Using sera from dogs experimentally infected with *R. rickettsii* or *Ehrlichia canis*, cross reactivity to *Bartonella* antigens was not detected. However, 36% and 52% of serum samples derived from dogs naturally infected with *E. canis* or *B. canis* were reactive to *B. vinsonii* antigens. Because both *E. canis* and *B. canis* are transmitted by *Rhipicephalus sanguineous*, this tick may be involved in the transmission of *B. vinsonii*. The possibility of tick transmission was further supported by two additional studies involving dogs infected with one or more *Ehrlichia* spp. from the same geographic region, in which seroreactivity to *B. vinsonii (berkhoffii)* antigens was 30% and 89%, respectively.[16,17] Seroprevalence, using *B. vinsonii (berkhoffii)* antigens, was 10% (4 of 40 dogs) in dogs with suspected tick-borne illness from Israel and 36% in dogs with fever and thrombocytopenia from Thailand.[15,18] Using an ELISA assay, 35% of 869 samples (derived from coyotes in California) contained antibodies to *B. vinsonii (berkhoffii)* antigens.[19] These data suggest that *B. vinsonii (berkhoffii)* is distributed throughout the world.

167.2 DISEASE MANIFESTATIONS

The spectrum of disease associated with *Bartonella* infection in dogs and most other animal species is currently unknown. Endocarditis, caused by *B. vinsonii (berkhoffii)*, occurs in large breed dogs with a potential predisposition for aortic valve involvement.[10,20,21] Intermittent lameness, bone pain or fever of unknown origin (FUO) can precede the diagnosis of endocarditis by several months. Multifocal areas of severe myocardial inflammation can be found in some dogs with *B. vinsonii* endocarditis. Recently *B. vinsonii (berkhoffii)*, originally isolated from a dog, was isolated from a human endocarditis patient.[22] Considering these preliminary observations, derived from naturally infected dogs and people, the role of *Bartonella* spp. as a cause of myocarditis in companion animals deserves additional research consideration.

Bartonella-induced granulomatous lymphadenitis, involving the left submandibular lymph node, was diagnosed in a dog on the basis seroreactivity to *B. vinsonii (berkhoffii)* antigens, visualization of Warthin-Starry silver staining bacteria within the lymph node, and PCR amplification followed by Southern blot hybridization.[23] Seven days prior to enlargement of the lymph node, the owners removed an engorged tick from the left ear. This case may be illustrative of a clinical presentation that is analogous to acute bartonellosis (cat scratch disease) in people, where a scratch or bite injects the inoculum, as compared with direct inoculation by the bite of a tick.

Based on recently obtained serologic evidence in dogs, *B. vinsonii (berkhoffii)* or closely related *Bartonella* species appear to contribute to the development of dermatologic lesions indicative of a cutaneous vasculitis, anterior uveitis, polyarthritis, meningoencephalitis, and immune-mediated hemolytic anemia.[24] Thrombocytopenia is found in approximately half of the dogs with disease manifestations. Eosinophilia is also found in approximately one third of infected dogs.

Based upon current evidence, *B. vinsonii (berkhoffii)* is considered the most frequent *Bartonella* species that causes disease in dogs. However, this conclusion may not be accurate, because sera from dogs have not been screened systematically against a large panel of *Bartonella* species antigens. Studies from Hawaii, the United Kingdom, and Japan identified *B. henselae* seroprevalences of 6.5% (2 of 31 dogs), 3.0% (3 of 100 dogs), and 7.7% (4 of 52 dogs).[25–27] However, it is becoming increasingly clear that other *Bartonella* species can infect dogs. For example, *B. henselae* was amplified and sequenced on two independent occasions from the liver of a dog with peliosis hepatis.[28] This is a unique pathologic lesion that is induced only by *B. henselae* infection in people.[1,8] Recently, *B. henselae* DNA was amplified from a dog with granulomatous hepatitis, a histopathologic lesion that is reported with some frequency in children infected with *B. henselae*.[29] Similarly, *B. clarridgeae* was cultured, and DNA was amplified from the aortic valve of a dog with vegetative valvular endocarditis.[21] *Bartonella clarridgeae* was also amplified and sequenced from the liver of a Doberman pincher with copper storage disease.[29] *Bartonella elizabethae*, a species that infects rodents, was PCR amplified and sequenced from an ethylenediamine tetra-acetic acid (EDTA) blood sample obtained from a dog that had experienced chronic weight loss culminating in sudden unexplained death.[30] The clinical importance of these observations, particularly as relates to causation, is unknown. However, although presumably infrequent, *Bartonella* spp. that frequently infect cats or rodents and are transmitted by fleas among reservoir hosts, may occasionally be found in dogs with disease manifestations.

167.3 DIAGNOSTIC CONSIDERATIONS

Thrombocytopenia, anemia (which frequently can be immune-mediated), and neutrophilic leukocytosis are the most commonly detected hematologic abnormalities. Monocytosis and eosinophilia can also occur in *B. vinsonii*–infected dogs. During a 149-day study, after experimental inoculation of SPF dogs with culture grown *B. vinsonii (berkhoffii)*, there was sustained suppression of peripheral blood CD8+ lymphocytes, accompanied by an altered cell surface phenotype and an increase in CD4+ lymphocytes in the peripheral lymph nodes.[31] Therefore infection with *B. vinsonii (berkhoffii)* could induce a degree of chronic immunosuppression that might predispose to secondary infections and result in a wide array of clinical manifestations in dogs naturally infected with *Bartonella* species. Because blood culture is insensitive, serology and PCR amplification of *Bartonella* DNA are the mainstays of diagnosis. As seroprevalence to *B. vinsonii (berkhoffii)* antigens is infrequently detected (<4%) in sick dog populations in endemic regions, detection of antibodies in a sick dog provides strong clinical evidence for prior exposure and potentially active infection. For this reason, treatment of seroreactive dogs is recommended. A reciprocal titer of 64 or greater is considered indicative of prior exposure to or active infection with *B. vinsonii (berkhoffii)*. Testing against other *Bartonella* spp. antigens, such as *B. henselae,* may prove to be of clinical use in the future.

167.4 TREATMENT

To date, an optimal protocol has not been established for the treatment of *Bartonella* infections in cats, dogs, or people.[32,33] Regardless of the antibiotic used for treatment, a long duration of antibiotic administration (4 to 6 weeks) may be necessary to eliminate the infection. Macrolides (erythromycin, azithromycin) most probably represent the oral antibiotic class of choice for treating *Bartonella* infections.[32,33] Fluoroquinolones alone (or in combination with amoxicillin) have also elicited a positive therapeutic response in dogs, which is accompanied by a progressive decrease in *B. vinsonii* antibody titers.[24] Doxycycline may be effective for treatment of *B. vinsonii (berkhoffii)* in dogs, but data from cats experimentally or naturally infected with *B. henselae* or *B. clarridgeae* indicates that a high dose (10 mg/kg every 12 hours) for 4 to 6 weeks may be necessary to eliminate *Bartonella* infection in dogs, cats, or other animal species.[34] Recently, retrospective analysis of the treatment of human *Bartonella* endocarditis identified a more favorable outcome if an aminoglycoside was prescribed for a minimum of 2 weeks.[35] In those situations in which *Bartonella* infection poses serious risk in dogs, such as endocarditis, myocarditis, or meningoencephalitis, use of an aminoglycoside may be warranted.

167.5 PREVENTION

Increasingly, veterinarians play an important role in advising the public as to the epidemiologic and zoonotic implications of vector-borne pathogens. Nondomestic animals frequently serve as the primary reservoir for *Bartonella* species. For example, the coyote appears to be an important reservoir host for *B. vinsonii (berkhoffii)*.[36] Although somewhat circumstantial, increasing evidence suggests that *Bartonella* species can be transmitted by fleas and ticks to cats, dogs, or human beings.[12,23,37] Therefore minimizing or eliminating flea and tick exposure is perhaps of greater public health importance today than during any previous time. When rigorous flea and tick control measures are instituted, it is highly probable that transmission of *Bartonella* species will be greatly reduced or eliminated.[38]

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168 CHAPTER • 168 Protozoal and Miscellaneous Infections

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Multiple pathogenic protozoans infect dogs and cats. The group can be divided into amoeba, ciliates, coccidians, flagellates, Microspora, and Piroplasmia. Protozoans generally cause gastrointestinal (GI) tract disease (enteric protozoans), polysystemic disease, or in the case of *Toxoplasma gondii*, both enteric and polysystemic disease.

168.1 ENTERIC PROTOZOAL DISEASES

The most common protozoal agents infecting the GI tract of dogs and cats are *Giardia* spp., *Cryptosporidium* spp., *Cystoisospora* spp., *Sarcocystis* spp., *Besnoitia* spp., *Hammondia* spp., *T. gondii*, *Neospora caninum*, *Entamoeba histolytica*, *Balantidium coli*, and *Tritrichomonas foetus*.[1–3] *Giardia* and *T. foetus* are flagellates, *Cystoisospora* spp., *Sarcocystis* spp., *Besnoitia* spp., *Hammondia* spp., *N. caninum*, *T. gondii*, and *C. parvum* are coccidians, *B. coli* is a ciliate, and *E. histolytica* is an amoeba. *Cystoisospora* spp., *Sarcocystis* spp., *Besnoitia* spp., *Hammondia* spp., *N. caninum*, and *T. gondii* only complete the intestinal cycle in one species. Some isolates of *Cryptosporidium* spp., *Giardia* spp., *E. histolytica*, and *B. coli* will replicate in multiple warm-blooded vertebrates and therefore can potentially be zoonotic.

Fecal oral transmission occurs with all the enteric protozoans. The coccidians produce oocysts. *Cryptosporidium* spp. oocysts are immediately infectious when passed by the host; *T. gondii*, *N. caninum,* and *Cystoisospora* spp. must sporulate outside the host to be infectious. Both trophozoites and cysts of *Giardia* spp. are potentially infectious; however, transmission occurs most frequently after ingestion of cysts because gastric secretions generally kill trophozoites. Ingestion of the organism in the tissues of transport hosts can also result in infection by *Cystoisospora* spp., *Besnoitia* spp., *Hammondia* spp., *N. caninum*, and *T. gondii*. Carnivorism can result in infection by *Cryptosporidium* spp., *Giardia* spp., *E. histolytica*, and *B. coli* if the organisms are present in the intestines of the prey species. Infections can be self-limiting for each of the agents; however, with the exception of *T. gondii,* fecal shedding periods are variable. After tissue cyst ingestion, infected cats rarely shed oocysts of *T. gondii* for more than 2 weeks.[4]

The enteric protozoans have worldwide distribution. Because they are maintained in nature primarily by fecal-oral transmission, more cases are associated with crowded and unsanitary environments. In general, *Giardia* spp., *T. gondii*, *Cystoisospora*, and *Cryptosporidium* spp., *T. foetus* (cats) infections are common in the United States; *E. histolytica*, *B. coli*, and infections are rare. Antibodies against *T. gondii* (40%) and *Cryptosporidium* spp. (8.3%) are commonly detected in serum from client-owned cats, suggesting that exposure is common.[4,5] Prevalence of the agents varies by region in coprologic studies.

Pathogenic mechanisms have not been ascertained for each of the enteric protozoans. *Cystoisospora* spp. and *T. gondii* replicate in intestinal cells and may result in clinical illness from cell destruction. Tissue invasion also can occur with *E. histolytica*.[6,7] *Giardia* spp. and *Cryptosporidium* spp. are found on the surface of enterocytes, so pathogenesis is unlikely secondary to direct cell damage. Some of the pathogenic mechanisms proposed for these enteric agents include production of toxins, disruption of normal flora, induction of inflammatory bowel disease (IBD), inhibition of normal enterocyte enzymatic function, blunting of microvilli, and induction of motility disorders. *Cystoisospora* spp. generally are only pathogens resulting in clinical disease in puppies or kittens, and *Sarcocytis* spp., *Besnoitia* spp., and *Hammondia* spp. are almost never pathogenic in dogs or cats. All other enteric protozoans can cause disease regardless of age. Clinical disease is more common, and duration of organism

shedding into the environment may be prolonged in dogs and cats with immunodeficiency inducing concurrent diseases.

Owner concerns in dogs or cats with enteric protozoal infections generally are vomiting, inappetence, or diarrhea; fever is uncommon. *Giardia* spp., *Cryptosporidium* spp., and *T. gondii* infections are most commonly associated with small-bowel diarrhea; *E. histolytica*, *B. coli*, and *T. foetus* infections are most commonly associated with large-bowel diarrhea. *Cystoisospora* spp. infections can cause clinical signs of large or small-bowel diarrhea. Physical examination findings in dogs or cats with enteric protozoal infections are nonspecific but can include abdominal discomfort, increased gas or fluid in the intestinal tract, or thickened intestinal loops.

All dogs and cats with large, small, or mixed bowel diarrhea should be assessed for enteric protozoal infections. Diagnosis of GI protozoal infection is based primarily on documentation of oocysts, trophozoites, or cysts on direct fecal examination or fecal flotation.

A direct smear of diarrheic stool can be used to examine for trophozoites of *E. histolytica*, *B. coli*, *T. foetus*, or *Giardia*. More frequently, a small quantity of fresh feces or mucous is mixed with a drop of 0.9% NaCl on a clean microscope slide and examined at 100X after placing a cover slip. When a motile organism is noted, examining at 400X assesses structural features. Application of a stain like Lugol's solution, methylene blue, or acid methyl green to the wet mount at the edge of the cover slip will aid in visualizing internal structures of protozoa.[8] Trophozoites are rarely found in formed stools. Duodenal aspiration for cytologic examination for *Giardia* trophozoites is effective for the diagnosis of giardiasis in the dog. However, this technique is not effective in the cat because the organism lives in the distal small intestine.

Protozoal cysts or oocysts are best demonstrated after fecal concentration; Sheather's sugar centrifugation and zinc sulfate centrifugation are two techniques commonly used in clinical practice.[8] These solutions are inexpensive and generally effective. Sugar solution is hypertonic and will distort *Giardia* spp. cysts; the cytoplasm is pulled to one side and appears as a half-or quarter-moon. Zinc sulfate centrifugation is considered by some to be the flotation solution of choice for *Giardia* spp. cysts.

Due to small size and limited number in feces of infected dogs and cats, *Cryptosporidium* spp. oocysts are almost never seen when concentrated feces are examined at 100X. Acid-fast staining or fluorescein-labeled monoclonal antibody staining of a fecal smear and fecal antigen testing can aid in the diagnosis of cryptosporidiosis in dogs and cats. Oocysts stain pink with acid-fast stain. A fluorescein-labeled monoclonal antibody system is also available for identification of *Giardia* spp. cysts. Antigens of *Giardia* spp. and *Cryptosporidium* spp. can be detected in feces by enzyme-linked immunosorbent assay (ELISA). However, it is now known that dog-and cat-specific *Giardia* spp. and *Cryptosporidium* spp. exist[9–12]; most currently available tests were titrated using isolates from human feces. A *Gardia* spp. antigen ELISA for veterinary use is currently being evaluated (IDEXX Laboratories, Portland, ME). Thus results of indirect fluorescent antibody (IFA) and antigen assays should be interpreted with results from fecal examination techniques. Polymerase chain reaction (PCR) assays for demonstration of *Giardia* spp., *Cryptosporidium* spp., and *T. foetus* DNA in feces are being studied. In addition, *T. foetus* can be cultured from feces.

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The presence of enteric protozoans in diarrheic stool does not prove that disease was due to the organism. Some enteric protozoans, especially *Giardia* spp., *Cryptosporidium* spp., *T. foetus*, and *Cystoisospora* spp. live chronically in the intestinal tract of normal animals; other conditions causing GI tract disease can induce shedding. Thus animals with enteric protozoal infections that do not respond to therapy should be evaluated for underlying causes of disease. *Giardia* spp., *Cryptosporidium* spp., *Cystoisospora* spp., and *Sarcocystis* spp. are commonly found in animals with normal stools; therefore yearly fecal examinations are indicated in all dogs and cats.

Withholding food for 24 to 48 hours is indicated for animals with acute vomiting or diarrhea. Highly digestible, bland diets are used most frequently if vomiting and small-bowel diarrhea are the primary manifestations of disease. High-fiber diets are generally indicated if large-bowel diarrhea is occurring. Feeding a high-fiber diet may also aid in the treatment of giardiasis due to inhibition of trophozoite attachment to duodenal epithelial cells.

Dogs and cats with *Giardia* spp. infections generally respond clinically to the administration of metronidazole, but infection may not be cleared; this drug may also be effective for dogs infected with *E. histolytica* (Table 168-1). Because dogs or cats with giardiasis could also be infected with these other potentially zoonotic enteric protozoans, metronidazole is a logical primary drug. Metronidazole also helps correct the anaerobic bacterial overgrowth that commonly accompanies giardiasis. If inflammatory changes exist, metronidazole may also be beneficial due to inhibition of lymphocyte function. In a recent study of cats, administration of liquefied metronidazole benzoate for 7 days was 100% effective during the time period studied.[13] Central nervous system (CNS) toxicity occasionally occurs with this drug; it is unlikely if no more than 50 mg/kg is given orally per day.[14,15] Fenbendazole and albendazole are commonly prescribed alternate anti-*Giardia* spp. drugs; albendazole is associated with neutropenia in dogs and cats and so should not be used.[16–19] Furazolidone (cats); paromomycin (dogs or cats); and febantel, pyrantel, and praziquantel (dogs) are other drugs with anti-*Giardia* effects.[20] Lastly, use of the commercially available *Giardia* spp. vaccines as immunotherapy has given variable treatment responses.[21–23] Cats with concurrent diarrhea and *T. foetus* infection will sometimes respond clinically to administration of metronidazole, fenbendazole, or tylosin; however, none of these drugs have eliminated the infection. Cats that fail to respond immediately to treatment often have resolution of diarrhea in approximately 9 months.

Paromomycin, tylosin, and azithromycin have all been used to lessen diarrhea in dogs and cats with cryptosporidiosis, but no treatment has consistently stopped *Cryptosporidium* spp. oocyst shedding.[24,25] The most commonly prescribed drugs to treat *Cystoisospora* spp. infections of dogs and cats are trimethoprim-sulfonamide, sulfadimethoxine, furazolidone, amprolium, or amprolium-sulfadimethoxine. Quinacrine, spiramycin, toltrazuril, and roxithromycin have been used on a limited basis. However, no drug eliminates infection.

Cryptosporidium spp., *T. gondii*, *Giardia*, *E. histolytica*, and *B. coli* are potentially zoonotic. *Entamoeba histolytica* and *B. coli* infections are extremely uncommon, and pets are unlikely sources of human infections. Most people are infected with *Cryptosporidium* spp. or *Giardia* spp. from contaminated food or water, not contact with pets.[26–28] It is now known that *Cryptosporidium* spp. and *Giardia* spp. exist that are specific to people or pets. For example, in one recent study of *C. hominis* of people, the organism failed to infect dogs and cats.[29] In one enzootic area, people were infected with a human *Giardia* and dogs were infected with a dog *Giardia*; cross-infection did not seem to occur.[11] Thus not all *Cryptosporidium* spp. and *Giardia* spp. are zoonotic. However, it is impossible to determine clinically if an individual strain is infectious to people; therefore infected animals should be managed as a potential zoonotic risk. (See the following section for a discussion of *T. gondii* associated zoonotic disease.)

168.2 POLYSYSTEMIC PROTOZOAL DISEASES

The primary protozoans that induce polysystemic disease in dogs and cats are *Acanthomoeba* spp., *Hepatozoon canis*, *Neospora caninum*, *Toxoplasma gondii*, *Leishmania* spp., *Trypanosoma cruzi*, *Cytauxzoon felis*, *Babesia* spp., and *Pneumocystis carinii*.

168.3 COCCIDIANS

168.3.1 Toxoplasmosis

Toxoplasma gondii is one of the most prevalent parasites infecting warm-blooded vertebrates.[4] Only cats complete the coccidian life cycle and pass environmentally resistant oocysts in feces. Dogs can pass oocysts in feces after the ingestion of feline feces.[30] Sporozoites develop in oocysts after 1 to 5 days of exposure to oxygen and appropriate environmental temperature and humidity. Tachyzoites disseminate in blood or lymph during active infection and replicate intracellularly rapidly until the cell is destroyed. Bradyzoites are the slowly dividing, persistent, tissue stage that form in the extraintestinal tissues of infected hosts as immune responses attenuate tachyzoite replication. Tissue cysts form readily in the CNS, muscles, and visceral organs.[4] Infection of warm-blooded vertebrates occurs after ingestion of any of the three life stages of the organism or transplacentally. Most cats are not coprophagic and are usually infected by ingesting *T. gondii* bradyzoites during carnivorous feeding; oocysts are shed in feces from 3 to 21 days. Sporulated oocysts can survive in the environment for months to years and are resistant to most disinfectants. Bradyzoites may persist in tissues for the life of the host. Approximately 30% to 40% of cats and people and 20% of the dogs in the United States are seropositive and therefore presumed to be infected.[4] Prior to 1988 many of the dogs diagnosed with toxoplasmosis based on histologic evaluation were truly infected with *Neospora caninum* (see Neosporosis section).[31]

Clinical disease associated with the intestinal phase of infection is rare. Approximately 10% to 20% of experimentally inoculated cats develop self-limiting, small-bowel diarrhea after primary oral inoculation with *T. gondii* tissue cysts. Detection of *T. gondii* oocysts in feces is rarely reported in studies of naturally exposed cats with diarrhea.

Death in dogs and cats can develop from overwhelming intracellular replication of tachyzoites after primary infection; hepatic, pulmonary, CNS, and pancreatic tissues are commonly involved.[32,33] Transplacentally or lactationally infected kittens develop the most severe signs of extraintestinal toxoplasmosis and generally die of pulmonary or hepatic disease.[34,35]

Common clinical findings in cats with disseminated toxoplasmosis include depression, anorexia, fever followed by hypothermia, peritoneal effusion, icterus, and dyspnea.[32] If a host with chronic toxoplasmosis is immunosuppressed, bradyzoites in tissue cysts can replicate rapidly and disseminate again as tachyzoites. Disseminated toxoplasmosis has been documented in cats concurrently infected with feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), feline infectious peritonitis (FIP) virus, and after renal transplantation.[4]

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Table • 168-1 Drugs Used in the Management of Protozoal and Miscellaneous Diseases

ORGANISM/DRUG NAME	COMMON CANINE DOSE	COMMON FELINE DOSE
Babesia spp.		
Clindamycin hydrochloride	12.5 mg/kg, q12h, for 14 days, PO	NA
Imidocarb dipropionate	5–6.6 mg/kg, q14 days, SC or IM	NA
Metronidazole	25 mg/kg, q8-12h, for 14 days PO	NA
Pentamidine isethionate	15 mg/kg, q24h, daily for 2 days, SC	NA
Balantidium coli		
Metronidazole	10–25 mg/kg, q12h, for 8 days, PO	NA
Tetracycline	22 mg/kg, q8h, for 7–10 days, PO	NA
Cryptosporidium spp.	Unknown	10 mg/kg, q24h, for 7–21 days, PO
Azithromycin	As for cats	10 mg/kg, q24h, for 7–21 days, PO
Paromomycin	As for cats	150 mg/kg, q12-24h, for 5 days, PO
Tylosin	As for cats	10–15 mg/kg, q12h, for 21 days, PO
Cystoisospora spp.		
Trimethoprim-sulfonamide	15–30 mg/kg, q12h, for 5 days, PO	15 mg/kg, q12h, for 5 days, PO
Sulfadimethoxine	50–60 mg/kg, daily, for 5–20 days, PO	50–60 mg/kg, daily, for 5–20 days, PO
Furazolidone	8–20 mg/kg, q12-24h, for 5 days, PO	8–20 mg/kg, q12-24h, for 5 days, PO
Amprolium	300–400 mg, daily, for 5 days	60–100 mg, daily, for 5 days
Paromomycin	As for cats	165 mg/kg, q12h, for 5 days, PO
Cytauxzoon felis		
Buparvaquone	NA	10 mg/kg, q24h, IM or SC
Diminazene	NA	2 mg/kg, q14 days, IM
Imidocarb	NA	2 mg/kg, q14 days, IM
Parvaquone	NA	10–30 mg/kg, q24h, IM or SC
Entamoeba histolytica		
Metronidazole	10–25 mg/kg, q12h, for 8 days, PO	25 mg/kg, q12h, for 7 days, PO
Giardia spp.		
Fenbendazole	50 mg/kg, q24h, for 3–7 days, PO	50 mg/kg, q24h, for 3–7 days, PO
Giardia vaccine	1 dose, q21days, for 2–3 inoculations	1 dose, q21days, for 2–3 inoculations
Metronidazole	10–25 mg/kg, q12h, for 8 days, PO	25 mg/kg, q12h, for 7 days, PO
Praziquantel, pyrantel and febantel	Daily PO for 3 days	NA
Hepatozoon americanum		
Clindamycin*	10 mg/kg, q8h, for 2–4 weeks, PO	NA
Decoquinate*	10 to 20 mg/kg, q12h, for life, PO	NA
Pyrimethamine*	0.25 mg/kg, q24h, for 2–4 weeks, PO	NA
Trimethoprim-sulfadiazine*	15 mg/kg, q12h, for 2–4 weeks, PO	NA
Imidocarb dipropionate	5–6 mg/kg, q14 days, IM or SQ	NA
Leishmania spp.		
Allopurinol	15 mg/kg, q12h, for months, PO	NA
Amphotericin B	3.0–3.3 mg/kg, q48h, 3–5 times, IV	NA
Meglumine antimonite	100 mg/kg, q24h, IV, IM, SC	NA
Sodium stibogluconate	30–50 mg/kg, q24h, IV, SC	
Neospora caninum		
Clindamycin*	10 mg/kg, q8h, for 4 weeks, PO	NA
Pyrimethamine*	1 mg/kg, q24h, for 4 weeks, PO	NA
Trimethoprim-sulfadiazine*	15 mg/kg, q12h, for 4 weeks, PO	NA
Pneumocystis carinii		
Pentamidine isethionate	4 mg/kg, q24h, for 2 weeks, IM	NA
Trimethoprim-sulfonamide	15–30 mg/kg, q8-12h, for 2 weeks, PO	NA

Tritrichomonas foetus		
Metronidazole	10–25 mg/kg, q12h, for 8 days, PO	25 mg/kg, q12h, for 7 days, PO
Toxoplasma gondii		
Azithromycin	5–10 mg/kg, q12h, for 5–7 days, PO	7–15 mg/kg, q12h, for 5–7 days, PO
Clindamycin hydrochloride	12.5 mg/kg, q12h, for 28 days, PO, IM	12.5 mg/kg, q12h, for 28 days PO, IM
Pyrimethamine	0.25–0.5 mg/kg, q24h, for 28 days PO	Usually not used due to toxicity
Trimethoprim-sulfonamide	15 mg/kg, q12h, for 28 days, PO	15 mg/kg, q12h, for 28 days, PO

IM, Intramuscular; *IV*, intravenous; *SC*, subcutaneous; *PO*, oral; *NA*, not applicable.

* Used in combination.

Chronic toxoplasmosis occurs in some dogs and cats. *Toxoplasma gondii* infection should be on the differential diagnoses list for cats with anterior or posterior uveitis, fever, muscle hyperesthesia, weight loss, anorexia, seizures, ataxia, icterus, diarrhea, and pancreatitis.[4,36] Based on results of *T. gondii*–specific aqueous humor antibody and PCR studies, toxoplasmosis appears to be a common infectious cause of uveitis in cats.[37,38] Kittens infected transplacentally or lactationally commonly develop ocular disease.[39] Immune complex formation and deposition in tissues and delayed hypersensitivity reactions may be involved in chronic, subfatal clinical toxoplasmosis. Because none of the anti-*Toxoplasma* drugs totally clear the body of the organism, recurrence of disease is common.

In dogs, respiratory, GI, or neuromuscular infection resulting in fever, vomiting, diarrhea, dyspnea, and icterus are most common and occur most frequently in immune-suppressed dogs, such as those with canine distemper virus (CDV) infection or those receiving cyclosporine to prevent rejection of a transplanted kidney.[4,40,41] Neurologic signs are dependent on the location of the primary lesions and include ataxia, seizures, tremors, cranial nerve deficits, paresis, and paralysis. Dogs with myositis have weakness, stiff gait, or muscle wasting. Rapid progression to tetraparesis and paralysis with lower motor neuron dysfunction can occur. Some dogs with suspected neuromuscular toxoplasmosis probably had neosporosis.[31] Myocardial infection resulting in ventricular arrhythmias occurs in some infected dogs. Dyspnea, vomiting, or diarrhea occur in dogs with polysystemic disease. Retinitis, anterior uveitis, iridocyclitis, and optic neuritis occur in some dogs with toxoplasmosis but are less common than in the cat.

Dogs or cats with clinical toxoplasmosis can have a variety of clinicopathologic and radiographic abnormalities but none document the disease. Nonregenerative anemia, neutrophilic leukocytosis, lymphocytosis, monocytosis, neutropenia, eosinophilia, proteinuria, bilirubinuria, increases in serum proteins and bilirubin concentration, as well as creatinine kinase, alanine aminotransferase, alkaline phosphatase, and lipase activity occurs in some animals.[4] Pulmonary toxoplasmosis most commonly causes diffuse interstitial to alveolar patterns or pleural effusion.[42] Cerebrospinal fluid (CSF) protein concentrations and cell counts are often higher than normal. The predominant white blood cells (WBCs) in CSF are small mononuclear cells, but neutrophils also are commonly found.

The antemortem definitive diagnosis of toxoplasmosis can be made if the organism is demonstrated; however, this is uncommon. Bradyzoites or tachyzoites are rarely detected in tissues, effusions, bronchoalveolar lavage fluids, aqueous humor, or CSF. Detection of 10 × 12 μm oocysts in feces in cats with diarrhea suggests toxoplasmosis but is not definitive, because *Besnoitia* and *Hammondia* infections of cats produce morphologically similar oocysts.

Toxoplasma gondii–specific antibodies (dogs or cats), antigens (cats), immune complexes (cats), and DNA (cats) can be detected in the blood of normal animals, as well as in those with clinical signs of disease; therefore it is impossible to make an antemortem diagnosis of clinical toxoplasmosis based on these tests alone.[4,37,38,43]

Of the serum tests, IgM correlates the best with clinical toxoplasmosis because this antibody class is rarely detected in serum of healthy animals. The antemortem diagnosis of clinical toxoplasmosis can be tentatively based on the combination of the following:

- Demonstration of antibodies in serum that documents exposure to *T. gondii*
- Demonstration of an IgM titer greater than 1:64 or a fourfold or greater increase in IgG titer that suggests recent or active infection
- Clinical signs of disease referable to toxoplasmosis
- Exclusion of other common causes of the clinical syndrome
- Positive response to appropriate treatment

Some animals with clinical toxoplasmosis will have reached their maximal IgG titer or will have undergone antibody class shift from IgM to IgG by the time they are serologically evaluated, so the failure to document an increasing IgG titer or a positive IgM titer does not exclude the diagnosis of clinical toxoplasmosis. Because some healthy animals have extremely high serum antibody titers and some clinically ill animals have low serum antibody titers, the magnitude of titer is relatively unimportant in the clinical diagnosis of toxoplasmosis. Because the organism cannot be cleared from the body, most animals will be antibody-positive for life; therefore repeating serum antibody titers after clinical disease has resolved is of little use.

The combination of aqueous humor or CSF *T. gondii*–specific antibody detection and organism DNA detection by PCR is the most accurate way to diagnose ocular or CNS toxoplasmosis in cats (Diagnostic Laboratory, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO 80523). Although *T. gondii*–specific IgA, IgG, and organism DNA can be detected in aqueous humor and CSF of both normal and clinically ill cats, *T. gondii*–specific IgM has only been detected in the aqueous humor or CSF of clinically ill cats and so may be the best indicator of clinical disease. Because *T. gondii* DNA can be detected in blood of healthy cats, positive PCR results do not correlate to clinical disease.

Supportive care should be instituted as needed. Clindamycin hydrochloride, trimethoprim-sulfonamide combination, and azithromycin have been used successfully for the treatment of clinical toxoplasmosis.[4,36] Pyrimethamine combined with sulfa drugs is effective for the treatment of human toxoplasmosis but commonly results in toxicity in cats. Cats or dogs with uveitis should be treated with topical, oral, or parenteral glucocorticoids to avoid secondary glaucoma and lens luxations.[4,44] *T. gondii* seropositive animals with uveitis that are otherwise normal can be treated with topical glucocorticoids alone, unless the uveitis is recurrent or persistent. In these situations, administration of a drug with anti-*T. gondii* activity may be beneficial.

T. gondii is a significant zoonosis. Primary infection of mothers during gestation can lead to clinical toxoplasmosis in the fetus; stillbirth, CNS disease, and ocular disease are common clinical manifestations. Primary infection in immunocompetent individuals results in self-limiting fever, malaise, and lymphadenopathy. As T-helper cell counts decline, approximately 10% of people with acquired immunodeficiency syndrome (AIDS) develop toxoplasmic encephalitis from activation of bradyzoites in tissue cysts. People most commonly acquire toxoplasmosis by ingesting sporulated oocysts, tissue cysts, or they acquire it transplacentally. To prevent toxoplasmosis, eating undercooked meats or ingesting sporulated oocysts should be avoided. Although owning a pet cat was epidemiologically associated with acquiring toxoplasmosis in one study of pregnant women,[45] touching individual cats is probably not a common way to acquire toxoplasmosis for the following reasons:

- Cats generally only shed oocysts for days to several weeks after primary inoculation.
- Repeat oocyst shedding is rare, even in cats receiving glucocorticoids, and in those infected with FIV or FeLV.[46,47]
- Cats with toxoplasmosis inoculated with tissue cysts 16 months after primary inoculation did not shed oocysts.[47]

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- Cats are fastidious and usually do not allow feces to remain on their skin for time periods long enough to lead to oocyst sporulation; the organism was not isolated from the fur of cats shedding millions of oocysts 7 days previously.[48]
- Increased risk of acquired toxoplasmosis was not associated with cat ownership in human immunodeficiency virus (HIV)-infected people or in veterinary health care providers.[49]

If infection is suspected on fecal examination, the oocyst shedding period can be shortened by administration of clindamycin (25 to 50 mg/kg a day orally), sulfonamides (100 mg/kg a day orally), or pyrimethamine (2.0 mg/kg a day orally).[4] Because humans are not commonly infected with *T. gondii* from contact with individual cats, testing healthy cats for toxoplasmosis is not recommended. No serologic assay accurately predicts when a cat shed *T. gondii* oocysts in the past, and most cats that are shedding oocysts are seronegative. Most seropositive cats have completed the oocyst shedding period and are unlikely to repeat shedding; most seronegative cats would shed the organism if infected. If owners are concerned that they may have toxoplasmosis, they should see their doctor for testing. Avoiding sporulated oocysts and tissue cysts in undercooked meat can lessen the risk of acquiring toxoplasmosis.

168.4 NEOSPOROSIS

Neospora caninum is a coccidian previously confused with *T. gondii* due to similar morphology.[31,50,51] The sexual cycle is completed in the GI tract of dogs and results in the passage of oocysts in feces.[52–55] Sporozoites develop in oocysts within 24 hours of passage. Tachyzoites (rapidly-dividing stage) and tissue cysts containing hundreds of bradyzoites (slowly-dividing stage) are the other two life stages. Dogs are infected by ingestion of bradyzoites but not tachyzoites.[53] Infection has been documented after ingestion of infected bovine placental tissue. Transplacental infection has been well documented; dams that give birth to infected offspring can repeat transplacental infection during subsequent pregnancies.[56] Although organism replication occurs in many tissues, clinical illness primarily reflects neuromuscular infection in dogs. Although encephalomyelitis and myositis develops in experimentally infected kittens, clinical disease in naturally infected cats has not been reported.[57] Canine neosporosis has been reported in many countries around the world. Whether other intermediate hosts play a role in maintenance of infection is unknown, but white-tailed deer are commonly seropositive.[58] Because repeated transplacental infections occur, increased risk exists for puppies from a bitch that has previously birthed infected puppies.

Congenitally infected puppies develop ascending paralysis with hyperextension of the hindlimbs; muscle atrophy occurs in many cases. Polymyositis and multifocal CNS disease can occur alone or in combination. Clinical signs can be evident soon after birth or may be delayed for several weeks. Neonatal death is common. Although disease tends to be most severe in congenitally infected puppies, dogs as old as 15 years have been clinically affected. In

some dogs, myocarditis, dysphagia, ulcerative dermatitis, pneumonia, and hepatitis occur.[59–63] Glucocorticoid treatment may activate bradyzoites in tissue cysts resulting in clinical illness. CNS inflammation is usually with mononuclear cell infiltrates, which suggests an immune-mediated component to the pathogenesis of disease. If not treated, most affected dogs die.

No specific hematologic or biochemical findings exist, but increased creatine kinase (CK) and aspartate transaminase (AST) activities are common in dogs with myositis. CSF abnormalities include increased protein concentration (20 to 50 mg/dL) and a mild, mixed inflammatory cell pleocytosis (10 to 50 cells/dL) consisting of monocytes, lymphocytes, neutrophils, and rarely, eosinophils. Interstitial and alveolar patterns can be noted on thoracic radiographs. Demonstration of the organism in CSF or tissues gives a definitive diagnosis. Tachyzoites are rarely identified on cytologic examination of CSF, imprints of dermatologic lesions, and bronchoalveolar lavage. Mixed inflammation with neutrophils, lymphocytes, eosinophils, plasma cells, macrophages, and tachyzoites was noted on transthoracic aspirate of one dog with lung disease.[63]

Oocysts can be detected in feces by microscopic examination after flotation or by PCR. *Neospora caninum* tissue cysts have a wall greater than 1 μm; *T. gondii* tissue cysts have a wall less than 1 μm. The organism can be differentiated from *T. gondii* by electron microscopy, immunohistochemistry, and PCR.[61]

The clinician can make a presumptive diagnosis of neosporosis by combining appropriate clinical signs of disease and positive serology or presence of antibodies in CSF with the exclusion of other causes inducing similar clinical syndromes, in particular, *T. gondii*. Immunoglobulin G antibody titers greater than or equal to 1:200 have been detected in most dogs with clinical neosporosis; minimal serologic cross-reactivity with *T. gondii* occurs at titers greater than or equal to 1:50.

The prognosis for dogs with severe neurologic involvement is grave. Some have survived after treatment with trimethoprim-sulfadiazine combined with pyrimethamine, sequential treatment with clindamycin hydrochloride, trimethoprim-sulfadiazine, and pyrimethamine, or clindamycin alone.[59–62]

Neospora caninum antibodies have been detected in people,[64] but in one study there was no link to repeated abortion.[65] There has been an epidemiologic link between dogs and cattle; therefore efforts should be made to lessen dog fecal contamination of livestock feed, and dogs should not be allowed to ingest bovine placentas.[66] White-tailed deer are commonly seropositive, so it is possible that intermediate hosts play a role in canine infection. Bitches that whelp clinically affected puppies should not be bred. Glucocorticoids should not be administered to seropositive animals, if possible, because a potential exists for activation of infection.

168.5 HEPATOZOONOSIS

Hepatozoonosis in dogs is caused by *Hepatozoon canis* and *H. americanum*.[67,68] In North America, *H. americanum* predominates, is transmitted by *Amblyomma maculatum*, and is most common in the Texas Gulf Coast, Mississippi, Alabama, Georgia, Florida, Louisiana, and Oklahoma.[69] In Africa, southern Europe, and Asia, *H. canis* predominates and is transmitted by *Rhipicephalus sanguineous*. A *Hepatozoon* species is occasionally found in the blood of cats in Europe.[71–73] The tick ingests the organism from infected dogs during a blood meal and oocysts develop. After a dog ingests an infected tick, sporozoites are released and infect mononuclear phagocytes and endothelial cells of the spleen, liver, muscle, lungs, and bone marrow, and they ultimately form cysts containing macromeronts and micromeronts. Clinical disease results from pyogranulomatous inflammation; glomerulonephritis or amyloidosis may occur secondary to chronic inflammation and immune complex disease.

H. americanum has resulted in illness in all age groups, but disease is most commonly recognized in puppies.[73–74] Fever, weight loss, and severe hyperesthesia over the paraspinal regions are common findings. Anorexia, pale mucous membranes from anemia, depression, oculonasal discharge, and bloody diarrhea occur in some dogs. Clinical signs can be intermittent and recurrent. Clinical disease associations are currently unclear, but the cats are commonly coinfected with FeLV or FIV.

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Neutrophilic leukocytosis (20,000 to 200,000 cells/μL) with a left shift is the most common hematologic finding. Thrombocytopenia is unusual unless coinfection by *Ehrlichia canis* occurs. Normocytic, normochromic nonregenerative anemia is common and is likely from chronic inflammation. Increased activity of alkaline phosphatase but not creatine kinase occur in *H. americanum* infected dogs. Hypoalbuminemia, hypoglycemia, and rarely, polyclonal gammopathy occur in some dogs. Periosteal reactions from the inflammatory reaction directed at tissue phases in muscle can occur in any bone excluding the skull, are most common in young dogs, do not occur in every case, and are not pathognomonic for hepatozoonosis. Presence of serum antibodies against *H. americanum* were compared with tissue biopsy; the sensitivity and specificity were 93% and 96%, respectively.[75] Definitive diagnosis is based on identification of gamonts in neutrophils or monocytes in Giemsa-or Leishman's-stained blood smears or by demonstration of the organism in muscle biopsy sections.

For treatment of *H. americanum*, the combination of trimethoprim-sulfadiazine, pyrimethamine, and clindamycin for 14 days is successful in the short-term.[73,74] Administration of decoquinate mixed with food lessens the likelihood of recurrence of clinical disease and prolongs survival time. Imidocarb dipropionate is the drug of choice for treatment of *H. canis* and may also be effective for *H. americanum*. Administration of nonsteroidal anti-inflammatory drugs (NSAIDs) may lessen discomfort for some dogs. No therapeutic regimen has been shown to eliminate *H. canis* or *H. americanum* infection from tissues.

Tick control is the best form of prevention. Glucocorticoid administration should be avoided because it may exacerbate clinical disease. No evidence exists for zoonotic transfer of *H. americanum* or *H. canis* from infected dogs to people.

168.6 PIROPLASMIA

168.6.1 Babesiosis

Multiple *Babesia* spp. infect dogs throughout the world.[76–85] *Babesia canis* has worldwide distribution including Africa, Asia, Australia, Europe, Central America, South America, Japan, and the United States. *B. canis rossi* is transmitted by *Haemaphysalis leachi* and is the most pathogenic. *B. canis canis* is transmitted by *Dermacenter reticulatus* and is moderately pathogenic. *B. canis vogeli* is the least pathogenic and is transmitted by *Rhipicephalus sanguineus. Babesia gibsoni* infects dogs in the United States, Japan, India, Sri Lanka, Korea, Malaysia, and Egypt. North American and Asian isolates of *B. gibsoni* vary genetically enough to be proposed as different species.[81] In countries other than the United States, *H. bispinosa* and *H. longicornis* are known vectors for *B. gibsoni. R. sanguineus* is proposed but not proven to be a vector in the United States. A *Babesia* spp. that genetically varies considerably from other *B. canis* or *B. gibsoni* isolates was described in Oklahoma. None of the *Babesia* spp. that infect cats—*B. cati* (India), *B. felis* (South Africa and Sudan), *B. herpailuri* (South America and Africa), or *B. pantherae* (Kenya)—are found in the United States.[85] *Babesia* spp. can also be transmitted by blood transfusion.

The organisms replicate intracellularly in red blood cells (RBCs) resulting in intravascular hemolytic anemia. Immune-mediated reactions against the parasite or altered self-antigens worsens the hemolytic anemia and commonly results in positive Coombs' test. Severity of disease depends on the species and strain of *Babesia* and the host immune status; chronic, subclinical infection can occur. Peracute or acute *Babesia* infections result in anemia and fever leading to pale mucous membranes, tachycardia, tachypnea, depression, anorexia, and weakness. Icterus, petechiation, azotemia, and hepatosplenomegaly are present in some dogs depending on the stage of infection and the presence of disseminated intravascular coagulation (DIC).[83–88] Severe, acute anemia potentiates the development of DIC, metabolic acidosis, and renal disease. The primary differential diagnosis for acute babesiosis is primary immune-mediated hemolytic anemia. Chronically infected dogs commonly have weight loss and anorexia. Ascites, GI signs, CNS disease, edema, and clinical evidence of cardiopulmonary disease occur in some dogs with atypical infection. Subclinical infection occurs as well. Administration of glucocorticoids or splenectomy may activate chronic disease.

Regenerative anemia, hyperbilirubinemia, bilirubinuria, hemoglobinuria, thrombocytopenia, metabolic acidosis, azotemia, polyclonal gammopathy, and renal casts are common in dogs infected with babesiosis. IFA tests for *B. canis* and *B. gibsoni* are available commercially. Demonstration of increasing titers over 2 to 3 weeks are consistent with recent or active infection. Currently no standardization exists between laboratories; therefore suggested positive “cutoff” titers vary. False-negative serologic test results can occur in peracute conditions or in dogs with concurrent immunosuppression. A titer of greater than 1:320 was suggested for *B. gibsoni*, but not all infected dogs achieve titers of this magnitude.[83] A presumptive diagnosis can be based on historical findings, physical examination findings, test results, and positive serology. Many dogs are seropositive but clinically normal; therefore serology alone cannot be used to make a definitive diagnosis.[89,90] Definitive diagnosis is based on organism demonstration in RBCs using Wright's or Giemsa stains on thin blood smears. *B. canis* is typically found as paired, piriform bodies measuring 2.4 × 5.0 μm. *B. gibsoni* is typically found as single, annular bodies measuring 1.0 × 3.2 μm. PCR is now available commercially and can be used to document organism presence, but positive results do not always correlate to clinical illness.[91]

Supportive care should be administered as indicated. Phenamidine isethionate and imidocarb dipropionate may be effective for the treatment of babesiosis.[83–88,92] Adverse effects include transient salivation, diarrhea, dyspnea, lacrimation, and depression. Metronidazole or clindamycin hydrochloride may lessen clinical disease if other drugs are not available. Diminazene aceturate, pentamidine isethionate, parvaquone, and niridazone have also been used. No drugs are available to eliminate infection; therefore it is unknown whether it is beneficial to treat healthy, seropositive dogs.

Ticks should be controlled if possible. Administration of immunosuppressive drugs and splenectomy should be avoided in previously infected dogs. Dogs used as blood donors should be assessed for infection by PCR or serologic screening. Currently no evidence exists to suggest that *Babesia* spp. infecting dogs and cats can cause human disease.

168.7 CYTAUXZOONOSIS

Cytauxzoon felis infects cats in the southeastern and south central United States. Bobcats are usually subclinically affected and are the likely natural host of the organism. The organism can be passed experimentally from infected bobcats to domestic cats by *Dermacentor variabilis*; clinical illness occurs after an incubation period of 5 to 20 days.[93] Infected macrophages line the lumen of veins throughout the body and merozoites released from the

infected macrophages infect erythrocytes. Clinical disease results from obstruction of blood flow through tissues by mononuclear infiltrates and from hemolytic anemia.

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Most cases of cytauxzoonosis are in cats allowed to go outdoors. Fever, anorexia, dyspnea, depression, icterus, pale mucous membranes, and death are the most common clinical findings.[94–96] A primary differential diagnosis is haemobartonellosis. Ticks are generally not identified on affected cats. Recently, cytauxzoonosis was described in cats of Oklahoma and Arkansas that did not result in death suggesting that variants that are less virulent to cats exist.[97,98]

Cytauxzoonosis is suspected in cats with regenerative anemia and neutrophilic leukocytosis; thrombocytopenia occurs in some cats. Hemoglobinemia, hemoglobinuria, bilirubinemia, and bilirubinuria are uncommon. Antemortem diagnosis is based on demonstration of the erythrocytic phase on thin blood smears stained with Wright's or Giemsa stains. Infected macrophages can be detected cytologically in bone marrow, spleen, liver, or lymph node aspirates. The organism is easily identified on histologic evaluation of most organs. Serologic testing is not commercially available. PCR can be used to amplify organismal DNA from blood.[98]

Supportive care should be administered as indicated. Treatment with diminazene or imidocarb were used in cats that survived infection.[95] Historically, paraquone, buparvaquone, thiacetarsemide therapies have been attempted. However, paraquone and buparvaquone are not routinely available, and thiacetarsemide is toxic for cats and should not be used for the treatment of this parasite. Ticks should be controlled, and cats in endemic areas should be housed during periods of peak tick activity. *Cytauxzoon felis* is not known to be zoonotic.

168.8 FLAGGELATES

168.8.1 Leishmaniasis

Leishmania spp. are flagellates that cause cutaneous, mucocutaneous, and visceral diseases in dogs, humans, and other mammals.[99,100] Rodents and dogs are primary reservoirs of *Leishmania* spp., people and cats are probably incidental hosts, and sandflies are the vectors. Leishmaniasis was considered unimportant in the United States until recently, with cases only reported occasionally.[101–103] In 2000, *Leishmania donovani* infection was confirmed in multiple dogs in a foxhound kennel in New York State.[104] Further investigation documented *L. donovani* or *Leishmania* spp. infection in 30 other foxhound kennels in 20 states and Ontario, Canada, suggesting a competent vector exists in North America. The organism has been transmitted by blood transfusion.[105] A clinically affected cat in Texas was infected by *L. mexicana mexicana*.[102] Flagellated promastigotes develop in the sandfly and are injected into the vertebrate host when the sandfly feeds. Promastigotes are engulfed by macrophages and disseminate through the body. After an incubation period of 1 month to 7 years, amastigotes (nonflagellate) form and cutaneous lesions develop; sandflies are infected during feeding. The intracellular organism induces extreme immune responses; polyclonal gammopathies (and occasionally monoclonal), proliferation of macrophages, histiocytes, and lymphocytes in lymphoreticular organs and immune complex formation resulting in glomerulonephritis and polyarthritis are common.

Dogs generally develop visceral leishmaniasis. Subclinical infection may persist for months or years. Weight loss, normal to increased appetite, polyuria, polydipsia, muscle wasting, depression, vomiting, diarrhea, cough, epistaxis, sneezing, and melena are common presenting complaints. Splenomegaly, lymphadenopathy, facial alopecia, fever, rhinitis, dermatitis, increased lung sounds, icterus, swollen painful joints, uveitis, and conjunctivitis are commonly identified on physical examination.[99,100,106] Cutaneous lesions are characterized

by hyperkeratosis, scaling, thickening, mucocutaneous ulcers, and intradermal nodules on the muzzle, pinnae, ears, and footpads. Cats are usually subclinically infected. One cat had cutaneous nodules on the ear pinna.[102]

Hyperglobulinemia, hypoalbuminemia, proteinuria, increased liver enzyme activities, thrombocytopenia, azotemia, lymphopenia, and leukocytosis with left shift are common. Hyperglobulinemia is usually polyclonal, but an IgG monoclonal gammopathy was reported in a dog.[107] Neutrophilic polyarthritis occurs in some dogs as a manifestation of a Type III hypersensitivity reaction. Antibodies against *Leishmania* can be detected in serum[108–110]; IgG titers develop 14 to 28 days after infection and decline 45 to 80 days after treatment. Because dogs are unlikely to eliminate infection spontaneously, a true positive antibody test indicates infection. Demonstration of amastigotes (2.5 to 5.0 μm × 1.5 to 2.0 μm) in lymph node aspirates, bone marrow aspirates, or skin imprints stained with Wright's or Giemsa stain gives a definitive diagnosis. The organism can also be identified by histopathologic or immunoperoxidase evaluation of skin or organ biopsy, culture, inoculation of hamsters, or PCR. PCR can be performed on EDTA anticoagulated blood, bone marrow, or lymph node aspirates.[109,110]

Leishmania cannot be eliminated from the body with drugs.[108,111,112] The combination of antimony and allopurinol was superior to treatment with either drug alone in one study.[112] Liposomal amphotericin B has also been prescribed.[113] The prognosis is variable; most cases are recurrent. Dogs with renal insufficiency have a poor prognosis.

Avoidance of infected sandflies is the only means of prevention.[114] If in endemic areas, pet owners should house animals during nighttime hours and control breeding places of sandflies. Potential blood donors from endemic areas should be serologically screened.[105] The primary zoonotic risk for canine leishmaniasis is from dogs acting as a reservoir host for the organism. Direct contact with amastigotes in draining lesions is unlikely to result in human infection.

168.9 AMERICAN TRYPANOSOMIASIS

Trypanosoma cruzi infection of mammals is diagnosed primarily in South America, but several cases have been detected in dogs of North America.[115–123] Infected reservoir mammals (dogs, cats, raccoons, opossums, armadillos) and vectors (reduviid bugs, kissing bugs) are found in the United States, but infection in dogs or people is rare; this may relate to differences in vector behavior and sanitation standards in the United States. In one study in Texas, the number of serologically positive dogs increased between 1987 and 1996.[116] The organism has three life stages: (1) trypomastigotes (flagellated stage found free in blood), (2) amastigotes (nonflagellated intracellular form), and (3) epimastigotes (flagellated form found in the vector). When infected kissing bugs defecate during feeding, epimastigotes enter the vertebrate host, are engulfed by macrophages and myocytes, and transform into amastigotes. Amastigotes divide by binary fission until the host cell ruptures, releasing trypomastigotes into circulation. The vector is then infected by ingesting trypomastigotes during a blood meal. Transmission can also occur by ingesting the vector, by blood transfusions, by ingestion of infected tissues or milk, or transplacentally.

Disease in dogs is primarily a cardiomyopathy that develops from parasite-induced damage to myocardial cells or immune-mediated reactions. Exercise intolerance and weakness are nonspecific presenting complaints that relate to myocarditis or heart failure during acute infection. Generalized lymphadenopathy, pale mucous membranes, tachycardia, pulse deficits, hepatomegaly, and abdominal distension can be detected on physical examination. Anorexia, diarrhea, and neurologic signs occasionally occur. Dogs that survive acute infection can present for

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evaluation of chronic dilative cardiomyopathy. In one study of 11 dogs with chronic infection, right-sided cardiac disease, conduction disturbances, ventricular arrhythmias, and supraventricular arrhythmias were most common.[116]

Common clinicopathologic abnormalities include lymphocytosis and increased activities of liver enzymes and creatine kinase. Thoracic radiographic, abdominal radiographic, and echocardiographic findings are consistent with cardiac disease and failure, but they are not specific for trypanosomiasis. The primary ECG findings are ventricular premature contractions, heart block, and T-wave inversion. Definitive diagnosis is based on organism demonstration. Tryptomastigotes (1 flagellum, 15 to 20 µm long) can be identified during acute disease on thick blood film or buffy coat smears stained with Giemsa or Wright's stain. The organism is sometimes detected in lymph node aspirates or in abdominal effusions. Histopathologic evaluation of cardiac tissue may reveal amastigotes (1.5 to 4.0 µm). Tryptomastigotes can also be cultured from blood or grown by bioassay in mice. In North American cases, positive serologic test results correlate with infection. PCR can also be used to detect infection.

Nifurtimox administered at 2 to 7 mg/kg orally every 6 hours for 3 to 5 months has been prescribed most frequently but is not routinely available. Glucocorticoid therapy may improve survival of infected dogs. Therapy for arrhythmias or heart failure should be instituted as needed. Most dogs that survive acute infection will develop dilative cardiomyopathy. Survival time in 11 dogs varied from 0 to 60 months.[116]

Dogs should be kept from other reservoir hosts such as opossums and should not be fed raw meat. Potential blood donors from endemic areas should be serologically screened. Infected dogs can serve as a reservoir of *T. cruzi* for vectors, and blood from infected dogs can be infectious to humans. Vector control is the primary means of prevention.

168.10 AMOEBA

168.10.1 Acanthamoeba Spp.

Acanthamoeba castellanii and *A. culbertsoni* are free-living amoeba rarely associated with disease in dogs.[124–126] Several cases have been reported in greyhounds. Young dogs seem to be affected most often. Clinical signs resemble CDV infection and consist primarily of oculonasal discharge, fever, anorexia, lethargy, dyspnea, and CNS disease. No pathognomic laboratory or radiographic abnormalities exist, but leukopenia is common. The organism can be demonstrated histologically or cultured; antemortem diagnosis is not usually made. No known effective treatment or zoonotic risk exists.

168.11 MICROSPORA

168.11.1 Encephalitozoon Cuniculi

Dogs and cats can develop clinical illness after exposure to *Encephalitozoon cuniculi*.[127–129] Schizonts and sporonts are found intracellularly in many cell types including renal tubular epithelial cells, endothelial cells, tissue macrophages, and hepatocytes. Spores are the extracellular stage of the organism that is passed in urine. Infection is probably from oronasal exposure to spores passed in urine. In utero infection can also occur; infected puppies are weak, have stunted growth, and develop renal failure and CNS disease. Muscle spasms, depression, paralysis, and death have been reported in naturally infected cats. No pathognomonic laboratory abnormalities exist; however, azotemia, increased activities of hepatic enzymes, and increased CSF cell counts

(neutrophils) and protein concentrations commonly occur. Diagnosis is based on demonstration of spores in urine sediment stained with Gram or Ziehl-Neelsen stains. Serologic testing is available but is not specific for *E. cuniculi*. Although no drug has been shown to be effective for treatment of *E. cuniculi* in infected dogs or cats, fumigillin and albendazole were effective in vitro.[130] Although the zoonotic risk is considered minimally important, a 10-year-old girl in a home with two infected puppies seroconverted to *E. cuniculi*.[129] Sanitation is the best form of control.

168.12 MISCELLANEOUS INFECTIOUS AGENTS

168.12.1 Pneumocystosis

Pneumocystis carinii is a saprophytic organism with worldwide distribution that has characteristics of protozoans, yeast, and fungi that has been detected in diseased dogs.[131–136] The organism is found in the alveoli of some normal animals. Disease only occurs in immune-suppressed individuals. Replication of the organism in the alveoli induces infiltrates of lymphocytes, plasma cells, and macrophages that induces an alveolar-capillary blockage. Disseminated infection is rare in dogs and people. Disease has been detected in cats given corticosteroids.[137] Pneumocystosis in animals is extremely rare and only associated with concurrent immune deficiency. Miniature dachshunds with common variable immunodeficiency syndrome are affected most frequently.[131–132]

Most affected dogs have been less than 1 year of age. Predominant findings are dry cough, dyspnea, and progressive weight loss. Dermatopathies such as demodicosis and pyoderma that likely reflect the immune deficiency occur with most.

Neutrophilic leukocytosis, polycythemia, eosinophilia, and monocytosis occur in some dogs but are nonspecific findings. Common blood gas abnormalities include hypoxemia, hypocapnia, and an increased arterial-alveolar gradient. On thoracic radiographs, interstitial to alveolar patterns predominate.[138] Cor pulmonale can develop. Cytologic demonstration of the organism in transthoracic aspirates, transtracheal wash specimens, or lung biopsies is used to make the final diagnosis. Immune function deficits have been documented in affected dachshunds. Diffuse interstitial pneumonia characterized by free and phagocytosed organism in the alveolar spaces is found on histopathologic examination.

Administration of potentiated sulfas give the best results.[131,132] Pentamidine, carbutamide, trimetrexate, the combination of clindamycin and primaquine, and the combination of dapsone and trimethoprim have been used to treat pneumocytosis in some dogs. Supportive care, including oxygen therapy, bronchodilators, nebulization, and mucolytic agents, should be administered as indicated. For most cases, death occurs or euthanasia is chosen within days to months after diagnosis. Infected dogs are not considered zoonotic risks for people.

168.13 PROTOTHECOSIS

Prototheca zopfii and *P. wickerhamii* are the two species in this genus of green algae incriminated as pathogens; protothecosis is a disseminated disease in the dog *(P. zopfii)* and a cutaneous disease in the dog and cat *(P. wickerhamii)*.[139–142] The organism is found in sewage and animal wastes and is transmitted by ingestion of contaminated food, water, or soil. Disease generally only occurs in individuals with decreased cell-mediated immune responses. There may be strain differences in virulence and genetic predispositions.

The disseminated disease is most common in dogs that present for evaluation of weight loss, large-bowel diarrhea, CNS disease, or uveitis. The cutaneous disease occurs in dogs and cats and appears as draining ulcers and crusts of the trunk, extremities, and mucous membranes in dogs and as firm cutaneous nodules on the limbs, feet, and head of cats. CSF abnormalities include pleocytosis with either lymphocytes or granulocytes as the predominate cell type and increased total protein. Diagnosis is confirmed by cytologic, histologic, or culture documentation of the organism in CSF, rectal scrapings, or rectal biopsies. Cutaneous lesions should be excised if possible. Liposomal amphotericin B, ketoconazole, itraconazole, tetracyclines, and fluconazole may be effective treatments. CNS and ocular manifestations have a poor prognosis; fluconazole may be the drug of choice for disease of these systems. Topical clotrimazole may be effective for treatment of cutaneous *P. wickerhamii* infections. *Prototheca* spp. are not thought to be transmitted between hosts; therefore zoonotic risk is minimal.

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168.14 References

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169 CHAPTER • 169 Canine Viral Diseases

Rance K. Sellon

169.1 CANINE PARVOVIRUS

169.1.1 Cause and Epidemiology

Parvovirus of dogs is caused by type 2 canine parvovirus (CPV-2), a nonenveloped single-stranded DNA virus, of which two pathogenic variants, types 2a and 2b are recognized. Evidence suggests an evolution of the type 2a variant to the type 2b, with the 2b variant the most common isolate infecting dogs in the United States. Both variants can be found in other parts of the world. A third variant, type 2c, has recently been found in cats in Southeast Asia.[1]

Wild and domestic canids are susceptible to infection with CPV-2. Canine parvovirus (CPV) infection has been described in minks and ferrets, and all variants are known to infect cats. The virus is transmitted primarily by the fecal-oral route after exposure of susceptible animals to contaminated feces. CPV is quite stable under many environmental and hospital conditions, contributing to maintenance of the virus in natural settings and creating the potential for transmission in veterinary clinics. CPV is resistant to many detergents and disinfectants, although it is inactivated by bleach solutions (1 part bleach to 29 parts water), formalin, and sunlight.

169.1.2 Pathogenesis

After exposure, CPV replicates in lymphoid cells in the oropharynx, mesenteric lymph nodes, and thymus, then within 3 to 5 days it spreads hematogenously to crypt cells of the small intestine and epithelial cells of the oral cavity, tongue, and esophagus. Lymphoid organs, lungs, liver, kidneys, bone marrow and (in very young animals) myocardial cells may also become infected. Virus excretion begins shortly after infection of intestinal epithelial cells and can occur as soon as 3 to 4 days after exposure; virus excretion typically occurs for 1 to 2 weeks. In the intestinal tract, necrosis of infected crypt cells leads to villus collapse and loss of intestinal epithelial integrity. The hemorrhagic diarrhea that is characteristic of the clinical disease results from a combination of increased intestinal permeability and malassimilation from abnormal mucosal function. Breakdowns in the intestinal epithelial barrier predispose to translocation of intestinal bacteria and absorption of bacterial endotoxins into the systemic circulation (common events in parvoviral-infected dogs).[2,3] Translocation of bacteria and endotoxins can lead to systemic bacteremia and the systemic inflammatory response syndrome, disseminated intravascular coagulation (DIC), and death. Activation of systemic immune responses increases the risk of thromboembolic complications of CPV infection.[4]

169.1.3 Clinical Signs

Clinical features in infected dogs range from asymptomatic infection to fulminant disease and rapid death. The majority of dogs will not develop obvious clinical signs, but in very young animals, immune-suppressed, heavily parasitized or stressed animals, or animals at risk of disease because of breed-related susceptibility, clinical signs often start with anorexia, lethargy, and fever that progresses within 1 to 2 days to vomiting and diarrhea, which is often hemorrhagic. More severe gastrointestinal (GI) signs can be expected in puppies with intestinal parasites or other intestinal disease.

Uncommonly, clinical signs of myocarditis may be observed in very young puppies, typically those less than 8 weeks of age that have not benefited from receipt of maternal antibodies. Puppies may die acutely with no warning, or they may die after signs of enteric disease. Puppies that survive acute myocardial infection may succumb at later times to congestive heart failure (CHF).

169.1.4 Diagnosis

The development of characteristic clinical signs in a dog at risk of infection often provides the first suspicion of CPV. Assays based on enzyme-linked immunosorbent assay (ELISA) techniques to detect CPV antigen in stool samples are commonly used for suspect animals as a first-line diagnostic tool and represent a quick, relatively accurate, and inexpensive means of supporting the diagnosis. Limitations of fecal ELISA testing include brief periods of antigen shedding, varying levels of antigen shedding, and the inability of current tests to discriminate modified-live viral (MLV) vaccine isolates, which can be present in feces for around 1 week starting about 5 days after vaccination, from pathogenic isolates. Thus false negatives and false positives are possible. The development of polymerase chain reaction (PCR)-based assays may prove valuable in the future for discrimination of vaccine from field isolates.

Laboratory abnormalities are common in dogs with clinical CPV infection. Leukopenia and neutropenia can reflect either marrow infection or sepsis and generally parallel the severity of clinical infection; recovery of circulating neutrophil counts often precedes clinical improvement. Anemia and hypoproteinemia, which can be a consequence of hypoalbuminemia, hypoglobulinemia, or both can develop from enteric blood loss. Vomiting and diarrhea can contribute to electrolyte abnormalities and dehydration leading to prerenal azotemia.

Intestinal intussusceptions are a recognized complication of CPV infection.[5] Puppies with refractory vomiting and diarrhea may need abdominal radiographs to rule out such obstructions.

169.1.5 Treatment

No treatment directed at the virus itself exists, so therapy revolves around supporting effective circulating volume, controlling secondary bacterial infections, and resting the GI tract.[6] Administration of replacement type crystalloid fluids such as lactated Ringer's or 0.9% saline at volumes sufficient to restore and maintain hydration in the face of ongoing fluid losses is a key element of therapy. Supplementation of fluids with potassium and dextrose may be needed to maintain normal serum potassium and glucose concentrations in ill puppies. Administration of crystalloid fluids may contribute to the development of anemia and hypoproteinemia as a consequence of rehydration in conjunction with previous and ongoing enteric blood loss. Puppies that become severely anemic are candidates for blood transfusions, with whole blood preferred for animals that are both anemic and hypoproteinemic. Colloid administration may be indicated in puppies that are hypoproteinemic but not anemic enough to require erythrocyte support.

Puppies with vomiting and diarrhea are typically maintained NPO (nothing by mouth) until such signs have resolved; partial parenteral nutrition may be considered for nutritional support of these animals.[6] Parenteral administration of broad-spectrum antimicrobials with good gram-negative spectra is considered a key aspect of treatment. Good combinations include an aminoglycoside or fluoroquinolone with a beta lactam in the penicillin (amoxicillin, ampicillin) or first-generation cephalosporin families. Fluaroquinolones may cause cartilage abnormalities if administered to puppies.

Other considerations in the supportive care of affected dogs include control of persistent vomiting with antiemetic drugs such as metoclopramide, phenothiazine derivatives (e.g., chlorpromazine), or serotonin antagonists (e.g., ondansetron), although the latter category of drugs is comparatively expensive. Administration of hyperimmune or antiendotoxin serum has also been advocated.[6] Use of recombinant human granulocyte colony–stimulating factor (rHuG-CSF) has been suggested as an adjunctive treatment of neutropenic dogs to improve neutrophil counts. However, one study of a small number of dogs suggested no clinical benefits in recipients of rHuG-CSF as compared with a control group, and an additional study found that peak endogenous granulocyte colony–stimulating factor (G-CSF) concentrations in CPV-infected dogs occurred at the peak of neutropenia, raising the question as to whether higher concentrations of G-CSF would be of any additional benefit.[7,8] Given the expense of rHuG-CSF, its use is not easily justified. Glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDS) may be considered for use in puppies suspected of endotoxemia or sepsis, although their benefits need to be carefully weighed against their potential risks.

Once vomiting has stopped, patients may be offered water. If no more vomiting occurs, food may then be offered. Diets in the initial feeding period should be easily digestible, low-fat foods because villus structure and function may require a number of days to return to normal. A number of diets are commercially available for the benefit of patients recovering from gastroenteritis. Administration of anthelmintics is appropriate at this time as well.

Given adequate supportive care, many affected puppies survive infection. Once recovered, puppies are considered immune to reinfection for long periods—possibly for life.

169.1.6 Prevention

The cornerstone of prevention of CPV infection is vaccination. CPV vaccines are available in live or killed forms, with the latter sometimes used in breeds considered at greater risk of clinical CPV infection, in pregnant animals in need of vaccination, or animals with diminished immune function. Live-virus vaccines produce an asymptomatic infection with a longer duration of immunity than is considered achievable with inactivated vaccines. The use of low-passage (increased antigenicity), high-titer (larger viral inoculum) vaccines incorporating highly immunogenic CPV-2 strains is advised for most dogs to provoke a protective immune response in the presence of maternal antibodies. Recommended schedules are to begin vaccinations at 6 weeks of age with boosters at 9 and 12 weeks of age. For breeds such as Doberman pinschers, Rottweilers, or others that are considered to be at greater risk of infection, an additional booster vaccination around 15 to 16 weeks of age or measurement of serum neutralization or hemagglutination inhibition (HI) antibody concentrations has been recommended. All dogs should receive a booster vaccine 1 year after completion of the initial series. The frequency of vaccination recommended in adult dogs is a subject of some controversy, and support for extending vaccine intervals beyond 1 year exists.[9] Recent recommendations from a canine vaccine advisory board are for adult dogs to receive boosters to CPV every 3 years.[10] The interval chosen should reflect assessment of the risks and benefits of vaccination for each patient. Measurement of serum neutralization or HI titers may be considered as a guide to dictate the need for vaccination because, in general, higher serum titers tend to correlate with protection from infection.

169.2 CANINE CORONAVIRUS

169.2.1 Cause and Epidemiology

Canine coronavirus (CCV) is an enveloped single-stranded RNA virus in the family Coronaviridae. CCV can infect many species of canids. The virus is relatively stable in the environment but can be disinfected by many compounds. The virus is spread primarily by the fecal-oral route to susceptible dogs.

169.2.2 Pathophysiology

CCV infects epithelial cells in the villus tips of the small intestine. A malabsorptive diarrhea results as a consequence of loss of villus surface area. After infection, CCV is shed in the feces for 6 to 9 days, but the duration of shedding can be longer in some animals. The development of a local intestinal immune response terminates clinical signs and ultimately viral shedding.

169.2.3 Clinical Signs

Diarrhea is the principle clinical sign in clinically affected dogs; blood in the feces is an infrequent finding. Vomiting may be seen before or after diarrhea in some animals. Anorexia and lethargy are common features, and if vomiting and diarrhea are severe, dehydration may ensue. Clinical disease from CCV is considered infrequent compared with other viral enteropathies and is usually more severe in neonatal animals, with diminishing severity of clinical disease in older animals. Clinical signs abate after 7 to 10 days in most dogs, but the clinical course may be longer in dogs that develop secondary complications or infection.

169.2.4 Diagnosis

The definitive diagnosis of CCV historically has required the demonstration of virus in the stool, usually by electron microscopy. PCR-based techniques, although not yet commercially available, have been developed as a means to detect viral nucleic acid in the stool.[11]

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169.2.5 Treatment

Treatment of CCV is primarily supportive during the time needed for the disease to run its natural course. Dehydrated animals may require parenteral fluids. The role of antibiotics in the treatment of CCV has not been assessed. The use of antibiotics in dogs with diarrhea, though not universally accepted, has been supported because bacteria may be primary or secondary pathogens and attempts to define viral causes may not always be made.[12]

169.2.6 Prevention

CCV vaccines are available, but efficacy of protection is questioned.[10] CCV vaccines are not considered core vaccines, but tend to be reserved for animals going into situations where the risk of exposure may be higher (kennels, shows).

169.3 CANINE ROTAVIRUS

169.3.1 Cause and Epidemiology

Canine rotavirus enteritis is most often caused by a group A rotavirus in the family Reoviridae, which are nonenveloped double-stranded RNA viruses. Recently, group C rotaviruses, which are more commonly found in other species such as pigs, have been documented in diarrheic dogs.[13] Infection usually occurs via the fecal-oral route, and causes subclinical or mild gastroenteritis in young animals, especially puppies less than 14 days of age. A high seroprevalence is found in adult dogs. Compared with other enteric viruses, clinical disease caused by rotavirus appears to be uncommon.[12,14]

169.3.2 Pathogenesis

After exposure, rotavirus infects epithelial cells of the villus tip of the jejunum and ileum. Loss of villus epithelial cells ensues with development of villus atrophy. Virus is shed early as infected, necrotic epithelial cells are sloughed from the villus.

169.3.3 Clinical Signs

Anorexia, vomiting, and mild diarrhea, which can occasionally be bloody, are the typical clinical signs of rotaviral gastroenteritis. Recovery is expected in most animals within 5 to 7 days of onset of clinical signs.

169.3.4 Diagnosis

A variety of tests to detect rotaviral antigens are commercially available but are not commonly used in small animal practice. Other methods to obtain a definitive diagnosis include demonstration of virus in stool samples by electron microscopy or PCR.

169.3.5 Treatment

Therapy of rotavirus gastroenteritis is supportive care, with attention to maintenance of hydration status the key element in puppies with anorexia and vomiting.

169.3.6 Prevention

No vaccine is currently available for prevention of rotaviral infection.

169.4 CANINE ADENOVIRUS

169.4.1 Cause and Epidemiology

Canine adenovirus type 1 (CAV-1), a nonenveloped double-stranded DNA virus in the Adenoviridae family, is the cause of infectious canine hepatitis (ICH) and causes disease in domestic and wild canids and bears. The

virus is relatively hardy, surviving in the environment for days to months, and is resistant to most disinfectants except quaternary ammonium compounds. Infection occurs after oronasal exposure to infectious secretions.

169.4.2 Pathogenesis

After exposure, CAV-1 replicates in lymphoid tissue of the tonsils and area lymph nodes. A viremia follows, leading to infection of other tissues. Direct cytopathic effects of the virus in the liver, eyes, and kidney contribute to early clinical signs, which can become apparent in naïve dogs 4 to 7 days after exposure. The extent of hepatic necrosis is a function of the level of antiviral antibody present at the time of infection: animals with minimal antibody exhibit extensive necrosis that is often fatal; dogs with high levels of antibody exhibit minimal clinical signs; and animals with intermediate antibody levels are susceptible to persistent hepatic inflammation. Clinical signs of anterior uveitis initially develop as a consequence of infection of corneal endothelial cells, then by inflammation provoked by deposition of immune complexes as antibody responses to the virus increase. Virus is shed during the acute infection in all body secretions including saliva, stool, and urine; excretion of virus in urine can persist for months after infection, but urinary virus is not thought to contribute greatly to transmission.

169.4.3 Clinical Signs

Initial clinical signs include fever, depression, and lethargy, with later development of abdominal discomfort, mucous membrane pallor, and inflammation of the tonsils and pharynx with tonsillar and cervical lymph node enlargement. Abdominal discomfort and hepatomegaly will be detected in some dogs, and coughing may be seen in cases of respiratory disease. Vomiting and diarrhea can also occur. In severe cases, petechial and ecchymotic hemorrhages may develop from coagulation abnormalities secondary to hepatic dysfunction and DIC. Icterus is uncommon despite the presence of hepatic necrosis. Neurologic signs may be seen as a consequence of hepatic encephalopathy or central nervous system (CNS) infection; measurement of bile acids or plasma ammonia concentrations, if elevated, would support a contribution of hepatic encephalopathy to observed neurologic signs. Dogs with severe disease may die within hours after showing clinical signs, whereas dogs with less severe disease may exhibit clinical improvement 5 to 7 days after onset of clinical signs.

169.4.4 Diagnosis

The diagnosis of CAV infection is usually based on finding evidence of acute hepatic disease in a dog with a poor vaccination history. No specific laboratory abnormalities pathognomonic for CAV infection are seen. There may be leukopenia or leukocytosis depending on whether the patient is seen early or later in the course of disease. Thrombocytopenia is possible and could contribute to coagulopathies in the setting of DIC or abnormal platelet function. Increases in alanine aminotransferase (ALT) and alkaline phosphate (ALP) activity are expected, but the magnitude of activity will depend on the extent of hepatic necrosis and the timing of sample collection. Prolongations of OSPT and APTT are common as a result of decreased hepatic synthesis of coagulation factors, DIC, or both. Proteinuria is also expected as a sequel to renal injury during viremia or immune complex injury later in the course of disease.

Definitive diagnosis of CAV infection can be established if needed through serological, viral isolation, or immunohistochemical techniques. Inclusion bodies observed during cytologic or histologic examination of tissue, particularly the liver, can be strongly supportive of the diagnosis.

169.4.5 Therapy

No specific treatments exist that address the virus, and therapy is directed at provision of supportive care and managing clinical signs and complications. Intravenous fluid therapy to replace losses from vomiting or diarrhea is important, as is administration of blood products (whole blood, fresh or fresh frozen plasma) to manage the complications of hemorrhage and DIC. In patients with neurologic signs from hepatic encephalopathy, administration of lactulose via enema (or orally if the patient is not vomiting and can tolerate oral medications) can help reduce circulating concentrations of encephalotoxins.

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169.4.6 Prevention

As with other important canine viral diseases, vaccination is the foundation of prevention of CAV-1 infection. Most commonly used vaccines to CAV-1 use CAV-2 isolates which, through the production of cross-reactive antibodies, will elicit a protective immune response without the complications, such as corneal edema, seen more often after vaccination with vaccines using CAV-1 isolates. The duration of immunity after immunization with CAV-2 MLV vaccines is likely long, and revaccination every 3 years after a routine initial series and booster at 1 year of age has been recommended.[10]

169.5 CANINE DISTEMPER VIRUS

169.5.1 Cause and Epidemiology

Canine distemper virus (CDV) is caused by an enveloped single-stranded RNA *Morbillivirus* in the Paramyxoviridae family and is closely related to viruses that cause measles, rinderpest, and distemper in other animals. CDV is capable of infecting a large variety of species including dogs, mustelids (e.g., ferrets, skunks), and procyonids (e.g., raccoons). The virus does not survive for long periods outside of the host and is susceptible to inactivation with a number of disinfectants such as phenolic or quaternary ammonium compounds. CDV is most often spread by inhalation of virus particles in respiratory aerosols or aerosols of other infected secretions such as urine.

169.5.2 Pathogenesis

After exposure, virus infects and replicates in macrophages, which spread virus to regional lymph nodes and tonsils, with virus reaching a peak in these tissues by 2 to 4 days after inoculation. By around 4 to 6 days postinfection (PI), virus has spread to, and is multiplying in, the stomach, small intestine, spleen, and hepatic macrophages. The widespread increase in virus production is associated with initial fever and lymphopenia.

After about 9 to 14 days PI, the outcome of infection is dictated by the strength and type of the host's immune response. Dogs with poor immune responses develop viral infection of several additional tissues including skin, CNS, and glandular and epithelial organs. Such animals generally exhibit severe clinical signs and are likely to die as a result of infection. Those animals that recover from the initial clinical signs maintain virus in tissues and are likely to subsequently develop clinical signs of CNS disease.

In animals that mount an intermediate level of immune response, mild or clinically silent infection may develop, with virus persisting in the lungs, skin, or CNS. Such animals may undergo a complete recovery or

may develop signs of CNS disease. Animals that mount strong immune responses are unlikely to develop signs of systemic infection but may still develop signs of CNS disease.

The pathogenesis of neurologic disease in CDV-infected dogs is complex. Dogs, especially those that are very young or immune-suppressed, may develop acute encephalitis, which is attributed to direct viral injury. Chronic encephalitis appears to be a consequence of inflammatory responses to viral antigens in CNS cells, with macrophage activation and release of cytotoxic mediators playing a role in destruction and demyelinization of CNS cells.

169.5.3 Clinical Signs

The severity of the clinical course is a function of the age of the animal at the time of infection, the viral strain, and immune responses. Affected dogs may be lethargic, anorexic, and febrile. Animals with respiratory infection may exhibit serous or mucopurulent oculonasal discharge and cough. More severely affected animals can show an initial conjunctivitis followed by cough, vomiting, and diarrhea that can be bloody or mucoid.

Neurologic signs may develop starting 1 to 3 weeks after recovery from systemic signs or can develop many more weeks to months later. Curiously, certain features of clinical disease tend to correlate with the likelihood of developing neurologic disease. Dogs that develop pustular skin lesions are less likely to develop CNS disease than dogs that exhibit hyperkeratosis of the nasal planum and digital footpads, which is frequently associated with the development of neurologic signs. Neurologic abnormalities can reflect lesions in any CNS site and include seizures, ataxia, hypermetria, and paraparesis or tetraparesis. Myoclonus, either generalized or focal, is a common clinical sign and is strongly suggestive of CDV infection.

Other clinical signs that can be seen include anterior uveitis and chorioretinitis; recovered animals may have hyper-reflective retinal lesions that develop from retinal atrophy and scarring. Optic neuritis may cause blindness or mydriasis; blindness can also result from serous retinal detachments. Some dogs, especially young large breed dogs, are susceptible to metaphyseal osteosclerosis of long bones, which is typically not associated with lameness. Puppies infected in utero or as neonates can develop CNS signs early in life, or have enamel hypoplasia if infected before the eruption of permanent teeth. Abortions or neonatal death may also be appreciated.

169.5.4 Diagnosis

Diagnosis of CDV is usually a clinical one, relying on compatible clinical signs in a young animal with a poor vaccination history. However, CDV should not be excluded as a differential in a dog with compatible clinical signs if the animal has a vaccination history.[15] No pathognomonic laboratory abnormalities are seen. Lymphopenia is the most consistent CBC abnormality. There may be CDV inclusions in monocytes, lymphocytes, neutrophils, or erythrocytes seen during examination of a stained blood smear. Biochemical profile abnormalities can include hypoalbuminemia and hypoglobulinemia. The CSF may have (1) increased numbers of lymphocytes and monocytes and increased protein, (2) increased protein only, or (3) may be normal.[15]

Dogs with respiratory disease may have interstitial or alveolar patterns on thoracic radiographs. Radiographs of long bones in lame animals may have metaphyseal lesions consistent with hypertrophic osteodystrophy.

Animals with CDV neurologic disease can be diagnostic challenges if no history of systemic signs exist. Definitive diagnosis of CDV can be made by demonstration of higher concentration of CDV antibody in the

CNS as compared with the serum, although not all animals will have CSF antibodies.[15] Demonstration of viral antigen in cells or tissues by immunohistochemical methods such as fluorescent antibody (FA) testing of conjunctival swabs or blood smears also confirms the diagnosis. Recently, reverse-transcriptase polymerase chain reaction (RT-PCR) assays have proven sensitive and specific for detection of CDV in experimental settings and can be performed on virtually any tissue type.[16] Such assays performed on whole blood, serum, or CSF may be more sensitive for detection of CDV than antigen or antibody demonstration techniques. The RT-PCR is not commercially available but holds future promise as a diagnostic tool.

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169.5.5 Treatment

Treatment of dogs with CDV is largely supportive. Parenteral administration of fluids may be needed in dogs with vomiting or severe diarrhea. Animals with secondary bacterial bronchopneumonia or other infections are candidates for antibiotics. Seizure control with diazepam, pentobarbital, or potassium bromide may be needed. The prognosis for dogs with neurologic disease is considered guarded to poor.

169.5.6 Prevention

The key to CDV prevention is vaccination. Current MLV or recombinant vaccines are effective at inducing immunity. Distemper-measles vaccines may be given to high-risk puppies 4 to 12 weeks of age to provide protection in the face of maternal CDV antibodies. The duration of immunity after immunization with MLV CDV products is considered long lasting, and vaccination intervals of 3 years have been supported.[10]

Immunization of dogs with MLV CDV vaccine has been associated with postvaccinal complications, the most common of which is encephalitis, which can produce clinical signs of neurologic disease and variable neurologic abnormalities 7 to 14 days after vaccination. Though not widely available, molecular techniques such as restriction fragment length polymorphism analysis may help distinguish clinical disease caused by vaccine isolates from that caused by field isolates.[17]

169.6 RABIES VIRUS

169.6.1 Cause and Epidemiology

Rabies virus is an enveloped single-stranded RNA virus in the family Rhabdoviridae. Rabies virus is capable of infecting all mammals, although differences exist in susceptibility to infection. Skunks, wild dogs, bats, raccoons, and cattle are most susceptible, whereas domestic dogs, cats, horses, sheep, and goats are considered to have moderate susceptibility. In the United States the principle reservoirs of rabies virus for domestic dogs are skunks, raccoons, and foxes.[18] The virus is not stable in the environment and is inactivated by most common disinfectants. Rabies virus is spread primarily by inoculation of a naïve animal with infected saliva, thus bite wounds are the most common mode of rabies virus transmission. Transmission by ingestion of infected tissue, inhalation of airborne virus, and transplacental transmission have been described but are considered rare.

169.6.2 Pathogenesis

After inoculation, virus replicates in local tissue then enters nerve endings through neuromuscular junctions or breaches in the axonal sheath of injured nerve fibers. Virus spreads along axons in the peripheral nerves to the

CNS. Once the CNS has been entered, virus spreads among adjacent axons to involve more neurons and spreads more rapidly to the brain stem and then forebrain. The virus replicates in the CNS and moves out of the CNS to other tissues along peripheral nerve fibers. Infection of salivary glands occurs during this time, and thus virus in the saliva is a reflection of CNS infection. Virus can be shed in the saliva up to almost 2 weeks before neurologic signs develop. In rare instances documented in experimentally infected dogs, virus excretion may persist for several months after resolution of neurologic signs.

169.6.3 Clinical Signs

Rabies can be variable in its clinical presentation, and suspicion can be delayed because of atypical signs. Clinical suspicion may be further delayed because of variable incubation periods after inoculation of virus; incubation periods reflect the size of the viral inoculum, the extent of nerve supply to injured tissue, the distance from the site of inoculation to the spinal cord, and host factors such as age and immune responses. Clinical signs often start with a prodromal phase of 2 to 3 days that is characterized by nervousness, anxiety, or other behavior changes. There may be paresthesia at the site of inoculation. As clinical signs progress, forebrain signs of irritability, restlessness, pica, as well as photophobia and hyperesthesia may be apparent. These clinical signs, often referred to as the *furious form of rabies*, can progress to incoordination, seizures, and death. Paralytic or dumb forms of rabies are characterized by lower motor neuron disease beginning in the area of initial injury and eventually involving the entire CNS. Dysphagia from paralysis of the muscles of deglutition causes accumulation of saliva in the oral cavity, which can be a source of infection to owners and veterinarians attending to such patients. Death follows as the animal develops coma and respiratory paralysis.

169.6.4 Diagnosis

Rabies should be suspected in any animal with an uncertain vaccination history exhibiting neurologic or behavioral abnormalities. Definitive diagnosis hinges on demonstration of virus in the brain, with direct FA testing considered the preferred method in many laboratories. Heads or bodies of suspect animals should be submitted to appropriate diagnostic laboratories without freezing to avoid damage to brain tissue associated with thawing. Detection of intracellular inclusions (Negri bodies) or direct FA testing of sensory vibrissae in the maxillary area is considered insensitive as compared with direct FA of nervous tissue. The application of molecular techniques such as the PCR may be of benefit in situations where brain tissue is not available or is not suitable for FA testing and offers potential advantages in detecting low levels of virus or virus in saliva.

169.6.5 Treatment

Treatment of animals suspected of having rabies is not recommended because of the human health hazard posed by such animals. Asymptomatic animals that are considered suspects should be isolated according to local laws and regulations or euthanized for collection and submission of brain tissue to diagnostic laboratories.

169.6.6 Prevention

Vaccination is an effective measure in the prevention of rabies in dogs and cats. Most commonly used vaccines contain inactivated virus given initially to animals older than 3 months of age with a booster at 1 year of age. The need for subsequent boosters either annually or every 3 years is predicated upon the product used and local laws regarding rabies prophylaxis. Recent epidemiologic studies have suggested that unvaccinated, owned animals represent the largest population of rabid dogs and cats.[18] Such findings emphasize the importance of client education, especially in areas in which rabies is endemic.

169.7 PSEUDORABIES

169.7.1 Cause and Epidemiology

Pseudorabies is caused by an enveloped double-stranded DNA virus in the alpha-herpesvirus family. Despite the presence of an envelope, pseudorabies virus is relatively stable in the environment. Affected dogs usually have a history of having been in contact with pigs, which are the main reservoirs of the virus. Most cases in dogs are believed to result from the ingestion of infected raw pork.

169.7.2 Pathogenesis

After ingestion, the virus enters nerve endings in the mucosa and spreads to the brain along nerve axons. Inflammation and functional abnormalities in brain cells result in neurologic signs after an incubation period of around 3 to 6 days.

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169.7.3 Clinical Signs

Signs of neurologic dysfunction are common features of the disease.[19] Neurologic abnormalities can be variable and have included ataxia, abnormal pupillary light responses, restlessness, trismus, and cervical rigidity. Ptyalism, tachypnea, and hyperpnea are common. Pruritus of the head and neck area can lead to self-induced excoriation. In some dogs, vomiting and diarrhea are the predominant signs. The clinical course of pseudorabies infection in dogs is usually swift, with most dogs dying within 48 hours after onset of clinical signs of acute neurologic disease.

169.7.4 Diagnosis

The diagnosis is suspected based on history of exposure to pigs or pork products and on clinical signs. Definitive diagnosis can be established by demonstration of virus by FA or PCR in the brain and tonsil.

169.7.5 Treatment

Treatment is supportive, although the fulminant nature of the clinical disease and poor prognosis have not seen many animals survive the infection.

169.7.6 Prevention

No approved pseudorabies vaccine exists for dogs, so prevention relies on limiting exposure of dogs to pigs or preventing ingestion of contaminated raw pork products.

169.8 CANINE PARAINFLUENZA VIRUS AND ADENOVIRUS-2

169.8.1 Cause and Epidemiology

Canine parainfluenza virus is a single-stranded RNA virus in the Paramyxoviridae family, and canine adenovirus-2 (CAV-2) is in the family Adenoviridae. The viruses are transmitted primarily from inhalation of aerosolized droplets from infected dogs and are part of a complex of pathogens causing infectious tracheobronchitis in dogs. Dense populations such as in kennels or shelters facilitate viral spread to naïve dogs.

169.8.2 Pathogenesis

Clinical signs develop after an incubation period of 3 to 10 days, during which time virus is replicating in epithelial cells of the upper respiratory tract of infected dogs, causing epithelial destruction. Damage to the epithelial barrier and disruption of normal respiratory defenses afforded by an intact epithelium predispose to infection with other respiratory tract pathogens such as mycoplasma or various bacteria. Viral shedding can occur for approximately 1 week after infection.

169.8.3 Clinical Signs

A hacking cough with a terminal retch and serous nasal discharge are the typical clinical signs of viral infection. Coughing bouts are often easily elicited with tracheal palpation or manipulation, and can be paroxysmal in nature. Coughing may produce foamy white mucus. Clinical signs are typically of short duration and often subside by 7 days after onset, although occasional dogs may exhibit clinical signs for up to 9 to 10 days.

169.8.4 Diagnosis

The diagnosis is typically established by the presence of clinical signs in an otherwise healthy animal with a history of risk factors for infection. No pathognomonic laboratory abnormalities are seen in affected dogs; thoracic radiographs should be normal unless severe infection creates a secondary bronchopneumonia from other respiratory pathogens or the animal has pre-existing respiratory disease. Isolation of virus from nasopharyngeal or tracheal swabs can establish a definitive diagnosis but is rarely performed in clinical practice.

169.8.5 Treatment

No specific treatment is effective for reducing viral loads, so treatment is largely supportive. Administration of antimicrobials such as amoxicillin, ampicillin, or trimethoprim-sulfa may limit the development of secondary bacterial infections that can prolong the clinical course. Antimicrobials are frequently used empirically because of the clinical difficulty in distinguishing clinical signs of viral infection from clinical signs caused by other upper respiratory pathogens such as *Bordetella bronchiseptica*. Judicious short-term use of anti-inflammatory doses of glucocorticoids or administration of cough suppressants, such as hydrocodone or butorphanol tartrate, may help ameliorate cough and improve patient comfort but are unlikely to shorten the clinical course.

169.8.6 Prevention

Vaccination is the mainstay of prevention of viral respiratory infection. Greater protection is afforded animals that receive MLV parainfluenza vaccines intranasally as compared with parenterally administered vaccines. CAV-2 vaccines are usually part of core vaccine programs because they provide cross protection to CAV-1.

169.9 CANINE HERPESVIRUS

169.9.1 Cause and Epidemiology

Canine herpesvirus (CH) is an enveloped, double-stranded DNA virus that infects domestic or wild canids. The virus is transmitted primarily during birth as a puppy passes through the birth canal, contacting infectious secretions of an infected bitch; transmission may also occur transplacentally, and via oronasal secretions from the infected mother. The virus is susceptible to inactivation with most common disinfectants and is not stable at usual environmental temperatures.

169.9.2 Pathogenesis

After oronasal exposure of neonatal puppies, CH first replicates in the epithelial cells of the oropharnyx and in the mucosa of the tonsils. Virus subsequently enters macrophages, which spread virus hematogenously to other tissues including the lymph nodes, spleen, adrenal glands, kidneys, lungs, liver, and CNS. The lower body temperature of neonates, in conjunction with a limited capacity to mount a febrile response, facilitates systemic spread of the virus, which replicates well at lower body temperatures but poorly at higher temperatures.

In older animals, infection tends to be confined to the respiratory and genital tracts, and signs of systemic infection do not develop. Viral DNA persists in neurons of the trigeminal ganglia and lymphocytes in the retropharyngeal lymph nodes.[20]

169.9.3 Clinical Signs

Abortions, or litters of stillborn puppies, may be seen after transplacental infections. Puppies less than 2 to 3 weeks of age are most likely to develop clinical disease. After an incubation period of 3 to 6 days, infected puppies become ill with signs of persistent crying, hypothermia, soft stool, and petechial hemorrhages in mucous membranes. Petechial hemorrhages in abdominal organs and lungs are also typical lesions observed on necropsy of infected puppies. Nursing stops and death usually follows 24 to 72 hours after the onset of clinical signs. Older puppies develop mild signs of respiratory disease with spontaneous recovery and latent infections that may emerge later as a cause of neurologic disease, with signs of ataxia, blindness, or central vestibular disease most common. Infection in adult dogs is usually associated with vaginal or preputial hyperemia, hyperplasia of vaginal mucosal lymphoid follicles, and sometimes submucosal hemorrhages.

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169.9.4 Diagnosis

Diagnosis is made by observation of clinical signs in puppies of susceptible age in conjunction with necropsy lesions. Viral inclusion bodies may be observed in cells surrounding areas of necrosis and hemorrhage. Definitive diagnosis of CH infection centers on demonstration of virus, viral antigen, or nucleic acids by electron microscopy, immunohistochemical techniques, or PCR of tissues or cell cultures inoculated with

infected tissue. Serologic testing for neutralizing antibodies confirms exposure but does not necessarily indicate active infection.

169.9.5 Treatment

Treatment is supportive but often ineffective at preventing neonatal losses. Injection of immune sera pooled from bitches that have had recent losses of litters may help reduce mortality during outbreaks. Keeping puppies warm and hydrated may lessen mortality in affected litters, primarily by limiting the spread of infection amongst uninvolved puppies.

169.9.6 Prevention

Currently no vaccine is available for CH. Spread of infection may be limited by not breeding infected dogs, although discrimination of infected versus exposed dogs is not easily achieved. Females that have previously lost litters to CH infection may raise healthy litters; thus caesarian sections or artificial insemination are not considered useful approaches to limit the spread of infection.

169.10 CANINE ORAL PAPILLOMA VIRUS

169.10.1 Cause and Epidemiology

Canine oral papillomavirus (COPV) is a nonenveloped double-stranded DNA virus in the family Papillomaviridae and is related to papillomaviruses affecting other species, including people. The virus is relatively stable in the environment.

169.10.2 Pathogenesis

The virus primarily infects cells in the basal layer of the epithelium of the oral cavity, penis, vulva, conjunctiva, and skin, and it is likely that different papillomaviruses account for differences in lesion distribution.[21] Once infected, basal cells increase mitotic activity to produce the characteristic warts.

169.10.3 Clinical Signs

The primary clinical sign of COPV infection is the appearance of papillomas, or warts, in the oral cavity or other epithelial sites. Young dogs are clinically affected more frequently than older animals. Papillomas develop 4 to 8 weeks after infection, and they typically regress within 4 to 8 weeks (and occasionally longer) after appearance when cell-mediated immune responses cause T-cell infiltration into the wart.[22] Humoral immune responses, although capable of preventing infection, do not seem to play a role in regression of lesions. Although lesions can become quite extensive, especially in the oral cavity, in a given dog, the functional impact of papillomas to the affected animal is usually minimal unless warts develop in locations that lead to dysphagia or respiratory obstruction.

169.10.4 Diagnosis

Diagnosis of COPV is usually based on the observation of characteristic lesions. Viral antigen in lesions can be documented by immunohistochemical techniques, electron microscopy, or PCR-based assays.

169.10.5 Treatment

Because the disease usually regresses spontaneously in the majority of dogs, treatment is not usually needed unless, as noted previously, warts compromise eating or respiration. In such cases, warts can be removed by surgical excision, cryosurgery, or electrosurgery. Refractory cases may benefit from autogenous vaccination in which a wart is removed, a crude vaccine is made, and then injected into the same dog.[22]

169.10.6 Prevention

No preventive vaccine is available for dogs. Dogs that have recovered from COPV are generally immune to reinfection, although occasional dogs, presumably dogs with immune defects, may be susceptible to repeated bouts of clinical disease.

169.11 EMERGING VIRUSES OF INTEREST

169.11.1 West Nile Virus

The West Nile virus (WNV) is a nonenveloped single-stranded RNA virus in the family Flaviviridae. WNV is found worldwide and is maintained in natural settings via transmission from infected to naïve birds via mosquitoes.[23] WNV has emerged recently in the United States as a cause of meningoencephalitis in people and horses, although occasionally other species, including dogs, can develop clinical disease. Epidemiologic studies have demonstrated that seropositive dogs can be found in areas where human infection is endemic.[24] It is currently suspected that nonavian species that become infected from the bite of an infected mosquito do not readily support viral replication leading to a dead-end infection. The pathogenesis of the infection in dogs is unknown. Although to date there have been no published reports describing canine infections, anecdotal reports suggest that clinically affected dogs develop an acute neurologic disease. Definitive diagnosis requires demonstration of viral antigen or nucleic acid in brain tissues. No specific treatments exist beyond supportive therapy, and no approved vaccine is available to prevent infection in dogs.

169.11.2 Bornavirus

The bornavirus (BV) is a enveloped single-stranded RNA virus in the family Bornaviridae. BV causes a fatal disease of the CNS in horses and other animals. Clinical disease in dogs appears to be relatively uncommon. However, reports documenting cases in Europe and Japan are relatively recent, and more cases may emerge as knowledge of the infection increases. The pathogenesis of the disease in dogs is unknown, but clinical signs in dogs have included tremors, salivation, mydriasis, and circling.[25,26] The infection is suspected based on the histopathologic observation of nonsuppurative encephalomyelitis predominantly in gray matter of the brain. Demonstration of viral RNA by in situ hybridization or PCR-based assays has provided definitive diagnosis.

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170 CHAPTER • 170 Feline Leukemia Virus

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170.1 VIROLOGY

Household clusters of lymphoma and lymphocytic leukemia were observed among young cats for many years, but it was not until the discovery of retrovirus particles in a leukemic cat in 1964 that an infectious cause was considered likely. Subsequently, feline leukemia virus (FeLV) was isolated and shown to be capable of transmitting lymphocytic neoplasia among cats. An indirect fluorescent antibody (IFA) test, developed in 1973 to detect antigenemia, made the clinical screening of privately owned cats possible. The mass testing that followed demonstrated that the virus was present at low levels throughout the world's domestic cat population, that it appeared to be spread both vertically (from queen to fetus) and horizontally (from cat to cat), and that infection was associated with a variety of illnesses in addition to neoplasia, including bone marrow suppression and immunodeficiency.

FeLV is a retrovirus; its genetic material is transmitted from host to host as RNA. In infected cells, DNA copies of the virus are transcribed, and it is these copies that are inserted randomly into the host genome. Once this DNA provirus is integrated, cell divisions will result in daughter cells that also contain the viral DNA. The virus encodes several major protein groups: *gag* (group-specific antigens), *pol* (reverse transcriptase), and *env* (envelope). One of the *gag* proteins, p27, is abundant in the plasma of infected cats and in the cytoplasm of individual infected cells. This protein is the basis for most currently used diagnostic tests. The envelope protein gp70 defines the virus subgroup and appears to be important for inducing immunity.

170.2 EPIDEMIOLOGY

The FeLV infection rate of cats is similar throughout the world, ranging from 1% to 8% of healthy cats. Prevalence in feral cats in the southeastern United States is 4%. To date, no large serosurveys have been performed on healthy pet cats in the United States. An infection rate of 21% among symptomatic cats was reported in a survey of 27,976 clinically ill and “at risk” cats, compared with 7% of asymptomatic cats; overall prevalence in this high-risk population was 13%. The study also found that males (15%) were more likely to be infected than females (11%) and that risk of infection was higher in mixed breed (13%) than purebred cats (10%) and outdoor (20%) compared with indoor cats (8%). The prevalence of FeLV was highest in cats aged 1 to 6 years and higher in cats from multicat households than single cat households. Similar results were reported in a survey of cases referred to veterinary medical teaching hospitals from 1972 to 1998. Of 409,417 cats seen at the teaching hospitals, 8756 (2.1%) were diagnosed with FeLV. Prevalence was greatest in male cats, mixed breed cats, and cats aged 2 to 7 years.

Susceptibility to FeLV infection is highest in young kittens, and resistance develops with age. After experimental inoculation with FeLV, 70% to 100% of neonatal kittens remain persistently infected, compared with 30% to 50% of 8-to 12-week-old kittens and 10% to 20% of adolescent and adult cats. This age resistance can be abolished by corticosteroid administration. When susceptible kittens were introduced into households with endemic FeLV, 70% became infected within 5 months, whereas only 18% of adult cats became infected within 5 years under the same circumstances. In nature, the prevalence of anti-FeLV antibodies increases with age, indicating continuous risk of exposure to FeLV throughout life. However, most cases of FeLV are diagnosed in cats less than 4 years of age.

Taken together with the antibody serosurveys, this suggests that exposure to FeLV accumulates with age but that susceptibility to infection simultaneously decreases.

The prevalence of FeLV has been decreasing since the mid-1980s. Widespread test and removal programs have eliminated FeLV from most breeding facilities. Testing of cats at animal shelters prior to adoption and separating infected cats are now common practices. Several FeLV vaccines are available and may also be contributing to the decline of FeLV prevalence. Concurrent with the decline in FeLV is a decline in FeLV-associated diseases, particularly lymphoma.

FeLV infection is slightly more common among male cats than females. Unlike FIV, which is spread primarily by biting during fights, FeLV is passed vertically from infected queens to kittens and horizontally among communal cats with prolonged close contact. The virus is shed in high amounts in the saliva and milk and to a lesser extent in urine and other secretions. Sharing food and water dishes, mutual grooming, and using common litter areas all contribute to virus spread. The wandering and fighting behavior of unneutered males is an additional risk factor for infection among this group.

Infected queens can pass the virus to their offspring in utero. Reproductive failure, taking the form of fetal resorptions, abortions, and neonatal deaths, is common in this situation, although up to 20% of vertically infected kittens may survive the neonatal period to become persistently infected adults. Queens may also infect their kittens after birth via their milk or during grooming. The distinction between vertical transmission from queen to kitten and horizontal transmission among a family group is a somewhat arbitrary one from a clinical perspective. It is common, however, to observe that newborn kittens from persistently or latently infected queens may test negative at birth, only to seroconvert one by one over the following weeks to months. Thus if the queen or any one of her litter tests positive, the entire family should be treated as suspect and isolated from other uninfected cats until their status is resolved.

170.3 DIAGNOSIS

Routine screening for FeLV infection became available when the IFA was developed in 1973. With enzyme-linked immunosorbent assay (ELISA) tests developed several years later, clinicians gained the ability to perform rapid and reliable in-house testing. Later, other immunochromatic lateral flow tests were developed for in-house use. These tests detect the FeLV core protein p27, which is produced abundantly in most infected cats, and are the mainstay of clinical FeLV testing. Immunochromatic tests are performed on serum, plasma, and whole blood samples. User error contributes to false-positive results and is most likely to occur during the washing steps of kits using a micro-well or wand format. The use of membrane-based tests offers the advantage of eliminating separate washing steps and of including both positive and negative controls for each test sample. Some test systems have been developed for use with tears or saliva samples in place of blood. In general, these tests are not as accurate, and, because the consequences of both false-positive and false-negative test results can be disastrous for individual cats or for multiple cat populations, tears and saliva are not recommended for routine screening.

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The IFA detects p27 antigen within the cytoplasm of infected blood cells. Because it requires special processing and fluorescent microscopy, a qualified reference laboratory must perform the IFA. Generally, two or more quality blood or bone marrow smears are air-dried and mailed, unfixed, to the laboratory. The antigen is present at highest concentrations in neutrophils and platelets, and false negatives may result when these two cell lines are deficient. False-positive results may occur when smears are too thick, when background fluorescence is high, and when the test is prepared and interpreted by inexperienced personnel.

Immunochromatic tests, such as ELISA, detect viral antigens circulating freely in the plasma. Because FeLV generally replicates in lymphoid tissue and other sites before the bone marrow, immunochromatic tests may detect

infection a few weeks earlier than the IFA. Some cats are apparently able to clear the infection at this stage and may revert to negative status within a few weeks to months. IFA-positive tests indicate that the bone marrow is infected with FeLV. In this case, most cats remain persistently infected for life. In general, immunochromatic tests are considered to be slightly more sensitive, and the IFA is slightly more specific. With either test, however, the reliability (predictive value) of the test is dependent on the prevalence of infection within different populations of cats. For example, FeLV is present in most cats with thymic lymphoma, so a positive test is likely to be accurate in this situation. In a lower-risk population, such as a closed cattery known to be free of FeLV, a positive test should be viewed with more suspicion and additional confirmatory tests should be performed.

Recently the polymerase chain reaction (PCR) test has been used for the diagnosis of FeLV infection. This test differs from earlier screening tests in that it detects viral nucleic acid sequences (RNA or DNA) instead of protein antigens. PCR may be useful in helping to determine the true status of cats with discordant results from other testing techniques and may be the most sensitive test available. Well-equipped and trained laboratories must perform PCR, because inappropriate sample handling can destroy the delicate nucleic acid material or introduce minute amounts of cross-contamination, leading to either false-negative or false-positive results. PCR is capable of detecting FeLV infection in blood, solid tissues, tissue cultures, and fixed specimens. Commercial FeLV PCR tests detect proviral DNA. FeLV provirus sequences have been detected in both transiently and latently infected cats, as well as in apparently uninfected cats that reside with FeLV-infected cats. This indicates that detectable viral fragments are not always associated with productive infection or clinical disease.

Because no test is accurate 100% of the time, and because various testing modalities target somewhat different specimens and disease stages, it is possible to have discordant test results. The challenge for the clinician is to determine which most likely reflects the true status of the cat. For example, it is possible for infected cats to be antigenemic (viral proteins circulating in the blood) but to have negative virus blood cultures or PCR if the active infection is sequestered in different tissue compartments such as the bone marrow or lymphoid system. In one study of cats positive by ELISA but negative by culture, viral DNA was detected by PCR in 13 of 39 samples, indicating that the cats were most likely infected with FeLV.

Immunochromatic tests are preferred for screening, with the IFA recommended for confirmation of positive results. The combination of routine screening and confirmatory tests will accurately determine the FeLV infection status of most cats. Some animals, however, will have repeatedly discordant test results or occult infections that remain undetected. Rarely, some cats that test negative for viremia have been shown to secrete infectious virus in body fluids such as milk and urine. These cats are infectious to other cats but test negative on routine screening tests. It is particularly difficult to know the true status of cats that have been “transiently” infected and have apparently recovered. In surveys conducted prior to the development of FeLV vaccines, most free-roaming cats acquired anti-FeLV antibodies (evidence of at least transient exposure and infection with the virus). Although almost all of these antibody-positive cats were seronegative for viral antigens, it is not possible to know whether they were truly clear of infection, resistant to further exposure, or latently infected.

The American Association of Feline Practitioners (AAFP) has developed recommendations for testing cats for FeLV. It states that the FeLV status of all cats should be known. Identifying infected cats provides an opportunity to prevent the spread of the disease and to institute appropriate health care for infected cats. The AAFP further recommends testing prior to vaccination for FeLV and retesting cats that become ill. Screening tests detect viral antigens (not antibodies), so neither vaccination nor maternal immunity has an effect on test results. Because cats may be in the early stage of infection at the time of the first test, it is further recommended that a follow-up test be performed at least 1 month after the initial test or after a potential exposure to FeLV. Although this interval is adequate for detection of most infections, periods of up to 6 months between exposure to FeLV and positive test results have been reported.

170.4 PATHOGENESIS

Horizontal transmission of FeLV among susceptible cats occurs most commonly via the oronasal route and by bite wounds. After mucosal or percutaneous inoculation of FeLV, the virus replicates in local lymphoid tissues. From there, infected cells carry the virus to other target tissues, such as thymus, spleen, and lymph nodes. At this stage of acute viral replication, fever, malaise, diarrhea, and leukopenia are common. In addition, generalized lymphadenopathy may be so marked as to be mistaken for lymphoma. The virus later infects the salivary glands and the mucosal glandular epithelium. These sites of infection may secrete most of the infectious virus that is responsible for horizontal transmission. About the same time, bone marrow cells become involved, producing infected leukocytes and platelets that circulate in the blood. In early infection, viral antigens may be detected in the circulation before the bone marrow is infected. This results in discordant test results (immunochromatic tests positive, IFA negative) and explains the slightly higher sensitivity of the immunochromatic tests. Acute infection may follow one of three courses: (1) a vigorous immune response may eliminate the virus, (2) the virus may be sequestered in an inactive latent form, or (3) persistent viremia may develop. It is difficult to differentiate cats that have cleared infection from those that have latent virus. PCR tests on bone marrow may be more sensitive than peripheral blood. Initially, latent infections can reactivate naturally or in response to immune suppression. As time passes, latent infections become more difficult to reactivate, even with the administration of high doses of corticosteroids. By 1 year after infection, reactivation of the virus is considered unlikely. If viremia persists more than 16 weeks, or if the bone marrow is infected, as indicated by a positive IFA test result, chances are high that the cat will remain persistently infected, viremic, and infectious to other cats for the remainder of its life. The ability of FeLV to integrate into the host's own genome is one of the most important factors in persistent infection. Once the pool of stem cells becomes infected, true elimination of the virus becomes unlikely.

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170.5 PREVENTION

When FeLV was first described in the mid-1960s, the highest rates of infection were found in large multicat households and catteries. In contrast, free-roaming cats had lower rates of infection, and cats housed singly indoors were rarely infected. The development of reliable tests allowed cat breeders to implement control programs. A dramatic example was a mandatory test and removal program imposed on all members of a cat breeding society in the Netherlands in 1974. When testing was first implemented, the prevalence of FeLV in purebred catteries was 11%. The rate was reduced to less than 2% within 4 years, and no infected cats have been reported since 1984. Cat fanciers in other countries responded similarly, although on a more voluntary basis, so FeLV is now considered an anomaly in well-run catteries.

The control of FeLV is facilitated by the fragility of the virus outside of the host's body. The virus begins losing viability immediately on dry surfaces and is completely inactivated within a few hours. Environmental contamination from infected cats is easily neutralized by routine disinfectants (detergent, quaternary ammonium, dilute bleach). Indirect exposure between cats at shows or veterinary clinics is not a risk for transmission as long as the cats are not allowed direct contact. FeLV-infected cats do not need to be housed in special isolation rooms at veterinary clinics as long as cats are kept in separate cages. Veterinarians and handlers, however, should take precautions to avoid inadvertent transmission of the virus via contaminated body fluids such as blood, urine, and saliva. Clinical practices that risk nosocomial transmission include serial surgeries performed with the same instruments, reuse of inadequately sterilized needles, reuse of saliva-contaminated endotracheal tubes and dentistry equipment, use of unscreened or latently infected blood donors, and fluid bags shared between patients. The same universal precautions used in human health facilities to prevent the spread of HIV should be incorporated into veterinary practices to prevent the transmission of FeLV and other infectious agents.

FeLV infection is primarily a concern for cats that are social with other cats, because close, intimate contact between cats is optimal for transmission. This type of contact occurs among cats as a result of mutual grooming and sharing of dishes and litter pans. If an FeLV-positive cat is identified in a household, the best method of preventing spread to other cats in the household is to isolate the infected cat in a separate room to prevent the infected cat from interacting with its housemates. Kittens less than 1 year of age are at a greater risk of infection than are adults. If owners choose not to separate housemates, uninfected cats should be vaccinated against FeLV in an attempt to enhance their natural level of immunity. However, it should be understood that FeLV vaccines do not necessarily protect all cats against FeLV infection, and vaccination is not as effective as isolation.

The simplest protection against infection is to keep susceptible cats confined indoors. For cats that are allowed to wander outdoors or that reside with infected cats, vaccination against FeLV may offer protection. Because no standard method exists to evaluate the efficacy of FeLV vaccines in challenge studies, the relative protection offered by the available products is subject to debate. Transient viremia is commonly observed in cats deemed to be protected against persistent viremia in challenge studies, and latent infection can be identified in some of these cats. All FeLV vaccines are inactivated, most contain adjuvants, and they are based on a variety of different virus strains. Vaccines may contain whole virus particles, viral subunits, or recombinants. The emergence of injection-site sarcomas and other problems associated with widespread annual vaccination has led the AAFP to develop revised vaccination guidelines for cats and recommends tailoring vaccine protocols for each patient. The AAFP recommends immunizing only those cats with potential risk of exposure to FeLV (i.e., cats allowed outdoors and cats residing in households with infected cats or with cats of unknown FeLV infection status). Furthermore, it is recommended that all cats be tested for FeLV prior to immunization, because FeLV vaccination of infected cats is not believed to be of benefit. Prevaccination screening also avoids the situation in which an undetected infected cat later develops FeLV-related disease, leading the client to suspect vaccine failure. The AAFP further recommends administering any vaccine with FeLV antigen in the lower left hind leg. This is to aid both the treatment of subsequent sarcomas (by amputation) and to help identify the offending product. It is important to keep detailed medical records of vaccine administration (including date, injection site and route, product, and lot number). The use of peel-off vaccine labels that are placed in the permanent medical record are helpful in this regard. It is also important to report adverse vaccine reactions (please contact the manufacturer).

170.6 CLINICAL DISEASE SYNDROMES

Many cats carry FeLV infections in an asymptomatic state. Clinical signs, when they occur, are varied and nonspecific, depending on the organ system involved and the presence of secondary diseases. In one study of 3712 FeLV-infected cats, 29% were free of clinical signs. This study may underestimate the proportion of asymptomatic cats, because cases were selected based on the presence of illness or a life style at high risk for FeLV infection. Weight loss was the most common clinical sign reported in symptomatic cats (63%), followed by fever (42%), dehydration (35%), rhinitis (18%), diarrhea (17%), conjunctivitis (17%), oral infections (15%), lymphadenopathy (13%), and abscesses (12%). FeLV infection increases the risk for a wide variety of conditions, but it is not always possible to determine whether concurrent diseases are a consequence of FeLV infection or are independent events. Anemia was the most common finding in a study of 8756 FeLV-infected cats seen at veterinary medical teaching hospitals and was diagnosed in 18% of infected cats. Other findings included upper respiratory infections (11%), lymphoma (10%), myeloproliferative diseases (6%), stomatitis (5%), leukopenia (3%), haemotrophic mycoplasmas (3%), lymphadenopathy (3%), and uveitis (2%).

170.6.1 Bone Marrow Disorders

Bone marrow suppression is the most common clinical syndrome associated with FeLV infection and results from primary viral infection of hematopoietic stem cells and from viral infection of stromal cells that constitute the supporting environment for hematopoietic cells. The most common form of FeLV-induced anemia is pure red cell aplasia, a severe nonregenerative anemia associated with marked depletion and maturation arrest of erythroid precursors in the bone marrow. Serum erythropoietin levels are markedly increased, and few cats with FeLV-associated anemia respond to exogenous erythropoietin therapy. A rarely encountered form of FeLV-induced anemia is associated with red blood cell (RBC) macrocytosis. This is believed to represent a virus-induced defect in cell division during RBC maturation.

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Regenerative anemia in FeLV-infected cats, indicated by increased reticulocytes and, in some cases, nucleated RBCs, is less common than nonregenerative anemia and usually occurs in the presence of *Mycoplasma haemofelis* and *Mycoplasma haemominutum* (formerly *Haemobartonella felis*). Approximately one third of cats with immune-mediated hemolytic anemia are FeLV-positive; in some cases, hemolysis precedes the emergence of myeloproliferative disease or lymphoma. Erythemic myelosis is a myeloproliferative disease characterized by high numbers of nucleated RBCs (sometimes exceeding 500 nRBC/100 white blood cells [WBCs]). Although the high number of nucleated RBCs may suggest a regenerative process, the absence of reticulocytes indicates that it is actually a nonregenerative anemia. Erythemic myelosis is resistant to chemotherapy and is virtually always fatal, although affected cats may survive while supported with blood transfusions. Diagnostic evaluation of anemic FeLV-infected cats should include a complete blood count (CBC), reticulocyte count, serum chemistry panel, Coombs' test, and bone marrow evaluation. Examination of blood smears for *Mycoplasma haemofelis* or *M. haemominutum* may be performed, but PCR is more sensitive. If a specific cause for anemia is not determined, treatment should include a course of doxycycline (10 mg/kg orally for a minimum of 21 days) to rule out occult *Mycoplasma* spp. infection. Prednisone at antiinflammatory or immunosuppressive doses or erythropoietin therapy may improve nonregenerative anemia in some cats, but many become transfusion-dependent. Regenerative anemia, which is less common, should be treated as an immune-mediated disease once infectious causes such as *Mycoplasma* spp. and *Babesia* spp. have been ruled out.

FeLV is the most common cause of thrombocytopenia and granulocytopenia in cats. FeLV and myeloproliferative diseases accounted for 44% of cases of feline thrombocytopenia in one report. Cyclic and persistent neutropenia have been observed. The cycles are regular, ranging from 8 to 14 days. In one such cat, platelet count and reticulocyte count also cycled. An immune-mediated mechanism may be involved, because some cats respond to treatment with prednisone. Various cytopenias may wax and wane in FeLV-infected cats, seemingly responding to a variety of therapeutic interventions. Some persistent cytopenias are associated with myelodysplasia and may eventually evolve into a terminal myelodysplastic syndrome or leukemia. In addition to the direct bone marrow suppressive effects of FeLV, nonregenerative anemia, leukopenia, and thrombocytopenia may also be due to secondary effects of the virus, including bone marrow infiltration with lymphoma, leukemia, infectious agents, myelofibrosis, and osteosclerosis.

If cytopenia is severe, or if treatable underlying causes are not identified, therapy may be attempted with hematologic growth factors. Erythropoietin (Epogen, Amgen; 35 to 100 IU/kg subcutaneously every other day to correct anemia, then weekly to sustain PCV) has been of benefit to some cats with FeLV-associated anemia, although most do not respond. Reasons for resistance to erythropoietin include iron deficiency, concurrent infections, FeLV infection of bone marrow stromal cells, and the development of antierythropoietin antibodies. In some nonresponsive cats, repeated blood transfusions may be the only treatment possible. Recombinant human granulocyte colony–stimulating factor (rhG-CSF; Neupogen, Amgen; 5 μg/kg subcutaneously each day)

was developed for neutropenia associated with aggressive human chemotherapy protocols. In cats, rhG-CSF has been used successfully to treat neutropenia due to drug toxicity, infectious diseases, FeLV-associated cyclic neutropenia, and idiopathic causes. Long-term use of the drug in cats is limited by its high cost and the development of neutralizing antibodies against the human protein within a few weeks, but it is often effective for acute or life-threatening neutropenia. Whether antibodies develop in cats that are immune suppressed by FeLV infection or with concurrent use of prednisone is unknown. No growth factor is currently available to stimulate platelet production, and recovery depends on identifying and correcting the underlying cause.

170.6.2 Neoplasia

FeLV-infected cats have sixtyfold increased risk of developing lymphoma compared with FeLV-negative cats. Lymphoma is expected to occur in approximately 25% of cats infected with FeLV, usually within 2 years after diagnosis of the viral infection. Multicentric and mediastinal lymphoma are the most common forms to occur in FeLV-positive cats. Although less common, spinal, renal, ocular and other forms of lymphoma are also reported in young FeLV-infected cats. As the prevalence of FeLV decreased since its discovery, so did its association with lymphoma. Currently, alimentary lymphoma is the most common form diagnosed and a majority of affected cats are now middle-aged or geriatric and FeLV negative. FeLV may also have a role in lymphoma development in some cats that test negative for infection. FeLV genetic sequences and antigens have been identified in the tumors of some cats with negative FeLV blood tests. FeLV-negative housemates of infected cats have a fortyfold increased risk of lymphoma compared with cats that do not reside with infected cats. Although some reports suggest that concurrent FeLV infection is associated with reduced rate or duration of remission in cats treated for lymphoma with chemotherapy, other reports found no such effect.

Myelodysplasia (preleukemia) is characterized by nonregenerative anemia accompanied by abnormalities in cellular maturation in the bone marrow. Granulocytopenia and thrombocytopenia may also occur. Most cats are positive for FeLV. Bone marrow is usually hypercellular, and many samples also exhibit myelofibrosis. Blast cells comprise less than 30% of the marrow elements, distinguishing myelodysplasia from leukemia. Progression to acute leukemia is common and may occur within weeks to months after the diagnosis of myelodysplasia. Treatment with immunosuppressive doses of corticosteroids and blood transfusions may palliate clinical signs, but the prognosis is poor for most cats that have cytopenias due to myelodysplasia. Nearly all cats with acute nonlymphoid leukemia (ANLL or acute myeloid leukemia) are FeLV positive. These leukemias can involve erythroid elements (erythemic myelosis, erythroleukemia, reticuloendotheliosis), myeloid elements (granulocytic, monocytic, or myelomonocytic leukemia), or megakaryocytes. Stem cell involvement may result in a sequential expression of leukemia of various cell lines. Prognosis is grave for ANLL because chemotherapy does not appear to alter the course. Most cats are euthanized within days to weeks of diagnosis. Heavy infiltration of bone marrow (and frequently other organs) with lymphoblasts characterizes acute lymphocytic leukemia (ALL). ALL is often accompanied by anemia and circulating blasts. Most cats with ALL are FeLV-positive. Differentiating ALL from advanced lymphoma can be difficult, although the treatment for both forms of lymproliferative disease are similar. Chronic lymphocytic leukemia is uncommon in the cat, tends to occur in older FeLV-negative cats, and carries a better prognosis than ALL. Hypereosinophilic syndrome, polycythemia vera, and multiple myeloma are proliferative hematologic disorders that are not associated with FeLV infection.

Although lymphoid and hematologic malignancies are the most common forms of neoplasia associated with FeLV, viral infection is also associated with specific tumors of other organ systems. Osteochondromatosis is a syndrome usually observed in young FeLV-infected cats in which multiple lesions affect the skeleton; solitary lesions in older cats are usually not associated with FeLV. Olfactory neuroblastoma is a rare FeLV-associated tumor involving the nasal cavity with frequent invasion through the cribriform plate. Multiple subcutaneous

fibrosarcomas require coinfection of FeLV and feline sarcoma virus, which arises as a recombination between FeLV and cellular oncogenes. Similar to the reduction in observed cases of lymphoma, the decreasing prevalence of FeLV has paralleled a decrease in cats diagnosed with ANLL and other FeLV-associated malignancies. Diagnosis and treatment of FeLV-associated neoplasms are discussed in detail in Chapter 181.

170.6.3 Secondary Infections

Diseases associated with immune suppression account for much of the morbidity and mortality in FeLV-infected cats. Thymic atrophy and depletion of lymph node paracortical zones are common findings, particularly in cats infected as kittens. Neutropenia and lymphopenia may further exacerbate immune suppression. Several immune function tests have been reported to be abnormal in FeLV-infected cats, including poor response to T-cell mitogens, prolonged allograft rejection, reduced immunoglobulin production, depressed neutrophil function, complement depletion, and cytokine dysregulation.

Many reports exist of FeLV-infected cats having concurrent bacterial, viral, protozoal, and fungal infections; however, few studies prove these cats have a higher rate of infection than FeLV-negative cats or that they have a less favorable response to therapy. Thus, although FeLV is well known to suppress immune function, it should not be assumed that all concurrent infections are a result of FeLV infection. The most common secondary infections associated with FeLV are respiratory viruses that persist longer and cause greater illness than observed in immune competent cats. *Mycoplasma* spp. infections (haemobartonellosis), which may be clinically silent in healthy cats, are more likely to be associated with severe hemolytic anemia in FeLV-coinfected cats. Cats residing in households endemic for both FeLV and coronavirus are more likely to develop fatal FIP if they are infected with FeLV. Treatment-resistant dermatophytosis and acute generalized toxoplasmosis are also associated with FeLV infection.

170.6.4 Miscellaneous Disorders

A variety of other disorders are associated with FeLV infection. Reproductive failures have been associated with abortion due to transplacental infection of fetuses and endometritis. Glomerulonephritis has been a histologic finding in FeLV-infected cats, but is not usually clinically significant. Generalized lymphadenopathy has been observed in several young cats and may be mistaken for lymphoma. The lymph node enlargement usually resolves after several months without treatment. A “panleukopenia-like syndrome” of FeLV mimics feline parvovirus infection and is characterized by panleukopenia, crypt necrosis, and high mortality. In some cats, parvovirus is identified as a coinfection, suggesting that FeLV may enhance the susceptibility of adult cats to parvoviral enteritis. Neurologic infection has been reported to cause urinary incontinence and papillary spasm leading to *D*-shaped pupils and anisocoria. FeLV-associated myelopathy results in vocalization, hyperesthesia, and paresis progressing to paralysis. Lymphocytic-plasmacytic stomatitis, although more common in cats infected with FIV, is also increased in FeLV-infected cats.

170.7 TREATMENT OF FELV-INFECTED CATS

Adherence to the AAFP guidelines to test all cats for FeLV is likely to result in the identification of many asymptomatic cats. Early identification allows steps to prevent the spread of infection and to optimize the health of infected cats. The AAFP recommends that cats infected with FeLV be confined indoors to prevent spread to other cats in the neighborhood and exposure of affected cats to infectious agents carried by other animals. As for all cats, good nutrition and husbandry are essential to maintaining health. Cats should be fed a nutritionally balanced and complete feline diet. Raw meat and eggs and unpasteurized dairy products should be avoided, because the risk

of food-borne bacterial and parasitic infections is greater in immune-suppressed individuals. A program for routine control of gastrointestinal parasites, ectoparasites, and heartworms, where applicable, should be implemented.

Cats infected with FeLV should receive wellness visits at least semiannually to promptly detect changes in their health status. Veterinarians should obtain a detailed history to help identify problems requiring more intensive investigation and perform a thorough physical examination at each visit. Special attention should be paid to the oral cavity, because dental and gum diseases are common in affected cats. Lymph nodes should be identified and carefully evaluated for changes in size and shape. The skin should be examined closely for evidence of external parasitic infestations and fungal diseases. The body weight should be recorded, because weight loss is often the first sign of deterioration in a cat's condition. A CBC should be performed semiannually for FeLV-infected cats, because of the high risk of hematologic disorders. Serum biochemical analyses and urinalyses should be performed yearly; urine samples should be collected by means of cystocentesis so that bacterial cultures can be performed, if necessary. Fecal examinations should be considered for cats with a history of possible exposure to internal parasites or with a history of GI tract disease.

Vaccination programs to prevent common, serious infectious diseases should be maintained. In general, vaccination programs for infected cats are similar to those for uninfected cats. Rabies vaccines should be given in accordance with state and local regulations. Feline viral rhinotracheitis-calicivirus-panleukopenia vaccines should be given in accordance with the AAFP guidelines (i.e., routine primary vaccination, followed by a booster vaccination 1 year later and every 3 years thereafter). Some clinicians recommend that only inactivated vaccines be used in infected cats. However, little evidence indicates that such cats are at increased risk of adverse effects with modified-live virus (MLV) vaccines. FeLV vaccines are of no benefit in and should not be given to FeLV-infected cats. Other vaccines should be evaluated carefully before being administered. Sexually intact cats should be sterilized to reduce stress associated with aggression, estrus, and mating behaviors. Neutered animals are also less likely to roam outside the house or to interact aggressively with their housemates. Surgery is generally well tolerated by infected cats that are not showing clinical signs of disease. Perioperative antibiotic administration may be considered for cats undergoing dental procedures and invasive surgeries.

Illnesses in cats infected with FeLV are often secondary diseases acquired because of immune dysregulation and not the direct effects of the FeLV infection. Prompt and accurate identification of secondary illnesses is essential to allow early therapeutic intervention and a successful outcome. Therefore intensive diagnostic testing may proceed earlier in the course of illness for infected cats than might be recommended for uninfected cats. Many cats infected with FeLV respond as well as their uninfected counterparts to appropriate treatment strategies, although a longer or more aggressive course of treatment may be needed. Owners should be forewarned and clinicians should not be discouraged if a response to treatment takes longer than expected. As in the case of asymptomatic cats, corticosteroids and other immunosuppressive drugs should be administered only to those patients with a clear indication for their use.

170.8 IMMUNE-MODULATOR AND ANTIVIRAL THERAPY

The evaluation of anti-FeLV therapies is hampered by the lack of well-controlled clinical trials in which new treatments are compared against standard care or placebo. Host factors, such as the age of the cat at the time of infection, genetics, immune function, and concurrent diseases interact with viral factors, including virus strain, dose, and route of infection in determining the clinical outcome of infection. The marked natural variation in disease expression among infected cats makes it risky to predict which cats will have rapid progression of disease and which will be long-term survivors. In addition to host and viral factors that affect infected cats, the attitude and motivation of both the owners and the treating veterinarians can have a profound influence on the clinical outcomes. Immune modulators are suggested to benefit FeLV-infected cats by restoring compromised immune

function, thereby allowing the patient to control the virus and recover from associated clinical syndromes. Antiviral agents directly inhibit virus infection and replication.

170.8.1 Immune-Modulating Agents

Acemannan (Carrisyn, Carrington Laboratories) is a complex carbohydrate (mannan) polymer derived from the aloe vera plant. In one uncontrolled open-label trial, 50 cats with natural FeLV infection were treated with acemannan (2 mg/kg intraperitoneally every week for 6 weeks). Whether concurrent supportive care was permitted was not described. At the end of the 12-week study period, nine cats had been excluded from evaluation. Of the remaining 41 cats, 29 (71%) were known to be alive. All cats remained ELISA-positive for FeLV antigen, and there were no significant changes in clinical or hematologic scores. Because the study did not include a control group, and because clinical and laboratory evaluations failed to document improvement from pretreatment evaluations, it is difficult to determine whether the use of acemannan improved the outcome of infection in treated cats.

Propionibacterium acnes (ImmunoRegulin, ImmunoVet) is a killed bacterial product. No prospective studies have been reported for use in FeLV-infected cats, but veterinarians have described their clinical experiences in anecdotal reports. In one discussion, 76 clinically ill cats with natural FeLV infections were treated with ImmunoRegulin (0.25 to 0.5 mL intravenously twice weekly, then every other week for 16 weeks) and supportive care, including prednisone, antibiotics, and vitamins. Although no specific clinical and laboratory evaluations were discussed, 55 (72%) of the cats reportedly became seronegative for FeLV antigens and survived for an unspecified period of time.

Interferons (IFNs) have been used as antiviral agents (at high doses) and as immune modulators (at low doses). Anecdotal reports of beneficial responses in cats with FeLV infection treated with low doses administered orally (0.5 to 30 U orally each day) have been described. In a review of more than 100 FeLV-infected cats treated with various protocols for low-dose rhIFNα in combination with antibiotics, blood transfusions, fluids, and other supportive care, it was recommended to treat cats with 15 to 30 U orally each day for 7 days on alternate weeks. The mechanism by which oral rhIFNα acts is unknown, but it is not believed to be present in the blood or oral cavity in concentrations high enough to exert a direct antiviral effect. In one study, rhIFNα failed to improve hematologic or lymphocyte subset abnormalities in cats with chronic FeLV infection. rhIFNα (Roferon, Hoffman LaRoche; Intron A, Schering-Plough) is supplied in 3,000,000 U vials. The protocol for diluting the drug for oral use is (1) mix 3,000,000 U in 1 liter sterile saline; (2) freeze in 1 or 10 mL aliquots; (3) as needed, thaw aliquots and mix into the working solution by further diluting into 100 mL (1 mL aliquot) or 1000 mL (10 mL aliquot); (4) the final working concentration of 30 U/mL is considered an appropriate cat dose. This working solution is reportedly stable in the refrigerator for 2 months.

Staphylococcus protein A (SPA, Sigma) is a bacterial polypeptide product purified from the cell wall of *Staphylococcus aureus* Cowan I. A variety of SPA sources and treatments have been used in FeLV-infected cats. In some studies, a high rate of tumor remission and conversion to FeLV-negative status was observed, whereas in others, responses were less dramatic and short-lived. In a study of kittens with experimental FeLV infection, treatment (20 μg/2.75 kg intraperitoneally twice weekly for 8 weeks) neither reversed viremia nor improved humoral immune function. A recent double-blind controlled trial compared treatment of naturally infected cats with SPA, rhIFNα, SPA+rhIFNα, or placebo. There were no significant differences in survival, hematology, or clinical findings.

PIND-ORF (Baypamune, Bayer) is derived from an inactivated *Parapox ovis* virus and is proposed to induce nonspecific or “para” immunity. After reports of curing infection and disease in hundreds of FeLV-infected cats, Baypamune (1.0 mL subcutaneously 1 to 3 times weekly for 4 to 30 weeks) quickly became the most

commonly used treatment for FeLV infections in Europe. In one of the only large-scale double-blind, placebo-controlled clinical trials of an immune modulator reported to date, 150 cats with natural FeLV infection were randomized to receive Baypamun (1.0 mL subcutaneously twice for 1 week, then weekly for 6 weeks) or placebo. There were no significant differences in clinical score, hematology score, lymphocyte subsets, FeLV p27 concentration, pterin concentration, reversion to negative status, or survival between the groups. Overall, between 7% and 12% of the cats in both groups became negative for FeLV p27 antigen. This study demonstrates the marked differences that can be observed in uncontrolled or retrospective studies compared with randomized, controlled clinical trials.

170.8.2 Specific Antiviral Agents

AZT/Zidovudine (Retrovir, GlaxoSmithKline) is the most widely used antiviral agent for both human and feline retroviral infections. It is a nucleoside analog inhibitor of the viral reverse transcriptase enzyme, preventing conversion of viral RNA into DNA, which would then enter the host genome. Only 1 controlled clinical trial has been reported in which cats with natural FeLV infections were treated with AZT. In this study, 32 FeLV-infected cats, all with chronic oral inflammation (stomatitis), were treated with AZT (5 mg/kg subcutaneously twice a day) or placebo for 3 weeks in a double-blind design. No other treatments were permitted. AZT-treated cats had improved stomatitis score and decreased FeLV p27 antigenemia compared with placebo. Previously, AZT was recommended at 15 mg/kg twice a day. The dose of 5 mg/kg twice a day used in this study was associated with decreased hematologic toxicity and cost.

Recombinant human interferon alpha (rhIFNαIntronA, Schering-Plough; Roferon, Hoffman LaRoche) has potent antiviral activity, preventing final virion assembly and budding. When administered to cats with experimental FeLV infection, rhIFNα (10^4 to 10^6 U/kg subcutaneously each day) effectively reduced FeLV p27 antigenemia. The effect was most rapid and complete in the high-dose treatment group. However, neutralizing antibodies developed against the human protein and appeared earliest in the high-dose group. Thus, the authors concluded that the intermediate dose of 10^5 U/kg provided the most beneficial balance of efficacy and duration of action, which persisted approximately 50 days until antibodies inhibited activity. Interestingly, the addition of AZT to a rhIFNα treatment did not enhance the antiviral effect in this study of chronically infected cats as it did in a study of FeLV prophylaxis. The cats in this study were healthy, so a clinical benefit could not be assessed. Theoretically, the observed suppression of virus load could benefit FeLV-infected cats because the immune system may achieve some level of reconstitution during this period. A recombinant feline rhIFNα omega product (10^3 to 10^6 U/kg subcutaneously each day) from Japan (INTERCAT, Toray) failed to decrease FeLV p27 levels or prevent lymphoma in experimentally infected cats. Recently, rfaIFN omega became available in Europe (Virbagen Omega, Virbac) and is approved for the treatment of parvoviral enteritis in dogs. The manufacturer reports that clinical condition and the proportion of cats surviving ±1 year are increased in FeLV-infected cats treated with IFN omega (10^6 U/kg subcutaneously each day for 5 days on day 0, day 14, and day 60) compared with cats treated with placebo.

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171 CHAPTER • 171 Feline Immunodeficiency Virus Infection and Related Diseases

Katrin Hartmann

In 1986, feline immunodeficiency virus (FIV), a T-lymphotropic lentivirus causing an acquired immunodeficiency syndrome (AIDS) in domestic cats, was isolated in Davis, California. FIV shares many morphologic and biochemical properties with human immunodeficiency virus (HIV) but is antigenetically distinct. The pathogenesis of both virus infections is characterized by a long period of clinical latency during which immune function gradually deteriorates. Triggered by factors as coinfections, ultimately the immunodeficiency syndrome develops and is accompanied by opportunistic infections, myelosuppression, tumors, or neurologic disease. No evidence links FIV infection to any human disease, including AIDS. Investigations have failed to identify antibodies in people that have been bitten by infected cats or who have inadvertently injected themselves with virus-containing material.

FIV has been detected worldwide in domestic cats. In the United States, antibody prevalence ranges from 1% to 24%; prevalence is higher in cats at high risk of exposure and in sick cats. In large surveys of stray and feral cats in the United States, overall percentage rates of 2% to 4% are reported. There seem to be no regional difference in the United States; in Europe, however, infection rates vary significantly (e.g., from 2% in Germany and The Netherlands to over 30% in Italy). Cats that are free roaming in areas of high cat density have an increased opportunity for exposure, largely because bite wounds are the most important mode of transmission. Male cats are infected 2 to 4 times more frequently than females, and the prevalence is higher in adult cats. In a survey study of 826 naturally FIV-infected cats examined at North American Veterinary Teaching Hospitals, 80% were male and 78% were at least 2 years old at the time of presentation. Adult male cats living outdoors consistently compose the majority of FIV-infected cats, and the risk is highest for sexually intact males.[1,2]

171.1 PATHOGENESIS

The pathogenesis of FIV infection is not completely understood. Despite the generation of antibodies and a strong cellular immune response, a latent infection arises and infection cannot be cleared. The hallmark of FIV pathogenesis is the progressive disruption of normal immune function. FIV replicates in $CD4^+$ and $CD8^+$ lymphocytes, B lymphocytes, macrophages, astrocytes, and microglia cells. Ability to replication in different cell types is thought to be associated with use of different cellular receptors and to be responsible for different clinical manifestations of FIV infection. Virus replication in cells of the monocyte and macrophage lineage can result in central nervous system (CNS) disease.[3]

FIV can be isolated from lymphocytes, at the earliest, 10 to 14 days after infection. Viremia rapidly increases until day 21, peaks between weeks 7 and 8, and then decreases gradually until the virus load increases in the terminal stage. Conversely, when the virus peaks, the number of $CD4^+$ cells decreases. In the first few weeks of infection, numbers of both $CD4^+$ and $CD8^+$ cells decline. The initial lymphopenia is followed by a strong immune response characterized by the production of anti-FIV antibodies and a rebound in $CD8^+$ cells above pre-infection levels. This results in a persistent inversion of the CD4/CD8 ratio. Over time, numbers of both $CD4^+$ and $CD8^+$ cells gradually decline. Decrease of $CD4^+$ cells is caused by a shortened life span in infected lymphocytes and apoptosis of uninfected cells. In HIV, distinctive clinical stages can be defined based on absolute $CD4^+$ cell count. A $CD4^+$ cell count of 200/μL or less is considered an AIDS-defining condition. It is more difficult to assign clinical stages of disease to cats based on $CD4^+$ cell counts, mainly because FIV appears to be less pathogenic

than HIV. Although chronic inflammatory conditions and opportunistic infections are more common in cats with low $CD4^+$ cells, other cats with low counts appear to remain healthy.

In addition to the quantitative decrease in $CD4^+$ cells, FIV-infected cats show dysfunction of immune cells (e.g., loss of ability of lymphocytes to proliferate in response to stimulation) and a significant perturbation of cytokine production. Cell-mediated immunity is more profoundly affected than humoral immunity. Despite being target cells of viral infection, no changes in number or proportions of B cells occur after FIV infection.[2] Consequently, chronic inflammatory conditions, neoplasia, and infections with intracellular organisms are more common than infections controlled by antibodies. FIV-infected cats respond adequately to vaccinations and frequently develop a polyclonal hypergammaglobulinemia characteristic of nonspecific stimulation of humoral immunity.

171.2 CLINICAL SIGNS

FIV infection progresses through several stages, much like HIV infection in humans. Clinical stages in cats include an acute phase, a clinically asymptomatic phase of variable duration, and a terminal phase. Attempts have been made to define the clinical course in different stages analogous to those of HIV infection; however, often no sharp distinction is seen between the phases in cats, and not all stages will always be apparent. The clinical disease caused by FIV is dependent on age and health at the time of infection, dose and route of virus inoculation, virus strain, and immunologic competence of the cat. Experimental infections of cats in different environments have helped to differentiate between primary viral effects and syndromes that develop only in the presence of cofactors. During a 4-year follow-up period, both SPF and random source FIV-infected cats experienced immunodeficiency with progressive inversion of the CD4/CD8 ratio. The random source cats went on to an AIDS-like syndrome characterized by stomatitis, recurrent respiratory disease, diarrhea, and weight loss. In contrast, SPF cats developed lymphoma or neurologic disease believed to be caused by direct viral effects and not to be the consequence of immunodeficiency.[2]

Many FIV-infected cats are healthy; others have a history of recurrent illnesses. In a follow-up study of naturally FIV-infected cats, 18% of infected cats died within the first 2 years of observation (5 years after the estimated time of infection) and 18% developed increasingly severe disease. However, more than 50% of infected cats remained asymptomatic during the 2 years.[1] In a survey study of 826 naturally FIV-infected cats examined at North American Veterinary Teaching Hospitals, the most common disease syndromes were stomatitis, neoplasia (especially lymphoma and cutaneous squamous cell carcinoma), ocular inflammation (uveitis and chorioretinitis), anemia and leukopenia, opportunistic infections, renal insufficiency, lower urinary tract disease, and endocrinopathies such as hyperthyroidism and diabetes mellitus.[2] Some of these diseases are most likely associated with the older age at which these cats presented (e.g., endocrinopathies, renal insufficiency) than with their FIV infection.

171.2.1 Stomatitis

Chronic ulceroproliferative stomatitis is the most common disease syndrome found in cats naturally infected with FIV, affecting up to 50% of infected cats. It characteristically originates in the fauces and spreads rostrally, especially along the maxillary teeth. Lesions are often painful and tooth loss is common. Severe stomatitis can lead to anorexia and emaciation. Histologically, the mucosa is invaded by plasma cells and lymphocytes, accompanied by variable degrees of neutrophilic and eosinophilic inflammation. The cause of the syndrome is uncertain, but the histologic findings suggest an immune response to chronic antigenic stimulation or immune dysregulation. Circulating lymphocytes of cats with stomatitis have greater than normal expression of

inflammatory cytokines,[2] further implicating immune activation in the pathogenesis of this condition. Concurrent calicivirus infection is often identified in the oral cavity of cats with FIV-associated stomatitis and may be one of the infectious cofactors. Other infectious agents, including *Trichomonas*, *Candida*, or *Bartonella* infections, may also play a role.

171.2.2 Neurologic Disease

Both central and peripheral neurologic disease are common in HIV-infected humans, and the same is true of FIV. Dementia of human AIDS is often characterized by a slight decline in cognitive ability or behavior, changes that may be too subtle to recognize in cats. About 5% of clinically affected FIV-infected cats have neurologic disease as a predominant clinical feature. Although the majority of FIV-infected cats do not show clinically observable neurologic signs, a much higher proportion of infected cats exhibit microscopic CNS lesions. Brain lesions may occur in the absence of massive infection, and abnormal neurologic function has been documented in FIV-infected cats with only mild to moderate histologic evidence of inflammation.[1]

Uncommonly, neurologic signs may be caused by opportunistic infections such as toxoplasmosis, cryptococcosis, or feline infectious peritonitis (FIP). Mostly abnormal neurologic function is the result from a direct effect of the virus on CNS cells. Neurologic expression of FIV infection is highly strain dependant. The virus infects the brain early, with virus-induced CNS lesions sometimes developing within 2 months of experimental infection.[1] Neurologic abnormalities seen in naturally infected cats tend to be more behavioral than motor. Twitching movements of the face and tongue, psychotic behavior, compulsive roaming, dementia, loss of bladder and rectal control, and disturbed sleep patterns have been observed. Other signs described include nystagmus, ataxia, seizures, and intention tremors. In addition, sensitive electrodiagnostic tests such as nerve conduction velocity and brain stem auditory evoked potentials have detected abnormalities in clinically normal FIV-infected cats. Pathologic findings include the presence of perivascular infiltrates of mononuclear cells, diffuse gliosis, glial nodules, and white matter pallor. These lesions are usually located in the caudate nucleus, midbrain, and rostral brain stem.[1] Microglia and astrocytes are infected by FIV. The virus does not infect neurons; however, neuronal death has been associated with FIV infection. In particular, forebrain signs are often a result of direct neuronal injury from the virus. The mechanism of neuronal damage by FIV is unclear but may include neuronal apoptosis, effects on the neuron-supportive functions of astrocytes, toxic products released from infected microglia, or cytokines produced in response to viral infection. In vitro studies support the hypothesis that FIV infection may impair normal metabolism in CNS cells, particularly astrocytes.[1] Documented abnormalities of astrocyte function include altered intercellular communication, abnormal glutathione reductase activity that could render cells more susceptible to oxidative injury, and alterations in mitochondrial membrane potential that disrupt energy-producing capacities of the cell.[4] Astrocytes are by far the most common cell type of the brain and are important in maintaining CNS neuronal microvascular microenvironment. One of the most important functions of astrocyes is to regulate the level of extracellular glutamate, a major excitatory neurotransmitter that accumulates as a consequence of neuronal activity. Excessive extracellular glutamate often results in neuronal toxicity and death. FIV infection of feline astrocytes can significantly inhibit their glutamate-scavenging ability, potentially resulting in neuronal damage.[4,5]

171.2.3 Tumors

FIV-infected cats have a higher incidence of certain types of tumors and are five times more likely to develop lymphoma or leukemia than noninfected cats, compared with a sixty-twofold increase in cats infected with feline leukemia virus (FeLV).[4] In contrast to lymphoma in FeLV-infected cats that is primarily of T cell origin,

the phenotype of FIV-associated lymphoma is mainly B cell. Other neoplastic diseases in FIV-infected cats include squamous cell carcinoma, fibrosarcoma, mast cell tumor, myeloid tumor, and leukemia. It is not known exactly how FIV is associated with these cancers. Lentiviruses are not directly oncogenic. Because increasing age is a risk factor both for FIV infection and development of neoplasia, it is difficult to determine the exact role of FIV in carcinogenesis. Infection with immunosuppressive lentiviruses is associated with increased cancer risk, but most studies suggest indirect mechanisms. With the exception of one recently published case,[5] integrated FIV sequences cannot been detected in lymphoma cells, suggesting that, unlike FeLV, the role of FIV in lymphoma development is generally indirect. Several theories exist concerning the association of tumors with FIV infection. FIV might increase cancer incidence by decreasing tumor immunosurveillance mechanisms. It might promote tumor development through the immunostimulatory effects of replicating in lymphocytes. Finally, it might impair immunologic control of FeLV infection or of transformed lymphoid cells.

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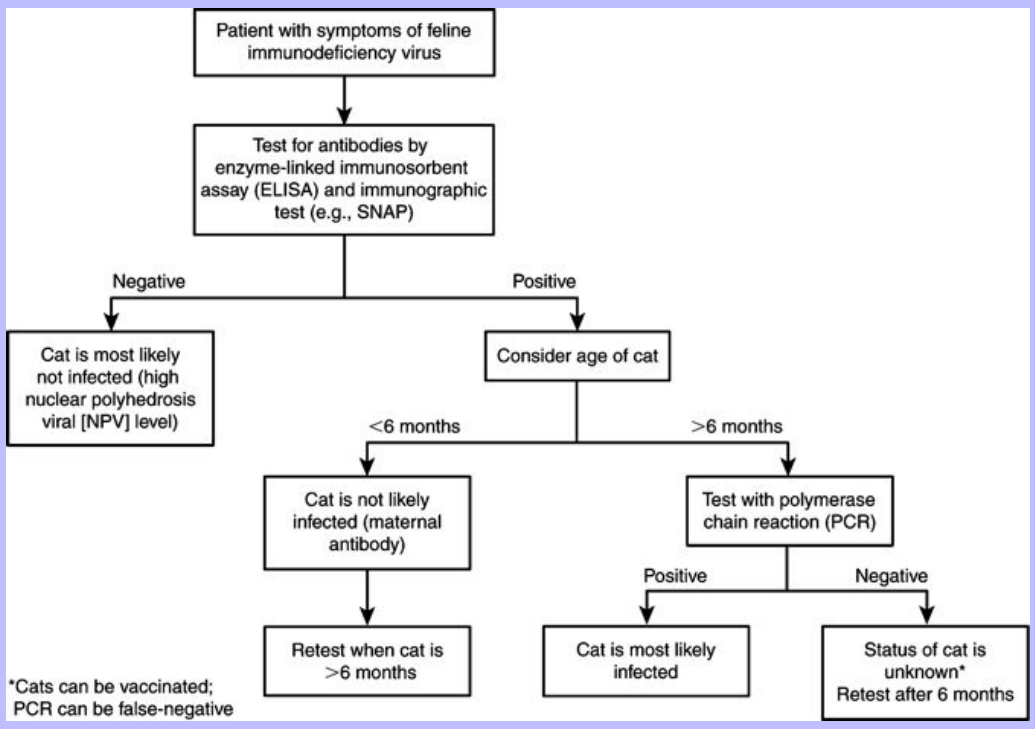
171.3 DIAGNOSIS

Currently available tests for FIV infection rely on the detection of antibodies to FIV (Figure 171-1). In contrast to FeLV, FIV antigen concentration in blood is too low to be detected. FIV-infected cats do, however, usually develop high levels of FIV-specific antibodies, and FIV produces a persistent infection from which cats do not recover. Therefore FIV-specific antibody detection was effectively used for diagnosis, and the presence of antibodies was predictive of infection in cats older than 6 months of age. In kittens less than 6 months of age, antibody tests must be interpreted carefully because kittens acquire anti-FIV antibodies by passive transfer in colostrum from infected or vaccinated mothers. It is very rare for kittens to become infected from their mothers under natural circumstances, so most kittens (that are truly uninfected) initially testing positive will eventually test negative when their maternal antibodies wane.

Antibodies to FIV can be detected by immunochromatographic tests like enzyme-linked immunosorbent assay (ELISA). These tests can produce false-positive results for a number of reasons, a fact that is of major importance in areas with low FIV prevalence (e.g., United States, Northern European countries). Therefore positive results should be confirmed with a Western blot or at least with a second immunochromatographic test.

Interpretation of positive FIV tests is unfortunately confounded by a recently approved vaccine (on the U.S. market) that interferes with all tests relying on antibody detection, including the confirmatory Western blot. This vaccine induces broad spectrum antibody production to FIV proteins and results in long-lasting titers. These antibodies are indistinguishable from those detected in infected cats. After vaccination a cat will test positive for at least 12 months and will transfer antibodies to kittens through colostrum. Polymerase chain reaction (PCR) and virus isolation have been suggested as alternative testing methodologies. Virus isolation is possible over the whole infection period, but is time-consuming, expensive, and requires expertise; therefore it is not practical for routine diagnosis. PCR is a very sensitive and specific method when used in experimental conditions. If appropriately inactivated the current vaccine should not result in viral genome production and should not interfere with PCR assays. PCR requires specialized equipment, is not available for patient-side testing, and is performed only by specialized laboratories. Current PCR tests in the field are not standardized, and information about sensitivity, specificity, and overall diagnostic performance in naturally infected cats is not available. Due to the marked variability of the viral genome in the field, failure rates to detect FIV infection by PCR of up to 50% have been reported; therefore false-negative results are common. Another concern is that the high sensitivity of PCR may lead to false positive results if even minor contaminations occur during handling of samples.[3,5]

Figure 171-1 Algorithm for feline immunodeficiency virus.



171.4 PREVENTION

FIV infection can be best prevented by keeping cats out of environments that encourage high-risk behavior. Cats should be neutered and not be exposed to untested homeless, feral, abandoned, or stray cats.

Development of an effective vaccine is difficult because of the nature of the retrovirus-host interaction and the relatively poor immunogenicity of lentiviral antigens in inducing vaccinal immunity. Cats typically mount a marked antibody response after exposure to FIV, but these antibodies are unable to clear infection. Many approaches have been taken toward the development of an effective vaccine against FIV, but the same hurdles facing HIV prevention also apply to FIV. Both viruses have an error-prone RT, which enhances the mutation rate of replicating virus and increases the opportunity for escape from immune surveillance. The viruses can even take advantage of specific antibody formation, using antibodies to enhance pathogenicity or to enter cells via immune complexes. To date, no vaccine approach has been completely successful in preventing infection, and in some cases immunization paradoxically enhanced viral replication and disease expression. Another major obstacle in designing an effective vaccine against FIV infection is the large genetic diversity among viral isolates. Five known subtypes of FIV exist, and sequence divergence ranges from 2% to 15% within a subtype (between subtypes it ranges up to 26%). The new vaccine (Fel-O-Vax FIV®) is a dual-subtype vaccine containing inactivated FIV subtype A and subtype D with an adjuvant. The combination of two genetically distinct subtypes elicits strong anti-FIV cellular immunity and broad-spectrum virus-neutralizing antibodies, but the range of protection is still unknown. This vaccine has not yet been field tested against natural FIV infection, and protection against the frequently found subtype B viruses (in USA and in Europe) is uncertain.[3,5]

171.5 TREATMENT

In most naturally infected cats, FIV infection does not cause a severe clinical syndrome. With proper care, FIV-infected cats can live many years and, in fact, may die in older age from causes unrelated to their FIV infection. Survival time is long and quality of life is usually good. The most important life-prolonging advice is to keep FIV-infected cats strictly indoors, not only to prevent spread to other cats but also to prevent exposure of the immunosuppressed cat to infectious agents carried by other animals. Secondary infections not only cause clinical signs in FIV-infected cats but also lead to progression of FIV infection.

171.5.1 Antiviral Chemotherapy

Clinical use of antiviral drugs is still not very common in veterinary medicine. With the exception of feline interferon-ω now on the market in Japan and some European countries, no antiviral drugs are licensed for veterinary use; therefore human drugs must be used in animals. Most antivirals are specifically intended for treatment of HIV infection, and many of those can be used to treat FIV infection because most enzymes of FIV and HIV have similar sensitivities to various inhibitors. In cell culture and experimental studies, several compounds have been shown to be active against FIV. However, many of these studies used FIV as a model for screening new compounds for HIV, and most of these drugs will never be accessible to veterinarians. Unfortunately, to date the drugs available to cats are limited, and only few controlled studies have been performed to support their use.

Licensed antiviral compounds that have been used in FIV-infected cats include zidovudin (3′-azido-2′,3′-dideoxythymidine, AZT), phosphonoformate (foscarnet), ribavirin, and interferons (human interferon-α, feline interferon-ω). Foscarnet and ribavirin are relatively toxic in cats, and their use is limited in feline medicine. AZT is the most thoroughly studied anti-FIV drug. It is a nucleoside analogue (thymidine derivative) that blocks the RT of retroviruses. It is integrated in the developing DNA strand and thus inhibits new infection of cells but not replication of viruses already present in infected cells. AZT reduces plasma virus load and improves the immunologic and clinical status of FIV-infected cats resulting in increased survival time. In a placebo-controlled trial, AZT improved stomatitis in naturally infected cats. It is used at a dose of 5 to 10 mg/kg every 12 hours (orally or subcutaneously). During treatment, regular blood cell counts are necessary because nonregenerative anemia is a common side effect, especially if the higher dose is used. Cats with myelosuppression should not be treated. Studies in which cats were treated with AZT for 2 years demonstrated that AZT is well tolerated in most FIV-infected cats. Some cats developed a mild decrease in hematocrit initially in the first 3 weeks that resolved even if treatment was continued. If hematocrit drops below 20%, discontinuation of AZT is recommended and anemia usually resolves within a few days. Unfortunately, as in HIV, AZT-resistant mutants of FIV can arise as early as 6 months of treatment.

Interferons have an immunomodulatory effect and a direct antiviral effect by inducing an antiviral state of cells that protects against virus replication. Human interferon-α used in cats with FIV infection can be given parenterally for a maximum of 6 to 7 weeks in high doses (10^5 to 10^6 IU/kg), leading to measurable serum levels. After 6 to 7 weeks, cats develop antibodies against the human interferon-α. If given orally, interferons are destroyed in the gastrointestinal (GI) tract and no measurable serum levels develop. The only potential effect that oral interferon could have is stimulation of the lymphoid tissue in the oral cavity with subsequent systemic immunomodulation. No placebo-controlled studies prove a positive effect of low-dose oral human interferon-α in FIV-infected cats. Interferons are species-specific and feline interferon-ω (recently licensed in some countries) is more effective in feline cells than human interferon. So far only one study has been performed with feline interferon-ω in FIV-infected field cats at 10^6 IU/kg every 24 hours subcutaneously for 5

consecutive days. This study failed to show a significant difference in survival rate, although some clinical improvement was noted.[3] Other trials are needed to assess the efficacy of feline interferon-ω against FIV infection.

171.5.2 Immune Modulatory Therapy

Nonspecific immunostimulatory agents (e.g., Acemannan, *Staphylococcus* protein A (SPA), *Propionibacterium acnes*, paramunity inducer) are probably the most widely used medications in FIV-infected cats. It has been suggested that these agents restore compromised immune function, allowing the patient to control viral burden and recover from associated clinical syndromes. Although reports of uncontrolled studies frequently suggest clinical improvement, these effects have not been observed when followed by controlled studies. No conclusive evidence from controlled studies shows that immunomodulators or alternative drugs have any beneficial effects on health or survival of asymptomatic or symptomatic FIV-infected cats. A nonspecific stimulation of the immune system might even be contraindicated. In HIV-infected people (and in FIV-infected cell cultures), nonspecific stimulation can lead to increased virus replication by activating latently infected lymphocytes and macrophages. Consequently this therapy can actually promote progression of disease. This is why unspecific immunomodulators with unknown effects should not be used in FIV-infected cats.

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172 CHAPTER • 172 Feline Infectious Peritonitis and Feline Enteric Coronavirus

Janet E. Foley

172.1 FELINE CORONAVIRUSES

Feline enteric coronavirus (FECV) and feline infectious peritonitis (FIP) virus are two feline coronavirus phenotypes of positive-stranded RNA virus. Like transmissible gastroenteritis virus of pigs, murine hepatitis virus, and others, the FEVC and FIP virus are in the family Coronaviridae. FECV is a fecal-orally transmitted virus that can infect intestinal epithelium of all Felidae but is not infectious to nonfelids or humans. FECV produces moderate villus pathology with no clinically detectable disease; the major clinical importance is that frequent RNA mutations confer a novel phenotype that allows the virus (now an FIP virus) to enter and replicate within feline macrophages.[1,2] If a cat fails to eliminate FIP virus–infected cells early in infection, the presence of FIP virus within macrophages may initiate an ultimately fatal Arthus-type immune-mediated vasculitis, which defines FIP. Affected cats may develop signs due to lesions in a sensitive target organ (central nervous system [CNS], kidney, or liver) or it may die due to fluid redistribution into second spaces, disseminated intravascular coagulopathy, or secondary sepsis.

172.2 DIAGNOSIS OF FELINE INFECTIOUS PERITONITIS

FIP is diagnosed on histopathologic examination of lesions, supported by signalment, history, physical examination, and laboratory findings (Figure 172-1). Cats with FIP may be any breed or either sex, with a peak age distribution from 6 months to 3 years (although FIP occurs in all ages). Commonly, affected cats come from a multiple-cat household (more than five cats), even though the cat may have been in a single-cat household for months or years. Often, cats with FIP have a history of failure to thrive or grow. On physical examination, affected cats may have antibiotic-unresponsive or cycling fever, lethargy, icterus, abdominal masses (especially associated with kidneys, liver, spleen, and mesenteric lymph nodes), and neurologic abnormalities. Diarrhea is not a sign of either FIP or FECV infection. Cats with ocular FIP may have keratic precipitates, anterior uveitis, hypopyon, hyphema, or retinal hemorrhage or detachment. Cats with effusive or “wet” FIP develop a yellow-tinged, high-protein, inflammatory exudate in their abdominal, pleural, pericardial, or scrotal cavities. Pleural effusion may cause dyspnea, and abdominal fluid may cause obvious ascites. Clinical pathologic examination of the fluid indicates either exudate (possibly turbid, specific gravity >1.017, 5 to 12 g/dL protein, moderate numbers of nondegenerate neutrophils, macrophages, plasma cells, and lymphocytes) or occasionally modified transudate. There may be bacteria present, reflecting the cat's immunosuppressed state. Synovial fluid may appear inflamed due to immune complex deposition. Blood testing for coagulopathy may demonstrate increases in prothrombin time (PT) and partial thromboplastin time (PTT) and increased fibrin degradation products.

Several hematologic changes occur in cats with FIP, although many affected cats have patterns differing from “classic.” Cats with FIP often have a mild neutrophilia and lymphopenia. Anemia secondary to red cell destruction or to chronic disease is common. Serum biochemistry results frequently demonstrate increases in serum protein concentration (>8.0 g/dL) consisting of hypergammaglobulinemia. Less commonly, abnormal liver enzyme activities occur due to hepatitis, hepatic lipidosis, or prehepatic sequelae of vasculitis, erythrocyte destruction, and hypoxia. Hyperbilirubinemia is common and secondary to vasculitis within the liver. Affected cats have severe liver disease.

Serology can be helpful as part of the diagnostic profile but is so often misinterpreted that results need to be evaluated carefully. Serology does not differentiate the FIP virus from FECV, is not correlated with severity of

disease, and is not indicative of active infection.[3–6] Most commonly, serology for anti-FECV and FIP virus IgG is an indirect immunofluorescent antibody (IFA) test using FIP virus–infected feline cell lines; enzyme-linked immunosorbent assay (ELISA) is available in some commercial laboratories. Dilution should start at 1:25; if a cat is negative at 1:25, one can assume that the cat is truly negative (or was only exposed within the last 10 days). Unfortunately, many laboratories only report high titers (ε1:400) as positive, despite the fact that FIP can occur in cats with titers lower than 400. Rising titers are not very helpful because cats with FIP and FECV can both have fluctuating titers. Titers greater than 16,000 are suggestive of FIP. In multiple-cat facilities, virtually all cats are seropositive. Kittens in catteries often have high titers (400 to 6400), but most do not develop FIP. Positive titers wane slowly, but cats held in single-cat households with no further exposure to coronavirus eventually become seronegative after months to years if they are not FECV carriers and do not have FIP. Rare cases occur in which cats appear to be seronegative and yet have FIP. In almost all such instances, the problem is with testing: low titers are not detected. Other reported, rare causes of seronegativity in cats with FIP include immune complex consumption of free antibodies, exhaustion of antibody-producing plasma cells, or acute fulminant disease less than 10 days after first exposure to coronavirus. It is technologically possible to generate antibodies to mutant FIP viruses. However, so many potentially different mutations exist that any single antimutant FIP virus antibody becomes useless for routine diagnostic purposes. Commercially available anti-7b antibody tests anecdotally suffer from poor positive and negative predictive values.

Reverse-transcription polymerase chain reaction (RT-PCR) can be performed to reverse-transcribe coronavirus RNA to cDNA and then make visually detectable large quantities of DNA. Although FIP viruses are genetic mutants of FECVs, numerous sites exist in the S, 3c, or 7b genes of FECV that can be mutated or deleted and confer on the virus the capability to infect and replicate within macrophages. Sometimes the change can be a single RNA base. As a result, PCR primers to discriminate between FECV and FIP virus cannot be designed. RT-PCR is sensitive and useful for documenting FECV or FIP virus RNA to confirm that a suspect lesion is due to FIP or that a cat is shedding FECV in feces. All samples for coronavirus PCR must be carefully handled, kept frozen, and protected from RNA-degrading enzymes (which are ubiquitous in most environments). PCR should be performed as quickly as possible after collection, even if samples are frozen; delays in testing may result in false-negative results. In feces, PCR-positive tests document FECV infection. The strength of the PCR signal in feces correlates with the level of infection.[7,8] Because cats with FECV vary in how much FECV is shed in feces, repeated PCR should be performed daily over 4 to 5 days to accurately detect whether a given cat sheds FECV.

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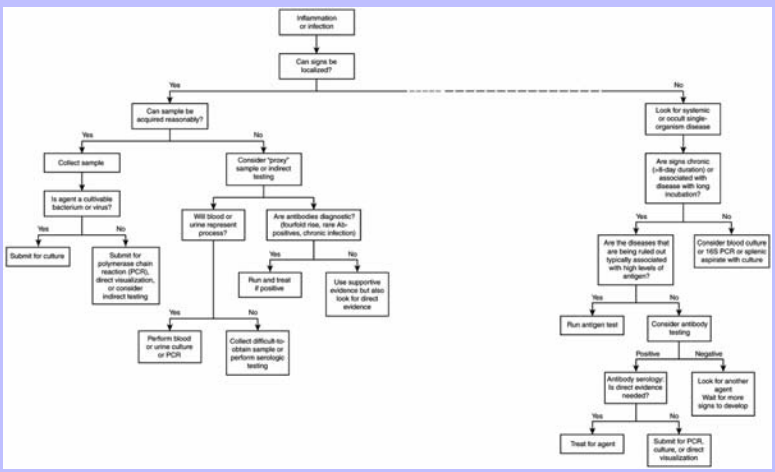
Figure 172-1 Algorithm for inflammation or infection.



Urine and cerebrospinal fluid (CSF) are not recommended for FIP PCR, because these fluids contain low numbers of virus. Ascites may be false negative because of PCR inhibitors. Blood and mesenteric lymph nodes may be false positive for FIP (small amounts of FECV). In other lesions, positive PCR can be interpreted as positive for FIP virus.

Confirmation of FIP is made by histopathology of biopsy or necropsy samples with pyogranulomas, coronavirus antigen, or nucleic acids. Hematoxylin and eosin-stained samples contain localized perivascular mixed inflammation with macrophages, neutrophils, lymphocytes, and plasma cells (or any combination of these). Pyogranulomas may be large and consolidated, sometimes with tissue necrosis, or numerous and small. To confirm coronavirus within the lesions, PCR may be performed or formalin-fixed, paraffin-embedded tissues may be stained with a chromagen-tagged monoclonal antibody such as 5.2D5 against the FIP N protein, then lightly counter stained with hematoxylin and eosin.[9]

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In the less commonly encountered cats with the neurologic form of FIP, several ante-mortem tests have a high probability of successfully ruling in or out a diagnosis of FIP. Clinical signs indicate disease in various parts of the spinal cord, cerebrum, and cerebellum and may include seizures, ataxia, paresis, paralysis, vestibular disease, peripheral neuropathy, hyperesthesia, urinary incontinence, and behavior changes. Cats with neurologic FIP are seropositive in blood and in CSF (and often in anterior chamber fluid), with a ratio of CSF: serum antibodies generally much higher than the ratio of CSF protein: serum total protein. The CSF often appears normal, or there may be mild increases in protein concentration and cell number. CNS inflammation often results in hydrocephalus. On magnetic resonance imaging (MRI), hydrocephalus may be observed, as well as contrast enhancement in ependyma, meninges, and other sites.

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172.3 TREATMENT AND PREVENTION OF FELINE INFECTIOUS PERITONITIS

Virtually every cat with confirmed FIP dies. Some veterinarians prescribe immunomodulators (*Propionobacterium acnes* (immunoregulin), interferon, acemannan) to treat cats with FIP with no documented, controlled evidence of efficacy. Immunosuppressive drugs such as prednisone (4 mg/kg, orally once a day) or cyclophosphamide (2 to 4 mg/kg, orally four times a week) may slow disease progression but do not produce a cure. Cats with FIP should also be treated with broad-spectrum antibiotics and supportive therapy (subcutaneous fluids, rest, good nutrition, lack of stress) for as long as they are comfortable. Once disease signs become debilitating and weight and appetite decline, the owner must be prepared for the reality that their cat is dying.

Unfortunately, preventing FIP is extremely difficult. Three prevention targets will be discussed: (1) preventing FIP in cats that were in contact with cats with FIP, (2) preventing FIP in cats harboring FECV, and (3) preventing FECV. After a cat in a household develops FIP, one can do virtually nothing to prevent FIP in other in-contact cats. All cats will have already been exposed to the same coronaviruses, although this is usually an FECV. Few healthy cats in the household will develop FIP, although the stress of being locked in a bathroom in the misguided attempt to prevent exposure would not help remaining cats fight infection. After a diagnosis of FIP, the probability of any other cat dying of FIP is no higher than in any other cattery with endemic FECV (which is all catteries). Exceptions exist to this rule. The first is full-sib littermates of cats with FIP, which have a 0.25 to 0.5 probability of dying of FIP as well. The second exception is during rare epidemics that may be associated with spread of FIP (in contrast to the typical scenario of spread of FECV and periodic mutations to FIP virus).[3] This type of spread of FIP virus has not been documented in natural epidemics and is unlikely, because FIP lesions are not in epithelial surfaces where the virus could be shed.

The second target is to prevent FIP in catteries with endemic FECV. This includes virtually all multiple-cat households, breeding catteries, shelters, foster homes, and other homes with more than five cats. Various tactics have been used. To be successful, they should focus on supporting cats' natural resistance to FIP virus phenotypes and reducing FECV challenge in these cats. In catteries, the major risk factor for FIP is the overall prevalence of FECV. Reducing the number of cats (especially kittens less than 12 months old) and keeping possibly FECV-contaminated surfaces clean can minimize population loads of FECV.

Vaccination is supposed to help cats fight FIP but has not proven to do so. Often cats do not seroconvert after vaccination, and study results are mixed as to whether vaccination has no effect versus a small effect. Although marginally if at all efficacious, the vaccine is safe and does not induce antibody-dependent enhanced FIP.

It is reasonable in breeding catteries to maximize heritable resistance to FIP. If a cat has two or more litters that develop FIP (at any age), then that cat should not be bred again. It would be rare for such a cat to have FIP, so it should be screened (complete blood count [CBC], serology, abdominal palpation, and possibly ultrasound). If no abnormalities are found, the animal should be neutered and placed for adoption. Particular attention should be paid to pedigrees of toms where FIP is over-represented. Because line breeding often uses valuable toms extensively, eliminating such toms may have a small but important effect on improving overall resistance.

Concurrently with palliative efforts, cattery managers should use education and communication to minimize adverse effects of FIP on cat populations. For example, if a shelter has a reputation for having FIP, adoptions may be reduced and cats may be euthanized for space. Cattery managers should have written information sheets or contracts informing buyers or adopters about FECV and FIP. They should understand that FECV is unavoidable in multiple-cat environments and that FIP is an unavoidable consequence of endemic FECV. It is particularly important that cats associated with the cattery be diagnosed accurately. For example, cats from shelters may have moderately high FECV titers *not* due to FIP and yet be euthanized inappropriately because of a history of having been at a shelter.

The last FIP-prevention scenario is to prevent or eliminate FECV, which is difficult. Isolation is not effective because of the ease with which FECV is transported on things such as clothes, shoes, dust, and cats' fur. As long as five or more cats live in a home, FECV infection maintains itself by infecting and reinfecting the same cats, whether or not the cats are separated. When the number of cats drops to five or fewer, it is much more difficult for the virus to sustain itself.

If depopulation is possible, a chance exists that endemic FECV can be induced to become extinct in the cat population. It is important to determine whether any cats are chronic FECV carriers so that they can be removed. Forty to 60% of cats in large multiple cat environments shed virus in their feces at any given time. About 20% will shed virus persistently, whereas 20% will be immune and not shed virus. Repeated PCR testing of feces should be performed at weekly intervals for 2 months or more to document carriers: if the cats remain persistently PCR-positive more than 6 weeks, they should be placed for adoption (only in very small catteries attempting to eradicate FECV).

Early weaning has been proposed as a means to interrupt transmission from adult cats to kittens. Unfortunately, queens may infect kittens as early as 5 to 6 weeks. This is prohibitively young to be removing kittens from the nurturing of the queen, particularly when the kittens likely will be exposed within a few weeks anyway. For early weaning to be effective, kittens should be taken to a new home (with no other cats) at 5 weeks of age. Even then, early weaning is not always successful.

To conclude, management of FIP should be directed at minimizing the population impact and accurately diagnosing and supporting individually affected cats. Vaccination neither prevents FIP nor FECV; testing and

removing is ineffective. Thus cattery managers have few effective management tools. However, veterinarians need to be knowledgeable regarding both successful and unsuccessful strategies to provide useful counsel to their clients with multiple-cat households.

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173 CHAPTER • 173 Other Feline Virus Diseases

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173.1 FELINE VIRAL RESPIRATORY DISEASE

Feline viral respiratory disease (Table 173-1) is most commonly seen where cats are grouped together, such as in breeding and boarding catteries and in rescue shelters. The two main causes of viral respiratory disease in cats are (1) feline herpesvirus 1 (FHV-1) (feline rhinotracheitis virus) and (2) feline calicivirus (FCV). FHV-1 generally induces a more severe disease than FCV, but FCV appears to be relatively more common.[1] Other viruses implicated in the syndrome include feline reovirus and cowpox virus (see following). Bacterial pathogens such as *Bordetella bronchiseptica* and *Chlamydophila felis* may also be involved in infectious respiratory disease in cats.

173.1.1 Causative Agents

FHV-1 is an alphaherpesvirus affecting both domestic cats and other members of the Felidae. Only one serotype of the virus exists, and genetically all isolates are very similar. The virus contains double-stranded DNA and is enveloped, making it relatively labile.

FCV is a small nonenveloped RNA virus. Only one genotype and one serotype of the virus exist, although a large degree of variability exists within both of these.[2,3] However, most strains of FCV are closely related enough antigenically to induce some degree of cross-protection, and this has been used in developing vaccines.

FCV affects both domestic cats and some nondomestic Felidae. Although dogs have their own genetically distinct calicivirus, some canine calicivirus isolates appear to be closely related to FCV and some epidemiologic evidence indicates of a link between the two.[4,5]

FCV is slightly more resistant than FHV-1 and is less susceptible to some disinfectants. However, a diluted hypochlorite and detergent mixture should be effective for both viruses.

173.1.2 Clinical Signs

FHV-1 causes upper respiratory tract (URT) disease, with oculonasal discharges, conjunctivitis, sneezing, and sometimes hypersalivation and coughing. Occasionally more severe signs including pneumonia and generalized disease may be seen, particularly in young or debilitated animals. Abortion occurs rarely and is probably due to severe systemic disease rather than a direct effect of the virus itself. The role of FHV-1 in ocular disease has been increasingly recognized, with keratitis, corneal sequestration and a possible association with uveitis having been reported.[6] Similarly, involvement of FHV-1 with skin ulcers and dermatitis has also been described.

FCV causes typical URT signs, but the disease is generally milder than that seen with FHV-1. Mouth ulceration is a characteristic feature of the disease, typically on the tongue, but lesions may occur elsewhere in the mouth or on the skin. Lameness and pyrexia may also occur, with or without respiratory or oral disease. In addition, FCV infection is associated with chronic stomatitis, although its precise role in the condition is not clear and other factors are likely to be involved.[1]

There is some strain variation in FCV with respect to pathogenic potential. Some isolates appear to be apathogenic, some may induce an interstitial pneumonia, and more recently very virulent strains have emerged in California that induce a hemorrhagic syndrome. Affected cats had variable signs, such as facial and paw edema, respiratory signs, pyrexia, icterus, and hemorrhages from the nose and in the feces.[7]

173.1.3 Diagnosis

Diagnosis of FHV-1 and FCV infection has classically been confirmed by virus isolation in cell culture from oropharyngeal or conjunctival swabs, although immunofluorescence has also been used (particularly for FHV-1). Increasingly, polymerase chain reaction (PCR) is being used for diagnosis of FHV-1, because it is significantly more sensitive than traditional methods.[8,9] However, the clinical and epidemiologic significance of PCR-positive and virus isolation–negative cats is currently unclear. For FCV, reverse-transcriptase polymerase chain reaction (RT-PCR) is less sensitive than isolation but it is useful for differentiating between strains in investigating the epidemiology of the disease.[10]

173.1.4 Treatment

Treatment involves both broad-spectrum antibacterial cover and supportive therapy. Tetracyclines are indicated if *Bordetella bronchiseptica* or *Chlamydophila felis* are involved. No specific antivirals are licensed for use in either FHV-1 or FCV infection. Some antiherpesvirus drugs used in human medicine, such as acyclovir, are not sufficiently active against FHV-1 or are too toxic for use in cats.[11] However, others have been used with some success in cats with ocular herpesvirus lesions.[12] For FCV, ribivarin has been shown to be effective in cell culture but was too toxic for use in cats. It has been suggested that recombinant interferon may be helpful in cats with viral respiratory or ocular disease.[12] In addition, some evidence reveals that orally administered L-lysine may be useful in treating acutely and latently FHV-1 infected cats.[13]

173.1.5 Epidemiology

Both viruses are primarily transmitted by direct contact between cats, although indirect transmission may also occur in the short term through contact with infectious discharges. Aerosols are not of major importance, although sneezed macrodroplets may transmit infection over a distance of 1 to 2 m.

Acutely infected cats are clearly an important source of virus, but infection also commonly occurs from clinically recovered carrier cats. In FHV-1 carriers, the virus persists in a latent form largely in trigeminal ganglia, although other tissues may also be involved. Periodically, particularly after a stress, virus reactivates in such carriers, and they can then infect other animals. Stresses that may induce virus shedding include a change of housing, kittening and lactation, and corticosteroid treatment. Some cats may show clinical signs during a reactivation episode, which can be a useful indicator that they are likely to be infectious.

Table • 173-1 Recognized Virus Infections of Cats

Upper Respiratory Tract (URT) Viruses	Feline herpesvirus type 1 (FHV-1)	URT disease
	Feline calicivirus (FCV)	URT and oral disease; sometimes lameness
	Feline reovirus	Conjunctivitis/respiratory lesions/diarrhea, experimentally; no evidence important in the field
Enteric Viruses	Feline parvovirus (FPV)	Enteritis and panleukopenia; cerebellar hypoplasia; fetal death
	Feline coronavirus	Mild enteritis; feline infectious peritonitis (FIP)
	Feline rotavirus	Mild diarrhea; disease uncommon
	Feline astrovirus	Persistent watery diarrhea; disease uncommon
	Feline torovirus	Putative torovirus detected in cats; possible association with protruding nictitating membrane and diarrhea syndrome in cats
Retroviruses	Feline leukemia virus (FeLV)	See Chapter 170
	Feline immunodeficiency virus (FIV)	See Chapter 170
	Feline foamy virus (FFV)	Previously feline syncytium-forming virus; no definite disease association
Miscellaneous Virus Infectious of Cats	Cowpox virus	Sporadic disease in cats; mainly skin lesions; cowpox virus endemic in small wild rodents
	Hantavirus	Endemic disease in rodents; serologic evidence of infection in cats; zoonotic (but cats are unlikely source)
	Rabies virus	See Chapter 177
	Aujeszky's disease virus/pseudorabies virus	Herpesvirus infection in pigs/swine; cats occasional host; disease signs are severe behavioral changes, pruritus, paralysis, coma, and death
	Feline herpesvirus type 2 (FHV-2)	Possible association with idiopathic feline lower urinary tract disease, now thought to be bovine herpesvirus 4; possible disease association unclear
	Canine distemper virus (CDV)	Evidence from field serology and experimental studies indicate that cats can be infected subclinically; however, severe disease with neurologic signs seen in large Felids
	Paramyxoviruses: hendra and nipah viruses	Newly emerged, fatal zoonotic respiratory disease of horses in Australia (Hendra virus) and pigs in Malaysia (Nipah virus); endemic in certain species of fruit bats; cats can be infected experimentally with both viruses
	Paramyxovirus: unclassified	Report of demyelinating lesions in central nervous system (CNS) of cats
	Influenza virus	Can replicate in cats after experimental inoculation but no disease signs; no evidence of cat-human transmission; may occur in reverse during human influenza outbreaks
	Borna disease virus (BDV)	Rare but fatal neurologic disease that occasionally occurs in cats
	Arthropod-borne viral infections	Cats in some parts of the world may become infected with several arthropod-borne diseases; usually asymptomatic, occasionally cause encephalitis

Unlike FHV-1 carriers, FCV carriers shed virus more or less continuously and are therefore always infectious to other cats. The virus persists in tonsil and other oropharyngeal tissues. In some cats the carrier state appears to

be lifelong, but most spontaneously recover at some point and appear to eliminate virus. FCV carriers appear to be very common, with approximately 20% to 30% of cats in the general population shedding FCV.[1]

173.1.6 Prevention and Control

Prevention and control may be achieved through a combination of vaccination and management. Both modified-live virus (MLV) vaccines and inactivated adjuvanted vaccines are marketed for parenteral injection against FHV-1 and FCV. Modified-live intranasal vaccines are also available in some countries but are not widely used. A number of recombinant vaccines have also been created, including FHV-1 deletion mutants, baculovirus constructs, a myxoma FCV recombinant, and an FCV DNA vaccine.

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Both MLV and inactivated FHV-1 and FCV vaccines are reasonably effective at protecting against disease, but none protects against infection or the development of the carrier state. For FCV, various strains are used in commercial vaccines, for example, strains F9 and 255. Most seem to protect against the majority of FCV isolates but not as well against all of them. Some evidence suggests that the percentage of isolates neutralized by such strains is decreasing.

Parenteral MLV vaccines are generally safe, but disease signs may occasionally occur after their use. This may be due to inadvertent oronasal exposure to the vaccine, for example, if the cat licks the injection site, and occasionally vaccine virus may generalize and spread.[10,14,15] Inactivated adjuvanted vaccines may therefore be safer in disease-free colonies. However, adjuvants can sometimes cause local or systemic reactions, and (very rarely) sarcomas may develop at the site of injection.

Intranasal MLV vaccines induce better protection but often at the expense of slight side effects, such as sneezing and oculonasal discharges. They are however useful for rapid onset of protection.

Primary vaccination in young kittens is generally at 8 to 9 weeks of age, with a second dose at 12 weeks. Boosters are traditionally recommended every year, but immunity may last longer in some cases.[16] In view of this and because of concerns over vaccine site reactions, it has been suggested that after the first annual booster, revaccination intervals may be extended to up to 3 years.[17] However, an individual risk-benefit assessment should be carried out to determine the most appropriate vaccination strategy for a particular animal[18] (see Chapter 164).

Management measures are aimed at preventing spread of viruses within a cattery, through both direct and indirect contact between cats. In boarding catteries and rescue shelters, cats should be individually housed with solid partitions between pens, and good hygiene and disinfection procedures should be used. In breeding colonies, young kittens are most at risk when they lose their maternally derived antibodies (MDA). Overcrowding should be avoided and cats kept as stress free as possible. Ideally, queens should kitten in isolation with early weaning of kittens or earlier vaccination schedules implemented if required. Such measures have been described in detail elsewhere.[1]

173.2 FELINE PANLEUKOPENIA/FELINE PARVOVIRUS (FPV) INFECTION

Feline panleukopenia is a highly infectious disease affecting members of the Felidae and a number of other species including mink, ferrets, and raccoons. The disease is characterized by enteritis and a panleukopenia and has a high mortality. Vaccination is generally highly effective in controlling the disease.

Feline panleukopenia is caused by a parvovirus, a small nonenveloped DNA virus similar to the canine parvovirus type 2 (CPV-2), which causes a severe hemorrhagic enteritis in dogs. Although feline panleukopenia is a long-established disease of cats, CPV-2 emerged suddenly in 1978 as a host range variant of FPV and spread rapidly within the dog population. The mechanism of its evolution is unknown, but it has been suggested that it may have originated from a wild carnivore intermediate host.[19] CPV-2 has largely been replaced by CPV-2a and CPV-2b, which now coexist in dog populations worldwide.[20] Although CPV-2 isolates did not replicate in cats, both CPV-2a and CPV-2b do so and have been reported to constitute a small proportion of isolates found naturally in cats.[21–23] In addition, some evidence suggests that the percentage of CPV isolates from cats in some parts of the world is increasing and that a potential new variant, CPV-2c, from leopards may also have emerged.[22]

Parvoviruses have an affinity and requirement for actively dividing cells. The main target tissues are the rapidly dividing cells of lymphoid tissue and the bone marrow, leading to panleukopenia, and the crypt epithelium of the intestinal mucosa, leading to enteritis. Infection early in pregnancy may lead to fetal death and resorption. From the middle third of gestation to immediately postnatally, infection results in cerebellar hypoplasia in kittens.

The severity of the disease varies considerably, ranging from a subclinical infection to a peracute syndrome with sudden death. In general, the disease appears to be more severe in young kittens. Other factors, such as a change of food or coinfection with other pathogens, which increase the mitotic rate in the intestinal villi, may increase the severity of disease. In a typical case the first signs of illness are lethargy, fever, and anorexia with apparent thirst but refusal to drink. Affected cats may vomit, particularly in the early stages. Profuse watery diarrhea or dysentery then develops, and cats may become severely dehydrated. Most fatalities occur within 3 to 5 days of the first signs of illness and are probably due to overwhelming bacterial infection, dehydration, and electrolyte imbalance. Experimental infections have suggested that infection with CPV in cats may lead to milder disease with reduced virus shedding compared with FPV, although the situation in the field is unclear.[24,25]

Kittens with cerebellar hypoplasia show ataxia, incoordination, hypermetria, and often intention tremors. These signs persist for life. Nevertheless, affected kittens may learn to compensate and otherwise function normally. Forebrain lesions have been reported and may lead to seizures and behavioral abnormalities.[26] Retinal lesions may also be present but are usually of no clinical significance. A possible role of FPV in myocarditis and idiopathic cardiomyopathy has also been suggested.[27]

A presumptive diagnosis of feline panleukopenia may be made based on history, vaccination status, and clinical signs. Disease is more commonly seen in rescue shelters and in groups of unvaccinated cats. Virus culture from fecal samples is difficult, and fecal shedding only occurs for a short period after infection. Enzyme-linked immunosorbent assays (ELISAs) and rapid immunomigration tests have been used for detection of viral antigen in fecal samples, with variable sensitivity and specificity. More recently, PCR tests for the detection of viral DNA in fecal samples have been used, and these have good sensitivity.[28] Antibody levels, which may reach very high titers after an active infection, may be useful as an aid to diagnosis.

Diagnosis may also be confirmed at necropsy, where characteristic histopathologic changes, including the presence of intranuclear inclusion bodies, may be seen in the crypt epithelium of the small intestine. Specific diagnosis using in situ hybridization and immunohistochemistry has also been reported.

Treatment is largely supportive and is aimed at restoring the fluid and electrolyte imbalance and covering against secondary bacterial infection.

Both MLVs and inactivated parenteral vaccines are available. Only one serotype of the virus exists, and the vaccines are generally highly effective in preventing disease. Protection against CPV-2b has also been shown experimentally,[24] and it is likely that FPV vaccines will protect against such isolates in the field. Primary vaccination usually takes place at 8 to 9 weeks of age, with a second dose at 12 weeks. However, the duration of MDA in kittens can be quite variable, and those born to unvaccinated queens or those who have not suckled colostrum may have no or very low levels of MDA. In contrast, kittens born to recovered queens may have very high levels of MDA lasting up to 20 weeks. MLV vaccines should not be used in kittens under 4 weeks of age or in pregnant queens because of the risk of the development of cerebellar hypoplasia.

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Boosters have typically been administered every 1 to 2 years, although some evidence suggests that immunity may last longer.[16] Consequently, and because of possible safety issues with respect to feline vaccines, three yearly intervals are now being suggested by some.[17]

Although the disease has largely been controlled by vaccination, cases still occur, particularly in rescue shelters and sometimes also in breeding colonies.[29] FPV is a remarkably stable virus and may persist in infected premises for up to 1 year: subclinical infection of susceptible cats can also help maintain the virus within a population. Not all disinfectants are active against FPV, but sodium hypochlorite and glutaraldehyde solutions are effective. Because of the ability of the virus to survive in the environment, thorough disinfection of premises must be carried out after any disease outbreaks and any new cats admitted to such infected premises should be fully vaccinated. Although persistent infections may occasionally occur after in utero or neonatal infection, carriers do not play a significant role in the epidemiology of the disease.

173.3 BORNAVIRUS DISEASE (FELINE "STAGGERING DISEASE")

Borna disease (BD) is a rare but fatal neurologic disease caused by a negative-stranded RNA virus, Borna disease virus (BDV). The disease occurs predominantly in horses and sheep; but a number of other species may also be affected, and increasing evidence indicates that cats are also susceptible.[30,31] The disease in cats has been reported mainly in Europe but also occurs in other parts of the world, including Japan.[32] Affected cats show motor dysfunction and behavioral changes including an unsteady "staggering" gait, depression, and progressive hindlimb ataxia and paresis. Other signs include anorexia, increased salivation, hyperesthesia, impaired vision, and seizures. The disease is generally progressive; despite supportive treatment, affected cats die or are euthanized. At necropsy a characteristic nonsuppurative meningoencephalomyelitis is seen mainly in the gray matter of the cortex, brain stem, and spinal cord. In some cases, evidence of BDV infection is seen in cats with no neurologic disease. It has been suggested that BDV or a related virus may be involved in psychiatric disorders in humans.[33]

173.4 POXVIRUS INFECTION

Cats are susceptible to cowpox virus, a member of the Orthopoxvirus family.[34,35] Occasional cases of parapoxvirus infection in cats have also been reported.[36] Cowpox virus is found only in Eurasia, and the reservoir hosts are small wild mammals such as voles and woodmice. The disease is mostly seen in rural cats that hunt rodents, and most cases are seen in summer and autumn when opportunities for contact with the reservoir hosts are highest. Cat-to-cat transmission rarely occurs and generally causes only subclinical infection.

The disease typically starts with a single primary lesion, generally on the head, neck, or forelimb, which may be ulcerated or scabbed and can become secondarily infected. Although some cats may only have a primary lesion, in

many cases widespread secondary skin lesions also develop after 1 to 3 weeks. These appear as randomly distributed, small epidermal nodules that increase in size over a few days to well-circumscribed ulcers about 1 cm diameter. These gradually become scabbed and heal over a period of 4 to 5 weeks, and most animals recover uneventfully. Occasionally, especially in immunosuppressed cats, systemic illness may develop. Some exotic felids (e.g., cheetahs) are particularly susceptible, and a rapidly fatal pneumonia often develops.

Diagnosis is by virus culture, electron microscopy (EM), or PCR of scab material, or by serology.[37,38] Characteristic histopathologic lesions include the presence of intracytoplasmic, eosinophilic inclusion bodies. Immunostaining is a useful aid to diagnosis.

Treatment includes broad-spectrum antibiotics to control secondary bacterial infection and general supportive therapy with fluids where necessary. Glucocorticoids are contraindicated because they can predispose to the development of secondary lesions, more severe disease, or both. Cidofovir has been shown to be active against cowpox virus in cell culture and some animal systems, although its use in cats has not been reported.[39] No vaccines are available, although vaccinia (smallpox vaccine) may be considered for valuable zoo collections.[40] Cowpox is zoonotic and may cause both a localized lesion and sometimes severe systemic illness in infected people, particularly those who are immunosuppressed. However, the risk of cat-human transmission is small if basic hygiene precautions are taken.

173.5 FELINE FOAMY VIRUS (FELINE SYNCITIUM-FORMING VIRUS) INFECTION

Feline foamy virus (FFV) is a member of the foamy virus group (spumaviruses) in the retrovirus family. Spumaviruses have been isolated from many species, but they generally do not appear to be pathogenic. Their main importance lies not in clinical medicine but as potential contaminants in research and vaccine production and, more recently, as possible viral vectors in recombinant vaccine technology.

FFV infection is very common in cats, with seroprevalences of up to 90%, depending on the population tested.[35,41] Infected cats harbor virus indefinitely; therefore seropositivity equates with infection. FFV is transmitted horizontally, and in some cases vertically, from infected queens to kittens.

The virus has been isolated from both clinically healthy cats and cats with a variety of diseases, although no clinical signs have been seen after experimental infection. However, FFV may predispose to disease in conjunction with other agents or particular MHC types. Such an association has been suggested for FFV in the feline progressive polyarthritis syndrome.[42]

173.6 ASTROVIRUS

Astroviruses have been detected in a number of species including cats, and in humans are a common cause of gastroenteritis. Astroviruses have been detected in the feces of kittens with diarrhea, and in normal cats.[43,44] The diarrhea has been described as persistent (4 to 14 days) and watery and may be accompanied by vomiting, pyrexia and depression. Mild diarrhea has also been reproduced experimentally.[43] It is not clear how commonly astrovirus-induced disease occurs in cats: a limited serologic study has reported that less than 10% of cats in the UK have antibody, although this may be an underestimate as only one serotype was examined.[45]

Serologic cross-reactivity has been reported between feline astrovirus and human sera and a close phylogenetic relationship shown between pig, human, and feline astroviruses. However, no evidence indicates on-going human-animal transmission, although it may have occurred in the past.

173.7 FELINE REOVIRUS INFECTION

Reoviruses have been isolated from both healthy and diseased cats with a variety of signs. Serologic surveys suggest infection is widespread, although the clinical importance of reovirus infection in cats is unknown.[35] Three serotypes of the virus exist. Experimental inoculation of kittens with serotype 3 induced predominantly conjunctivitis, photophobia, and serous ocular discharges; type 2 induced mild diarrhea[46]; and newborn kittens inoculated with type 1 nursed poorly and died 2 days later with respiratory lesions identified at necropsy.[35,47] However, little evidence suggests that these conditions occur in the field.

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173.8 ROTAVIRUS

Rotaviruses are a major cause of enteritis in humans and in many animal species such as cattle and pigs. Typically rotavirus infections occur in neonatal animals, although older animals may also be affected.

In cats, rotavirus infection is widespread, with between 28% to 100% of cats seropositive depending on the population sampled.[35,48] However, clinical disease appears to be uncommon, and diarrhea, when it occurs, tends to be mild and of only short duration.[35,49,50] Diagnosis of rotavirus infection may be carried out from fecal samples by EM, polyacrylamide gel electrophoresis of viral RNA, or by PCR.[45] Because of serologic differences between strains, ELISAs developed for diagnosis of human rotavirus infections may not necessarily detect all feline rotaviruses.[45]

Cross-species transmission is known to occur with rotaviruses experimentally, although to what extent this happens under natural conditions is not known. A number of recent reports have shown close phylogenetic relationships between some feline and some human rotavirus strains, and it has been suggested that cross-infection between cats and humans may sometimes occur.

173.9 HANTAVIRUS INFECTION

Hantaviruses are enzootic worldwide in wild and laboratory rodents, and they are zoonotic.[51] However, strains vary in their pathogenicity to humans. Disease syndromes seen in humans include hemorrhagic fever with renal syndrome in Asia and hantavirus pulmonary syndrome in North America. Only mild or subclinical disease is seen with most European strains.[52]

Hantavirus antibody has been detected in laboratory-housed cats in Belgium and in up to 10% cats from a variety of backgrounds in the United Kingdom, Austria, and Canada.[53–55] In addition, virus has been isolated from a cat in China.[56] However, the clinical significance of Hantavirus infection in cats is not known. There is little evidence to suggest that in most parts of the world cats are likely sources of human infection; however, an increased risk of human infection associated with cat ownership has been reported in China.

173.10 TOROVIRUS INFECTION

Toroviruses are a group of viruses similar to coronaviruses, but with a characteristic rod-or doughnut-shaped core. They have been detected in a number of species including cattle (Breda virus), horses (Berne virus), and humans and tend to be associated with enteritis. There is some evidence for a torovirus of cats that may be associated with

protruding nictitating membrane and diarrhea syndrome.[48] However, other workers have been unable to substantiate this.[57]

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174 CHAPTER • 174 Systemic Mycoses

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Systemic mycoses are fungal infections that disseminate from a single portal of entry. The respiratory system serves as the portal of entry for most systemic fungi that affect the dog and cat, but the gastrointestinal (GI) system is occasionally implicated.[1]

Systemic mycoses are becoming more worrisome in human medicine because of immune-suppressive diseases such as acquired immunodeficiency syndrome (AIDS) and the expanded use of immune-suppressive therapy for cancer and organ transplantation. Immune suppression does not play as important a role in veterinary patients, but the importance of such diseases in humans has led to tremendous pharmacologic advances in the treatment of fungal infections.

Systemic fungal infections cause disease, the clinical signs of which are dependent on which systems are involved (Table 174-1). Weight loss, lymphadenopathy, and fever are typical of most systemic mycoses. Because the respiratory system is the usual portal of entry, clinical signs such as cough, dyspnea, and exercise intolerance are common. If the GI system is the portal of entry, as may occur with histoplasmosis, malabsorption may lead to severe diarrhea and weight loss.

In most cases, diagnosis of a systemic mycosis is dependent on demonstrating the presence of the organism in tissue. For yeasts such as *Cryptococcus* or *Candida,* or for dimorphic fungi that have a yeast phase in tissue, such as *Blastomyces dermatitidis* or *Histoplasma capsulatum*, the diagnosis can usually be made cytologically. For other fungi that grow as hyphal organisms in infected tissue, the diagnosis is usually dependent on histopathology, culture, or molecular techniques. Serology is used extensively in practice to support the diagnosis of fungal infections, but with the exception of tests for cryptococcal antigen, most commercially available assays determine the presence of antibody and may indicate only previous exposure.

Many treatment regimens have been reported for the management of various systemic mycoses, but few veterinary studies have been performed that have critically evaluated these agents in a prospective manner, and studies comparing treatment regimens are practically nonexistent. A lack of controlled observations has led to recommendations that are based primarily on anecdotal information, extrapolation from what is done in people, and small retrospective studies. The “best” treatment regimen for any given systemic fungal infection is therefore largely a matter of opinion.

Table • 174-1 Differential Diagnoses for Systemic Manifestations of Systemic Mycoses

Multisystemic granulomatous, neoplastic, and immune-mediated diseases must be differentiated from disseminated systemic mycoses.

Differential Diagnosis for Nodular Skin Disease

Bacterial skin disease

Actinomycosis
Mycobacteriosis
Botryomycosis
Brucellosis
Rhodococcus equi infection
Bartonella vinsonii Subs, *berkhoffi infection*

Mycotic and miscellaneous infectious skin disease

Cryptococcosis
Coccidioidomycosis
Sporotrichosis
Basidiobolomycosis
Conidiobolomycosis
Phaeohyphomycosis
Hyalohyphomycosis
Eumycotic mycetoma
Dermatophytic mycetoma
Protothecosis
Pythiosis
Lagenidiosis
Nodular leishmaniasis

Noninfectious pyogranulomatous skin disease

Foreign body reaction
Idiopathic nodular panniculitis
Sebaceous adenitis (nodular form)
Canine cutaneous sterile pyogranuloma/granuloma syndrome

Neoplasia

Squamous cell carcinoma
Cutaneous lymphoma
Mycosis fungoides (cutaneous T-cell lymphoma)
Cutaneous histiocytosis

Miscellaneous diseases

Systemic lupus erythematosus (SLE)
Systemic vasculitis
Cutaneous embolic disease

Differential Diagnosis for Chorioretinitis, Exudative Retinal Detachment, and Panophthalmitis

Fungal

Cryptococcosis
Coccidioidomycosis
Geotrichosis
Histoplasmosis
Aspergillosis

Neoplasia

Lymphosarcoma
Metastatic neoplasia

Miscellaneous infectious causes

Protothecosis
Brucellosis

Toxoplasmosis *Neosporum caninum* infection Leishmaniasis Lymphadenopathy must be differentiated from numerous causes, including lymphosarcoma, other fungal infections, rickettsial diseases, brucellosis, mycobacteriosis, protothecosis, and leishmaniasis. Solitary bone lesions must be differentiated from primary or metastatic bony neoplasia and other fungal or bacterial osteomyelitis.

The principal antifungal agents are antibiotics produced by microorganisms (e.g., amphotericin B, griseofulvin) and synthetic agents (e.g., potassium iodide, flucytosine, azole derivatives, allylamine derivatives, chitin synthesis inhibitors). The options for treatment of fungal infections increased substantially during the 1990s with the Food and Drug Administration's approval of the azole derivatives fluconazole and itraconazole. Clinical trials have been performed using itraconazole,[2–4] and case reports and retrospective reviews documenting the use of both drugs are available in the veterinary literature. The high cost of most antifungal agents and the long treatment protocols required affect the number of cases that are treated, both limiting and probably epidemiologically biasing the data that have been generated to date. Adding to the difficulty of assessing the efficacy of antifungal agents are that the pharmacologic principles of antifungal therapy are only partially understood, in vitro testing of fungi for resistance to antifungal agents provides little clinically useful information, susceptibility testing yields variable results, and tissue distribution of antifungal agents correlates variably with the clinical outcome.

174.1 ANTIFUNGAL AGENTS

174.1.1 Amphotericin B

Amphotericin B is a polyene macrolide antibiotic produced by the aerobic actinomycete *Streptomyces nodosus*. It was discovered in the 1950s and was one of the first antifungal agents found to be widely useful in treating systemic fungal infections. It has become the gold standard against which the efficacy of new antifungal agents is compared; despite significant toxicity and poor oral bioavailability, it remains the drug of choice for the treatment of many invasive mycoses. The traditional formulation of amphotericin B is a desoxycholate preparation (Fungizone) that, after intravenous administration, is highly protein bound (91% to 95%), primarily to lipoproteins, erythrocytes, and cholesterol in the plasma, and then is redistributed from the blood to the tissues. Penetration into the cerebrospinal fluid (CSF) is poor. Tissue accumulation accounts for the majority of drug disposition. Only 5% to 10% of amphotericin B is excreted in the urine and bile. Although great care should be used when treating animals in renal or hepatic failure, no modification of the dose is necessary unless the renal or hepatic damage is attributable to the drug. Amphotericin B acts by binding to sterols in cell membranes, especially ergosterol in fungal cell membranes. Binding alters membrane permeability, causing leakage of sodium, potassium, and hydrogen ions and eventually leading to cell death. Amphotericin B probably also has important immunostimulatory effects by oxidation-dependent stimulation of host macrophages.[5] Stimulation of macrophages may play an important role in the treatment of some systemic fungal infections with amphotericin B. Toxic effects are attributable to affinity for sterols such as cholesterol in mammalian cell membranes.

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Amphotericin B has been effective in the treatment of blastomycosis, histoplasmosis, coccidioidomycosis, cryptococcosis, systemic candidiasis, zygomycosis, and occasionally pythiosis. It is administered as a series of intravenous infusions (0.22 to 0.5 mg/lb [0.5 to 1 mg/kg] every 48 hours to a cumulative dose of 2 to 4 mg/lb [4 to 8 mg/kg] or until azotemia occurs). Bolus dosing over 5 to 10 minutes is common, but clinicians can reduce renal toxicity by infusing the drug in 5% dextrose over 1 to 5 hours. Nephrotoxicity is the most signi-ficant adverse effect and is dose dependent.[6] Generally, renal azotemia is reversible, and renal function returns to

normal after cessation of therapy. However, return to pretreatment values may take several months. Irreversible renal dysfunction is more likely in animals with pre-existing azotemia or in those receiving other nephrotoxic agents such as aminoglycosides. Blood urea nitrogen (BUN) should be monitored before each administration of amphotericin B. If the BUN is greater than 50 mg/dL, the drug should be discontinued until the azotemia has resolved. Clinicians believe nephrotoxicity is caused by disruption of renal tubular epithelial cell permea-bility resulting in increased delivery of chloride ions to the distal tubule, with subsequent decreased glomerular filtration rate (GFR) being the result of tubuloglomerular feedback. This feedback is amplified by sodium depletion and suppressed by sodium loading. Administration of 0.9% sodium chloride (5 to 10 mL/lb) before amphotericin B administration decreases the incidence of nephrotoxicity in people. Other possible mechanisms of nephrotoxicity include decreased renal blood flow and direct renal cellular toxicity. Tumor necrosis factor (TNF) may also play a role in mediating amphotericin B–induced azotemia. Pentoxifylline, a hemorrheologic drug, seems to exert protective effects in people and rats. Mannitol and dopamine have also been shown to decrease nephrotoxicity in experimental situations. Other possible toxic effects include thrombophlebitis, pyrexia (usually ameliorated by pretreatment with nonsteroidal anti-inflammatory drugs or anti-inflammatory doses of glucocorticoids), hypokalemia, distal renal tubular acidosis, hypomagnesemia, cardiac arrhythmias, and nonregenerative anemia. Calcinosis cutis has been reported in dogs with blastomycosis 2 to 4 weeks after beginning treatment with amphotericin B.[7]

Recently the use of novel delivery systems have been effective in reducing nephrotoxicity and improving site-specific delivery of amphotericin B, allowing higher doses to be administered. Currently three new formulations of amphotericin B are available for clinical use in human patients: (1) amphotericin B lipid complex (ABLC) (Abelcet®, Enzon), (2) amphotericin B colloidal dispersion (Amphotec®, Intermune, Inc.), and (3) liposome-encapsulated amphotericin B (AmBisome®, Gilead Sciences).[8] Of these three formulations, ABLC has been the most extensively evaluated in small animal patients and is the least expensive. In dog studies, lipid-complexed amphotericin B was determined to be 8 to 10-fold less nephrotoxic than conventional amphotericin B. The decreased toxicity is due to decreased renal cell uptake, reduced tubular toxicity, reduced free amphotericin in solution in plasma, and a selective transfer of amphotericin directly to fungal cell membranes. The reduced toxicity allows higher cumulative doses to be used, which increases drug efficacy. This increase in efficacy is also thought to be related to rapid uptake of lipid complexes by phagocytic cells of the reticuloendothelial (RE) system, which allows sites of inflammation and organs with high RE system activity such as liver, spleen, and lung to receive higher doses of amphotericin B despite minimal renal uptake.

Clinical trials in people have documented improvement in treatment outcomes for many types of fungal infections. ABLC has been used successfully to treat blastomycosis in dogs without significant nephrotoxicity being noted.[9] ABLC can be used in dogs at a dose of 1 to 1.5 mg/lb (2 to 3 mg/kg) intravenously three times a week to a cumulative dose of 24 to 27 mg/kg. Azotemia is rare.

174.1.2 Oral Azole Antifungal Drugs

The azoles are classified as imidazoles (ketoconazole [Nizoral Janssen]) or triazoles (fluconazole [Diflucan Pfize] and itraconazole [Sporanox Janssen]), according to whether they contain two or three nitrogen atoms, respectively, in the five-member azole ring. Ketoconazole and itraconazole have similar pharmacologic profiles, but fluconazole is unique because of its comparatively small molecular size and low lipophilicity. The azole antifungal agents act by inhibiting ergosterol synthesis through interaction with 14-α-demethylase, a cytochrome P-450 enzyme that is necessary for the conversion of lanosterol to ergosterol. Similar interaction in mammalian cells with enzymes dependent on cytochrome P-450 also mediates some of the major toxic effects. The imidazoles are much more potent inhibitors of mammalian cell cytochrome P-450 than are the triazoles. Other antifungal effects include inhibition of endogenous respiration, toxic interaction with membrane

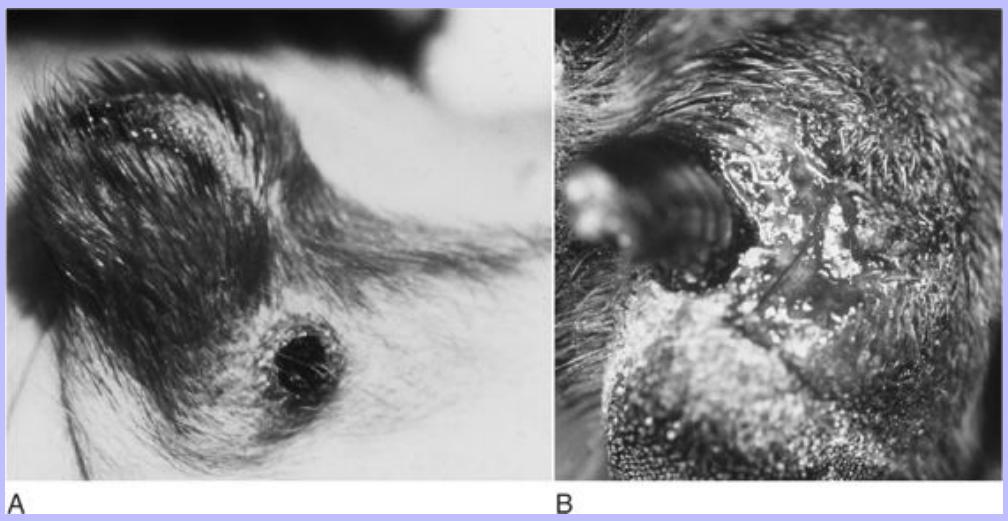
phospholipids, and inhibition of morphogenetic transformation of yeasts to the mycelial forms. Some of the azole antifungal drugs, especially itraconazole and ketoconazole, are potent immune-suppressive agents, suppressing T-lymphocyte proliferation in vitro. Ketoconazole has anti-inflammatory properties that are probably mediated through inhibition of 5-lipoxygenase activity.

Ketoconazole and itraconazole are weak bases that require an acid environment for maximal oral absorption. Antacid administration inhibits oral bioavailability, and the bioavailability of itraconazole is two to three fold higher when taken with food. Recently, itraconazole has been solubilized in cyclodextrins in an effort to increase its absorption after oral dosing and to allow development of a parenteral formulation. Pharmacokinetic studies in both humans and cats have demonstrated increased absorption of itraconazole after administration of the oral solution in comparison to capsules. Both the oral solution (10 mg/mL) and the parenteral formulation (200 mg ampules diluted in 50 mL 0.9% sodium chloride for intravenous administration) are currently available.

Fluconazole is not affected by gastric pH, and food does not affect its oral bioavailability. Peak plasma concentrations of itraconazole and fluconazole do not occur until 6 to 14 days after treatment is begun. This may account for the clinical lag time often seen between the time the drug is started and the time the patient begins to improve. A loading dose can be given for the first 3 days of treatment to reduce the time until steady-state concentrations are attained. Ketoconazole and itraconazole are extensively bound to plasma proteins (>99%), but because of their lipophilicity, both drugs distribute well throughout most tissues; however, 673
concentrations in urine and CSF are typically very low. Neither drug crosses the blood-brain, blood-prostate, or 674
blood-ocular barriers well. Despite this, central nervous system (CNS), prostatic, and ocular fungal infections respond well to treatment with itraconazole. Itraconazole is concentrated in the skin, with delivery being via sebum. Sebum concentrations are 5 to 10 times higher than plasma concentrations, and detectable amounts persist for up to 14 days after the drug is discontinued. Detectable concentrations can be found in the hair and stratum corneum for up to 4 weeks. This property makes itraconazole ideal for treating dermatophyte infections and other fungal infections with cutaneous manifestations. Fluconazole is minimally protein bound and highly water soluble and distributes similarly to free water. High concentrations can be found in urine, CSF, and ocular fluids, and the drug crosses the blood-brain, blood-prostate, and blood-ocular barriers well. Ketoconazole and itraconazole are extensively metabolized in the liver and excreted in the bile and, to a lesser extent, in the urine. In contrast, fluconazole is minimally metabolized, and approximately 80% is excreted unchanged in the urine; consequently, the dose of fluconazole should be reduced in animals with decreased GFR.

The azole antifungal agents are widely used in veterinary medicine for treating systemic fungal infections.[2–4,10] Ketoconazole has been effective as a sole therapeutic agent in the management of blastomycosis, histoplasmosis, cryptococcosis, and coccidioidomycosis. However, with the possible exception of coccidioidomycosis, ketoconazole is probably not as effective as amphotericin B. Ketoconazole is primarily used in conjunction with amphotericin B when managing systemic infections, allowing lower doses of amphotericin B to be used and thus limiting nephrotoxicity. Itraconazole and fluconazole are safer and more effective than ketoconazole and can be used as sole agents in the management of most systemic mycoses. Itraconazole appears to be more effective than fluconazole in most situations, but fluconazole may be superior in the management of cryptococcosis and CNS, prostatic, and urinary tract infections. Itraconazole is the treatment of choice for blastomycosis in dogs and probably cats. Itraconazole has proven very effective as a sole treatment agent for histoplasmosis in cats.[3] The authors have found itraconazole to be effective in treating about 15% of dogs with GI pythiosis, despite the fact that *Pythium insidiosum* does not contain significant concentrations of membrane ergosterol. In treating most systemic fungal infections, a lag occurs between the initiation of treatment and clinical improvement. In severely affected animals, amphotericin B should probably be used initially or in conjunction with the triazole during this lag period.

Figure 174-1 **A**, Lesion on the prepuce of a dachshund being treated for blastomycosis with itraconazole. The lesion is caused by an itraconazole-induced cutaneous vasculitis. **B**, Paronychial lesion caused by an itraconazole-induced cutaneous vasculitis in a Doberman pinscher.



The dose of ketoconazole is 4.5 to 13.6 mg/lb (10 to 30 mg/kg) divided twice a day. Side effects are often limiting, especially at higher doses. Fluconazole (1 to 4.5 mg/lb; 2.5 to 10 mg/kg) and itraconazole (2.2 to 4.5 mg/lb; 5 to 10 mg/kg) are usually better tolerated. Pharmacokinetic studies of itraconazole have been performed in cats.[11] Based on these studies, the oral itraconazole solution is preferred to the capsules, with a 24-hour dosing interval being sufficient at 4.5 mg/lb (10 mg/kg). Steady-state concentrations take up to 3 weeks to achieve. Most adverse effects of itraconazole are related to high serum concentrations, and animals that exhibit adverse effects usually do well on half the original dose. Adverse effects of the azole antifungal agents are similar across the class. Ketoconazole is the least tolerated, and itraconazole appears to be the best.
Dose-related GI side effects (anorexia and vomiting) are most common, especially in cats. When these occur, dividing the dose into two treatments or reducing the dose may be of benefit. Azole-induced anorexia in cats is often ameliorated by the use of appetite stimulants such as oxazepam or cyproheptadine. Liver enzymes should be periodically monitored in animals being treated with azole antifungals. Asymptomatic increases in transaminase concentrations are seen in about half of animals treated with itraconazole, but this does not necessitate a change in therapy unless the animal also has anorexia, vomiting, depression, or abdominal pain. Enzyme concentrations often return to normal over time without intervention. Symptomatic hepatotoxicity is occasionally seen with ketoconazole use but is unusual after fluconazole or itraconazole administration.
Cutaneous reactions are seen in approximately 7% of dogs receiving itraconazole at a dose of 4.5 mg/lb (10 mg/kg).[2] A local ulcerative dermatitis due to a cutaneous vasculitis (Figure 174-1) usually resolves shortly after the drug is discontinued. More severe reactions such as erythema multiforme or toxic epidermal necrolysis are rare. Thrombocytopenia has been associated with fluconazole use in people but has not been documented in animals. Adrenal insufficiency is possible with ketoconazole use. Azole interference with the activity of hepatic

microsomal enzymes can lead to increased concentrations of coadministered drugs such as cyclosporine, digoxin, phenytoin, sulfonylureas, and warfarin.

The emergence in human patients of itraconazole-resistant fungal pathogens has prompted a search for new triazoles with greater potency. One of these newly developed triazoles, voriconazole, has recently gained FDA approval and is available to veterinarians. Voriconazole (Vfend™, Pfizer) is a fluconazole derivative that has potent in vitro and in vivo activity against common endemic and opportunistic fungal pathogens, including molds other than the zygomycetes. It has demonstrated efficacy for invasive aspergillosis and oropharyngeal candidiasis in phase III clinical trials and can be administered either orally or intravenously. Its indications in human patients are for the treatment of invasive aspergillosis and other infections caused by molds (such as *Fusarium*) in immunocompromised individuals. Unfortunately, its high cost makes it unlikely to be used extensively in veterinary patients.

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174.1.3 Flucytosine

Flucytosine is a synthetic antifungal drug with activity attributed to disruption of protein synthesis by inhibition of DNA and RNA synthesis. The drug is synergistic with amphotericin B and is used almost exclusively as an adjunct to amphotericin B in the treatment of cryptococcosis in cats. Flucytosine has good oral bioavailability. It is widely distributed and crosses the blood-brain barrier. The most common side effects are diarrhea, anorexia, and vomiting. Dose-dependent bone marrow suppression manifesting as neutropenia, thrombocytopenia, or pancytopenia is a less common but more signi-ficant toxicity. Cutaneous or mucocutaneous drug eruptions consisting of depigmentation followed by ulceration, exudation, and crust formation (occurring most frequently on the scrotum and nasal planum) have been described in a series of dogs. The dose of flucytosine used in cats is 125 to 250 mg orally divided two to four times a day.

174.1.4 Allylamines

Terbinafine is a synthetic allylamine antifungal drug that interferes with squalene epoxidase and is a potent inhibitor of ergosterol biosynthesis. Squalene accumulation in the fungal cell may account for the drug's fungicidal activity. A keratinophilic compound that is well distributed in skin, it has been used primarily for the treatment of dermatophytosis and onychomycosis in both human and veterinary patients. It may also have efficacy for the treatment of sporotrichosis. The efficacy of terbinafine for invasive or systemic fungal infections has not been well evaluated. However, the authors' clinical observa-tions support the use of this drug in combination with itraconzole for the medical treatment of pythiosis when complete surgical resection of infected tissues is not possible. Potential side effects of terbinafine include GI toxicity, cutaneous reactions, and hepatitis. The drug dose ranges from 2.5 to 9 mg/lb (5 to 20 mg/kg) orally once daily.

174.1.5 Chitin and Glucan Synthesis Inhibitors

Drugs that inhibit the synthesis of chitin or β-glucan, two substances important to the structural and functional integrity of the fungal cell wall, hold promise as antifungal therapeutic agents because their targets are unique to fungi. Chitin synthase inhibitors include lufenuron [program] Novaris (a nonspecific inhibitor of chitin synthase) and drugs in the nikkomycin class, which are competitive inhibitors of chitin synthase. Although one drug in this class (nikkomycin Z) has been highly effective for the treatment of coccidioidomycosis in animal models, the spectrum of activity of nikkomycins for other systemic mycoses is limited and they are no longer being developed. Lufenuron has not been well-evaluated for the treatment of systemic mycoses in animals, but the limited spectrum of the nikkomycins suggest that the usefulness of lufenuron will be limited.

Echinocandins and pneumocandins, which are β-glucan synthase inhibitors in the new lipopeptide class of antifungal agents, hold perhaps the greatest promise for changing the way that clinicians will treat systemic mycoses in the next decade. The most studied of these agents, caspofungin (Cancidas®, Merck) is a potent broad-spectrum parenteral formulation that has potent activity against *Aspergillus* spp. and *Candida* spp. In addition, it is highly effective for the treatment of *Pneumocystis carinii* pneumonia because of its ability to prevent development of the glucan-rich cyst form. The primary limitation of this class of antifungals is its ineffectiveness against *Cryptococcus neoformans*, which contains very little glucan synthase. To date, the use of caspofungin in veterinary patients has not been evaluated, and its extremely high cost will certainly limit its otherwise tremendous potential.

174.2 SPECIFIC SYSTEMIC MYCOSES

174.2.1 Blastomycosis

Blastomycosis is a systemic fungal infection that usually originates in the lungs and then disseminates to the lymphatics, skin, eyes, bones, and other organs. The dog is most commonly affected. Young, male, large breed dogs (especially sporting breeds and hounds) living near water are at an increased risk.[12] In endemic areas, blastomycosis usually occurs as a sporadic event, but outbreaks are occasionally observed in both dogs and people.[13–15] Epidemiologically, outbreaks can often be traced back to a common point source of exposure to a focal area in the environment from which infective spores had been aerosolized for a short time. Confirmation of the source is rarely achieved by organism isolation because of the transient nature of the environmental contamination and the difficulties inherent in laboratory isolation.

The dimorphic fungus *Blastomyces dermatitidis* is the causative agent of blastomycosis. In infected tissue or when cultured at 37°C, the organism is a thick-walled yeast that reproduces by budding. Most often, organisms in tissue have a single bud, attached to the mother cell by a broad base. When cultured at 25°C, mold colonies grow slowly and contain branching, septate 1 to 2 μm mycelia that form round to piriform 2 to 10 μm conidia. In nature, *Blastomyces dermatitidis* is probably a soil saprophyte, but the reservoir remains unresolved because the organism can rarely be cultured from the environment. When cultured, it is usually cultured from wet, acidic or sandy soil containing decaying wood, animal feces, or other organic enrichment.[16] Moisture appears to be important to growth and transmission.

Disease occurrence is reported primarily in a geographically restricted distribution that follows the Mississippi, Ohio, Missouri, Tennessee, and St. Lawrence Rivers, the southern Great Lakes, and the southern Mid-Atlantic states (Figure 174-2). Within these geographic regions, infections are generally limited to smaller geographic pockets, with most affected animals living within a quarter of a mile of water.[15,17] It is not unusual for one veterinary practice within an endemic area to diagnose blastomycosis commonly, whereas another practice located within the same county rarely encounters the infection.

174.2.1.1 Pathophysiology

Blastomycosis is not a contagious disease. It follows contact with the organism in the environment. Infection usually occurs via a respiratory route after the host inhales infective conidiophores. Rarely, disease may be seen after direct inoculation.[18] The incubation period varies from 5 to 12 weeks. Rain, dew, fog, or mist may play a critical role in liberating conidiophores from the environment. In addition, activities that disrupt the

soil such as digging or construction may play a role in the aerosolization of spores. After inhalation, conidia are phagocytized by alveolar macrophages and transform from the mycelial phase to the yeast phase.

The yeasts stimulate local cell-mediated immunity, which results in a marked suppurative to pyogranulomatous inflammatory response. In some cases the cell-mediated immune response controls the infection locally; in others, phagocytized yeasts are transported into the pulmonary interstitium, where they gain access to both the lymphatics and the vascular system.

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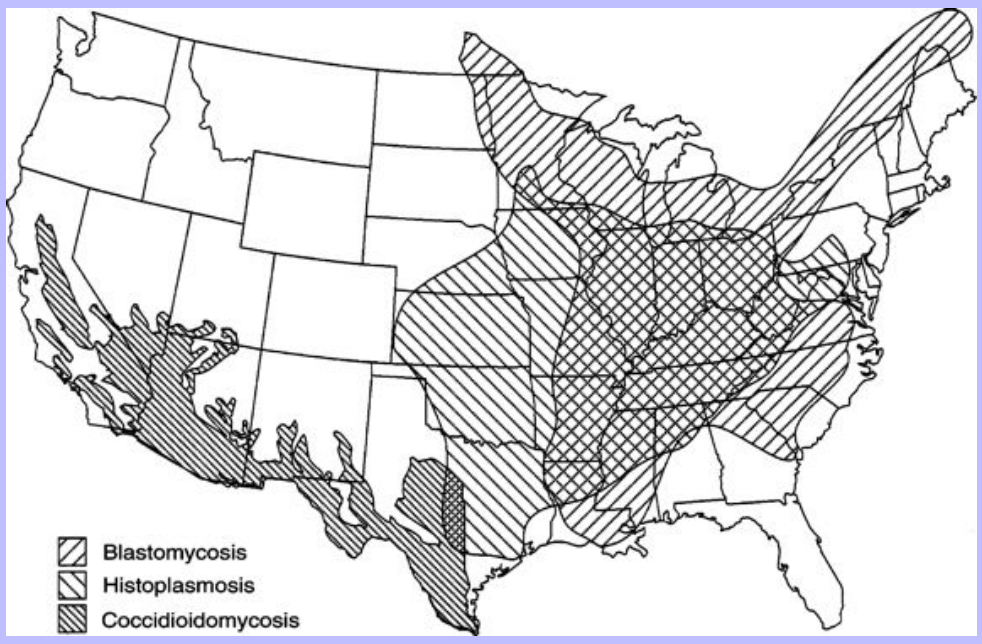
Figure 174-2 Areas in the United States endemic for blastomycosis, coccidioidomycosis, and histoplasmosis.



Hematogenous and lymphatic dissemination then results in multisystemic pyogranulomatous disease. Although dissemination can be to any organ system, the lymph nodes, eyes, skin, bones, subcutaneous tissues, and prostate are common organs affected in dogs[2,17,19]; skin, subcutaneous tissues, eyes, CNS, and lymph nodes are most commonly affected in cats.[20]

The immune response determines the severity of clinical disease, but blastomycosis is not considered an opportunistic infection. Antibody production occurs in most but not all cases, with the highest titers usually found in dogs with severe disseminated disease. Antibodies are not considered protective but can be used as a clinical marker of recent exposure or current disease. Recovery from infection is dependent on cell-mediated immunity. An adequate immune response may result in mild respiratory disease that resolves spontaneously. If dissemination has occurred, disease may be obvious in other organ systems, even without apparent pulmonary involvement. A poor immune response may result in severe pulmonary and disseminated disease.

174.2.1.2 Clinical Signs

Bluetick coonhounds, treeing-walker coonhounds, pointers, and Weimaraners have the highest risk of infection.[12] Males are affected more commonly than females, and although any age dog can be affected, those in the 2-to 4-year age group have the highest incidence of disease. Exposure to possible environmental sources of infection, close proximity to water, and the likelihood of being housed in outdoor kennels probably explains the breed association. Clinical findings in animals with blastomycosis vary greatly because of the multisystemic nature of the disease. One or more organ systems may be involved.

Nonspecific signs such as anorexia, depression, weight loss, cachexia, and fever are common. Approximately 40% of dogs are febrile, and dogs with chronic pulmonary disease are most likely to be cachectic. Because the lungs serve as the portal of entry for the *Blastomyces* organism, it is not surprising that pulmonary signs are seen in 65% to 85% of affected dogs. Signs of pulmonary involvement range from mild respiratory distress when exercised to severe dyspnea at rest. Hypoxemia resulting in cyanosis is seen in the most severely affected cases and has a negative prognostic significance.[2] A dry, hacking cough is common. Mildly affected dogs may initially be diagnosed as having kennel cough. Enlarged perihilar lymph nodes compressing primary bronchi, as well as infiltrative bronchointerstitial and alveolar disease, contribute to the cough. Rapid, shallow respiratory efforts may be noted and can be caused by pleural effusion or pleuritic pain. Chylothorax, solid granulomatous masses, and pulmonary thromboembolism are uncommonly reported complications of blastomycosis.

Diffuse lymphadenopathy is seen in about 40% to 60% of dogs with blastomycosis. The lymph node enlargement can be marked and may be mistaken for lymphosarcoma if cytology or histopathology is not performed.

Cutaneous signs are reported in about 30% to 50% of affected dogs and are also commonly noted in affected cats. Reported prevalences of skin disease in cases of blastomycosis may underestimate the actual prevalence, because lesions are sometimes small and easily overlooked unless a thorough dermatologic examination is performed. Single or multiple papules, nodules, or plaques that can ulcerate and drain a serosanguineous to purulent exudate characterize typical skin lesions. The nodular lesions are often quite small in dogs, but large abscesses occasionally occur, especially in cats. Paronychia is common in dogs, so the feet and nail beds should be closely examined.

Ocular involvement is noted in 20% to 50% of cases. Posterior segment disease, characterized by chorioretinitis, retinal separation, subretinal granulomas, and vitreitis, usually occurs initially. Approximately 50% of affected dogs have bilateral ocular involvement. Optic neuritis is occasionally noted and may signify more diffuse CNS involvement and a poorer prognosis. Anterior segment disease is usually, but not always, secondary to the posterior segment involvement. It may be characterized by conjunctivitis, keratitis, iridocyclitis, and eventually anterior uveitis and endophthalmitis. Secondary glaucoma is common in dogs with anterior segment disease. Dogs that are blind at the time of initial diagnosis rarely regain vision, even with aggressive treatment and good systemic response. Dogs that have vision and only posterior segment disease at the time of diagnosis have a better prognosis for vision.

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Lameness caused by fungal osteomyelitis or painful paronychia is noted in about 25% of dogs with blastomycosis, and fungal osteomyelitis is noted in about 10% to 15% of dogs with blastomycosis. The pain and swelling are usually noted over epiphyseal regions below the elbow or stifle. Single lesions are more common than multiple lesions. Fungal mono-or polyarthritis is a rare cause of lameness.

The reproductive system is affected in approximately 5% to 10% of affected dogs. Orchitis was noted in 16% of 61 intact male dogs with blastomycosis seen at Louisiana State University. Fungal prostatitis or mastitis is reported in less than 5% of affected dogs.

The nervous system is affected in less than 5% of canine cases but is commonly affected in feline cases (Figure 174-3). Advanced CNS imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) should be considered in any cat diagnosed with blastomycosis, even if obvious neurologic signs are not apparent. The clinical signs associated with nervous system involvement are dependent on which parts of the CNS are involved, but often neurologic localization indicates diffuse or multifocal disease. Other potential sites of infection include cranial mediastinum, liver, spleen, kidney, and nasal cavity.[21]

Feline blastomycosis is less common than canine blastomycosis. The veterinary literature contains only scattered case reports and small case series.[20] Most of the clinical signs observed in dogs are also noted in cats. The main differences are that large abscesses are more common in cats than in dogs, and neurologic involvement is often noted.

174.2.1.3 Diagnosis

Blastomycosis is usually fairly easy to diagnose because of the large numbers of characteristic yeasts found within lesions, especially within infected skin, eyes, and lymph nodes.[17,22]

Complete blood count (CBC) results are often normal. A mild nonregenerative anemia and mature neutrophilia or neutrophilia with mild left shift may be seen. Clinical chemistry results are also often unremarkable. Hypoalbuminemia is the most consistent abnormality. Mild hypercalcemia is noted in up to 10% of cases.[17] Severe hypercalcemia requiring treatment is occasionally seen.

Radiographic assessment can be very helpful in the diagnostic evaluation of a dog or cat suspected of having blastomycosis (Figures 174-4, 174-5, and 174-6). Thoracic radiographs reveal an interstitial pattern in about 70% of canine cases. Although a nodular interstitial pattern is classically observed (41% of cases), diffuse interstitial (24%) and bronchointerstitial (5%) patterns may also be prominent findings. An alveolar or mixed interstitial-alveolar pattern is observed in about 20% of canine cases, and tracheobronchial lymphadenopathy is noted in about 30%. Radiographic patterns mimicking other diseases such as mediastinal mass (8%) or solitary pulmonary mass (8%) are not as common. Pleural effusion (7%) is rarely observed and when present may obscure pulmonary parenchymal changes. Pneumothorax induced by pulmonary blastomycosis is rare. 677
Bone lesions may be noted on radiographs of long bones, especially those of the distal limbs. Lesions are 678
osteolytic and typically occur at the ends of the long bones (Figure 174-7). The forelimbs are affected more commonly than the rear limbs, with most extremity lesions being below the elbow or the stifle. Periosteal proliferation and soft tissue swelling are noted in about 50% of lesions.

Figure 174-3 Cross-sectional magnetic resonance image (MRI) revealing a contrast-enhancing mixed-intensity lesion in the rostral portion of the right cerebral cortex in a cat with blastomycosis.

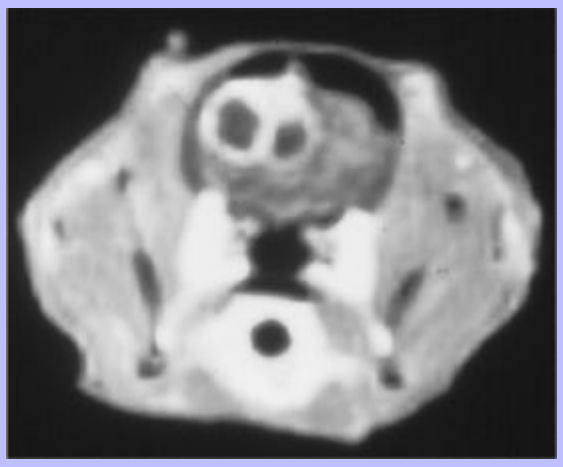


Figure 174-4 Lateral thoracic radiograph revealing a diffuse nodular interstitial pattern in a cat with blastomycosis.

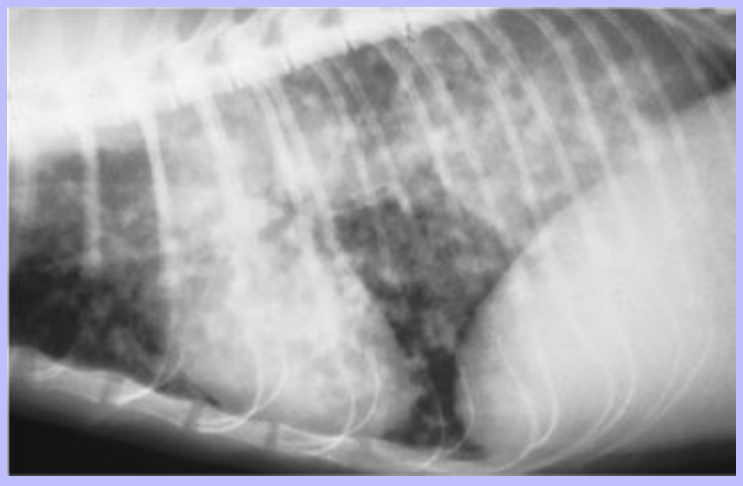
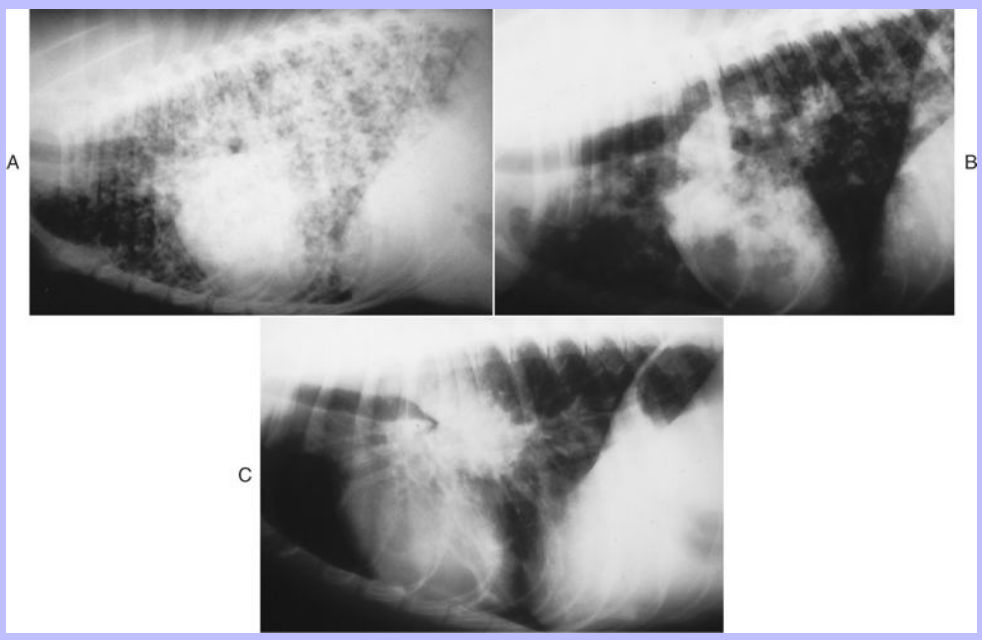


Figure 174-5 Consolidation of the right cranial lung lobe in a cat with blastomycosis. Consolidating and abscessing lesions are often seen in cats with systemic fungal infections.

Figure 174-6 **A,** Lateral thoracic radiograph from a dog with blastomycosis revealing the classic "snowstorm" appearance of the nodular interstitial pattern commonly seen in systemic mycotic infections. **B,** Lateral thoracic radiograph from a dog with blastomycosis showing multiple large, ill-defined nodules and a bronchointerstitial pattern. **C,** Lateral thoracic radiograph from a dog with blastomycosis showing perihilar lymphadenopathy and a patchy interstitial pattern. Perihilar lymphadenopathy is common in systemic fungal infections, especially histoplasmosis and coccidioidomycosis.



Definitive diagnosis is made by organism identifica-tion. This can be done by cytology, histopathology, or fungal culture. Cytology from affected tissue typically reveals pyogranulomatous or suppurative inflammation, often with thick-walled yeasts (8 to 12 µm in diameter, with 0.5 to 0.75 µm thick walls) that bud to form daughter cells from a broad base (Figure 174-8).[22,23] The yeast cells lack a capsule, helping to differentiate them from *Cryptococcus*. Skin lesions yield organisms about 80% of the time. This is the easiest and most useful site for cytologic diagnosis. Impression smears, skin scrapings, and fine needle aspirate of nodular lesions can be used. Vitreal aspirates yield organisms from almost all affected eyes, and lymph node aspirates yield organisms approximately 60% of the time. Bone and lung aspirates, transtracheal wash cytology, and bronchoalveolar lavage each yield organisms less than 50% of the time.[17,24] Urinalysis or prostatic wash cytology rarely reveals organisms.

Figure 174-7 Lateral and anteroposterior view of the distal radius, ulna, and carpus from a Brittany spaniel with *Blastomyces* osteomyelitis. The reader should note the bony lysis and periosteal proliferation involving the distal aspect of the proximal radius.

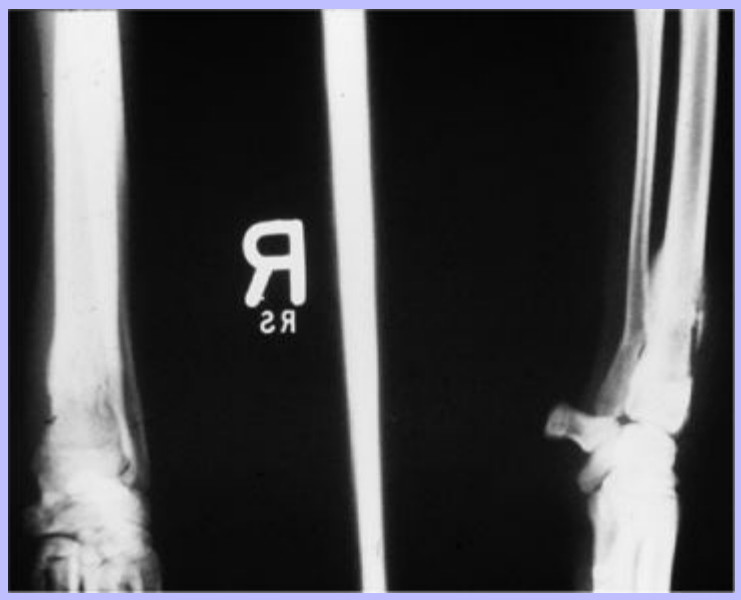


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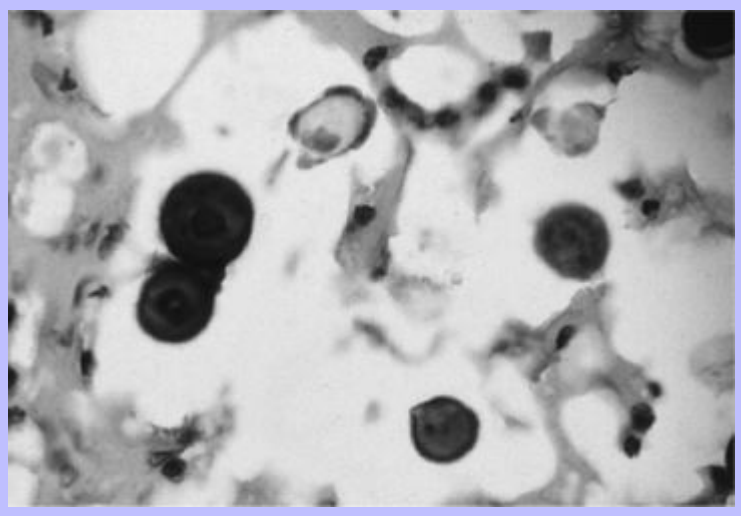
Figure 174-8 Impression smear from a dog with cutaneous lesions revealing thick-walled, budding yeast typical of *Blastomyces dermatitidis*.



Rarely, organisms may be coughed up and swallowed and appear in the stool on fecal examination.[25] Care must be taken when handling samples that may contain yeast cells. Direct inoculation of organisms from needle-stick injury may result in localized cutaneous disease.[26] This is seen as an occupational hazard in laboratory workers who handle infective material and cultures and in veterinary personnel who sample infected tissue via fine needle aspirate or biopsy. Local inoculation is probably rare as a cause of subcutaneous disease in dogs and cats.

Histopathology is generally characterized by purulent to pyogranulomatous inflammation, with broad-based organisms usually being apparent. Special stains such as periodic acid–Schiff (PAS), Gridley's fungal, and Gomori's methenamine silver (GMS) stain are best for demonstrating organisms. PCR has recently been used to identify organisms in tissue.[27]

Culture is not needed for definitive identification in clinical cases. If tissue is cultured, mycelial growth on Sabouraud's dextrose agar may take 1 to 4 weeks at 37°C, whereas yeast will grow on blood or brain-heart infusion agar in 1 to 2 weeks at 25°C. Culturing the organism from the environment is rarely achieved. The microbiology lab should be alerted if blastomycosis is suspected, because viable cultures of *Blastomyces dermatitidis* present a potential danger of infection for laboratory personnel if the plates are handled inappropriately.[28]

Serology should be used only when a high degree of suspicion for blastomycosis exists and repeated attempts have failed to demonstrate the organisms. Several different types of serologic tests have been evaluated, including agar-gel immunodiffusion (AGID), complement fixation, enzyme-linked immunosorbent assay (ELISA), counterimmunoelectrophoresis, and agar-gel precipitin tests. An AGID test is most commonly used. This test detects antibodies directed against the fungal organism and has a sensitivity and specificity of approximately 90%. Serology may be negative early in the disease course, and in some cases it may revert back to negative as the disease progresses. Antibody titers have not proven useful as an assessment tool in following response to therapy.

174.2.1.4 Treatment

Spontaneous recovery from symptomatic blastomycosis has been reported in people but rarely occurs in dogs and has not been reported in cats. Therefore all cases of symptomatic blastomycosis in dogs and cats should be treated. Itraconazole is presently considered the treatment of choice, except in cases of moderate to severe hypoxemia, when amphotericin B should still be considered the drug of first choice.[2] Clinical cures can be expected in 70% to 75% of treated cases. Treatment failure is most likely in dogs that are hypoxemic or have three or more organ systems affected. The dose of itraconazole that has proven effective is 2.2 mg/lb (5 mg/kg) orally once a day or divided twice a day. The drug should be continued for 2 to 3 months or until active disease is not apparent. Response to itraconazole treatment is minimal during the initial 1 to 2 weeks. A loading dose of 4.5 mg/lb (10 mg/kg) daily for the first 3 days of treatment may minimize this lag time. Treatment for an extra month after signs have resolved does not appear to reduce the likelihood of recurrence. Recurrence occurs in approximately 20% of treated dogs from months to years after treatment has been discontinued.[2,17] Thoracic radiographs are an insensitive tool in monitoring recovery, because significant radiographic abnormalities continue to improve for months after itraconazole treatment has been discontinued. Cats require 4.5 mg/lb (10 mg/kg) once a day or divided twice a day, and longer courses of treatment are usually required.

Ketoconazole is effective in less than 50% of cases at an oral dose of 4.5 to 13.6 mg/lb (10 to 30 mg/kg) divided twice daily for a minimum of 3 months. The response rate is much lower, and the relapse rate is higher when compared with treatment with itraconazole; in addition, dogs generally have to be treated longer. Toxicity is more likely with ketoconazole. Fluconazole has not been investigated for the treatment of blastomycosis in dogs and cats. The author's clinical impression is that it is not as effective as itraconazole, and fluconazole is more expensive. Fluconazole has been used successfully at high doses to treat blastomycosis in people.[29] In addition, because fluconazole does not require a low gastric pH for maximal bioavailability and is not affected by the presence or lack of food, it may be a better initial choice in animals that will not eat. Because it is excreted in the urine and crosses the blood-brain, blood-ocular, and blood-prostatic barriers well, it may be a more appropriate treatment choice for urinary tract, prostatic, and CNS infections. Studies evaluating efficacy in these situations in dogs and cats have not been performed, however. Parenteral forms of fluconazole and itraconazole are available and may be useful for treating severely affected or hypoxemic animals in which amphotericin B is not an appropriate option.

Amphotericin B has very good efficacy against *Blastomyces* organisms. It is recommended that amphotericin B be used in combination with itraconazole or ketoconazole for severely affected or hypoxemic animals.

ABLC (Abelcet), a lipid complexed formulation of amphotericin B is recommended. It allows relatively high doses to be used with low toxicity.[9] A dose of 1 to 1.5 mg/lb (2 to 3 mg/kg) intravenously every other day to a total dose of 24 to 27 mg/kg has been recommended for dogs with blastomycosis. ABLC is expensive when compared with the deoxycholate form, but the authors consider it the treatment of choice for severely affected dogs.

The deoxycholate formulation, although much less expensive, carries a higher risk of toxicity. When using this formulation, reconstituted, amphotericin B is mixed with 5% dextrose in water (D5W) and administered as a rapid infusion over 10 minutes or as a longer infusion over 1 to 6 hours. The longer infusion is less likely to cause toxicity. The dose is 0.22 mg/lb (0.5 mg/kg) for dogs, 0.1 mg/lb (0.25 mg/kg) for cats, intravenously every other day to a total dose of 1.8 mg/lb (4 mg/kg) when used in combination with azole antifungal drugs. A higher dose of 0.22 to 0.45 mg/lb (0.5 to 1 mg/kg) to a total dose of 3.6 mg/lb (8 mg/kg) is recommended in dogs if amphotericin B is the sole treatment agent. The BUN or creatinine should be monitored before each treatment, and amphotericin B should be discontinued if the dog or cat becomes azotemic (BUN >50 mg/dL, creatinine >3 mg/dL). The efficacy of amphotericin B when combined with ketoconazole or itraconazole is equal to that seen with itraconazole alone, but side effects are much more likely.

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Ancillary therapy in hypoxemic animals should include oxygen, bronchodilators, and possibly antibiotics. Anterior uveitis should be treated with topical steroids and atropine; secondary glaucoma with dichlorphenamide (0.9 to 1.8 mg/lb [2 to 4 mg/kg], orally two to three times a day). Atropine should not be used in animals with glaucoma.

Approximately 70% to 75% of dogs treated with either itraconazole or ketoconazole-amphotericin B combination respond completely to therapy. Dogs that die are usually those with severe respiratory disease and hypoxemia. Dogs that live through the first 10 days of therapy generally do well. Hypoxemia and the involvement of three or more systems are poor prognostic factors.[2] Relapse occurs in 15% to 20% of treated dogs. It usually occurs in the first 6 months after treatment but can occur after a year or more. Relapses should be treated as new infections and are no less likely to respond.

174.2.1.5 Public Health Significance

Blastomycosis is not likely to be transmitted from animal to animal or from animal to person. Localized *Blastomyces* infections have occurred after needle-stick injuries when obtaining fine needle aspirate from infected lesions, and laboratory workers can potentially be infected from fungal cultures. Outbreaks in which both people and dogs are affected are due to exposure to a common environmental source rather than to zoonosis.

174.2.2 Histoplasmosis

Histoplasmosis is a systemic fungal infection that usually originates in the lungs and potentially the GI tract, then disseminates to the lymphatics, liver, spleen, bone marrow, eyes, and other organs. A wide variety of mammalian species can be affected, and cats may be more susceptible to infection than dogs. As with most systemic fungal diseases, animals younger than 4 years old are at an increased risk, but any age can be affected.

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*. In infected tissue or when cultured at 30° to 37° C, the organism is a yeast. In the environment, *H. capsulatum* is a soil saprophyte that survives a wide range of moistures and temperatures. Nitrogen-rich soils, especially those containing bird or bat guano, appear ideal for supporting growth. The fungus is endemic throughout most of the temperate and subtropic regions of the world. Most cases of histoplasmosis in the United States occur in the central states, with the geographic distribution following the Mississippi, Ohio, and Missouri Rivers. The geographic distribution is wider than that of blastomycosis.

174.2.2.1 Pathophysiology

Histoplasmosis is not a contagious disease. Infection is probably via inhalation or ingestion of infective conidia from the environment. The respiratory system is likely the primary route of infection in cats, humans, and dogs, but the GI system may also be an important route in the dog.

After inhalation or ingestion, conidia transform from the mycelial phase to the yeast phase and are phagocytized by cells of the macrophage monocyte system, where they grow as facultative intracellular organisms. Hematogenous and lymphatic dissemination results in multisystemic disease. Dissemination can be to any organ system, resulting in a granulomatous inflammatory response. The lungs, GI system, lymph nodes, liver, spleen, bone marrow, eyes, and adrenal glands are common organs affected in dogs; lungs, liver, lymph nodes, eyes, and bone marrow are most commonly affected in cats. The incubation period is 12 to 16 days in dogs and humans.

The cell-mediated immune response determines the severity of clinical disease, with subclinical infection probably being common. Most cases of infection are sporadic events, but point-source outbreaks of disease are occasionally reported in both dogs and humans. Epidemiologically, these outbreaks are usually associated with exposure to areas heavily contaminated with *Histoplasma* organisms such as chicken coops, bat habitats, or starling roosts.

174.2.2.2 Clinical Signs

Feline histoplasmosis occurs most commonly in cats younger than 4 years of age. No breed or sex predilection exists. Disease in cats is usually insidious in onset and nonspecific, with clinical findings

varying greatly because of the multisystemic nature of the infection. Depression, anorexia, fever, pale mucous membranes, and weight loss are common. Pulmonary involvement, as evidenced by dyspnea, tachypnea, or abnormal lung sounds, is seen in about 50% of affected cats. Cough is uncommon. Hepatomegaly, splenomegaly, or lymphadenopathy is noted in about a third of affected cats. Ocular involvement may result in abnormal retinal pigment proliferation, retinal edema, granulomatous chorioretinitis, anterior uveitis, panophthalmitis, or optic neuritis. Retinal detachment and secondary glaucoma are less common than in animals affected with blastomycosis. Fungal osteomyelitis may cause lameness in one or more limbs. Cutaneous lesions consisting of multiple small nodules that may ulcerate and drain or crust over are noted less commonly than in animals affected with blastomycosis. GI signs other than anorexia are uncommon in cats with histoplasmosis. Oral and lingual ulceration has been reported as an unusual manifestation. Icterus is occasionally seen in cats with hepatic involvement.

Canine histoplasmosis is also most commonly seen in dogs younger than 4 years of age. Male dogs are affected 1.2 fold as frequently as female dogs, and pointers, Weimaraners, and Brittany spaniels may be over-represented. The clinical findings are related to the route of infection and the extent of systemic dissemination. Clinically inapparent infection is probably common after inhalation of organisms. In those dogs showing clinical signs, findings vary greatly, but GI signs are most common (Table 174-2). Large-intestine diarrhea with tenesmus, mucus, and fresh blood is most common early in the disease course. Small-intestine diarrhea that may be voluminous and associated with malabsorption, protein-losing enteropathy, or both may become apparent as the disease progresses. Nonspecific clinical signs such as fever, anorexia, depression, and severe weight loss are common and may be caused by elaboration of inflammatory mediators such as TNF and interleukin-1 (IL-1). Abnormal lung sounds with or without coughing, tachypnea, or dyspnea are seen in less than 50% of affected dogs. Pleural effusion is seen in rare cases and may contribute to respiratory signs.[30] Splenomegaly, hepatomegaly, and lymphadenopathy are occasionally seen.

174.2.2.3 Diagnosis

A normocytic-normochromic nonregenerative anemia is the most common CBC abnormality. It is caused by chronic inflammation, GI blood loss, and bone marrow infection. Neutrophilia and monocytosis are often seen, but leukocyte counts are variable. Neutropenia or pancy-topenia (or both) is noted in a minority of affected animals, especially in cats. The CBC rarely results in a definitive diagnosis, because *Histoplasma* organisms are only occasionally seen in monocytes or neutrophils and rarely in eosinophils. Thrombocytopenia due to increased use or platelet destruction is seen in as many as one half of affected dogs and one third of affected cats. Serum chemistry abnormalities are nonspecific. Hypoalbuminemia is the most consistent abnormality. Increases in serum alanine aminotransferase (SALT), serum aspartate aminotransferase (SAST), alkaline phosphatase, and total bilirubin may indicate hepatic involvement. Hypercalcemia, although not as common as in dogs with blastomycosis, has been reported. Hypercalcemia is more common in cats than in dogs.[3] It should be noted that hypoalbuminemia lowers total serum calcium and may mask subtle hypercalcemia. Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) tests are usually negative in cats.

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Table • 174-2 Differential Diagnosis for Gastrointestinal Signs Seen in Dogs and Occasionally in Cats With Histoplasmosis

Large-Intestine Disease
Diet-associated colitis
Dietary hypersensitivity
Foreign material–induced colitis
Idiopathic colitis
Lymphocytic-plasmacytic colitis
Eosinophilic colitis
Granulomatous colitis
Histiocytic ulcerative colitis of boxer dogs
Suppurative colitis
Parasitic and protozoal colitis
Trichuriasis (whipworms)
Ancylostomiasis (hookworms)
Strongyloidiasis
Entamebiasis
Balantidiasis
Giardiasis
Bacterial colitis
Salmonella spp.
Campylobacter jejuni
Yersinia enterocolitica, Y. pseudotuberculosis
Mycobacteria
Clostridium perfringens, C. difficile
Candidiasis
Gastrointestinal (GI) pythiosis
Protothecosis
Cecocolic or ileocolic intussusception

Pancreatitis-associated colitis
Small-Intestine Disease
Idiopathic inflammatory bowel disease
Lymphocytic-plasmacytic enteritis
Eosinophilic enteritis
Granulomatous enteritis
Intestinal lymphosarcoma
Parasitic enteritis (ancylostomiasis, toxocariasis)
Chronic giardiasis
Small-intestine bacterial overgrowth
Gastrointestinal (GI) pythiosis
Lymphangiectasia
Exocrine pancreatic insufficiency
Partial intestinal obstruction
Chronic enteropathy of Shar Peis
Immunoproliferative enteritis of basenjis

Thoracic radiographs often reveal a diffuse interstitial or linear interstitial pattern that tends to coalesce to a nodular interstitial pattern (Figure 174-9). Alveolar infiltrates are rarely reported. Hilar lymphadenopathy is common in dogs but unusual in cats. Calcified pulmonary infiltrates or hilar lymph nodes may indicate inactive disease in dogs. Osseous lesions consisting of osteolysis, periosteal new bone formation, and subperiosteal bone proliferation are rarely noted. Bones of the distal appendicular skeleton, especially carpal and tarsal bones, are affected most commonly.

Organism identification is required for definitive diagnosis. The most common means of organism identification is cyto-logy. Cytology from affected tissue reveals pyogranulomatous inflammation, often with numerous small, round to oval intracellular yeast cells (2 to 4 μm in diameter) characterized by a basophilic center and a light halo caused by shrinkage of the cell away from the cell wall during fixation (Figure 174-10). Although multiple *Histoplasma* organisms are usually found within phagocytic cells of the mononuclear phagocyte system, a small number of the organisms are released from cells during slide preparation and may be seen free on the slides stained with a Wright-Giemsa–type stain. Samples for cytology should be collected from tissue with apparent abnormalities. In the cat, aspiration cytology from bone marrow or lymph nodes or cytology from tracheal wash or bronchoalveolar lavage is most likely to yield organisms. In the dog, cytology from rectal scrapings or biopsies and aspiration cytology from bone marrow, liver, lymph nodes, spleen, or tracheal wash or bronchoalveolar lavage are most likely to yield organisms. Buffy coat smears, cytology of pleural or peritoneal effusions, aspirates of lytic bone lesions, and aspirates or impression smears of nodular skin lesions may also yield organisms.

If organisms are not cytologically apparent, histopathology may be diagnostic. Pyogranulomatous lesions with multiple intracellular organisms are usually apparent. Histoplasmosis should be considered when granulomatous hepatitis or other granulomatous or pyogranulomatous disease is seen on biopsy.[31] The yeast does not stain well with routine hematoxylin-eosin (H&E) stains, so special stains such as PAS, Gridley's fungal, and GMS stain are often used to demonstrate organisms.

Fungal culture from affected tissue can be used for diagnosis but is rarely needed in clinical cases. The organism grows as buff-brown mycelial growth on Sabouraud's dextrose agar. It usually takes 7 to 10 days to grow at room temperature. The yeast produces white, moist colonies on blood agar when grown at 30° to 37° C. The cultured organism is of pathogenic potential, which precludes culture attempts in a practice setting.

Serology is presently an ineffective method of diagnosis. Both false-positive and false-negative results are common. Poor correlation between necropsy findings and complement-fixation tests has been seen in multiple studies.

174.2.2.4 Treatment

Pulmonary histoplasmosis may be self-limited, but antifungal treatment is still recommended because of the potential for chronic dissemination. Dogs or cats with other systemic findings indicative of disseminated histoplasmosis usually die without treatment. Treatment protocols are similar to those described for blastomycosis, although they have not been as well studied. Longer treatment times are probably needed in most cases, but this is highly variable, depending on the severity of the infection and the response of the animal.

Itraconazole (4.5 mg/lb [10 mg/kg] orally once a day or divided twice a day) is considered the treatment of choice for feline histoplasmosis. At least 2 to 4 months of therapy is required. Few studies have evaluated the efficacy of itraconazole treatment, but in one study, all eight of eight treated cats were cured.[3] Ketoconazole is effective in about one third of affected cats. The addition of amphotericin B to ketoconazole treatment regimens may improve the efficacy, especially in severely affected cats. Fluconazole is likely effective but has not been well studied.

In dogs with histoplasmosis, ketoconazole has been described as the treatment of choice. Amphotericin B should be added to the protocol in fulminant cases. Itraconazole or fluconazole is safer and may result in better efficacy than ketoconazole, but evaluation has been minimal. For dogs with GI disease, ancillary therapy should be considered along with antifungal therapy. A highly digestible diet should be fed to dogs with small-intestine involvement, and fiber may be useful in dogs with signs of colitis. Small-intestine bacterial overgrowth may occur in dogs with histoplasmosis and should be treated with tylosin (4.5 to 9 mg/lb [10 to 20 mg/kg] orally twice a day), metronidazole (3.4 to 4.5 mg/lb [7.5 to 10 mg/kg] orally two to three times a day), tetracycline (6.8 to 9 mg/lb [15 to 20 mg/kg] orally three times a day), or amoxicillin (4.5 to 9 mg/lb [10 to 20 mg/kg] orally twice a day). Nonspecific therapy for diarrhea can include loperamide (0.045 to 0.09 mg/lb [0.1 to 0.2 mg/kg] orally twice a day) for small-intestine diarrhea and sulfasalazine (4.5 to 13.6 mg/lb [10 to 30 mg/kg] orally two to three times a day) for large-intestine diarrhea. Ancillary respiratory therapy may include oxygen and bronchodilators in hypoxemic animals and antibiotics in dogs with secondary bacterial pneumonia. Corticosteroids have been recommended for treating dogs with airway obstruction secondary to hilar lymphadenopathy caused by histoplasmosis.[32]

Figure 174-9 Lateral thoracic radiograph of an 8-year-old Siamese cat with a 2-week history of dyspnea caused by *Histoplasma capsulatum* infection. This coalescing pattern of interstitial infiltrates is commonly seen in cats with pulmonary histoplasmosis.

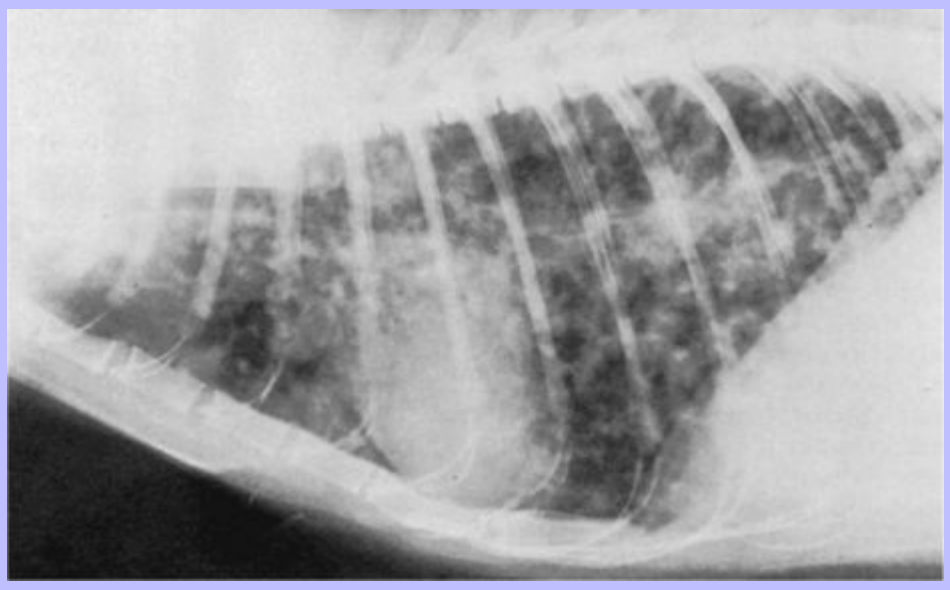
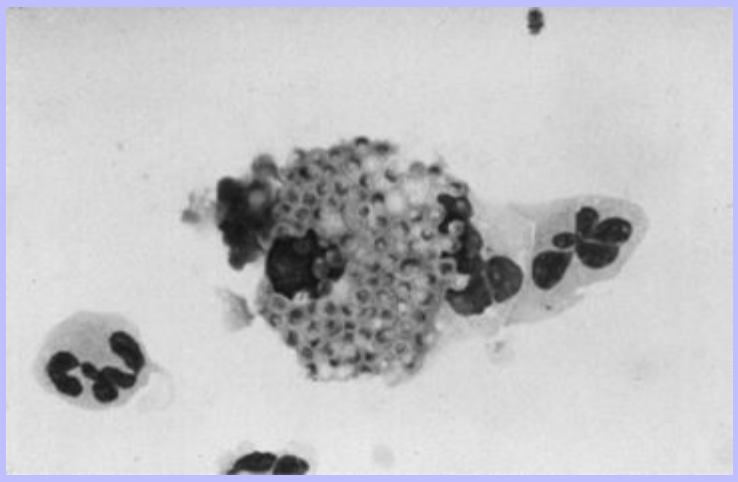


Figure 174-10 Cytology from a bronchoalveolar lavage sample revealing a macrophage containing many round to oval-shaped *Histoplasma* organisms in a cat with histoplasmosis. (Courtesy of Dr. Jan VanSteenhouse.)



Resolution of clinical signs is the best means of patient monitoring. Rechecks should be performed monthly while dogs or cats are being treated and should include physical and ocular examinations and a chemistry panel to evaluate liver enzymes in animals receiving azole antifungals. Treatment should be continued for 1 month beyond resolution of clinical signs, and animals should be reevaluated 3 and 6 months after discontinuing therapy to assess for relapse. Serology is not useful in monitoring response to therapy or evaluating for relapse.

The prognosis is good for dogs with only pulmonary signs, but dogs with GI or severe dissemination have a guarded prognosis. The prognosis is fair to good for cats treated with itraconazole, although long-term therapy may be required. Severely debilitated cats have a guarded prognosis.

174.2.3 Cryptococcosis

Cryptococcosis is an opportunistic systemic fungal infection of worldwide significance that usually originates in the nasal cavity, paranasal tissues, or lungs. It can then disseminate, most commonly to the skin, eyes, or CNS. Disease occurs in a wide variety of mammalian species. Among domestic animals, it occurs most commonly in the cat, in which it is the most common of the systemic mycoses. Unlike the other systemic mycoses, cryptococcosis does not follow strict geographic boundaries but is most common in the Southeastern and Southwestern United States, Southern California, and the east coast of Australia.

Cryptococcosis is caused by *Cryptococcus neoformans*, a saprophytic, round, yeastlike organism with a restricted ecologic niche. *C. neoformans* var. *neoformans* is the subspecies that most commonly causes disease and is environmentally associated with pigeon droppings or other avian habitats. *C. neoformans* var. *gattii* is a second subspecies that is capable of causing disease and is associated with bark and leaf litter of certain eucalyptus trees. In infected tissue, and often when cultured, the organism is a variable-sized yeast (3.5 to 7 μm) with a large heteropolysaccharide capsule (1 to 30 μm). Both subspecies have been shown to cause disease in cats and humans. *C. neoformans* reproduces primarily by budding from a narrow base.

The pigeon is thought to be the most important vector of *C. neoformans*. The *Cryptococcus* organism can be found in high numbers in pigeon roosts, barn lofts, haymows, and along cupolas and cornices where pigeons often sit. In the desiccated state, the *Cryptococcus* organism may be no larger than 1 μm and may survive up to 2 years.

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174.2.3.1 Pathophysiology

Cryptococcosis is not a contagious disease. Infection occurs most commonly via inhalation of yeast from the environment. Debris and droppings in and around avian habitats, especially pigeon habitats, contain the largest numbers of *Cryptococcus* organisms. Most yeasts are probably too large to be inhaled into the lungs and settle out in the nasal cavity or nasopharynx, where they can produce disease or result in animals becoming asymptomatic carriers of the organism. In one study, cryptococcal organisms could be cultured from nasal washings in 14% of asymptomatic dogs and 7% of asymptomatic cats.[33] The small, desiccated forms of the yeast are also infective and can be inhaled into the small airways and alveoli, leading to pulmonary disease. After inhalation into the nasal cavity, paranasal sinuses, or lungs, cell-mediated immune response results in granuloma formation. Dissemination can occur by either direct extension or hematogenous spread. Direct extension from the nasal cavity through the cribriform plate to the CNS or to the paranasal soft tissues and skin is common. Although dissemination can be to any organ system, the skin, eyes, and CNS are most commonly affected.

Lesions consist of either granulomatous inflammation with few organisms or gelatinous masses of organisms with little inflammation. The large capsule surrounding the cryptococcal organism contributes to pathogenicity by inhibiting phagocytosis, plasma cell function, and leukocyte migration. As with the other systemic mycoses, the immune response determines the severity of clinical disease. Antibodies are readily produced by the humoral immune system but are not considered protective. Recovery, therefore is dependent on cell-mediated immunity. Most human cases of cryptococcosis are associated with immune suppression, especially lymphoreticular neoplasia and AIDS. However, immune suppression has not been as apparent in most affected cats and dogs. An association with FeLV and FIV infections in cats has been reported, and chronic glucocorticoid use has been implicated as a predisposing factor in both cats and dogs.[4,30,34,35]

174.2.3.2 Clinical Signs

Cats are more commonly affected by cryptococcosis than dogs. No apparent breed, sex, or age predilection exists in cats. Clinical findings are usually related to upper respiratory, nasopharyngeal, cutaneous, ocular, or CNS involvement. Unlike in other systemic mycoses, the lungs are not commonly affected. Nonspecific signs such as depression and anorexia are common in chronic cases, but fever is uncommon. Upper respiratory signs related to nasal cavity involvement are seen in 50% to 80% of affected cats. In these cats, sneezing and snuffling are common, and unilateral or bilateral mucopurulent nasal discharge with or without blood is typically seen. Proliferative soft tissue masses or ulcerative lesions within the nasal cavity or over the bridge of the nose are seen in approximately 70% of cases with upper respiratory involvement (Figure 174-11). Oral ulcerations are occasionally noted but are not common. Nasopharyngeal mass lesions causing snoring, stertor, and inspiratory dyspnea are occasionally noted.[36] The skin or subcutaneous tissues are affected in approximately 40% to 50% of infected cats. Primary lesions include papules or nodules that may ulcerate and drain. Multiple lesions are typical, and regional lymphadenopathy is common. Hematogenous spread from the respiratory system may result in lameness secondary to osteomyelitis, renal failure secondary to renal disease, and generalized lymphadenopathy.

The eyes are affected in 20% to 25% of infected cats, especially those with CNS involvement. Granulomatous chorioretinitis with or without exudative retinal detachment is the most common ocular manifestation and can lead to panophthalmitis. Less often, optic neuritis can be seen, resulting in blindness. Anterior uveitis is not as common as posterior segment disease. CNS involvement is reported in approximately 20% of affected cats. This may be an under-representation of the actual number of cases with nervous system involvement.[35] The forebrain is most commonly affected, because invasion through the cribriform plate is thought to be common. Signs may include depression, behavior changes, seizures, circling, ataxia, blindness, head pressing, cranial nerve deficits, and paresis. Nasopharyngeal granulomas may occlude the auditory tube resulting in otitis media interna and resultant peripheral vestibular signs.[37] Cats with concurrent FeLV or FIV infection tend to be more severely affected and may be more likely to develop neurologic or ophthalmic signs.

Figure 174-11 Nasal cryptococcosis in a cat. (Courtesy Dr. Carol Foil.)

Canine cryptococcosis is typically seen in dogs younger than 4 years of age. No apparent sex predilection exists, and American cocker spaniels, Labrador retrievers, Great Danes, and Doberman pinschers appear to be over-represented. In dogs, clinical findings are most often related to CNS, upper respiratory, ocular, or cutaneous involvement.[38] As in cats, depression and anorexia are common but fever is not. CNS involvement is reported in approximately 50% to 80% of affected dogs. The brain is affected in most of these dogs.[39,40] The spinal cord may be affected along with the brain, and rarely the spinal cord alone is affected, causing signs consistent with either meningitis or an extradural compressive lesion.[41] Signs of nervous system involvement may include mental depression, vestibular syndrome, ataxia, cranial nerve deficits (especially cranial nerves V, VII, and VIII), seizures, paresis, blindness, hypermetria, and cervical pain. In dogs with CNS signs, other systems are usually affected as well, reflecting multisystemic dissemination.

The upper respiratory system or perinasal tissues are affected in approximately 50% of dogs with cryptococcosis (Figure 174-12).[38] The caudal nasal cavity and frontal sinuses are affected more commonly than the rostral nasal cavity. Signs may include upper airway stridor, nasal discharge and sneezing, epistaxis, or firm swellings over the bridge of the nose. The eyes or periorbital tissues are affected in approximately 20% to 40% of dogs with cryptococcosis. Granulomatous chorioretinitis with or without exudative retinal detachment is the most common ocular manifestation and can lead to panophthalmitis. In addition to chorioretinitis, fundic examination may reveal retinal hemorrhage or retinal scarring. Optic neuritis may be noted as a cause of blindness. As with the other systemic mycoses, anterior uveitis is less common than posterior segment disease. The skin is affected in approximately 10% to 20% of dogs with cryptococcosis. Subcutaneous nodules with ulcerative draining lesions, often on the head, feet, nail beds, and mucous membranes of the mouth, occur most commonly. Proliferative lesions in the ear canals may result from cryptococcal otitis externa. Direct extension from the ears to the CNS may occur. Multiorgan dissemination is more common in dogs than in cats. Disease may be subclinical or may result in clinical signs referable to the organ systems affected.

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Figure 174-12 Periocular swelling in a female Siberian husky, caused by cryptococcal infection.

174.2.3.3 Diagnosis

Hematology and clinical chemistries are often normal in animals with cryptococcosis. Mild nonregenerative anemia and mature neutrophilia or neutrophilia with a mild left shift may be seen. Because the nervous system is so commonly affected, CSF tap for culture and cytology should be considered. CSF commonly yields increased opening pressure, increased protein, and mixed mononuclear and neutrophilic pleocytosis. Organisms are visualized in approximately 90% of dogs with CNS cryptococcosis.[42]

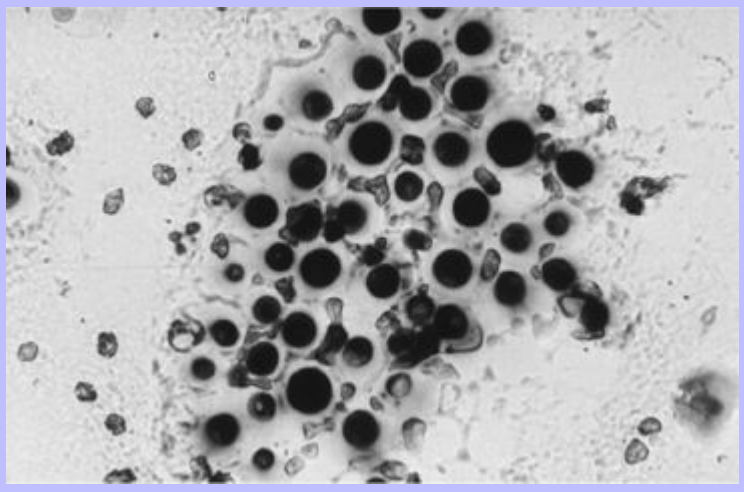
Nodular infiltrates, an interstitial pattern, pleural effusion, and tracheobronchial lymphadenopathy are occasionally seen on thoracic radiographs. Nasal radiographs may demonstrate increased soft tissue density and bone destruction in the nasal passages and frontal sinuses.

Organism identification allows for definitive diagnosis and can usually be made cytologically or histologically. Cytology from affected tissue is the quickest and easiest means of identifying cryptococcal organisms. Nasal swabs, exudate from cutaneous lesions, aspirates of masses, subretinal or vitreal aspirates, and CSF often reveal organisms. Organisms are apparent in approximately 75% of cases. The large capsule makes identification easy (Figure 174-13).

Gram's stain is useful in looking for cryptococcal organisms, because the cells retain the crystal violet and the capsule stains lightly red with the safranin. If India ink is used, the organism and capsule appear unstained and silhouetted against the black background (Figure 174-14). Care must taken in interpreting India ink preparations, as lymphocytes, fat droplets, and aggregated ink particles may be confused with the organism. Budding is occasionally noted. The thin wall and the large capsule differentiate *Cryptococcus* from *Blastomyces*.

Histopathology should be used if cytology fails to identify organisms. Nodular to diffuse granulomatous lesions or areas of degeneration with little inflammation are seen in infected tissue. Yeastlike organisms are usually numerous. Special stains such as PAS, Gridley's fungal, and GMS stain are best at demonstrating organisms. Mucicarmine stains best demonstrate the capsule.

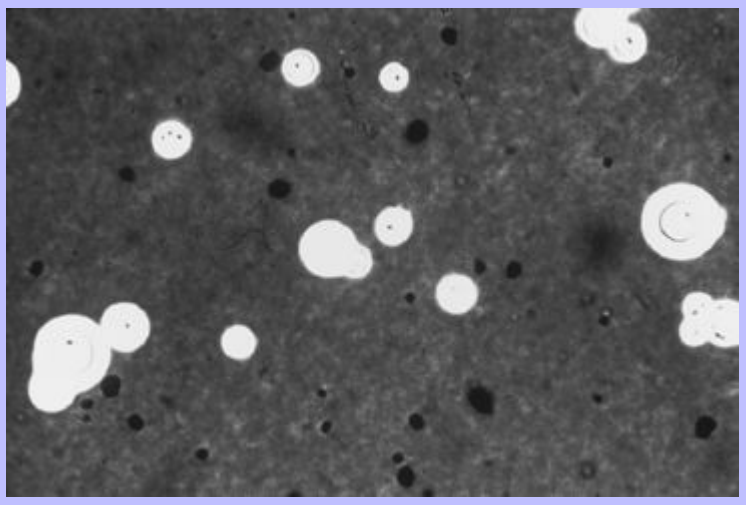
Figure 174-13 Cryptococcal organism noted on fine-needle aspirate cytology from the dog in Figure 174-12. Note the large capsules surrounding the organisms and the minimal inflammatory response.



Cryptococcal organisms grow readily when cultured. The organism can be cultured from infected tissue, exudate, CSF, urine, joint fluid, and blood if large enough samples are submitted. Yeastlike growth occurs in 2 days to 6 weeks on Sabouraud's dextrose agar. Hyphae rarely grow, even at 37° C. Care must be taken in interpreting positive cultures from the nasal cavity, because 14% of asymptomatic random-source dogs and 7% of asymptomatic random-source cats were culture-positive in one study.[33] Animals in the previously mentioned study were all negative on serum latex agglutination tests and did not have macroscopic or microscopic findings supportive of cryptococcal infection.

Serology is useful as an inexpensive and noninvasive diagnostic test when cytology has failed to demonstrate organisms. Latex agglutination procedures are used to detect cryptococcal capsular antigen. Antibody titers are not useful diagnostically, because most infected animals do not mount a humoral immune response.[43] The commercially available latex cryptococcal antigen agglutination tests can be used on serum, urine, or CSF. CSF is the best sample to use in animals with neurologic signs, and serum is the best sample to use in animals with upper respiratory or cutaneous signs but without neurologic signs. Most cases are positive with titers between 1:10 and 1:100,000. The median titer in infected cats in one study was 1:1000.[43] False-negative antigen titers are rare but may occasionally be seen in localized disease. False-positive antigen titers are uncommon and are usually related to technique or interfering substances such as rheumatoid factor (RF). The latex agglutination antigen titer tends to correlate well with the extent of disease but does not correlate well with prognosis.[44] It may be used to evaluate the treatment progress.

Figure 174-14 India Ink preparation revealing cryptococcal organisms. (Courtesy of Dr. Carol Foil.)



174.2.3.4 Treatment

Amphotericin B is the most effective drug in vitro against cryptococcal isolates, but both itraconazole and fluconazole have proven to be equally efficacious in treating CNS cryptococcosis in people. Little information is available evaluating amphotericin B in the treatment of cryptococcal infections in dogs and cats. Amphotericin B is synergistic with flucytosine. Flucytosine can be used at a dose of 11.4 to 22.7 mg/lb (25 to 50 mg/kg) orally four times a day and has been used in dogs and cats. The combination of amphotericin B and flucytosine may be especially useful for treating CNS infections. Cryptococcal organisms may rapidly develop resistance to flucytosine, so it has limited efficacy as a sole treatment agent. The dose of flucytosine should be adjusted downward in animals with concurrent renal failure. Toxicity to flucytosine includes ulcerative drug eruptions on the skin (especially on the face) and mucocutaneous junctions, enterocolitis, leukopenia, and thrombocytopenia. Amphotericin B has also been effective when combined with azole antifungal agents.

Subcutaneously administered amphotericin B in combination with azole antifungals or flucytosine has been used to successfully treat both feline and canine cryptococcosis.[45] Amphotericin B (0.22 to 0.36 mg/lb; 0.5 to 0.8 mg/kg) is diluted in 0.45% saline containing 2.5% dextrose (400 mL for cats, 500 mL for dogs <20 kg, 1000 mL for dogs >20 kg) and administered subcutaneously two to three times per week. This protocol may allow larger cumulative doses of amphotericin B to be given with reduced toxicity. Concentrations greater than 20 mg/L of amphotericin B resulted in local irritation and sterile abscess formation; therefore more concentrated formulations of amphotericin B should not be used subcutaneously.

Ketoconazole is variably effective as a sole treatment agent but is ineffective in cases with CNS involvement. There were only scattered reports of successful treatment of cryptococ-cal infections in dogs and cats before the availability of the triazole antifungals, but since they became available, successful treatment has been reported more commonly. Fluconazole (50 mg/cat orally twice a day; 2.2 mg/lb [5 mg/kg] orally once to twice a day for dogs) is very effective and is the treatment of choice for cryptococcosis

in cats and probably dogs. Itraconazole (4.5 mg/lb [10 mg/kg] orally daily) is effective in cats and dogs but appears to be less effective than fluconazole. Controlled trials in people have revealed the two drugs to be equally efficacious. Ketoconazole (4.5 to 13.6 mg/lb [10 to 30 mg/kg] orally twice a day) is even less effective but can be used if other drugs are unavailable.

Resolution of clinical signs is the best means of patient monitoring, but serially monitoring latex agglutination antigen titers can significantly augment the clinician's clinical observations.[30,44] Rechecks should be performed monthly while dogs or cats are being treated and should include a chemistry panel to evaluate liver enzymes in animals receiving azole antifungals and a latex agglutination antigen titer. Sequential titers should differ by two or more dilutions before they are considered significantly different. A decline of two-to fourfold per month during the initial few months of antifungal therapy generally corresponds to an adequate clinical response. Ideally, treatment should be continued until the titer is negative or for at least 2 months beyond resolution of clinical signs. In some animals, detectable cryptococcal polysaccharide antigen persists in the circulation long after the infection has been successfully treated. This is thought to be caused by continued elimination of unviable organisms and capsular material from infected tissues and macrophages. Most of these animals have low titers. High residual titers may indicate insufficient therapy and thus persistence of viable organisms.[30] One author's recommendation is to continue antifungal drug treatment to a titer of less than 1.[44] In cases in which there has been a thirty-twofold decrease and resolution of clinical signs, treatment may be discontinued; however, titers should be reevaluated periodically to ensure that they continue to decline or at least remain stable. Animals should be reevaluated at least 3 and 6 months after discontinuing treatment to assess for relapse. Negative antigen titers are occasionally seen in animals with localized disease, so they do not always indicate clinical cure.

The prognosis is good for cats with extraneural disease, and it is guarded for dogs with any form of the disease and for cats with CNS involvement.

174.2.4 Sporotrichosis

Sporotrichosis is a chronic granulomatous disease of worldwide significance caused by the dimorphic saprophytic fungus *Sporothrix schenckii*. The organism lives as a mycelium in the soil and when cultured at room temperature and as a yeast at body temperature. The mycelia are thin, finely branched, and septate. They produce clusters of conidiophores, which are the infective stage. The yeast form exists in infected tissue and is characterized as pleomorphic round, oval, or cigar-shaped cells that measure 2 by 3 µm to 3 by 10 µm (Figure 174-15). The yeast is fairly characteristic, and a diagnosis can usually be made from a cytologic preparation. Both dogs and cats can be infected. Dogs are infected less commonly and usually have only cutaneous or subcutaneous disease. Cats are infected more frequently and commonly have systemic dissemination.

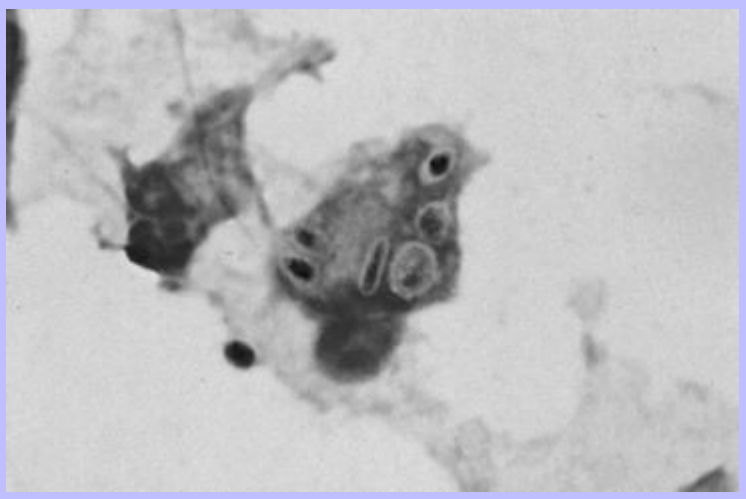
174.2.4.1 Pathophysiology

Infection with *S. schenckii* in dogs and cats usually occurs after trauma that results in inoculation of infective conidiophores. Yeast from cutaneous lesions can be infective and is a potential zoonotic source of infection via contamination of wounds or via scratches or bites. The skin is the primary organ system affected, but dissemination via lymphatics is common in cats and less common in dogs. Immune suppression predisposes to infection and increases the likelihood of dissemination.

Sporotrichosis occurs in three primary forms: (1) cutaneous, (2) cutaneolymphatic, and (3) disseminated disease. In the dog, the infection is usually cutaneous or cutaneolymphatic. Disseminated disease is rare and usually follows immune suppression with corticosteroids. The cutaneolymphatic form is common in the cat, 685 686

and dissemination is seen in more than 50% of feline cases. The lesions in cats are characterized by large numbers of yeasts, making zoonotic transmission more likely from cats than from dogs.

Figure 174-15 Impression smear from a skin lesion on a cat, revealing pleomorphic organisms characteristic of sporotrichosis.



174.2.4.2 Clinical Signs

Most affected cats are younger than 4 years of age, and males are affected approximately twice as commonly as females.[46] Young hunting dogs may be predisposed. Multiple subcutaneous or dermal nodular lesions that occur most commonly on the head, neck, trunk, and distal limbs characterize the cutaneous form of the disease. The tail base may also be involved in cats. The nodules typically ulcerate, drain a purulent exudate, and crust over (Figure 174-16). They are often confused with bite wound abscesses or cellulitis. Lesions on the distal limbs commonly result in regional lymphadenitis, which is manifested as linear ulcerating lesions and regional lymphadenopathy. Lesions in cats may be associated with extensive areas of necrosis. Otitis externa has been reported.

Dissemination may occur and be subclinical or may result in serious systemic disease. Too few cases have been reported to develop a clear picture of a dissemination pattern, but internal lymph nodes, spleen, liver, lungs, eyes, bones, muscles, and CNS have all been affected.

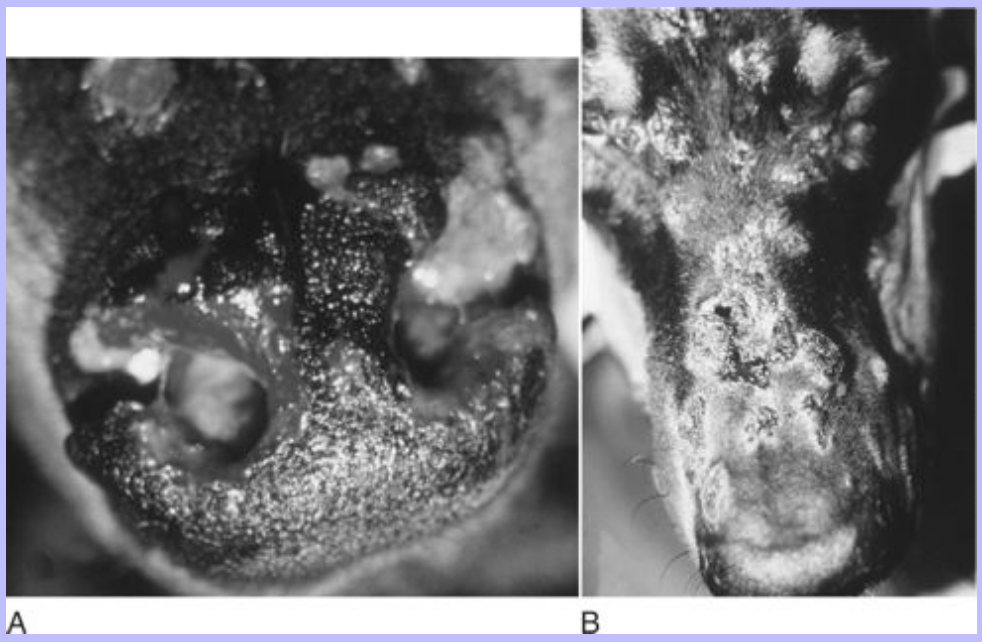
174.2.4.3 Diagnosis

Cytology from skin lesions is the most common means of diagnosis. Lesions from cats contain large numbers of organisms, making diagnosis fairly easy; lesions from dogs usually contain very few organisms. The organisms may be seen intracellularly within macrophages or neutrophils or may be present extracellularly. Culture can be used to make a definitive diagnosis.

Material for culture should include exudate from deep within a draining tract and tissue samples from biopsy specimens. Cultured organisms pose a serious threat to persons working in the laboratory, so the laboratory should be notified whenever a sample is submitted from a dog or cat with suspected sporotrichosis.

Histopathology reveals pyogranulomatous inflammation. Numerous organisms are commonly seen in lesions from cats, even when stained with H&E. Fungal stains such as PAS or immunofluorescent techniques may aid in finding organisms in dogs. Immunofluorescent testing can be performed by the Centers for Disease Control and Prevention in Atlanta, Georgia.

Figure 174-16 A and B, Sporotrichosis affecting the skin and nasal mucosa of a Doberman pinscher.



174.2.4.4 Therapy

Traditionally, sporotrichosis has been treated with potassium iodide, ketoconazole, or combinations of the two. Approximately 55% of treated cats in the literature responded to one or both of these drugs.[46] Itraconazole is the treatment of choice in people and is effective in dogs and cats. It is especially valuable in cats because of the species' tendency to develop iodism on potassium iodide.

The response to itraconazole treatment in cutaneous and cutaneolymphatic cases is generally good. The prognosis must be guarded for disseminated disease, but too few cases have been reported to give a well-informed likelihood of response.

174.2.4.5 Public Health Significance

Canine sporotrichosis is of minimal zoonotic potential, but feline sporotrichosis is a significant zoonotic disease. Veterinarians and veterinary assistants are at the highest risk of infection. Care should be taken to limit contact with exudate and lesions from infected cats. Gloves should always be worn when handling cats suspected of having sporotrichosis, and owners should be advised of the possibility of infection and the need

for strict hygiene. After any contact, gloves should be removed carefully and disposed of, and hands, wrists, and arms should be washed thoroughly with either chlorhexidine or povidone-iodine scrub.

174.2.5 Candidiasis

Candida spp. are normal inhabitants of the GI, genitourinary, and upper respiratory systems. *Candida* may overgrow in cases of immune suppression or prolonged broad-spectrum antibiotic use, especially in wounds, the oropharynx, or the GI tract. Animals with neutropenia are especially predisposed to infection. Infections may be localized, or dissemination may occur via a hematogenous route, resulting in microabscesses at multiple sites.

Localized candidiasis is usually characterized as a nonhealing ulcer covered by a whitish-gray plaque in the oral cavity, in the GI tract, or on the genitourinary mucosa. Chronic moist, exudative lesions may occur on the skin or at the nail beds.

Disseminated disease is typified by fever and the acute appearance of multiple raised erythematous skin lesions in dogs. In dogs, pain is often caused by myositis and osteomyelitis, and other signs are referable to the systems affected. Cats are less likely to have multiple skin lesions. The CBC in systemically affected animals is often characterized by leukopenia and thrombocytopenia. Renal involvement is common, and yeast may be found in the urine, especially in cats.

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Itraconazole and ABLC are considered the treatments of choice, but few reports of successful treatment are available.

174.2.6 Pythiosis

Pythiosis is a devastating and often fatal cause of chronic GI or cutaneous disease in dogs and cats. It is caused by *Pythium insidiosum*, an aquatic pathogen belonging to the class Oomycetes in the Kingdom Stramenopila (Chromista). Recent phylogenetic studies have confirmed that oomycetes are more closely related to algae than to fungi. Chitin, an essential component of the fungal cell wall, is generally lacking in oomycetes, which instead contain predominately cellulose and β-glucan. In addition, oomycetes differ from fungi in that ergosterol is not a principal sterol in the oomycete cell membrane. In the United States, pythiosis is encountered most often in the Gulf Coast states, but has been recognized in animals living as far north as New Jersey, Virginia, Kentucky, and southern Illinois and Indiana, and as far west as Arizona, California, Oklahoma, and Kansas. Globally, pythiosis is most often encountered in Southeast Asia, eastern coastal Australia, and South America.

174.2.6.1 Pathophysiology

The infective form of *P. insidiosum* is thought to be the motile biflagellate zoospore, which is released into aquatic environments and likely causes infection by encysting in damaged skin or GI mucosa. Many dogs with pythiosis have a history of recurrent exposure to warm freshwater habitats. However, some cases are observed in suburban house dogs with no history of access to lakes or ponds. Affected animals are typically immunocompetent and otherwise healthy.

174.2.6.2 Clinical Findings

Pythiosis occurs most often in young, large breed dogs and is especially common in outdoor working breeds such as Labrador retrievers. Affected dogs are presented to the veterinarian more often in the fall, winter, and

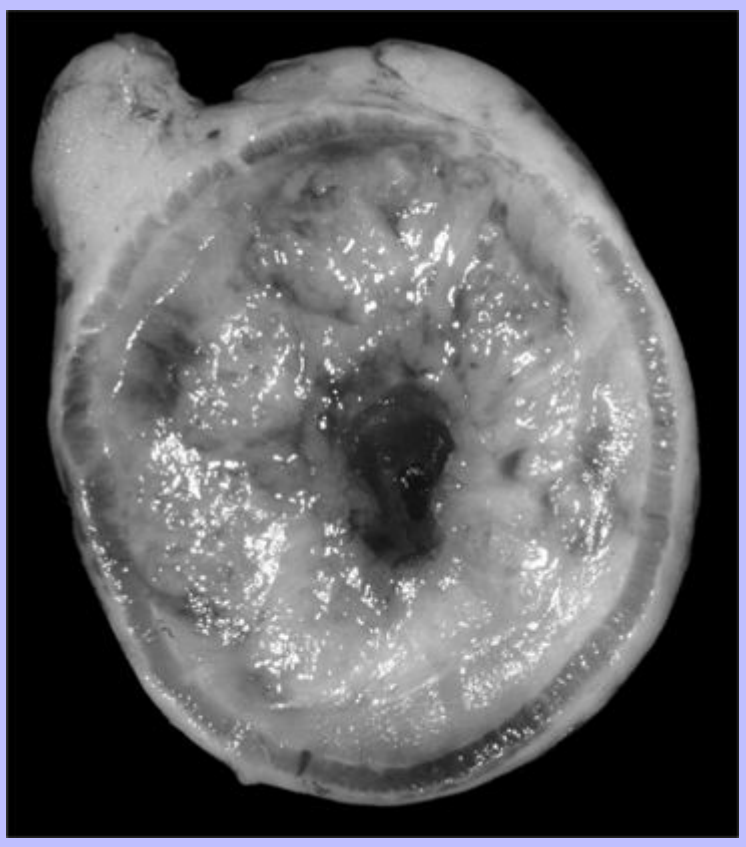
early spring than in the summer months. In cats, specific breed and sex predilections have not been observed in the few cases that have been reported to date. However, of ten cats with cutaneous pythiosis diagnosed through our laboratory since 1999, five were less than 10 months old, with an age range of 4 months to 9 years.

Cutaneous pythiosis in dogs typically causes nonhealing wounds and invasive masses that contain ulcerated nodules and draining tracts, most often involving the extremities, tail head, ventral neck, or perineum.[47,48] Cats with pythiosis may have nasopharyngeal lesions, invasive subcutaneous masses in the inguinal, tail head, or periorbital regions, or they may have draining nodular lesions or ulcerated plaquelike lesions on the extremities, sometimes centered on the digits or footpad.[48,49]

GI pythiosis in dogs is characterized by severe segmen-tal transmural thickening of the stomach, small intestine, colon, rectum, or (rarely) the esophagus or pharyngeal region (Figure 174-17).[50] Mesenteric lymphadenopathy is common and is occasionally observed without accompanying GI tract lesions. The gastric outflow area, duodenum, and ileocolic junction are the most frequently affected portions of the GI tract. Involvement of the mesenteric root may cause severe enlargement of mesenteric lymph nodes, which are often embedded in a single, large, firm granulomatous mass in the midabdominal region. Extension of disease into mesenteric vessels may result in bowel ischemia, infarction, perforation, or acute hemoabdomen. Clinical signs associated with GI pythiosis include weight loss, vomiting, diarrhea, and hematochezia. Physical examination often reveals a thin body condition and palpable abdominal mass. Signs of systemic illness are not typically present unless intestinal obstruction, infarction, or perforation occurs.

Laboratory abnormalities that may be associated with pythiosis include eosinophilia, anemia, and hyperglobulinemia. In dogs with GI pythiosis, abdominal radiographs usually reveal an abdominal mass or thickened segment of the GI tract. Ultrasonography typically demonstrates severe segmental thickening of the GI tract and mesenteric lymphadenopathy.

Figure 174-17 Cross-section of a segmental colonic lesion resected from a 3-yr old female Doberman with gastrointestinal (GI) pythiosis. The reader should note the thickening of the submucosa and narrowing of the colonic lumen.



174.2.6.3 Diagnosis

Histologically, pythiosis is characterized by eosinophilic pyogranulomatous inflammation. Although *P. insidiosum* hyphae are difficult to visualize on H&E-stained sections, they are easily identified in sections stained with GMS as broad (mean, 4 μ; range, 2 to 7 μ), rarely septate, occasionally branching structures. Because inflammation in GI pythiosis centers on the submucosal and muscular layers rather than mucosa and lamina propria, the diagnosis may be missed on endoscopic biopsies that fail to reach deeper tissues. Therefore pythiosis should be considered when endoscopic biopsies reveal eosinophilic or pyogranulomatous inflammation without identification of a causative agent.

Isolation of *P. insidiosum* from infected tissues is not difficult when appropriate sample handling and culture techniques are used. For best results, unrefrigerated tissue samples should be wrapped in a saline-moistened gauze sponge and shipped at ambient temperature to arrive at the laboratory within 24 hours. Identification of *P. insidiosum* should be based on morphologic features; growth at 37° C; production of motile, reniform,

biflagellate zoospores; and, if possible, specific PCR amplification or ribosomal RNA gene sequencing.[51] Although the production of zoospores is an important supporting feature for the identification of pathogenic oomycetes, it is not specific for *P. insidiosum*.

An ELISA for the detection of anti-*P. insidiosum* antibodies in dogs and cats has been found to be highly sensitive and specific for the diagnosis of pythiosis.[51] In addition to providing a means for early, noninvasive diagnosis, this assay also appears to be useful for monitoring response to therapy. Immunohistochemical techniques have previously been used to confirm the diagnosis of pythiosis. However, the specificity of these antibodies has not always been well established. A new polyclonal anti-*P. insidiosum* antibody raised in chickens and adsorbed with *Lagenidium* and *Conidiobolus* hyphae appears to be highly specific for the immunohistochemical detection of *P. insidiosum* hyphae in tissues.

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174.2.6.4 Therapy

Aggressive surgical resection is the treatment of choice for pythiosis. When cutaneous lesions are limited to a single distal extremity, amputation is recommended. In animals with GI pythiosis, segmental lesions should be resected with 3 to 4 cm margins if possible. Unfortunately, most dogs with GI pythiosis are not presented until late in the course of disease, when complete excision is not possible. Local postoperative recurrence of pythiosis is common and can occur either at the site of resection or in regional lymph nodes. For this reason, medical therapy with a combination of itraconazole (10 mg/kg orally every 24 hours) and terbinafine (5 to 10 mg/kg orally every 24 hours) is recommended for at least 2 to 3 months after surgery. To monitor for recurrence, ELISA serology should be performed prior to and 2 to 3 months after surgery. In animals that have had a complete surgical resection and go on to have no recurrence of disease, serum antibody levels drop significantly within 3 months of surgery.[51] If this occurs, medical therapy can be discontinued, with subsequent reevaluation of serum antibody levels in 2 to 3 months.

Medical therapy for pythiosis is typically unrewarding, likely because ergosterol (the target for most currently available antifungal drugs) is generally lacking in the oomycete cell membrane. Despite this fact, clinical improvement has been documented in a small number of *P. insidiosum*–infected dogs treated with either itraconazole (10 mg/kg every 24 hours for 6 to 9 months) or ABLC (2 to 3 mg/kg administered three times weekly to a cumulative dose of 24 to 27 mg/kg). More recently, clinicians have observed clinical and serologic improvement or cure in several patients treated with a combination of itraconazole (10 mg/kg every 24 hours) with terbinafine (5 to 10 mg/kg every 24 hours). Although the percentage of animals responding is still poor (<20%), the combination protocol seems superior to itraconazole or amphotericin B alone.

174.2.7 Lagenidiosis

Until recently, *Pythium insidiosum* was considered to be the only mammalian pathogen in the class Oomycetes. However, in 1999, a second pathogenic oomycete was isolated from a dog with multifocal cutaneous lesions and regional lymphadenopathy. The dog died acutely after rupture of a caudal vena caval aneurysm, and necropsy revealed severe sublumbar lymphadenitis and pyogranulomatous vasculitis. Sequencing of a portion of the ribosomal RNA gene of the isolate recovered from this dog identified it as member of the genus *Lagenidium*.[52] Presently, more than 40 dogs with serologic, histologic, or culture evidence of *Lagenidium* spp. infection have been identified.

The majority of species in the genus *Lagenidium* are parasites of algae, fungi, nematodes, crustaceans, and insect larvae. The most well-studied species, *Lagenidium giganteum*, is a mosquito larval pathogen approved

for use as a biocontrol agent for mosquito populations. Although antigenic and molecular similarities suggest that the canine pathogenic *Lagenidium* species is closely related to *L. giganteum,* differences in their *in vitro* growth characteristics and the failure of *L. giganteum* to infect rodents in mammalian safety studies suggest that they are likely distinct species. Although little is currently known about the life cycle of the canine pathogenic *Lagenidium* species, it is likely similar to that of *P. insidiosum*.

174.2.7.1 Clinical Findings

The epidemiologic and clinicopathologic features of lagenidiosis are similar in many respects to those previously associated with cutaneous pythiosis. Affected animals are typically young to middle-aged dogs living in the Southeastern United States. Although most of these dogs have been from Florida or Louisiana, cases in Texas, Tennessee, Virginia, and Indiana have been identified as well. A number of infected dogs have had frequent exposure to lakes or ponds.

Dogs with *Lagenidium* spp. infection are typically presented for progressive cutaneous or subcutaneous lesions (often multifocal) involving the extremities, mammary region, perineum, or trunk.[52] Grossly, these lesions appear as firm dermal or subcutaneous nodules or as ulcerated, thickened areas with areas of necrosis and numerous draining tracts (Figure 174-18). Regional lymphadenopathy is often noted and may occur in the absence of cutaneous lesions. Similar to the clinical course associated with cutaneous pythiosis, skin lesions in dogs with lagenidiosis tend to be progressive, locally invasive, and poorly responsive to therapy. In contrast to pythiosis, however, the majority of dogs with lagenidiosis have been found to have lesions in distant sites, including great vessels, sublumbar and inguinal lymph nodes, lung, pulmonary hilus, and cranial mediastinum.

Figure 174-18 Ulcerative dermatitis caused by *Lagenidium* sp. infection in a 2-year-old female border collie presented for progressive skin lesions and generalized lymphadenopathy. This dog had similar lesions on all four limbs. The reader should note a large eschar distal to the ulcerative lesion.

174.2.7.2 Diagnosis

The histologic features of lagenidiosis are similar to those associated with pythiosis and zygomycosis and are characterized by pyogranulomatous and eosinophilic inflammation associated with broad, irregularly branching, sparsely septate hyphae. In contrast to *P. insidiosum*, *Lagenidium* spp. hyphae are usually visible on H&E-stained sections. On GMS-stained sections, numerous broad, thick-walled, irregularly septate hyphae are easily recognized. *Lagenidium* hyphae typically demonstrate a great deal of variability in size but in general are much larger than *P. insidiosum*, ranging from 7 to 25 μ in diameter, with an mean of 12 μ.

Immunoblot serology for the detection of anti-*Lagenidium* antibodies in canine serum can provide a presumptive diagnosis of lagenidiosis but must be interpreted in conjunction with results of serologic testing for *P. insidiosum* infection.[52] The definitive diagnosis of *Lagenidium* spp. infection is best made by culture. Because of current limitations associated with its morphologic characterization, definitive identification of *Lagenidium* spp. should be based on ribosomal RNA gene sequencing or specific PCR amplification.

174.2.7.3 Treatment

Aggressive surgical resection of infected tissues is the treatment of choice for lagenidiosis. In animals with lesions limited to a single distal extremity, amputation is recommended. Because dogs with lagenidiosis often have occult systemic lesions, radiographic imaging of the chest and abdomen and sonographic imaging of the abdomen is recommended to determine the extent of disease prior to attempting surgical resection of cutaneous lesions. Unfortunately, the vast majority of *Lagenidium*-infected dogs have nonresectable disease in regional lymph nodes or distant sites by the time the initial diagnosis is made. Medical therapy for lagenidiosis is typically ineffective, and in general, the prognosis for dogs with lagenidiosis is grave.

Table • 174-3 Drug Appendix

GENERIC	TRADE	DOSE	ROUTE	FREQUENCY
Amphotericin B	Fungizone	Dog: 0.22–0.5 mg/lb (0.5–1 mg/kg) Cat: 0.11–0.25 mg/lb (0.25–0.5 mg/kg)	IV	q48h
		Dog/cat: 0.22–0.36 mg/lb (0.5–0.8 mg/kg) diluted in 0.45% NaCl and 2.5% dextrose	SQ	q48h
Lipid amphotericin B complex (ABC)	Abelcet	Dog: 0.5–1.5 mg/lb (1–3 mg/kg)	IV	q48h
Flucytosine	Ancobon	Dog: 11.4–22.7 mg/lb (25–50 mg/kg)	PO	q6h
Ketoconazole	Nizoral	Dog: 4.5–13.6 mg/lb (10–30 mg/kg)	PO	q12h
Itraconazole	Sporanox	Dog: 2.2–4.5 mg/lb (5–10 mg/kg) Cat: 4.5 mg/lb (10 mg/kg)	PO	q24h
Fluconazole	Diflucan	Dog/cat: 1–4.5 mg/lb (2.5–10 mg/kg)	PO	q12h
Enilconazole		Dog: 4.5 mg/lb (10 mg/kg)	Intranasal	q12h
Clotrimazole	Lotrimin	Dog: 1 g	Intranasal	Once
Sodium iodide		Dog: 20 mg/lb (44 mg/kg) Cat: 10 mg/lb (22 mg/kg)	PO	q8
Terbinafine	Lamisil	Dog/cat: 4.5–9 mg/lb (10–20 mg/kg)	PO	q24h
Lufenuron	Program	Dog: 2.2–4.5 mg/lb (5–10 mg/kg)	PO	q24h

174.2.8 Zygomycosis

The term *zygomycosis* refers to infections caused by fungi in the class Zygomycetes, including the genera *Basidiobolus* and *Conidiobolus* in the order *Entomophthorales*, as well as the genera *Rhizopus, Absidia, Mucor*, *Saksenaea,* and others in the order *Mucorales*. Although infections caused by the *Mucorales* have not been well documented in small animals, the *Entomophthorales* have been reported in dogs to cause pyogranulomatous lesions that are grossly and histologically similar to those caused by *P. insidiosum* and *Lagenidium* spp. *Basidiobolus ranarum*, *Conidiobolus coronatus*, *Conidiobolus lamprauges,* and *Conidiobolus incongruus* are saprophytes found in soil and decaying plant matter. Cutaneous infection likely occurs by direct implantation of spores via minor trauma or insect bites. Systemic infection may result from inhalation or ingestion of spores. Affected animals are typically immunocompetent.

174.2.8.1 Clinical Findings

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In humans and other mammals, conidiobolomycosis occurs most often as a nasopharyngeal infection with or without local dissemination into tissues of the face and retropharyngeal region. In two dogs evaluated in the authors' hospital, culture-confirmed conidiobolomycosis was associated with ulcerative lesions of the hard palate.[53] In two additional dogs, a presumptive diagnosis of nasopharyngeal conidiobolomycosis was made based on histologic and serologic findings. One of these dogs was presented for signs of chronic nasal cavity disease, and the other had a severe chronic ulcerative dermatitis of the nasal planum. In a fifth dog described in the literature, *Conidiobolus* infection was associated with multi-focal nodular draining subcutaneous lesions and regional lymphadenopathy.[54]

Basidiobolomycosis is a rare cause of ulcerative draining skin lesions in dogs and has also been reported in a single case as a cause of respiratory disease.[55] Disseminated *Basidiobolus* spp. infection involving the GI tract and other abdominal organs has been described in two dogs.

174.2.8.2 Diagnosis

The histologic features of zygomycosis are similar to those associated with pythiosis and lagenidiosis. On GMS-stained sections, hyphae appear broad, thin-walled, and occasionally septate. The histologic hallmark of entomophthoromycosis is the presence of a wide eosinophilic sleeve surrounding the hyphae. In general, hyphal diameter tends to be significantly larger for *Basidiobolus* spp. (mean, 9 μ; range, 5 to 20 μ) and *Conidiobolus* spp. (mean, 8 μ; range, 5 to 13 μ) than for *P. insidiosum* (mean, 4 μ; range, 2 to 7 μ).

The diagnosis of zygomycosis is based on isolation of the pathogen from infected tissues. Identification of zygomycetes in the laboratory is based on morphologic characteristics of asexual reproductive structures (conidia) and sexual reproductive structures (zygospores).

174.2.8.3 Treatment

Attempted therapy has only been described in a few patients with confirmed zygomycosis. Although anecdotal information and a small number of cases in the literature suggest that cutaneous entomophthoromycosis may be less aggressive than pythiosis or lagenidiosis, progression of cutaneous lesions and sometimes even dissemination despite treatment have also been described. Perhaps the most appropriate current recommendation for the treatment of entomophthoromycosis is aggressive surgical

resection of infected tissues whenever possible, followed by itraconazole therapy for 2 to 3 months. If resection is not possible, therapy with either itraconazole or ABLC should be recommended (Table 174-3).

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175 CHAPTER • 175 Coccidioidomycosis and Aspergillosis

Autumn P. Davidson

175.1 INTRODUCTION

Unique among the continents, North America is host to three of the geographically defined major endemic mycoses: histoplasmosis, blastomycosis, and coccidioidomycosis. The three endemic pathogenic fungi share several characteristics. All are soil-dwelling organisms existing only within defined geographic regions based on specific environmental (soil and climatic) conditions. All are dimorphic, capable of undergoing morphologic change from a native saprophytic form (infectious to mammals; also found in vitro) to the parasitic form causing disease in vivo. *Histoplasma capsulatum* and *Blastomyces dermatitidis* convert in vivo into a "yeast form", and *Coccidioides immitis* converts to a "spherule." Infection in mammals occurs most commonly by inhalation of airborne spores. Inhaled saprophytic spores cannot be killed by neutrophils and are small enough (3 to 5 μm) to lodge in host alveoli. Recovery from infection depends on the competence of the host's cell-mediated immunity. Compromised cell-mediated immunity, due to chemotherapy for neoplasia, organ transplant, or immune mediated disease or as a consequence of immunocompromising viral infection, renders the host less able to resist colonization and dissemination of these fungi.[1]

Fungi and the infectious diseases they cause have become increasingly important in modern human and veterinary medicine, challenging mycologists to better understand their epidemiology, pathophysiology, and the host response. Popular current therapeutic targets include ergosterol in the fungal cell membrane and fungal RNA and DNA synthesis. Novel targets include enzymes involved in cell wall biosynthesis (1,3-beta glucan synthase and chitin synthase), as well as nonergosterol cell membrane molecules, DNA-related enzymes, intermediary fungal metabolism, and fungal virulence factors. Unfortunately, the prevalence of antifungal drug resistance appears to be increasing. Antifungal susceptibility testing is becoming more available and standardized. Data concerning combination therapy and sequential therapy as compared with single-agent therapy are accumulating. Adjunctive therapy with cytokines capable of immunohematologic modulation (granulocyte colony–stimulating factor [G-CSF], granulocyte macrophage colony–stimulating factor, macrophage colony–stimulating factor, and interferon-gamma) also have potential roles in the treatment and prevention of fungal infections. Stem cell and granulocyte transfusions and effective and safe vaccinations offer other avenues under development for restoration and improvement of host defense against mycotic disease.[2]

175.2 COCCIDIOIDOMYCOSIS

175.2.1 History and Mycology

Coccidioidomycosis ("valley fever," "valley rheumatism") was experimentally studied in dogs in the 1890s, but it was not described as a clinical entity in the veterinary literature until 1940. Coccidioidomycosis was recognized as a fatal granulomatous disease in humans during the late nineteenth century. Initially, the pathophysiology of coccidioidomycosis was thought to be neoplastic, a cancer induced by a protozoal organism because of the coccidial-like appearance of the spherule detected in biopsy specimens from affected individuals. Recognition of the mycotic cause of coccidioidomycosis and fulfillment of Koch's postulates occurred in 1900. *Coccidioides immitis* (within California) and *C. posadasii* (in all other endemic Southwestern regions) are the two pathogenic species causing coccidioidomycosis.[3–6]

The alkaline sandy soil environment characteristic of the lower Sonoran life zone in the southwestern United States, western Mexico, and Central and South America is the normal habitat for *Coccidioides* spp., which produce mycelia during seasonal rainfall. Arthroconidia (arthrospores) develop with soil drying, subsequently becoming airborne under appropriate environmental (dry and windy) conditions. In the dog and cat, inhalation of infectious and hardy arthroconidia is the major route of infection. Cutaneous contamination via a penetrating wound occurs less commonly. Experimentally, the canine infectious dose of inhaled arthroconidia is low (<10).[7]

175.2.2 Pathophysiology and Epizootiology

The severity and extent of clinical disease resulting from an infectious exposure depends upon the immunocompetence of the host, and ranges from a mild, clinically silent pulmonic form to fatal, multisystemic dissemination. *C. immitis* transforms in tissue to its parasitic form, the spherule, which undergoes internal division (endosporulation) and ruptures at maturity. Each endospore can become an endosporulating spherule, promoting continuation and expansion of the parasitic phase (Figure 175-1). Spherules or endospores can revert to the mycelial form of growth under appropriate environmental conditions, such as might be found under bandages covering a draining tract. As such, the disease is not believed to be directly contagious among mammals except by direct innoculation of infectious body fluids (blood, semen). Pulmonary infection is characterized by extension from the bronchioles and alveoli, through peribronchiolar tissues, to the subpleura and the tracheobronchial and mediastinal lymph nodes. Dissemination is defined as spread of coccidioidal infection beyond the tracheobronchial and mediastinal lymph nodes. Disseminated disease most commonly involves the axial and appendicular skeleton and overlying skin, abdominal viscera, central nervous system (CNS) (including the eye), pericardium, myocardium, and the prostate gland (Figures 175-2 and 175-3).[8]

The incidence of coccidioidomycosis is increased in young, male, medium to large breed outdoor dogs. The boxer, pointer, Australian shepherd, beagle, and Scottish terrier were found to have increased incidence in one study, although it is not believed that pure breed dogs are generally at greater risk than mixed breed dogs. A breed-specific susceptibility based in host immunocompetence may exist.[9]

Figure 175-1 *Coccidioides immitis* endosporulating spherule.

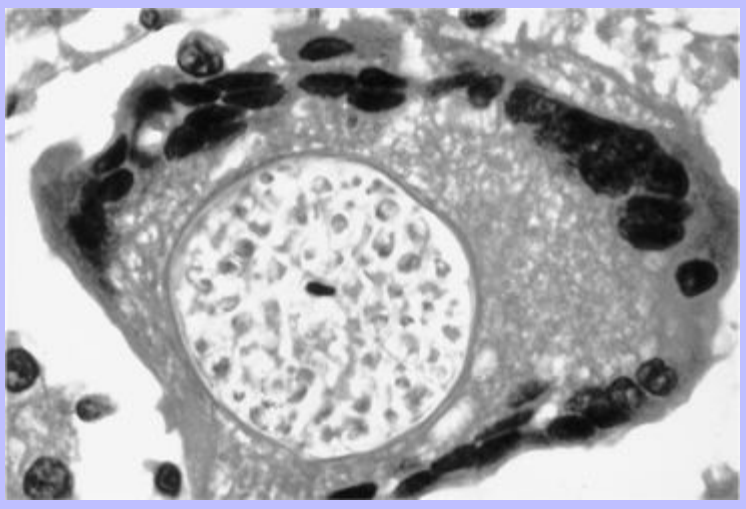


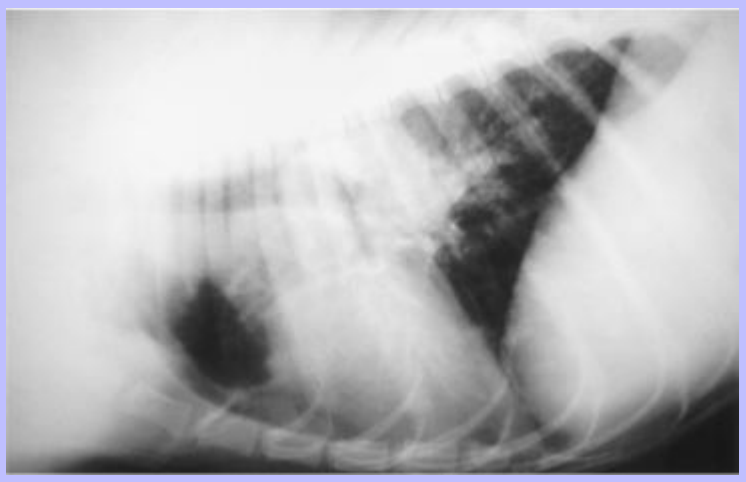
Figure 175-2 Prescapular lymphadenopathy secondary to disseminated coccidioidomycosis in a dog.

175.2.3 Diagnosis

The diagnosis of coccidioidomycosis should be first based on clinical signs compatible with the infection (most commonly cough, lethargy, anorexia, fever, chronic lameness, cervical or head pain, and weight loss) and positive serologic findings. Early in the course of disease (2 to 5 weeks), a positive precipitin test reflects increased IgM levels. Subsequent (8 to 10 weeks) positive complement fixation (CF) testing marks the presence of IgG antibodies. Canine anticomplementary factors can interfere with CF testing, making quantitative immunodiffusion with concentration techniques more reliable than CF. Persistence or reappearance of a positive precipitin test can indicate dissemination. Early CF titers of greater magnitude may suggest more likelihood of dissemination. CF titers may persist at low levels (1:4) during recuperation. Negative serology in an infected individual reflects fulminating disease or anergy.[2,10]

Figure 175-3 Osseous coccidioidomycosis, dissemination to the carpi of a dog.

Figure 175-4 Marked sternal and tracheobronchial (perihilar) lymphadenopathy caused by pulmonary coccidioidomycosis in a dog.



Radiographic changes occurring with coccidioidomycosis are well described. Pulmonary lesions vary in character and severity. Most commonly, peribronchiolar and interstitial nodular lesions are associated with hilar lymphadenopathy (Figures 175-4 and 175-5). Skeletal lesions also vary, productive lesions are more common than lytic lesions, and both may be present simultaneously (Figures 175-6 and 175-7). Characteristic laboratory changes associated with coccidioidomycosis include a mature neutrophilic leukocytosis, mild anemia, monocytosis, hyperglobulinemia, and hypoalbuminemia. Histopathology, mycology, and cytology can also enable a positive diagnosis of coccidioidomycosis but are more invasive (biopsy), are hazardous to laboratory personnel (culture), and are less sensitive (cytology) than serology. A specific and sensitive polymerase chain reaction (PCR) assay for detection of *Coccidioides immitis* DNA is anticipated to assist with earlier diagnoses and subtle cases.[11–13]

Figure 175-5 Nodular pulmonary infiltrates caused by pulmonary coccidioidomycosis in a dog.

Figure 175-6 Disseminated coccidioidomycosis with vertebral (L3) spondylitis in a dog.

Coccidioidomycosis is a reportable disease in humans and considered a serious biohazard due to the highly infectious nature of the saprophytic phase (present in laboratory cultures and the soil). One half to two thirds of humans with primary coccidioidal pulmonic infection are subclinical and resolve their disease and then have durable cellular immunity. The intradermal skin test has been used in humans to identify individuals with such immunity. The outcome of infection in humans is highly correlated with patient profiling (age, sex, race, and reproductive status). The elderly, young, dark-skinned races, and women in the third trimester of pregnancy are at increased risk of serious infection. Five to 10% of primary pulmonary infections in humans result in pulmonary sequelae (nodules or cavities), and only 0.5% to 1.0% progress to chronic pulmonary infection or significant extrapulmonary dissemination. Humans with primary uncomplicated respiratory coccidioidomycosis usually resolve their infection without specific therapy, and it is not believed that therapy adds significant benefit. Pulmonary sequelae may not cause symptoms but warrant close clinical monitoring for evidence of progression to extrapulmonary infection. Treatment of dogs showing clinical signs of pulmonary coccidioidomycosis has traditionally been encouraged and is thought to reduce the potential for dissemination that results in a poorer prognosis. It is not known how many dogs in endemic areas recover from occult, clinically inapparent pulmonary infection with coccidioidomycosis. Epizootiologic studies evaluating serologic evidence of previous infection are underway in parts of the endemic area. A 20% rate of exposure adequate to cause seroconversion is apparent. The intradermal skin test is not reliable in the dog. The incidence of actual illness resulting from *Coccidioides* infection in animals living within endemic areas is not known. Treatment of symptomatic cats is supported by the fact that disseminated disease is already likely present once the diagnosis is made. Weight loss and cutaneous lesions (chronic draining tracts) are the most commonly reported symptoms in the cat. A lack of familiarity with the disease in nonendemic areas may hamper diagnosis in dogs and cats having traveled through endemic regions.[13,14]

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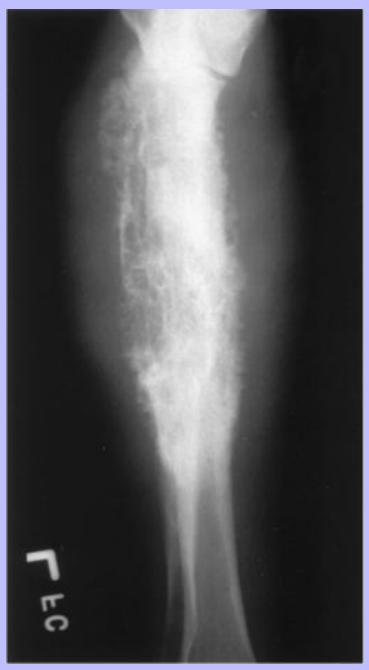
Figure 175-7 Disseminated coccidioidomycosis with radial and ulnar osteomyelitis in a dog.



175.2.4 Therapy

Therapy of coccidioidomycosis has involved both amphotericin B (standard and novel lipid formulations) and the azoles (ketoconazole, itraconazole or fluconazole) as sole agents, in combination, or in succession. Numerous clinical reports exist in the veterinary literature regarding therapy for coccidioidomycosis, with variable recommendations for length of treatment based on the assessment of clinical cure. Treatment for a minimum of 4 to 6 months beyond clinical cure, with marked reduction or resolution of positive serologic findings, is advised. Relapse reportedly occurs commonly and it is not known if resolution of disease in the dog and cat results in lifelong immunity as is believed in humans. Humans living in endemic areas and undergoing immunosuppressive therapy associated with organ transplant experience a 3% (approximate) infection rate. If past exposure to coccidioidomycosis can be documented pretransplant, concurrent antifungal and immunosuppressive therapy is given. Immunosuppression-induced recrudescence of disease in a dog after occult infection has recently been reported.[16]

The soil organism *Streptomyces nodosus* is the source of the gold standard antimycotic agent amphotericin B. Amphotericin B is a polyene antibiotic with antifungal activity due to binding ergosterol, a sterol moiety in the fungal cell membrane, forming channels that increase the permeability of the membrane. Amphotericin B is both fungistatic and fungicidal, depending on the concentration of the drug and the sensitivity of the fungal organism. It is not absorbed to any large extent through the skin or across mucous membranes. Amphotericin B (Fungizone) was introduced in the 1950s and was the first effective parenteral drug available for the treatment of invasive mycoses. Amphotericin B has the widest spectrum of activity of the clinically available antifungal agents. Its major limitation is its narrow therapeutic window. Amphotericin B is administered as an intravenous or intrathecal agent, usually every 48 hours. The intravenous dose, given in 5% dextrose, is 0.25 (feline) to 0.5 (canine) mg/kg intravenously Q 48 hr to a final dose of 5 to 10 mg/kg. The intrathecal dose is up to 0.5 mg in 3 to 5 mL spinal fluid, three times weekly. Amphotericin B is cumulatively nephrotoxic and its use is limited by associated azotemia). Phlebitis, chills, fever, anorexia, renal tubular acidosis, hypokalemia, hypomagnesemia, anemia, thrombocytopenia, leukopenia, and anaphylaxis are other side effects associated with its use. Slow intravenous infusions and pretreatment saline diuresis reduce nephrotoxicity. Recent reports suggest success using amphotericin B subcutaneously diluted in large volumes of saline (0.5 mg/kg in 400 ml 0.45% saline, given every 2 to 3 days to a cumulative dose of 10 to 20 mg/kg). The original formulation of amphotericin B is a micellar suspension with sodium deoxycholate. Recently, novel preparations of amphotericin B in lipid and liposomal-based formulations have been developed that are significantly less nephrotoxic but more costly. Slightly higher doses of these lipid formulations are required for efficacy equal to Fungizone, but the higher doses are well tolerated. Nephrotoxicity is still possible with lipid formulations, and infusional reactions remain a complication. Amphotericin B lipid complex (ABLC) (Abelcet) is dosed at 1 mg/kg intravenously Q 48 hr to a total dose of 12 mg/kg. ABLC and amphotericin B in colloidal dispersion (ABCD) are other lipid formulations. Amphotericin is recommended for serious disseminated coccidioidal infections.

Azole agents for treating mycotic infections were developed during the 1980s and 1990s. Miconazole and clotrimazole were early azoles intended for topical use (see Aspergillosis, Therapy). Ketoconazole (Nizoral), an imidazole, was the first oral agent with an acceptable performance against the endemic mycoses and permitted outpatient therapy. The development of the triazoles, itraconazole (Sporanox) and fluconazole (Diflucan), followed. Azoles are usually fungistatic, inhibiting ergosterol synthesis from lanosterol by interacting with C-14 alpha demethylase, an enzyme dependent on cytochrome P-450. The result is increased cell membrane permeability and inhibition of fungal cell growth. At high concentrations achievable topically, some azoles may be fungicidal due to direct damage to fungal cell wall components (disturbed membrane lipid organization resulting in cell lysis). Other antifungal actions of the azoles include inhibition of endogenous respiration,

toxicity to membrane phospholipids, and inhibition of the transformation of yeasts to their mycelial form. The interaction with cytochrome P-450 enzyme systems causes some of the side effects in mammals associated primarily with ketoconazole. Inhibition of adrenal and gonadal steroid synthesis can occur with ketoconazole administration. Ketoconazole, itraconazole, and fluconazole are available as oral preparations (pill form). Itraconazole and fluconazole are also available as parenteral preparations. Itraconazole has recently become available as an oral solution and a novel intravenous formulation, both in a beta cyclodextrin carrier that vastly improves absorption and bioavailability, allowing higher concentrations in affected tissues. Ketoconazole and itraconazole undergo hepatic metabolism and can be associated with hepatotoxicity, gastrointestinal (GI) intolerance, and cutaneous reactions. Fluconazole is excreted largely unchanged through the kidneys, is well absorbed orally, and has good CNS penetration. With increased prophylactic and long-term use of the azoles, fungal resistance is emerging, especially in immunocompromised humans on extended periods of therapy. The recommended dose of ketoconazole (brand name or its newly available generic equivalent) is 5 to 15 mg/kg orally every 12 hours (given with food). The recommended dose for itraconazole is 5 mg/kg orally (given with food) or intravenously every 12 to 24 hours, and for fluconazole it is 2.5 to 5.0 mg/kg orally or intravenously every 24 hours.

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Currently, ketoconazole therapy, although expensive by veterinary standards, is less cost prohibitive than the expense of hospitalization, supportive care, and renal monitoring required by the appropriately conservative use of amphotericin B. In addition, it is less costly than the later generation azoles, itraconazole, and fluconazole. Amphotericin B therapy in rapidly progressing, serious fungal infection should be followed by long-term oral azole therapy. The use of amphotericin should thus probably be reserved for refractory, disseminated, or fulminating cases. The increased cost of itraconazole and fluconazole may be offset by the suspected, but not yet well-documented, increased efficacy in animals. The improved bioavailability of itraconazole solution supports its use in serious or refractory disease. Fluconazole is indicated for animals with CNS involvement. The use of liposomal amphotericin will permit higher doses to be administered for longer periods of time with less nephrotoxicity. Voriconazole (Pfizer) is a newly approved azole being used in humans with refractory fungal infection. It has excellent oral absorption and favorable pharmacokinetics. Little data are available on its use in coccidioidomycosis.[2,17,18]

Chitin makes up a higher percentage of the fungal cell wall when the organism is in a mycelial phase. Nikkomycin Z, discovered in the 1970s and currently undergoing development, is a natural chitin synthase inhibitor, resembling the precursor substrate. Nikkomycin Z holds great promise as a fungicidal agent, also exhibiting marked in vitro synergism with the azoles.

Lufenuron, a benzoylphenyl urea, is a nonspecific insect chitin synthase inhibitor used in veterinary medicine to sterilize female fleas. Anecdotal clinical reports suggested that lufenuron was useful against coccidioidal infection. Controlled studies have subsequently shown no apparent efficacy or synergy of the compound as an antifungal agent in vitro or in vivo.[19–21]

175.3 ASPERGILLOSIS

175.3.1 Mycology and Epizootiology

Aspergillus species are filamentous fungi that are ubiquitous under appropriate environmental conditions and not typically infectious due to host resistance (Figure 175-8). Aspergillosis in humans is typically a pulmonary hypersensitivity reaction rather than an infectious disease entity, except in immunocompromised individuals where disseminated infection with *Aspergillus* species is problematic. Pets acquire infectious aspergillosis in two forms: (1) localized (usually sinonasal) and (2) disseminated (involving two or more noncontiguous

organs), both more common in the dog than cat. Aspergillus species typically proliferate by producing spores in vegetative decaying soil and water (Figure 175-9).

Figure 175-8 Methenamine-silver stain of histologic section of *Aspergillus* spp. showing characteristic parallel septate hyphae with acute angle branching.

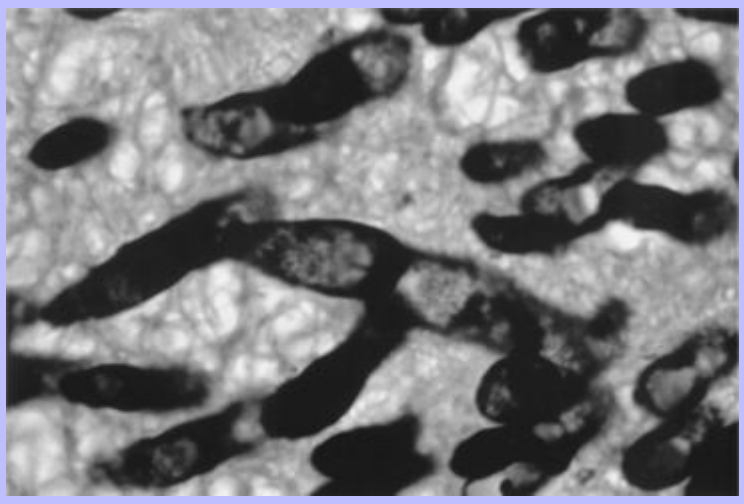
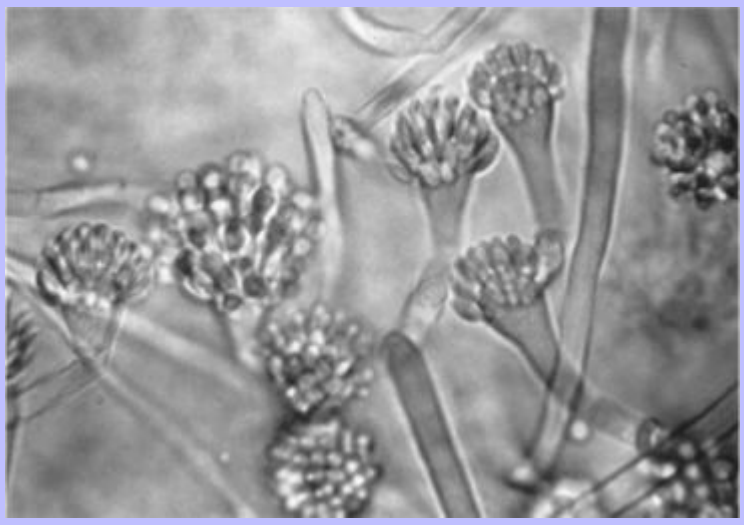


Figure 175-9 *Aspergillus flavus* in culture showing conidiophores bearing fruiting heads.



175.3.2 Localized (Sinonasal) Aspergillosis

Canine sinonasal aspergillosis is characterized by colonization and invasion of the nasal passages and frontal sinuses by the saprophytic fungus, *Aspergillus fumigatus*. *A. fumigatus* is regarded as an opportunistic pathogen, suggesting that some pre-existing local nasal mucosal immunocompetence allowed its establishment in the upper respiratory tract. Alternatively, an in vitro inhibition of B and T lymphocyte transformation by *A. fumigatus* products has been described, suggesting that immunosuppression may both result from or be perpetuated by infection. Sinonasal aspergillosis may occur as an opportunistic primary infection or it may occur secondary to the presence of a foreign body (foxtail, splinter), nasal trauma, or neoplasia (Figure 175-10). The primary form of the disease most commonly affects young to middle-aged mesaticephalic and dolichocephalic breeds and is progressive unless effective specific therapy is given. German shepherds and Rottweilers are the breeds more commonly affected.[22,23]

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Figure 175-10 Foxtail removed from the nasal passage of a dog with sinonasal aspergillosis.

175.3.3 Pathophysiology

Colonization and invasion of the nasal mucosa by *A. fumigatus* results in destruction and necrosis of the nasal turbinates, often accompanied by frontal sinus osteomyelitis. The cribriform plate, palatine bones, and orbit are sometimes involved. Facial pain, anorexia, sneezing, and copious mucoid to hemorrhagic nasal discharge and crusting are common clinical signs (Figure 175-11). Life-threatening epistaxis can occur secondary to erosion of the nasal vasculature. With chronicity, depigmentation and ulceration of the nares and masticatory muscle atrophy result (Figures 175-12 and 175-13). CNS involvement (encephalitis, meningitis) precipitating seizures can result after erosion of the cribriform plate.

175.3.4 Diagnosis

The condition should be differentiated from other inflammatory causes of rhinitis such as infestation with nasal mites, idiopathic lymphocytic-plasmacytic rhinitis, bacterial or other mycotic rhinitis, chronic nasal foreign body, and nasal neoplasia. The diagnosis of sinonasal aspergillosis is best made by direct observation and microscopic demonstration of invasive fungal plaques on the nasal mucosa (Figure 175-14). Culture of *A. fumigatus* from affected tissues is supportive of the diagnosis, but fungi can contaminate nasal mucosa diseased from other causes. It is a good rule to suspect neoplasia as the primary condition in older dogs with confirmed aspergillosis. Serologic evaluation of sinonasal aspergillosis is unreliable, both false-positive and false-negative results occur. Additionally, serology is not prognostic in aspergillosis. Biopsy of affected tissue and histopathologic evaluation for mucosal invasion is confirmatory.[24]

Radiology of the nasal passages and frontal sinuses (radiography and computed tomography [CT]) is useful in the diagnosis of sinonasal aspergillosis but must be performed before rhinoscopic evaluation to avoid artifacts resulting from lavage, tissue manipulation, and hemorrhage. Radiography shows loss of fine nasal turbinate detail and fluid density in the nasal passages and frequently the frontal sinuses (Figure 175-15). In advanced cases, an aspergilloma may exist in the frontal sinus (Figure 175-16). CT evaluation is useful because characteristic lesions may be identified and evaluation of the extent of disease is optimized. CT has provided a new appreciation for the aggressive nature of fungal rhinitis. Mild cases of sinonasal aspergillosis result in relatively little structural change within the nasal cavity other than the regional lysis of nasal turbinates. Dogs that are chronically infected often demonstrate dramatic turbinate destruction, gross epithelial thickening, formation of dense fungal colonies and granulomas, and penetration into adjacent bone causing hyperostosis and in some instances gross bony destruction. Dogs with sinonasal aspergillosis frequently have copious, thick nasal exudate obscuring radiographic identification of granulomas. Administration of intranasal iodinated contrast medium can help define mass lesions in the presence of surrounding fluid.[24–26]

Figure 175-11 Severe crusting of nasal planum and nares in a dog with sinonasal aspergillosis.

Figure 175-12 Ulceration and depigmentation of the nares of a dog with chronic sinonasal aspergillosis.

Numerous techniques have been described to obtain tissue specimens for the definitive histopathologic diagnosis of sinonasal aspergillosis. General anesthesia is usually required, with a cuffed endotracheal tube placed to prevent aspiration of blood and lavage fluids. The external surface of the nasal cavity is visually and digitally examined for evidence of swelling, asymmetry, and ulceration. This includes a thorough oral examination and visualization of the nasopharynx with either a flexible fiber-optic scope or an angled, warmed dental mirror. Placement of precounted gauze sponges in the pharynx, for further protection of the airways, is then performed. Larger laparotomy sponges should be used if possible because these are less easily swallowed by dogs that may react to manipulation of sensitive nasal tissues. The clinician should then measure the distance from the nares to the area of interest noted on the nasal radiographs or CT. This distance serves as a guide for obtaining nasal biopsy and culture specimens. In addition, prior to inserting any instrument in the nasal cavity, the distance from the nares to the medial canthus of the ipsilateral eye is noted and should not be exceeded or penetration of the cribriform plate may result (Figure 175-17). Rhinoscopy should be performed while the animal is in sternal recumbency. Only a limited examination of the rostral nasal cavity can be performed with an otoscope. A rigid arthroscope with a 1.9 to 2.7 mm outside diameter and a 5 to 25 degree angle of view (Richard Wolf Medical Instruments Corp., 7046 Lyndon Avenue, Rosemont, IL 60018) permits a more comprehensive evaluation of the nasal passages. A flexible bronchoscope with a 3.5 to 4.8-mm outside diameter (Olympus Corporation, 4 Nevada Drive, Lake Success, NY 11042-1179) has the added benefit of allowing visualization of the nasopharynx by retroflexing the scope around the soft palate, but it is more difficult to manipulate through the nasal passages. Light resistance is usually felt while inserting the scope through the nares. The scope can then be directed ventrally into the ventral nasal meatus toward the nasopharynx or dorsally into the dorsal nasal meatus toward the olfactory epithelium, openings (ostia) of the frontal sinuses, and the cribriform plate. The advantages of direct visualization of the nasal cavity are that a more thorough understanding of the nature of the disease process might be obtained and placement of a biopsy instrument at the area of interest is facilitated.

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Figure 175-13 Masticatory muscle atrophy in a Labrador retriever previously diagnosed with sinonasal aspergillosis.

Figure 175-14 Fungal plaque, nasal passage of a dog, viewed rhinoscopically.

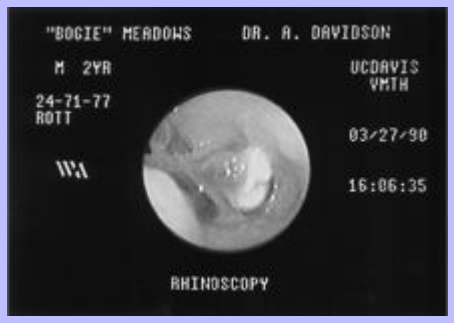


Figure 175-15 Nasal radiography showing loss of turbinate detail and fluid density associated with nasal aspergillosis in a dog.

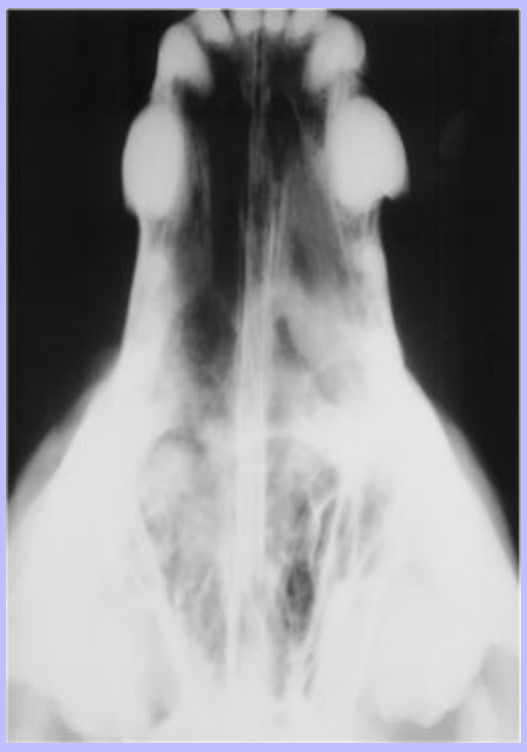
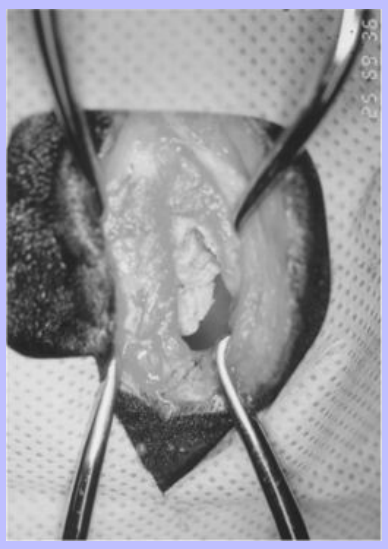


Figure 175-16 Aspergilloma in the frontal sinus of a dog.



Indirect methods of obtaining tissue specimens via the nares have also been described. As with rhinoscopic examination, prebiopsy imaging studies are recommended. Biopsy instruments should never be inserted beyond the level of the ipsilateral medial canthus, and protection of the airways under general anesthesia is recommended. The simplest of these techniques involve flushing the nasal cavity with saline in an attempt to dislodge diagnostic tissue. A catheter should be placed in the nares, or retroflexed 180 degrees around the soft palate. Gauze sponges are used to catch tissues that are flushed out through the nares or into the pharynx. More aggressive blind techniques include flushing the nasal cavity while reaming the area of interest with a stiff plastic tube or biopsy with a biopsy needle (Tru-Cut® Disposable Biopsy Needle; Travenol Laboratories Inc., Morton Grove, IL 60053), a plastic catheter, or by applying suction to a Foley urethral catheter. These techniques do not allow the characterization of the disease process that is possible with direct visualization and 696
may result in nondiagnostic or misleading tissue samples. However, they do not require specialized equipment, 697
are easy to perform, and may result in a definitive diagnosis. If the cytologic diagnosis is inconsistent with the signalment, history, or imaging studies, the clinician should repeat the procedure or consider one that allows direct visualization of the area of interest.[24]

Figure 175-17 Marking the distance from the rostral nares to the ipsilateral medial canthus before rhinoscopic evaluation.

175.3.5 Therapy

Therapeutic recommendations for sinonasal aspergillosis have included surgery and systemic and topical antimycotic medications. Rhinotomy and turbinectomy with perioperative thiabendazole administration resulted in improvement in 50% or less of dogs in one study. Oral ketoconazole administration was reportedly efficacious in 47%, oral itraconazole in 60% to 70%, and oral fluconazole in 60% of infected dogs. Enilconazole applied topically through frontal sinus tubes (twice daily for 7 to 10 days) was reportedly efficacious in 80% to 90% of dogs but is cumbersome and not readily available in the United States. Extensive débridement of the nasal cavities and frontal sinuses followed by infusion of 1% to 2% enilconazole via endoscopically placed catheters has been advocated. Invasive surgical exposure of the nasal passages and

frontal sinuses, topical application of 10% povidone iodine, and delayed closure 6 to 8 weeks postoperatively was recommended for refractory cases but had poor client acceptance and a small study size.[22]

Clotrimazole is a synthetic imidazole derivative. At concentrations achieved during systemic use, imidazoles impair the biosynthesis of ergosterol, the major component of fungal cell membranes, resulting in interference with certain membrane-bound enzyme systems and fungistatic inhibition of growth. In addition, clotrimazole is fungicidal topically, reaching higher concentrations (1.5×10^{-4}M). Electron microscopic observations indicate that at high concentrations, clotrimazole causes alteration in the fungal cell membrane with consequent changes in permeability and leakage of cellular constituents in a manner similar to the effect of polyene antifungal antibiotics. This drug is available in human topical preparations for cutaneous, oral or vaginal applications. Administered orally, it is poorly absorbed and rapidly absorbed undergoes hepatic metabolism and biliary excretion. GI irritation and contact hypersensitivity are reported human side effects.[23,27]

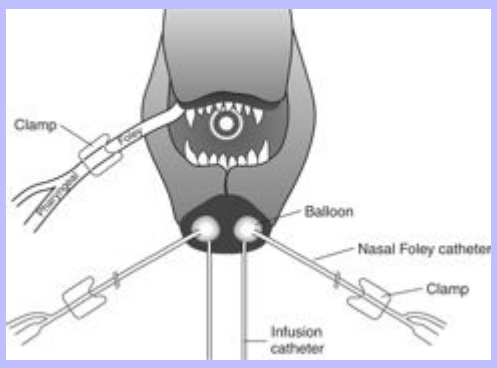
Clotrimazole solution has been used successfully for the topical treatment of nasal aspergillosis in the dog. The topical delivery of clotrimazole has been accomplished using two techniques. In the first, an infusion of clotrimazole is delivered through infant feeding tubes placed into the frontal sinuses and caudal nasal passages through the skull (a somewhat invasive procedure requiring surgical expertise for trephination and tube placement). An alternative technique, based on studies of the distribution of topical agents in the frontal sinuses and nasal passages, involves the retrograde infusion of clotrimazole through polypropylene catheters placed into the nares. This technique is equally successful, technically simpler, and associated with less morbidity. Based on a previous study in cadavers, the average volume of the frontal sinuses in breeds predisposed to fungal rhinitis is 25 mL per side. Flooding the nasal cavity and sinuses with a larger volume of infusate (50 to 60 mL per side) results in distribution to all areas of the nasal cavity and frontal sinuses. Delivery by trephination and feeding tube placement can bypass areas within the frontal sinuses. At present, the recommendation is to use 50 to 60 mL per side in middle to large breed dogs, regardless of head size.

Catheters should be placed with the dog in lateral recumbency. A 24 F Foley catheter is placed per os so that the tip of the catheter lays dorsal to the soft palate. This process can be aided initially by grasping the catheter tip with a pair of right-angle forceps (Meeker) or long-handled needle holders so that the catheter tip is directed rostrally. A mouth gag is then placed, and an assistant should retract the tongue rostrally to improve visualization during catheter placement. The catheter can then be advanced until its balloon is dorsal to the junction of the hard and soft palates. The balloon of the Foley catheter is then inflated to occlude the nasopharynx. The balloon can be palpated through the soft palate to confirm its position just caudal to the hard palate. Moistened laparotomy sponges should be counted and then placed in the pharynx so that the catheter cannot migrate caudally and will absorb any infusate that might escape around the balloon. During sponge placement the index finger of the opposite hand is used to maintain balloon position. Once this process is complete, the mouth gag is removed. One 10 F polypropylene infusion catheter is then advanced through each nostril, beginning dorsomedially; each is advanced into the dorsal nasal meatus to the level of the medial canthus of the ipsilateral palpebral fissure. A Foley catheter (12 F) is then inserted into each nostril and the balloons inflated so that they lay just caudal to and occluding the nostrils. Occasionally a nylon suture is placed across each nostril to prevent cranial migration of the nasal balloons. After three Foley catheters (one nasopharyngeal, two nasal) are placed, and their balloons should be inflated to slow the leakage of clotrimazole from the nasal cavity and frontal sinuses (Figures 175-18 and 175-19). The dog is then repositioned in dorsal recumbency, and an additional laparotomy sponge is placed just caudal to the upper incisors (between the endotracheal tube and the incisive papilla) to absorb leakage of clotrimazole through the incisive ducts.

Clotrimazole (1 g) in 100 mL of polyethylene glycol 200 (a 1% solution) is then evenly divided between two 60 mL syringes (50 mL per syringe). Initially the nasal passages and frontal sinuses must be filled with solution.

When clotrimazole is noted within the lumen of a Foley catheter it should be clamped shut, eventually creating a closed system for saturation of the nasal and frontal sinus mucosa. The clotrimazole should then be continuously and slowly infused over a 1-hour period (50 mL per infusion catheter). The polypropylene catheters are maintained in a horizontal position, parallel to the table, throughout infusion. Positioning the dog so that its nose protrudes beyond the edge of the treatment table allows clotrimazole escaping around the nasal catheters to drip into a receptacle. While the dog's body is maintained in dorsal recumbency, the head can be tilted and maintained in the following positions to ensure drug contact with all mucosal surfaces: dorsal 697
recumbency (15 minutes), left lateral recumbency (15 minutes), right lateral recumbency (15 minutes), and 698
dorsal recumbency (15 minutes). The dog is then placed in sternal recumbency, the catheters and sponges removed and counted, the clotrimazole allowed to drain rostrally, and the pharynx and proximal esophagus suctioned before recovery from anesthesia.

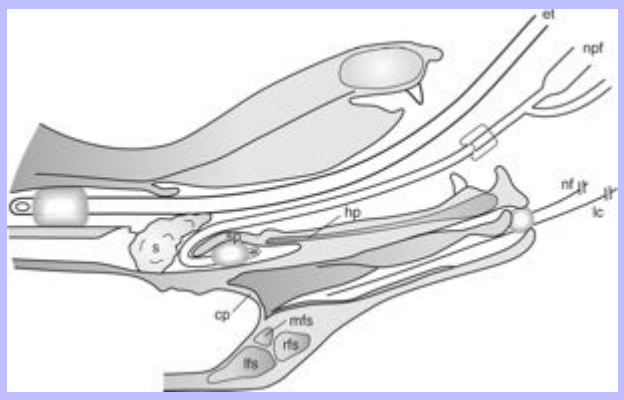
Figure 175-18 Catheter position with the dog in dorsal recumbency. A Foley catheter with the balloon inflated in the nasopharynx and pharyngeal gauze sponges (not shown) minimize leakage of infusion caudally. A cuffed endotracheal tube *(et)* further diminishes the risk of aspiration. Syringes (60 mL) are used to inject infusion into the dorsal nasal meatus via polypropylene infusion catheters. Inflated Foley catheter balloons obstruct the nares to diminish leakage of infusion rostrally. Tubing clamps on Foley catheters are closed when fluid is observed within the catheter lumen. (Adapted from Mathews KF et al: Computed tomographic assessment of noninvasive intranasal infusions in dogs with fungal rhinitis, *Vet Surg* 25:309, 1996.)



Topical administration of clotrimazole into the frontal sinuses and nasal passages is generally well tolerated. Pharyngitis, conjunctivitis, and pharyngeal edema have been reported as transient side effects. The success rate with one or more topical clotrimazole applications has been reported to be 86%. The infection will resolve in most dogs after a single treatment. A favorable response to clotrimazole therapy is usually indicated by resolution of nasal discharge by 2 weeks after therapy. Unabated persistence of nasal discharge 2 weeks after therapy is an indication for repeat evaluation and treatment if aspergillosis persists. Concurrent systemic antibiotic therapy may be indicated if secondary bacterial rhinitis is present. Some dogs with advanced disease may require multiple 1-hour clotrimazole infusions. Cases selected for topical therapy should have aspergillosis

limited to the frontal sinuses and nasal passages, without CNS involvement. Pretreatment CT scans are encouraged so that the extent of the disease is determined and the integrity of the cribriform plate evaluated. Remember, however, that no test (including CT scan) is 100% reliable in determining if the cribiform is intact. 698
Informed consent should be obtained from clients. Topical infusion of clotrimazole solution is not advised if the 699
cribriform plate is not intact, because serious meningitis and encephalitis may result. Cases with CNS involvement, characterized by a lack of integrity of the cribriform plate or orbit (ocular or retrobulbar involvement), should receive systemic antifungal therapy (preferably fluconazole). Only the formulation of clotrimazole in polyethylene glycol is advised. The use of clotrimazole in propylene glycol-isopropyl alcohol vehicles is problematic due to the tendency of the latter to significantly irritate oronasal mucosa. Topical therapy with itraconazole oral suspension in refractory cases is currently under clinical investigation.[28–30]

Figure 175-19 Sagittal section showing the position of the endotracheal tube *(et)*, pharyngeal sponges *(s)*, infusion catheter *(ic)*, and rostral nasal Foley catheter *(nf)* in relation to the hard palate (*hp*), soft palate *(sp)*, cribriform plate *(cp)*, rostral frontal sinus *(rfs)*, medial frontal sinus *(mfs)*, and lateral frontal sinus *(lfs)*. (From Mathews KG et al: Computed tomographic assessment of noninvasive intranasal infusion in dogs with fungal rhinitis, *Vet Surg* 25:309, 1996.)



175.3.6 Disseminated Aspergillosis

Disseminated aspergillosis is most commonly diagnosed in dogs and cats that are terminally ill from the disease. Disseminated aspergillosis typically involves multiple organ systems with no history of nasal or pulmonary involvement. *Aspergillus terreus*, *A. deflectus*, *A. flavipes,* and rarely *A. fumigatus* have been reported in cases where the species has been identified. Disseminated aspergillosis is believed to occur after inhalation of small spores (<8 μm) and hematogenous spread. The pathogenicity of the causative species is reported to be associated with their production of highly infective aleuriospores in tissue and their inherent ability to invade blood vessels. In dogs, disseminated aspergillosis has been most commonly reported in the German shepherd between 2 and 8 years of age. Genetic predisposition and dysfunctional mucosal immunity are suspected. Defective IgA production or regulation has been identified in some affected German shepherds.

Cats with disseminated aspergillosis generally have identifiable concurrent immunosuppressive disease (usually viral) or other debilitation and are less than 2 years of age.

The clinical signs associated with disseminated aspergillosis are nonspecific and related to organ involvement. Uveitis, enophthalmitis, and chorioretinitis may precede the onset of generalized disease. Osteomyelitis and mycotic granulomas of the kidneys, liver, spleen, intervertebral discs, pancreas, lymph nodes, myocardium, prostate, brain, uterus, and thyroid gland have been reported. Bone pain, paraparesis, draining sinus tracts, anorexia, weight loss, pyrexia, lethargy, muscle wasting, and fever are the most common signs. Animals with disseminated aspergillosis may have fungal hyphae observed on cytologic examination of urine sediment, serum, synovial fluid, lymph node centesis, bone biopsy, or intervertebral disc aspiration. The diagnosis is confirmed by culture on Sabouraud's dextrose agar. Serology is not reliable (false negatives have been reported).

The prognosis for recovery is poor despite aggressive antifungal therapy and supportive care. Intravenous amphotericin B, itraconazole, or fluconazole are advised initially. Long-term (sometimes for life) oral azole therapy can be attempted if an initial positive response to intravenous antimycotic drug administration occurs. Surgical excision of fungal granulomas may be helpful, if feasible.[31–33]

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176 CHAPTER • 176 Tropical Diseases

Remo Lobetti

In the past, the term *tropical diseases* referred to diseases that occurred only in the tropic regions of the world. However, the distinction between tropical and nontropical disease is becoming increasingly blurred, and diseases that traditionally were considered tropical now occur in many nontropical places. Moreover, some of the parasitic infections formerly thought to be uncommon or very localized are now recognized to have a wide distribution. Possible reasons for the expansion of tropical diseases to other parts of the world include global warming, especially with diseases that are vector borne, and the ever-increasing movement of both people and animals, which allows dissemination and spread of disease. The presence of tropical diseases is compounded by socioeconomic factors, pet-owner relationships, and nutritional disorders. Diseases that may still be considered of a tropical nature are listed in Table 176-1.

176.1 AFRICAN HORSE SICKNESS

African horse sickness is caused by a double-strand RNA orbivirus. In addition to equines, the dog is the only other species that can contract African horse sickness.[1] Dogs usually contract the disease by ingesting infected horsemeat, but they can also become infected through vector-borne transmission by *Culicoides* midges.[2] Typical clinical signs include fever, cough, and diarrhea, and the disease progression is often acute. Postmortem examination demonstrates severe pulmonary edema, pleural effusion, and splenomegaly.[1] Antibodies to African horse sickness have been detected in healthy dogs from Egypt, India, and South Africa.[2] No specific therapy is available for the disease.

176.2 FLAVIVIRIDAE

Flaviviridae are vector-borne, single-strand RNA viruses.[3] Of all the viruses in this group, the two that are of a tropical nature and that affect the dog and cat are yellow fever and Wesselsbron disease.

Yellow fever, which is transmitted by *Aedes* mosquitoes, produces a subclinical infection in cats that is characterized by a transient viremia, whereas dogs are resistant to the virus.[4] Affected cats may show a transient febrile reaction. Wesselsbron disease has been reported in a dog that died from encephalitis. When three dogs were challenged with the viral isolate from the succumbed dog, two showed a transient febrile reaction and one developed transient paresis.[5] Antibodies to Wesselsbron disease have been detected in healthy dogs from Botswana and South Africa.[5] The diagnosis is usually made retrospectively on postmortem examination. No specific therapy is available for the disease.

Table • 176-1 Diseases That May Still Be Considered of a Tropical Nature

ORGANISMS	DISEASE
Viruses	Orbivirus (African horse sickness)
	Wesselsbron disease
	Yellow fever
	Rift Valley fever
Bacteria	Melioidosis
	Anthrax
Protozoa	Southern African canine babesiosis
	Feline babesiosis
	Trypanosomiases
	Sarcocystosis
Ectoparasites	*Hyalomma* tick bite necrosis
	Cordylobia infestation
Endoparasites	Spirocercosis

It is likely that transient, nonspecific signs of encephalitis in dogs and cats may in fact be the result of infection with Flaviviridae.

176.3 BUNYAVIRIDAE

Bunyaviridae, the largest family of vector-borne, single-strand RNA viruses, includes many important pathogens of both humans and animals.[6] Of all the viruses in this group, the only one of a tropical nature is Rift Valley fever. The *Aedes* mosquito is the most common vector, although midges, ticks, and sand flies also can transmit the infection. Direct trans-mission, by inhalation or ingestion, from affected animals is also possible.[6] In young puppies and kittens, infection with Rift Valley fever virus results in viremia, hepatic and myocardial necrosis, meningitis, diffuse petechial hemorrhages, and death.[4] Although adult animals do not succumb to the infection, they can develop a viremic state, and infection in a pregnant animal can result in abortion or stillbirths.[4,6] The diagnosis is usually made retrospectively on postmortem examination. No specific therapy is available for the disease.

176.4 MELIOIDOSIS

Melioidosis is a bacterial infection caused by *Burkholderia (Pseudomonas) pseudomallei*. The disease occurs in Southeast Asia, northern Australia, and the South Pacific. The organism is a ubiquitous soil saprophyte that results in chronic nodular or purulent generalized systemic inflammatory disease in dogs, cats, and other species.[7] The route of infection is by inhalation, ingestion, or direct transmission into wounds or tissues by bites of arthropod vectors or by direct contact with contaminated soil.[7,8] Isolation of the organism from blood or lesions is diagnostic. Therapy is aimed at surgical drainage of large abscesses and long-term systemic antibiotic therapy.[8]

176.5 ANTHRAX

Anthrax is an acute bacterial systemic disease of mammals caused by *Bacillus anthracis*. In dogs and cats the infection is rare and is manifested by local inflammation, necrosis, and edema of tissues of the upper gastrointestinal tract, which first come into contact with the organism.[9] Although death is usually by asphyxiation,

the toxin can also exert systemic effects. The cat and dog are usually infected by the ingestion of meat from contaminated carcasses of animals that have died from anthrax.[9,10] The diagnosis is made by detection of the bacillus on a blood or edema fluid smear. Postmortem examination is not recommended, because this results in dissemination of the bacterial spores.[10] Treatment is with penicillin antibiotics.[10]

176.6 CANINE BABESIOSIS

Canine babesiosis is an important worldwide, tick-borne disease that ranges in severity from relatively mild to fatal. The causative organism is either *Babesia canis* or *Babesia gibsoni*. Three subtypes of *B. canis* are recognized: *B. canis canis, B. canis vogeli,* and *B. canis rossi*. The first two subtypes occur in Europe and North Africa, respectively, and the third subtype occurs in Southern Africa.[11] *B. gibsoni* occurs in Asia, North America, and North and East Africa.[12] *B. canis canis, B. canis vogeli,* and *B. gibsoni* all result in mild clinical disease; *B. canis rossi* results in severe clinical disease and is the focus of this section.

Canine babesiosis may be clinically classified as uncomplicated and complicated forms.[13] Uncomplicated cases typically present with signs relating to acute hemolysis, including fever, anorexia, depression, pale mucous membranes, splenomegaly, and a waterhammer pulse. This form is further characterized as mild, moderate, or severe disease, according to the severity of the anemia.

With the complicated form of babesiosis, clinical manifestations include acute renal failure, neurologic dysfunction, coagulopathies, liver dysfunction, acute respiratory distress syndrome, myocarditis, hypotension, and pancreatitis. Rare complications include myalgia, ocular involvement, upper respiratory signs, necrosis of the extremities, and fluid accumulation.[14]

Primary hematologic abnormalities include anemia, thrombocytopenia, and leukocytosis. Alterations in biochemical parameters vary, depending on the severity of the case. Typically, uncomplicated cases may show no biochemical changes. However, increased liver enzyme activities, hypokalemia in more severely affected cases, and an increased blood urea nitrogen (BUN) with a normal serum creatinine may be evident. In complicated cases, biochemical changes reflect the underlying complication.[14]

The diagnosis of babesiosis is made by demonstrating *Babesia* organisms (2 × 5 μm, pear-shaped organisms, usually in pairs) in infected erythrocytes on a blood smear stained with a Romanowsky-type stain.

The primary therapeutic aim in the treatment of babesiosis is the reversal of life-threatening anemia through blood transfusions and elimination or suppression of the parasite with specific antibabesial drugs, such as diminazene aceturate and imidocarb. Mild to moderate, uncomplicated cases require only antibabesial therapy; severe uncomplicated cases require antibabesial therapy and blood transfusions. The complicated forms of the disease require additional therapy aimed at treating the complication present.[14]

176.7 FELINE BABESIOSIS

Feline babesiosis is caused by *Babesia felis*, a small *Babesia* parasite that has been reported from France, Germany, Thailand, and Zimbabwe but that only appears to cause clinical disease in South Africa.[15] 700 701

Common clinical signs include anorexia, weight loss, and anemia. Less common signs may include icterus, vomiting, pica, and respiratory signs. The disease can be protracted and often is clinically silent until fairly far advanced. Anemia is the most consistent hematologic finding; white cell and thrombocyte counts are variable and

inconsistent. The most remarkable changes on serum biochemistry are increased alanine aminotransferase (ALT) activity and hyperbilirubinuria. Other biochemical parameters are generally variable and inconsistent.[15] The diagnosis of babesiosis is made by demonstrating *Babesia* organisms in infected erythrocytes on a blood smear stained with a Romanowsky-type stain.

The drug of choice for treating feline babesiosis is the antimalarial drug primaquine phosphate, given at a dosage of 1 mg per cat every 36 hours for four treatments, then 1 mg per cat per os every 7 days for four treatments. The drug does not sterilize the infection. Another drug that reportedly has some effect is doxycycline, given at a dosage of 5 mg/kg per os twice a day for 21 days.[16]

176.8 AFRICAN TRYPANOSOMIASES

Trypanosomiasis is a hemoparasitic protozoal disease that in the dog is caused either by *Trypanosoma brucei* or *Trypanosoma congolense*.[17] The disease is transmitted by the tsetse fly, although dogs may become infected by eating infected fresh meat.[18]

Relapsing fever, anemia, weakness, anorexia, and emaciation are common clinical signs. Other clinical signs include anasarca, conjunctivitis, keratitis, and occasionally neurologic signs (depression, incoordination, circling, and paralysis).[18] In untreated cases, death may occur in 1 week to 3 months.

The diagnosis is made by direct visualization of parasites on blood smear evaluation. Indirect fluorescent antibody (FA) and enzyme-linked immunosorbent assay (ELISA) methods and species-specific monoclonal antibodies can also be used in the diagnosis.[19] Hematologic changes include regenerative anemia, leukopenia, and thrombocytopenia.[17]

Few drugs are effective against African trypanosomiases; however, drugs that have been used include diminazine (most effective), difluoromethylornithine, ethidium, isometamidium, and quinapyramin.[17,18]

176.9 SARCOCYSTOSIS

Sarcocystosis is a protozoal disease caused by organisms of the genus *Sarcocystis*.[20] The dog and cat are definitive hosts, and cattle, sheep, and pigs are intermediate hosts. When a dog or cat ingests meat containing sarcocysts, bradyzoites develop into macrogametocytes and microgametocytes in the epithelial and goblet cells of the intestine. Oocysts then form, which sporulate in situ within the intestinal wall; they are released into the intestinal lumen, where they leave the host via the feces. Sarcocystosis in the dog and cat is usually asymptomatic, but acute to chronic diarrhea may occur.

In the dog and cat the diagnosis is made by finding the small sporocysts in the feces using a supersaturated sodium chloride solution. Potentiated sulfonamides can be used in the dog and cat to eliminate the intestinal infection.[20]

176.10 *HYALOMMA* TICK BITE NECROSIS

Skin necrosis induced by the bite of the *Hyalomma* tick is a common disease of southern Africa. Dermatrophic skin necrosis is thought to be caused by a cytotoxin produced in the salivary gland of the tick.[21] The initial stage the disease is characterized by severe pain at the site of the tick attachment. This is followed by erythema and

edema at the site of the tick bite. Full-thickness skin necrosis follows. The size of the necrotic area, which can vary from 5 to 30 cm, appears to be directly related to the length of time the tick was attached.

The diagnosis is based on clinical signs and the presence of one or more *Hyalomma* ticks. Treatment involves removal of the tick and general principles of wound management.

176.11 *CORDYLOBIA ANTHROPOPHAGA*

The larvae of the *tumbu* or mango fly *(Cordylobia anthropophaga)* produce myiasis in humans and animals in sub-Saharan Africa. The adult fly deposits the eggs on skin that usually is soiled with urine or feces. Within 2 days the larvae hatch and penetrate the skin to form a furuncular lesion with a small central opening. The larvae are obligate parasites and usually provoke a localized furuncle, but aberrant migrating larvae may result in necrotic and inflammatory lesions in many tissues.[23{22}] The larave pupate after 8 or 9 nine days, and the whole life cycle can be completed in less than 4 weeks.[22{23}]

Therapy includes mechanical removal of the larvae, covering the breathing hole in the skin with petroleum jelly, or the use of systemic ivermectin drugs. Prevention involves grooming, good hygiene, and the use of topical insecticidal shampoos and repellants.

176.12 SPIROCERCOSIS

Spirocerca lupi is a nematode parasite of carnivores found primarily in dogs but that also can occur in numerous wild carnivores.[24] Spirocercosis occurs throughout the world, having a tropical and subtropical distribution, although some colder regions have a high incidence.[24,25] Infection depends on the canine population density and the degree of contact between definitive, intermediate, and transport hosts.[24] The adult parasite is most commonly found embedded in a nodule in the host's thoracic esophagus, although it can occur in other parts of the body.[25] In the esophagus the adult worm passes larvated eggs into the lumen; these hatch only after being ingested by an intermediate host (coprophagous beetles).[24,25] Transport hosts (birds, amphibians, reptiles, and small mammals) can become infected if they ingest the intermediate host.[24]

The definitive host becomes infected by ingestion of the intermediate or the transport host. Once ingested, the larvae are liberated in the stomach. From there they penetrate the stomach wall, enter an arteriole, and migrate in the wall of the gastric and gastric-epiploic arteries to the celiac artery and then to the thoracic aorta. From the aorta, the larvae emerge and migrate to the adjacent esophagus. This process takes approximately 6 months.[24,25] The pathology of spirocercosis results from larval migration, the presence of adult worms in granulomas in the esophagus, and secondary bacterial infections.[24] In some cases, the esophageal granuloma can undergo malignant transformation to form a sarcoma, with and without metastases.[26]

Clinical signs of spirocercosis include vomiting, regurgitation, weight loss, salivation, and dysphagia.[24,27] Aortic infection is asymptomatic unless rupture occurs, in which case hemo-thorax and sudden death may occur. The diagnosis is based on survey and contrast radiographs, esophagoscopy, and the finding of larvated eggs on fecal flotation.[24,25,27] The larvated eggs are not a common finding, however, because the adult female can shed eggs only if an opening exists in the granuloma; also, the eggs are shed only for an unpredictable short period.[24] Because the eggs are heavier than other helminth eggs, a flotation fluid of higher specific gravity is required. Doramectin has been shown to be effective in the therapy of spirocercosis.[28]

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It has been speculated that in endemic areas, the incidence of spirocercosis infection may be 100%, a rate probably associated with the many opportunities for acquiring infection from the various intermediate and transport hosts.

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177 CHAPTER • 177 Public Health Aspects of Small Animal Practice

Leonard C. Marcus

Veterinarians must protect clients, staff, and the general public from diseases acquired from animals. This chapter reviews prevention and control of zoonoses in small animal practice. The diagnosis and treatment of these diseases in animals are discussed elsewhere in this text.

177.1 BITE-AND SCRATCH-RELATED INFECTIONS

Animal bites and scratches can range from trivial and self-healing to severely mutilating or fatal. Rabies is the most feared consequence of an animal bite. Almost all cases of dog rabies and all cases of cat rabies in the United States and Canada are acquired from wildlife. The last focus of enzootic domestic canine rabies is along the U.S. -Mexican border, and the disease there is being brought under control. Because dogs and cats remain an important bridge of infection between wildlife and humans, veterinarians should vigorously support animal control legislation and mandatory rabies immunizations for dogs and cats.

All veterinary clinical staff in the United States and Canada (except Hawaii, which is rabies free) should be immunized against rabies before exposure.[1] A vaccine grown on human diploid cells (Imovax; Aventis Pasteur, Swiftwater, PA) or on chick embryo cells (RabAvert; Chiron Corp., Emeryville, CA) is currently available. Both are inactivated. They are given on days 0, 7, and 21 or 28.

Anyone exposed to rabies after completing the pre-exposure series should be given two booster immunizations 3 days apart. Anyone who was not previously immunized should be given one weight-based dose of rabies immune globulin (RIG), with as much as possible infiltrated into the area of the bite or scratch; also, rabies vaccine should be given on days 0, 3, 7, 14, and 28. RIG should not be given to anyone who had pre-exposure immunization. Rabies vaccine should be given to adults in the deltoid muscle, not in the buttocks, to avoid injection into fat rather than muscle. Intradermal vaccine is not available in the United States at this time.

After completion of the pre-exposure series, veterinary staff should have titers checked every 2 years, and a booster should be given if the indirect fluorescent focus inhibition test (IFFIT) result drops below a titer of 1:5 or 0.5 IU/mL.

Testing for antibody before administration of a rabies booster is advisable to reduce adverse side effects, which are more common with boosters than with the primary series. It is also cost-effective, because most individuals maintain an adequate titer for many years, and the cost of testing is much lower than that of immunization.

In addition to transmission through bites or scratches, rabies can be transmitted through contact of saliva, cerebrospinal fluid (CSF), or infected tissue with a mucous membrane or opening in the skin. Possible veterinary occupational exposures include being cut with a surgical or necropsy instrument, using bare hands while performing an oropharyngeal examination, or being sprayed in the eyes or mouth with saliva during a dental procedure or with CSF while decapitating an animal or performing a spinal tap. The use of gloves, masks, and goggles reduces risk. Areas exposed to infective material should be cleaned thoroughly; soap and water should be used for cutaneous exposure, and flushing or rinsing with water should be done for ocular and oral exposures. Contact with blood, urine, or feces is not considered an exposure risk.

Bacterial infections associated with dog and cat bites include *Pasteurella multocida, Pasteurella canis, Staphylococcus* and *Streptococcus* species, plague, tularemia, and *Capnocytophaga canimorsus*.[2] Bite wounds should be washed immediately with soap and water to reduce the risk of infection. Bite victims should be advised to consult a physician about further treatment. Tetanus boosters, rabies immunizations, suturing, or prophylactic antibiotics may be indicated, depending on the circumstance, location, and condition of the wound, the likely pathogen, and the underlying health status of the individual.

Bartonella henselae causes several human ailments, the most common in immunocompetent people being cat scratch disease. Other forms of infection (e.g., bacillary angiomatosis, peliosis hepatis, endocarditis, and retinitis) occur mostly in immunocompromised individuals, such as those with acquired immunodeficiency syndrome (AIDS).[3]

B. henselae is usually transmitted to humans through a scratch from a cat. Cats are infected by interfeline fights and by fleas *(Ctenocephalides felis)*. Fleas may possibly infect humans as well. Transmission can be reduced by eliminating fleas and avoiding actions that are likely to result in a bite or scratch, such as teasing a cat with a short string.

The occupational risk of bites and scratches can be reduced through proper animal restraint, including the use of protective gloves, muzzles, and tranquilizers. Staff, not clients, should handle animals in the veterinary office. Signs to that effect (available from the American Veterinary Medical Association [AVMA] Professional Liability Insurance Trust) should be on display. Clients should be educated about bite prevention, including selection of appropriate pets and avoiding situations that result in bites, especially with small children. The AVMA has brochures for clients on these topics. Aggressive animals should receive behavior modification therapy.

177.2 FECAL-ORAL TRANSMITTED INFECTIONS

Animal feces are an important source of human disease. *Salmonella, Campylobacter, Giardia,* and *Cryptosporidium* spp. are major fecal pathogens with a wide host range, including cats and dogs.

Most cases of human giardiasis and cryptosporidiosis are transmitted person to person. When pets and humans are infected in the same household, it usually cannot be determined if all were infected through a common or different source or if the humans acquired the infection from the animals (or vice versa). Animals can be infected by drinking from toilet bowls, a practice that should be discouraged. Although differences in strains exist, all feline and canine cases of salmonellosis, campylobacteriosis, giardiasis, and cryptosporidiosis should be considered potentially zoonotic.[4]

Toxoplasma gondii has an indirect life cycle, with felids as the only definitive host. Although humans can be infected transplacentally, by organ transplant, or by ingestion of oocysts in soil or cysts in meat, traced back far enough, all human cases ultimately have a feline source.[5]

Most cats acquire toxoplasmosis within the first year of life. The patent period is only 1 to 2 weeks. Infection usually induces protective immunity, with little likelihood of much additional shedding of oocysts. Therefore the proba-bility of finding *Toxoplasma* oocysts in randomly collected feline feces is small and has little public health value. Serologic testing for toxoplasmosis may be useful to diagnose clinical disease in the cat. It has little value in public health, except (if negative) to exclude a particular cat as the source of human toxoplasmosis.

Hydatid disease is infection with the larval stage of *Echinococcus* tapeworms, usually *E. granulosus* or *E. multilocularis*. The space-occupying lesions cause severe disease in humans; *E. multilocularis* is frequently fatal.[6,7] Infection is acquired through ingestion of eggs passed in animal feces.

Veterinarians should know the geographic distribution of adult *Echinococcus* infections and should screen definitive host species for these infections if they come from enzootic areas. *E. granulosus* is an adult tapeworm in the small intestine of wild and domestic canids. It is found in sheep dogs and, less commonly, other dogs in some western states. It is also found in canids from parts of Canada, South America, Europe, the Middle East, Africa, and Australia.

E. multilocularis is found in wild and domestic canids and domestic cats in Canada, the north-central United States, northern and central Europe, and parts of the Middle East and Asia. It may have been introduced into the U.S. southern states with the importation of foxes from Canada for hunting.

Visceral and ocular cases of larva migrans are most commonly caused by the larvae of *Toxocara canis* and less commonly by *Toxocara cati* or *Baylisascaris procyonis*.[6,7] Humans become infected by ingesting embryonated eggs. Cutaneous larva migrans, or *creeping eruption,* is usually caused by the larvae of cat and dog hookworms; infection occurs through skin contact with contaminated soil.[6,7] The pinworm *(Enterobius vermicularis)* is host specific for humans and is never acquired from dogs or cats.

Because of the long external incubation period (which averages 2 weeks), transmission of ascarids and hookworms in a veterinary hospital is unlikely. *Salmonella, Campylobacter, Giardia, Cryptosporidium,* and *Echinococcus* species are infective at the time of passage and can be transmitted in veterinary hospitals. *Toxoplasma* oocysts have an external incubation period of 2 to 3 days, therefore daily disposal of feline feces should eliminate the risk of transmission.

Prevention of fecally transmitted diseases requires education of clients and staff in hygiene and sanitation. Hands should be washed with soap and water or alcohol skin cleaners after animals, cages, or fecally contaminated equipment has been handled, even if gloves were worn.[8] Feces should be flushed down toilets or incinerated. Veterinarians should promote “pooper scooper” laws to reduce the risk of fecally transmitted diseases in public areas. Personnel that clean cages and kennels should wear protective masks and eyewear to avoid ricocheting water from high-pressure hoses. Two-inch wide slides are safer than the standard 1-inch slide for microscopic fecal examinations. Sealing the edges of cover slips with Permount or nail polish further increases safety. Gloves should be worn to clean cages or handle fecal specimens in the laboratory. Tools used for cage cleaning should be disinfected between cages to reduce nosocomial and zoonotic infections.

Fecally soiled surfaces should be decontaminated using approved disinfectants. Steam or flaming may be needed to kill ascarid eggs.

Prophylactic deworming schedules should be followed to reduce the infection of dogs and cats with ascarids, hookworms, and *Echinococcus* organisms.[7] Treatment for other parasites and pathogenic bacteria should be given if they are diagnosed by stool examination or culture. However, antibiotic treatment of intestinal *Salmonella* infection usually is contraindicated because of the risk of the development of antibiotic resistance.

Intestinal infections can be reduced by feeding cooked, canned, or dry food and by preventing predatory behavior by cats and dogs (e.g., keeping cats indoors).

177.2.1 Cutaneous Zoonoses

Various infections can be transmitted by direct contact between an animal and human skin. Several species of ringworm are zoonotic, the most common being *Microsporum canis*. Sporotrichosis is a fungal infection usually acquired by inoculation of spores in soil or organic matter. Transmission by contact with feline lesions has occurred in rare instances.

Parasitic mites vary considerably in host specificity. *Notoedres cati* very rarely infects humans; *Sarcoptes scabiei* var. *canis* does occasionally, usually transiently; *Cheyletiella* spp. readily bite humans but do not remain on them, therefore the diagnosis is made by finding mites on contact animals. Dermanyssid mites thrive in the nests of birds and rodents and bite the animals while they are nesting. These mites also bite humans, but diagnosis and control may depend on finding the nesting site.

Ctenocephalides felis and *C. canis* commonly bite humans, but their life cycle depends on the use of cats and dogs as preferred hosts. *C. felis* transmits *B. henselae* to cats and possibly to humans. *C. felis* and *C. canis* are intermediate hosts for *Dipylidium caninum,* a tapeworm that rarely infects humans because transmission requires ingestion of the flea. Because there is no approved (human) medical treatment for fleas in the United States, the animal hosts and their environment must be treated.[9] Lice are host specific. Pediculosis in humans is transmitted person to person, not from animals.

Dogs and cats that hunt can acquire fleas from prey (e.g., rodents) and bring them home. The fleas can bite humans and transmit infections such as plague and murine typhus. Dogs and cats can also bring ticks into a house. If the ticks are unattached, they could transfer to a person, but humans usually acquire ticks outdoors.

Zoonotic skin disease can be reduced through prompt diagnosis and treatment of animals, disinfection or removal of fomites, and adequate hand washing.

177.2.2 Zoonoses Associated with Animal Genitourinary Products

Leptospirosis is acquired through contact with infected animal urine. Dogs are commonly infected, cats rarely are. The disease can vary from mild to severe or fatal in humans. Occupational risk can be reduced by ensuring that personnel wear gloves, a mask, and goggles while cleaning cages or handling urine specimens in the laboratory, by disinfecting exposed surfaces, and by washing the hands. Exposure would appear to be high in veterinary facilities, but reported cases are rare among veterinary staff in the United States. In a high-risk situation, a single dose of doxycycline (200 mg given orally) is prophylactic.[10]

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Q fever, caused by *Coxiella burnetii,* is usually transmitted by aerosol or by ticks. The source of infection often is the products of conception. Individuals who assist in obstetrical delivery of animals are at risk. Although most infections are associated with cattle, sheep, and goats, dogs and cats also harbor the organism.[11]

Brucella canis is rarely transmitted to people by contact with canine genital secretions or products of conception or abortion.

177.2.3 Zoonoses Associated with Respiratory Infections in Animals

The worst respiratory infection of cats and dogs directly transmissible to humans by aerosol is plague, which is enzootic in the western United States and parts of Asia, Africa, and South America. Suspected human or animal

cases should be reported immediately to the appropriate health agencies and confirmatory diagnostic procedures done. Suspect and proven cases and their contacts (human and animal) must be quarantined and treated. Veterinarians have contracted fatal pneumonic plague from cats.[12]

Bordetella bronchiseptica is a rare cause of human disease. “Strep throat” in humans is caused by *Streptococcus pyogenes*. It is transmitted person to person, and rarely, if ever, by an animal. Animals often carry other, non-group A streptococci in their oropharynx or skin. Definitive diagnosis of *S. pyogenes* requires Lancefield group serotyping.

Dogs and cats rarely get *Mycobacterium tuberculosis*. It is more often transmitted from humans to pets than vice versa, therefore the human source should be traced and treated.

Systemic mycoses, such as histoplasmosis, coccidioidomycosis, and blastomycosis, are transmitted by contact with or inhalation of spores from the soil. They can cause pulmonary, cutaneous, or multiorgan infection in humans and animals. Finding these infections in animals indicates an environmental source to which humans may be exposed.

177.2.4 Zoonoses in Immunocompromised People, Pregnant Women, and Children

Individuals with AIDS or some forms of leukemia, those who are undergoing chemotherapy or corticosteroid or other immunosuppressive therapy for cancer, autoimmune disease, arthritis, or organ transplant, or those who have congenital immunodeficiency are uniquely susceptible to opportunistic infections. Many of these are zoonoses (e.g., cryptosporidiosis, toxoplasmosis, salmonellosis, and bartonellosis). Asplenia increases the risk for potentially fatal sepsis with *C. canimorsus* and babesiosis.

If a woman acquires toxoplasmosis during pregnancy, the fetus could become infected and suffer severe congenital defects. Infection in the woman before conception provides protective immunity for the fetus, therefore antibody screening could provide assurance (if positive) that future pregnancies are not at risk.

It is inappropriate for veterinarians to delve into a client's health status, because such inquiry could be interpreted as practicing human medicine.[13] However, if a person volunteers the information that he or she is immunocompromised, it is appropriate for the veterinarian to advise the person to be especially careful to avoid zoonotic diseases.[14,15] If an opportunistic zoonosis is diagnosed in an animal, the owner can be advised in an open-ended way that the organism can infect humans and could cause severe illness in pregnant or immunocompromised individuals.

Because of their behavior, ignorance of risk, and poor sanitary habits, children are more at risk than adults of being injured or infected by animals. Special efforts should be made to educate parents of young children about the prevention of zoonoses and injuries from animals.

177.3 GENERAL PRINCIPLES OF VETERINARY PUBLIC HEALTH

Animals often carry *Salmonella, Campylobacter, Giardia, Cryptosporidium, Toxoplasma, Echinococcus,* and roundworms in the intestine asymptomatically. They also can harbor ringworm without dermatitis and can shed *Leptospira* organisms in the urine and appear well. Therefore the practice of putting warning signs on cages and applying precautions only with sick animals ignores the risk from subclinical carriers.

Hands should be washed after animals or items contaminated by their excretions have been handled. Veterinary staff should wash hands between each patient. Items soiled by urine or feces should be disposed of in a sanitary manner. Food should not be stored in refrigerators used to hold laboratory specimens. Veterinary hospitals should have effective isolation rooms and procedures for animals with contagious diseases, including the use of antiseptic footwear baths, eyewear, disposable booties, gowns, gloves, and masks; and safe sharps disposal.

Clients and staff should be educated about disease prevention, and this information should be reinforced with pamphlets and written protocols. Posting signs about washing hands, no smoking zones, and safe food storage helps. Written guidelines can cover specific situations, such as who will feed and handle rabies suspects and the way in which feces will be handled in the laboratory.

People seeking to reduce zoonotic risks when acquiring a pet can be advised to get a healthy-appearing, mature animal from a known source with no recent history of fleas, diarrhea, or respiratory or cutaneous disease. Pets should be immunized and dewormed according to standard protocols and examined regularly (e.g., annually as adults). Pets with diarrhea, cough, dermatitis, or fever should be evaluated and treated definitively and promptly.

Veterinarians should interact constructively with physicians, educating them about the transmission of zoonoses but avoiding litigious risk of involvement with individual patient care. Consultation between knowledgeable veterinarians and physicians is mutually beneficial.

177.4 BIOTERRORISM

Most potential agents of germ warfare directed against humans are zoonoses (e.g., anthrax, brucellosis, glanders, plague, Q fever, tularemia, viral encephalitides, and viral hemorrhagic fevers). Some of these occur naturally in dogs and cats, others do not, but genetic manipulation could change the host range of pathogens. It is possible that animals could become a persistent reservoir of infection after an initial attack. Veterinarians should promptly report unusual presentations or patterns of disease suggestive of bioterrorism to appropriate government authorities.

177.5 MEDICAL-LEGAL ASPECTS OF VETERINARY PUBLIC HEALTH[13]

Veterinarians can be sued if their malpractice results in human injury or zoonotic disease. Damages can include medical expenses, lost wages, and pain and suffering. Malpractice includes failure to diagnose a zoonotic disease, treat it properly, or warn potential human contacts of the risk of transmission. The veterinary record should include the advice given to clients and others in potential contact with the animal (e.g., ways to reduce exposure and to seek medical care). Records should be kept of injuries and disease exposures that occur among staff and the response to those incidents.

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Veterinarians should not offer (human) medical advice or treat human patients. The only exception might be immediate first aid that would reasonably be expected of any lay person (e.g., washing a bite or scratch wound or applying pressure to reduce bleeding from an injury inflicted by an animal).

Reportable diseases must be reported. Criminal as well as civil consequences can ensue if damages occur because of failure to report.

177.6 SUMMARY AND CONCLUSION

The great majority of zoonoses are preventable through education of clients, staff, and the general public, as well as sanitation and treatment of animal carriers. Veterinarians are obligated to incorporate public health measures into their practice. Even with these precautions, the benefits of pet ownership far outweigh the risks.

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178 CHAPTER • 178 Principles of Chemotherapy

Angela E. Frimberger

178.1 INTRODUCTION

Chemotherapy is the principal modality used to treat systemic cancers such as hematologic malignancies and metastatic solid tumors. In managing chemotherapy, communication between the veterinarian and the owner is essential, and it must be frank and compassionate. All options should be presented to the owner without regard to the clinician's preconceptions of the owner's preferences. The goal of chemotherapy in human oncology is usually to cure the patient; however, in veterinary medicine, palliation is often a more appropriate goal. It is important to determine the goal of treatment at the outset because it often determines the course of therapy. If treatment is to be undertaken with curative intent, a greater likelihood of side effects is accepted because of greater long-term benefit. In palliative treatment it is accepted that survival is likely to be relatively short, and the primary goal is to improve quality of life, which in veterinary medicine may result in prolonged survival because euthanasia is delayed. Therefore the drug doses and schedules used are less likely to result in side effects. Because quality of life for humans depends largely on preservation of body image and essential organ function, owners may interpret their pet's well being in similar terms; the clinician can help them to understand that these are not necessarily valid for animals. A continuing, open dialogue will allow an owner to make an informed decision and will ultimately create a “team” approach to treatment of the pet's cancer.

178.2 TUMOR BIOLOGY IN CHEMOTHERAPY

In general, chemotherapy drugs are most active against cells that are actively dividing and in a particular phase of the cell cycle. In the cell cycle, cells may be in mitosis (M phase), or undergoing RNA and protein synthesis (G_1 and G_2 phase) or DNA synthesis (S phase, which occurs between G_1 and G_2). Cells may also exit the active cell cycle and enter G_0, during which time they are mitotically quiescent and may not be affected by chemotherapy. The proportion of cells in G_1, G_2, S, and M phases (the active phases of the cell cycle) compared with G_0 is referred to as the *growth fraction*. Thus it is most advantageous to use chemotherapy when tumors have a relatively high growth fraction.

Tumors grow most rapidly when they are small. As they grow larger, the growth rate decreases due to a decrease in the proportion of cells in active phases of the cell cycle, increased loss of cells, and cell death due to poor circulation, poor nutrition, and hypoxia. This decrease in growth fraction as tumors age is referred to as *Gompertzian growth*. Larger tumors may also have a poor blood supply; thus chemotherapy drugs may not be delivered to cancer cells at cytotoxic levels. In addition, resistance to chemotherapy can occur through spontaneous mutations that occur with each cell division at a rate intrinsic to each tumor. Thus the likelihood that mutation resulting in drug resistance has occurred is related to the number of cell divisions that have taken place, and therefore resistance to chemotherapy is more likely in large tumors. Furthermore, the larger the absolute number of tumor cells present, the higher the likelihood that a resistant clone is present. Finally, chemotherapy cytotoxicity follows fractional-kill kinetics; for example, if a particular dose of drug kills 4 logs of cells, then it will reduce a tumor of 10^{13} cells to 10^{9} cells and a tumor of 10^{10} cells to 10^{6} cells. Either will appear clinically as a complete response; however, the latter scenario is obviously preferable. Therefore it is most advantageous to begin treatment with the smallest tumor, and in general, chemotherapy will be most active either after early detection or after a cytoreductive (“debulking”) procedure such as surgery or radiation therapy. Except in

vincristine treatment for canine transmissible venereal tumor and combination chemotherapy for lymphoma, chemotherapy is rarely effective for large bulky tumors.

178.3 CHEMOTHERAPY STRATEGIES

Before undertaking any treatment, it is important to determine a definitive diagnosis of tumor type, the clinical stage of disease, and the patient's overall health. The histologic diagnosis and stage are important both in establishing a prognosis and prescribing a treatment plan. The prognosis assists the client in choosing a goal of treatment. The general health screen is necessary to determine if other conditions are present that may affect the patient's life expectancy (i.e., other systemic disease), conditions that need to be resolved prior to starting chemotherapy (e.g., subclinical urinary tract infection), or conditions that need to be taken into account in planning chemotherapy (e.g., subclinical cardiac or renal disease).

178.3.1 Goal of Treatment

As discussed previously, it is important to determine the goal of treatment at the start of therapy, because the goal usually determines the course of treatment.

Cure is the eradication of all tumor cells and is an ideal outcome, although not always realistic in veterinary oncology. The restriction on chemotherapy doses to keep side effects within an acceptable range in veterinary oncology means that cures are only possible in a small number of patients. Often defined as 2 years of unmaintained remission (not receiving chemotherapy), cure is possible for up to 15% of dogs with lymphoma and 20% of dogs with osteosarcoma.

Palliation is designed to improve quality of life—and thus possibly to extend life—but without expectation of cure. Palliative treatment is often done when the prognosis is poor and significant toxicity cannot be justified in the face of a short expected survival. It is rarely effective to begin treatment with palliative intent and then later to switch to a more aggressive approach. However, it is common to begin treatment with curative intent and then later switch to a palliative course.

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178.3.2 Treatment Response

To determine if a given treatment is effective, it is necessary to evaluate treatment response at each visit. This is important to avoid unneeded expense and toxicity from continuing to administer an ineffective drug and so that a more effective treatment can be instituted. Clinicians can determine the tumor volume by measuring each tumor in three dimensions when possible and multiplying them. If multiple masses are present, they are each measured and the total tumor volume for the patient is determined. The response to treatment is then determined as follows:

- Clinical remission/complete response (CR)—No evidence of any detectable tumor by routine physical exam and imaging techniques but not necessarily the same as cure
- Partial response (PR)—A decrease in tumor volume of greater than 50% and no new masses
- Stable disease (SD)—A decrease of less than 50% or increase of less than 10% in tumor volume
- Progressive disease (PD)—An increase in tumor volume of greater than 10% or the appearance of any new masses

178.3.3 Combination Chemotherapy

To understand combination chemotherapy, it is necessary to have a brief overview of the common classes of drugs in use in veterinary oncology.

Alkylating agents create cross-links in DNA, causing strand breaks. An interesting feature of this class of drugs is the apparent lack of cross-resistance between different alkylating agents or with other classes of drugs.

Antitumor antibiotics (anthracyclines) act by interfering with topoisomerases, DNA intercalation, and other mechanisms. These drugs usually exhibit cross-resistance with others in their class and with drugs in other classes, particularly mitotic inhibitors.

Mitotic inhibitors act to inhibit assembly (vinca alkaloids) or disassembly (paclitaxel) of the mitotic spindle.

Platinum compounds create cross-links in DNA. These drugs are similar to alkylating agents, and no cross-resistance with other classes of chemotherapeutic drugs is seen.

Antimetabolites are analogs of normal metabolites and are incorporated into DNA where they interfere with enzyme activity, transcription, or translation. These drugs often have significant toxicity with low efficacy at veterinary doses and so are not in frequent use in veterinary oncology.

Early therapeutic trials for the treatment of lymphoma using single-agent chemotherapy drugs, such as vincristine or cyclophosphamide, produced dramatic clinical responses in both dogs and cats. However, these responses were often of short duration, and further treatment using the same drug did not provide further response. In other words, these animals had resistant tumors. Tumor resistance to chemotherapy is common even before treatment is started, and tumor cells acquire resistance rapidly after drug exposure due to their high mutation rate.

Combination chemotherapy may overcome some of these problems by affecting different metabolic pathways in cells that are resistant to other drugs in the combination. The object is to kill cells that may be resistant to drug A by a different mechanism using drug B before the drug A–resistant clone has a chance to expand and develop cross-resistance. Although combination chemotherapy could potentially be more toxic to normal cells, patterns of toxicity vary between drugs, and judicious scheduling of chemotherapeutic agents so that their toxicities do not overlap appears to improve tumor kill without compounding toxicity. For example, drugs that do not produce significant bone marrow suppression (such as vincristine or L-asparaginase) may be scheduled to be given 1 week after a myelosuppressive agent (doxorubicin, cyclophosphamide) or even on the same day in combination. When chemotherapy combination regimens are designed, each drug included must be at least partially effective against the target tumor as a single agent. When drugs are given in combination on the same day it is sometimes necessary to reduce the dose of each individual drug for a higher total dose intensity. However, care must be taken not to reduce the dose of a highly effective drug to allow administration of a less effective one. The drugs are then scheduled, taking into account both the mechanism of action and the toxicity profile of each drug, to expose the tumor to the highest possible number of agents and maximize dose intensity while minimizing toxicity.

To reduce the risk of drug resistance occurring, it is important not to administer drugs at subtherapeutic doses; the highest dose intensity possible should be delivered. It is important not to modify the planned doses or schedule in anticipation of a toxicity that has not occurred. For example, a dog that became neutropenic after receiving doxorubicin is not at increased risk for myelosuppression from other chemotherapeutics such as

cyclophosphamide, so doses should not be reduced. It is also important not to change the protocol for short-term or nonlife-threatening toxicities such as emesis or diarrhea. On the other hand, if tumor growth occurs, it is not good practice to continue the same treatment protocol at the same doses. Instead, an alternative, noncross-resistant regimen should be used.

Although bacterial culture and sensitivity testing appears reliable, similar tests for chemotherapeutic sensitivity using tumor cells do not appear to have the same power of prediction. Such tests appear able to predict drug resistance and may have a role in identifying agents that could cause side effects without antitumor effects. However, because the ability of such tests to predict tumor sensitivity is low, combination chemotherapy is recommended over single agents suggested by assays.

178.3.4 Chemotherapy in Combination with Other Treatment Modalities

Chemotherapy can be used in combination with other modalities, including surgery, radiation therapy, or both.

Adjuvant chemotherapy is used after resection of a primary tumor, when the animal is at significant risk of recurrence or metastasis. The most obvious veterinary example is the effectiveness of adjuvant cisplatin, doxorubicin, or carboplatin in the treatment of canine osteosarcoma. The effectiveness of adjuvant chemotherapy lies in the fact that it is used at the earliest stages of growth. When a primary tumor is resected, micrometastatic foci of tumors cells have a high growth fraction and a low number of resistant cells. As the tumors grow, the growth fraction decreases, the cell cycle time increases, cellular heterogeneity increases (leading to a higher level of spontaneous resistance), and areas of poor vascular perfusion increase. The disadvantage of adjuvant chemotherapy is that some patients may be cured with surgery, and the animals are exposed to needless risks of toxicity. For tumors such as osteosarcoma and hemangiosarcoma in dogs and mammary tumors in cats, this percentage is small, but for animals with other tumors, the decision may be more difficult.

Neoadjuvant chemotherapy is used prior to localized treatment modalities such as surgery or radiation therapy with the objective of reducing the size of the primary tumor and reducing the scope and side effects of other definitive treatment.

Chemoradiotherapy refers to the use of chemotherapy drugs primarily as radiation sensitizers rather for their direct antitumor effect.

178.3.5 Modes of Administration

The majority of chemotherapy is delivered either intravenously or orally, and occasionally subcutaneously or intramuscularly. However, other modes of administration are sometimes used, particularly for cisplatin. *709* *710*
Cisplatin can be delivered to dog as an intracavitary infusion into the pleural or peritoneal cavities to successfully control malignant effusions or intravesicularly (into the urinary bladder) for bladder tumors. Cisplatin has also been injected intralesionally, in a collagen or oil-based vehicle, to control localized tumors. In this method, great care must be taken to avoid exposure of personnel because spillage occurs easily and drug may leak from the injection sites. Topical administration is available (5-fluorouracil—dogs only) but is rarely used because of drug toxicity and the risk of exposure to humans who apply the medication and play with the dog. Certain drugs can also be administered intra-arterially and intrathecally for specific treatment protocols; however, this is rarely done in veterinary medicine.

Encapsulation in liposomes can reduce or alter the toxicity of some chemotherapy drugs. Conjugation of the liposome with polyethylene glycol reduces clearance by the reticuloendothelial system, producing “stealth”

liposomes with greater circulating time. A liposome-encapsulated doxorubicin formulation has been reported to be less cardiotoxic in veterinary patients but resulted in a new cutaneous toxicity.

178.3.6 Chemoprotection

The administration of a second drug specifically to reduce the host organ toxicity of a chemotherapy drug is termed *chemoprotection*. Chemoprotectants in use in human and veterinary oncology include mesna, which reduces the risk of cystitis associated with ifosfamide and cyclophosphamide by binding toxic metabolites in the urine, and dexrazoxane, which protects against doxorubicin-associated chronic cardiotoxicity.

178.3.7 Metabolic Dosing

Because their desired effect is cellular cytotoxicity, most chemotherapy drugs have a very narrow therapeutic margin; that is, the host toxic dose is very close to the effective dose. Therefore it is important to be as accurate as possible when calculating doses. For some drugs, dosing is based on a “metabolic body size” to decrease the risk of toxicity to the patient. Although imperfect, current dose recommendations for these drugs are based on body surface area (BSA, m^2). This scheme implies that smaller animals have a higher metabolic rate and therefore should receive a higher dose on a body weight basis. For other drugs (e.g., doxorubicin) dose based on BSA is imperfect, and small dogs and cats should be dosed at lower rate than larger dogs. Until further guidelines are available, the veterinarian should check the dosing basis for any drug to be used, become familiar with the individual drugs that require lower dose for small pets, and use a BSA conversion table when metabolic dosing is indicated.

In human oncology, dosing is sometimes tailored to the individual patient either by monitoring drug levels or based on patient characteristics. For example, the appropriate dose of carboplatin can be determined from a formula based on the patient's glomerular filtration rate (GFR) and the desired area under the curve (AUC). This type of calculation is not usually done in veterinary oncology; however, similar principles are recognized: in patients with reduced GFR reflected as elevated serum creatinine level, carboplatin dosing should be adjusted based on the serum creatinine level (see Practical Chemotherapy).

178.3.8 Dose Intensity

The concept of dose intensity is an important principle of chemotherapy. It is defined as mg/m^2 of drug per week of therapy and should be the highest tolerated by the animal with minimal toxicity. For example, in dosing of myelosuppressive drugs, because there will be variation in individual metabolism of drugs and in the sensitivity of normal tissues, the aim should be to deliver doses that produce a neutrophil nadir of between 1000 and 1500 cells per μl. Ample evidence in both human and veterinary oncology suggests that optimal dose intensity improves the outcome for chemotherapy.

Chemotherapy dose intensification with bone marrow support has been used with success in veterinary oncology. The use of autologous (patient's own) bone marrow transplant to allow higher doses of a myelosuppressive drug has been used in myeloablative bone marrow transplantation in human patients and dogs, but the toxicity of such dose intensification is high. Intensifying chemotherapy doses with autologous bone marrow support, but only into the submyeloablative range, appears to improve remission times without increasing toxicity for selected dogs with lymphoma.

178.3.9 Toxicity After Chemotherapy

Because most chemotherapy drugs are effective in the active phases of the cell cycle, toxicity from chemotherapy is most common in tissues that are renewing and is usually related to the dose of the drug. This has implications for both the patient (toxicity and efficacy) and for owner and veterinary staff safety in handling the drugs during administration and patient care. (See Practical Chemotherapy for more on chemotherapy safety.) Although most tumor cells are in active phases of the cell cycle, most normal tissues have a relatively low growth fraction. Normal tissues can be classified as static (nerve, striated muscle) in which the capacity for mitosis is limited; expanding (organs, glands) in which mitosis can be induced; and renewing (hematopoietic cells, mucosa, epidermis, gametes, fetal tissues) in which the growth fraction approaches that of tumor tissue. The major toxicities of chemotherapy affect the latter group.

Myelosuppression is a general term applied to the toxic effects of chemotherapy on the bone marrow (Table 178-1). In general the prognosis for uncomplicated myelosuppression is good, and most veterinary patients recover within a few days. Most dogs and cats that have myelosuppression have no clinical signs at all. The most chemosensitive cells in the bone marrow are the proliferating hematopoietic progenitors and precursors, which are starting to commit to a particular lineage but are still immature. The more differentiated cells form a nonproliferating pool of maturing hematopoietic cells that will be unaffected by chemotherapy and will provide mature cells for 5 to 10 days. This means that the nadir (or low point) of peripheral cell counts occurs at this time. The time at which the nadir occurs also depends on the life span of the hematopoietic cell. Neutrophils live only hours in both dogs and cats, and their nadir occurs first at 5 to 10 days postchemotherapy; platelets live for approximately 10 days, and their nadir occurs 1 to 2 weeks after chemotherapy. Erythrocytes live for 120 days in the dog and 70 days in the cat; although anemia may occur over a prolonged course of chemotherapy, it is rarely clinically significant. Like the maturing cells, hematopoietic stem cells are largely nonproliferating and so are relatively resistant to chemotherapy toxicity. However, they are stimulated to divide by the loss of proliferating precursor cells and rapidly replace the lost cells so that nadirs after chemotherapy rarely last more than several days. This also has implications for the interval between administrations of myelosuppressive drugs. If these drugs are given when the stem cell pool is dividing (i.e., soon after the previous administration), then severe prolonged myelosuppression due to stem cell destruction may occur. The usual timing for myelosuppressive drug administration is every 2 to 3 weeks. Some drugs (such as lomustine and carboplatin) may have delayed or prolonged nadirs, and dosing intervals are longer for these drugs.

When administering chemotherapy, a complete blood count (CBC), including a platelet count, should be collected at the expected neutrophil nadir, usually 1 week after administration. The absolute neutrophil count (not the total leukocyte count) should be evaluated. Although many animals have a low neutrophil count without clinical signs, a count of less than 1000 cells per µl is sufficient reason to reduce all subsequent doses of that myelosuppressive drug.

Table • 178-1 Myelosuppressive Potential of Some Commonly Used Chemotherapeutic Agents

HIGHLY MYELOSUPPRESSIVE	MODERATELY MYELOSUPPRESSIVE	MILDLY MYELOSUPPRESSIVE
Doxorubicin	Melphalan	L-asparaginase*
Vinblastine	Vincristine (0.75 mg/m2)*	Vincristine (0.5 mg/m2)*
Cyclophosphamide	Methotrexate	Corticosteroids
Carboplatin	Cisplatin	Bleomycin
Mitoxantrone	Chlorambucil	
Lomustine (CCNU)	Hydroxyurea	
	5-Fluorouracil	

* However, the combination of vincristine and L-asparaginase can be highly myelosupportive.

Thrombocytopenia rarely causes clinical signs; however, at counts less than 50,000, the risk of bleeding increases and the veterinarian should be alert to petechiation, ecchymoses, or mucosal bleeding.

The gastrointestinal (GI) mucosa is another site of renewing tissue, and toxicity may occur anywhere in the GI system. Clinical signs include nausea, vomiting, inappetence, anorexia, or diarrhea. The management of this toxicity will depend on the severity of signs. Again, most GI toxicity is mild, self-limiting, and carries a good prognosis. For inappetence, tempting with palatable foods or using appetite stimulants such as cyproheptadine may be helpful. For occasional or mild vomiting, withholding food for 24 hours, then introducing multiple small feedings of a bland diet is usually sufficient. Metoclopramide may reduce the severity of vomiting; for diarrhea in dogs, subsalicylate may be therapeutic. For severe GI signs, intravenous fluid support and antiemetic treatment should be considered. Antiemetics include metoclopramide infused at a constant rate, chlorpromazine, or ondansetron (a serotonin antagonist that is an excellent antiemetic). Cisplatin is a powerful emetogen, and the prophylactic administration of butorphanol immediately after cisplatin administration reduces both the incidence and severity of vomiting. Ondansetron may also be used in the same setting. If vomiting occurs after cisplatin treatment (and particularly if it is prolonged or associated with anorexia), intravenous fluids should be administered, because dehydration may exacerbate the nephrotoxic effects of cisplatin. Severe hemorrhagic colitis after doxorubicin administration increases the risk of subsequent sepsis due to breakdown of the protective mucosal barrier to gram-negative intestinal bacteria at a time when the animal is myelosuppressed. Antibiotics should be administered to these animals in addition to supportive and symptomatic care.

In veterinary oncology, cardiotoxicity is only clinically a problem with doxorubicin chemotherapy. Although both cats and dogs show histologic cardiac changes, cats have not been reported to have clinical cardiotoxicity. Acute cardiotoxicity is related to peak plasma level and occurs during administration that is too rapid. Although the arrhythmias are self-limiting, they can cause collapse. The infusion should be stopped and then restarted at a slower rate. Chronic cardiotoxicity is related to the total cumulative dose of doxorubicin rather than the amount of each individual dose, and it carries a poor to grave prognosis. The end result resembles dilated cardiomyopathy and may progress to congestive heart failure (CHF). Although cardiotoxicity in dogs can occur at any cumulative dose, it is most frequent above 180 mg/m^2, and doxorubicin should not be given above this level without echocardiographic monitoring. Electrocardiographic changes are inconsistent and a poor indicator of early cardiac damage. Although echocardiographic changes usually occur before clinical signs, the damage will progress even after doxorubicin has been discontinued. Breeds susceptible to dilated cardiomyopathy, particularly Dobermans, appear to be more sensitive to this toxicity; pretreatment cardiac evaluation and close monitoring is mandatory in these dogs. The risk of cardiotoxicity is reduced by delivering the drug as a

continuous infusion over several hours, by using liposome-encapsulated doxorubicin, or by pretreatment with the cardioprotectant drug, dexrazoxane. The latter two options are yet to be fully evaluated in clinical veterinary practice.

Nephrotoxicity is the primary dose-limiting toxicity of cisplatin and depends on both the individual and cumulative dose. This toxicity also carries a poor prognosis. Cisplatin should not be administered to dogs with pre-existing renal disease and should be used with caution in dogs with urinary tract tumors. It is important to check the serum creatinine level before each cisplatin treatment. Cisplatin should not be administered if the serum creatinine is above normal range. In addition, cisplatin should always be delivered with appropriate saline diuresis. Doxorubicin has been anecdotally associated with nephrotoxicity in cats.

Urothelial toxicity (sterile hemorrhagic cystitis) is associated with cyclophosphamide and ifosfamide administration. Although this toxicity is uncommon after cyclophosphamide administration, it will occur after ifosfamide treatment unless the urothelial protectant, mesna, is given concurrently. When it occurs, it is usually self-limiting and carries a fair to good prognosis. Clinical signs of stranguria, dysuria, and hematuria can be severe and prolonged over many weeks. This toxicity should be distinguished from infectious cystitis by bacterial culture; however, even if bacteria are isolated and signs resolve with antibiotic administration, the drug should not be administered again because infectious cystitis could have been secondary to chemical cystitis. Chlorambucil is usually substituted for cyclophosphamide if urothelial toxicity occurs in lymphoma patients. If urothelial toxicity occurs, steroidal or nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the severity of signs. In persistent cases, intravesicular instillation of 25% dimethyl sulfoxide (DMSO) for 20 minutes may help reduce signs and may be repeated weekly.

Extravasation is rarely a problem if chemotherapy is administered carefully through a “first-stick” venous catheter. The catheter should be tested with a saline flush both before the drug is administered and after infusion is complete.

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Although a butterfly catheter is acceptable for volumes less than 1 mL, larger volumes should be administered through a secure over-the-needle catheter. If any drug is extravasated, the clinician should aspirate as much drug as possible before removing the catheter. If vincristine is extravasated, the area should be flooded with 10 mL of 0.9% NaCl and warm compresses applied. The resulting reaction is rarely severe and will be reduced further by preventing self-trauma. If doxorubicin is extravasated, ice compresses should be applied for 6 to 12 hours. Dilution of drug will only increase the area affected. Doxorubicin extravasation results in a slough that can be severe, and the full extent of the reaction may not be apparent for 3 to 4 weeks. Surgical resection or débridement may be necessary.

Hypersensitivity reactions may occur during doxorubicin administration due to histamine release from mast cells. This effect only occurs with rapid administration and is not a problem if the drug is given as a slow infusion or an intravenous injection at a rate of 1 mL per minute. A similar but more severe reaction occurs after intravenous administration of etoposide and paclitaxel due to “carrier” solutions in these formulations. Both carriers cause massive histamine release, the effects of which are only partly prevented by pretreatment with antihistamines and corticosteroids. True anaphylaxis may occur after L-asparaginase administration, particularly by the intravenous or the intraperitoneal route. This toxicity occurs very rarely if L-asparaginase is administered intramuscularly or subcutaneously. If anaphylaxis occurs, treatment with corticosteroids and antihistamines plus any necessary supportive measures should be instituted. The patient should not receive any further L-asparaginase. Attachment of polyethylene glycol conjugates to the L-asparaginase abrogates the immune response, and extends its half-life while preserving efficacy.

Hair loss is rarely a problem in pets that have fur. However, in dog breeds with hair (e.g., poodles, terriers, old English sheepdogs), alopecia can be significant although regrowth usually occurs in 4 to 8 weeks. In addition, dog breeds with “feathers” will lose these (e.g., golden retrievers). Cats will lose whiskers and sometimes body fur, and they may experience hair coat color changes. These problems are cosmetic and rarely of consequence to an adequately prepared owner.

Specific cat toxicities may occur with chemotherapy. Cisplatin causes a fatal, acute pulmonary edema in cats and should not be administered systemically. Intralesional administration of a colloidal suspension of cisplatin may be safe in cats, but care should be taken if this route is to be used. Topical and systemic administration of 5-fluorouracil causes acute fatal neurotoxicity in cats, and products containing this drug should not be used.

The major dose-limiting toxicity in veterinary cancer chemotherapy is myelosuppression. Recombinant hematopoietic growth factors and autologous bone marrow transplantation are widely available in human oncology practice and are in the initial stages of evaluation in veterinary oncology. Such techniques may allow the use of higher dose intensity without increasing the risk of myelosuppression. Similarly, advances that are being made in the treatment of pain and nausea and in the prevention of toxicities such as cystitis (mesna with ifosfamide or cyclophosphamide) will reduce the incidence of other toxicities. These will improve the ability of the veterinary oncologist to deliver adequate chemotherapy doses and result in better quality of life for pets with cancer.

178.3.10 Chemotherapy Drug Resistance

Resistance to chemotherapy may be either inherent or acquired. Drugs may be physically unable to reach tumors that are in sanctuary sites such as the central nervous system (CNS) or that are poorly perfused. Tumor cells may inherently lack receptors for a drug or not be susceptible to the mechanism in some other way (e.g., cells that have asparagine synthetase will be resistant to L-asparaginase).

Tumor cells may develop drug resistance spontaneously through mutation. The mutation rate is higher in tumors than in normal tissue because of the genetic instability characteristic of malignancy. With each cell division comes the risk of a resistance mutation; therefore the larger a tumor is (i.e., the more cell divisions it has undergone), the higher the likelihood that this has occurred. Tumor cells can also develop drug resistance specifically. Exposure to sublethal drug concentrations can result in gene amplification of detoxifying proteins.

Although combination chemotherapy may circumvent individual drug resistance, it does not avoid the problem of cross-resistance to multiple unrelated chemotherapy drugs. The transmembrane pump protein (P-glycoprotein) is present at increased levels in some tumor cells, and both the level and prevalence increases with exposure to chemotherapy. This phenomenon of multiple drug resistance (mdr) occurs between anthracyclines, mitotic inhibitors, and others. However, alkylating agents are not substrates for the mdr pump, and so they become the mainstay of treatment in patients that appear to have this type of drug resistance.

178.4 ADDITIONAL READING

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5. AE Frimberger, CA London: Principles of oncology. In RV Morgan (Ed.): *Handbook of small animal practice*. ed 4, 2003, WB Saunders Co, Philadelphia.

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179 CHAPTER • 179 Pratical Chemotherapy

Antony S. Moore

This chapter is best read in conjunction with Chapter 178, Principles of Chemotherapy. The two chapters include many of the same topics, but they are complementary in their treatment of those topics.

179.1 CLIENT PREPAREDNESS

The greatest challenge the veterinarian faces in using chemotherapy is addressing owners' preconceptions, biases, and negative experiences with chemotherapy. The side effects of treatment in human patients, which the owner may have experienced or may have heard about from television, the Internet, or family and friends, usually are inconsistent with the quality of life clients want for their pet. It is important for the veterinarian to acknowledge these feelings and to inform the owner that the goal of chemotherapy in cats and dogs is different; that is, that the pet should be given the maximum dose that improves quality of life without causing undue toxicity, as defined by the veterinarian and the owner. For some owners, this definition may mean preventing *any* loss of quality of life; for other clients, it may have a much different meaning. In any situation, the veterinarian should establish the goals of therapy before starting treatment. If owners understand that quality of life takes precedence in their pet's treatment they are more likely to trust the veterinarian and to treat their pet. The reality of supportive care for cancer chemotherapy patients in veterinary medicine is that component transfusions, sterile wards, and allogeneic transplant support are unavailable. For these reasons, lower drug dosages must be used, and dosages must be reduced even further if toxicity is observed. This should be emphasized to owners.

Provision of accurate information in understandable terms about the type of cancer, the prognosis, and the predictable side effects of treatment is an important responsibility of any veterinarian. Being honest while maintaining a feeling of hope and caring is one of the most important aspects of establishing trust with the owners of a pet with cancer. Encouraging owners to ask questions and to communicate their concerns is equally important.

Supplementation of verbal instructions with written information about the specific disease, the treatment protocol, and the drugs to be used greatly assists owners in making their decision. Many such information sheets can be obtained from veterinary oncologists and the Internet.

Furthermore, it is important to discuss with owners not only the potential toxicities of treatment, but also the owners' goals for chemotherapy, in particular what they would consider a successful outcome.

179.1.1 Palliative Intent Treatment

For many older veterinary patients, the diagnosis of cancer is made at a time when other diseases may limit survival to a greater extent than does the cancer. For these animals, palliative care may be most appropriate, and the choice of chemotherapy must be weighed against the risk of toxicity. An example would be a Doberman pinscher with cardiomyopathy and osteosarcoma. Such a dog may benefit from pain relief for the bone cancer. Cardiac disease makes doxorubicin a poor choice for chemotherapy, and the diuresis required for cisplatin administration may result in cardiac decompensation. An alternative, therefore, would be carboplatin. However, if a poor prognosis due to cardiac disease makes it unlikely that the benefits of extended survival through chemotherapy will be realized, chemotherapy may not be a good choice for this pet, and treatment should focus on pain relief.

179.1.2 Curative Intent Treatment

For younger dogs and cats that are in good health and have no concurrent illnesses and for which chemotherapy holds the possibility of prolonged control of the cancer with little risk of toxicity, chemotherapy with curative intent may be undertaken. An example would be an asymptomatic, middle-aged dog with stage 3, B-cell lymphoma, for which the prognosis is guardedly optimistic. The owners of such a dog may even elect to try more aggressive combination chemotherapy to improve the chance of long remission.

179.2 SUITABILITY OF THE PATIENT

When evaluating an animal for treatment of cancer, it is important not only to obtain a definitive diagnosis, but also to assess the pet's general health through clinical examination and ancillary diagnostics. Prognostic information gained by determining the extent of organ involvement by the tumor and by identifying unrelated or secondary conditions that must be treated or controlled before the appropriate therapy can be instituted is mandatory in order to make recommendations regarding the suitability of a patient for chemotherapy. This information is also vital for individualizing the type and intensity of a treatment regimen.

179.2.1 Staging and Health

Staging is a clinical process that enables the veterinarian to quantitate the extent of cancer involvement in the dog or cat. Staging is sometimes confused with *grading,* which characterizes the histopathologic features of a tumor. Staging often carries prognostic significance that may help both the veterinarian and the client make informed, rational decisions about the type of therapy best suited for a pet. Most staging systems are based an assessment of three major components of the malignant process: the size of the primary tumor (T), lymph node metastasis (N), and distant metastasis (M). Ancillary diagnostics, often incorporating sophisticated imaging techniques, are important for obtaining this information. The majority of pets for which chemotherapy may have therapeutic benefit have systemic or metastatic disease that either is physically evident or is presumed through historical knowledge of tumor behavior (e.g., osteosarcoma and hemangiosarcoma in dogs).

The likelihood of a successful outcome for a dog or cat treated with chemotherapy is as dependent on drug metabolism and elimination (and drug absorption for orally administered chemotherapy) as it is on the sensitivity of the tumor.

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Consequently, information gained during staging may identify problems that can affect the type and dosage of chemotherapy, in order to optimize efficacy while limiting toxicity. For example, hepatic dysfunction may lead to delayed elimination of some drugs (e.g., vinca alkaloids, doxorubicin) and therefore to greater toxicity, such as myelosuppression. In contrast, because cyclophosphamide is activated in the liver, hepatic dysfunction may result in poor efficacy.

Similarly, renal dysfunction may worsen toxicity for some drugs that are themselves nephrotoxic. For example, cisplatin and streptozocin should not be used in animals with renal azotemia. Reduced renal excretion of carboplatin exacerbates myelosuppression.

Particularly in breeds with a predisposition to the development of cardiomyopathy, treatment with doxorubicin should be accompanied by cardiac evaluation. Pretreatment echocardiography should be performed, and dogs with reduced contractility should not be given doxorubicin. Although valvular dysfunction should not be a reason to withhold doxorubicin, mild changes in cardiac muscle function may exacerbate the valvular disease.

In these dogs, echocardiography should be performed periodically, ideally prior to each doxorubicin treatment. Treatment with doxorubicin should be discontinued if contractility is below normal and while the dog is still asymptomatic. Cardiac dysfunction caused by doxorubicin is irreversible and usually progressive. For this reason, monitoring for signs of early cardiac failure before discontinuing doxorubicin is unacceptable practice.

179.3 SUITABILITY OF THE TUMOR

The most rapidly changing aspect of veterinary oncology involves published data on tumor sensitivity to chemotherapy. Although good published data are available on dogs with osteosarcoma and lymphoma, information on the most effective chemotherapy for adjunctive treatment of other, even common, malignancies often is unavailable or is based on small case series. As larger, multi-institutional and organizational studies are completed and the results published, this will change. For example, the recent finding that high-grade soft tissue sarcomas in dogs are more likely to metastasize implies that it may be possible to assess adjunctive chemotherapy for efficacy in this select group of dogs. In contrast, appendicular osteosarcoma in cats rarely metastasizes (approximately 25%), and it would be difficult to demonstrate adjuvant efficacy for any chemotherapeutic agent, given the rarity of the tumor.

179.4 CHOOSING A DRUG

Clinical veterinary chemotherapy research is advancing at a great rate. However, even when studies are completed, it may be a year or more until the results are published, and they often appear in less accessible journals. The best resources for veterinarians are veterinary oncologists, the Veterinary Cancer Society (www.vetcancersociety.org), other Internet-based resources and Internet literature data bases, such as Medline.

In addition to efficacy, and possibly more important, the final choice of a drug (or protocol) depends on toxicities, an owner's tolerance for side effects, the treatment goals, the cost, and the veterinarian's level of comfort in delivering chemotherapy and supportive care.

179.5 CHEMOTHERAPEUTIC DRUGS

No chemotherapeutic drugs are labeled for veterinary use only. All veterinary cancer chemotherapy is performed off label. However, most of the available drugs have an established track record, particularly those that have been used to treat lymphoma and osteosarcoma. The body of literature available means that veterinarians should feel secure in using dosages and schedules provided in published protocols. Treatment using most veterinary drugs is expected to result in less than 5% risk of life-threatening toxicity (hospitalization, severe neutropenia) when established dosages are used. The risk of death from chemotherapy should be considerably lower than that.

179.5.1 Drug Cost

The cost of many of these drugs may be high. However, generic versions of several chemotherapeutic agents (e.g., vincristine, doxorubicin, cisplatin) are available, making them more affordable. Some pharmacies supply small amounts of injectable drugs to veterinarians, and compounding pharmacies will reformulate smaller dosages of oral medications (e.g., lomustine [CCNU] or procarbazine for cats and small dogs). The cost of therapy often is not as much a deterrent to owners interested in chemotherapy for their pet as is quality of life. Veterinarians should inform owners of the best available options and allow them to make the decision on cost.

179.6 WHEN TO GIVE CHEMOTHERAPY

Veterinary chemotherapy protocols are often simple, consisting of one or two chemotherapy agents given at an interval that minimizes the risk of toxicity but maintains the highest possible dose intensity (e.g., cisplatin as an adjuvant to surgery for dogs with osteosarcoma). In contrast, lymphoma protocols are often complex, with many agents scheduled in combination (see Tufts VELCAP-SC, Figure 179-1). Descriptions of different "phases" of a protocol apply best in these lymphoma treatment schedules.

179.6.1 Timing

179.6.1.1 Primary Treatment

In veterinary oncology, primary chemotherapy usually is reserved for hematopoietic tumors (lymphoma, leukemias, multiple myeloma). The phases of a primary treatment protocol for lymphoma are presented in Box 179-1. Chemotherapy for dogs with metastatic solid tumors (carcinomas and sarcomas) is rarely successful and is better considered to be palliative.

179.6.1.2 Adjuvant Treatment

After surgery, adjuvant chemotherapy may be given to slow the progress of metastatic disease or possibly to provide a cure. The optimum time to administer primary chemotherapy is when the dog or cat has microscopic disease, rather than when gross metastases have developed. An example of successful adjuvant veterinary chemotherapy is the use of platinum compounds and doxorubicin after surgery for canine osteosarcoma.

179.7 ADMINISTRATION OF CHEMOTHERAPY

The proper administration of chemotherapy has been covered in great detail by many authors. In brief, the regulations set by the U.S. Occupational Safety and Health Administration (OSHA) should be followed, and owners, as well as all personnel coming in contact with chemotherapeutic agents, should be protected to the best of the veterinarian's abilities. A chemotherapy logbook, which includes identification of animals treated and the personnel involved in the treatments, should be maintained to track exposures.

179.7.1 Box • 179-1 Phases of a primary treatment protocol for lymphoma

179.7.1.1 Induction

The induction phase encompasses the often intensely scheduled initial treatments. During this phase, a dog or cat has a relatively higher risk of toxicity but usually also the greatest chance of response (e.g., during the first 12 weeks of VELCAP; see Figure 179-1).

179.7.1.2 Consolidation

Consolidation is sometimes used at the end of induction; unrelated, effective drugs are administered to further reduce the proportion of surviving cancer cells (e.g., the combination of mechlorethamine, vincristine (Oncovin), procarbazine, and prednisone [MOPP] and CCNU in VELCAP; see Figure 179-1).

179.7.1.3 Maintenance

Maintenance is a less intense phase (usually involving decreased frequency of administration) during which the drugs previously used for induction are administered. Maintenance therapy probably has little influence on whether an animal is cured, but it may prolong survival by increasing the time to relapse.

179.7.1.4 Rescue

Rescue is therapy given when the drugs used during the other three phases no longer result in remission. Unrelated drugs (often alkylating agents because they are less likely to show cross-resistance) are used for rescue therapy.

179.7.2 Handling

Veterinarians can greatly reduce the risk of exposure by familiarizing themselves with the hazardous properties included in the Material Data Safety Sheet (MSDS) for each drug and by using appropriate protective equipment. The information contained in each MSDS covers specific health hazards, including carcinogenicity; primary routes of exposure; protective equipment; treatment of personnel acutely exposed; chemical activators; solubility; stability; volatility; and specific procedures to be undertaken in case of a spill. The MSDS should be requested with the initial shipment of any chemotherapeutic agent and should be kept on file in an easily accessible location.

Most chemotherapeutic agents are both toxic and mutagenic. Alkylating agents have been associated with the highest risks to handlers. Organ damage and increased risk of fetal loss have been reported in individuals handling and administering chemotherapy with inadequate attention to personal safety. Precautions should be taken in handling chemotherapeutic drugs during any phase of preparation, administration, and disposal of drugs or waste. Ideally, a vertical laminar flow biologic safety cabinet would be used to prepare all chemotherapeutic drugs. If this is not available, protective eyewear, a respirator mask, and a disposable gown with closed-cuff sleeves and latex (not vinyl) gloves should be worn. All these items usually are available through distributors of chemotherapeutic agents. Hydrophobic filters that insert into chemotherapeutic drug vials can prevent aerosolization of drugs during preparation for dosing. If a filter is not used, gauze moistened with alcohol should be wrapped around the vial top and needle to protect personnel from aerosolized drug. Latex gloves should be worn when the drugs are administered, whether parenterally or orally. With parenteral administration, Luer-Lok syringes reduce the risk of drug leakage or spills. Pills should not be broken.

If owners are administering drugs orally at home, gloves and a waste bag should be provided. For drugs excreted in the urine (particularly cisplatin), the pet should be encouraged to urinate on soil where urine drains quickly, and any urine in other areas should be handled and disposed of as chemotherapy. These precautions should be followed for approximately 48 hours after administration.

179.7.3 Route of Administration

For most intravenous chemotherapy administrations, injection through a peripherally located over-the-needle catheter is safest, reducing the risk of extravasation even when a small volume is to be administered. For longer infusions (more than 30 minutes), a through-the-needle catheter is less likely to become dislodged.

When long infusions are required, either for prolonged drug delivery or for the saline diuresis that accompanies nephrotoxic drugs such as cisplatin or streptozocin, an infusion pump is recommended. Free-flowing fluid administration, even when monitored continuously, may not ensure continued diuresis or could result in uneven delivery of the drug dose. Both of these factors could affect the risk of toxicity. A calibrated infusion pump allows predictable administration of the chemotherapeutic dose.

Some cats and many dogs are small, and their vascular integrity may be compromised by multiple administrations of anesthesia (e.g., surgery, radiation therapy) prior to receiving chemotherapy. Because the risk of extravasation reactions is greater in these animals, an indwelling, subcutaneously located, implantable vascular access port may ensure timely drug delivery and reduce stress during restraint for catheter placement and administration of chemotherapy. Such a port may be maintained for the duration of therapy and then removed. The implantable vascular access port must be placed surgically, in a similar manner to a tunneled catheter, with a subcutaneous pocket for positioning of the port. Ports for veterinary use are available from Norfolk Vet Products, Skokie, Illinois.

Most oral medications are administered as tablets or capsules, although a cyclophosphamide elixir can be compounded using the injectable form of the drug. Tablet formulations should not be split, because distribution of the drug may not be uniform throughout the tablet; this is particularly true of cyclophosphamide. For small animals, reformulation of oral medications by a compounding pharmacy is more accurate and safer (e.g., CCNU or procarbazine for cats).

Intracavitary chemotherapy (intrathoracic, intra-abdominal, intrapericardial, or intravesicular [urinary bladder]) has been reported. The drugs used for this purpose logically should have little vesicant activity. The drugs most commonly used are the platinums (cisplatin may have greater tissue penetration than carboplatin) and mitoxantrone.

Intralesional chemotherapy usually involves a suspension of a chemotherapeutic agent in a vehicle (the use of cisplatin or 5-fluorouracil in sterile sesame oil or bovine collagen matrix has been reported). The mixture should be injected into a tumor, creating high drug exposure to tumor cells. This involves minimal systemic drug levels, avoiding the risk of systemic toxicity. Intralesional chemotherapy is used to treat only small, easily accessible tumors.

179.7.4 Dosing

The initial treatment with an individual drug should be given at a dosage known to result in minimal toxicity in the majority of animals. Because the risk of toxicity is highest when an animal receives a drug for the first time, the temptation may exist to begin with a low dose and increase the dosage incrementally after each administration that is toxicosis free. The logic of that approach is flawed, however, because the reduction in dose intensity can only reduce the chance for successful remission and accelerate the development of drug resistance. Effective treatment is more likely to result from the highest tolerated dosage, and prophylactic supportive strategies (see below) are preferable to an arbitrary reduction in the initial dosage.

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The selection of drug dosage can also be influenced by organ function. Although no guidelines have been established, it may be safest to reduce the dosage of hepatically metabolized drugs by 50% if the serum bilirubin is greater than 1.5 mg/dL and by 75% if the serum bilirubin is greater than 3 mg/dL. Dosages can then be slowly increased after each cycle that occurs without toxicity.

Because carboplatin is renally excreted, carboplatin dosage ideally is based on the glomerular filtration rate (GFR). If the GFR cannot be estimated, an arbitrary dose reduction of 50% to 75% should be made for animals with renal azotemia; dosages then can be increased after each cycle that occurs without toxicity.

The frequency of drug administration is determined by the length of time required from administration of the drug to the recovery of normal tissues (bone marrow, gastrointestinal tract). For example, doxorubicin can be given every 2 weeks to most animals because neutropenia has usually completely resolved by this time. However, some individual patients may not be able to receive the drug any more often than every 3 weeks because of a neutrophil count that is still too low (see the section on monitoring, below). The drug that is the most common example of individual variability for dosing interval in veterinary medicine is carboplatin. In some animals (particularly cats), it may take 5 weeks or longer for hematologic parameters to recover to a level at which a subsequent dose can be delivered safely.

179.7.5 Drug Resistance

Chemotherapeutic drugs act through a multitude of mechanisms. Resistance to individual drugs may occur at the cellular level (e.g., altered target) or as a result of host factors (e.g., antibody formation to L-asparaginase). When combination chemotherapy is used, cross-resistance between different classes of agents is a serious threat to successful treatment. In particular, multiple drug resistance (MDR) due to a transmembrane efflux pump protein (gp170) can reduce intracellular levels of vinca alkaloids, anthracyclines, and other “naturally” derived chemotherapeutics to nontoxic levels. Because these drugs are often used in the treatment of lymphoma, it is wise *not* to overly rely on them in the rescue stage, but rather to use them in combination for first-line therapy. Interestingly, drugs classified as alkylating agents are not susceptible to the MDR mechanisms. There is very little cross-resistance, even between different alkylating agents. This may explain the successful strategy of using alkylating agents as rescue therapy for animals with lymphoma. It is also possible that the use of alkylating agents in combination with MDR-type drugs during the early phases of treatment (induction) may slow the onset of resistance. Trials of agents that competitively block MDR have not yet led to practical veterinary treatment strategies.

179.7.6 Drug Combinations

Combination chemotherapy has two major aims. The first is to slow the onset of drug resistance in tumor cells. As mentioned above, the use of agents with differing targets and mechanisms of action is most likely to provide long-term tumor control. In particular, the use of alkylating agents may slow the development of MDR (e.g., adding cyclophosphamide or the combination of mechlorethamine, vincristine (Oncovin), procarbazine, and prednisone [MOPP] to a chemotherapy protocol for lymphoma rather than using doxorubicin alone). The second aim of combination chemotherapy is to maximize tumor cell kill while minimizing toxicity. The combination of drugs that are myelosuppressive with drugs that are minimally myelosuppressive may fulfill this aim (e.g., cyclophosphamide and vincristine; doxorubicin and cisplatin). It is important that combinations comprise *effective* drugs; there is little use to using a nontoxic combination if one of the drugs has not been shown to be efficacious against the particular tumor type. Combinations, therefore, use drugs that have shown activity as single agents.

Some combinations may result in altered toxicity due to changes in the way a drug is metabolized or excreted. For example, L-asparaginase is thought to slow hepatic metabolism of drugs such as vincristine and doxorubicin, thereby increasing the risk of myelosuppression.

It is recommended that practitioners use only combinations for which published efficacy and toxicity data are available.

179.8 MONITORING OF ANIMALS WITH CANCER

179.8.1 History

Before chemotherapy is administered, drug dosages and toxicities, as well as the administration schedule, must be reviewed with the owner. After the chemotherapeutic treatment, the pet should be monitored at home for gastrointestinal or other toxicoses. In general, the use of antiemetics and appetite stimulants can prevent mild toxicities; diarrhea may be treated with dietary management or with sulfasalazine or metronidazole, as long as specific causes have been eliminated. Gastrointestinal toxicity usually occurs in the 4 to 5 days after treatment.

Chemotherapeutic doses should be reduced if the pet requires hospitalization for gastrointestinal signs or if such signs are unacceptable to the owner. A dose reduction of 25% for all subsequent administrations of that drug is a good rule of thumb, because with this reduction, it is unlikely that subsequent chemotherapy administration will be associated with toxicity. Supportive care, as both treatment and further prophylaxis, is mandatory.

179.8.2 Complete Blood Count

Neutropenia is a toxicity of many chemotherapy agents, and the nadir (lowest point) generally occurs 5 to 10 days after administration. A complete blood count (CBC) should be obtained 7 days after most treatments. Monocytosis on a CBC often predicts imminent neutrophil recovery, because monocytes have one fewer maturation step than granulocytes and therefore are released from the bone marrow earlier.

Neutrophil recovery is usually rapid; however, a nadir of less than 1000/μL should prompt a 25% dosage reduction for all subsequent administrations of that drug. It is not necessary to reduce the dosage of other myelosuppressive drugs, because they may not cause the same degree of suppression. Each drug should be assessed individually. If a dosage reduction is made, the nadir should again be assessed.

Neutropenia at the time of the next chemotherapy treatment is a reason to delay administration of a myelosuppressive drug (but not of a nonmyelosuppressive drug, such as L-asparaginase or prednisone). In general, a neutrophil count of less than 3000/μL requires a delay in chemotherapy, usually of 1 week, before the CBC is rechecked. If the pet takes a long time to recover (as occurs for many cats and some dogs after receiving carboplatin), it may be necessary to reduce the dosage so that the optimal intertreatment interval and dose intensity can be maintained.

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Thrombocytopenia may be dose limiting for select chemotherapy agents (carboplatin, cumulative for CCNU), but is rarely clinically significant for other drugs. Platelet nadirs occur later than neutrophil nadirs, but are rarely as severe and recovery is slower but complete. Thrombocytopenia in a pet due to receive CCNU should prompt a dose reduction or discontinuation.

179.8.3 Serum Chemistry Profile

Renal function should be assessed by serum creatinine and urine specific gravity determinations prior to administration of nephrotoxic drugs (cisplatin in dogs; doxorubicin in cats) or renally excreted drugs (carboplatin). The dosages of these drugs should be adjusted as described above under Dosing.

Liver enzyme serum activity (alanine aminotransferase [ALT]) should be assessed prior to administration of lomustine. Irreversible hepatic toxicity can result if lomustine therapy is continued despite increases in serum ALT activity.

Increases in serum bilirubin should prompt dose reductions in hepatically metabolized drugs. Guidelines are provided under Dosing, above.

179.9 THERAPEUTIC SUPPORT OF ANIMALS WITH CANCER

In order that pets maintain the highest quality of life, and that chemotherapy dosages be maintained at the highest level, the veterinarian should, whenever possible, use prophylactic strategies to circumvent common toxicities.

179.9.1 Antiemetics

The recent introduction of serotonin antagonists such as ondansetron (Zofran) and dolasetron (Anzemet) has markedly altered toxicity patterns for animals treated with many drugs. Vomiting and nausea, leading to inappetence and weight loss, are common after treatment with drugs such as cisplatin (in dogs) and doxorubicin (in cats and dogs). Anzemet, given intravenously once at a dosage of 0.5 to 1 mg/kg or given orally once 20 to 30 minutes prior to treatment may markedly reduce the risk of this toxicity.

179.9.2 Appetite Stimulants

Anorexia is a common side effect of chemotherapy in cats (particularly doxorubicin or vincristine). Cyproheptadine (Periactin; 0.35 to 1 mg/kg given orally in cats and 0.1 to 0.2 mg/kg given orally in dogs) may stimulate appetite. The drug may be dosed every 12 hours, or less frequently if inappetence is mild. Megestrol acetate is an effective appetite stimulant in cats at a dosage of 0.25 to 0.5 mg/kg per day given orally for 3 to 5 days, then every 2 to 3 days. In humans, megestrol acetate not only improves appetite but also enhances the enjoyment of food.

Vincristine may result in intestinal ileus in cats and less commonly in dogs. Prokinetic drugs such as metoclopramide may act to reverse this toxicity. Some practitioners recommend prophylactic use of metoclopramide to reduce the risk of inappetence caused by vincristine or doxorubicin (perhaps by central action to reduce nausea). For prophylactic purposes, treatment is started at the time of chemotherapy and continued for 4 to 5 days. Prior to administering strong emetogens (e.g., cisplatin), owners should withhold food, because this reduces the risk of vomiting and may prevent future “aversion” to that food.

179.9.3 Antidiarrheal Drugs

The pet's diet should remain as stable as possible during chemotherapy to avoid exacerbation of gastrointestinal damage. Prophylactic absorbents (e.g., Kaopectate) may reduce the risk of diarrhea. If diarrhea occurs, a bland diet should be offered; if the diarrhea persists, and causes such as parasitism in these often immunosuppressed patients have been eliminated, sulfasalazine or metronidazole may reduce the severity. Prophylactic trimethoprim-sulpha (TMPS) antibiotics should be considered (see below).

179.9.4 Urothelial Bladder Wall Protection

Cyclophosphamide and ifosfamide are hepatically metabolized to their active forms and also to compounds that can cause bladder wall damage (acrolein). Prolonged contact time between the bladder wall and acrolein results in hemorrhagic cystitis. Furosemide, given as a single dosage (2 mg/kg either IV or PO) at the time of cyclophosphamide administration, almost completely abrogates this toxicity and is recommended even in dogs receiving prednisone concurrently. Allowing ample opportunity for the dog to void urine is equally important, and cyclophosphamide is preferably administered in the morning rather than late in the day. Mesna is a thiol drug that is active only in urine; it binds to acrolein, preventing the toxicity of urothelial damage. Because mesna is expensive, its use usually is limited to dogs receiving ifosfamide that have a high risk of urothelial damage.

Treatment of hemorrhagic cystitis includes the use of anti-inflammatory drugs (e.g., piroxicam, 0.3 mg/kg given orally once a day); with prolonged cases, intravesicular dimethyl sulfoxide (DMSO) may accelerate recovery. Most cases resolve with time, but because the condition may require several weeks to subside, it is a toxicity best prevented. Sterile hemorrhagic cystitis is extremely rare in cats.

179.9.5 Prevention of Neutropenic Sepsis

Neutropenia is a common side effect of many chemotherapeutics and may occasionally be severe (e.g., neutrophil count less than 500/μL at the nadir). The risk of sepsis is low in animals receiving antibiotics concurrently, because the nadir rarely persists longer than a couple of days. Many oncologists recommend prophylactic use of a broad-spectrum, oral antibiotic (e.g., TMPS) in animals receiving a myelosuppressive agent for the first time. If the nadir is greater than 1000/μL, subsequent administrations may be given without prophylactic antibiotics.

Administration of TMPS to dogs for 14 days from the day of treatment with doxorubicin markedly reduced the likelihood of gastrointestinal toxicity (vomiting or diarrhea), hospitalization, and reduced quality of life (Karnovsky score). These effects, most marked in dogs with lymphoma, may be due to reduced bacterial translocation in damaged intestinal epithelial layers.

When a pet is severely neutropenic, it is tempting to use recombinant granulocyte-colony stimulating factor (G-CSF). Neutropenic dogs should have high endogenous G-CSF and are unlikely to benefit from exogenous administration. Also, the available human recombinant product (hr-G-CSF [Neupogen, Amgen]) carries a risk of induction of neutralizing and cross-reacting antibodies. Appropriate use of hr-G-CSF would be in cases in which an inadvertent and potentially lethal chemotherapy overdose has been delivered. For such a patient, hr-G-CSF therapy from the time of chemotherapy administration to beyond the neutrophil nadir has the best chance of preventing sepsis and death.

179.10 SPECIFIC CHEMOTHERAPEUTIC AGENTS

179.10.1 Commonly Used Alkylating Agents

Commonly used alkylating agents are listed in Table 179-1. Cyclophosphamide (Cytoxan) is used primarily for the treatment of lymphoma in dogs and cats. Chlorambucil (Leukeran) is used primarily for the treatment of chronic lymphocytic leukemia or low-grade lymphoma in dogs and cats and as a substitute for

cyclophosphamide if hemorrhagic cystitis occurs. Melphalan (Alkeran) is used primarily in combination with prednisone for the treatment of multiple myeloma in dogs and cats.

179.10.2 Less Commonly Used Alkylating Agents

Less commonly used alkylating agents are listed in Table 179-1. Mechlorethamine (Mustargen) is used in the MOPP protocol for lymphoma in dogs and cats. Procarbazine (Matulane) is used in the MOPP protocol for lymphoma in dogs and cats. Dacarbazine (DTIC) is used in combination with doxorubicin for the treatment of lymphoma, and some anecdotal activity has been indicated for melanoma. Lomustine (CCNU, Ceenu) is used for the treatment of lymphoma, mast cell tumors, brain tumors (response in gliomas and meningiomas) and possibly histiocytosis. Ifosfamide (Ifex) is active against lymphoma and soft tissue sarcomas, particularly in cats.

179.11 ANTITUMOR ANTIBIOTICS

Antitumor drugs act by interfering with topoisomerases, deoxy-ribonucleic acid (DNA) intercalation, and other mechanisms. These drugs usually exhibit cross-resistance with others in their class and with drugs in other classes, such as vincristine, paclitaxel, and etoposide. This resistance is mediated by the MDR glycoprotein.

179.11.1 Commonly Used Antibiotics

Commonly used antibiotics are listed in Table 179-2. Doxorubicin (Adriamycin; generic form) is the most active single agent in the treatment of lymphoma in dogs and is highly effective in combinations for lymphoma treatment in dogs and cats. It has broad-spectrum efficacy in the treatment of solid tumors, particularly osteosarcoma, and in combination with cyclophosphamide. Low-dose doxorubicin may be used for "sensitization" of tumor cells to radiation therapy. Mitoxantrone (Novantrone) shows moderate efficacy against lymphoma in dogs but low efficacy in cats. It also has low efficacy in the treatment of carcinomas and sarcomas. However, in combination with radiation therapy it may be efficacious for oral squamous cell carcinoma (SCC) in cats and in combination with piroxicam for transitional cell carcinoma in dogs. Dactinomycin (Actinomycin-D, Cosmegen) is a low-cost alternative to doxorubicin for canine lymphoma. However, it has low efficacy in the treatment of carcinomas and sarcomas.

Table • 179-1 Commonly Used Alkylating Agents

DRUG	FORM	POTENTIAL SIDE EFFECTS	REGIMEN
Cyclophosphamide (Cytoxan)	25, 50 mg tablets; 500 mg vials	Myelosuppression	250 mg/m^2 PO
		Hemorrhagic cystitis	200 mg/m^2 IV q3wk
			50 mg/m^2 PO every other day
Chlorambucil (Leukeran)	2 mg tablets (refrigerate)	Mild myelosuppression	2–8 mg/m^2 PO every other day
			14 mg/m^{2}PO daily for 4 days q3wk
Melphalan (Alkeran)	2 mg tablets (refrigerate)	Myelosuppression	1.5 mg/m^2 PO daily for 10 days, then a 10-day "rest"
Less Commonly Used Alkylating Agents			
Mechlorethamine (Mustargen)	10 mg vials	Myelosuppression	In MOPP: 3 mg/m^2 IV weekly
		Extravasation reaction	
Procarbazine (Matulane)	50 mg capsules	Nausea, anorexia, diarrhea	In MOPP: 50 mg/m^2 PO daily (dogs); 10 mg/cat PO daily
		Myelosuppression	
Dacarbazine (DTIC)	200 mg vials	Myelosuppression	800 mg/m^2 q3-4wk
		Anorexia, vomiting, diarrhea (Anzemet is used prior to treatment.)	
Lomustine (CCNU; Ceenu)	10, 40, and 100 mg capsules	Myelosuppression, neutropenia, and delayed thrombocytopenia in dogs; delayed neutropenia in cats	70–90 mg/m^{2}PO q4-6wk (dogs)
		Irreversible renal and liver toxicity (uncommon)	50 mg/m^2 PO q6wk (cats)
Ifosfamide (Ifex)	1 g with mesna (1 g) vials	Myelosuppression	375 mg/m^2 IV (dogs)
		Hemorrhagic cystitis (must be given with mesna and diuresis protocol)	900 mg/m^2 IV (cats)
			Given q3wk in 0.9%
		Renal toxicity in cats	NaCl with mesna

179.11.2 Less Commonly Used Antibiotic

Bleomycin (Blenoxane) is a less commonly used antitumor antibiotic (Table 179-2). Its possible efficacy in the treatment of squamous cell carcinoma and lymphoma is unproven.

179.12 PLATINUMS

Cisplatin (Platinol) has efficacy in the treatment of canine osteosarcoma and many carcinomas. It is not for use in cats. Carboplatin (Paraplatin) has efficacy similar to cisplatin with no apparent renal toxicity (Table 179-3).

179.12 ENZYME

The enzyme L-asparaginase is used primarily for lymphoma in dogs (Table 179-4).

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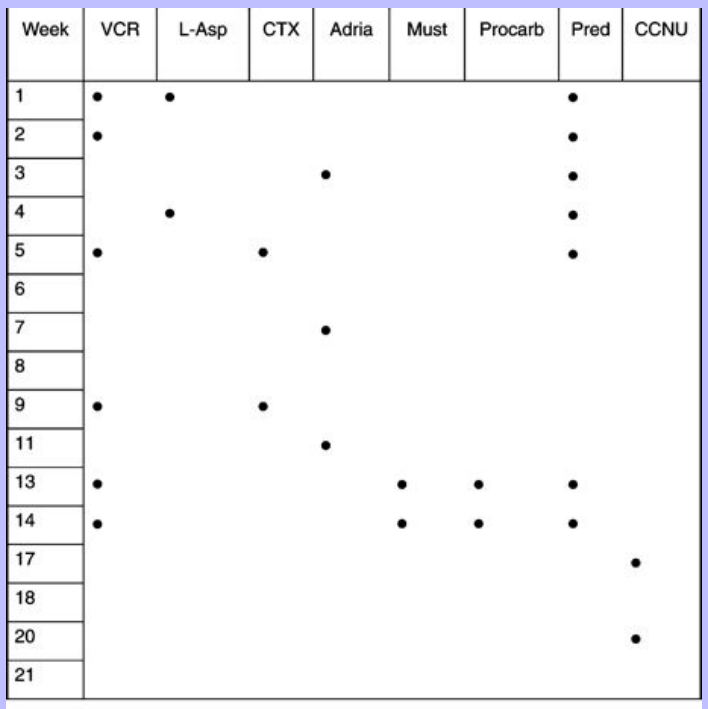
Table • 179-2 Commonly Used Antibiotics

DRUG	FORM	POTENTIAL SIDE EFFECTS	REGIMEN
Doxorubicin, (Adriamycin; generic)	200 mg	Myelosuppression	30 mg/m^2 IV (large dogs)
		Cumulative cardiotoxicity	25 mg/m^2 or 1 mg/kg IV (cats and small dogs)
		Anorexia, vomiting, diarrhea	
		Allergic reaction (infusion rate should not exceed 2 mg/min)	Given q2-3wk
		Possible renal toxicity in cats	
		Extravasation reaction	
Mitoxantrone (Novantrone)	20 mg	Myelosuppression	6 mg/m^2 IV (dogs)
		GI effects (uncommon)	6.5 mg/m^2 IV (cats)
			Given q3wk
Dactinomycin (Actinomycin-D, Cosmegen)	0.5 mg (extravascular) vials	Myelosuppression	0.7–1 mg/m^2 IV (not used in cats to date)
		Diarrhea, vomiting	
		Requires slow infusion rate	Given q3wk
		Extravasation reaction	
Less Commonly Used Antibiotic			
Bleomycin (Blenoxane)	15 IU (15 mg) vials	In humans: allergic reaction, pulmonary fibrosis	0.3–0.5 IU/kg IV or SQ weekly

Figure 179-1 Tufts VELCAP-SC protocol for treatment of lymphoma in dogs. Patients are induced over 11 weeks with a combination of vincristine (0.75 mg/m^2 IV), L-asparaginase (10,000 IU/m^2 SQ, maximum dose 10,000 IU), doxorubicin (<1 m^2 = 1 mg/kg IV, >1 m^2 = 30 mg/m^2 IV), cyclophosphamide (250 mg/m^2 PO), and a tapering dose of prednisone starting at 40 mg/m^2 PO daily. All dogs in complete remission (CR) at week 13 receive consolidation treatments of MOPP (mechlorethamine [3 mg/m^2 IV], vincristine [0.75 mg/m^2 IV], procarbazine [50 mg/m^2 PO once a day for 14 days], and prednisone [40 mg/m^2 PO once a day for 14 days]) at weeks 13 and 14, followed by CCNU (90 mg/m^2 PO) at weeks 17 and 20. The protocol is reinstituted if clinical relapse is noted. The total cumulative dosage of doxorubicin should not exceed 180 mg/m^2. Dogs that are in CR by week 21 discontinue chemotherapy. Dogs receiving cyclophosphamide are treated concurrently with furosemide, 2 mg/kg PO once.



VCR = vincristine, L-Asp = L-asparaginase, CTX = cyclophosphamide, Adria = doxorubicin, Must = mechlorethamine, Procarb = procarbazine, Pred = prednisone.

Table • 179-3 Platinums Used as Chemotherapeutic Agents

DRUG	FORM	POTENTIAL SIDE EFFECTS	REGIMEN
Cisplatin (Platinol)	50 mg (aqueous) vials	Renal toxicity Vomiting and (less commonly) diarrhea Myelosuppression Fatal pulmonary edema in cats	50–70 mg/m^2 IV with 0.9% saline diuresis q3-4wk
Carboplatin (Paraplatin)	50 mg, 150 mg vials	Myelosuppression	250–300 mg/m^2 IV q3-4wk

Table • 179-4 Enzyme Used as a Chemotherapeutic Agent

DRUG	FORM		REGIMEN
L-asparaginase (Elspar)	10,000 IU vials	Anaphylaxis	10,000 IU/m^2 SQ or IM weekly

Table • 179-5 Commonly Used Mitotic Inhibitors

DRUG	FORM	POTENTIAL SIDE EFFECTS	REGIMEN
Vincristine (Oncovin; generic)	1 mg vials	Mild myelosuppression (dose related) Anorexia in cats, rarely dogs (dose related) Peripheral neuropathy (rare) Extravasation reaction	0.5–0.75 mg/m^2 IV weekly
Vinblastine (Velban)	10 mg vials	Myelosuppression Peripheral neuropathy (very rare) Extravasation reaction	2–2.5 mg/m^2 IV weekly

179.14 MITOTIC INHIBITORS

Mitotic inhibitors act to inhibit assembly (vinca alkaloids) or disassembly (paclitaxel) of the mitotic spindle. Paclitaxel is rarely used in veterinary medicine, and dosages have not been published.

The commonly used mitotic inhibitor vincristine (Oncovin; generic form) is curative for canine transmissible venereal tumor. It also is very effective in combination chemotherapy for lymphoma in dogs and cats. It is included in some combinations for the treatment of sarcomas. Vinblastine (Velban) is effective in combination chemotherapy against lymphoma in dogs and cats; however, it is seldom used because of its myelosuppressive effect, which makes it more problematic than vincristine to include with other drugs. Vinblastine also appears to have efficacy for mast cell tumors in dogs (Table 179-5).

179.15 SUGGESTED READINGS

1. AS Moore, et al.: lomustine (CCNU) for the treatment of relapsed lymphoma in dogs. *J Vet Intern Med.* **13**, 1999, 395–398.

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5. KM Rassnick, et al.: Evaluation of ifosfamide for treatment of various canine neoplasms. *J Vet Intern Med.* **14**, 2000, 271–276.

6. KM Rassnick, et al.: Phase I evaluation of CCNU (lomustine) in tumor-bearing cats. *J Vet Intern Med.* **15**, 2001, 196–199.

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180 CHAPTER • 180 Practical Radiation Therapy

Alain P. Théon

Radiation therapy is the use of ionizing radiation for local and regional treatment of patients with malignant tumors and, occasionally, selected benign diseases. In veterinary medicine, it is a consultative discipline in which veterinary radiation oncologists see animals referred by other veterinarians. The objective of radiation therapy is eradication of a tumor with preservation of normal tissue structure and function.

The availability of appropriate equipment and the evolution of veterinary oncology into a multidisciplinary specialty have led to an increasingly important role for radiation therapy in the management of cancer in small animals. New developments in radiation therapy technology permit treatment of arbitrary tumor volumes anywhere in the body. Radiation therapy can be used alone or in combination with surgery or chemotherapy. The increase in the use of radiation therapy has led to a progressive decrease in the need for radical surgery as the sole treatment for many common cancers.

180.1 BIOLOGIC PRINCIPLES OF RADIATION THERAPY

180.1.1 Biological Effect of Radiation

The radiation used in radiation therapy is called *ionizing radiation* because it is sufficiently energetic to cause ionization and excitation of atoms and molecules in cells, resulting in a variety of short-lived ions and chemically unstable free radicals that cause molecular damage. With therapeutic radiation doses, the molecular damage most detrimental to cell survival is that involving the structure and function of genomic deoxyribonucleic acid (DNA).[1] Most of the damage to DNA results indirectly from interaction of DNA with free radicals derived from the ionization of cellular water molecules, the most common molecule in cells. Ionizing radiation produces many types of DNA damage, including single-strand breaks (SSB), double-strand breaks (DSB), base damage, and DNA-DNA or DNA-protein crosslinks. During the processing and enzymatic repair of the damage or during DNA replication, DNA damage may be completely repaired or may become irreversible. Radiation repair is usually more efficient in normal cells than in tumor cells. Although the majority of DNA damage can be repaired, heterologous DNA double-strand breaks are most often irreparable. Irreversible damage to the DNA results in chromosomal aberrations, gene mutations, cell degeneration, and cell death.

At clinically achievable doses, the damage induced by radiation results in cell death or terminal growth arrest.[2] Depending on the cell type and numbers and the kind of DNA damage, cell death occurs through two distinct pathways, proliferative cell death (mitotic cell death) and programmed cell death (apoptosis).[3] Mitotic cell death is the main form of cell death induced by ionizing radiation. It occurs during postirradiation mitosis in proliferating cells entering mitosis with unrepaired DNA damage. Mitotic cell death is selective for cells engaged in the mitotic cycle. This form of cell death is particularly relevant to radiotherapy of tumors, because one of the most important characteristics of a tumor is its ability to divide indefinitely. The difference in proliferative activity in normal cells and tumor cells accounts in part for the selective cytotoxic effects of radiation against tumors. Mitotic cell death is not immediate, but rather occurs after the cell passes through one or more consecutive aberrant mitoses, during which the number of chromosomal aberrations and genomic dysfunctions increases, leading to metabolic failure and cell death.[1] This mechanism of cell death leads to cell necrosis and results in local inflammation.

Cell death through apoptosis is a normal, noninflammatory physiologic process that occurs spontaneously or in response to cellular stress, including ionizing radiation. Apoptosis occurs regardless of the cell cycle and does not require cell division. Susceptibility to radiation-induced apoptosis is cell type specific and is most prominent in hematopoietic or lymphoid cells, but not in stromal-or epithelial-derived tissues. Apoptosis requires intact cellular mechanisms that are often compromised in tumor cells. The tumor suppressor gene protein p53 plays a pivotal role in radiation-induced apoptosis. Its mutation, which is common in some cancers, results in a decreased contribution from apoptosis to the overall cell death in different cell types.

While mitotic cell death and apoptosis kill and eliminate cancer cells, radiation-induced terminal growth arrest irreversibly prevents further tumor evolution. Terminal growth arrest is a process similar to senescence in which the cells remain physiologically active but have lost their ability to proliferate. This cytostatic effect on tumor cells results in a delayed tumor response to irradiation.

180.1.2 Tissue Response

The degree and speed of tumor regression after therapeutic irradiation is determined by several factors, including the susceptibility to ionizing radiation related to tumor type and the contribution of inhibition of cell proliferation and cell death; tumor cell kinetics (i.e., the rate of cellular proliferation, cell death, and cell loss); the proportion of clonogenic cells; and the amount of vasculoconnective tissue in or around the tumor.[4]

Tumor response during or shortly after treatment is not a reliable index of tumor curability, but slow regression of a tumor type that usually regresses quickly is often associated with an unfavorable prognosis. Tumors that regress quickly and completely (e.g., mast cell tumors in dogs and oral squamous cell carcinomas in cats) may also recur quickly. Incomplete tumor regression at the completion of treatment does not necessarily indicate treatment failure. Some soft tissue sarcomas, meningiomas, and pituitary adenomas may remain detectable for weeks or even months after the course of radiotherapy is finished and yet ultimately disappear and never recur. Tumor disappearance may also be delayed when bony changes associated with bone invasion are present. Anatomic deformity caused by tumors with an abundant intercellular stroma may be slow to resolve, which may be interpreted as a treatment failure. Slowly regressing oral epulides in dogs are in fact one of the few highly curable tumors with radiation therapy. A practical implication of the complex reasons for different rates of tumor response is that only persistent or continual growth is a reliable sign of treatment failure. Therefore, as long as a tumor is regressing after radiotherapy, biopsy is contraindicated. A prematurely positive result from a biopsy specimen may lead to unnecessary salvage surgery, and repeated biopsies interfere with the healing of normal tissues.

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The effects of radiation on normal tissues are restricted to the treatment site. Chronologically, the clinical effects of irradiation are subdivided into *acute effects,* which occur during or immediately after treatment (during the first 3 months) and *late effects,* which occur months to years after completion of treatment. The rate of appearance of injury depends not only on the proliferative activity of the stem cells but also on the lifetime of the differentiating progeny of these cells.

Acute effects result primarily from radiation-induced stem cell depletion, which exceeds cell production in actively proliferating parenchymal tissues. The most common acute radiation reactions involve the skin and mucous membranes and result from stem cell proliferation that is inadequate to maintain the epithelial surface. The acute effects of radiation therapy always accompany curative radiotherapy, because to some extent they mirror the damage done to tumor tissue. Although acute effects may be temporarily painful and require supportive therapy, they are not complications but normal tissue reactions, which are usually self-limited and resolve naturally after treatment. Acute reactions of the skin (skin desquamation and epilation) and oral mucosa

(mucositis) may be lessened by cleansing the tissue with a 1:1 solution of hydrogen peroxide and normal saline and using topical ointments, systemic antibiotics, and corticosteroids to minimize infection and inflammation.[5]

Table • 180-1 Role of Radiation Therapy in the Treatment of Specific Neoplastic Diseases

ANATOMIC SITE	ROLE OF RADIOTHERAPY	RESULTS	ACUTE REACTIONS	COMPLICATIONS
Skin and Subcutaneous Tissues				
Squamous cell carcinoma	Curative treatment alternative to surgery for carcinomas not invading bone; treatment of choice for lesions of eyelids and nasal plane in cats and over cartilage; performed preoperatively for advanced tumors; palliative treatment with modest increase in survival for carcinoma of nasal plane in dogs.	*Nasal plane in cats:* 2-yr LCR: 77% for lesions <2 cm; 37% for advanced lesions[16]; comparable results for tumors of pinnae and forehead.	Erythema, moist desquamation, epilation; rarely, ulceration	Permanent epilation, skin atrophy, subcutaneous fibrosis; rarely, soft tissue necrosis
Mast cell tumor (dogs)	Primary treatment for small lesions; used postoperatively for microscopic or gross residual disease; adjuvant postoperative treatment for completely resected grade II/III lesions; preoperative treatment for unresectable tumors; low histologic grade and location on an extremity are favorable prognostic factors; used in combination with surgery and chemotherapy in dogs with regional metastasis.	2-yr LCR: 70%-92% for postoperative microscopic disease; 50%-85% for lesions <2 cm; 20%-58% for large tumor and gross residual tumor[11,12,36]; 60% for postoperative locoregional irradiation for node-positive dogs.[37]	Same as for squamous cell carcinoma	Same as for squamous cell carcinoma

	Soft tissue sarcomas	For operable tumors: postoperative treatment when risk of surgical complication exists due to tumor size or location; preoperative treatment when increased risk of radiation complications exists due to radiosensitive normal tissue (brain, spinal cord, lung, guts) in treatment field. For advanced inoperable lesions: primary treatment followed by limited resection if lesion rendered operable.	*Dogs:* 2-yr LCR: 33% for primary radiotherapy of all histologic types and sizes[15]; 40%-50% for hemangiopericytoma (HPA)[18,38] and 30% for fibrosarcoma (FSA)[18] after subtotal resection; 85% for postoperative radiotherapy of all histologic types; 76% for FSA and 100% for HPA after microscopically incomplete resection[18]; 40 months median survival for postoperative irradiation of infiltrative lipomas.[39] *Cats with cutaneous FSA at vaccination sites:* 2-yr LCR: 55% with preoperative treatment,[29] 30% with postoperative treatment.[40]	Same as for squamous cell carcinoma	Same as for squamous cell carcinoma
	Perianal gland	Postoperative treatment for adenocarcinomas and regional irradiation to local lymph nodes for high-risk or node-positive dogs; primary treatment for large adenomas.	Median survival: 12–18 months for perianal adenomas/carcinomas with postoperative irradiation.[41,42]	Same as for squamous cell carcinoma ADD: diarrhea and bleeding	Same as for squamous cell carcinoma ADD: Stenosis
	Head and Neck				

	Oral cavity	*Dogs:* Curative radiotherapy for small, caudally located squamous cell carcinoma (SCC), mycosis fungoides (MF), fibrosarcoma (FSA) of the gingiva/palate, buccal mucosa; alternative to surgery for small, rostrally located SCC, plasmacytoma of the gingiva/palate and floor of the mouth, and epulides; used postoperatively for advanced resectable SCC and FSA; used alone or with chemo-therapy to improve survival for advanced unresectable lesions; palliative for advanced melanomas (MMA) and tumors of the base of the tongue and tonsils. *Cats:* Curative for odontogenic tumors and epulis; palliative for SCC with modest increase in survival.	*Dogs:* 2-yr LCR for lesions <2 cm : 100% for epulides; 74% for SCC; 67% for FSA; 54% for MMA[25]; comparable results for postoperative treatment of advanced resectable (2–4 cm) epulides, SCC, and FSA. Prolongs survival in advanced SCC (median survival, 7.5 months) and FSA (median survival, 7.1 months); palliative for symptoms of advanced MMA (median survival, 7–8 months).[14,23] *Cats:* 2-yr LCR : 100% for postoperative irradiation of odontogenic tumors.[43]	Painful mucositis, resulting in dysphagia, xerostomia, and weight loss	Persistent xerostomia, dental decay; rarely, fistulas, bone exposure, and osteoradio-necrosis of mandible and maxilla
	Nasal cavity/paranasal sinuses	Primary treatment to improve survival for carcinomas and sarcomas; combination with surgery or chemotherapy may not increase survival. Curative alone or in combination with chemotherapy for localized lymphoma.	*Dogs:* Median survival for nonlymphoproliferative tumors: 10–13 months (all tumors)[17,44]; 12–14 months for carcinomas[14,45]; 15 months for chondro-sarcomas.[14] *Cats:* Median survival for nonlymphoproliferative tumors: 12 months (all tumors)[46]; 28 months for lymphoma.[47]	Nasal and oral mucositis; conjunctivitis ± keratitis for eye in radiation field; skin epilation	Loss of smell, chronic keratitis, cataract, kerato-conjunctivitis; rarely, bone necrosis
	Ear canal	Primary treatment alternative to surgery for small ceruminous adenocarcinoma or squamous cell carcinomas; used postoperatively for advanced lesions.	2-yr LCR: 56%[48]	Otitis, dysphagia	Damage to middle and inner ear and cranial nerves syndrome)

Thyroid	*Dogs:* Irradiation used alone or as a postoperative treatment with subtotal resection of adenocarcinomas; used preoperatively for inoperable lesions, followed by limited resection if lesion is rendered operable. *Cats:* Primary treatment with radioiodine for functional adenomas and adeno-carcinomas; used as postoperative treatment with subtotal resection for carcinomas.	*Dogs with carcinomas treated with teletherapy:* 2-yr survival rate: 50% after irradiation alone[49]; 66% after subtotal resection in dogs with no evidence of metastasis.[50] *Cats treated with radioiodine:* 2-yr cure rate for adenomas: 92%[51]; >50% for carcinomas given postoperative treatment.[52]	Teletherapy: Skin epilation, dysphagia (esophagitis), hoarseness, cough (tracheitis)	Teletherapy: Subcutaneous fibrosis; rarely, spinal cord damage
Central Nervous System				
Pituitary gland	Effective in controlling signs of mass effects, in dogs with macroadenoma/carcinomas and no/mild neurologic signs; used in combination with medical treatment for pituitary-dependent hyperadrenocorticism (PDH). Ineffective for dogs with severe neurologic signs.	*Dogs with Cushing's disease:* 2-yr survival: No neurologic signs, 100%[53]; mild to moderate neurologic signs, 45%[54]; median survival in dogs with severe neurologic signs, 4 months.[54] *Cats with acromegaly:* Median survival, 15 months [55,56]	Hair loss, skin erythema, otitis, dullness (brain edema)	Hearing loss, cataract formation if eye is in the field; rarely, brain necrosis
Intracranial meningioma	Postoperative irradiation after incomplete resection for cure and primary radiation therapy (RT) for inoperable lesions.	Postoperative irradiation 2-yr LCR: 70%[20]; median survival in dogs with inoperable tumors: 9 months.[34]	Exacerbation of neurologic signs dullness	Somnolence, Seizure, behavioral modification, local motor or sensory signs
Spinal cord	Postoperative treatment to improve neurologic signs and survival.	Median survival for postoperative irradiation of meningiomas: 17 months.[57]	Subtle exacerbation of Neurologic signs	Decrease in sensa-tion or motor weakness pain; rarely, irreversible spinal cord myelopathy
Bone				

Primary bone tumors	For appendicular osteosarcomas: preoperative treatment combined with chemotherapy (cisplatin/carboplatin) for limb-sparing procedure; palliative treatment as alternative to amputation or for pain relief in advanced disease. For axial and skull tumors: postoperative irradiation concurrent with chemotherapy.	Median survival of dogs with osteosarcoma (OSA) treated with limb-sparing surgery, irradiation, and cisplatin: 9 months[33]; treated with irradiation and cisplatin: 5 months[34]; treated with palliative irradiation alone: 2–4 months.[58]	Skin erythema, dry/moist desquamation	Subcutaneous fibrosis, ankylosis, distal edema; rarely, bone/soft tissue necrosis
Metastatic bone tumors	Palliative local treatment or systemic administration of bone-seeking radioisotopes for pain relief.	Mean survival in dogs treated with radioactive Sm-153: 8 months.[9]	Depression of platelet and white blood cell count	
The local control rate (LCR) is provided as a cure rate; the median survival or local control is provided if a cure rate has not been determined or if it cannot be computed because of small sample size.				

Late effects are considered complications of radiation therapy. They are caused primarily by damage to the vasculoconnective stroma and slowly proliferating parenchymal tissues, such as the kidneys, cartilage, bone, or lungs. Clinically, radiation complications appear to be less severe in cats than in dogs. In cats, feline immunodeficiency virus (FIV) infection may be associated with a higher risk of radiation complications. Unlike acute effects, radiation complications are not self-limited and tend to be progressive. They are usually irreversible. In practice, with appropriate treatment techniques, the risk of severe complications is low and should be weighed against the probability of tumor control.[6] Radiation complications are usually managed conservatively. Occasionally, severe complications, including chronic ulcers, radionecrosis of soft tissues or bone, intestinal or rectal stenosis, or cystitis may require surgical resection of the involved tissue or organ (Table 180-1).

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180.1.3 Radiocurability

The radiation doses delivered and the volume of tissue treated in clinical radiotherapy are determined as much by the tolerance of normal tissue that is included in the irradiated volume as they are by the tumor being treated. Normal tissue in the radiation field is said to be dose limiting with respect to the maximum dose that can be safely administered. Therefore tumors are typically treated within a narrow range of doses, thus commonly achieving a narrow range of tumor control rates. Maximal doses are therefore limited even for tumors with high local failure rates. This is true in spite of the fact that one can confidently assume that a sufficient dose of radiation will control virtually any localized tumor. Thus a radiocurable tumor is one that can be eradicated by a dose of radiation that is well tolerated by the surrounding normal tissues. A practical implication of this is that a tumor that is curable in one anatomic site may not be curable in another. The art of clinical radiotherapy is to find the right balance between tumor control and injury to normal tissues, to achieve what is called *uncomplicated cure*. A curative dose of radiation is a dose that will potentially cure or control the disease and result in a probability of serious complications of less than 5% for bone or soft tissue necrosis and less than 1% for spinal cord injury.

Because curative radiation doses are often by necessity close to the maximum dose tolerated by normal tissues, the radiation dose must be planned and delivered accurately to the tumor with as little radiation dose to the uninvolved normal structures as possible. Accurate tumor localization with modern imaging technology

(computed tomography [CT] and magnetic resonance imaging [MRI]) and optimum use of the radiation therapy techniques allow delivery of a high radiation dose to the tumor relative to the surrounding normal tissue. The choice of a treatment technique depends on the location, size, and extension of the tumor and adjacent normal structures. Each technique exploits the specific differences in patterns of dose distribution in tissues according to the type (photons versus electrons) and energy of radiation and the distance from the source of radiation to the lesion to be treated.

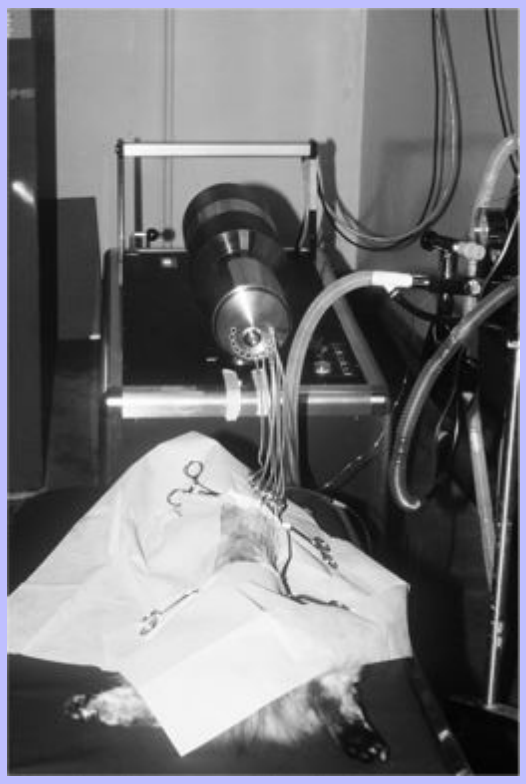
In *teletherapy* (also called *external beam therapy*), the distance between the source of radiation and the patient (50 to 100 cm) allows delivery of a relatively uniform dose of radiation to a large volume of tissue. The higher the energy of the radiation, the more significant the sparing of superficial structures (skin and subcutaneous tissues) and the greater the penetration of the beam. Medium energy x-rays (200 to 300 kV) produced by orthovoltage units are useful for the treatment of superficial tumors because their limited penetration in tissue minimizes the radiation dose to deeper, uninvolved tissues. High energy radiation (greater than 1 MV [1 MV = 1 million electron-volt]), including x-rays produced by linear accelerators and gamma rays produced by telecobalt units, are used for the treatment of large and deep-seated tumors. The availability of high energy radiation therapy units in veterinary medicine has expanded the number and types of cancers that can be cured with irradiation. High energy electrons produced by a linear accelerator have a tissue penetration range of a few centimeters, which allows complete sparing of the underlying tissues. Electron beams are useful in the treatment of superficially located tumors or those overlying radiosensitive normal tissue (spinal cord, brain, lung, and gastrointestinal tract).

Brachytherapy is a technique in which sealed radioactive sources are applied directly to the area to be treated. The short distance between the source of irradiation and the tumor provides a rapid decrease in dose as distance from the radiation source increases. This allows delivery of a high radiation dose to the tumor-bearing structures while sparing uninvolved adjacent normal tissues. When radioactive sources (usually iridium-192) are implanted directly into the tissues (Figure 180-1), the technique is called *interstitial brachytherapy* or *curietherapy*. It is used for small lesions that cannot be completely excised and for operable cutaneous tumors with indistinct margins for which there is a high probability of recurrence.[7] It may also be used in combination with teletherapy to boost the radiation dose to a specific area. When radioactive sources (usually strontium-90) are applied to the tumor's surface (Figure 180-2), the technique is called *surface brachytherapy* or *plesiotherapy*. Treatment is curative for superficial lesions of the skin, including carcinoma in situ and early squamous cell carcinoma (SCC) lesions less than 2 mm thick. Surface brachytherapy may also be used as primary or ancillary treatment for superficial fibrovascular infiltrates of the cornea that are not responsive to medical treatment. The shortest distance between the radiation source and the tumor cells is achieved by use of organ-seeking radiopharmaceuticals that are administered systemically. Irradiation is then selective to the tissue that concentrates the radioisotope. Clinical applications of systemic radiotherapy include radioactive iodine-131 for the treatment of feline hyperthyroidism and functional thyroid cancer in dogs and cats; phosphorus-32 for myeloproliferative and lymphoproliferative diseases, such as polycythemia vera and essential thrombocythemia[8]; and samarium-153 or strontium-89 for metastatic bone tumors.[9]

Another way to achieve uncomplicated cure with radiation therapy is to divide the dose into a series of equal-sized fractions given over several weeks, a process called *fractionation*. Fractionated irradiation allows selective regeneration of normal tissues due to their greater ability to repair radiation injury between treatments and to repopulate during the course of radiotherapy relative to the majority of tumors. As a result, curative treatment may be given while not exceeding the tolerance of the surrounding normal tissues. Clinical data, essentially in people, indicate that large doses per fraction are preferentially damaging to slowly proliferating tissues responsible for radiation complications. As a rule, when the dose of radiation per fraction decreases, the

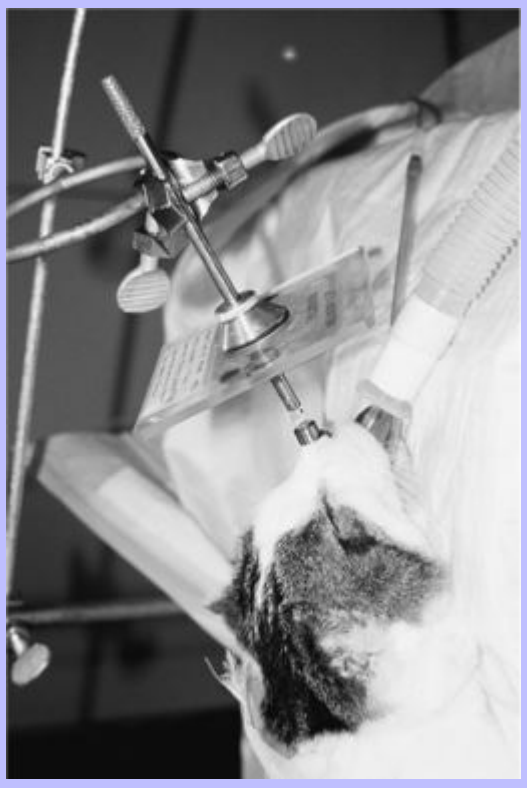
risk of radiation complications decreases, which allows the use of higher total doses and inclusion of a larger volume of normal tissues.

Figure 180-1 Setup for interstitial brachytherapy using a remote afterloader for postoperative irradiation of an interscapular fibrosarcoma in a cat. The technique is ideal for this location because a high radiation dose can be delivered, yet dose-limiting normal tissue, including the spinal cord and lungs, is spared. The treatment is done on an outpatient basis and poses no radiation hazard to personnel. The head of the remote after-loader (Gammamed Iii; RTS Technology, North Andover, Massachusetts), which contains a radioactive source (10 Ci, iridium-192) in a shielded container, is connected by source guide tubes to plastic needles implanted in the tumor bed below the skin. After all personnel have left the treatment room, the afterloader is activated from a shielded control room, and the radioactive source is driven through the array of applicators to deliver the planned dose. When treatment is complete, the radioactive source returns to the shielded container, and personnel can safely enter the treatment room.



In people, the standard fractionation for external beam therapy includes daily (5 days a week) dose fractions of 1.8 to 2.0 Gy (Gray [1 Gy=100 rad]). In teletherapy, various treatment schedules have evolved over the years, with dose fractions decreasing from 4 Gy given on an alternate-day schedule (Monday-Wednesday-Friday) to 3 Gy given on a daily schedule (5 days a week), and total radiation doses have increased from 40 to 60 Gy. The current recommendation for curative treatment is delivery of daily radiation doses (5 days a week) of 3 Gy or less in an overall treatment time that is as short as is consistent with acute reactions (over 3 to 4 weeks). Longer overall treatment times or intertreatment times (three fractions/week) increase the risk of "tumor escape" through accelerated repopulation. The benefit of daily treatment compared with alternate-day treatments has been shown in cats with oral carcinomas[10] and dogs with mast cell tumors.[11] In addition, in people, treatment prolongation caused by interruptions due to severe acute reactions, intercurrent illness, public holidays, or machine breakdown has been shown to have a negative influence on the outcome. The detrimental effect of treatment interruptions increases as treatment progresses. An early interruption in the treatment course is less detrimental for the patient than a late interruption.

Figure 180-2 Cat undergoing surface brachytherapy for early-stage squamous cell carcinoma of the nasal plane. The strontium-90 radioactive source at the tip of the applicator is a fission byproduct (half-life, 30 years) that produces an electron beam (2.3 MeV maximum energy). Electrons have shallow penetration in tissues, which allows delivery of high radiation doses to the tumor without exposure to the underlying normal tissues. The dose is 100% at the surface and decreases rapidly with depth: 40% at 1 mm, 20% at 2 mm, and less than 1% at the surface of the nasal cartilage. The applicator is carefully positioned directly on the surface of the lesion. The Lucite shield protects the operator's hands from scattered electrons. Because each treatment takes 3 to 4 minutes, the applicator is held with a stand to minimize radiation exposure to personnel. The surface dose ranges from 200 to 250 Gy. Usually one treatment is sufficient.



Because brachytherapy is used to treat smaller target volumes and the volume irradiated outside the target volume is minimized, the potential for complications is lower than with teletherapy. As a result, dose

fractionation with large doses per fraction may be used for interstitial brachytherapy (five doses of 5 to 7.5 Gy given once a week) or plesiotherapy (one or two doses of 150 to 200 Gy) without increasing the risk of serious complications.

180.2 CLINICAL RADIATION THERAPY

The basic principle of clinical radiation therapy is that treatment should always benefit the patient, even though the treatment outcome may not be entirely predictable. The selection of patients for radiation therapy should involve consultation with a radiation oncologist, preferably in a multidisciplinary clinic setting, and should include consideration of all aspects of the individual patient. The only contraindication for radiation therapy in dogs and cats is inability to tolerate the multiple episodes of anesthesia necessary for positioning and immobilization during treatment. Concurrent disease, particularly of the heart and liver, may be more limiting to survival than cancer.

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180.2.1 Treatment Goals

After the extent (staging) and pathologic characteristics of the tumor have been evaluated, the objective of radiation therapy must be determined based on the likelihood of tumor spread, the expected cure rate, and treatment morbidity. The treat-ment goal should be defined at the onset of formulation of the therapeutic strategy, because it affects the selection of the appropriate treatment modalities (irradiation alone or in combination with other modalities) and the radiation treatment plan (technique and target volume). A correct assessment of the treatment goal is one of the most important decisions in radiation therapy. Overly aggressive treatment plans can expose animals that are not curable to needless morbidity, prolonged and expensive treatment, and unnecessary radiation effects. On the other hand, therapeutic decisions that are too pessimistic deprive the animal of a small but real chance for cure.

180.2.1.1 Curative Radiotherapy

Radiation therapy is most commonly used with curative intent when there is no evidence of widespread dissemination of metastases. Animals are treated with curative intent when it is expected that a finite probability exists that the tumor will be destroyed after adequate therapy, even if that chance is low. Radiation therapy given with curative intent is called *definitive therapy* if it is used for a localized, primary tumor that has been biopsied or incompletely resected. Radiation therapy is called *adjuvant therapy* if it is applied to a primary tumor or to sites of potential spread when the malignant cell burden is microscopic or below the level detectable by current imaging methods. Local and regional tumor control is an absolute necessity for cure of a patient with a solid tumor. *Tumor control* refers to complete eradication of the tumor at the primary site and in adjacent involved tissues and lymphatics. Failure to achieve control results in an increased likelihood of metastases and death. Tumors that are diagnosed and treated at an early stage, before distant metastases have occurred, are often curable by radiation therapy. Tumors arising from or involving organs highly vulnerable to radiation injury and tumors with a high propensity to develop distant metastases are rarely cured with radiation therapy alone.

The probability of tumor control depends on several clinical factors, including the tumor's size, extent, histologic grade, proliferative activity, and location and whether there is a history of previous treatment. Other factors, such as the patient's species, gender, age, and performance status, also may affect tumor control. One of the most important factors influencing the probability of local control is the tumor's size and extent. An inverse relationship between the probability of local control and tumor volume has been shown for mast cell tumors,[12] oral tumors (squamous cell carcinomas, fibrosarcomas, melanomas, and

epulides),[13,14] and soft tissue sarcomas[15] in dogs; squamous cell carcinomas of the nasal plane in cats[16]; and intranasal tumors (carcinomas, chondrosarcomas) in dogs.[17] Although invasion of bone or cartilage is not a contraindication to irradiation, local control rates are higher when the tumor is confined to the site of origin.

Histologic identification and grading of tumors are useful pretreatment predictors of biologic behavior. In practice, some tumors (e.g., round cell tumors) are easily controlled with low radiation doses, but most of the common tumors that can be cured with radiation (carcinomas, soft tissue sarcomas) require high doses. A few tumor types (e.g., glial tumors) are rarely cured, even with high doses. Usually, microscopic tumor deposits of any histologic type can be cured with moderate doses of radiation.[18] Histologic grading and tumor cell kinetics have been shown to be prognostic factors. High histologic grades are associated with a poorer prognosis after irradiation for mast cell tumors[12] and soft tissue sarcomas.[19] A high tumor growth fraction is associated with a poorer prognosis for SCC of the nasal plane, meningiomas in dogs, and oral SCC in cats.[10,16,20]

Tumors of similar histologic types arising from different anatomic sites have different biologic characteristics. In some instances, cancers arising from sites only 1 or 2 cm apart show markedly different responses that are not explainable by current knowledge. For example, in cats, squamous cell carcinoma of the facial skin is curable with radiation therapy alone, but squamous cell carcinoma of the oral cavity is rarely controlled. Paradoxically, in dogs, squamous cell carcinoma of the oral cavity is radiocurable, but squamous cell carcinoma of the nasal plane cannot be controlled with irradiation.

180.2.1.2 Palliative Radiotherapy

The goal of palliation is to relieve pain or other complications resulting from an incurable tumor but not to prolong life. Although life may be prolonged through the use of palliative irradiation, this is not the primary goal. For pets with extensive and rapidly progressive tumors and anticipated short survival, radiation therapy may be used to slow local progression of the disease and relieve distressing symptoms. Palliative radiation therapy offers an opportunity for rapid improvement in the quality of a pet's life. In this setting, the treatment course is as short as possible, using a few larger dose fractions and lower total doses. However, the use of large dose fractions is associated with a high risk of complications, and palliative treatment regimens should not be used for animals with a life expectancy greater than 6 to 12 months. Administration of palliative versus curative treatment for purposes other than alleviating pain or suffering amounts to substandard care. Palliation is acceptable for animals with a short life expectancy because the probability of developing late complications is limited. Palliative irradiation is not a less expensive, less complicated alternative treatment for pets that would benefit from treatment given with curative intent. The use of palliative radiation therapy has been investigated for management of selected tumors, including thyroid tumors,[21] pituitary tumors,[22] oral melanomas,[23] and nasal tumors[24] in dogs and oral squamous cell carcinomas in cats.[25] Tumor control duration has proved to be inferior compared with that obtained with standard fractionation and is associated with significant risk of complications in animals surviving longer than 6 months.

Palliative radiation therapy is useful to relieve discomfort associated with both skeletal tumors (primary and metastatic bone lesions) and soft tissue tumors. Pain, compression of vital structures such as the brain, ulcerating skin lesions, and bone tumors or bone metastases in weight-bearing bones susceptible to fracture can be managed effectively with palliative radiation. Dogs with appendicular osteosarcomas that are not candidates for amputation may benefit from palliative radiation therapy. Treatment consists of three to four weekly large-dose fractions (8 to 10 Gy). Pain relief occurs in 75% to 90% of these dogs, with the period of pain control lasting 2 to 3 months.[26,27] The duration of pain relief may be slightly longer for appendicular

than for axial bone tumors and may be increased by use of higher radiation doses and concurrent use of platinum-based chemotherapy.[26,27]

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180.2.2 Clinical Role of Radiation Therapy

Ideally, the radiation oncologist should be involved at the time of diagnosis and initial decision making so that if and when radiation therapy is used, the oncologist will be knowledgeable about all the factors involved in the treatment planning. Seeing the intact, untouched lesion before surgery can be of immense help in planning definitive treatment. The best results are achieved by an initial integrated treatment plan with combined modalities tailored to the particular pet's cancer rather than by ad hoc attempts to salvage the failures of another modality. Treatment of localized tumors often involves the use of surgery or radiation therapy or a combination of the two (Figure 180-3). Treatment of tumors with a high probability or evidence of metastasis at the time of diagnosis involves a combination of local treatment and systemic chemotherapy.

180.2.2.1 Primary Radiation Therapy

Radiation therapy plays an important role in the curative treatment of small malignant solid tumors. It is also used in the management of benign tumors, including adenomas of the pituitary and perianal glands and oral epulides in dogs and thyroid adenomas in cats. Surgery is essentially a local treatment, whereas radiotherapy offers locoregional treatment covering a wider area, less constrained by anatomic boundaries and surgical techniques. Local control rates for radiation therapy are equivalent to those for surgery for small, localized tumors (2 to 4 cm) in many sites, and irradiation has the advantage of controlling the disease in situ, thus avoiding disruption of anatomic structure and preserving function. In practice, radiation therapy is used for lesions that are technically difficult to completely resect without excessive functional and cosmetic mutilation. Radiation therapy is particularly well suited for lesions of the facial skin, including carcinomas of the nose, eyelids, ear canals, or pinnae, and certain more extensive lesions of the forehead and cheeks. Radiation therapy may be preferred at specific sites on the trunk or extremities for tumors that have extended near or around critical structures such as the spinal cord, nerves, large vessels, or tendons. For certain early-stage lesions in less strategic locations, surgery can be carried out expediently and effectively and therefore is preferred. For example, surgery is preferred for oral tumors that are rostrally located, where a wide excision is possible. Radiation therapy is preferred, on the other hand, for caudally located tumors when a high risk of oral incompetence is anticipated after radical excision or when regional lymph node involvement is observed or anticipated.

Less frequently, primary radiotherapy is used for tumors that are highly radiocurable or that are technically unresectable. Tumors of any size, including transmissible venereal tumors at all sites, localized mycosis fungoides of the oral mucosa in dogs, and extranodal solitary lymphomas (stage I), can be cured with radiation therapy alone. Radiation therapy is the mainstay of treatment for central nervous system (CNS) and intranasal tumors because most such lesions are inoperable.

Radiation therapy is also used as primary treatment for control of invasive and inoperable cancers. The goal is not to cure the pet, because extensive disease or potential distant metastases obviate this goal, but to prolong survival. This setting is different from palliative radiation therapy, in which the quality, rather than the duration, of survival is of utmost importance. Many animals may live for long periods in comfort with residual tumor or metastasis. Some animals have good prospects of prolonged survival with inoperable regional disease without demonstrable metastases. The goal of radiation therapy in this situation is to achieve lasting local control and improve the duration and quality of survival. Here, control indicates that the local disease can be kept within bounds for extended periods. In dogs with large intracranial tumors (gliomas,

pituitary adenomas, meningiomas) or inoperable soft tissue sarcomas, the treatment goal is to control the growth of the tumor and extend the dog's survival. Thus the radiation therapy technique and dose are similar to those used in curative radiation therapy.

Reirradiation of recurrent tumors that are unresectable because of their strategic location may be used in selected cases to prolong survival.[28] Because of the poor radiation tolerance of previously irradiated adjacent normal tissues, recurrences are best managed by resection.

Combinations of surgery and radiation therapy may be used for advanced locoregional disease.

Radiation therapy and surgery may be “equally” beneficial for the treatment of small lesions, but they also can be mutually beneficial in the treatment of advanced tumors. The goals of a combined approach are to preserve function and cosmetic appearance and to reduce the chance of local failure when the probability of cure by either modality alone is low.

The timing and dose of radiotherapy and its sequencing with surgery depend on (1) the tumor's resectability (preoperative irradiation may be used if complete resection is not feasible); (2) the dose desired (high doses must follow surgery); and (3) the extent of the planned surgery (extensive procedures must precede radiotherapy). The interval between the application of each treatment method should be planned to minimize additive complications without losing any advantage in tumor control.

The main combinations of surgery and radiation therapy involve preoperative and postoperative radiation therapy. The optimal sequencing depends on the tumor's size, location, and histologic characteristics. The best interval between preoperative radiation and surgery or between surgery and postoperative radiation has not been clearly established. When radiation therapy is given preoperatively, the optimal interval between irradiation and surgery is usually 3 to 4 weeks. This allows acute radiation reactions to resolve before fibrosis begins to develop. When radiation therapy is given postoperatively, an interval of 2 to 3 weeks after surgery usually allows satisfactory wound healing.

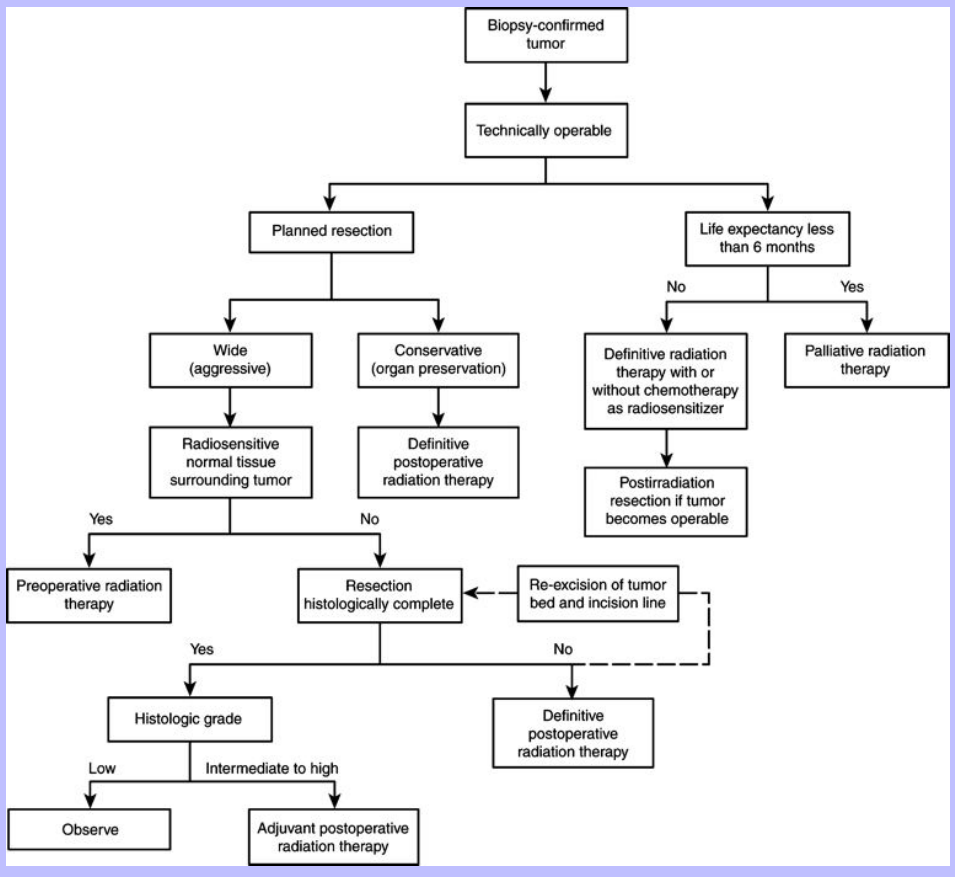
180.2.2.1.1 Postoperative radiation therapy.

Radiation therapy may be used postoperatively as an adjuvant treatment for control of postoperative microscopic disease or with curative intent for control of residual gross disease. The advantages of postoperative irradiation are that the entire surgical specimen is available for review for exact histopathologic classification; the extent of microscopic tumor can be assessed directly; and a high dose of radiation can be given without increasing surgical morbidity. In wounds that are healing poorly, such as those with postoperative infection or dehiscence, irradiation will further hinder healing. In pressing instances, irradiation may be given to animals with an open wound. Depending on the size of the wound, this may be accomplished without complication; however, the wound may have difficulty healing by secondary intention and may require skin grafting or plastic reconstructive techniques.

Adjuvant radiation therapy is used to improve local control and functional results for treatment of operable tumors. A tumor is considered operable if it is anticipated to be highly likely that all gross disease can be resected, leaving at most microscopic disease. Operable tumors include accessible, medium-sized or advanced tumors in locations where wide resection is possible. Adjuvant radiation therapy is used to improve local control and functional results. In this setting, clinically apparent disease is surgically resected and irradiation is given to eliminate tumor microextension present at the periphery of the gross tumor and in regional lymph nodes. In clinical practice, animals with resectable tumors are treated with postoperative irradiation when histopathologic evidence of microscopic residual disease is

present (close to or positive for tumor at surgical margins) or when the risk of local recurrence is high after surgery because of extensive tumor invasion and high histologic grade. Clean surgical margins are not a guarantee that all tumor cells have been removed, because cell aggregates greater than $10^6/cm^3$ or higher are required for histopathologic detection. Aggressive intermediate or high-grade fibrosarcomas, hemangiopericytomas, cutaneous hemangiosarcomas, infiltrative lipomas and liposarcomas, myxosarcomas, synovial cell sarcomas, and mast cell tumors resected with clean surgical margins benefit from adjuvant postoperative irradiation.

Figure 180-3 Integration of radiation therapy in the management of solid tumors in patients with no evidence of systemic disease. The term *definitive radiation therapy (RT)* refers to therapy given at full dose when gross disease is present; *adjuvant RT* refers to radiation therapy given at moderate dose for treatment of microscopic or subclinical disease.



Unfortunately, radiation therapy is too frequently used after a partial resection in which gross residual disease is present. This is the setting in which the treatment combination is the least effective. Irradiation is most effective for treatment of microscopic or subclinical residual disease.[18] Partial removal of gross

disease (surgical debulking) provides little therapeutic advantage. For example, a surgical excision that removes 99% of a tumor containing 10^{10} cells (about 10 g of tissue) leaves 10^{8} tumors cells. In fact, subtotal resection may lessen the chance of cure by irradiation in some situations, because tumor cells may be disseminated throughout the surgical bed and may be implanted in relatively hypoxic scar tissue, where they are less sensitive to irradiation. In addition, reduction of tumor volume may result in a compensatory burst of accelerated regrowth of residual tumor cells, which can decrease the efficacy of radiation therapy.

180.2.2.1.2 Preoperative irradiation

Advantages of preoperative radiation are that it can eradicate subclinical or microscopic disease beyond the margins of the surgical resection; it may theoretically diminish tumor implantation within the operative field; and it can decrease the potential for dissemination of tumor cells that might produce distant metastases. In some cases it may convert a nonresectable tumor into one that can be resected.

Preoperative irradiation is more “dose effective” than postoperative radiotherapy; that is, a lower dose is needed preoperatively to reduce rates of local recurrence to the same extent as postoperative radiation. Although radiation doses are lower and radiation treatment fields are smaller than those used with postoperative radiation therapy, preoperative treatment may be associated with an increased risk of surgical morbidity. The decision to accept increased short-term morbidity from wound healing complications with preoperative radiation therapy must be balanced against the potential effects of larger radiation doses and larger treatment volumes associated with postoperative radiotherapy. Practical measures have proved useful in avoiding treatment complications. At the time of surgery, it is extremely important to handle irradiated tissues with care. Whenever possible, the fascia and underlying muscle should be left attached to the skin and subcutaneous tissue as they are reflected from the tumor. Potential dead spaces should be avoided, and wounds should be drained and closed without tension. Seromas and hematomas should be drained, because they are likely to increase the incidence of late wound breakdown and subsequent infection, thus delaying the administration of radiation therapy.

For large operable tumors with anticipated extensive regional microextensions or for those that arise from or are located close to radiosensitive normal tissue (brain, spinal cord, lung, abdominal cavity), there is an advantage in using adjuvant preoperative irradiation. In contrast to postoperative irradiation, preoperative treatment can be given to a smaller treatment volume with lower radiation doses. Although there is a potential increase in postoperative morbidity, the risk of long-term, radiation-induced complications is reduced. In this setting, irradiation is followed by wide-margin surgical resection according to the original extent of the disease. This treatment combination is effective for most operable cutaneous soft tissue sarcomas in dogs and cats. The benefit of this approach has been demonstrated for the treatment of feline fibrosarcomas at vaccination sites overlying the spinal cord and lungs.[29]

180.2.2.1.3 Sequential combination of surgery and radiation therapy.

A subset of animals with advanced, incompletely resectable cancer may be treated with definitive irradiation followed by surgery if the tumor undergoes significant regression and becomes resectable. In this setting, the timing between irradiation and surgery is longer (8 to 10 weeks) to allow tumor shrinkage and normal tissue recovery than in planned preoperative irradiation. This approach requires careful monitoring of tumor response after irradiation while planning the surgery. This treatment combination is different from that in which surgery is used for attempted salvage of those that experience a locoregional recurrence after definitive irradiation.

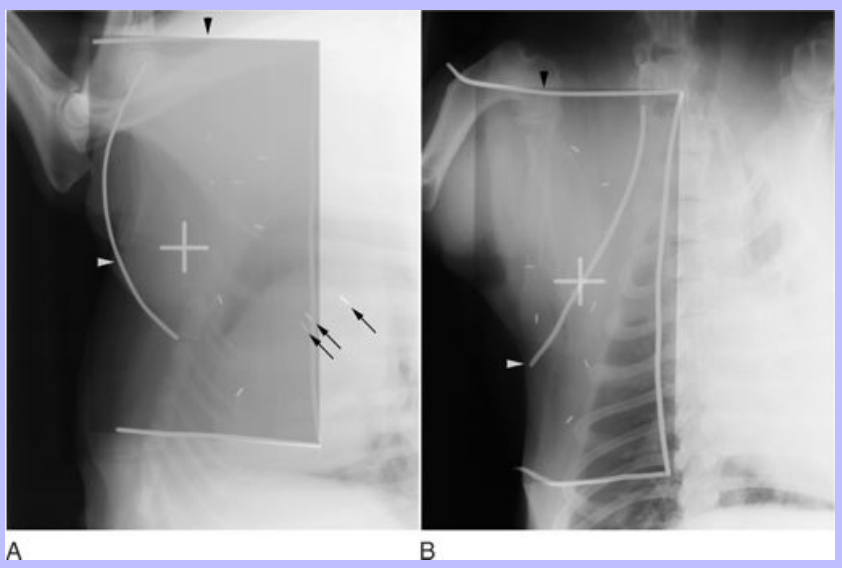
In clinical practice, the sequential combination of irradiation followed by surgery is reserved for situations in which either the tumor is initially thought to be unresectable or the original boundaries are obscured. In this setting, a definitive dose of radiation is used, followed by limited surgical resection to eliminate the residual gross disease that has not been sterilized by irradiation. This approach has been found effective, with minimal surgical morbidity in expert hands, for advanced lesions arising from the head (carcinomas and soft tissue sarcomas of the face and oral cavity) and neck region (thyroid carcinomas) and the extremities (fibrosarcomas, hemangiopericytomas, and mast cell tumors).

180.2.2.1.4 Surgical procedures helpful for radiation therapy.

Because the most common treatment combination is irradiation given after surgery, the surgeon plays a critical role in treatment. Unless the primary tumor can be removed in *toto*, it usually is preferable to perform a biopsy of the site, visualize the extent of the tumor, and then end the procedure. The treatment options can then be reconsidered. This approach is better than performing heroic surgical procedures that will compromise the efficacy of radiation therapy. Because the radiation treatment field must incorporate all areas that have potentially been contaminated by surgical dissection, single incisions, rather than multibranched ones, should be made. Drain sites should be positioned close to the wound to be included in the treatment field. Good communication between the radiation oncologist and the surgeon is imperative. Information regarding the total extent of tissue involvement, the estimated volume of residual tumor, and the quality of the surgical margins is required for radiation treatment planning. To excise the tumor and then refer the pet for radiation therapy treatment imposes a severe handicap on the therapist and the pet. The location of the cutaneous surgical scar, the palpable postoperative indura-tion, the owner's recollection, and the surgical notes are usually inadequate to determine the location of the tumor bed. Radiation treatment fields devised primarily on the location of the skin incision are associated with a risk of geographic treatment miss. For the radiation dose to be delivered precisely to the tumor confines, as identified at the surgical procedure, the walls of the excision cavity must be marked with radiopaque markers (i.e., steel or titanium surgical hemostatic clips or wire) to document the boundaries of the tumor bed and residual disease.

Radiographic documentation of the clips is used to localize the entire tumor volume for treatment planning and to verify that the treatment setup provides adequate coverage of the entire tumor volume (Figure 180-4). If markers are not present for guidance, the radiation oncologist must use larger than usual fields to decrease the likelihood of inadequate coverage, with subsequent increased risk of complications.

Figure 180-4 Dog with a mast cell tumor in the axillary region treated postoperatively with two orthogonal radiation fields: **A,** Lateral view. **B,** Dorsoventral view. The tumor bed is defined by radiopaque surgical hemostatic clips. The clinical setup was based on the location of the scar and surgical induration, the surgeon's recollection of the tumor location, and the surgical report, which provided anatomic landmarks (rib number) and measurements of tumor extension. Postoperative portal films were done to verify the treatment setup. The radiation fields marked with solder wire *(black arrowhead)* taped on the skin were determined clinically (*X* at center of treatment field). Although the skin incision was made almost directly over the tumor, the location of the skin incision marked with solder wire *(white arrowhead)* was not immediately above the tumor because the position of the underlying tissues was different on the treatment table than that on the operating table. The dorsoventral radiation field **(B)** was barely adequate. The lateral field **(A)** was clearly inadequate because surgical clips *(black arrows)* extended outside the dorsal border of the radiation field. Correction of the treatment setup would not have been possible without demarcation of the tumor volume with surgical clips. The geographic treatment miss would have resulted in tumor recurrence.



Integration of Radiation Therapy, Surgery, and Chemotherapy for Inoperable or Metastatic Disease

The use of combinations of radiation therapy and chemotherapy has increased. Radiation therapy alone or in combination with surgery is usually directed at primary tumor masses and involved regional nodes, whereas systemic treatment is aimed at distant metastases.

Radiation therapy and chemotherapy play important roles in the management of metastases that are either documented (radiographically, histopathologically, or cytologically) or suspected (subclinical disease). Radiation therapy is effective for the treatment of subclinical disease in the regional lymphatics and in the treatment of clinically positive lymph nodes. For tumors with a high potential for regional spread (invasive tumors with intermediate to high histologic grades), a large treatment field is used to include the first-echelon lymph nodes along with the primary lesion. The benefit of large-field irradiation can be demonstrated by the lower rate of metastasis observed in dogs with malignant oral tumors treated with irradiation when compared with dogs treated with surgery.[14] When clinically positive nodes are present, the radiation field includes the gross disease (primary and positive nodes) and contiguous nodes that are at risk. In this setting, radiation therapy is often used with palliative intent.

Adjuvant chemotherapy is used for treatment of subclinical disease after effective local treatment (surgery and/or irradiation) has been completed. The initial decision to use local treatment alone or both a local and systemic approach depends on the risk of occult distant disease and the availability of effective chemotherapy. As local treatment becomes more effective, animals live longer and a higher number develop metastasis. This pattern of failure is seen with some tumors that previously had the reputation of low metastatic rates, including squamous cell carcinomas of the oral cavity, fibrosarcomas in any location, and hemangiopericytomas. As a result, chemotherapy may have a bigger part to play as an adjuvant to local treatment. Adjuvant chemotherapy with cisplatin, carboplatin, or doxorubicin is indicated for control of subclinical disease in tumors with a high risk of distant failure, including osteogenic sarcomas and high-grade soft tissue sarcomas. Preliminary data on the use of chemotherapy to prevent metastasis for oral melanoma[23] and mast cell tumors[30] in dogs and vaccine-associated sarcomas[29] and oral carcinomas[25] in cats have failed to show a therapeutic benefit.

For the treatment of locally advanced, unresectable disease, concomitant chemoradiotherapy is the most promising approach. Schedules of concomitant chemoradiotherapy can be synchronous, with the two modalities administered close together, or alternating, with the treatments administered in a nonoverlapping fashion. Administration of radiotherapy and chemotherapy concomitantly is a dose-intensive approach that exploits the independent, complementary activity of radiotherapy locally and chemotherapy distantly (spatial cooperation). In cats with mediastinal lymphoma and severe respiratory compromise secondary to pleural effusion, radiation therapy may be used along with induction chemotherapy to improve the likelihood of rapid and complete remission. The beneficial effects of concurrent chemotherapy and radiation therapy result from the added toxic effects of the two modalities in the treatment field, with less than additive effects against dose-limiting normal tissues. Cisplatin and carboplatin are ideal agents for concomitant chemoradiotherapy. They have established single-agent activity, as well as synergistic interaction but nonoverlapping toxicities with radiotherapy. The drugs may be used as a systemic cytotoxic agent in addition to irradiation or as a radiosensitizer administered as small, frequent doses systemically[31] or intratumorally.[32] Several clinical trials are underway to test the efficacy of irradiation combined with carboplatin and mitoxantrone for the treatment of advanced tumors in dogs and cats. The benefit of adding chemotherapy to irradiation has been shown with cisplatin in dogs

with appendicular osteosarcomas, regardless of whether they are resectable, and for carboplatin in dogs with intranasal carcinomas.[33–35]

180.3 ROLE OF RADIATION THERAPY IN THE MANAGEMENT OF CANCER PATIENTS

Radiation therapy can be used in the clinical management of virtually every type of solid tumor in dogs and cats. Table 180-1 outlines the role of radiotherapy for specific tumors, the results obtained, and the possible treatment complications that should be discussed with owners before treatment. This table is not intended for use as a manual of radiation therapy. Most of the results are given as local control rates at 2 years because in general, the risk of local failure 2 years after irradiation is low in animals that have survived disease free. As a result, the 2-year local control rate represents a reliable estimate of the cure rate in dogs and cats that have no evidence of metastasis before treatment. The local control rates given here represent a lower limit, because they were obtained with treatment protocols that may not have been optimum. It is anticipated that the current use of higher radiation doses given with effective fractionation schemes and optimum irradiation techniques will result in higher local control rates. Specific results according to tumor size, location, and other prognostic factors are given in the other chapters of this text.

A great improvement in the treatment of cancer could be achieved immediately if all animals received what is currently acknowledged as the best available treatment. This requires that individual veterinarians appreciate the potential of available treatment modalities, especially the advantage of multidisciplinary consultation, at the time of initial diagnosis and treatment.

The role of radiation therapy for the treatment of brain tumors and in combination with surgery for mammary and salivary gland adenocarcinomas, thymomas, and intra-abdominal carcinomas (prostate, bladder, and rectum) needs to be established in animals because of its important role in people.

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181 CHAPTER • 181 Hematopoietic Tumors

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181.1 LYMPHOMA

Lymphoma (lymphosarcoma [LSA]) is the most common hematopoietic tumor affecting dogs and cats. It is defined as a proliferation of malignant lymphoid cells affecting primarily the lymph nodes or solid visceral organs, such as the liver or spleen. The management of LSA initially is quite gratifying in both species, because response rates approach 90% in dogs and 70% in cats treated with multiagent chemotherapeutic approaches. Unfortunately, most animals eventually succumb to relapse of chemotherapy-resistant, disseminated disease.

181.1.1 Etiology

The etiology of LSA in companion animals is for the most part unknown. Although certain varieties of LSA in cats have been directly and indirectly associated with feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV), respectively, no strong evidence exists as yet of a retroviral etiology in dogs. A weak to moderate association between canine LSA and the use of herbicides, exposure to strong magnetic fields, or residence in industrial areas has been observed in preliminary epidemiologic studies,[1–5] and a recent study found a meaningful association between environmental tobacco smoke exposure and the risk of feline gastrointestinal LSA.[6] More thorough studies are necessary to evaluate these associations further. Both somatic and germ line mutations in the tumor suppressor gene p53 have been reported in some cases of canine LSA,[7] and occasional clustering of LSA in related dogs has suggested a heritable component in limited instances.[8]

181.1.2 Classification of Lymphoma

Various classification schemes for LSA have been evaluated, including those based on the anatomic site, the World Health Organization (WHO) clinical stage (Table 181-1), the histologic/cytologic phenotype, and the immunophenotype.

181.1.2.1 Canine Classification

In the dog, 80% to 85% of cases are the multicentric anatomic type and present as WHO stage III or IV.[9–13] Alimentary (~7%), cutaneous (~6%), mediastinal (~3%) and miscellaneous extranodal sites (central nervous system [CNS], bone, heart, nasal cavity, and primary ocular locations) are less frequently encountered. Regardless of the histologic classification scheme used (e.g., Kiel, NCI-Working Formulation), most cases (80%) equate to medium-or high-grade non-Hodgkin's LSA in humans.[14–16] Most canine LSA is of the B-cell immunophenotype, with approximately 20% to 30% being of T-cell derivation.[9,14–16]

Table • 181-1 World Health Organization Clinical Staging for Domestic Animals With Lymphoma

STAGE	CRITERIA
I	Single lymph node
II	Multiple lymph nodes in a regional area
III	Generalized lymphadenopathy
IV	Liver and/or spleen involvement (with or without stage III)
V	Bone marrow or blood involvement and/or any nonlymphoid organ (with or without stages I to IV)
Substage a	Without clinical signs of disease
Substage b	With clinical signs of disease

World Health Organization: TNM Classification of Tumors in Domestic Animals. World Health Organization, Geneva, 1980.

181.1.2.2 Feline Classification

In the cat, a definite and repeatable shift in anatomic type, immunophenotypic derivation, and retroviral associa-tion has occurred concomitant with the initiation of wide-spread FeLV testing and vaccination programs over the past 15 to 20 years.[17–19] Studies prior to this era reported that the mediastinal and multicentric forms of LSA predominated and that these represented younger, FeLV-positive cats. Contemporary reports document that currently, LSA primarily affects older, FeLV-negative cats and that the alimentary form predominates (Table 181-2). Only 10% to 20% of cases are now associated with FeLV antigenemia, compared with the 60% to 70% figure published before FeLV testing and vaccination became available.

Along with a shift away from FeLV antigen–associated tumors has come an alteration in the traditional signalment and relative distribution of anatomic sites. The median age of 9 to 10 years now reported is considerably higher than the 4-to 6-year medians reported prior to this era. The median age of cats within various anatomic tumor groupings has not changed, however, and sites traditionally associated with FeLV (i.e., mediastinal and multicentric locations) still occur primarily in younger, FeLV-antigenemic cats. Similarly, the alimentary form occurs most often in older, FeLV-negative cats. It is unclear whether this change in the epidemiology of LSA in cats is due to FeLV vaccination itself or whether the procedure of FeLV antigen testing before vaccination has allowed separation of potentially infective cats from the susceptible population. Either situation would result in a reduction in the number of FeLV-positive LSA cases. Recently, European oncologists have reported mediastinal LSA in young, Oriental breed cats that are uniformly FeLV negative.[19]

Table • 181-2 Characteristics of Feline Lymphoma by Anatomic Site

ANATOMIC SITE	RELATIVE FREQUENCY	AGE	T CELL ASSOCIATION	FeLV POSITIVE
Alimentary	50%-70%	~10–14 yr	High	Low (5%)
Multicentric	10%-25%	Depends on feline leukemia virus (FeLV) status*	Depends on FeLV status*	Approximately one third
Mediastinal/thymic	10%-20%	Young	High	High (>80%)
Nasal	~10%	Aged	Low	Low
Renal	5%-10%	Middle-aged	Low to moderate	Low to moderate
Other	5%-25%	Mixed	Mixed	Mixed

* FeLV-positive cats tend to be younger, and the cancer is more commonly of T cell derivation.

A distinct class of LSA in cats has more recently been reported.[20–23] This lesion, a granulated, round cell tumor, has been termed either *globule leukocyte tumor* or *large granular lymphocyte LSA,* although these are likely variations of the same disease. The tumor usually involves the intestinal tract and abdominal viscera, with systemic involvement being the norm. Affected cats are generally FeLV negative. A series of cats with LSA resembling human Hodgkin's disease also has been recently reported.[24]

181.1.3 Clinical Presentation and Signs

181.1.3.1 Canine Multicentric Lymphoma

LSA affects primarily middle-aged to older dogs. No sex predilection is observed, and many different breeds are represented. Only 10% to 20% of dogs are clinically ill (WHO substage b) at presentation,[9–13] therefore most cases present as healthy dogs with incidental generalized lymphadenopathy. In dogs with substage b disease, the clinical signs are nonspecific and can include inappetence, weight loss, and lethargy. Paraneoplastic hypercalcemia may result in presentation for polyuria and polydipsia. In stage V disease, if bone marrow involvement is marked, peripheral cytopenias may result in presentations reflecting neutropenic sepsis, thrombocytopenic hemorrhage, or anemia.

181.1.3.2 Canine Lymphoma of Other Sites

The presentation and associated clinical signs of LSA reflect the anatomic form present in each individual case. Alimentary forms present with signs specific to the gastrointestinal tract, including vomiting, diarrhea (with or without blood), weight loss, and inappetence. Mediastinal forms may present with respiratory signs, including dyspnea and muffled heart sounds. Mediastinal LSA may also present with precaval syndrome, characterized by pitting edema of the head, neck, and forelimbs secondary to tumor compression of the cranial vena cava (Figure 181-1). Nearly half of mediastinal LSA cases are associated with paraneoplastic hypercalcemia,[25] therefore polydipsia and polyuria are common presenting complaints for this anatomic form.

Cutaneous LSA has been called the “great imitator” because of its ability to present in many varying forms. Single or multiple cutaneous lesions can occur, which may appear as mild, eczematous plaques or more impressive nodular tumors (Figure 181-2).

Figure 181-1 Precaval syndrome in a dog with mediastinal lymphoma. Pitting edema of the head and neck are noted.

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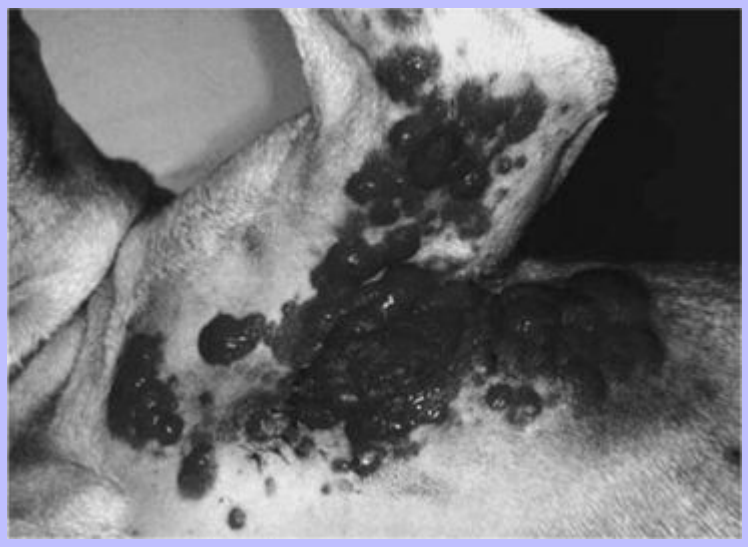
Lesions may or may not be pruritic and can occur anywhere on the skin and in the oral cavity.

Miscellaneous sites of disease result in signs attributable to the location (i.e., lameness for bone lesions, neurologic compromise for CNS lymphoma).

181.1.3.3 Feline Lymphoma

No breed or sex predilections have been identified. Age and its association with FeLV status have been discussed previously. In general, cats are more likely than dogs to present with clinical illness; 75% or more present with substage b signs.[17,18] The clinical presentation of LSA in cats depends on the anatomic sites involved. Cats with alimentary LSA or large granular lymphocyte LSA present with varying degrees of weight loss, unkempt haircoat, inappetence, chronic diarrhea, and vomiting. Cats with mediastinal disease are often in severe respiratory distress due to the effects of an intrathoracic mass or the presence of significant pleural effusion. Cats with renal LSA may present with polyuria/polydipsia secondary to renal failure. In the case of nasal LSA, sneezing, chronic serosanguineous nasal discharge, exophthalmos, and facial deformity are common presentations. Cats with FeLV-associated LSA are more likely to present with pale mucous membranes as a result of anemia.

Figure 181-2 Cutaneous T-cell lymphoma (mycosis fungoides) in a dog.



181.1.4 Diagnosis

181.1.4.1 Physical Examination

A thorough physical examination should include palpation of all assessable lymph nodes and a rectal examination in the dog. The clinician should inspect the mucous membranes for pallor or petechiae indicative of anemia or thrombocytopenia secondary to myelophthisis and should look for evidence of major organ failure, including the presence of icterus or uremic ulcers. Abdominal palpation may reveal organomegaly, intestinal wall thickening, or mesenteric lymphadenopathy. The presence of a mediastinal mass and/or pleural effusion may be suspected based on thoracic compression in cats and auscultation in both dogs and cats. An ophthalmic examination, including funduscopic assessment, may reveal abnormalities (e.g., uveitis, retinal hemorrhage, ocular infiltration) in approximately one third to one half of dogs with LSA.[26]

181.1.4.2 Hematologic Abnormalities

A complete blood count (CBC), including a numeric platelet count, is a necessary part of any evaluation of dogs or cats suspected of having LSA. Hematologic abnormalities occur in most cases of multicentric LSA.[27] Anemia, when present, is usually normocytic, normochromic, and nonregenerative, reflecting anemia of chronic disease. Regenerative anemias may reflect concomitant blood loss or hemolysis. Cats with FeLV-associated disease may have a macrocytic anemia. If significant myelophthisis is present, the anemia may be accompanied by thrombocytopenia and leukopenia. Circulating atypical lymphocytes may be indicative of bone marrow involvement and leukemia. It is important to differentiate multicentric LSA with bone marrow involvement (i.e., stage V disease) from primary lymphoblastic leukemia (discussed later in

this chapter), because these two diseases have entirely different prognoses. Hypoproteinemia is more commonly observed in animals with alimentary LSA.

Bone marrow aspiration cytology is recommended for staging because of the prognostic significance of marked marrow involvement; it is also recommended for cases in which LSA is suspected but has not yet been documented.

181.1.4.3 Serum Biochemical Abnormalities

The serum biochemical abnormalities seen in LSA often reflect the anatomic site involved. In addition, approximately 15% of dogs with LSA (40% of dogs with mediastinal involvement) are hypercalcemic, often owing to the ectopic production of parathyroid hormone–related peptide.[25,27,28] In cases of hypercalcemia of unknown origin, LSA should always be considered high on the differential disease list, and diagnostics directed at this possibility should be undertaken. In addition, the presence of hypercalcemia can serve as a marker for response to therapy. Elevations in blood urea nitrogen and serum creatinine can occur secondary to renal infiltration with tumor, hypercalcemic nephrosis, or dehydration. Liver-specific enzyme or bilirubin elevations may result from hepatic parenchymal infiltration. Serum globulin elevations, usually monoclonal, occur infrequently with B cell–derived LSA.

181.1.4.4 Retroviral Status

In the cat, retroviral screening (i.e., FeLV and FIV) is important from diagnostic, prognostic, and husbandry standpoints.

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The relative frequency of FeLV associations is presented in Table 181-2.

181.1.4.5 Imaging

Imaging (radiographic, ultrasonographic, or computed tomography [CT]) may be important for diagnosis, especially in cases lacking peripheral lymphadenopathy. Imaging is equally important for clinical staging (i.e., determining the extent of disease), because results may significantly affect the overall prognosis and alter the caregiver's willingness to pursue therapy.

Abnormalities on thoracic radiographs are noted in approximately two thirds to three fourths of dogs with LSA[29,30]; these include one third with evidence of pulmonary infiltrates (Figure 181-3) and two thirds with thoracic lymphadenomegaly. It is important to note that 20% of dogs present with cranial mediastinal lymphadenopathy, which correlates negatively with both remission and survival duration.[29]

Abdominal radiographs or ultrasound may reveal evidence of sublumbar/mesenteric lymph node, spleen, or liver involvement in approximately 50% of dogs. Abdominal ultrasound is most important in cats when intestinal LSA is suspected.

Special studies, including contrast studies of the gastrointestinal tract, CT or myelographic studies of the central nervous system, and skeletal radiograpic/scintigraphy surveys are reserved for cases in which involvement of the appropriate anatomic site is suspected.

In the authors' practice, for the typical cases of canine multicentric LSA, imaging is limited to thoracic radiographs, because there is no prognostic difference between dogs with stage III and stage IV disease (i.e.,

liver/spleen involvement); however, the presence of cranial mediastinal lymphadenopathy is of prognostic significance.[29]

181.1.4.6 Cytologic and Histopathologic Diagnosis

Microscopic conformation of LSA is the cornerstone of diagnosis in both cats and dogs. Fine needle aspirate (FNA) cytologic assessment by a skilled clinical pathologist is often adequate to make a diagnosis of LSA in dogs; however, conclusive histologic conformation is the gold standard. The predominance of a homogenous population of immature lymphoid cells is suggestive of LSA (Figure 181-4), although small cell variants do exist. Avoidance of nodes draining reactive areas (e.g., submandibular nodes in the presence of periodontal disease) is recommended, because reactive hyperplasia may mask (or mimic) the true neoplastic condition.

Figure 181-3 Lateral thoracic radiographic projection of a dog illustrating interstitial pulmonary infiltration with tumor typical of lymphoma at this site.

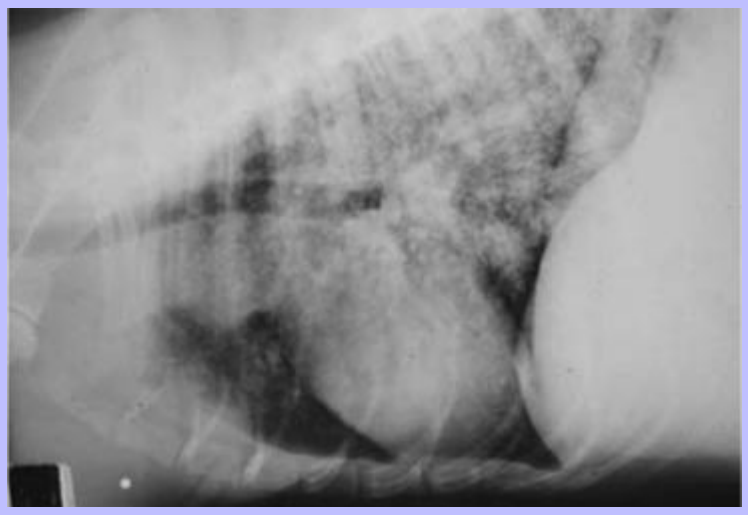
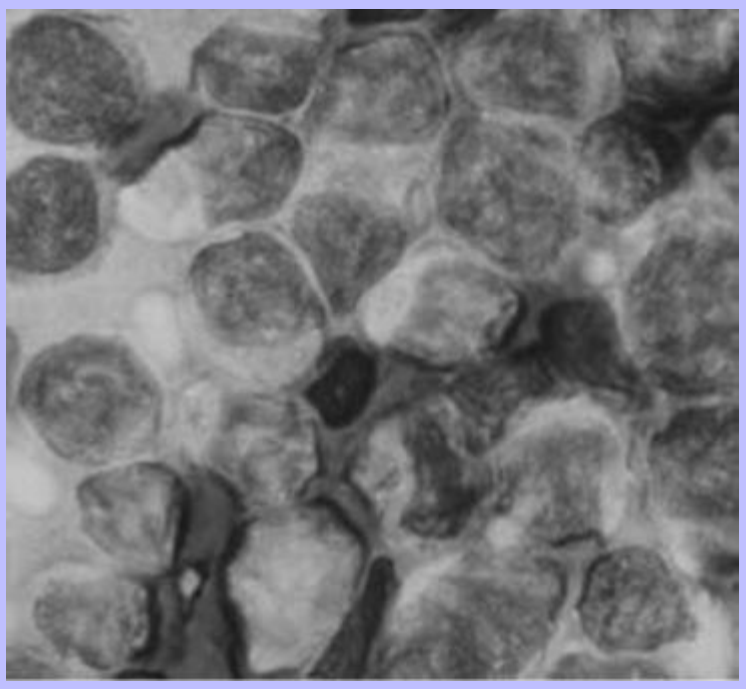


Figure 181-4 Fine needle aspirate cytology (Wright-Giemsa stain, ×1000) of a peripheral lymph node in a dog with high-grade lymphoma. The node is effaced with an homogenous population of immature lymphoid cells.



In the cat, FNA assessment alone is not sufficient in most cases because of the difficulties encountered in distinguishing LSA from benign hyperplastic lymph node syndromes unique to the species. These syndromes include idiopathic peripheral lymphadenopathy, plexiform vascularization of lymph nodes, and peripheral lymph node hyperplasia of young cats.[31–34] In these cases, whole lymph node excision is preferred, because evaluation of orientation, invasiveness, and architectural abnormalities may be necessary for diagnosis.

Besides their role in confirming a diagnosis of LSA, histologic and cytologic samples can be analyzed by various histochemical and immunohistochemical techniques to determine the immunophenotype (B cell versus T cell), tumor proliferation rates (e.g., Ki-67, proliferating cell nuclear antigen [PCNA], argyrophilic nucleolar organizer regions [AgNOR]), and histologic subtype (high-, intermediate-, or low-grade tumors).[9,15,16,35–38] The availability of such analysis is increasing; however, currently only immunophenotype in dogs is consistently predictive of prognosis. Histologic assessment of markers of multidrug resistance and apoptotic pathways (e.g., P-glycoprotein, p53) are currently being evaluated in dogs and cats with LSA, but their significance requires further evaluation.[7,37,39–43]

Additional site-specific cytologic or histologic assessments may be warranted when extranodal sites are suspected. Thoracocentesis followed by cytologic evaluation of pleural fluid is often diagnostic in cats with mediastinal LSA but is less likely to be of value in dogs with effusions secondary to mediastinal

involvement. Conversely, cerebrospinal fluid (CSF) analysis is more commonly helpful in dogs than cats with CNS LSA because the more common spinal form of LSA in cats is generally extradural.[44,45] In cats suspected of having CNS LSA, bone marrow and renal involvement are often present, and cytologic assessment of these organs is generally more easily attainable than CNS sites.

181.1.5 Differential Diagnosis

The differential diagnoses for LSA, which vary with the anatomic form of the disease, are presented in Table 181-3.

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Table • 181-3 Common Differential Diagnoses for Lymphoma

ANATOMIC FORM	DIFFERENTIAL LIST
Generalized lymphadenopathy	•Disseminated infections (e.g., bacterial, viral, rickettsial, parasitic, and fungal) •Immune-mediated disorders (e.g., lupus, polyarthritis, vasculitis, dermatopathy) •Other hematopoietic tumors (e.g., leukemia, multiple myeloma, malignant or systemic histiocytosis) •Tumors metastatic to nodes •In cats, many benign reactive hyperplastic syndromes (see text)
Alimentary	•Infiltrative enteritis (e.g., lymphocytic, plasmacytic enteritis) •Nonlymphoid intestinal neoplasms •Granulomatous enteritis •Granulated round cell tumors in cats •Gastrointestinal mast cell tumors in cats
Cutaneous	•Infectious dermatitis (e.g., advanced pyoderma) •Immune-mediated dermatitis (e.g., pemphigus) •Other cutaneous neoplasms
Mediastinal	•Thymoma •Heart base tumor (chemodectoma) •Ectopic thyroid tumor •Pulmonary lymphomatoid granulomatosis •Granulomatous disease (e.g., hilar lymphadenopathy with blastomycosis)

181.1.6 Therapy

Untreated dogs and cats live an average of 4 to 6 weeks once a diagnosis has been established. In general, LSA is a systemic disease and requires a systemic approach to therapy (i.e., chemotherapy). Exceptions to this occur in cases of solitary site or extranodal LSA, for which local therapy involving either surgery or radiotherapy may be indicated.

181.1.6.1 Systemic Chemotherapy in Dogs with Lymphoma

There are almost as many chemotherapy protocols for dogs with LSA as there are veterinary oncologists. This likely reflects our inability to achieve cure in the majority of cases. LSA in the dog can be an initially gratifying disease to treat, because remission rates approach 80% to 90% with available combination chemotherapy protocols, and quality of life is generally excellent during the period of remission.[46] However,

the majority of dogs eventually succumb to drug-resistant recurrence of the disease, on average, 1 year after diagnosis.

Due to the large and ever increasing number of available chemotherapeutic protocols, several factors should be considered and discussed with caregivers when choosing a protocol, which can be done on a case-by-case basis. These factors include the cost, time commitment involved, efficacy, toxicity, and experience of the clinician with the protocols in question. With the availability of generic drugs, chemotherapy protocols are becoming affordable to a larger segment of veterinary clientele. In general, more complex combination chemotherapy protocols are more expensive, more time-consuming (i.e., requiring repeated office visits and closer monitoring), and more likely to result in toxicity than are simpler, single-agent protocols. However, as a general rule, more complex combination protocols result in longer remission and survival durations than do single agent protocols.

A complete listing of all available chemotherapy protocols for dogs with LSA is beyond the scope of this review, therefore the reader is referred to a recent review and other reports.[11,16,46] This discussion presents an example of the combination protocol used by the authors and the most widely used single agent protocol. Most complex combination protocols are modifications of CHOP protocols initially designed for human oncologic use. The CHOP protocol represents combinations of cyclophosphamide *(C),* doxorubicin (hydroxydaunorubicin *[H]*), vincristine (Oncovin *[O]*), and prednisone *(P)*. Regardless of which CHOP-based protocol is used, the overall median remission and survival times are approximately 8 and 12 months, respectively.[12,13,46,47] Approximately 20% to 25% of treated dogs are alive 2 years or longer after initiation of these protocols. Response rates and the length of response vary, depending on the presence or absence of prognostic factors discussed under Prognosis. Historically, the treatment protocol begins with an intensive *induction phase,* during which drugs are given weekly; this is followed by a *maintenance phase,* during which treatment intervals are slowly spread out and the drugs are given less frequently.

An important question is how long chemotherapy should be continued beyond the point at which complete remission has been achieved; that is, how long should the maintenance phase last or, for that matter, should maintenance therapy be used at all? In most human LSA protocols, after a 6-month induction phase, no benefit has been shown with continued maintenance therapy, therefore no further therapy is given until recurrence is observed. Recent evidence suggests that use of a DOX-containing, multiagent protocol (Table 181-4) for 6 months, followed by monthly re-evaluation, results in remission and survival times similar to those achieved with protocols involving a prolonged maintenance phase.[12,13]

The most effective and commonly used single agent chemotherapy protocol available for dogs with LSA is DOX.[11,48–50] DOX is administered at a dosage of 30 mg/m^2 given intravenously every 3 weeks for five treatments. Response is observed in 75% to 80% of cases, and median remission and survival durations of approximately 5 and 7 months, respectively, are reported. The advantages of this single agent protocol are that it is less time-consuming and expensive, and fewer hospital visits are required. Because only one drug is used, any side effects encountered are attributable to that drug.

If financial or other client concerns preclude the use of more aggressive systemic chemotherapy, prednisone therapy alone (2 mg/kg given orally daily) often results in short-lived remissions of approximately 1 to 2 months. In these cases, it is advisable to inform clients that if they should decide to pursue more aggressive therapy at a later date, dogs with prior prednisone therapy may be more likely to have drug-resistant disease and to experience shorter remission and survival durations with subsequent chemotherapy protocols. This is especially true after long-term prednisone use or in dogs that have experienced a recurrence while receiving prednisone.[51]

Modifications in the chemotherapy dose and/or frequency may be necessary under conditions of excess toxicity, as discussed in Chapters 178 and 179. When hypercalcemia is present, if the dog has substage A disease and continues to eat and drink, ancillary therapy for the hypercalcemia is usually unnecessary, because initiation of chemotherapy results in eucalcemia within a few days. If the animal is ill, azotemic, or showing signs attributable to hypercalcemia, therapy directed specifically at hypercalcemia (see Chapter 237) concurrent with the initiation of systemic chemotherapy is warranted.

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Table • 181-4 University of Wisconsin–Madison Combination Chemotherapy Protocol for Dogs With Lymphoma

TREATMENT WEEK	DRUG, DOSAGE, AND ROUTE	TREATMENT WEEK	DRUG, DOSAGE, AND ROUTE
1	Vincristine: 0.5–0.7 mg/m^2 IV[a] L-asparaginase: 400 U/kg SC[b] Prednisone: 2 mg/kg PO[c]	11	Vincristine: 0.5–0.7 mg/m^2 IV
2	Cyclophosphamide: 250 mg/m^2 IV Prednisone: 1.5 mg/kg PO	13	Cyclophosphamide: 250 mg/m^2 IV
3	Vincristine: 0.5–0.7 mg/m^2 IV Prednisone: 1 mg/kg PO	15	Vincristine: 0.5–0.7 mg/m^2 IV
4	Doxorubicin: 30 mg/m^2 IV Prednisone: 0.5 mg/kg PO	17	Doxorubicin: 30 mg/m^2 IV
6	Vincristine: 0.5–0.7 mg/m^2 IV	19	Vincristine: 0.5–0.7 mg/m^2 IV
7	Cyclophosphamide: 250 mg/m^2 IV	21	Cyclophosphamide: 250 mg/m^2 IV
8	Vincristine: 0.5–0.7 mg/m^2 IV	23	Vincristine: 0.5–0.7 mg/m^2 IV
9*	Doxorubicin: 30 mg/m^2 IV	25†	Doxorubicin: 30 mg/m^2 IV

NOTE: A CBC should be performed before each chemotherapy treatment. If the neutrophil count is less than 2000 cells/μL, the clinician should wait 5 to 7 days and then repeat the CBC; the drug is administered if the neutrophil count has risen above the 2000 cells/μL cutoff.

* If the patient is in complete remission at week 9, treatment continues to week 11.

† If the patient is in complete remission at week 25, therapy is discontinued and the dog is rechecked monthly for recurrence.

181.1.6.2 Systemic Chemotherapy in Cats with Lymphoma

Several combination chemotherapy protocols for cats have been reported and reviewed previously.[17–19,52] It has become clear that the addition of DOX to COP-based protocols (*C,* cyclophosphamide; *O,* Oncovin [vincristine]; *P,* prednisone) is superior to COP alone in the cat.[17,52] However, in one European study, cats receiving COP experienced remission and survival durations comparable to cats treated with CHOP protocols in North America.[19] In contrast to dogs, DOX does not appear to be as effective single agent for

feline LSA.[53] In general, cats do not enjoy as high a response rate or as long remission and survival durations as dogs with LSA. Complete response rates vary between 50% and 75%, and overall median remission and survival durations are approximately 4 to 8 and 6 to 8 months, respectively.[17,19,54] However, a larger proportion of cats (30% to 40%) that achieve a complete response with combination chemotherapy enjoy more durable overall remission and survival times (i.e., 2 years) than that seen in dogs. Response rates and length of response vary according to the presence or absence of prognostic factors discussed under Prognosis. The modified CHOP-based protocol preferred by the authors for cats is represented in Table 181-5.

A recent preliminary report suggests that cats with low-grade gastrointestinal LSA may respond favorably and enjoy comparably long survival times using a protocol of oral chlorambucil (15 mg/m^2 given daily for 4 days, repeated every 3 weeks) and prednisone.[55]

Cats with large granular LSA or globule leukocyte tumors tend to respond more poorly to chemotherapy, although durable responses have been reported.[20]

181.1.6.3 Reinduction or Rescue Therapy

Ultimately, most dogs and cats with LSA successfully treated with chemotherapy relapse. This often represents a recrudescence of the tumor in a more drug-resistant form. Evidence suggests that recurrent LSA in dogs is more likely to express the gene encoding the P-glycoprotein transmembrane drug pump that is often associated with multiple drug resistance.[39–41] At the first recurrence of LSA, it is recommended that reinduction first be attempted by repeating of the induction protocol that was initially successful. In general, the likelihood of a response and the length of the response are half those seen with the initial therapy; however, a subset of animals will enjoy long-term reinductions. Recently it was shown that dogs that reached the observation phase using a no-maintenance protocol had a very high likelihood of a second response to the identical protocol.[13]

If reinduction fails or if the patient does not respond to the initial induction, so-called rescue agents or rescue protocols can be utilized. These drugs or drug combinations typically are not found in the standard CHOP protocol and are withheld for use in drug-resistant cases. A number of rescue protocols have been reported in the veterinary literature and have previously been reviewed.[46] The most common protocols used in dogs include single agent use or combination use of Actinomycin-D, mitoxantrone, lomustine (CCNU), DOX (if DOX was not part of the original induction protocol), DOX/dacarbazine combination, D-MAC (*D,* dexamethasone; *M,* melphalan; *A,* Actinomycin-D; *C,* cytosine arabinoside) and MOPP (*M,* methclorethamine; *O,* Oncovin; *P,* procarbazine; *P,* prednisone). Mitoxantrone, DOX, and MOPP have also been advocated in cats with resistant relapse. In general, overall rescue response rates of 25% to 50% are reported; however, these responses are usually not durable. Median response durations of 1.5 to 2 months are the norm. A small subset of animals will enjoy longer remission durations.

181.1.6.4 Therapy for Extranodal Lymphoma

If extranodal involvement is part of a more generalized or multicentric disease process, the systemic therapies previously discussed should be instituted. Conversely, if the extranodal site is solitary and not part of a multicentric presentation, local therapy may be performed without institution of systemic chemotherapy. In these latter cases, strict adherence to staging diagnostics, including bone marrow evaluation and

radiographic/ultrasonographic imaging of the thorax and abdomen, are warranted to ensure that the process is localized. If the disease is confined, local surgery and/or radiotherapy is often effective (Figure 181-5). Clients should be informed that systemic LSA is likely to occur months to years later, and a regular recheck schedule should be instituted. It is the authors' opinion that systemic therapy should be withheld until systemic disease has been documented. 738

Table • 181-5 University of Wisconsin–Madison Combination Chemotherapy Protocol for Cats With Lymphoma

TREATMENT WEEK	DRUG, DOSAGE, AND ROUTE	TREATMENT WEEK	DRUG, DOSAGE, AND ROUTE
1	Vincristine: 0.5–0.7 mg/m^2 IV L-asparaginase: 400 U/kg SC Prednisone: 2 mg/kg PO	11	Vincristine: 0.5–0.7 mg/m^2 IV
2	Cyclophosphamide: 200 mg/m^2 IV Prednisone: 2 mg/kg, PO	13†	Cyclophosphamide: 200 mg/m^2 IV
3	Vincristine: 0.5–0.7 mg/m^2 IV Prednisone: 1 mg/kg PO	15	Vincristine: 0.5–0.7 mg/m^2 IV
4	Doxorubicin: 25 mg/m^2 IV Prednisone: 1 mg/kg, PO*	17	Doxorubicin: 25 mg/m^2 IV
6	Vincristine: 0.5–0.7 mg/m^2 IV	19	Vincristine: 0.5–0.7 mg/m^2 IV
7†	Cyclophosphamide: 200 mg/m^2 IV	21†	Cyclophosphamide: 200 mg/m^2 IV
8	Vincristine: 0.5–0.7 mg/m^2 IV	23	Vincristine: 0.5–0.7 mg/m^2 IV
9‡	Doxorubicin: 25 mg/m^2 IV	25§	Doxorubicin: 25 mg/m^2 IV

NOTE: A CBC should be performed before each chemotherapy treatment. If the neutrophil count is less than 2000 cells/L, the clinician should wait 5 to 7 days and then repeat the CBC; the drug is administered if the neutrophil count has risen above the 2000 cell/μ L cutoff.

† If renal or CNS lymphoma is present, substitute cytosine arabinoside (600 mg/m^2 SC bid over 2 days) at these treatments.

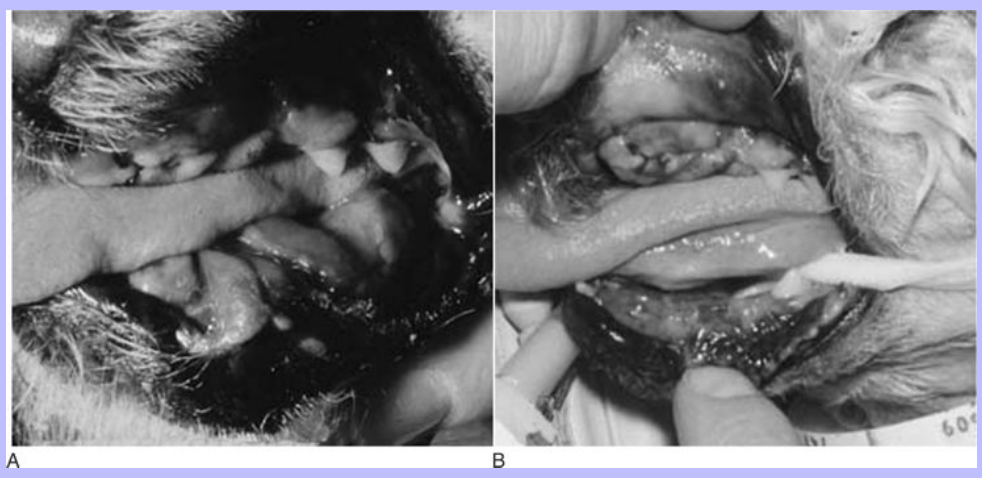
* Prednisone (1 mg/kg, PO) is continued every other day from this point on.

‡ If the patient is in complete remission at week 9, continue to week 11.

§ If the patient is in complete remission at week 25, therapy is discontinued and the cat is rechecked monthly for recurrence.

In cases in which CNS involvement is part of a more generalized process, penetration by chemotherapeutic drugs through the blood-brain barrier (BBB) may be a concern, and additional therapies are recommended. In standard CHOP protocols, only prednisone consistently penetrates the BBB. The addition of cytosine arabinoside, which achieves therapeutic CSF levels, to a CHOP-based protocol is recommended in such cases. Radiotherapy can also be effective, directed either to the entire neural axis (multifocal CNS lymphosarcoma) or to specific CNS locations (solitary central or spinal LSA). Cytoreductive surgery has been attempted in a small number of cases of extradural LSA in both cats and dogs, with mixed results.[44–46] 738 739

Figure 181-5 **A,** Solitary gingival lymphoma in a dog staged negative for systemic involvement. **B,** The same dog 6 months after external beam radiation therapy (48 Gy total dose). A complete response and long-term survival were achieved.



Cutaneous LSA in solitary sites has been effectively treated with local surgery or radiotherapy, but the likelihood of ultimate systemic involvement is high. Multiple cutaneous lesions are more commonly encountered (see Figure 181-2), and systemic therapy is necessary. In general, cutaneous LSA tends to be less responsive to chemotherapy than multicentric LSA, and clinical signs can wax and wane considerably over time. Responses have been reported with oral cis-retinoic acid therapy (Accutane®, 1 to 3 mg/kg given orally twice a day), Doxil® (a liposome encapsulated form of DOX), L-asparaginase, dacarbazine, lomustine, topical nitrogen mustard, and standard CHOP-based protocols.[57–60] Response rates are approximately 40% to 50%, and long-term survival is uncommon.

181.1.7 Prognosis

181.1.7.1 Prognostic Factors in Dogs

A list of factors known or suspected to affect remission rates and/or remission and survival durations in dogs with LSA is presented in Table 181-6. Age and breed do not affect the duration of remission or survival, and most studies fail to correlate the clinical stage to the prognosis except in dogs with marked stage V disease; that is, if bone marrow is heavily infiltrated, if overt leukemia is present, or if peripheral cytopenias exist secondary to myelophthisis. The two factors that most consistently correlate with the prognosis in dogs with LSA are the immunophenotype and the WHO substage.[9–14,16,29] Many reports have confirmed that dogs with CD3 immunoreactive tumors (i.e., T cell derived) have significantly shorter remission and survival durations (Figure 181-6). Similarly, dogs presenting with substage b disease (i.e., clinically ill) do poorly compared with dogs with substage a disease (Figure 181-7).

Other factors reported to correlate with the prognosis are less consistent; that is, they are not found to correlate in all studies, are preliminary reports, or contradictory reports exist in the literature. Some correlate after univariate analysis; however, when scrutinized by multivariate analysis (in which all factors are considered together), they are no longer significant. An example is the presence of hypercalcemia. In several reports, the presence of hypercalcemia is associated with a poor prognosis; however, if multivariate analysis is performed, hypercalcemia is no longer predictive, primarily because dogs with hypercalcemia are more likely to have T cell–derived LSA, which is a much stronger prognostic factor.

Table • 181-6 Factors Known or Suspected to Affect the Prognosis in Dogs With Lymphoma

FACTOR	STRENGTH OF ASSOCIATION	COMMENTS
World Health Organization (WHO) clinical stage	Weak	This factor is likely predictive of the outcome only in stage V disease with marked marrow involvement.[16]
WHO substage	Strong	Dogs with substage b disease have shorter remission and survival durations.[9,10,11,13,14]
Immunophenotype	Strong	Dogs with T-cell lymphoma have shorter remission and survival durations than dogs with B-cell tumors[9,14,16,19,29]
Hypercalcemia	Moderate	Poorer prognosis is not independent; rather, it is more likely due to T-cell association.[10,11]
Prolonged steroid pretreatment	Moderate	Most studies show previous steroid use shortens response durations.[9,10,29,113]
Sex	Weak	Some studies report that males have shorter remission and survival durations; other reports are contradictory.[9,35]
Proliferation rate Cranial mediastinal lymphadenomegaly	Weak Moderate to strong	Reports are contradictory.[25,29] Large compilation of cases shows association with shorter remission and survival durations; other reports arecontradictory.[16]
Histologic grade	Moderate	Low-grade tumors are less likely to respond to chemotherapy; however, patients may live longer despite this.[40,41]
P-glycoprotein expression	Moderate	This factor is associated with poor response rates and shorter remission and survival durations.

181.1.7.2 Prognostic Factors in Cats

Unlike in the dog, CD3 immunoreactivity has not been established as a negative prognostic factor in the cat.[17] This may reflect the wider variations in frequency of the different anatomic forms of LSA encountered in cats and the difficulty of distinguishing differences. Factors most strongly associated with a more positive prognosis in cats appear to be complete response to therapy (which unfortunately cannot be determined prior to treatment), negative FeLV status, early clinical stage, substage a disease, and the addition of DOX to the treatment protocol.[17,19,52,54,61] Early reports may contradict more recent studies, partly because FeLV associated LSA is declining, and early literature may not equate to more recent populations studied.[19] In

general, FeLV-negative cats that achieve a complete response on CHOP-based protocols have a high likelihood of long-term survival, with approximately 35% alive at 1.5 years after diagnosis. Cats with nasal LSA, overall, have the best prognosis, because local radiotherapy (or chemotherapy, if radiotherapy is not available) results in excellent control, with median survival times approaching 1.5 years.

181.1.7.3 The Future of Lymphoma Therapy

Based on the similarity of results achieved using the many and varied combination chemotherapy protocols, it is unlikely that currently available chemotherapeutics will significantly improve the outcome in dogs and cats with LSA. All combination protocols reported to date stop short of the same 10-to 12-month median survival "brick wall." Advances in remission and survival durations await the development of new agents or novel treatment modalities. Mechanisms of avoiding or abrogating multidrug resistance, enhancing tumor apoptosis (programmed cell death), utilization of chemotherapy/radiotherapy combinations, and novel immunomodulatory therapies (e.g., antibodies, vaccination strategies) are all active areas of investigation in both human and veterinary oncology. As practitioners who experience both the gratification that comes with high initial response rates and the frustration of equally high relapse rates, we eagerly await the advancement of these treatment modalities.

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Figure 181-6 Kaplan-Meier survival duration estimates for a group of 55 dogs with lymphoma treated with an identical CHOP-based combination chemotherapy protocol at the University of Wisconsin. Dogs with CD3 immunoreactive (T-cell) lymphoma had significantly shorter survival durations.

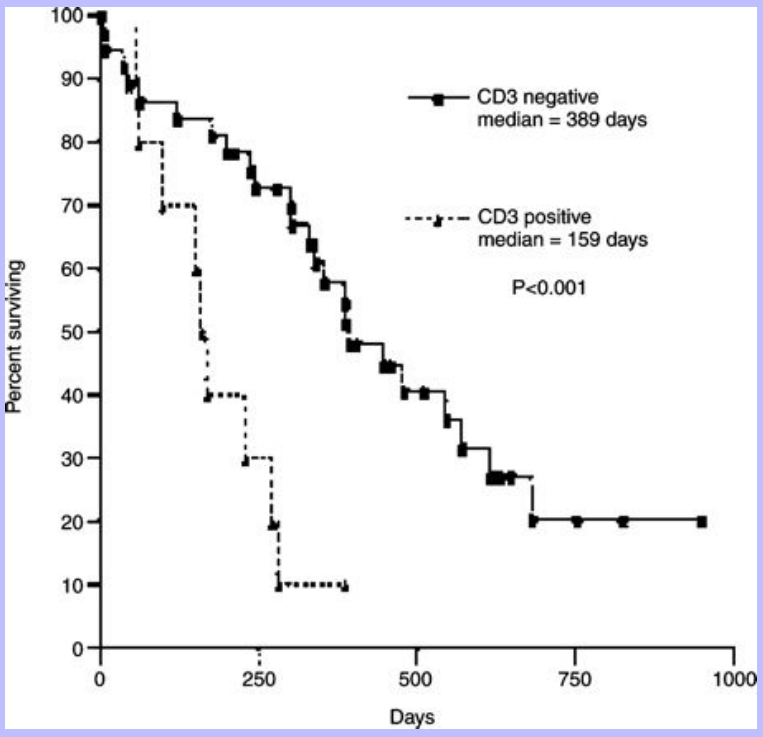
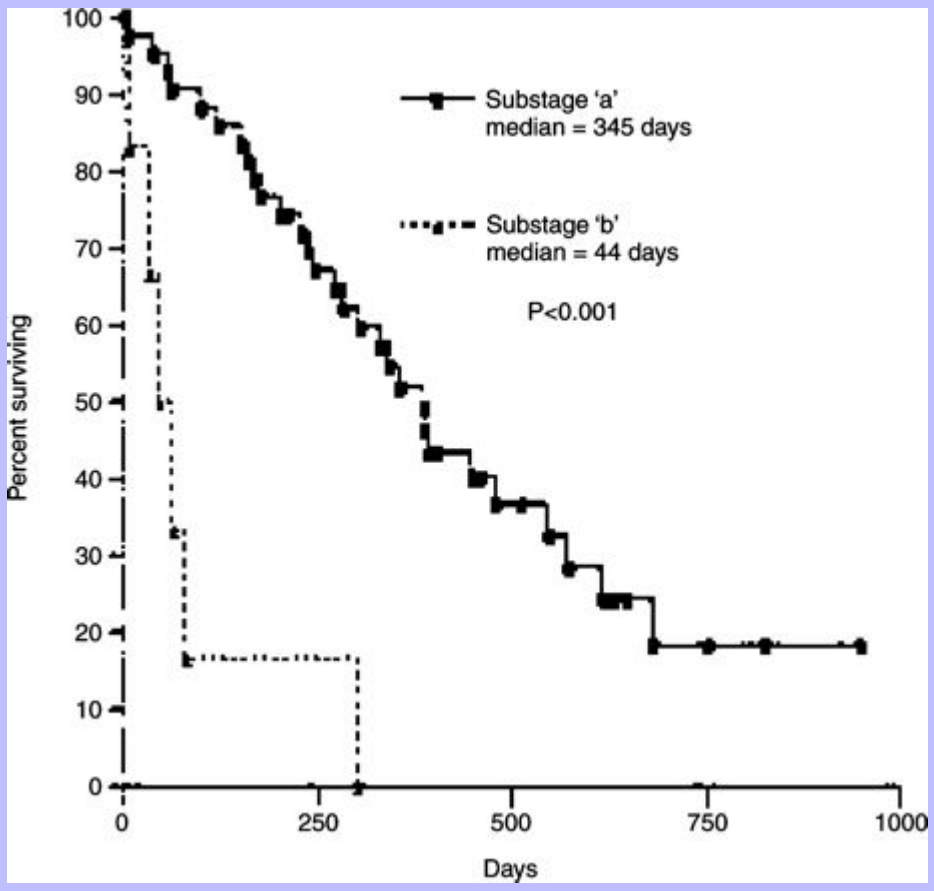


Figure 181-7 Kaplan-Meier survival duration estimates for a group of 55 dogs with lymphoma treated with an identical CHOP-based combination chemotherapy protocol at the University of Wisconsin. Dogs with substage b disease (i.e., those that were clinically ill) had significantly shorter survival durations.



181.2 LYMPHOID LEUKEMIA

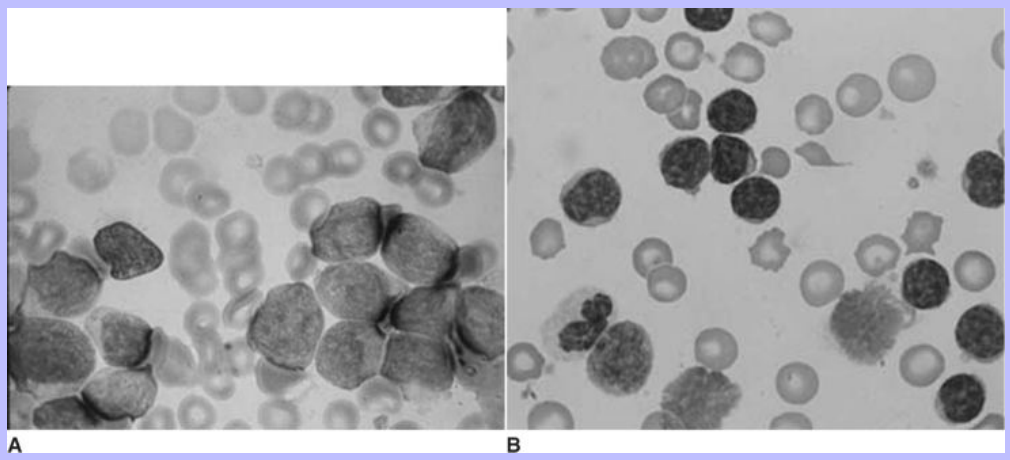
Leukemia is defined as a proliferation of neoplastic cells in the bone marrow. An important distinction is that by definition, the malignant cells may or may not be present in the peripheral blood circulation. Categorization of lymphoid leukemia into acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL) is important from a diagnostic, prognostic, and therapeutic standpoint (Figure 181-8). Both forms are relatively rare in companion animals.[62–66]

181.2.1 Acute Lymphoblastic Leukemia

ALL is characterized by proliferations of morphologically immature lymphoblasts in the bone marrow or peripheral blood. ALL may be confused with multicentric LSA in dogs that also have advanced stage V disease (i.e., secondary bone marrow infiltration). However, the primary component of ALL is leukemia. The clinical course is rapid, progressive, and poorly responsive to therapy.[62,64]

No breed or sex predilection exists for dogs with ALL. Middle-aged to older dogs are typically affected. Cats with ALL are usually younger and are often FeLV antigenemic.[66] Presentations are nonspecific and commonly include lethargy, weight loss, intermittent pyrexia, hepatosplenomegaly, and nonspecific abdominal pain. Neurologic signs, both central and peripheral, have been reported. The majority of affected animals are anemic, and varying degrees of thrombocytopenia and leukopenia are commonly present.

Figure 181-8 **A,** Peripheral blood smear (Wright-Giemsa stain, ×1000) from a dog with acute lymphoblastic leukemia (ALL). Note the morphologically immature lymphoblasts characteristic of ALL. **B,** Peripheral blood smear (Wright-Giemsa stain, ×1000) of a dog with chronic lymphocytic leukemia (CLL). Note the morphologically mature lymphocytes characteristic of CLL. (Courtesy Dr. Karen Young, University of Wisconsin—Madison.)



The diagnosis is confirmed by documentation of marked lymphoblast proliferation in the bone marrow or peripheral blood. Bone marrow aspirate or core biopsy and a complete blood count are usually all that are required for diagnosis. Aspiration cytology of lymph node and involved organs and conformation of retroviral status in cats may be contributory. The presence of 30% or more lymphoblasts in the bone marrow is considered diagnostic. Approximately 10% of cases are classified as “aleukemic” leukemia because bone marrow infiltration is present but peripherally circulating lymphoblasts are absent. ALL may be further differentiated clinically from stage V multicentric LSA by its more rapid progression, lack of significant lymphadenopathy in approximately 50% of cases, poor chemoresponsiveness, and short survival times.

The prognosis is generally poor for dogs and cats with ALL.[62,64–66] Combination chemotherapy protocols designed to treat LSA result in remission in approximately 25% of cases, but remission durations are usually quite short, and survival times of more then a few months are rare. A short-term response to low-dose cytosine arabinoside (10 mg/m^2 given subcutaneously twice a day) has been reported in a cat.[67]

181.2.2 Chronic Lymphocytic Leukemia

CLL is characterized by the proliferation of phenotypically mature lymphocytes rather than lymphoblasts. Interestingly, recent immunophenotypic and clonotypic analysis has shown that the majority of CLL cases in dogs arise from CD8+ T cells, many of which show a large granular lymphocytic morphology.[68] CLL is reported primarily in older dogs and cats. The clinical presentation is nonspecific and may include lethargy, organomegaly, pyrexia, polyuria/polydipsia, hemorrhage (from thrombocytopenia), intermittent lameness, and collapse.[63] Most dogs present with mild to moderate lymphadenopathy, splenomegaly, and pale mucous membranes. However, asymptomatic lymphocytosis may be detected on routine geriatric or preanesthetic screening in some animals.

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A normocytic, normochromic, nonregenerative anemia usually accompanies a marked mature peripheral lymphocytosis, which may range from 10,000 to 300,000/μL or more. Thrombocytopenia and neutropenia may be present as a result of myelophthisis. Although a minority of cases present with hyperglobulinemia, after immunoelectrophoresis, approximately half have evidence of a monoclonal gammopathy, often with Bence Jones proteinuria. No association with FeLV infection has been documented in the cat. Unlike ALL, CLL can have a protracted clinical course and is usually initially responsive to chemotherapy.[63] Treatment is not instituted unless significant clinical signs, organomegaly, or peripheral cytopenias (anemia, neutropenia, thrombocytopenia) are present that affect or threaten the animal's quality of life. Cases of CLL have been followed for many months without the necessity for therapy. If therapy is indicated, chlorambucil (*dogs:* 0.2 mg/kg given orally daily for 10 days, then 0.1 mg/kg/day; *cats:* 2 mg/cat given orally every other day) is combined with prednisone (2 mg/kg given orally daily). The dosage is adjusted based on the response. Approximately 75% of animals respond and enjoy a normal quality of life, with a median survival time of approximately 1 year. Although the prognosis is good in the short term, eventually CLL becomes resistant to therapy or progresses to ALL. When this happens, lymphoblasts replace mature lymphocytes as the abnormally proliferating population, and survival is short.

181.3 NONLYMPHOID LEUKEMIAS AND MYELOPROLIFERATIVE DISORDERS

Myeloproliferative disorders (MPDs) are defined as a group of nonlymphoid bone marrow cell disorders in which proliferation of one, several, or all of the marrow cell lines occurs. The disorders may represent preneoplastic or neoplastic conditions that may have a benign or malignant course. These are rare conditions in companion animals. With few exceptions (see Polycythemia Vera [Primary Erythrocytosis], p. 743), the veterinary literature on MPDs is sparse at best and is composed almost entirely of single case reports. Our experience with MPDs, therefore, is almost exclusively anecdotal, and specific characterizations and therapeutic recommendations are lacking.

Table • 181-7 Myeloproliferative Disorders Reported in Dogs and Cats

CLASSIFICATION	CELL LINEAGE	SELECTED REFERENCES
Acute Myeloproliferative Disorders		
Acute myelogenous leukemia (AML)	Myeloblasts	64–66
Acute myelomonocytic leukemia (AMML)	Myeloblasts/monoblasts	64–66, 69–71
Acute monocytic leukemia (AmoL)	Monoblasts	64–66, 72
Acute megakaryoblastic leukemia (AmkL)	Megakaryoblasts	73–79
Erythroleukemia	Erythroblasts	66, 80
Chronic Myeloproliferative Disorders		
Chronic myelogenous leukemia (CML)	Neutrophils, late precursors	82–84
Primary thrombocythemia	Platelets	84, 85
Basophilic leukemia	Basophils and precursors	86, 87
Eosinophilic leukemia	Eosinophils and precursors	88, 89
Polycythemia vera	Erythrocytes	84, 90–94

181.3.1 Classification

In general, MPDs are classified first on the basis of the derivation of the cell in question and second on the degree of cellular differentiation. If the proliferating cell population is mature or microscopically typical of a well-differentiated bone marrow cell line, the disorder is classified as chronic; if an immature or poorly differentiated cell line is present, the disease is classified as acute. Table 181-7 lists the MPDs reported in the veterinary literature. Because pluripotent bone marrow stem cells are involved, one MPD may evolve into another, and more often than not, more than one cell line is involved in the same disorder.

181.3.2 Clinical Presentation

Animals with a chronic MPD may have no clinical signs until organ involvement or bone marrow myelophthisis results in systemic disease. Clinical signs in dogs with late-stage chronic MPD or acute MPD are generally nonspecific and can include organomegaly, pallor, sepsis, and hemorrhage from thrombocytopenia. Most MPDs have been associated with FeLV infection in cats.

181.3.3 Diagnosis

The diagnosis of MPD is based on demonstration of the proliferating cell line in the absence of non-neoplastic diseases associated with bone marrow hyperplasia or hypoplasia. Differential diagnoses therefore include chronic inflammatory diseases (e.g., ehrlichiosis), multicentric LSA, estrogen toxicity, lead poisoning and, in the case of essential or primary thrombocytosis, iron deficiency. Because many of the acute MPDs are poorly differentiated and/or represent combinations of cell lineages, light microscopic morphology often is insufficient to determine the specific cellular derivation. Histochemistry, immunohistochemistry, and flow cytometric analysis are ultimately necessary in many instances for precise classification. Several private and academic laboratories perform these analyses. A complete listing of available tests is beyond the scope of the present chapter; these have been reviewed elsewhere.[95,96]

181.3.4 Therapy

The acute MPDs are generally poorly responsive to single agent or combination chemotherapy protocols, therefore their prognosis is grave. Several agents and combinations have been tried, including DOX, cytosine

arabinoside, 6-thioguanine, and CHOP-based protocols.[64–66,76] Response rates are low, and overall survival times are generally short. If chemotherapy is pursued, aggressive supportive therapy is usually necessary and may include whole blood or blood-component therapy to address cytopenias secondary to myelophthisis, antibiotic support, and aggressive fluid therapy.

Chronic MPDs carry a guarded prognosis; however, initial durable responses to therapy are more likely than with an acute MPD. Therapy is not required until clinical signs or significant peripheral cytopenia develops. Hydroxyurea has been used successfully in the treatment of several types of chronic MPD, particularly polycythemia vera (see below), essential thrombocythemia, basophilic leukemia, and chronic myelogenous leukemia (CML).[81,85–87,97,98] In dogs with CML, hydroxyurea is administered at an initial dosage of 20 to 25 mg/kg given orally twice daily. This dosage is continued until the leukocyte count drops to less than 20,000 cells/μL, at which time the dosage is reduced to 10 to 15 mg/kg daily or switched to 50 mg/kg given orally once every 2 to 3 weeks. A common side effect of hydroxyurea therapy in dogs is onychomadesis (sloughing of the claw or toenail). In dogs that respond to hydroxyurea therapy, survival times of many months have been reported. Ultimately, many of the chronic MPDs shift into a terminal phase or *blast crisis,* in which a fatal acute leukemic phase is observed.

181.3.5 Polycythemia Vera (Primary Erythrocytosis)

Polycythemia vera (PV) is defined as an abnormal proliferation of erythroid precursors in the bone marrow; this occurs independent of erythropoietin (EP), and the cells follow a normal, orderly pattern of maturation. The result is an abnormally elevated packed cell volume, erythroid count, and blood hemoglobin level. PV must be differentiated from so-called relative polycythemia or secondary polycythemia. Relative polycythemia is a result of hemoconcentration secondary to severe dehydration, body fluid shifts, or acute splenic contraction in dogs. It is readily corrected with fluid-based therapies. Secondary polycythemia is defined as EP-mediated erythrocytosis. Conditions associated with secondary polycythemia include right-to-left cardiac shunts, congestive heart failure, severe chronic pulmonary disease, some forms of renal disease, and neoplasms that secrete EP or EP-like substances.

Middle-aged dogs and cats are typically affected.[84,90–94] Clinical signs and physical findings associated with PV include hyperemic mucous membranes, injected scleral and retinal vessels, weakness, exercise intolerance, frank hemorrhage (epistaxis, hematuria, melena), neurologic signs (dementia, seizures, paralysis, ataxia), and occasional splenomegaly. Cardiac or renal compromise may also be present. The majority of signs reported occur secondary to hyperviscosity syndrome, discussed at length in the plasma cell tumor portion of this chapter.

The diagnosis is made by documentation of significant erythrocytosis (60% to 75% hematocrit) with normal to decreased serum EP levels and the absence of conditions associated with relative or secondary polycythemia. Thoracic and abdominal radiographs, abdominal ultrasound, arterial blood gas determinations, bone marrow aspirate testing, and serum EP levels should be procured to rule out differentials. Erythroid hyperplasia with relatively normal patterns of maturation is found on bone marrow cytology. Radioactive chromium determinations of red blood cell mass may contribute to the diagnosis.

Therapy for PV involves reduction of the red blood cell mass and suppression of erythroid production in the bone marrow. Reduction of the red blood cell mass can easily be achieved by phlebotomy (15 to 20 cc/kg body weight) and reinfusion of the patient's plasma after removal of the red blood cells.[91–93] Several techniques can be used to suppress erythrocyte production, including the use of radioactive phosphorous (^{32}P) or, more commonly available, chemotherapy.[84,97] The antineoplastic drug of choice is hydroxyurea, although alkylating

agents such as melphalan, cyclophosphamide, and busulfan have also been used, with mixed results. Hydroxyurea therapy is instituted at a dosage of 20 to 25 mg/kg given orally twice a day in dogs (10 to 15 mg/kg in cats). Once the hematocrit is below 60%, hydroxyurea is given every other day. Complete blood counts must be carefully monitored for potential myelosuppression of other cell lineages. Most cases of PV respond to therapy, and survival times of a year or longer are the norm. Progression to leukemia is reported in some humans with the disease.

181.4 PLASMA CELL NEOPLASMS

Plasma cell neoplasms are defined as neoplastic proliferations of cells of the B-lymphocyte plasma cell lineage. This population is believed in most instances to be monoclonal (i.e., derived from a single cell), because it typically produces homogenous immunoglobulin. Plasma cell neoplasms include multiple myeloma, IgM (Waldenstrom's) macroglobulinemia, and solitary plasmacytoma (including solitary osseous plasmacytoma and extramedullary plasmacytoma). Multiple myeloma is the most important plasma cell neoplasm based on incidence and severity.

181.4.1 Multiple Myeloma

Multiple myeloma (MM) is responsible for approximately 8% of all canine hematopoietic tumors.[99] The true incidence of MM in the cat is unknown; however, it is much less common than in the dog.[100] In MM, malignant plasma cells produce an overabundance of a single type, or component, of immunoglobulin, which is referred to as the M-component. Rarely, biclonal immunoglobulin production has been reported.[101] The M-component may represent any class of immunoglobulin or only a portion of the molecule, such as the light-chain (Bence Jones protein) or heavy chain (heavy chain disease) of the molecule.

181.4.2 Etiology

The etiology of MM is for the most part unknown. Genetic predispositions, viral infections, chronic immune stimulation, and exposure to carcinogens have all been suggested as contributing factors.[102–104] MM has not been associated with either FeLV or FIV infection.

181.4.3 Pathophysiology

A wide array of pathologic abnormalities and related clinical syndromes can occur as a result of tumor infiltration of various organ systems, the presence of high levels of circulating M-component, or a combination thereof.

Hyperviscosity syndrome (HVS) represents one or a constellation of clinicopathologic abnormalities resulting from greatly increased serum viscosity. The magnitude of HVS is related to the type, size, shape, and concentration of the M-component in the blood. It is more common with IgM macroglobulinemias because of their high molecular weight; however, IgA-and IgG-associated HVS can occur, albeit less frequently.[99,105,106] High serum viscosity occurs in approximately 20% of dogs with MM and can result in bleeding diathesis, neurologic signs (e.g., dementia, depression, seizure activity, coma), ophthalmic abnormalities (e.g., dilated and tortuous retinal vessels, retinal hemorrhage, retinal detachment), and increased cardiac workload with the potential for subsequent development of cardiomyopathy or congestive failure.[99,105–110] These consequences are thought to be a result of sludging of blood in small vessels, ineffective delivery of oxygen and nutrients, and

coagulation abnormalities. HVS is less common in cats but has been reported in association with IgG-, IgA-, and IgM-secreting tumors.[106,111–114]

Renal disease is present in 30% to 50% of dogs with MM.[99] This can occur as a result of Bence Jones (light chain) proteinuria, tumor infiltration into renal tissue, hypercalcemia, amyloidosis, diminished perfusion secondary to hyperviscosity syndrome, dehydration, or ascending urinary tract infection. Bence Jones proteinuria (BJP) occurs in approximately 25% to 40% of dogs with MM; the true incidence of BJP in cats is not well established.

Hypercalcemia occurs in 15% to 20% of dogs with MM and is thought to result primarily from the production of osteoclast-activating factor or other cytokines (e.g., interleukin-6) by neoplastic cells.[99,106] In two dogs with MM and hypercalcemia, serum elevations in circulating N-terminal parathyroid hormone–related protein were noted, although its relative contribution to hypercalcemia is unknown.[115] Hypercalcemia may be exacerbated by associated renal disease. Hypercalcemia is rare in cats with MM.[116,117]

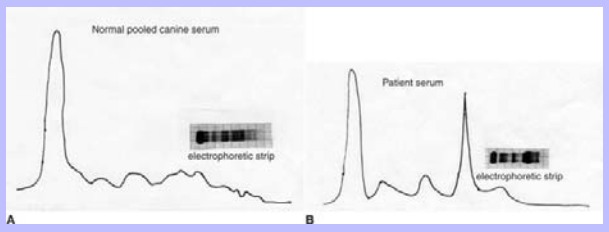
Susceptibility to infection and immunodeficiency are often the ultimate causes of death in animals with MM. Normal immunoglobulin levels are usually severely depressed, and leukopenias may be present secondary to marrow infiltration (myelophthisis).

Variable cytopenias may be observed in association with MM. A normocytic, normochromic, nonregenerative anemia is encountered in approximately two thirds of dogs.[99,106] This can result from myelophthisis, blood loss from coagulation disorders, anemia of chronic disease, or increased erythrocyte destruction secondary to high serum viscosity. Similar factors lead to thrombocytopenia and leukopenia in 25% to 30% of affected dogs.

Bleeding diathesis can result from one or a combination of events. M-components may interfere with coagulation in a number of ways, including inhibition of platelet aggregation and the release of platelet factor-3, adsorption of minor clotting proteins, generation of abnormal fibrin polymerization, production of heparin-like anticoagulants, and a functional decrease in calcium.[118]

Cardiac disease, if present, is usually a result of excessive cardiac workload and myocardial hypoxia secondary to hyperviscosity. Myocardial infiltration with amyloid and anemia may be complicating factors.

Figure 181-9 **A,** Serum protein electrophoresis from pooled normal dogs. Stained cellulose acetate electrophoretic strip with accompanying densitogram. **B,** Serum protein electrophoresis from a dog with multiple myeloma. Note the large M component spike (representing an IgA monoclonal gammopathy) in the gamma region.



181.4.4 Clinical Presentation and Signs

MM occurs in aged dogs and cats, and no breed or sex predilection has been consistently reported. Clinical signs are variable due to the wide range of pathologic effects possible and may be present up to one year prior to diagnosis.[99] The most common clinical signs in decreasing order of frequency are lethargy and weakness, lameness as a result of bone destruction, hemorrhage, polyuria/polydipsia, and neurologic deficits. Bleeding diathesis is usually represented by epistaxis and gingival bleeding. Central nervous system signs may include dementia, seizure activity, and deficiencies in midbrain or brain stem localizing reflexes secondary to HVS or extreme hypercalcemia. Signs reflective of transverse myelopathies secondary to vertebral column infiltration, pathologic fracture, or extradural mass compression can also occur.

In the cat, anorexia and weight loss are the most common clinical signs.[116,119,120] A history of chronic respiratory infections may be present. Skeletal lesions are uncommon in cats, but hepatosplenomegaly is more commonly seen due to organ infiltration.[116] Epistaxis, pleural and peritoneal hemorrhagic effusions, retinal hemorrhage, and central neurologic signs have been reported.[106,111–114,120] Polydipsia and polyuria can occur secondary to renal disease, and dehydration may develop. Hindlimb paresis secondary to osteolysis of lumbar vertebral bodies has been reported in a cat.[121]

181.4.5 Diagnosis

The diagnosis of multiple myeloma usually follows demonstration of bone marrow plasmacytosis and serum or urine myeloma proteins (M-component), as well as detection of osteolytic bone lesions (primarily in the dog). In the absence of osteolytic bone lesions, a diagnosis can be made if marrow plasmacytosis is associated with a progressive increase in the M-component.

All animals suspected of plasma cell tumors should receive a CBC, platelet count, serum biochemistry profile, and urinalysis. Particular attention is paid to renal function and serum calcium levels. Serum electrophoresis and immunoelectrophoresis are performed to detect a monoclonal spike (Figure 181-9) and to categorize the isotype of immunoglobulin involved. In the dog, the M-component is usually of the IgG or IgA class in nearly equal incidence.[99,106] If IgM constitutes the M-component, the term *macroglobulinemia* (i.e., Waldenstrom's macroglobulinemia) is used. Biclonal gammopathy has also been reported.[101,122] In the cat, MM is usually associated with IgG elevations; only a few cases of IgA or IgM gammopathies have been reported.[106,111–114,120,123] Occasionally, cryoglobulinemia has been reported in dogs and cats with MM.[106,124–126] Cryoglobulins are paraproteins that are insoluble at temperatures below 37° C and that require blood collection and clotting to be performed at 37° C before serum separation. If Bence Jones proteinuria is suspected, heat precipitation and electrophoresis of urine are necessary, because commercial urine dipstick methods are not capable of this determination. “Nonsecretory” varieties of multiple myeloma have been reported rarely in dogs.[127,128]

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Definitive diagnosis usually requires a bone marrow aspirate or core biopsy. Normal marrow contains less than 5% plasma cells, whereas myelomatous marrow often greatly exceeds this level. Malignant plasma cells can have a varied microscopic appearance, ranging from that of normal plasma cells to early stages of differentiation.

Skeletal survey radiographs are recommended to determine the presence and extent of osteolytic lesions, which may have diagnostic, prognostic, and therapeutic implications. Rarely, biopsy of osteolytic lesions (i.e., Jamshidi core biopsy) is necessary for diagnosis. Bone lesions may be isolated, discrete lesions (including pathologic fractures) or diffuse osteopenias (Figure 181-10). Approximately 25% to 30% of dogs with MM have evidence of bony lysis or diffuse osteoporosis.[99,106] Bones engaged in active hematopoiesis are more commonly affected (e.g., vertebrae, ribs, pelvis, skull, and proximal long bones). Skeletal lesions are rare in cats with MM and in dogs with IgM (Waldenstrom's) macroglobulinemia.[106,119,120] In macroglobulinemia, malignant cells often infiltrate the spleen, liver, and lymphoid tissue rather than bone.[124,129]

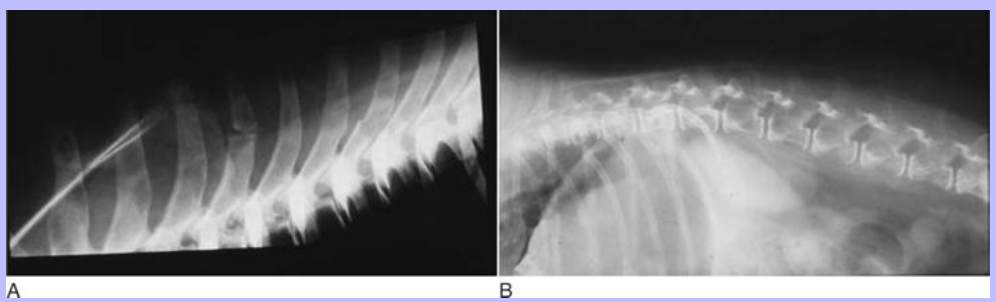
If clinical evidence of hemorrhage is present, coagulation assessment (e.g., platelet count, prothrombin time [PT], and partial thromboplastin time [PTT]) and serum viscosity measurements should be undertaken. Nearly half of these patients have abnormal PT and PTT values.

All animals should undergo a careful funduscopic examination; abnormalities may include retinal hemorrhage, venous dilatation with sacculation and tortuosity, retinal detachment, and blindness.

181.4.6 Differential Diagnosis

Disease syndromes other than MM can be associated with monoclonal gammopathies and should be considered in any list of differential diagnoses. These disorders include other lymphoid tumors (LSA, CLL, and ALL), chronic infections (e.g., ehrlichiosis, leishmaniasis, feline infectious peritonitis [FIP]), and monoclonal gammopathy of unknown significance (MGUS). MGUS (i.e., benign, essential, or idiopathic monoclonal gammopathy) is a benign monoclonal gammopathy that is not associated with osteolysis, bone marrow infiltration, or Bence Jones proteinuria.[130,131]

Figure 181-10 **A,** Lateral thoracic radiographs of a dog showing multiple expansile, lytic lesions in the axial skeleton, most apparent in the spinous processes of the vertebrae, as can be seen with multiple myeloma. **B,** Lateral vertebral radiographs of a dog with multiple myeloma. Note the overall decreased opacity of the lumbar vertebrae secondary to diffuse marrow involvement with tumor, which causes a loss of bone trabeculae and thinning of the cortices. (Courtesy Dr. Lisa Forrest, University of Wisconsin—Madison).



181.4.7 Treatment

181.4.7.1 Initial Therapy of Multiple Myeloma

Therapy should be directed at both the tumor cell mass and its secondary systemic effects. Chemotherapy is highly effective at reducing the myeloma cell burden, relieving bone pain, initiating skeletal healing, and reducing levels of serum immunoglobulins.[99,106] It significantly extends both the quality and length of most patients' lives. Complete elimination of neoplastic myeloma cells is rarely achieved, however, and although MM remains a gratifying disease to treat, eventual relapse is to be expected.

Melphalan, an alkylating agent, in combination with prednisone, is the treatment of choice. In the dog, the initial starting dose for melphalan is 0.1 mg/kg given orally once daily for 10 days; it is then reduced to 0.05 mg/kg given once daily continuously. Prednisone is initiated at a dosage of 0.5 mg/kg given orally once daily for 10 days, then reduced to 0.5 mg/kg every other day. Therapy continues until clinical relapse occurs or myelosuppression necessitates a dose reduction. The most clinically significant toxicity of melphalan is myelosuppression, particularly thrombocytopenia. Complete blood counts, including numeric platelet counts, should be performed biweekly for 2 months after initiation of therapy and monthly thereafter. If significant myelosuppression occurs, reduction of the dosage or the treatment frequency may be necessary. An alternative pulse dosing regimen for melphalan (7 mg/m^2 given orally daily for 5 consecutive days every 3 weeks) has been used successfully at the University of Wisconsin in a small number of cases in which myelosuppression limited more conventional continuous low-dose therapy. Melphalan and prednisone therapy can also be used in cats with multiple myeloma, although the results are generally less rewarding.

Cyclophosphamide can be used as an alternate alkylating agent, sometimes in combination with melphalan; however, there is no evidence to suggest that it is superior. In the authors' practice, cyclophosphamide is limited to cases presenting with severe hypercalcemia or widespread systemic involvement, in which a faster acting alkylating agent may more quickly alleviate the systemic effects of the disease. Cyclophosphamide is administered at a dosage of 200 mg/m^2 given intravenously once at the same time oral melphalan therapy is started. Chlorambucil, another alkylating agent, has been used successfully for the treatment of IgM macroglobulinemia in dogs at an initial dosage of 0.2 mg/kg given orally once daily.[106]

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181.4.7.2 Evaluation of Response to Therapy

Response is based on improvement in clinical signs, clinicopathologic parameters, and radiographic improvement of skeletal lesions. Subjective improvement in bone pain, lameness, lethargy, and anorexia should be evident within 3 to 4 weeks. Objective laboratory improvement, including a reduction in serum immunoglobulin levels or Bence Jones proteinuria, is usually noted within 3 to 6 weeks. Radiographic improvement in osteolytic bone lesions may take months, and resolution may only be partial.

As previously discussed, complete resolution of multiple myeloma rarely occurs, and a good response is defined as a reduction in measured M-component (i.e., immunoglobulins or Bence Jones proteins) to at least 50% of pretreatment values.[106] For routine follow-up, quantitation of serum immunoglobulins via radial immunodiffusion or measurement of urine Bence Jones proteins is performed monthly until a good response is noted and then every 2 to 3 months. Repeat bone marrow aspiration is performed if warranted.

181.4.7.3 Therapy Directed at Complications of Multiple Myeloma

Long-term control of complications, including hypercalcemia, hyperviscosity syndrome, bleeding diathesis, renal disease, immunosuppression, and pathologic skeletal fractures, depends on control of the tumor mass. However, therapy directed more specifically at these complications may be indicated in the short term.

If hypercalcemia is marked and significant clinical signs exist, standard therapies are indicated (see Chapter 237). Moderate hypercalcemia typically resolves within 2 to 3 days of initiation of melphalan/prednisone chemotherapy.

Hyperviscosity syndrome is best treated in the short term by plasmapheresis. Whole blood is collected from the patient and centrifuged to separate plasma from packed cells. Packed red cells are resuspended in normal saline and reinfused into the patient. Bleeding diathesis usually resolves along with HVS; however, platelet-rich plasma transfusions may be necessary with thrombocytopenia.

Renal impairment may necessitate aggressive fluid therapy. Careful attention to secondary urinary tract infections and appropriate antimicrobial therapy are indicated. Patients with MM can be thought of as "immunologic cripples," and prophylactic antibiotic therapy in dogs with multiple myeloma has been advocated by some.[106] In humans, however, prophylactic antibiotic use is not superior to diligent monitoring and aggressive antimicrobial management when indicated.[132] Cidal antimicrobials with low potential for nephrotoxicity are preferred.

Pathologic fractures of weight-bearing long bones and vertebrae, resulting in spinal cord compression, may require immediate intervention in conjunction with systemic chemotherapy. Orthopedic stabilization of fractures should be undertaken and may be followed with external beam radiotherapy. Recently, inhibition of osteoclast activity by bisphosphonate drugs has been shown to reduce the incidence and severity of skeletal complications of MM in humans.[133] This class of drugs may hold promise for use in dogs and cats in the future.

181.4.7.4 Rescue Therapy

At the time of relapse or in cases initially resistant to melphalan, rescue therapy may be attempted. The authors have had success with a combination of DOX (30 mg/m^2 given intravenously every 21 days), vincristine (0.7 mg/m^2 given intravenously on days 8 and 15 of the cycle), and prednisone (1 mg/kg given orally daily) administered in 21-day cycles. Although most dogs initially respond to a rescue protocol, the duration of response tends to be short, lasting only a few months. High-dose cyclophosphamide (300 mg/m^2 given intravenously every 7 days) has also been used as a rescue agent, with limited success. A durable rescue with liposome-encapsulated DOX has been reported in a dog with MM.[134] In humans, the antiangiogenic and anticytokine drug thalidomide is an active agent in chemotherapy-refractory MM.[135] To the authors' knowledge, thalidomide has not been evaluated in veterinary MM patients.

181.4.8 Prognosis

The prognosis for dogs with MM is good for initial control of the tumor and a return to good quality of life. In a group of 60 dogs with MM, 43% achieved complete remission (i.e., serum immunoglobulins normalized) and

49% achieved partial remission (i.e., immunoglobulins less than 50% of pretreatment values); only 8% did not respond to melphalan and prednisone chemotherapy.[99] Long-term survival is the norm, with a median of 540 days reported. Hypercalcemia, Bence Jones proteinuria, and extensive bony lysis are known negative prognostic factors in the dog. The long-term prognosis for dogs is poor, because recurrence is expected. Eventually, the tumor no longer responds to available chemotherapeutics, and death follows from renal failure, sepsis, or euthanasia for intractable bone or spinal pain.

The prognosis for MM in the cat is not as favorable as in the dog.[112,116,119,120] Although most cats transiently respond to melphalan/prednisone or cyclophosphamide-based protocols, responses are not durable, and most patients succumb within 2 to 3 months. One long-term feline survivor has been reported.[117]

In nine dogs with IgM macroglobulinemia, response to chlorambucil occurred in the majority, and a median survival time of 11 months was reported.[106]

181.5 SOLITARY PLASMACYTOMA

Solitary collections of monoclonal plasmacytic tumors can originate in bone or soft tissues and are referred to as *solitary osseous plasmacytoma (SOP)* and *extramedullary plasmacytoma (EMP),* respectively. The majority of SOPs eventually progress to systemic MM.[128,136] Cutaneous EMP, including oral cavity EMP, is typically a benign disorder in dogs.[137] Conversely, the natural behavior of noncutaneous EMP appears to be much more aggressive. Gastrointestinal EMPs have been reported to involve the esophagus, stomach, and small and large intestine.[138–143] Metastasis to associated lymph nodes is common in these cases, although bone marrow involvement and monoclonal gammopathies are less commonly encountered. One report exists of subcutaneous EMP in a cat with IgG gammopathy; the EMP progressed to lymph node disease and distant metastasis.[144]

181.5.1 Clinical Signs

Clinical signs associated with solitary plasmacytomas relate to the location of involvement; in rare cases with high levels of M-component, HVS may occur. SOP usually is associated with pain and lameness if the appendicular skeleton is affected or with neurologic signs if vertebral bodies are involved. Cutaneous EMP usually has a benign course with no related clinical signs. Gastrointestinal EMP, however, typically presents with relatively nonspecific signs that may suggest alimentary involvement. One case of ataxia and seizure activity in a dog with EMP secondary to tumor-associated hypoglycemia has been reported.[145]

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181.5.2 Diagnosis

The diagnosis of SOP and EMP requires tissue biopsy. It is important to thoroughly stage such cases of SOP and noncutaneous EMP with bone marrow aspirate, serum electrophoresis, and skeletal survey radiographs to ensure that disease is confined to a local site prior to initiation of therapy. In the case of poorly differentiated solitary plasmacytic tumors, immunohistochemical studies, directed at detecting immunoglobulin light and heavy chains and thioflavin-T, may be helpful in confirming a diagnosis.

181.5.3 Therapy

Animals with solitary plasma cell tumors may be treated with local therapy in the absence of systemic chemotherapy, provided thorough clinical staging does not reveal systemic involvement. Effective local control has been achieved with surgical excision or external beam radiotherapy, alone or in combination. Most dogs with noncutaneous SOP and EMP eventually develop systemic myeloma, and there exists controversy among veterinary oncologists as to whether systemic chemotherapy should be initiated at the time of local therapy. Systemic dissemination may not occur for many months to years beyond diagnosis in humans, and studies in humans reveal no benefit from initiation of systemic chemotherapy prior to the documentation of subsequent systemic involvement.[132]

Long-term follow-up of patients with solitary plasmacytoma is indicated to detect both recurrence of disease and systemic spread.

181.5.4 Prognosis

Dogs with cutaneous plasmacytomas are usually cured by means of surgical excision. Dogs with SOP or EMP of the alimentary tract treated by surgical excision (in combination with systemic chemotherapy once systemic disease is documented) enjoy long-term survival in the majority of cases.

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182 CHAPTER • 182 Tumors of the Skin

Kenneth M. Rassnick

The skin is the most common site of occurrence for neoplasms in the dog and the second most common site in the cat. Subcutaneous and cutaneous tumors together account for at least one third of all canine tumors. Approximately 20% to 30% are histologically malignant.[1] Mast cell tumors, perianal adenomas, lipomas, histiocytomas, sebaceous gland adenomas, and papillomas are the most common histologic types of canine tumors.[1–4] Skin and subcutaneous tissues account for approximately one fourth of all tumors in the cat, and 50% to 65% are histologically malignant.[1,2,5] The histologic appearance of malignancy does not necessarily correlate with the tendency to metastasize. The most common skin tumors found in cats include basal cell tumors, mast cell tumors, squamous cell carcinoma, and fibrosarcoma.[2,5,6]

Tumors of the skin and subcutis can be broadly classified histologically according to their tissue of origin: epithelial, mesenchymal, round cell, or melanocytic (Box 182-1). Tumors can be further classified according to individual cell of origin as long as sufficient differentiation is present. This chapter focuses primarily on tumors of epithelial origin, melanocytic tumors, and some of the round cell tumors.

182.1 GENERAL APPROACH TO SKIN TUMORS

182.1.1 History and Physical Examination

Because lesions and masses involving the skin are easily seen, they are common reasons for owners to seek veterinary care. General history taking should include duration and rate of tumor growth, change in appearance over time, response to previous treatments, and related medical problems. All tumors should be accurately reported in the medical record. Topographic maps are helpful in making this documentation a permanent part of the record. Three-dimensional caliper measurements and the actual anatomic locations of masses should be recorded. The record should also include gross appearance (color, alopecia, ulceration), consistency (firm, soft), borders (circumscribed, infiltrative), and attachments to underlying tissues (fixed, movable). In addition to a complete physical examination of the animal, lymph nodes draining a skin mass should always be thoroughly evaluated.

182.1.2 Diagnostics

The key to the appropriate management of skin tumors is a specific diagnosis. In many circumstances, diagnosis and characterization of a skin mass should be done before a definitive surgical excision. Knowledge of the tumor type allows the clinician to plan an appropriate surgical approach, make decisions about the need for adjuvant radiation therapy or chemotherapy, and discuss realistic outcomes of therapy and prognosis with clients. Figure 183-2 in Chapter 183 shows an approach to the diagnosis of superficial masses based on initial fine needle aspiration cytology and tissue biopsy.

Routine hematologic and biochemical analyses are rarely helpful in the diagnosis of cutaneous masses; however, some skin tumors may be associated with hematologic or paraneoplastic complications (see Chapter 189). “Screening” blood tests are recommended before a definitive procedure is planned.

Radiographs of the thorax are required in the clinical staging of malignant skin tumors, and ultrasound evaluation of abdominal organs may be useful in the assessment of potential sites of metastases for some tumors. For tumors that deeply attach to underlying tissues, imaging modalities such as radiographs, computed tomography (CT), or magnetic resonance imaging (MRI) may be helpful for delineating tumor borders prior to surgical excision. 748

182.1.2.1 Box • 182-1 Common Skin and Subcutaneous Tumors

182.1.2.1.1 Epithelial Tumors

Papilloma

Intracutaneous cornifying epithelioma

Squamous cell carcinoma

Basal cell tumors

Trichoepithelioma

Pilomatricoma

Trichoblastoma

Sebaceous gland tumors

Hepatoid gland tumors (perianal gland tumors)

Sweat gland tumors (apocrine gland tumors)

Ceruminous gland tumors

Anal sac apocrine gland tumors

182.1.2.1.2 Mesenchymal Tumors

Soft tissue sarcomas (see Chapter 183)

182.1.2.1.3 Round Cell Tumors

Plasmacytoma

Mast cell tumor (see Chapter 186)

Lymphoma (see Chapter 181)

Histiocytoma (see Chapter 187)

Transmissible venereal tumor (see Chapter 188)

182.1.2.1.4 Melanocytic Tumors

Melanoma

Enlarged lymph nodes should always be evaluated cytologically or histologically. For some tumors (e.g., mast cell tumors), metastases may be present in lymph nodes that are palpably normal, therefore lymph node evaluation should be a routine part of the evaluation of an animal with a cutaneous mass.

182.1.2.2 Fine Needle Aspiration

Fine needle aspiration is easy and quick and often provides information about the neoplastic cell type. Fine needle aspiration cytology is most useful in the diagnosis of round cell tumors (e.g., mast cell tumors, cutaneous lymphoma) and for identifying benign skin tumors or papules, nodules, and masses that are non-neoplastic. When cytology is nondiagnostic, a biopsy should be performed. Likewise, when a cytologic diagnosis of neoplasia is obtained, a biopsy should always be done to confirm the diagnosis and assess important prognostic information, such as the degree of differentiation or the tumor grade, a description of vessel invasion, and an evaluation of tissue margins if an excisional biopsy is performed.

182.1.2.3 Biopsy

A number of biopsy techniques can be used, depending on the size and anatomic location of the mass. Incisional, needle core, or punch biopsies are indicated for large, infiltrative masses or for tumors in a difficult area for reconstruction (e.g., extremities, perineal or periocular regions). For superficial exophytic lesions, shave biopsies done with a scalpel blade may be adequate. For small, freely movable dermal masses, excisional biopsy can be both diagnostic and therapeutic. Even when the diagnosis is known prior to the excisional biopsy, the histopathology of the final specimen should also be determined because it may provide information useful for treatment planning.

When performing nonexcisional biopsies, clinicians should always carefully examine the region to be sampled. The biopsy site should be in an area that can easily be included in the definitive resection or, if indicated, radiation field. As a general rule, all biopsy incisions on extremities should be longitudinal along the axis of the limb. Injection of local anesthetics into cutaneous and subcutaneous tumors should be avoided. Tumor tissue is poorly innervated, and the mass itself does not require anesthesia. Local injections cause tissue distortion and make margin evaluation difficult. The biopsy should be taken deep enough to avoid superficial necrotic tissue and surrounding areas of inflammation. The biopsy procedure should never disrupt tissue planes. A biopsy that opens new and previously uninvolved tissue planes generally necessitates a wider surgical resection or radiation field to control local disease. Drain placement should be avoided, because it allows fluid that has been contaminated with neoplastic cells to contact all tissues through which the drain is placed. Similarly, formation of seromas or fluid pockets may allow tumor cells to invade previously uninvolved tissue planes.

An ideal histologic specimen should include the junction of the tumor with adjacent normal tissue. This allows the pathologist to assess the degree of invasiveness of the tumor. Sample size and consistency are important for obtaining accurate pathologic diagnoses. Most tumors are not homogenous, containing areas of inflammation, necrosis, and reactive tissue, and small samples may not be representative of the entire lesion. Samples smaller than 1 × 1 mm are usually inadequate. Needle core samples 1 mm wide and 5 mm long can be adequate. Samples that fall apart in formalin are often blood, mucus, or necrotic material and are not

sufficient for a diagnosis. Large biopsy samples or multiple biopsy specimens from different areas of the tumor (collected through the same incision) can improve chances for an accurate diagnosis.

Cautery and radiofrequency surgical instruments should not be used during the biopsy procedure because they alter tissue and cellular morphology, which may complicate interpretation. Cautery for hemostasis may be used once the sample has been removed.

Finally, applying India ink or other marking dyes to the cut surfaces of excised tumors prior to fixation in formalin is an effective way to ensure that the pathologist can distinguish surgical margins from preparation artifacts.

182.2 EPITHELIAL TUMORS

182.2.1 Papilloma

Cutaneous papillomas are benign proliferations of the epidermis and are common in the dog but relatively rare in cats. Grossly, they are whitish or gray, pedunculated or cauliflower-like masses and are often referred to as *warts* or *verrucae*. Both viral and nonviral forms exist. The papillomaviruses are species-specific deoxyribonucleic acid (DNA) viruses. They are fairly stable in the environment and can survive for longer than 2 months at 4° to 8° C and for 6 hours at 37° C.[7] Papillomaviruses can be transmitted by direct and indirect (e.g., fomite) contact. In general, infection occurs in damaged skin, and incubation times vary from 1 to 2 months.[7]

Cutaneous papillomas occur in older dogs, and single or multiple lesions may be seen. They most commonly occur on the head, eyelids, and feet and are not associated with papillomavirus. *Canine oral papillomatosis* is a contagious disease of viral origin that often affects young or immunocompromised dogs.[8] Multiple lesions occur in the mouth, pharynx, face, and skin. *Cutaneous inverted papillomas,* cup-shaped lesions seen in young dogs, are also caused by infection with a papillomavirus. They occur on the ventral abdomen and groin.[9] Rare cases of multiple, pigmented plaques, or *papular papillomas,* have been reported in dogs.[10]

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In cats, most solitary cutaneous papillomas are not caused by papillomavirus. In contrast, papillomas that occur on the ventral tongue in cats are generally viral in origin, as are multiple cutaneous papillomas. These viral papillomas may be precursors to feline multicentric squamous cell carcinoma, or Bowen's disease (see Feline Squamous Cell Carcinoma, below).[11]

Surgical excision of solitary cutaneous papillomas is curative. Canine oral papillomatosis usually undergoes spontaneous regression within 3 months, and the dog is then immune to reinfection.[7] Oral administration of retinoids has been reported to be effective in the treatment of canine inverted papillomas,[12] and anecdotal reports indicate that interferon may be effective in the treatment of severe oral or cutaneous viral papillomatosis.[13]

182.2.2 Intracutaneous Cornifying Epithelioma

Intracutaneous cornifying epitheliomas (keratoacanthomas) arise from the outer portion of the hair follicle. They usually occur in relatively young, purebred dogs. Most are solitary, but generalized forms exist. Norwegian elkhounds and keeshonds are predisposed to the generalized form.[14] These tumors often have a

central pore filled with inspissated keratinous material. Gentle digital pressure applied to the mass results in expulsion of a gray-white keratinous material.

Intracutaneous cornifying epitheliomas are benign and do not recur after adequate surgical removal. In the generalized form, new tumors may develop throughout a dog's life. Oral retinoids may be useful in the treatment of multiple intracutaneous cornifying epitheliomas. In one study of seven dogs, five complete remissions and two partial remissions occurred.[12] Spontaneous regression has also been reported to occur in a dog with the generalized form.[15]

182.2.3 Canine Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is a common malignant neoplasm in the dog. The etiology usually is not known. Tumors that develop in unpigmented or lightly pigmented skin, such as the abdomen and inguinal areas, are believed to be induced by ultraviolet radiation (sun damage).[16] Occasionally SCC may be caused by burns, chronic infectious or immune-mediated diseases, or progression from viral papillomas.[13,17] In an immunohistochemistry study of 40 dogs with SCC, 100% of lesions showed expression of cyclo-oxygenase-2 (COX-2).[18] COX-2 has been implicated in the oncogenesis of various human cancers, but the precise mechanisms leading to upregulation of COX-2 are not known.

SCC in the dog may be proliferative, ulcerative, or erosive. The clinical features and management of canine SCC are highly dependent on the anatomic location.

182.2.3.1 Canine Cutaneous Squamous Cell Carcinoma

Cutaneous SCC may first be diagnosed as a preneoplastic lesion, but it ultimately progresses to an invasive tumor. Rarely, metastases to regional lymph nodes and the lungs may occur.[19] Canine cutaneous SCC is best managed with adequate surgical excision. Preneoplastic lesions may be responsive to oral retinoids,[16] and intralesional therapy with sustained-release cisplatin, 5-fluorouracil, or carboplatin may have a role in the management of some dogs with superficial SCC.[20] Aggressive surgical excision is the treatment of choice for invasive cutaneous SCC. Radiation therapy for incompletely excised tumors and chemotherapy with platinum drugs or doxorubicin for metastatic tumors can be considered, but their efficacy is unproven.

182.2.3.2 Canine Nasal Planum Squamous Cell Carcinoma

Nasal planum SCC can be treated with aggressive surgical excision of the nasal planum and premaxilla, but the prognosis is extremely guarded. Case selection is important when this procedure is considered. In a study of six dogs treated surgically, two recurred in less than 2 months, probably because of incomplete resections.[21] The results of radiation therapy for SCC in this location have been largely disappointing. In one study, all seven dogs treated with radiation for incompletely excised tumors suffered recurrences in 8 to 12 weeks.[21]

182.2.3.3 Canine Digital Squamous Cell Carcinoma

SCC originates from the subungual epithelium or occasionally from other tissues of the digit and is the most common digital tumor in dogs. Approximately 80% of digital SCCs invade bony tissue of the third phalanx.

Metastases are uncommon at initial diagnosis but may be diagnosed in as many as 30% of dogs after treatment. Rarely, dogs may develop SCC on multiple digits, either simultaneously or over time.[22] Wide amputation that includes disarticulation of the first phalanx and metacarpal or metatarsal bone is the treatment of choice. In one study, the 1-and 2-year survival rates were 95% and 74%, respectively, for 19 dogs with SCC arising from the subungual epithelium; the rates were 60% and 40%, respectively, for 10 dogs with SCC arising from other parts of the digit.[22]

182.2.4 Feline Squamous Cell Carcinoma

As with dogs, SCC in cats occurs most frequently in sun-damaged skin and is usually preceded by actinic (solar) keratosis.[13] Viruses may also be underlying etiologies for feline SCC. In one study, 24% of cats infected with feline immunodeficiency virus (FIV) developed SCC.[23] It is unclear whether a direct causal relationship exists, or whether the condition is due to outdoor sunlight exposure in these cats. Papillomavirus has been identified in lesions of multicentric SCC in situ (Bowen's disease).[11]

182.2.4.1 Feline Cutaneous Squamous Cell Carcinoma

Cutaneous SCC in the cat usually starts as a crusted area that eventually develops into an erosive or ulcerative lesion. The most common sites are unpigmented areas exposed to sunlight, including the external nares, pinnae, eyelids, and lips. Multiple lesions occur in approximately 45% of affected cats.[24] Metastases are rare.

Several treatment options exist for feline cutaneous SCC, including aggressive surgical excision (“pinnectomy,” “nosectomy”), cryotherapy, external beam radiation, strontium-90 plesiotherapy, photodynamic therapy, and intralesional chemotherapy. These treatments are most successful in small (less than 5 cm), superficial lesions, therefore early diagnosis and prompt therapy are essential. Small, minimally invasive SCC lesions can be controlled for longer than 1 year in most cats, and long-term control (e.g., 2 to 7 years) is possible in 10% to 60%. Treatment of larger (greater than 5 cm) or more invasive tumors is disappointing, with control times generally less than 2 years.[24–28] In all cats, avoidance of sunlight is important to prevent additional lesions.

182.2.4.2 Feline Multicentric Squamous Cell Carcinoma in Situ (Bowen's Disease)

Bowen's disease is a condition of small, plaquelike, crusted SCC lesions that histologically do not invade the basement membrane. Unlike solar-induced SCC, multicentric SCC in situ is found in haired, pigmented areas and may be caused by infection with a papillomavirus.[11] Lesions are multifocal over the head, neck, thorax, abdomen, and limbs. Occasionally focal areas of invasive SCC may be present. When possible, surgical excision is the treatment of choice. Strontium-90 plesiotherapy may be effective for lesions less than 5 mm in diameter.[11] Therapy with oral retinoids is variably successful.[11]

182.2.5 Basal Cell Tumors

Basal cell tumors are benign neoplasms that arise from the basal cells of the epidermis. They are the most common skin tumor affecting the cat.[29] The tumor previously classified as basal cell tumor in the dog has been reclassified as trichoblastoma. Basal cell tumors are usually solitary, firm, rounded, and well circumscribed.

Occasionally they may be cystic. Basal cell tumors are often pigmented, which can lead to a clinical misdiagnosis of melanoma. Adequate surgical excision is the treatment of choice.

182.2.6 Basal Cell Carcinoma

Basal cell carcinomas are usually solitary and similar to basal cell tumors; they are often pigmented brown/black. This tumor is locally invasive, therefore clinical management should include wide surgical excision. Animals with proven metastases have rarely been reported.[30] Adjunctive radiation therapy can be considered when adequate surgical margins cannot be achieved.

182.2.7 Trichoepithelioma

Trichoepitheliomas are benign neoplasms derived from the hair follicle sheath. They are relatively common in the dog and uncommon in the cat. Surgical excision is the treatment of choice. Malignant trichoepithelioma with metastases to lymph nodes and lungs has rarely been reported.

182.2.8 Pilomatricoma

Pilomatricomas are uncommon, benign tumors that arise from the hair follicle. They usually are solitary and well circumscribed. On cut section, the tumor consists of several layers of gray-white chalky tissue. Surgical excision is the treatment of choice. Rare cases of malignant pilomatricomas have been reported. Lymphatic invasion is seen histologically, and metastases to lymph nodes, the lungs, and the nervous system may occur.[31]

182.2.9 Trichoblastoma

Trichoblastomas are common benign tumors that predominately derive from primitive hair germ epithelium. This neoplasm was previously classified as basal cell tumor. Trichoblastomas are generally solitary and may be pigmented. Surgical excision is curative.

182.2.10 Other Follicular Tumors

Other uncommon follicular tumors include tricholemmoma, trichofolliculoma, dilated pore of Winer, and warty dyskeratoma. These are benign lesions, and adequate surgical excision should be curative.

182.2.11 Sebaceous Gland Tumors

Sebaceous gland tumors are derived from sebocytes and are among the most common skin tumors in dogs. They are uncommon in cats. Histologically, they are classified as sebaceous hyperplasia, epitheliomas, adenomas or, rarely, carcinomas. The lesions are wartlike or cauliflower-like in appearance and can occur throughout the body, including on the eyelids. They are usually solitary, but multiple sebaceous gland tumors can occur.

Surgical excision is the treatment of choice for all types of sebaceous gland tumors. Local recurrence is rare, but up to 10% of dogs may develop lesions at other sites.[32] Dogs with sebaceous hyperplasia may respond to therapy with oral retinoids.[12] Sebaceous carcinomas appear to have a low potential for metastasis.[32]

182.2.12 Hepatoid Gland Tumors (Perianal Gland Tumors)

Perianal gland tumors arise from canine circumanal glands, which are modified sebaceous glands. They are referred to as *hepatoid glands* because the cells morphologically resemble hepatocytes. Circumanal glands contain receptors for both testosterone and estrogen, and intact males are at increased risk for tumor development. The occurrence of these tumors in female dogs or in males that were castrated early in life suggests a need for evaluation for hyperadrenocorticism. The vast majority of perianal gland tumors are benign and histologically may include hyperplastic lesions, adenomas, or epitheliomas. Rarely, hepatoid gland carcinomas occur.

Most perianal gland tumors occur adjacent to the anus, but they can also occur on the ventral aspect of the tail and perineum. Fine needle aspiration cytology may help differentiate perianal gland tumors from other tumors of the perineum; however, it may be difficult to distinguish adenomas from carcinomas.

Castration is the treatment of choice for perianal gland hyperplasia and adenomas in intact males; 95% of lesions regress. Surgical excision is necessary in female dogs and castrated animals or when the tumors are ulcerated. Radiation therapy may cause nonresectable adenomas to regress, but limited information is available on this treatment.

Carcinomas do not regress after castration, therefore aggressive surgical excision must be done. In one study, 70% of dogs with tumors less than 5 cm in diameter survived for 2 years when treated by surgical excision alone.[33] Ten percent to 30% of tumors may metastasize to the iliac lymph nodes, liver, and lungs.[34] Radiation therapy can be considered for tumors that are incompletely excised or if metastasis to iliac lymph nodes is confirmed. Occasionally, lymphadenectomy may be an option. Doxorubicin and platinum compounds may be useful, but their efficacy is unproven.

182.2.13 Sweat Gland Tumors (Apocrine Gland Tumors)

Sweat gland tumors in dogs and cats commonly occur in the inguinal or axillary regions. These tumors have various clinical presentations, including solitary nodular masses or a diffuse, inflammatory and ulcerative, plaquelike growth. Cats with a histologic diagnosis of apocrine gland carcinoma of the digit may actually have digital metastases from a pulmonary carcinoma.

The majority of sweat gland tumors are histologically malignant (carcinomas), and more than 20% may have evidence of lymphatic or vascular invasion.[35,36] Wide surgical excision is the treatment of choice. In two retrospective studies, fewer than 2% of canine sweat gland carcinomas developed distant metastases.[35,36] Metastatic disease may have been correlated with intravascular invasion.[36]

182.2.14 Ceruminous Gland Tumors

Ceruminous gland tumors originate from modified apocrine sweat glands found in the external ear canal. Chronic otitis may be a predisposing factor.[37] Common clinical signs associated with ear canal tumors include the presence of a mass, aural discharge, odor, pruritus, and pain. Neurologic signs, including Horner's syndrome and vestibular disease, may also be present. Radiographs of the skull and/or computed tomography are important imaging modalities that should precede surgery. Careful evaluation of the mandibular and periauricular lymph nodes is essential.

Ceruminous gland adenomas can be managed by conservative surgical resection. For ceruminous gland carcinomas, however, aggressive surgical excision, including ear canal ablation and lateral bulla osteotomy, is the treatment of choice. Sixteen cats treated by ear canal ablation and bulla osteotomy had a 42-month median remission, a 25% recurrence rate, and a 75% 1-year survival rate. Six cats treated only with lateral ear resection had a 10-month median remission, four of the cats had recurrence, and the 1-year survival rate was only 33%.[38] In seven dogs, aggressive ear canal ablation with lateral bulla osteotomy resulted in no recurrences during follow-up for a median of 36 months, compared with a 75% recurrence rate within 4 months for four dogs treated by a more conservative lateral ear canal resection.[39]

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Radiation therapy can be used as an adjunct to incomplete resection. A median progression-free interval of 40 months and a 56% 1-year survival rate were achieved in one study of six cats and five dogs treated with radiation therapy after incomplete resection of ceruminous gland adenocarcinoma.[40]

182.2.15 Anal Sac Adenocarcinoma

Anal sac adenocarcinomas arise from the apocrine glands in the ventrolateral aspects of the anus. They occur almost equally in female and male dogs but are rare in cats. The tumors are usually unilateral, occasionally can be bilateral, and are either discrete or infiltrative when palpated rectally. Twenty-five percent to 50% of anal sac adenocarcinomas produce parathyroid hormone–related protein (PTHrP), leading to hypercalcemia of malignancy.[41,42] Metastases generally arise in the iliac lymph nodes, although distant metastases may also be seen in the liver, spleen, lungs, and other sites. Occasionally extension from the iliac lymph nodes into the lumbar vertebrae may occur.[42]

Aggressive surgical excision with or without chemotherapy and radiation therapy is recommended for treatment of anal sac adenocarcinoma. Hypercalcemia generally resolves quickly after resection of the primary tumor. The rate of local recurrence after surgical excision is approximately 50%. It is unclear whether this correlates with incomplete histologic margins.[41,42] In one study, dogs underwent surgical excision of the primary mass. Some also had surgical removal of metastatic lymph nodes. The median survival for dogs with metastases (n = 11) or hypercalcemia of malignancy (n = 5) was 6 months, compared to 15.5 months for dogs without metastases (n = 10) and 11.5 months for dogs with normocalcemia (n = 16).[41] In another study of 34 dogs, the overall median survival was approximately 8 months.[42]

Adjunctive treatment with radiation to the anal sac and iliac lymph node regions and chemotherapy with platinum agents or doxorubicin may improve outcome. However, this has not been substantiated.

182.3 ROUND CELL TUMORS

Round cell tumors may also be called *discrete cell tumors*. Cytologically, they appear as individually oriented, round cells that have no obvious attachments to each other. The round cell tumors include lymphoma, mast cell tumors, plasmacytomas, histiocytomas, and transmissible venereal tumors. Occasionally melanomas and basal cell tumors may mimic round cell patterns.

182.3.1 Lymphoma, Mast Cell Tumor, Histiocytoma, and Transmissible Venereal Tumor

For a discussion of these tumor types, the reader is referred to detailed information presented in other chapters of this text.

182.3.2 Plasmacytoma

Cutaneous plasma cell tumors (cutaneous extramedullary plasmacytomas) are usually solitary, and common locations of occurrence are the digits, lips, pinnae, oral cavity, and rectum.[43,44] The majority of cutaneous plasmacytomas in the dog are benign and are unrelated to multiple myeloma. The behavior of canine plasmacytomas does not seem to have any relationship to the degree of histologic atypia or pleomorphism.[43,44]

The treatment of choice for cutaneous plasmacytomas is surgical excision. Local recurrence may be associated with incomplete margins.[43] Radiation therapy can be considered for cases that are nonresectable, but information is limited.

182.4 MELANOCYTIC TUMORS

182.4.1 Melanoma

The etiology of cutaneous melanomas in dogs and cats is unknown, but breed predilection in dogs suggests a genetic basis. Breeds reported to be at risk include Scottish terriers, Airedales, Boston terriers, cocker and springer spaniels, boxers, golden retrievers, miniature schnauzers, and Doberman pinschers.[13] In dogs, lesions are usually solitary and are brown to black in appearance. Common sites include the eyelid, muzzle, trunk, interdigital skin, and subungual epithelium (nail bed). Digital melanomas are the second most common digital tumor in dogs, next to squamous cell carcinoma. In cats, the most common pigmented cutaneous tumor is a basal cell tumor. However, melanomas also are black. Common sites in cats include the pinna, nose, and neck.

Cutaneous melanomas can be behaviorally benign or malignant. Of critical importance is the location of the tumor. As a general rule, tumors arising from the haired skin are benign. Those arising from mucocutaneous junctions are malignant, the only exception being those arising on the eyelids. Melanomas of the digit may be highly malignant. Malignant melanomas commonly spread via lymphatics to draining lymph nodes and the lungs. Metastases to distant sites such as the liver, spleen, brain, heart, and bone marrow occasionally occur.

In dogs, the histologic mitotic index is highly predictive of biologic behavior.[45–47] A mitotic index of less than 3 per 10 high-power fields is generally associated with benign behavior.[45] It is difficult to predict the biologic behavior of cutaneous melanomas in cats based on the mitotic index, because 25% of malignant tumors may show no mitotic figures.[48]

The treatment of choice for cutaneous melanomas in both the dog and the cat is surgical excision. In one study, 59 dogs had a median survival of 26 months and a 2-year tumor-related death rate of 10% if the mitotic index of the tumor was less than 3. In contrast, 26 dogs had a median survival of 7.5 months and a 2-year tumor-related death rate of 73% if the mitotic index of the tumor was 3 or higher.[45] With digital melanomas in dogs, more than 50% may develop metastases. A median survival time of 12 months has been reported for dogs treated by amputation of the affected digit.[22] Other studies have reported median survival times of 18 to 24 months.[45,46]

The prognosis for cats with cutaneous melanomas is guarded. In one study of 57 cats with the tumors, metastases were documented at initial diagnosis in 11 (19%). Forty-five cats were treated by surgical excision, and 22 of these animals developed local recurrence or metastases.[49]

Coarsely fractionated radiation therapy is useful for treating dogs with oral melanoma and may be beneficial for local control of nonresectable cutaneous melanomas in dogs and cats.[50] Also, a clinical response to treatment with carboplatin can be seen in dogs with oral melanomas, therefore this may be considered as an adjunct therapy in dogs with digital melanomas or in dogs and cats with malignant or nonresectable tumors or metastatic disease.[51]

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183 CHAPTER • 183 Soft Tissue Sarcomas

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Soft tissue sarcomas represent a significant group of cancers in companion animals. Collectively, sarcomas include numerous histologic subcategories that are derived from neoplasms of mesenchymal origin. Box 183-1 lists the individual histologic categories of canine soft tissue sarcomas included in most discussions. In some instances, distinct biologic behaviors have been described for specific subcategories. However, the collective experience of pathologists and specialists managing sarcomas in dogs has permitted development of a histologic grading scheme that more uniformly describes clinical behavior by the degree of differentiation rather than specific histologic type (Table 183-1). The histologic grade of a tumor can dictate radical versus functional surgery or may determine the addition of radiation therapy or chemotherapy. In addition, the size of the tumor and its location will obviously affect the surgical options available for local control. Despite the general consensus that grade may influence the ultimate control of a tumor, debate continues about the universal applicability of histologic grade of sarcomas as a clinically meaningful predictor of response in dogs. To date, no convincing evidence exists for comparison of grade with outcome for feline sarcomas. Specific histopathologic types of sarcomas include fibrosarcoma, undifferentiated sarcoma, osteosarcoma, rhabdomyosarcoma, liposarcoma, malignant fibrous histiocytoma (or myofibrosarcoma) and leiomyosarcoma. Hemangiosarcomas (HSAs), synovial cell sarcomas, and mast cell tumors (MCTs) are discussed separately in this text due to the common occurrence of these cancers and their unique biologic and clinical features. Other, less common sarcomas are not included, because they cannot be considered as part of the collective terminology due to insufficient information (e.g., rhabdomyosarcoma).

Soft tissue sarcomas are typically focal, solitary, palpable, soft to firm lumps found in the dermis, subcutaneous tissue, or deeper muscular and musculofascial compartments. The most common owner concern is the identification of a palpable or visible nonpainful mass (or both) that may be growing. Masses that have grown rapidly or have been present for a prolonged time with resultant substantial growth can have an ulcerated surface and may be painful. The majority of masses are 2 to 4 cm in diameter at the time of initial examination. Tumor size can vary depending on a number of factors including location on the body, particularly whether it is located superficially in the dermis or deep in a muscle, whether an owner frequently handles or grooms the pet and identifies a new lump early, the overall body condition with masses more easily observed on a trim pet, and the length and thickness of the hair coat. Soft tissue sarcomas can develop in any location on the body but are most commonly identified on the limbs or head. In cats, soft tissue sarcomas are frequently associated with sites of previous vaccination and therefore are more commonly located on the trunk either in the interscapular region, dorsal lumbar, or flank region.

183.1 Box • 183-1 Histologic Categories of Soft Tissue Sarcomas in Dogs and Cats

Fibrosarcoma

Hemangiopericytoma

Malignant fibrous histiocytoma

Synovial sarcoma

Neurofibrosarcoma

Rhabdomyosarcoma

Leiomyosarcoma

Liposarcoma

Undifferentiated sarcoma

Schwannoma

An accurate diagnosis is critical for appropriate treatment planning. An incisional biopsy is recommended for all but the smallest of nodules to prevent disruption of the surrounding normal tissue prior to definitive surgical planning. Excisional biopsies should be avoided unless the mass is small (<1 to 2 cm proportional to the size of the dog or cat) and surrounded by abundant normal tissue. In addition, all biopsy procedures should be carefully planned for all subcutaneous nodules to avoid inadvertent contamination of surrounding tissues. Although local control is expected with complete surgical removal, local recurrence is often observed after suboptimal surgical procedures. Aggressive tumor management at the first opportunity is required for successful management of soft tissue sarcomas. The challenge of surgical planning, the need for multimodality therapy in many instances, and the potential for metastases despite local control in high-grade sarcomas add complexity to the treatment decision-making process. These challenges are particularly important for successful management of injection-site sarcomas in cats.

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Table • 183-1 Proposed Grading Criteria for Canine Soft Tissue Sarcomas*

SCORE	DEGREE OF DIFFERENTIATION	MITOTIC INDEX†	NECROSIS
1	Normal appearance	<10	None
2	Histologic type	10–19	<50%
3	Undifferentiated	>19	>50%
Grade (Cumulative Score)			
1	<5		
2	5 or 6		
3	>6		

* Adapted from Kuntz CA et al: Prognostic factors for surgical treatment of soft-tissue sarcomas in dogs:75 cases (1986–1996), *J Am Vet Med Assoc* 211:1147, 1997.

† Number of mitotic figures/10 high-powered fields (40×).

183.2 CAUSE

The genetic or specific biochemical mechanisms responsible for development of sarcomas in both dogs and cats remain unknown. It is believed that most sarcomas that develop in dogs occur sporadically. Germ-line mutations

or familial forms of sarcomas have been confirmed in humans, and provocative anecdotal epidemiologic evidence suggests similar processes may be present in dogs. However, detailed genetic or pedigree characterization of dogs that develop sarcomas at a young age (<2 years) or where a breed prevalence seems likely have not been conducted. In one recent study, chromosomal translocation was identified in 1 of 30 canine sarcomas, although its significance remains unknown.[1]

It is well established that exposure to irradiation, viral infection (feline sarcoma virus), trauma, or chronic inflammatory conditions are associated with development of sarcomas in dogs and cats. Conventional irradiation schedules for management of a primary cancer carries less than 5% risk of a radiation-induced tumor occurring 3 to 5 years later.[2] Clearly, the benefits of primary tumor control outweigh the risk of radiation-induced second tumors. High, single doses of radiation used for intraoperative therapy are more likely to produce sarcomas (20% to 25%) in dogs with a median latency of 4 years postirradiation.[3]

The molecular development of injection-associated sarcomas in cats is not yet defined. There have been several reports eliminating the most common feline viral infections (oncorna, papilloma, polyoma viruses) as causes.[4–6] Unique molecular features of injection-associated sarcomas have been identified. Epidermal growth factor/receptor (EGFR), platelet-derived growth factor/receptor (PDGF), and transforming growth factor–beta expression is abundant on tumor cells and infiltrating lymphocytes in injection-site sarcomas but are not expressed in cells from noninjection site sarcomas of cats.[7] C-Jun overexpression, a proto-oncogene, has also been identified in feline injection site sarcomas and may be the result of persistent growth factor stimulation.[7]

P53 abnormalities have been reported in vaccine-associated sarcomas. In one report, approximately 43% of samples from sarcomas strongly overexpressed the p53 protein.[8] In another report, five of eight tumor samples overexpressing this protein had a mutated gene. No cats from a control group of 13 injection sarcomas without p53 protein overexpression had gene mutations.[9] In this study, no surrounding tissue had p53 mutations, suggesting that abnormalities in p53 function did not exist prior to tumor development. These data taken collectively indicate that molecular and cellular abnormalities exist and suggest several hypotheses; however, no specific cause has been associated with the development of feline injection sarcomas.

Abnormalities in p53 and MDM2, a gene with a product that suppresses p53 expression, have recently been reported in canine sarcomas.[10] Twenty percent (6/30) of sarcomas had base substitutions resulting in single amino acid misreads in the p53 gene. Three of these six tumors with mutations were malignant nerve sheath tumors. Interestingly, canine MDM2 gene amplification (threefold or greater) was identified in five of the 30 sarcomas. In all but one of these combined samples there was coordination of these abnormalities, resulting in p53 disruption (mutations) or secondary p53 suppression due to MDM2 overexpression. Thus directly or indirectly, almost one third of canine sarcomas appear to have altered p53 function. Interestingly, five of seven malignant peripheral nerve sheath tumors had p53 functional abnormalities.

183.3 INITIAL CLINICAL EVALUATION

Routine evaluation of the patient should be conducted, including a thorough physical examination and laboratory evaluations. Tumor staging includes the assessment of the extent of local disease and detection of any evidence of regional or distant metastasis. A thorough description and measurement of the mass in three dimensions is essential and is important for documenting subsequent growth if initiation of therapy is delayed, or for documentation of therapeutic response. Soft tissue sarcomas, in general, have a relatively low metastatic rate, but the rate of metastasis increases with increasing tumor grade. The greatest concern of metastasis is with high-grade

sarcomas. The regional lymph node should be evaluated by aspiration, biopsy, or both techniques, particularly if the lymph node is enlarged or if it is a high-grade tumor. Metastasis can occur to the regional lymph node, although this is not the most common site of metastasis. The incidence of metastasis for sarcomas at initial diagnosis is low, but without specific examination of regional lymph nodes or careful follow-up, the actual incidence of metastasis remains unknown. The most common route of metastasis is via the hematogenous route, and the most common sites of metastasis are the lung and liver. In cats with vaccine-associated fibrosarcomas, sites of metastasis that have been reported include lung, skin, or subcutaneous sites, regional lymph nodes, mediastinum, liver, and pelvis.

Appropriate imaging for evaluation of the primary tumor, as well as thoracic radiographs and abdominal ultrasound, should be conducted during the staging process if malignancy is confirmed. Imaging techniques may also aid in planning biopsy and treatment options. An ultrasound evaluation of the primary tumor may aid in determining the best site for biopsy; for deep-seated tumors, ultrasound guidance may be necessary for accurate tumor sampling. Imaging of soft tissue sarcomas increasingly involves more advanced cross-sectional imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI). CT with the administration of intravenous contrast can assist in delineating the extent of the local disease and extension into the surrounding tissues. It is highly recommended that imaging precede therapeutic intervention. The extent of invasion into surrounding tissues for vaccine-associated sarcomas in cats can be substantial, and an initial excisional biopsy can impair the ability to achieve local tumor control. It was recently determined that tumor volume measured from contrast-enhanced CT studies of feline sarcomas exceeded the physical measurements by two-to fivefold, and attachment of the tumor to surrounding muscle and tissue was much more extensive than predicted.[11] Figure 183-1 illustrates an infiltrative sarcoma in the prescapular and interscapular space of a cat. Obviously, a surgical procedure without accurate knowledge of tumor extent in feline injection sarcomas is not recommended. Furthermore, in dogs, soft tissue sarcomas frequently occur on the extremities where it is difficult to resect the tumor with the necessary margins. An initial biopsy and imaging can provide both a diagnosis and understanding of the extent of disease, with preplanning possible so that an owner can be appraised of whether or not combination therapy may be indicated, with the potential for increased duration and cost of therapy.

183.4 BIOPSY CONSIDERATIONS

As with any suspected tumor, the clinician needs a definitive diagnosis to determine the best treatment strategy. Aspiration cytology can provide initial information on a dermal or subcutaneous lump that may support the diagnosis of a non-neoplastic process. Additionally, aspiration cytology can be diagnostic for neoplasia and indicative of a round cell (e.g., MCT), epithelial or mesenchymal tumor. Mesenchymal tumors are less likely to exfoliate during aspiration, and for soft tissue sarcomas, aspiration cytology is performed primarily to rule out other disease processes. At times, cytology may be diagnostic for a sarcoma. An incisional biopsy is recommended to obtain a definitive diagnosis of a soft tissue sarcoma and to determine the specific histopathologic type. The biopsy procedure for sarcomas should be carefully planned to obtain a representative sample of the tumor and prevent any unnecessary complications or contamination of surrounding tissue with tumor. If a cutting needle is to be used, care should be taken not to penetrate beyond the known tumor perimeter. Sarcomas are often adhered to adjacent tissue, and extension along fascial planes can be difficult to appreciate on physical examination. Therefore biopsy samples such as those obtained from limited incisions, punch biopsy tools, or cutting needles are preferred to excisional biopsy to minimize any tissue disruption. The acquisition of a biopsy sample allows grading of the tumor based on assessment of a number of histopathologic features. The histologic features assessed in soft tissue sarcomas to arrive at a tumor grade include degree of differentiation, percentage of necrosis, and mitotic rate (see Table 183-1). Tumor grade for soft tissue sarcomas in dogs can have prognostic significance with a more progressive course and higher likelihood of metastasis with a high-grade tumor. One report on prognosis in cats after surgical excision of fibrosarcomas showed a correlation between mitotic index (sum of mitotic figures in

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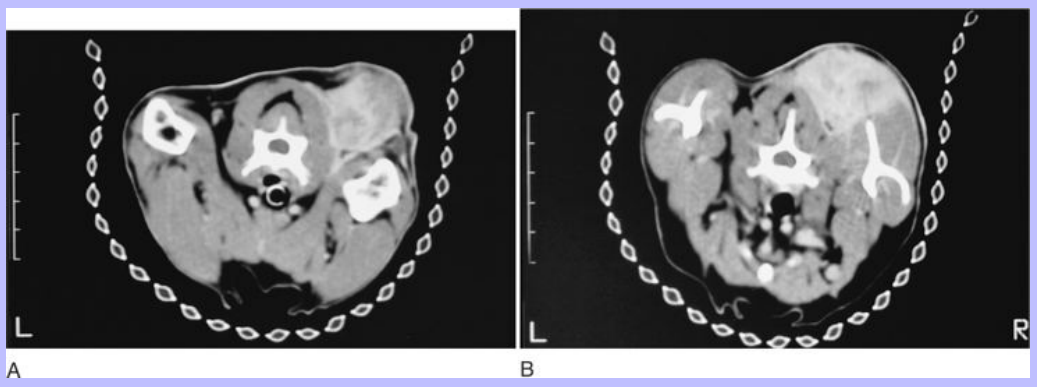
ten high-power fields) and median survival. For cats with a mitotic index less than six the median survival was 32 months as compared with 4 months if the mitotic index was greater than or equal to six. More recent studies have not shown a correlation between tumor grade and survival in cats with vaccine-associated sarcomas. Such tumors may have a cell population that is generally more aggressive than many other sarcomas.

Figure 183-1 Computerized tomography (CT) image with contrast agent of a feline vaccine-associated sarcoma in prescapular space. Extensive soft tissue infiltration is obvious with numerous muscles adjacent to tumor tissue.



183.5 GENERAL TREATMENT CONSIDERATIONS

Surgical excision of any tumor without preplanning can result in incomplete removal and the need for a second, more extensive surgical procedure, radiation therapy, and potentially a higher complication rate. Soft tissue sarcomas in particular are likely to be incompletely removed with close marginal excision due to tumor extension beyond what is visible. Higher morbidity and cost associated with incomplete resection justify the referral of pets with large or high-grade soft tissue sarcomas for consideration of multidisciplinary evaluation and possibly multimodality therapy. Figure 183-2 represents a decision-making algorithm for soft tissue sarcomas, or any superficial nodule, based on the initial determination of surgical success. Pivotal decision points in this algorithm include the determination of whether curative surgery is possible, the success of the surgical procedure based on thorough evaluation of the surgical margins, and the need for any adjuvant chemotherapy determined by tumor grade and stage.

Decision regarding surgical resection of a soft tissue sarcoma is perhaps the most critical point in the algorithm. The decision to attempt resection should be made from accurate measurement of the mass and its deep tissue attachments, the location of the tumor and surrounding normal tissue limitations for deep resection, and the surgeons' skill. The surgical procedure should be well planned to accomplish the goal of complete resection and reduce or prevent the likelihood of inadvertent seeding of the tumor resection bed and surrounding tissue. Referral to a surgical specialist that has had extensive experience with cancer surgery should be considered for most sarcomas. New techniques are being evaluated and implemented that require advanced technology and training.[12]

After a surgical procedure it must be assumed that the entire operating field could be contaminated, including the scar. The use of appropriate technique is essential. This includes incision planning, avoidance of unnecessary manipulation of the tumor itself, or placement of drains with distant tissue dissection. During the procedure,

hemoclips may be used to define the deep and lateral extent of the surgical plane. This will be of benefit to determine the area of resection if a second surgery is indicated or for radiation treatment planning if needed.

Examination of the deep margins for completeness of resection is of critical importance for determining local tumor control. The histopathologic analysis of tumor margins is aided by deep surface marking with permanent dye and a thorough description of the sites that might be suspect for closer examination by the pathologist.[13–15] Adequate margins around the tumor tissue can be difficult to estimate once the tissue has been processed for fixation and microscopic evaluation. For classification of complete resection, most pathologists recommend a minimum of ten cell diameters between tumor and deep surface. This arbitrary designation should be carefully examined with more defined measurements of distance that could be correlated to the required margin necessary to prevent recurrence for different grades of sarcoma.

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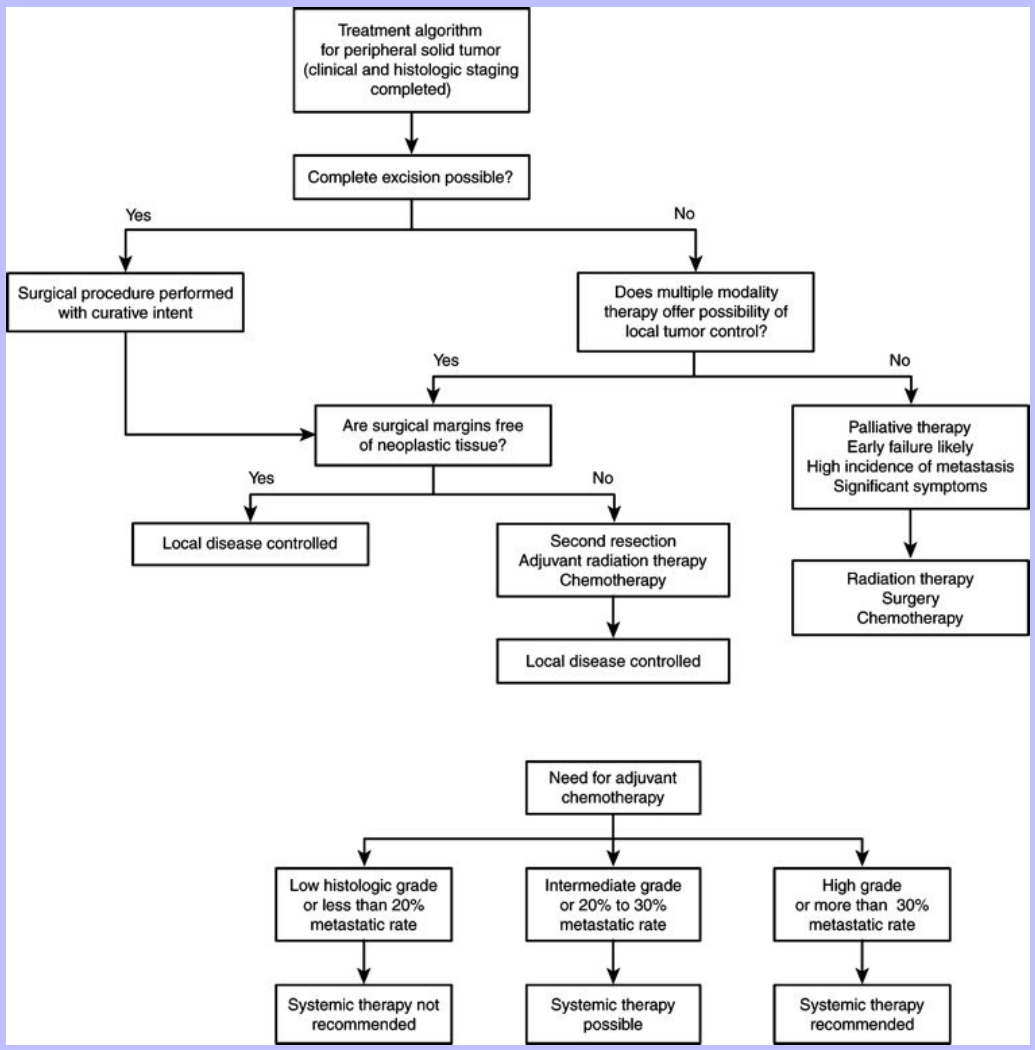
Figure 183-2 Soft tissue sarcomas.



Palliative therapy may be necessary for tumors that are not amenable to aggressive surgery or multimodality therapy. Palliative therapy should be actively pursued, and numerous treatment options have been devised specifically for management of dogs and cats with noncurable tumors or those with significant signs associated with the presence of tumors.

183.6 MANAGEMENT OF CANINE SOFT TISSUE SARCOMAS

To date, no known risk factors exist for the development of canine sarcomas. Therefore general recommendations for cancer screening and detection such as frequent physical examinations, radiographs, and other imaging studies should become more routine for earlier identification of sarcomas. Any mass that is apparent should be characterized early with measurements, appropriate imaging, and biopsy. If a sarcoma is identified, the procedures outlined previously for treatment planning should be implemented.

Figure 183-2 summarizes the treatment recommendations for management of the primary tumor and whether chemotherapy for adjuvant treatment should be instituted after local control. Surgical resection should be the first consideration for any sarcoma. The conclusion that a mass is potentially curable with surgery should be closely scrutinized because local recurrence represents a serious complication of inadequate surgery and will impact future treatment options.[16] Referral for more extensive tumor evaluation and aggressive management is warranted for tumors occurring in areas of complex musculofascial anatomy because adequate normal tissue removal around the sarcoma improves local control.[17] Multimodality therapy is an appropriate consideration for tumors that are not easily resectable.

Radiation therapy has been shown to be of significant benefit for local control in tumors that are not controllable with surgery alone. The use of preoperative or postoperative irradiation can be considered, although ideally, the schedule for application of radiation therapy should be made before the treatment is initiated rather than using radiation as a means to manage residual disease after an inadequate surgical procedure.[18] Several studies have demonstrated that irradiation results in long-term control of soft tissue sarcomas in dogs.[19,20] Local relapse-free survival has been estimated at 75% to 85% for 3 or more years, and this combination should be recommended for all incompletely excised sarcomas in dogs. Current treatment schedules and technology make irradiation of tumor sites less likely to result in limiting side effects than previous techniques. However, soft tissue sarcomas can arise in any tissue, and adjacent normal structures can be difficult to avoid in some instances without compromising tumor control.

Chemotherapy also has a role in management of canine soft tissue sarcomas. A recent review thoroughly describes the indications, options, and strategies for chemotherapy in sarcoma management.[21] Chemotherapy is indicated when animals have inoperable sarcomas because of size or location because a measurable reduction might allow function-preserving resection; pets with recurrent sarcomas that are not amenable to second surgical procedures; dogs with high-grade sarcomas to reduce or delay metastatic nodules; and those with sarcomas that have inherently greater likelihood of metastasis such as oral sarcomas, liposarcomas, and dogs with soft tissue sarcomas of the spleen. Adriamycin is the most active single agent for canine sarcomas.[21] Other options include platinum-containing agents and ifosfamide. Although no definitive evidence exists to make adjuvant chemotherapy a general recommendation for dogs with high-grade sarcomas, many specialists feel the chance for distant spread of the tumor even with local control (~40%) warrants a recommendation of treatment with chemotherapy.[17]

Palliative therapy is also available for dogs with tumors that have significant functional abnormalities directly related to the tumor. Irradiation schedules for palliative management are designed to deliver a significant dose to the tumor without debilitating side effects and with minimal hospitalization. Tumors associated with dysphagia, dyspnea, dyschezia, or dysuria, and that are assumed to be incurable with surgery should be considered for palliative irradiation. Palliative chemotherapy may also be offered in hopes of reducing the mass associated with debilitating clinical symptoms. Any response to treatment should be observed after the initial treatment course and is unlikely to occur after the second course of treatment. Therefore continuation of the chemotherapy is unnecessary if no response is observed. Surgical procedures designed specifically for improved quality of life in dogs with extensive disease include resolution of ulceration and management of secondary infection.

183.6.1 Management of Canine Soft Tissue Sarcomas with Unique Clinical Features

The majority of tumors listed in Table 183-1 can be managed with the principles described after considering the histologic grade and the likelihood of local control. Special consideration should be given to several sarcomas due to unique presentations or tumor biology. Discussion of synovial cell sarcoma, malignant fibrous histiocytoma, and HSAs are discussed in chapters 181, 184, and 187.

183.6.1.1 Leiomyosarcoma

Sarcomas of smooth muscle occur most often in the intestinal tract and are singled out here due to special considerations of management related to their site of origin. Because second approaches are unlikely, it is recommended that intestinal tumors be resected widely and any lymph nodes or other sites of concern in the abdomen be resected to aid in staging during the laparotomy. Several retrospective reviews have reported clinical outcome of approximately 100 dogs with leiomyosarcoma of the intestine.[22–24] In addition, data is available describing the site or origin and metastases of 158 dogs and 22 cats with leiomyosarcomas.[25] Leiomyosarcomas are most often located in the small intestine, cecum, spleen, or urogenital tract. Feline leiomyosarcomas are uncommon but occur in the intestinal tract more often than other sites. If complete surgical resection can be accomplished, median survival times (MSTs) are approximately 18 to 21 months, and many dogs succumb to diseases other than recurrence or metastasis. Metastatic lesions are reported in 15% to 30% of dogs with leiomyosarcomas and are most likely to be found in the mesentery, spleen, or liver. Metastases may be slow to develop (1 to 2 years) and relatively slow to progress to clinical signs. No reports on postoperative chemotherapy are available.

183.6.2 Management of Feline Sarcomas

Surgical excision of soft tissue sarcomas in cats represents the best chance of affecting local tumor control.[26,27] If an initial biopsy is suggestive of soft tissue sarcoma in a cat, imaging (CT or MRI) will provide the most accurate assessment of the extent of disease and assist in developing an appropriate treatment plan. An excisional biopsy of a vaccine-associated sarcoma will rarely result in a complete resection and is likely to result in local recurrence and a second, more difficult surgery will be necessary. Tumor recurrence has been documented to occur as early as 2 weeks after surgery and will typically occur by 6 months after incomplete surgical resection.[28] An aggressive surgical resection is necessary to effect local control, and this can entail resection of the tumor with 3 to 5 cm margins, removal of associated bone (e.g., dorsal spinous processes, partial scapulectomy), and at least one fascial plane deep to the involved tissues. Vaccine-associated sarcomas have commonly occurred in the interscapular space. This is a difficult location for surgery because it may require removal of dorsal spinous processes and the surrounding musculature. For this reason the

Vaccine-Associated Feline Sarcoma Task Force has made the recommendation to vaccinate with rabies and feline leukemia virus (FeLV) in the distal hind limb. Therefore amputation would be possible to effect local tumor control. Even with amputation or hemipelvectomy, it may not be possible to completely excise a vaccine-associated sarcoma. It is often necessary to use a multimodality approach, combining radiation therapy and surgery. For instance, preoperative irradiation of a proximal limb sarcoma may be necessary prior to amputation. The use of radiation therapy in the preoperative setting will often result in reduction in tumor size, and theoretically sterilization of the peripheral components of the tumor that would otherwise be problematic and result in an incomplete resection and resultant rapid tumor regrowth.

Chemotherapy may be used in the management of vaccine-associated sarcomas as adjuvant therapy to address potential metastatic disease, as neoadjuvant therapy to reduce the tumor in size prior to surgical resection, or as palliative therapy for nonresectable tumors. The use of combination doxorubicin and cyclophosphamide has been reported in 12 cats with nonresectable tumors.[29] There was a 50% overall response rate. The MST was significantly longer in those cats that responded (242 days) than in those that did not respond (83 days).

A combination of surgery, radiation therapy, and chemotherapy may result in the greatest potential for long-term tumor control. The largest report to date details the results of preoperative radiotherapy in 92 cats with vaccine-associated sarcomas.[30] The median time to first event (time from the start of treatment to local recurrence, metastasis, or date of death or euthanasia) was significantly longer at 986 days (n = 59 cats) if a complete resection was accomplished compared with 292 days (n = 28 cats) with an incomplete resection. There was a trend toward improved survival with the addition of chemotherapy (carboplatin, other) with a median time to first event of 1059 days (n = 33 cats) in cats that received chemotherapy versus 584 days (n = 59 cats) in those cats that were treated with radiation and surgery alone. The overall rate of metastasis was 21.7% (20/92), although complete follow-up was not available for all cats. Ongoing investigations are being carried out to determine the optimal treatment approach for vaccine-associated sarcomas, but it is likely that the best chance for success will lie in early detection and aggressive management or prevention of the development of vaccine-associated sarcomas.

183.7 PREVENTION

The cause of the majority of canine soft tissue sarcomas is unknown and therefore it is not feasible to develop strategies for prevention. However, for cats where there has been an association between vaccination and the development of soft tissue sarcomas, it is possible to decrease the risk of development of a soft tissue sarcoma. It is important to limit the number of vaccinations that are administered to cats and to only give those vaccines that are necessary to maintain health. For instance, it is not necessary to vaccinate cats for FeLV when they are indoor cats that are not exposed to other FeLV-positive cats. It is also important to follow the recommendations that have been provided by the Vaccine-Associated Feline Sarcoma Task Force: limiting one vaccine per site and documenting the location of each of the vaccines (right hind limb for rabies, left hind limb for FeLV, and right lateral scapular region for feline viral rhinotracheitis calcivirus panleukopenia [FVRCP]). In this way even if a tumor is to develop, an owner can be informed as to what to watch for and where to check for a possible tumor. Additionally, vaccines have been developed that do not appear to result in a local inflammatory response and may therefore translate into a decreased risk of tumor development at that site, although no long-term studies have confirmed this. There have been isolated reports of tumor development in cats at sites not associated with vaccination but rather due to some other inciting event that has resulted in a local inflammatory response. For instance, a report exists of a cat that developed a condition similar to a vaccine-associated fibrosarcoma at the site of a deep nonabsorbable suture.[31]

183.8 SUMMARY

Soft tissue sarcomas include a diverse group of histologic types classified based on the cell of origin but, as a group, exhibit similar biologic behavior. Tumor grade has proven to be important and predictive for outcome in dogs with soft tissue sarcomas but has not been shown to be of prognostic significance in cats. Wide surgical resection is required for local control in dogs and cats with soft tissue sarcomas. Radiation therapy will control the majority of tumors after incomplete resection in dogs; however, complete surgical removal, with or without irradiation, is necessary for control of vaccine-associated sarcomas in cats. Currently, a multimodality approach including surgery, radiation therapy, and chemotherapy seems reasonable to optimize the chance of tumor control in dogs with high-grade soft tissue sarcomas and cats with vaccine-associated sarcomas.

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184 CHAPTER • 184 Hemangiosarcoma

Philip J. Bergman

184.1 GENERAL FEATURES, PATHOLOGY, AND BIOLOGIC BEHAVIOR

Hemangiosarcoma (HSA) (angiosarcoma, malignant hemangioendothelioma) is an extremely malignant cancer of vascular endothelial origin. With this cellular origin, virtually any anatomic site can have HSA as a primary or secondary tumor diagnosis. HSA occurs most frequently in dogs (approximately 2% of all tumors), and the most common site of origin is the spleen; however, additional sites include right atrium, pericardium, liver, muscle, lung, skin and subcutis, bone, kidney, central nervous system (CNS), peritoneum and oral cavity.[1–3]

In three large canine splenic disease studies encompassing approximately 2000 dogs, a “rule of two thirds” was found, suggesting that approximately two thirds of dogs with a splenic mass have a malignancy (therefore one third are not malignant) and two thirds of the malignant tumors of the spleen are HSA.[2,4,5] It cannot be overemphasized that only histology can confirm the diagnosis of HSA. The differential diagnosis for a splenic mass should include lymphoma, leiomyosarcoma, fibrosarcoma, osteosarcoma, malignant fibrous histiocytoma, and other sarcomas (e.g., undifferentiated, liposarcoma, mesenchymoma), as well as non-neoplastic entities such as nodular hyperplasia, splenic hematoma, and hemangioma.[4,6,7] HSA can be single or multiple, and in those dogs with multiple tumors it can be extremely difficult to identify which is the primary tumor. HSAs are typically grossly soft, nodular, and dark red due to hemorrhagic and necrotic regions; however, extremely undifferentiated HSAs can lose this grossly vascular appearance and be more firm and pale gray, like other sarcomas. Immunohistochemistry (IHC) using antibodies against factor VIII, PECAM, and other antigens can be helpful to distinguish HSA from other undifferentiated neoplasms.[8,9]

Importantly, the right atrium and auricle is the third most common site for HSA in the dog, and HSA is the most common heart tumor.[10–15] Pericardial effusion, cardiac tamponade, or both are common sequelae to cardiac HSA.[16,17] Twenty-five percent of dogs with splenic HSA also have right atrial HSA.[18] It is not known whether the splenic or atrial lesion is primary or secondary. It seems most likely that right atrial lesions in dogs with splenic HSA are metastatic, because many dogs with right atrial HSA do not have splenic HSA. In addition to the aforementioned metastatic sites, HSA metastasizes to the brain in approximately 15% of cases.[19] HSA generally metastasizes via hematogenous routes (e.g., lungs, liver, brain) or by direct extension via transabdominal implantation via tumor rupture (e.g., omentum, mesentery).[13,18]

HSA tends to be a disease of older dogs and cats with a median age of 9 to 10 years. However, reports exist of extremely young dogs and cats with this disease (5 to months to a few years of age).[20–23] German shepherd dogs are the most common breed of dog diagnosed with HSA.[10] Other large breed dogs, such as golden retrievers and Labrador retrievers, may also be over-represented. In cats, the most common breed is the domestic shorthair (DSH).[24–26] HSA appears to be less common in cats (< 0.5% of all tumors) than dogs, with the most common primary tumor sites including spleen, liver, or mesentery.[27–29] Intra-abdominal HSA in the cat appears to be a highly malignant neoplasm, similar to that in dogs; metastatic sites commonly include lungs, liver, omentum, diaphragm, and occasionally pancreas.[21–26] There does not appear to be an overt gender predisposition for HSA in dogs or cats; however, some reports suggest that male dogs are redisposed.[10,12,20,23]

The cause of HSA in dogs and cats is unknown. Exposure to toxins such as vinyl chloride, dioxides, radiation, and arsenicals have been reported in humans to be associated with HSA.[30–32] Radiation exposure in dogs has been implicated as a potential cause of HSA[33]; however, the implanted doses of radiation were high and lengths of time of implantation and subsequent exposure were long in these studies. Interestingly, the ingestion of methylnitrosamines from fish meal by mink has been implicated in the carcinogenesis of HSA.[20] Ultraviolet (UV) light exposure may be a potential cause of HSA in dogs because cutaneous HSAs are commonly seen in dogs with light hair and poor pigmentation (e.g., salukis, whippets, white bulldogs).[34]

184.2 HISTORY AND CLINICAL SIGNS

Due to its cell of origin, HSA can be found in dogs or cats in almost any anatomic locale; therefore the history and clinical signs can vary. At the most extreme, HSA can cause sudden death due to tumor rupture, acute blood loss, or both. At the other end of the spectrum, nonspecific signs such as anorexia, vomiting, and lethargy can be seen in dogs and cats with HSA. It is quite common for HSA patients with intra-abdominal or intrathoracic disease to have a history of weakness, pale mucous membranes, or collapse (or a combination of these signs). Other potential historical abnormalities that may be noted by owners are abdominal distension, dyspnea, and weight loss. Episodes with weakness and collapse can last for minutes to hours with recovery from the episode being a common feature. It is surmised that the weakness, pale mucous membranes and collapse are due to acute blood loss, whereas the dramatic recovery is likely due to discontinuation of the acute blood loss, autotransfusion of the blood lost into a body cavity, or both.

In those situations where the heart is involved, the acute blood loss from the HSA can result in pericardial or thoracic effusion (or both), which can result in cardiac tamponade. On physical examination, these dogs may have clinical signs of right heart failure, muffled heart sounds, and arrhythmias.[16,35] The neurologic form of HSA can cause a variety of neurologic signs that include seizures.[19] The cutaneous form of HSA generally causes discrete nonulcerative dermal to subcutaneous masses that are firm, raised, and dark purple to red. When involving the deeper tissues such as muscle, deep fascia, or both, dogs may have a large mass, firmness in the muscle, lameness, or a combination of these signs. Swelling distal to the lesion can be seen with extremely large intra-or intermuscular HSA.

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184.3 DIAGNOSIS AND STAGING

Presumptive diagnosis of HSA can be based on the history, signalment, and physical examination findings. In addition, other diagnostics such as radiography, ultrasound, and fine needle aspiration or paracentesis (or both) are valuable. Serosanguineous effusions associated with HSA generally do not clot and upon cytologic examination only reveal a confirmatory diagnosis in 25% of dogs.[35]

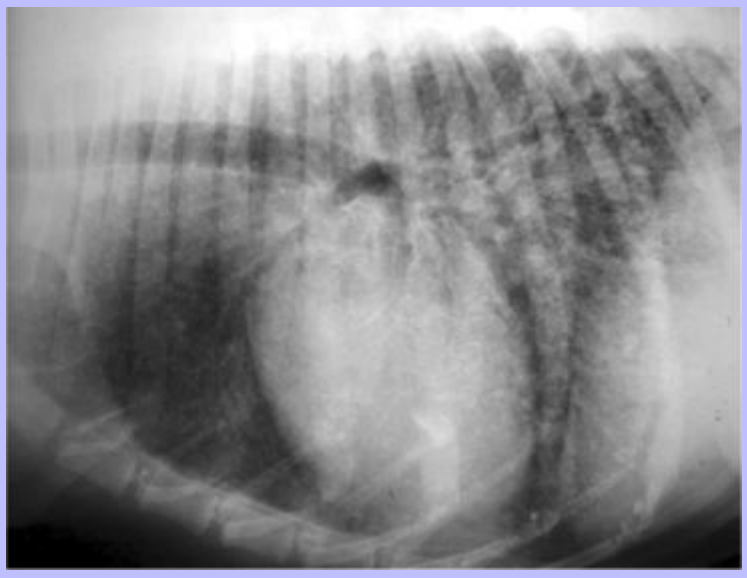
It cannot be overemphasized that the definitive diagnosis of HSA can only be made via biopsy and histopathologic examination (or in the rare instance of the aforementioned cytologic-based diagnosis). After surgical removal, large lesions should be “bread-loaf” sectioned to allow for full fixation by formalin, and then the entire sample submitted whenever possible. In those situations in which the sample and concomitant formalin represent too large a volume for transport to the pathology laboratory, one can either (1) fully fix the bread-loafed specimen overnight, remove the specimen, and submit in formalin-wetted towels to prevent sample drying or (2) submit representative smaller samples from a variety of regions of the lesion. Whenever possible the entire resection should be submitted no matter what type of neoplasia is suspected, because this best allows the pathologist to discern a final diagnosis with delineation of resection margins. If the diagnosis of HSA is suspected and

histopathologic review does not document the presence of HSA, then further consultation with the histopathologist and additional review of submitted tissues may be helpful.

Nondermal HSA is commonly a metastatic neoplasm based on necropsy studies. Because the prognosis (discussed later in this chapter) and potential need for additional therapy is highly dependent on clinical stage, a thorough evaluation for evidence of metastatic disease is highly recommended. Thoracic radiographs with right and left lateral views and ventrodorsal views should be performed for delineation of possible lung metastasis, cardiac involvement, or both with the presence of pericardial effusion. Although many sarcomas with pulmonary metastasis will have a classic nodular or "cannonball appearance," HSA pulmonary metastases can have a military to coalescing miliary pattern as seen in Figure 184-1.[36,37] Radiography was able to detect pulmonary HSA metastasis and cardiac involvement (because of an abnormal silhouette) in 78% and 47% of dogs, respectively.[37] The most accurate diagnostic for cardiac involvement from HSA is echocardiography.[38,39] The value of echocardiography for staging HSA is continuing to be evaluated. Echocardiography is recommended for HSA staging whenever available and financially feasible.

Use of abdominal ultrasound is strongly recommended for additional staging of HSA. It can be a valuable tool for evaluation of a primary intra-abdominal tumor and delineation of the presence of metastatic spread. The echo pattern most commonly seen in dogs with splenic HSA is mixed or nonhomogenous (or both), whereas hepatic metastases generally appear anechoic or hypoechoic.[40] If metastatic spread is felt to be highly likely on ultrasound examination, it must be emphasized that a tissue-based histopathologic or cytopathologic diagnosis (or both) is necessary to prove that metastatic disease is indeed present. Importantly, abnormalities seen on abdominal exploratory for a splenic HSA, such as masses on the liver, omentum, diaphragm, should all be biopsied and evaluated histopathologically. The clinical staging system for HSA is shown in Box 184-1.

Figure 184-1 Lateral chest radiograph of a 6-year-old castrated male golden retriever 52 days after splenectomy for a splenic hemangiosarcoma. The reader should note the non-nodular miliary metastatic pattern.



The most common hematologic finding in dogs with HSA is anemia.[13,20,41] The anemia is generally a regenerative normocytic-normochromic anemia with polychromasia, reticulocytosis, nucleated red blood cells (RBCs), and anisocytosis.[13,20,41] The anemia associated with HSA is generally felt to be due to microangiopathic hemolysis and possibly intracavitary hemorrhage (with subsequent autotransfusion), which results in RBC fragmentation and schistocytosis in canine and human HSA but not feline HSA.[42] Other common hematologic abnormalities in dogs and cats with HSA also include neutrophilic leukocytosis, band neutrophilia, and thrombocytopenia. Significant thrombocytopenia can be seen in approximately one half of dogs with HSA.[43,44] In addition, spontaneous hemorrhage and disseminated intravascular coagulation (DIC) may occur in dogs and cats with HSA, and therefore a coagulogram is strongly recommended prior to the use of invasive diagnostics, surgery, or both.

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184.3.1 Box • 184-1 Canine Hemangiosarcoma TNM Clinical Staging System

184.3.1.1 T = Tumor (Primary Tumor)

T0 = No evidence of tumor

T1 = Tumor confined to primary site and/or dermis and <5 cm in diameter

T2 = Tumor invading SQ tissues and/or ≥ 5 cm in diameter

T3 = Any T1 or T2 with tumor invading adjacent structures and/or muscle

184.3.1.2 N = Node (Regional Lymph Nodes)

N0 = No evidence of regional lymph node involvement

N1 = Regional lymph node involvement

N2 = Distant lymph node involvement

184.3.1.3 M = Metastasis (Distant Metastasis)

M0 = No evidence of distant metastasis

M1 = Distant metastasis

184.3.1.4 TNM-Based Stages

I = T0 or T1, N0, M0

II = T1 or T2, N0 or N1

III = T2 or T3, N0 or N1 or N2, M1

184.4 TREATMENT AND PROGNOSIS

184.4.1 Surgery

Surgery continues to be the gold standard treatment for dogs and cats with HSA. Due to the metastatic propensity of nondermal HSA, this disease should be one that is routinely thought of as having two problems: (1) local tumor control and (2) systemic tumor control. Therefore even though surgery remains the gold standard, it is almost always used in concert with some systemic therapy modality in nondermal HSA because the prognosis for dogs with splenic HSA treated with surgery alone remains poor to grave with a median survival time (MST) of only 19 to 86 days.* The prognosis for cats is also poor. Cats have a MST after splenectomy for splenic HSA of only 20 weeks.[26] Surgery should be used as aggressively as possible for HSA to remove all diseased tissue whenever possible. For example, for dogs with intramuscular HSA, a radical myectomy or amputation would be recommended, whereas with splenic HSA a splenectomy would be the surgical methodology of choice. Due to aforementioned staging concerns, any suspicious lesions (e.g., omentum, diaphragm, liver, lymph nodes) noted at the time of surgery should also be biopsied and histopathologically examined. For dogs undergoing splenectomy for splenic HSA, development of ventricular arrhythmias, thought to be due to hypovolemia, anoxia, and anemia, occurred in approximately one quarter of dogs postoperatively.[47]

Local tumor control is especially problematic for dogs with HSA of the pericardium, right atrium, or both due to anatomic constraints. Exploratory thoracotomy may be performed with removal of the tumor by pericardiectomy for pericardial HSA, as well as the use of staples and hand suturing for right auricular and atrial tumors.[14,16,48] Unfortunately the prognosis for HSA at this anatomic location is also poor to grave, with death being reported within 3 to 5 months (median survival only weeks) after surgery.[14,16] Thoracoscopy appears to be a promising less-invasive diagnostic modality and has also been reported as a methodology for pericardiectomy.[48,49]

Cutaneous HSA without hypodermal invasion is less metastatic than nondermal HSA. The median survival of dogs with dermal only HSA (treated by surgical resection) was 780 days, whereas in dogs with hypodermal or deeper involvement of their cutaneous HSA (or both) have MSTs of 172 and 307 days, respectively.[50] Therefore it appears that hypodermal involvement in canine cutaneous HSA warrants a poorer prognosis and probable need for adjuvant therapy when compared with dermal HSA. Cats with cutaneous HSA treated by surgical excision had a MST of 44 weeks.[26]

* References 1, 4, 5, 13, 45, 46.

184.4.2 Chemotherapy

Hypodermal or deeper canine and feline HSA appears to be routinely metastatic, and therefore adjuvant therapy is considered necessary after surgery. As shown in Box 184-2, doxorubicin-based protocols are most commonly reported. Similar MSTs are noted whether doxorubicin is used adjuvantly as a single agent or in combination with cyclophosphamide (i.e., adriamycin and cyclophosphamide) and vincristine (i.e., vincristine, adriamycin, and cyclophosphamide [VAC]) as shown in Table 184-1.[45,51–53] Because single-agent doxorubicin appears to have similar activity to VAC and AC with less toxicity, doxorubicin may be the therapy of choice for HSA.[45] However, doxorubicin appears to have limited therapeutic benefit. For those dogs with nondermal HSA

receiving five doses of doxorubicin after surgery, negative prognostic factors included (1) younger age, (2) higher grade and degree of anaplasticity and undifferentiation, and (3) incomplete gross tumor removal.[45] Other chemotherapy regimens such as single-agent vincristine and VCM (vincristine, cyclophosphamide, and methotrexate) have been reported in dogs with HSA[13,54]; however, their use is not recommended due to limited therapeutic activity. 760 761

184.4.2.1 **Box • 184-2 Canine Hemangiosarcoma Adjuvant Chemotherapy Protocols**

184.4.2.1.1 **1. A (Adriamycin)**

Doxorubicin IV every 3 weeks for 5 treatments

30 mg/m2 for dogs >10 kg

1 mg/kg for dogs ≤10 kg OR cats

Note: Pretreatment CBC/platelet counts required.

Need >3000 neutrophils and >75,000 platelets to treat

Nadir CBC/Plt at 7–10 days

184.4.2.1.2 **2. AC (Adriamycin and Cyclophosphamide)**

Day 1—Doxorubicin (see "A" protocol) and 100–150 mg/m2 cyclophosphamide IV

Can substitute IV Cytoxan with Oral at 50 mg/m2 on days 3, 4, 5, 6

Day 22—Repeat cycle for 4–6 total cycles

Note: Antibiotics may be required due to significant myelosuppression.

184.4.2.1.3 **3. VAC (Vincristine, Adriamycin, and Cyclophosphamide)**

Day 1—Doxorubicin (see "A" protocol) and cyclophos phamide 100–200 mg/m2 IV

Day 8—Vincristine at 0.75 mg/m2

Day 15—Vincristine at 0.75 mg/m2

Day 22—Repeat cycle for 4–6 total cycles

Note: Clinician should stop chemotherapy for 1 week if any pretreatment CBC has <3000 neutrophils. Antibiotics may be required prophylactically and/or therapeutically because this protocol is extremely myelosuppressive.

Table • 184-1 Survival Times for Canine Hemangiosarcoma

TREATMENT	MEDIAN SURVIVAL IN DAYS	REFERENCES
Splenectomy	19–86	1, 5, 13, 45
Splenectomy and MBVacc +/–VMC	91–117	13
Splenectomy and VAC	145	51
Splenectomy and AC	141–179	53, 62
Splenectomy and AC and L-MTP-PE	273	55
Complete Surgery and A	172	45
Incomplete Surgery and A	60	45

Dogs with earlier-stage hypodermal or deeper HSA treated with surgery and chemotherapy appear to have a better prognosis compared with dogs with more advanced stage disease based on multiple studies.[13,55,56] When taken in concert with the aforementioned negative prognostic factor of incomplete tumor resection,[45] it appears that the use of adjuvant chemotherapy is most beneficial in dogs with earlier-stage, nonruptured, and completely resected HSA. It therefore cannot be overstated that preoperative staging is imperative for preoperative prognosis in dogs suspected of having HSA.

184.4.3 Immunotherapy and Biologic Therapy

Relatively few studies have been published investigating the therapeutic efficacy of biologic response modifiers in canine HSA. Modest improvement in survival was noted for dogs receiving a killed bacterial vaccine after splenectomy compared with splenectomy alone.[13] Macrophage-activating agents such as L-MTP-PE (liposome-encapsulated muramyl tripeptide phosphatidylethanolamine) appear to have tumoricidal activity against a variety of neoplasms.[57–59] In a surgical adjuvant-chemotherapy canine HSA study, L-MTP-PE significantly prolonged disease-free survival and overall survival[55]; unfortunately, this compound is presently not commercially available.

Based on the cell of origin, antiangiogenic approaches are thereby logical anticancer approaches to HSA. Minocycline is an antibiotic with antiangiogenic activity.[60,61] Dogs with HSA were treated with surgery, AC (i.e., doxorubicin and cyclophosphamide), and minocycline; however, no statistically significant change in survival was noted in comparison to historical controls.[53,56] Although these results are discouraging, additional investigations using novel rationally targeted therapies for HSA are desperately needed and encouraged.

184.4.4 Radiation

Due to HSA's predilection for visceral anatomic sites in concert with its metastatic nature, radiation is rarely used. It has been noted anecdotally that significant decreases in bulky disease has followed externally located HSA treated with palliative radiation, but the impact on prolongation of survival has not yet been published.

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185 CHAPTER • 185 Bone and Joint Tumors

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185.1 PRIMARY APPENDICULAR TUMORS

185.1.1 Canine Osteosarcoma

The four primary bone tumors are osteosarcoma (OSA), chondrosarcoma (CSA), fibrosarcoma (FSA), and hemangiosarcoma (HSA).[1] Liposarcoma, rhabdomyosarcoma, plasma cell tumors (solitary plasmacytoma and multiple myeloma), and lymphoma are also reported to involve bone; however, these tumors more typically involve bone as a secondary process.[1] OSA is the most common primary bone tumor accounting for greater than 85% of all appendicular bone tumors.[1] OSA occurs in the axial skeleton and may occur in extraskeletal tissues, including visceral organs, skin, and mammary glands.

OSA is a tumor of unknown cause. Repetitive injury to the physis has been proposed due to the high incidence of OSA in the metaphyseal region of large breed dogs with late-closing physes, however, recent evidence fails to support this theory.[1,2] Other potential causes include viral transmission and a genetic predisposition.[1,3] OSA has been reported in association with previous fractures, particularly in the femoral diaphysis, and other bone diseases, such as infarcts and bone cysts.[3] Radiation-induced OSA has also been documented and may be associated with protocols involving radiation doses greater than 3.5 Gy per fraction.[1]

185.1.1.1 Signalment

Appendicular OSA is usually a disease of large to giant breeds of dogs.[1] OSA also affects smaller breeds but they are 20 times less likely to develop OSA.[4] Breed predispositions have been reported; however, size, and particularly height, are more important risk factors than breed.[1,5] Neutered dogs, regardless of sex, have a two-fold risk of developing OSA compared with sexually intact dogs.[5] The age distribution at diagnosis is bimodal, with most dogs between 7 and 9 years of age and a smaller population between 1 and 2 years of age.[1,5]

185.1.1.2 Diagnosis

Lameness and localized limb swelling are the most common signs.[1] Pain and lameness are caused by microfractures, disruption of the periosteum with tumor extension, and pathologic fracture.[1] Appendicular OSA occurs in the metaphyseal region of long bones. The thoracic limb is involved 1.7 times more frequently than pelvic limb.[1,6] The distal radius (23.1% of OSA cases) and proximal humerus (18.5%) are the two most common sites for OSA.[1,6] In the hind limb, OSA occurs in the tibia and femur with equal frequency. The femur is the most common site in dogs weighing less than 15 kg.[4]

An orthopedic examination is necessary to localize the source of lameness and differentiate metaphyseal pain from other common orthopedic diseases in large breed dogs, such as osteoarthritis, cranial cruciate ligament rupture, and hip dysplasia. Physical examination and a minimum data base, consisting of hematology, serum biochemistry, and urinalysis, is important to evaluate general health status and ability to tolerate surgery and chemotherapy. Three basic types of OSA exist: (1) endosteal, (2) periosteal, and (3) parosteal.[1,7] Periosteal and parosteal OSA are uncommon and originate from the periosteal surface or, less commonly, the endosteum and medullary canal.[1,7] Endosteal OSA is far more common.[1] Regional radiographs are recommended to establish a tentative diagnosis and differentiate primary bone tumors from other orthopedic diseases. The radiographic appearance of endosteal OSA can range from lytic to blastic and is usually a mixture of both patterns.[1,7] Other characteristic radiographic signs of primary bone tumors include cortical lysis, periosteal proliferation, palisading new bone formation perpendicular to the axis of cortical bone (sunburst effect), periosteal lifting due to subperiosteal hemorrhage (Codman's triangle), loss of the fine trabecular pattern in metaphyseal bone, and pathologic fracture with metaphyseal collapse.[1,7] Appendicular FSA and CSA have a similar radiographic appearance to OSA and cannot be differentiated radiographically. However, classic signalment and radiographic findings are often sufficient for the diagnosis of a primary bone tumor.[1,7]

Differential diagnoses for primary bone tumors include fungal osteomyelitis, especially *Coccidioides immitis* and *Blastomyces dermatitidis*.[1,7] A thorough history is necessary to determine whether the dog lives or has traveled through an area endemic for fungal disease. Dogs with fungal osteomyelitis often have systemic illness and polyostotic bone disease.[1,7] Conversely, dogs with primary bone tumors rarely have systemic illness and bone involvement is usually confined to a single site.[1,7] Bacterial osteomyelitis, atypical bone cysts, and metastatic neoplasia are other potential differential diagnoses.

Bone biopsy can be performed to confirm the diagnosis using closed or open techniques.[8–11] Fine needle aspiration, with or without ultrasound guidance, is a useful, minimally invasive technique to diagnose sarcoma and differentiate primary bone tumors from metastatic disease and fungal osteomyelitis.[8,9] Closed needle-core biopsy, using either a Jamshidi needle or Michele trephine, is invasive and requires general anesthesia.[1] Biopsies should be planned and performed meticulously, preferably by the primary surgeon, so the biopsy does not compromise surgical options.[1] The biopsy should be performed to ensure that the biopsy tract can be excised en bloc with the tumor and unaffected tissues are not contaminated during the biopsy procedure or by postbiopsy hematoma formation.[1] Large core samples can be obtained with a Michele trephine, resulting in a diagnostic accuracy rate of 94%, but the larger bone defect also increases the risk of pathologic fracture.[1,10] Bone biopsies procured with a Jamshidi needle have an accuracy rate of 82%, and the smaller gauge needle decreases the risk of complications and creates a significantly smaller biopsy tract.[11] Two to four biopsies should be collected from the center and periphery of the lesion through a single stab incision in the skin. The risk of pathologic fracture increases if the biopsy needle penetrates both the near and far cortices.[1] Multiple biopsies are preferred to increase diagnostic accuracy because small biopsy samples can be misdiagnosed due to the heterogeneous nature of OSA.[1] Central bone biopsies are recommended because the peripheral aspects of bone tumors often contain reactive bone.[1] After definitive surgery the entire tumor should be submitted for histology to confirm the diagnosis.

Appendicular OSA is a highly aggressive tumor. More than 90% of dogs have micrometastatic disease; however, less than 15% of dogs have clinically detectable metastasis at the time of initial diagnosis[1] Metastasis occurs primarily through hematogenous routes, particularly to the lungs and other bone, although metastasis to the regional lymph node is reported in up to 37% of dogs with OSA.[1,6,9,12] Palpation of regional lymph nodes, thoracic radiographs, and nuclear scintigraphy are essential tools for thorough staging of dogs with a suspected primary bone tumor. The presence of detectable metastatic disease significantly influences the management options for dogs with OSA.[1,13–15] High-detail three-view inspiratory thoracic radiographs, including right and left lateral and ventrodorsal or dorsoventral projections, are required for the diagnosis of pulmonary metastases.[1,7] Lesions of 6 mm diameter or greater can be detected with good-quality radiographs.[1] Computed tomography (CT) provides greater sensitivity to detect lesions less than 6 mm in diameter, but advanced imaging may be cost prohibitive for some clients and has been associated with false-positive diagnoses of metastatic lesions.[1,13] Whole-body bone scintigraphy, using radiolabeled technetium pertechnetate, is highly sensitive for the detection of concurrent skeletal abnormalities, including both primary and metastatic tumors, but is not specific for the diagnosis of neoplasia.[1,14,15] In a recent study a second asymptomatic bone lesion, consistent with metastatic disease, was identified in 7.8% of 399 dogs with OSA.[15] If a suspicious lesion is identified, fine-detail radiographs should be performed of that region. Bone biopsy may be performed for confirmation if radiographic results are equivocal. Alternatively, survey radiographs of the skeleton, consisting of lateral radiographs of long bones and ventrodorsal radiographs of the pelvis, can be used to screen for bone metastases if nuclear scintigraphy is unavailable.[16] When present, metastatic skeletal disease is a negative prognostic indicator. This becomes extremely important for dogs in which limb amputation is planned, because occult skeletal metastases may become clinically symptomatic after surgery, rendering the dog nonambulatory.

185.1.1.3 Palliative Management

Management options for dogs with appendicular OSA are broadly classified into two distinct pathways: (1) palliative-intent or (2) curative-intent. Palliation is indicated for dogs with metastatic disease or when owners do not want to pursue more aggressive treatment options. Palliative therapy is geared toward management of pain and lameness associated with the primary bone tumor but does not improve survival time. Analgesia is the cornerstone for the palliative management of dogs with primary bone tumors (Table 185-1).[17] Nonsteroidal anti-inflammatory drugs (NSAIDS) may initially be sufficient to manage pain and improve quality of life. Cyclooxygenase-1-sparing NSAIDS are preferred as adverse effects are reduced.[17] More potent analgesic drugs, or combinations of drugs, are often required for effective pain relief.[17] These include codeine acetaminophen, partial mu agonists or agonist-antagonists, sustained-release oral morphine, fentanyl patches, and adjunctive drugs, such as N-methyl-D-aspartate (NMDA) antagonists and tricyclic antidepressants.[17] Multiple drug combinations are most efficacious for refractory pain because different aspects of the pain pathway are targeted and result in an additive or synergistic analgesic effect. The median survival time (MST) for dogs with appendicular OSA treated with analgesic drugs alone has not been reported, although anecdotal evidence suggests that 1 to 3 months is a reasonable expectation.

Radiation therapy is effective for palliation of dogs with primary bone tumors. A number of different protocols have been described, most commonly 4 to 10 Gy administered on a 0-7–21 day or monthly protocol.[18–22] These protocols are relatively inexpensive and do not require prolonged hospitalization. Radiation reduces local inflammation, minimizes pain, slows progression of metastatic lesions, and improves

quality of life in dogs with primary and metastatic lesions.[18–23] A 50% to 92% response rate has been reported with the median onset of response 11 to 14 days after initiation of radiation therapy and median duration of response lasting 73 to 130 days.[18–22] The duration of response is significantly improved when less than 50% of bone length is affected by tumor. Proximal humeral OSA has been reported to have the best response.[21,22] Higher cumulative doses, higher intensity of treatment, and the addition of chemotherapy to palliative radiation protocols have been reported to improve response rate and duration of response.[20–22] Palliative radiation therapy is not associated with acute effects and does not negatively influence quality of life.[18–22] The MST for dogs with appendicular OSA treated with palliative radiation is 122 to 313 days.[18–22] Radiopharmaceuticals, such as samarium, have been used for the palliation of primary and metastatic bone lesions but are expensive and, at this time, are not widely available in veterinary medicine.[24,25]

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Table • 185-1 Oral and Transdermal Analgesic Drugs Used for the Palliation of Dogs with Appendicular Osteosarcoma

ANALGESIC DRUG	DOSE	INTERVAL	COMMENTS
NSAIDS			
Carprofen	2.2 mg/kg	12 hr	Idiosyncratic hepatic failure, gastric ulceration, renal failure, lethargy
Deroxicab	1–2 mg/kg	24 hr	Gastric ulceration, renal failure
Etodolac	10–15 mg/kg	24 hr	Gastric ulceration, renal failure
Meloxicam	0.05–0.1 mg/kg	24 hr	Gastric ulceration, renal failure
Ketoprofen	0.5–1.0 mg/kg	24 hr	Gastric ulceration, renal failure, platelet aggregation inhibition
Piroxicam	0.3 mg/kg	48 hr	Gastric ulceration, renal failure
Partial Agonists			
Butorphanol	0.55 mg/kg	1–2 hr	Controlled substance, short duration of activity, ceiling effect of analgesia, sedation, respiratory depression
Opioids Morphine	0.5–1.0 mg/kg	8–12 hr	Controlled substance, sedation, euphoria, bradycardia, vomiting, urine retention, constipation
Fentanyl patch	50 µg/hr (10–20 kg)	72 hr	Controlled substance; variable serum concentration due application site, skin blood flow and
	75 µg/hr (20–30 kg) to	72 hr	temperature, and hydration; correct disposal required because residual dose lethal to humans
	100 µg/hr (>30 kg)	72 hr	
Miscellaneous			
Codeine-acetaminophen	0.5–2.0 mg/kg	6–8 hr	Controlled substance, anemia
Amantadine	3 mg/kg	24 hr	NMDA antagonist
Prednisone	0.5–1.0 mg/kg	12–24 hr	Anti-inflammatory, synergistic activity with opiates, contraindicated with NSAIDs
Amitriptyline	1–2 mg/kg	12–24 hr	Tricyclic antidepressant, alters serotonin and norepinephrine activity

185.1.1.4

Limb Amputation

Limb amputation can be used as palliative therapy and as part of the curative-intent treatment in dogs with primary bone tumors.[1,26,27] Amputation is an effective means of pain control, particularly in dogs with pathologic fracture and lameness unresponsive to analgesic drugs or radiation therapy. Osteoarthritis, neurologic disease, obesity, and large body size have been cited as relative contraindications.[1,26,27] Experience has shown that osteoarthritis, weight, and body size are rarely problematic. The majority of dogs

with OSA are middle-to older-aged, large breed dogs with moderate pre-existing osteoarthritis. They rarely have difficulties after amputation.[27] Dogs with neurologic disease or *severe* clinical osteoarthritis are exceptions, and palliative management or limb-sparing techniques should be considered in these dogs. When thoracic limb amputation is performed, the scapula should be removed. Tumor control, particularly for dogs with proximal humeral OSA, and cosmetic appearance is improved.[1] In the pelvic limb, coxofemoral disarticulation should be performed for dogs with OSA distal to the proximal femur, whereas dogs with proximal femoral OSA should be treated with either en bloc acetabulectomy or subtotal hemipelvectomy to achieve adequate tumor control and minimize the risk of local recurrence. Most dogs are able to ambulate unassisted within 12 to 24 hours after limb amputation. Amputees should be encouraged to ambulate at home by the owners after discharge to speed recovery. Studies have shown that most dogs fully adapt to amputation by 4 weeks after surgery. If the dog was significantly lame from the tumor prior to surgery, full recovery often occurs more quickly than 4 weeks once the painful limb is removed. In addition, a positive attitude by the owners shortens the time to adaptation after amputation.[27] Body weight and thoracic or pelvic limb amputation do not have a significant influence on the time to adaptation after amputation; however, early in the postoperative period, dogs with thoracic limb amputation have greater difficulty in balancing.[27] Behavioral changes, such as increased anxiety and loss of dominance, have also been observed but are relatively uncommon.[27] Complications associated with limb amputation are rare. Intraoperative complications may include hemorrhage, air embolism, and inadvertent thoracotomy (front-limb amputations). Possible postoperative complications include infection and stump recurrence. The survival time of dogs treated with amputation alone is significantly better than with the use of analgesic drugs or palliative radiation therapy.[9] The MST for dogs with OSA treated with limb amputation alone is 103 to 175 days with a 6-month survival rate of 47% to 52%, 12-month survival rate of 11% to 21%, and 24-month survival rate of 0% to 4%.[12,28–31]

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185.1.1.5 Limb-Sparing Surgery

Limb-sparing techniques are becoming more common, despite the success of limb amputation in dogs with primary bone tumors.[1,26,32–42] In fact, the most common reason for performing limb sparing in dogs with OSA is owner reluctance to proceed with amputation. Medical indications for limb sparing include previous amputation of another limb, severe concurrent osteoarthritis, or neurologic disease.[1,26]

Limb-sparing surgery is most successful for dogs with primary bone tumors in the distal radius and ulna.[26,32–34] Limb-sparing surgery for other anatomic locations is often associated with a high complication rate and poor postoperative limb function.[35,36] Candidates for limb-sparing surgery include dogs with tumors confined to the bone, minimal extension into adjacent soft tissue, and involvement of less than 50% of the bone length.[1,26] The extent of bone involvement is most accurately determined using CT scans.[43] Bone involvement is overestimated by radiographs, nuclear scintigraphy, and magnetic resonance imaging (MRI).[43–45] The use of imaging techniques that overestimate the degree of bone involvement may be acceptable because adequate surgical margins and complete resection of the bone tumor may be more readily achieved.[44] Pathologic fractures are a relative contraindication due to soft tissue contamination via hemorrhage and hematoma, although the risk of local tumor recurrence can be reduced by preoperative chemotherapy or radiation therapy.[26]

A number of surgical techniques have been reported to preserve limb function.[1,26,32–42] Marginal resection of the soft tissue component of the bone tumor is common to all techniques. After resection, the osseous defect is traditionally filled with a massive cortical allograft (Figure 185-1), although other options include vascularized ulna grafts, endoprostheses, and segmental bone transport osteogenesis.[1,26,32–42] Arthrodesis of the adjacent joint is often required due to the metaphyseal and periarticular location of appendicular OSA.[1,26] Pancarpal arthrodesis is well tolerated in dogs, but arthrodesis of the shoulder, stifle, and tarsal joints results in poor limb function. Rarely, joint preservation is possible with ulnar or diaphyseal OSA. The limb is placed in a lightly padded bandage postoperatively with dressing changes every 3 to 5 days for 2 to 3 weeks.[1,26] Weight-bearing and range-of-motion exercises can be started immediately postoperatively but should be restricted to leashed walks for the first 4 weeks.[1,26] Exercise is important in preventing flexure contracture of the digits and minimizing swelling of the foot and digits, both of which can occur as a result of resection of the digital extensor muscles and tendons and vascular structures during surgery. Good to excellent limb use is achieved in over 80% of dogs.[1,2,6,32,33]

The most commonly reported complications with limb-sparing surgery are implant failure, local tumor recurrence, and infection.[1,26,32,33,37–39] Implant failure occurs in approximately 10% of cases.[1,26,32,33,37] The injection of methylmethacrylate into the medullary canal of the allograft increases screw pullout strength and reduces the incidence of screw loosening, implant failure, and allograft fracture.[37]

Local tumor recurrence is caused by incomplete resection or, more commonly, residual neoplastic cells in the soft tissue adjacent to the tumor capsule after marginal resection of the primary bone tumor.[1,26] Local recurrence has been reported in up to 28% of cases[33]; however, this rate can be reduced to less than 10% with locally released chemotherapy agents, such as cisplatin from open-cell polylactic acid biodegradable implants, appropriate case selection, and experience.[1,26,38] Local recurrence either has no effect[2] or a negative influence on survival time depending upon the study cited.[35] Local recurrence can be managed with a second limb-sparing surgery, amputation, or palliative radiation therapy.[26]

Figure 185-1 Lateral radiographic projection of limb-sparing surgery of the distal radius using a cortical allograft.

Infection is the most significant postoperative complication encountered with limb-sparing surgery.* The cause of infection is unknown, although the extensive soft tissue resection with vascular compromise to a poorly perfused site, poor soft tissue coverage, implantation of orthopedic implants and nonvascularized and possibly immunogenic cortical bone, and administration of local and systemic chemotherapy are thought to contribute.[26]

Infection occurs in over 40% of limb spare cases where reconstruction is performed with an allograft.[32,33,37,39] Several different bacterial organisms have been cultured with mono-and polymicrobial infections occurring in approximately 50% of cases each.[39] Initially, infections are treated with appropriate antibiotics based on culture and sensitivity results, isotonic saline lavages, and wet-to-dry bandages.[1,39] If the infection is unresponsive or recurrent, antibiotic-impregnated methylmethacrylate beads can be surgically implanted adjacent to the infected bone.[39] Limb amputation may be used as a salvage procedure in dogs with uncontrollable infection.[1,37,39]

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* References 1, 26, 32, 33, 37, 39.

185.1.1.6 Radiation Therapy

Radiation therapy is most commonly used for palliation but can be used for control of the primary bone tumor in dogs where surgical options are either not indicated or refused.[46,47] Full-course external beam radiation therapy has been investigated.[46,47] The fractionation and radiosensitization protocols have varied, with total doses ranging between 24 to 54 Gy.[46,47] Complications include moist desquamation, alopecia, depigmentation, bone marrow suppression, and pathologic fracture.[46,47] The MST for dogs with OSA treated with curative-intent radiation therapy and adjuvant chemotherapy (AC) is 7 months.[46,47]

185.1.1.7 Chemotherapy

Definitive management of dogs with appendicular OSA requires treatment of both the local bone tumor and micrometastatic disease. The efficacy of chemotherapy in other types of primary bone tumors is less clear. Surgery, unless combined with chemotherapy, is considered a palliative measure.[28–31,48–54] Conversely, chemotherapy without surgery does not provide a survival benefit over other palliative techniques.[55,56] In most institutions and oncology practices, chemotherapy is initiated at the time of suture removal. Current chemotherapy protocols include the use of cisplatin, carboplatin, and doxorubicin, either as a single agent or in combination (Table 185-2).[1,28–31,48–54] Studies have not shown large differences in survival times between the different protocols using single or multiple agents. Practically speaking, protocol selection is often dependent on drug cost, adverse effects, and intensity of treatment. If cisplatin is used, saline diuresis is necessary to minimize the risk of nephrotoxicity (Table 185-3).[1] Nephrotoxicity can also be reduced by using carboplatin instead of cisplatin or concurrently administering amifostine, which is used to prevent cisplatin-induced nephrotoxicity in humans.[1,42,53,54] Doxorubicin has been associated with myocardial toxicity, particularly with cumulative doses greater than 180 mg/m^2. Hence, an echocardiogram is recommended prior to starting chemotherapy, especially in high-risk breeds.[1]

After administration of chemotherapy, especially after the first chemotherapy dose, dogs should be discharged with antibiotics and antiemetics for palliation of gastrointestinal (GI) disease and nausea if needed at home. Hematology should be performed at the time of nadir, generally 7 to 10 days postchemotherapy, and again immediately prior to subsequent doses of chemotherapy to assess the presence and degree of myelosuppression. Chemotherapy administration should be delayed or the dose decreased if the neutrophil count is less than 2000/μL or platelet count is less than 100,000/μL.[1] The MST for dogs treated with surgery and chemotherapy is 235 to 366 days, with a 33% to 65% 12-month survival rate and 16% to 28% 24-month survival rate.[28–31,48–54]

Table • 185-2 Chemotherapy Protocols Used in the Management of Dogs with Appendicular Osteosarcoma[*†]

AGENT OR AGENTS	DOSE	INTERVAL	NUMBER	COMMENTS
Cisplatin	70 mg/m^2	3 weeks	5	Vomiting during administration, nephrotoxicity, gastrointestinal (GI) toxicity, mild myelosuppression; nadir at 10 days; MST 262–413 days
Carboplatin	300 mg/m^2	3 weeks	4	Myelosuppression, GI toxicity; nadir at 11–14 days; MST 321–366 days
Doxorubicin	30 mg/m^2	2–3 weeks	5	Anaphylaxis during administration, GI toxicity, myocardial toxicity, myelosuppression, nadir at 10 days; MST 366 days
Cisplatin	50 mg/m^2	3 weeks	4	Cisplatin administered on day 1 and doxorubicin on day 2; MST 300–540 days
Doxorubicin	15 mg/m^2			
Carboplatin	300 mg/m^2	3 weeks	6	Carboplatin and doxorubicin administered alternately every 3 weeks for 3 doses each, for a total of 6 doses; MST 388 days
Doxorubicin	30 mg/m^2			

* Adapted from Dernell WS et al: Tumors of the skeletal system. In Withrow SJ, MacEwen EG, editors: *Small animal clinical oncology*, ed 3, Philadelphia, 2001, WB Saunders.

† Liptak JM et al: Survival analysis of dogs with appendicular osteosarcoma treated with limb-sparing surgery and adjuvant carboplatin or carboplatin and doxorubicin, *Pers Comm, Proc Vet Cancer Soc Conf* 21:39, 2001.

The role of immunotherapy in the treatment of dogs with OSA is undefined. A significant improvement in disease-free interval (DFI) and survival time has been reported in dogs treated with a nonspecific immunostimulant, muramyl tripeptide phosphatidylethanolamine.[57,58] Increased immune stimulation is also suspected in the prolonged survival times in dogs with infected limb-sparing surgery and four dogs with spontaneous regression of OSA lesions.[53,59]

185.1.1.8 Digit Osteosarcoma

OSA arising in bones distal to the carpus or tarsus are rare.[1,6] Treatment recommendations include limb salvage (i.e., amputation of the affected digit and metacarpal or metatarsal bones) followed by chemotherapy.[1,60] Similar to humans, the prognosis for dogs with OSA distal to the carpus or tarsus is better

than other appendicular sites, with a MST of 466 days.[60] However, the biologic behavior is still aggressive with most dogs euthanatized due to metastatic disease.[60]

185.1.1.9 Metastasis

Metastatic disease is the most common cause of death or euthanasia in dogs with appendicular OSA after definitive treatment.[1] Pulmonary and skeletal sites are most frequently involved, although other metastatic sites include subcutaneous tissue, mediastinum, myocardium, diaphragm, kidneys, spleen, small intestine, spinal cord and brain, and lymph nodes.[1,9,12]

Interestingly, metastatic disease rarely occurs in dogs undergoing palliative, nonsurgical treatment but is the major cause of death in dogs treated with surgery alone, despite the minimal difference in survival time. A recent study, using a mouse OSA model, showed that primary tumor resection enhanced systemic angiogenesis resulting in progression of distant metastatic lesions.[61] The distribution of metastatic lesions depends on the type of treatment. Pulmonary metastases are more common when only the local tumor is ablated, whereas skeletal metastases are more prevalent when chemotherapy is added to the treatment regimen. Pulmonary metastasis accounts for 61% of all metastatic lesions in dogs treated with amputation alone and 26% when treated with amputation and cisplatin.[12,50] In comparison, skeletal metastases develop in 47% of dogs after surgery and postoperative cisplatin.[50]

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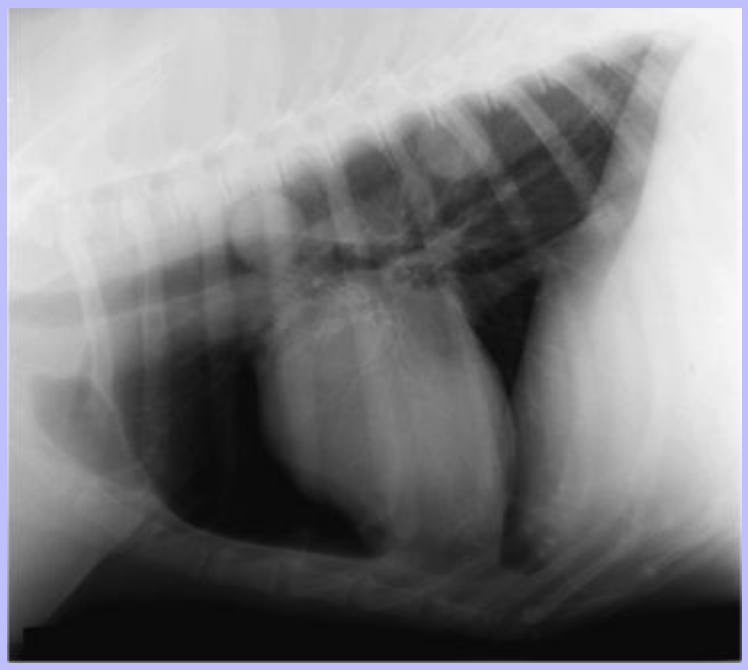
Table • 185-3 Saline Diuresis Protocols Used to Minimize Cisplatin-Associated Nephrotoxicity*

PROTOCOL	PHASE I	PHASE II	PHASE III
6 hr	Saline, 18.3 mL/kg/hr, 4 hr	Cisplatin for 20 min	Saline, 18.3 mL/kg/hr, 2 hr
24 hr	Saline, 3.75 mL/kg/hr, 16 hr	Cisplatin for 16 hr	Saline, 3.75 mL/kg/hr, 6 hr

* Adapted from Dernell WS et al: Tumors of the skeletal system. *In* Withrow SJ, MacEwen EG, editors: *Small animal clinical oncology*, ed 3, Philadelphia, 2001, WB Saunders.

Generalized malaise is the most common sign in dogs with pulmonary metastasis. Respiratory signs are usually a late development (Figure 185-2). Occasionally, hypertrophic osteopathy may be the first indication of pulmonary metastasis. Chemotherapy, using platinum and antibiotic agents, is ineffective in prolonging survival time in dogs with measurable pulmonary metastasis.[62] Surgical resection of metastatic lesions, by either subpleural resection or partial lung lobectomy, can significantly improve survival time in select cases (Figure 185-3).[63] Candidates for pulmonary metastasectomy include dogs that develop pulmonary metastasis greater than 300 days after initial diagnosis of appendicular OSA, have no more than three radiographically evident metastatic lesions, and have lesions that do not double in size or no new lesions that develop in a 4-week period.[63] The MST for dogs with metastasis to the lungs is 61 days when treated with chemotherapy and 176 days after metastasectomy.[62,63]

Figure 185-2 Lateral radiographic projection of a dog 8 months after limb-sparing surgery for a distal radial osteosarcoma (OSA). Two metastatic lesions are seen in the dorsal lung fields.



Management options for dogs with skeletal metastasis include pain control with analgesic drugs, bisphosphonates, and palliative radiation therapy. Bisphosphonates block osteoclast activity, thereby minimizing the risk of pathologic fracture.[6465] Limb-sparing surgery and curative-intent radiation therapy have been used to treat metastatic skeletal lesions for select cases but are not routinely recommended.

185.1.1.10 Prognostic Factors

In dogs with appendicular OSA, a number of factors have been identified as being prognostic. OSA can be histologically subclassified into osteoblastic, chondroblastic, fibroblastic, telangiectatic, and undifferentiated OSA; however, histologic subtype has not been shown to be prognostic in dogs or humans.[1] Poor prognostic factors in dogs with OSA include age less than 7 years and older than 10 years, body weight greater than 40 kg, large tumor volume, proximal humeral location, increased preoperative total and bone-specific serum alkaline phosphatase (ALP) activities and failure to normalize within 40 days of surgical removal of the tumor, high tumor grade, and presence of metastatic disease.[*] Dogs with proximal humeral OSA have a significantly shorter DFI and MST than other appendicular OSA sites; however, this may be a function of tumor volume rather than site.[48] The MST for dogs with normal and elevated total serum ALP is 12.5 and 5.5 months, respectively.[66] The MST for dogs with normal and elevated bone-specific serum ALP is 16.6 and 9.5 months.[66] For both bone-specific and total serum ALP, each increase of 100 IU/L increases the risk of death due to OSA by 25%.[66,67]

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Figure 185-3 Intraoperative image of a metastatic lesion from an appendicular osteosarcoma (OSA). Partial lung lobectomy was performed and the dog is still alive 256 days after metastasectomy.

* References 1, 9, 12, 48, 66, 67.

185.1.2 Other Canine Appendicular Tumors

185.1.2.1 Chondrosarcoma

CSA is the second most common primary bone tumor in dogs.[1] Appendicular CSA accounts for 9% to 17% of all canine CSA cases.[68–71] The cause is unknown, although CSA has been reported to arise from osteochondroma or sites of previous trauma.

Golden retrievers, German shepherds, and boxers are over-represented, and the median age at presentation is 6 to 8.7 years.[68–71] Clinical findings are similar to dogs with appendicular OSA, and biopsy is required to

differentiate tumor types. The femur is most commonly involved, and CSA may have a more lytic radiographic appearance than OSA.[70,71] Limb amputation and limb salvage procedures can be used to manage the local tumor. Metastatic disease is reported in up to 21% of dogs with CSA but usually occurs late in the course of disease.[68–71] Chemotherapy does not provide a survival benefit in humans with CSA, and a similar situation probably exists in dogs.[72]

Fluoroquinolones may have a role in the management of dogs with CSA because these antibiotics are toxic to chondrocytes and, in in vitro studies, inhibit chondrocytic proliferation and induce chondrocyte apoptosis.[73] The MST for dogs with untreated CSA is 46 days compared with 540 days for dogs treated with limb amputation alone.[71] Prognostic criteria in dogs include tumor location and histologic grade, although these are not well defined.[70,74]

185.1.2.2 Fibrosarcoma

FSA is the third most common skeletal neoplasm in dogs and occurs more commonly in axial than appendicular sites.[69] Two distinct appendicular FSAs exist: (1) central and (2) parosteal.[75] A palpable mass is often present in dogs with parosteal but not central FSA. Parosteal FSA may represent a tumor of soft tissue origin with secondary invasion into bone.[69,75] The radiographic features of appendicular FSA are similar to OSA, although lytic lesions and pathologic fracture are reported in up to 50% of dogs with FSA.[75] Amputation and limb salvage are the main surgical treatment options. The role of AC is unknown. Appendicular FSA metastasizes late in the course of disease, often to sites other than the lungs, such as myocardium, pericardium, skin, and other bones.[75] Survival times are difficult to interpret because more than 50% of fibroblastic OSAs are misdiagnosed as FSA.[1,75] The 12-month survival rate for dogs with appendicular FSA treated with limb amputation alone is 66%.[75]

185.1.2.3 Hemangiosarcoma

HSA is rare and accounts for 3.6% of all primary bone tumors. German shepherd, Great Dane, and boxer dogs are over-represented, with a mean age at presentation of 6.2 to 8.2 years. This is a younger age at presentation than what is reported with most other primary bone tumors.[69] A relatively equal distribution exists between appendicular and axial sites, with 43% of cases occurring in the appendicular skeleton.[69,76] The proximal humerus is the most common appendicular site.[76] Skeletal HSA has a different biologic behavior than other primary bone tumors. The majority of appendicular HSAs have a lytic radiographic appearance. Cortical and periosteal changes may be minimal.[69,76] Polyostotic disease, soft tissue extension, and pathologic fractures are common.[69,76] In dogs with appendicular HSA, abdominal ultrasonography and echocardiography are recommended (in addition to the other standard staging tests), because 82% of dogs are reported with extraosseous disease or metastasis.[76] The value of local and systemic treatment is uncertain because the majority of dogs develop metastatic disease before 6 months and the 12-month survival rate is less than 10%.[69,76] However, limb amputation and doxorubicin-based chemotherapy protocols may be indicated for dogs with nonmetastatic monostotic appendicular HSA.[77] Palliative radiation therapy may be used in dogs with polyostotic disease.

185.1.2.4 Multiple Cartilaginous Exostoses

Multiple cartilaginous exostosis (MCE) is a developmental disease of immature dogs.[78–86] A hereditary predisposition is suspected. The true pathogenesis of MCE in dogs is unknown. Bony lesions in metaphyseal areas near endochondral ossification sites characterize MCE. The lesions can be single (osteochondroma) or multiple.[78–80] They originate at the metaphysis but move away from the physis with progressive longitudinal bone growth.[1] MCEs usually stop growing when dogs reach skeletal maturity. Continued growth beyond skeletal maturity is suggestive of malignant transformation, although continued non-neoplastic growth has been reported.[78–80] Malignant transformation to OSA or CSA of single osteochondromas has been reported.[80–85] A persistent cartilage cap on the apical margins of the MCE has been present in the majority of dogs with malignant transformation and, in humans, where up to 25% of MCE become neoplastic, the potential for malignant transformation can be predicted from the thickness of the apical cap on MRI.[85,86]

The incidence of MCE is difficult to determine because many dogs are clinically asymptomatic. When they occur, clinical signs are caused by interference or compression of adjacent structures, such as the spinal cord, peripheral nerves, or high motion tendons.[78–80] Regional radiographs will reveal a bony mass on the surface of the affected bone.[78–80] The radiographic appearance is consistent with a benign, nonaggressive proliferative process and minimal cortical disruption. Bilaterally symmetrical lesions may be present. The medullary cancellous bone is radiographically and histologically contiguous with the parent bone.[78–80] Epiphyseal bone is nearly never involved.[1,78–80] Vertebral and rib MCE lesions are typically spherical, with a sessile or pedunculated base. Long bone MCE lesions have a more irregular surface.[78–80] The radiographic features of malignantly transformed MCE include an indistinct, poorly mineralized mass with a thickened cartilage cap.[78–85]

Treatment options for MCE vary with age, location, and severity of symptoms. For appendicular lesions, conservative management with analgesic drugs is appropriate until skeletal maturity. Local excision is indicated if the dog is unresponsive to medical management.[1] The entire lesion, including the cartilage cap, should be submitted to ensure accurate histologic interpretation. Neutering is recommended in dogs with MCE due to its possible heritable nature.[1]

The prognosis for dogs with monosteal or bilaterally symmetrical appendicular MCE is good. However, the prognosis for MCE may be guarded when multiple lesions are present. In one review, 38% of dogs were euthanized before 12 months of age due to progressive clinical signs. Malignant transformation of MCE, particularly solitary lesions, was reported in 83% of 6 dogs older than 6 years.[79,80]

185.1.3 Cats

185.1.3.1 Osteosarcoma

Primary bone tumors are uncommon in cats.[87–90] Unlike dogs, 10% to 33% of primary bone tumors in cats are benign.[88] OSA is the most common tumor, accounting for 70% to 80% of all feline bone tumors, whereas FSA, CSA, HSA, and rhabdomyosarcoma have also been reported.[87–89,92] The mean age at diagnosis of

appendicular OSA is 10.2 years, and males are over-represented with a male-to-female ratio of 1.7:1.[88] A number of differences are seen in the presentation and biologic behavior of OSA in cats versus dogs. In feline OSA, bones of the pelvic limb are involved 1.6 times more frequently than the thoracic limb.[88] The proximal humerus is the most common site, closely followed by the distal femur and proximal tibia.[87–91] The radiographic features of primary bone tumors in cats are similar to dogs, although lytic and juxtacortical lesions are more common.[87,88,90,91] Metastasis is uncommon and is diagnosed in less than 10% of cats with OSA.[87–91] Metastatic sites include lungs, brain, liver, kidneys, and spleen. Due to the infrequency of metastatic disease, limb amputation without chemotherapy is recommended for the treatment of cats with appendicular OSA. The MST after limb amputation alone is reported to be 11.8 to 49.2 months.[87,88,90,91]

185.1.3.2 Other Feline Appendicular Tumors

FSA and CSA have a similar biologic behavior to OSA (Figure 185-4). Limb amputation may be curative although metastatic disease has been reported for both tumor types.[87,88]

185.2 PRIMARY AXIAL TUMORS

185.2.1 Canine Osteosarcoma

OSA of the axial skeleton accounts for 25% of all OSA and 59% of OSA in dogs weighing less than 15 kg.[4,93] However, medium to large breed dogs are commonly affected.[93,95] Boxers may be over-represented, and a female predisposition is reported for all axial sites except the ribs and vertebrae.[93,94] The most common sites of axial OSA, in order of frequency, are mandible (27% of axial OSA), maxilla (16% to 22%), vertebrae (7% to 15%), scapula (13%), skull (11% to 12%), ribs (10% to 11%), nasal and paranasal sinuses (9%), and pelvis (4% to 5%).[93,94] OSA of the hard palate and patella have also been reported.[96,97]

Figure 185-4 Juxtacortical chondrosarcoma (CSA) of the proximal humerus of a cat.

Advanced imaging, particularly CT scans, are useful for staging and surgical planning of tumors of the axial skeleton. Surgical resection is recommended although radiation therapy can also be used for control of the local tumor.[93–95] Local recurrence is reported in up to 80% of dogs, and the metastatic rate varies between 11% to 46%.[93–95] Local recurrence, rather than metastasis, is the most common cause of death and chemotherapy has not been shown to improve metastatic rate or survival time.[93–95,98–103]

Overall, the MST for dogs with axial OSA is 120 to 154 days, with a 12-and 24-month survival rates of 26.3% and 18.4%, respectively.[93–95] Prognostic factors include anatomic site, body size, breed, and surgical margins.[94,95,98–103] Smaller breed dogs have a significantly better survival than large breed dogs.[94] The MST of golden retrievers with axial OSA is 100 days, compared with 182 days in pure bred dogs and 264 days in mixed-breed dogs.[95] Mandibular OSA has a better prognosis than OSA of the ribs, scapulae, and skull.[94] The MST after palliative and curative-intent radiation therapy of axial OSA in large breed dogs is 79 and 265 days, respectively.[95] Incomplete surgical resection significantly increases the risk of local recurrence and metastasis.[98–103]

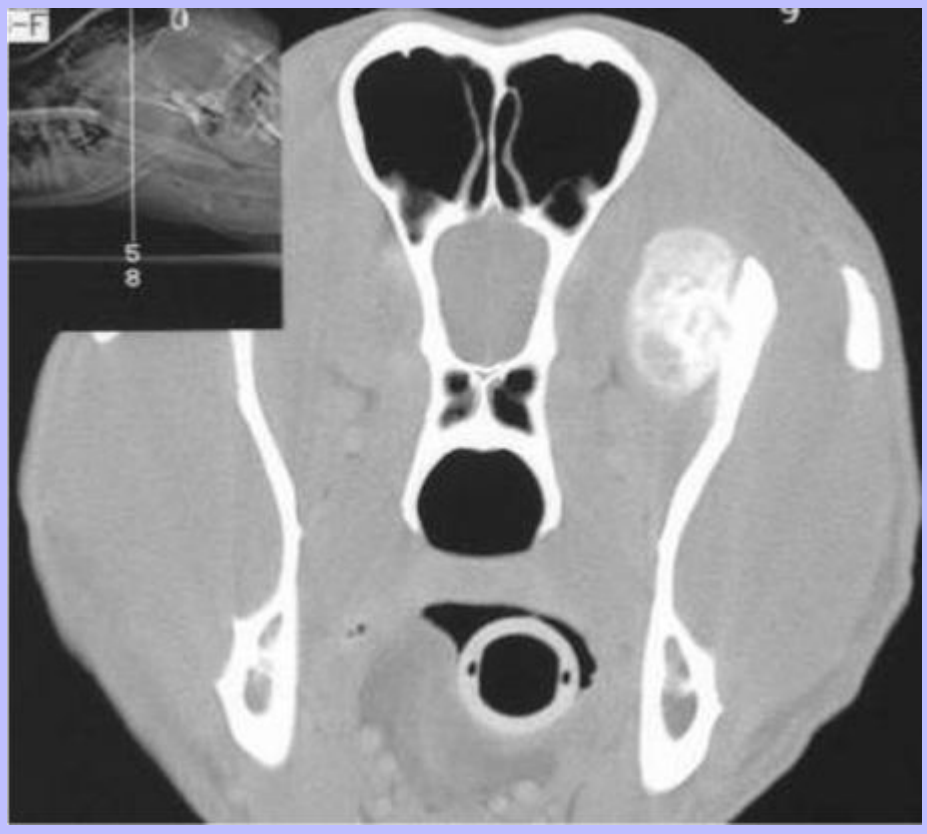
185.2.2 Skull Tumors

OSA of the skull can involve the calvarium, nasal and paranasal sinuses, maxilla, and mandible. Calvarial OSA accounts for 11% to 12% of axial OSA.[93,94] Signs include a visible external mass and neurologic signs due to extradural compression of the brain. Direct invasion of the brain is rare.[1] Surgical resection is recommended after CT imaging. Intra-and postoperative complications include cerebral edema, brain herniation, pneumo-meningocoele, aspiration pneumonia, and death.

Axial OSA may also involve the maxilla and mandible; however, it is less common than the other tumors affecting these bones. The most common canine oral tumors are malignant melanoma, squamous cell carcinoma, FSA, OSA, and the benign epulides.[98–102] In the majority of these tumors, except for OSA, mandibular and maxillary bone is secondarily involved by tumor invasion.[98–102] Signs include a visible mass, halitosis, ptyalism, exophthalmos, and jaw pain; eating difficulties and dyspnea are also reported.[98–102] Regional radiographs are sufficient for local staging of most mandibular tumors, although CT imaging is recommended for tumors of the vertical mandibular ramus (Figure 185-5) and maxilla. Surgical resection (i.e., mandibulectomy, maxillectomy) provides the best opportunity for local tumor control. Postoperative cosmesis is usually excellent.[98–102]

The most common cause of death in dogs with axial OSA is local tumor recurrence rather than metastasis. Metastasis is reported in up to 30% of skull OSA. The MST for mandibular OSA treated with mandibulectomy is 7 to 18 months with a 12-month survival rate of up to 71%.[98–100] Histologic grade and score are predictive of survival in dogs with mandibular OSA.[100] In contrast, the MST for maxillary OSA treated with maxillectomy is 4.5 to 10 months, with a 12-month survival rate of 17% to 27%.[101,102] Aggressive surgical excision, with complete histologic resection, results in a significant improvement in local recurrence and survival rates, with a reported MST greater than 1503 days.[103] Postoperative radiation therapy and chemotherapy have not been shown to provide a survival benefit, even in dogs with incomplete tumor resection.[95,103]

Figure 185-5 Sagittal computerized tomographic (CT) image of a grade III multilobular osteochondrosarcoma (MLO) of the vertical ramus of the mandible. Complete resection was performed with a caudal mandibulectomy and the dog is alive and disease free 308 days postoperatively.



185.2.3 Scapular Tumors

Scapular OSA is relatively uncommon and accounts for up to 13% of all axial OSA.[69,93–95] CSA, FSA, and HSA have also been reported to involve the scapula.[70,104–106] Lameness is the most common clinical sign. Radiographic changes are consistent with appendicular OSA, with a mixed pattern of lytic and productive changes most common.[104] However, due to positioning difficulties and superimposition of the body wall, the extent of disease may be difficult to determine. CT imaging is helpful to determine the location and extent of scapular involvement. Surgical resection (partial scapulectomy) is recommended with good to excellent limb function after subtotal scapulectomy of up to 90% of the scapula.[104,105] Because a high metastatic rate has been reported in dogs with scapular OSA, postoperative chemotherapy is recommended.[93,94]

185.2.4 Pelvic Tumors

OSA of the pelvic bones accounts for 4% to 6% of axial OSA.[69,93,94] Pelvic FSA, CSA, and OSA occur at relatively equal frequencies.[68,70,71,107] Boxer dogs may be predisposed to pelvic CSA.[68] Lameness is common, although tenesmus, due to compression of the rectum, and neurologic deficits, as a result of peripheral nerve compression, have also been observed. Radiographic abnormalities are similar to appendicular OSA (Figure 185-6). CT imaging is helpful for local staging and surgical planning. Surgical resection, with either subtotal or total hemipelvectomy, is the recommended treatment for dogs with pelvic tumors.[107] If necessary, the lateral third of the sacrum, lateral to the dorsal sacral foramina, can be resected en bloc with the affected pelvis. Limb salvage is possible if the weight-bearing axis can be preserved by internal hemipelvectomy. Chemotherapy is recommended for dogs with pelvic OSA because their biologic behavior is similar to appendicular OSA with a high metastatic rate.[107] However, the metastatic rate of pelvic FSA and CSA is low and chemotherapy is probably not required.[107]

185.2.5 Rib Tumors

Rib tumors are uncommon and reported tumor types include OSA, CSA, FSA, HSA, multilobular osteochondrosarcoma (MLO), and mast cell tumor.[1,93–95,108,109] OSA is the most common rib tumor accounting for 73% of rib tumors and 11% of axial OSA.[93,94,108,109] No breed or sex predispositions have been reported, but rib tumors tend to occur in younger, large breed dogs with a mean age of 4.5 to 6 years.[93–95,108,109]

Rib tumors usually occur in the distal third of the rib adjacent to the costochondral junction.[108,109] A palpable firm and fixed mass is the most common clinical sign, although pain and dyspnea are also reported. Radiographic changes include lysis, sclerosis, or a mixture of lytic and blastic patterns, with displacement of adjacent ribs and intrathoracic structures, such as the heart and lungs, and medial displacement of the parietal pleura resulting in an extrapleural sign (Figure 185-7).[108,109] Intrathoracic extension and invasion of adjacent pericardium and lung lobes are relatively common. Pulmonary metastasis is common, particularly with telangiectatic OSA, and up to 45% of dogs with rib OSA have metastatic disease at diagnosis.[108,109] Metastasis was detected in 100% of dogs with rib OSA, 53% to 57% with CSA, 67% with HSA, and 100% of dogs with rib FSA at the time of death.[108,109] Due to the similar biologic behavior of rib and appendicular OSA, rib OSA should be treated with rib resection and postoperative chemotherapy. The role of chemotherapy in other tumor types is undefined but warrants consideration due to the high metastatic rate.

Tumor type and surgical margins are prognostic. The MST after rib resection alone for OSA and CSA is 90 and 1080 days, respectively.[108,109] Completeness of surgical margins is an important prognostic indicator. Dogs with incomplete excision are 5.6 times more likely to develop local recurrence and possibly metastatic disease.[109] In dogs with rib OSA, postoperative treatment with chemotherapy extends the MST to 240 days.[109]

185.2.6 Vertebral Tumors

OSA is the most common extradural tumor of the nervous system and accounts for up to 16% of axial OSA.[93,94,110,111] Other vertebral tumors include CSA, FSA, HSA, MCE, lymphoma, liposarcoma, giant cell

tumor, plasma cell tumors, either as solitary plasmacytoma or multiple myeloma, and metastatic carcinomas and sarcomas.[110,111] A breed predisposition has not been reported, although German shepherd dogs, Labrador retrievers, and standard poodles were over-represented in one study.[110] Large breeds are commonly affected. Only 5% of dogs with vertebral tumors weighed less than 20 kg.[110,111] Primary vertebral tumors tend to occur in a younger subset of dogs than metastatic tumors of the vertebrae. The median age for dogs with primary vertebral tumors is 6 to 8 years and 8 to 9 years for secondary tumors.[111] A thorough physical examination should be performed to identify possible occult primary tumors. Carcinomas of the mammary and thyroid glands, bladder, and prostate, and visceral HSA are known to metastasize to the vertebrae. Thoracic and lumbar vertebrae are most commonly involved.[110]

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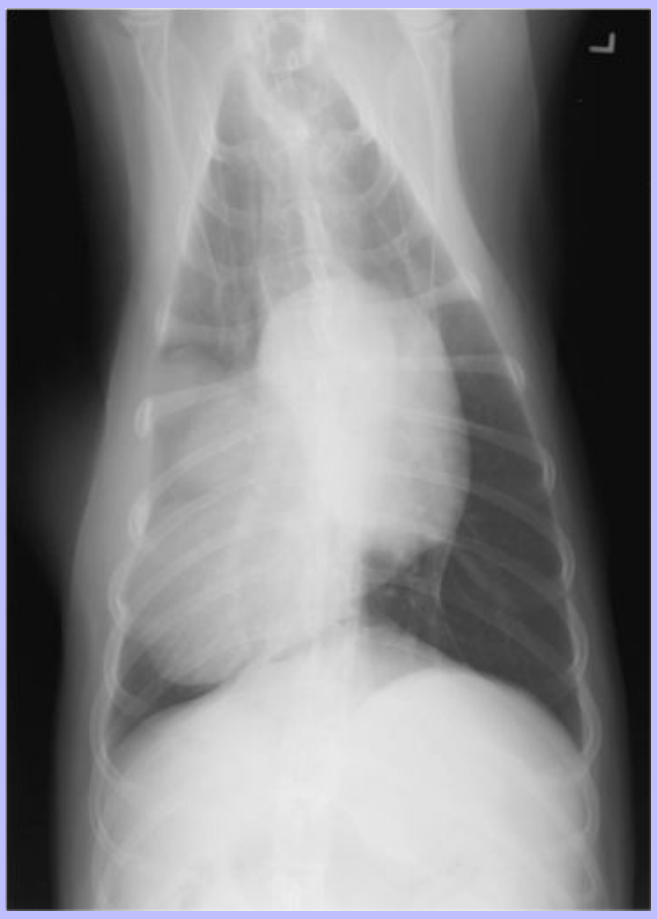
Figure 185-6 Ventrodorsal radiograph of a grade I chondrosarcoma (CSA) of the right ilium. The reader should note the large tumor volume and compression rather than invasion of the transverse processes of the sixth and seventh lumbar vertebra. Hemipelvectomy was performed, and the dog is alive and disease free 516 days postoperatively.

Pain and neurologic deficits are the two most common signs in dogs with vertebral tumors.[110,111] Neurologic deficits are caused by compression of nerve roots or the spinal cord.[110,111] Neurologic signs are typically slowly progressive, but pathologic fracture will cause an acute deterioration in neurologic function. A neurologic scoring system has been devised and is prognostic for outcome and survival.[111]

A spectrum of radiographic changes is observed in dogs with vertebral tumors. These changes can be difficult to detect due to inconsistent vertebral shape and superimposition of overlying ribs and soft tissue.[110] Cortical lysis with vertebral body collapse is a characteristic finding in primary vertebral tumors but a late event in metastatic tumors.[110,111] Skip and multiple tumors are reported in up to 25% of dogs with vertebral OSA and can be difficult to differentiate from metastatic tumors.[110] Osteochondromas and MCE are well-circumscribed benign lesions that frequently involve the dorsal spinal elements, such as the dorsal lamina and spinous process, rather than the vertebral body.[78,79] Other imaging techniques include myelography, CT and MRI, and nuclear scintigraphy.

Figure 185-7 Ventrodorsal radiograph of an osteosarcoma (OSA) of the seventh rib is displacing the heart and caudal lung lobes to the left side.



Nuclear scintigraphy can be beneficial in identifying the location of single and multiple lesions but cannot differentiate multifocal OSA from multiple metastatic lesions. Furthermore, most plasma cell tumors are photophenic due to marked osteo-lysis and minimal new bone production. Myelographic changes include collapse of the subarachnoid space and unilateral or asymmetric displacement of the spinal cord.[110] Advanced imaging provides the most accurate information for evaluating the degree of vertebral involvement but differentiating intra-and extradural involvement can be difficult.[112]

Surgical resection, with vertebrectomy, is rarely feasible, although dorsal decompression can provide meaningful palliation in dogs with localized dorsal tumors.[111,113] Radiation therapy, either with palliative-or curative-intent, can be beneficial in dogs with vertebral tumors.[111] The role of chemotherapy is unknown, even in dogs with vertebral OSA, because most dogs are euthanatized due to the local tumor rather than metastatic disease.[111]

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Overall, the MST for dogs with malignant vertebral tumors is 135 days.[111] Survival time is not significantly influenced by preoperative neurologic score, tumor type (OSA or FSA), primary or metastatic disease, anatomic location (cervical, thoracic, or lumbar), chemotherapy, or radiation therapy.[111] Although not significant, neurologic score can provide useful information as dogs with a preoperative score of 1 had a survival time of 330 days compared with 120 days if the neurologic score was greater than 1.[111] Furthermore, dogs with a posttreatment neurologic score of 1 or 2 were 12 times more likely to survive than dogs with posttreatment score of 3 or 4.[111] Curative-intent radiation therapy provides a significant improvement in survival time when compared with palliative radiation, with survival times of 150 and 15 days, respectively.[111]

185.2.7 Nasal and Paranasal Tumors

Adenocarcinoma is the most common tumor of the nasal and paranasal sinuses.[114–116] Sarcomas, such as CSA and OSA, are uncommon.[68–71,93–95,114–116] Dolichocephalic breeds are predisposed, particularly if living in an urban environment with exposure to smoke. Nasal and paranasal tumors, regardless of tumor type, are characterized by local invasiveness and a low metastatic rate, although up to 50% of dogs have metastasis to the regional lymph nodes and lungs at necropsy.[114–116] Unilateral epistaxis is the most common sign. Other less frequent signs include sneezing, dyspnea, stertorous respiration, facial deformity, and seizures.[114–116] Advanced imaging is recommended for local staging and determination of the caudal extent of the tumor in relation to the cribriform plate. Unlike tumors of other axial and appendicular sites, nasal and paranasal tumors are usually not amenable to surgical resection. Full-course fractionated radiation therapy is the recommended treatment resulting in a MST of 424 to 580 days.[114–116] An improved survival time is seen when radiation is combined with radiation sensitizers, such as local or systemic cisplatin.[114]

185.2.8 Other Canine Axial Tumors

185.2.8.1 Multilobular Osteochondrosarcoma

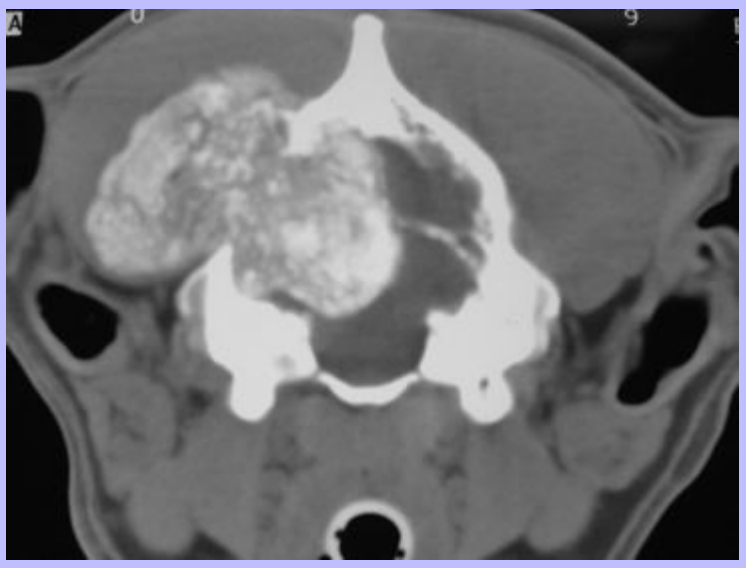
MLO is an uncommon tumor arising from the periosteum of bones formed by intramembranous ossification.[117,118] The skull is most commonly involved, including the calvarium, orbit, zygomatic arch,

mandible, and maxilla.[117,118] Other sites include the pelvis, ribs, and hard palate. Cats have also been reported with MLO.

MLO is usually a disease of middle-aged, large breed dogs.[117,118] No known sex or breed predisposition exists. Clinical signs are dependent on tumor location and include a palpable firm and fixed mass, neurologic signs with calvarial MLO, pain on opening of the jaw with mandibular and zygomatic arch MLO, exophthalmos with orbit MLO, and dyspnea with MLO of the tympanic bulla.[117,118] The imaging changes associated with MLO are characteristic with the tumor described as having a popcorn appearance with well-defined borders and a lobulated pattern on both radiographs and CT scans.[117–120] Advanced imaging is indicated for surgical planning of calvarial MLO because the extent of intracranial involvement can be extensive (Figure 185-8).[119,120]

Treatment options include surgical resection and radiation therapy.[117,118] Cranioplasty, using either allografts or bone cement, has been described after calvarial resection but is probably unnecessary. Neurologic recovery, particularly with marked intracranial involvement, can be prolonged, although the majority of dogs will return to normal function within 2 weeks. MLOs have a slow growth rate, and this would usually result in a relative resistance and poor response to radiation therapy. Although not well investigated, good responses have been reported using external beam radiation therapy and radiopharmaceuticals.[118]

Figure 185-8 A sagittal computerized tomographic (CT) image of a grade I multilobular osteochondrosarcoma (MLO). The reader should note the characteristic popcorn appearance of the mass and significant intracranial involvement.



A histologic grading scheme for MLO is prognostic for local recurrence and metastasis.[117] Other prognostic factors include site and completeness of surgical resection.[117,118] The overall rate of local recurrence is 47%

to 58%, with a median DFI of 426 to 797 days, although this rate varies with histologic grade.[117,118] The local recurrence rate for grade I MLO is 30%, grade II is 47%, and grade III is 78%.[117,118] Furthermore, an aggressive surgical approach is recommended because incomplete resection significantly increases the risk of local recurrence. The median DFI after incomplete resection is 330 days, but median DFI was not reached and greater than 1332 days with completely resected MLO.[117,118]

Metastasis is reported in up to 58% of dogs with MLO. The lungs are the most common metastatic site, accounting for 90% of cases, although other sites include brain, pancreas, kidneys, mediastinum, and ribs.[117,118] Surgical margins and histologic grade are prognostic for the development of metastatic disease.[118] Metastasis is diagnosed in 25% of dogs after complete resection and 75% of dogs with incompletely resected MLO.[118] The metastatic rate for grade I MLO is 30%, grade II MLO is 60%, and grade III MLO is 78%.[118] The MST after diagnosis of recurrent or metastatic disease is 239 days, and many dogs with pulmonary metastasis from MLO are good candidates for pulmonary metastasectomy.[117,118]

The MST for untreated MLO is 24 days compared with 669 to 797 days for surgically resected MLO.[117,118] Tumor site is prognostic with mandibular MLO having a significantly better MST than other sites, with 1487 days for mandibular MLO and 528 days for nonmandibular MLO.[118] The MST for grade I MLO is greater than 897 days, whereas the MST for grade II and III MLO is 520 and 405 days, respectively.[118]

185.2.8.2 Osteoma

Osteomas account for 6% of all primary bone tumors in cats and dogs.[1,69,87] Osteomas are formed by intramembranous bone and occur in the axial skeleton, particularly the skull. A palpable, nonpainful mass is usually present and appears as well-circumscribed dense bony projections on regional radiographs. Osteomas have similar histologic features to reactive bone. Surgical resection is recommended for problematic or uncosmetic lesions.[1]

185.2.9 Cats

185.2.9.1 Osteosarcoma

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OSA is the most common tumor of the feline axial skeleton.[87,91] FSA and CSA are also reported to involve the axial skeleton.[87,88] The mean age at presentation for cats with axial OSA is 10.4 years, which is significantly older than cats with appendicular OSA.[91] The skull and pelvis are frequently affected, although other sites include ribs, vertebrae, and scapulae.[87–91] The presenting signs, radiographic features, and treatment recommendations are similar to malignant canine axial tumors. Periosteal new bone formation and juxtacortical tumors are more common in cats with axial OSA.[87,90] Complete surgical resection is complicated by tumor location, resulting in incomplete resection and poor tumor control. The MST for cats with axial OSA is 5.5 to 6.1 months, with most euthanized due to local recurrence rather than metastatic disease.[90,91]

185.2.9.2 Feline Multiple Cartilaginous Exostosis

In contrast to dogs, feline MCE develop after skeletal maturity, appendicular skeletal involvement is rare, and the majority have a viral or familial cause.[88] The mean age at diagnosis is 3.2 years.[88] A sex or breed predisposition is unlikely, although Siamese were over-represented in early reports.[1] The vast majority of cats with MCE are positive for feline leukemia virus (FeLV).[1,88] In these cats the disease is rapidly progressive with firm, painful swelling of axial sites such as the scapula, vertebrae, and ribs. Radiographically, feline MCEs appear as sessile or pedunculated masses arising from the surface of affected bones with bony lysis and loss of smooth bony contour.[1,88] Surgical resection is indicated for painful lesions, although complete resection is difficult, because the cartilage caps tends to infiltrate adjacent tissue and local recurrence is common.[1,88] Malignant transformation and metastasis are also possible.[88]

185.3 METASTATIC BONE TUMORS

Metastatic bone tumors are infrequently diagnosed in cats and dogs. Metastasis usually occurs via the hematogenous route. In dogs, urogenital carcinomas, particularly bladder and prostate, are the most common primary tumors to metastasize to bone.[4,121] Skeletal metastasis is also reported in dogs with OSA, mammary carcinoma, thyroid carcinoma, pulmonary carcinoma, nasal carcinoma, apocrine gland anal sac adenocarcinoma, and renal tumors.[1,4,121–124] Metastatic lesions represent 24% of all bone tumors in dogs weighing less than 15 kg and only 5% in large breed dogs.[1,4,123] The most common metastatic sites are the axial and proximal appendicular skeleton with less than 11% of dogs having metastatic lesions distal to the elbow or stifle.[121] In contrast, acrometastasis involving one or more digits is the most common presentation for cats with metastatic pulmonary carcinoma.[122–125]

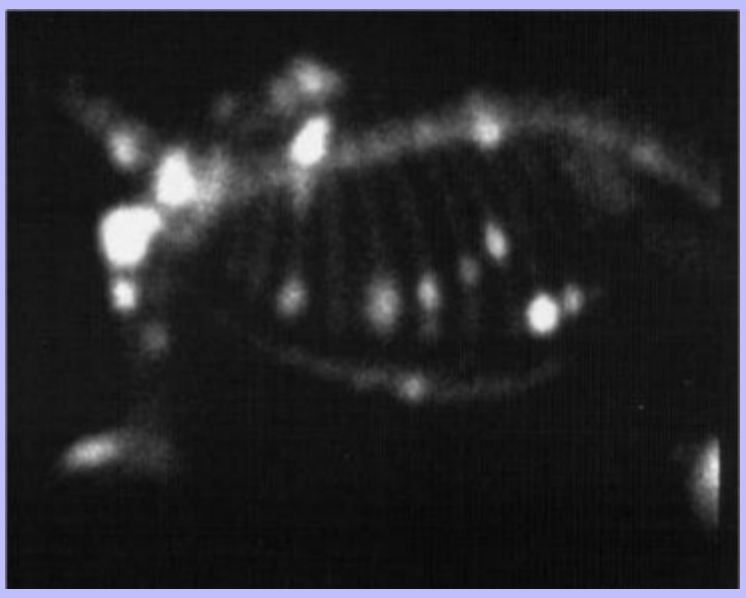
Nuclear scintigraphy is recommended for the identification of multiple bone lesions (Figure 185-9). Treatment options for skeletal metastasis include surgery, radiation therapy, and pharmaceutical agents.[64] Surgical curettage and stabilization of metastatic lesions is uncommonly performed in veterinary medicine but may provide a meaningful response in select cases. Radiation therapy is indicated for management of pain and inflammation.[22]

185.4 PRIMARY JOINT TUMORS

185.4.1 Dogs

Joint tumors are usually primary and malignant.[126–130] Previously, synovial cell sarcoma was considered the most common tumor of the canine joint.[126,127] However, recent evidence suggests that other soft tissue sarcomas of periarticular tissue are more prevalent and immunohistochemistry (IHC) is required to differentiate these tumor types.[128,129] Other reported joint tumors include histiocytic sarcoma and malignant fibrous histiocytoma, synovial myxoma and myxosarcoma, OSA, FSA, CSA, HSA, liposarcoma, rhabdomyosarcoma, and undifferentiated sarcoma.[1,128,129]

Figure 185-9 Nuclear scintigraphy of a dog with prostatic transitional cell carcinoma. The reader should note the numerous metastatic lesions in the proximal radius, proximal humerus, cervical and thoracic vertebrae, ribs, and sternum.



Synovial cell sarcomas are malignant tumors arising from mesenchymal cells within tenosynovial tissue of joints, bursa, and tendon sheaths.[126] The stifle, elbow, shoulder, carpal, tarsal, and hip joints are most commonly involved, in decreasing order.[1,126] The mean age at presentation is 6 to 8 years, and a sex and breed predisposition has been reported.[126–130] Males are over-represented and flat-coated retrievers are predisposed.[26–130] Metastasis to the regional lymph nodes and lungs is reported in up to 32% of dogs at diagnosis and in 41% to 54% of dogs during the course of disease.[126–130]

185.4.1.1 Diagnosis

Typically, dogs have lameness, joint pain, and synovial effusion. Dogs with suspected joint tumors should be staged with palpation of regional lymph nodes and regional and three-view thoracic radiographs. Regional radiographs will often reveal a soft tissue opacity adjacent to the affected joint. Mineralization of the soft tissue mass is occasionally seen in humans but rarely in dogs. Bone involvement is observed in 11% to 100% of cases and can either be smooth and well delineated, due to pressure necrosis from the expansile mass, or permeative to punctate lysis as a result of bony invasion.[126–130]

Biopsy is required for a definitive diagnosis. Analysis of synovial fluid is usually consistent with chronic, low-grade inflammation, and neoplastic cells are rarely identified. Large core biopsies, using either a Jamshidi needle or open wedge, are sufficient to establish a diagnosis and histologic grade.

Synovial cell sarcomas have two distinct populations of cells: (1) epithelioid and (2) spindle.[1,126] Based on these cells, synovial cell sarcomas are subclassified as either monophasic, with one cell type, or biphasic, with both cell types.[126] However, this histologic appearance is not adequate to differentiate synovial cell sarcoma from other types of soft tissue sarcoma. Recently, IHC stains have been used to differentiate joint tumors with synovial cell sarcomas staining positive with cytokeratin antibody AE1/AE3, histiocytic sarcomas staining positive with CD18 antibody, and malignant fibrous histiocytomas staining positive with smooth muscle actin.[129]

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185.4.1.2 Treatment

Limb amputation is the recommended treatment for dogs with a histologically confirmed joint tumor.[126–130] Local recurrence is common after conservative excision and has also been reported with relative frequency in the stump of the amputation site.[126] The role of radiation therapy and chemotherapy is unknown. Chemotherapy does not improve survival time in humans with synovial cell sarcoma.[131] However, doxorubicin-based chemotherapy protocols are recommended for high-grade synovial cell sarcoma due to their high metastatic potential.

185.4.1.3 Prognosis

Several prognostic factors have been identified in dogs with synovial cell sarcoma, including clinical stage, treatment, histologic grade, and IHC staining.[126–130] Synovial cell sarcoma is locally staged as well-defined with no evidence of invasion into regional structures (T_1), invading soft tissue (T_2), and invading bone and joints (T_3).[126] Local staging is not prognostic; however, dogs with metastatic disease, to either regional lymph nodes (N) or lungs (M), have a MST less than 6 months. Aggressive surgical treatment is important in prolonging both DFI and survival time. Local tumor control is poor after conservative local excision with a median DFI of 4.5 months compared with 30 months after limb amputation.[126,130] Furthermore, survival time is significantly improved with more aggressive local treatment regimens: 93 days with no treatment, 455 days with conservative resection, and 840 days with limb amputation.[130] Histologic grade is also prognostic because the MST for dogs with grade I synovial cell sarcoma is greater than 48 months, grade II is 36 months, and grade III only 7 months.[126]

185.4.2 Cats

Synovial cell sarcoma is rarely diagnosed in cats. As a result, the disease has not been investigated in detail, and management and prognostic criteria have not been established. Seven cases have been reported in the veterinary literature, three with benign and four with malignant disease.[132,133] Based on these reports, synovial cell tumors in cats may have a more benign behavior than dogs. However, two cats have recently been diagnosed with metastatic synovial cell sarcoma at Colorado State University. Regional lymph node metastases were present at diagnosis in both cases, and one cat was diagnosed with pulmonary metastasis 12 months postoperatively. Limb amputation is recommended for the local management of synovial cell sarcomas because, similar to dogs, local recurrence has been reported after conservative excision.[132,133] The role of chemotherapy in malignant or metastatic synovial cell sarcomas is unknown.

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186 CHAPTER • 186 Mast Cell Disease

Kenita S. Rogers

186.1 OVERVIEW OF CANINE AND FELINE MAST CELL DISEASE

Differences in the incidence, clinical forms, and biologic behavior associated with canine and feline mast cell disease are remarkable enough that separate discussions are required. Briefly, the incidence of cutaneous mast cell disease is higher in the dog and constitutes the most important form in this species; primary noncutaneous forms are uncommon. The biologic behavior of mast cell disease in the dog is also more variable and unpredictable, with a greater risk of systemic spread. Like dogs, cats can develop cutaneous mast cell disease, but primary visceral mastocytosis appears to be an equally important disease process. A primary gastrointestinal (GI) form is infrequently reported in the cat.

186.2 INCIDENCE OF CANINE MAST CELL DISEASE

Mast cell tumors (MCTs) remain one of the most important and frequent neoplasms affecting the canine dermis and subcutis, having been reported to account for 7% to 21% of all canine skin tumors and 11% to 27% of all cutaneous malignancies.[1,2] Mast cell disease can occur in any breed, but those that appear to be at increased risk are most of the brachycephalic breeds and Golden retrievers. Although boxers are at increased risk for developing MCTs, they often develop a well-differentiated form of the disease, which has a more favorable prognosis. Other breeds with an apparent predisposition in some reports include Bassett hounds, Labrador retrievers, Bernese mountain dogs, Chinese Shar Peis, Scottish terriers, pointers, beagles, and German shorthaired pointers. The average age of dogs that develop MCTs is 8.5 to 9.5 years, but they can develop at any age, with no apparent gender predisposition. Development of multiple tumors is a common clinical observation, occurring in approximately 10% to 15% of cases.

186.3 BIOLOGY OF MAST CELLS

Mast cells are a heterogenous cell population that originate in the bone marrow from a CD34+ pluripotential hematopoietic stem cell that is promoted to mast cell differentiation by a hemopoietin called stem cell factor or c-*kit* ligand.[3] Undoubtedly, the development of MCTs involves many factors including genetic propensity, but alteration of c-*kit* receptor expression for stem cell factor in a proportion of canine MCTs suggests that loss of normal regulation may be an important factor in tumor development.[4] Cytoplasmic receptors for estrogen and progesterone have been identified in canine MCTs, but their importance in the pathogenesis of disease is unclear. Committed mast cell precursors move from marrow to blood to tissues where maturation occurs. Besides the skin, the GI tract and lungs are rich in normal mast cells, but development of tumors at these sites is rare.

Normal mast cells play an important role in mediating inflammatory responses. Mast cell activation stimulates release of a variety of substances from the variably sized intracytoplasmic granules, including vasoactive amines (histamine, seratonin), enzymes (acid hydrolases, cathepsin G, phospholipase A, chymase, tryptase, carboxypeptidase) and proteoglycans (heparin, chondroitin sulfate).[3] Mast cells can also synthesize and release lipid mediators and cytokines. The ability to release these active substances and mediators explains many of the clinical manifestations of these tumors. Mast cell functions include promoting hypersensitivity reactions, modulating immune responses by stimulating T cells, defending the host against tissue parasites, and promoting

acute and chronic inflammatory responses by stimulating leukocyte migration, endothelial-leukocyte adhesion, angiogenesis, fibrin deposition, and fibroblast proliferation.[3]

Local release of biologically active substances from the granules can lead to recruitment of other cytokines and inflammatory cells. Unique local clinical signs that are related to these cellular products can range from nonpainful swelling to pruritus, ulceration, erythema, bruising, or prolonged hemorrhage. Poor wound healing may be attributed to proteolytic enzymes and vasoactive amines, but mouse studies suggest that histamine binds to H_1 and H_2 receptors on macrophages, resulting in release of a fibroblastic suppressor factor that decreases normal fibroplasia and results in delayed wound healing.[2] MCTs may cyclically wax and wane in size; manipulation on examination may also lead to degranulation and subsequent swelling or wheal formation. Systemic effects can also occur as part of a paraneoplastic syndrome because plasma histamine concentrations in dogs with MCTs are significantly greater than normal.[5] Increased concentrations of circulating histamine can be associated with gastric hyperacidity and GI ulceration, because binding of histamine to H_2 receptors of gastric mucosal parietal cells stimulates gastric acid secretion and hyperacidity. Histamine also increases GI motility and capillary permeability, promoting intravascular thrombosis and subsequent mucosal ulceration. With marked systemic histamine release, potential also exists for arrhythmias, systemic hypotension, and shock due to H_1 and H_2 receptor binding on blood vessels, cardiac muscle, and smooth muscle.[1]

186.3.1 Biologic Behavior of Canine Mast Cell Tumors

Cutaneous MCTs are likely to arise from tissue mast cells in the dermis. The clinical course of mast cell disease is somewhat unpredictable, but all tumors are considered potentially malignant due to their ability to metastasize. The typical metastatic pattern for MCTs is to the reticuloendothelial system. The first and most common site of metastasis is the regional lymph node, followed by the spleen, liver, and bone marrow.

One of the unique features of MCT behavior is the concurrent development of multiple dermal or subcutaneous tumors. When it occurs, the tumors may seem to erupt simultaneously or develop over months to years. It is unknown if each of the masses is a new individual tumor or whether each tumor represents metastatic spread. The best way to describe the typical biologic course of MCTs is “predictably unpredictable.” MCTs may have a very slow nonprogressive clinical course, they may be present for long periods prior to disseminating, or they may be locally invasive with systemic spread early in the disease course.

Histologically, canine MCTs have been graded 1 through 3, with the grade of the tumor having substantial impact on overall prognosis. Some confusion has existed because of two distinct grading systems. The Patnaik scale is more popular because it uses the more conventional nomenclature of Grade 1 representing the most well-differentiated tumors that are confined to the dermis, Grade 2 representing more pleomorphic tumors that extend into lower dermis and subcutaneous tissues, and Grade 3 representing pleomorphic tumors that replace subcutaneous and deep tissues.[6,7]

186.3.1.1 Clinical Presentation

Tremendous variation exists in the clinical appearance of MCTs. They may be soft and fluctuant or firm, discrete or diffuse, small or large, solitary or multiple, haired or hairless, and dermal or subcutaneous. A good rule of thumb is that MCTs can look like anything! They remain one of the most important reasons that any dermal or subcutaneous mass should be evaluated cytologically, because they can mimic lipomas and other nonneoplastic lesions. At least one half of these tumors have been reported on the trunk and perineum,

but the extremities, head, and neck remain common sites. Although most commonly located within the dermis, some tumors, particularly those that are rapidly growing, extend into the underlying subcutaneous tissues and muscle. Disseminated mastocytosis without an associated cutaneous MCT is reported infrequently in dogs.[8,9] Equally uncommon are reports of MCTs of GI origin.[10] Rare reports exist of MCTs arising from a variety of sites, including the oral cavity, nasal cavity, larynx, and conjunctiva.

Dogs with MCTs often have a solitary nonpainful mass, but more profound local clinical signs that should raise clinical suspicion of a MCT include swelling that may wax and wane (particularly after manipulation of the mass), pruritus, erythema, ulceration, or bruising. Systemic signs of GI ulceration, abdominal discomfort, vomiting, melena, hypotension, or coagulation abnormalities are less common but remain clinically important. If GI ulceration and hemorrhage is persistent, anemia will develop that is progressively less regenerative as external iron loss occurs.

186.3.1.2 Diagnosis and Staging

Early diagnosis of mast cell disease is important because a number of precautions may be taken if the diagnosis is known preoperatively, most notably premedication with H_1 and H_2 receptor blockers and more extensive planning for wide surgical margins. Most MCTs are easily diagnosed with fine needle aspiration due to distinctive cytologic characteristics. It has been suggested that manual quick stains, such as Diff Quick, may stain mast cell granules poorly.[3] Because the lack of adequate staining may be associated with dissolution of the mast cell granules by these largely aqueous stains if fixation is inadequate, particular care should be taken to adequately fix the slides when using these in-hospital stains. MCTs are categorized as round cell tumors because they typically have round cytoplasmic borders, do not cluster, and exfoliate well. Specific cytologic characteristics include a round to ovoid nucleus, a moderate amount of cytoplasm, and the presence of red-purple variably sized intracytoplasmic granules. In heavily granulated cells, the nucleus may stain pale blue due to the high affinity of the mast cell granules for the stain, with subsequent understaining of nuclear DNA. Well-differentiated tumors are typically homogenous in appearance with few malignant characteristics, even though the tumor remains potentially malignant. As tumors become more poorly differentiated, the number and size of granules within the cell may diminish and the degree of cellular pleomorphism will increase. The most poorly differentiated or anaplastic MCTs may have no visible granules on light microscopy and require special stains such as toluidine blue for definitive diagnosis. A subset of tumors remains that is cytologically and histologically defined only as *anaplastic round cell tumors*, with MCT being only one possible diagnosis within a list of differentials that may include lymphoma, transmissible venereal tumor, histiocytic disorder, plasma cell tumor, amelanotic melanoma, and anaplastic carcinoma. Immunohistochemical techniques may be helpful for differentiating these tumors (MCTs are vimentin + and most are alpha-1 antitrypsin +), but electron microscopy of ultrastructural features may be required in some cases for definitive confirmation.[3] Another useful cytologic characteristic supporting the diagnosis of MCT is the presence of a concurrent eosinophilic infiltrate due to chemotactic attraction of these inflammatory cells to histamine.

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Histologic examination of MCTs is important, not only to confirm the diagnosis but also to accurately grade the tumor and evaluate for completeness of surgical resection. Histologic tumor grade plays a substantial role in prognosis by correlating with both recurrence and survival. Four-year survival rates after surgical excision are 83% for Grade 1 tumors, 44% for Grade 2 tumors, and 6% for Grade 3 tumors.[6] Many studies have confirmed the trend that well-differentiated tumors are least likely to metastasize and have longer postoperative survival times. Although it is recognized that even with wide resection, well-differentiated MCTs can locally recur and metastasize, it is usually considered that the metastatic potential of

well-differentiated tumors is low (<10%) and that of intermediate-grade tumors is low to moderate.[2] Poorly differentiated MCTs are associated with the greatest risk of metastasis and shortest survival times.

Clinical staging also provides important information regarding prognosis (Box 186-1). Because metastasis is typically to the reticuloendothelial system, the regional lymph nodes, liver, spleen, and bone marrow are usually targeted for evaluation. The first site of mast cell metastasis is the regional lymph node. If an apparent regional node exists, it should always be aspirated, even if palpably normal in size. Early in the course of disease, MCTs may metastasize without causing a concomitant lymphadenopathy. It is important to remember that a palpably normal node does not rule out metastasis. Conversely, an enlarged regional lymph node may represent only reactive changes associated with lymphoid hyperplasia or secondary inflammatory changes. It is quite common for a peripheral lymph node to contain a small population of normal mast cells, particularly if the animal has allergic or parasitic skin disease, making definitive diagnosis of nodal metastasis problematic. In a population of 56 healthy nontumor-bearing beagles, approximately 24% of lymph node aspirates contained mast cells, with a range of one to 16 mast cells per slide.[11]

Differentiating inflammatory from neoplastic mast cells within a node can be difficult at best. Typically, inflammatory mast cells are spread somewhat evenly throughout a node and on the cytologic preparation. Tumor mast cells have a greater tendency to arrange themselves in groups within a node, and this may be apparent on the smear. Another helpful finding may be noting the degree of differentiation of the mast cells within the node. Inflammatory mast cells are usually well differentiated and heavily granulated. Tumor mast cells may also have this appearance, but if the cells in the node are more poorly differentiated with few granules, the cells are more likely to represent metastatic tumor.

186.3.1.2.1

Box • 186-1 World Health Organization Clinical Staging of Canine Mast Cell Tumors

Stage 0: One tumor incompletely excised from the dermis, identified histologically, without regional lymph node involvement

Stage I: One tumor confined to the dermis, without regional lymph node involvement

Stage II: One tumor confined to the dermis, with regional lymph node involvement

Stage III: Multiple dermal tumors; large infiltrating tumors with or without regional lymph node involvement

Stage IV: Any tumor with distant metastasis (including blood or bone marrow involvement) or recurrence with metastasis

Substage a: without systemic clinical signs

Substage b: with systemic clinical signs

As is true with lymph nodes, buffy coat smears and aspirates of spleen and bone marrow must also be interpreted carefully because small numbers of mast cells can normally be seen in these preparations, particularly if concurrent inflammatory disease exists. When few mast cells are present in potential metastatic sites, it is difficult or impossible to determine if the mast cell infiltrate represents metastatic neoplasia, mast cell hyperplasia, or a nonpathologic condition.[3] Mastocytemia is uncommon in dogs, but unless extensive blood involvement occurs, the number of mast cells seen in blood samples cannot be used to accurately distinguish nonmalignant from malignant disease. Indeed, more than 1000 mast cells per buffy coat preparation were described in nonneoplastic disorders in dogs.[12] A few mast cells may be present normally in a bone marrow smear, and mast cell hyperplasia associated with marrow hypocellularity has been reported.

Because the lymph node is the first site of metastasis, nodal assessment with cytology or histology is the single most important diagnostic step in staging. In the dog with no evident lymph node involvement, evaluation of the spleen, liver, and bone marrow is unlikely to yield useful information. Unfortunately, several areas of the body (particularly on the trunk) do not drain to a single, easily accessible peripheral lymph node. In these cases the regional node may be within the thoracic or abdominal cavities, and access for aspiration or biopsy is more difficult.

Diagnostic evaluation of splenic or hepatic involvement may include radiographs, ultrasound, and aspiration. The bone marrow is most commonly assessed with aspiration cytology; the presence of more than 10 mast cells/1000 nucleated cells can indicate systemic spread of mast cell disease. In a study of 16 dogs with systemic mastocytosis, bone marrow aspiration was deemed superior to blood smear and buffy coat examination.[8] In dogs with low and intermediate-grade cutaneous MCTs, the value of bone marrow examination is questionable due to the low incidence of finding metastasis in this location, particularly if the regional node can be evaluated. Because pulmonary metastasis is rare, thoracic radiographs are only indicated for assessing intrathoracic lymphadenopathy for MCTs located on the cranial portion of the body. A complete blood count (CBC) may show nonspecific eosinophilia, basophilia, and anemia if GI hemorrhage has occurred.

186.3.1.3 Treatment

As is true with most types of neoplasia, the conventional choices for therapy are surgery, radiation, and chemotherapy. Each of these treatment modalities has a role in mast cell disease. The location of the mass, the number of masses, the grade of the tumor, and the presence or absence of metastasis are all important factors in choosing the most appropriate course of therapy for dogs with mast cell disease. However, the unpredictable biologic behavior of MCTs must always be kept in mind when making therapeutic decisions.

186.3.1.3.1 Surgery

Complete surgical excision has been the mainstay of therapy for canine MCTs, and remains the treatment of choice. Curative intent can be expected with surgery of Grade 1 and 2 tumors that have no evidence of metastasis and are located in areas where surgery will allow adequate resection while maintaining cosmesis and function. The preoperative diagnosis of MCT allows the clinician to prepare the dog with prophylactic H_1 and perhaps H_2 receptor blockers, if appropriate. In addition, decisions regarding the size of surgical margins is often altered when the clinician has made a preoperative diagnosis of mast cell disease. Classically, it has been recommended that 2-3 cm margins be obtained if possible when resecting

a MCT due to often inapparent extension of the tumor into surrounding tissues. Equally important is the recommendation that excision include at least one fascial plane beyond the apparent extent of the tumor (i.e., if the tumor is dermal, underlying subcutaneous tissue should be removed; if the tumor is located in the subcutis, at least one layer of underlying muscle should be excised to routinely obtain adequate surgical margins free of tumor cells). All surgical margins should be clearly identified to allow the pathologist to examine for remaining tumor cells. Interestingly, many clinicians have noted that even when adequate surgical margins have not been obtained, a subset of patients exist in which the tumor does not occur.[13] Regardless, the current recommendation remains to widely excise tissue to obtain clean margins or follow with radiation therapy of the tumor bed and immediate surrounding tissues. For low to intermediate-grade MCTs on a distal extremity, limb amputation is also a surgical option for obtaining wide margins (albeit with less remaining function). Alternatives for limb salvage for tumors in this area include radiation alone, or more ideally, a combination of cytoreductive surgery followed by radiation therapy (Figure 186-1). The use of deionized water to treat surgical wounds after MCT removal has been reported, but this approach must not delay the use of more conventional therapy.

186.3.1.3.2

Radiation

Radiation alone for gross mast cell disease has generally been considered poorly effective with variable control rates cited; 1-year control rates using doses of 40 to 45 Gy are approximately 50%.[2] Use of more aggressive doses or different fractionation schemes may improve these results. A palliative course of radiation (coarse weekly fractions of 800 to 1000 Gy) for 3 to 4 weeks may result in responses that improve quality of life and decrease local clinical signs for unresectable MCTs but may also result in GI upset and weakness, most likely associated with mast cell degranulation.[14]

Radiation therapy is best applied as adjunctive therapy for incompletely resected tumors where further surgery is not deemed possible (i.e., Stage 0 disease). The prognosis after radiation for Grade 1 and 2 MCTs is good, with 1-and 2-year disease-free intervals of 79% to 97% and 77% to 85%, respectively.[15–18] Common toxicities associated with the use of conventional radiation include alopecia, haircoat color changes within the treatment field, and temporary moist desquamation. Prophylactic irradiation of cytologically negative regional lymph nodes is controversial with little guidance in the literature to suggest improved survival times with use of this technique. However, after cytoreductive surgery of the primary mass, radiation of regional nodes with metastasis in 19 dogs (16 with Grade 2 tumors) resulted in a median disease-free survival of 1240 days.[19]

Whether surgery or radiation is chosen as local therapy, dogs should be evaluated regularly for local recurrence and metastasis. For dogs with high-grade, poorly differentiated MCTs, surgery, and radiation may be used as local therapies but will not address the high risk of systemic spread that will typically occur within weeks to months of the local therapy. It is extremely important that clients be fully educated regarding the high risk of metastasis in this subset of dogs, prior to initiating surgery or radiation therapy.

186.3.1.3.3

Chemotherapy

With poorly differentiated MCTs or documented metastasis, local treatments such as surgery and radiation may provide only palliative therapy. Systemic adjuvant chemotherapy can be offered in an attempt to decrease the likelihood of systemic involvement or potentially to improve disease-free intervals.[2] MCTs appear to be quite resistant to the effects of chemotherapy, because many different agents have been used

with little reported efficacy and most responses have been of short duration. P-glycoprotein and multidrug resistance–associated protein have been detected in canine cutaneous MCTs.[20]

Prednisone is commonly advocated for treatment of MCTs, but the reported response rates are low. One prospective clinical trial with daily oral prednisone at 1 mg/kg demonstrated disappointing results.[21] Only 4 of 25 dogs had a partial response (PR) and only one dog had a complete response (CR). Most responses lasted only a few weeks. However, it must be recognized that many dogs in this study had poorly differentiated tumors that may respond differently to prednisone than lower-grade tumors, potentially due to differences in numbers of steroid receptors. As an anti-inflammatory agent, prednisone may be helpful by decreasing swelling and edema associated with mast cell degranulation and concomitant inflammation, as well as stabilizing cytoplasmic membranes and helping to prevent further degranulation. Intralesional use of triamcinolone at 1 mg/1 cm of tumor diameter at 2-week intervals has been anecdotally reported to be effective at controlling local tumor volume. Corticosteroids may also be useful in combination with other chemotherapy agents.

Although the response rate to vincristine was low in a study of dogs with Grade 2 and 3 tumors (0 CR and 3 PR) and administration caused an unacceptable rate of GI toxicity, the use of vinblastine has met with more favorable results.[22,23] As adjuvant therapy to incomplete surgical resection, a combination of prednisone and vinblastine conferred a 57% 1-and 2-year disease-free rate. In dogs with evaluable gross disease, the overall response rate was 47% with 5 CR and 2 PR. Lomustine is an oral alkylating agent in the nitrosourea subclass. It was evaluated in 19 dogs with measurable MCT.[24] Eight of the 19 dogs (42%) had a measurable response; one dog had CR for 440 days and 7 dogs had PR for a median duration of 77 days. Six dogs (32%) had stable disease for a median duration of 78 days. The dose-limiting toxicity was neutropenia. Combination chemotherapy may improve response rates.[25,26] Supportive medical management of patients with MCTs may include H_1 and H_2 receptor antagonists, omeprazole, misoprostol, sucralfate, metoclopramide, and prednisone in an anti-inflammatory dose.

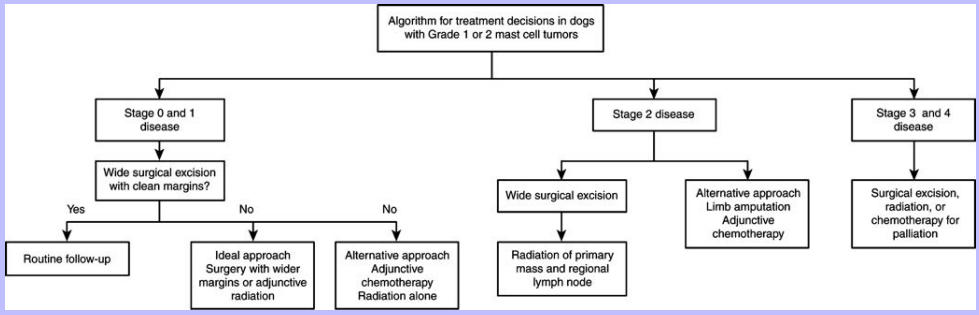
186.3.1.4 Prognosis

Although the biologic behavior of each individual MCT is unpredictable, the prognosis roughly follows the Patnaik grade, with other recognized prognostic factors being the stage of disease, tumor location, tumor duration, and several proliferation markers. As the Patnaik grade increases, average survival times diminish. Dogs with Stage 0 or 1 disease have a better prognosis than those with higher stage disease. Visceral or bone marrow involvement represents advanced disease and a poor prognosis. In 16 dogs with visceral MCT, the median survival was 90 days, and all dogs with follow-up died of their disease.[8] Dogs with systemic signs such as GI ulceration and vomiting do more poorly than dogs with no evidence of illness on presentation, because these signs are associated with more advanced and aggressive forms of mast cell disease.

Dogs with tumors on the extremities may have longer survival than those with tumors on the trunk. Tumors located on the perineal, inguinal, preputial, and subungual areas and noncutaneous sites, such as the oral cavity and GI tract, have a poorer prognosis and are often more poorly differentiated. The growth rate of a tumor can be prognostic, because tumors that remain localized and are present for months without metastasizing are often cured with complete surgical excision. The length of time that a tumor has been present prior to surgical resection is inversely related to survival time.[7] Recent rapid growth is a poor prognostic sign.

Although not routinely performed, at least four laboratory tests can provide further prognostic data: argyrophilic nucleolar organizer (AgNORs), proliferating-cell nuclear antigen (PCNA), Ki-67–positive nuclei, and ploidy. The relative frequency of AgNORs is predictive of postoperative success because higher AgNOR counts are associated with a poor prognosis.[27,28] In addition, a higher percentage of PCNA immunopositivity and a higher number of Ki-67–positive nuclei are associated with a more guarded prognosis.[27,29] These tests represent indirect measures of cellular proliferation. Dogs with aneuploid tumors have a trend toward shorter survivals and higher-stage disease.[30]

Figure 186-1 Algorithm for treatment decisions in dogs with Grade 1 or 2 mast cell tumors (MCTs).



186.3.2 Feline Mast Cell Disease

The three forms of mast cell disease in the cat are (1) cutaneous, (2) visceral (systemic, splenic), and (3) GI. Although mast cell disease is diagnosed less frequently in the cat than the dog, it remains among the four most common skin tumors in the cat (with basal cell tumor, squamous cell carcinoma, and fibrosarcoma) and accounts for 12% to 20% of all skin neoplasms.[31] Visceral MCT and lymphoma are the two most common hematopoietic tumors of the spleen, and MCT is the third most common intestinal tumor in the cat after lymphoma and adenocarcinoma. MCTs are most commonly diagnosed in middle-aged to older cats with no gender predilection, but Siamese appear to be over-represented in many studies.

186.3.2.1 Cutaneous Form

Cutaneous lesions in the cat appear as solitary or multiple dermal nodules that are discrete, nodular, papular, or plaquelike, and occasionally, diffusely swollen. Plaquelike lesions can be confused with eosinophilic granuloma complex, and indeed, some eosinophilic plaques contain mast cells as a part of the inflammatory component. Unlike the dog, feline cutaneous MCTs appear to occur more frequently on the head and neck, although some reports have not documented a site predilection. Occasionally, cutaneous lesions may represent metastasis from the visceral form of the disease, and it is recommended that any cat with multiple cutaneous lesions be evaluated for primary visceral disease. There has been no evidence of a relationship between the development of MCTs and feline leukemia virus (FeLV), but there has been a suggestion of a relationship between multiple cutaneous MCTs and feline immunodeficiency virus (FIV) infection.[1]

Diagnostic techniques used in the dog are similar for cats, with cytology and histology being the most useful for the mast cell variety of MCT. Some feline mast cells have fine granules that are difficult to visualize, even with additional stains such as toluidine blue or Wright-Giemsa. Unfortunately, the histologic grading systems used for canine MCTs do not provide prognostic information in the cat.[32] Metastasis is less common, but when it occurs it is primarily to a regional node. In several studies few cats demonstrated metastasis, but development of new cutaneous lesions occurred in one third to one half of the cats.[31,33,34] A histiocytic variety of MCT exists that has been reported primarily in young Siamese. These cats often have multiple lesions, typically developing in the same region of the body. The mast cells are poorly granulated, and the tumors are often infiltrated by numerous lymphoid aggregates. Many of these tumors are small and may spontaneously regress.

The treatment of choice for feline cutaneous mast cell disease is complete surgical excision. The overall survival of cats with cutaneous mast cell disease is long. If tumors are incompletely resected or evidence of systemic disease exists, radiation and chemotherapy may be considered. Because vinblastine and CCNU (Lomustine) are active agents in canine MCTs, they may have role in the cat. Although histamine may play a role in the clinical signs associated with feline mast cell disease, seratonin may be a more important inflammatory mediator in feline mast cells.[35] Therefore cyproheptadine may be a more effective agent than diphenhydramine for cats with clinical signs related to mast cell degranulation. The effectiveness of corticosteroids is also less clear in cats.

186.3.2.2 Visceral Form

Visceral or systemic mastocytosis is a disease that is relatively unique to the cat. This form of disease has been reported to comprise up to 50% of all feline mast cell disease and typically involves the spleen, liver, and often abdominal lymph nodes; infrequently it has been diagnosed involving mediastinal or peripheral lymph nodes.[1,2] The disease affects older cats (average age of 10 years) with no breed or gender predilection and occurs most often in domestic shorthair and longhair breeds. Clinical signs include a palpable or visible intra-abdominal mass, vomiting with or without hemorrhage, weight loss, anorexia, abdominal discomfort, ascites, and lethargy. GI signs are due to either the space-occupying nature of the large mass or histamine release with resultant gastric ulceration. An acute abdominal crisis can occur with intestinal perforation secondary to ulceration or with splenic rupture. Laboratory abnormalities may include anemia and mastocytemia, with circulating mast cells noted in up to 50% of affected cats. In addition, there may be mast cells noted within body cavity effusions. Neoplastic cells frequently spread from the spleen to the liver, abdominal lymph nodes, and bone marrow. Cytology of these organs is typically consistent with a mast cell infiltrate, and occasionally neoplastic cells will demonstrate erythrophagocytosis. Manipulation of the enlarged spleen for aspiration poses modest risk, and pretreatment with antihistamines and vigilance for precipitation of shock must accompany fine needle aspiration. Use of a 25-gauge needle allows for adequate cellular collection while minimizing the risk of hemorrhage or degranulation. Abdominal radiographs or ultrasound can demonstrate enlargement of the spleen, liver, or mesenteric nodes and may aid in obtaining diagnostic aspirates. Thoracic radiographs may be helpful in identifying pleural effusion that may occur in up to one third of cats with visceral mastocytosis. Treatment of these cats can consist of supportive care (prednisone, H_1 and H_2 antagonists, cyproheptadine), splenectomy, or chemotherapy. In most cases supportive care measures alone fail to ameliorate the clinical signs of disease. The longest survival times have been associated with successful splenectomy, even without the benefit of other therapies and in the presence of overt metastatic disease. Median survival time after splenectomy is between 12 and 19 months, but some cats live 2 to 3 years postsplenectomy.[2] Intraoperative risks include excessive hemorrhage, as well

as hypotension and shock when the splenic mass is manipulated. Prior to splenectomy, cats should be medicated with H_1 and H_2 receptor blockers and cyproheptadine to mitigate the adverse effects of intraoperative mast cell degranulation. Although not reported in the cat, use of chemotherapy may have a role in management of visceral mast cell disease.

186.3.2.3 Gastrointestinal Form

This form of mast cell disease has been infrequently reported and arises primarily from the small intestines. Clinical signs are associated with GI upset, including vomiting, diarrhea, anorexia, and weight loss. Interestingly, ulceration has not been reported, so the vomiting noted in these cats is most likely due to mechanical obstruction.[1] Many cats have a palpable mass that can be localized with imaging to the intestinal wall. Most of these tumors are solitary, but multiple tumors have been reported. Intestinal MCT are often poorly differentiated and may be difficult to definitively diagnose, particularly with cytology. These tumors usually have systemic involvement, so surgical resection is often not curative. Reported sites of metastasis have been the regional lymph nodes, liver, spleen, bone marrow, and lung. Life span is typically less than 4 months, but occasionally cats will survive long-term.

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187 CHAPTER • 187 Canine and Feline Histiocytic Diseases

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187.1 OVERVIEW OF CANINE HISTIOCYTIC DISEASES

At least four well-defined histiocytic proliferative diseases have been recognized in dogs. They are a frustrating group of diseases because it may be difficult to differentiate them from granulomatous, reactive inflammatory diseases or from lymphoproliferative diseases by examination of regular paraffin sections. The clinical presentation and behavior and responsiveness to therapy vary tremendously between the syndromes observed. Clinical and pathologic images of canine histiocytic diseases and details of histiocytic lineages are available on a web site maintained by the authors (http://www.histiocytosis.ucdavis.edu). *Canine cutaneous histiocytoma* usually occurs as a single lesion in young dogs and spontaneously regresses. Multiple histiocytomas and metastatic histiocytomas are examples of less common but more aggressive subgroup of this tumor. *Langerhans' cell histiocytosis* (LCH) is a rare disease characterized by extensive regional cutaneous infiltration by histiocytes, which otherwise resemble those in histiocytoma, although rapid systemic metastasis is observed. *Cutaneous histiocytosis* (CH) typically occur as single or multiple lesions, which tend to wax and wane and may even spontaneously regress. Few cases respond to corticosteroids; the remainder persist and may require more aggressive immunosuppressive therapy. *Systemic histiocytosis* (SH) is a familial disease of Bernese mountain dogs and also occurs sporadically in other breeds. SH causes prominent skin manifestations identical to those seen in CH, but mucous membranes (ocular and nasal) and a variety of other organ systems, including lymphoid organs, lung, and bone marrow, may also be involved. Although the lesions may wax and wane, SH is a progressive disease that often requires continuous immunosuppressive therapy. *Histiocytic sarcoma* (HS) and *malignant histiocytosis* (MH) occur with high incidence in Bernese mountain dogs, Rottweilers, flat-coated retrievers, golden retrievers, and sporadically in many other breeds. HSs occur as localized lesions in spleen, lymph nodes, lung, bone marrow, skin and subcutis, brain, and periarticular tissue of large appendicular joints.

HS can also occur as multiple lesions in single organs (especially spleen) and rapidly disseminate to involve multiple organs. Hence, disseminated HS is difficult to distinguish from MH, which is a multisystem, rapidly progressive disease that includes simultaneous involvement of multiple organs such as spleen, lymph nodes, lung, bone marrow, skin, and subcutis. Response of HS and MH to chemotherapy is at best brief.

187.1.1 Histiocytic Differentiation and Canine Histiocytosis

The development of canine-specific monoclonal antibodies for many of the functionally important molecules of macrophages and dendritic antigen presenting cells (DCs) has enabled the identification of the cell lineages involved in canine histiocytic disorders.[1–4] Despite the large variation of clinical and pathologic features of canine histiocytic diseases, the majority represent proliferations of cells of various DC lineages.

Histiocytes differentiate from CD34+ committed stem cell precursors into *macrophages* and several DC lineages, which include *epithelial DCs* or *Langerhans' cells* (LC), *interstitial DCs* in many organs (e.g., dermal DCs in skin), and *interdigitating DCs* of T-cell domains in peripheral lymphoid organs. Cytokines influencing DC development include GM-CSF and TNF-alpha. Macrophage development from CD34+ precursors is influenced by GM-CSF and M-CSF. Blood monocytes can differentiate into either macrophages under influence of M-CSF or into DCs under influence of GM-CSF and interleukin (IL)-4.[5,6] Recently a new human

dendritic lineage of myeloid origin was identified. These DCs differentiate under the influence of GM-CSF and IL-3 and are the major source of nonactivated resident DCs in T-cell domains of peripheral lymphoid organs.[7] They are supplemented by migration of activated DCs from skin and interstitial tissues, which arrive in lymph nodes as veiled cells in afferent lymph after contact with antigen.

Dendritic cells are the most potent antigen presenting cells (APCs) for induction of immune responses in naïve T cells. Canine DCs have been best defined in canine skin. They occur in two major locations: (1) within the epidermis (LC) and (2) within the dermis especially adjacent to postcapillary venules (interstitial DCs or dermal DCs). Canine DCs abundantly express CD1 molecules,[3,4] which together with MHC class I and MHC class II molecules are responsible for presentation of peptides, lipids, and glycolipids to T cells. Hence, DCs are best defined by their abundant expression of molecules essential to their function as APC. Of these, the family of CD1 proteins is largely restricted in expression to dendritic APC in skin; whereas MHC class I and II are more broadly expressed.

The beta-2 integrins (CD11/CD18) comprise the major family of adhesion molecules on leukocytes and as such are useful markers of leukocytic differentiation. CD11/CD18 expression is highly regulated in normal canine macrophages and DCs. CD11c is frequently expressed by DCs; whereas macrophages predominately express CD11b (or CD11d in the splenic red pulp and bone marrow).[8,9] In diseased tissues these beta-2 integrin expression patterns may be diversified.

Langerhans' cells (epidermal DCs) and interstitial DCs are distinguishable by their differential expression of E-cadherin (LC+) and Thy-1 (CD90) (interstitial DC+). Lineage distinctions among histiocytes are best made via immunohistochemistry (IHC) performed on frozen sections (CD1, CD11b, CD11c, CD11d, CD18, CD90, MHC II, and E-cadherin expression). Less definitive but useful distinctions can also be attained via IHC on formalin-fixed paraffin sections with panels of leukocytic markers developed for use in this format (CD3, CD11d, CD18, CD45, CD45RA, CD79a, and E-cadherin).

Regardless, dendritic APC arise in bone marrow and migrate through blood to a variety of epithelial sites (cutaneous and mucosal), where they take up residence either within epithelia or in dermis and lamina propria. 779
In these sites they function as antigen processing cells and ultimately APCs, which interact with T cells. 780
Migration of DCs (as veiled cells) beyond the skin to the paracortex of lymph nodes occurs after contact with antigen. The interdigitating dendritic APCs of lymph node paracortex are partially derived from such migration. Aspects of this developmental and migratory program of cutaneous DCs are recapitulated in the DC proliferative disorders of canine skin.

Successful interaction of dendritic APC and T cells in response to antigenic challenge also involves the orderly appearance of costimulatory molecules (B7 family—CD80 and CD86) on dendritic APC, as well as their ligands (CD28 and CTLA-4) on T cells. Defective interaction of dendritic APC and T cells appears to contribute to the development of reactive cutaneous histiocytic proliferative diseases (CH and SH), which are related DC disorders arising out of disordered immune regulation (see following). Much research is currently directed at the molecular events associated with maturation and migration of dendritic APC and the costimulatory function of dendritic APC. To some extent this research should be of future benefit to understanding the pathogenesis of proliferative diseases of dendritic APC in both human and dog.

187.1.2 Cutaneous Histiocytoma Complex

Several discrete clinical entities exist, in which proliferation of histiocytes, which resemble those encountered in histiocytoma, are seen. *Histiocytoma* is a common, benign, cutaneous neoplasm of the dog. Histiocytomas

usually occur as solitary lesions, which undergo spontaneous regression. The age-specific incidence rate for histiocytomas drops precipitously after 3 years, although histiocytomas do occur in dogs of all ages.[10] Recurrence of histiocytomas at the same or other sites is uncommon. The occurrence of multiple tumors is also uncommon. Epidermal invasion by cells of histiocytoma frequently occurs (incidence about 60%), and intraepidermal nests of histiocytes resemble Pautrier's aggregates, characteristically found in epidermotropic lymphoma (mycosis fungoides [MF]). Epidermal invasion in histiocytoma, or presence of simultaneous *multiple histiocytomas* especially in aged dogs, can present a diagnostic dilemma, and distinction from MF and nonepidermotropic cutaneous lymphoma (NECL) is difficult on purely morphologic grounds.[3,11,12] It is imperative to request IHC stains to resolve these issues particularly in older dogs or if equivocal comments appear in the pathology report.

Multiple histiocytomas can be confused with CH on clinical appearance. Morphologically, however, histiocytomas are consistently epidermotropic and commonly epidermally invasive; these are not features of CH. Multiple histiocytomas appear to be more common in Shar Pei dogs but can occur in any breed. Delayed regression of multiple histiocytomas can occur, and lesions can persist for up to 10 months before onset of regression.

187.1.2.1 Metastatic Histiocytoma

Several dogs with histiocytomas have been observed in which histiocytes had migrated to and completely obliterated draining lymph nodes. Each dog had been diagnosed as having HS, and each was assigned a poor prognosis. However, three dogs had complete spontaneous regression of their lesions within 3 to 4 weeks of diagnosis.[3] In other instances the metastatic lesions of histiocytoma persisted without regression and the dogs were euthanized. The disease course in these dogs extended over several months. Spread from lymph nodes to lung has also been observed in some dogs but is rare. Veterinarians should remember that the primary lesion in most of these dogs looked no different from an uncomplicated histiocytoma.

187.1.2.2 Langerhans' Cell Histiocytosis

The presence of multiple histiocytomas is now a well-recognized syndrome. However, another presentation exists in which widespread cutaneous lesions histologically identical to histiocytoma are observed. Clinically the lesions are almost confluent in affected regions. Rapid internal spread is observed, and affected dogs have all been euthanized. One published account of such a case exists,[13] and the authors have data on four dogs with similar signs. This disease is most like cutaneous LCH of humans.[14]

187.1.2.3 Immunophenotypic Studies

IHC is best performed on frozen sections of tumor or cytologic preparations (not formalin fixed material). Histiocytoma is readily distinguished from other histiocytic disorders and cutaneous lymphoma with the aid of IHC. Histiocytomas have the phenotype of epidermal Langerhans' cells.[3] They express CD1a, CD1b, CD1c, MHC class II, CD11c, and E-cadherin. In leukocytes, E-cadherin expression is unique to Langerhans' cells. Langerhans' cells use E-cadherin to localize in the epidermis via homotypic interaction with E-cadherin expressed by keratinocytes. E-cadherin expression has only rarely been observed in HS in canine skin and subcutis. Histiocytomas lack expression of CD4 and Thy-1, which are consistently expressed by histiocytes in CH and SH. Therefore cutaneous histiocytoma is a localized epidermal Langerhans' cell tumor. The rare dogs with multiple histiocytoma and metastasis to local lymph nodes can be compared with dogs with

confluent histiocytic lesions that occur in many cutaneous sites with rapid systemic spread. These two conditions may represent one disease with a spectrum of diverse clinical behavior and are perhaps best characterized as LCH. LCH is also recognized as a rare disease of humans in which marked variation in clinical behavior is recognized.[14,15]

187.1.2.4 Regression of Histiocytomas

The factors that determine the onset of regression in canine histiocytomas are unknown. Evidence of regression is usually observed in lesions that have been present for only a few weeks, although regression can be delayed for many months. Regardless, CD8+ alpha beta T cells mediate regression; only scant numbers of CD4+ T cells are observed in histiocytoma lesions. Migration of tumor histiocytes, tumor infiltrating reactive DCs to draining lymph nodes, or both could activate CD4+ T cells, which would assist in CD8+ cytotoxic T-cell recruitment. Because massive CD8+ T-cell infiltration is observed in all instances of histiocytoma regression, therapeutic intervention with the aim of immunosuppression should be avoided once a definitive diagnosis of histiocytoma has been reached (to allow unfettered cytotoxic T-cell function).

187.1.3 Histiocytic Sarcoma Complex

The *HS complex* encompasses a number of distinctive clinical entities (see following). Some definitions are in order and reflect the preferred nomenclature of the Histiocyte Society. Histiocytic neoplasia that originates at a single site is called *HS*. This form of HS, which is often encountered on the extremities, has the best prognosis if treated early by surgical excision or by amputation of a limb. When spread to distant sites beyond the local lymph node occurs, the disease is then termed *disseminated HS*; this is more likely to occur unnoticed when primary lesions are located in cryptic sites (e.g., spleen, lung, bone marrow). This latter form of HS is most like MH. MH is an aggressive, histiocytic neoplasm that arises in multiple sites simultaneously. Most lesions previously defined as MH are probably more correctly termed *disseminated HS*. The occurrence of true MH is difficult to establish because the lesions often occur in cryptic sites, and the existence of histiocytic neoplasia is only recognized after clinical signs have appeared and disease progression is advanced. HS and MH are capable of widespread metastasis, hence in time the two syndromes merge clinically and it is not always possible to 780
differentiate true multicentric origin (i.e., MH) from widespread metastasis of disseminated HS. In addition, it 781
is never possible to know exactly how long the disease process has been operative. Hence, the perception is that both disseminated HS and MH follow a rapid clinical progression despite therapeutic intervention. This is certainly true once clinical signs are apparent, but the subclinical period is of unknown duration.

The HS complex of diseases is best recognized in the Bernese mountain dog, in which a familial association is apparent. Other breeds predisposed to HS complex diseases include Rottweilers, Golden retrievers, and flat-coated retrievers. HS complex is not limited to these breeds and can occur in any. Primary lesions of HS occur in spleen, lymph node, lung, bone marrow, skin and subcutis (especially of extremities), and in periarticular tissues of the limbs. Secondary sites are widespread but consistently include liver and lung (with splenic primary) and hilar lymph node (with lung primary). Clinical signs include anorexia, weight loss, and lethargy. Other signs depend on the organs involved and are a consequence of destructive mass formation. Accordingly, pulmonary symptoms such as cough and dyspnea have been seen. Central nervous system (CNS) involvement (primary or secondary) can lead to seizures, incoordination, and paralysis. Regenerative and nonregenerative anemias have been consistently documented in hemophagocytic HS/MH. Lameness is often observed in periarticular HS.

187.1.3.1 Treatment of Histiocytic Sarcoma Complex

Localized HS affecting skin and subcutis have been cured by early surgical excision. In others, surgery supplemented by local radiation therapy has been curative. In the case of periarticular HS, which occurs in the subsynovial tissues of the extremities, amputation of the affected limb is necessitated by the inoperable nature of the primary lesion, which usually ensnare structures vital to limb function. Prior to amputation it is important to support absence of metastasis with thoracic radiographs, abdominal ultrasound, and draining lymph node aspiration cytology. Disseminated HS (including MH) is not readily treated surgically, because even in the splenic form, early metastasis to the liver has been documented. Response to chemotherapy has been at best brief, and the disease progresses rapidly (weeks to months) to death or euthanasia.

187.1.3.2 Morphologic Features of Histiocytic Sarcoma

Lesions of HS are typically destructive mass lesions with a uniform, smooth cut surface and a white or cream to tan color. Lesions have a soft consistency and may contain discolored areas (typically yellow and extensive), which indicate area of necrosis. Lesions can be solitary or multiple within an organ (especially spleen). Periarticular HS has a distinctive appearance: it occurs as multiple tan nodules located in the subsynovium. These lesions may encircle the affected joint. Hemophagocytic HS does not initially form mass lesions in the primary sites (spleen and bone marrow). Typically, diffuse splenomegaly and ill-defined mass lesions are observed; the cut surface is dark red and the consistency is firm. The liver is usually bile stained (jaundice), and disruption of the lobular pattern due to metastasis is observed—marked liver involvement can occur before destructive liver masses are noticeable.

The histological appearance of HS lesions is consistent regardless of location. Lesions are most frequently composed of sheets of large, pleomorphic, mononuclear cells and multinucleated giant cells, which show marked cytologic atypia and numerous bizarre mitotic figures. Some lesions may include spindle cell forms either alone or mixed with the mononuclear cells and multinucleated giant cells. Pure spindle cell lesions resemble spindle cell sarcomas of diverse cell lineage. Confirmation of histiocytic lineage can only be achieved with IHC in these instances. Phagocytosis of red cells, leukocytes, and tumor cells occurs but is not prevalent in most forms of HS. However, in *hemophagocytic HS* this behavior is amplified. Neoplastic histiocytes manifest marked erythrophagocytosis, and the infiltrates obliterate the splenic red pulp and invade red pulp sinuses. Foci of extramedullary hemopoiesis (EMH) occur within and adjacent to the tumor infiltrates in the splenic red pulp. Simultaneous involvement of bone marrow is frequent, and erythrophagia is observed here as well; these cases are probably equivalent to hemophagocytic MH in recognition of the simultaneous involvement of multiple sites. In some instances the neoplastic infiltrates can be deceptively cytologically bland. The cytologic appearance can be asynchronous between sites (e.g., spleen and bone marrow), which can contribute to diagnostic ambivalence if only one site is evaluated. Invasion of splenic red pulp sinuses portends invasion of the hepatic sinusoids. In the early stages, liver metastases can easily be overlooked grossly and histologically, because histiocytic infiltrates creep along sinusoids and do not form discrete masses until later. Neoplastic histiocytes in hemophagocytic HS express a distinctive surface antigen profile much like that expressed by macrophages in splenic red pulp and bone marrow (see following).

187.1.3.3 Immunophenotypic Studies

MH and HS lesions express leukocyte surface molecules characteristic of DCs (CD1, CD11c, and MHC II). Diffuse expression of E-cadherin, Thy-1, and CD4 has not been observed in HS or MH in skin or other sites; this, together with cytomorphology, assists in the distinction of MH and HS from histiocytoma and reactive

histiocytosis (SH and CH). In histiocytoma the phenotype is quite similar to that of HS, except for the expression of E-cadherin, which occurs in histiocytoma (especially in the cellular infiltrate immediately adjacent to the epidermis). E-cadherin expression is visibly weaker in tumor cells in the deep dermis. In reactive histiocytosis, infiltration and proliferation of activated interstitial (dermal) DCs (CD1+, CD11c+, MHC II+, E-cadherin-), which consistently express CD4 and Thy-1 is observed.

In hemophagocytic HS, histiocytes express CD11d (instead of CD11c) and MHC II. Expression of CD1 molecules is uniformly low or occasionally moderate but with a patchy distribution. This phenotype is consistent with macrophage differentiation rather than DC differentiation, in which abundant expression of CD1 and CD11c is expected.

The exact sublineages of DCs involved in HS have not been determined in most instances. The most likely candidates include interdigitating DCs in lymphoid tissues and perivascular interstitial DCs in other involved tissues. Immunophenotyping and careful morphologic assessment should also avoid confusion of HS and MH with the large cell form of T-cell lymphoma (CD3+) and with poorly differentiated mast cell tumors (CD18+ variable, CD45+, CD45RA+, Tryptase+, c-kit+).

187.1.4 Reactive Histiocytosis

187.1.4.1 Systemic Histiocytosis

SH was originally recognized in related Bernese mountain dogs.[16] SH is a generalized histiocytic proliferative disease with a marked tendency to involve skin, ocular and nasal mucosae, and peripheral lymph nodes. The disease predominately affects young to middle-aged dogs (2 to 8 years). SH has been observed less commonly in other breeds (Irish wolfhounds, Basset hounds, and others). Clinical signs vary with the severity and extent of the disease and include anorexia, marked weight loss, stertorous respiration, and conjunctivitis with marked chemosis. Multiple cutaneous nodules may be distributed over the entire body but are especially prevalent in the scrotum, nasal apex, nasal planum, and eyelids. Ulceration of the skin overlying the nodules is common. Peripheral lymph nodes are often palpably enlarged. The disease course may be punctuated by remissions and relapses, which may occur spontaneously (especially early in the disease course). In severe disease, lesions become persistent and do not respond to immunosuppressive doses of corticosteroids.

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187.1.4.2 Cutaneous Histiocytosis

CH is a histiocytic proliferative disorder that primarily involves skin and subcutis and does not extend beyond the local draining lymph nodes.[17] CH occurs in a number of breeds. Evidence of spread beyond the skin would invoke the diagnosis of SH—a closely related disorder. Lymphadenopathy has not been emphasized in published reports and has only been documented in a small number of the authors' cases. The lesions occur as multiple cutaneous and subcutaneous nodules up to 4 cm diameter. Overlying skin ulceration is common. Lesions may disappear spontaneously or regress and appear at new sites simultaneously. Topographically, lesions may be found on the face, ears, nose, neck, trunk, extremities (including foot pads), perineum, and scrotum.

187.1.4.3 Treatment Options in Systemic Histiocytosis and Cutaneous Histiocytosis

SH has proven to be a difficult and frustrating condition to treat. Consequently, many dogs were euthanized. Originally dogs were treated with thymosin (derived from bovine thymus) because of reports of its effectiveness in human LCH cases. Some dogs appeared to respond to this but not consistently. The original rationale for using thymosin was that SH was likely an immunoregulatory disorder and not cancer.[16] In the majority of instances, corticosteroid treatment is ineffective, although in about 10% of dogs with CH, steroid administration is effective. Hence, steroids are worth trying in this disease, given the expense of the alternatives.

Intractable cases are best treated with immunosuppressive doses of cyclosporine A (Neoral, Sandoz, East Hanover, NJ) or leflunomide (Arava, Aventis Pharmaceuticals, Bridgewater, NJ). These drugs are potent inhibitors of T-cell activation, and their ability to abrogate clinical disease supports the hypothesis that SH and CH are disorders of immune regulation. Treatment with these drugs is expensive and may be needed for life. It is preferable not to invoke such powerful immunosuppressive therapy until disease progression is evident or troublesome sites are involved, because in some cases of CH (and even SH) spontaneous regression of lesions or episodic disease activation can occur. Cost of treatment can be substantially reduced by coadministration of cyclosporine A and ketoconazole. It is imperative to measure 12-hour plasma trough levels of cyclosporine A (with twice-daily dosing); this is especially important if ketoconazole is coadministered! The 12-hour plasma trough target for cyclosporine A is 500 to 600 ng/mL. Neoral is the preferred cyclosporine A drug, because it is a microemulsion preconcentrate with superior gastrointestinal (GI) absorption compared with Sandimmune (Sandoz) (cyclosporine A in an olive oil base). Hence, Neoral can be used at a lower dose.[18]

187.1.4.4 Microscopic Features of Systemic Histiocytosis and Cutaneous Histiocytosis

The lesions of SH in most tissues consist of perivascular infiltrates of large histiocytes and variable populations of lymphocytes, neutrophils, and eosinophils. The histiocytes frequently invade vessel walls, and this may lead to vascular compromise and infarction of surrounding tissues, which contributes to ulceration of the cutaneous lesions. The widespread distribution of lesions of SH is only fully appreciated at necropsy. Histiocytic lesions have been observed in skin, lung, liver, bone marrow, spleen, peripheral and visceral lymph nodes, kidneys, testes, orbital tissues, nasal mucosa, and other sites.

In skin, the lesions of SH and CH are virtually identical. The lesions usually involve the deep dermis and subcutis. Involvement of the superficial dermis is inconsistent, and epidermotropism of the histiocytes is not observed. In CH the lesions are limited to the skin but may involve the draining lymph nodes.

187.1.4.5 Immunophenotypic Studies

Histiocytes in SH and CH express markers expected of DCs such as CD1, C11c, and MHC II. However, the lack of consistent epidermotropism in SH and CH lesions and the expression of Thy-1 (expressed by dermal DCs) and CD4 (a marker of DC activation) suggest that histiocytes in these diseases are activated interstitial-type DC[1]. In skin, dermal DCs are mostly of interstitial DC type. Expression of Thy-1 and CD4 in SH and CH clearly distinguishes these diseases from histiocytoma, in which an epidermal LC phenotype is observed. LCs are epithelial DCs; they express CD1, CD11c, MHC II, and E-cadherin. LCs lack expression of Thy-1 and do not express CD4 in the nonactivated state.

187.1.4.6 Pathogenesis

The clinical behavior and consistent clinical response to immunosuppressive therapy with agents capable of profoundly inhibiting T-cell activation has reinforced the concept that SH and CH occur in the context of disordered immune regulation arising from defective interaction of DC and T cells. The end result of this dysregulated immune interaction is chronic proliferation of DC and T cells. The initiation of the process is probably antigen driven, although studies to identify the nature of the antigens involved have been unrewarding. Hence, it is important to perform tests to rule out infectious agents in the initial evaluation of a dog suspected of having reactive histiocytosis (i.e., culture, special stains for microorganisms in tissue). The lesions can wax and wane over a considerable period of time, and spontaneous regression without therapy has been observed. The lymphoid component of the lesion consists of predominately CD8+ alpha beta T cells, which have numbers that can vary markedly between lesions. These T cells can comprise up to 50% of the cells in some instances. The role played by T cells is unknown. T cells may be involved in a key way in the exaggerated proliferation and activation of DCs via T-cell-derived cytokines such as GM-CSF and TNF alpha, which are known to influence the proliferation and differentiation of DCs.

187.1.4.7 Concluding Remarks

The continued distinction of SH and CH as separate entities is probably no longer justifiable. It would be preferable to consider them within the spectrum of reactive histiocytoses of interstitial DC origin, in which clinical outcome is predictable more by the distant migratory potential of the proliferating histiocytes beyond the skin. In this view, CH and SH would be regarded as skin-limited and systemic interstitial DC proliferations, respectively. A wide range of clinical behavior is to be expected within each grouping, with SH usually exhibiting more aggressive disease. CH and SH should not be confused with malignant DC disorders (HS and MH), which can occur in the same topographic locations. Cytologic and immunophenotypic differences can distinguish these diseases in most instances. Clear evidence of progression of reactive histiocystosis to HS or MH is not evident.

187.2 FELINE HISTIOCYTIC PROLIFERATIONS

True histiocytic proliferative diseases in cats have not been extensively documented. The lesion referred to as *malignant fibrous histiocytoma* is most likely a soft tissue sarcoma with giant cells; the neoplastic population does not express histiocytic markers. At least two different histiocytic proliferative diseases have been recognized in cats: (1) progressive histiocytosis and (2) HS/MH.

187.2.1 Feline Progressive Histiocytosis

Data on 19 cats with feline progressive histiocytosis have been accumulated since 1995. The incidence and recognition of cases seems to be increasing. Clinical presentation and progressive behavior resemble LCH in humans and multiple persistent histiocytomas or LCH in dogs. Affected cats may have a solitary skin nodule, but usually multiple papules, nodules, or plaques develop, measuring up to 1.5 cm in diameter. The nodules are firm, nonpruritic, and nonpainful. The surface is often alopecic and may be ulcerated. The lesions are mostly located on the head, lower extremities, or trunk. Occasionally, the lesions are limited to one extremity. Feline progressive histiocytosis is a disease of middle-aged to older cats, the age ranging from 7 to 17 years. Sex or breed predilection has not been seen. The lesions may wax and wane, but spontaneous regression does not occur. In general, the nodules progress in size and may coalesce to large plaques. In addition, new lesions may

develop. Some cats develop lesions in lymph nodes and internal organs including the lungs, kidneys, spleen, and liver. Additional clinical signs vary depending on the internal organ systems involved. Feline progressive histiocytosis has a guarded to poor long-term prognosis, because no successful treatment has been recognized to date.

187.2.1.1 Morphologic Features

Lesions consist of diffuse dermal histiocytic infiltrates, which may extend into the subcutis. The overlying epidermis is either intact or ulcerated. Histiocytes have irregular, vesicular nuclei and finely dispersed chromatin. Cytologic atypia is present in a minority of lesions. Multinucleated tumor cells and occasional intralymphatic tumor cell aggregates may be present. The mitotic activity varies, and atypical mitoses are seen. Some cases are epitheliotropic (epitheliotropic progressive histiocytosis), characterized by intraepidermal single cells or cell aggregates, other cases lack epithelial involvement (nonepitheliotropic progressive histiocytosis). As the lesions progress the cells may exhibit numerous cytoplasmic vacuoles and hence have a foamy appearance. The extent of reactive infiltrates, composed of dispersed lymphocytes and fewer neutrophils, varies between cases.

Feline progressive histiocytosis has to be differentiated from xanthomas and from multicentric round cell tumors, such as lymphomas and mast cell proliferations. Xanthomas often have small areas of hemorrhages and deposition of cholesterol crystals, and they are composed of markedly vacuolated macrophages. Xanthomas are usually associated with underlying metabolic disorders such as diabetes mellitus or hypertriglyceridemia. Cutaneous papular mastocytosis (urticaria pigmentosa) is usually composed of well-granulated mast cells and Toluidine blue or Giemsa stains demonstrate their metachromatic granules. However, IHC may be required to rule out xanthomas, lymphomas, or poorly granulated mast cell tumors (“histiocytic” mast cell tumors).

187.2.1.2 Immunophenotypic Studies

Histiocytes of feline progressive histiocytosis consistently express CD18, CD1a, CD1c, and MHC II. This immunophenotype is consistent with a DC origin.[4] However, both the epitheliotropic and nonepitheliotropic forms lack expression of E-cadherin, and Birbeck's granules could not be found in the only case evaluated by electron microscopy. These features indicate that feline progressive histiocytosis is not composed of Langerhans' cells, despite the existence of epitheliotropic infiltrates. The DCs are most likely of interstitial (dermal) type. The admixed reactive lymphocytes are CD8+ cytotoxic T cells.

187.2.2 Feline Histiocytic Sarcoma

Localized HS has been observed in cats. The poorly demarcated tumor masses were located in the subcutis of the ventral abdomen or the extremities. Metastasis to draining lymph nodes occurs. Alternatively, primary HS may occur in the spleen.[19] In essence, feline HS resembles the canine counterpart in terms of location of lesions and disease progression, but the incidence of feline HS is markedly lower. Feline HSs have a guarded to poor prognosis and most cats have been euthanized.

187.2.2.1 Morphologic Features

Feline HS shares morphologic features with canine HS, including variable cytology encompassing mononuclear and multinucleated round cells and discrete to aggregated spindle cells. Anisocytosis and

anisokaryosis exist in tumor cells of all types. A moderate to high mitotic rate with bizarre mitotic figures is common. IHC is required to differentiate between HSs and vaccine-induced sarcomas or anaplastic sarcomas with giant cells (incorrectly referred to as *malignant fibrous histiocytoma*).

187.2.2.2 Immunophenotypic Studies

The round and spindle-shaped tumor cells express CD18, CD1, and MHC II. This immunophenotype is consistent with a DC origin, although the precise sublineage of DC has yet to be determined. The tumor cells lack expression of E-cadherin and hence are not of Langerhans' cell origin.

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188 CHAPTER • 188 Urogenital and Mammary Gland Tumors

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Laura Garrett

188.1 KIDNEY

Renal tumors are uncommon in cats and dogs, but they are almost always malignant. The most common renal tumor in cats is lymphoma; up to 50% of these cats are FeLV positive. Affected cats are usually middle aged (6 years) with no breed or sex predilection. In dogs the most common primary renal tumors are epithelial in origin (i.e., carcinoma or adenocarcinoma). Older dogs are affected, with an average age of 9 years, and males are overrepresented (1.5:1). Rare tumors include cystadenocarcinoma with concurrent nodular dermatofibrosis in German shepherd dogs and tumors of embryonal origin (e.g., Wilm's tumor) that are typically recognized in younger dogs. Animals with renal tumors usually have nonspecific signs of weight loss, anorexia, and lethargy. Less commonly, they have abdominal distention, lameness, and pain. Gross hematuria is a possible but uncommon finding. Physical examination may reveal unilaterally or bilaterally enlarged kidneys. A rare physical examination finding in dogs is palpable thickening and warmth in the distal long bones—a finding compatible with the paraneoplastic syndrome of hypertrophic osteopathy. Renal cystadenocarcinoma may be associated with firm, nodular dermal lesions and benign uterine growths. The genetic determinant of this unusual triad has yet to be identified.

Diagnosis may be obtained via cytology, especially in cats with lymphoma. However, biopsy is the gold standard for definitive diagnosis of most renal tumors. Ancillary tests such as a complete blood count (CBC), serum chemistry profile, and urinalysis provide important information regarding the overall health of the pet and the presence of paraneoplastic syndromes. Animals with renal tumors may have either anemia or polycythemia secondary to decreased or increased erythropoietin production, respectively. Another rare paraneoplastic syndrome of uncertain etiology in dogs with renal adenocarcinoma is neutrophilic leukocytosis. Animals with bilateral disease may have renal failure, as evidenced by increases in BUN and creatinine and a low urine specific gravity. Although tumor cells are only infrequently recognized on evaluation of urine sediment, finding RBCs and proteinuria on urinalysis is common. Up to one third of dogs and cats with epithelial renal tumors have radiographic evidence of pulmonary metastases. Abdominal radiographs show renomegaly but abdominal ultrasonography is both more sensitive and specific for identifying renal tumors. Ultrasound may also be helpful in obtaining preoperative biopsy specimens. Renal carcinomas are often bilateral and biologically aggressive, invading into the vena cava and metastasizing to regional lymph nodes, liver and bone.

Treatment with chemotherapy is indicated for cats with renal lymphoma. In addition to being bilateral, this is typically a systemic disease. With treatment, the average survival time is 6 months.[1] A doxorubicin-based combination chemotherapy protocol is recommended with the caveat that doxorubicin may be associated with nephrotoxicity in cats and thus renal parameters should be closely monitored before, during, and after use of doxorubicin.[2] As central nervous system (CNS) involvement has been documented in cats with renal lymphoma, the addition of a drug that reaches effective concentrations within the CNS (e.g., cytosine arabinoside) into a multidrug protocol is recommended. Nephrectomy is the most effective treatment for dogs with unilateral tumors, with average survival of 6 to 10 months. Renal cystadenocarcinomas in German shepherds, although malignant and metastatic, progress more slowly than other renal malignancies and survival times may be longer.[3] Ovariohysterectomy (OHE) is indicated for treatment of the uterine leiomyomas if the animal is symptomatic for those lesions.

188.2 URINARY BLADDER

Tumors of the urinary bladder are uncommon in dogs and rare in cats. Transitional cell carcinoma (TCC) is the most common primary tumor of the urinary bladder in both species. Other differentials include squamous cell carcinoma, leiomyosarcoma, leiomyoma, and rhabdomyosarcoma. The bladder may also be invaded by prostatic neoplasia or metastatic disease (e.g., hemangiosarcoma, lymphoma). Bacterial cystitis and urolithiasis are common differentials for the clinical signs seen, and a rare but important differential diagnosis for mass lesions is benign polyps of the urinary bladder.

Affected cats are usually middle aged and male. No underlying causes have been identified in cats. Older (10 years) female dogs of small breeds such as West Highland white and Scottish terriers, beagles, Dachshunds, and Shetland sheepdogs are reportedly at higher risk. Potential etiologies in dogs include obesity, cyclophosphamide therapy, and organophosphate, carbamate, pyrethrin, or pyrethroid-based flea dips.[4,5] Client complaints of recurrent stranguria, pollakiuria, hematuria, dysuria, urinary incontinence, or any combination of the above signs in an older dog should initiate a search for bladder cancer. In advanced cases, a mass is palpable in the caudal abdomen or abnormalities, such as a thickened urethra or enlarged sublumbar or intrapelvic lymph nodes, are identified on rectal examination. TCC can also metastasize to the inguinal lymph nodes and thus palpation of the inguinal fat pads may reveal firm nodes. Rarely, dogs have shifting leg lameness, or warm, swollen, and painful limbs. Palpation of the affected limbs reveals a firm, irregular, periosteal proliferation—a finding suggestive of hypertrophic osteopathy.

Diagnostic evaluation of any animal with the above clinical signs should begin with careful abdominal palpation and a rectal examination. CBC and biochemistry may be normal or may show azotemia. The urine sediment may reveal carcinoma; the presence of inflammation may cause “reactive” epithelial cells to exhibit criteria of malignancy. When a bladder tumor is suspected, urinalysis should be obtained by free catch, catheterization, or ultrasound-guided cystocentesis, with caution to avoid penetrating the bladder through the tumor mass. Ideally, urine culture and sensitivity should be performed to rule out concurrent lower urinary tract infection. Unless the lesion is mineralized, abdominal radiographs will not reveal urinary bladder disease but may show sublumbar lymphadenomegaly or bony metastases. Although contrast cystography may be indicated for identification of urethral involvement, imaging of the urinary bladder via double contrast cystography has been widely replaced by ultrasonography. Ultrasound (Figure 188-1) is a highly sensitive tool in localizing and defining the extent of disease and for monitoring response to therapy.[6] Cytology may be diagnostic, with the finding of characteristic pink, intracytoplasmic transitional bodies (Figure 188-2). Failing a cytologic diagnosis, biopsy (traumatic catheter, surgical, or cystoscopic) and histologic examination may be necessary. Ultrasound-guided biopsy is not recommended as seeding of the biopsy tract with viable tumor cells is a possible complication.[7]

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TCC often involves the apex of the bladder in cats. As this tumor is uncommon, the disease may go undiagnosed until it is diffusely invasive. However, even in cases of extreme local invasion, metastatic disease is not a common finding. In dogs, TCC typically involves the trigone. Obstruction of the ureters and urethra as well as invasion and disruption of the normal function of the urethral sphincter are common. TCC in dogs is metastatic; up to 40% of cases show spread by the time of diagnosis, 17% involve the lungs.[8]

Localized cases of TCC are treated with surgical resection if possible. TCC is highly exfoliative; caution is warranted to avoid “seeding” the tumor into the abdomen or along the surgery site.[9] The use of stay sutures to lift the bladder out of the abdominal cavity and moistened gauze sponges to pack off the rest of the abdomen can greatly decrease the risk of tumor seeding. Instruments and gloves that touch the tumor are contaminated. Once the

tumor is exposed, use “clean” instruments to resect the tumor, switch gloves and use “clean” instruments to close the abdomen. Because the trigone region is most commonly involved in dogs, complete resection with acceptable postoperative function is rarely feasible. Most dogs with TCC should be managed medically or, less commonly, with radiation therapy.

Although no published studies discuss the medical management of TCC in cats, treatment of dogs is well described. Single agent therapy with piroxicam or cisplatin has a response rate of 20% with median survival times of 6 months.[10,11] Other studies report that single agent mitoxantrone or the combination of doxorubicin and cyclophosphamide have some activity.[12,13] Although cisplatin and piroxicam combination therapy has a response rate of 70%, 12 of 14 dogs treated with this protocol went into renal failure; most required early termination of their therapy and, in spite of the impressive response rate, median time to tumor progression or death was 4 months.[14] Mitoxantrone and piroxicam combination therapy has a response rate of 35% with a median survival time of 11½ months.[15] The current treatment recommendations are either single agent therapy with piroxicam (0.3 mg/kg orally once daily), or combination therapy of piroxicam and mitoxantrone (5 mg/m^2 IV every 21 days) with response to therapy used as a guideline for continued treatment.

Figure 188-1 Transverse ultrasonographic image of a thickened, irregularly marginated circumferential urinary bladder wall mass in a spayed female collie with TCC. (Courtesy Todd Henrikson, Kansas State University.)

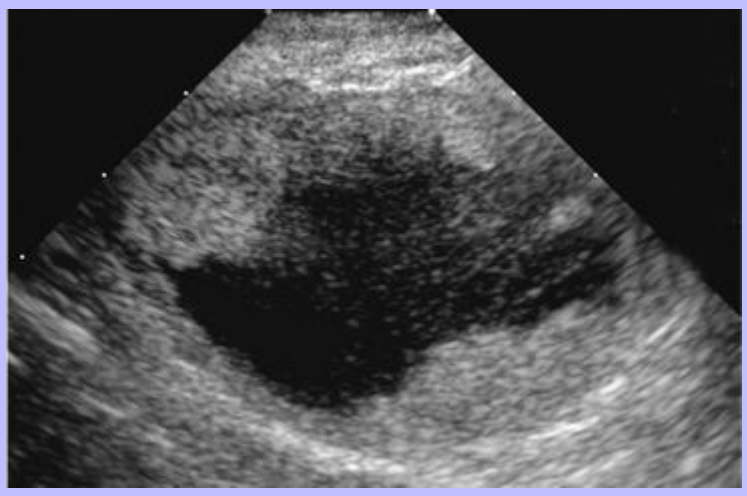
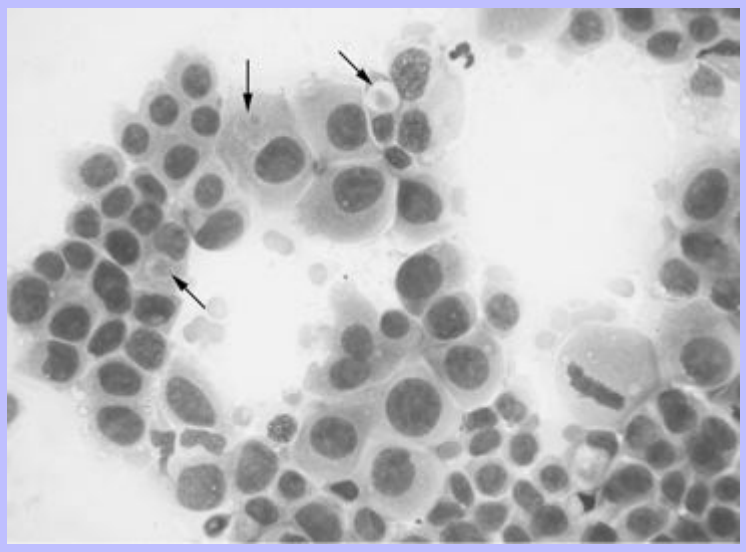


Figure 188-2 Large clustering epithelial cells showing criteria of malignancy from a male neutered Scottie with a urinary bladder mass, note transitional bodies *(arrows)*. Sample obtained via traumatic catheterization. (20×, Diff Quick stain.)



Although radiation therapy may also play a role in the management of TCC, survival times are not reported.[16] Surgical palliation for TCC obstructing the urethra ranges from ureterocolonic anastomosis to tube cystostomy. Ureterocolonic anastomosis has been described but this procedure is commonly associated with neurologic and gastrointestinal complications secondary to hyperammonemia, metabolic acidosis, and uremia, as well as chronic pyelonephritis, and survival times following this procedure ranged from only 0 to 5 months.[17] A tube cystostomy is a much simpler and better tolerated procedure that allows pets to survive an average of 3 months beyond when they would have been euthanized for urethral obstruction.[18] With disadvantages limited to recurrent urinary tract infections and occasional mechanical complications (e.g., tube is pulled out, animal chews through tube), the tube cystostomy is an excellent palliative option.

188.3 PROSTATE

Prostatic tumors are rare in dogs and are even less common in cats. Older, neutered, or intact dogs are typically affected. The most common histologic types are prostatic adenocarcinomas (ADC) and TCC, with many tumors having features of both.[19] Clinical signs include stranguria, hematuria, weight loss, tenesmus, rear limb lameness/pain, lumbar pain, and polyuria/polydipsia. Important differentials to consider are benign prostatic hypertrophy, prostatic cyst, prostatic abcess, and prostatitis. Prostatic carcinomas are aggressive; the majority of dogs have metastatic disease at the time of diagnosis. Metastases may be seen in the regional lymph nodes, vertebral bodies, or lungs.

Figure 188-3 Lateral abdominal radiograph of a male neutered sheltie dog with prostatic carcinoma, note the irregular proliferative changes along the ventral aspects of lumbar vertebral bodies 5 through 7. (Courtesy David Biller, Kansas State University.)

Diagnostic evaluation should begin with a rectal examination. A neoplastic prostate is usually asymmetric, fixed, and firm. Careful rectal palpation for intrapelvic lymph node enlargement is also warranted. The CBC, chemistry profile, and urinalysis do not usually have pathognomonic findings; however, malignant cells may be observed occasionally in the urine sediment. As with any evaluation for metastatic disease, three view thoracic radiographs are recommended. The finding of mineralization in the prostate on abdominal radiographs or ultrasound is suggestive of neoplasia. Other areas that should be examined closely on abdominal radiographs and/or ultrasound include sublumbar lymph nodes and lumbar vertebrae (Figure 188-3), as these are common areas for metastases. Samples for cytologic examination may be collected via traumatic catheterization, prostatic massage, or transrectal needle aspiration. Although ultrasound guided aspiration of the prostate provides an accurate sampling technique, there is a possibility of seeding the tumor with this procedure.[7] Cytology is often diagnostic for malignancy but histologic examination remains the gold standard for diagnosis. Tissue may be obtained surgically or via ultrasound-guided biopsy, but caution is warranted as ultrasound-guided techniques may result in tumor seeding.

Curative treatment has not been identified for prostatic carcinomas. Castration is not beneficial. Palliative therapies including either tube cystostomy or piroxicam (0.3 mg/kg orally once daily) may provide up to 6 months of survival. The role of radiation therapy for the treatment of prostatic cancer is under investigation and seems promising, but the actual value of this therapy in prolonging survival is undefined. The overall prognosis for animals with prostatic neoplasia is guarded.

188.4 PENIS AND PREPUCE

The prepuce is affected by tumors that occur on haired skin elsewhere (e.g., mast cell tumor, squamous cell carcinoma). As with other cutaneous sites, evaluation of regional lymph nodes (i.e., inguinal and sublumbar lymph nodes) is an important component of the diagnostic examination. For the majority of penile and preputial tumors

the diagnostic evaluation and treatment is the same as for other locations. Mast cell tumors tend to be more aggressive when arising on the prepuce, and thus even lower grade mast cell tumors in this location may require systemic chemotherapy for effective management.

The most common penile neoplasm is transmissible venereal tumor. This round cell tumor rarely metastasizes, is readily diagnosed via cytology, and is usually curable with vincristine (0.5 mg/m^2 IV weekly).[20] The number of treatments required varies between cases. Lesions tend to resolve within 2 weeks of the first treatment, but therapy should be continued for a minimum of 2 doses beyond complete visible resolution. Lesions that are resistant to chemotherapy may be successfully treated with radiation therapy.

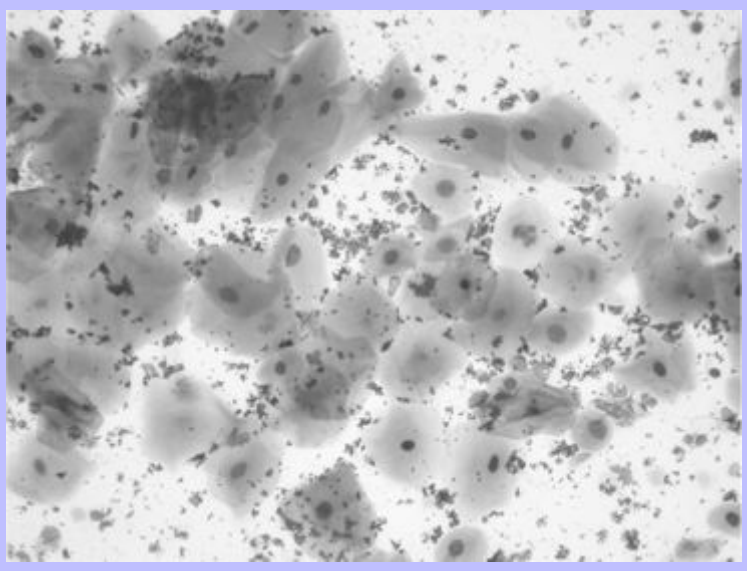
188.5 TESTICLE

Testicular tumors are the second most common tumor of the male dog but are extremely rare in cats. Middle-aged to older dogs (9 to 11½ years) are affected. The three main histologic types seen include Sertoli cell, seminoma, and interstitial cell tumor. These tumors occur with roughly the same frequency, but cryptorchid individuals have 13.6 times greater risk of developing a Sertoli cell tumor or seminoma, and animals can be affected at a younger age. Roughly 25% to 50% of Sertoli cell tumors are functional and can cause hyperestrogenemia. The Sertoli cell tumor is also the type most likely to metastasize, usually to regional lymph nodes, but still with a low rate of 2% to 14%.

Although most testicular tumors are incidental findings on physical examination, clinical signs may include decreased libido, signs of prostatomegaly (e.g., stranguria or tenesmus), and inappetance and/or weakness secondary to anemia. Asymmetric testicles, scrotal or inguinal swellings, prostatomegaly, or signs of hyperestrogenism including alopecia, gynecomastia, a pendulous prepuce, and a poor haircoat may be seen on physical examination. Both testes are palpated simultaneously to compare size, shape, and firmness. A rectal examination should also be performed on these dogs; prostatomegaly secondary to estrogen-induced squamous metaplasia (Figure 188-4) is common.

Evaluation of dogs with testicular tumors should include a CBC with a platelet count and evaluation of regional lymph nodes via radiographs and/or ultrasonography with fine needle aspiration if indicated. Bone marrow suppression is a rare complication of hyperestrogenism. This syndrome is characterized initially by thrombocytopenia and neutrophilic leukocytosis, which ultimately progresses into pancytopenia. As pulmonary metastases are extremely rare, thoracic radiographs may not be cost effective as a staging test; however, they may be indicated for evaluation of concurrent disease in these older patients.

Figure 188-4 Squamous metaplasia of prostatic cells from a mixed-breed cryptorchid dog with a Sertoli cell tumor. Sample acquired via traumatic catheterization, debris in background is lubricating jelly. (20×, Diff Quick stain.)



Castration is curative for most testicular tumors. Scrotal ablation may be necessary if the tumor is fixed to scrotal skin. If the affected testicle is cryptorchid caution is warranted during surgery as the testicle may be friable. Any enlarged lymph nodes should be biopsied and ideally excised at the time of surgery. Cisplatin has been reported to be of benefit in a small number of dogs with metastatic disease.[21] Radiation has been used to treat sublumbar lymph node metastases in patients with seminoma.[22] If estrogen-induced myelosuppression has occurred, the patient may require months of hematologic support; some dogs with such myelosuppression never recover.

188.6 VAGINA AND VULVA

Tumors of the vagina and vulva are the second most common reproductive tumors in female dogs but are extremely rare in cats. Most are benign smooth muscle tumors that arise within the vestibule and occur in older intact dogs, with an increased incidence in nulliparous bitches. Histologic terminology used for these benign tumors includes leiomyoma, fibroleiomyoma, fibroma, or polyp, depending on the amount of connective tissue present in the mass. Lipomas may also be seen in this area. Malignant tumors are rare, with leiomyosarcoma the most likely. Transmissible venereal tumors may also occur (Figure 188-5).

Tumors may be intraluminal or extraluminal. Intraluminal tumors are often associated with stranguria; owners may see the mass protrude during urination or defecation. Other possible clinical signs include bleeding, discharge, dysuria, and licking. Extraluminal tumors are usually slow-growing perineal masses. Diagnostic evaluation of any straining dog should include a rectal and vaginal examination. For intraluminal masses, cytology can often be performed from an impression smear made by gently scraping the mass with a gloved fingertip. Fine needle aspirates can be performed on extraluminal masses or on intraluminal masses that do not exfoliate with the

digital technique. Other diagnostic tests include vaginoscopic exam to determine the local extent of disease as well as abdominal radiographs and/or abdominal ultrasound to evaluate for lymph node involvement.

Figure 188-5 Large, irregular friable vaginal TVT protruding from vulva of mixed breed intact dog.

Chemotherapy with vincristine as described above is the treatment of choice for bitches with TVT, for all other types of vaginal tumors surgical resection and OHE is usually curative. OHE is recommended for these hormonally responsive tumors as recurrence is likely in dogs treated with mass removal only. Excise intraluminal tumors at the pedicle; wide excision is not needed. Approach extraluminal tumors via dorsal episiotomy; these tend to be well encapsulated and are easy to resect.

188.7 UTERUS

Uterine tumors are rare in dogs and cats, likely because the vast majority of female dogs and cats under veterinary care within the United States have undergone OHE. In dogs the majority of uterine tumors are mesenchymal; 85% to 90% are leiomyomas and 10% are leiomyosarcomas. German shepherd dogs may be overrepresented in the literature due to the well-described syndrome of renal cystadenocarcinomas and associated uterine leiomyomas.[23] As expected with their benign nature, most uterine tumors in dogs are slow-growing, non-invasive into surrounding structures, and not metastatic. In cats uterine adenocarcinoma is the most common primary tumor of the uterus, a disease associated with an aggressive biologic behavior and widespread metastases.

Although clinical signs in dogs may be organ-related, such as vaginal discharge or evidence of pyometra, uterine tumors are more commonly an incidental finding. Cats may have specific signs of discharge or suspected

pyometra, or they may have signs related to metastatic disease (e.g., pulmonary distress, lymphadenopathy, anorexia).

Diagnostic evaluation of animals with suspected uterine tumors should include a minimum database to establish overall metabolic status as well as thoracic and abdominal radiographs and abdominal ultrasound. A technique that may be useful in imaging uterine tumors if ultrasound is unavailable is compression radiography.[24] This procedure employs the use of a radiolucent device (e.g., a wooden or plastic spoon or paddle) to apply pressure to the area of interest during the making of a radiograph, increasing visualization of the region by moving overlying structures out of the way. Ovariohysterectomy is often curative for dogs, but due to the aggressive biologic behavior in cats OHE alone is unlikely to provide long-term control. Although the efficacy of chemotherapy in both dogs and cats remains largely unknown, one case report describes the successful use of OHE followed by epirubicin in a young dog with a uterine carcinoma.[25] Thus anthracycline based chemotherapy may be efficacious in the rare cases of uterine malignancy.

188.8 OVARY

Similar to uterine neoplasia, ovarian tumors are rare in dogs and cats, again in part related to the high rate of neutering in companion animals. Asymptomatic ovarian tumors are most commonly found during routine OHE in older animals; an important differential in this situation are ovarian cysts. However, as some ovarian tumors are malignant, any abnormal ovary should be submitted for histologic examination. Specific clinical signs associated with ovarian tumors include a palpable mass, signs of ascites, or systemic effects of hormone production. These tumors may attain a large size prior to detection. Three categories of ovarian tumors are seen, depending on the cell of origin of the neoplasm: epithelial, germ, and sex-cord stroma.[26] All three of these categories include benign and malignant forms. The malignant forms may metastasize to the peritoneum and can cause a malignant effusion; metastases are also seen in the lymph nodes, liver, and lungs.

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In dogs, roughly one half of ovarian tumors fall into the epithelial category and include the histologic diagnoses of papillary adenoma, cystadenoma, papillary adenocarcinoma, and undifferentiated adenocarcinoma. These tumors can occur bilaterally, are rarely functional, and have malignant forms with a metastatic rate of approximately 50%. Epithelial tumors are rare in cats.

Germ cell tumors make up roughly 10% of ovarian neoplasms in dogs, are rarely bilateral or functional, have a metastatic rate of 10% to 30%, and may be seen in young as well as older animals. These tumors are further categorized into three histologic types: dysgerminomas, teratomas and teratocarcinomas. Dysgerminomas (i.e., ovarian seminomas) arise from undifferentiated germ cells and have a similar histologic appearance to their testicular counterpart. Teratomas are made up of more than one germ cell layer (ectoderm, mesoderm, and/or endoderm) and the majority are well differentiated. Teratocarcinomas have differentiated and undifferentiated components; metastatic lesions are composed of the undifferentiated components and have been reported in the abdomen, lung, mediastinum, and bone. In cats approximately 15% of ovarian tumors are dysgerminomas; these may occur bilaterally and are malignant.

Sex-cord stromal tumors make up 35% to 50% of ovarian tumors, are rarely bilateral, are functional in approximately 50% of cases, and have a metastatic rate of less than 20%. These tumors can produce estrogen and progesterone. Clinical signs seen may be related to estrogenic effects (e.g., vulvar enlargement, vaginal discharge, persistent estrus) or progesterone effects (e.g., pyometra). The most common sex-cord stromal cell tumor is the granulosa cell tumor; this is the only tumor in this category that can metastasize. Less commonly, the benign thecoma or luteoma may be diagnosed. In cats germ cell tumors make up roughly 50% of ovarian tumors; greater

than 50% of these are malignant. The most common histologic type in cats is granulosa cell tumors, and hyperestrogenism is commonly seen.

Diagnostic evaluation of dogs or cats with ovarian tumors should include a minimum data base, thoracic radiographs, and abdominal radiographs or ultrasound. If ascites is present, cytologic examination of the fluid may be diagnostic for malignancy. The ultrasonographic characteristics of ovarian tumors in dogs has been reported, with the tumors ranging from solid to cystic in appearance.[27] Uterine changes (i.e., findings consistent with cystic endometrial hyperplasia or pyometra) were commonly found with sex-cord stromal tumors.

Treatment of ovarian tumors relies primarily on OHE and carries, in general, an excellent prognosis. In the rare cases of peritoneal metastases or malignant ascites, intracavitary chemotherapy may be of benefit.[28]

188.9 MAMMARY GLAND

Mammary gland tumors (MGT) are the third most common tumor overall in cats and one of the most common tumors in female dogs. Older females of either species are more likely to develop these tumors. Breeds at risk include Siamese; Poodles; English, cocker, and Brittany spaniels; English setters; and fox and Boston terriers. A hormonal etiology is well described for dogs and is likely for cats. Ovariohysterectomy can greatly decrease the risk of developing mammary gland tumors. Dogs spayed before their first estrus have a risk of 0.5%, after their first estrus the risk jumps to 8%, and after their second estrus the risk goes to 26%. There is no protective effect if dogs are spayed after their third estrus cycle. Estrogen and progesterone receptors have been identified in dog and cat MGT; for dogs the less well differentiated the tumor the more likely the tumor is to be hormone receptor negative. Prolonged administration of estrogens to dogs does not increase the incidence of MGT, although progesterone administration may result in benign nodule formation. However, there is an association between the use of megestrol acetate and the development of MGT in cats.[29]

On physical examination, animals may have single or multiple nodules associated with the nipple or the gland itself. Benign lesions tend to be small, well-circumscribed, and firm on palpation. The caudal mammary glands are most often involved in dogs; feline tumors occur with equal frequency in all glands. MGT may be freely movable or adherent to the skin or abdominal wall. They may be ulcerated (Figure 188-6), inflamed and edematous, or associated with discharge from the nipple. Differentials for MGT include other neoplasms (e.g., mast cell tumors, squamous cell carcinoma), mastitis, lobular hyperplasia, and fibroepithelial hyperplasia in cats.

Diagnostic evaluation of animals with mammary neoplasia should include a CBC, chemistry profile, and urinalysis. Cytologic evaluation of the mass is warranted. Although cytology cannot generally differentiate benign from malignant lesions, it can be helpful in ruling out other differentials. Also, cytology may be diagnostic if strong criteria of malignancy are present. Thoracic radiographs are important to evaluate for pulmonary metastatic disease and sternal lymphadenopathy. Pleural effusion, a common occurrence in cats with metastatic MGT, may also be identified. Assessment of inguinal, sublumbar, mesenteric, and pelvic lymph nodes is an important component of thorough staging. These nodes can be evaluated via physical and rectal examination, fine needle aspiration, and abdominal radiographs, or ultrasound. Biopsy of the mammary mass, typically excisional, will provide a definitive diagnosis.

In dogs 50% of MGT are benign, most often fibroadenomas (i.e., benign mixed tumor). The most common types of malignancies in dogs are solid carcinomas, followed by tubular adenocarcinomas; only about 3% are sarcomas and 1% are inflammatory carcinomas. Of the 50% that are malignant, 50% will recur or metastasize following the first surgical resection. Poor prognostic factors for survival in dogs with MGT include histologic type (poorly differentiated tumors, sarcoma, and inflammatory carcinomas have a worse prognosis), tumor size greater than 3

cm, lymph node involvement, histologic evidence of lymphatic or vascular invasion, minimal to no lymphocytic infiltration into the tumor, ulceration, and distant metastases.

Figure 188-6 Large multi-lobulated and ulcerated MGT in a spayed female domestic shorthaired cat.

The majority of feline MGT are malignant, most often adenocarcinomas, and they exhibit highly metastatic behavior. Prognosis depends primarily on tumor size at the time of diagnosis. Tumors less than 2 cm in diameter are associated with survival times over 3 years, whereas tumors larger than 3 cm are associated with survival times of 4 to 6 months. The type of surgery performed (see below) has been shown to be prognostic for disease free interval but not for survival time.

Surgery is the mainstay of treatment of MGT in dogs and cats. A major contraindication to surgery is in the case of inflammatory carcinomas, as it is virtually impossible to remove the entire tumor and regrowth may occur within days of the surgery. In dogs with MGT the goal of surgery is to remove the entire tumor by the simplest procedure possible. For example, a “lumpectomy” is acceptable for a small (less than 1 cm diameter) and superficial mammary nodule, whereas lesions 1 to 2 cm in diameter may require a mammectomy. If masses are present in multiple glands, they may be resected individually or in a chain mastectomy, again choosing the surgery based on the easiest way to remove all affected tissue. As malignant MGT do rarely express estrogen or progesterone receptors, there is theoretical benefit to spaying the pet; however, no controlled studies have shown an actual therapeutic benefit of OHE at the time of mammary tumor excision. OHE may be recommended at the time of mastectomy to prevent ovarian or uterine diseases in the future. As described above, the majority (75%) of canine mammary gland tumors can be cured with surgery alone. In cats, full chain mastectomy (i.e., removal of all five glands on one side without removal of underlying musculature) is recommended, with bilateral staged mastectomy for bilateral disease. Cats with minimal resections reportedly had recurrent disease sooner than cats with a full mastectomy but had similar survival times. Radiation therapy is not routinely used for this disease in dogs or cats.

Little information is available regarding the efficacy of chemotherapy for canine or feline MGT. In dogs with malignant mammary tumors and the presence of poor prognostic factors, a doxorubicin or doxorubicin/cyclophosphamide protocol is the conventional treatment. Recently, a 5-FU/cyclophosphamide protocol was shown to be of benefit in a small case series. Additionally, piroxicam has been shown to have some effect against this disease and may be particularly indicated for inflammatory carcinomas. Since the vast majority of feline mammary tumors are malignant and metastatic, chemotherapy postoperatively is recommended. As in

dogs, single agent doxorubicin or a doxorubicin-based protocol is used. 5-FU should not be administered to cats as the drug is associated with neurotoxicity.

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189 CHAPTER • 189 Paraneoplastic Syndrome

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Paraneoplastic syndromes (PNS) result from indirect effects of tumors due to the production and release of biologically active substances such as hormones, growth factors, and cytokines. The immune system may be affected, and autoimmunity, immune complex production, or immune suppression can occur. Occasionally, PNS may have a higher morbidity than the original tumor itself.

PNS are divided in different categories depending on their target organ. They include endocrinopathies, disorders of hematopoiesis and hemostasis, neuromuscular disorders, and cutaneous syndromes. Cancer cachexia is usually treated separately as it affects multiple organ systems.

A timely detection of PNS is essential for several reasons: (1) they may be the first clinical manifestation of tumor, and early diagnosis may improve the prognosis for the underlying neoplasia; (2) the severity of the PNS can reflect the activity of the tumor cells, and give information on the progressive or regressive nature of the tumor; (3) the clinical signs caused by a PNS could be falsely interpreted as direct effects of the tumor itself or side effects of treatment, and lead to false prognostic considerations; (4) finally, PNS may affect the general condition of the animal, and significantly alter the prognosis of a specific tumor.

189.1 GENERAL MANIFESTATIONS OF CANCER

189.1.1 Cancer Anorexia-Cachexia

The cancer anorexia-cachexia syndrome (CACS) affects more than one half of all human cancer patients and represents the most common paraneoplastic disorder. A decline in body weight of more than 10% in these patients negatively influences survival, in part due to secondary infections and wound healing complications.[1,2] In addition to CACS, anorexia and weight loss are often compounded by the side effects of treatment in cancer patients. Although no comparable epidemiologic data are available in small animal oncology, CACS is also recognized in canine and feline cancer and is likely to adversely affect prognosis.

Anorexia, nausea, and weight loss clinically characterize CACS. In contrast to wasting due to severe starvation, a massive decrease in muscle protein mass accompanies body fat depletion in CACS. In addition to wasting, this syndrome is frequently accompanied by changes in food perception (taste, smell), which diminishes the pleasure of eating. The metabolic alterations associated with CACS are, at least in part, mediated by the production of substances such as IL-1β, TNF-α, IL-6, IFN-γ, and serotonin by both the tumor and the host immune system.[1] The pathophysiologic mechanisms triggered by these cytokines include alterations in carbohydrate, fat, and protein metabolism as well as in energy expenditure.

Several studies have investigated the metabolic alterations associated with lymphoma in dogs. Abnormalities in *carbohydrate metabolism* include an increased concentration of insulin and lactate in response to an intravenous glucose challenge[3], which does not resolve when complete clinical remission following doxorubicin chemotherapy is achieved.[4] Moreover, intravenous infusions with lactated Ringer's solution seem to exacerbate this aberration and should therefore be avoided in canine lymphoma patients.[3] The authors of these studies

concluded that an insulin receptor or post-receptor defect is present in dogs with lymphoma, and that hyperlactatemia is the result of preferential anaerobic glucose metabolism by lymphoma cells. Large amounts of lactate produced by anaerobic glycolysis in tumor cells are then reconverted into glucose via the hepatic Cori cycle, which creates a futile energy-consuming cycle for the host.[2]

Abnormalities in *lipid metabolism* associated with CACS result in severe loss of body fat. Decreased lipoprotein lipase activity impedes the extraction of fatty acids from plasma lipoproteins by adipocytes. Moreover, increased hormone-dependent lipase activity, which acts in concert with a recently isolated lipid mobilizing factor in some tumors, contributes to lipolysis and lipid mobilization.[5] In dogs with lymphoma, lipoprotein profiles were found to be altered and did not improve following complete remission with doxorubicin therapy.[6]

Studies on *resting energy expenditure* (REE) in cancer patients have yielded disparate results. Although some tumors in humans are associated with an increased REE, others are not. Similarly, despite a decreased REE observed in canine lymphoma patients, dogs with osteosarcoma (OSA) were found to have a higher REE before limb amputation than healthy controls.[7] In addition to the abnormalities in glucose metabolism, an altered expression of uncoupling proteins has recently been postulated to be an important determinant in the increase in REE associated with cancer. Uncoupling proteins are mitochondrial membrane proteins that impede the coupling of respiration to ADP phosphorylation, which results in the generation of heat instead of ATP.[5]

The effects of CACS on *protein metabolism* encompass both increased protein catabolism and decreased protein synthesis and result in significant muscle atrophy. Dogs that suffer from OSA were found to have a negative nitrogen balance following limb amputation.[7] In these animals, the rate of protein synthesis was only 72.4% that of healthy dogs, whereas the urinary nitrogen excretion was 65% greater.[7] The role of cytokines, such as TNF-α, IL-6, and IFN-γ, as mediators of muscle catabolism and abnormal protein metabolism has been called into question, and these substances may merely serve as markers of these phenomena. Moreover, a recently isolated circulatory skeletal muscle proteolysis-inducing factor (PIF) is thought to play a central role in eliciting cancer-associated protein catabolism. Indeed, human cancer patients with severe weight loss were found to frequently excrete PIF in their urine.[5]

The objectives of nutritional support in cancer patients are to limit the adverse effects of CACS and enhance immune system function as well as the response to and tolerance of cancer therapy. Recently, a diet rich in polyunsaturated omega-3 fatty acids was found to have beneficial effects on the disease-free interval and survival of dogs with stage-III lymphoma treated with doxorubicin.[8] This fish-based diet was also associated with a more rapid decline in circulating levels of the inflammatory cytokines IL-6 and TNF following treatment. Moreover, insulin resistance and hyperlactatemia diminished to a greater extent and more rapidly in dogs fed with this diet than in control animals.[8] In addition to aspects of diet composition, current treatment recommendations for CACS in human patients emphasize the advantages of gastrointestinal over parenteral nutritional support.[1]

The metabolic alterations responsible for CACS are usually present in cancer patients long before clinical signs of CACS are recognized. This implies a need for early nutritional support. In persistently anorectic animals, naso-esophageal, esophagostomy, or gastrostomy tubes are recommended to administer food safely and provide adequate nutrients. Most pharmacologic interventions aimed at prevention of weight loss in human cancer patients have thus far been largely unsuccessful and are unlikely to be beneficial in veterinary cancer patients.[1,2]

189.1.2 Fever

Although common in human cancer patients, fever is rarely a genuine PNS. In patients with neutropenia, fever is often the consequence of an infectious process. Paraneoplastic fever is generally suspected in human patients who are not neutropenic, and those affected by certain neoplasms, including renal cell carcinoma, hepatoma, and non-Hodgkin's diseases.[1] The pathomechanisms of paraneoplastic fever include the elaboration of pyrogenic cytokines by the tumor and/or host immune system. In particular, IL-1, IL-6, and TNF may act as endogenous pyrogens on the thermoregulatory center of the anterior hypothalamus. Despite the lack of studies on the prevalence of paraneoplastic fever in dogs and cats, numerous case reports and experience indicate that it also occurs in small animals.

189.2 HEMATOLOGIC PARANEOPLASTIC SYNDROMES

Tumors, or their metastases, can have profound effects on hematopoietic cell lines by infiltration of the bone marrow. Further suppression of the bone marrow can be caused by treatment with cytostatic drugs. In addition to these direct effects on the bone marrow, mechanisms involved in PNS sometimes have even more serious effects on hematopoiesis, which may be better understood when data from ongoing research on hematopoietic growth factor are available.

189.2.1 Anemia

Anemia is one of the more common PNS in dogs and cats. Although exact figures are not available for all tumor types, anemia has been reported to occur in 30% to 40% of dogs with malignant lymphoma and up to 69% of those with splenic hemangiosarcoma. Different mechanisms are involved: anemia of chronic disease, immune-mediated hemolytic anemia, myelophtisis, blood loss, and microangiopathic hemolytic anemia.[9]

Anemia of chronic disease (ACD) is caused by shortening of the erythrocyte life span and is a mild, normocyticnormochromic, nonregenerative anemia. It is not associated with particular types of cancer and its cause is unknown. The characteristic features of ACD are disordered iron metabolism as manifested by a low serum iron, decreased serum transferrin, decreased transferrin saturation, increased serum ferritin, increased reticuloendothelial iron stores, and reduced iron absorption.[9] In humans, erythropoietin production is usually normal but the responsiveness of erythroid progenitor cells to the hormone is impaired by inflammatory cytokines. The anemia is mild and disappears after treatment of the tumor.

When *immune-mediated hemolytic anemia* (IMHA) occurs as a PNS in dogs and cats, it is usually associated with hematopoietic tumors, especially lymphoid malignancies and less frequently with solid tumors. Cross-reacting antibodies against cell-membrane antigens or direct interference with the immune system through suppressor T-cells lead to a premature destruction of red cells by the reticuloendothelial system.

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The anemia can be acute or chronic, mild or severe and is regenerative in most cases. The most common clinical signs are lethargy, weakness, pale mucous membranes, icterus, hepatosplenomegaly, hemoglobinuria, and anorexia. Diagnosis is made by a direct antiglobulin test for detection of erythrocyte-bound immunoglobulin (IgG and IgM) and complement (C3). Treatment with corticosteroids, with or without immunosuppressive agents such as azathioprine or cyclophosphamide, has been evaluated mainly in dogs with primary idiopathic IMHA, but not in cancer patients. Elimination of the primary tumor remains as the most important factor for control of the IMHA.

Blood loss anemia associated with paraneoplastic gastroduodenal ulceration occurs with mast cell tumors and gastrinomas as well as primary gastrointestinal neoplasms. The anemia is initially regenerative but becomes nonregenerative, microcytic, and hypochromic, accompanied by decreased serum iron concentration and increased iron-binding capacity. Blood loss anemia occurs with some renal tumors and with any tumor in which bleeding occurs, such as splenic or hepatic tumors. Treatment should be directed at the primary tumor. Supportive treatment with transfused blood and oral ferrous sulfate is usually not necessary in animals with chronic blood loss, unless they undergo surgery for the tumor.

Microangiopathic hemolytic anemia is usually associated with microvascular tumors but can occur with any tumor that leads to disseminated intravascular coagulation (DIC). Fragmentation of erythrocytes can be caused by abnormal vascular structures with fibrin deposits, fibrin threads formed in the course of DIC, pulmonary intraluminal tumor emboli, or narrowing of pulmonary arterioles by intimal proliferation.[10] Hemangiosarcoma is the most frequent tumor associated with this type of anemia in dogs.

189.2.2 Erythrocytosis

Erythrocytosis, or polycythemia, is a rare PNS in dogs and cats. It is usually associated with primary or secondary tumors of the kidney, but it has also been documented in dogs with nasal fibrosarcoma, bronchial carcinoma, and cecal leiomyosarcoma. In contrast to primary eryrhocytosis (polycythemia vera), in which there is a neoplastic disorder of the erythroid cell lines in the bone marrow, the cause of secondary erythrocytosis is an increased level of erythropoietin. Possible mechanisms are ectopic erythropoietin production by the tumor,[11] increased erythropoietin production by the kidney in response to hypoxia of the kidney caused by tumor compression, and increased production of so-called *hypoxia-inducible transcription factors*, which stimulate erythropoietin production.[12] The clinical signs result from hyperviscosity of the blood and dilatation and decreased perfusion of small blood vessels, which result in tissue hypoxia, bleeding, polyuria, and thrombosis.

189.2.3 Leukocytosis

Increased peripheral granulocytosis without evidence of infection or leukemia has been reported to occur in association with several tumor types in humans but less frequently in the dog and cat. The excessive leukocytes are mature neutrophils and there are usually no clinical signs. In the dog, neutrophilic leukocytosis has been reported as a PNS with renal carcinoma, malignant lymphoma, metastatic fibrosarcoma, rectal adenomatous polyps, and pulmonary carcinoma. It has been described in a cat with dermal tubular adenocarcinoma. The diagnosis is made by exclusion of other causes of leukocytosis and resolution of the leukocytosis after removal of the tumor. Differentiation from a coexistent chronic myelogenous leukemia can be difficult. In paraneoplastic leukocytosis the tumor itself produces colony-stimulating factors (CSF). With the help of immunohistochemical staining techniques and reverse transcription polymerase chain reactions, the presence and production of both granulocyte-CSF (G-CSF) and granulocyte-macrophage-CSF (GM-CSF) have been demonstrated in tumor tissue in the dog, while in the cat only G-CSF could be demonstrated.[13,14]

Hypereosinophilia is a rare manifestation of cancer. Although it has been found with T-cell lymphoma,[15] mammary carcinoma, and oral fibrosarcoma, it is usually associated with disseminated mast cell tumors. Thoracic and abdominal eosinophilic effusions may accompany the peripheral blood eosinophilia.[16] The hypereosinophilia appears to be a response to cytokines such as IL-2 and IL-5. It is associated with disseminated, metastatic disease and hence signifies a poor prognosis.

189.2.4 Thrombocytopenia

Thrombocytopenia is one of the most common hemostatic abnormalities in cancer patients. It has been reported to occur in 10% to 36% of dogs with solid cancers and up to 50% of animals with malignant lymphoma.[17,18] Myeloproliferative neoplasms are responsible for 20% of the cases of thrombocytopenia in cats. Several different mechanisms may be responsible for thrombocytopenia in cancer patients. The life span of platelets can be shortened, especially in animals with metastatic tumors. Proposed mechanisms for this include binding of platelets to abnormal endothelium of blood vessels in tumors such as hemangiosarcomas, and accelerated removal from the circulation because of tumor-stimulated microaggregation of the platelets or because of binding of tumor proteins to the platelets. Immune-mediated thrombocytopenia (ITP) is another frequent cause of depletion of platelets in animals with cancer. It may result from anti-platelet antibody production or cross-reactivity between platelet and tumor antigens. Another cause of increased platelet destruction is microangiopathy, which leads to fragmentation of both red cells and platelets. Thrombocytopenia can also be the result of decreased platelet production caused by massive tumor infiltration of the bone marrow. Clinical signs of thrombocytopenia do not usually become evident until the platelet count decreases below 30,000/μL. Treatment of thrombocytopenia associated with cancer should be directed at removal of the tumor. ITP is treated with immunosuppressive drugs such as corticosteroids.

189.2.5 Thrombocytosis

Thrombocytosis (platelet counts above 500,000/μL) is a very common PNS in humans but is rare in dogs and cats. It has been described in animals with osteosarcoma, gingival carcinoma, chronic myeloid leukemia, bronchoalveolar carcinoma, and metastatic squamous cell carcinoma. It can cause thrombotic or hemorrhagic tendencies, but in most cases there are no clinical signs. The mechanism leading to the thrombocytosis is still unclear. Although elevated levels of IL-6, GM-CSF, and G-CSF have been found in some human patients, the levels were generally lower than required for *in vitro* induction of megakaryocytic differentiation. There may be other thrombopoietins in affected patients that have not yet been identified.[19] For the diagnosis of thrombocytosis as a PNS, other causes of thrombocytosis such as vinca alkaloids, splenectomy, iron deficiency, and myeloproliferative disorders should be ruled out.

189.2.6 Thrombocyte Hyperaggregability

Functional changes in platelets have also been demonstrated in patients with cancer. Hyperaggregation of platelets was demonstrated in a study of 59 dogs with cancer.[20] Proposed explanations for hyperaggregation include (1) an increase in serum factors that induce platelet aggregation, (2) a change in plasma membrane lipid composition, and (3) increased numbers of younger platelets, which have a higher activity. Platelet hyperaggregability may not only lead to thromboembolism but may also aid metastasis by the release of factors influencing stroma and blood vessels.

189.2.7 Pancytopenia

In dogs, bone marrow aplasia can be caused by administration of estrogens and by estrogen-producing tumors such as Sertoli cell tumors of the testis and granulosa cell tumors of the ovary. Although the exact pathomechanism is unknown; estrogens may not directly damage the bone marrow granulocyte-macrophage progenitor cells. A myelopoiesis-inhibitory factor produced by canine thymic stromal cells is probably a

mediator of the bone marrow suppression.[21] The prognosis is guarded, for the pancytopenia is often irreversible in spite of removal of the tumor. In addition to large individual differences in sensitivity to estrogens, age is a major factor that influences the prognosis.[22]

189.2.8 Coagulation Disorders

Coagulation disorders often develop in late stages of aggressive malignancies. The mechanism of this cancer-related hypercoagulability is not completely understood. It has been postulated that tumor-specific physiologic changes such as decreased oxygenation (tumor hypoxia) stimulate expression of blood-clotting regulators such as tissue factor and plasminogen activators, by both tumor cells and host cells.[23] In dogs and cats, however, disseminated intravascular coagulation (DIC) is the most frequent clinical abnormality and is probably caused by a complex of factors. As in humans, coagulation-activating substances can be produced by tumor cells. Hemangiosarcoma can release tissue thromboplastin into the circulation causing increased platelet aggregation. Tumor necrosis factor (TNF), produced by inflammation-activated macrophages, can change the endothelium of blood vessels, which increases the tendency for intravascular coagulation. The DIC-induced depletion of coagulation factors and the inhibitory properties of fibrinogen degradation products may cause hemorrhagic diathesis. DIC is often associated with hemangiosarcomas, thyroid carcinomas, and mammary gland carcinomas. Hemostatic abnormalities occurred more frequently with canine mammary carcinomas in the presence of extended tumor necrosis, inflammatory carcinoma, infiltration of the stroma by tumor cells, and distant metastases.[24]

189.2.9 Hyperproteinemia

Hyperproteinemia occurs as a PNS more often in animals with multiple myeloma or chronic lymphatic leukemia (CLL).[25,26] In approximately 75% of cases of multiple myeloma there are monoclonal immunoglobulins, usually IgG or IgA, which can be secreted in large quantities, producing paraproteinemia. Incomplete molecules, heavy or light chains, may also be secreted. The light chains have molecular weights ranging from 20,000 to 25,000 Daltons and are readily excreted in the urine. They are referred to as *Bence Jones proteins* and in patients with multiple myeloma are either only kappa type or only lambda type. Excretion of Bence Jones proteins occurs in about 30% to 40% of dogs with monoclonal gammopathy. In many dogs with CLL, serum globulin concentrations are normal, but in most a monoclonal gammopathy is revealed by serum protein electrophoresis. IgM is the most frequent paraprotein and these monoclonal gammopathies are described as *Waldenström's macroglobulinemia*. Bence Jones proteinuria can also be found. Hyperviscosity in these patients results from the protein-protein interactions of large, long molecules with high intrinsic viscosity, such as IgM M-components, or from high concentrations of specific IgG or IgA M-components, which have a tendency to form multimolecular aggregates. It rarely or never occurs in patients with light-chain-only myeloma, because of the small molecular size of Bence Jones proteins.

Multiple clinical signs of variable severity are associated with paraproteinemia. Bleeding disorders occur as the result of poor platelet aggregation and release of platelet factor III secondary to platelet coating by immunoglobulins. Prolongation of PT and APTT sometimes occurs as the result of interference by the immunoglobulins with the function of coagulation factors. There may be an increased susceptibility to infections because of severe depression of immunoglobulin levels.

Serum hyperviscosity causes sludging of blood and tissue hypoxia, which may lead to a plethora of clinical signs. Both the increased vascular volume and bleeding tendencies may lead to ocular changes, including distended and tortuous retinal vessels, cysts of the pars plana, papilledema, and retinal hemorrhage and

detachment. These changes can result in acute blindness. Severe central nervous system deficits (dementia with concurrent deficiency in midbrain or brainstem reflexes) were reported in 11% of dogs with myeloma. The cause of cardiac disease or failure associated with hyperviscosity is thought to be the large volume of hyperviscous blood. It is rare in the dog, more frequent in the cat. In patients with hyperviscosity of the serum, plasmapheresis may be necessary to reduce paraprotein concentration.[27] Therapy consists of treating the underlying cause of hyperproteinemia, multiple myeloma or CLL, with chemotherapy.

189.3 ENDOCRINE MANIFESTATIONS OF CANCER

Hormonally active tumors can arise in endocrine tissues, including the parathyroid glands, adrenal cortex and medulla, and pancreatic islet cells, as well as in tissues of nonendocrine origin. PNS associated with primary endocrine neoplasia are discussed in more detail in the section dealing with endocrine disorders. The following paragraphs focus on PNS due to ectopic hormone production by neoplasms of nonendocrine tissues.

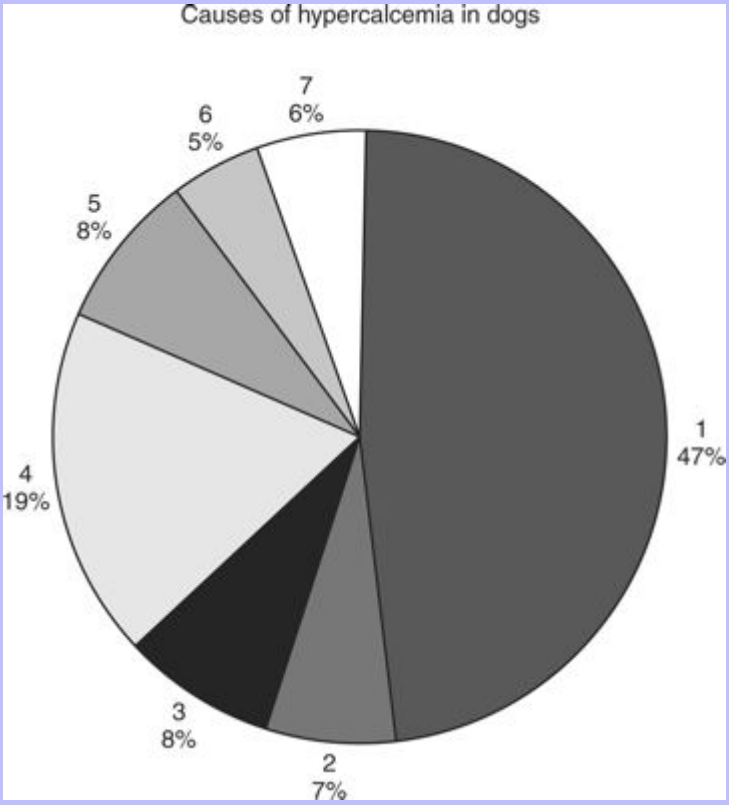
189.3.1 Hypercalcemia of Malignancy

Hypercalcemia is a relatively uncommon problem in small animals, diagnosed more often in dogs than in cats. Numerous disorders are associated with increased serum calcium concentrations, and the general approach to and differential diagnosis of hypercalcemia is discussed in detail in Chapter 237. The most common cause of hypercalcemia in dogs is hypercalcemia of malignancy (HM), which is diagnosed in 57% to 67% of hypercalcemic dogs (Figure 189-1).[28,29] In contrast, neoplasia is diagnosed in only 30% of hypercalcemic cats.[30]

The central mechanism of HM is the promotion of bone resorption by osteoclasts and subsequent release of calcium into the circulation. Patients with primary hyperparathyroidism are predictably affected with HM resulting from increased parathormone (PTH) levels. Interestingly, a variety of tumors originating outside of the parathyroid glands cause increased serum calcium concentrations. The most widely documented mechanism of tumor-associated hypercalcemia is humoral hypercalcemia of malignancy due to the synthesis of PTH-related peptide (PTHrP) by neoplastic cells. PTHrP shares structural homology with PTH in the first 13 amino acids of its N-terminal portion, which bind to the PTH receptor with an affinity equal to that of PTH and result in similar biologic effects.[31]

Other mechanisms of HM are more complex and have not been investigated in much depth in dogs and cats. They include tumor production of various substances that stimulate bone resorption, including cytokines, notably interleukin-1, and growth factors such as transforming growth factor beta (TGF-β). Furthermore, a recently elucidated novel pathway for HM involves the production of soluble forms of receptor activator of nuclear factor kappa B ligand (RANKL), a membrane-associated protein capable of stimulating the activity of osteoclasts by binding to a receptor on their surface. Hypercalcemia occurs when the interactions between ligand, receptor, and their natural inhibitors allow osteoclastic activation to predominate.[32]

Figure 189-1 Causes of hypercalcemia in 86 dogs. 1. lymphoma; 2. anal gland adenocarcinoma; 3. other neoplasias (2 mammary tumors, 1 of each anaplastic carcinoma, lung tumor, malignant histiocytosis, osteosarcoma, thymoma); 4. hypoadrenocorticism; 5. renal disease (2 acute, 2 chronic renal failure); 6. miscellaneous (primary hyperparathyroidism, vitamin D intoxication, panniculitis); 7. no diagnosis. (Compiled from references 28 and 29.)



HM in dogs is most frequently associated with lymphoma (10% to 40% of all cases), anal sac adenocarcinoma (ASAC, 25% to 53% of all cases), and multiple myeloma (15% to 20% of cases). In ASAC, a linear correlation was found between serum concentrations of calcium and PTHrP, attesting to the central etiological role of PTHrP in causing hypercalcemia by this tumor. No such correlation could be detected in dogs with lymphoma, suggesting that PTHrP is only partially responsible for HM in this neoplasia.[33] In canine lymphoma, hypercalcemia occurs most frequently in dogs with T-cell lymphomas and anterior mediastinal masses. In canine multiple myeloma, hypercalcemia is thought to be the result of local processes that increase bone resorption in the immediate proximity of neoplastic foci. HM is less prevalent in cats and has been associated with a variety of tumors, the most frequent of which are lymphoma and a variety of carcinomas. In squamous cell carcinomas, HM was most often detected in cases involving the mandible with radiographic evidence of bone lysis.[30]

The most significant effects of hypercalcemia are those exerted on the kidneys. Furthermore, dogs with HM are more frequently azotemic than those with parathyroid-dependent hypercalcemia.[34] Decreased responsiveness of the distal tubules to antidiuretic hormone (ADH) and subsequent polyuria and polydipsia are early features of hypercalcemia in dogs. Moderate to severe hypercalcemia may lead to decreased renal plasma flow and glomerular filtration rate, which significantly decrease renal function. In addition, parenchymal calcium salt deposition leading to nephrocalcinosis can compound azotemia.[34]

Clinical signs observed in hypercalcemic dogs are relatively nonspecific and include inappetence or anorexia, polyuria and polydipsia, weakness, vomiting, twitching and shaking, and weight loss. In cats, hypercalcemia also causes anorexia and lethargy, but the frequency of polyuria and polydipsia, and gastrointestinal signs is markedly lower than in dogs. Moreover, signs of lower urinary tract disease were observed in approximately one quarter of hypercalcemic cats and were probably associated with calcium oxalate urolithiasis, although there was not always a clear explanation for their appearance.[30]

Once spurious hypercalcemia has been ruled out, several parameters may provide useful diagnostic clues in elucidating the cause of hypercalcemia. These include serum phosphorus and ionized calcium concentrations, as well as circulating levels of PTH and PTHrP. Typically, dogs and cats with HM have increased serum ionized calcium, normal or low serum phosphorus, low PTH and increased PTHrP concentrations. In addition to these specific laboratory parameters, a systematic search for malignancy should be undertaken, including a meticulous clinical examination, CBC, chemistry profile, imaging of both body cavities, and bone marrow cytology.

Treatment of hypercalcemia of malignancy includes symptomatic therapy to avert or curtail complications of hypercalcemia as well as treatment of the primary disease. A detailed review of therapy is available in Chapter 181. Among the particularities for the treatment of HM, glucocorticoids may hamper diagnosis, especially in lymphoma, and should be avoided until a diagnosis is reached. Alternatively, in cases with a high level of suspicion of lymphoma, the administration of cytostatic drugs with few side effects, such as L-asparaginase may result in both diagnostic confirmation and resolution of hypercalcemia.

The prognosis is generally guarded to poor in animals with HM and depends greatly on the prognosis of the primary neoplasia. Relevant factors are the rapidity of onset, duration, and severity of hypercalcemia, and the degree of renal involvement. In dogs with lymphoma, hypercalcemia has been identified in the past as a negative prognostic factor. However, several studies have demonstrated that the shorter survival is only due to the frequent association of HM with T cell tumors in these dogs.

189.3.2 Hypoglycemia

Hypoglycemia is recognized infrequently in dogs and only rarely in cats. The most common cause of hypoglycemia is insulin-producing islet cell pancreatic tumor. Diagnosis and therapy of insulinomas and associated hypoglycemia are described in detail in Chapter 240. Hypoglycemia associated with other neoplasia is unusual PNS in humans[1] and small animals. In dogs, it has been described in association with hepatoma, hepatocellular carcinoma, intra-abdominal leiomyoma or leiomyosarcoma, and hemangiosarcoma of the liver and spleen.

Paraneoplastic hypoglycemia is probably caused by tumor production of insulin-like growth factors (IGFs) or somatomedins, a family of peptide hormones normally produced in the liver under growth hormone regulation.[1]

Increased levels of IGF-II have been documented in hypoglycemic humans with various cancers as well as in one dog with leiomyoma of the gastric wall.

Treatment of hypoglycemia caused by non–islet cell cancers optimally resides in the surgical removal of the neoplasm. However, management of hypoglycemia is also essential. If signs of neuroglycopenia are present, treatment includes the immediate administration of glucose and glucagon infusions,[35] followed by feeding of diets with complex carbohydrates. Low doses of corticosteroids (0.5 to 1 mg/kg/day) can be administered to curtail further hypoglycemic episodes.

189.3.3 Miscellaneous Endocrine Paraneoplastic Syndromes

The syndrome of inappropriate ADH secretion (SIADH) is characterized by hyponatremia, serum hyposmolality, and urine hyperosmolality in the absence of renal function disorders or adrenal dysfunction. Only very rare clinical cases of paraneoplastic SIADH in dogs have been reported. SIADH probably occurs very exceptionally in dogs and cats but should be considered when typical laboratory findings are observed.

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189.4 GASTROINTESTINAL MANIFESTATIONS OF CANCER

189.4.1 Gastroduodenal Ulceration

Although gastroduodenal ulceration is not a very frequent problem in small animals, the diagnostic workup of gastric and/or duodenal ulcers includes a thorough search for neoplasia. Beside primary gastrointestinal tumors, the presence of mast cell tumor (MCT) and gastrinoma must also be ruled out. The latter two stimulate gastric acid secretion through histamine release and activation of histamine-type 2 (H2) receptors, or binding to the gastrin receptors on the basal wall of the gastric parietal cells, respectively.

Mast cell tumor is a common neoplasm in dogs and accounts for up to one fifth of all skin and subcutaneous tumors in that species. MCT can be difficult to differentiate clinically from other skin tumors as they sometimes mimic the appearance and the indolent behavior of benign subcutaneous tumors such as lipomas. Mast cell granules contain biologically active substances such as histamine, heparin, and proteolytic enzymes, and canine MCT have been associated with a variety of complications of which gastrointestinal ulceration is probably the most frequently encountered.

To date, two studies have investigated the role of hyperhistaminemia associated with MCT in a total of 28 dogs.[36,37] Although only 10 of 28 dogs with MCTs confirmed histologically had gastrointestinal signs at initial presentation, plasma histamine concentrations were increased in 21 animals, mostly those with macroscopically evident MCT. An inverse relationship between plasma histamine and gastrin concentrations was documented in one study, providing indirect evidence for gastric hyperacidity secondary to hyperhistaminemia.[36] Severe hyperhistaminemia and increasing histamine levels following surgery represent a negative prognostic factor in dogs with MCT.[37] Dogs affected with MCT should receive treatment with an H2 receptor blocker such as ranitidine, famotidine, or cimetidine at the time of diagnosis.

Gastrinomas are rare pancreatic islet cell tumors that secrete excessive amounts of gastrin.[38] A discussion on diagnosis, biologic behavior, and treatment of gastrinoma can be found in the section on pancreatic tumors.

189.5 RENAL MANIFESTATIONS OF CANCER

In human cancer patients, glomerular disorders may be associated with non-renal neoplasia, especially in the elderly. Neoplasia is also an important differential diagnosis in dogs and cats with glomerulonephritis due to the potential for tumor-related immune complexes to be deposited in the renal glomeruli. In addition, hypercalcemic nephropathy can affect dogs and cats with paraneoplastic hypercalcemia (see above).

189.6 CUTANEOUS PARANEOPLASTIC SYNDROMES

PNS affecting the skin are rare in dogs and cats and mostly affect older animals.

Superficial necrolytic dermatitis (SND) is a condition reported rarely in dogs and cats.[39] Other names previously used to describe this disorder are *necrolytic migratory erythema, hepatocutaneous syndrome,* and *diabetic dermatopathy*. Cutaneous lesions associated with SND include erythema, crusting, exudation, ulceration, and alopecia without severe pruritus. These lesions may involve the face, anogenital region, and pressure points on the trunk and extremities. Additionally, marked crusting, fissuring and ulceration of the footpads is observed in most dogs with SND, and secondary infections with bacteria, yeast, or dermatophytes are common. Histopathologic examination typically reveals epidermal parakeratosis, inter-and intracellular edema, degeneration of keratinocytes in the upper epidermis, and hyperplastic basal cells. Plasma amino-acid concentrations were severely decreased (as low as 30% of the normal plasma concentrations) in all dogs affected with SND that were examined. Underlying conditions observed in dogs with SND include glucagon-producing pancreatic tumors, hepatic disease, and diabetes mellitus. Dogs with SND often have a poor to guarded prognosis. Treatment is aimed at fighting the primary cause if it can be identified. Surgical removal of pancreatic tumors has been associated with resolution of SND and intravenous administration of amino-acid solutions has been effective in prolonging survival in some cases.

Nodular dermatofibrosis is a rare paraneoplastic disorder typically affecting middle-aged to older German shepherd dogs (GSD) with hereditary multifocal renal cystadenocarcinomas. Skin nodules are typically small (2 to 5 mm), very firm, and round. They can easily be overlooked initially and grow slowly. Most are located subcutaneously on the limbs and head region, are freely mobile, and consist of densely packed collagen fibers.[40] At the time of diagnosis, abnormal kidneys are detected on abdominal palpation in 60%, and on radiographs in more than 85% of dogs. Additionally, uterine tumors can be detected in a high proportion of affected bitches. The prognosis is poor due to renal disease and no curative treatment is known for this disorder. The syndrome seems to be inherited as an autosomal dominant trait in some GSD families.[40]

189.7 NEUROMUSCULAR MANIFESTATIONS OF CANCER

Neurologic paraneoplastic disorders occur in less than 1% of human cancer patients and encompass diseases affecting the brain, cerebellum, peripheral nerves, and neuromuscular junction.[1] Neurologic PNS are also infrequently reported in dogs and cats, and clinical relevance is limited to the peripheral neuropathies, myasthenia gravis, and polymyositis.

Myasthenia gravis (MG) has been reported in up to 50% of dogs affected with thymoma.[41] Among the associated clinical signs, megaesophagus was present in many reported cases and was frequently associated with aspiration pneumonia. Detection of circulating auto-antibodies against the acetylcholine receptor (AchR) and, to a lesser degree, the edrophonium (Tensilon) test and electromyography with repetitive nerve stimulation were helpful in

confirming the diagnosis. Megaesophagus is a negative prognostic factor that significantly shortens median survival in dogs with thymoma.[41] Surgical removal of the tumor is associated with improvement of the clinical signs, although anti-AchR titers do not always significantly decrease. Conservative treatment using immunosuppressive doses of glucocorticoids and/or cholinesterase inhibitors may be attempted in cases in which surgery is not an option (see Chapter 192).

Peripheral neuropathy has been reported in association with a variety of tumors in dogs, including multiple myeloma, lymphoma, and various carcinomas and sarcomas. The disease is likely due to auto-antibodies targeting antigens shared between the tumor and the peripheral nerves. Expected clinical signs are weakness and progressive paraparesis to tetraparesis, characterized by lower motor neuron type disease. Polyneuropathy, a generally rare and subclinical disease, may be present. Besides screening tests for cancer, electrodiagnostics (such as electromyography and motor nerve conduction studies) may also be of value.

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189.8 MISCELLANEOUS SYNDROMES

189.8.1 Hypertrophic Osteopathy

Hypertrophic osteopathy (HO) is a well-documented paraneoplastic disorder in dogs and occurs only rarely in cats. HO is characterized by progressive periosteal hyperostosis that occurs on the bones of distal extremities and occasionally on other long bones of the appendicular skeleton. The disease is associated with chronic space-occupying lesions located in the thorax or, rarely, in the abdomen. These include a variety of intrathoracic tumors as well as non-neoplastic processes such as abscesses, granulomas, foreign bodies, and parasites. The pathogenesis of HO is still largely unknown but is believed to be associated with irritation of the vagal and/or intercostal nerves and subsequent enhanced blood flow to the distal extremities.

Animals with HO are typically presented with a history of shifting leg lameness and reluctance to move especially if several limbs are affected. Frequently, a painful swelling of the distal extremities is clinically detected. At the time of diagnosis of HO, clinical signs attributable to the primary disease process are usually discrete. The diagnosis of HO is confirmed on radiographs and should be followed by a search for a space-occupying intracavitary process. The focus of treatment of HO is the removal of the thoracic or abdominal lesion. Administration of steroidal or non-steroidal anti-inflammatory drugs may be useful in the management of pain associated with HO.

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190 CHAPTER • 190 Neurologic Manifestations of Systemic Disease

Michael Podell

190.1 GENERAL PRINCIPLES

Systemic diseases can induce a variety of neurologic manifestations that affect the central (CNS) and peripheral nervous system (PNS) in small animals. In theory, identification of a systemic illness as the underlying cause of the neurologic sign(s) is diagnostically simple, with historical signs that suggest a multi-organ problem that can be quickly identified with appropriate laboratory tests. In reality, when the neurologic signs are the sole manifestation of the illness, or when an unrelated, coincidental metabolic disease is present, the diagnosis of a systemic disease as the underlying cause can be challenging. Manifestation of a metabolic encephalopathy should be taken as a warning sign of organ deterioration or failure. The purpose of this chapter is to help clinicians identify the presence of a systemic disease associated with preceding neurologic signs and to realize the potential neurologic complications associated with systemic illnesses. The goal is to develop an efficient diagnostic plan to provide rapid reversal of many of the neurologic signs resulting from the metabolic derangement before permanent deficits occur.

Metabolic-induced neurologic disorders (MIND) of the CNS (metabolic encephalopathies, ME) or PNS (myopathies and/or neuropathies) are syndromes that are not due to primary structural problems of that part of the nervous system. The underlying mechanisms are either the inability to generate energy, to use energy in a normal fashion, changes in baseline excitability of the membrane potential, or direct toxic effects. A common mechanism of pathogenesis is the cascade phenomenon related to excessive glutamate neurotransmission in the brain, known as excitotoxicity[1] (Figure 190-1). As extracellular glutamate uptake increases in the brain secondary to hypoxia, ischemia, hypoglycemia, and other metabolic disturbances, calcium channels open to raise intracellular calcium concentration, leading to neuronal death. Differential sensitivity exists, however, between patients, and within the nervous system of each patient. This selective vulnerability is most apparent in the brain. Here, the more metabolically active regions are most susceptible to injury, so that gray matter is more vulnerable than white matter, and within the gray matter, layers 3, 5, 6 of the neocortex, and portions of the hippocampus, amygdala, thalamus, basal ganglia, and cerebellum are highly sensitive to the effects of metabolic derangement. Although the brain makes up only 2% of body mass, it receives 20% of the cardiac output and oxygen supply of the body, with 75% of this oxygen consumed by the gray matter for aerobic glycolysis.[2] Over 60% of the body's glucose is used in the brain, with the majority of this energy used to preserve normal ionic gradients responsible for maintaining the delicate balance of excitation and inhibition of the nervous system.

In general, the clinical signs of MIND are initially diffuse, non-fixed in time, and reversible. The onset of clinical signs of ME ranges from peracute (e.g., hypoxia) to chronic (e.g., hepatic encephalopathy). Waxing-waning behavior changes are the predominant early clinical signs in the majority of small animal ME. Aimless wandering, non-directional circling, and disorientation are common early changes.[3] As the disease progresses, clinical signs progress in a rostral (cerebrocortical) to caudal (brain stem) fashion. Over time, animals can develop stupor or coma with untreated ME. Oculomotor abnormalities are common and range from symmetric, reactive miosis in early ME, to symmetric, fixed mydriasis with prolonged hypoxia. Marked motor abnormalities are unusual early in the course of ME, with the exception of epileptic seizure activity. As more brain stem involvement occurs, ataxia and paresis can be seen. Respiratory pattern irregularities are common with ME. Diffuse cortical disease can result in an irregular cycle of hyperventilation followed by apnea (Cheynes-Stokes respiration). The presence

of ataxic breathing (very irregular inspiratory and expiratory pattern) indicates caudal brain stem involvement, a poor prognostic sign.

In the PNS, similar mechanisms, as seen in the brain, are responsible for loss of function. Long and large diameter nerve fibers are affected first via disruption in axonal transport of integral substances necessary for nerve viability. Nerves will then undergo a dying back process, with degeneration of the axons in a distal to proximal fashion.[4] The clinical signs include a chronic systemic disease, preferential lower and pelvic limb involvement, sensory loss prior to motor loss, muscle wasting, and slow return to normal with treatment. In contrast, in myopathies, the proximal muscles are typically affected, muscle mass is preserved, and muscles may be painful. Since muscle contraction and relaxation are both energy dependent activities, failure to maintain normal ionic gradients is a common mechanism for myopathies associated with systemic illness.

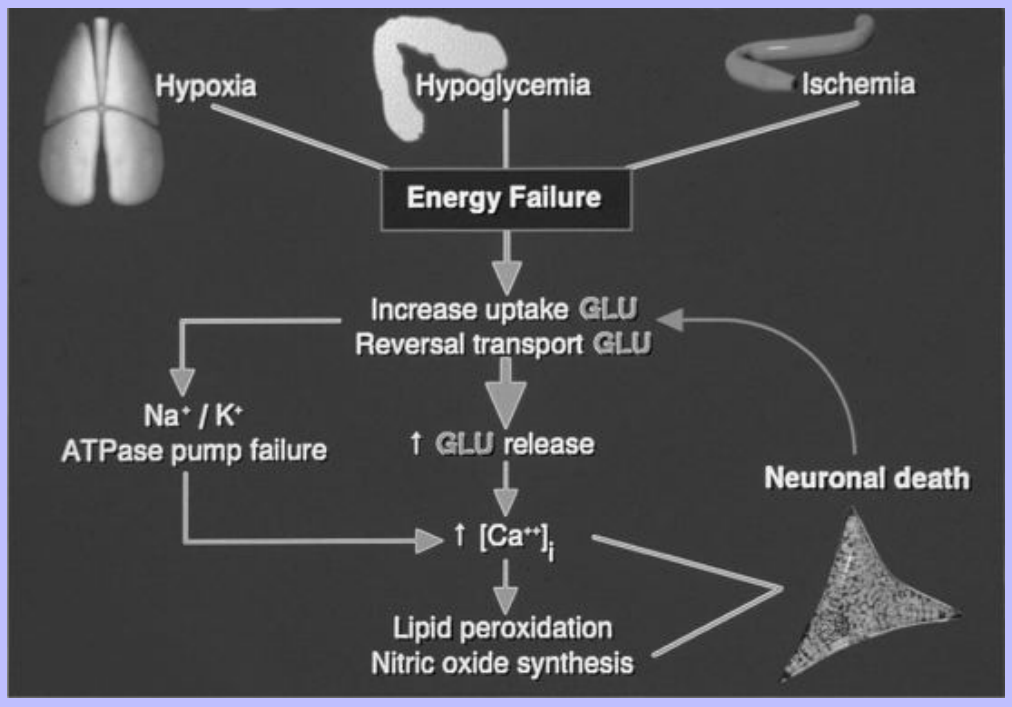
Five major classifications of systemic diseases are listed in Box 190-1. Examples of the more common systemic diseases associated with neurologic manifestations in the cat and dog are presented with emphasis placed on the pathophysiology and identification of the disease process.

190.2 FUEL DEPRIVATION

190.2.1 Oxygen Deprivation

Hypoxic-ischemic encephalopathy is the result of loss of cerebral oxygen supply either through decreased arterial oxygen tension (PaO_2 <50 mm Hg), or reduced to absent cerebral blood flow. Irreversible brain injury occurs within 20 seconds after anoxia, and 2 to 4 minutes after hypoxia-ischemia. Moreover, in dogs, a PaO_2 less than 45 mm Hg is sufficient to cause heart failure and systemic hypotension, thus exacerbating the condition with cerebral perfusion deficit.[5] This circulatory collapse cascade phenomenon in acute hypoxia is due to a primary CNS-induced reflex depression of cardiac function. In this setting, a common cause of hypoxia-ischemia in small animals is an anesthetic complication. Other causes for acute respiratory insufficiency include pneumonia, pulmonary thromboembolism, pneumothorax, and bronchospasm. Surviving animals may initially be comatose with fixed dilated pupils, leading to dementia, cortical blindness, and motor abnormalities. Since the degree of necrotic neuronal death is proportional to the lack of oxygen, the prognosis is greatly dependent upon the total duration of the hypoxic-injury. The longer the duration of hypoxia, the greater the chance for brain stem signs to occur.

Figure 190-1 Schematic diagram of glutamate (GLU)-induced excitotoxicity secondary to fuel deprivation of the brain.[1]



190.2.1.1 Box • 190-1 Classification of Systemic Diseases With Neurologic Manifestations

I. Fuel deprivation

A. Oxygen

1. Hypoxia

a) Primary pulmonary disease

b) Decreased O_2 transport

c) Secondary heart failure

2. Vascular disease

a) Ischemia

(1) Decreased peripheral vasomotor tone (shock)

(2) Decreased cardiac disease

(3) Thromboembolic disease

b) Hemorrhage

(1) Vessel rupture secondary to hypertension

(2) Coagulopathies

(3) Vasculitis

B. Glucose utilization (hypoglycemia)

1. Increased uptake

a) Hyperinsulinemia

(1) Islet cell tumors

(2) Insulin overdose

b) Non-islet cell neoplasia (hepatoma, leiomyoma)

c) Excessive metabolism (sepsis, breed or activity-related)

2. Decreased output or metabolism

a) Primary liver disease

b) Malnutrition

c) Thiamine deficiency

3. Increased uptake of amino acids by extrahepatic tissues

II. Water and ionic imbalances

A. Water

1. Hypoosmolar states (retention of free water)

a) Hyponatremia

2. Hyperosmolar states (loss of free water)

a) Hypernatremia (diabetes insipidus)

b) Hyperglycemia (diabetes mellitus)

B. Ions (excess or deficiency)

1. Potassium

2. Calcium

III. Endogenous neurotoxins

A. Renal failure

B. Hepatic failure

C. Endocrine disease

1. Adrenal

a) Cortisol and mineralcorticoid dysregulation

(1) Hyperadrenocorticism (Cushing's disease)

(2) Hypoadrenocorticism (Addison's disease)

b) Adrenergic dysregulation

(1) Pheochromocytoma

2. Thyroid

a) Hypothyroidism (myxedema, neuromyopathy)

b) Thyrotoxicosis

IV. Exogenous neurotoxins

A. Sedative depressant drugs (e.g., antiepileptic drugs)

B. Plant toxicity and poisons

C. Heat stroke

V. Remote neurologic manifestations of cancer

A. Metastases to the nervous system

B. Vascular accidents and infection

C. Adverse effects from therapy

D. Paraneoplastic syndromes

Therapy consists of reversal of the underlying event and supportive care to reintroduce energy to the brain by instituting proper ventilation and oxygenation, maintenance of normal hydration, and early enteral nutritional support. Steroid therapy does not improve neurologic recovery in people,[6] and in general, increases metabolic demand on the body, produces adverse effects, and has minimal benefit to the brain. Many animals may become functional pets over time and take several weeks to recover.

Cerebrovascular disease that results in focal lesions often is related to underlying systemic illness in the cat and dog.[7] Historical signs may be vague initially (e.g., lethargy, inap-pettance), leading to acute, focal cerebrocortical signs. Thromboembolic disease from sepsis, tumor metastasis, atherosclerotic disease, and hemorrhage from systemic causes of hypertension have been documented.

190.2.2 Glucose Deficiency

Hypoglycemia is a common cause of neurologic signs associated with systemic diseases. The brain requires an average of 100 g of glucose/day to function. Blood glucose below 40 mg/dL induces a stress response to release counter-regulatory hormones and induce gluconeogenesis. Progressive and/or persistent hypoglycemia results in cerebrovascular constriction, thus reducing oxygen delivery. Eventually, neuronal cell death occurs. Neuroglycopenic effects range from behavior changes (e.g., hiding) and weakness early and progress to tremors, partial and generalized seizures, blindness, and unresponsiveness.

The most common causes of hypoglycemia in small animals are increased uptake or decreased output. Increased uptake is seen with insulinoma, non-islet cell tumors, excessive exogenous insulin, and excess metabolism in certain toy and sport breed dogs. Most dogs with pancreatic islet cell tumors have clinical signs for several months with multiple episodic events interspersed with normalcy. In addition to neuroglycopenic signs, affected dogs may develop weakness secondary to a paraneoplastic peripheral neuropathy[8] and lacunar infarcts related to cerebral microangiopathy.[9] No correlation exists between severity or frequency of clinical signs, degree of hypoglycemia, and survival time post-treatment.[10] Non-islet cell tumors that arise from the

liver, smooth muscle, and other areas can produce insulin-like growth factor or other counter-regulatory hormones, which results in reversible hypoglycemia once the tumor is removed.[11]

Insulin overdosing is a serious complication of diabetes mellitus management. This problem appears to be more common in heavier cats receiving more than 6 U per injection of insulin, regardless of type.[12] Persistent cortical blindness and epileptic seizures after restoration of euglycemia may occur. Initial treatment is an IV bolus of 50% dextrose at 1 g/kg over 3 to 5 minutes, followed by continuous rate infusion of a dextrose containing solution to maintain blood glucose more than 80 mg/dL. Thiamine supplementation should be provided to allow for proper mitochondrial aerobic glycosis to occur.

190.2.3 Thiamine Deficiency

Thiamine (vitamin B1) is essential for the oxidative decarboxylation of pyruvic acid in the Kreb's cycle. Failure to complete this cycle will result in decreased gluconeogenesis. Thiamine deficiency occurs in cats and dogs fed primarily diets of over-cooked meats or fish that contains thiaminase, or with prolonged anorexia. Clinical signs are related to a progressive, bilateral, symmetric polioencelomalacia, which predominantly involves the subcortical gray matter. Cats can initially develop central vestibular disease, head tremor, mydriasis, and cervical ventroflexion, which may progress to opisthotonus, coma, and death. In dogs, ataxia, paresis, vestibular signs, and seizures have been observed. Parenteral administration of thiamine (10 to 20 mg IM for cats; 25 to 50 mg IM for dogs) will resolve clinical signs early in the course of the disease.

190.3 WATER AND IONIC IMBALANCES

190.3.1 Hypoosmolality with Hyponatremia

Hyponatremic encephalopathy is the result of an osmotic shift between extracellular fluid and brain cells, which results in a net movement of water into the brain, with its associated cerebral edema. Although the cause of hyponatremia may differ depending on the patient's volume status, the clinical signs are more dependent on the onset of the osmolar shift. Acute hyponatremia (hours) can lead to pressure necrosis of the cerebral hemispheres after an expansion of at least 5%, followed by brain herniation.[13] Little intracranial compensation can occur during the acute stage. With chronic (days) hyponatremia, the brain compensates with a loss of cation to lower intracellular osmolality with minimum water gain. Animals may exhibit little to no clinical signs. A rapid correction in serum sodium of at least 20 mEq/L of hyponatremia (<130 mEq/L) over 24 to 48 hours can lead to a potentially fatal demyelination of the brain stem, known as *central pontine myelinolysis*.[14]

Sodium replacement with 0.9% NaCl in volume depleted patients is calculated by the following equation:

$$\text{Na Deficit (mEq)} = 0.3 \times \text{BW kg} \times (\text{Normal Na} - \text{Patient Na})^{15}$$

Appropriate volume correction is simultaneously administered. The goal is to raise serum sodium at a rate of 6 to 12 mEq/L per day.

190.3.2 Hyperosmolality

Acute plasma hypoosmolarity leads to shifting of intracellular water into the extracellular space, which results in disruption of the neuronal ionic gradients, cell shrinkage, progression to brain shrinkage, and potentially leading to tearing of arachnoid blood vessels, with intracranial bleeding. With chronic hyperosmolar shifts, the

brain adapts by *de novo* synthesis of idiogenic osmoles to increase intracellular osmolarity. Rapid correction of the resultant hypernatremia can lead to cerebral edema, as the brain is now hyperosmolar to the plasma.

Common causes of plasma hyperosmolality with neurologic signs include central (CDI) or nephrogenic diabetes insipidus (free water loss) and diabetes mellitus (hypotonic fluid loss). Antecedent clinical signs include intense polydipsia and polyuria. Since CDI may cause similar neurologic signs indirectly through fluid shifts or directly from a pituitary mass, brain imaging is recommended after diagnosis of CDI in all dogs.[16]

Neurologic complications associated with diabetes mellitus related to CNS changes related due to hyperosmolality, electrolyte imbalances, and metabolic acidosis and to PNS changes with chronic inability to maintain Na-K ATPase activity in the nerve membranes. Diabetic neuropathy is typically a subclincal, electrophysiologic phenomenon in the dog[17] but results in a pronounced tibial neuropathy in the cat. These cats have a marked, symmetric plantigrade stance with pelvic limb weakness. Many cats will improve after sustained euglycemia.

Initial correction of hypernatremia to replace total body water can be calculated with the following formula:

$$\text{Water deficit} = \text{BW (kg)} \times [(\text{Patient Na}/\text{Normal Na}) - 1]^{15}$$

The deficit should be given over a 48-hour period to prevent cerebral edema starting with 0.45% NaCl/2.5% dextrose solution. A 5% dextrose in water solution can be used if serum sodium is not declining adequately.

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190.3.3 Ionic Imbalances

Potassium and calcium imbalances have a direct effect on muscle membrane stability. Hypokalemia (≤3.0 mEq/L) from excessive urine loss or dietary depletion decreases membrane excitability, which leads to episodic weakness, cervical ventroflexion, and bizarre postures in the cat[18] (Figure 190-2) but can also be seen in the dog. Clinical signs resolve with appropriate potassium supplementation. Oral potassium gluconate supplement at an initial dose of 5 to 10 mEq/day is preferable, as parenteral supplementation may exacerbate the hypokalemia through volume expansion and enhanced potassium diuresis.

Generalized weakness with or without tetanic muscle contractions are commonly seen with hypocalcemia (ionized calcium <5.0 mg/dL in dogs and <4.5 mg/dL in cats) due to increased membrane excitability. The more acute the onset, the more severe the clinical signs, with progression to status epilepticus possible. Initial treatment consists of 10% calcium gluconate IV at dosage of 0.5 to 1.5 mL/kg over 10 to 20 minutes while heart rate is monitored.[19] Identification and treatment of the underlying cause is essential to prevent recurrence.

190.4 ENDOGENOUS NEUROTOXINS

The blood-brain barrier is a highly specialized, integrated network of capillaries and glial cells to maintain the internal environment of the brain and cerebrospinal fluid. Certain endogenous neurotoxins and/or consequences of systemic diseases have been identified to alter the brain's neurochemical balance by either bypassing the blood-brain barrier or through direct changes in neurotransmitter activity.

190.4.1 Uremic Encephalopathy

Neurologic clinical signs associated with acute or chronic renal failure can be seen when glomerular filtration rate decreases below 10% to 20% of normal. Extensive data suggests that parathyroid hormone is the putative

neurotoxin.[20] Clinical signs in cats and dogs include depression, stupor, myoclonic movements, generalized weakness, and partial and generalized seizures. Animals may not have prolonged antecedent mental depression prior to more pronounced neurologic signs, as seen in people.[21] Calcitriol (1,25 dihyroxyvitamin D, 1.5 to 3.5 ng/kg/day), by lowering parathyroid hormone serum concentration, reverses the neurologic depression in the majority of chronically treated uremic small animals.[20] Attention to blood pressure control should also be provided.

Figure 190-2 Cervical ventroflexion in a 2-year-old female spayed DSH cat with hypokalemic polymyopathy secondary to potassium-losing nephropathy.

190.4.2 Hepatic Encephalopathy

Advanced congenital or acquired liver disease can produce a complex of neurologic signs, known as hepatic encephalopathy (HE). Waxing-waning bizarre, unpredictable behavior, dementia, progressive loss of arousability, myoclonus, and seizures can all occur. Clinical signs can worsen after protein digestion. Although most animals with HE will have an elevated plasma ammonia concentration, there is minimal correlation between the severity of clinical signs and ammonia level. Irish wolfhound pups can exhibit hyperammonemia of a metabolic and non-hepatic origin, with a low likelihood of a portosystemic shunt (PSS) if the ammonia level is less than 120 mumole/L.[22] There are several potential pathophysiologic causes of the neurologic syndrome of HE, which include (1) hyperammonemia, (2) synergistic neurotoxins, (3) altered monoamine (tryptophan) and “false” neurotransmitter synthesis, (4) alterations in amino acid neurotransmitters, and (5) increased cerebral concentrations of an endogenous benzodiazepine.[23] Recent studies demonstrated increased cerebrospinal fluid concentrations of tryptophan, tryptophan metabolites, glutamine, and quinolinic acid in dogs with naturally occurring PSS as compared with control dogs. The results support the theory of an increased flux and metabolism of tryptophan through the CNS serotonin metabolic pathway as a contribution to the neurologic complications with PSS and ensuing encephalopathy in dogs.[24]

Medical therapy for HE is directed to the reduction of by-products of protein metabolism and subsequent neurotoxins. Initial medical therapy includes a low-protein diet, antibiotic therapy to reduce ammonia producing bacteria, lactulose to decrease production and absorption of ammonia, and H_2-blockers as needed to treat for gastrointestinal bleeding. Surgical correction of congenital porto-caval shunts is most successful in dogs less than 2 years of age for reduced mortality[25] and neurologic morbidity. Generalized seizures may persist post-ligation despite lack of other evidence of HE.[26] The recommended antiepileptic drug therapy for these dogs is either potassium bromide at an initial maintenance therapy at 40 mg/kg/day or gabapentin at 20 mg/kg/day with increases to 60 to 80 mg/kg/day divided TID as needed. Both of these drugs are renal excreted, non-protein bound drugs with good antiepileptic properties in the cat and dog. Bromide therapy should be used with caution in the cat due to the potential for induction of an allergic induced asthmatic reaction.[27] Continuous rate infusion of sodium bromide at 600 to 1200 mg/kg/24 hours for 1 day is an alternative method to rapidly raise bromide serum concentrations to a therapeutic range.[28] Benzodiazepine therapy should be avoided to prevent potentiation of inhibitory neurotransmission in the brain. Sarmazenil, a benzodiazepines antagonist and partial inverse agonist, at 3 to 8 mg/kg IV ameliorated neurologic signs in dogs with experimentally induced HE secondary to PSS.[29]

190.4.3 Thyroid Diseases

Primary hypothyroidism is a common endocrinopathy of the older dog with multiple neurologic manifestations. The most severe form is myxedema, associated with bradycardia, hypothermia, dementia, stupor or coma, generalized lower motor neuron weakness, and possible seizures. Concurrent complications of hyponatremia, hypoventilatory hypoxia, and cerebral ischemia make this a life-threatening condition. Treatment consists of gradual rewarming, correction of serum sodium and osmolarity, steroid therapy (prednisolone sodium succinate 10 mg/kg IV BID for 24 hours), and injectable levothyroxine replacement (5 ug/kg IV once), followed by maintenance thyroid supplementation. Marked improvement is usually seen within 24 hours.

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Chronic, progressive peripheral or central vestibular disease can also occur in hypothyroid dogs.[30] These dogs are typically older (more than 7 years), with progressive ataxia and head tilting as primary signs. Other clinical syndromes are related to motor unit dysfunction. Generalized lower motor neuron weakness with exercise intolerance can be the result of hypothyroid neuro-myopathy. Concurrent or separate signs of megaesophagus and facial and/or laryngeal paralysis may be present. Many, but not all, dogs will improve with appropriate thyroid supplementation.[31]

Thyrotoxicosis (hyperthyroidism) in cats can produce multiple neurologic abnormalities. Predominant behavior changes include irritability, hyperactivity, aggression, and reduced sleep cycles. Some cats may exhibit a paradoxic “apathy,” characterized by excessive dullness. Progressive neuromuscular weakness with cervical ventroflexion, exercise intolerance, and loss of jumping ability can be seen with more advanced disease, and associated muscle wasting. Signs are reversible with appropriate treatment of the underlying hyperthyroid condition.

190.4.4 Adrenal Diseases

Adrenal hormone excess or deficiency has been associated with a variety of neurologic disturbances. Signs attributed to hypoadrenocorticism (Addison's disease) include episodic, progressive lethargy, dullness, tremors, vomiting, and possible acute collapse.[32] Glucocorticoid deficient hypoglycemia may exacerbate these signs.

Rapid reversal of neurologic signs is seen with mineral-and/or glucocorticoid replacement and restoration of metabolic homeostasis.

Cushing's disease (hyperadrenocorticism) can produce CNS and PNS abnormalities through direct or indirect mechanisms. Direct compression of a pituitary macroadenoma onto the brain results in early signs of dullness and dementia, with progression to obtundation, tetraparesis and ataxia, visual impairment, and seizures. Up to 35% of dogs with pituitary dependent Cushing's with a visualized (CT or MRI scan) tumor of more than 4 mm may develop neurologic signs.[33] Cerebrovascular accidents may also occur, secondary to systemic arterial hypertension or thromboembolic disease. In the PNS, an irreversible progressive fibrosing myopathy can occur, regardless of duration, severity, or onset of treatment with canine Cushing's disease. A progressive stiff gait leading to inability to flex the limbs is characteristic of this condition.

Pheochromocytoma can induce neurologic signs in approximately 10% of clinically symptomatic dogs.[34] Generalized weakness, pelvic limb weakness, focal forebrain signs, and seizures may develop. Signs can be the result of direct intracranial metastasis or secondary intracranial hemorrhage due to hypertension.

190.5 EXOGENOUS NEUROTOXINS AND INJURY

A variety of environmental or iatrogenic substances will produce diffuse forebrain disturbances. More common conditions are toxic reactions to antiepileptic drugs, rodenticides, and heat stroke. Removal of the inciting cause and appropriate supportive care are often corrective.

190.5.1 Neurologic Complications of Cancer

More neurologic complications secondary to systemic cancer are being observed with the advancement of diagnostic and treatment capabilities in veterinary oncology. These complications can be serious to life-threatening, may be diagnostically challenging, yet early treatment can be quite beneficial to the patient. Moreover, the nervous system problems are unique to the rest of body, in that small lesions can create major clinical signs (as compared with the liver), heterogeneous function is present, barriers must be kept intact for proper function, and damage to CNS tissue has limited capacity to repair itself, so that clinical signs may be irreversible.[35]

Direct and extensional metastases to the nervous system are the most common neuro-oncologic complications in the cat and dog. Hemangiosarcoma, mammary and thyroid carcinoma, and melanoma, spread preferentially to the end-arterial vasculature of the gray-white matter regions of the cerebrum.[36] Clinical signs are related to tumor location and the secondary effects. Dogs with intracranial extension of nasal carcinoma may present only with CNS signs. Chemo-and radiation therapy can directly or indirectly affect the nervous system. Paraneoplastic disorders are due to autoimmunity as a result of tumor cells expressing “onconeural” antigens identical or antigenically related to molecules normally expressed by neurons or other receptors.[37] In small animals, the primary paraneoplastic syndromes recognized are related to PNS disease, including neuropathy (e.g., secondary to insulinoma, carcinoma, sarcoma) and myasthenia gravis (e.g., secondary to thymoma, osteogenic sarcoma).

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191 CHAPTER • 191 Brain Disease

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"All the most acute, most powerful, and most deadly diseases, and those most difficult to be understood… fall upon the brain." Hippocrates

For as long as people have been aware of disease, they have been frustrated by brain disease. Recent advances in brain imaging and molecular approaches to understanding disease hold the promise of changing these concerns. This chapter will outline the diagnostic approach to brain disease and discuss the major diseases of dogs and cats that primarily affect the brain.

191.1 RESPONSE OF THE BRAIN TO DAMAGE

The nervous system has relatively few ways to respond to damage, and the complexity of neurologic signs depends upon the localization of that response within the nervous system. Because neurons are excitable cells, one potential response to disease is excessive discharge of these cells. The most dramatic example of this is seizure activity. Conversely, if the disease destroys the neurons of a functional system, there will be a loss of function of that system. For example, the destruction of a cranial nerve nucleus in the brain stem will lead to paralysis of the muscles innervated by that nerve. If the system that is lost happens to be an inhibitory pathway, then the system that is no longer inhibited may show an exaggerated response. The classic example of such disinhibition is the exaggerated reflexes seen with upper motor neuron (UMN) loss. When dealing with higher brain functions, such responses can be complex. For example, the paradoxical aggression sometimes seen with benzodiazepines or barbiturates in dogs may represent a disinhibition of aggressive behavior.

In addition to local effects, a disease process in the brain can produce generalized effects secondary to increased intracranial pressure. Because the calvarium is a rigid structure, the three major components within it (brain, cerebrospinal fluid [CSF], and blood) are confined to a fixed volume. Any increase in one of these components would then have to be accompanied by a decrease in one of the others (the Monro-Kellie doctrine). A gradual increase in volume of one component, such a slowly progressive hydrocephalus, can be compensated for to some extent, in this case by atrophy of brain tissue. More acute disease would not allow time for compensatory atrophy, and even chronic disease, such as a brain tumor, will eventually exceed the ability of the other components to compensate. The result is increased intracranial pressure. With increasing intracranial pressure, generalized forebrain signs will develop, even if the inciting cause is a localized process such as neoplasia. As intracranial pressure increases, blood pressure will increase to maintain cerebral perfusion. This can sometimes result in a reflex increase in vagal tone and bradycardia (the Cushing's response). Vomiting may also occur.

Continued increases in intracranial pressure will lead to herniation. Brain tissue can herniate laterally under the falx cerebri, or it can herniate caudally under the tentorium or through the foramen magnum. Tentorial herniation leads to a progressive rostral-caudal deterioration of neurologic status when the midbrain, pons, and terminally the medulla are compressed. The progression can be rapid or can evolve slowly over a mater of hours or even days. Herniation is most commonly associated with forebrain lesions, such as neoplasia or trauma. Increased pressure arising below the tentorium (e.g., a cerebellar tumor) will cause herniation of the cerebellum through the foramen magnum, mimicking the terminal events of tentorial herniation without any of the earlier signs.

191.1.1 Neurologic Examination

Regardless of whether the signs reflect focal damage or diffuse disease, the first step in diagnosing any neurologic disease is to localize the lesion. The neurologic exam requires care to perform, but it is the most cost-effective diagnostic procedure available. A neurologic exam form can be used to ensure a complete exam and to accurately record observations (Figure 191-1). Even in cases with obvious brain disease, a complete neurologic exam should be done to rule out multifocal disease. The focus of this chapter is on the aspects of the neurologic exam that are important for evaluating brain function: (1) observation of behavior, posture, and gait; (2) postural reactions; and (3) cranial nerves. Although not technically a part of the neurologic exam, a fundic exam should be considered. Because the retina and optic nerve are basically extensions of the brain, the clinician should take advantage of the one place where they can look directly at the nervous system (Figure 191-2). A disease process visualized in the fundus is likely to be the same process producing signs elsewhere in the nervous system.

191.1.1.1 History and Behavior

Because changes in behavior or episodic events like seizures will be important clues to brain disease, an adequate history is essential. The clinician must elicit descriptions of the animal's behavior that will allow identification of the changes without leading the client. Clients will misinterpret the nature of many neurologic signs, including seizures, so they should be encouraged to describe what they observed rather than their conclusions. Many clients have access to video cameras, and a tape of an episodic event can be useful in determining the nature of the episode.

If allowed to freely roam the exam room, the animal's behavior can be observed while a history is being taken. Looking at how an animal interacts with the environment assesses the mental status. A normal animal will be aware and observant of its surroundings. How the animal interacts with its owner or other people should be noted. Any spontaneous noises or movements may be used to see if the pet is attentive to these stimuli. The odors of the exam room floor can also be an interesting stimulus to many animals. An animal that is lethargic or obtunded will withdraw from its surroundings unless stimulated. A stuporous animal responds only to strong or noxious stimuli, and the response may not be at all appropriate. A comatose animal does not respond even to noxious stimuli. A demented animal may appear alert, but its response to its environment will be inappropriate.

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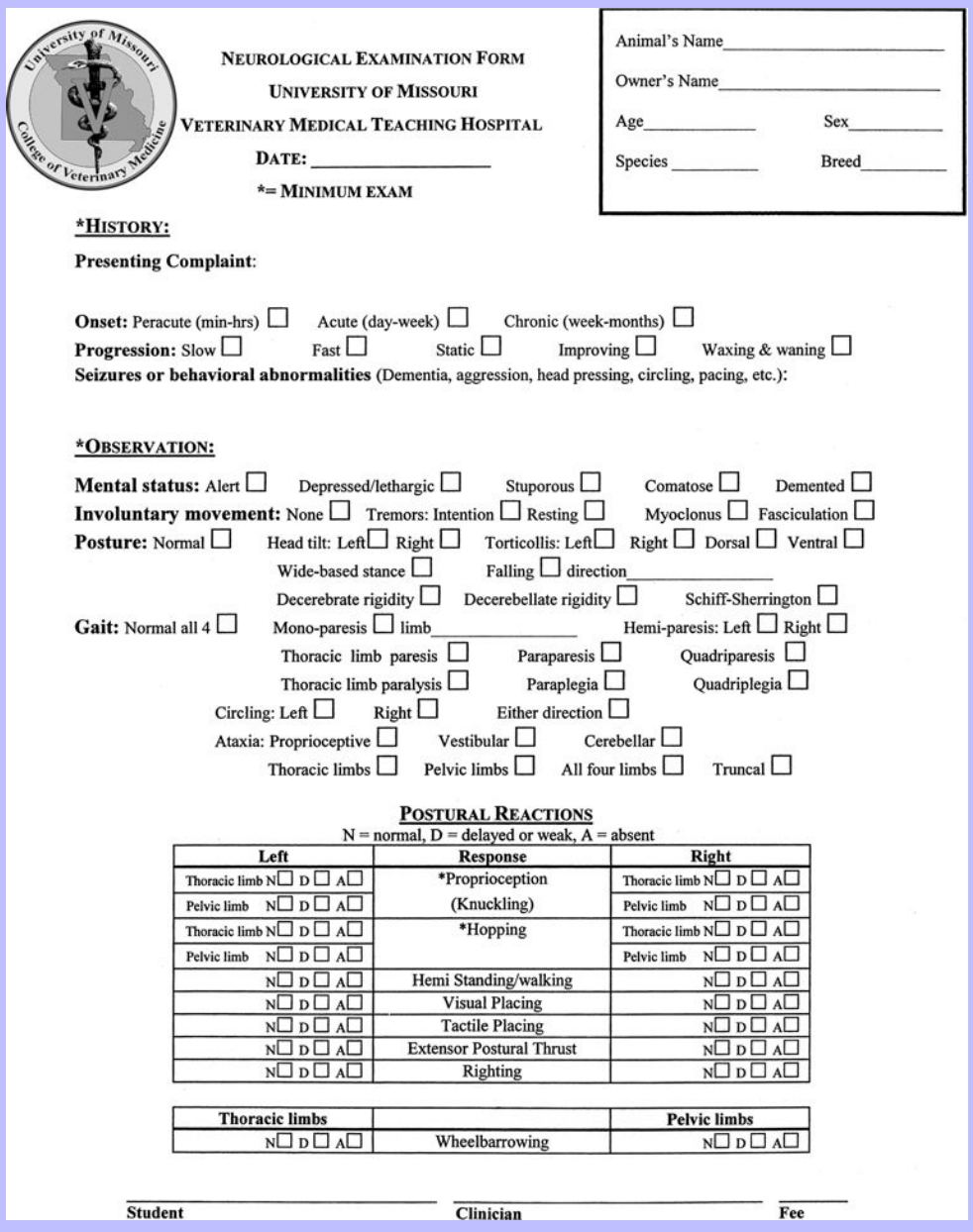
Figure 191-1 Neurologic examination form.



NEUROLOGICAL EXAMINATION FORM
UNIVERSITY OF MISSOURI
VETERINARY MEDICAL TEACHING HOSPITAL
DATE: _____
*= MINIMUM EXAM

Animal's Name_____
Owner's Name_____
Age_____ Sex_____
Species _____ Breed_____

*HISTORY:

Presenting Complaint:

Onset: Peracute (min-hrs) ☐ Acute (day-week) ☐ Chronic (week-months) ☐
Progression: Slow ☐ Fast ☐ Static ☐ Improving ☐ Waxing & waning ☐
Seizures or behavioral abnormalities (Dementia, aggression, head pressing, circling, pacing, etc.):

*OBSERVATION:

Mental status: Alert ☐ Depressed/lethargic ☐ Stuporous ☐ Comatose ☐ Demented ☐
Involuntary movement: None ☐ Tremors: Intention ☐ Resting ☐ Myoclonus ☐ Fasciculation ☐
Posture: Normal ☐ Head tilt: Left ☐ Right ☐ Torticollis: Left ☐ Right ☐ Dorsal ☐ Ventral ☐
Wide-based stance ☐ Falling ☐ direction_____
Decerebrate rigidity ☐ Decerebellate rigidity ☐ Schiff-Sherrington ☐
Gait: Normal all 4 ☐ Mono-paresis ☐ limb_____ Hemi-paresis: Left ☐ Right ☐
Thoracic limb paresis ☐ Paraparesis ☐ Quadriparesis ☐
Thoracic limb paralysis ☐ Paraplegia ☐ Quadriplegia ☐
Circling: Left ☐ Right ☐ Either direction ☐
Ataxia: Proprioceptive ☐ Vestibular ☐ Cerebellar ☐
Thoracic limbs ☐ Pelvic limbs ☐ All four limbs ☐ Truncal ☐

POSTURAL REACTIONS
N = normal, D = delayed or weak, A = absent

Left	Response	Right
Thoracic limb N☐ D☐ A☐	*Proprioception (Knuckling)	Thoracic limb N☐ D☐ A☐
Pelvic limb N☐ D☐ A☐		Pelvic limb N☐ D☐ A☐
Thoracic limb N☐ D☐ A☐	*Hopping	Thoracic limb N☐ D☐ A☐
Pelvic limb N☐ D☐ A☐		Pelvic limb N☐ D☐ A☐
N☐ D☐ A☐	Hemi Standing/walking	N☐ D☐ A☐
N☐ D☐ A☐	Visual Placing	N☐ D☐ A☐
N☐ D☐ A☐	Tactile Placing	N☐ D☐ A☐
N☐ D☐ A☐	Extensor Postural Thrust	N☐ D☐ A☐
N☐ D☐ A☐	Righting	N☐ D☐ A☐

Thoracic limbs		Pelvic limbs
N☐ D☐ A☐	Wheelbarrowing	N☐ D☐ A☐

Student Clinician Fee

CRANIAL NERVE EXAM

N = normal A= absent/abnormal (describe)

Left	Reflex or Response	Right
	Olfaction (I) N☐ A☐	
N☐ A☐	Vision (II)	N☐ A☐
N☐ A☐	*Menace response (II, VII)	N☐ A☐
N☐ A☐ Direct N☐ A☐ Consensual	*PLR (II, III) Direct / Consensual	N☐ A☐ N☐ A☐
N☐ Y☐ I☐	Pupil size & Anisocoria (II, III, Sympathetics) mYdriasis or mIosis	N☐ Y☐ I☐
N☐(absent) Present☐	Other Horner's Signs (Sympathetics)	N☐(absent) Present☐
N☐(absent) L☐ X☐ M☐	Strabismus: III-ventroLateral, IV- eXtorsion (outward rotation), VI-Medial Positional ☐:	N☐(absent) L☐ X☐ M☐
N☐(present) Absent☐	*Physiologic nystagmus (Doll's eye) (III, IV, VI, VIII)	N☐(present) Absent☐
N☐(absent) H-L☐ R☐ O-L☐ R☐ V☐ P☐	Pathologic nystagmus (VIII) Horizontal, rOtary (Left or Right) Vertical or Pendular, Positional ☐:	N☐(absent) H-L☐ R☐ O-L☐ R☐ V☐ P☐
N☐ A☐	*Masticatory muscle mass (V)	N☐ A☐
N☐ A☐	*Palpebral (Ophth V, VII)	N☐ A☐
N☐ O☐ X☐ D☐	Facial Sensation (V: if absent check branch: Ophthalmic, maXillary or manDibular)	N☐ O☐ X☐ D☐
N☐ A☐	Facial muscles (VII)	N☐ A☐
N☐ A☐	Hearing (VIII)	N☐ A☐
N☐ A☐	*Gag reflex / swallowing, eating, voice (IX, X, XII)	N☐ A☐
N☐ A☐	Trapezius / brachiocephalicus (XI)	N☐ A☐
N☐ A☐	Tongue: paralysis, atrophy, fasciculations (XII)	N☐ A☐

SPINAL HYPERESTHESIA

Absent /Present	Localize
Cervical A☐ P☐	
Thoracic A☐ P☐	
Lumbar A☐ P☐	
Sacral A☐ P☐	

SPINAL REFLEXES

0 = absent, 1+ = decreased,
2+ = normal, 3+ = increased,
4+ = very exaggerated, clonus or crossed extension

Left	Reflex or Response	Right
	Triceps (C7-T2 - radial)	
	Extensor Carpi Radialis (C7-T2 - radial)	
	*Thoracic limb withdrawal (C6-T2 - radial, ulnar, median, musculocutaneous)	
Superficial N☐ weak☐ A☐ Deep (if no SP) N☐ weak☐ A☐	Thoracic limb pain perception	Superficial N☐ weak☐ A☐ Deep (if no SP) N☐ weak☐ A☐
	*Patellar (L4-L6 - femoral)	
	Cranial Tibial (L6-S1 – peroneal)	
	Gastrocnemius (L6-S1- tibial)	
	Pelvic limb withdrawal (L6-S1 - sciatic)	
Superficial N☐ weak☐ A☐ Deep (if no SP) N☐ weak☐ A☐	Pelvic limb pain perception	Superficial N☐ weak☐ A☐ Deep (if no SP) N☐ weak☐ A☐
N☐ A☐	Perineal reflex & sphincter tone (S1-S3 - pudendal)	N☐ A☐
N☐ A☐ Ends:	Panniculus (T3-L3 & C8-T1)	N☐ A☐ Ends:

PALPATION: Normal ☐ Abnormal ☐ (muscle atrophy, spasms, rigidity, peripheral hyperesthesia, etc - describe.)

BLADDER & BOWEL FUNCTION:

*Voluntary urination: Yes☐ No☐ N/A(not assessed)☐

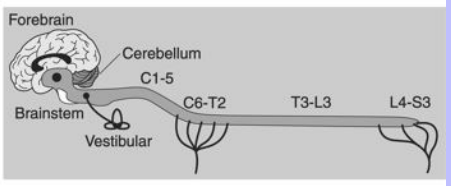
*Incontinence: No☐ Urinary☐ Fecal☐

Bladder size: Small☐ Large☐ N/A☐

Bladder expression: Difficult☐ Easy☐ N/A☐

TAIL MOVEMENT/TONE: Normal ☐ Abnormal ☐

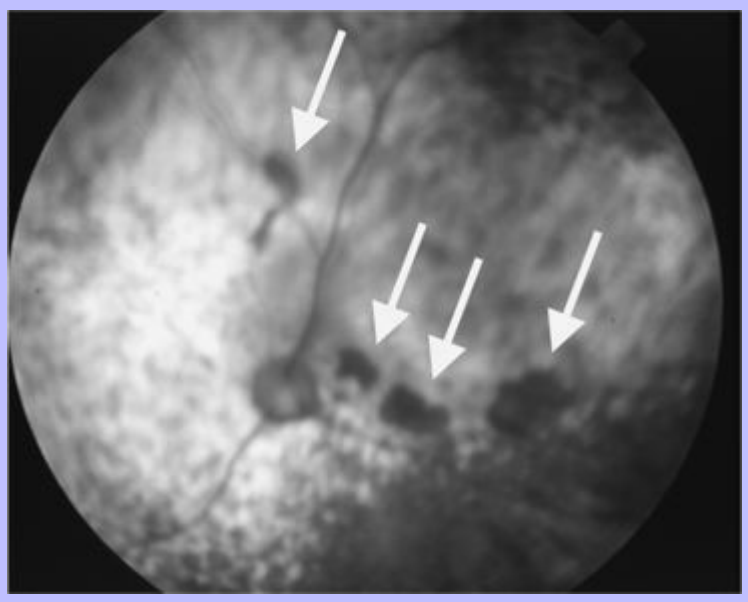
***LESION LOCALIZATION/SUMMARY:**



***DDx:**

***Plan:**

Figure 191-2 The retina is a direct extension of the brain. Thus retinal hemorrhages (*arrows*) in this dog with histoplasmosis suggest the same process is occurring within the brain. (Photo courtesy Dr. Elizabeth Giuliano.)



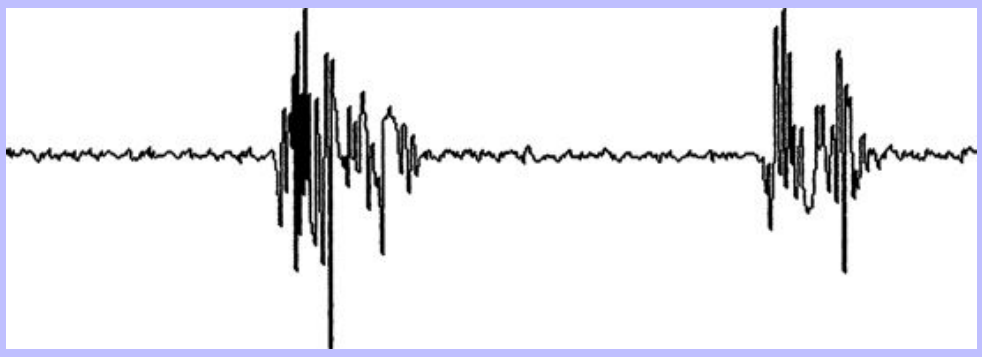
Because a tendency to circle can reflect asymmetrical damage to the brain, the direction the animal turns when it reaches a corner should be noted. If the animal is not clearly circling but has a bias toward turning one direction, the clinician should set up situations in which a turn in the opposite direction is required and see if the animal does so effortlessly. The character of the circling can provide clues to the localization. Forebrain disease tends to produce larger, wandering circles (sometimes the animal only makes a turn when it reaches a place where it cannot continue forward). Typically the circling will be toward the side of the forebrain lesion. Brain stem disease will more commonly produce tight circling or a tendency to lean against the wall with one side. The direction can be variable with brain stem lesions.

191.1.1.2 Abnormal Movements

While observing the animal's behavior in the exam room, any abnormal movements should be noted. In addition to the character of the movement, it is important to note when the abnormal movement occurs, whether at rest, when standing still, or when moving.

Tremors are probably the most common abnormal movement because they can be the result of a wide variety of causes. A tremor is a rhythmic oscillation of at least one functional region of the body such as a limb or the head. Tremors can be classified based on the frequency of the tremor, the part of the body affected, and the activity that precipitates the tremor.

Figure 191-3 Myoclonus is visible as brief bursts of muscle activity in the electromyography (EMG) of a dog with canine distemper.



Normally a subclinical tremor called the *physiologic tremor* occurs in all muscles. This is a high-frequency tremor (6 to 12 Hz) that disappears when the muscles are at rest. A variety of diseases can produce an enhanced physiologic tremor. Such a tremor is still a high-frequency tremor, and it tends to be most noticeable when the animal is standing quietly (postural tremor).

Goal-directed movements activate an intention tremor. This is seen most clearly in the head when the animal attempts to eat or drink or otherwise tries to fix its attention on something. Such tremors are characteristic of cerebellar disease but may be seen in other conditions such as hypocalcemia. The tremors are courser and slower (3 to 5 Hz) than physiologic tremors.

Myoclonus refers to a brief contraction of a muscle, group of muscles, or occasionally the entire body. Although myoclonus can repeat rhythmically, it does not have the oscillating character of tremors. Instead a rapid jerk occurs, followed by a quiet period (Figure 191-3). Myoclonus is seen most commonly in dogs after distemper infection but can be seen in other conditions such as myoclonic epilepsy, toxicities such as lead poisoning, or metabolic encephalopathies.

Dyskinesia is a general term to describe abnormal movement. The specific dyskinesias described in human neurology, such as chorea, ballism, or athetosis, have not been well characterized in animals. It is important to recognize that in a quadruped, fine motor control is more important in the head and facial muscles than the limbs. For example, star thistle toxicity in horses produces a degeneration of the substantia nigra comparable to Parkinson's disease of humans. The tremors and motor difficulties in the horse, however, are most dramatic in the facial muscles.

191.1.1.3 Gait and Posture

The posture of a normal animal should be square with the feet directly beneath the body and the head straight. A wide-based stance would indicate a problem with proprioception or balance. Unilateral balance or motor problems, usually related to a brain stem or inner ear lesion, may cause the animal to lean toward one side, possibly against a wall for support. With forebrain disease, the animal may tend to curl toward the side of the lesion as they orient toward that direction. With vestibular disease, the head tends to be rotated on the long axis so that one ear is lower than the other. The nose may be kept straightforward or sometimes turned away from the lower ear. Except for the paradoxical vestibular syndrome seen with cerebellar disease, the

head tilt will be toward the lesion (Figure 191-4). If abnormal head posture occurs in forebrain disease, the head will be pulled around to the side but usually not rotated. This type of head posture is sometimes referred to as an *adversion*, but the direction of the movement is typical toward the side of the lesion. *Dystonia* refers to a sustained abnormal contraction or posturing from basal ganglia disease.

Figure 191-4 With vestibular disease the head is rotated on its long axis with one ear lower than the other. This can be compared with a head adversion shown in Figure 191-17 in which the nose is pulled around toward the flank. (From O'Brien DP: Circling. In August JR, editor: *Consultations in feline internal medicine*, Philadelphia, 1994, WB Saunders Co, p 449.)

If the animal is stuporous or comatose, it may adopt abnormal postures that help to localize the lesion. A lesion affecting the midbrain will produce decerebrate rigidity. The neck is extended dorsally, and all four limbs are extended. Lesions of the cerebellum can sometimes produce a similar posture (decerebellate posture). The neck and thoracic limbs are extended, but the pelvic limbs are flexed.

The gait can be observed while the animal explores the exam room or while the owner walks the animal on lead. Walking in tight circles or up and down stairs may exacerbate subtle deficits. If an animal is weak from brain disease, it will be a UMN weakness. As a result, the limbs will tend to be stiff and the stride lengthened as opposed to the short, shuffling stride and buckling of the limbs seen with lower motor neuron (LMN) weakness. An animal with cerebellar disease will have normal strength with dysmetria. This is most apparent in the thoracic limbs as a goose-stepping gait, but the pelvic limbs may also show hyperflexion. Typically marked truncal ataxia is also noted as a swaying of the pelvis. Truncal ataxia may also be observed with proprioception deficits, but limb ataxia is different. An animal with proprioception deficits tends to drag the

toes and may stand with the foot knuckled under. It misplaces the feet and may cross over or step on itself, especially during tight circles.

191.1.1.4 Postural Reactions

The postural reactions are complex responses requiring integration of sensory information and coordination of motor responses at the brain level (Figure 191-5). Thus they are more involved than simple reflexes but still occur in direct response to a sensory stimulus, usually a perturbation of proprioception or balance. This makes them useful for evaluating brain function and spinal tracts.

Figure 191-5 Postural reactions, such as hopping, assess the ability of the brain to integrate sensory information and produce a coordinated motor response. The entire circuit (sensory afferents, long tracts, higher integration, and motor efferents) must be functional for a postural reaction to be executed. (From O'Brien DP; Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004.)

Conscious proprioception is evaluated by balancing the animal with one hand under the thorax or abdomen and knuckling one foot under so that the animal bears weight on the dorsum of the paw. Although clinicians are mainly interested in the perception of the sensation, they are looking for a motor response (replacing the foot to a normal position), thus this qualifies as a postural reaction. Proprioception deficits with forebrain disease may not be as obvious as the deficits seen with spinal cord disease. An alternative method for assessing proprioceptive awareness is placing a sheet of paper under one foot and slowly pulling the paper laterally. An animal with proprioception deficits may allow the foot to slide far laterally, even though it may replace the foot when knuckled.

Hopping also assesses proprioception, specifically where the foot is relative to the animal's center of gravity. The required motor response is more complex and thus allows the clinician to assess motor function and sensory perception. A small animal may be held with all its weight on one paw, whereas in a larger animal, only one paw is lifted and the animal pivoted. As the animal moves laterally, it should begin to hop to the side before its center of gravity passes over the paw. Proprioception deficits result in a delayed or absent initiation of the response. Cerebellar disease would result in an exaggerated movement, whereas UMN lesions would result in a weak or absent response.

Hemistanding and hemiwalking are good for comparing strength and coordination on one side of the body versus the other. First, both legs on one side are lifted off the ground so that the animal has to support all of its weight on one side and strength can be assessed. Then the animal is moved laterally so that it has to walk sideways on one side. This is a sensitive test of the ability of the contralateral forebrain to control those limbs.

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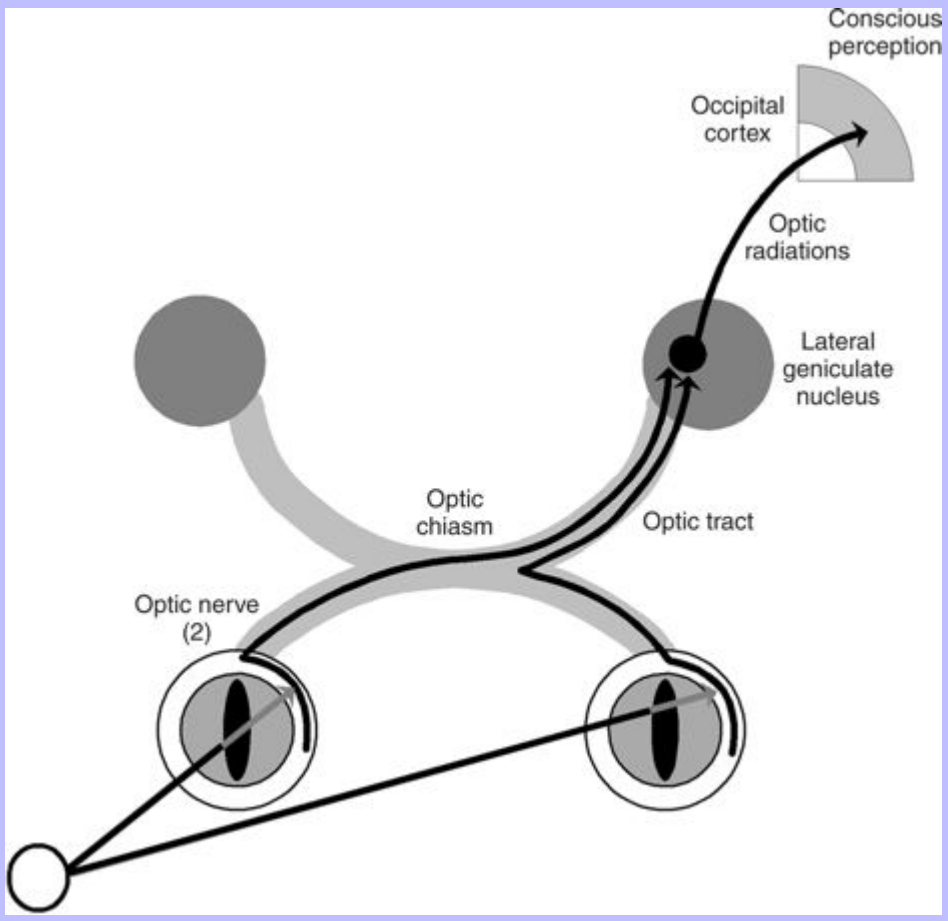
Visual placing assesses the animal's ability to use a visual stimulus to coordinate a motor response. As with proprioceptive positioning, the clinician is mainly interested in the sensory perception, in this case, vision. The animal must be small enough to be lifted off the ground, and then it is brought forward and downward toward the edge of a table. The normal response is to reach out and place one or both thoracic paws on the table. Tactile placing can be used to evaluate light touch perception of the thoracic limbs. The procedure is like visual placing, except the animal is blindfolded and the dorsum of the paw lightly touched against the table. Perception of touch in the pelvic limb is evaluated by the extensor postural thrust. The animal is picked up under the axilla and slowly lowered down. The normal response when the paws touch the ground is an extension of the limb and a shuffle to get the feet underneath the body.

The righting response is also a postural reaction. In this case the main sensory modality evaluated is the vestibular system. Proprioception and vision can also play a role, particularly in animals with vestibular deficits. Blindfolding the animal to remove visual compensation will exacerbate a vestibular deficit. Suspending the animal by the pelvis with the head down removes most proprioception clues, and the clinician can assess the animal's ability to orient to gravity. A normal animal will attempt to keep the head upright, whereas an animal with vestibular deficits may curl or move the head regardless of orientation to gravity. Alternatively the animal can be placed in lateral recumbency and allowed to right itself. A normal response would be a rostral-caudal righting, whereby the animal brings up the head, then neck, then shoulders, and sometimes also the pelvis.

Figure 191-6 The decussation of fibers within the optic chiasm ensures that images from one visual field are transmitted to the contralateral visual cortex.



191.1.1.5 Cranial Nerves

Because the cranial nerves originate in the brain, careful evaluation assesses the function of not only the nerve itself but also the associated brain areas. Although there can be UMN type of deficiencies in cranial nerves (just as for spinal reflexes), these are difficult to detect in animals. Thus with a few exceptions (see following discussion), a deficiency in a cranial nerve reflects damage either to the nerve itself or the brain area where the nucleus resides. Cranial nerve deficits will generally be ipsilateral to the lesion with the exception of the optic (II) and trochlear (IV)[4] nerves, which may be contralateral. Forebrain lesions may produce a loss of response to sensory information originating from the contralateral side.

The olfactory nerve (I) is the only sensory nerve that does not relay through the thalamus. Instead, it projects to the pyriform cortex and limbic areas such as the septal nuclei and amygdala, areas important in emotional

responses. This may explain why odors can have a profound emotional effect. Evaluating olfactory function can be difficult. If the animal investigates an odor, such as concealed food or urine odor on the exam room floor, then they have some olfactory function, but a unilateral loss could not be ruled out. A failure to orient to an odor could reflect a loss of the sense of smell or simply a lack of interest in the odor. Any withdrawal from an odor must be interpreted cautiously, because irritating substances such as alcohol could stimulate pain receptors in the nasal mucosa (carried by the trigeminal nerve [V]).[5]

The optic nerve (II) is evaluated by assessing vision and the pupils. *Vision* refers to the conscious perception of a visual stimulus, so clinicians rely on observing a behavioral response to determine if the animal has perceived the stimulus. The decussation of the optic nerves ensures that all visual information from one side goes to the contralateral visual cortex (Figure 191-6). The most effective way to evaluate vision is by tossing a cotton ball from behind, toward one side or the other, and observing whether the animal tracks the cotton ball (Figure 191-7). By avoiding the area directly in front of the animal where stereoscopic vision occurs, it is easier to differentiate loss in one visual field. The cotton ball will not create any noise and will typically surprise the animal enough to elicit some response.

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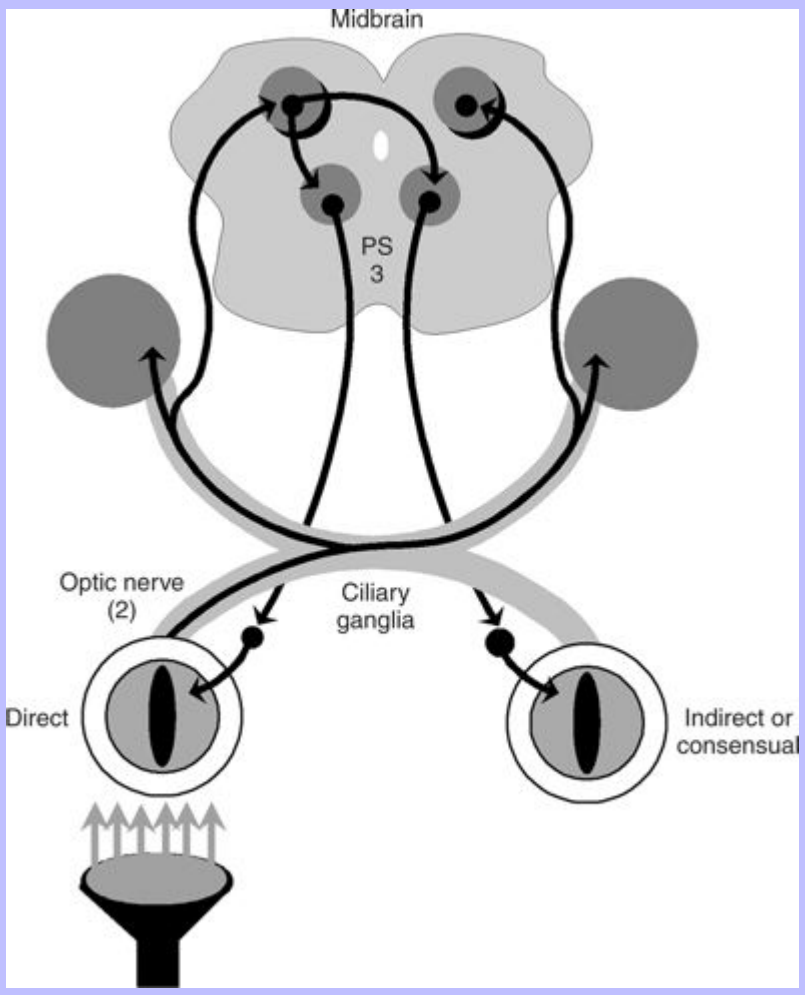
Figure 191-7 Most normal animals will track a cotton ball tossed from behind them. By keeping the cotton ball off to the side, vision in the left and right fields can be independently evaluated.

Figure 191-8 Light in one eye activates afferents in the optic nerve *(2)*. These synapse on efferents for the parasympathetic portion of the oculomotor nerve *(PS3)*, which in turn synapse in the ciliary ganglia. Crossover in the optic chiasm and the midbrain ensure that both the ipsilateral (direct response) and contralateral (indirect or consensual response) pupils constrict. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).



The ability of the animal to negotiate obstacles in the exam room, such as the exam table or a chair, can also assess vision. One eye can be covered to detect unilateral deficits. If the animal appears blind, the room can be darkened to dilate the pupils and the door opened to a bright hallway. If it cannot perceive the doorway,

then it is unlikely that the animal has any functional vision. If the animal is small enough to be picked up easily, visual placing can be used to assess vision.

The menace response is an acquired and complex response, not a simple reflex. It is one of the last cranial nerve responses to develop and may not be apparent until the animal is 12 weeks of age. It is best assessed with a quick movement of the hand parallel to the head, starting from behind the ear outside the animal's visual field. By moving parallel to the head, the whiskers can be avoided and fewer air currents are generated. By staying lateral, the stereoscopic field is avoided and one visual field evaluated. Most animals will respond to a quick movement from outside their vision with a blink. Because it is a complex pathway, a menace loss does not precisely localize a lesion without clues from the rest of the examination.

The optic nerve (II) provides the sensory afferents for the pupillary light reflex (PLR). These fibers synapse in nuclei in the midbrain and control the parasympathetic constriction of the pupil via the oculomotor nerve (III). In mammals, crossover in the optic chiasm and the midbrain ensures that both pupils respond together (Figure 191-8). Thus a light in one eye produces a constriction of the ipsilateral eye (direct response) and the contralateral eye (indirect or consensual response). A unilateral lesion of the retina or the optic nerve distal to the optic chiasm will produce blindness in that eye; thus if the other eye is blindfolded, the animal will have no vision. Shining a light in the affected eye will not produce a response in either pupil. Because the consensual innervation from the unaffected eye would be intact, pupil size and consensual response in the affected eye would be normal. With bilateral disease, both pupils would be dilated and completely unresponsive to light in either eye. A lesion affecting the parasympathetic third nerve, either in the brain stem or peripherally, would cause a dilated pupil in the ipsilateral eye that did not respond to light in either eye. Vision in that eye, however, would be normal, and shining a light in the affected eye would still elicit constriction of the contralateral pupil (consensual response).

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The sympathetic innervation of the pupil controls dilation. The first sympathetic fibers to leave the spinal cord at the T1–T2 cord segments run cranially in the vagosympathetic trunk to synapse in the cranial cervical ganglia at the base of the skull. From there, the postganglionic fibers course through the middle ear and into the calvarium, where they join with the ophthalmic branch of the trigeminal nerve and project through the retrobulbar area to innervate the eye. A lesion anywhere along this path can produce the classic signs of Horner's syndrome. The pupil cannot dilate normally in darkness but constricts normally in response to light, so the anisocoria will be most evident in dim lighting. Loss of sympathetic innervation to other structures around the eye would produce enophthalmos, ptosis, elevated third eyelid, and vasodilation.

Eye movements are controlled by the oculomotor (III), trochlear (IV), and abducens (VI) nerves. Damage to one of these nerves results in deviation of the eye (strabismus), because the muscles innervated by the functioning nerves pull the eye away from the denervated muscles. Thus with loss of the oculomotor nerve (III), a ventrolateral strabismus occurs. Trochlear nerve (IV) loss results in an outward rotation of the top of the eye. In an animal with a round pupil like the dog, this can be detected by the position of the vessels in the fundus. The trochlear nerve (IV), like the oculomotor nerve (III), originates in the midbrain, but it is the only cranial nerve to completely decussate. The abducens nerve (VI) originates near the vestibular nucleus in the medulla. Loss of this nerve results in a medial strabismus. The abducens nerve (VI) also innervates the retractor bulbi muscle; thus lesions will abolish retraction of the globe when the cornea is touched. With lesions sparing one or two of the nerves, some eye movement will be apparent even though the eye is deviated. With retrobulbar or cavernous sinus lesions, all three nerves may be lost, resulting in an eye that is positioned normally but unable to move (external ophthalmoplegia).

The doll's eye reflex (physiologic nystagmus or oculocephalic reflex) can be used to induce eye movements, and thus evaluate the vestibular system, and the innervation of the extraocular muscles. The vestibular

apparatus detects movement of the head. The vestibular nuclei feed information about the direction and speed of movement to the third, fourth, and sixth nerve nuclei, which move the eyes in the opposite direction at exactly the same speed. This allows the animal to maintain a fixed image on the retina even when the head is moving. Once the eyes have reached the limit of their range of movement in that direction, a center in the pons takes over to quickly flick the eyes back in the direction of the head movement, and the process begins again. Clinicians can observe this physiologic nystagmus by rotating the head to one side at a moderate speed and observing the eye movements. It is often easier to see the eye movements if the eyelid is pulled back to reveal the sclera. Because the pathway between the vestibular nucleus in the medulla and the third and fourth nerve nuclei in the midbrain (the medial longitudinal fasciculus) runs through the area of the reticular activating system, it is also a useful reflex in animals with stupor or coma.

Facial sensation is carried by the three branches of the trigeminal nerve (V). The ophthalmic branch innervates the skin medial to the eye and the cornea. Touching the medial canthus of the eye or the cornea will produce a blink (the palpebral or corneal reflex, respectively) if sensation is present and the motor innervation of the eyelid muscles by the facial nerve (VII) is intact. Because the sympathetic fibers to the eye travel with the ophthalmic branch, Horner's syndrome can accompany the sensory loss. The maxillary branch innervates the skin of the side of the face and the nostrils. A blink can frequently be elicited by touching the dog on the lateral aspects of the muzzle as well. Alternatively, maxillary sensation can be evaluated by touching the inside of the nostril. A normal animal will withdraw the head, but this response is sensitive to altered consciousness and nerve damage. The mandibular branch carries sensation for the skin of the chin and just ventral and rostral to the ear.

The muscles of mastication are innervated by the motor portion of the mandibular branch of the trigeminal nerve (V). Bilateral trigeminal paralysis will result in a dropped jaw and an inability to prehend food. The animal will be able to swallow normally when food is placed into the back of the mouth because pharyngeal function is normal. With unilateral paralysis, the animal will be able to eat normally, and the only sign will be atrophy of the temporalis and masseter muscle on the ipsilateral side.

Facial nerve (VII) palsy results in loss of function of the small muscles of the face. The most obvious sign will be an inability to blink the eye on the ipsilateral side, either spontaneously, in the palpebral and corneal reflex, or in the menace response. The lip and cheek may sag, and food may become lodged in the cheek. The nostrils will not flair with respiration, and cats will not be able to move their whiskers forward. The animal will not be able to lay the ear back, and in droop-eared dogs the ear will sag further. With chronic denervation, the muscles may contract, producing a grimacing facial expression.

Because the parasympathetic innervation of the lacrimal glands is also carried by the facial nerve, a dry eye may accompany the loss of blinking, predisposing the eye to exposure keratitis. Tear production can be evaluated by the Schirmer's tear test. The facial nerve also conveys taste sensation from the rostral two thirds of the tongue. Taste can be evaluated by touching the lateral aspect of the tongue just behind the canine tooth with a cotton tip soaked in a bitter substance like atropine. If the animal can taste, it immediately begins to salivate and lick. Taste from the caudal one third of the tongue is carried in the glossopharyngeal nerve but is more difficult to evaluate in animals. Finally, sensation from the skin in the concave surface of the pinna is carried by the facial nerve.

The vestibular portion of the eighth cranial nerve transmits information about the position of the head relative to gravity and head movement from the inner ear. The vestibular nuclei use this information to control eye movements (discussed previously) and maintain balance. Acute unilateral lesions affecting the vestibular apparatus will cause profound disruption of balance. The imbalance in vestibular input between the two sides creates the perception of spinning, leaning, or both. In response to this, the animal will be

anxious and may be nauseated and vomit. It will lean and may even roll toward the side of the lesion. There will be a head tilt toward the affected side, sometimes dramatically. If able to walk, affected animals may circle or lean against a wall for balance. When lifted off the ground, they may curl toward the side of the lesion with the contralateral limbs extended and the ipsilateral limbs flexed.

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Spontaneous nystagmus occurs because the imbalanced vestibular input creates a perception that the animal is spinning when it is not. With peripheral vestibular disease, the nystagmus may be horizontal or rotary with the fast phase away from the lesion. With time, the animal can compensate even if vestibular function does not return on the affected side. The disorientation and rolling will subside within a few days, and within 1 week the nystagmus may stop. Often signs like nystagmus can be precipitated again by rolling the animal onto its back or quickly extending the neck with the nose pointed toward the ceiling. Blindfolding will exacerbate the balance problems. With time, a residual head tilt may be the only sign that the vestibular system has not recovered completely. When the head is tilted, the eye position appears normal. If the clinician straightens the animal's head, the eye ipsilateral to the lesion will deviate ventrally. This is referred to as a *positional strabismus*.

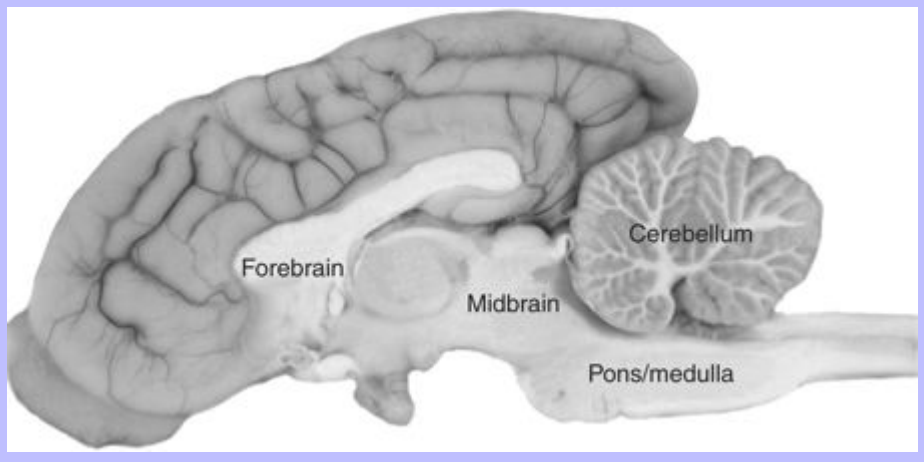
Because no asymmetry exists in the vestibular afferents, bilateral vestibular lesions do not produce the classic vestibular signs of nystagmus, head tilt, and circling. Instead the animal is wide based and apprehensive. It may hug the ground, refusing to move. Head movements are exaggerated. The doll's eye response is absent, and when blindfolded the animal has deficient righting responses.

The auditory portion of the eighth cranial nerve mediates hearing. Like vision, *hearing* refers to the conscious perception of a sensory stimulus and is assessed by observing the response to a noise such as clapping or a squeaky toy. When assessing the animal's ability to orient to a sound, it is important to avoid vibrations, shadows, or air currents that might provide a nonauditory cue. Animals with unilateral hearing loss may orient abnormally, turning away from a sound, but some can locate sound accurately even with unilateral hearing loss. The brain stem auditory evoked response (BAER) can detect unilateral damage to the cochlea or auditory pathways, but only a behavioral response truly tests hearing.

Swallowing entails coordination of the tongue, pharynx, larynx, and esophagus. The glossopharyngeal nerve (IX) and cranial branches of the vagus nerve (X) innervate the pharyngeal muscles and carry sensory information from the caudal tongue and pharynx. Damage to these nerves would affect the ability to swallow but not the ability to prehend food. Clinicians can use the gag reflex to assess pharyngeal function by placing the finger or a tongue depressor on the caudal aspect of the tongue. A normal animal will gag and swallow, whereas an animal with glossopharyngeal paralysis will not respond. An animal with unilateral damage may still be able to swallow, but it will choke, gag, or lose food through the nostrils. Regurgitation of swallowed food occurs with disorders of esophageal motility. The vagus nerve (X) is the major nerve of the esophagus. Contrast radiography may be necessary to evaluate esophageal motility.

Figure 191-9 Unilateral hypoglossal paralysis interferes with swallowing. The ipsilateral half of the tongue will atrophy, and the tongue will deviate. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).

Figure 191-10 For purposes of localization, the brain can be divided into four areas: the forebrain, midbrain, pons and medulla, and cerebellum. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).



The larynx is also innervated primarily by the vagus nerve (X) through the cranial and recurrent laryngeal nerves. Unilateral paralysis produces laryngeal hemiplegia and inspiratory stridor. Because the left recurrent laryngeal nerve follows a longer course through the thorax, that side is more susceptible to some disease processes, such as dying back neuropathies. Observing the movement of the vocal folds under light sedation will confirm paralysis. Voice change and dysphagia may also accompany laryngeal paralysis.

The spinal accessory nerve (XI) may contribute to some of the laryngeal and pharyngeal muscles, but it primarily innervates the trapezius, brachiocephalicus, and sternocephalicus. Denervation of these muscles is difficult to detect clinically.

The intrinsic and extrinsic muscles of the tongue are supplied by the hypoglossal nerve (XII). Unilateral damage will denervate the ipsilateral muscles and result in deviation of the tongue (Figure 191-9). Bilateral lesions abolish tongue movement, preventing normal prehension and swallowing.

191.1.2 Localizing the Lesion

Once a neurologic exam has been performed, that information is synthesized to localize the lesion. For localization purposes, the brain can be divided into four broad areas: (1) the forebrain (cerebrum and diencephalon), (2) the midbrain, (3) the pons and medulla, and (4) the cerebellum (Figure 191-10). It is often possible to further localize within these areas, but placing the lesion within one of the broad divisions is sufficient to have a reasonable list of differential diagnoses and diagnostic plan. When localizing the lesion, the first question the clinician must answer is whether the signs reflect focal, diffuse, or multifocal disease. A focal lesion is suspected if strong lateralization to the clinical signs occurs (e.g., circling, focal onset seizures, lateralized cranial nerve deficits). A focal lesion suggests localized damage to the brain as might occur from a neoplasia, vascular disease, or localized infection. A metabolic or toxic insult or a degenerative process would be expected to affect the brain more generally and not preferentially affect one side or the other. Although symmetrical forebrain signs suggest a diffuse disease process, they do not rule out focal disease. Focal disease can produce diffuse signs through mechanisms like obstructive hydrocephalus and increased intracranial pressure. Every effort should be made to explain the clinical signs based on a single lesion. If a single lesion cannot explain some signs; multifocal disease is suspected. For example, a single lesion cannot explain an animal that has both seizures (cerebral cortex) and unilateral facial palsy (medulla or facial nerve).

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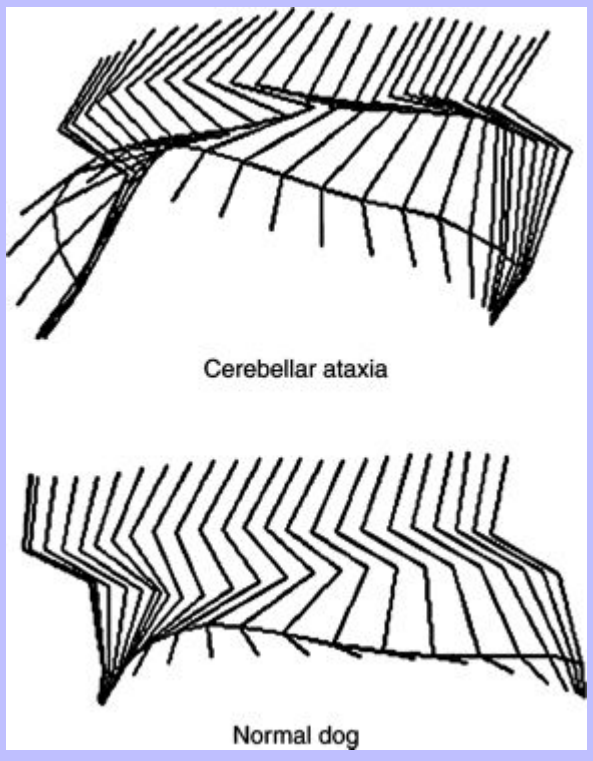
191.1.2.1 Cerebellum

The cerebellum receives input from higher motor command centers and sensory feedback from proprioceptive afferents and the vestibular system. It uses this information to coordinate movement and help maintain balance. The connections to and from the cerebellum via the cerebellar peduncles form a large part of the pons. A disease affecting the cerebellum or its peduncles will produce dysmetria, tremors, and vestibular signs. Dysmetria is most noticeable in the thoracic limbs as a goose-stepping gait (Figure 191-11) but will also be apparent as a wide base, truncal swaying, and exaggerated flexion of the pelvic limbs. The tremors of cerebellar disease are coarse tremors that disappear at rest. In acute cerebellar disease the tremors can be almost constant and the most dramatic manifestation of dysfunction. In more chronic disease, such as congenital cerebellar deficits, the tremors may be more subtle and only noticeable when the animal attempts to make a directed movement such as eating (intention tremors). The cerebellum works intimately with the vestibular system to control balance and eye movements. Lateralized lesions, such as in one cerebellar peduncle, can produce head tilt, imbalance, and horizontal or rotary nystagmus similar to a peripheral vestibular lesion. With cerebellar disease, the direction of the head tilt (away from the lesion) and nystagmus

(fast phase toward the lesion) are the opposite direction as in peripheral vestibular disease. This is referred to as *paradoxical vestibular syndrome*. With more diffuse disease of the cerebellum, a vertical nystagmus can be present as in central vestibular disease. In either case the animal may also lose its balance, especially in response to quick movements, such as shaking the head or sudden turns. Severe cerebellar lesions can produce decerebellate posturing, extension of neck, and thoracic limbs with flexion of the pelvic limbs. Because the menace response is a learned motor response and the cerebellum plays an important role in motor learning, animals with cerebellar disease may lose the menace response.

Figure 191-11 Lesions of the cerebellum disrupt the control of movement, resulting in dysmetria. This is most obvious as a goose-stepping gait in the thoracic limbs demonstrated by this stick figure representation of the limb in a Chinese crested dog with multiple system degeneration compared with a normal littermate. The line connecting the limb positions follows the trajectory of the carpus. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).



191.1.2.2 Pons and Medulla

The pons and medulla are the most caudal portions of the brain stem (Figure 191-12). The sensory and motor tracts of the spinal cord traverse these areas as well; thus lesions in this area can produce deficits in these long tracts similar to cervical spinal cord disease. Lateralization to the weakness or proprioception deficits would be common, and the side affected would depend on where the lesion was relative to the decussation of that particular tract. Because the respiratory centers reside in the medulla, an animal with a lower brain stem lesion producing complete paralysis would die from respiratory compromise. In addition to respiration, other autonomic centers reside in the brain stem, although clinical signs associated with their malfunction may not be as readily apparent.

Cranial nerve deficits are the signs that point most directly to a brain stem lesion. In isolation, such deficits could reflect a peripheral nerve lesion or small focal brain stem disease. Multiple nerve deficits or concurrent long tract signs (e.g., hemiparesis, proprioception deficits) point toward brain stem involvement. Cranial nerves V to XII arise from the pons and medulla. They all remain ipsilateral, and thus a lateralized deficit will be on the side of the lesion. The facial nerve (VII), vestibulocochlear nerve (VIII), and nerves controlling the pharynx, larynx, and tongue (IX, X, XII) run laterally from the brain stem out their respective foramina. Thus a lesion on the lateral aspects of the brain stem, such as a meningioma of the cerebellopontine angle, may affect combinations of these nerves (Figure 191-13). The trigeminal nerve (V) originates from the pons in close proximity to these nerves but runs rostrally to exit retrobulbar. The abducens nerve (VI) also runs rostrally from the medulla to innervate the lateral rectus and retractor bulbi muscles. A lesion produces a medial strabismus.

191.1.2.3 Midbrain

In addition to the nuclei of cranial nerves III and IV, the midbrain contains important motor nuclei and serves a major role in regulation of consciousness (Figure 191-14). The red nucleus is the origin of one of the major UMN tracts in quadrupeds, and damage to this nucleus in the midbrain will cause paresis or paralysis. Because the vestibulospinal tracts originate in the medulla and would be spared by a midbrain lesion, their excitatory effects on extensors of the limbs and neck would be unopposed by the normal inhibitory effects of the rubrospinal tracts. Thus midbrain lesions can produce decerebrate rigidity, a posture with dorsal extension of the neck and extension of the limbs. Because the respiratory centers reside more caudally in the medulla, the animal can continue to breathe even if completely paralyzed from a midbrain lesion. Conscious proprioception tracts must also course through the midbrain on their way toward higher centers. Thus deficits in postural reactions may be apparent with a midbrain lesion if the animal is still capable of voluntary movements.

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Figure 191-12 Lesion of the pons and medulla can affect cranial nerves V to XII, proprioception, and motor tracts. Severe lesions cause death by affecting respiratory centers. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).

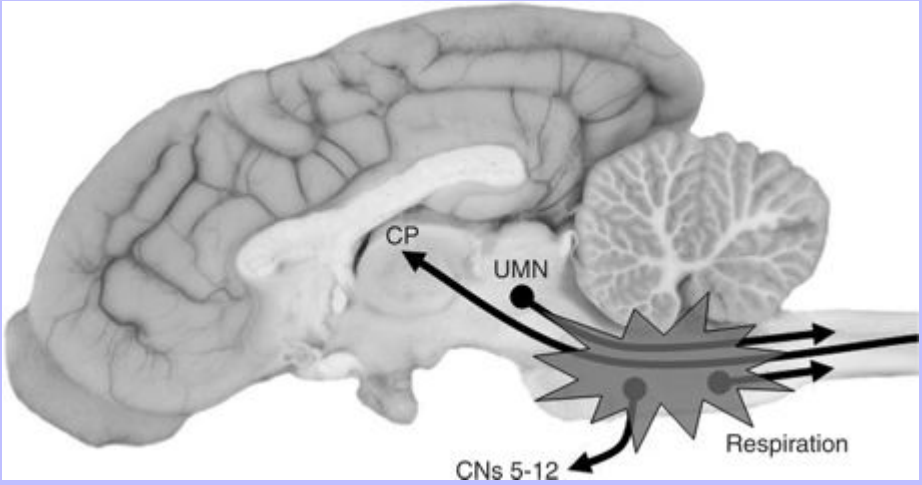
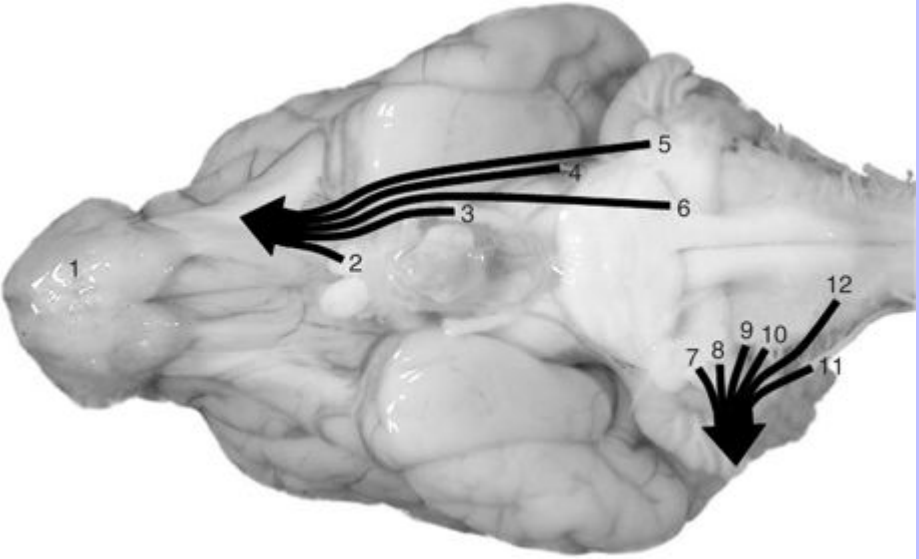
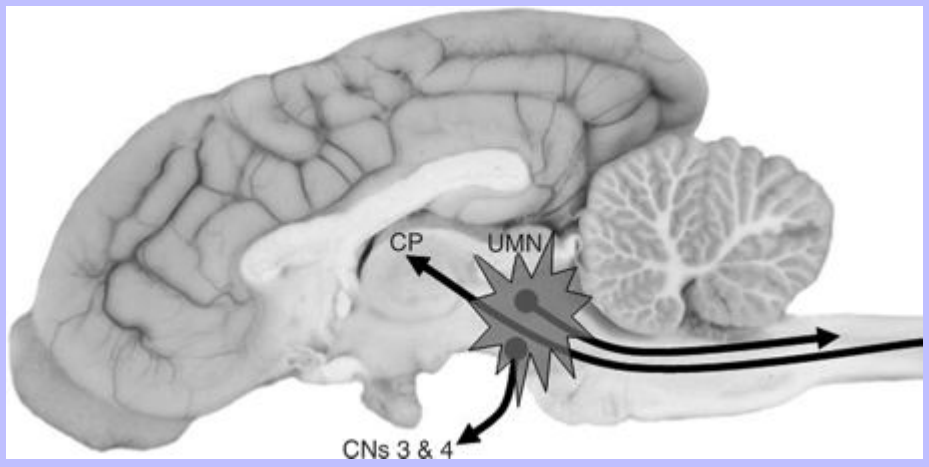


Figure 191-13 The cranial nerves form two anatomic clusters. Cranial nerves VII to XII run laterally from the brain stem and could be affected by a lesion such as a meningioma of the cerebellopontine angle. Cranial nerves II to V course rostral below the forebrain to exit in the retrobulbar area. Thus lesions in the cavernous sinus or retrobulbar area could affect combinations of these nerves. The olfactory nerve *(1)* crosses the cribriform plate and projects directly to the limbic areas. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).



Lesions below the midbrain may produce complete paralysis and respiratory compromise but may not directly alter consciousness or behavior. The midbrain marks the beginning of the reticular activating system (RAS), a group of loosely defined areas that project from the cranial pons, midbrain, and hypothalamus to the cerebral cortex and regulate consciousness and goal-directed behavior. Lesions of the midbrain will affect these functions (see following discussion).

Figure 191-14 Lesions of the midbrain affect cranial nerves III and IV. Damage to the origin of upper motor neurons (UMNs) in the red nucleus can lead to decerebrate rigidity and damage to the reticular activating system (RAS) will affect consciousness. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).



The trochlear nerve (IV) innervates the dorsal oblique muscle. Deficits result in outward rotation of the eye and, because the trochlear nerve is the only cranial nerve to completely decussate, a midbrain lesion will produce strabismus in the contralateral eye. In animals with round pupils such as the dog, this can only be detected by looking at the orientation of the vessels in the fundus. Because the trochlear nerve will seldom be damaged without affecting other cranial nerves, this is usually not an issue. The oculomotor nerve (III) innervates the remaining extraocular muscles. Damage results in ventrolateral strabismus and loss of the normal doll's eye response in the ipsilateral eye. The third nerve also contains the parasympathetic fibers to the pupil. Damage to these fibers will produce mydriasis and loss of the PLR, although vision is unaffected.

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191.1.2.4 Forebrain

The forebrain encompasses the cerebral cortex, basal nuclei, thalamus, and hypothalamus. These areas mediate higher brain functions such as personality and learned behavior, motor planning, sensory processing, and emotional, endocrine, and autonomic functions, respectively. The olfactory (I) and optic (II) nerves are also primarily forebrain nerves. All the nerves of the eye and extraocular muscles (II, IV, VI), along with the trigeminal nerve (V), course rostrally along the floor of the calvarium to exit through their retrobulbar foramina. Thus a lesion in the area of the cavernous sinus may produce deficits in combinations of these nerves and affect the overlying forebrain. These nerves can also be affected after they exit the calvarium by retrobulbar lesions.

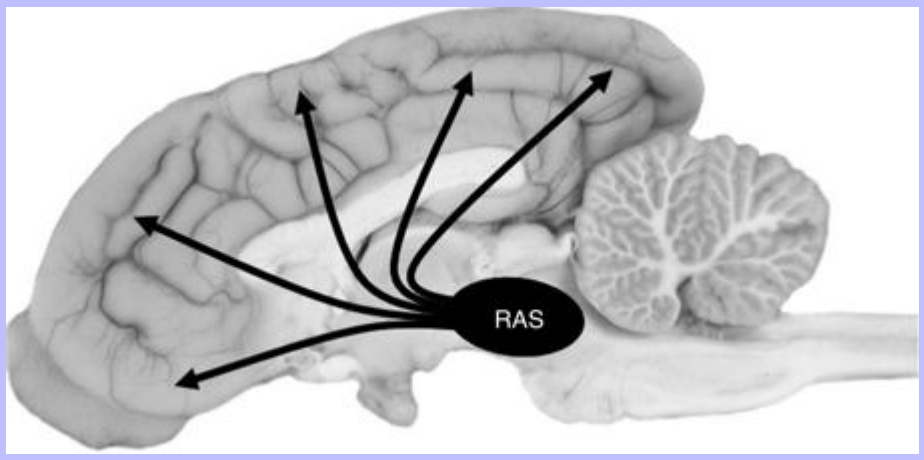
Although the pupilomotor fibers of the optic nerve project to the midbrain to control the PLR, the main projection of the optic nerve to the forebrain mediates vision. Lesions of the optic tract, lateral geniculate

nuclei, or occipital lobes can produce a loss of vision with normal PLR (central blindness). If unilateral, the vision loss is limited to the contralateral visual field.

In addition to vision, other sensory modalities such as conscious proprioception or hearing are relayed through the thalamus to the appropriate area of the cerebral cortex. Thus the ability of the animal to respond meaningfully to a sensory stimulus may be disrupted by lesions of the appropriate thalamic nuclei or region of the cerebral cortex. Like the PLR, some other simple responses such as the startle response to a loud noise or the dazzle response to a bright light are mediated at a subcortical level. Vision appears to be the most sensitive to diseases such as hypoxia that diffusely affect the forebrain. The olfactory nerve projects directly to the olfactory bulbs and from there to the limbic areas of the forebrain, thus bypassing the thalamus. Olfactory deficits, however, are difficult to detect in animals.

The hypothalamus controls endocrine function through the pituitary gland. It also regulates a variety of other homeostatic functions such as body temperature, osmolality, and autonomic functions. Together with limbic areas, the hypothalamus is also involved in learning and memory, goal-directed behaviors, and emotions.

Figure 191-15 The nuclei of the reticular activating system (RAS) in the rostral brain stem project to the cerebral cortex and regulate attention and goal-directed behavior. Lesions of either the cortex or the RAS can affect consciousness. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).



Epileptic seizures are caused by abnormal electrical activity in the cerebral cortex; thus they should be considered an unambiguous sign of forebrain disease. Either focal damage to the cortex or diffuse metabolic effects can produce seizures (see Chapter 48).

Alterations of consciousness and behavior are hallmarks of forebrain disease. The traditional view of regulation of consciousness is that the RAS in the brain stem projects to the cerebral cortex and “activates” it to produce normal consciousness (Figure 191-15). This concept is useful when considering causes of stupor

and coma. Such profound alterations of consciousness can result from either a lesion in the brain stem affecting the RAS nuclei, the projections pathways of these systems toward the cortex, or diffuse disease affecting the cerebral cortex. Lesions of the brain stem caudal to the RAS can render the animal quadriplegic without necessarily disrupting consciousness.

The function of these RAS systems, however, is more complex than just turning on or off the cerebral cortex. Different nuclei and neurotransmitter systems are responsible for different aspects of attention, arousal, and goal-directed behavior. One of the main projections from the RAS nuclei to the cerebral cortex is the medial forebrain bundle—a tract running from the midbrain through the lateral hypothalamus to project diffusely to the cortex and limbic forebrain. Brain damage can lead to complex behavioral abnormalities, which are a manifestation of functional subsystems of behavior operating without direction toward a goal.[1,2]

Sensory neglect refers to a loss of meaningful response to stimuli in multiple sensory modalities without a lesion in the classic sensory pathways or a significant depression of consciousness. With unilateral lesions of the medial forebrain bundle or cerebral hemisphere, these signs can be limited to one side (hemineglect or hemi-inattention).[3] Unilateral loss of hearing and proprioception with tumor of the medulla would not fit the definition of hemineglect. The classic sensory pathways are affected in this example, and other sensory modalities, such as vision, are unaffected. Likewise, a comatose animal has simply severely altered consciousness and not neglect.

Hemineglect provides the most interesting illustration of the difference between sensory neglect and loss of consciousness or classic sensory or motor pathway lesions. The decussation of sensory and motor pathways means that all sensory information originating from the right half of the animal's perceptual world goes to left forebrain, and all control of motor activity directed toward the right side of that world originates from the left forebrain. The reader should note that this motor control extends beyond simply control of the right limbs. The activation of the left cortex is necessary for the animal to direct its attention and behavior toward the right half of the world (Figure 191-16). Thus a unilateral lesion may be immediately apparent as a tendency to circle (Figure 191-17). Such circles can be large, wandering circles where turning only occurs when the animal reaches a corner or other obstacle that requires a decision. Because all their attention is directed toward the side of the world associated with the functional cortex, they orient and turn in that direction (i.e., they circle toward the side of the lesion).[1,4]

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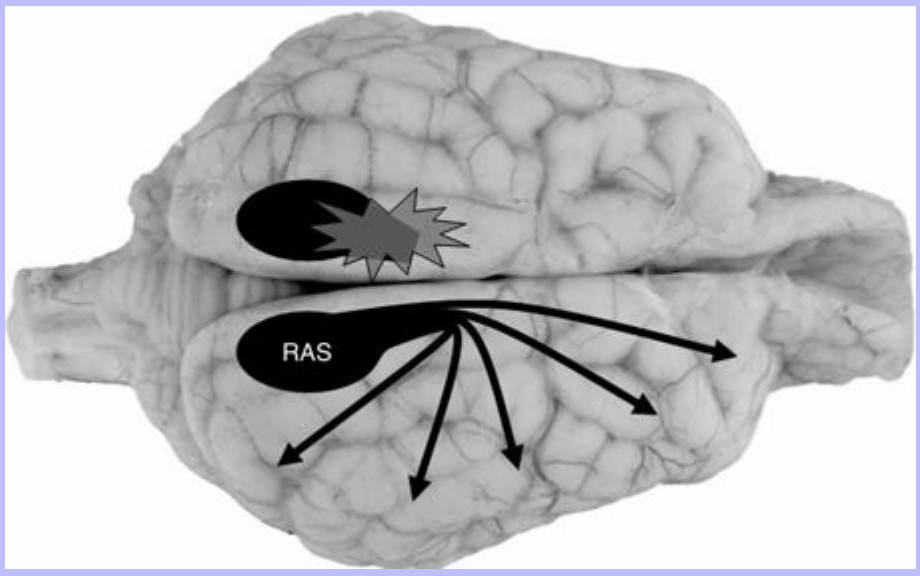
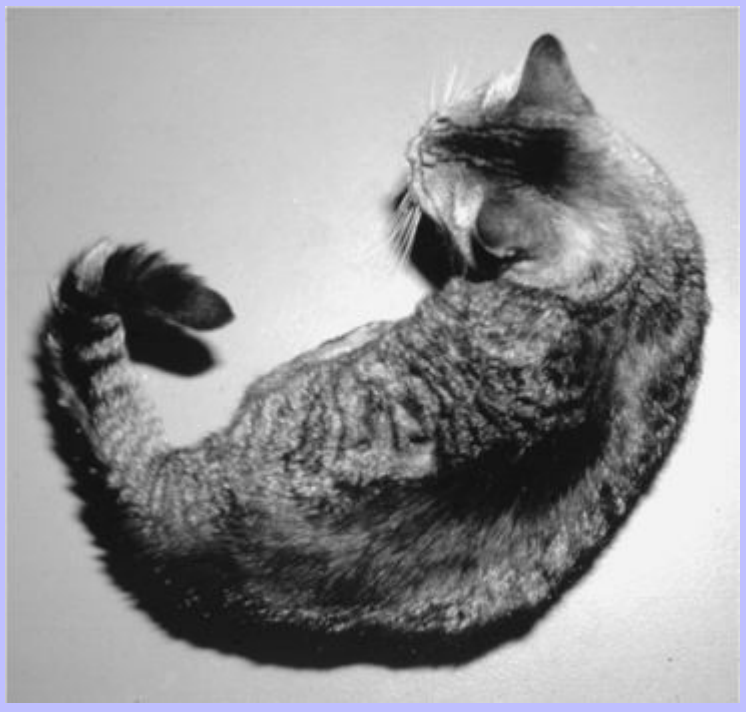
Figure 191-16 The RAS nuclei project to the ipsilateral cortex. A focal lesion of the RAS or diffuse cortical disease on one side will produce hemineglect. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).



Conversely, they neglect all sensory information arising from the side contralateral to the lesion. They do not track cotton balls or menace in the contralateral visual field. They have deficient conscious proprioception and postural reactions on that side. They do not orient to sounds in that direction but may turn a circle in the opposite direction to localize the sound. Noxious stimuli may produce arousal, but no meaningful behavior (e.g., biting the clinician) will be directed toward the source of the pain.[1,4,5]

Figure 191-17 With forebrain lesions the animal may curl and circle toward the side of the lesion. In contrast to vestibular disease (see Figure 191-4), the ears are level but the nose is pulled around toward the flank (adversion). (From O'Brien DP: Circling. In August JR, editor: *Consultations in feline internal medicine*, Philadelphia, 1994, WB Saunders Co, p 449.)



In humans the difference between neglect and simple sensory deficits is readily illustrated by asking the patient to perform tasks such as drawing a picture (they would only draw the half corresponding to the functional half of the brain).[3] In animals this splitting of the world into neglected and normal halves is most apparent at feeding time. A hungry animal with sensory neglect will eat the food from half the food bowl (Figure 191-18). Olfactory inputs would tell them that food is around, but they will not eat from the neglected half because they cannot direct their attention toward that side of the world.[1,4,5]

The red nucleus in the midbrain is responsible for generating the gait in quadrupeds, and the corticospinal system is less important than in humans. Postural reactions require forebrain control and may be deficient, but an animal with bilateral forebrain damage that is not severe enough to produce stupor may still be able to walk relatively normally. The walking, however, may not be directed toward any meaningful goal; instead the animal may pace aimlessly. As in the hemineglect cases, it may not respond to sensory stimuli. In the extreme case, it will not even be aware of the fact that it has walked into a corner and will continue to push forward, head pressing against the corner.

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Figure 191-18 An animal with hemineglect will eat the food from half the food bowl. Even though still hungry, the dog cannot direct its attention toward the food contralateral to the lesion. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).

Forebrain lesions disrupt higher control, releasing some subcortical behaviors from their normal regulation.[2] For example, dogs and cats have a bite reflex whereby they will turn and snap at anything that touches them around the mouth. Normally this reflex is regulated by higher centers, activated when needed, such as in a fight, and inhibited when not needed, as in nuzzling the owner. Like a spinal reflex, it can be exaggerated when released from inhibition, and the animal with forebrain disease may snap without warning or emotion when touched around the mouth. In contrast to sensory neglect, where the animal ignores all stimuli, some brain-damaged animals develop magnet responses, whereby they compulsively orient and move toward a stimulus. These orienting responses are subcortical responses released from normal forebrain control and become autonomous. Emotional responses such as rage or fearfulness are also subcortical, and it is not unusual for a demented animal to respond excessively (e.g., when restrained).

Many behaviors such as sleeping and feeding are goal-directed behaviors that can be disrupted by forebrain disease. The same way the animal cannot direct its attention toward external stimuli, it cannot respond to internal needs to accomplish these behaviors. Thus it may be insomniac or anorexic.[1,2] Learned behaviors, such as tricks or housebreaking, may also be lost with forebrain disease. The micturition response is mediated in the pons, thus the animal is able to empty its bladder but is unable to regulate when micturition occurs.

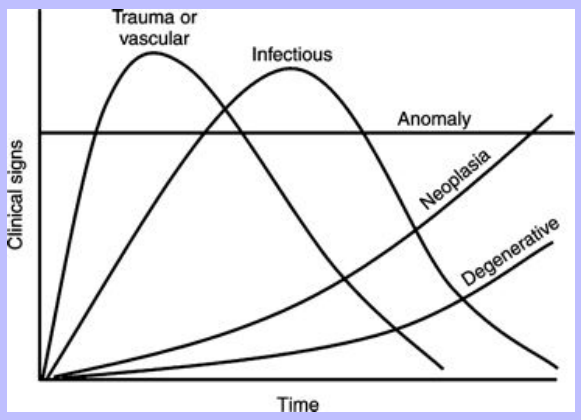
191.2 DIFFERENTIAL DIAGNOSES

Once the lesion has been localized, a list of differential diagnoses can be generated and a diagnostic plan developed. The signalment provides the first clues to organizing the differential list. Congenital and hereditary diseases will be much more frequent in young, purebred animals. Although infectious diseases, traumatic injury, and toxicities can occur anytime, young animals are more likely to be affected. Some diseases, such as idiopathic epilepsy, will have their onset in young adulthood. With increasing age neoplasia, metabolic encephalopathies, and degenerative diseases become increasingly common. Breed predilections are most noticeable in hereditary diseases. Tables of breed predilections are available.[6,7]

Onset and progression of signs is the other important clue to ordering the differential diagnosis list (Figure 191-19). A congenital malformation would be present from birth and relatively static, although some, such as hydrocephalus, could progress over time. An acute onset of signs would be expected with vascular disease, trauma, most toxins, and many infectious, inflammatory, and metabolic diseases. Some infectious and inflammatory or metabolic diseases will be chronic and progressive, as will most neoplastic or degenerative conditions.

Finally the neurologic exam will suggest the type of disease process. Some diseases will have predilection for specific parts of the brain (see following discussion). Generally, lateralized neurologic signs such as circling, hemiparesis, or unilateral cranial nerve deficits suggest a localized disease process such as an infection, vascular disease, neoplasia, or traumatic injury. Likewise, focal onset seizures would suggest localized cortical damage, although idiopathic epilepsy can rarely produce focal seizures.[8,9] Infectious and inflammatory, vascular, or metastatic neoplasia would be the most likely to produce multifocal signs. A metabolic or toxic insult should not affect the brain asymmetrically, and diffuse, symmetrical signs would be expected. Because the cerebral cortex is the most metabolically demanding part of the brain, forebrain signs tend to predominate. As discussed in the introduction, however, a localized disease process can result in diffuse forebrain signs through increased intracranial pressure.

Figure 191-19 The progression of signs over time provides important clues to the underlying cause. A mental "sign-time graph" can help to categorize diseases. (From Lorenz M, Kornegay JN: *Handbook of veterinary neurology*, ed 4, Philadelphia, 2004, WB Saunders Co.)



191.3 DIAGNOSTIC APPROACH TO BRAIN DISEASE

When considering the diagnostic approach to diseases affecting the brain (Figure 191-20), the clinician must weigh cost, availability, risks, and potential yield. The value of a thorough history and neurologic examination should never be underestimated. Even if advanced imaging reveals a clear lesion, if that lesion does not correspond to the localization on the neurologic examination, its significance needs to be questioned.

Routine clinical pathology is the most readily available, most cost-effective, and least invasive procedure. Even though the yield may be low with focal disease, it is still an important minimum data base for any ill animal, and in cases with diffuse disease, ruling out a metabolic cause is essential. A complete blood count (CBC) may suggest infectious causes and provide clues to other causes. It is important to recognize, however, that a normal blood count does not rule out encephalitis as a cause. Serum biochemistry profile and urinalysis will be essential to rule out energy deficiencies, electrolyte disturbances, or accumulation of endogenous toxins. Particularly with diffuse forebrain signs or seizures, a liver function test such as bile acids or ammonia tolerance should be included. If inborn errors of metabolism are suspected, urine assays for abnormal metabolites may be necessary. Assays for specific exogenous toxins, such as lead or organophosphates, may be indicated if signs and history suggest likely candidates, but a screen for all possible neurotoxins is not feasible. Because neurologic signs can accompany endocrine diseases such as hypothyroidism and hyperadrenocorticism, endocrine function tests should be considered if the clinical signs and signalment warrant. Thoracic and abdominal imaging will be important, particularly in geriatric animals, to rule out metastatic or cardiac disease.

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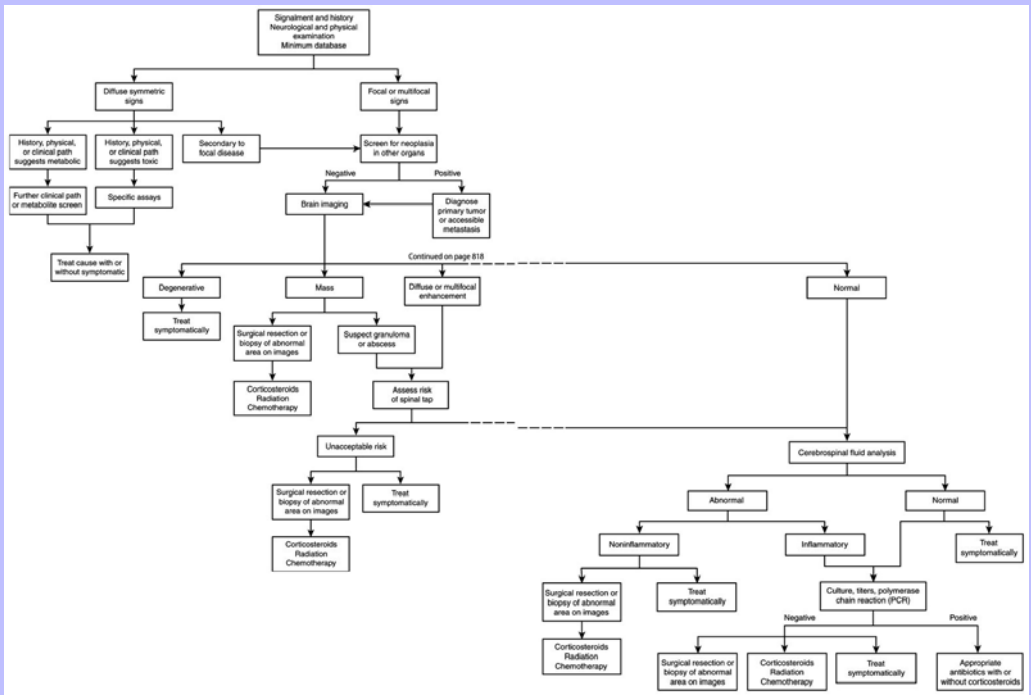
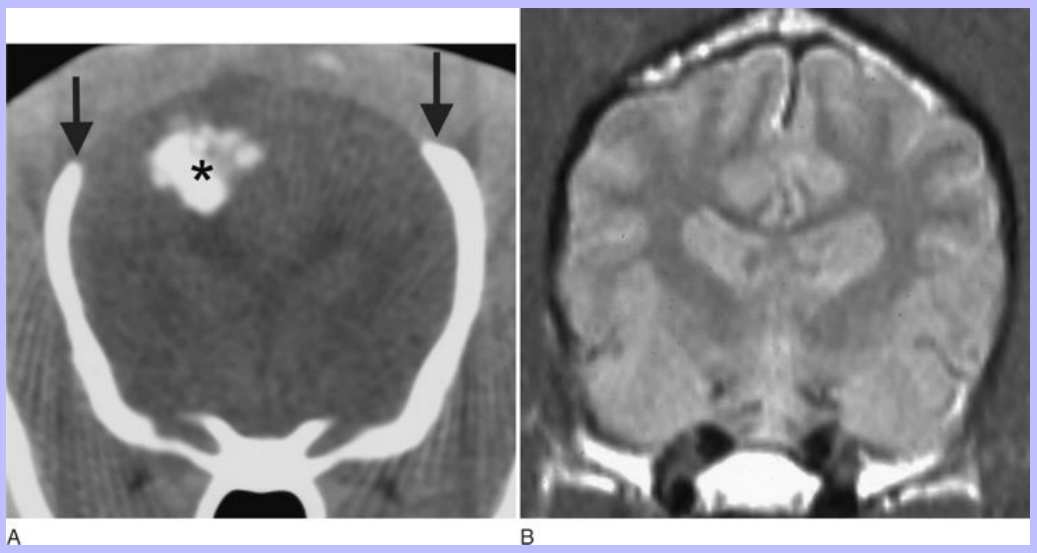
Figure 191-20 Diagnostic approach to brain disease.



The increasing availability of advanced brain imaging techniques for animals has revolutionized the practice of neurology. Although advanced imaging is expensive, the high return usually justifies the expense. Routine skull radiographs are of very limited value in diagnosing brain disease, because only the skull can be imaged without invasive contrast studies. The superimposition of the structures on radiographs makes interpretation difficult. Ultrasound imaging of the brain, although useful, is only an option when an open fontanelle or craniotomy provides an acoustic window.

Computed tomography (CT) and magnetic resonance imaging (MRI) allow detection of structural changes of the brain itself (Figure 191-21).[10,11] CT is more readily available and less expensive. CT relies on traditional radiographic principles; thus the image consists of similar graded densities, with bone being white and air black. The attenuation of the x-rays will be similar to that of the gamma rays used in radiation therapy, so CT images are used to calculate dose delivery. Only cross-sectional images are acquired, although computer reconstructions can generate sagittal or dorsal planes. CT has the advantage of being able to image bone, which is useful in diseases such as osteochondrosarcomas of the skull. The ventricular system is readily appreciated on CT, but fine anatomic detail is often not visible. Edema may be visible as a reduced density of the parenchyma, whereas other processes, such as acute hemorrhage or calcification, produce an increased density. CT resolution is limited by the attenuation of the x-rays by the surrounding skull. The petrosal bones at the base of the skull are dense, thus limiting the quality of CT images of the area below the tentorium.

Figure 191-21 **A,** Computed tomography (CT) scans are more readily available and can image many intracranial diseases. Bone is readily visible as in this recurrent osteochondrosarcoma *(asterisk)* after a prior craniectomy *(arrows)*. **B,** Magnetic resonance image (MRI) provides much greater detail, especially in the caudal fossa. This proton density image of normal brain clearly delineates gray and white matter.



MRI uses magnetic resonance of charged particles to generate radio waves that can then be detected and reconstructed into an image in any plane desired. The MRI unit generates a large magnetic field through the brain, which aligns charged particles with the field. It then conducts a sequence of radio wave pulses through the brain while a radio frequency detector listens for the echo from the interaction of those pulses with the charged particles and the magnetic field. The hydrogen ion (proton) generates a large portion of the radio wave signal in most MRI sequences, and because water contains a high proportion of free protons, the MRI can be thought of as imaging free water content. This is particularly useful in the nervous system, where marked differences exist in water density between gray matter, white matter, edema, and the ventricular system. In contrast, bone generates little signal. By altering the sequence used, different weight is given to the signals producing different contrasts between the tissues. In a T1-weighted image, water in the ventricular system is black and white matter is light, whereas in a T2-weighted image, the ventricles appear white and the white matter dark. Edema is readily apparent as an increase signal on T2 images. An in-between sequence (proton density) decreases the contrast between the ventricles and the brain, but increases contrast between gray and white matter, revealing fine anatomic detail. More advanced techniques such as FLAIR (fluid attenuated inversion recovery), MRI spectroscopy, and MRI angiography can also be useful for special applications. One disadvantage of MRI is that it cannot be used when metal implants are present.

For both CT and MRI, the initial evaluation is for differences in density and signal in the brain parenchyma, which may be readily apparent as asymmetry. Even without clear differences within the parenchyma, a mass effect may produce a shift of the midline structures or distortion of the ventricles. Contrast agents are available for both imaging modalities. After IV injection, the blood-brain barrier would normally exclude such agents from the brain. Breakdown of this barrier by neoplasia or inflammation will result in accumulation and contrast enhancement of the lesion. Contrast enhancement is most apparent on the T1-weighted MRI.

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Although advanced imaging may provide an unprecedented view of the nervous system, it still may not provide a definitive diagnosis. Brain biopsy is not commonly used as a diagnostic procedure in veterinary medicine, except when accompanying tumor resection. Imaging-guided biopsy techniques will decrease the morbidity associated with biopsy and increase the availability.

Because a mass lesion producing increased intracranial pressure significantly increases the risk of complications of a spinal tap, imaging should be recommended before performing the tap. The CSF is most useful in inflammatory disease but can provide clues to other diseases such as an increased protein with neoplasia. In some cases, such as cryptococcosis, the organism may be found in the CSF. More commonly, the CSF simply confirms inflammation in the central nervous system (CNS). Then auxiliary tests are necessary to make the definitive diagnosis. Cultures of the CSF are rarely positive, but the importance of ruling out a treatable condition warrants the expense if the CSF analysis, and signs are compatible with bacterial meningoencephalitis. Most infectious diseases will be identified by titers on the serum, CSF, or both. Although some titers such as the antigen titer for cryptococcosis are highly reliable, most are highly subjective. It is hoped that the increasing availability of PCR testing for infectious agents will relieve the problems clinicians have interpreting titers.

Electrodiagnostic tests allow functional testing of the nervous system. The electroencephalogram (EEG) is used primarily to confirm epileptic activity in the brain in suspected seizure cases. It is particularly useful in cases of status epilepticus to confirm that seizure activity has been stopped. The brainstem auditory evoke response (BAER) is used primarily to assess cochlear function, but can also assess brain stem conduction. Somatosensory and visual evoked potentials can assess function of these systems.

Response to therapy can be an important diagnostic tool, particularly when financial or other factors limit the diagnostic tests pursued. Therapy for the most likely treatable condition can be instituted and the response

monitored. For example, dramatic improvement with doxycycline would support a presumption of rickettsial disease. Although corticosteroids play an important role in treating brain disease, the risks of side effects, including exacerbation of an infectious disease, need to be weighed carefully. Dramatic improvement with corticosteroids would be consistent with a neoplasia or infectious and inflammatory disease. Improvement with neoplasia is usually short-lived because it relieves the peritumoral edema but does nothing about the neoplasia. Some inflammatory disease may be kept in remission with prolonged treatment. Infectious diseases will also often respond dramatically to corticosteroids, only to worsen if appropriate antibiotics are not also instituted. Response to anticonvulsant drugs helps to confirm a seizure disorder but does not rule out an underlying cause to the seizures.

191.4 PRIMARY BRAIN DISEASES

The brain is the most metabolically demanding organ in the body. A large portion of the body's energy supply goes toward maintaining resting membrane potentials and neurotransmission. The nervous system has more limited energy metabolism pathways than other tissues; thus it is more sensitive to disturbances of glucose or oxygen supply. The brain is also quite sensitive to exogenous or endogenous toxins. The higher the level of function of a portion of the nervous system, the more sensitive it tends to be to metabolic insults. Thus forebrain signs are a common manifestation of systemic diseases. The brain can also be affected in disease processes such as infections, most of which are multifocal in nature (discussed in Chapter 192). This chapter will focus on diseases that primarily affect the brain and are not covered in other chapters. They are organized roughly by typical age of onset.

191.4.1 Congenital and Hereditary Diseases

Congenital refers to any disease or malformation present at birth. It encompasses both genetic conditions and the results of external influences during gestation such as toxins, malnutrition, birth trauma, or infections. If more than one individual in a family is affected, then the condition is familial. However, a familial disease does not necessarily have to be genetic, because families may share some things (e.g., diet, environment, infection exposure). Breed predilection for a disease suggests a genetic contribution, but again, could reflect other factors such as the typical use of a particular breed or supplements in vogue with those breeders. Multiple litters must be evaluated before any estimate of genetic contribution to a disease can be formulated. Many hereditary neurologic diseases will be congenital or at least apparent at an early age, but notable exceptions exist. Some lysosomal storage diseases require time for accumulation of byproducts. Animals with hereditary cerebellar ataxia (abiotrophy) may be normal clinically and histologically for a variable period of time and then develop clinical signs as the Purkinje cells undergo premature cell death. Finally some, like idiopathic epilepsy or ceroid lipofuscinosis (CL) will not show signs until early or even late adulthood.

Most hereditary disease will be due to autosomal recessive traits or have a complex inheritance, because dominant traits can be eliminated from a breed by simply not breeding affected dogs. The nervous system is especially sensitive to genetic disease. Many genes are expressed for brief periods to appropriately direct the complex development of the nervous system. Because few neurons are capable of reproducing after maturity, defective neurons cannot be replaced. Mutations that interfere with the ability of the cell to deal with insults such as oxidative stress can lead to accumulated damage and early onset of degeneration.

191.4.1.1 Congenital Malformations

Congenital malformations of the brain would typically be present from birth and be nonprogressive. A few exceptions, such as congenital hydrocephalus, can manifest later in life with progressive signs. The nervous

system originates from a plate on the dorsal surface of the embryo, which folds in to form the neural tube. This infolding begins in the thoracic area and extends rostrally and caudally. Genetic defects and in utero infection, toxins, or malnutrition may cause failure of normal closure of the neural tube, which is typically manifested at rostral or caudal end of the developing nervous system. These malformations can range in severity from complete failure of cerebral development (anencephaly) to clinically unapparent malformations such as agenesis of the corpus callosum. Typically the effects are most apparent in the midline structures. In some cases, concurrent malformation of overlying tissues allows protrusion of meningeal or brain tissue through the defect.[12] Severe malformations will be apparent on physical exam, whereas brain imaging or postmortem examination may be necessary to detect more subtle deficits. Brain anomalies may accompany other defects such as cleft palate or cardiac anomalies.

Once the neural tube has formed, differentiation of the various parts of the brain occurs and can be disrupted by similar genetic or environmental influences. Migration of neurons within the cerebral cortex leads to the characteristic sulci and gyri and the normal laminar arrangement of neurons within the cortex. In lissencephaly, this normal migration is disrupted (Figure 191-22). Some, or all, of the surface of the cortex is smooth and abnormally thickened (pachygyria), which can be visualized on MRI. In humans a variety of mutations have been associated with lissencephaly, and a genetic cause is suspected in dogs because it has been recognized primarily in Lhasa apsos.[12–14] Affected dogs showed behavioral changes, vision deficits, and seizures.[13,14] Excessive production of small gyri (polymicrogyria) has also been reported.[12] In other conditions the gross structure of the brain is normal, but the laminar arrangement of neurons and white matter within the cortex is disrupted, leading to abnormally placed nests or rows of neurons. Such dysplasia has been observed in the cerebellar cortex but was associated with severe motor problems, suggesting that more than cerebellar function was disrupted even though dysplasia was not apparent in other areas.[15]

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Figure 191-22 The lack of normal gyri in lissencephaly could be visualized with magnetic resonance imaging (MRI). Like most congenital anomalies, signs are present from birth and are static.

Cerebellar hypoplasia is seen most commonly in cats after in utero or early neonatal infection with the feline panleukopenia virus. The rapidly multiplying granule cells of the cerebellum are sensitive to damage by the virus at this stage of development.[12] Although apparently much less common, evidence indicates that canine parvovirus infection can produce similar damage to the developing cerebellum of dogs.[16] Cerebellar hypoplasia can also occur as isolated malformation without evidence of infection or as part of a more generalized brain development abnormality. The Dandy-Walker syndrome of humans is characterized by agenesis of the cerebellar vermis. A similar malformation has been described in dogs and cats.[12]

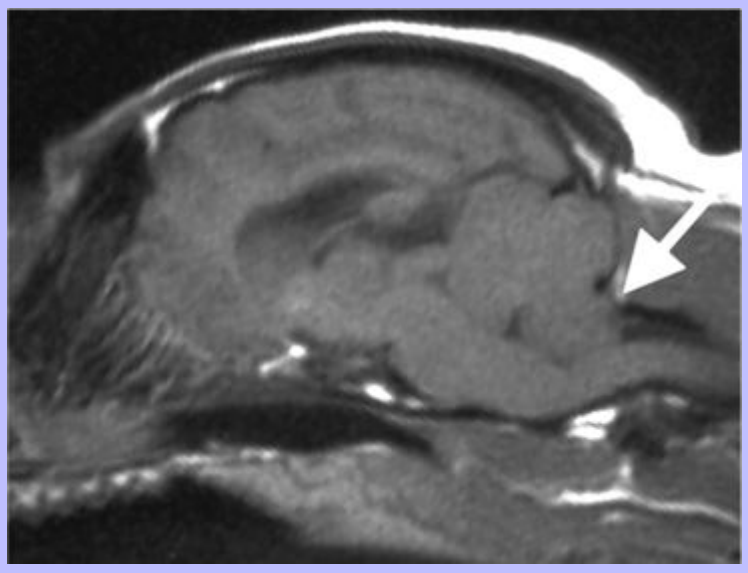
For most congenital malformations, treatment is symptomatic and the prognosis will depend upon the severity of the neurologic deficits. History and serology can rule out toxic or infectious causes that may potentially be treatable. Genetic and nutritional counseling may help prevent future occurrences in breeding kennels.

191.4.1.2 Chiari-like Malformations

Signs associated with abnormal conformation of the foramen magnum and cerebellar vermis were described as early as 1965 but were initially attributed to an enlargement of the dorsal aspect of the foramen (occipital dysplasia).[17,18] Subsequently it was demonstrated that a great deal of variation exists in the dorsal extent of the foramen magnum in normal dogs.[19] With the advent of MRI it became easier to image this area of the brain and spinal cord, and a malformation of the cerebellum similar to the Chiari type I malformation of humans was identified in the Cavalier King Charles spaniel, other dog breeds, and a cat.[20-22,22A] The Chiari type I malformation consists of an elongation of the caudal, ventral cerebellum through the foramen magnum, and in humans it is thought to be the result of small caudal fossa (the area caudal to the tentorium) crowding the enclosed structures. In addition to compressing the medulla, the herniated cerebellum obstructs normal outflow of CSF from the calvarium that can lead to secondary hydrocephalus. As the brain expands with each heart beat, the herniated cerebellum is forced caudally, generating pulsatile compression of the cervical spine. This leads to syringomyelia of the cervical spinal cord.[23] In addition to those referable to hydrocephalus and cerebellar compression, clinical signs include cervical myelopathy signs: ataxia, proprioception deficits, weakness, and cervical pain. The malformations appear to create paraesthesias, and excessive scratching of the ear, neck, or shoulder may be the major presenting complaint.[22]

The Chiari-like malformation also referred to as caudal occipital malformation syndrome,[22A] is readily diagnosed on a midsagittal MRI on which the herniation of the cerebellum and any concurrent hydrocephalus or syringomyelia can be visualized (Figure 191-23). Although some improvement can be achieved with antiinflammatory drugs and rest, definitive treatment consists of enlarging the foramen magnum via a suboccipital craniectomy and resecting any dural bands that are constricting the cerebellum. Sometimes the herniated portion of the cerebellum should be removed as well. With the improved CSF dynamics after such decompressive surgery, the hydrocephalus and syringomyelia may resolve.

Figure 191-23 Midsagittal magnetic resonance image (MRI) of a Cavalier King Charles spaniel showing protrusion of the cerebellar vermis through the foramen magnum *(arrow)* similar to the Chiari type I malformation in humans.



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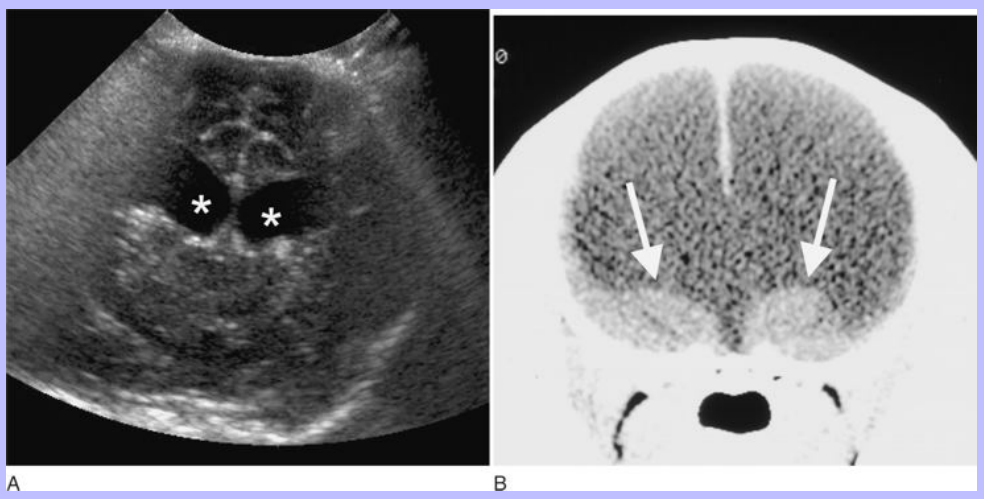
191.4.1.3 Hydrocephalus

Hydrocephalus can be either congenital or acquired. It can also be categorized as either obstructive or communicating. Obstructive hydrocephalus occurs when a blockage occurs in the flow of CSF through the ventricular system. The obstruction typically occurs at the bottlenecks of CSF flow, the connection between the lateral ventricle and the third ventricle (the intraventricular foramen), or the connection between the third and fourth ventricle (the mesencephalic aqueduct). Obstruction of one intraventricular foramen will result in unilateral dilation of the lateral ventricle. With obstruction of the mesencephalic aqueduct, both lateral ventricles and the third ventricle will dilate. Obstructive hydrocephalus is acquired when a disease process such as neoplasia, hemorrhage, or inflammation occludes the pathway. In communicating hydrocephalus, no obstruction to flow is seen and all of the ventricular system dilates. Such diffuse dilation can be seen when absorption of CSF from the subarachnoid space into the venous drainage is impeded (e.g., by inflammation or neoplastic infiltrates in the meninges). The ventricles will also dilate in response to atrophy of surrounding brain tissue and is called *compensatory hydrocephalus* or *hydrocephalus ex vacuo*.

In spite of the fact that congenital hydrocephalus is common in some breeds, little published research exists on the condition in animals. It is occasionally seen in conjunction with other congenital problems such as Chiari-like malformations[22] or cerebellar ataxia in bull mastiffs,[24] but it most commonly occurs as an isolated finding. Toy and brachycephalic breeds appear to be at highest risk for the disease.[25] In some cases a congenital stenosis or aplasia of the mesencephalic aqueduct exists.[12] Neonatal infections, such as parainfluenza virus in dogs, can result in stenosis without leaving any indications of the cause once the initial

ependymitis has resolved.[26] The strong breed predilection, however, suggests a hereditary basis in many of these dogs. Congenital hydrocephalus can lead to an enlarged calvarium and failure of normal closure of the suture lines of the skull. A small open fontanel is common in many toy breeds and does not necessarily indicate hydrocephalus.

Figure 191-24 **A,** Ultrasound can be used to image dilated ventricles *(asterisks)* if an open fontanel provides an acoustic window. **B,** Otherwise magnetic resonance imaging (MRI) or computed tomography (CT) scan is necessary. Some severe hydrocephalics may show minimal signs. The dog in **B** had minimal forebrain tissue left on CT scan *(arrows)*, yet the only complaint of the owners was irritability and polydipsia and polyuria. After a fall the dog developed adipsia and hypernatremia, which prompted referral.



Clinical signs of hydrocephalus include behavioral changes, ataxia, and seizures. A ventrolateral strabismus is common in congenital hydrocephalus, but it is not clear whether this is due to cranial nerve compromise or malformation of the skull. Lateralized signs such as circling will be evident with obstruction of the intraventricular foramen causing dilation of one lateral ventricle. Even in congenital cases, the disease may follow a waxing and waning course. Sometimes dramatic hydrocephalus may be present, and the owners report few clinical signs other than slowness to learn. Increased intracranial pressure can lead to tentorial herniation, particularly in acute, obstructive hydrocephalus.

The EEG may show a characteristic pattern of high-voltage synchronous activity, but imaging the dilated ventricles is necessary to confirm the diagnosis. If a large fontanel is present, the ventricles can often be adequately imaged with ultrasound. If not, then CT or MRI will be necessary to image the dilated ventricles and rule out obstructive disease (Figure 191-24). Normal ventricle size is 1.5 mm; anything exceeding 3.5 mm is considered to be characteristic of hydrocephalus.

The ideal treatment for hydrocephalus is to place a shunt into the dilated ventricle and drain the excess CSF into the peritoneal cavity. This may be indicated to relieve pressure even if a treatable condition is causing the hydrocephalus. A special valve is necessary to prevent excessive drainage of CSF (which could lead to collapse of the overlying cerebrum and subarachnoid hemorrhage) and to prevent pressure in the abdomen during coughing or exertion from being transmitted to the ventricles. Complications such as infection or occlusion of the shunt are common, and only a few centers perform this operation. Another mode of surgery is to enter the skull from above, open the third ventricle, and then fenestrate the floor of the third ventricle. 822
This procedure allows drainage of CSF directly into the subarachnoid space and is less invasive. It is 823
considered the treatment of choice for humans in most situations.

Medical management of hydrocephalus is largely symptomatic. Anticonvulsant drugs may be used to control seizures. Furosemide, corticosteroids, or both may help decrease intracranial pressure. Mannitol can be used in cases of acute decompensation, but the benefits are transient. Carbonic anhydrase inhibitors have been used to decrease CSF production but the side effect of acidosis limits their usefulness. Although medical therapy may ameliorate the signs, hydrocephalus tends to be a progressive disease.

191.4.2 Inborn Errors of Metabolism

Although some congenital diseases cause structural malformations of the nervous system, others interfere with function at a biochemical level or lead to premature death of neurons. Ultimately the hereditary disorders will be classified based on the gene or its product that is altered. Most such cases in veterinary medicine are classified according to the clinical presentation, pathologic changes, or both. For many, however, the clinical signs are relatively nonspecific. The clinician should have a high index of suspicion in young, purebred animals with diffuse, symmetrical signs of brain disease when toxic, routine metabolic and infectious causes have been ruled out. Breed tables can be consulted for specific diseases that have been reported.[6,7]

Some inborn errors of metabolism may be apparent on routine clinical pathology tests. Deficiencies in urea cycle enzymes will result in elevated blood ammonia, whereas ketonuria or acidosis, without a clear underlying cause like diabetes mellitus, may reflect errors in mitochondrial metabolism. If the error leads to the accumulation of an abnormal metabolite, that product can often be detected. Urine is the ideal sample to assay because the metabolite may be excreted into the urine in high concentrations, and sufficient volume of urine can be collected even in neonates. Simple urine screening tests are available for some inborn errors of metabolism, but most require testing at specialized labs. Serum or spinal fluid may need to be assayed for metabolites that are not excreted in the urine in detectable amounts. Others may require culturing fibroblasts and measuring specific enzyme activity.

Many inborn errors of metabolism will affect other organs that can be evaluated more readily than the brain. If peripheral nerve is involved, a nerve biopsy may yield clues such as the presence of vacuolated macrophages in globoid cell leukodystrophy (Figure 191-25). Occasionally such vacuolated cells may be visible on routine blood smears or CSF analysis. Because muscle also has a high metabolic demand, diseases affecting energy metabolism may show changes on muscle biopsy. If hepatomegaly or lymphadenopathy accompany neurologic signs, a biopsy of one of these more accessible organs may reveal storage products.[27,28]

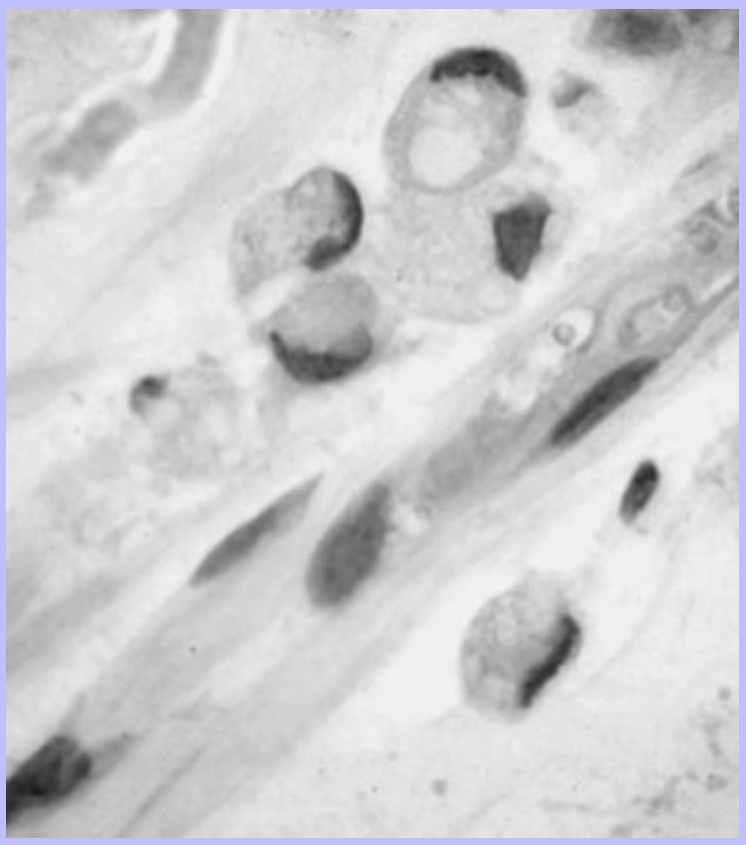
191.4.2.1 Organic Acidurias

These diseases are characterized by the presence of abnormal organic acids as the result of an error in the metabolic pathway. Although relatively few have been described in veterinary medicine, as a whole they are

common diseases in humans and probably occur in purebred dogs with greater frequency than has been recognized. They can be diagnosed by urine organic acid screens and have the potential for therapeutic intervention if the deficient pathway can be bypassed.

Malonic acid levels in a cell regulate the switch between carbohydrates and fatty acids as an energy source in the fed versus fasted state respectively. A Maltese dog from a family with malonic aciduria developed seizures, stupor, hypoglycemia, acidosis, and ketonuria when it experienced a brief period of anorexia. Altering the diet to frequent feedings of a high-carbohydrate, low-fat diet eliminated the need to rely on fatty acids as an energy source and ameliorated the clinical signs.[29]

Figure 191-25 Evidence of inborn errors of metabolism can sometimes be found in more accessible tissues such as white blood cells (WBCs), liver, or peripheral nerve. Macrophages with lysosomal storage product in vacuoles (globoid cells) were found in this peripheral nerve of a Cairn terrier with globoid cell leukodystrophy.



Cobalamin (vitamin B_{12}) is a necessary cofactor in the conversion of methylmalonyl-CoA to succinyl CoA, a significant step in gluconeogenesis. Cobalamin deficiency has been associated with elevated methylmalonic

acid and ammonia, as well as hypoglycemia in a cat (presumably due to a deficiency of intrinsic factor necessary for absorption of B_{12}).[30] Dogs with congenital cobalamin deficiency present primarily with anemia and failure to thrive, although one case presented with seizures.[30A]

Abnormal increases of methylmalonic and malonic acid (and other intermediary metabolites) were found in the urine of a 12-week-old Labrador retriever pup with progressive neurologic signs. The pup was not ketoacidotic or hyperammonemic, and cobalamin levels were normal. Diffuse atrophy of the CNS was found at necropsy, but no specific metabolic defect was identified.[31]

Staffordshire terriers with L-2-hydroxyglutaric aciduria develop seizures, ataxia, and altered behavior between 6 months and 7 years of age. On T2-weighted MRI, dramatic hyperintensity was seen in the cerebral, cerebellar, thalamic, and brain stem gray matter.[32]

191.4.2.2 Spongiform Encephalopathies

The spongiform encephalopathies compromise a heterogenous group of diseases that have in common spongiform change within the brain at necropsy.[33] Some lysosomal storage diseases (see following) may also be characterized by vacuolation of neurons, but in those cases the vacuoles are lysosomes distended with storage products. In the spongiform encephalopathies, vacuoles appear empty and, if intraneuronal, they are not membrane bound. They can be subdivided depending on whether the vacuolation occurs within the myelin sheaths in the white matter (discussed in Leukoencephalopathies) or in the gray matter within neurons or their process (Figure 191-26). The gray matter spongiform encephalopathies include both hereditary and acquired (transmissible) diseases.

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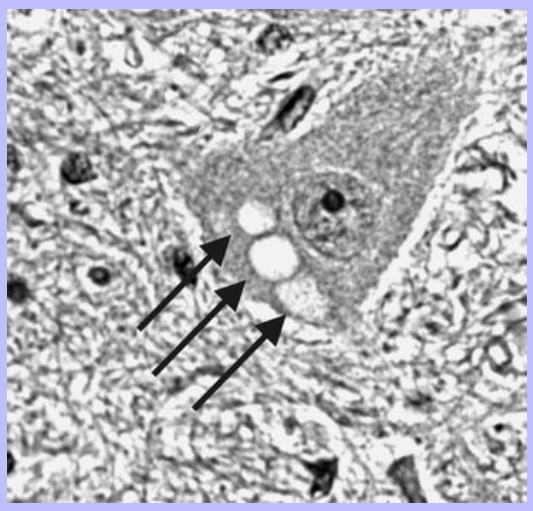
Figure 191-26 Spongiform change in the gray matter should arose suspicion of a transmissible spongiform encephalopathy (TSE), but such vacuolation *(arrows)* of neurons and their processes can be seen in hereditary diseases, such as hereditary spongiform encephalopathy in this rottweiler dog.



Most researchers believe an enigmatic agent, the prion, causes transmissible spongiform encephalopathy (TSE). Scrapie was the first TSE to be described and, for a long time, these diseases were of little concern to small animal practitioners. The outbreak of the TSE bovine spongiform encephalopathy (BSE) in England, and the subsequent recognition that this disease may be spread to cats and humans by ingestion of meat products from affected cows, has made these diseases of more general interest.[34,35] The prion is unique in that it is not a nuclei acid-based organism but rather a rogue isoform of a protein (the prion protein). An alpha-helical isoform of the prion protein is found in normal neurons. The disease isoform (usually referred to as the *scrapie isoform*) of the protein forms a beta-sheetlike amyloid, which renders it resistant to degradation by proteases. These abnormal prions then accumulate in the neurons as scrapie-associated fibrils, interfere with cell function, and produce intraneuronal vacuolation. The scrapie isoform apparently propagates by inducing the normal cellular isoform to convert to the beta-sheet conformation. Exactly how this process occurs is still a matter of much research.[36] A long latency period characterizes the TSEs.

Cats affected with feline spongiform encephalopathy (FSE) show signs reminiscent of BSE: ataxia, behavioral changes, and hyperesthesia to touch or sound. At necropsy, the TSEs are characterized by vacuolation of nerve processes and to a lesser extent their cell bodies. In cats such lesions occur throughout the gray matter of the brain.[35] Although it is hoped that the control of BSE will mean that TSEs are no longer an issue for the small animal clinician, the potential exists for a similar outbreak in the future. Maintaining an index of suspicion will permit early recognition of the disease should it occur in dogs or cats.

Spongiform change in the gray matter also occurs in other diseases including rabies and hereditary disease. A hereditary spongiform encephalopathy has been recognized in rottweiler dogs. Beginning at 6 to 8 weeks of age, affected dogs develop progressive laryngeal paralysis, tetraparesis, and proprioception deficits most prominent in the pelvic limbs and cerebellar ataxia.[37] No abnormal prion proteins were detected in these dogs,[37] and no mutations were found in the gene for the prion protein.[37A]

A hereditary polioencephalomyelopathy of Australian cattle dogs appears to be an autosomal recessive trait. The first signs recognized in affected dogs were seizures beginning at less than 1 year of age. After a variable period of time, progressive ataxia, vestibular signs, and thoracic limb atrophy and muscle rigidity developed, ultimately resulting in recumbancy.[38,39] Symmetrical increased signal was apparent on T2-weighted MRI in the cerebellar, vestibular, and other brain stem nuclei.[39] At necropsy, degeneration of the ventral horn of the spinal cord and in the cerebellar and brain stem nuclei is seen. Within these areas, vacuolar degeneration occurs in the neuropil, astrocytes, and myelin. A mitochondrial defect in astrocytes is suspected.[38]

A litter of Malinois shepherd crosses with congenital generalized tremors has been reported with diffuse vacuolation of the gray matter,[40] and the bull mastiffs with hydrocephalus and cerebellar ataxia have spongiform change in the cerebellar nuclei.[24] Although such diseases are rare, it is important to differentiate them from the TSEs, which carry significant public health implications.

191.4.2.3 Polioencephalopathies

Other conditions affect the gray matter without producing vacuolation. The selective involvement of gray matter suggests a metabolic deficit that creates a dysfunction in neurons or in some cases glia. The clinical signs of polioencephalopathies vary widely, but because neurons of the cerebral cortex are often affected,

seizures and behavior changes are common, as are cerebellar ataxia and sensory or motor deficits. The hereditary movement disorders typically affect neurons of the cerebellum and motor nuclei but will be considered as a separate class of diseases because of the limited distribution of the lesions and hence clinical signs.

Because neurons have a high metabolic demand, they are particularly susceptible to disturbances of energy metabolism. Disorders of mitochondrial metabolism can thus produce polioencephalopathies. In human medicine, such encephalopathies can also be associated with pathology in the muscles, another cell with high-energy demands. Such an association has not been shown in any of the veterinary diseases to date. Two mitochondrial polioencephalopathies have been described in dogs. One English springer spaniel, at 16 months of age, had progressive ataxia, mild behavior changes, visual deficits, and vestibular signs. At necropsy, abnormal mitochondrial changes were associated with degeneration in the cerebellar and cerebral cortex, brain stem nuclei, and optic nerves (a nerve selectively affected in the human mitochondrial encephalopathy: Leber's optic neuropathy).[41] A suspected mitochondrial encephalopathy similar to Leigh's syndrome of humans was recognized in a family of Alaskan huskies that typically are less than 1 year of age when they exhibit an acute onset of ataxia, seizures, behavior changes, blindness, and facial sensation deficits. Dramatic cavitation was seen symmetrically in the gray matter of the thalamus that extended to a variable degree into the brain stem.[42] These lesions are clearly visible on MRI as high T2 signal.[43] The lesions are similar to those seen in acquired energy metabolism problems such as a deficiency of thiamine, a vital cofactor in the Krebs cycle.[44] The sudden onset of signs in huskies could reflect an incident where metabolic demand outpaced supply or susceptibility to an outside insult such as a low thiamine level. One severely affected dog improved dramatically with supportive care that would support this hypothesis.[43] A similar condition has been reported in Yorkshire terriers.[45]

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Chromatolysis refers to loss of Nissl bodies, the dense staining aggregates of ribosomes that give neurons their characteristic granular cytoplasm. Chromatolysis is most commonly seen in wallerian degeneration after destruction of an axon, but also occurs in hereditary diseases such as spinal muscular atrophy. A more diffuse multisystemic chromatolysis has been reported in Cairn terriers and Swedish Lapland pups. Affected pups develop progressive weakness, ataxia, head tremors, and cataleptic episodes.[12,46]

191.4.2.4 Neuroaxonal Dystrophy

Swellings within the axons, called *spheroids*, characterize neuroaxonal dystrophies. They are thought to represent disorders of trafficking of cytoskeletal elements, which then accumulate in axons or synaptic terminals. Because longer axons have further to transport these elements, changes are often most prominent in the termination of the long proprioception tracts in brain stem nuclei. If peripheral nerve is involved, the disease can be diagnosed by nerve biopsy.

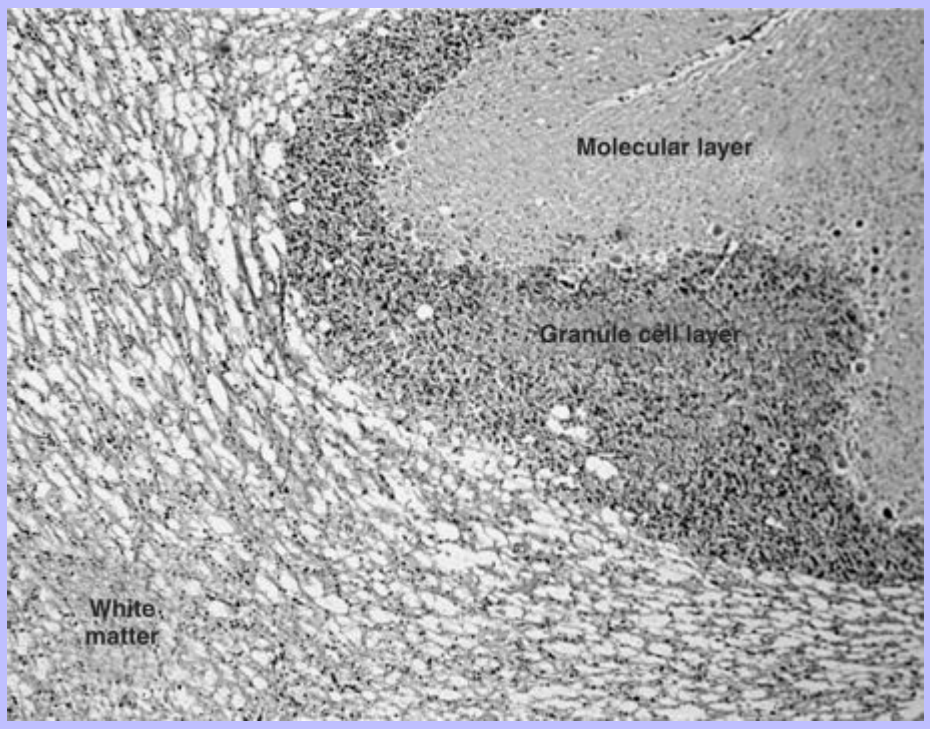
Neuroaxonal dystrophy has been reported in a variety of breeds including Chihuahua, collie, Jack Russell terrier, Papillon, and Siamese,[12,47–49] but it has been best characterized in a family of rottweilers. Affected dogs begin showing signs of hypermetria of the thoracic limbs at 1 year of age. Signs progressed over the next few years to include more pronounced dysmetria, truncal ataxia, intention tremors, menace deficits, nystagmus,[47,50] and laryngeal paralysis.[51] In a family of Scottish terriers, pups developed progressive tremors, ataxia, and paraparesis beginning at a much younger age (10 to 12 weeks). They differed from the neuroaxonal dystrophies previously described in that the axons were diffusely swollen rather than

concentrated in spheroids.[52] Similar diffuse swelling of axons in the CNS is seen in giant axonal neuropathy where peripheral nerve signs predominate.

191.4.2.5 Leukoencephalopathies

Leukoencephalopathies are diseases of myelin and thus affect predominantly the white matter. Such conditions typically produce cerebellar or long tract signs, although many variations exist. The spongiform encephalopathies that affect the white matter are often referred to as *spongy degenerations of the white matter* or *spongy leukodystrophies* to clearly differentiate them from the TSEs that affect primarily gray matter. In spongy degeneration of white matter, splitting of the myelin sheaths causes the vacuolation.[33] Other leukoencephalopathies disrupt myelin or axons without producing vacuolation and would be referred to as *leukodystrophies. Hypomyelinogenesis* refers to the conditions where myelin never forms normally. In dysmyelinogenesis, myelin formation is present but delayed or abnormal.[12] Many of the myelin diseases, such as the leukoencephalomyelopathy of rottweilers, are predominantly spinal cord diseases.[12]

Figure 191-27 In spongy degeneration of white matter, the myelin lamellae are separated, producing vacuolation primarily within the white matter, such as in this section of the cerebellum.



Congenital disorders of myelin formation most commonly begin with generalized tremors and dysmetria noticeable from the first attempts at walking. In some breeds, such as the chow chow, improvement occurs with time, whereas others, such as the Springer spaniel, are permanently disabled. Typically, myelin

throughout the CNS is affected; however, peripheral nerves are spared, so reflexes are normal or exaggerated. Both X-linked and autosomal recessive forms have been described, and mutations of one of the myelin proteins has been identified in the Springer spaniels.[12,53,54] Diagnosis is based on the typical clinical signs in a breed at risk and, if necessary, confirmed at necropsy.

Later age onset leukodystrophies have also been described in dogs. Alexander's disease (fibrinoid leukodystrophy)[12] has been reported as a sporadic occurrence in several breeds. They presented for progressive ataxia, weakness, and, in one case, seizures between 3 and 6 months of age. Perivascular accumulations of characteristic eosinophilic (Rosenthal's) fibers at necropsy permitted the definitive diagnosis.[12]

Spongy degeneration of the white matter similar to Canavan's disease of humans has been reported sporadically in a variety of breeds of dogs and cats.[12] Affected Labrador retrievers began showing signs at 4 to 6 months of age. Initial signs were episodes of extensor rigidity and dorsiflexion of the neck with retained consciousness. These were followed by progressive dysmetria, intention tremors, tetraparesis, hyperreflexia, and spasticity. Behavior, autonomic, and sensory functions remained normal. At necropsy, splitting of the myelin resulted in vacuolation of the whiter matter throughout the brain and to lesser extent the spinal cord (Figure 191-27).[55,56] In the familial spongiform leukodystrophy described in Shetland sheepdogs, the clinical signs began at less than 3 weeks of age and included progressive seizures, weakness, lethargy, and dysphagia. Spongiform degeneration was most prominent in the cerebellum and corona radiata. Biochemical screening tests in the sheepdogs failed to identify any of the abnormal organic acids or amino acids associated with spongy degeneration in people or cattle.[57]

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191.4.2.6 Lysosomal Storage Disease

Storage diseases are characterized by an accumulation of metabolic byproducts within lysosomes. Lysosomes are cellular organelles responsible for breaking down complex macromolecules. This compartmentalization allows for a more acidic pH within the lysosome and protects the rest of the cell from digestion. The substrates for catabolism within lysosomes include sphingolipids (a major component of myelin), oligosaccharides, mucopolysaccharides, glycoproteins, and proteins. The storage diseases are typically caused by a deficiency in a key enzyme in the breakdown of one of these molecules, and without the enzyme the substrate accumulates within the lysosome. The syndromes are usually named for the accumulated product. Proteases are less substrate specific, thus a deficiency in a single enzyme is less likely to produce problems. As a result, disorders of protein catabolism are uncommon, although CL may represent such a defect.[27,28,58] Alternatively the defect can interfere with cell's ability to use a normal enzyme. In I-cell disease (mucolipidosis) of cats, for example, the disorder appears to be one of trafficking of the enzymes into the lysosome. As a result, multiple enzymes are affected.[59] Recent reviews of the storage diseases in animals have been published and should be consulted for details on the individual syndromes in different breeds.[27,28,58] Some drugs and toxins, such as locoweed, can interfere with the activity of these enzymes, producing similar clinical signs and histologic lesions; however, this has not been documented in small animals.[27]

Accumulation of the storage product takes time; thus most storage diseases have a delayed onset of signs even though the enzyme has been deficient from birth. The age of onset and severity can depend upon how much residual function is left in the altered enzyme. Many of the storage diseases affect multiple organs, whereas others, such as those affecting degradation of myelin, only affect the nervous system. How the

accumulated storage product produces neurologic disease is not always clear. In globoid cell leukodystrophy, one of the storage products is clearly toxic to oligodendroglia. In others, spheroid formation may be related to neuronal death.[27,28,60]

Cerebellar signs of dysmetria, truncal ataxia, and nystagmus are often the first signs of storage diseases.[28] The cerebellum is dependant on fast conduction to get sensory feedback during execution of a movement, and complex integration of sensory and motor information is necessary. Thus the cerebellum is sensitive to disorders affecting myelin or information processing. In addition, even subtle cerebellar deficits may be recognized, whereas more profound learning or mentation deficits may be necessary to reach a threshold of recognition. Signs often progress to weakness, behavior abnormalities, and seizures.[28] In some diseases, such as CL (see following), forebrain signs will be the earliest signs.[61] Peripheral nerves are involved in some conditions such as globoid cell leukodystrophy. Few imaging studies have been performed on the brains of animals with storage disease. In dogs with globoid cell leukodystrophy, increased signal intensity in white matter has been shown on T2-weighted MRI.[62] Cats with alpha-mannosidosis also show white matter changes on MRI.[63]

In some lysosomal storage diseases, signs of other organ involvement may be apparent. Ocular abnormalities can include visible changes in the retina or cataract formation. Skeletal or facial malformations are especially prominent in the mucopolysaccharidoses and may be apparent on radiographs. Cardiac, hepatic, splenic, or lymph node enlargement may accompany the neurologic signs.

Storage vacuoles may be apparent in white cells on a peripheral blood smear or, in the case of globoid cell leukodystrophy or fucosidosis, on CSF analysis. Alternatively, lymphoid tissue can be examined via biopsy of the spleen or lymph node. If the liver is enlarged, aspirate or biopsy may also reveal storage vacuoles. When peripheral nerve is involved, biopsy of the nerve may reveal vacuolated mononuclear cells. Muscle biopsy will be most useful when glycogen storage disease is suspected. Necropsy may be necessary to demonstrate storage product when only the nervous system is involved. Electron microscopy can demonstrate that the storage material is contained within lysosomes. Abnormal metabolites may be detectable in urine with some of the storage diseases. Definitive diagnosis depends upon demonstration of deficient enzyme activity in serum, leukocytes, or cultured fibroblasts.

191.4.2.7 Ceroid Lipofuscinosis

Although a lysosomal storage disease, CL differs from the other diseases in that the storage products are proteins. These products have a characteristic autofluorescence similar to ceroid and lipofuscin, pigments that accumulate normally with aging. Although named for this similarity, ceroid and lipofuscin are not found in any appreciable amounts in these diseases. Among the known storage products in CL are subunit c of mitochondrial adenosine triphosphate (ATP) synthase and sphingolipid activator proteins (saposins) A and D.[64] The enzymes responsible (saposin A and D) have been identified in humans and sheep, respectively.[65] In addition to lysosomes, evidence exists that these enzymes may be involved in mitochondrial and synaptic functions, which may explain some of the neuropathology seen.[65,66]

The original classification of CL was based on age of onset and rapidity of progression. As discussed previously, this is probably more of a reflection of the degree of residual enzyme activity than differences in enzymes responsible. Nonetheless, because purebred dogs usually have a single mutation responsible for a genetic disease, there will be consistency between individuals within a breed, making such classifications useful. The earliest reported onset of signs in CL (<6 months of age) has been reported in a cat and in

dalmatians, but affected dogs can live up to 7 to 8 years.[61,67] English setters, border collies, and other breeds have an early adult onset (about 1 year of age), acute disease, and die by 2 years of age.[61] The Tibetan terrier is the best characterized breed with adult onset, slowly progressive disease. Signs of visual impairment begin at 2 to 3 years of age, and behavior changes do not become apparent until 4 to 6 years of age.[61]

Diminished vision is usually the first sign of CL. This can be especially noticeable in dim-light situations. Behavior changes are prominent in the disease and include timidness, hyperesthesia, confusion, and unprovoked aggression. Seizures, jaw chomping, bruxism, and myoclonus are also reported. Ataxia and hypermetria are also reported but tend to be later manifestations in many breeds.[61] Brain atrophy and dilation of the ventricles can be seen on CT scan in later stages of the disease,[68,69] but definitive diagnosis relies upon identification of the characteristic autofluorescent material in the brain or other tissues.

Currently no effective therapy exists for any of the storage diseases. Gene therapy holds the promise of restoring function to affected individuals, but cost will limit its application to veterinary medicine. DNA testing is already available for some diseases and will become more readily available in the future. This will permit breeders to make informed decisions that are likely to decrease the incidence of some diseases in the future. Symptomatic therapy such as anticonvulsants and behavior-altering drugs can help ameliorate some of the symptoms.

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191.4.3 Movement Disorders

Most of the movement disorders that are recognized in veterinary medicine are hereditary diseases, although acquired conditions are beginning to be characterized. The hereditary ataxias encompass a heterogeneous group of diseases. As with other hereditary diseases, these will ultimately be classified based on the gene responsible and its product. However, even then, signalment and clinical signs will be the initial clues that direct clinicians toward those answers. The most common movement disorders in animals are the cerebellar disorders, although in some breeds other motor systems are affected.[12,70]

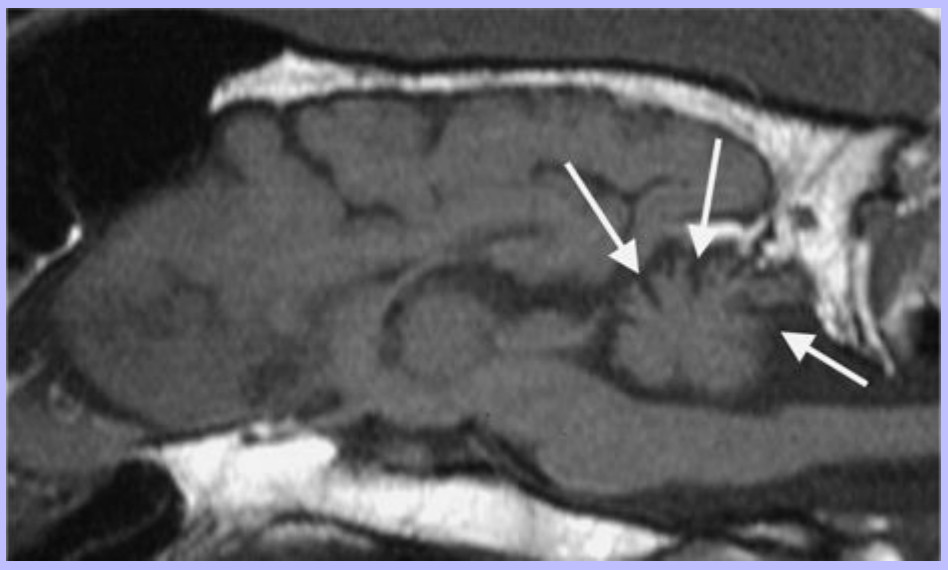
191.4.3.1 Hereditary Cerebellar Ataxia

The cerebellar ataxias can be divided into neonatal, early, and delayed onset.[70] Many neonatal conditions are associated with gross malformations of the cerebellum (discussed previously). In certain breeds with neonatal onset ataxia, such as beagles and Samoyeds, the loss of Purkinje cells is similar to that seen in later age onset conditions.[12] Others, such as neonatal ataxia in Coton de Tulear dogs, show minimal histologic changes and are presumably a biochemical dysfunction.[71]

Other hereditary ataxias are characterized by a variable period of normal development followed by progressive cerebellar ataxia as specific populations of neurons die prematurely. The age of onset of signs can vary from weaning age (e.g., English pointers, Kerry blue terriers)[72,73] to adulthood (e.g., Gordon setters, Old English sheepdogs)[74,75] to later life (e.g., Brittany spaniels).[76] This process is sometimes referred to as *abiotrophy*, based on the original hypothesis that lack of a trophic substance was responsible for the degeneration. The term is now used to emphasize the fact that these diseases have a delayed onset of degeneration and clinical signs.[12,70] The specific genetic deficit responsible has yet to be identified in any of these diseases in dogs or cats. Most are autosomal recessive, although the ataxia in English pointers is X linked.[73]

In most of these delayed onset ataxias of dogs and cats, the Purkinje cells of the cerebellum degenerate. Because the Purkinje cell is the sole efferent from the cerebellar cortex, degeneration results in a loss of cerebellar function. In addition to the period of normal function, clinicians can tell that the Purkinje cells formed and then degenerated by the presence of "empty baskets." Basket cells are interneurons that form a dense meshwork of dendrites around the Purkinje cell body. When the Purkinje cells degenerate, these empty baskets of dendrites remain, but they would not form if the Purkinje cell body had not been there initially.

Figure 191-28 In the hereditary ataxias, atrophy of the cerebellar cortex *(arrows)* may be apparent as shrinkage and flattening of the cerebellum with an increased space between the folia.



Although Purkinje cell degeneration is the most common type of degeneration described, other parts of the cerebellum can be affected. In Jack Russell terriers, the granule cell layer is primarily affected.[76A] In beagles both cell types are affected.[77] In bull mastiffs, the cerebellar roof nuclei along with some brain stem nuclei undergo spongiform degeneration.[24]

Hereditary cerebellar ataxia should be suspected when a breed at risk or other young, purebred dog develops progressive cerebellar ataxia. Atrophy of the cerebellum may be apparent on MRI of the brain (Figure 191-28). CSF analysis may be helpful in ruling out infectious and inflammatory causes, but histologic examination may be necessary to determine the character of the lesion. The severity of signs varies a great deal. Some dogs and cats with pure cerebellar cortical degeneration have only mild to moderate ataxia and may be able to live with their disabilities. Ensuring against injury due to falls is the most pressing management concern. Feeding difficulties may require the use of a high-calorie food to maintain weight. In other cases the degree of ataxia may be severe enough to warrant euthanasia.

191.4.3.2 Multiple System Degeneration

The basal ganglia, such as the caudate nucleus and substantia nigra, are also important in movement and are affected in Huntington's and Parkinson's disease in humans. When the cerebellum and basal ganglia are involved, these conditions are referred to as *multiple systems degenerations*. The best-characterized syndrome of this type in animals is the disease of Kerry blue terriers and Chinese crested dogs called *progressive neuronal abiotrophy* (PNA) by breeders. In these breeds, cerebellar ataxia begins at 8 to 12 weeks of age, but is followed at 6 to 12 months of age by degeneration of the basal ganglia.[72,78] As the basal ganglia degenerate, affected dogs have increasing difficulty initiating movements and maintaining balance. This results in a festinating locomotion in which the dog begins to lose balance and then runs in that direction to keep from falling (Figure 191-29). The degeneration of the basal ganglia is visible on MRI as an increased T2 signal. The severe motor difficulties associated with these conditions necessitate euthanasia by 1 to 2 years of age.

191.4.3.3 Dyskinesias and Dystonias

Dyskinesia is a general term for a disorder of movement usually characterized by involuntary, stereotyped movements caused by disease affecting the basal ganglia (extrapyramidal) motor systems or their neurotransmitters. In human medicine, dyskinesias are classified based on the character of the movements. 827
Chorea refers to arrhythmic, rapid, jerky movements, which are more sustained than the brief jerks of 828
myoclonus. The rhythmic jerking associated with canine distemper has been called *chorea* in the past but is actually a myoclonus. When chorea affects proximal muscles producing flinging movements of the limbs, they are called *ballismus*. *Athetosis* describes slower, flowing movements. *Dyskinesias* can involve the entire body or be limited to one side or to the face. *Dystonia* refers to a sustained abnormal contraction often producing abnormal posturing or torticollis.

Figure 191-29 As Chinese crested dogs with multiple system degeneration progress from cerebellar ataxia to basal ganglia degeneration, they develop difficulty initiating movements. They may shift weight forward until they begin to fall, and then they are able to move forward.

Such movement disorders have not been well documented in animals. In part, this may reflect a difference in the rolls of the cortical (pyramidal) and basal ganglia (extrapyramidal) motor systems in primates versus quadrupeds. More likely it is simply a failure to recognize movement disorders. Some idiopathic head tremors (see following discussion) may well represent basal ganglia disease. Oral-facial dyskinesias in animals have been observed that undoubtedly represent movement disorders. Increased availability of MRI will allow recognition of structural lesions of the basal ganglia. For example, infarcts of the basal ganglia have been identified in dogs with acute torticollis.[79]

191.4.3.4 Paroxysmal Dyskinesias

Seizures are by far the most common neurologic disorder that occurs as discrete episodes of involuntary movement, and they are discussed in detail (see Chapter 48). Reports exist of paroxysmal abnormal movements in dogs that do not appear to be seizures. Episodic ataxia and paroxysmal dyskinesia are two examples of human diseases that occur in episodes but do not have the EEG changes that define seizure disorders. Generalized seizures are distinguished by a loss of consciousness, but in focal motor seizures, consciousness may not be impaired. Thus distinguishing between a focal seizure and a paroxysmal dyskinesia can be difficult without an EEG recording during an episode. The character of the movement in paroxysmal dyskinesias tends to be different from that observed with seizures. Focal motor seizures frequently produce an erratic twitching of one side of the face and may progress to affect the limbs on the same side. This reflects the origin of the seizure in the area with largest representation in the motor cortex of the dog followed by spread of seizure activity in that hemisphere. The movements in paroxysmal dyskinesias are more of the character of a dyskinesia or dystonia. In addition, the episodes may last much longer than the 2 minutes typical of most seizures and may be precipitated by excitement or exercise.

Scotty cramp is a condition of Scottish terriers characterized by episodes of rigidity with excitement or exercise. Affected dogs develop limb rigidity, which can result in recumbency in severely affected dogs.[80] The cause of the muscle hypertonicity is not clear, but a central motor problem is suspected. Serotonin antagonists will worsen the attacks, whereas alpha noradrenergic blocking drugs and benzodiazepines are reported to help alleviate the episodes. An autosomal recessive inheritance is suspected. Similar signs have been reported in dalmatians and a Shetland sheepdog.

A movement disorder characterized by episodes of flexion of the limbs has been described in adult Bichon frises. Affected dogs develop a kyphotic stance and alternately flex various limbs. This flexion is not limited to one side of the body and appears to affect pelvic limbs or thoracic limbs randomly rather than in set progression. These episodes resemble root signature seen with intervertebral disk disease. The dogs are not in pain, however, and herniated disks are not found on myelography. Facial grimacing also occurs.[81] Similar episodes have been described in two litters of young boxers.[82] Chinook dogs have a familial disorder characterized by prolonged episodes of inability to stand with dystonic posturing and sometimes rhythmic limb or tongue movements. Whether these episodes are focal seizures, a paroxysmal dyskinesia, or some other disorder is still not clear. Dancing Doberman disease is characterized by alternating flexion and extension of the pelvic limbs, resulting in the dog “dancing” from one foot to the other. It is thought to be a peripheral neuropathy, however, rather than a central movement disorder.[83]

191.4.3.5 Tremors

Fine, fast tremors (enhanced physiologic tremors) are common with a wide variety of conditions such as weakness, fatigue, fear, pain, hypoglycemia, pheochromocytoma, hyperthyroidism, and certain drugs or toxins such as pyrethrins or caffeine. Benign tremors are common in older animals, particularly in the hind limbs. Beta-blocking drugs can ameliorate physiologic tremor, but usually the tremor does not interfere with the animal's function. The major concern is ruling out treatable underlying causes of the tremor.

An idiopathic tremor syndrome was first reported in Maltese and West Highland white terriers and called *little white shakers* syndrome.[84–86] Although these breeds appear to have a predilection of the disease, a wide variety of breeds have been reported with the disease[84,87]; *idiopathic tremors* is a more appropriate name for the condition. Most affected dogs are young adults (6 months to 5 years of age) with an acute onset of tremors. The tremors affect the entire body, including the eye, and vary from mild to severe enough to interfere with the dog's ability to stand or walk. They are exacerbated by excitement or movement and disappear at rest (intention tremors). Other signs such as absent menace response, ataxia, head tilt, or paresis may accompany the tremors. CSF analysis typically includes mild lymphocytic and monocytic pleocytosis, and a few dogs that have been necropsied have shown mild inflammatory changes on histopathology.[12,86,87] Most dogs respond very well to immunosuppressive doses of corticosteroids for 1 to 3 weeks, though relapses can occur. Benzodiazepines or propranolol may help relieve the tremors.[85–87]

A syndrome of head tremors is seen in some breeds. Doberman pinschers sometimes develop a head tremor after administration of droperidol when that drug was used in an injectable neuroleptic and analgesic combination that is no longer marketed. Because droperidol is a dopamine antagonist, the assumption was that the head tremor was akin to the tremors in human patients with Parkinson's disease. Occasionally, isolated head tremors are seen without any history of intoxication in Doberman pinschers, boxers, bulldogs, and Shetland sheepdogs. The exact cause of the tremors is not known. Often they are discrete episodes, which could represent a focal motor seizure, but response to the anticonvulsant drugs has been variable. Generally they appear to be benign.

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191.4.4 Encephalitis

Encephalitis refers to an inflammation of the brain. Most infectious or inflammatory diseases of the nervous system involve the spinal cord and the brain, producing multifocal disease (discussed in Chapter 192). Potential causes include viral, bacterial, rickettsial, protozoal, fungal, and parasitic. A few diseases affect the brain almost exclusively. Encephalitis is typically an acute disease, but in some cases, such as canine distemper or FIV, can be chronic and insidious. Some infections can be quite focal, and signs will reflect the area of the brain affected; however, others will produce more diffuse signs. Altered mentation with focal facial muscle twitching, seizures, or both is a typical presentation. If the meninges are involved, pain may be a prominent feature. Signs of systemic illness may or may not be present. CSF analysis can confirm inflammation, but prior treatment with corticosteroids may mask any CSF changes. With a few exceptions such as cryptococcosis, organisms are rarely seen or cultured in CSF and titers or PCR testing is necessary to identify the cause.

Because results of culture or titers may be delayed, symptomatic therapy is usually instituted when encephalitis is suspected based on signs or CSF results. Corticosteroids are usually indicated in acute encephalitis to decrease inflammation and the attendant morbidity. Immunosuppression can lead to subsequent worsening of the condition, however, if the underlying cause is not identified and treated appropriately. CSF analysis should

be completed before corticosteroids are administered, but the pet should not be sacrificed for the sake of a definitive diagnosis.

Appropriate antibiotics are instituted based on the most probable organism. The choice of antibiotics is influenced by disease prevalence in an area, evidence from physical exam or clinical pathology, and ability to penetrate the blood brain barrier in significant concentrations. During tick season in endemic areas, doxycycline can be administered to treat rickettsial disease, especially if other signs, such as thrombocytopenia or polyarthritis, are present. Clindamycin or potentiated sulfonamides can be used if protozoal infection is suspected. Trimethoprim-sulfonamide and enrofloxacin are bactericidal, broad-spectrum antibiotics that have good to fair blood-brain barrier penetration respectively. They can be used if bacterial infection, such as spread from an otitis media or septicemia, is suspected. If better activity against anaerobes were needed, metronidazole and clindamycin would be logical choices. In areas where coccidiomycosis is endemic or if cryptococcosis is suspected, antifungals may be necessary.

191.4.4.1 Viral Encephalitis

Though rabies is uncommon in dogs and cats, the public health risk requires that it always be considered in the differentials for unvaccinated animals with brain disease. If the virus gains entry through a wound on the limbs, rabies may affect the spinal cord, producing an ascending LMN paralysis prior to brain signs. Commonly, however, the bite occurs on the face, and the signs will reflect cranial nerve and forebrain involvement. For the first few days after infection there may be a fever, pruritus of the bite site, and anxious or irritable behavior. Progression and signs of the disease are quite variable, with considerable overlap between the two general forms of the disease. In the paralytic or dumb form of rabies, LMN paralysis of cranial nerves can produce a dropped jaw, dysphagia, laryngeal paralysis, and voice change. Signs progress over days to coma and respiratory arrest. The furious form consists of the classic behavior changes of rabies. Animals become hyperesthetic, irritable, and restless. They may be photophobic and hide or avoid contact with people. They may attack inanimate objects such as their cage and pica is common. As signs progress, ataxia, disorientation, and generalized seizures develop. The animal may develop a brief paralytic stage before death.[88]

A herpes virus causes pseudorabies (Aujeszky's disease). Dogs and cats typically acquire the infection from eating tissue from infected pigs. It produces a fulminate encephalitis characterized by dementia, seizures, and intense pruritus, often to the point of self-mutilation. No effective treatment is available; affected animals typically die within 48 hours, although cats may be more resistant to the infection.[88]

Increasing evidence suggests that feline immunodeficiency virus (FIV) infection can cause an encephalopathy not related to secondary infection. Affected cats develop progressive, symmetrical forebrain signs including depression, restlessness, learning and memory deficits, and mild coordination difficulties.[89] Diagnosis is based on serology and compatible clinical signs. Encephalitis due to a secondary infection such as toxoplasmosis needs to be ruled out or treated appropriately. Drugs used in treating acquired immunodeficiency syndrome (AIDS) in humans may prove useful in FIV infected cats, but currently the prognosis is poor.

191.4.4.2 Encephalitis of Unknown Cause

Pug encephalitis is a necrotizing meningoencephalitis that affects young adult pug dogs.[90] Affected dogs typically develop an acute onset of seizures and other forebrain signs. Maltese and Yorkshire terriers develop

a similar encephalitis, although brain stem involvement is more common in the Yorkshires. CSF analysis shows a lymphocytic pleocytosis. Histologically, asymmetrical necrosis and inflammation exists that affects both gray and white matter.[12] The cause is unknown. Immunosuppressive therapy may slow the course of the disease. Many affected dogs die within days of the onset of signs, though some may survive for months.

Granulomatous meningoencephalomyelitis (GME) can affect the spinal cord, but primarily causes encephalitis. Affected dogs tend to be young adults but any age may be affected. Onset of signs is typically acute. CSF typically shows a marked elevation in white cells (lymphocytes and monocytes) and protein, but may be unremarkable, especially after corticosteroid therapy. Imaging may reveal multifocal areas of contrast enhancement or a single mass. Histologically, GME shows perivascular cuffs of inflammatory cells often with epithelioid differentiation. Lesions are most prominent in the white matter.[12,91,92] Unless confirmed by brain biopsy, GME is a diagnosis of elimination once other causes of meningoencephalitis are ruled out. Immunosuppressive doses of corticosteroids will often achieve remission of signs for a variable period of time. When the disease becomes refractory to corticosteroids, radiation therapy or chemotherapeutic agents such as lomustine or cytosine arabinoside have been used with some success, but the prognosis is poor.

191.4.5 Vascular Disease

Stroke is uncommon in animals compared with humans because of the lower incidence of atherosclerosis and primary hypertension. With advanced imaging, however, vascular disease is being recognized with increasing frequency in veterinary medicine. Cerebrovascular disease can be subdivided into infarction and hemorrhage, although the two categories overlap in the case of hemorrhagic infarcts.

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Infarction can occur due to thrombosis or embolism of the arterial supply or due to thrombosis of venous drainage. Thrombosis typically occurs when a clot forms in vessels compromised by atherosclerosis. In dogs, atherosclerosis is seen in hypothyroidism and idiopathic hyperlipidemia, and stroke can occur in these patients. Embolism will be secondary to some systemic disease such as sepsis, cardiac disease, neoplasia, or coagulopathy. Venous occlusion can occur secondarily to thrombosis or compression of the vein. Although a rich collateral drainage usually prevents signs with venous thrombosis, a severe occlusion may result in impaired blood flow to the tissues drained.

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Intracranial hemorrhage occurs most commonly secondary to head trauma. When venous thrombosis occurs, the arterial supply is still intact and hemorrhage into the area of infarction may occur. Primary intraparenchymal hemorrhage can occur with hypertension. Hypertension in animals is most commonly secondary to hyperthyroidism, renal disease, pheochromocytoma, or hyperadrenocorticism.

Feline ischemic encephalopathy is a cerebral infarction syndrome in cats. Some cases have been associated with aberrant migration of *Cuterebra* larvae into the brain. Not all cases have obvious vascular lesions, leading to the hypothesis that the larvae induce vasospasm.[12]

Vascular disease is characterized by a peracute onset of signs. Unilateral forebrain signs of circling, hemiparesis, seizures, and personality changes would be most common, though any part of the brain could be affected. Some progression of signs could be expected from increased intracranial pressure. CT is good at detecting acute hemorrhage, whereas MRI is more sensitive for infarction. The signal changes with time, allowing estimation of the chronicity of the lesion (Figure 191-30).[93] Because infarction is rarely due to thrombosis in animals and the therapeutic window is a matter of hours, the thrombolytic drugs used in human stroke patients hold little promise in veterinary medicine. Thus treatment will be largely symptomatic,

controlling seizures and intracranial pressure and treating any underlying cause such as vasculitis or hypertension.

191.4.6 Brain Tumors

Brain tumors in dogs are more properly classified as intracranial neoplasms, because not all tumors that arise inside the cranium originate from brain tissue (Table 191-1). Regardless of the tissue origin, intracranial neoplasms result in a characteristic milieu of clinical signs in dogs. Signs typically develop as a result of a focal tumor and can be due to the disturbance of surrounding normal brain tissue from expansive growth of the tumor or the result of the peritumoral effects, such as edema and compromised blood flow. As the disease progresses the clinical signs may change to reflect further damage within the cranial vault. This is especially true when intracranial pressure rises and causes a shift in the intracranial contents. Additional damage and clinical signs can result from expansion of the tumor into non-neural tissues, such as the nasal cavity, periorbita, or the surrounding cranial bones. Rarely, primary intracranial neoplasms can disseminate throughout the CNS either by hematogenous or CSF routes. Intracranial neoplasms rarely spread systemically, although metastasis is not unprecedented. When this occurs it generally spreads to the lungs, most likely through venous drainage from the venous sinus plexuses in the cranial vault.

Although intracranial tumors in the dog and cat have been well described, the prevalence is largely unknown due to the lack of a comprehensive screening system. The incidence for primary CNS tumors in the dog have been reported as 14.5 in 100,000 dogs and 3.5 in 100,000 cats.[94,95] The tumor incidence in dogs is virtually identical to that in humans (11.8 per 100,000).[96] Interestingly, primary CNS tumors in humans, specifically malignant gliomas and CNS lymphomas, are becoming recognized at a higher rate in some studies.[97] However, as is probably the case in small animals, this data may only be reflecting an increased availability of imaging modalities that are necessary to identify the tumors.

Figure 191-30 T1-weighted magnetic resonance imaging (MRI) with contrast enhancement from a dog with two suspected strokes of the cerebellum 1 year apart. The older infarct on the right *(black arrow)* shows the atrophy of a wedge-shaped portion of the cerebellum replaced with cerebrospinal fluid (CSF). The left side shows an area contrast enhancement *(white arrow)* 4 days after an acute recurrence of cerebellar signs.

Clear risk factors for the development of intracranial neoplasms in the dog have not been identified. In humans, much press has been devoted to the role of cellular phones, exposure to high-tension wires, the use of hair dyes, head trauma, and exposure to N-nitrosourea compounds and other nutritional factors. To date, none of these have been definitively linked to the development of a brain tumor. Ionizing radiation, however, has been identified as an unequivocal risk factor for the development of glial and meningeal neoplasms. Exposure of the cranium to even low doses of radiation can increase the incidence of glial tumors in humans by a factor of 3 to 7, with a latency period of 10 years or more after exposure.[98] It is unknown whether small animals respond similarly to ionization radiation.

This section will focus on the diagnosis of the most common intracranial neoplasms and general treatment guidelines. It is important to note that an in-depth analysis of tumor behavior and of specific treatment regimes for intracranial neoplasms is difficult to perform in companion animals, because this information has not been comprehensively gathered and disseminated. To compensate for the relative paucity of information, data derived from the diagnosis and treatment of human tumors will be provided when appropriate.

191.4.6.1 Diagnostic Procedures

An intracranial mass can be confirmed on brain imaging with MRI or a CT scan. A CT scan, though adequate for identifying tumors in the majority of the cerebral cortex, is more prone to artifact production when imaging the caudal fossa because of interference from the surrounding petrous temporal bone. An MRI is the preferred diagnostic modality, because it provides images with superb soft tissue detail and is not interfered by the surrounding bony structures. It is important to remember that any ferrous substance locating in the magnetic field will dramatically alter the image, resulting in poor tissue detail. As such, it is a good practice to perform a radiograph of the target area prior to performing an MRI to ensure a clean field. An MRI should be performed both with and without the addition of gadolinium, an intravenous contrast agent. Although it is not a definitive test, the degree of contrast enhancement and specific tumor location will aid the clinician in making a presumptive tumor diagnoses. This will be discussed in more detail with each individual tumor. The quality of images with an MRI has reached the point that a normal gadolinium-enhanced MRI of the brain essentially rules out the possibility of a brain tumor in both small animals and humans.

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Table • 191-1 World Health Organization Classification System for Intracranial Neoplasia[93A]

TYPE	EXAMPLES
Astrocytic tumors	Astrocytoma
	Anaplastic (malignant) astrocytoma
	Glioblastoma multiforme
	Pilocytic astrocytoma
	Subependymal giant cell astrocytoma
	Pleomorphic xanthoastrocytoma
Oligodendroglial tumors	Oligodendroglioma
	Anaplastic (malignant) oligodendroglioma
Ependymal cell tumors	Ependymoma
	Anaplastic ependymoma
	Myxopapillary ependymoma
	Subependymoma
Mixed gliomas	Mixed oligoastrocytoma
	Anaplastic (malignant) oligoastrocytoma
	Others (e.g., ependymoastrocytomas)
Neuroepithelial tumors of uncertain origin	Polar spongioblastoma
	Astroblastoma
	Gliomatosis cerebri
Tumors of the choroid plexus	Choroid plexus papilloma
	Choroid plexus carcinoma (anaplastic choroid plexus papilloma)
Neuronal and mixed neuronal-glial tumors	Gangliocytoma
	Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)
	Ganglioglioma
	Anaplastic (malignant) ganglioglioma
	Desmoplastic infantile ganglioglioma
	Central neurocytoma
	Dysembryoplastic neuroepithelial tumor
	Olfactory neuroblastoma (esthesioneuroblastoma)
Pineal parenchyma tumors	Pineocytoma
	Pineoblastoma
	Mixed pineocytoma/pineoblastoma
Tumors with neuroblastic or glioblastic elements (embryonal tumors)	Medulloepithelioma
	Primitive neuroectodermal tumors with multipotent differentiation
	Medulloblastoma
	Cerebral primitive neuroectodermal tumor
	Neuroblastoma
	Variant: ganglioneuroblastoma
	Retinoblastoma
	Ependymoblastoma
Tumors of the sellar region	Pituitary adenoma
	Pituitary carcinoma
	Craniopharyngioma
Hematopoietic tumors	Primary malignant lymphomas
	Plasmacytoma
	Granulocytic sarcoma
Germ cell tumors	Germinoma
	Embryonal carcinoma
	Yolk sac tumor (endodermal sinus tumor)
	Choriocarcinoma
	Teratoma

	Mixed germ cell tumors
Tumors of the meninges	Meningioma: variants include meningothelial, fibrous (fibroblastic), transitional (mixed), psammomatous, angiomatous, microcystic, secretory, clear-cell, chordoid, lymphoplasmacyte-rich, and metaplastic subtypes Atypical meningioma Anaplastic (malignant) meningioma

Other diagnostic modalities, including CSF analysis, EEG, and brain stem–evoked responses may provide evidence of an intracranial neoplasm or other CNS disease process. In a recent clinical study of 115 dogs with seizures, 36 of 37 dogs (97%) with an abnormal neurologic examination and abnormal CSF analysis (protein >25 mg/dL or nucleated cell count >5 cells/μL) were found to have MRI abnormalities.[99] Statistical analysis of the data indicated that a CSF protein concentration greater than 25 mg/dL was associated with a 76% sensitivity and 70% specificity for prediction of MRI abnormalities, whereas a CSF protein greater than 35 mg/dL resulted in 52% sensitivity and 96% specificity. Although this does show some value to CSF analysis as a screening test, disadvantages still exist. Prediction of MRI abnormalities is not the same as diagnosis of a brain neoplasm (non-neoplastic diseases may also result in MRI abnormalities). Even if a neoplasm is suspected based upon the CSF, the cytology is usually nonspecific for tumor type and tumor location.[100] Although CSF collection generally carries a low-level of risk for the patient, if a brain neoplasm is suspected, it is recommended to perform MRI before CSF tap (due to the risk of tentorial herniation with CSF tap under conditions of increased intracranial pressure).

EEG has been used in humans as a useful aid to imaging studies in the localization of structural and functional brain lesions. An EEG is not as useful for lesion localization in companion animals as it is in humans because dogs and cats have a relatively small brain that is extremely well protected by a thick calvarium and masticatory muscle mass. In addition, EEG abnormalities are not specific for different types of intracranial neoplasia, so the value in the diagnosis of neoplasia is limited to screening at best.

The BAER test reflects audiologic and neurologic function at the level of the brain stem, and is used in human beings to aid in the diagnosis and localization of lesions of the cochlea, the vestibulocochlear nerve, and brain stem auditory pathways. In a prospective study of 26 dogs with naturally occurring brain tumors, BAER was abnormal in 13 of 15 dogs with tumors of the brain stem but only in 1 of 11 dogs with forebrain lesions.[101] Although this type of information may be useful in localizing a lesion, it is nonspecific as to lesion type, and like an EEG, is useful only as a screening tool.

Functional brain imaging, combined with structural data gleaned from either MRI or CT, is becoming more integrated in the identification and management of intracranial neoplasms and other CNS diseases. Specifically, flourodeoxyglucose (FDG) positron emission tomography (PET) and functional MRI are gaining widespread use in the human field for diagnosing and staging neurologic diseases. These imaging modalities are limited to few veterinary institutions, but they may be used more frequently in the future as the technology becomes widely accepted.

Once an intracranial structural lesion (tumor suspect) is identified, it is necessary to specifically identify the type of tumor present to tailor a specific treatment regime. The primary method of obtaining tissue for histopathologic diagnosis is by surgical exploration and excisional biopsy. This is most often accomplished when the lesion is located in the superficial aspect of the cerebral or cerebellar cortex. The surgeon is often able to remove or debulk these tumors at the time of surgery, thereby affecting not only a diagnosis but also substantial cytoreduction and potential cure. Disadvantages include cost, morbidity, and mortality associated with the surgery itself; tumor seeding of the surgical site; and the potential of enhancing the biologic activity

of the tumor itself. Additionally, the possibility exists of the tumor being responsive to chemotherapy, in which case the risks of surgery would not be warranted.

Less invasive biopsy techniques are available. Fine needle aspiration and needle core biopsy using stereotaxic CT or ultrasonographic guidance are routinely available at some institutions and have proved invaluable in diagnosing tumors that are located in surgically inaccessible areas of the brain. The inherent advantages and disadvantages of fine needle and needle core biopsies relate to the small sample that is obtained. Small needle diameter limits the amount of damage to nontarget tissues, but also limits the amount of tissue available for examination. Fine needle aspiration limits the method of examination to cytology. This offers the advantages of superior assessment of individual cell morphology and rapid turnaround for intraoperative use. The disadvantages of cytology are poor ability to assess histologic architecture and limited ability to apply special staining techniques. The accuracy of fine needle aspiration for diagnosis of intracranial neoplasia has been compared with histopathology in a number of studies, both human and veterinary. In a recent study of 10 clinical cases with necropsy confirmation of the diagnosis, fine needle aspiration had an exact agreement with the histopathologic diagnosis in 60% of the cases and made the correct diagnosis with regard to neoplasia and degree of malignancy in 100% of the cases.[102] In these cases, fine needle aspiration was performed after the brains had been removed en bloc from the cranium and the lesions were located with MRI. Whether similar results can be obtained antemortem in clinical cases remains to be evaluated.

191.4.6.2 Meningioma

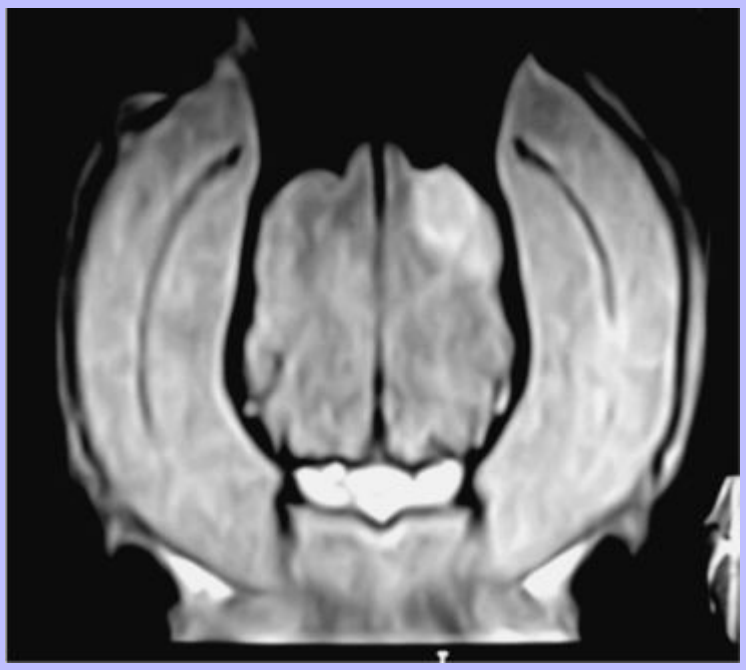
Meningiomas are the most common intracranial neoplasm in dogs and cats. They are mesenchymal tumors that arise from the cells of the three layers of the meninges: (1) the dura mater, (2) the arachnoid, and (3) the pia mater.[93,103,104] However, most commonly from the meningiocytes of the arachnoid layer. These neoplasms are in most cases benign, solitary tumors that grow slowly, often adhering to the dura mater or leptomeninges. Intracranial and extracranial metastases have been reported but are extremely rare. Meningiomas can also occur within spinal cord and intraorbital locations, although greater than 80% are reported to be intracranial.[105]

There does not appear to be a particular breed or sex of dog predisposed to meningiomas; however, it has been suggested that dolichocephalic breeds may be at increased risk.[106] Meningiomas are characteristically a neoplasm of older dogs, with 95% occurring in dogs over 7 years of age.[107]

Clinical signs in dogs with meningioma depend on the location of the tumor.[108] The majority of canine meningiomas are located in the cerebrum and often arise from over the convexities of the cerebral cortex or the falx cerebri.[104,106,109] The most common clinical signs in these dogs are seizures and changes in behavior or attitude. Cerebellar meningiomas may cause dysmetria, circling, ataxia, or intention tremors, and meningiomas that arise from the brain stem can potentially result in cranial nerve deficits or paresis.[108]

Although definitive diagnosis of an intracranial meningioma can only be made by histopathologic tissue examination, CT images and MRI are often highly suggestive of this tumor type. Meningiomas are usually visualized as a solitary, contrastenhancing, broad-based mass (Figure 191-31).[110] Typically, the tumor is homogenous in appearance with a low-intensity capsule separating the mass from adjacent brain parenchyma. In some cases, meningiomas are cystic in appearance.[111]

Figure 191-31 Meningiomas appear as a solitary, contrast-enhancing mass with a broad base on the dural surface. They are found most commonly over the convexity of the cerebrum.



The three major treatments that are used in veterinary medicine today for treatment of canine meningiomas are (1) surgery, (2) radiation therapy, or (3) a combination of the two.[112] Gene therapy has also been attempted in a limited number of studies, and some reduction in tumor size has been achieved; however, this practice has not yet gained wide acceptance.[112,113] Efficacy of chemotherapeutic compounds for the treatment of meningioma has not been demonstrated.[114] In humans the role of chemotherapy for the treatment of meningiomas is unclear and is usually reserved as a rescue protocol in nonresponders.[115] Studies in the past have reported extended survival times in dogs with brain tumors that received radiation therapy with or without surgery.[116–118] Cobalt-60 has been the most common source of radiation therapy used for treatment of canine brain tumors in the past and has been used successfully for several years to treat intracranial meningiomas.[103,119] Orthovoltage radiation has also been used successfully, although it is not considered ideal due to poor beam penetration, profile, and limited field configuration. Linear accelerators are becoming increasingly available for animal treatment at large referral institutions, and external beam megavoltage irradiation is the current recommendation for brain tumors in dogs and cats.[120]

Past radiation treatment protocols have varied from total doses of 30 to 36 Gy in 5 to 6 fractions over 14 to 19 days to the more recent total doses of 45 to 48 Gy in 12 fractions over 26 days.[116] Acute effects have been minimal and usually remain limited to the temporary disruption of normal epithelial tissue within the radiation field. Early delayed effects due to transient demyelination can cause recurrence of presenting signs or mental depression and usually occur within a few weeks to a few months after treatment. These changes

are typically steroid responsive and transient. Late delayed effects can occur more than 6 months after treatment, are not responsive to therapy, and are usually associated with brain necrosis.[121] In the human literature, daily fractions of 3 Gy or less given over 4 weeks with a total normal tissue dose of 50 to 55 Gy appears to induce fewer late effects, and this approach has been advocated by some in veterinary medicine.[122] The use of stereotaxic delivery of radiation may be of benefit because it decreases the dose of ionizing radiation to the surrounding healthy tissue. This method has been used recently to treat canine meningiomas with encouraging results.[123]

The prognosis for dogs with intracranial meningiomas that receive no treatment is poor. One study found that untreated dogs had a median survival time (MST) of 75 days after CT diagnosis.[124] Dogs receiving only palliative therapy (corticosteroids and anticonvulsants) after diagnosis by CT or MRI have shown average survival times ranging from 59 to 81 days.[118,121] However, extended survival times of greater than 16 months have been noted when surgical resection of the meningiomas is followed by radiation treatment.[117,125]

191.4.6.3 Neuroepithelial Tumors

Neuroepithelial tumors or gliomas are comprised of both astrocytic and oligodendroglial cell lines, as well as other neuroepithelial tissues (see Table 191-1). Although the true incidence in dogs is unknown, these tumors are second only to meningiomas when an intracranial neoplasm is histopathologically diagnosed. Astrocytomas are the most common human intracranial neoplasm; much effort has been devoted to the identification of imaging and histopathologic findings associated with rapidly growing, aggressive tumors. The World Health Organization (WHO) classification scheme characterizes astrocytomas based upon aggressiveness and allows for treatment planning and prognostication. High-grade (malignant) astrocytomas may arise alone or from a preexisting low-grade tumor. Low-grade astrocytomas (secondary) are much less invasive and carry an improved prognosis. Regardless, astrocytomas are usually fatal in both dogs and humans, although the survival time is unpredictable. In humans, the MST of patients with low-grade astrocytomas is 5 years. Interestingly, death usually results from malignant transformation into a high-grade tumor.

The characteristic appearance of an astrocytoma or oligodendroglioma on an MRI is that of a diffuse, nonenhancing or variably enhancing mass (Figure 191-32) that is hypointense on T1-weighted images and best seen on T2-weighted images. Typically the lesion exhibits a local mass effect. The borders of the tumor often appear distinct on MRI but histologically these tumors are usually invasive. Occasional evidence of invasion can be imaged if a powerful MRI is used.

Treatment of gliomas, whether an undifferentiated tumor, oligodendroglioma, or astrocytoma, is similar to that of a meningiomas: surgery and radiation therapy. These tumors, depending on the classification, tend to be invasive. As such, surgery would be expected to be less curative than it would for meningiomas. Chemotherapy may play a larger role in the adjunctive treatment of malignant gliomas compared with meningiomas. Although still controversial, sole-drug and multidrug chemotherapy has been shown to increase the proportion of long-term survivors in humans from less than 5% to approximately 15% to 20%.[126] The most commonly used drugs are procarbazine, lomustine, and vincristine. The role of these drugs and others has yet to be defined in dogs.

Choroid plexus tumors typically display homogenous contrast enhancement with discrete borders and appear hyperintense on (postcontrast) T1-weighted images. They can occur in the lateral, third, or fourth ventricle,

because these locations are where the choroids plexus resides (Figure 191-33). The most common location, however, is in the lateral aspect of the fourth ventricle.[127] Choroid plexus tumors are well vascularized, leading to good contrast enhancement and increased bleeding if the tumors are excised. These tumors often cause obstructive hydrocephalus due to their location in the ventricular system. This will be evident on imaging studies and may contribute to the overall morbidity of the animal. Embryologically the choroid plexus and ependymal cells are derived from similar tissues. As such, the MRI appearance and tumor distribution for choroid plexus papillomas and ependymomas are similar. However, ependymomas appear to be more uncommon and have a predilection for brachycephalic breeds of dogs.[128] Treatment for choroids plexus and ependymal tumors is largely conjectural, because no study has clearly defined the role of surgery, radiation therapy, or chemotherapy. When accessible, surgery is probably the treatment of choice. However, the high vascularity of these tumors, combined with the relative inaccessibility, indicate that chemotherapy or radiation therapy may play a vital role in effective management.

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Figure 191-32 Gliomas appear as intraparenchymal masses with variable enhancement.

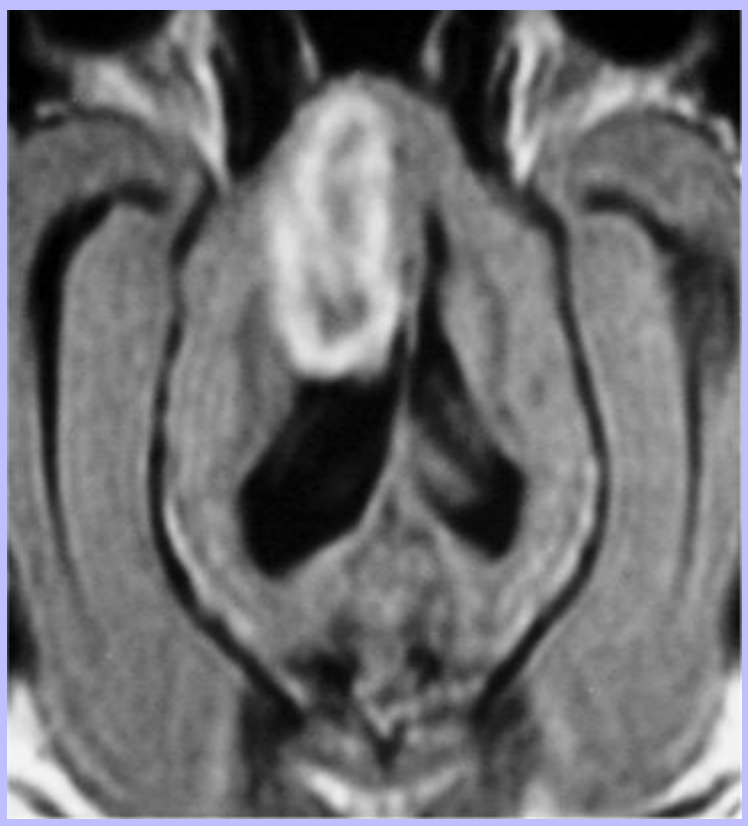

Figure 191-33 Choroid plexus papillomas arise within the ventricular system and have discrete borders. They usually are more uniformly enhancing than this example.

191.4.6.4 Central Nervous System Lymphoma

Primary CNS lymphoma is a result of neoplastic transformation of native lymphocytes within the CNS, whereas secondary CNS lymphoma results from spread of systemic disease. Regardless, involvement of the CNS provides the clinician with a challenge in both disease diagnosis and treatment. The blood-brain barrier effectively excludes many common drugs that are used to treat systemic disease and can hide involvement of the brain, making it difficult to confirm the presence of a neoplastic process within the brain. Diagnosis of CNS lymphoma is made by CSF analysis and, in cases of systemic disease, the presence of atypical lymphocytes in other body systems. In one study, 7 out of 7 dogs with CNS lymphoma had atypical lymphocytes noted in the CSF.[129] The clonal expansion of lymphocytes in lymphoma will all express identical unique DNA sequence in the variable region of the antigen receptor gene. A PCR assay that detects clonal rearrangement of these genes has been developed for dogs and hold promise as a means of diagnosing CNS lymphoma from CSF.[129a] Localized radiation therapy of the brain may be effective in cases of primary CNS lymphoma. Intrathecal administration of cytosine arabinoside at 20 mg/m^2, diluted in 2 to 4 mL of lactated Ringer's solution, given twice weekly for a total of 6 treatments, has been advocated by one author.[129] Another treatment method uses 100 mg/m^2 of cytosine arabinoside (intrathecal) given weekly 1

week beyond the point at which the CSF is devoid of all atypical lymphocytes. Lomustine (CCNU), an alkylating nitrosourea chemotherapeutic, is effective at crossing the blood-brain barrier and has gained support for the treatment of resistant systemic lymphoma in dogs.[130] CCNU and other chemotherapeutics that cross the blood-brain barrier (e.g., hydroxyurea, methotrexate) may also be considered a good choice for systemic treatment of lymphoma when the CNS is involved.

Intravascular lymphoma, a type of systemic lymphoma that is limited to the lumen and walls of blood vessels, has also been reported in the dog. This disease has a propensity for the brain and lungs in both dogs and humans and ultimately results in the occlusion of blood vessels.[131] Diagnosis is difficult, because both the CSF and peripheral blood analysis are not diagnostic for this disease. Imaging of the brain with MRI could yield evidence of multifocal abnormalities. In one case report, an MRI revealed diffuse postcontrast enhancement of the brain parenchyma and multifocal areas of hyperintensity.[132] Definitive diagnosis is made by histopathologic examination of a biopsy specimen. Treatment for intravascular lymphoma is similar to that for systemic disease: chemotherapy. However, specific treatment regimes and survival data for a large case series is not available.

191.4.6.5 Metastatic Neoplasms of the Central Nervous System

Metastatic neoplasms of the CNS are common in both humans and dogs. Generally, systemic tumors spread to the brain; spread to other parts of the CNS occurs with less frequency. Although the exact incidence of CNS metastasis in veterinary patients is unknown, it is known that in humans metastasis occurs in 20% to 30% of cases of systemic neoplasia. It has been noted in some studies that the rate of CNS metastasis has increased over the last 2 to 3 decades.[133] However, this finding may only reflect an increased ability to detect antemortem evidence of metastasis with advanced imaging procedures or increased longevity of animals with systemic neoplasia as a result of better treatment regimes. Regardless, CNS metastasis has become a real concern for veterinarians and, like treatment of CNS lymphoma, presents a unique challenge in both the diagnosis and treatment of these tumors.

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Although it is true that any form of neoplasia has an inherent ability to spread, certain tumor types have been found to metastasize to the CNS with some regularity. Involvement of the CNS can be accomplished by direct invasion from the surrounding structures or systemic spread through the vascular system. Nasal adenocarcinomas tend to be locally invasive, and systemic tumors such as melanomas, hemangiosarcomas, and lymphosarcomas tend to spread hematogenously.

Recognizing CNS metastasis in an animal with systemic disease requires paying careful attention to the neurologic examination and questioning of the animal's caregiver. Because neurodiagnostic procedures are expensive and require anesthesia, reasonable suspicion is necessary to justify the search for CNS metastasis. CSF analysis may be beneficial as a screening test. Although CSF cytology rarely yields abnormal cells, it can provide other clues to CNS involvement. Albuminocytologic disassociation, or increased protein without an increased cell count, is a common finding in cases of tumors within the CNS. In other cases the CSF may have increased white cells. To confirm a diagnosis, however, advance imaging with MRI or CT should be performed. Metastatic tumors will lack a defined blood-brain barrier; therefore they commonly exhibit well-defined contrast enhancement (Figure 191-34) and are best visualized on MRI that is T1-weighted. Biopsy would be necessary to confirm a diagnosis.

In some instances an animal with systemic neoplasia may have signs limited to the CNS. In these cases a tumor may be diagnosed on MRI and treatment begun prior to diagnosis of a systemic tumor. Therefore it is

good practice to perform a thorough systemic workup, including thoracic and abdominal radiographs and, potentially, abdominal ultrasonography on every animal that is diagnosed with a brain tumor.

191.4.6.6 Pituitary Tumors

Pituitary tumors can be considered one of the most common intracranial neoplasms in dogs. Cushing's disease, or pituitary-dependent hyperadrenocorticism (PDH), comprises 80% to 85% of dogs with naturally occurring Cushing's syndrome. Virtually 100% of dogs with PDH have a functional tumor of either the pars distalis (80%) or pars intermedia (20%) of the anterior pituitary. These tumors are generally less than 1 cm in diameter and cause little damage to surrounding neural tissue. However, these tumors may continue to grow throughout the animal's life, ultimately resulting in both neurologic deterioration and death. Pituitary macrotumors—tumors greater than 1 cm in diameter—are also fairly common in dogs. These tumors are generally nonfunctional and cause clinical signs related to a space-occupying mass in the cranium. Most animals with expansive pituitary tumors exhibit signs related to hypothalamic disturbance (diencephalic syndrome), such as propulsive and constant pacing, behavior changes, endocrine disturbances, loss of vision, and potentially proprioceptive deficits.

Figure 191-34 Because they lack a blood-brain barrier, metastatic tumors such as this hemangiosarcoma of the diencephalon show well-defined contrast enhancement.

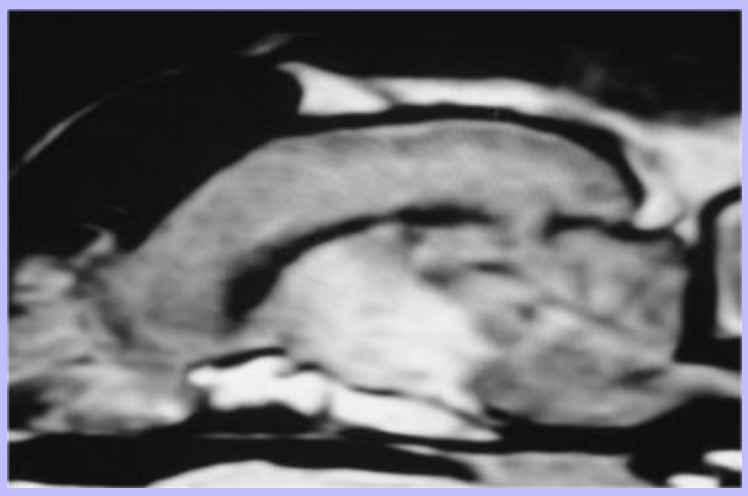
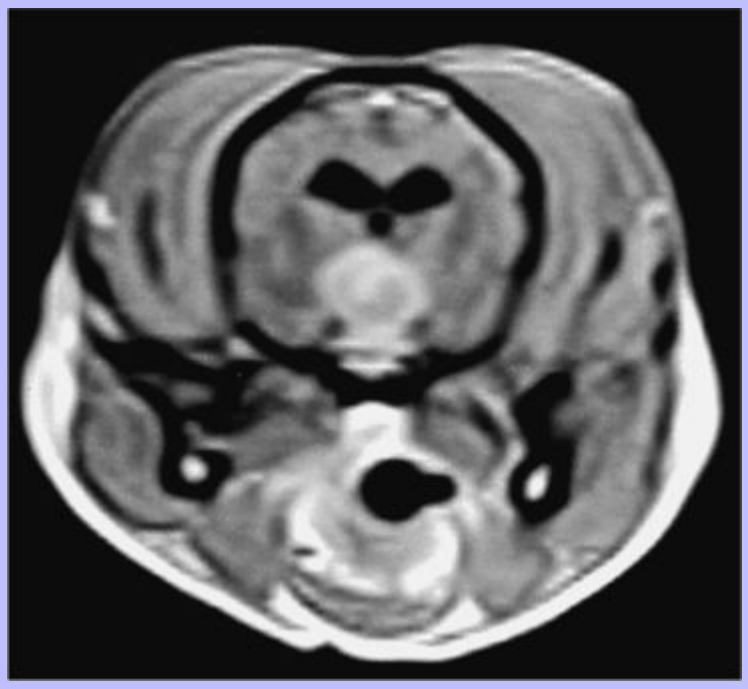


Figure 191-35 Pituitary macrotumors arise from the sella and invade the hypothalamus. They typically show marked contrast enhancement.



Diagnosis of a pituitary tumor is made with an MRI or CT (Figure 191-35). These tumors exhibit bright homogenous contrast enhancement with distinct borders. Peritumoral edema can be extensive in animals with large pituitary tumors. It is important to note that the anterior pituitary lacks a functional blood-brain barrier, because this tissue embryologically is derived from Rathke's pouch of the oral ectoderm. As such the tissue will normally enhance with the addition of a contrast agent. However, a pituitary microtumor can generally be visualized as an asymmetrical enhancement of the anterior pituitary.

Some pituitary tumors in humans are responsive to chemotherapy, but the treatment of choice is surgical excision. The cure rate is high, and perioperative morbidity and mortality is low. In dogs, pituitary surgery is rarely performed. Where it is performed in dogs with pituitary microtumors and PDH, a remission time of up to 39.4 months has been noted. The 1-year estimated survival rate was 84%, the 2-year survival was 80%, and the overall success rates of hypophysectomy around 73.1%.[134] The growth rate of pituitary tumors in dogs with PDH is unknown, but in one study 36% of dogs that had a tumor greater than or equal to 4 mm exhibited continued tumor growth and developed CNS signs within 1 year.[135] This finding may indicate that surgical removal of the tumor should be performed early in the disease process, prior to expansive tumor growth and CNS dysfunction.

Surgery for pituitary macrotumors is rarely performed, because the size of the tumor and location make complete excision improbable. In these cases, radiation therapy is generally recommended.

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192 CHAPTER • 192 Multifocal Neurologic Disease

Rodney S. Bagley

Many diseases occur primarily or exclusively in specific areas within the nervous system. These conditions cause clinical signs that allow clinicians to localize lesions to discrete areas within the nervous system. Some diseases, however, affect the nervous system in a number of anatomically and functionally distinct areas (Box 192-1). In these instances, a constellation of clinical signs result from dysfunction of these differing neuroanatomic areas. It is also possible that, when clinical signs reflect more than a single level of neuroanatomic involvement, more than one disease is present within the nervous system in the same animal (e.g., a brain tumor and a cervical disk extrusion). Therefore it is reasonable to expect that signs of neurologic dysfunction will be found in multiple areas within the nervous system in animals with more than a single disease process. Diseases that primarily affect specific areas of the nervous system, such as the spinal cord or brain, are discussed in those chapters pertaining to those discrete neurologic regions. In this chapter the more clinically important diseases that often result in multifocal or diffuse clinical signs are reviewed. If the neurologic signs present in an animal cannot be localized to one functional area within the nervous system, consideration should be given to these diseases.

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192.1 Box • 192-1 Diseases That Commonly Result in Multifocal Nervous System Signs

192.1.1 Degenerative

Storage disease

Multineuronal degeneration

192.1.2 Anomalous

Hydrocephalus/syringomyelia/hydromyelia complex

192.1.3 Metabolic

Hepatic

Renal

Hypoglycemia

Thyroid (hypo and hyper)

Hyperadrenocorticism

Hyperosmolar syndromes

Adipsia

192.1.4 Neoplastic

Lymphoma

Leukemias

Metastatic tumors

192.1.5 Nutritional

Thiamine

192.1.6 Inflammatory

Infectious

Viral

Distemper

Herpes

Parvo

Parainfluenza

FIP (Feline infectious peritonitis virus)

FIV (Feline immunodeficiency virus)

Bacterial

- Bacterial encephalitis
- Tetanus

Fungal

- Cryptococcosis
- Blastomycosis
- Coccidiomycosis
- Candidiasis
- Aspergillosis

Protozoal

- Toxoplasmosis
- Neosporosis

Parasitic

- *Toxocara*
- *Cuterebra*

Rickettsial

- Rocky Mountain spotted fever (RMSF)
- *Ehrlichia*

Unclassified

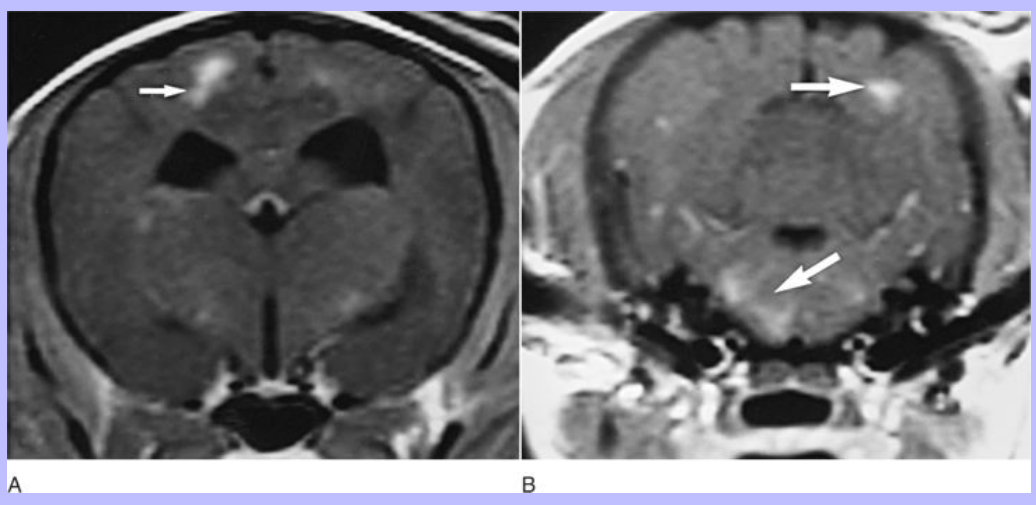
- Protothecosis
- Noninfectious
  - Granulomatous meningoencephalitis (GME)
  - Breed-associated CNS inflammation
    - Pug encephalitis
    - Maltese encephalitis
    - Yorkshire terrier encephalitis
  - Spinal cord vasculitis
  - Nonclassified
    - Steroid-responsive meningitis
- Idiopathic
  - Dysautonomia
- Toxins
- Vascular disease
  - Intracranial hemorrhage
  - Thromboembolism
  - Hypertension
  - Spinal hemorrhage

192.2 INFLAMMATORY DISEASES

Encephalitis and meningitis often exist concurrently in dogs and cats and are the most common group of diseases that result in multifocal nervous system signs.[1–3] Causes include both infectious and noninfectious causes. Infectious agents associated with encephalitis and meningitis include viral (distemper, parvovirus, parainfluenza, herpes, feline infectious peritonitis [FIP], pseudorabies, rabies), bacterial, rickettsial (Rocky Mountain spotted fever [RMSF], *Ehrlichia*), spirochete (Lyme disease, leptospirosis), fungal (blastomycosis, histoplasmosis, cryptococcosis, coccidiomycosis, aspergillosis), protozoal (toxoplasmosis, neosporosis), parasitic, and unclassified organisms (protothecosis). Incidence of infectious agents causing meningitis varies with geographic location. Additionally, infectious causes of encephalitis and meningitis exist that have not been identified or well-clarified as causes of inflammatory central nervous system (CNS) disease in small animals.

Encephalitis and meningitis may affect the nervous system at multiple levels. Intracranial signs (behavior changes, mental status abnormalities, visual deficits) including cranial nerve dysfunction and spinal cord signs (paresis, ataxia) are commonly seen. Neck pain is a prominent clinical feature of meningitis but may be less obvious with pure parenchymal involvement (e.g., myelitis). Pain may be assessed by vocalization during direct palpation or by reluctance to move the head and neck freely or with manipulation (decreased range of motion). Diffuse spinal pain is also possible. Because these diseases are often polysystemic, diffuse pain may also result from an associated articular facet polyarthritis or myositis. Some animals will react as if painful to minimal palpation (hyperesthestic) anywhere on the body, especially of the limbs and face. Many animals become irritable and uncharacteristically aggressive. Because chorioretinitis is often concurrent, fundic examination may yield important clues to the polysystemic nature of the problem.

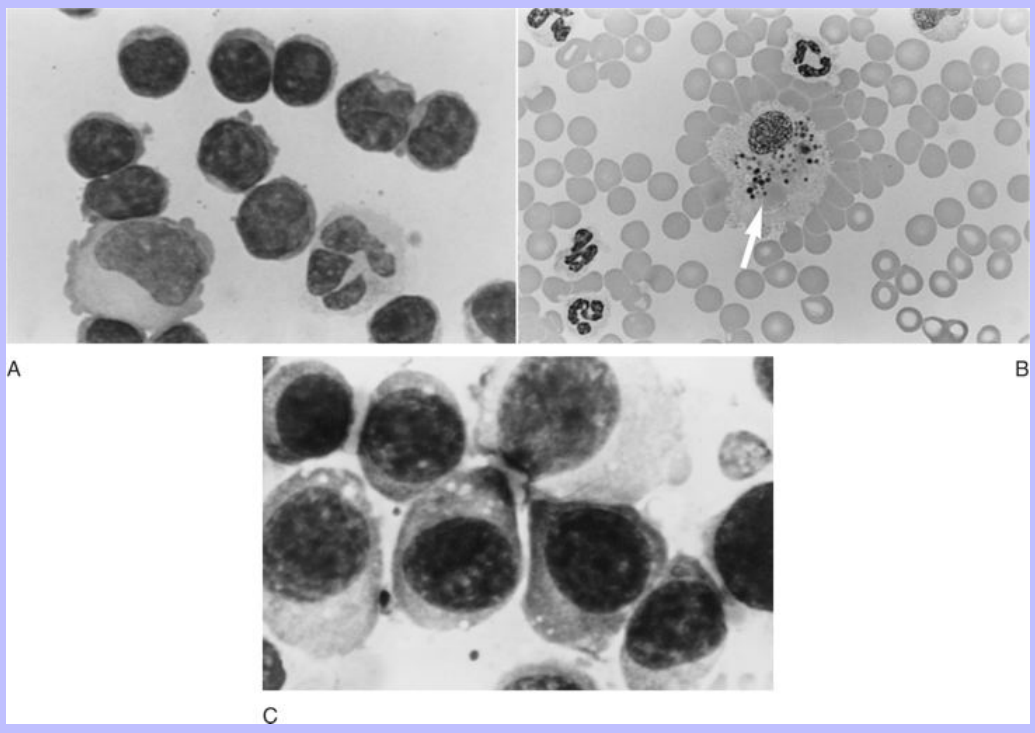
Figure 192-1 Transaxial, T1-weighted, contrast-enhanced (Magnevist [gadolinium DTPA], Berlex Laboratories, Inc., Cedar Knolls, NJ) magnetic resonance image (MRI) at the level of the thalamus **(A)** and brain stem **(B)** from a dog with multifocal clinical signs. Multifocal lesions are present in the cortex and brain stem *(arrows)*. Diagnosis was granulomatous meningoencephalitis (GME).



In many animals with encephalitis and meningitis, the cardinal signs of systemic inflammatory processes, such as the presence of a fever and increases in white blood cells (WBCs) in the leukograms, may not be found as localized inflammatory disease in the CNS and may not elicit a systemic inflammatory response. For ultimate diagnosis, imaging studies such as magnetic resonance imaging (MRI) and computed tomography (CT) are helpful in defining structural lesions (Figure 192-1).[4] Multifocal, discrete, anatomic lesions are often present within the nervous system and may be especially conspicuous after intravenous contrast medium administration, suggesting alterations in the blood-brain barrier to the cerebral vasculature. Cerebrospinal fluid (CSF) analysis is often important in diagnosis of an inflammatory CNS disease. CSF results alone, however, rarely yield a definitive causative diagnosis and are most helpful when evaluated concurrently with CNS anatomic imaging. Increased numbers of nucleated cells and increased protein concentrations commonly present in CSF from animals with inflammatory CNS disease may also be present with a variety of CNS diseases that result in secondary inflammation (i.e., tumors, trauma, vascular disease) (Figure 192-2). Nucleated cell numbers and types are variable depending upon the cause. In most primary inflammatory CNS conditions, however, mononuclear cells and neutrophils are the predominant cell types present. Eosinophils may indicate a parasitic or allergic response but have also been seen with certain infection conditions, such as *Cryptococcus* in cats and protothecosis in dogs. If prior CNS hemorrhage has occurred, erythrophagocytosis may be noted (see Figure 192-2). Primary CNS hemorrhage may also secondarily result in inflammation.

Unfortunately, evidence of inflammation on CSF evaluation alone is not specific for primary encephalitis because other CNS diseases (e.g., neoplasia, trauma, infarction) may result in a CSF pleocytosis and protein elevations. Therefore evaluation of serum or CSF titers for the aforementioned infectious diseases is often necessary to establish associated infectious diseases. It is recommended to assess several titers in animals with inflammatory CNS disease in an effort to establish an infectious cause. Common infectious causes for dogs include toxoplasmosis, neospora, distemper, and some fungi. Common infectious causes in cats include toxoplasmosis, FIP, *Cryptococcus*, and other as yet unclassified but suspected viral agents. In up to 60% or more of cases of encephalitis, however, an infectious cause is not identified.

Figure 192-2 Cerebrospinal fluid (CSF) cytology from various dogs with multifocal clinical signs. **A,** Predominantly small mononuclear cells with some neutrophils and monocytes are seen, consistent with a lymphoid pleocytosis (×100). **B,** Numerous red blood cells (RBCs), some neutrophils, and erythrophagocytosis *(arrow)* are seen (×50). **C,** The predominant cell is a large blast-type cell, consistent with lymphosarcoma (×100).



Occasionally, CSF from an animal with inflammatory CNS disease will be normal at a single sampling. This is especially true when the disease is primarily intraparenchymal and sometimes after previous corticosteroid administration.

Treatment of meningitis is ideally directed at a specific causative organism. However, treatment often needs to be initiated prior to establishing the exact cause of inflammation because results of serologic testing may delay diagnosis. More aggressive treatment is warranted in animals with severe to rapidly deteriorating clinical signs prior to a definitive diagnosis being rendered.

In this situation, multiple drug therapies are recommended and treatment should begin earlier rather than later in the disease course. Trimethoprim-sulfadiazine (30 mg/kg every 12 hours), clindamycin (20 to 25 mg/kg every 12 hours), doxycycline (10 mg/kg orally every 24 hours), and corticosteroids (prednisone 1 to 4 mg/kg every 12 hours) can be used in combination. Although corticosteroids may seem to be contraindicated with infectious diseases, they are often beneficial in the acute treatment of brain inflammation and edema and have proven

beneficial even with bacterial meningitis in children. It is often the associated inflammatory reaction in the CNS that is more detrimental to CNS function than the primary pathophysiologic effects of the organism itself. If rickettsial diseases are suspected, chloramphenicol (15 to 25 mg/kg orally every 8 hours) can be substituted or added to the regime; however, this drug is becoming infrequently used in veterinary medicine in general. If the animal is receiving phenobarbital, the clinician should not use chloramphenicol, because this drug will decrease the metabolism of the barbiturate and the animal could become comatose and die. Therefore in animals with encephalitis and seizures, it is probably wise to avoid chloramphenicol in case barbiturates are needed for seizure control.

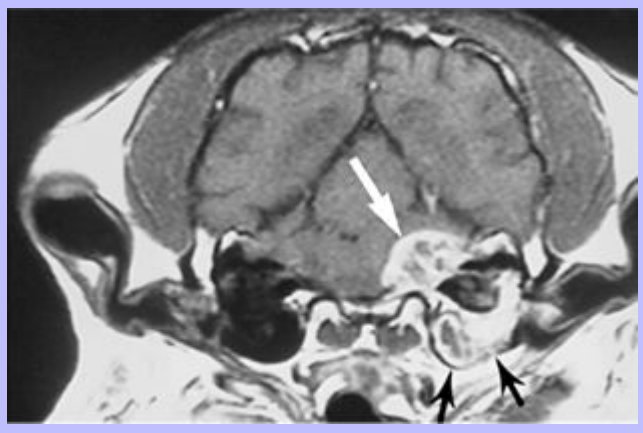
192.3 SPECIFIC INFLAMMATORY DISEASES

192.3.1 Bacterial Diseases

Bacterial meningitis is rare in dogs and cats.[1] Often, a concurrent disease that results in persistent bacteremia is present. Notable examples in dogs are endocarditis and pyometra. Extension of a local bacterial disease process, most commonly from the nasal passages or middle ear, is also possible (Figure 192-3). Dogs and cats with bacterial meningitis usually have rapidly progressing clinical signs, and the disease is often fatal. Abscesses may form, resulting in focal clinical signs.[5] A variety of causative bacteria may be present.

Diagnosis is aided by CSF analysis. CSF collection should be performed with caution, however, because the associated intracranial alterations associated with fulminant bacterial encephalitis may result in an increased intracranial pressure and resultant brain herniation. Although attempts have been made to classify CSF changes commonly associated with septic inflammatory CNS diseases, the degree of crossover in CSF nucleated cell counts and types makes it difficult to presumptively diagnose a specific inflammatory disease from the CSF results alone. One clue to the presence of bacterial component is a decreased glucose concentration in CSF as compared with plasma, presumably due to consumption of glucose by the organisms. If bacterial encephalitis is suspected, additional CSF should be collected in a sterile container without fixative or other chemicals for culture and sensitivity. Glass tubes containing ethylenediamine tetra-acetic acid (EDTA), commonly used for submission of CSF for cytologic analysis, are not appropriate for culture because the EDTA is bacteriostatic and may hinder organism growth. Because the number of organisms in CSF can be small, the greater amount of CSF cultured the more likely an organism will be isolated.

Figure 192-3 Transaxial, T1-weighted, contrast enhanced (Magnevist [gadolinium DTPA], Berlex Laboratories, Inc., Cedar Knolls, NJ) magnetic resonance image (MRI) at the level of the vestibular area from a snow leopard with seizures and a head tilt. A brain abscess is present, extending from the middle and inner ear to the brain stem *(arrows)*. A surgical biopsy and culture found both fungal and bacterial organisms were present.



Because identification of the organism may take a few days and the clinical signs are often rapidly progressive, treatment is often initiated prior to culture analysis. As stated previously, prior to a specific cause being identified, trimethoprimsulfadiazine, clindamycin, doxycycline, and corticosteroids can be used in combination for treatment of CNS inflammation and infection. Methylprednisolone sodium succinate (30 mg/kg) can be administered intravenously initially if the animal is severely impaired, rapidly deteriorating, or unable to swallow. If the animal is more mildly affected and can swallow effectively, prednisone or prednisolone can then be initiated at anti-inflammatory doses. In some instances, the infection will form a discrete abscess. Because this abscess and its associated inflammation can rapidly increase intracranial pressure, surgical decompression of a focal abscess should take place as soon as possible. Similarly, penetrating intracranial wounds may require débridement to avoid infectious complications.

Although not associated with meningitis per se, tetanus can result in both confusing and diffuse clinical signs. Tetanus is due to a neurotoxin secreted by the organism *Clostridium tetani*. This toxin binds to interneurons and inhibits the release of inhibitory neurotransmitter (glycine) in inhibitory interneurons (Renshaw cells). The organism gains access to the body through a wound, which often cannot be seen in dogs. Cats, which are more resistant to the disease than dogs, usually have a visible wound.

Clinical signs include extensor rigidity, inability to open the mouth, salivation, prolapsed nictitating membrane, inability to urinate, and seizures. Bradycardia, megaesophagus, and hiatal hernia may be seen.[6,7] Tetanus localized to one part of the body is occasionally found. Diagnosis is based upon clinical signs. Anaerobic culturing of a wound may reveal the organism. A serum test for antibodies has occasionally been useful but is not readily available. Treatment includes wound débridement, antitoxin (administered once intravenously),

penicillin, muscle relaxants, enteral or parenteral nutrition support, a quiet environment, and good supportive care. Anticonvulsants are given if seizures occur.

192.3.2 Viral Diseases

Canine distemper remains a surprisingly common cause of neurologic dysfunction in dogs. This disease is caused by a paramyxovirus. Clinical signs can occur at any age, regardless of vaccination status. Most commonly, young dogs with inadequate vaccinations are affected with the polysystemic signs (i.e., gastrointestinal [GI], respiratory) and the neurologic signs of infection. However, in the modern era of prophylactic vaccination for distemper, distemper infection may only result in nervous system signs. Nervous system disease associated with distemper is characterized pathologically by two main forms: (1) neuronal and glial cell death (polioencephalopathy) and (2) demyelination (leukoencephalopathy).[3,8–10] It has been suggested that those animals with a poorer antibody response to the virus tend to have the former form and those with an adequate immune response to the virus tend to have the latter—immune-mediated demyelination. Any region of the nervous system can be involved. Myoclonus, a rhythmic, shocklike contraction of a muscle or group of muscles, is usually the result of previous or concurrent distemper infection and lends a clue to the virus' presence. Muscles of the limbs are commonly involved, but other muscles, including the tongue, may be affected.[11]

Clinical signs of a prior or concurrent systemic illness (respiratory, GI) are not always found in dogs with distemper. Diagnosis is suggested by finding inclusion bodies in pathologic specimens. Elevated CSF antibody titer (immunoglobulin G [IgG] and immunoglobulin M [IgM]) against distemper virus is supportive of a diagnosis, especially if concurrent serum distemper titers are not elevated or if a CSF electrophoresis suggests intrathecal antibody production. Occasionally, dogs with CNS distemper do not have positive CSF distemper titers.[12] No specific treatment is effective against the distemper virus. Corticosteroids, although seemingly contraindicated, may decrease inflammation and improve clinical signs in some dogs.

Other viruses of dogs that result in encephalitis and meningitis do so primarily in very young animals. Examples include herpes virus, parvovirus, and parainfluenza virus. Occasionally, these viruses will cause encephalitis and meningitis in adult dogs. Parainfluenza virus has a propensity for causing hydrocephalus.

FIP results from a coronavirus-induced vasculitis. This disease can involve various areas of the nervous system, primarily the intracranial structures and spinal cord. Very young and, conversely, very old cats seem predisposed.[13] Of the two forms of FIP that exist in cats, the “dry” form commonly affects the nervous system. This viral infection results in an immune complex vasculitis that is responsible for most of the pathologic effects. CSF analysis may show a pleocytosis, with either mononuclear cells or neutrophils as the predominant cell type and elevated protein concentration, often greater than 1 g/L (0.1 g/dL). No specific treatment is effective. Immunosuppressive therapy may result in short-term improvement of clinical signs.

Feline immunodeficiency virus has been associated with nervous system signs including behavior changes, seizures, anisocoria, and muscle twitching.[3] As the clinical spectrum of this disease evolves, it may represent an important CNS pathogen of cats. Feline leukemia virus (FeLV) has also been associated with a myelopathy independent of the presence of lymphoma.[14]

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Toxoplasma gondii and *Neospora caninum* are protozoal organisms that can affect any area of the nervous system resulting in encephalitis, myelitis, peripheral neuropathy, or myositis in dogs.[15] These organisms are the most common cause of infectious encephalitis and myelitis in the Pacific Northwest. A classic sign of the

infection in young animals is a hyperextended pelvic limb or limbs. Other systemic signs such as chorioretinitis may also be present. Cats also commonly have toxoplasmosis within the nervous system; however, neosporosis has only been established experimentally in this species. CSF analysis often contains a pleocytosis and increased protein concentration. In some instances, discrete granulomas may be found within the CNS and peripheral nerves. Diagnosis of toxoplasmosis is based on the presence of IgM or rising IgG titers to the organism (toxoplasmosis), on visualization of the protozoan in biopsy specimens, or on both.[16] Clinical distinction between the two organisms is not always possible but is increased by awareness of the later protozoal organism and special staining and electron microscopic characteristics. Although sometimes helpful in the diagnosis, CSF titers to toxoplasmosis antibodies may be negative in the presence of CNS toxoplasmosis infection. Serum titers may be more often positive compared with CSF titers with CNS toxoplasmosis. Serologic titers to the presence of Neospora are also available to support the diagnosis of this infection. As with most systemic titer results, the presence of antibodies against these organisms does not ensure the presence of active CNS infection.

Treatment for toxoplasmosis currently is clindamycin[17]; however, this drug is often used in combination with a potentiated sulfa drug in immunosuppressed humans with toxoplasmosis.[18] Trimethoprim sulfa antibiotics have also been used successfully to treat CNS toxoplasmosis. Treatment courses of antibiotics are usually administered for as long as 4 weeks. In some animals, constant treatment with antibiotics is necessary to control clinical signs. A similar treatment is used for neosporosis; however, few cases with definitive treatment success have been reported.[19]

192.3.3 Rickettsial Diseases

Infection with rickettsial organisms associated with RMSF and *Ehrlichia* commonly involve the brain stem, particularly the vestibular system.[20] With RMSF a history of systemic illness (usually with a thrombocytopenia) often exists 5 to 10 days prior to development of neurologic signs. As the animal's fever is decreasing, neurologic signs commonly appear. Diagnosis is based on lack of mass lesion with intracranial imaging studies and a pleocytosis on CSF evaluation. Occasionally, increased contrast enhancement is noted in the choroid plexus area in affected dogs. This must be differentiated from the degree of contrast enhancement normally seen in these structures. CSF usually contains mild increases in nucleated cells (<50 nucleated cells/µl; normal <5 nucleated cells/µl) and mild increases in protein concentration (<50 mg/dL; normal <25 mg/dL). Increasing serum titers to the organism supports diagnosis, but results are often available after the disease has progressed. Prognosis is dependent primarily on the severity of clinical signs prior to treatment. Dogs that are severely obtunded prior to treatment are less likely to recover. Dogs with clinical features of vestibular disease after a systemic febrile illness associated with thrombocytopenia should be treated with tetracycline or doxycycline prior to establishing a definitive diagnosis with titers.

192.3.4 Fungal Diseases

Of the fungal diseases that can affect the nervous system, *Cryptococcus*, blastomycosis, coccidiomycosis, candidiasis, and aspergillosis are most common.[2,3] Immunodeficiency may play a role in these uncommon nervous system infections. Definitive diagnosis is made through viewing the organism in CSF or biopsy samples and fungal culture of infected nervous tissues. Treatment can be attempted with antifungal agents; however, the presence of an intact blood-brain barrier may interfere with drugs reaching therapeutic concentration in CNS tissue. Fluconazole and itraconazole hold the most promise for treating fungal

encephalitis and meningitis. These drugs have historically been rather expensive and owner financial constrains often limit effective long-term therapy.

With cryptococcosis, identification of the organism from cytologic evaluation of samples such as CSF, nasal discharge, and skin lesions supports the diagnosis. A neutrophilic pleocytosis, and occasionally an eosinophilic pleocytosis, may be found on CSF analysis. Detection of the cryptoccal capsular antigen in serum is usually diagnostic. Tissue biopsy and fungal culture or fungal culture of CSF may be more definitive in establishing a diagnosis.

192.3.5 Parasites

Involvement of the intracranial nervous system can occur with parasites such as *Cuterebra* larvae, *Toxocara*, and aberrant heartworm migration. These parasitic conditions may result in inflammation with eosinophils.

192.4 NONINFECTIOUS DISEASES

Most meningitis syndromes (~60%) in dogs do not have a definable infectious cause. Noninfectious disease of the supratentorial structures includes some specific diseases such as granulomatous meningoencephalitis (GME), breed-specific encephalitis and meningitis, and many nonspecific entities. GME can occur as a disseminated disease, a focal mass-lesion, or as a primary ocular disease. Unfortunately, many nonspecific encephalities are inappropriately diagnosed as GME. The cause of true GME is not known.[1] Some animals initially thought to have this disease have been shown to have lymphoma. CSF usually shows a mononuclear pleocytosis but is rarely pathognomonic for the disease. Occasionally the CSF will be normal or contain only increases in protein. CT or MRI may show diffuse inflammatory changes or a mass lesion.[4] Biopsy is needed for definitive diagnosis. Treatment options include immunosuppression (corticosteroids, azathioprine), surgery (if a focal mass), or radiation therapy. The latter has shown the most promise recently for definitive treatment of this disease.[21] Most dogs with GME die within 6 months to 1 year after diagnosis unless radiation therapy is used. Newer medical treatments under investigation that show promise in treatment of GME include cytosine arabinoside and procarbazine.[22]

192.4.1 Breed-Associated Encephalitis, Meningitis, and Vasculitis

Multiple primary CNS inflammatory and CNS vasculitis diseases are inherent in specific breeds of dogs. Pug encephalitis is an example of a breed-associated inflammatory brain disease[23]; it usually occurs in young pugs but has been reported in dogs up to 7 years of age. The disease is characterized histologically by forebrain inflammation and necrosis, primarily of the cerebral hemispheres.[23] It is not unusual, however, that initial clinical signs include neck pain, and that the disease is misinterpreted as a primary spinal cord disease such as intervertebral disk disease. Usually this disease has been fatal, and therapy (corticosteroids) has not altered the course of the disease; however, the prognosis with this disease is debatable. A similar disease has been described in Maltese terriers, Yorkshire terriers, and some other breeds.[24–26]

Other inflammatory diseases that do not have a definitive cause are also often grouped together under the heading of "steroid-responsive meningitis."[2,3] Almost assuredly, multiple diseases exist within this group. Younger, large breed dogs such as retrievers are often affected. Clinical signs often include cervical pain as a prominent feature. Additionally, there exists a syndrome of spinal cord vasculitis that occurs in beagles and Bernese mountain dogs. Other dogs such as German shorthaired pointers and Nova Scotia duck trolling

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retrievers have an apparent breed-associated meningitis syndrome.[2,3] Clinical signs are similar to other meningitis syndromes. CSF from affected dogs often contains a preponderance of neutrophils. In some cases associated hemorrhage will make the CSF bloody upon collection. This is often misinterpreted as iatrogenic at time of collection; however, the presence of erythrophagocytosis is helpful in establishing previous CNS hemorrhage. Some of these animals will have positive LE (Lupus erythematous) cell tests, suggesting a possible immune-mediated component to the disease, although LE is quite nonspecific in dogs. Corticosteroid therapy often is rapidly beneficial in these dogs.

192.4.2 Generalized Tremors

Adult animals that have generalized tremors often have associated encephalitis. Many of these dogs also have additional clinical signs that reflect dysfunction of multiple regions with the nervous system. Generalized tremor syndrome occurs in numerous dog breeds.[27–29] Diffuse, low-amplitude tremors are the norm. Many dogs are initially thought to be hypothermic or apprehensive. Historically, dogs with white haircoats were more often affected, thus the term *white shakers*. However, dogs with a variety of haircoat colors, like the miniature pinscher, can be affected.[29] Clinical signs usually occur in young (1 to 4 years of age) dogs and include generalized tremor, ocular muscle tremor, vestibular signs (head tilt, ataxia), cerebellar signs, and seizures. The disease is often associated with a mild encephalitis. CSF from affected animals usually contains mild increases in nucleated cell counts and mild to normal protein content. No obvious cause of the encephalitis has been found. Clinical signs usually respond to immunosuppressive doses of corticosteroids. After the clinical signs have initially resolved, the corticosteroid dose can be slowly decreased (over weeks to months) to prevent recurrence. The disease, in some dogs, will only remain in remission with continual corticosteroid administration.

192.4.3 Dysautonomia

Dysautonomia is a disease that seems to have regional prevalence in the United States with primary concentration in the Midwest (Kansas, Missouri).[30–35] Animals with this disease can have numerous clinical signs reflective of both a diffuse neurologic and systemic process. Clinical signs may include vomiting, diarrhea, ileus, decreased GI motility, dry mucous membranes, dry eyes (keratoconjunctivitis sicca [KCS]), dramatic loss of body mass, pupillary changes with decreased pupillary light reflex (PLR) (mydriasis), dilated anal sphincter, dysuria, and bradycardia. In some instances, decreased to absent spinal reflexes suggest lower motor neuron (LMN) involvement. A regional infectious or toxin cause is suspected. Diagnosis is suspected based on the presence of the aforementioned constellation of clinical signs. Some pharmacologic manipulations may also be helpful, such as assessment of response to 0.1% pilocarpine instillation in the eyes and assessment of wheal and flare reaction subsequent to intradermal histamine administration. Radiographic assessments may show evidence of ileus, distended intra-abdominal organs, decreased intestinal motility after barium administration, megaesophagus (with or without aspiration pneumonia), and distention of the bladder. Treatment is directed at supporting body functions; however, the overall prognosis is poor because clinical signs are persistent.

192.4.4 Central Nervous System Hemorrhage

Hemorrhage in or around the CNS may also result in a multifocal clinical picture.[36,37] Hemorrhage may be associated with systemic bleeding disorders, thrombosis and other vascular occlusive disease, vasculitis, and hypertension. Vascular and other hemorrhagic diseases involving the nervous system are uncommonly reported

in animals, as compared with human beings. With the advent of the increased use of advanced imaging studies such as MRI, vascular disease and CNS hemorrhagic phenomenon are increasingly recognized. Thrombosis, infarction, and hemorrhage can occur spontaneously—secondary to drug therapy (L-asparaginase, anticoagulants)—with thrombocytopenia and other bleeding disorders, anticoagulant rodenticide toxicity, trauma, hypertension (hyperthyroidism, hyperadrenocorticism), atherosclerosis from hypothyroidism, infection (septic emboli), and diseases that result in hypercoagulability such as glomerulonephritis. Of special note, many dogs with idiopathic thrombocytopenia have CNS bleeding complications. Greyhounds appear predisposed to cerebrovascular problems. Clinical signs are usually acute in onset and may be initially progressive because the vascular event results in secondary ischemia, inflammation, and edema. Hemorrhage and infarction may be seen with CT and MRI. Acutely, the associated mass effect and edema can mimic other intracranial structural diseases such as tumor. Diagnosis is supported by cerebral angiography; however, this is uncommonly performed in dogs and cats. Treatment is directed at any underlying cause of thrombosis or hemorrhage. If the hemorrhage results in mass effect, acute surgical decompression may be necessary to avoid severe brain or spinal cord dysfunction. Blood product support, procoagulant, or anticoagulant drugs (as necessary) may be needed during the perioperative and postoperative time.

192.5 METABOLIC DISEASES

Many metabolic diseases may affect the nervous system at multiple levels and result in diffuse or multifocal clinical signs.[38] Hypoglycemia secondary to insulinoma can result in clinical signs of CNS (depression, seizures, tremors) and peripheral (weakness, decreased spinal reflexes, muscle atrophy) dysfunction.[39–44] The dichotomy of seizures (a supratentorial sign) and decreased to absent reflexes (an LMN sign) may initially result in confusion during neuroanatomic localization. Clinical signs of weakness with insulinomas are often attributed to the hypoglycemia, and the concurrent neuropathy is often overlooked.

Hyperthyroidism of cats has been associated with both central and peripheral nervous system abnormalities.[45] CNS signs include restlessness, hyperexcitability, irritability, aggression, wandering, pacing, circling, insomnia, and seizures. Apathy, lethargy, and depression occur infrequently. Focal neurologic deficits may result from associated cerebrovascular accidents, most likely secondary to hypertension. Clinical signs of peripheral nervous system involvement include generalized weakness, neck ventroflexion, muscle tremors, gait abnormalities, and muscle atrophy. Muscle weakness often manifests as a decrease or inability to jump. Neck ventroflexion may occur with other diseases, including myasthenia gravis (MG), polymyopathy (including hyperkalemic polymyopathy), and organophosphate toxicity.

Conversely, hypothyroidism has been associated with various nervous system abnormalities in dogs.[46] Whether these signs reflect a primary metabolic disturbance or secondary structural abnormalities associated with underlying vascular disease is not always determined. Cranial (vestibular, facial, trigeminal) and appendicular peripheral nerves may be abnormal. Morphologic changes in nerves included demyelination, remyelination, and axonal necrosis. These changes, however, are not specific for hypothyroid neuropathy.

Hyperadrenocorticism may result in abnormalities of the muscle and peripheral nervous system.[47] Affected dogs usually are weak, but an extremely small percentage of dogs (<1%) have a stiff gait, most obvious in the pelvic limbs. An associated pseudomyotonic state has been described. In some instances, myotonia may predominate. Whether this secondary consequence of hyperadrenocorticism is primarily a myopathy or neuropathy has not been determined. If hyperadrenocorticism is the result of a pituitary tumor, clinical signs of intracranial disease are also possible. Macroadenomas may enlarge dorsally from the sella and compress the diencephalon. The most common

abnormalities are listlessness, decreased appetite, and, less commonly, disorientation. Seizures and blindness are extremely rare.

192.5.1 Neoplasia

Tumors of the nervous system include primary and secondary (metastasis) neoplasms.[48] Often tumors of the nervous system result in focal clinical signs. Some tumors, however, are diffuse and therefore result in diffuse clinical signs. Prominent examples include lymphosarcoma and carcinomatosis. Multiple cranial nerves (III, IV, V, VI, VII) may be involved with hematogenous neoplasia (leukemias) due to direct involvement with the tumor cells.[49] Choroid plexus tumors, which often arise within the ventricles of the brain, may metastasize within the neural axis by metastasis through the CSF.[48] If the spinal cord is affected, clinical signs of spinal dysfunction may occur concurrent with intracranial signs from the primary tumor. Diagnosis is aided by advanced imaging and CSF analysis.

Neoplasia secondarily involves the brain via metastasis or via direct extension from extraneural sites.[50–52] Clinical signs may be localized or multifocal depending upon the number and location of metastasis and associated pathophysiologic sequelae such as hemorrhage and edema.[51]

192.6 OTHER DISEASES

Many degenerative neurologic diseases of dogs and cats are inherited or congenital; therefore they are seen primarily in young animals.[1] Storage diseases are prominent examples. Diseases that involve the neuronal cell body are more likely to have cerebral, cranial nerve, or peripheral nerve signs, whereas diseases that primarily involve myelin are more likely to result in ataxia and paresis of the limbs.[1] The storage diseases and other degenerative diseases of dogs and cats have been reviewed previously.[1]

Numerous toxins can affect the nervous system, often at multiple sites.[53,54] Examples of primary toxins include organophosphates, metaldehyde, lead, and bromethalin. Diagnosis can be difficult if exposure has not been documented historically. Treatment is directed toward the specific toxin.

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193 CHAPTER • 193 Diseases of the Spinal Cord

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193.1 MECHANISMS OF DISEASE

Spinal cord diseases can be divided into two groups.[1] The first group comprises diseases that affect both the nervous system and other organ systems. The second group includes diseases that are unique to the nervous system, such as disorders of myelin, neurons, or supporting cells (glial cells and the like). Categories of disease that may be included in either of these two groups are congenital and familial disorders, toxicities, nutritional disorders, degenerative diseases, neoplasia, and idiopathic disorders.

The localization of specific functions in the nervous system has important effects on the clinical presentation and progression of spinal cord diseases. Localization of function in the spinal cord causes a pathologic process to result in many different clinical presentations, depending on the part or parts of the spinal cord it affects. For example, a spinal cord neoplasm at the level of the C3 vertebra may result in tetraparesis, whereas the identical neoplasm at the level of the T13 vertebra may result in paraparesis, leaving the thoracic limbs unaffected. Furthermore, localization of function in the spinal cord renders the cord inherently vulnerable to focal lesions that in other organs, where function is more uniformly distributed, might not result in detectable clinical signs. For example, a small infarction of the cervical spinal cord may result in tetraplegia, whereas a similar lesion in the hepatic parenchyma probably would not compromise liver function.[1]

The unique susceptibility of the nervous system to a localized lesion is compounded by its strictly limited capacity to restore function in damaged tissue. Because the pathologic reactions of the spinal cord to disease are to a degree nonspecific, various disorders may induce a somewhat similar histologic appearance.[2,3]

Clinical syndromes that affect the spinal cord may be characterized by a single focal lesion (transverse myelopathy) or by several focal lesions (multifocal disorders). Myelopathies may be *extrinsic,* meaning that spinal cord dysfunction occurs secondary to diseases of the vertebrae, meninges, or epidural space, or it may be *intrinsic,* which means the disease begins as an intramedullary lesion. Extrinsic myelopathies are almost always transverse myelopathies.

Because the nervous system can respond in only a limited number of ways to the numerous causes of myelopathies, a systematic diagnostic approach must be taken for an animal with a spinal cord disorder.

193.2 APPROACH TO A SPINAL CORD PROBLEM

193.2.1 Diagnosis

193.2.1.1 Signalment

Accurate diagnosis of a spinal cord disorder must include consideration of the animal's age, breed, and gender. Diseases may be specific to certain species and breeds.[4–8]

193.2.1.2 History

An accurate and complete history constitutes the initial step in the diagnosis of all neurologic problems. Important aspects of the history include the rapidity of onset of the problem and the nature of its progression. This information may be helpful for determining the cause of a problem. For example, neoplastic diseases that affect the spinal cord often result in focal signs that have an insidious onset and a gradual progression. In contrast, vascular disorders, such as infarction or hemorrhage, may manifest an acute onset of focal signs without evidence of progression. Inflammatory, degenerative, or metabolic disorders generally cause a diffuse distribution of signs with an insidious onset and gradual progression. Traumatic and congenital diseases may result in either a focal or multifocal distribution of signs, most often with an acute onset and without progression, although such diseases may have a progressive course.

Although careful consideration of these factors is helpful in determining the cause of a spinal cord problem, so many exceptions to general statements exist that such information must be used with caution. For example, an acute onset of signs does not rule out neoplasia as a possible cause of myelopathy, because a neoplasm may be associated with rapid decompensation of neural tissue, particularly if vascular factors, such as infarction or hemorrhage, are involved.

193.2.1.3 Physical Examination

The physical examination consists of a series of observations that provide information about the general health of all body systems. The results of this examination supplement the information collected in the history and may implicate involvement of body systems other than the nervous system. For example, an animal suspected of having spinal pain may in fact have abdominal pain. A thorough orthopedic examination should be performed for any dog or cat suspected of having a spinal cord disorder. Particular attention should be paid to examination of the joints. Rupture of anterior cruciate ligaments bilaterally or bilateral patellar luxations may mimic paraparesis caused by a neural disorder.

193.2.1.4 Neurologic Examination

The neurologic examination is an extension of the physical examination. When spinal cord disease is suspected, it is essential to complete a thorough, comprehensive, and unbiased examination of the nervous system. Errors in diagnosis commonly occur when the examiner focuses on only the region of an obvious neurologic deficit and overlooks more subtle alterations in other parts of the nervous system. The objectives of the neurologic examination are to detect any disorder of the nervous system and to determine its location and extent.[4–8]

193.2.1.5 Problem List and Differential Diagnosis

A comprehensive list of problems should be compiled after the physical and neurologic examinations have been completed. All identified problems should be included, even though some may not appear to be directly related to the presenting complaint. A list of the possible causes of each problem should be compiled, with the most probable causes listed first. Ranking of the differential diagnoses is based on the information collected in the history (e.g., signalment, nature of onset and progression of signs) and on the results of the physical and neurologic examinations.

193.2.1.6 Minimum Database

Initial clinicopathologic tests include a complete blood count, blood chemistry profile, and urinalysis. The results of the initial blood and urine tests may support a diagnosis of an infectious or a metabolic or toxic disorder that is either producing or complicating signs of spinal cord dysfunction. Additional diagnostic tests may be required for investigation of disorders suspected on the basis of the results of the initial screening tests. For example, hyperglobulinemia detected in a cat with signs of myelopathy may support completion of a serum feline infectious peritonitis (FIP) virus titer.

Thoracic radiographs should be obtained as part of the minimum database in dogs or cats with a spinal cord disorder. This is especially necessary in older animals, in animals in which abnormalities of cardiovascular or respiratory function are suspected, and in animals in which neoplasia is included on a list of differential diagnoses. Abdominal radiography or ultrasonography should also be performed.

193.2.1.7 Ancillary Diagnostic Investigations

The recommended essential procedures for diagnosis of a myelopathy, in advised order of completion, are noncontrast vertebral radiography, cerebrospinal fluid (CSF) analysis, and myelography. Other procedures, such as electrophysiologic testing or advanced imaging (computed tomography [CT] or magnetic resonance imaging [MRI]), may be added to this list, depending on the nature of the problem investigated.

193.2.1.7.1 Noncontrast vertebral radiography

Noncontrast vertebral radiography is essential to the accurate diagnosis of a disorder affecting the spinal cord.[4–8] Owing to the limitations of a neurologic examination in outlining multiple lesions of the spinal cord and for the purpose of comparison if problems related to other regions of the vertebral column occur in the future, the entire vertebral column must be radiographed. Correct technique, exact positioning, and use of appropriate projections are essential.[9–12] Further diagnostic investigations may be indicated based on the initial interpretation of the noncontrast vertebral radiographs. For example, a finding of discospondylitis may be followed by culture and sensitivity testing of the blood, urine, or an aspirate from an infected disk or by serologic testing for *Brucella canis*. Differentiation of an infectious lesion from a vertebral neoplasm may be difficult on the basis of noncontrast vertebral radiography alone. In such cases, a biopsy, by means of needle aspiration or surgical excision, may be indicated.

193.2.1.7.2 Cerebrospinal fluid analysis

Collection and analysis of the CSF are essential when noncontrast vertebral radiographs do not completely define the location, nature, and extent of a spinal cord disorder.[13] CSF may be collected by means of a cisternal or a lumbar subarachnoid puncture. It has been recommended that CSF be collected from a cisternal site if cervical spinal cord disease is suspected and from a lumbar location if a thoracolumbar disorder is involved. However, a lumbar collection site (most often between the L4 and L5 or L5 and L6 vertebrae) may be used for most dogs or cats with a spinal cord disorder regardless of the suspected location of the problem. Precautions must be taken in the collection of CSF from animals suspected of having increased intracranial pressure.

Analysis of CSF collected from a dog or cat suspected of having a spinal cord disorder should always include a total red blood cell count, total and differential white blood cell (WBC) count, and quantitative estimation of protein content. The results for CSF from normal dogs and cats have been published.[14–17] It should be noted that normal values for CSF collected from lumbar sites differ from those for CSF collected from cisternal sites.[17,18]

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The results of CSF analysis may support further examination of the cerebrospinal fluid, such as bacterial or fungal culture and sensitivity testing, completion of titers, or CSF protein electrophoresis and determination of the immunoglobulin G (IgG) index.[19–21]

193.2.1.7.3

Myelography

Myelography is the radiographic examination of the spinal cord and emerging nerve roots after injection of contrast material into the subarachnoid space. Myelography should be done when the results of noncontrast vertebral radiography and CSF analysis do not fully define a disorder affecting the spinal cord or when spinal surgery is contemplated.[11,12] Patterns of myelographic alteration may be used to differentiate intramedullary, intradural-extramedullary, and extradural space-occupying lesions.[11,12]

Myelography should be considered only if positive findings are essential for diagnosis and prognosis, or to determine a precise site for surgery, because it is a difficult procedure to complete and may have undesirable consequences.[22–24] A lumbar injection site is preferred for dogs or cats with spinal cord disease at any level of the vertebral column. Dynamic radiographic techniques and oblique projections may augment the diagnostic information gained from a myelographic study.

193.2.1.7.4

Electrophysiology

The role of electrophysiologic testing in the diagnosis of spinal cord disease is limited. Abnormal findings on electromyographic (EMG) examination are seen only when the lower motor neurons in the ventral horn of the spinal cord, or their axons in the ventral root are affected by a pathologic process. EMG examination may be performed to define the extent of a lesion affecting the brachial or lumbar enlargement of the spinal cord; the examination maps the distribution of EMG abnormalities caused by denervation and correlates this information with the spinal nerve root origins of the nerves supplying the affected muscles.[1] Electrophysiologic findings may be valuable for defining precisely the location and extent of a spinal cord lesion, because EMG may help distinguish between disuse atrophy and atrophy secondary to denervation.[25,26]

Determination of the sensory or motor nerve conduction velocities of the thoracic or pelvic limbs may aid in the identification of the nerve roots affected by a spinal cord disorder. Spinal cord potentials (cord dorsum potentials) evoked by stimulation of a peripheral sensory nerve may be used, along with the sensory nerve conduction velocities, to determine involvement of sensory nerve roots proximal to the dorsal root ganglia. However, in animals with spinal cord disorders, evoked spinal cord potentials are of limited usefulness for localizing lesions, determining the disease's severity and prognosis, or evaluating the response to therapy.[25,26]

A variety of pressure, flow, and electrophysiologic techniques have been developed to assess the function of the lower urinary tract.[5] Cystometry, profile recording of the urethral closure pressure, electromyography of the urethral sphincter, uroflowmetry, and evoked spinal cord potential measurements after pudendal nerve stimulation have all been investigated in dogs or cats.[5] Combinations of these electrophysiologic tests may provide the information needed about the functional status of spinal cord segments involved in micturition.

193.3 CLINICAL SIGNS OF SPINAL CORD DISEASES

Assessment of an animal's gait and posture, postural reactions, spinal reflexes, cranial nerve function, and state of consciousness is essential in determining whether a spinal cord disease exists, the most likely location or locations of a spinal cord lesion, and whether a focal, multifocal, or disseminated disease process is present that involves the spinal cord and/or other parts of the nervous system.[1]

Five groups of clinical signs are seen to a varying degree in all animals with disease that affects the spinal cord: depression or loss of voluntary movement, alteration of spinal reflexes, changes in muscle tone, muscle atrophy, and sensory dysfunction. Careful assessment of these groups of clinical signs in an animal suspected of having a disease affecting the spinal cord facilitates localization of the lesion and diagnosis. Neurologic disorders that result in either loss of voluntary movement alone or sensory dysfunction alone are unlikely to be spinal cord disorders, because most spinal cord diseases do not affect selected tracts while sparing anatomically adjacent pathways.

Diseases of the spinal cord may also result in dysfunction of the bladder, urethral sphincter, and anal sphincter and in loss of voluntary control of urination and defecation. This may be due to interruption of spinal cord pathways connecting the brain stem and cerebrum to the bladder and rectum that are important in normal detrusor reflex function and voluntary control of micturition and defecation, or it may be due to interruption of the parasympathetic nerve supply to the bladder and urinary and anal sphincters (L7 to S3 spinal cord segments and spinal nerves). Spinal cord diseases also indirectly interferes with excretory functions by impairing the animal's ability to assume the posture necessary for normal defecation or urination.

193.3.1 Voluntary Movement

Loss of voluntary movement as a result of interruption of motor pathways at any point from the cerebrum to the muscle fibers is referred to as *paralysis (plegia)*. Lesser degrees of motor loss are referred to as *paresis*. The terms *tetraplegia* (or *quadriplegia*) and *tetraparesis* (or *quadriparesis*) refer to an absence of voluntary movement in the thoracic and pelvic limbs and to depression of movement in the thoracic and pelvic limbs, respectively. The terms *paraplegia* and *paraparesis* describe the absence of voluntary movement and depression of voluntary movement in only the pelvic limbs. *Hemiplegia* and *hemiparesis* refer to paralysis or motor dysfunction, respectively, of a pelvic limb and a thoracic limb on the same side.

Voluntary movement must be differentiated from reflex movement by means of neurologic examination findings and general observation.

Ataxia (incoordination) is seen in association with paresis and probably occurs as a result of interference with both the ascending and descending spinal cord pathways. Many ascending spinal cord tracts contribute to the transmission of sensory information to the cerebrum for coordination of voluntary movements; however, interference with the spinocerebellar tracts probably causes a large part of the ataxia seen in association with

spinal cord disease in animals. Observation of gait is the only clinical testing technique for assessing these pathways.

193.3.2 Spinal Reflexes

Spinal reflexes are stereotyped involuntary actions that occur independent of brain input and that may be elicited consistently by specific stimuli. The central nervous system (CNS) components of spinal reflex arcs are located entirely in the spinal cord. Disturbance of spinal reflexes occurs in almost all animals with spinal cord disease. A spinal reflex may be normal, depressed *(hyporeflexia)*, absent *(areflexia)*, or exaggerated *(hyper-reflexia)*. Classification of spinal reflexes into one of these categories is helpful for localizing a spinal cord lesion.

Depression of a spinal reflex in association with spinal cord disease most frequently occurs as a result of involvement by a pathologic process of spinal cord segments that mediate the reflex. It must be remembered that involvement of motor nerves arising from or of sensory nerves traveling to such spinal cord segments, or abnormalities of the effector organ (muscle), may also result in depression of spinal reflexes.

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Exaggeration of a spinal reflex in association with spinal cord disease occurs when a lesion affects the spinal cord cranial to segments that mediate a reflex. The neural mechanisms that result in spinal reflex exaggeration are not completely understood. The concept that reflex exaggeration simply results from interruption of descending inhibitory pathways is useful for lesion localization; however, other factors are likely to be involved, such as collateral axonal sprouting or the development of denervation supersensitivity. Exaggeration of a reflex may result from a brain lesion, as well as from a spinal cord lesion.

Spinal cord lesions that affect both gray and white matter may result in depression of spinal reflexes mediated by spinal cord segments involved in a pathologic process and in exaggeration of spinal cord reflexes mediated by spinal cord segments caudal to a lesion. This is useful for lesion localization, particularly lesions that affect the cervical enlargement (C6 to T2 spinal cord segments), where thoracic limb hyporeflexia and pelvic limb hyper-reflexia may be present.

Interpretation of reflex abnormalities must be approached with the knowledge that two (or more) lesions in the same anatomic division of the spinal cord may produce reflex changes identical to those seen with a single lesion. For example, two lesions between the T3 and L3 spinal cord segments cause hyper-reflexia in the pelvic limbs indistinguishable from that resulting from a solitary lesion in this location. Furthermore, hyporeflexia produced by one spinal cord lesion may mask hyper-reflexia that would otherwise result from a second lesion in a more cranial location. For example, a lesion in the lumbar enlargement (L4 to S3 spinal cord segments) causes hyporeflexia in the pelvic limbs that masks the hyper-reflexia that otherwise would result from a second lesion cranial to the L4 spinal cord segment.

Depression of spinal reflexes caudal to a lesion may be seen for several days after spinal cord injury in humans or primates and is called *spinal shock*. Spinal shock may occur in quadrupeds; however, it is too brief to be of clinical significance. Hyporeflexia observed immediately after spinal cord injury should be attributed to damage to spinal cord segments that mediate the reflexes or to other systemic complications (e.g., hypovolemic shock) that frequently accompany spinal cord trauma.

193.3.3 Muscle Tone

Maintenance of normal muscle tone is a function of spinal reflexes (tonic muscle stretch reflexes). Alterations in muscle tone therefore are interpreted in a fashion similar to that for alterations in spinal reflexes described

above. Abnormal muscle tone may be depressed *(hypotonia),* absent *(atonia),* or exaggerated *(hypertonia),* depending on the location of the spinal cord lesion.

193.3.4 Muscle Atrophy

Two types of muscle atrophy may occur in association with a spinal cord disease. *Denervation atrophy* is seen when the lower motor neurons (LMNs) innervating a muscle are damaged by a lesion that affects their spinal cord segment or segments of origin. Denervation atrophy is evident within a week of injury, usually is severe, and is associated with EMG abnormalities. *Disuse atrophy* may be seen in muscles innervated by LMNs caudal to a spinal cord lesion. Disuse atrophy commonly is slower in onset and progression than denervation atrophy, most often is less severe, and usually is not associated with EMG alterations.

193.3.5 Sensory Dysfunction

Abnormalities of sensory (ascending) pathways of the spinal cord contribute to the ataxia of spinal cord disease; however, specific clinical tests of their function do not exist. Perception in animals must be inferred from certain behavioral responses that indicate that ascending sensory signals have reached the cerebral cortex (e.g., aversive response to a noxious stimulus). Interruption of sensory signals at any point between (and including) sensory receptors in the periphery and cerebral cortex may depress or obliterate normal sensory function. Therefore the results of a clinical examination for signs of sensory dysfunction alone may not be of value in localizing a lesion to the spinal cord. However, combined with the results of other parts of a neurologic examination, signs of sensory dysfunction may provide important diagnostic and prognostic information.

Proprioceptive positioning (perception of body position or movement) and pain perception are tested during a neurologic examination. Proprioceptive positioning is a sensitive indicator of spinal cord function, and depression or loss of proprioceptive positioning frequently is the sign first caused by a myelopathy.

Pain perception may be normal, depressed *(hypesthesia),* absent *(anesthesia),* or exaggerated *(hyperesthesia)*. Two types of pain perception may be distinguished in animals. *Cutaneous ("superficial") pain perception* is manifested by a response to pricking or pinching of the skin; *deep pain perception* is manifested by reaction to pinching of the toes or tail across bone with hemostatic forceps. Areas of decreased or absent cutaneous pain perception may aid the identification of specific nerves, nerve roots, and spinal cord segments involved in a pathologic process. This technique of cutaneous mapping is especially useful with lesions that affect the cervical or lumbar enlargements.

Deep pain perception appears to be the sensory function most resistant to a spinal cord disease, and it is the last spinal cord function to disappear in myelopathies of any type. An animal with complete bilateral loss of deep pain perception due to a transverse myelopathy is necessarily paralyzed caudal to the lesion. Loss of deep pain perception, therefore, is a grave prognostic sign.

Hyperesthesia in association with a spinal cord disease may indicate nerve root or spinal nerve involvement, or it may be consistent with meningeal irritation. A focal area of hyperesthesia over the vertebral column may indicate the location of a spinal cord lesion.

193.4 LOCALIZATION OF SPINAL CORD DISEASES

Motor, sensory, reflex, and sphincter abnormalities may help determine the location of a lesion in one of four major longitudinal divisions of the spinal cord: the cervical region (C1 to C5 spinal cord segments), the cervical

enlargement (C6 to T2), the thoracolumbar region (T3 to L3), and the lumbar enlargement (L4 to Cd5). It is essential to remember that these divisions refer to spinal cord segments, not vertebrae, and that spinal cord segments do not correspond exactly with vertebrae of the same number. Some variations may be encountered because of slight differences among animals in segments that form the cervical and lumbar enlargements. The diseases most commonly associated with neurologic signs referable to each of these four regions are listed in Boxes 193-1 to 193-4.

A disorder of any of the four regions of the spinal cord results in a combination of neurologic signs specific for that region.[6] Recognition of these clinical signs allows accurate localization of a spinal cord lesion. The presence of neurologic deficits indicative of involvement of more than one region of the spinal cord is highly suggestive of multifocal or disseminated spinal cord disease.

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193.4.1 Box • 193-1 Diseases Affecting the Cervical Region (Spinal Cord Segments C1 to C5)*

193.4.1.1 Hereditary/Congenital Causes

Atlantoaxial subluxation

Congenital vertebral anomalies

Spina bifida

Myelodysplasia

Syringomyelia/hydromyelia

Globoid cell leukodystrophy

Hereditary ataxia

Pilonidal sinus/epidermoid cyst/dermoid cyst

Spinal stenosis

193.4.1.2 Degenerative Causes

Intervertebral disk disease

Cervical spondylomyelopathy

Leukoencephalomyelopathy of rottweilers

Neuroaxonal dystrophy of rottweilers

Spondylosis deformans

Dural ossification

Synovial cyst

193.4.1.3 Inflammatory/Infectious Causes

Discospondylitis

Corticosteroid responsive meningitis-arteritis

Granulomatous meningoencephalomyelitis

Distemper myelitis

Feline infectious peritonitis meningitis/myelitis

Bacterial/fungal/rickettsial/protothecal meningitis/myelitis

Protozoal myelitis

Feline polioencephalomyelitis

Spinal nematodiasis

193.4.1.4 Neoplastic Causes

Neoplasia

193.4.1.5 Traumatic Causes

Spinal cord trauma

193.4.1.6 Vascular Causes

Ischemic myelopathy

Progressive hemorrhagic myelomalacia

Hemorrhage

Vascular malformations and benign vascular tumors

193.4.1.7 Nutritional Causes

Hypervitaminosis A (cats)

193.4.1.8 Idiopathic Causes

Spinal intra-arachnoid cysts

Osteochondromatosis

Calcinosis circumscripta

* Common causes are in italics.

193.4.2 Box • 193-2 Diseases Affecting the Cervical Enlargement (Spinal Cord Segments C6 to T2)*

193.4.2.1 Hereditary/Congenital Causes

Congenital vertebral anomalies

Spina bifida

Myelodysplasia

Syringomyelia/hydromyelia

Globoid cell leukodystrophy

Hereditary ataxia

Pilonidal sinus/epidermoid cyst/dermoid cyst

Spinal stenosis

193.4.2.2 Degenerative Causes

Intervertebral disk disease

Cervical spondylomyelopathy

Spondylosis deformans

Dural ossification

Synovial cyst

193.4.2.3 Inflammatory/Infectious Causes

Discospondylitis

Distemper myelitis

FIP meningitis/myelitis

Bacterial/fungal/rickettsial/protothecal meningitis/myelitis

Protozoal myelitis

Feline polioencephalomyelitis

Granulomatous meningoencephalomyelitis

Spinal nematodiasis

193.4.2.4 Neoplastic Causes

Neoplasia

193.4.2.5 Traumatic Causes

Spinal cord trauma

193.4.2.6 Vascular Causes

Ischemic myelopathy

Progressive hemorrhagic myelomalacia

Hemorrhage

Vascular malformations and benign vascular tumors

193.4.2.7 Nutritional Causes

Hypervitaminosis A (cats)

193.4.2.8 Idiopathic Causes

Spinal intra-arachnoid cysts

Osteochondromatosis

* Common causes are in italics.

193.4.3 Box • 193-3 Diseases Affecting the Thoracolumbar Region (Spinal Cord Segments T3 to L3)*

193.4.3.1 Hereditary/Congenital Causes

Congenital vertebral anomalies

Spina bifida

Myelodysplasia

Syringomyelia/hydromyelia

Mucopolysaccharidosis

Globoid cell leukodystrophy

Pilonidal sinus/epidermoid cyst/dermoid cyst

Spinal stenosis

193.4.3.2 Degenerative Causes

Intervertebral disk disease

Degenerative myelopathy

Spondylosis deformans

Dural ossification

Synovial cyst

Diffuse idiopathic skeletal hyperostosis

193.4.3.3 Inflammatory/Infectious Causes

Discospondylitis

Distemper myelitis

Feline infectious peritonitis (FIP) meningitis/myelitis

Bacterial/fungal/rickettsial/protothecal meningitis/myelitis

Protozoal myelitis

Feline polioencephalomyelitis

Spinal nematodiasis

Granulomatous meningoencephalomyelitis

193.4.3.4 Neoplastic Causes

Neoplasia

193.4.3.5 Traumatic Causes

Spinal cord trauma

193.4.3.6 Vascular Causes

Ischemic myelopathy

Progressive hemorrhagic myelomalacia

Hemorrhage

Vascular malformations and benign vascular tumors

193.4.3.7 Idiopathic Causes

Osteochondromatosis

Spinal intra-arachnoid cyst

Calcinosis circumscripta

* Common causes are in italics.

193.4.4 Box • 193-4 Diseases Affecting the Lumbar Enlargement (Spinal Cord Segments L4 to Cd5) and Cauda Equina*

193.4.4.1 Hereditary/Congenital Causes

Spina bifida

Sacrocaudal dysgenesis

Congenital vertebral anomalies

Myelodysplasia

Syringomyelia/hydromyelia

Globoid cell leukodystrophy

Pilonidal sinus/epidermoid cyst/dermoid cyst

Spinal stenosis

193.4.4.2 Degenerative Causes

Intervertebral disk disease

Lumbosacral vertebral canal stenosis

Spondylosis deformans

Dural ossification

Diffuse idiopathic skeletal hyperostosis

Synovial cyst

193.4.4.3 Inflammatory/Infectious Causes

Discospondylitis

Protozoal myelitis

Distemper myelitis

FIP meningitis/myelitis

Bacterial/fungal/rickettsial/protothecal meningitis/myelitis

Feline polioencephalomyelitis

Spinal nematodiasis

Granulomatous meningoencephalomyelitis

193.4.4.4 Neoplastic Causes

Neoplasia

193.4.4.5 Traumatic Causes

Spinal cord trauma

193.4.4.6 Vascular Causes

Ischemic myelopathy

Progressive hemorrhagic myelomalacia

Hemorrhage

Vascular malformations and benign vascular tumors

193.4.4.7 Idiopathic Causes

Osteochondromatosis

Spinal intra-arachnoid cyst

* Common causes are in italics.

The functional differences between upper motor neurons (UMNs) and LMNs may be used to localize lesions to one of the longitudinal regions of the spinal cord. Cell bodies of spinal cord LMNs are located in the spinal cord gray matter. Their axons leave the spinal cord via the ventral nerve roots to become part of a peripheral nerve and terminate in a muscle. The cell bodies of the LMNs of the thoracic limb are in the C6 to T2 spinal cord segments,

which form the cervical enlargement, whereas the LMNs of the pelvic limb arise from the L4 through S1 spinal cord segments of the lumbar enlargement. Anal and urethral sphincter LMNs originate from the S1 through S3 spinal cord segments. Signs of LMN dysfunction, which in diseases affecting the spinal cord reflect damage to the spinal cord segment or segments from which the LMNs originate, include decreased or absent voluntary motor activity; decreased or absent muscle tone; normal, decreased, or absent segmental spinal reflexes; and rapid, severe atrophy of an affected muscle as a result of denervation.

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UMNs arise from cell bodies in the brain. Their axons form the descending pathways of the spinal cord and terminate on interneurons, which in turn synapse with LMNs. Lesions that affect UMNs result in UMN signs, which are the result of an increase in the excitatory state of LMNs. UMN signs include depression or loss of voluntary motor activity, normal or exaggerated segmental spinal reflexes, appearance of abnormal spinal reflexes (e.g., crossed extensor reflex), increased muscle tone, and muscle atrophy as a result of disuse.

Unilateral signs caused by spinal cord disease are unusual; however, signs frequently are asymmetric. In most cases a lesion that results in asymmetric signs is located on the side of the greater motor and sensory deficit.

193.4.5 Cervical Region (C1 to C5 Spinal Cord Segments)

Fatal respiratory paralysis resulting from interruption of descending respiratory motor pathways or damage to motor neurons of the phrenic nerve (C5 to C7 spinal cord segments) occurs in a complete transverse myelopathy. Lesions that are less than complete may not affect respiration, but other signs may be detectable.

Ataxia and paresis of all four limbs usually are seen. Tetraplegia rarely is seen, because lesions severe enough to cause tetraplegia also cause respiratory paralysis. Hemiparesis occasionally may be present in association with a cervical lesion. Lesions of the cervical spinal cord may result in paraparesis with minimal neurologic deficits in the thoracic limbs. The reasons for this are poorly understood.

Spinal reflexes and muscle tone are intact in all limbs and may be normal or exaggerated. Muscle atrophy generally is not present; however, disuse atrophy may develop in disease that has a chronic course. Anal reflexes are intact, and anal tone usually is normal. Bladder dysfunction may occur as a result of detrusor muscle areflexia, with normal or increased urinary sphincter tone and loss of voluntary control of micturition. Reflex dyssynergia may also be seen. Although voluntary control of defecation may be lost, reflex defecation occurs when feces are present in the rectum. Horner's syndrome (ptosis, miosis, and enophthalmos) rarely may be present in an animal with a severe destructive cervical lesion. Proprioceptive positioning and other postural reactions usually are depressed or absent in all limbs. Complete loss of proprioceptive positioning may occur without detectable loss of pain perception.

Cervical hyperesthesia (“spasms,” apparent pain on palpation, cervical rigidity, and abnormal neck posture) may be seen in some animals with cervical myelopathy. It should be noted that apparent cervical pain may also be seen in association with lesions affecting the brain stem and cerebrum. Occasionally an animal may hold a thoracic limb in a partly flexed position, a posture that may be consistent with C1 to C5 nerve root or spinal nerve entrapment *(root signature),* although this posture is seen more commonly with a disorder affecting the cervical enlargement.

Disorders that affect the cervical region of the spinal cord must be differentiated from brain lesions that result in tetraparesis. This may be accomplished with a complete neurologic examination; however, occasionally the distinction may be difficult to make. In most circumstances, a cervical lesion does not result in neurologic deficits attributable to involvement of the medulla oblongata; however, there are several notable exceptions to this rule. Positional strabismus, resulting from loss of the vertebral joint proprioceptive input to the attitudinal

reflexes, may be seen in association with a cranial cervical lesion (C1 to C3 spinal cord segments). A cranial cervical lesion may also cause facial hypesthesia as a result of involvement of the spinal nucleus and tract of the trigeminal nerve. Cranial cervical trauma often results in clinical signs referable to injury of the caudal brain stem (head tilt, pharyngeal paresis, facial paresis) or cerebellum.

The Schiff-Sherrington sign (syndrome or phenomenon), which consists of hypertonicity of thoracic limb muscles and hyperextension of the neck, is seen in association with spinal cord lesions caudal to the cervical enlargement. It is essential to differentiate this sign from thoracic limb hypertonicity caused by a cervical lesion.

193.4.6 Cervical Enlargement (C6 to T2 Spinal Cord Segments)

Ataxia and paresis of all four limbs usually are present with lesions of the cervical enlargement. Occasionally paresis of the thoracic limbs and paralysis of the pelvic limbs may be seen.

Spinal reflexes and muscle tone may be normal or decreased in the thoracic limbs and normal or exaggerated in the pelvic limbs. The nature of thoracic limb reflex alterations depends on the exact craniocaudal location of a lesion in this region. Muscle atrophy often is severe in the thoracic limbs. The panniculus reflex may be depressed or absent unilaterally or bilaterally as a result of interruption of the LMNs involved in this reflex (C8 and T1 spinal cord segments). If bladder dysfunction occurs, it is similar to that observed with a lesion in the cervical region, with loss of voluntary control of urination. Anal reflexes and anal tone most often are normal, although voluntary control of defecation may be absent. Unilateral Horner's syndrome is commonly observed with a spinal cord lesion of the cervical enlargement, particularly a lesion involving the Tl to T3 spinal cord segments or nerve roots.

Proprioceptive positioning and other postural reactions usually are depressed in all four limbs. Alterations in these functions may be more pronounced in the pelvic limbs than the thoracic limbs. Occasionally, proprioceptive positioning is absent only in a thoracic and pelvic limb on the same side. Severe depression or loss of pain perception rarely is seen in association with a lesion of the cervical enlargement, except in intrinsic myelopathies (e.g., ischemic myelopathy). Hyperesthesia at the level of a lesion of the cervical enlargement, thoracic limb lameness, or apparent neck pain may be seen.

193.4.7 Thoracolumbar Region (T3 to L3 Spinal Cord Segments)

Most spinal cord lesions of dogs or cats occur in the thoracolumbar region. Typically the thoracic limb gait is normal, and paresis and ataxia, or paralysis, is seen in the pelvic limbs. The thoracic limb spinal reflexes are normal. Pelvic limb spinal reflexes and muscle tone are normal to exaggerated, depending on the severity of the lesion. Muscle atrophy is not seen in the thoracic limbs. Pelvic limb muscle atrophy, if present, is the result of disuse and is seen in animals with a severe, chronic lesion.

Anal reflexes and anal tone usually are normal or exaggerated. Voluntary control of defecation may be lost. Reflex defecation occurs when the rectum is filled with feces; however, it may not be at an appropriate time or place. The degree of bladder dysfunction varies, depending on the severity of the spinal cord lesion. There may be loss of voluntary control of urination, detrusor muscle areflexia with normal or increased urinary sphincter tone, or reflex dyssynergia, in which initiation of voiding occurs and is stopped by involuntary contraction of the urethral sphincter. The bladder can be manually expressed in some animals, but not others, as a result of increased tone of the urinary bladder sphincter; this is often referred to as a *UMN bladder*. Although “overflow” incontinence may occur with lesions of the spinal cord in this region, secondary to overfilling of the bladder,

detrusor muscle tone and urinary sphincter tone are present, which distinguishes this type of incontinence from that due to lesions of the lumbar enlargement and cauda equina (LMN bladder).

Proprioceptive positioning and other postural reactions are normal in the thoracic limbs and depressed or absent in the pelvic limbs. Pain perception is normal in the thoracic limbs and may be normal, depressed, or absent in the pelvic limbs. The panniculus reflex may be reduced or absent caudal to a lesion. In the lumbar region, the panniculus reflex may be present in lesions caudal to L3 as a result of the pattern of cutaneous innervation of lumbar spinal nerves.[1] There may be an area of hyperesthesia at the level of a lesion. The Schiff-Sherrington sign may be seen with a lesion in the thoracolumbar region. It usually is an indication of an acute, severe spinal cord lesion, although such a lesion may be reversible.

193.4.8 Lumbar Enlargement (L4 to Cd5 Spinal Cord Segments) and Cauda Equina

Involvement of the lumbar enlargement and cauda equina by a pathologic process results in varying degrees of pelvic limb paresis and ataxia, or paralysis, and is often accompanied by dysfunction of the bladder and by paresis or paralysis of the anal sphincter and tail. Thoracic limb function is normal. Pelvic limb reflexes and muscle tone are reduced or absent. Muscle atrophy often is present in the pelvic limbs. Conscious proprioception and other postural reactions may be reduced or absent in the pelvic limbs.

Anal tone and anal reflexes are reduced or absent. The rectum and colon may become distended with feces, and fecal incontinence, with continual leakage of feces, is often seen. Constipation may result from the inability to void feces. Paresis or paralysis of the urethral sphincters and detrusor muscle result in overfilling of the bladder and "overflow" incontinence. Affected animals have a large residual volume of urine in the bladder, and the bladder is easily expressed manually (LMN bladder). The Schiff-Sherrington sign occasionally may be seen with an acute lesion that affects this region of the spinal cord.

The term *cauda equina* is used to describe the lumbar, sacral, and caudal nerve roots and spinal nerves as they extend caudally from the caudal tip (conus medullaris) of the spinal cord in the vertebral canal. Lesions that affect the cauda equina result in clinical signs that are indistinguishable from those produced by lesions affecting the spinal cord segments from which the nerves of the cauda equina arise (L6 to Cd5).

193.5 ALPHABETIC LISTING OF DISEASES

193.5.1 Atlantoaxial Subluxation (Atlantoaxial Instability) and Malformations of the Odontoid Process

193.5.1.1 Etiology and Pathogenesis

Subluxation, instability, or malformation of the atlantoaxial joint that permits excessive flexion of the joint may result in compression of the spinal cord as a result of dorsal displacement of the cranial portion of the body of the axis into the vertebral canal. Such conditions may result from congenital or developmental abnormalities, trauma, or a combination of these factors.[9,10,27,28]

Agenesis or hypoplasia of the dens, nonunion of the dens with the axis, absence of the transverse ligament of the atlas, and dorsal angulation of the odontoid process with compression of the spinal cord have been associated with atlantoaxial instability in dogs.[29,30] Traumatic atlantoaxial luxation may occur in any breed of dog or cat and usually results from rupture of the atlantoaxial ligaments or fracture of the dens at its

junction with the axis. The onset of signs usually is acute and coincides with the trauma, but occasionally it is delayed.

193.5.1.2 Clinical Findings

Congenital or developmental malformations occur most frequently in small dog breeds.[31] Animals with congenital atlantoaxial joint abnormalities usually develop clinical signs during the first year of life. Occasionally a dog with a congenital atlantoaxial abnormality appears normal until trauma occurs at an older age, at which time clinical signs may occur.

Clinical signs associated with congenital atlantoaxial instability may have an acute onset, may be slowly progressive, or may be intermittent. Signs are indicative of a transverse myelopathy between C1 and C5 and vary from mild cervical pain to tetraparesis or tetraplegia and possibly death as a result of respiratory paralysis. Occasionally, signs of brain stem dysfunction may follow an atlantoaxial luxation (e.g., dysphagia, facial paralysis, or vestibular deficits).

Atlanto-occipital luxation results in trauma to the medulla oblongata and clinical signs indicative of a caudal brain stem or cranial cervical spinal cord injury. Severe injuries may result in respiratory paralysis and death.

193.5.1.3 Diagnosis

Atlantoaxial instability is best demonstrated by radiography. Radiographically, the body of the axis is displaced dorsally and cranially into the vertebral canal, and the distance between the dorsal arch of the atlas and the spinous process of the axis is increased. If lateral views are not diagnostic, slight flexion of the head may be necessary. Extreme care must be taken when manipulating an animal suspected of having atlantoaxial instability while it is under anesthesia or during radiography, because flexion of the animal's neck may result in further spinal cord compression. Splinting the animal's neck and head in extension beforehand may help prevent excessive flexion of the head during induction of anesthesia, intubation, and positioning for radiography. Abnormalities of the dens may be seen on ventrodorsal views or slightly oblique lateral views such that the wings of the atlas are not superimposed on the dens (Figure 193-1). An open mouth view may show agenesis, nonunion, or fracture of the dens; however, the degree of cervical flexion required for completion of this view may result in further spinal cord compression. Therefore obtaining an open mouth view usually is not recommended.

Animals with congenital or developmental abnormalities of C2 may have additional vertebral abnormalities, such as shortening of C1 or abnormal atlanto-occipital articulation. Agenesis or malformation of the dens may be an incidental finding and is probably not of clinical significance unless associated with radiographic findings of atlantoaxial instability. However, spinal cord compression associated with hypoplasia of the dens without radiographic evidence of atlantoaxial instability has been reported in a dog. Similarly, abnormal angulation of the dens may cause spinal cord compression. In these cases, myelography or advanced imaging (especially CT) may be necessary to demonstrate spinal cord compression (Figure 193-2).

193.5.1.4 Treatment

Animals with an acute onset of neurologic deficits resulting from atlantoaxial instability or traumatic atlanto-occipital luxation should be treated medically, as described for other forms of spinal cord trauma. In addition, the head and neck should be splinted in extension. Animals with mild luxations and cervical pain only or with minimal neurologic deficits, or animals with multiple vertebral abnormalities, such as

atlantoaxial instability and shortening of the body of C1, may respond to splinting of the head and neck in extension and strict cage rest for at least 6 weeks. Casting material or a metal metacarpal splint may be used for this purpose. Care must be taken to ensure that respiration is not compromised. Splinting the head and neck may permit the formation of fibrous tissue to stabilize the atlantoaxial joint and is most successful in small dogs. However, clinical signs may recur.

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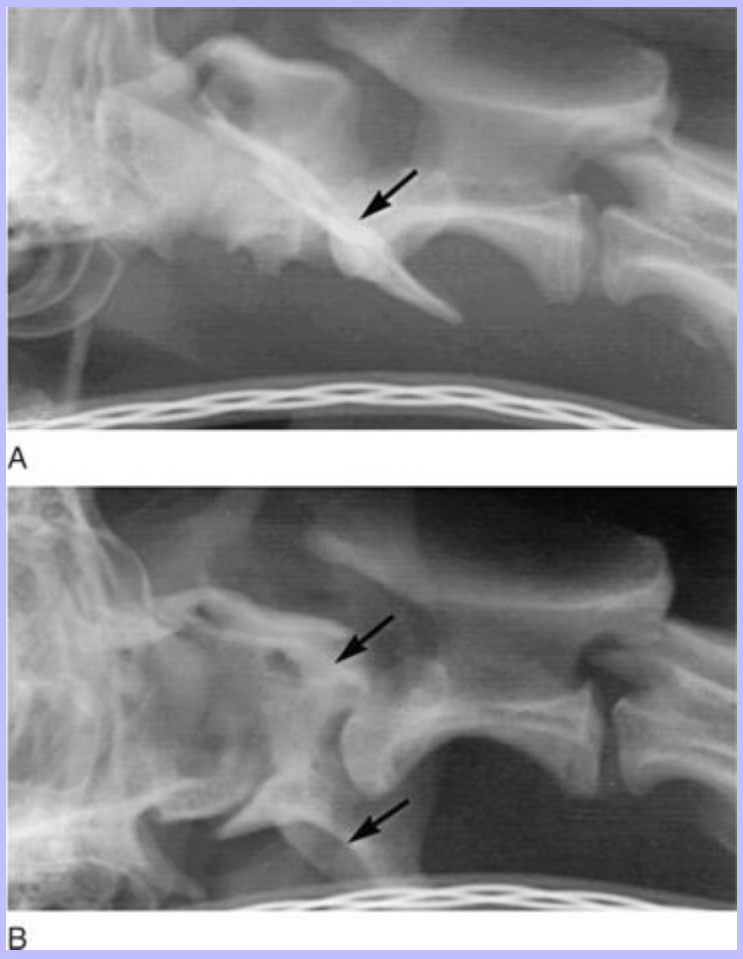
Figure 193-1 Atlantoaxial subluxation and agenesis of the dens. Lateral **(A)** and oblique **(B)** radiographs of the cranial cervical vertebrae of a 10-month-old female miniature dachshund that was tetraparetic after a minor trauma. In the lateral projection **(A),** the wings of the atlas are superimposed *(arrow),* obscuring the cranial aspect of the axis. In the oblique projection **(B),** the cranial aspect of the axis is visible because the wings of the atlas *(arrows)* are rotated out of the primary area of interest, and absence of the dens is confirmed.



Surgical stabilization or decompression (or both) is indicated in animals with moderate to severe neurologic deficits or recurrent episodes of neck pain unresponsive to medical therapy or splinting and in animals in which angulation of the dens results in spinal cord compression. Various surgical techniques that use either a dorsal or a ventral approach have been described.[32–34]

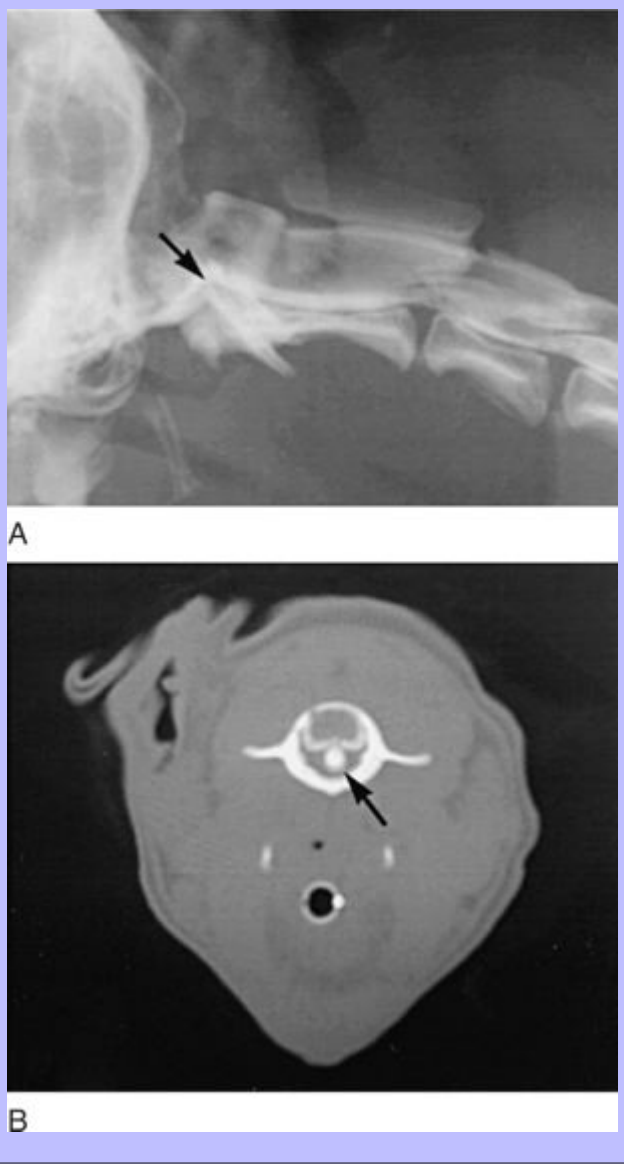
The prognosis for animals with atlantoaxial instability varies, depending on the severity of the spinal cord injury that occurs. The prognosis is fair to good for those with mild to moderate neurologic deficits and guarded for those with an acute onset of tetraplegia.

193.5.2 Bacterial, Fungal, Rickettsial, or Protothecal Meningomyelitis

193.5.2.1 Etiology and Pathogenesis

Dogs and cats are affected infrequently by bacterial or fungal meningitis and/or myelitis.[3–6,35,36] Several routes of infection exist. Direct implantation of organisms may occur with a bite wound, spinal puncture, or surgery or may accompany migration of a foreign body, such as a grass awn. Extension may occur from a focus of infection, such as a paravertebral infection, discospondylitis, or dermoid sinus, or from infection following tail docking. Infection may also result from hematogenous spread of systemic infection (e.g., endocarditis). Because clinical signs produced by bacterial or fungal agents depend more on the neural structures affected than on the agent responsible, these agents are discussed together.

Figure 193-2 Dorsal angulation of the dens. Lateral myelogram **(A)** and transverse computed tomography (CT) image **(B)** taken after myelography of the cranial cervical vertebrae of a 3-year-old male Chihuahua that had an acute onset of tetraparesis and generalized ataxia. The myelogram **(A)** confirms ventral compression of the spinal cord *(arrow)* in the region of the dens. The CT image **(B)** confirms that the dens *(arrow)* is causing compression of the overlying spinal cord.



Meningitis may be accompanied by infection of the underlying parenchyma of the spinal cord (myelitis). Meningitis and/or myelitis may be focal, multifocal, or disseminated in distribution and is frequently accompanied by meningoencephalitis. Pathologically, meningitis is characterized by infiltration of inflammatory cells into the leptomeninges. Inflammation may occur throughout the entire subarachnoid space of the brain and spinal cord. Myelitis is characterized by necrosis and infiltration of inflammatory cells into the spinal cord parenchyma.

Bacteria that have been isolated from cats or dogs with meningitis and myelitis include *Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus albus,* and *Pasteurella, Actinomyces,* and *Nocardia* spp. Fungal infections have been caused by *Cryptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum,* and *Coccidioides immitis. C. neoformans* is found ubiquitously and frequently causes infection in immunosuppressed animals. Cryptococcosis is more common in cats than in dogs, and infection may result from extension of nasal infection through the cribriform plate. *Blastomyces, Histoplasma,* and *Coccidioides* infections are found in certain geographic areas in the United States, and in such cases the CNS is infected by hematogenous spread.[1]

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Focal epidural infections have been reported to occur, generally as a result of migrating grass awns or penetrating wounds.[37] Proliferation of inflammatory tissue may result in an extradural space-occupying lesion that causes spinal cord compression and clinical signs of a transverse myelopathy.[38] Abscessation may occur within the spinal cord and may have the radiographic appearance of an intramedullary mass.[39]

Rickettsial or protothecal infections may cause meningomyelitis similar in clinical presentation to that resulting from bacterial or fungal infection of the CNS. Ehrlichiosis (*Ehrlichia canis* infection) and Rocky Mountain spotted fever ([RMSF] caused by *Rickettsia rickettsii*) may cause meningo-encephalitis or meningomyelitis in dogs. Rocky Mountain spotted fever is transmitted primarily by two outdoor ticks (*Dermacentor variabilis* and *Dermacentor andersoni*), whereas ehrlichiosis is transmitted by a tick that is frequently found inside houses *(Rhipicephalus sanguineus)*. Acutely, both diseases may induce immune-mediated vasculitis in a variety of tissues, including the CNS. Borreliosis, caused by *Borrelia burgdorferi,* has been reported to occur in dogs and may be expected to cause meningomyelitis, as it does in humans.[40] *Prototheca wickerhamii* and *Prototheca zopfii,* species of ubiquitous, colorless, unicellular algae, have been isolated from pyogranulomatous lesions of the spinal cord and other organs. Protothecosis rarely occurs, and infection may depend on inadequate host immune response.[40]

193.5.2.2 Clinical Findings

193.5.2.2.1 Bacterial or fungal infections

Clinical signs of meningitis include apparent spinal pain, hyperesthesia, and cervical or thoracolumbar rigidity, occasionally manifested as a “sawhorse” posture.[40] Irritation of the numerous nerve endings in the meninges results in reflex muscle spasms when affected animals are stimulated. Fever is intermittent and is more likely to occur in association with concurrent bacteremia or disseminated fungal infection. Fever may occur in association with primary CNS infections as a result of leukocytic pyrogens in the CSF or hypothalamic circulation.

Neurologic deficits are indicative of associated myelitis or radiculitis, and abnormalities depend on the location and extent of infection. Focal myelitis may result in signs of transverse myelopathy.

Disseminated bacterial meningomyelitis often is associated with meningoencephalitis, and clinical signs usually are acute and rapidly progressive. Focal bacterial meningitis and/or myelitis and fungal meningomyelitis may be associated with the development of more slowly progressive clinical signs.

Paraparesis and pelvic limb ataxia are common in animals with cryptococcal meningitis and/or myelitis. Progressive paralysis of a single pelvic limb has been reported in two cats with cryptococcal infection of the lumbar spinal cord. Cats with CNS cryptococcal infections may show an acute onset of clinical signs despite chronic destruction of nervous tissue.

The clinical signs of bacterial or fungal meningitis and myelitis in animals are indistinguishable from those of other causes of meningitis and myelitis, such as granulomatous meningoencephalitis and corticosteroid-responsive meningitis; necrotizing vasculitis of the meningeal arteries and distemper virus myelitis in dogs; and CNS toxoplasmosis and FIP meningomyelitis in cats. The differential diagnosis of meningitis also includes intervertebral disk protrusion (especially in the cervical spine), spinal fracture, discospondylitis, polymyositis, and polyarthritis.

193.5.2.2.2 Rickettsial infections

Central depression is the most consistent clinical finding in dogs with rickettsial infection. Other abnormalities indicative of spinal cord and/or meningeal involvement include paraparesis, tetraparesis, ataxia, and generalized or localized hyperesthesia.[41,42] Cervical rigidity and apparent pain may occur in animals with RMSF.[1] Neurologic abnormalities indicative of cerebral involvement include vestibular disturbances, seizures, cerebellar abnormalities, and coma. Other clinical signs that occur in dogs with rickettsial infections include listlessness, depression, fever, anorexia, lymphadenopathy, dyspnea, diarrhea, vomiting, hemorrhagic diathesis, and joint pain. Dogs of all ages may be infected, and the clinical signs are often indistinguishable from those of systemic viral infections (especially canine distemper), septicemia, and immune-mediated disorders.

193.5.2.2.3 Protothecal infections

Clinical signs reported in dogs with CNS protothecosis have included ataxia, circling, and paresis or paralysis. Only the cutaneous form of this disease has been reported in cats.[40]

193.5.2.3 Diagnosis

193.5.2.3.1 Bacterial or fungal infections

A diagnosis of bacterial or fungal meningitis and/or myelitis is made on the basis of the results of CSF analysis and isolation of a causative organism by culture of CSF. Clinical signs may reflect meningeal irritation or myelopathy that may be indistinguishable from signs caused by other, noninfectious myelopathies, such as intervertebral disk disease. The presence of fever or an abnormal hemogram cannot be relied upon for diagnosis of meningitis/myelitis, because neither may be seen in affected animals.

Bacterial or fungal meningitis has been reported to result in moderate to severe CSF pleocytosis that reflects the degree of leptomeningeal or ependymal involvement.[13] A finding of more than 5000 WBCs/μL may be noted in some cases. Polymorphonuclear (PMN) cells predominate. Mixed mononuclear and PMN pleocytosis occurs with fungal meningitis, and eosinophils may be present,

especially in cases of cryptococcal meningitis. The CSF appears turbid if the cell count is greater than 500 WBCs/μL. Disseminated bacterial meningomyelitis is rarely recognized antemortem in dogs or cats. Focal bacterial epidural, meningeal, or parenchymal infections more commonly occur.

CSF protein may be moderately to markedly increased as a result of increased capillary permeability and leakage of serum proteins into the CSF and probably also owing to local production of immunoglobulins.[13,43] If the CSF protein content is high, fibrin clots may develop. The CSF pressure is usually normal but occasionally is increased, especially in animals with cryptococcal meningitis. Hemorrhage into the CSF may occur; a red or pink supernatant is indicative of recent hemorrhage. Xanthochromia develops if more than 48 hours have elapsed since the hemorrhage. The CSF glucose content (normally 60% to 80% of a simultaneously determined plasma glucose concentration) may be decreased as a result of glucose utilization by micro-organisms and possibly by PMN leukocytes. However, a low CSF glucose concentration is not a consistent finding in animals with bacterial meningitis.

Bacteria or fungal organisms may be identified by staining (i.e., Gram stain or acridine orange) of sedimented or centrifuged CSF. Cryptococcal organisms often are observed in cell preparations of CSF and can be identified with Wright's stain or Gram stain or by use of a wet mount preparation with India ink.

CSF from all animals with CSF abnormalities consistent with meningitis should be submitted for both aerobic and anaerobic bacterial culture and for antibiotic sensitivity testing of any cultured bacterial isolates. CSF fungal culture may also be performed. Negative CSF culture results are common, even in animals in which bacteria or fungal organisms have been identified in the cerebrospinal fluid. Culturing the sediment of centrifuged CSF or filtering CSF and culturing the filter may increase the likelihood of obtaining a positive CSF culture. Causative organisms may be isolated from blood cultures of animals that are bacteremic or that have a systemic fungal infection. *Histoplasma* organisms may be found in buffy coat or bone marrow neutrophils or monocytes. A large volume of CSF (preferably 2 or 3 mL) should be collected for bacterial and/or fungal culture. If a delay in processing of a CSF sample is anticipated, CSF may be aseptically inoculated into a blood culture bottle for submission to a diagnostic laboratory.

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Serology may also be useful in the diagnosis of CNS fungal infections. The titer of antibody-coated latex agglutination to cryptococcal (capsular) antigen may be useful in supporting a diagnosis of cryptococcal meningitis and in assessing the response to therapy. The latex cryptococcal agglutination titer (LCAT) is more sensitive than the indirect fluorescent antibody test and may be used on CSF. However, animals with a localized CNS infection may have a negative titer.[44]

Focal epidural inflammatory lesions may appear as an extradural mass on myelography. Chronic focal meningitis may result in obstruction of CSF flow and blockage of contrast material on myelography as a result of arachnoid adhesions.

193.5.2.3.2 Rickettsial infections

The characteristic histopathologic lesions of RMSF are necrotizing vasculitis, perivascular accumulation of PMN cells, and lymphoreticular cell infiltration into most tissues of the body, including the meninges and CNS. The histopathologic lesion in canine ehrlichiosis is generalized lymphoid and plasma cell accumulation in the bone marrow, meninges, kidneys, and other organs. The results of CSF analysis of dogs with RMSF may be normal or may show a mild increase in protein (less than 60 mg/dL) and nucleated cells (fewer than 80cells/μL) with lymphocytes the predominant cell type. Currently, little

information is available on the expected CSF findings in animals with ehrlichiosis. In one reported case, the CSF protein and nucleated cell levels were increased, with lymphocytes the predominant cell type. Diagnosis of both diseases is based on serology.[45]

193.5.2.3.3 Protothecal infections

Neutrophilic or eosinophilic leukocytes often are increased in the CSF of animals with protothecosis. Culture of CSF on fungal media may result in isolation of the organism. Rectal scrapings should also be performed. Fluorescent antibody examination may demonstrate the organism in tissue sections.[40]

193.5.2.4 Treatment

193.5.2.4.1 Bacterial infections

In the treatment of bacterial meningitis and/or myelitis, it is desirable to use an antimicrobial that is specific for the causative organism and that crosses the blood-brain barrier (or the blood–spinal cord barrier) in therapeutic concentrations, so that drug concentrations may be maintained after the acute phase of inflammation has subsided[46] (Box 193-5). The blood-brain, blood-spinal cord, and blood–spinal fluid barriers are most permeable to antimicrobials with high lipid solubility, low ionization potential, and low protein-binding affinity.[41,46,47] Antibiotics may be administered to animals suspected of having bacterial meningitis before the results of culture and sensitivity testing have been obtained. The selection of antibiotic should be based on tentative organism identification (by Gram or acridine orange staining) from the CSF, the suspected source of infection, and on the drug's ability to reach effective tissue concentrations in the CNS. High-dose intravenous therapy with a bactericidal drug should be used when possible, although many bactericidal drugs penetrate the CSF poorly. Penicillin and penicillin derivatives in high doses have been recommended for the treatment of CNS infections caused by gram-positive cocci (e.g., penicillin G, 10,000 to 20,000 U/lb given intravenously every 6 hours for at least 7 days). Oxacillin may be used for the treatment of meningitis caused by penicillin-resistant *Staphylococcus* strains (Box 193-5).

193.5.2.4.1.1 Box • 193-5 Antibiotic Penetration of the Cerebrospinal Fluid

193.5.2.4.1.1.1 Good Levels without Meningeal Inflammation

Chloramphenicol

Sulfonamides

Metronidazole

Trimethoprim-sulfamethoxazole

Isoniazid

Rifampin

Pyrazinamide

193.5.2.4.1.1.2

Therapeutic Levels with Meningeal Inflammation

Penicillin

Ampicillin

Nafcillin

Oxacillin

Cefotaxime

Ceftriaxone

Ceftizoxime

Vancomycin

193.5.2.4.1.1.3

Poor or No Penetration, Even with Meningeal Inflammation

Aminoglycosides

Erythromycin

Tetracycline

Clindamycin

First-generation cephalosporins

From Gormley WB et al: Cranial and intracranial bacterial infections. *In* Youmans JR (ed): Neurological Surgery, 4th ed. Philadelphia, WB Saunders, 1996, p 3191.

Most cephalosporins penetrate the CNS poorly.[48] Several third-generation cephalosporins (e.g., cefotaxime) reach effective CNS concentrations and are considered the drugs best suited for treatment of gram-negative meningitis. First-and second-generation[48,49] cephalosporins do not reach effective CSF concentrations and should not be used in the treatment of CNS infections.

Metronidazole is useful for the treatment of most anaerobic infections, is bactericidal, and diffuses well into all tissues, including the CNS.[50] Metronidazole has played an increasingly greater role in the therapy of brain abscesses of humans and is used in combination with high doses of penicillin when aerobes are present. Toxicity (central vestibular signs and cerebellar dysfunction) has been reported in dogs treated with metronidazole.[51] Chloramphenicol reaches higher CSF concentrations than most other antibiotics; however, it is bacteriostatic, and many *Staphylococcus* strains have been shown to be resistant to this drug.[52] Most sulfonamides penetrate the CSF effectively. Sulfadiazine (which is less protein bound than other sulfonamides) penetrates the CSF and nervous tissue better than sulfamethoxazole and is effective if given orally. Data are not available on the concentration of trimethoprim in the CSF of dogs.

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Intrathecal administration of antibiotics has been used in humans. Although its use is possible in dogs or cats, multiple CSF punctures, each requiring anesthesia, are needed. Some drugs are toxic when introduced directly into the CNS (e.g., penicillin may cause seizures), and drugs may not diffuse freely through the cerebrospinal fluid, especially if CSF flow is blocked.

Treatment with antibiotics should be started as soon as possible after submission of CSF for culture. After the results of culture and sensitivity are known, therapy may be altered. Treatment is continued for 4 to 6 weeks; however, treatment for longer periods often is necessary, and relapses are possible. It is also important to identify possible sources of infection outside the CNS (e.g., endocarditis, discospondylitis, and paravertebral abscess). Localized spinal cord or meningeal infections that are well encapsulated may be resistant to antibiotic therapy. Surgical exploration is indicated if focal meningeal or epidural infection refractory to medical therapy is suspected.

Use of corticosteroids in cases of bacterial meningitis and myelitis is controversial. Corticosteroids may reduce inflammation and thereby decrease the resulting spinal cord and nerve root damage; however, such treatment may also decrease host defense mechanisms, resulting in worsening of clinical signs and a higher incidence of relapse.

The prognosis in cases of bacterial meningitis and myelitis depends both on the ability to eliminate the causative organism and on the extent of neurologic deficits. Neurologic deficits that occur as a result of spinal cord or nerve root inflammation may be permanent.

193.5.2.4.2

Fungal infections

Fungal infection of the CNS of dogs or cats is extremely difficult to eliminate.[40,41] The disease is often multisystemic and is seldom recognized in the early stages of CNS involvement. Amphotericin B is frequently used to treat systemic fungal infections, although it is poorly absorbed into the CSF and nervous tissue. Intrathecal administration of amphotericin B has been recommended, especially in animals with *C. immitis* meningitis, but it may result in arachnoiditis and cranial nerve toxicity.

Combinations of drugs have been recommended. Amphotericin B, ketoconazole (poor CNS penetration), and flucytosine (good CNS penetration) are the main agents used. Rifampin has been used to enhance amphotericin B activity. Combined treatment with amphotericin B and 5-fluorocytosine (5-FU) has been recommended for use in cases of cryptococcosis. Long-term, high-dose ketoconazole therapy is reported to be effective for treatment of cryptococcosis in cats.[53] Sequential LCAT determinations may provide a quantitative indication of the clinical response to treatment of cryptococcosis.[44,54]

Because obtaining therapeutic concentrations of antifungal agents in nervous tissue is difficult, the prognosis for CNS mycotic infections is poor.[55] Newer generation azole antifungal agents (e.g., fluconazole, itraconazole) are currently under investigation for treatment of fungal infections of the CNS.[56–60]

193.5.2.4.3

Rickettsial infections

Rickettsial organisms appear to be extremely sensitive to tetracyclines (10 mg/lb given orally three times a day for 14 days).[40] Tetracyclines are bacteriostatic, and elimination of the organisms from the body

depends on the immunocompetence of the affected animal. Doxycycline has better CNS penetration than oxytetracycline or tetracycline and is used in animals with meningitis or myelitis resulting from RMSF or ehrlichiosis. Chloramphenicol, rather than tetracycline, is used to treat young dogs prior to the eruption of permanent teeth. Severely affected dogs, especially those with neurologic involvement, may die despite therapy. Neurologic deficits may be permanent in affected dogs. Recovery may be prolonged, and pancytopenia persistent, in dogs with chronic ehrlichiosis.

193.5.2.4.4 Protothecal infections

Treatment of cutaneous protothecosis in a dog with a 6-month course of oral ketoconazole has been reported.[61] Effective therapy for disseminated proto-thecosis has not been described.

193.5.3 Calcinosis Circumscripta

Calcinosis circumscripta is usually an idiopathic condition that results in circumscribed single or multiple calcium deposits, often in periarticular connective tissue.[62] It occurs mainly in young dogs of large breeds, with an apparently high incidence in German shepherds.[63–65] The clinical signs of spinal cord compression caused by these slow-growing deposits vary, depending on the location of the mass. The diagnosis is made on the basis of radiography. Myelography usually reveals a solitary, rounded, mineralized mass dorsal to the spinal cord that results in extradural spinal cord compression (Figure 193-3). Advanced imaging (CT or MRI) may further delineate the extent of mass lesions. Complete surgical removal of the mass provides long-term resolution of clinical signs.[62–64]

193.5.4 Cervical Spondylomyelopathy

193.5.4.1 Etiology and Pathogenesis

Several terms have been used to describe this disease of the cervical vertebral column of Great Danes, Doberman pinschers, and other large breed dogs.[66–71] These terms include *wobbler syndrome, caudal cervical malformation-malarticulation, cervical spondylopathy, cervical vertebral instability,* and *cervical vertebral stenosis*. The term *wobbler* is nonspecific; it describes a dog with generalized ataxia and tetraparesis that may be seen with a variety of cervical myelopathies. The number of different terms that have been used reflects the many unanswered questions that remain regarding the etiology and pathogenesis of this condition. The term *cervical spondylomyelopathy* accurately reflects the complexity of the syndrome and therefore has become widely accepted. Although the etiology remains undetermined, the high incidence of the syndrome in certain dog breeds suggests that heredity is a contributing factor. Osteochondrosis resulting from overnutrition and rapid growth may also be a factor.[66–71] In humans, stenosis of the vertebral canal may be clinically “silent” as long as it is not complicated by other factors, such as vertebral instability or intervertebral disk protrusion.

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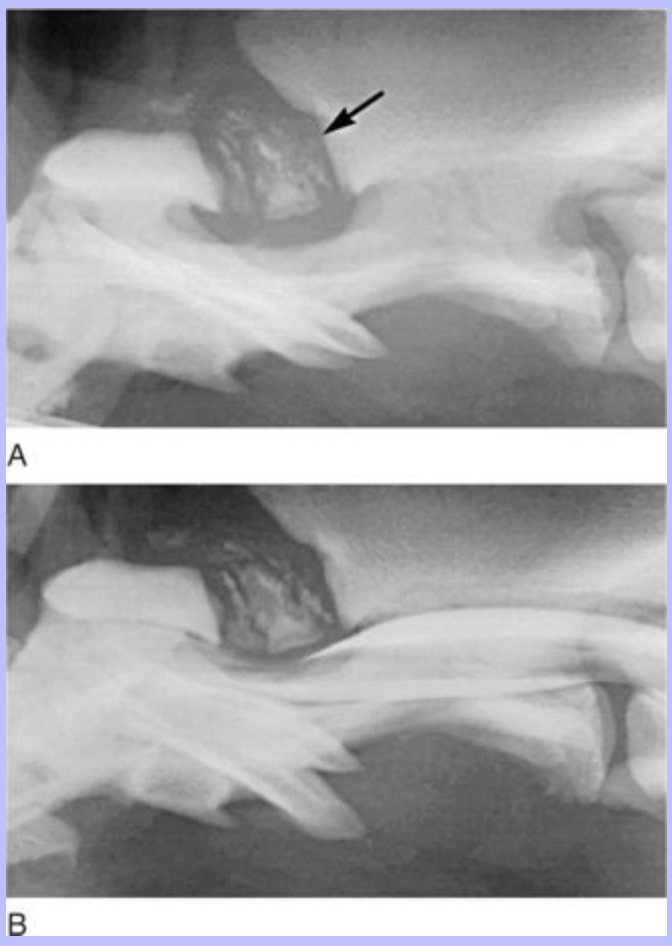
Figure 193-3 Calcinosis circumscripta. Lateral radiograph **(A)** and myelogram **(B)** of the cranial cervical vertebrae of a 10-month-old neutered male German shepherd with signs of worsening tetraparesis and generalized ataxia. The radiograph **(A)** confirms a focal area of soft tissue mineralization between the dorsal arch of C1 and the spinous process of C2 *(arrow)*. The myelogram **(B)** shows dorsal spinal cord compression caused by this mass.



Vertebral instability, either alone or in combination with vertebral malformation and/or soft tissue stenosis, has been suggested as an initiating cause of spinal cord compression and associated neurologic abnormalities.[68] The histopathologic alterations seen in the spinal cord are characteristic of chronic compression and usually involve both white and gray matter. White matter degeneration is noted in tracts cranial and caudal to the level of focal compression. Myelin degeneration appears to predominate over axonal degeneration.

Cervical spondylomyelopathy occurs most frequently in young Great Danes (less than 2 years of age) and middle-aged or older Doberman pinschers (3 to 9 years of age).[66–71] Other breeds that have been reported to be affected are the Saint Bernard, weimaraner, Labrador retriever, German shepherd, boxer, basset hound, Rhodesian ridgeback, Dalmatian, Samoyed, Old English sheepdog, and bull mastiff. Males appear to be affected more often than females. The C5–C6 and C6–C7 vertebrae and disks appear to be affected most commonly, although alterations consistent with a diagnosis of cervical spondylomyelopathy may be seen at the level of C4–C5 and less frequently at C3–C4. Spinal cord compression may be present at more than one site in the cervical spine. Stenosis of the vertebral canal of basset hounds has been reported to occur at C2–C3. Although the lesions seen in all breeds of dogs of all age groups are similar, certain pathologic changes are more characteristic of each particular group. Younger Great Danes frequently have dorsal spinal cord compression as a result of elongation of the cranial aspect of the dorsal arch of affected vertebrae. Older Doberman pinschers frequently have severe ventral spinal cord compression centered over the anulus fibrosus of the affected intervertebral disk.

193.5.4.2 Clinical Findings

The clinical signs reflect chronic compression of the cervical spinal cord. These signs are most often gradually progressive over several months or years; however, they sometimes may develop acutely, perhaps after an apparently insignificant traumatic episode. Gait deficits are frequently noted initially in the pelvic limbs. A mild pelvic limb ataxia progresses in severity until a wide-based, crouching stance and dragging or knuckling of the toes of the pelvic limbs may be seen. Abnormalities may be more easily observed when an affected dog rises from a lying position, turns, or negotiates stairs or a curb.

Neurologic abnormalities that may be noted in the pelvic limbs include depression or loss of proprioceptive positioning reactions and exaggerated spinal reflexes. Thoracic limb abnormalities most often occur after the development of neurologic deficits in the pelvic limbs, and thoracic limb deficits seldom progress to the level of severity of the pelvic limb abnormalities. Thoracic limb deficits usually are mild and may be evident only during intensive evaluation of postural reactions, particularly thoracic limb hopping reactions. Neurogenic atrophy of the supraspinatus or infraspinatus muscles may be detected; however, widespread LMN involvement in the thoracic limbs is rarely seen. In dogs with a chronic course, a stiff, “choppy” thoracic limb gait may be seen, often in combination with a rigid flexion of the neck. Although affected dogs may resist extension of the neck, apparent neck pain, as seen frequently with an acute cervical disk protrusion, seldom is elicitable.

193.5.4.3 Diagnosis

Radiography is the most accurate means of delineating the pathologic alterations of cervical spondylomyelopathy.[72,73] A diagnosis of cervical vertebral canal stenosis has been made on the basis of noncontrast lateral radiographs of the cervical spine; however, numerous studies have emphasized that noncontrast radiographs of the cervical spine may be normal in affected dogs. Abnormalities that may be present on noncontrast radiographs include malalignment of vertebrae, remodeling of vertebrae with cranial stenosis of the vertebral canal, new bone formation (spondylosis deformans), narrowing or collapse of one or more intervertebral disk spaces, calcification of the nucleus pulposus of one or more intervertebral disks, sclerosis of vertebral endplates, and degenerative changes of vertebral articular facets. It is important to note that features such as vertebral remodeling with spondylosis deformans, narrowing of intervertebral disk spaces, and asymmetry of articular facets may not be associated with clinically significant vertebral canal

stenosis. “Tilting” of adjacent vertebrae, which may be apparent on plain spinal radiographs, may be within normal limits.

Myelography is essential for determining the location or locations, nature, and extent of spinal cord compression. Myelographic findings are essential in the consideration of treatment options and any surgical repair that is to be attempted. The importance of ventrodorsal projections in defining lateral spinal cord compression, and that of dynamic or “stressed” radiographs in outlining dorsal spinal cord compression, in combination with myelography, has been emphasized by several authors. Lateral and ventrodorsal “traction” radiographs are recommended as a method of showing the dynamic nature of a lesion.[68–71]

The myelographic abnormality most frequently recognized in Doberman pinschers is ventral spinal cord compression resulting from a hypertrophied, hyperplastic, or “redundant” dorsal anulus fibrosus. Other findings include dorsal spinal cord compression resulting from hypertrophied or hyperplastic ligamentum flavum, dorsolateral spinal cord compression resulting from malformed articular processes, and spinal cord compression resulting from malformed or malaligned vertebrae.

Dynamic or “stress” radiography, after myelography, may be of value in demonstrating instability, ventral spinal cord compression as a result of dorsally protruding intervertebral disks, or dorsal spinal cord compression as a result of ventrally protruding interarcuate ligament or joint capsule. A dorsal extended view is appropriate for demonstrating dorsal spinal cord compression due to interarcuate ligament hypertrophy/hyperplasia. It has been reported, however, that routine use of “stressed” views is not warranted because of the possibility of misinterpretation of alterations and because of the risk of further injury to a spinal cord that may already be severely compromised.

“Traction” radiography, for which firm traction is placed on the cervical spine during exposure of a lateral or ventrodorsal radiograph, may further delineate the dynamic nature of a lesion. With this technique, spinal cord compression resulting from “redundant” or protruding anulus fibrosus may be relieved by the procedure. Failure to relieve the compression with “traction” may indicate a static lesion, such as a disk protrusion. It should be noted that “traction” may relieve the compression evident on lateral radiographs, whereas the lateral compression seen on ventrodorsal radiographs may remain. “Traction” views in both the lateral and ventrodorsal projections are recommended after myelography, because they do not appear to increase spinal cord compression and they provide useful information for the selection of an appropriate surgical technique.

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Advanced imaging modalities (e.g., CT or MRI) may be useful for further defining the nature and extent of spinal cord and nerve root involvement in caudal cervical spondylo-myelopathy and for differentiating this condition from other causes of caudal cervical spinal cord compression.[74]

193.5.4.4 Treatment

Numerous regimens have been recommended for the management of dogs with cervical spondylomyelopathy.[66–78] Treatment is directed toward relief of clinical signs through medical therapy and management practices or toward surgical relief of spinal cord compression. The large number of recommended treatments reflects the variety of lesions demonstrated by various diagnostic techniques, the variable results achieved by investigators, and the personal bias of individual surgeons. In most dogs the disease course is chronic and progressive, and the prognosis, in the absence of treatment, is guarded to poor.

Medical therapy consists of the use of anti-inflammatory medications and management procedures that reduce neck movement, such as close confinement or use of a neck brace.[68–71] Some affected dogs may be maintained at an acceptable level of neurologic function for months to years with corticosteroid administration. In some dogs, corticosteroid therapy may be discontinued during periods of improved neurologic function and re-established during periods of relapse of neurologic abnormalities. The adverse effects of long-term corticosteroid therapy must be considered, and it must be remembered that in most cases, this approach does not address the underlying sustained spinal cord compression.

Techniques for surgical management attempt to correct the underlying spinal cord compression.[66–82] The high potential for morbidity and postoperative complications associated with surgical management of cervical spondylomyelopathy must be considered before surgery is recommended. These considerations must be balanced against the current knowledge of the natural progression of the disease. Surgical procedures may use either a dorsal or a ventral approach to the vertebral column. The primary objective of all surgical procedures is decompression of the spinal cord or stabilization of affected vertebrae, or both.

The prognosis for dogs with cervical spondylomyelopathy is difficult to determine. In general, medical therapy may be expected to provide clinical improvement for a variable period (weeks to years). Medical therapy does not alter sustained and often progressive spinal cord compression. Surgical therapy that relieves spinal cord compression may be associated with postoperative complications; however, the following statements may be made: (1) The prognosis for dogs with a chronic history of worsening signs is not as favorable as for dogs with an acute onset of signs; (2) mildly affected dogs have a fair prognosis for recovery; (3) dogs with a single level of compression appear to have a better prognosis after surgery than those with multiple-level compressions; (4) long-term follow-up of dogs treated by fusion reveals that up to 19% of dogs develop spinal cord compression at an adjacent interspace an average of 20 months after surgery.[83]

Overall, the prognosis for long-term resolution of clinical signs must be considered guarded, regardless of the type of therapy.

193.5.5 Congenital Vertebral Anomalies

193.5.5.1 Etiology and Pathogenesis

Vertebral anomalies frequently occur in cats or dogs as a result of disturbances in embryonic development.[31,84,85] Most such anomalies are not clinically significant. If a vertebral anomaly causes instability or deformity of the vertebral canal, or spinal cord or nerve root compression, clinical signs may result. Multiple spinal anomalies may occur in a single dog or cat.

The most frequently recognized vertebral anomalies are alteration in location of the anticlinal vertebrae, anomalies of articular processes, variations in numbers of vertebrae, transitional vertebrae, butterfly vertebrae, block vertebrae, nonfusion of sacral vertebrae, or hemivertebrae. Of these anomalies, hemivertebrae are the most significant as a cause of neurologic abnormalities.[31]

193.5.5.1.1 Hemivertebrae

Hemivertebrae are wedge shaped, and the apex may be directed dorsally, ventrally, or medially across the midline.[31] Hemivertebrae may be associated with moderate to severe angulation of the spine and may be displaced dorsally during growth by pressure from adjacent vertebrae. Hemivertebrae occur most commonly in the thoracic spine of "screw-tailed" brachycephalic breeds (French and English bulldogs, pugs, and Boston terriers), but they may occur at any location in any breed of dog. Thoracic hemivertebrae are the development of caudal hemivertebrae. Kyphosis, scoliosis, and lordosis are commonly associated with hemivertebrae.

193.5.5.1.2 Block vertebrae

Block vertebrae may involve the vertebral bodies, vertebral arches, dorsal spinous processes, or entire vertebrae, at any level of the vertebral column. The sacrum is considered a "normal" block vertebra. Block vertebrae may be the same length as the number of involved vertebrae or shorter and can result in abnormal angulation of the spine. Partial "blockage" of vertebral bodies may occur, allowing partial development of an intervertebral disk.

193.5.5.1.3 Butterfly vertebrae

Butterfly vertebrae result from persistence of the notochord. In some instances, sagittal cleavage of the notochord may result in a sagittal cleft dorsoventrally through the vertebral body. On a dorsoventral radiograph, such vertebrae resemble a butterfly with wings spread. Compensatory growth of the adjacent normal vertebrae often fills in the funnel-shaped depression of the vertebral endplates. Butterfly vertebrae are most commonly seen in brachycephalic "screw-tailed" breeds.

193.5.5.1.4 Transitional vertebrae

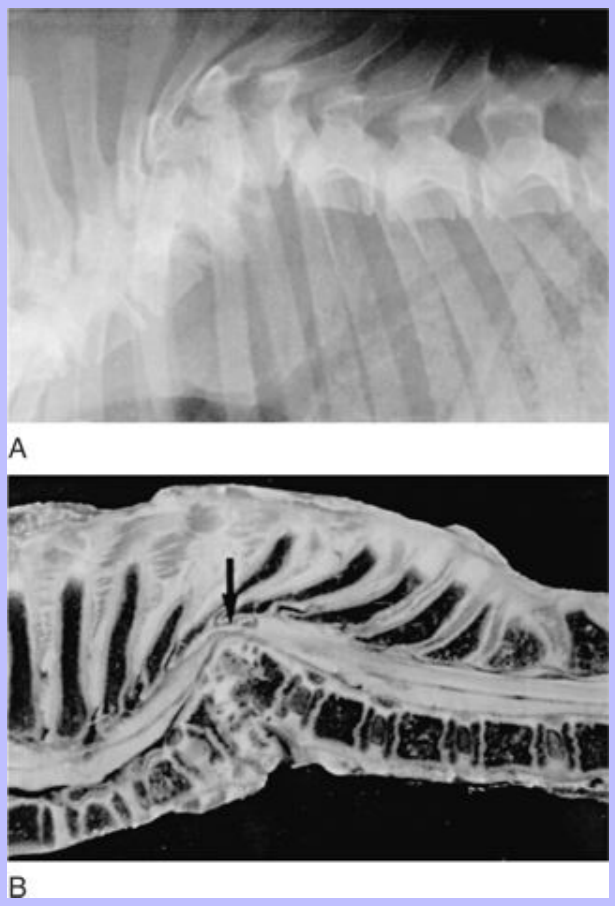
Dogs may have variations in the number of cervical, thoracic, lumbar, or sacral vertebrae. Furthermore, congenital absence or alteration in the shape of vertebral articular processes and variation in the location of the anticlinal (usually T11) and diaphragmatic (usually T10) vertebrae may occur. Vertebrae that have the characteristics of two major divisions of the vertebral column are referred to as *transitional vertebrae*. Observed alterations include transverse processes of C7 resembling a rib, a transverse process on the most caudal thoracic vertebra in place of a rib, the first sacral vertebra having a transverse process, and the last lumbar vertebra having a transverse process that has fused with the ilium. These alterations may be accompanied by an alteration in the size and shape of the vertebral body or in the plane of the vertebral body or intervertebral disk.

193.5.5.2 Clinical Findings, Diagnosis, and Treatment

Congenital vertebral anomalies frequently occur; however, clinical signs related to anomalous vertebrae are not present in most affected animals. In most animals in which clinical signs develop, trauma to the spinal cord has occurred secondary to vertebral instability or progressive deformity with growth. Diagnosis of a vertebral anomaly is made using radiographs of the vertebral column (Figure 193-4). Radiographically, hemivertebrae and adjacent vertebrae appear to be formed of normal bone, and disk spaces are usually normal or widened. Vertebral bodies appear to have a portion absent and do not appear to be compressed.

Adjacent vertebrae frequently have an altered shape that conforms to the defect found in the congenitally affected segment. Vertebral endplates are smooth and of normal thickness. Hemivertebrae should be differentiated from vertebral compression caused by a traumatic fracture, pathologic fracture as a result of vertebral neoplasia, or osteomyelitis. In most cases myelography is necessary to detect spinal cord compression resulting from a congenital anomaly. Advanced imaging (CT or MRI) may be useful in further defining the extent of vertebral and spinal cord involvement. Vertebral anomalies resulting in spinal cord compression and instability of the vertebral column may be treated through surgical decompression, vertebral realignment, and stabilization.[86]

Figure 193-4 Hemivertebrae. Lateral radiograph **(A)** of the midthoracic region of the vertebral column of a 3-month-old male malamute that had a history of inability to use the pelvic limbs since birth. Pain perception was absent in the pelvic limbs. Note the kyphosis associated with hemivertebrae affecting three midthoracic vertebrae. Severe spinal cord compression *(arrow)* is seen in a gross necropsy specimen **(B)** of the vertebral column sectioned in the midsagittal plane.



193.5.6 Corticosteroid-Responsive Meningitis-Arteritis

193.5.6.1 Etiology and Pathogenesis

Corticosteroid-responsive meningitis-arteritis, which occurs in young, medium to large breed dogs, may be the most frequently occurring form of meningitis.[87–89] The etiology is unknown; however, immunopathologic mechanisms are suspected, because IgA seems to play a central role in the pathogenesis.[21,90–92] It has been suggested that repeated vaccinations with multivalent modified live vaccines may be a cause. The clinical and clinicopathologic findings associated with this disease are similar to those seen in dogs with necrotizing vasculitis of the spinal meningeal arteries.[49,93–98]

193.5.6.2 Clinical Findings

Affected dogs are usually 7 to 16 months of age. Clinical signs include reluctance to move, arched back, stiff gait, apparent cervical and/or thoracolumbar pain, fever, muscle rigidity or spasms, apparent pain on opening the mouth and, less commonly, neurologic deficits, such as decreased proprioceptive positioning, paraparesis, or tetraparesis. Optic neuritis has been reported in an affected animal.[87] The clinical signs are indistinguishable from those of meningitis and myelitis of other causes (bacterial, fungal, viral) and from necrotizing vasculitis of spinal meningeal arteries. Clinical signs may be acute in onset and progressive, or they may follow a waxing and waning course over a period of weeks or months.

193.5.6.3 Diagnosis

The diagnosis is made on the basis of increased white blood cells in the CSF, failure to isolate an infectious agent from the CSF, and response to therapy with corticosteroids. Most affected dogs may have a mature neutrophilia in peripheral blood. The WBC count of the cerebrospinal fluid may be normal or may range from 50 to more than 3000 cells/μL, with predominantly mature neutrophils. Neither bacteria nor fungi are seen in the white blood cells. The CSF protein concentration most often is increased (40 to 350 mg/dL). Bacterial (aerobic and anaerobic) and fungal cultures of the CSF, urine, and blood are negative. It may be difficult to differentiate this disease from granulomatous meningoencephalomyelitis on the basis of CSF analysis. Examination of the IgG index and the IgM and IgA contents of the CSF may be useful in distinguishing corticosteroid-responsive meningitis from other causes of meningitis, such as chronic distemper encephalitis or granulomatous meningoencephalitis of dogs.[21]

193.5.6.4 Treatment

Early diagnosis is essential for successful treatment.[92] Initially, a corticosteroid is given at a dosage sufficient to produce remission of clinical signs (prednisone, 1 to 2 mg/lb/day). Corticosteroids are reduced slowly over several months to the lowest dose necessary to maintain remission of the clinical signs. Maintenance treatment using every other day dosing is preferred. Approximately 50% of affected animals have recurrence of clinical signs after corticosteroid therapy is discontinued. Increasing the corticosteroid dose may be necessary if clinical signs recur. Therapy for up to 6 months may be necessary to prevent recurrence of clinical signs. Ideally, CSF analysis results should be within normal limits before therapy is

stopped.[92] The prognosis for eventual resolution of clinical signs is good. Treatment with antibiotics may be indicated initially if the diagnosis is uncertain and bacterial meningitis is suspected.

193.5.7 Degenerative Myelopathy

193.5.7.1 Etiology and Pathogenesis

Degenerative myelopathy is characterized by slowly progressive ataxia and paresis of the pelvic limbs. Histologically, demyelination, axonal degeneration, and astrocytosis in the white matter of the spinal cord are seen. These changes are found throughout the spinal cord and are most severe in the thoracic spinal cord segments, especially in the dorsolateral and ventromedial funiculi.[99–101] The etiology of degenerative myelopathy is unknown in dogs.[102,103] Dural ossification, spondylosis deformans, chronic intervertebral disk protrusion, or infectious or vascular disorders may occur concurrently with degenerative myelopathy. The occurrence of degenerative myelopathy predominantly in German shepherds suggests a genetic basis for the disease, although there is no direct evidence to support this.

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193.5.7.2 Clinical Findings

Degenerative myelopathy generally occurs in dogs 6 years of age or older, although a similar condition has been reported in German shepherds 6 and 7 months of age.[104] Males are affected more often than females. It has been reported most commonly in German shepherds and German shepherd–mixed breed dogs, although it does occur in other large and medium breeds.[99–101]

Affected dogs usually have a slowly progressive paraparesis and pelvic limb ataxia. The onset of clinical signs is gradual. Neurologic deficits often are more noticeable when the dog walks on a smooth surface. Affected dogs may have worn pelvic limb toenails. Although neurologic deficits are most often present bilaterally, they may be asymmetric. Paraparesis and ataxia progressively worsen, so that most affected dogs become nonambulatory within several months to 1 year after neurologic deficits are first detected. Paralysis of the pelvic limbs rarely occurs, probably because most large dogs are euthanized if they become nonambulatory.

Apparent pain or discomfort is not evident in affected dogs. Voluntary control of urination and defecation is retained, although affected dogs may not be able to urinate or defecate in an appropriate place owing to severe paraparesis or inability to assume a voiding posture. This is important, because some dogs have apparent incontinence in the house, which may suggest a lesion of the cauda equina or sacral spinal cord segments. Muscle atrophy is not severe in the initial stages of the disease but may become noticeable in later stages; it is due to disuse rather than denervation. Cutaneous and deep pain perception remain intact throughout the course of the disease.

The neurologic examination findings usually are indicative of a transverse myelopathy between T3 and L3. Abnormalities include decreased or absent conscious proprioception and placing reactions in the pelvic limbs, normal to exaggerated patellar reflexes, normal to exaggerated withdrawal reflexes in the pelvic limbs, normal anal sphincter tone and anal reflex, normal muscle tone in the tail and, in some cases, crossed extensor reflexes in the pelvic limbs. The panniculus reflex usually is normal bilaterally. It is important to note that patellar reflexes may be decreased or absent unilaterally or bilaterally in some cases, possibly as a result of degeneration of the dorsal root ganglia or dorsal gray matter of the lumbar spinal cord (i.e., an afferent rather than a LMN lesion).

193.5.7.3 Diagnosis

Diagnosis of degenerative myelopathy is based on the clinical findings, the age and breed of the dog, and the ruling out of all other causes of a transverse myelopathy in the T3 to L3 region of the spinal cord. Diseases to be considered in the differential diagnosis include discospondylitis, myelitis, spinal cord compression due to type II intervertebral disk protrusion, and spinal neoplasia. Radiographs of the vertebral column may be normal or may demonstrate degenerative changes, such as dural ossification, spondylosis deformans, or narrowed intervertebral disk spaces. An increased protein content (40 to 100 mg/dL) is often found in CSF collected from the lumbar subarachnoid space. The CSF protein level is usually normal in samples collected from the cisternal subarachnoid space. The WBC count is normal in both lumbar and cisternal CSF. Significant myelographic abnormalities are not found.

193.5.7.4 Treatment

Effective treatment has not been reported, and affected dogs usually progress to severe nonambulatory paraparesis within a year of initial diagnosis. Therapy with vitamin supplementation, epsilon-aminocaproic acid (EACA), N-acetylcysteine, and exercise has been recommended by one author.[99–101] However, to date no controlled studies have shown that this therapeutic regimen is of any benefit.

193.5.8 Diffuse Idiopathic Skeletal Hyperostosis

193.5.8.1 Etiology and Pathogenesis

Diffuse idiopathic skeletal hyperostosis (DISH) is a diffuse ossifying condition of young dogs (predominantly large and giant breeds) or cats.[105,106] It has been suggested that four of the following five criteria be met for confirmation of DISH in dogs: (1) flowing calcification and ossification along ventral and lateral aspects of three contiguous vertebral bodies, leading to segmental bony ankylosis; (2) relative preservation of disk width in involved areas, and absence of extensive radiographic changes of degenerative disk disease (e.g., endplate sclerosis, nuclear calcification, or localized spondylosis deformans); (3) periarticular osteophytes surrounding true vertebral joints; (4) formation of pseudoarthrosis between the bases of spinous processes; and (5) periarticular osteophytes and calcification and ossification of soft tissue attachments (enthesiophytes) in both the axial and the peripheral skeleton.[105] Other associated findings may include periarticular osteophytes, sclerosis and ankylosis of sacroiliac joints, and bony ankylosis of the symphysis pubis.

The etiology of this condition is obscure. DISH is a disease that most likely represents a “vulnerable state” in which extensive vertebral ossification results from some stimulus that causes only modest new bone formation in most animals. These “bone formers” have a high incidence of associated extraspinal hyperostosis at the sites of ligament or tendon attachment. The pathologic alterations in DISH include findings consistent with spondylosis deformans; however, DISH differs quantitatively and qualitatively from spondylosis deformans and represents a regional ossification encompassing ligaments, paraspinal connective tissue, and anulus fibrosus, as well as periosteal new bone formation on the ventral surface of the vertebrae.[107–109] Spinal rigidity of several vertebrae resulting from DISH may result in syndromes caused by “dynamic overload” of an adjacent “mobile segment” of the vertebral column. Typically, a rigid fusion of several lumbar vertebrae may result in degenerative changes (e.g., sclerosis, spondylosis deformans, disk

protrusion) that affect the "overloaded" disk immediately cranial to the fused segments. The degenerative changes in the adjacent disk may result in clinical signs associated with spinal cord compression or nerve root entrapment.

193.5.8.2 Clinical Findings

Clinical signs, which may be minimal compared with the dramatic radiographic changes, include mild apparent spinal pain, stiff or stilted gait, and difficulty jumping. Rarely, clinical signs of spinal cord compression resulting from extreme bony proliferation and spinal canal stenosis may result in a transverse myelopathy between T3 and S3. Nerve entrapment may result from bony proliferation at the level of the intervertebral foramen.

193.5.8.3 Diagnosis and Treatment

The diagnosis is based on radiographic confirmation of the diagnostic criteria listed above (Figure 193-5).[105] Analysis of CSF and myelography are necessary to rule out other disorders that may result in similar clinical signs. Advanced imaging (CT or MRI) may be useful for accurately investigating the possibility of spinal cord compression or nerve root entrapment resulting from bony proliferation.

Treatment for DISH has not been described. Conservative (medical) management is recommended unless clinical signs of spinal cord compression or nerve root entrapment are present, in which case surgical decompression may be considered.

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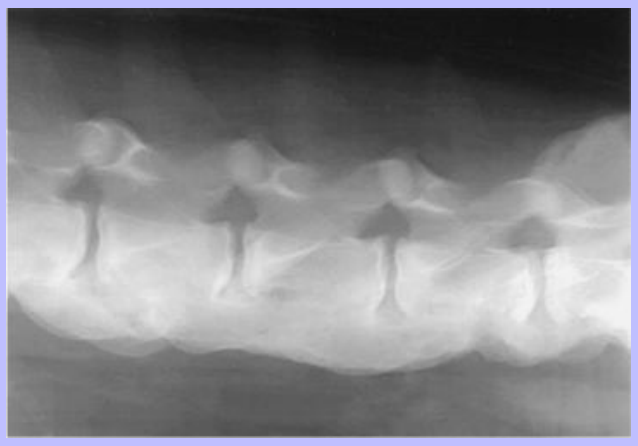
Figure 193-5 Diffuse idiopathic skeletal hyperostosis (DISH). Lateral radiograph of the lumbar region of a 4-year-old neutered male Akita. Note the smooth proliferative laminar bridging of the ventral aspects of L4 through L7, consistent with a diagnosis of DISH. The intervertebral disks in this region do not appear to be narrowed. Spondylosis deformans is present at L7–S1. Proliferative remodeling changes are observed at multiple articular facets along the lumbar spine.



193.5.9 Discospondylitis (Spondylitis, Vertebral Osteomyelitis)

193.5.9.1 Etiology and Pathogenesis

Bacterial or fungal infection of the intervertebral disks and adjacent vertebral bodies (discospondylitis) or of only the vertebral bodies (spondylitis) may cause extradural spinal cord or cauda equina compression as a result of granulation tissue, bony proliferation, or pathologic fracture or luxation. Less commonly, discospondylitis may lead to diffuse or focal meningitis and myelitis.[110–113] These conditions result from implantation of bacteria or fungi introduced by migrating plant awns (grass seeds, foxtails), hematogenous spread, extension of a paravertebral infection, a penetrating wound, or previous disk or vertebral surgery.

Discospondylitis and spondylitis occur more commonly in dogs in areas where grass awn infections are a problem. Several theories attempt to explain the migration of grass awns to the vertebral column. Awns may be swallowed and migrate through the bowel wall (possibly at the caudal duodenal flexure), through the mesentery to the attachment to ventral epaxial muscles, and to the vertebral column. Evidence of scarring, however, has not been found in the gut or abdomen of dogs with discospondylitis. Because dogs with discospondylitis thought to be due to plant awn migration have lesions most commonly in the cranial lumbar spine (L2–L4), it has been suggested that awns may be inhaled and migrate through the lungs to the diaphragm, lodging at the crural insertion on the lumbar vertebrae. Plant awns may also migrate through skin and paravertebral or abdominal muscles to the vertebral column. Grass seeds are able to travel long distances owing to the direction of the barbs. Forward progress may be aided by muscle movements.

Hematogenous spread of bacteria or fungi is probably the most common cause of discospondylitis. Sources of infection include bacterial endocarditis, dental disease, and urinary tract infections. Retrograde flow in the vertebral veins has been suggested as a possible route of infection to the vertebral column. It is not known whether discospondylitis associated with urinary tract infection is due to venous or arterial dissemination of bacteria or whether a direct causal relationship exists between urinary tract infection and discospondylitis. Many dogs with discospondylitis have concurrent urinary tract infection. Discospondylitis caused by *Brucella canis* infection most likely results from bacteremic spread from a genital infection.

Affected intervertebral disks may show evidence of degeneration (collapsed disk space, spondylosis deformans) or trauma (traumatic disk protrusion, vertebral luxation). Discospondylitis may occur with increased frequency in immunocompromised animals.[114–116] The organisms most commonly isolated from the blood, affected vertebrae, and urine of dogs with discospondylitis are coagulase-positive *Staphylococcus* spp. *(S. aureus, S. intermedius),* although a number of other organisms have been identified.[110–112,116–120] Discospondylitis has been reported to occur in cats.[121]

193.5.9.2 Clinical Findings

Discospondylitis may occur in dogs or cats of any age, but it is most commonly seen in giant and large breed dogs. Any level of the vertebral column may be affected, and multiple lesions may be seen in either adjacent or nonadjacent vertebrae. Discospondylitis occurs more commonly in the thoracic and lumbar spine than in the cervical spine. The lumbosacral disk space frequently is involved.

Clinical findings depend on the location of the affected vertebra or vertebrae. The most common clinical signs are weight loss, anorexia, depression, fever, reluctance to run or jump, and apparent spinal pain (which

may be severe). Hyperesthesia may be present only over the site of the lesion or may be poorly localized, especially with involvement of multiple sites.[110]

193.5.9.3 Diagnosis

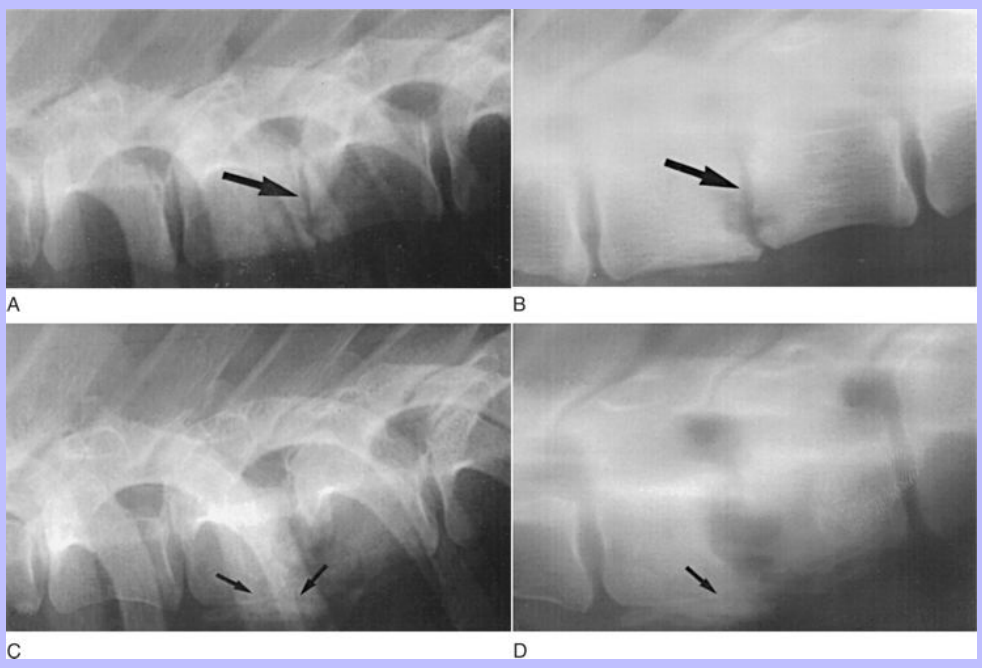
Diagnosis may be difficult, because clinical signs often are nonspecific. Discospondylitis should always be considered in an animal with fever of unknown origin. If the lumbosacral intervertebral disk is involved, dogs often show a stilted, short-strided pelvic limb gait and shifting pelvic limb lameness. Clinical signs may be present for several weeks or months before diagnosis.

Neurologic deficits associated with spinal cord or cauda equina compression may be present and may reflect either a transverse or a multifocal myelopathy. Neurologic deficits associated with a transverse myelopathy (T3–L3) occur most commonly and include paraparesis, decreased conscious proprioception, exaggerated spinal reflexes and, much less commonly, paraplegia. Cervical lesions most commonly cause only apparent cervical pain, and lumbosacral lesions may cause neurologic deficits due to compression of nerves of the cauda equina. Rarely, animals may demonstrate clinical signs of diffuse suppurative meningitis associated with extension of infection to involve the spinal meninges. Dogs may have a history of draining tracts in the paravertebral area associated with grass seed migration. Discospondylitis has been described in dogs with osteomyelitis in other sites (femur and sternum).

Affected animals may have a normal or elevated peripheral WBC count. Typical radiographic findings are destruction of the bony endplates adjacent to an infected disk, collapse of the intervertebral disk, and varying degrees of new bone production. Early lesions may consist only of lytic areas in affected vertebral endplates. More advanced lesions show a mixture of bone lysis and extensive new bone production, with osteophytes bridging adjacent vertebrae containing a central destructive focus (Figure 193-6). Affected vertebral bodies may be shortened, and bony proliferation may result in fusion of one or more vertebrae. Discospondylitis may be superimposed on other vertebral abnormalities, including fracture and associated callus formation, spondylosis deformans, or a surgical site.

Because discospondylitis may be present in more than one site in the vertebral column, it is important that the entire spine be radiographed in animals suspected of having discospondylitis. Occasionally clinical signs may occur before characteristic radiographic changes are evident. Tomography may also be a useful method of radiographic diagnosis of discospondylitis, particularly at the lumbosacral junction (Figure 193-7). Bone scintigraphy may be useful for detection of early lesions prior to the development of radiographically evident lesions and for investigation in animals in which it is uncertain whether lesions are due to infection or other causes (e.g., severe spondylosis deformans). Advanced imaging (CT or MRI) may be useful in the identification of subtle vertebral lesions.[110,122]

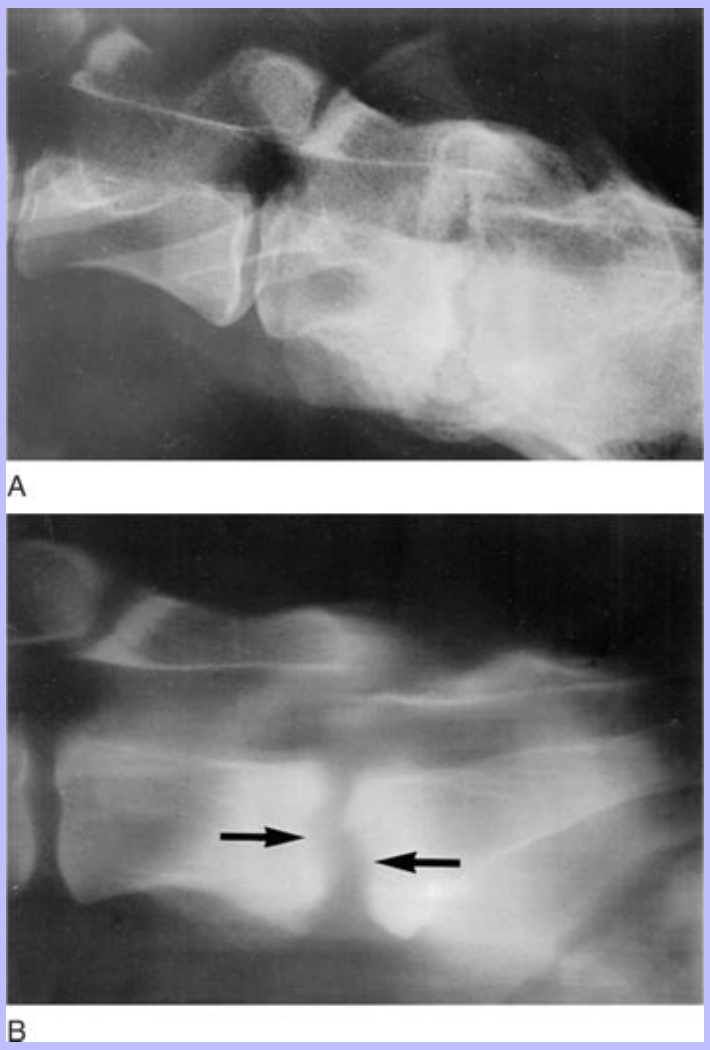
Figure 193-6 Discospondylitis. Lateral radiograph **(A)** and linear tomogram **(B)** of the midthoracic vertebral column of a 1-year-old female Doberman pinscher 8 weeks after the onset of apparent back pain. Note the collapse of the T6–T7 disk *(large arrow)*, the destruction of the vertebral endplates, and the well-delineated lysis of the T6 and T7 vertebral bodies. These changes are easily observed on the tomogram, where superimposed ribs are not a factor. Lateral radiograph **(C)** and linear tomogram **(D)** of the midthoracic vertebrae completed 3 months after **A** and **B.** The dog had undergone a 4-week course of a broad-spectrum antibiotic that resulted in clinical improvement after the initial radiographic examination; however, signs of spinal pain had returned. Note the progression of the radiographic changes seen 3 months earlier and the bony proliferation *(small arrows)* at T6–T7. After surgical biopsy and culture of the T6–T7 disk, therapy with an appropriate antibiotic drug was commenced. Complete radiographic resolution of the discospondylitis and fusion of the T6–T7 vertebrae were apparent after 6 months of continued antibiotic therapy.



Collection of CSF is indicated for animals with neurologic deficits. The CSF may be normal or may have an increased WBC count and/or protein content when discospondylitis lesions cause extradural compression of the spinal cord or result in meningitis and/or myelitis. Myelographic findings usually indicate extradural compression that results from extension of granulation tissue and bony proliferation in the spinal canal. Clinical signs do not always correlate well with the degree of compression seen on myelography and depend on factors such as the rate, duration, and degree of compression. Aerobic, anaerobic, and fungal cultures of blood and urine should be done prior to treatment in an attempt to isolate causative organisms. Some authors consider any organism other than *S. intermedius* cultured from the urine unlikely to be the causative organism unless it is also cultured from the blood or a vertebral lesion. Cultures of CSF are indicated if the WBC count is elevated. Cultures of fluid from draining sinuses may also be performed. In all dogs with discospondylitis, efforts should be made to determine whether *B. canis* infection is present.[117]

Surgical biopsy may be indicated in affected dogs in which a causative organism is not isolated from blood or urine and/or in animals that are unresponsive to treatment with broad-spectrum antibiotics. Fluoroscopy-guided needle aspiration of lesions is possible in some animals.[123] However, cultures of samples collected in this way are often negative, especially if animals have been treated with antibiotics prior to the biopsy.

Figure 193-7 Discospondylitis. Lateral radiograph **(A)** and linear tomogram **(B)** of the lumbosacral region of the vertebral column of a 4-year-old German shepherd that had a 1-month history of apparent pain and pelvic limb weakness. Note the sclerosis of the vertebral endplates, spondylosis deformans, new bone formation, and collapsed disk seen on the radiograph of L7–S1. A tomogram of this region confirms the presence of bone lysis *(arrows)* consistent with a diagnosis of discospondylitis. *Staphylococcus aureus* was cultured from the urine and blood and from material obtained from the L7–S1 disk by needle aspiration.



193.5.9.4 Treatment

Treatment consists of long-term use of an antimicrobial that is effective against the causative organism or organisms detected by blood and/or urine cultures. If an organism is not cultured, dogs without severe neurologic deficits may be treated empirically, assuming infection with the most common organism isolated from animals with discospondylitis (coagulase-positive *Staphylococcus* spp.). The antibiotics most effective for this purpose are cephalosporins or beta lactamase–resistant penicillins (e.g., oxacillin and cloxacillin). A trimethoprim/sulfonamide combination or chloramphenicol is less effective, but it is less expensive and may be effective in some cases.

Clinical signs may recur if the infection is not completely eliminated prior to cessation of antibiotic therapy, and repeated cultures of blood and urine, as well as ongoing treatment with an appropriate antibiotic, may be necessary. Treatment is continued for at least 6 weeks, and vertebral radiographs are taken every 2 to 3 weeks to monitor the progression or regression of a lesion and to monitor for the development of new lesions. Antibiotic administration may be necessary for up to 6 months before radiographic evidence of resolution of lesions is seen. Clinical improvement in animals with discospondylitis (resolution of fever, improved appetite, reduction of apparent spinal pain) should be seen within 2 weeks of initiation of antibiotic therapy. Surgical exploration of a lesion should be considered in animals that are unresponsive to treatment or that have persistent draining tracts suggestive of grass seed migration. The objectives of surgery are curettage of lesions and harvesting of material for bacterial and fungal culture. A cancellous bone graft has been recommended after curettage of a disk space. Decompressive surgery is indicated if evidence of spinal cord compression is found on myelography and if the animal shows severe or progressive neurologic deficits. Surgical stabilization of the vertebrae may be necessary after decompression.[124]

193.5.10 Distemper Myelitis

193.5.10.1 Etiology and Pathogenesis

Canine distemper (CD) virus is a neurotropic virus that may cause focal or diffuse demyelination in both gray and white matter of the CNS.[125] The mechanism by which demyelination occurs is not known, but the condition may be a primary effect of the virus on glial cells or may occur secondary to immunologic mechanisms. The white matter of the cerebellum, cerebellar peduncles, optic nerves, optic tracts, and spinal cord are most severely affected. Focal or diffuse demyelination may occur in the white matter of the spinal cord.[126,127] Further histopathologic changes seen in the spinal cord and throughout the CNS include perivascular cuffing by mononuclear cells, gliosis, microglial proliferation, inflammatory cell infiltration of the pia arachnoid, and neuronal changes (nuclear pyknosis, chromatolysis, shrunken cells, and neuronophagia). Intranuclear and intracyloplasmic inclusions may or may not be present.

193.5.10.2 Clinical Findings

Affected animals may or may not have a history of systemic illness. Dogs of any age may be affected, but those with myelitis due to CD infection are usually less than 3 years of age. Dogs that have been vaccinated according to recommended schedules may be affected. Clinical signs of CD myelitis reflect the location of the lesion or lesions, which may be focal or diffuse, at any point in the spinal cord. The T3 to L3 spinal cord segments are affected most often, and clinical signs indicative of a transverse myelopathy in this region are seen. Neurologic abnormalities include paraparesis or paraplegia and normal to exaggerated reflexes in the

pelvic limbs. Neurologic deficits are progressive and bilateral; however, they may be asymmetric. Affected dogs may have clinical signs indicative of current or previous systemic CD infection. Neurologic deficits commonly seen in dogs with CD infection are vestibular and/or cerebellar abnormalities and visual deficits.[128] Self-mutilation occasionally is seen in dogs with CD infection. The limbs and tail are the common sites of mutilation. Paresis or paralysis of the limbs may also be present.

193.5.10.2.1 Distemper myoclonus

Myoclonus, the rhythmic twitching of a muscle or muscle group, is most often associated with CD infection.[129] Any muscles may be involved, including the facial and masticatory muscles or the limb muscles. The pathogenesis of myoclonus is unknown. It is thought to result from an abnormality in the motor neuron and interneuron pools of the medulla and spinal cord. Animals may recover from systemic CD infection and occasionally from CNS infection; however, myoclonus may persist. Myoclonus is generally permanent and may persist during sleep. It may be alleviated by oral therapy with procainamide.

193.5.10.3 Diagnosis

Antemortem diagnosis often is difficult.[130] Clinical signs of multifocal CNS disease, particularly neurologic deficits indicative of spinal cord and cerebellovestibular disease, are highly suggestive of CD infection. Hematologic findings in dogs with CD infection are nonspecific. Abnormalities of the cerebrospinal fluid may be useful in the diagnosis of CD infection; however, the CSF may be normal. The WBC count and protein content of the cerebrospinal fluid are usually mildly to moderately increased. Cells seen in the CSF are predominantly lymphocytes (10 to 60 cells/μL). The presence of interferon in the CSF appears to be a reliable indicator of virus persistence.[129] CSF electrophoresis may also be performed and is useful for predicting the histopathologic changes in dogs with CD encephalomyelitis.[131] Determination of the IgG index may also aid the diagnosis of CD encephalomyelitis.[126]

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Increased CD virus–specific antibody titers in the CSF may be useful in the diagnosis of CD infection. Increased anti–CD virus antibody in the CSF may offer evidence of chronic CD infection, because antibody is produced locally in the CNS, and significantly increased titers have rarely been present in vaccinated dogs or dogs with systemic CD infection without CNS involvement. Cerebrospinal CD antibody may be artifactually increased if whole blood contamination of the CSF occurs during collection. Negative CD antibody results do not rule out a diagnosis of CD.[40,129]

193.5.10.4 Treatment

Clinical signs of CD myelitis may be either rapidly or more slowly progressive. Periods of apparent improvement may be followed by progression of clinical signs. A specific antiviral drug that has an effect on CD in dogs is not currently available. Favorable results have been reported by some investigators with short-duration (1 to 3 days) corticosteroid therapy.[40] Intravenous administration of a modified live vaccine in dogs with CD is effective only if given before clinical signs appear. Treatment of CD myelitis is almost always unrewarding. The prognosis for recovery is poor. In dogs that recover from CD infection, residual signs such as myoclonus or optic neuritis may improve with time. Immunization by vaccination is the only effective approach to the prevention of CD.[126]

193.5.11 Dural Ossification

193.5.11.1 Etiology and Pathogenesis

Dural ossification is the formation of bony plaques on the inner surface of the dura mater.[6] Bony plaques are found most commonly in the cervical and lumbar spine and may occur laterally, ventrally, or dorsally. Dural ossification is found in more than 40% of large and small breed dogs over 2 years of age and in more than 60% of dogs 5 years of age or older. Although many dogs with dural ossification also have spondylosis deformans, no direct correlation exists between the two conditions. The etiology of dural ossification is unknown.

193.5.11.2 Clinical Findings

Dural ossification rarely results in neurologic deficits or apparent spinal pain in dogs. Other causes of spinal cord disease should be ruled out before clinical significance is attributed to dural ossification.

193.5.11.3 Diagnosis and Treatment

Radiographically, bony plaques appear as thin, radiopaque lines (linear shadows) that are most easily viewed at the site of intervertebral foramina. These linear shadows must be distinguished from calcified herniated disk material in the spinal canal, from vertebral osteophytes, and from the accessory processes of the lumbar vertebrae. No specific treatment exists for dural ossification; however, in rare cases surgical removal of a bony plaque from the vicinity of a nerve root may be necessary to alleviate apparent pain due to nerve root compression.

193.5.12 Feline Infectious Peritonitis, Meningitis, and Myelitis

193.5.12.1 Etiology and Pathogenesis

Feline infectious peritonitis is a serious, almost always fatal disease caused by a coronavirus.[132–137] Pyogranulomatous meningitis and myelitis may occur in cats with FIP, which is most commonly seen in younger animals between 6 months and 5 years of age. Meningeal and spinal cord lesions are probably the result of immune complex–mediated vasculitis. Involvement of the CNS is more frequently observed in the noneffusive (dry) form than in the effusive (wet) form of the disease.

193.5.12.2 Clinical Findings

Focal, multifocal, or diffuse involvement of the spinal cord, brain, and meninges may occur with FIP, and clinical signs reflect the location of these lesions. The most commonly recognized neurologic signs are pelvic limb ataxia, hyperesthesia (especially over the back), and generalized ataxia.[137] Affected animals usually manifest other clinical signs indicative of disseminated disease, such as persistent fever (frequently exceeding 105° F), weight loss, enlarged kidneys, chorioretinitis, panophthalmitis, or anterior uveitis.[137]

193.5.12.3 Diagnosis

Histopathologic examination of biopsy specimens is the only conclusive method for diagnosing FIP. Short of this, a variety of factors may be considered to support a diagnosis of FIP.[138–140] The CSF usually is abnormal, with an elevated WBC count and protein level. The differential WBC count for the CSF is variable, but PMN cells, lymphocytes, and monocytes usually are present.

PMNs may be the predominant cell type in the CSF. The protein concentration may be high (greater than 2000 mg/dL), and the CSF may be viscous and may clot. This should be taken into consideration when a CSF puncture is performed, because fluid may flow into the needle slowly. The results of cytologic examination of the CSF depend on the degree of meningeal involvement. Meningeal inflammation may be extensive, and the CSF in these cases is generally highly abnormal. With focal or parenchymal inflammation, the CSF may be normal.

193.5.12.4 Treatment

The prognosis for cats with FIP of the central nervous system is poor. The feline leukemia virus (FeLV) status of cats suspected of having FIP should be determined before treatment is started, because the prognosis for cats with both viruses is hopeless.[141] The most effective treatment protocols combine high levels of corticosteroids (prednisolone, 1 to 2 mg/lb given orally once daily in the evening), cytotoxic drugs (either cyclophosphamide [1 mg/lb given orally once daily for 4 consecutive days of each week] or melphalan [1 mg given orally every third day]), and broad-spectrum antibiotics (ampicillin, 10 mg/lb given orally every 8 hours), together with maintenance of nutrient intake and electrolyte balance. Cats receiving cytotoxic drugs should be routinely monitored for evidence of kidney dysfunction or bone marrow suppression. If a positive response to therapy is seen, treatment should be continued for at least 3 months.[141]

193.5.13 Feline Polioencephalomyelitis (Feline Nonsuppurative Meningoencephalomyelitis)

Feline polioencephalomyelitis is a chronic, slowly progressive encephalomyelitis of unknown etiology that has been described in immature and mature cats.[40,142] A viral etiology is suspected based on the histopathologic changes, although a specific viral agent has not been isolated. The chronic clinical course, distribution of lesions, and lack of inclusions distinguish this disease from rabies, pseudorabies, and FIP. It has been proposed that a tick-borne virus may be the causative agent in Sweden.[143–146]

Clinical signs include ataxia, paraparesis, tetraparesis, hypermetria, head tremors, and localized hyperesthesia. Spinal reflexes, pupillary light reflexes, and postural reactions may be normal or depressed. Clinical signs usually are indicative of multifocal CNS disease but may be suggestive of focal transverse myelopathy in the thoracolumbar region or lumbar enlargement. Clinical signs are slowly progressive over several months. Antemortem diagnosis is difficult and is made by ruling out other multifocal CNS diseases. Treatment of affected cats has not been reported.

193.5.14 Globoid Cell Leukodystrophy (Krabbe-Type Leukodystrophy)

193.5.14.1 Etiology and Pathogenesis

Globoid cell leukodystrophy is an inherited lysosomal storage disease that results from a deficiency of galactocerebrosidase (GALC) activity.[6,147] Globoid cell leukodystrophy is characterized by bilaterally symmetric demyelination of the white matter of the brain, spinal cord, spinal nerve roots, and peripheral nerves and by accumulation, especially perivascularly, of large phagocytic cells with foamy-appearing cytoplasm (globoid cells). Globoid cell leukodystrophy is inherited as an autosomal recessive trait in cairn terriers and West Highland white terriers, and findings in other dog breeds suggest a recessive factor. The condition may not be inherited as a simple autosomal recessive trait in cats. Cloning of the GALC cDNA has been completed and the disease–Causing mutation identified in both West Highland white and cairn terriers.[147]

193.5.14.2 Clinical Findings

Clinical signs generally are first seen between 2 and 6 months of age and are progressive. However, neurologic abnormalities were not evident in an affected basset hound until 4 years of age. Affected cats usually show abnormalities by 6 weeks of age. Progressive paraparesis and paraplegia predominate in some affected animals, whereas cerebellar signs predominate in others. Spinal reflexes in the pelvic limbs may be normal or exaggerated, indicative of T3–L3 transverse myelopathy. Neurologic signs in affected animals usually progress to quadriparesis, dysmetria, head tremor, behavioral changes, and/or blindness. Spinal reflexes may be decreased or absent and muscle atrophy may be evident in some animals, indicative of LMN disease. Clinical signs usually progress over 2 to 6 months, although they were observed to progress for 2 years in one dog. Clinical signs in cats with globoid cell leukodystrophy are generally more indicative of cerebellar disease and are more rapidly progressive than in dogs.

193.5.14.3 Diagnosis

The diagnosis is made on the basis of the animal's age and breed and the presence of progressive neurologic deficits, as well as by ruling out other causes of progressive myelopathy (e.g., CD myelitis). The CSF may have phagocytic cells containing periodic acid–Schiff (PAS)-positive material (globoid cells), and the CSF protein content may be increased. In some animals the CSF may be normal. Brain and/or peripheral nerve biopsy may show characteristic demyelination and globoid cell accumulation and may be done to confirm a diagnosis of globoid cell leukodystrophy. A rapid test for identification of the genotype at cDNA position 473 has been developed.[147] The results of this test may allow breeders to screen their dogs for this problem and may result in elimination of this disease in the future.

193.5.14.4 Treatment

Treatment for globoid cell leukodystrophy has not been described.[6] Selective breeding based on genetic testing may eventually eliminate this disease.[147]

193.5.15 Granulomatous Meningoencephalomyelitis

193.5.15.1 Etiology and Pathogenesis

Granulomatous meningoencephalomyelitis (GME) is a nonsuppurative meningoencephalomyelitis of undetermined etiology in dogs.[6,148–150] It is characterized histopathologically by large perivascular accumulations of mononuclear cells throughout the brain, spinal cord, and meninges. A recent immunomorphologic study suggested that inflammatory lesions in canine GME consist of a heterogeneous population of major histocompatibility complex (MHC) class II antigen–positive macrophages and predominantly CD3 antigen–positive lymphocytes.[151] These data suggest T cell–mediated, delayed-type hypersensitivity of an organ-specific autoimmune disease.[151]

193.5.15.2 Clinical Findings

A higher incidence of GME has been found in female dogs, small breed dogs, poodles, poodle–mixed breed dogs, and Airedale terriers. Affected dogs usually are between 1 and 9 years of age, although dogs may be affected at any age. Clinical signs may indicate focal or multifocal cerebral, brain stem, cerebellar, and/or spinal cord involvement. GME may involve the spinal cord at any level; however, lesions appear to be most severe in the cervical spinal cord, and clinical findings are often indicative of cervical spinal cord disease. Findings include apparent cervical pain, rigidity, reluctance to move, hyperesthesia, cervical paraspinal muscle spasms, exaggerated spinal reflexes, decreased conscious proprioception, paraparesis, tetraparesis, and paraplegia. Affected animals usually have an acute onset of clinical signs, which progress over several days to months.[148,149]

193.5.15.3 Diagnosis

Antemortem diagnosis is difficult and usually is made on the basis of clinical findings and the results of CSF analysis. Dogs with GME may have intermittent fever. The findings for a complete blood count and on spinal and skull radiographs frequently are within normal limits. The CSF is abnormal in most affected dogs. The WBC count of the cerebrospinal fluid is usually increased (may be greater than 1000 WBCs/μL). Mononuclear cells predominate. The percentage of lymphocytes and monocytes varies considerably. PMN cells may also be present and in one study constituted 0 to 62% of the differential WBC count.[152] In the same study, less than 1% of the differential WBC count consisted of macrophages with ingested debris, plasma cells, and cells undergoing mitosis. The total and differential CSF white blood cell counts do not reflect the severity of meningeal involvement or the degree of necrosis. The CSF protein concentration is usually elevated, and the CSF pressure may be normal or increased. Alterations in the CSF were similar in untreated and corticosteroid-treated dogs in one study.[152]

Meningeal lesions may render CSF collection from cisternal puncture difficult. Although CSF collected from the lumbar subarachnoid space of affected dogs may have fewer white blood cells than cisternal CSF, it is useful for diagnosis. The difference in WBC counts probably reflects the greater distance of the lumbar subarachnoid space from the site of most lesions. Bacterial and fungal cultures are negative, and organisms are not identified in CSF cell preparations. Noncontrast radiography, myelography, and advanced imaging (CT or MRI) may confirm an intramedullary space-occupying lesion of the spinal cord.

193.5.15.4 Treatment

GME is either continuously or episodically progressive, and the prognosis for recovery is poor. Treatment with cortico-steroids may result in improvement of clinical signs for several days to several months or years. Immunosuppressive doses of corticosteroids should be given, and therapy must be sustained indefinitely. The corticosteroid regimen used for treatment of corticosteroid-responsive meningitis should be used for therapy of dogs with GME. Clinical remissions of greater than 1 year occur in some cases; however, clinical signs usually recur with discontinuation of treatment with corticosteroids. Radiation therapy may be an effective treatment for dogs with focal GME.[150] Alternative immunomodulatory drugs may also play a role in the treatment of GME in the future.[153]

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193.5.16 Hemorrhage

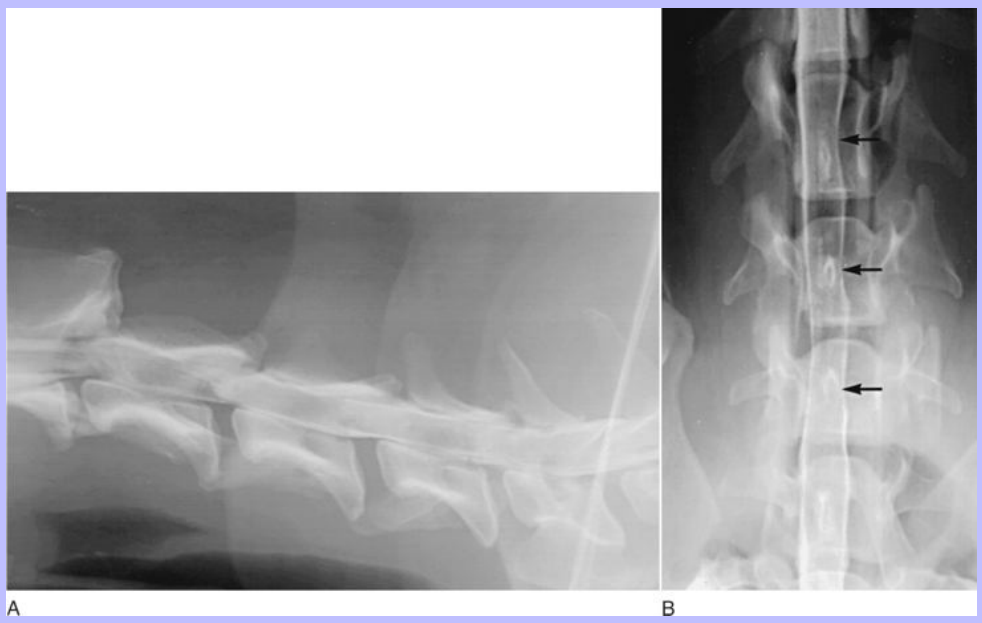
193.5.16.1 Etiology and Pathogenesis

Intramedullary, intrameningeal, or epidural hemorrhage may be due to coagulopathies, including thrombocytopenia, clotting factor deficiencies, disseminated intravascular coagulation, and anticoagulant poisonings (e.g., warfarin).[154] Acute hemorrhage may also occur in association with tumors, vascular malformations, acute intervertebral disk protrusion, trauma, parasitic migration, or meningitis (Figure 193-8). Spontaneous intramedullary hemorrhage with hematoma formation has been reported in the cervical spinal cord of a dog.[155] Spontaneous subperiosteal vertebral hemorrhage and hematoma formation associated with spinal cord compression and transverse myelopathy have been reported in dogs.

193.5.16.2 Clinical Findings

Neurologic deficits depend on the location of the hemorrhage and usually indicate a focal or multifocal myelopathy. Clinical signs most often are acute in onset, and neurologic deficits may be severe. Extensive gray matter necrosis may occur with intramedullary hemorrhage, resulting in LMN signs over a relatively large area of the spinal cord, especially if the cervical or lumbosacral spinal cord is involved. Subarachnoid hemorrhage may result in clinical signs suggestive of meningitis, including cervical rigidity, hyperesthesia, and elevated body temperature.

Figure 193-8 Hemorrhage. Lateral **(A)** and ventrodorsal **(B)** myelogram of the cervical vertebrae of a 10-year-old neutered male mixed-breed dog with an acute onset of tetraparesis. Narrowing of the C5–C6 intervertebral disk can be seen. The lateral myelogram **(A)** demonstrates inconsistent filling of the subarachnoid space. The ventrodorsal projection **(B)** confirms lateral deviation of the right contrast column and attenuation of the left contrast column *(arrows)*, owing to an extradural space-occupying mass. Exploratory surgery demonstrated that the extradural compression was caused by hemorrhage that had occurred secondary to the acute C5–C6 disk extrusion.



193.5.16.3 Diagnosis

Animals with coagulopathies may have evidence of hemorrhage elsewhere in the body. Diagnostic tests for coagulopathies should be undertaken. Subarachnoid CSF puncture may be contraindicated in animals with a coagulopathy because of the high probability of inducing further hemorrhage. Red blood cells may be present in the CSF for a short time after subarachnoid hemorrhage, and CSF supernatant may be red or pink in color. Xanthochromia may be present in the CSF 48 hours or more after the hemorrhage. The CSF white blood cell count and protein concentration may also be elevated.

Myelography is indicated when epidural hemorrhage is suspected to be the cause of spinal cord compression and when noncontrast radiographs and the results of CSF analysis are normal and no evidence of coagulopathy has been found. Epidural hemorrhage is not distinguishable from other extradural

space-occupying lesions on myelography. Hemorrhage may occur secondary to other abnormalities, such as intervertebral disk extrusion, as a result of laceration of a vertebral venous sinus.

193.5.16.4 Treatment

Treatment is directed at the underlying cause in animals with coagulopathies. Epidural and intramedullary hematomas not associated with coagulopathy may be removed surgically. The prognosis depends on the severity of the neurologic deficits at the time of diagnosis.

193.5.17 Hereditary Ataxia (Ataxia in Smooth-Haired Fox Terriers and Jack Russell Terriers)

193.5.17.1 Etiology and Pathogenesis

An inherited, progressive, generalized ataxia has been reported to occur in young, smooth-haired fox terriers and Jack Russell terriers.[6] This disease is characterized pathologically by demyelination bilaterally throughout the dorsolateral and ventromedial white matter of the spinal cord. In Jack Russell terriers, wide-spread wallerian-type degeneration in the white matter of the brain and degenerative changes in the central auditory pathways and peripheral nerves may be seen. Hereditary ataxia is inherited as an autosomal recessive trait in smooth-haired fox terriers. The etiology of ataxia in Jack Russell terriers is not known; however, clinical and pathologic findings suggest that it may be congenital. Degenerative myelopathies have been described in several dog breeds other than fox terriers and Jack Russell terriers, including English foxhounds, harriers, beagles,[156–158] boxers,[1] German shepherds,[99–104] poodles,[1] Afghan hounds,[1] a Pyrenees mountain dog,[159] a cairn terrier,[160] Dutch Kooiker dogs,[161] and Australian cattle dogs.[162] The pathogenesis of these conditions is unclear.

193.5.17.2 Clinical Findings, Diagnosis, and Treatment

Both males and females are affected. Neurologic abnormalities, first seen between 2 and 6 months of age, include pelvic limb ataxia and swinging of the hindquarters. The ataxia progressively worsens over 6 months to 2 years and involves all four limbs. Affected animals often have a prancing pelvic limb gait. Dysmetria may be severe, and affected dogs fall to the ground with a slight change in position. The diagnosis is made on the basis of the animal's age and breed and the clinical findings. Treatment is not effective. Affected animals are eventually unable to walk.

193.5.18 Hypervitaminosis A of Cats

193.5.18.1 Etiology and Pathogenesis

Hypervitaminosis A in cats is characterized by extensive, confluent exostosis that is most prominent in the cervical and thoracic spine.[6,7,163] It is caused by a chronic excess of dietary vitamin A and is usually a result of feeding of a diet consisting largely of liver. Exostosis may extend to involve the entire spine, ribs, and pelvic and thoracic limbs, with complete fusion of the spine and joints. Compression of spinal nerve roots or nerves may occur if new bone formation extends into the intervertebral foramina.

193.5.18.2 Clinical Findings, Diagnosis, and Treatment

Clinical signs in affected cats include apparent cervical pain and rigidity, thoracic limb lameness, ataxia, reluctance to move, paralysis, and hyperesthesia or anesthesia of the skin of the neck and forelimbs. The three most proximal diarthrodial joints of the cervical spine are almost always first affected. Osseous lesions develop insidiously, and clinical disease usually is advanced in cats older than 2 years of age before significant clinical features are recognized. Radiographic evidence of extensive exostosis of the cervical vertebral column and a history of excessive dietary intake of vitamin A or liver are necessary for the diagnosis. Reduction of dietary intake of vitamin A prevents the development of further exostosis, but it may be difficult to persuade affected cats to eat anything other than liver.

193.5.19 Intervertebral Disk Disease

193.5.19.1 Etiology and Pathogenesis

Degeneration of intervertebral disks may result in protrusion or extrusion of disk material into the spinal canal, causing spinal cord compression and clinical signs ranging from apparent pain to complete transverse myelopathy. Degenerative changes may occur in any of the intervertebral disks; however, they occur most commonly in the cervical, caudal thoracic, and lumbar spine. Because the intervertebral disks between T1 and T11 are stabilized dorsally by the intercapital ligaments, disk protrusion or extrusion is less likely in this region.[164–166]

Two types of disk herniation have been reported to occur in dogs.[167] Type I disk herniation occurs with degeneration and rupture of the dorsal anulus fibrosus and extrusion of the nucleus pulposus into the spinal canal. Type I disk extrusion is most commonly associated with chondroid disk degeneration (Figure 193-9). Although chondroid disk degeneration and type I disk extrusion occur most commonly in chondrodystrophoid breeds (dachshund, beagle, Pekingese, Lhasa apso, Shih Tzu) and in breeds with chondrodystrophoid tendencies (miniature poodle and cocker spaniel), these conditions may occur in any breed, including large breeds. Type II disk protrusion is characterized by bulging of the intervertebral disk without complete rupture of the anulus fibrosus. Type II disk protrusion is most commonly associated with fibroid disk degeneration (Figure 193-10). Chondroid metaplasia of the nucleus pulposus, chondroid disk degeneration, and type I disk extrusion may occur in any breed, including large breeds. The author (RAL) has noted an unusually high incidence of type I disk extrusion in Doberman pinschers. The smaller lumbar epidural space in dachshunds may explain the severe clinical signs seen in this breed in association with apparently small amounts of extruded disk material. Likewise, the larger epidural space in large breed dogs may account for the fact that small amounts of extruded disk material in the spinal canal in these breeds may not cause spinal cord compression and associated clinical signs.[168]

Chondroid degeneration of disks is characterized by an increase in the collagen content of the disk, alteration of the specific glycosaminoglycan concentration of the nucleus pulposus, and a decrease in the water content of the disk. The normally gelatinous nucleus pulposus becomes progressively more cartilaginous and granular and eventually may mineralize (calcify). Extrusion of degenerative nucleus pulposus occurs through fissures in or rupture of the anulus fibrosus. In chondrodystrophoid breeds of dog, 75% to 100% of all disks undergo chondroid metaplasia by 1 year of age.[169]

Fibroid disk degeneration occurs in older dogs of all breeds; however, it is most often recognized as a clinical problem in older, large breed, nonchondrodystrophoid dogs and is characterized by fibrous metaplasia of the nucleus pulposus. An increase in the noncollagenous glycoprotein content of the intervertebral disks occurs in nonchondrodystrophoid breeds with aging. Calcification of the disk may occur but is rare. Protrusion of the disk occurs, with a bulging of the anulus fibrosus as a result of partial rupture of the anular bands. Rupture of the anulus fibrosus and extrusion of the nucleus pulposus (characteristic of type I disk extrusion) infrequently is seen in association with type II disk protrusion.

Intervertebral disk protrusion or extrusion may occur in a ventral, dorsal, or lateral direction. In most instances only dorsal protrusions or extrusions are of clinical significance, because meningeal irritation and nerve root and/or spinal cord compression may occur. Occasionally a lateral disk protrusion or extrusion may result in nerve root or spinal nerve compression with associated clinical signs. The cause of intervertebral disk degeneration is unknown. Trauma does not appear to play a major role; mechanical and anatomic factors are probably important. Disk extrusions are most common in the cervical and T11 to L3 regions of the vertebral column. Genetic factors probably also play a role.

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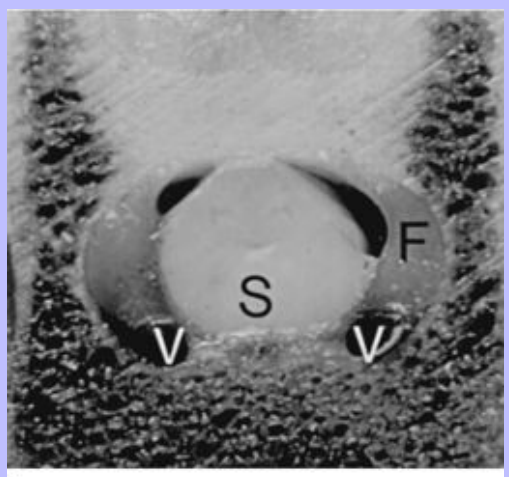
Figure 193-9 Type I disk extrusion. Gross necropsy specimens from a 4-year-old male dachshund that had an acute onset of pelvic limb paralysis. Pain perception was absent in the pelvic limbs. Myelography confirmed acute disk extrusion at T11–T12 that had caused severe spinal cord compression. **A,** Transverse section of the T12 vertebral canal 1 cm caudal to the extruded T11–T12 disk. Note the normal appearance of the spinal cord *(S)* in the spinal canal. Epidural fat *(F)* and internal vertebral venous plexus or vertebral sinuses *(V)* are also present in the spinal canal. **B,** Transverse section of the vertebral canal at the level of the T11–T12 disk. Calcified material *(C)* is present in the nucleus pulposus. A fissure (*arrows*) is present in the dorsal anulus fibrosus, and calcified material from the nucleus pulposus *(D)* has extruded through the fissure into the spinal canal. Dorsal displacement and compression of the spinal cord *(S)* have occurred. **C,** Transverse section of the vertebral canal 5 mm cranial to **B.** Extruded calcified material *(D)* from the nucleus pulposus is compressing the spinal cord *(S)* at this level.



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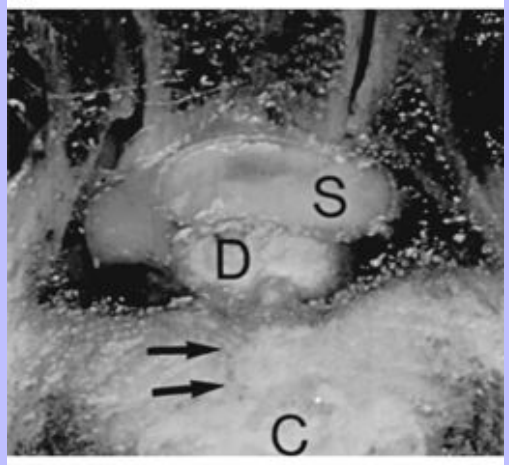

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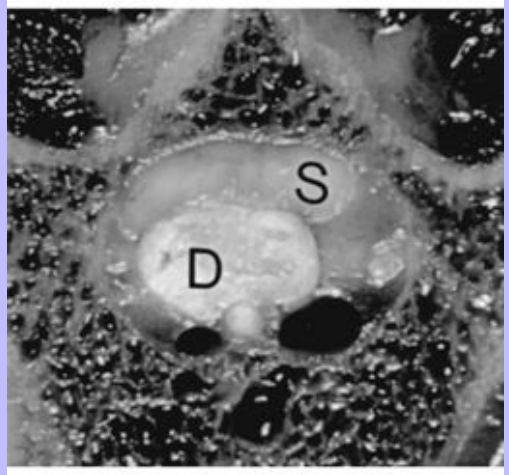

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Type I disk extrusion often results in more severe clinical signs than type II protrusion, although the mechanical distortion and compression of the spinal cord caused by type II protrusion may be greater. The nucleus pulposus is most often extruded into the spinal canal acutely (minutes to hours) or subacutely (days) from disks undergoing chondroid degeneration, whereas slowly progressive spinal cord compression most often accompanies protrusion of disks undergoing fibroid degeneration, as the bulging fibrous mass increasingly enlarges within the spinal canal. The spinal cord changes seen in acute versus chronic spinal cord compression differ and are reflected in the difference in clinical signs and response to treatment seen in these two types of intervertebral disk disease. The severity of spinal cord injury depends on the velocity at which the compressive force is applied, the degree of compression, and the duration of the compression. Vascular factors, as well as mechanical distortion of the spinal cord as a result of herniated disk material, are important in the pathogenesis of resulting spinal cord lesions. Severe spinal cord lesions may be found without evidence of compression, presumably as a result of vascular changes.

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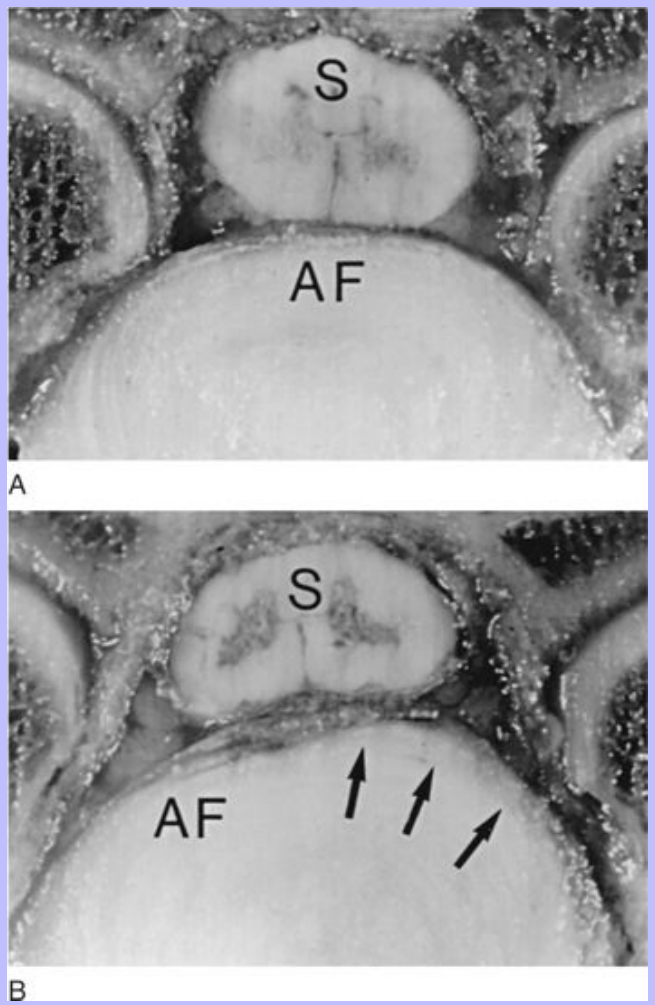
Figure 193-10 Type II disk protrusion. Gross necropsy specimens from a 7-year-old female Doberman pinscher that had a history of progressively worsening tetraparesis and generalized ataxia. Myelography confirmed type II disk protrusion at C6–C7. The disk protrusion appeared to be predominantly on the left. **A,** Transverse section of the vertebral canal at the level of the C5–C6 disk. Note the normal appearance of the spinal cord (*S*) in the spinal canal, and the close anatomic relationship of the dorsal anulus fibrosus (*AF*) to the spinal cord. **B,** Transverse section of the vertebral canal at the level of the C6–C7 disk. Note the compression of the left spinal cord (*S*), caused by dorsal bulging (*arrows*) of the anulus fibrosus (*AF*) at this level.



Hemorrhage, edema, and necrosis of spinal cord gray and white matter are characteristic of acute spinal cord injury associated with acute type I disk extrusion. Hemorrhage and edema are not major features of chronic spinal cord compression in which white matter changes (e.g., demyelination, focal malacia, vacuolization, and loss of axons) are seen. Type I disk extrusions often are associated with rupture of vertebral venous sinuses, and hemorrhage into the epidural space may increase the degree of spinal cord compression. Pulmonary emboli arising from the nucleus pulposus have been described in three chondrodystrophoid dogs with acute thoracolumbar transverse myelopathies as a result of type I disk extrusions, presumably as a result of disk material entering the vertebral venous sinuses. The nucleus pulposus may also penetrate the dura mater. Traumatic rupture of the anulus fibrosus and extrusion of normal nucleus pulposus may occur, resulting in spinal cord compression and acute onset of clinical signs indicative of a transverse myelopathy.[170,171]

Degenerative disk disease also occurs in cats,[7,170,171] although the incidence of clinical signs associated with disk protrusion is low. The degenerative changes, distribution of disk protrusions, and clinical signs are similar to those seen with type II disk protrusions in nonchondrodystrophoid dogs. Type I disk extrusion associated with a calcification of intervertebral disks and an acute onset of neurologic deficits may occur in cats.

193.5.19.2 Clinical Findings

Chondroid degeneration and type I disk extrusion most commonly occur in dogs 3 years of age and older. Fibroid degeneration and type II disk protrusion most commonly occur in dogs older than 5 years of age. Clinical signs seen in association with type I disk extrusion include apparent pain and/or motor and/or sensory deficits. These clinical signs usually develop rapidly, within minutes or hours of disk extrusion. However, clinical signs may progress slowly over several days or may manifest periods of improvement and subsequent worsening over weeks or months. These findings are probably associated with extrusion of small amounts of disk material into the spinal canal over a period of time.

Clinical signs associated with type I disk extrusion in the cervical spine usually are less severe than those associated with extrusions in the thoracolumbar region because the vertebral canal in this region is larger in diameter in relation to the spinal cord than is the case in the thoracolumbar region. Apparent neck pain is the most common clinical finding in dogs with cervical disk extrusion. Affected dogs often hold the head and neck rigidly and cry out when moved, and they may show spasms of cervical musculature. Neurologic deficits indicative of a cervical myelopathy (e.g., proprioceptive deficits, tetraparesis, or tetraplegia) are seen less commonly.

Ipsilateral Horner's syndrome and hyperthermia have been described in cases of acute, severe, dorsolateral cervical disk extrusions. LMN deficits in the thoracic limbs may be seen in caudal cervical disk extrusions. Thoracic limb lameness may also be seen in caudal cervical disk extrusions as a result of nerve root compression, particularly from lateral disk extrusions in which disk material enters an intervertebral foramen.

Clinical findings with thoracolumbar type I disk extrusion, which depend on the severity of spinal cord injury, range from apparent back or abdominal pain to complete paraplegia and loss of deep pain perception. Neurologic deficits usually are indicative of a transverse myelopathy between T3 and L3, because most disk extrusions in this region occur between T11 and L3. LMN signs may be seen in the pelvic limbs if disk extrusion occurs caudal to L3 as a result of compression of the lumbosacral spinal cord or the nerves of the

cauda equina. LMN signs also may be seen in paraplegic animals with progressive hemorrhagic myelomalacia (PHM).

The panniculus reflex may be depressed or absent caudal to the site of disk extrusion. The site of a lesion is usually one or two vertebral spaces cranial to the loss or depression of the panniculus reflex. The Schiff-Sherrington sign may be seen in animals with acute type I disk extrusion caudal to T2.

The clinical signs seen in both cervical and thoracolumbar type I disk extrusion may be asymmetric, especially if the extrusion occurs dorsolaterally within the spinal canal.[172,173] Apparent pain associated with disk extrusions results from inflammation and/or ischemia caused by compression of meninges and/or spinal nerve roots. Extruded disk material initiates an extradural inflammatory reaction that results in fibrous adhesions between the dura mater and the extruded disk material. Pain may also arise from stimulation of sensory nerve endings in the anulus fibrosus and dorsal longitudinal ligament. The nucleus pulposus of each disk does not contain nerve fiber endings.

The clinical signs associated with type II disk protrusion generally progress slowly over a period of months. However, in some animals they may develop acutely over days. Neurologic deficits usually are indicative of a cervical or thoracolumbar myelopathy. Paraparesis or tetraparesis, depending on the site of the lesion, is the most common clinical finding, and deficits may be asymmetric. In the cervical spine, type II protrusions most commonly occur in caudal cervical disks. In some cases caudal cervical type II disk protrusion may be part of the spectrum of abnormalities associated with cervical spondylomyelopathy. Apparent neck or back pain may or may not be a feature of type II disk protrusion.

193.5.19.3 Diagnosis

A tentative diagnosis of type I disk protrusion or extrusion may be made on the basis of the patient's age, breed, history, and clinical signs; however, other causes of transverse myelopathy or apparent pain should be considered in the differential diagnosis. It must be remembered that apparent spinal pain is seen in animals with meningitis. Dogs with thoracolumbar disk extrusions may appear to have abdominal pain. The differential diagnosis in animals with type II disk protrusion includes other causes of progressive transverse myelopathy, the most likely being neoplasia or degenerative myelopathy.

Spinal radiographs and, in almost all cases, CSF analysis and myelography are necessary to confirm a diagnosis of disk extrusion or protrusion. General anesthesia is required to achieve the precise positioning needed to obtain radiographs of diagnostic value. Foam wedges or sandbags are usually needed to align the vertebral column parallel to the table top for lateral projections. Care must be taken, however, in anesthetizing and positioning animals suspected of having acute type I disk extrusions, because further extrusion of disk material and further spinal cord compression may occur with manipulation and movement of the spine.

Calcification of the nucleus pulposus is best seen on lateral radiographic views and usually is seen in one or more disks of most chondrodystrophoid dogs more than 1 year of age. Calcified disks also may be seen in older nonchondrodystrophoid breeds. The presence of calcified material in the nucleus pulposus is indicative of disk degeneration but by itself is not of clinical significance.

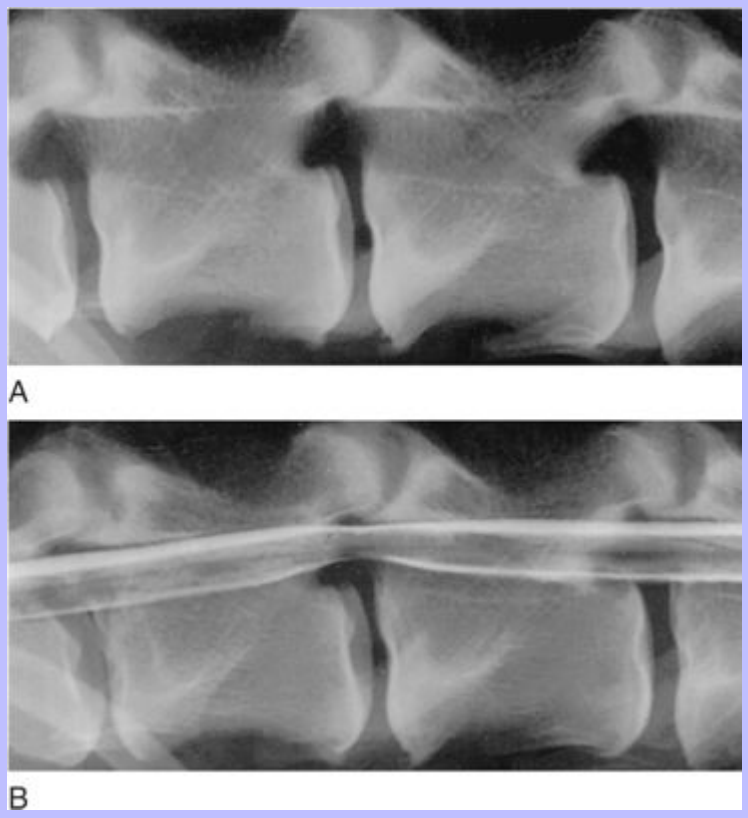
The disk space of an extruded disk may be narrower than adjacent disk spaces; it may be wedge shaped, with a decrease in the width of the disk space dorsally. However, positioning is important, because some disk spaces (C7–T1, T9–T10 or T10–T11, and L7–S1) are normally narrower than adjacent spaces, and cervical and lumbosacral disks are normally wedge shaped on hyperextension and flexion of the spine. “Spikes” of

calcified material suggestive of disk extrusion may extend dorsally from a disk. Calcified material may be present in the vertebral canal, but it often is difficult to visualize because of overlying vertebral articular processes or ribs. The intervertebral foramina are larger in the lumbar spine, and calcified material often is easily visualized in the spinal canal in this region. Disk material in the spinal canal may appear as a hazy, indistinct shadow or as a dense mass with distinct margins. In many cases of disk extrusion, calcified material is not visualized in the spinal canal, because the disk material is probably not sufficiently mineralized to be visible on radiographs. Ventrodorsal views, and in some cases oblique views, are important for determining the laterality of any visible mineralized material in the spinal canal. Vertebral osteophytes and vertebral endplate sclerosis may be seen in association with chronic disk degeneration and extrusion or, in cases of chronic disk degeneration, without disk extrusion or protrusion.

Type II disk protrusion may be associated with narrowing of the disk space, osteophyte production, and endplate sclerosis. Calcification of disk material rarely is seen with type II disk protrusion. In some animals with type I or type II disk herniation, obvious abnormalities are not seen on noncontrast vertebral radiographs (Figure 193-11).

Myelography is almost always necessary to confirm that disk material has herniated into the spinal canal, resulting in spinal cord compression.[173–175] Myelography is most important for determining the site (or sites) of disk herniation and for lateralizing disk material in the spinal canal prior to surgical decompression.[176] Myelography is necessary to distinguish disk protrusion from other causes of slowly progressive transverse myelopathy, such as spinal neoplasia and degenerative myelopathy.

Figure 193-11 Type II disk protrusion. Lateral radiograph **(A)** and myelogram **(B)** of the midlumbar vertebral column of a 7-year-old castrated male Great Dane with a 3-month history of corticosteroid-responsive back pain. The dog was neurologically normal at the time of this study. Slight narrowing of the L2–L3 disk and mild ventral spondylosis deformans are seen on the lateral radiograph. The myelogram confirms severe ventral spinal cord compression at the level of L2–L3 associated with a type II disk protrusion.



CSF should be collected and analyzed before myelography to rule out inflammatory or infectious disease of the spinal cord and/or meninges.[177] Clinical signs in animals with GME, distemper myelitis, FIP, spinal lymphoma, and other disorders may mimic those of cervical or thoracolumbar disk disease.

The characteristic myelographic findings in both type I and type II disk herniation into the spinal canal are extradural compression of the spinal cord with displacement of the spinal cord and narrowing of the subarachnoid space on lateral and/or ventrodorsal views, depending on the location of the compressive mass. Type II and most type I disk herniations result in a ventral or ventrolateral epidural mass that causes dorsal

displacement of the spinal cord. Disk material may extend over more than one vertebral segment in type I extrusions and may result in deviation or narrowing of contrast columns over more than one vertebral length. Disk material may completely encircle the spinal cord. Acute type I disk extrusions often are accompanied by spinal cord edema and swelling and occasionally by dural laceration.[178] The spinal cord may be widened over several segments, and the myelographic appearance is similar to that of an intramedullary mass, making precise determination of the site of disk extrusion difficult. In some animals, disk material is scattered along the spinal canal without obvious mechanical distortion of the spinal cord.

Rarely, in the cervical region type I disk extrusion may occur laterally or intraforaminally, resulting in neck pain or thoracic limb pain due to nerve root compression. In such cases myelograms may be normal; however, increased density associated with calcified disk material may be visualized intraforaminally on ventral oblique radiographs of the cervical spine. Traumatic disk protrusion is usually associated with narrowing of the intervertebral disk space on radiographs. Other abnormalities, such as vertebral fracture, luxation, or instability, also may be seen. Myelography is useful for determining whether spinal cord compression is present in such cases and therefore whether surgical decompression is indicated.

The use of advanced imaging techniques (CT or MRI) may aid in the exact localization of intervertebral disk extrusions, particularly in cases of intraforaminal disk extrusion.[179–181]

193.5.19.4 Treatment

193.5.19.4.1 Type I disk extrusion

The appropriate treatment for animals with type I disk extrusion depends on the individual animal's neurologic status. Medical treatment directed at reducing spinal cord edema with corticosteroid therapy is indicated only in animals with an acute onset of neurologic deficits that are examined within 8 hours of injury. The recommended agents and dosages are the same as those described for spinal cord trauma. The use of corticosteroids in dogs with type I disk extrusion has been associated with pancreatitis, gastrointestinal bleeding, and colonic perforation.

Nonsurgical (medical or conservative) treatment is recommended for animals with apparent pain only or animals that have mild neurologic deficits but are ambulatory and have not had previous clinical signs associated with disk disease. These animals should be strictly confined to a small area, such as a hospital cage or a quiet place away from other pets, for at least 2 weeks and walked (on a leash or harness) only to urinate and defecate. The objective of confinement is to allow fissures in the anulus fibrosus to heal, thus preventing further extrusion of disk material and allowing resolution of the inflammatory reaction caused by the small amounts of extruded disk material.

The use of analgesics, muscle relaxants, or nonsteroidal anti-inflammatory agents is not recommended in most cases, because it is believed that the pain relief they bestow encourages animals to exercise and thus risk further disk extrusion. Cautious use of analgesics or nonsteroidal anti-inflammatory agents occasionally may be indicated; however, strict confinement, followed by a period of restricted exercise, is imperative. Owners should also be warned that an animal's neurologic status may deteriorate, owing to extrusion of further disk material, despite this treatment. If the neurologic status worsens, treatment should be re-evaluated immediately. Owners should also be warned that recurrence of clinical signs is common, as a result of further disk extrusion at the same or a different site, and subsequent episodes may be more severe, especially in the thoracolumbar spine.

Animals with severe cervical pain frequently do not respond to cage rest. These dogs often have large amounts of disk material in the spinal canal. Dogs that do not show improvement after 7 to 10 days of confinement should be evaluated further using radiography and myelography, and ventral cervical decompression should be considered.

Surgical disk fenestration has been recommended as a prophylactic measure to prevent further extrusion of disk material into the spinal canal.[182,183] Fenestration of the disks most likely to herniate (C2–C3 through C6–C7 in the cervical spine and T11–T12 through L3–L4 in the thoracolumbar spine) is recommended in animals that have had one or more episodes of apparent neck or back pain and that have radiographic evidence of intervertebral disk disease. Various surgical techniques have been described.[164–166] However, fenestration of disks does not remove disk material from the spinal canal and therefore is not recommended as the sole surgical procedure in dogs that have radiographic and myelographic evidence of disk material in the spinal canal and of spinal cord compression.

The role of disk fenestration in the management of intervertebral disk disease is controversial.[182–185] Disk fenestration in the thoracolumbar region is not easily accomplished, and complications such as scoliosis, pneumothorax, and hemorrhage may occur. Disk fenestration in the cervical region is achieved more easily and rarely is associated with such complications. Fenestration does not prevent the recurrence of disk extrusion in all animals. The effectiveness of fenestration depends largely on the amount of nucleus pulposus removed. Completion of disk fenestration is recommended at the time of spinal cord decompression.

Animals with neurologic deficits such as paresis or paralysis in which deep pain perception is intact; animals with recurrent bouts of apparent back or neck pain; and animals with apparent back or neck pain (or mild neurologic deficits) unresponsive to strict confinement should be evaluated by means of spinal radiographs, CSF analysis, and myelography. Surgical decompression of the spinal cord and removal of disk material from the spinal canal should be considered. Although many dogs with moderate or severe paresis improve neurologically if treated with cage rest, neurologic recovery is often more rapid and more complete after surgical decompression of the spinal cord. In addition, the neurologic status of some dogs with type I disk extrusion, especially in the thoracolumbar spine, suddenly worsens over a period of hours or days despite medical treatment. Such deterioration usually results from further disk extrusion, which may cause irreversible spinal cord damage and permanent paralysis. This progression of signs always is a risk with medical treatment of animals with thoracolumbar disk disease. Progression is impossible to predict on the basis of the history, clinical signs, or radiography. Owners should be made aware of treatment options and offered the opportunity of referral to an appropriate surgical facility when animals are initially presented. Surgical decompression should be performed as soon as possible to prevent further spinal cord damage from sustained compression or further extrusion of disk material. Also, if surgery is delayed 2 to 3 weeks, disk material hardens and becomes adherent to the dura mater and is difficult or impossible to remove from the spinal canal.

The prognosis for neurologic recovery in animals that retain deep pain perception after surgery is fair to very good. The major factors that correlate with the degree of postsurgical neurologic improvement are the animal's neurologic status before surgery, the rapidity of onset of clinical signs, and the time interval between the onset of clinical signs and surgical decompression. Animals that have severe neurologic signs, a rapid onset of clinical signs (hours), and a long period before surgery generally have a prolonged recovery and may have varying degrees of permanent neurologic deficit.

The incidence of recurrence of clinical signs due to disk extrusion is greater in nonsurgically than surgically treated dogs. One author found that one third of dogs with type I disk herniation that were treated nonsurgically had a recurrence of clinical signs and generally showed greater severity of neurologic deficits at the time of recurrence.[1] Another author reported a recurrence rate of 40% in nonsurgically treated dogs.[1]

The advantages and disadvantages of various techniques for spinal cord decompression have been discussed.[125–127] Surgical treatment is not without risks. Anesthesia is necessary, and surgery occasionally results in further spinal cord damage, incurred through surgical manipulation. Nonsurgical treatment should be attempted in animals that are poor anesthesia or surgical candidates or if surgical treatment is not possible financially.

In animals that have clinical signs of a complete transverse myelopathy and in which deep pain perception has been absent for more than 24 hours, the prognosis for return of spinal cord function is poor despite medical or surgical treatment. Some of these animals may improve neurologically if given sufficient time; however, it is a matter of controversy whether surgical treatment increases the probability of improvement. When deep pain perception has been absent for less than 24 hours, the prognosis for return of spinal cord function is poor; however, surgical treatment may increase the likelihood of neurologic improvement.

Regardless of whether medical or surgical treatment is instituted, animals that are paretic or paralyzed require intensive nursing care.[186] Neurologic improvement may take weeks or months, and this requires owner co-operation and enthusiasm regarding care and physical therapy. Manual expression, intermittent catheterization, and/or indwelling catheterization of the bladder are often required to ensure emptying of the bladder. Weekly urinalysis, especially in animals that do not have voluntary control of micturition, is important in monitoring for urinary tract infection. It is also important to keep animals well padded, clean, and dry to prevent the formation of pressure sores, and to ensure that caloric and water intake is adequate. Physical therapy does not result in neurologic improvement but helps prevent disuse muscle atrophy associated with paraplegia or tetraplegia. Physical therapy should not be attempted in animals treated medically for at least the first 2 weeks after the onset of signs, because further extrusion of disk material may occur.[140]

193.5.19.4.2 Type II disk protrusion

Treatment with corticosteroids may result in neurologic improvement for variable periods in animals with type II disk protrusion. However, corticosteroid therapy is not curative. The reason for this improvement is not clear, because the intramedullary hemorrhage and edema seen in cases of acute spinal cord injury are not a feature of chronic spinal cord compression. In the thoracolumbar spine, surgical removal of protruded disk material may result in clinical improvement; however, the neurologic status of some dogs is worsened permanently despite careful surgical technique. The reasons for this are not known, but increased vascular permeability in the spinal cord has been described in association with release of chronic spinal cord compression, and this probably plays a role in the phenomenon. Ventral decompression in the cervical spine allows removal of protruded type II disk material, and neurologic improvement may occur over several months; however, some dogs, especially those with moderate to severe neurologic deficits prior to surgery, may manifest temporary or permanent worsening of clinical signs postoperatively.

193.5.19.4.3 Acupuncture

The use of acupuncture for the treatment of intervertebral disk extrusion in dogs is controversial. Acupuncture may be an excellent adjunctive therapy in nonsurgical management of affected dogs.[187] However, the use of acupuncture as an alternative to surgery for dogs that have severe spinal cord compression resulting from disk extrusion is not recommended.

193.5.19.4.4 Chemonucleolysis

Injection of the proteolytic enzyme chymopapain into the nucleus pulposus of intervertebral disks to cause discolysis has been used infrequently in veterinary medicine.[81,188–191] The precise mechanism by which chymopapain causes dissolution of the nucleus pulposus is unknown. In one study in dogs, dissolution of the nucleus pulposus was demonstrated histologically in all cervical intervertebral disks injected with chymopapain via a ventral surgical approach. Similar pathologic findings were found in the lumbar disks of dogs injected with chymopapain transcutaneously under fluoroscopic guidance via a lateral approach. Significant postoperative clinical complications were not seen. Radiographic narrowing of the intervertebral disk spaces was found in both the cervical and lumbar chymopapain-injected spaces. Cervical injection resulted in a more noticeable narrowing than did lumbar injection. However, successful injection, as determined histologically, was not always detected radiographically. These studies have described only the acute response to chymopapain. Another study has shown that chymopapain injection results in progressive dissolution of the nucleus pulposus and eventual regeneration of nuclear ground material.

Chemonucleolysis may be of benefit in animals with intervertebral disk disease when the nucleus pulposus is still contained within an intact or partly ruptured anulus fibrosus. Dissolution of the nucleus pulposus in these cases may relieve the pressure exerted by the protruding disk on the spinal cord and nerve roots. Chemonucleolysis may also be useful as a prophylactic measure in animals with evidence of intervertebral disk degeneration to prevent acute type I disk extrusion.

Chemonucleolysis is not indicated in cases of type I disk extrusion, because the enzyme is unable to reach sequestered nucleus pulposus in the spinal canal. Chemonucleolysis has been used in the treatment of type II disk protrusion in the cervical spine of large breed dogs. Most of the dogs in one study improved clinically despite a persistence or only slight decrease in the degree of spinal cord compression on myelography. Injection of chymopapain to the intervertebral disks via a surgical approach is recommended to prevent inadvertent intrathecal injection or accidental penetration of the vertebral arteries, spinal arteries, or spinal nerve roots. Further evaluation of the effect of chemonucleolysis in dogs with intervertebral disk disease is needed; however, it seems likely that this technique may have advantages over the methods used at present for surgical disk fenestration.

193.5.20 Ischemic Myelopathy Caused by Fibrocartilaginous Embolism

193.5.20.1 Etiology and Pathogenesis

Ischemic myelopathy results from ischemic necrosis of spinal cord gray and white matter associated with fibrocartilaginous emboli that occlude arteries and/or veins of the leptomeninges and spinal cord parenchyma of dogs[192–194] or cats.[195,196] This disease is characterized by an acute onset of neurologic deficits and is

generally nonprogressive after several hours. In most cases the substance occluding the spinal cord arteries and veins has histologic and histochemical properties similar to those of fibrocartilage of intervertebral disks and is presumed to originate from the nucleus pulposus of an intervertebral disk. The pathogenesis of this fibrocartilaginous embolism is not known. Acute spinal cord infarction has been reported secondary to neoplastic emboli and intravascular coagulation.[197] Most affected animals do not have evidence of degenerative intervertebral disk disease and are dog breeds that have a low incidence of degenerative disk disease and type I disk extrusion.

193.5.20.2 Clinical Findings

Ischemic myelopathy most commonly occurs in large and giant breed dogs, generally between 1 and 9 years of age, of either gender, but it has also been described in many other breeds, including smaller dogs such as miniature schnauzers and Shetland sheepdogs.[192–194] It has been described in cats.[195,196]

Ischemic myelopathy is characterized by an acute onset of neurologic deficits that may be severe. Clinical signs may progress over several hours but are generally not progressive after 12 hours. Affected animals usually do not have a history or evidence of trauma but may have a history of exercise prior to the onset of clinical signs. Apparent pain usually is not present at the time of examination or during the course of the disease, although dogs are often reported to cry out at the onset of clinical signs.

Neurologic deficits usually are bilateral and are often but not always asymmetric. The clinical signs seem to depend on the location and extent of the spinal cord lesion. Many spinal cord segments may be involved, and the neurologic deficits present may indicate extensive gray and white matter necrosis. If fibrocartilaginous embolism occurs in the cervical enlargement, unilateral or bilateral LMN signs in the thoracic limbs and UMN signs in the pelvic limbs are seen. The absence of the panniculus reflex unilaterally or bilaterally often is noted in lesions involving the T1 spinal cord segment. An ipsilateral Horner's syndrome commonly is seen in dogs with fibrocartilaginous embolism of the cervical enlargement as a result of damage to preganglionic sympathetic cell bodies in spinal cord segments T1 and T2. Horner's syndrome may also be seen in severe lesions in the cervical spinal cord, owing to interruption of the tectotegmental spinal tract.

Fibrocartilaginous embolism in the lumbosacral spinal cord causes unilateral or bilateral LMN signs in the pelvic limbs, anal and urinary sphincters, and tail. Lesions may also occur in the C1 to C5 and T3 to L3 spinal cord segments and may result in symmetric or asymmetric UMN signs in all four limbs or in the pelvic limbs, respectively. Neurologic deficits may range from decreased conscious proprioception and mild paresis to complete paralysis and analgesia in affected limbs.

193.5.20.3 Diagnosis

Ischemic myelopathy should be suspected in any dog (especially large and giant breed dogs) with an acute onset of nonprogressive neurologic deficits that are not associated with apparent spinal pain, especially if the deficits are asymmetric or indicate that at least several spinal cord segments are involved. A diagnosis is made by ruling out other causes of myelopathy. Spinal radiographs are normal. The CSF may be normal or may have an elevated protein concentration as a result of leakage of protein through damaged vascular endothelium. Xanthochromia may be present 48 hours or more after a subarachnoid hemorrhage. The myelographic appearance usually is normal, although mild intramedullary swelling as a result of spinal cord edema may be seen for as long as 24 hours after the onset of clinical signs.

193.5.20.4 Treatment

Corticosteroids (as recommended for spinal trauma) may be given initially to reduce any secondary spinal cord edema; however, such edema usually resolves after several days. Good nursing care is essential in recumbent animals to prevent pressure sores, urinary tract infections, and contracture of denervated muscles. The prognosis depends on the severity of an animal's neurologic deficits. Animals that retain pain perception in the affected limbs and tail usually regain neurologic function, although recovery may take several weeks to months, and LMN signs may persist (muscle atrophy and/or paresis). Animals with absent pain perception for 24 hours are likely to have irreversible spinal cord damage and have a poor prognosis for return of function in the affected limb or limbs. Many animals show improvement within 2 weeks of the onset of signs unless extensive gray matter destruction has occurred.

193.5.21 Leukoencephalomyelopathy of Rottweilers

193.5.21.1 Etiology and Pathogenesis

Leukoencephalomyelopathy is a demyelinating disorder of the brain and spinal cord that has been reported to occur in rottweilers. It is characterized by progressive tetraparesis and hypermetria, especially of the thoracic limbs.

Leukoencephalomyelopathy has been reported in two dogs in the United States,[198] and a similar disorder has been reported in 16 rottweilers in the Netherlands.[199] Histopathologic examination showed demyelination in the white matter of the spinal cord, brain stem, and cerebellum, with intact naked axons and thinly myelinated axons accompanied by reactive astrogliosis. The spinal cord lesions were found in the lateral funiculi and occasionally the dorsal funiculi, predominantly in the cervical and thoracic spinal cord, and tended to be bilaterally symmetric. The lack of neuronal fiber degeneration makes primary demyelination more likely than secondary demyelination.

The etiology of this disease is unknown. It may be the result of an acquired primary demyelinating disease, but whether the lesions seen are due to a single demyelinating event or are the result of repeated demyelination and remyelination is not known. The lesions' bilaterally symmetric character indicate that toxic, metabolic, and nutritional mechanisms may be involved. Infectious causes (e.g., CD virus) may also result in demyelination. Vascular mechanisms may be involved, because the lesions have a segmental distribution; however, axon degeneration would be expected. An inherited condition in which myelin formation is defective and cannot be maintained (leukodystrophy) is also possible. The two dogs in the U.S. report were related, as were the 16 dogs in the Netherlands.

Other leukodystrophies have been reported in young animals, although an adult-onset leukodystrophy has not been described in dogs. The relationship of this disease to neuroaxonal dystrophy of rottweilers is not known.[200] Histopathologic lesions and clinical findings differ from those described in dogs with neuroaxonal dystrophy; however, a dog related to a dog with leukoencephalomyelopathy was diagnosed as having neuroaxonal dystrophy.

193.5.21.2 ### Clinical Findings

Both males and females have been reported to be affected. Clinical findings included tetraparesis, hypermetria (especially of the forelimbs), decreased conscious proprioception (especially of the pelvic limbs), and exaggerated spinal reflexes. The clinical signs became apparent between 18 and 42 months of age, and the abnormalities progressed slowly over several months to 1 year. The neurologic abnormalities were consistent with a transverse myelopathy of the cervical spinal cord. Neurologic deficits referable to structures rostral to the foramen magnum were not detected.

193.5.21.3 ### Diagnosis and Treatment

The diagnosis may be made on the basis of the dog's age and breed and by ruling out other causes of cervical myelopathy, such as CD myelitis, GME, cervical spondylomyelopathy, and spinal neoplasia. The results of radiography, CSF analysis, and myelography were normal in the dogs reported. Treatment of leuko-encephalomyelopathy of rottweilers has not been effective.

193.5.22 ## Lumbosacral Vertebral Canal Stenosis

193.5.22.1 ### Etiology and Pathogenesis

The term *lumbosacral vertebral canal stenosis* encompasses a spectrum of disorders that result in narrowing of the lumbosacral vertebral canal, with consequent compression of the cauda equina. The term *cauda equina syndrome* describes a group of neurologic signs that result from compression, destruction, or displacement of the nerve roots and spinal nerves that form the cauda equina and that have a variety of causes, including lumbosacral vertebral canal stenosis (Box 193-6).[201]

Lumbosacral vertebral canal stenosis is defined as an acquired disorder of large breed dogs that results from several or all of the following: type II disk protrusion (dorsal bulging of the anulus fibrosus), hypertrophy and/or hyperplasia of the interarcuate ligament, thickening of the vertebral arches or articular facets and, infrequently, subluxation/instability of the lumbosacral junction. It is likely that several separate disorders currently are included in this definition. Other terms have been used to describe this syndrome, including *lumbo-sacral spondylolisthesis, lumbar spinal stenosis,* and *lumbosacral instability*. In humans, the term *spondylolisthesis* refers specifically to a forward (anterior) movement of a lower lumbar vertebra relative to a lumbar vertebra or sacrum directly below it. This problem rarely occurs in dogs, in which the most frequently encountered problem is a ventral slippage of the sacrum relative to the body of the L7 vertebra. The term *retrolisthesis* has been proposed to describe this “reverse spondylolisthesis” of dogs. *Lumbar spinal stenosis* is a term that perhaps is best used to describe a congenital (“idiopathic”) syndrome reported to occur in young dogs. *Lumbosacral instability* is a misleading term, because instability is not demonstrated consistently in association with lumbosacral vertebral canal stenosis.

193.5.22.1.1 **Box • 193-6 Disorders that Produce Signs of Cauda Equina Dysfunction in Dogs**

193.5.22.1.1.1 **Congenital Disorders**

Vertebral and/or nerve root anomalies (e.g., spina bifida)

Idiopathic lumbar stenosis

193.5.22.1.1.2 Acquired Disorders

Infections (e.g., discospondylitis)

Neoplasia (e.g., malignant nerve sheath neoplasia)

Intervertebral disk disease

Iatrogenic stenosis (e.g., postsurgical scarring)

Lumbosacral vertebral canal stenosis (with/without "retrolisthesis")

193.5.22.1.1.3 Combined Disorders

Combination of congenital and acquired disorders (e.g., disk degeneration and lumbosacral vertebral canal stenosis)

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Certain similarities between vertebral and soft tissue alterations seen in dogs with lumbosacral vertebral canal stenosis and in Doberman pinschers with caudal cervical spondylomyelopathy have been noted. Because the etiology and pathogenesis of both conditions are incompletely understood, such comparisons are of little significance at the present time. An association has been reported between lumbosacral stenosis and transitional vertebrae in German shepherds.[202] In another report, more than 30% of German shepherds with clinical signs of cauda equina compression had radiographic and pathologic abnormalities consistent with osteochondrosis of the sacral endplate.[203]

193.5.22.2 Clinical Findings

Acquired degenerative lumbosacral vertebral canal stenosis occurs most commonly in large breed dogs, especially German shepherds.[204] Males appear to be affected more frequently than females. The congenital ("idiopathic") form appears to affect smaller breed dogs. Affected dogs in both categories are between 3 and 7 years of age, although the problem can occur at any age. Degenerative lumbosacral vertebral canal stenosis is rarely recognized in cats.[7,171,193]

Signs of cauda equina compression seen frequently in affected dogs include apparent pain on palpation of the lumbosacral region, on caudal extension of the pelvic limbs, or on elevation of the tail; difficulty rising; pelvic limb lameness (often unilateral); pelvic limb muscle atrophy; paresis of the tail; scuffing of the toes; urinary and/or fecal incontinence or inappropriate voiding as a result of an inability to assume a voiding posture; self-mutilation of the perineum, tail, or pelvic limbs; and rarely, paraphimosis. These signs most often are insidious in onset and progress gradually over months, and they are easily confused with the signs of hip dysplasia or degenerative myelopathy.[204–206]

Abnormalities detected on neurologic examination include gait deficits related to sciatic nerve paresis (e.g., dragging of toes). Depression or loss of conscious proprioception, normal or slightly exaggerated patellar reflexes ("pseudoexaggeration" related to loss of antagonism to femoral nerve–innervated muscles by sciatic nerve–innervated muscles), depressed or absent flexion reflexes in pelvic limbs, decreased anal tone and anal

sphincter reflexes, atonic bladder, hypesthesia of the perineum and tail, and muscle atrophy may be seen. These abnormalities relate to deficits of the sciatic, pudendal, caudal, and pelvic nerves, the nerve roots of which make up the cauda equina.[204–206]

193.5.22.3 Diagnosis

Characteristic clinical findings may be consistent with a diagnosis of degenerative lumbosacral vertebral canal stenosis. Careful mapping of areas of loss of cutaneous sensation may assist the detection of involved nerve roots. However, the syndrome must be confirmed with plain radiographs and special radiographic procedures.[207] Rarely can this condition be diagnosed on the basis of plain radiographic findings alone. Plain radiographic findings include spondylosis deformans ventral and lateral to the lumbosacral articulation, sclerosis of vertebral endplates, "wedging" or narrowing of the L7–S1 disk space, and secondary degenerative joint disease in the region of the L7–S1 articular facets (Figure 193-12). Ventral displacement of the sacrum with respect to L7 (retrolisthesis) and diminished dorsoventral dimensions of the lumbosacral spinal canal may be seen; however, such findings must be interpreted with caution, because they may be seen in normal dogs in association with slight rotation of the vertebral column on lateral radiographs. General anesthesia is mandatory for obtaining radiographs of the lumbosacral vertebral column. A ventrodorsal projection also is recommended.

"Stressed" plain radiographic projections (flexed and extended views), obtained with careful attention to avoid rotation, often help detect instability or retrolisthesis. Several attempts to separate normal dogs from dogs with lumbosacral vertebral canal stenosis by means of objective measurements made from radiographs have not been successful.[208] The appearance on plain radiographs helps eliminate other causes of cauda equina syndrome (e.g., discospondylitis or vertebral neoplasia). Linear tomography, when available, may provide specific information about the diameter of the lumbosacral vertebral canal that cannot be obtained from plain radiographs.

Electromyography may complement information available from a neurologic examination and from plain spinal radiographs by confirming denervation in muscles innervated by the nerves of the cauda equina. Motor nerve conduction velocity determinations in the sciatic and tibial nerves and measurement of evoked spinal cord potentials may also provide indirect evidence of cauda equina dysfunction.[209,210] Several contrast radiographic techniques can be used to examine the lumbosacral vertebral canal. Such techniques must be used to demonstrate soft tissue vertebral canal stenosis.[209,211] Myelography most often is useful in the diagnosis of lumbosacral problems, because the terminal portion of the subarachnoid space of dogs may fill with contrast material at this level. Many investigators have used transosseous vertebral sinus venography (filling of vertebral sinuses with contrast material) and epidurography (filling of the lumbosacral epidural space with contrast material) in an attempt to outline soft tissue stenosis of the lumbosacral vertebral canal. Th results obtained with either of these techniques must be interpreted cautiously, because false-positive studies occur with both.

Discography is useful for confirming the presence of lumbosacral soft tissue stenosis.[209,212] Discography consists of radiography performed after injection of contrast material into the nucleus pulposus of an intervertebral disk (Figure 193-13). This technique has special application in the lumbosacral disk space.

CT, either alone or combined with the contrast techniques listed above, and MRI may provide further information about soft tissue stenosis of the lumbosacral vertebral canal, particularly with regard to the L7–S1 intervertebral foramen.[213–217]

Surgical exploration may be indicated in dogs (with the appropriate history and clinical signs) in which the results of ancillary diagnostic tests do not provide a definitive diagnosis of soft tissue stenosis.

193.5.22.4 Treatment

Some affected dogs in which the clinical signs are mild or the apparent lumbosacral pain is the sole problem improve temporarily after strict confinement and restricted leash exercise for 4 to 6 weeks. The use of analgesic drugs or corticosteroids has been recommended; however, such use must be accompanied by strict confinement.

Clinical signs commonly recur in affected dogs treated only with medical therapy. Dogs with recurrence of signs and dogs that are moderately to severely affected at the time of initial presentation (especially those with urinary/fecal incontinence) should be considered candidates for surgery. Dorsal decompressive laminectomy of the L7 and S1 vertebrae is recommended. This procedure may be combined with foraminotomy or facetectomy in dogs in which compression of the spinal nerves at the level of the intervertebral foramina is suspected. In animals with radiographically confirmed instability or significant retrolisthesis, fusion of the lumbosacral articulation may be necessary. A dorsal approach for fusion has been recommended.[218]

Patients should be confined for 2 to 4 weeks after surgery. Postoperative complications include seroma formation at the surgical site and formation of a laminectomy scar at the site of the laminectomy. Both may be avoided by use of appropriate surgical technique and postoperative patient management.

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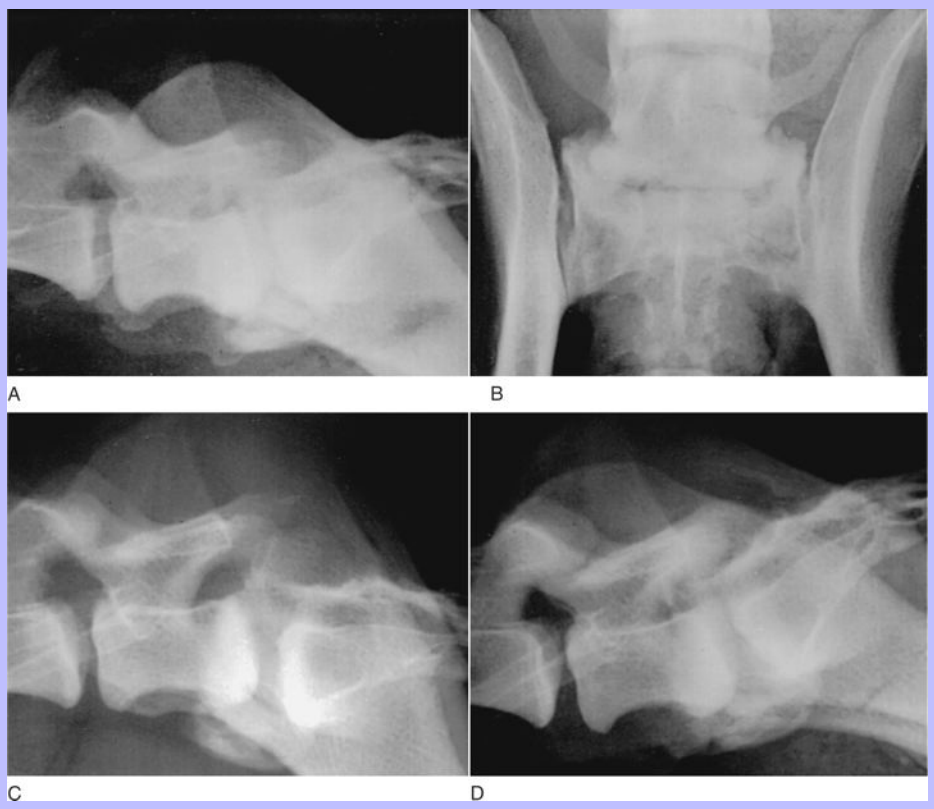
Attention to bladder emptying may be necessary in dogs with bladder atony prior to surgery. The bladder should be manually expressed three times a day in such dogs. Urine should be submitted for culture and sensitivity testing before and 2 weeks after surgery, and appropriate antibiotic therapy should be instituted as indicated by the results.

The prognosis for affected dogs depends on the severity of signs before surgery. Return to normal function may be expected in dogs that are mildly affected prior to surgery. Dogs with bladder atony or a flaccid anal sphincter prior to surgery have the poorest prognosis.

Figure 193-12 Lumbosacral vertebral canal stenosis. Lateral **(A)** and ventrodorsal **(B)** radiographs of the lumbosacral region of the vertebral column of a 7-year-old female vizsla. The dog had a history of apparent spinal pain, hypotonic tail, urinary incontinence, and pelvic limb paresis. Sclerosis of the vertebral endplates of L7 and S1, L7–S1 spondylosis deformans, "wedging" of the L7–S1 disk, and malalignment of L7–S1 are evident on the neutrally positioned lateral projection. Spondylosis deformans is seen lateral to the L7–S1 vertebral articulation on the ventrodorsal projection. A flexed lateral projection **(C)** confirms the presence of "retrolisthesis" with excessive ventral movement of the sacrum with respect to the body of L7. Instability of the lumbosacral articulation is further suggested by the extended projection **(D),** in which "wedging" of the L7–S1 disk can be seen. Use of these stressed projections is essential for confirmation of instability associated with lumbosacral vertebral canal stenosis.



193.5.23 Mucopolysaccharidosis

193.5.23.1 Etiology and Pathogenesis

The mucopolysaccharidoses are a group of genetic diseases that result from defects in the metabolism of glycosaminoglycans. Two subclasses have been recognized in cats, and paraparesis associated with spinal cord compression has been reported in Siamese cats with mucopolysaccharidosis VI (MPS VI).[6,7] MPS VI is the result of a deficiency of the lysosomal enzyme arylsulfatase B; in addition to causing characteristic physical deformities, it can result in (1) skeletal changes, including fusion of the cervical vertebrae, variable fusion of thoracic and lumbar vertebrae, and bony proliferation and protrusion into the vertebral canal in the thoracic and lumbar spine, causing compression of the spinal cord, and (2) bony proliferation in the intervertebral foramina, causing nerve root compression.[219] Bony proliferative changes and associated spinal cord compression occur prior to or at the time of epiphyseal closure (about 9 months of age) and are probably nonprogressive after this time. MPS VI is an inherited abnormality with an autosomal recessive mode of inheritance.

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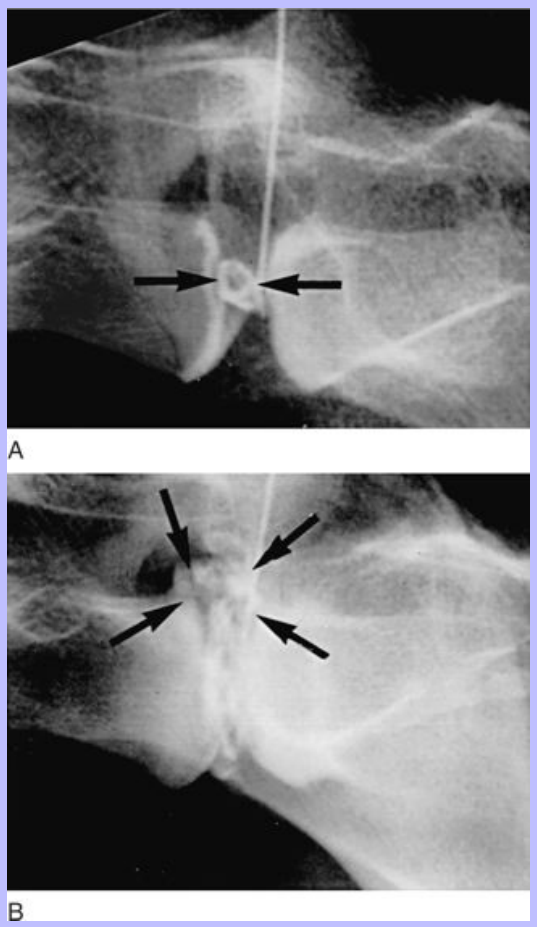
Figure 193-13 Lumbosacral vertebral canal stenosis. **A**, Discogram at L7–S1 in a normal 5-year-old male Saint Bernard. Note the placement of a spinal needle in the nucleus pulposus of the L7–S1 disk. Contrast material (0.2 mL) is confined to the region of the nucleus pulposus *(arrows)*. **B,** Discogram at L7–S1 in a 6-year-old male Great Dane with a history of apparent spinal pain and self-mutilation of the right side of the tail. Note the irregular pattern of contrast filling of the disk and the dome-shaped region of contrast material that has accumulated in the vertebral canal *(arrows)*. This abnormal discogram is consistent with a diagnosis of L7–S1 disk degeneration with bulging of the dorsal anulus fibrosus into the vertebral canal. This diagnosis was confirmed through dorsal laminectomy over this site.



MPS I, which is due to a deficiency of alpha$_l$-iduronidase, has been reported in a domestic short-hair cat. The clinical features were similar to those of MPS VI, but bony proliferative changes and associated spinal cord compression were not found. Although vacuolar changes were observed in the neurons of the brain and cervical spinal cord, presumably as a result of storage of glycosaminoglycans, neurologic deficits were not found clinically. MPS I probably has an autosomal recessive mode of inheritance.

193.5.23.2 Clinical Findings

The characteristic physical findings with MPS VI are a small head; a flat, broad face; widely spaced eyes; corneal clouding; small ears; depressed bridge of the nose; large forepaws; and a concave deformity of the sternum. Affected kittens are smaller than normal littermates, and physical deformities are noticeable by 8 weeks of age. Neurologic deficits due to skeletal changes and spinal cord compression are seen between 4 and 7 months of age and progress over 2 to 4 weeks. Neurologic findings, which are indicative of a transverse myelopathy between T3 and L3, include absent conscious proprioception, normal to exaggerated pelvic limb reflexes, and decreased pain perception in the pelvic limbs. The thoracic limb gait may be normal, or affected cats may have a crouching posture. Spinal reflexes in the thoracic limbs are normal.

193.5.23.3 Diagnosis

Radiographs of the spine show vertebral fusion and bony protrusions into the spinal canal and intervertebral foramina of the thoracolumbar spine.[219] However, bony proliferation is not an indication of neurologic dysfunction. Myelography is necessary to demonstrate spinal cord compression. Subarachnoid CSF puncture may be difficult, owing to proliferative changes around the vertebrae. MPS VI can be confirmed by measurement of arylsulfatase B activity in leukocytes.

193.5.23.4 Treatment

Because skeletal changes are nonprogressive after about 9 months of age, decompressive surgery may result in improvement in neurologic signs. However, spinal cord compression may be present at more than one site. The underlying lysosomal enzyme deficit is not amenable to treatment at present. Bone marrow transplantation is being investigated as a possible therapy for MPS VI.[220]

193.5.24 Myelodysplasia

193.5.24.1 Etiology and Pathogenesis

The term *myelodysplasia* describes a number of malformations of the spinal cord believed to result from incomplete closure or development of the neural tube.[6,7,221] Malformations identified histopathologically include anomalies of the central canal (hydromyelia, duplication of the central canal, or absence of the central canal); anomalies of the central gray matter, ventral median fissure, and dorsal median septum; gray matter ectopias, chromatolysis, and loss of nerve cell bodies; and syringomyelia, usually in the dorsal columns. Lesions are found throughout the spinal cord but are more severe in the lumbar region.

Myelodysplasia is considered to be an inherited condition in the weimaraner, transmitted by a mutant gene.[222] Both males and females are affected. Myelodysplasia has been described in other breeds of dogs

and cats, including a Dalmatian, a rottweiler, a West Highland white terrier, an English bulldog, mixed-breed dogs, and Manx cats.[7,221,223] The etiology and pathogenesis of the condition in these animals are unknown.

193.5.24.2 Clinical Findings

Clinical signs vary in severity and usually are referable to a transverse myelopathy between T3 and L3. Clinical abnormalities usually are evident at 4 to 6 weeks of age, when puppies become ambulatory, although abnormal reflexes have been reported in affected newborn puppies. The major clinical finding in affected dogs is a symmetric, "bunny hopping" pelvic limb gait. Other clinical findings are crouching stance, abduction or overextension of one or both pelvic limbs, decreased conscious proprioception in the pelvic limbs, scoliosis and, in one case, torticollis. The spinal reflexes and pain perception usually are normal. In weimaraners, other findings include abnormal hair "streams" in the dorsal neck region, koilosternia (a gutterlike depression in the chest) and, occasionally, a head tilt.

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193.5.24.3 Diagnosis

The diagnosis is made on the basis of the history, signalment, clinical signs, plain radiography, CSF analysis, and myelography. Advanced imaging techniques (CT and MRI) have also been used.[223]

193.5.24.4 Treatment

No effective treatment exists. In weimaraners, and probably in other dogs and in cats, the clinical signs are not progressive, and affected animals may be acceptable pets.

193.5.25 Neoplasia

193.5.25.1 Etiology and Pathogenesis

The spinal cord may be a site of primary or metastatic neoplasia, or it can be compressed or invaded by primary or metastatic tumors arising from the vertebrae and surrounding tissues.[224–227] Primary neural tumors include astrocytoma, glioma, ependymoma, neuroepithelioma, malignant nerve sheath neoplasm (schwannoma, neurofibroma, neurofibrosarcoma), meningioma, meningeal sarcoma, and reticulum cell sarcoma. Primary lymphosarcoma of the spinal cord also has been reported in a dog.

Tumors of spinal nerves that extend into the spinal canal or spinal nerve roots may cause extradural or intradural compression of the spinal cord.[228] These tumors may also invade the spinal cord parenchyma. The distinction between schwannoma, Schwann cell sarcoma, neurofibroma, and neurofibrosarcoma is difficult to make histologically, but all have similar features clinically and on gross pathology.[224] The term *malignant nerve sheath neoplasm* has been proposed for this tumor.[224] These tumors may involve any cranial or spinal nerve or dorsal or ventral nerve root and commonly spread to involve adjacent nerves and nerve roots. Malignant nerve sheath tumors commonly arise from nerve roots or spinal nerves contributing to the brachial plexus. The tumors may arise from more than one site. Lymphosarcoma may also involve peripheral nerves and may extend along spinal nerves and nerve roots into the spinal canal, resulting in clinical signs of spinal cord disease.[229] Meningeal sarcomatosis is a rare condition characterized by diffuse infiltration of the leptomeninges by neoplastic mesenchymal cells.

The spinal cord may also be compressed by tumors originating from surrounding structures. These tumors most commonly arise from bone, cartilage, fibrous tissue, and blood vessels of vertebrae and less commonly from the hematopoietic elements of bone and tissue outside the vertebral column, including muscle, fat, and paraganglia.[224] Primary vertebral tumors, which may cause compression of the spinal cord as a result either of extension of the tumor mass into the spinal canal or of pathologic fracture of the vertebra, include osteosarcoma, chondrosarcoma, fibrosarcoma, hemangioma, hemangiosarcoma, plasma cell myeloma, giant cell sarcoma (arising from primitive stromal elements of bone marrow), and undifferentiated sarcomas.[224] Tumor metastases from sites elsewhere in the body may also be found in vertebrae, epidural space, meninges, and rarely the parenchyma of the spinal cord.

Secondary tumors, which result from hematogenous or lymphatic spread of tumor emboli, include hemangiosarcoma, lymphosarcoma, mammary adenocarcinoma, pulmonary carcinoma, prostatic carcinoma, and malignant melanoma. Clinical signs associated with secondary spinal tumors may occur early or late in the course of the disease. With the prolonged survival times that accompany recent therapeutic regimens for osteosarcoma of long bones, an increased frequency of vertebral metastases can be expected, particularly in cranial thoracic vertebrae. Embolic tumor cells may pass directly to the lumbar vertebrae from tumors in the pelvic area by reversal of blood flow in the vertebral veins with increases in central venous pressure.

Retrospective studies have shown the most commonly occurring spinal tumors in dogs to be primary and secondary bone tumors and tumors of spinal nerves and nerve roots. Primary intramedullary tumors occur less commonly than extradural or intradural-extramedullary tumors. Spinal tumors of all types occur more frequently in large breed dogs. Epidural lymphosarcoma is the most commonly occurring spinal tumor in cats.[229–233] Primary intramedullary tumors rarely occur in cats. The etiology of vertebral and spinal cord tumors is unknown. Lymphosarcoma in cats may be associated with FeLV or feline immunodeficiency virus (FIV) infection; however, not all cats with spinal lymphosarcoma test positive for FeLV or FIV.[230]

Spinal tumors may occur in animals of any age. Although tumors more commonly occur in animals more than 5 years of age, spinal cord blastoma (nephroblastoma) in dogs[234] and lymphosarcoma in cats are found most commonly in young animals. Spinal cord blastoma has been reported in large breed dogs 6 months to 3 years of age. German shepherds have a higher incidence of this tumor than other breeds. These tumors are generally found in an intradural and extramedullary location, closely associated with the pia mater of the spinal cord and separated from the spinal cord by a thin band of connective tissue. The tumor may replace most of the spinal cord and may also have an intramedullary component. These tumors occur in the T10 to L2 spinal cord segments and may be the result of neoplastic transformation of remnants of embryonic medullary (neuro)epithelium in this region of the spinal cord. However, immunocytochemical studies do not support a neuroectodermal origin. The mixed epithelial and mesenchymal patterns seen in these tumors are similar to those of nephroblastomas.[234]

Metastatic spinal tumors have also been reported to occur in dogs.[226] Primary spinal cord, meningeal, and nerve root tumors rarely metastasize outside the spinal canal; however, tumors may arise from multiple sites or may metastasize along CSF pathways (meningioma, ependymoma). Primary vertebral tumors commonly metastasize to other organ systems.

193.5.25.2 Clinical Findings

The clinical signs depend on the location of the tumor. Tumors may involve more than one spinal cord segment, and more than one spinal tumor may be present, resulting in multifocal signs. However, most animals have clinical signs referable to a transverse myelopathy. Tumors may occur anywhere in the spinal cord or spinal canal and usually result in progressive neurologic deficits. The duration of clinical signs may vary considerably (from 1 week to 1 year in one study). Animals may have acute onset of severe neurologic deficits associated with pathologic fracture of a vertebra, resulting in spinal cord compression; epidural, subarachnoid, or intramedullary hemorrhage; or spinal cord ischemia associated with tumor expansion. Neurologic deficits are usually bilateral but may be asymmetric.

Tumors of nerves of the brachial plexus initially cause progressive LMN signs in the ipsilateral thoracic limb, including muscle atrophy and paresis. The affected limb is often painful on palpation or movement; cutaneous sensation generally remains intact.[224] If the tumor extends into the spinal canal, UMN signs in the pelvic limbs may become apparent. Tumors of nerves of the cauda equina or lumbosacral plexus, with extension into the spinal canal, may cause unilateral or bilateral LMN signs in the pelvic limbs, tail, perineum, urinary bladder, and anal sphincter.

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Apparent pain is a common finding with extradural and intradural tumors[227] and was the predominant clinical sign in a study of dogs with vertebral tumors. Apparent pain may be intractable, especially in animals with a tumor that affects spinal nerve roots. This may be due to stretching or inflammation of the meninges surrounding the expanding tumor. Intramedullary tumors are reported to cause a more rapid progression of clinical signs and are much less likely to be painful than extradural or intradural-extramedullary tumors. In general, however, extradural, intradural-extramedullary, and intramedullary tumors cannot be distinguished on the basis of clinical findings.

193.5.25.3 Diagnosis

A tentative diagnosis of spinal tumor can be made on the basis of radiographic, CSF, and myelographic findings. A definitive diagnosis can be made only after biopsy of a suspected lesion.

193.5.25.3.1 Radiography

Bone lysis with a cortical break is the most common radiographic finding in animals with vertebral tumors. Other radiographic findings include destruction of vertebral endplates, collapse of an adjacent disk space, collapse and shortening of a vertebral body, pathologic fracture, bone sclerosis and bony production, cystlike expansile lesions, and adjacent soft tissue masses. Bone tumors most commonly occur in the vertebral body but may also be found in the dorsal spinous processes, transverse processes, and articular facets. Primary and secondary bone tumors or specific tumor types cannot be distinguished radiographically. Primary bone tumors usually but not always involve one vertebra. More than half of the secondary bone tumors in one study involved more than one vertebra. Rarely, metastatic tumors (e.g., carcinoma) may arise in a disk space. The radiographic appearance of such tumors may resemble that of discospondylitis. Metastases from intrapelvic soft tissue tumors often produce periosteal new bone on the ventral aspect of multiple lumbar vertebral bodies in association with the formation of a paravertebral soft tissue mass. The characteristic vertebral lesions of multiple myeloma are “punched out” lytic lesions.

Vertebral lesions may also occur with the spread of tumors from surrounding soft tissues into the vertebrae. Bone tumors are not always easily detected radiographically because of inconsistent vertebral shape, overlying rib and soft tissue shadows, and improper positioning. Other diseases, such as bacterial or fungal discospondylitis, spondylitis, or vertebral osteomyelitis, must be considered in the differential diagnosis of vertebral tumors.

Expanding tumors in the spinal canal may result in widening of the vertebral canal and loss of bone density because of ischemia and necrosis of overlying bone. Similarly, tumors of spinal nerves extending into the spinal canal may cause widening of intervertebral foramina.

193.5.25.3.2 Cerebrospinal fluid analysis

The CSF may be normal or may have an elevated protein concentration and/or WBC count.[13] A mild to moderate increase in the WBC count of the cerebrospinal fluid may occur in animals with tumors that arise from or invade the leptomeninges. PMN cells may predominate, probably as a result of meningeal inflammation and necrosis. Tumor cells rarely are found in the CSF, except in CSF from animals with lymphosarcoma, in which abnormal lymphocytes are often present in association with meningeal infiltration. Collection of CSF from the lumbar subarachnoid space may yield more cells than cisternal collection, owing to probable caudal flow of the CSF in animals. Inability to demonstrate tumor cells in the CSF may be the result of the methods used to analyze it. Cell-concentrating techniques, which show a greater percentage of cells present in the CSF, may result in preservation of more neoplastic cells. Xanthochromia, which suggests previous subarachnoid hemorrhage, occasionally is present. The CSF protein concentration may be increased because of abnormal permeability of the blood–spinal cord or blood–meningeal barrier, the result of extradural compression or meningeal or parenchymal tumor infiltration.

193.5.25.3.3 Myelography

Myelography may be helpful in differentiating intramedullary, intradural-extramedullary, and extradural tumors. Cisternal and lumbar injection of contrast material may be necessary to outline both the cranial and caudal extent of a tumor. It is important to obtain survey radiographs of the entire vertebral column prior to and after the injection of contrast, because more than one tumor may be present, and the neurologic deficits of one tumor may mask those produced by another. Several radiographic views (at least lateral and ventrodorsal views) are necessary to determine whether a tumor is intramedullary, intradural-extramedullary, or extradural. Tumors may have a mixed myelographic appearance, with extradural, intradural, and/or intramedullary components (e.g., nerve root tumors, meningioma, and spinal cord blastoma). Myelographic findings may also be misleading, because extradural tumors may appear intramedullary on some views, or spinal cord edema associated with acute extradural compression may appear the same as an intramedullary mass. Other mass lesions that result in spinal cord compression, intramedullary swelling, and intradural lesions must be considered in the differential diagnosis of spinal tumors.

Both CT (Figure 193-14) and MRI aid the exact determination of the location and extent of spinal tumors.[235,236] Use of these advanced imaging modalities also helps in the planning of precise surgical approaches and radiation therapy.

193.5.25.3.4 Biopsy

Biopsy of suspected lesions is necessary to differentiate neoplasms from other vertebral and spinal cord abnormalities and to determine the histologic type.[237]

193.5.25.4 Treatment

Most vertebral tumors are not surgically resectable because of their malignant characteristics and because of the decreased stability of the vertebral column that may result from extensive surgery. Surgical decompression of the spinal cord and debulking of the tumor mass may be palliative in some cases. Some tumors in the spinal canal are surgically resectable, including some tumors that appear intramedullary on myelography, such as spinal cord blastoma.[238] Surgical exploration of solitary tumors in the spinal canal is recommended for animals with clinical signs indicative of an incomplete transverse myelopathy, even those in which myelographic findings are consistent with an intramedullary mass.[231] Intradural nerve root tumors are rarely completely surgically resectable, and the recurrence rate is high. Resection of ventral nerve roots that contribute to the brachial or lumbosacral plexus may necessitate amputation of the affected limb.[224]

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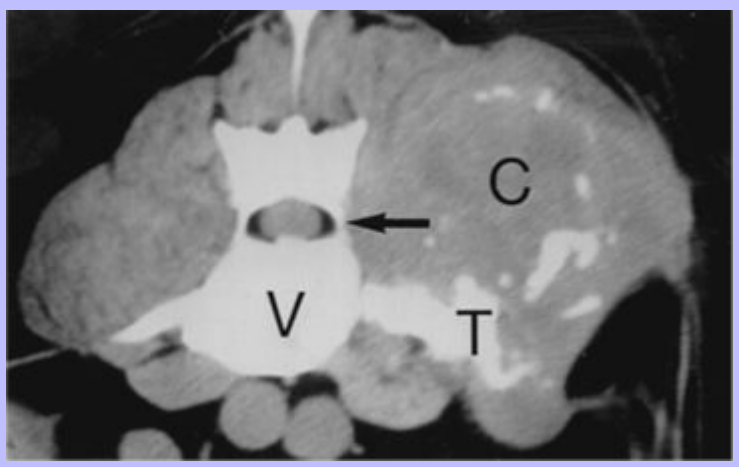
Figure 193-14 Vertebral neoplasia. Transverse computed tomography (CT) image of the vertebral column of a 13-year-old spayed female Old English sheepdog at the level of the L4 vertebral body *(V)*. Note the chondrosarcoma *(C)* arising from the transverse process *(T)* of L4. Areas of calcification can be seen in the neoplasm. The tumor involves the lateral lamina *(arrow)* of L4. CT allows exact determination of the location and extent of a neoplasm.



No direct correlation exists between tumor size and the severity or rate of progression of clinical signs. The spinal cord is able to compensate for pressure applied gradually, and animals with spinal tumors may remain

ambulatory despite having little normal spinal cord tissue remaining. Compression applied to the spinal cord rapidly, such as may occur with a pathologic fracture, may cause severe, irreversible spinal cord damage.

Corticosteroids may reduce spinal cord edema associated with spinal cord tumors and may produce clinical improvement for a variable period. Radiation therapy and chemotherapy may be helpful in animals with spinal lymphosarcoma. Most chemotherapeutic agents do not cross the blood–spinal cord or blood-CSF barrier in concentrations sufficient to eliminate tumor cells in the meninges or spinal cord. Several chemotherapeutic agents, including methotrexate and cytosine arabinoside, may be given intrathecally and have been used in the treatment of meningeal lymphosarcoma and leukemic meningitis. Complications of intrathecal use of chemotherapeutic agents include arachnoiditis and seizures. Chemotherapy may be helpful in the treatment of plasma cell myeloma.

Chemotherapy and radiation therapy have not been used in the treatment of a sufficient number of primary spinal cord, nerve root, or meningeal tumors to allow assessment of the results; however, initial experience suggests that further use of radiation therapy is warranted.[239] Various chemotherapeutic regimens have been used in the treatment of bone tumors and tumors that metastasize to bone, generally with poor results. Chemotherapy regimens in the future may offer more hope in the treatment of vertebral tumors. In general, the prognosis for animals with nonresectable spinal tumors is poor.

193.5.26 Neuroaxonal Dystrophy of Rottweilers

193.5.26.1 Etiology and Pathogenesis

Neuroaxonal dystrophy is a disease of rottweilers characterized by the accumulation of axonal spheroids throughout the neuraxis.[200,240,241] Clinically, affected animals have progressive ataxia in all limbs and severe hypermetria, especially of the thoracic limbs. Histologically, axonal spheroids are found in massive numbers throughout the brain and spinal cord, especially in the dorsal horns of the spinal cord and in the nucleus gracilis and nucleus cuneatus. The cerebellum is mildly atrophic in some dogs. Afferent fibers entering the sensory nuclei in the spinal cord, brain stem, and diencephalon are primarily affected. Electron microscopy has shown axonal spheroids to be enlarged, distal portions of axons and synaptic terminals that contain accumulations of smooth membrane–bound vesicles, membranous lamellae, dense bodies, and other organelles. Histologic lesions may be mild in young dogs.

A recessive mode of inheritance, with variable penetrance in rottweilers, is suspected from preliminary breeding studies. The etiology and pathogenesis of distal membranous axonopathies are not understood, but the location of the lesions suggests a derangement in the presynaptic portion of neurons or abnormalities in axonal transport. Axonal dystrophies have been associated with toxins, nutritional deficiency, aging, and genetic disorders in other species and in humans. A progressive neuroaxonal dystrophy was reported in a Jack Russell terrier pup, with pathologic alterations similar to those reported in rottweilers.[242]

193.5.26.2 Clinical Findings

Affected dogs may be clumsy as puppies, or clinical signs may not be seen until the dog is more than 12 months of age. Both male and female dogs are affected. Clinical signs may progress slowly over several years. The initial clinical finding is progressive ataxia of all limbs. Paresis or abnormalities in conscious proprioception have not been found in affected dogs. The patellar reflexes may be exaggerated, but other reflexes are normal. These findings are consistent with a transverse myelopathy of the cervical spinal cord or

multifocal spinal cord disease. As the disease progresses, other signs become apparent, including hypermetria (especially of the thoracic limbs), incoordination, tremors of the head, positional nystagmus, decreased menace response, and crossed extensor reflexes. Thoracic limb hypermetria may be severe in older dogs, especially when they climb stairs. The neurologic deficits seen in older dogs are predominantly referable to abnormalities in the cerebellum or input to the cerebellum.

193.5.26.3 Diagnosis

The diagnosis is made on the basis of the animal's age and breed, as well as the neurologic findings, and by ruling out other causes of cervical spinal cord and cerebellar disease. This disease is unusual in that it is slowly progressive over several years, but in the initial stages it may appear clinically similar to other causes of a cervical myelopathy, including CD myelitis and cervical spondylomyelopathy. The CSF may have an elevated protein concentration (40 mg/dL was reported in one dog[240]). Spinal radiographs and myelograms are normal.

193.5.26.4 Treatment

Currently, no effective treatment is available. Clinical improvement has not been detected during treatment with corticosteroids. Owing to the slow progression of the disease, affected dogs may be acceptable pets for several years. Affected dogs should not be used for breeding, although a diagnosis of neuroaxonal dystrophy may not be made until after these dogs have produced litters.

193.5.27 Osteochondromatosis (Multiple Cartilaginous Exostoses)

193.5.27.1 Etiology and Pathogenesis

A skeletal osteochondroma is a cartilage-capped exostosis arising from the surface of a bone formed by endochondral ossification. An animal with a monostotic lesion has a *solitary osteochondroma*. Polyostotic skeletal involvement is called *osteochondromatosis* (also *multiple cartilaginous exostoses, hereditary multiple exostoses, multiple osteochondromatosis, diaphyseal aclasis, dyschondroplasia,* and *hereditary deforming chondrodysplasia*). Consistent differences exist between cats and dogs with regard to the age of onset of lesions, patterns of skeletal involvement, and pathogenesis.[243,244]

The incidence of feline osteochondromatosis is unknown.[7] Feline osteochondromatosis is characterized by an initial appearance of lesions in the skeleton of mature cats (2 to 4 years of age). Growth of the lesions is progressive. In cats, the disease has no apparent gender or breed predilection, and a hereditary pattern has not been demonstrated. Malignant transformation to osteosarcoma was reported to have occurred in an osteochondroma of a cervical vertebra in a cat.

The incidence of osteochondromatosis in dogs remains undetermined. The disease is frequently demonstrated in the skeleton of dogs radiographed for unrelated reasons. The onset of clinical disease usually occurs in dogs less than 18 months of age.[245] Onset in mature dogs is infrequently recognized.[246] A hereditary basis has been indicated in dogs, but a gender or breed predilection is not apparent. Continued growth or reactivation of growth of exostoses in dogs is suggestive of neoplastic transformation.

The etiology of canine osteochondromatosis is unknown. The current view of the pathogenesis of feline osteochondromatosis is that the disease is virus related and probably virus induced. The random distribution

of the lesions is compatible with hematogenous distribution of a virus. The virus may be FeLV, feline fibrosarcoma virus acting in an atypical manner, or another member of the feline retrovirus family.

193.5.27.2 Clinical Findings

Osteochondromatosis may occur anywhere in the vertebral column but most commonly is found in the thoracic and lumbar spine. The disease may result in spinal cord compression and clinical signs indicative of a progressive transverse myelopathy between T3 and L3. Neurologic deficits are often asymmetric.

193.5.27.3 Diagnosis

Radiographically, vertebral lesions tend to be circular and smooth with sclerotic borders. The lesions are usually multiple and may be cystic or proliferative, with an increased radiodensity. Myelography is necessary to demonstrate associated spinal cord compression. Extension of exostoses into the spinal canal results in extradural compression of the spinal cord. Surgical biopsy is necessary to differentiate osteochondromatosis from benign bone tumors (osteomas), neoplastic lesions, or infectious processes.

193.5.27.4 Treatment

Treatment of canine osteochondromatosis affecting the vertebral column is unnecessary unless a lesion results in clinical sequelae. An osteochondroma should be removed if it impinges on the spinal cord or if malignant transformation is suspected. Surgical excision of cartilaginous exostoses and spinal cord decompression are the recommended treatments for lesions causing spinal cord compression and neurologic deficits. Intraoperative spinal stabilization may be indicated after removal of the lesion.[247] The prognosis for dogs that have stopped growing is good; however, the prognosis for animals that are still growing is guarded, because lesions may continue to expand and may subsequently cause spinal cord compression.

Treatment of feline osteochondromatosis is complicated by the association with FeLV and the progressive nature of the lesions in cats. It seems that at best, surgical removal of a lesion may provide only temporary relief to a cat because of the tendency for excised lesions to recur and for new lesions to develop.

193.5.28 Pilonidal Sinus, Epidermoid Cyst, and Dermoid Cyst (Dermoid Sinus, Pilonidal Cyst)

193.5.28.1 Etiology and Pathogenesis

A pilonidal sinus is an invagination of the skin dorsal to the spine that extends below the skin to variable depths and in some cases as far as the dura mater, where it may communicate with the subarachnoid space. The formation of pilonidal sinuses is related to failure of complete separation of the neural groove from the epidermis during embryonic development. Pilonidal sinuses may occur anywhere along the dorsal midline from the cervical to the sacrocaudal regions and may be single or multiple. Purebred and crossbred Rhodesian ridgeback dogs are most commonly affected, although other dog breeds may be affected.[248] There have been no reports of sinuses occurring along the ridge of hair of Rhodesian ridgebacks. The sinuses contain inspissated sebum, hair, and exfoliated cells and commonly become inflamed or infected. If the sinuses communicate with the subarachnoid space, extension of infection results in meningitis or myelitis. Pilonidal sinuses are likely to occur as a hereditary defect in Rhodesian ridgebacks, but the mode of inheritance is not definitely known.[6]

Dermoid cysts have been reported to occur in the brain and spinal cord of dogs and cats.[249] In one report, a dermoid cyst in the spinal cord of a cat at the level of T3 was considered a congenital anomaly.[1]

Epidermoid cysts have been reported to occur in the brain and spinal cord of dogs.[191] Such cysts are thought to arise from entrapment and subsequent growth of primordial epithelial cells during closure of the neural tube. Morphologically similar cysts have developed in humans after injury or after repeated lumbar subarachnoid punctures for CSF collection, presumably from mechanical implantation of epidermal cells. An intramedullary spinal epidermoid cyst reported in a dog was thought to have a congenital cause. Apparently, spinal epidermoid cysts rarely occur in dogs.[250]

193.5.28.2 Clinical Findings

Clinical signs of meningitis and myelitis may be seen in animals as a result of extension of infection from a pilonidal sinus to the subarachnoid space. Localized or generalized spinal pain and rigidity may be seen associated with meningitis. Neurologic deficits indicative of a transverse or diffuse myelopathy may be seen as a result of myelitis. Signs resulting from a spinal dermoid or epidermoid cyst depend on its location.

193.5.28.3 Diagnosis

A pilonidal sinus may be palpable as a cord of fibrous tissue under the skin of the dorsal midline. Palpation may be painful if the sinus is infected. An opening in the skin on the dorsal midline is usually found, and hair may or may not be seen protruding from this opening. The CSF in animals with meningitis or myelitis is generally abnormal and indicative of bacterial infection. Fistulography (performed by injecting a radiographic contrast material, such as metrizamide, which is not an irritant to nervous tissue, into the sinus) demonstrates whether pilonidal sinuses are continuous with the subarachnoid space. Myelography may also demonstrate communication.

The diagnosis of a spinal dermoid or epidermoid cyst is based on the clinical signs and on the results of plain spinal radiography, CSF analysis, and myelography. Typically an epidermoid cyst should be suspected with an intramedullary, expansile lesion on myelography in a young dog with progressive neurologic deficits. The diagnosis is confirmed by open surgical biopsy, which may provide the only means of ruling out spinal neoplasia (e.g., spinal cord blastoma). Advanced imaging (CT or MRI) may be useful for fully delineating the extent and location of these cystic structures.

193.5.28.4 Treatment

Animals with meningitis and/or myelitis associated with a pilonidal sinus should be treated as an animal with meningitis and myelitis due to another cause. Antibiotic therapy should be selected on the basis of the CSF culture, culture of the contents of the pilonidal sinus, and sensitivity testing. Complete surgical excision of the pilonidal sinus is essential.[251] Laminectomy may be necessary to remove portions of a pilonidal sinus from within the spinal canal. Recurrence of infection is likely in dogs in which a pilonidal sinus is incompletely removed. The prognosis depends on the severity of the neurologic deficits before surgery, the response to antibiotic therapy, and whether the pilonidal sinus was removed completely. Complications of surgical removal include wound dehiscence and seroma formation. Affected animals should not be used for breeding.

Treatment of spinal dermoid or epidermoid cysts of dogs has not been reported. Surgical excision may be possible in some animals.

193.5.29 Progressive Hemorrhagic Myelomalacia

193.5.29.1 Etiology and Pathogenesis

Acute, severe spinal cord injury may result in progressive ascending and descending infarction and hemorrhagic necrosis of the spinal cord parenchyma. Progressive hemorrhagic myelomalacia occurs infrequently and usually follows peracute explosive extrusion of a thoracolumbar disk, but it may also be seen after other types of spinal cord trauma.[6] PHM previously was known as hematomyelia. Most dogs with thoracolumbar disk extrusions have evidence of a localized myelopathy affecting up to four spinal cord segments. In animals with PHM, hemorrhagic necrosis of a large number of spinal cord segments may occur over a period of hours to days. The etiology of this syndrome is not known; however, spinal cord pathology indicates severe ischemia.

193.5.29.2 Clinical Findings

The clinical signs depend on the location of the lesion; however, most affected animals initially have clinical signs indicative of a transverse myelopathy between T3 and L3. Neurologic deficits usually are severe (paraplegia and absent deep pain perception in pelvic limbs) and peracute in onset (over several hours). Clinical signs indicating a diffuse myelopathy progress over a period of hours to 1 to 2 days. As infarction and hemorrhagic necrosis of the spinal cord progress caudally, LMN signs may be seen in the pelvic limbs and anus. As PHM progresses cranially, the level of cutaneous anesthesia and LMN signs in intercostal muscles extend cranially until thoracic limbs exhibit LMN signs. The Schiff-Sherrington sign may be present before involvement of the spinal cord cranial to T3. Diaphragmatic paralysis and bilateral Horner's syndrome may be seen with involvement of the cervical spinal cord. Affected animals often are in extreme pain, are anxious, and have an increased body temperature.

193.5.29.3 Diagnosis

The diagnosis is made on the basis of progressive clinical signs indicative of a diffuse myelopathy. Any animal with an acute onset of paraplegia due to a lesion between T3 and L3 that shows LMN signs in the pelvic or thoracic limbs should be suspected of having more than one lesion or PHM.

193.5.29.4 Treatment

In most cases PHM is fatal within 24 to 48 hours as a result of respiratory paralysis. There is no effective medical or surgical treatment, and euthanasia is recommended. Difficulty often arises in the treatment of animals that have an acute onset of paraplegia, with or without deep pain perception, within hours after the onset of clinical signs. Ideally, if decompressive surgery is indicated, it should be performed as soon as possible; however, a small percentage of these cases may show clinical signs of PHM after surgery. Hemorrhagic myelomalacia in some cases may not progress to involve the cervical cord, and affected animals may survive; however, the spinal cord damage incurred and the associated severe neurologic deficits are permanent.

193.5.30 Protozoal Myelitis

193.5.30.1 Etiology and Pathogenesis

Toxoplasma gondii is an obligate, intracellular, coccidian parasite. Cats are the only known definitive host of the organism and as such pass environmentally resistant oocysts in feces. The seroprevalence of infection varies by region but is approximately 30% in cats in the United States. Despite this high seroprevalence, clinical disease caused by *T. gondii* is rare.[252,253]

T. gondii infection may cause a focal or disseminated myelopathy in dogs or cats.[6] Animals are infected after ingesting meat containing *Toxoplasma* bradyzoites and/or tachyzoites; after ingesting cat feces containing sporulated oocysts; or by transplacental or congenital infection. The infective organism is spread hematogenously to most organs of the body, including the CNS. Although the incidence of disease associated with *T. gondii* is low, opportunistic infection in immunosuppressed animals may be more widespread than previously reported. Immaturity and concurrent CD virus infection may result in an increased susceptibility of dogs to toxoplasmosis. In dogs with systemic toxoplasmosis, the incidence of CNS involvement is high. In cats, concurrent infection with FeLV or FIV or administration of corticosteroids may predispose the animal to the development of clinical signs of toxoplasmosis through immunosuppression and reactivation of latent infection.[254–256]

Neospora caninum is a recently discovered, cyst-forming coccidium in the phylum Apicomplexa that is structurally similar to but distinct from *T. gondii*.[257–264] This protozoal parasite is associated most commonly with natural infection in dogs and cattle. The organism forms meronts in many tissues of dogs, especially the brain and spinal cord, resulting in meningoencephalomyelitis. Clinical signs result from host cell death caused by rapid intracellular multiplication of the parasite and the ensuing inflammatory response of the host. Cats have been infected experimentally and have been shown to develop clinical disease. *N. caninum* organisms do not react to *Toxoplasma* immunoperoxidase staining techniques, and the life cycle is unknown. Clinically, this protozoal disease appears similar to toxoplasmosis; however, CNS signs (progressive ascending paralysis) and myositis are seen more commonly than in toxoplasmosis, and *T. gondii* almost always has been associated with concurrent disease in dogs (e.g., CD infection), whereas *N. caninum* appears to be a primary pathogen.

193.5.30.2 Clinical Findings

Animals with CNS involvement by *T. gondii* usually have clinical signs of progressive multifocal or disseminated disease. Clinical signs indicating a focal transverse or diffuse myelopathy may be seen initially. Neurologic deficits depend on the site of involvement and may be either UMN or LMN deficits. If lower motor neurons are involved, denervation may result in severe muscle atrophy.

In dogs less than 1 year of age, a syndrome of progressive paralysis and rigid extension of one or both pelvic limbs may be seen in association with *T. gondii* infection. Muscle atrophy and contracture of affected limbs are seen, and limbs cannot be flexed. Muscle changes may be the result of myositis and myonecrosis and/or denervation caused by myelitis or radiculitis in the caudal lumbar and sacral spinal cord segments. Animals with CNS toxoplasmosis may or may not have other clinical signs indicative of systemic infection, such as fever, lymphadenopathy, pneumonia, apparent muscle pain, gastrointestinal tract disease, iritis, or chorioretinitis.

Overall, neosporosis is an increasingly prevalent infectious disease that merits consideration in juvenile and adult dogs with progressive paraparesis. Neosporosis may cause fatal disease in dogs of all ages (several weeks to 15 years). Puppies are affected more severely than older dogs. Young dogs develop an ascending paralysis, with the pelvic limbs affected more severely than the thoracic limbs. Other signs of dysfunction include difficulty swallowing, paralysis of the jaw, muscle flaccidity, and muscle atrophy.

193.5.30.3 Diagnosis

Antemortem confirmation of CNS toxoplasmosis or neosporosis in dogs or cats is extremely difficult and may be tentatively based on all of the following: (1) demonstration of serologic evidence of infection, (2) clinical signs of disease referable to toxoplasmosis or neosporosis, (3) exclusion of other common causes of these clinical signs, and (4) positive response to appropriate treatment.

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193.5.30.4 Treatment

Several antibacterial agents have been recommended for the treatment of both toxoplasmosis and neosporosis in dogs as well as cats.

193.5.31 Sacrocaudal Dysgenesis in Manx Cats

193.5.31.1 Etiology and Pathogenesis

Manx cats have varying degrees of taillessness associated with sacral and/or caudal vertebral deformities.[6,7,267] Some tailless cats have a normal sacrum, spinal cord, and cauda equina. Others show varying dysgenesis or agenesis of the sacral and/or caudal vertebrae that may be associated with spina bifida and/or malformations of the terminal spinal cord and/or cauda equina. Spinal cord malformations include the absence or partial development of the sacral and caudal spinal cord segments or the cauda equina; myelodysplasia; meningocele; meningomyelocele; diastematomyelia of sacral segments (duplication); myeloschisis (cleft within the spinal cord); syringomyelia in the lumbar and sacral spinal cord segments; shortening of the spinal cord and subcutaneous cyst formation. These spinal cord and cauda equina malformations are associated with a variety of neurologic deficits.

Sacrocaudal dysgenesis is inherited as an autosomal dominant trait and may be lethal in some homozygote cats. Sacrocaudal dysgenesis and associated malformations have been recognized in most breeds of cats, many not of true Manx breeding.

193.5.31.2 Clinical Findings

Clinical signs vary, depending on the degree of spinal cord and cauda equina malformation; they include paraparesis, paraplegia, megacolon, atonic bladder, absent anal and urinary bladder sphincter tone, absent anal reflex, urinary and fecal incontinence, and perineal analgesia. Affected cats often walk plantigrade in the pelvic limbs with a “bunny hopping” gait. Vertebral abnormalities may be palpable in the lumbosacral region, and in some cats a meningocele (congenital or the result of necrosis of the overlying skin) may exit through the skin and drain CSF.

Clinical signs usually are evident soon after birth and may remain static or may progress. Worsening of neurologic deficits may be due to progressive syringomyelia in the lumbar and sacral spinal cord.

193.5.31.3 Diagnosis

The diagnosis is made on the basis of clinical findings, in addition to radiographic findings indicative of dysgenesis or agenesis of the sacral and caudal vertebrae. Myelography may demonstrate meningocele or attachment of the spinal cord to subcutaneous tissues in the lumbosacral region. The degree of spinal deformity does not always correspond with the degree of neurologic impairment. Clinical findings are the most important factors to consider in the determination of the prognosis.

193.5.31.4 Treatment

The prognosis for severely affected cats is hopeless, and treatment is not available. Cats with urinary and fecal incontinence may be managed with manual bladder expression and fecal softening agents; however, recurrent urinary tract infection, megacolon, and chronic constipation are common problems. Meningocele in cats with minimal neurologic deficits may be surgically correctable. Many tailless cats do not have neurologic deficits, and sacral and caudal deformities often are an incidental radiographic finding.

193.5.32 Spina Bifida

193.5.32.1 Etiology and Pathogenesis

Spina bifida, which occurs in both dogs and cats, describes a group of developmental defects characterized by failure of fusion of the vertebral arches with or without protrusion or dysplasia of the spinal cord and meninges.[6,7] This defect is part of the complex of spinal dysraphism and is the most commonly occurring dysraphic defect. *Dysraphism* is a defective fusion of parts that normally unite. Spina bifida is the absence of a portion of the dorsal elements of the vertebrae. The spinal cord and meninges may be normal (spina bifida occulta), or they may be abnormal, and the meninges and/or spinal cord may protrude through the vertebral defect.

Myelodysplasia consisting of hydromyelia, syringomyelia, anomalies of the dorsal septum, anomalies of the central gray matter, abnormal position of the central gray matter, anomalies of the dorsal and ventral horns, and myeloschisis (cleft in the dorsal part of the spinal cord) may occur in association with spina bifida. The most severe defects involve myelorachischisis, with superficial location of the neuroectoderm that is continuous with the skin. Spina bifida with myelorachischisis has been reported to occur in dogs and cats.

The etiology of spina bifida is unknown and probably is multifactorial, with genetic and environmental components. The relatively high incidence of spina bifida in some breeds of animals (e.g., bulldogs and Manx cats) suggests a heritable basis for the disorder. Teratogenic compounds, nutritional deficiencies, and environmental changes during pregnancy are also known to induce this defect.

193.5.32.2 Clinical Findings

Spina bifida is usually an incidental radiographic finding; however, if associated with spinal cord malformations, it may result in clinical signs of spinal cord or cauda equina dysfunction. English bulldogs

have a high incidence of spina bifida. Spina bifida may be found anywhere in the spinal column but most commonly occurs in the caudal lumbar spine, where clinical signs are indicative of a transverse myelopathy from the L4 to the S3 spinal cord segments. Clinical signs usually become evident when affected animals start to walk.

Spina bifida also has been reported in the thoracic spine of a dog and may be associated with other spinal deformities, such as scoliosis. Other associated anomalies include dimpling of the skin or "streaming" (abnormal direction) of the haircoat over the affected region or a palpable abnormality in the spinal column. Meningoceles may cause necrosis of the overlying skin and drainage of CSF. Meningoceles may be present in the absence of clinical signs associated with spinal cord malformation.

193.5.32.3 Diagnosis

Radiographically, absence of the vertebral arch or failure of fusion of the spinous processes in one or more vertebrae may be seen (Figure 193-15). Myelography may demonstrate meningocele. Advanced imaging (CT or MRI) may be used to accurately define the location and extent of bony and soft tissue abnormalities in animals with spina bifida.

193.5.32.4 Treatment

Treatment of spina bifida rarely is attempted. Treatment is not effective for affected animals with clinical signs of spinal cord malformation. Meningocele may be amenable to surgery if neurologic abnormalities are not evident. Treatment is not necessary for animals with vertebral defects in the absence of spinal cord dysfunction. When planning therapy, the veterinarian must consider the possible existence of additional spinal cord malformations (e.g., hydromyelia) seen in association with spina bifida.

193.5.33 Spinal Intra-Arachnoid Cysts

193.5.33.1 Etiology and Pathogenesis

Intra-arachnoid cysts are intra-arachnoid membrane accumulations of CSF that may occur in any location along the cerebrospinal axis of cats or dogs.[268–273] The intra-arachnoid accumulation of CSF in the cyst results in expansion of the cyst between the overlying dura mater and the underlying pia mater, causing compression of the spinal cord. Intra-arachnoid cysts may be congenital in origin or may occur secondary to trauma, infection, inflammation, or subarachnoid hemorrhage.

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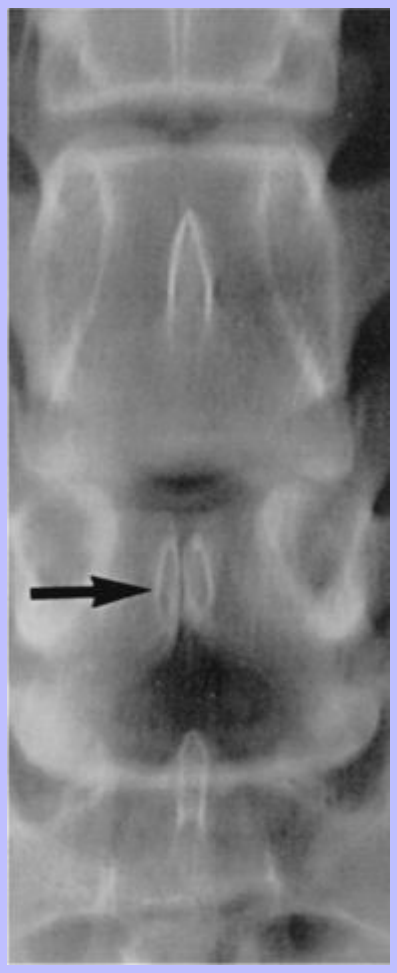
Figure 193-15 Spina bifida. Ventrodorsal radiograph of the caudal lumbar vertebral column of an 8-year-old spayed female chow chow. A deficit in fusion of the embryologic neural tube has resulted in nonfusion of the spinous process of L7 *(arrow)*. This congenital defect was an incidental finding in this dog.



193.5.33.2 Clinical Findings

A single intra-arachnoid cyst has been described in either the cranial cervical or caudal thoracic spinal canal. The author (RAL) has diagnosed multiple intra-arachnoid cysts in the caudal cervical region of three rottweilers. The neurologic deficits were indicative of a progressive transverse myelopathy in either the C1 to C5 or the T3 to L3 spinal cord region. Apparent cervical pain and spasms of the cervical muscles were a feature of cervical lesions; however, apparent pain was not evident in dogs with thoracic lesions. Neurologic deficits may be asymmetric.

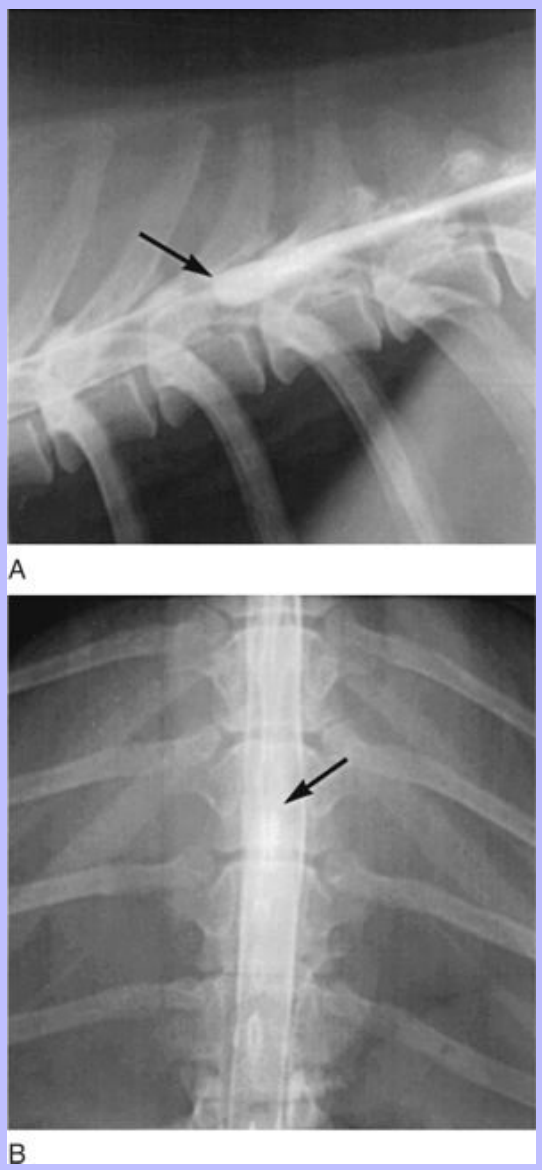
193.5.33.3 Diagnosis

The diagnosis is made on the basis of myelographic or advanced imaging (CT or MRI) findings. Surgical findings and histopathologic examination of excised tissues confirm the diagnosis.

Plain radiographs of the spine may be normal or may show enlargement of the vertebral canal with smooth cortical margins, presumably as a result of pressure atrophy of bone overlying the cyst. Abnormalities in the results of CSF analysis have not been reported. Care should be taken in attempting a cisternal subarachnoid puncture in an animal suspected of having a cervical arachnoid cyst, because lesions may be located on the dorsal midline. One reported dog was injured inadvertently during an attempted cisternal puncture.

On myelography, pooling of contrast material in the subarachnoid space may be seen, resulting in a characteristic widening of the subarachnoid space and spinal cord compression (Figure 193-16). In all reported cases, the lesions have been intradural-extramedullary and located on the dorsal midline. The author (RAL) has seen intra-arachnoid cysts in dorsolateral and ventral locations in the cervical region of dogs. The lesions may extend over more than one spinal cord segment.

Figure 193-16 Spinal intra-arachnoid cyst. Lateral **(A)** and ventrodorsal **(B)** projections of a myelogram of the midthoracic region of a 2-year-old toy poodle that had a 1-year history of progressive pelvic limb paresis and ataxia. Note the widening of the dorsal subarachnoid contrast column at T9–T10 on the lateral projection *(arrow)*. The ventrodorsal projection shows apparent intramedullary expansion of this area *(arrow)*. An intra-arachnoid cyst was removed by dorsal laminectomy.



Advanced imaging (CT or MRI) may be used to fully delineate intra-arachnoid cysts. Although intra-arachnoid cysts have a characteristic appearance on advanced imaging, they must be differentiated from other cystic lesions (e.g., cystic neoplasms or cysts associated with infections).

193.5.33.4 Treatment

Surgical exploration is necessary to confirm a diagnosis of intra-arachnoid cyst and to decompress the spinal cord. Complete surgical excision of an intra-arachnoid cyst usually is not possible, although partial excision of the cyst (called *surgical fenestration*) may result in decompression of the spinal cord and permanent clinical improvement. 880 881

193.5.34 Spinal Nematodiasis

193.5.34.1 Etiology and Pathogenesis

Aberrant migration and growth of parasites in the spinal canal rarely occur in dogs or cats. The route of migration of most parasites that enter the CNS is unknown, with the exception of hematogenous-borne *Dirofilaria immitis*. Parasites may cause extensive damage to neural parenchyma as a result of infarction, spinal cord compression, or granuloma formation. Parasites reported to occur in the CNS of dogs include *D. immitis*, *Toxocara canis* larvae, *Angiostrongylus cantonensis* (rat lungworm of Australia), *Ancylostoma caninum* (Australia),[274–276] *Baylisascaris* sp.,[277] and *Spirocerca lupi*.[278]

193.5.34.2 Clinical Findings

Clinical signs depend on the location of the migrating parasite, and the lesions may be focal or multifocal. Spinal nematodiasis usually is seen in immature animals, with the exception of *D. immitis*. Clinical signs often have an acute onset and usually are progressive. Clinical signs rarely occur with aberrant *Toxocara* migration in dogs; however, a single *Toxocara* larvae has been found in the cauda equina of a dog. Clinical signs reported to be associated with *A. cantonensis* infestation in the dog include paraparesis, paraplegia, urinary and fecal incontinence, paralysis of the tail, and apparent pain. *A. caninum* migration in the spinal cord has been reported to result in paraparesis, apparent neck pain, and tetraplegia.

193.5.34.3 Diagnosis

Definitive diagnosis is difficult antemortem because it requires isolation or demonstration of the parasite in the CNS.

The CSF may show an increase in the WBC count, especially in eosinophils, and/or in the protein concentration.[275] Affected animals usually have a large parasite burden, and nematode eggs or larvae may be found in the feces. Dogs with *D. immitis* infestation may have circulating microfilaria. Lesions may be located by means of myelography or advanced imaging (CT or MRI).

193.5.34.4 Treatment

The prognosis for animals with spinal nematodiasis depends on the severity of resulting neurologic deficits, and it usually is poor. Medical therapy often is ineffective at eliminating parasites in the CNS. Surgical removal of *D. immitis* adults from the spinal epidural space has been reported.

193.5.35 Spinal Cord Trauma

193.5.35.1 Etiology and Pathogenesis

Acute spinal cord injuries of dogs or cats result most commonly from direct physical trauma, such as missile injury or vertebral fracture or luxation. Also, spinal cord trauma is the underlying cause of neurologic signs in numerous myelopathies (e.g., intervertebral disk disease). Chronic spinal cord compression usually is seen in association with chronic progressive diseases such as neoplasia or type II disk protrusion.[279] After injury, the spinal cord may undergo sustained compression or distraction, or both. The severity of a spinal cord injury, as determined by the eventual degree and quality of recovery, is related to three factors: the velocity with which the compressive force is applied, the degree of compression (transverse deformation), and the duration of the compression. An understanding of the differences between acute and chronic spinal cord injury is essential for effective management and determination of the prognosis in cats or dogs with spinal trauma.[280]

193.5.35.1.1 Acute spinal cord injury

Blunt traumatic injury to the spinal cord causes neurologic deficits through both direct and indirect mechanisms. The direct effects are due to immediate mechanical disruption of neural pathways, and these effects have been considered by most investigators not to be amenable to therapy. Indirect effects develop during the first few hours after injury and result in delayed secondary injury to the spinal cord. It is likely that they result in part from the release of endogenous pathophysiologic factors in response to the initial trauma and that such factors produce injury by reducing spinal cord blood flow or by altering the local metabolic environment in injured spinal cord tissue. The spinal cord remains physically intact but is functionally deranged. A common feature of acute spinal cord injury is early, often progressive hemorrhage in the central region of the injured spinal cord, especially in the gray matter. Direct mechanical disruption of vessels at the site of injury is expected; however, the loss of circulation spreads for a considerable distance cranial and caudal to the site of injury. Angiographic studies have consistently shown that the large arteries remain patent, and the major loss of microcirculation involves capillaries and venules. The secondary damage has been considered potentially reversible through the use of either physical (e.g., hypothermia) or pharmacologic interventions.

Trauma to the spinal cord triggers a series of progressive, autodestructive events that lead to varying degrees of tissue necrosis, depending on the severity of the injury.[280] Despite extensive investigation, the mechanisms responsible for the initiation and propagation of these pathophysiologic and biochemical events remain undetected. However, recent evidence suggests that the overall initiator of this autodestructive cascade of events is mechanical deformation of any type (i.e., impact or compression injury), and that the primary sites of injury are the cellular and subcellular membranes of glia, neurons, and vascular endothelial cells. Lipid peroxidation and activation of membrane lipases, with the release of

fatty acids, leading to production of eicosanoids, are the earliest mechanically stimulated biochemical events described.

Within 5 minutes of spinal cord injury, postcapillary venules become congested. This is followed by opening of endothelial gap junctions there and at the capillary level, resulting in diapedesis of red blood cells and extravasation of fluid proteins and electrolytes through the "leaky" vasculature. Within 30 minutes of injury, microscopic hemorrhages appear in the central gray matter and coalesce over the following several hours (central hemorrhagic necrosis). Vacuolization develops in endothelial cells, indicating a profound ischemic or hypoxic insult, and subsequently leads to coagulative necrosis of the neuronal population. Adjacent white matter is relatively less severely affected; however, periaxonal swelling and retraction balls may be observed. These events may lead to autodissolution of the spinal cord within 24 hours, even in the absence of ongoing mechanical compression.

These phenomena would appear to have an ischemic basis, and considerable effort has been expended in characterizing the associated microcirculatory alterations. One cause of the ischemia may be direct mechanical irritation that results in vasospasm and biochemical damage due to the release of glutamate, intracellular calcium, catecholamines, and prostaglandins. Other studies point to intravascular thrombosis, possibly owing to the release of thromboxane, as an additional cause of post-traumatic ischemia. One of the most damaging biochemical alterations to the injured spinal cord is the accumulation of the excitatory amino acid neurotransmitter glutamate. Glutamate also causes an elevation of intracellular calcium that may in turn cause activation of calcium-dependent proteases or lipases, leading to further breakdown of cytoskeletal components.

A special feature of acute spinal cord injury is progressive hemorrhagic myelomalacia. This condition may occur after spinal cord injury, and appears to be a progression of central hemorrhagic necrosis and edema to areas of the spinal cord not directly involved in the initiating injury. 881 882

193.5.35.1.2 ## Chronic spinal cord compression

It has been shown experimentally that when slow compression of the spinal cord is compared with rapid compression of an equal amount, the extent of spinal cord dysfunction is determined by the contact velocity of compression. The major pathologic substrate for neural dysfunction after slow balloon compression is thought to be physical injury to the neural membranes, irrespective of blood flow changes, and the ability of that membrane to recover appears to be related to the rapidity and duration of compression. Clinical observations support the conclusion that spinal cord conduction is resistant to slow compression. Furthermore, it has been demonstrated that levels of compression that do not have an effect when applied slowly cause an immediate loss of conduction through the injured site when applied rapidly.[281]

Chronic spinal cord compression results either from a slowly developing lesion (e.g., neoplasia) or from an acute compression that is sustained. In contrast to acute spinal cord injury, chronic compression injury affects the white matter more severely than the gray matter. Hemorrhage and edema, the major findings of acute trauma, are not significant in chronic compression. Characteristic lesions are degeneration of myelin, focal areas of malacia, vacuolization, and loss of white matter axons. Mechanical deformation is likely to be the major factor in the pathogenesis of these lesions; however, ischemia and venous obstruction also may be important considerations.

193.5.35.2 Clinical Findings

193.5.35.2.1 Acute spinal cord injury

Dogs or cats with a spinal injury frequently have serious injuries to other organ systems. A primary concern is to balance the relative urgency of non-neurologic injuries (hemorrhage, shock, airway obstruction, or limb fractures) and the need for early treatment of spinal cord injury.[279]

A complete neurologic examination is performed to localize the site or sites of injury and to determine the severity of injury. Careful palpation of the vertebral column may aid identification of a vertebral fracture or luxation. Administration of tranquilizers or analgesic drugs should be delayed until the neurologic examination has been completed, because such medications may alter an animal's responses. The neurologic examination should be performed with care to prevent further injury from excessive movement of a vertebral instability.

Several aspects of the neurologic examination are of special importance in the assessment of a dog or cat with a spinal cord injury. Recognition of the Schiff-Sherrington sign is important. After trauma, this sign must be differentiated from other postures associated with cranial injury (e.g., decerebrate rigidity or decerebellate posture). Both deep and cutaneous pain perception should be assessed, because the results of these tests are important in the determination of the prognosis. It should be remembered that vertebral column injuries may be multiple and that a neurologic examination may not detect a second lesion.

193.5.35.2.2 Chronic spinal cord compression

Clinical signs of chronic spinal cord compression may progress over weeks or months or may be seen to occur acutely. Acute onset of neurologic signs with chronic spinal cord compression frequently is seen with such disorders as spinal neoplasia or type II disk protrusion. Sudden onset of signs may accompany pathologic fracture of a vertebra or spinal cord hemorrhage or infarction. In some cases sudden decompensation of a chronically compressed spinal cord may occur in the absence of pathologic changes. In these cases it is assumed that compensatory mechanisms in the spinal cord have been exhausted, allowing the sudden decompensation.

193.5.35.3 Diagnosis

193.5.35.3.1 Acute spinal cord injury

The results of a neurologic examination are used to determine the site and severity of a spinal injury. Radiographs of the entire spinal column should be taken. Two radiographic views are essential only when ventrodorsal views may be accomplished by means of a horizontal beam. The objectives of radiographic examination of an animal after acute spinal trauma are to determine precisely the location and extent of a lesion; to demonstrate the presence of multiple lesions, which may not be apparent from a neurologic examination; and to assess the need for surgical therapy and determine the most appropriate surgical procedure. Accurate interpretation of radiographs depends on a knowledge of the results of a neurologic examination.

Myelography is recommended for animals that have sustained spinal trauma. The results of a myelogram may determine the extent of spinal cord swelling caused by concussion in animals without evidence of a spinal fracture or luxation and may confirm that surgical decompression through laminectomy is not necessary in animals with a fracture that is evident on plain radiographs. In the diagnosis of intervertebral disk disease, a myelogram is essential prior to surgery.

The use of advanced imaging (CT or MRI) in acute spinal cord injury may be reserved for patients in which the results of the above diagnostic techniques do not fully explain the results of a neurologic examination.

193.5.35.3.2 Chronic spinal cord compression

The methods for diagnosing chronic spinal cord compression are the same as those used to diagnose acute spinal cord injury. A myelogram is considered essential in all such cases.

193.5.35.4 Treatment

The management of an animal with spinal trauma follows a list of priorities, and the focus of treatment is the prevention of secondary spinal cord damage that occurs after the initial injury. Immediate treatment of non-neural injuries is limited to life-threatening problems, such as shock or hemorrhage.

193.5.35.4.1 Acute spinal cord injury

Treatment of acute spinal cord trauma should always be instituted as soon as possible after injury. The specific objectives of therapy are relief of edema, control of intramedullary or extramedullary hemorrhage, relief of spinal cord compression and, in cases of vertebral fracture/luxation, removal of bone fragments from the spinal canal and realignment and stabilization of the vertebral column. Treatment of acute spinal cord trauma may be medical or surgical or a combination of these two therapies. The goal of medical therapy is to control the chemical and vascular changes that result in secondary spinal cord injury. Numerous drugs have been described for the treatment of spinal cord injury; however, the efficacy of many of these drugs for such injuries remains undetermined.

Corticosteroids are routinely and widely used in the treatment of acute spinal cord injury. Despite a positive clinical impression that corticosteroids have beneficial effects, their use is controversial. Some studies have failed to demonstrate significant improvement of neurologic recovery with cortico-steroid administration. The use of low versus high doses of corticosteroids in the treatment of spinal trauma also has yielded conflicting results. Use of corticosteroids may result in complications leading to increased morbidity and mortality (e.g., gastrointestinal bleeding, pancreatitis, colonic perforation).

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The only corticosteroid with proven efficacy in the management of spinal cord injury is methylprednisolone sodium succinate (MPSS). MPSS has been studied intensely in both the research and clinical settings for the past 10 years.[282–289] The drug must be administered as soon as possible after injury, and the effective dose range and the interval after injury when the drug may be given are narrow. Spinal cord uptake of MPSS rapidly decreases with time after injury, probably owing to secondary post-traumatic tissue loss and progressive blood flow decrease to the injury site. The molecular mechanism of action of MPSS may involve intercalation into the cell membrane and suppression of lipid peroxidation and hydrolysis. Inhibition of injury-induced lipid peroxidation results in attenuation of

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progressive post-traumatic ischemia and hypoxia, together with reversal of intracellular calcium accumulation. MPSS also directly retards secondary neuronal degeneration. The beneficial effects of antioxidant doses of MPSS support the contention that post-traumatic lipid peroxidation is a critical degenerative mechanism that may be interrupted with an antioxidant agent.

Current recommendations in humans are that patients with acute spinal cord injury receive MPSS (30 mg/kg given intravenously over 15 minutes) within 3 hours of injury; that they be maintained on an infusion of 5.4 mg/kg/hr for 24 hours; and that those that receive the initial bolus 3 to 8 hours after injury receive the infusion for 48 hours. Higher doses and initiation of treatment more than 8 hours after injury may exacerbate spinal cord damage. Complications include an increase in the incidence of pneumonia (2.6-fold in humans), gastrointestinal hemorrhage, and perforation. Although some experimental and clinical studies have found an improved recovery in research animals and humans treated with MPSS after spinal cord injury, a number of other studies have not found a significant improvement. One of the conclusions of the Third National Acute Spinal Cord Injury Randomized Controlled Trial[284] was that although the improvements in spinal cord injury patients after MPSS treatment were statistically significant, the actual functional differences were relatively small and benefited upper body function as opposed to actual locomotion.

The 21-aminosteroid tirilazad mesylate is a potent inhibitor of lipid peroxidation. In the Third National Acute Spinal Cord Injury Randomized Controlled Trial,[284] administration of tirilazad (2.5 mg/kg every 6 hours for 48 hours) after an initial 30 mg/kg bolus of MPSS to spinal cord injury patients resulted in motor recovery rates equivalent to those of patients who received MPSS for 24 hours. The reasons cited for failure of a 48-hour tirilazad regimen to improve neurologic recovery as much as the 48-hour MPSS regimen included the possibility that important mechanisms other than lipid peroxidation are involved in spinal cord injury and that a less than optimal dose was used. Another randomized, controlled trial of the drug in humans with spinal cord injuries is currently underway.

One of the most damaging effects of spinal cord injury is the accumulation of intracellular calcium in injured neurons, and neuronal death is closely related to the rise in intracellular calcium. Administration of a calcium channel antagonist (i.e., nimodipine or flunarizine) after spinal cord injury has had mixed results.

A decision on surgical therapy must be made as soon as non-neural injuries have been treated and medical management has been instituted. Ideally, this is within 2 hours of injury. Indications for surgery after spinal cord injury are moderate to severe paresis, or paralysis, associated with myelographic evidence of spinal cord compression; progressive worsening of neurologic signs despite adequate medical therapy; and luxation or fracture of the vertebral column in association with distraction, malalignment, instability, or myelographic evidence of spinal cord compression. Any animal with sustained compression of the spinal cord after injury, regardless of the cause, must be considered a candidate for surgical decompression of the spinal cord. In general, it is best to initiate surgical therapy in any animal in which uncertainty exists regarding the indications for surgical versus medical therapy. Neurosurgical procedures require specialized knowledge and equipment, and prompt referral to a qualified surgeon may be indicated.

The major objectives of surgical management of spinal trauma are decompression of sustained spinal cord compression and realignment and stabilization of vertebrae if necessary. Laminectomy alone is not sufficient for decompression in most cases, and the compressing mass (e.g., disk material, hematoma, bone fragments) should be removed when possible. When spinal cord swelling is the major source of compression or when discoloration of the spinal cord is present, durotomy or myelotomy may be combined with laminectomy.

No satisfactory methods of external fixation of spinal fractures exists for cats and dogs.[290] The author (RAL) favors the use of polymethyl methacrylate and Steinmann pin fixation for most spinal fractures or luxations.[291,292] Surgical management of spinal cord injuries provides the best opportunity for rapid, complete recovery in animals with sustained compression or instability and also facilitates postinjury care, because the risk of further injury from movement of an unstable vertebral column is minimized. However, conservative management, including strict confinement for 4 to 6 weeks, may be efficacious in animals with minimal neurologic deficits and without myelographic evidence of sustained spinal cord compression or vertebral displacement or instability.

Regardless of the type of stabilization used, strict confinement is recommended for 6 weeks after surgery. Potential complications encountered in dogs or cats with a spinal injury include the development of a urinary tract infection and pressure sores. Careful nursing care is essential, regardless of the type of therapy.[293]

The prognosis for an animal with an acute spinal cord injury depends on numerous factors; however, the results of the neurologic examination should be the main determinant. Assessment of pain perception is essential for an accurate prognosis. Perception of a painful stimulus must be differentiated from reflex activity mediated at the level of the spinal cord. Owners of affected animals should be made aware at the outset of therapy of factors such as the prognosis, the expense involved, the expected time from treatment to recovery, and the need for prolonged physical therapy in most cases. After a severe spinal injury, an animal may require many months to recover, and residual neurologic deficits may persist.

193.5.35.4.2

Chronic spinal cord compression

The approach to treatment of chronic spinal cord compression is different from that for acute spinal cord injury. As previously stated, hemorrhage and edema usually are not prominent factors in chronic compression, therefore medical management with corticosteroids would not be expected to be efficacious; however, many animals with chronic spinal cord compression improve clinically with corticosteroid administration. The reason for such a response has not yet been determined; however, it may be due to the effects of corticosteroids at the membrane level, resulting in improved conduction in remaining axons. Occasionally, animals may be maintained for months or years with corticosteroid therapy alone.

Surgical decompression and stabilization should be considered in dogs or cats with neurologic deficits associated with chronic spinal cord compression. Surgical decompression in such animals should be approached cautiously, because pathologic alterations in the spinal cord may be irreversible, and the most that may be achieved is arrest of the progression of neurologic deficits. In some cases, compensation for the irreplaceable loss of neural tissue may occur. Neurologic status may be worsened by surgical decompression, even with meticulous surgical technique. Such deterioration may be the result of reactive hyperemia that follows decompression, which in turn results in vascular protein leakage in the affected spinal cord segments.

193.5.36 Spinal Stenosis

193.5.36.1 Etiology and Pathogenesis

The term *spinal stenosis* indicates a narrowing of the vertebral canal, a condition that may produce a variety of neurologic syndromes.[31] The stenosis may be focal, segmental (affecting several adjacent vertebrae), or generalized (present throughout the vertebral column). Spinal stenosis may result either from bony impingement on neural elements (congenital stenosis, developmental stenosis resulting from inborn errors in skeletal growth, idiopathic developmental stenosis, or acquired stenosis) or from compression of neural tissue by nonosseous components of the walls of the vertebral canal (hypertrophy of the dorsal longitudinal ligament or ligamentum flavum or disk extrusion/protrusion).

Congenital spinal stenosis Congenital stenosis may occur as a primary lesion or may be seen in association with other congenital anomalies of the spinal cord or vertebral column.[294,295] In dogs, congenital stenosis may occur with block vertebrae or hemivertebrae.[31] Congenital spinal stenosis has been reported in association with transitional vertebrae, especially at the lumbosacral junction of dogs.[31,204] Despite the congenital origin of this stenosis, the initial manifestation of clinical signs may not occur until after an animal has reached skeletal maturity.

193.5.36.1.1 Thoracic vertebral canal stenosis

Segmental vertebral stenosis frequently occurs in the cranial thoracic spine of several dog breeds (e.g., Doberman pinscher).[31] Vertebrae T3 through T7 are affected most frequently. A decrease in the dorsoventral diameter of the vertebral canal, compared with adjacent vertebrae, is seen, and spinal cord compression may be seen. Mild lordosis, kyphosis, or scoliosis may be seen in association with the stenosis.

193.5.36.1.2 Developmental stenosis resulting from inborn errors in skeletal growth

This condition has been reported to occur in dogs.[168] The term *inborn errors* indicates incoordination of ossification and bone growth as a result of hereditary transmission or fresh mutation of a normal gene.[31] The errors are based on metabolic or other disturbances of cells involved in skeletal development. The disproportionate bone growth is already present at birth; however, the causative agents remain active during maturation. Therefore the term *developmental* is used to distinguish this group from the congenital stenoses. These conditions result in generalized spinal stenosis, which is more pronounced in the lumbar vertebral column. The vertebrae have a narrowed vertebral canal; however, the spinal cord and cauda equina are of normal size. This results in a disproportion between the dimensions of the vertebral canal and the volume of its contents. The relative spinal stenosis of chondrodystrophic dog breeds may contribute to the increased incidence of disk extrusion in these breeds. As with congenital stenosis, clinical signs may not develop until later in life and may be related only to a single level of the stenotic vertebral canal.

193.5.36.1.3 Idiopathic developmental stenosis

A genetic disturbance in which pathologic effects are apparent in their entirety only when growth is complete and the vertebrae have attained full size is termed *developmental*.[31] Clinical signs of spinal stenosis may result if some additional factor (e.g., disk protrusion) compromises the available diameter of the spinal canal in adult life. Hypertrophy of the bone of the vertebral arch or of the ligamenta flava may be present in this condition, which has been reported to occur in dogs.

193.5.36.1.4 Hypertrophy of the nonosseous components of the vertebral canal

Spinal stenosis resulting from ligamentous proliferation at C2–C3 has been reported in young rottweilers.[31,296]

193.5.36.2 Clinical Findings

Clinical signs of spinal stenosis reflect the location of the lesion, regardless of the precise cause.

193.5.36.3 Diagnosis

The diagnosis of spinal stenosis is made primarily by radiography. Myelography is essential for precise localization of the spinal stenosis. Other contrast-enhanced radiographic techniques may be used to define stenosis affecting the lumbosacral junction. Advanced imaging (CT or MRI) may aid in the determination of the location and extent of lesions associated with spinal stenosis.

193.5.36.4 Treatment

Spinal stenosis may be treated either medically or surgically. Relief of apparent pain with analgesic or anti-inflammatory drugs, combined with exercise restriction, may be adequate in dogs with mild clinical signs. In animals in which apparent pain persists or the stenotic condition worsens, decompressive surgery is indicated. Surgery is best performed early in the course of the disease. Internal spinal stabilization or fusion may be necessary when instability is evident on stress radiographs or after extensive decompressive procedures.

193.5.37 Spondylosis Deformans

193.5.37.1 Etiology and Pathogenesis

Spondylosis deformans is characterized by the formation of osteophytes (bony spurs) around the margins of vertebral endplates.[297] Osteophytes may form at one or more intervertebral disk spaces and may appear to bridge or almost bridge intervertebral disk spaces. The radiographic appearance of solid bony bridges may represent only an interdigitation of the adjacent osteophytes. Osteophyte production in spondylosis deformans is the noninflammatory bony response to degenerative changes in the intervertebral disks. These degenerative changes involve the anulus fibrosus and lead to the formation of intradiskal fissures.

The incidence and size of vertebral osteophytes increase with age. All dog breeds are affected, although large canine breeds may have a higher incidence of spondylosis deformans.[298] The caudal thoracic, lumbar, and lumbosacral spinal segments are affected most frequently. Because these segments are the areas of greatest spinal mobility, dynamic and mechanical factors may play a role in osteophyte formation. Spondylosis deformans is uncommon in the cervical and cranial thoracic segments in dogs. In cats, the incidence of spondylosis deformans forms a bell-shaped curve, with the highest incidence at the level of T7–T8.

The terms *ankylosing spondylosis* and *ankylosing spondylitis* have been used by some authors to describe spondylosis deformans, despite the fact that it is not an inflammatory condition and ankylosis is uncommon.

193.5.37.2 Clinical Findings

In most affected animals, spondylosis deformans is not of clinical significance. Rarely, bony spurs may project into the spinal canal or intervertebral foramina, resulting in compression of the spinal cord or spinal nerves. In such affected animals, the clinical signs, which depend on the location of the lesion, include apparent spinal pain, lameness, and signs of transverse myelopathy or peripheral neuropathy. Other causes of spinal cord disease, peripheral nerve disease, and apparent spinal pain should be investigated and ruled out before clinical signs are attributed to spondylosis deformans. Localized pain or lameness is reported to occur in animals with fracture of vertebral osteophytes.

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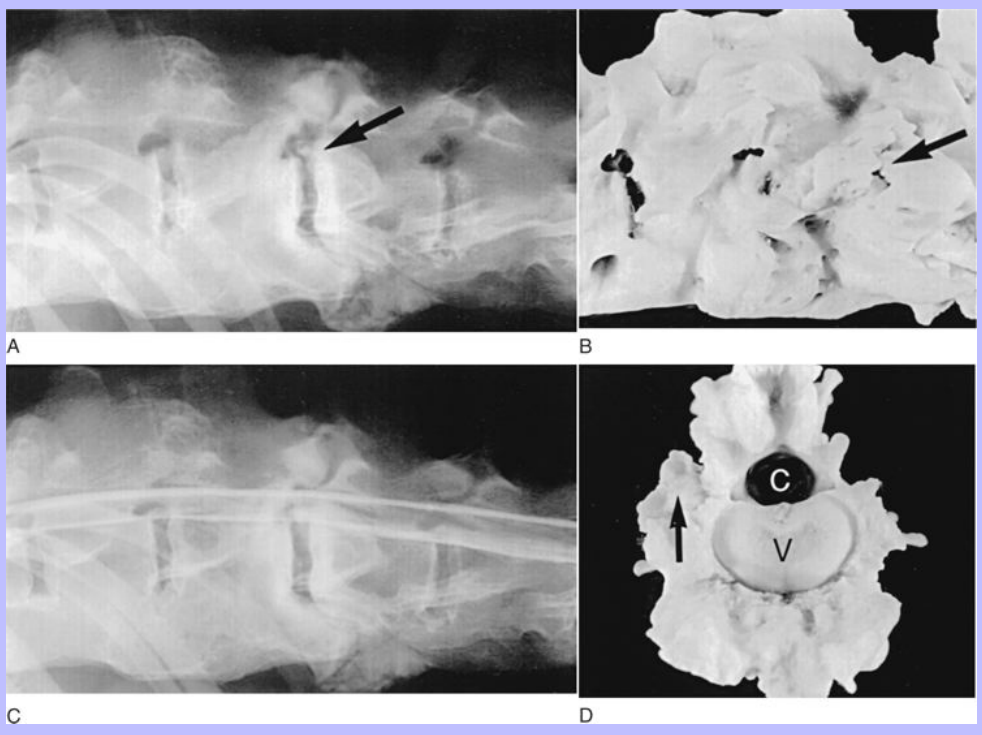
193.5.37.3 Diagnosis

A diagnosis of spondylosis deformans is based on the results of radiographs of the spine (Figure 193-17). Bony osteophytes associated with spondylosis deformans may be seen at one or more intervertebral disk spaces ventral to the vertebral bodies on lateral projections and lateral to the vertebral bodies on ventrodorsal views. These osteophytes have a curved, beaklike appearance with smooth ventral and lateral borders. Osteophytes range in size from small bony spurs to those that equal the dorsoventral dimensions of the vertebral body. Spurs from adjacent vertebrae may interdigitate. Osteophytes form predominantly around the ventral and lateral margins of the vertebral endplates, and those seen on lateral radiographs appear to be projecting dorsally into the spinal canal. Such osteophytes generally are located lateral to the spinal canal. Extensive osteophyte production dorsolateral to the vertebral body may compress spinal nerves at the level of the intervertebral foramina.

Figure 193-17 Spondylosis deformans. Lateral radiograph **(A),** gross pathologic specimen **(B),** and lateral myelogram **(C)** of the cranial lumbar vertebral column of a 12-year-old male golden retriever. Note the extensive spondylosis deformans present in the absence of myelographic abnormalities. Osteophytes *(arrow)* may appear to project into the vertebral canal on the lateral projection; however, these are actually dorsolateral and do not result in spinal cord compression. The typical location of osteophytes is seen in **D,** in which the spinal canal *(C)* of the L2 vertebrae *(V)* is not encroached upon by the ventrally and laterally located osteophytes. The arrow in **D** indicates osteophytes located close to the intervertebral foramen. This dog was neurologically normal.



Bone may form in the mass of connective tissue formed between developing osteophytes and may remain unattached to the vertebral bodies. These apparently free bone fragments are usually seen ventral to the intervertebral disk and may eventually become incorporated into developing osteophytes. These bone fragments may appear radiographically to be fractured osteophytes, but in fact they are not formed as a result of trauma.

Vertebral osteophytes may occur at either normal or narrowed disk spaces. Dorsally or dorsolaterally projecting osteophytes need to be distinguished from calcified disk material on lateral radiographs. Vertebral osteophytes may also form as a result of instability between adjacent vertebrae as a result of vertebral fracture or luxation, discospondylitis, congenital vertebral malformations, and surgery (e.g., disk fenestration). However, the term *spondylosis deformans* is used specifically to define the formation of vertebral osteophytes secondary to disk degeneration. Disk protrusion may occur at the same site as spondylosis deformans, resulting in spinal cord compression. Myelography or advanced imaging (CT or MRI) is necessary to determine whether disk protrusion or dorsal vertebral osteophyte formation is causing spinal cord compression. 885 886

193.5.37.4 Treatment

Spondylosis deformans rarely results in spinal cord compression. However, should spinal cord compression or nerve root entrapment be demonstrated in an animal with neurologic deficits, surgical decompression may result in clinical improvement. Analgesics may be of benefit in animals with evidence of pain suspected to be the result of spinal nerve compression by the production of vertebral osteophytes. In most animals, spondylosis deformans is not of clinical significance, and treatment is not necessary.

193.5.38 Synovial Cysts

Spinal synovial cysts may arise from the articular facets and surrounding connective tissues of the cervical and thoracolumbar vertebrae of dogs. These cysts may result in progressive extradural compression of the spinal cord. The etiology of synovial cysts is unknown; however, both degenerative changes and trauma have been suggested as likely causes.[299,300] Clinical signs resulting from compression of the spinal cord by a synovial cyst reflect the location of the cyst (or cysts) and are usually slowly progressive. The diagnosis of synovial cyst is made primarily by means of radiography. Myelography is essential for precise localization of the cyst or cysts. Advanced imaging techniques, particularly CT, may further delineate the location and extent of a synovial cyst. Surgical decompression of the spinal cord and excision of the cyst appear to provide long-term resolution of clinical signs.

193.5.39 Syringomyelia and Hydromyelia

193.5.39.1 Etiology and Pathogenesis

Syringomyelia (cavitation of the spinal cord) and hydromyelia (dilatation of the central canal) result in similar signs of spinal cord dysfunction. Syringomyelia may occur secondary to hydromyelia (communicating syringomyelia) or may not communicate with the central canal (noncommunicating syringomyelia). Syringomyelia may be associated with spinal cord tumors, myelitis, meningitis, and spinal cord trauma. The cause of syringomyelia is not known, but the condition may result from venous obstruction or distention or may be due to mechanical disruption or shearing of spinal cord tissue planes.

Hydromyelia with or without syringomyelia may be idiopathic or it may be associated with congenital malformations such as myelodysplasia, meningomyelocele or hydrocephalus, or lesions resulting in obstruction of CSF flow into the spinal subarachnoid space at the foramen magnum (e.g., chronic arachnoiditis, trauma, congenital malformations, and vascular malformations).[301–304] Hydromyelia and

syringomyelia in these animals probably results from intracranial and spinal cord venous or arterial pressure changes and associated CSF pressure changes.

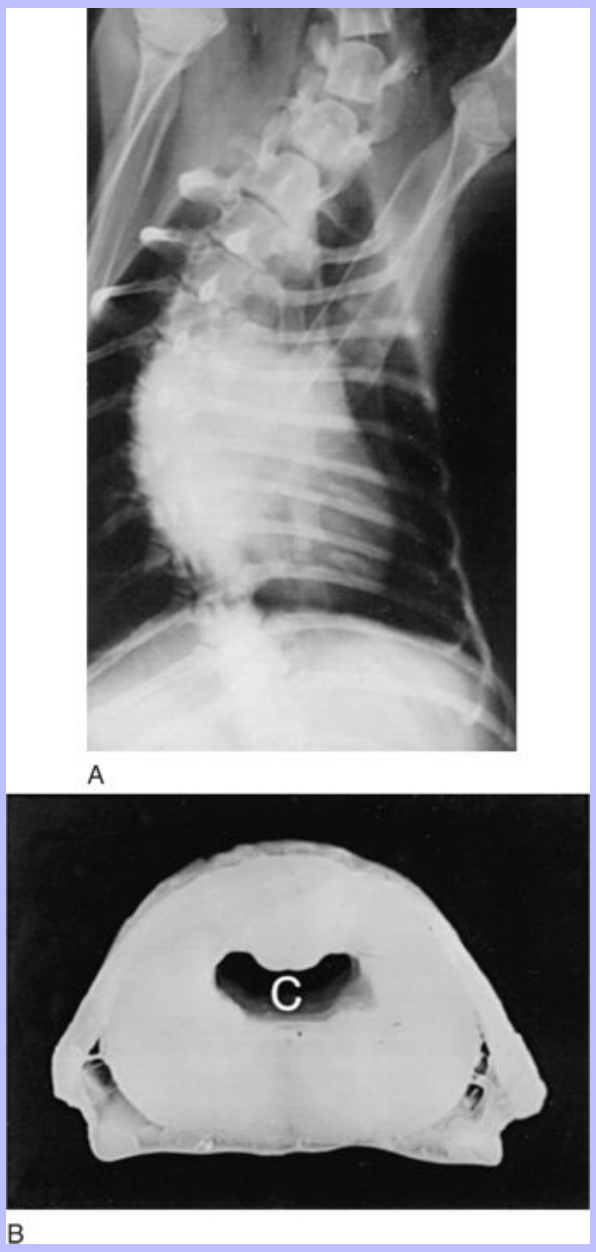
Syringomyelia in weimaraners with myelodysplasia may be the result of progressive hydromyelia, abnormalities in the central canal, or abnormal vascular patterns in local areas of the spinal cord leading to low-grade ischemia, degeneration, rarefaction, and cavitation in the spinal cord.

Regardless of the cause, cavitation may be progressive, probably along planes of structural weakness, such as the gray matter of the dorsal horns, and subsequent necrosis and edema of the spinal cord parenchyma around such a cavitation (or dilated central canal) can result in the onset and progression of clinical signs.

193.5.39.2 Clinical Findings

Clinical signs depend on the location of the lesion and whether other spinal cord lesions are present. Clinical findings include progressive spinal deformity (scoliosis, torticollis); LMN or UMN signs, depending on the location; and apparent spinal pain (Figure 193-18). Clinical signs may be acute or may be progressive over weeks to several years. In weimaraners with myelodysplasia, clinical signs do not appear to be progressive.

Figure 193-18 Hydromyelia and scoliosis. Ventrodorsal radiograph **(A)** of the caudal cervical and thoracic vertebral column of a 1-year-old female beagle. Note the scoliosis of the vertebral column. The spinal cord throughout the region of scoliosis **(B)** had an enlarged central canal *(C)* consistent with a diagnosis of hydromyelia.



193.5.39.3 Diagnosis

Myelography may show obstruction of the flow of CSF at the foramen magnum if hydromyelia or syringomyelia is due to chronic arachnoiditis or arachnoid adhesions. Cisternal puncture for the collection of CSF is contraindicated in these animals, owing to likely inadvertent puncture of the spinal cord. Lumbar CSF may show evidence of chronic inflammation. Myelographic results in other cases may be normal or may show intramedullary swelling of the spinal cord. Advanced imaging (CT or MRI) is extremely useful for identifying the location and extent of cavitary lesions of the spinal cord.[305]

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193.5.39.4 Treatment

Treatment of scoliosis in a dog after drainage of an intraspinal cystic lesion has been reported.[306] Surgical drainage of cavitary lesions in humans has resulted in improvement in some cases.

193.5.40 Vascular Malformations and Benign Vascular Tumors

193.5.40.1 Etiology and Pathogenesis

Spinal arteriovenous malformations and benign vascular tumors (hemangioma, cavernous angioma) have been reported in dogs. Arteriovenous malformations consist of one or more anomalous arteries arising from radicular arteries that drain without a capillary bed into one or more veins communicating with veins on the surface of the spinal cord, resulting in the formation of tangles of tortuous distended vessels on or in the spinal cord. These malformations may be extramedullary or intramedullary, or both. Hemangioma is regarded as a benign neoplasm of endothelium that consists of discrete masses of tangled capillaries with or without cavernous or solid areas. Multiple hemangiomas may occur. These tumors, which arise from the meninges, are predominantly extramedullary but may be intramedullary.

193.5.40.2 Clinical Findings

Arteriovenous malformations and vascular tumors may occur anywhere in the spinal canal, and clinical signs usually reflect a progressive transverse myelopathy. An acute onset or sudden worsening of clinical signs may occur as a result of hemorrhage or thrombosis associated with abnormal vasculature of the malformation or tumor. Clinical signs may be the result of spinal cord compression or ischemia.

193.5.40.3 Diagnosis

The CSF may be normal or may have an elevated protein concentration. It may be xanthochromic, and the WBC count may be mildly elevated if subarachnoid hemorrhage has occurred or if a meningeal inflammatory response is associated with tumor growth.

Myelography may show evidence of an intradural or intramedullary mass. Advanced imaging (CT or MRI) may be used to further define the lesions. Surgical biopsy is necessary to distinguish these lesions from other neoplasms, subarachnoid cysts, and other intradural and intramedullary lesions.

193.5.40.4 Treatment

Surgical removal of a vascular malformation or vascular tumor may be possible.

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194 CHAPTER • 194 Peripheral Nerve Disorders

Karen Dyer Inzana

The peripheral nervous system can be defined as those portions of the nervous system that reside partially or entirely outside the central nervous system (CNS) and are invested by a unique set of glial elements, Schwann cells, fibroblasts, and satellite cells. Using this definition, the peripheral nervous system includes cranial nerves II through XII, all of the spinal nerves with their roots, peripheral nerves, and the peripheral components of the autonomic nervous system.[1] Collectively they function to relay information about the environment to the CNS and in turn provide motor control of peripheral structures. Because peripheral nerves are the sole neural structure that controls skeletal muscle, they provide the most elemental level of motor control to the nervous system.

Structurally, peripheral nerves are collections of neuronal cell processes enveloped in fibrous connective tissue.[1] Three distinct supportive tissue sheaths (the endoneurium, the perineurium, and the epineurium) surround individual axons, fascicles of axons, or the entire peripheral nerve, respectively (see Figure 194-1). Neurons are the principle cells that make up the peripheral nerves.[1] Cell bodies are located in the brain stem and spinal cord (motor neurons) or in clusters of cells (ganglia; sensory and autonomic) located in the periphery. Cell bodies extend processes (axons) outside the nervous system, which either receive information from sensory receptors (sensory or afferent neurons) or transmit information regarding movement to peripheral muscles (motor or efferent neurons). All axons are invested with a Schwann cell covering. In most axons 1 μm in diameter, the Schwann cell also generates a myelin sheath that facilitates propagation of action potentials along the axon. Motor axons terminate on multiple skeletal muscle endplates, whereas sensory axons either terminate in secondary neurons, many of which form connections with the motor axons of the same or nearby peripheral nerves, or they continue uninterrupted to the brain stem as sensory spinal tracts.

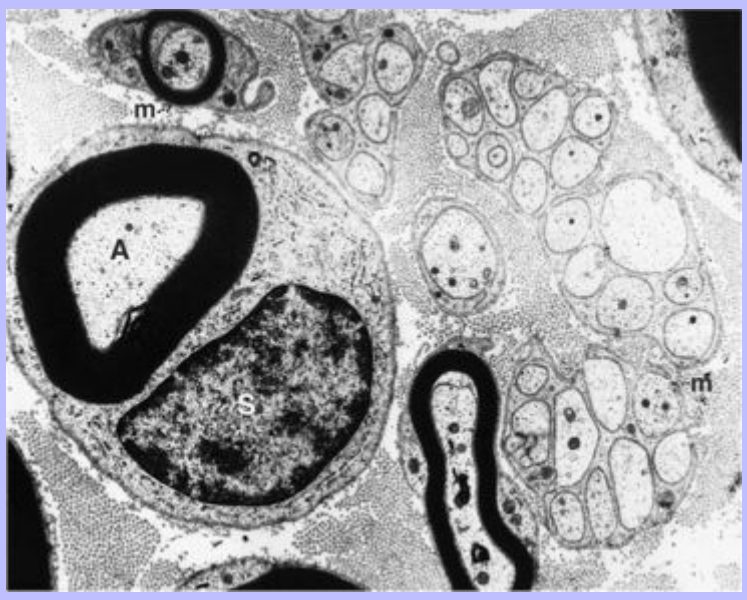
Functionally, information is transmitted along axons electrically in the form of an action potential.[1] The action potential is created by ion influxes, primarily sodium, that change the electrical gradient across the axonal cell membrane. In myelinated axons, sodium ion channels are concentrated at nodes of Ranvier and action potentials are propagated along the axon from node to node (saltatory conduction), whereas ion channels are uniformly located along the entire length of nonmyelinated axons and conduction is continuous along the cellular membrane. Information is transmitted to muscles or other neurons—most commonly chemically—by the physical release of a neurotransmitter at the axon terminal, which interacts with receptors linked to additional ion channels on the receptor surface.

194.1 METHODS OF EVALUATION

There are main methods of evaluating the peripheral nervous system: (1) clinical evaluation, (2) electrophysiological evaluation, and (3) histological evaluation. Clinically, the hallmarks of peripheral nerve disease are motor deficits ranging from weakness to paralysis, hypotonic muscles with rapid muscle atrophy, and diminished or absent spinal reflexes. Sensation may be altered if the disease process affects sensory nerves. These clinical signs may be diffuse or confined to one or more peripheral or cranial nerves. The clinical signs attributed to individual peripheral nerve or cranial nerve injury are outlined in Tables 194-1 and 194-2. Most peripheral neuropathies are “diffuse.” Weakness is often more pronounced in the pelvic limbs. With the exception of the recurrent laryngeal, hypoglossal, and vagal nerves, cranial nerves are usually only affected in more severe cases. Clinical signs of laryngeal paralysis including stridor, inspiratory dyspnea, voice change, and exercise intolerance may be an early sign of a more diffuse peripheral neuropathy.[1] Similarly, dysphagia and megaesophagus have

been associated with generalized peripheral nerve disease.[1] In rare cases where sensory nerves are affected alone, weakness is less apparent than poor coordination. Muscle atrophy is less marked, but spinal reflexes are uniformly depressed.

Figure 194-1 Electron micrograph of a peripheral nerve (×12000). Cross-sections of both myelinated (*A*) and unmyelinated (*a*) axons are present, surrounded by Schwann cell membranes (*m*). The section of the medium-sized myelinated axon in the center was taken through the Schwann cell nucleus (*S*).



Measuring the electrical activity of skeletal muscle via needle electromyography (EMG) is useful to confirm suspicions of peripheral nerve or muscle disease and to map the distribution of injury.[1] A variety of spontaneous electrical potentials may be recorded from denervated or otherwise injured skeletal muscle. These spontaneous potentials have been broken down into several characteristic potentials including fibrillation potentials, positive sharp waves, and high-frequency discharges.[1]

Because nervous tissue is electrically excitable tissue, the functional integrity of specific regions can be evaluated by measuring their ability to conduct an action potential evoked by electrical stimulus or stimulation of specific receptors. Using a combination of neuroanatomic and physiologic principles, any region of the central and peripheral nervous system can be electrophysiologically evaluated. The techniques most useful for peripheral nerve disease include motor and sensory nerve conduction, brain stem auditory evoked potentials, and occasionally spinal cord evoked potentials. These have been described in detail elsewhere.[1] Briefly, in demyelinating neuropathies, motor and sensory nerve conduction is slowed but the evoked action potential remains near normal in amplitude and duration. With axonal loss, significant reduction in nerve conduction velocity is not seen but the evoked action potential is often reduced in amplitude and prolonged. The distinction

between axon or myelin loss is not as readily apparent in central conduction studies. Instead, either conduction block or changes in the evoked potentials are simply an indication of disease.

Finally, the peripheral nervous system can be evaluated histologically without creating marked functional impairment. Muscle biopsies may be useful at distinguishing denervation from primary muscle disease. Denervated skeletal muscles develop characteristic changes of angular atrophy. By evaluating histologic types of muscle fibers in unfixed, frozen samples, both type grouping and large grouped atrophy can be useful indicators of chronicity of disease and regenerative attempts.[1] Fascicular biopsies of peripheral nerves can be obtained from both motor and sensory nerves. Briefly, the peripheral nerve to be sampled is surgically isolated, and a thin strip, less than one third the nerve diameter and extending 2 to 3 cm, is excised. Nerve samples should then be secured in a stretched position prior to fixation in 2.5% glutaraldehyde. Samples may then be sent to a laboratory that specializes in neuromuscular evaluation, where they will usually be osmicated and embedded in plastic for both light and electron microscopy. Postosmicated peripheral nerve biopsies can also be suspended in resin and individual fibers teased apart so that the pathology of successive internodes can be appreciated.[1]

194.2 MECHANISMS OF DISEASE

Because at least a portion of most peripheral nerves resides in the CNS, CNS diseases can affect them. However, this chapter concentrates on diseases unique to the peripheral nervous system and neuromuscular junction. Before considering individual diseases, it is useful to understand some of the complex interrelationships between neurons, axons, and Schwann cells that might contribute to disease processes.

The neuron is a specialized cell with an unusually large surface area that aids in recognition of synaptic inputs from adjacent cells. The neuron contains many of the typical cellular organelles, including a single nucleus, one or more nucleoli, Golgi, and mitochondria. Under most conditions the cytoplasm of neuronal cell bodies contains abundant rough endoplasmic reticulum or Nissl substance.[1] Unlike most cells, neurons must support cellular processes that often extend great distances from the cell body. Damage to a neuron results in degeneration of all of its cellular processes and dissolution of the myelin sheath produced by Schwann cells. Unlike damage to other peripheral nerve structures, regeneration is extremely limited in neuropathies.

Damage to the axon results in wallerian degeneration of all distal sections no longer in contact with the cell body. Histologically, this appears initially as dissolution of the myelin sheath with some clumping of the cytoskeletal elements and degenerating organelles within the axon. This is followed by progressive loss of axonal contents. Schwann cells survive, but peripheral nerve myelin degenerates with the axon. Complete severance of the axon and attendant wallerian degeneration is not difficult to identify histologically. More subtle lesions that result from metabolic alterations of the neuron or its ability to supply constitutive elements to the distal axon are more problematic.

Any disease process that injures the axon will cause secondary demyelination. However, examples of neuropathies exist that primarily target Schwann cells. In cross-section, myelin degeneration appears first as vacuolation, followed by separation of lamellae and finally removal of myelin debris by macrophages. This is usually associated with attempts at remyelination by surviving Schwann cells. Finding inappropriately thin myelin sheaths surrounding large axons or numerous "onion bulbs," concentric layers of Schwann cell membranes surrounding demyelinated or remyelinated axons, are indications of remyelination.[1]

Table • 194-1 Nerves of the Brachial Plexus

NERVE	SPINAL CORD SEGMENT	MUSCLES INNERVATED	SPINAL REFLEX ALTERATIONS WITH INJURY	MOTOR FUNCTION	CUTANEOUS DISTRIBUTION	CLINICAL SIGNS OF DYSFUNCTION
Suprascapular	C6–C7	Supraspinatus, infraspinatus	None	Extension and lateral support of the shoulder	None	Little gait abnormality
Axillary	C6–C8	Deltoid	No deficits or incomplete withdrawal reflex	Flexion of shoulder	Dorsolateral brachium, behind scapular spine	Little gait abnormality
Musculo-cutaneous	C6–C8	Biceps brachii	Decreased or absent biceps tendon reflex; no elbow flexion with withdrawal reflex	Flexion of elbow	Medial forelimb, medial humeral condyle	Little gait abnormality; unable to raise paw to table top (flex elbow)
Radial	C6–T2	Triceps brachii, extensor carpi radialis, ulnaris lateralis common and lateral digital extensors	Decreased or absent triceps tendon reflex and extensor carpi radialis response	Extension of elbow, carpus, and digits	Dorsolateral forelimb, dorsal surface of paw	Loss of weight bearing; unable to fix limb in extension
Median and ulnar	C8–T2	Flexor carpi radialis, superficial digital and deep digital flexors, flexor carpi ulnaris	Decreased or absent flexion of carpus and digits during withdrawal reflex	Flexion of carpus and digits	Palmar surface of paw, caudal forelimb	Little gait abnormality
Nerves of the Pelvic Plexus						
Obturator	L4–L6	Pectineus, gracilis	None	Adduction of pelvic limb	None	Little gait abnormality; limb may slide laterally on slick floor
Femoral	L3–L6	Quadratus femoris	Decreased or absent patellar reflex	Extension of stifle	Saphenous branch supplies medial thigh and digit	Inability to extend stifle
Sciatic	L6–S3	Gluteus semimem-branosus semitendinosus, all muscles innervated by peroneal and tibial nerves	Decreased or absent withdrawal reflex	Flexion and extension of hip	Caudal and lateral surfaces of limb	Cannot flex or extend digits and hock or flex stifle
Peroneal	L6–S3	Peroneus longus, cranial tibial, lateral and long digital extensor	Decreased or absent cranial tibial response	Flexion of hock extension of digits	Dorsal aspect of paw, hock and distal limb	Cannot extend paw (therefore knuckles on dorsum), poor hock flexion
Tibial	L6–S3	Gastrocnemius, superficial and deep digital flexors	Decreased or absent gastrocnemius tendon reflex	Extension of hock, flexion of paw	Plantar surface of paw	Unable to fix hock in extension

Table • 194-2 Cranial Nerves

CRANIAL NERVE	ANATOMIC COURSE	FUNCTION	EVALUATION
CN I: olfactory	Sensory ending in nasal mucosa, entercribriform plate to olfactory bulb ofpyriform cortex	Smell	Not routinely evaluated
CN II: optic	Retinal ganglion cells form optic nervethat traverses optic foramen to opticchiasm and optic tracts in diencephalons	Vision and pupillarylight reflexes (PLRs)	Menace reaction, PLRs, avoids objects
CN III: oculomotor	Cell bodies in mesencephalon sendprocesses through the orbital fissureto extraocular eye muscles and iris	Motor to extraoculareye muscles, parasympathetic to eye	Eye movement, PLRs; damage causesventrolateral strabismusand mydriasis
CN IV: trochlear	Cell bodies in mesencephalon; processescross in rostral medullary velum andpass through orbital fissure toextraocular eye muscles	Motor to dorsal obliquemuscle that rotates globe	Not routinely tested in dogs; damage causes rotationaldeviation of globe
CN V: trigeminal	Motor bodies in metencephalon; sensory cell bodies in trigeminalganglion terminate on metencephalicneurons; axons divide in to mandibular, maxillary, and ophthalmic branchesthat pass through oval foramen, around foramen, and orbitalfissure respectively	Motor to muscles ofmastication includingmasseter, temporal, pterygoids, rostraldigastricus, and myohyoidsensory to the face	Jaw tone, masticatorymuscle mass, sensationto face
CN VI: abducent	Cell bodies in metencephalon; have a long intracranial course toexit the orbital fissure to eye	Motor to extraocular eyemuscles including lateralrecturs and retractor bulbi	Eye movement; damagecauses ventromedialstrabismus
CN VII: facial	Cell bodies in myelencephalon; passthrough internal acoustic meatusand petrous temporal bone tostylomastoid foramen	Motor to muscles of facialexpression; sensory tosmall area of pinna; parasympatheticinnervation to lacrimalglands, mandibular andsublingual salivary glands	Ability to blink, retract lip, move ear, produce tears
CN VIII: vestibulocochlear	Sensory neurons arise fromreceptors in inner ear, traverse internal acousticmeatus to myelencephalon	Balance, linearacceleration, hearing	Body posture, eyemovement, hearing; damage causespositional strabismusand nystagmus
CN XI: glossopharyngeal	Cell bodies in myelencephalon exitexternal jugular foramen	Sensory and motor to thepharynx; parasympatheticinnervation to zygomaticand parotid salivary glands	Gag reflex, swallowing
CN X: vagus	Cell bodies in myelencephalonexit external jugular foramen	Sensory and motor topharynx; parasympathetic tocardiac, pulmonary, and gastrointestinal(GI) systems	Gag reflex, swallowing, oculocardiac reflex

CN XI: accessory	Cell bodies in myelencephalon androstral spinal cord exit externaljugular foramen	Motor to larynx, trapezius, andsternobrachiocephalicus	Vocalization, muscle tone
CN XII: hypoglossal	Cell bodies in myelencephalon exithypoglossal canal	Motor to tongue muscles	Tongue movement

194.2.1 Developmental and Congenital Disorders

Developmental and congenital disorders are peripheral neuropathies that occur in specific breeds with a predictable clinical course and characteristic pathology. A genetic basis is likely. The age of onset, specific clinical signs, and rate of progression varies from disease to disease. Because these disorders are, together, quite rare, the names and brief descriptions are listed in Table 194-3. More complete descriptions are available in neurology textbooks.

194.2.2 Metabolic and Toxic Disorders

194.2.2.1 Diabetes Mellitus

Diabetic neuropathy represents one of the most significant late complications of diabetes mellitus in human beings. The reported incidence in human diabetic populations varies with diagnostic criteria but ranges from 5% to 100%.[1] Although similar incidence statistics have not been reported in animals, a casual relationship between diabetes mellitus and peripheral nerve disease has been identified in dogs and cats as well. In dogs the neuropathy is usually subclinical.[1] In cats clinical signs are much more common.[1] Diabetic cats may develop a plantigrade stance, pelvic limb weakness, muscle wasting, and depressed myotatic reflexes. Electrodiagnostic abnormalities in some cats consists of spontaneous activity in skeletal muscle and slowed nerve conduction with smaller evoked muscle responses suggestive of an axonal neuropathy. In others a relative paucity of abnormal muscle activity with slowed nerve conduction or conduction block suggests demyelination may be more prominent.[23,24]

Pathologic findings are equally mixed. Some have described a loss of axons in distal nerves similar to distal sensorimotor axonal neuropathy in human diabetic patients.[1] Others have focused on changes in Schwann cell structure and suggested that some cases of diabetic neuropathy result from primary Schwann cell injury and demyelination.[24–27] Recently, significant changes in perineural thickness caused by perineural cell hyperplasia, basement membrane thickening, and increased interlamellar space was described in dogs with diabetes mellitus, whereas another study found thickening of endoneurial capillary basement membrane along with an increase in endoneurial capillary density and luminal area.[28,29] These findings suggest that the pathogenesis of diabetic neuropathy, regardless of the primary neural target, includes compression of endoneurial structures by a nondistensible perineurium, alterations in the nerve and blood barrier, and changes in vascular perfusion.

A number of metabolic derangements are thought to be involved, including increased aldose reductase activity leading to the accumulation of sorbitol and fructose, increased production and decreased scavenging of reactive oxygen species leading to cellular oxidative stress and impaired mitochondrial function, together with activation of protein kinase C, which promotes vasoconstriction and nerve ischemia. Altered protein synthesis and delayed axonal transport of molecules necessary to maintain distal axonal segments, together with immunologic mechanisms, may also play a role.

194.2.2.2 Hypothyroidism

The frequent association between hypothyroidism and a vast array of neurologic symptoms has lead to a casual association between the two conditions. Despite hypothyroidism being one of the most widely recognized causes of neuromuscular disease in both man and animals, it remains one of the least well characterized.

The most common neurologic problem described is paresis. This varied from monoparesis to hemiparesis to quadriparesis, with an equally variable onset and rate of progression. Cranial neuropathies are the second most common disorder with the facial, vestibulocochlear, and trigeminal nerves appearing most susceptible. Megaesophagus and laryngeal paralysis are also possible in dogs with hypothyroidism. Whether these are manifestations of a more generalized neuromuscular disorder or represent a unique form of the disease is unclear. Electrophysiologic evidence of a generalized neuropathy including spontaneous activity in all limb muscles and slowed nerve conduction velocities has been found. In addition, brain stem auditory evoked potentials are often reduced in amplitude and have prolonged latencies.[1]

In human patients and experimental models, hypothyroidism has been associated with both Schwann cell and primary axonal injury, with glycogen aggregates occurring in the cytoplasm of both cells.[1] Remaining axons often appear to have shrunken axons with inappropriately thick myelin sheaths, suggesting that axonal atrophy may be a feature of the neuropathy in some cases.

194.2.2.3 Botulism

Botulism in an acute, rapidly progressive, generalized lower motor neuron (LMN) paralysis that results from ingestion of the exotoxin produced by *Clostridium botulinum*.[1] *C. botulinum* is a saprophytic soil organism with a worldwide distribution. Under anaerobic conditions the toxin is elaborated from both vegetative cells and, to a lesser extent, spores. Although eight antigentically different types of botulinum neurotoxins have been identified; most cases of botulism in dogs are caused by type C.[1]

Clinical signs may begin within hours of toxin ingestion or may be delayed for up to 6 days. The severity of signs varies with both the amount and potency of toxin ingested, as well the susceptibility of the individual animal. Most often, clinical signs begin as an ascending paralysis in the rear limbs preceding forelimb involvement. In severe cases, complete flaccid paralysis is accompanied by weakness of facial, pharyngeal, and esophageal musculature.

Electrophysical changes characteristic of botulism include a marked reduction in the amplitude of the muscle action potential evoked by electrical stimulation of a motor nerve, whereas motor conduction velocities are normal or only mildly reduced. EMG is usually normal. The diagnosis of botulism is confirmed by identifying toxin in the food, serum, stomach contents, or feces. A mouse neutralization is available. By injecting toxin alone and in combination with specific antitoxins, both the type and potency of the botulinum toxin can be identified. Radioimmunoassay, enzyme-linked immunosorbent assay (ELISA), and passive hemagglutinations tests have been developed that will evaluate the toxin and type but do not evaluate potency. Recovery of *C. botulinum* from fecal culture is also presumptive evidence of intoxication because the organism rarely colonizes the normal canine intestine.

Pathophysically, ingested toxin is absorbed from the gastrointestinal (GI) tract and is transported to cholinergic nerve terminals. The toxin binds to presynaptic terminals, is internalized, and then blocks

acetylcholine release, presumably by inhibition of calcium ion increases necessary for transmitter release. Recovery usually occurs in 2 to 3 weeks, after regrowth of terminal motor branches. Because most animals recover within weeks, treatment is largely supportive. Antibiotics should only be used to treat secondary infections because they may facilitate intestinal colonization of *C. botulinum* by altering the normal GI flora. An antitoxin is available and should either be a polyvalent antitoxin or specific for type C. Antitoxin is not effective after the toxin has entered nerve terminals; therefore it will only halt the progression of the disease and not reverse clinical signs. Recommended antitoxin dose is 10,000 to 15,000 U, intravenously or intramuscularly administered twice at 4-hour intervals. Anaphylaxis is possible, so a test injection of 0.1 mL interdermally 20 minutes prior to antitoxin administration is advisable.

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Table • 194-3 Developmental/Congenital Disorders in Dogs and Cats Involving the Peripheral Nervous System

SPECIFIC NEUROPATHY, BREED AFFECTED, AND REFERENCE(S) CITED	INITIAL SIGNS	HISTOLOGY
Loss of Motor Neurons		
Progressive neuropathy in Cairn terriers[1]	Rear limb weakness	Central and peripheral chromatolysis
Focal spinal muscular atrophy in German shepherd dogs[1]	Forelimb weakness	Asymmetrical degeneration of somatic motor neurons
Hereditary progressive spinal muscle atrophy in English pointers[1]	Generalized weakness	Chronic denervation
Spinal muscular atrophy in rottweilers[1]	Regurgitation and generalized weakness	Central chromatolysis and marked cell body swelling
Neuronal abiotrophy in Swedish Lapland dogs[1]	Weakness to tetraplegia	Neuronal degeneration and central and peripheral chromatolysis
Spinal muscle atrophy in Brittany spaniels[2,3]	Weakness to tetraplegia	Neuronal chromatolysis and proximal axonal swelling
Loss of Peripheral Axons		
Giant axonal neuropathy in Alsatians[1]	Rear limb weakness	Swelling in axons
Peripheral neuropathy in aged German shepherds[1]	Rear limb weakness	Endoneural fibrosis
Hereditary polyneuropathy in Alaskan malamutes[1]	Rear limb weakness	Demyelination of axons
Idiopathic polyneuropathy in Alaskan malamutes[1]	Rear limb weakness and hyperesthesia	Axonal degeneration
Neuropathy in Birman cats[1]	Rear limb weakness and hypermetria	Loss of myelinated fibers
Polyneuropathy in rottweiler dogs[1]	Paraparesis then tetraparesis	Degeneration of peripheral nerves
Progressive axonopathy in boxer dogs[1]	Rear limb weakness	Mild axonal swellings
Laryngeal paralysis-polyneuropathy in dalmatians and rottweilers[1,4]	Respiratory distress and syncope	Peripheral neuronal degeneration
Schwann Cell Dysfunction		
Hypomyelinating neuropathy in golden retrievers[1]	Rear limb weakness	Hypomyelination and elevated Schwann cell cytoplasm
Hypertrophic neuropathy in Tibetan mastiffs[1]	Tetraparesis	Extensive demyelination
Loss of Sensory Neuron or Axon and Laryngeal Nerves		
Sensory neuropathy in long-haired dachshunds[1]	Abnormal rear limb abduction	Distal loss of sensory nerve fibers
Acryl mutilation in English pointers and shorthaired pointers[1]	Biting paws to severe self-damage	Lowered number of ganglionic cell bodies
Laryngeal paralysis in Bouvier des Flanders[1]	Inspiratory stridor and dyspnea	Axonal degeneration
Laryngeal paralysis in Siberian huskies[1]	Inspiratory stridor and dyspnea	Neuronal loss
Inborn Errors in Metabolism		
Hyperchylomicronemia in cats[1,5–8]	Horner's syndrome tibial/radial nerve compression	–
Hyperoxaluria type 2 in domestic shorthaired cats[1,9–11]	Acute renal failure	–
α-L-fucosidosis in English springer spaniels[1,12–18]	Behavior changes and generalized ataxia	Neuronal infiltration with macrophages

Atypical GM2 gangliosidosis in cats[1]	CNS dysfunction	Wallerian degeneration of peripheral axons, lamellar inclusions of Schwann cells
Globoid cell leukodystrophy[1,19,20]	Paraparesis and/or cerebellar signs	Axonal degeneration
Neiman-Pick disease in Siamese cats[1]	Tetraparesis and hypotonia	Marked demyelination; vacuolated and granular nerve distention
Glycogen storage disease IV in Norwegian forest cats[1,21,22]	Hyperthermia, tremors, ataxia	Peripheral asymmetrical Schwann cell accumulations throughout nervous tissue

194.2.2.4 Tick Paralysis

Tick paralysis is an acute, rapidly progressive generalized LMN paralysis caused by a salivary neurotoxin produced by ticks.[1] Adult female *Dermacentor andersoni* (the Rocky Mountain wood tick) and *D. variabilis* (the American dog tick) are most often incriminated in North America, whereas *Ixodes holocyclus* is most often incriminated in Australia. Adult females, nymphs, and larvae of *Ixodes* ticks may produce the neurotoxin. Although additional sites of neuronal dysfunction may result from intoxication, the predominate clinical signs are produced by inhibition of acetylcholine release from motor nerve terminals.

In the United States, clinical signs are restricted to dogs. Cats are also susceptible to the effects of *Ixodes* neurotoxin in Australia and have similar clinical signs. In most cases, rear limb weakness begins 5 to 7 days after tick attachment. This is rapidly followed by generalized weakness and eventually complete flaccid paralysis and areflexia within 24 to 72 hours. Cranial nerves, especially the facial nerve, may be mildly affected by the *Dermacentor* neurotoxin, but pain sensation is preserved and the animals do not appear hyperpathic. In contrast, *Ixodes* neurotoxin causes more profound signs of facial paralysis, dysphagia, and megaesophagus. Autonomic signs include mydriasis with loss of pupillary light reflex (PLR), peripheral vasoconstriction and arterial hypertension, pulmonary hypertension and edema, and either tachycardia or bradycardia. Failure to diagnose tick paralysis can result in death from respiratory paralysis within days.

Electrodiagnostic changes are similar in both forms of tick paralysis. EMG is usually normal. The evoked muscle action potential is reduced in amplitude or nonexistent, and mild slowing of both motor and sensory nerve conduction velocities occurs.[1] The diagnosis is made by exclusion of other causes of rapidly progressive generalized LMN paralysis (i.e., botulism, acute polyradiculoneuritis, myasthenia gravis [MG]) and response to tick removal. Clinical signs improve within 24 hours after *Dermacentor* tick removal, and the animals are usually normal within 48 hours. In Australia, clinical signs may progress for 24 to 48 hours after tick removal.

Table • 194-4 Toxic Neuropathies Recognized in Dogs and Cats

COMPOUND	SUCCEPTABLE SPECIES	PATHOLOGY
Vincristine	Dogs and cats	Distal axonopathy, loss of neurotubules with neurofilamentous accumulations in axons
Pyridoxine	Dogs	Neuronal loss in sensory, dorsal root ganglia, and trigeminal ganglia
Mercury	Dogs and cats	Neuronal loss in sensory, dorsal root ganglia, and trigeminal ganglia
Thallium	Dogs and cats	Gastrointestinal (GI) irritation, skin lesions, neuronal loss in cerebrum, cerebellum, and sensory ganglia
Lead	Dogs and cats	Central nervous system (CNS) signs predominate, rare megaesophagus; Schwann cell pathology in other species
Organophosphates	Cats (experimental)	Distal axonopathy with tubovesicular profiles in axons
Acrylamide	Cats and dogs (experimental)	Distal axonopathy with neurofilament accumulation in axons
Hexacarbons	Cats (experimental)	Distal axonopathy with giant neurofilamentous axonal swellings
Lasalocid	Dogs	Pathology not described; dogs recovered in 2–50 days.

Administration of canine hyperimmune serum at 0.5 to 1 mL/kg intravenously has been recommended to bind circulating neurotoxin and prevent further progression. Because the only available hyperimmune serum is derived from dogs, cats should be pretreated with 30 mg/kg hydrocortisone, and epinephrine (1 mL of a 1:10,000 solution) should be available to counteract anaphylaxis. Autonomic dysfunction may be improved by administration of a combination of phenoxybenzamine hydrochloride 1 mg/kg as a 0.1% solution administered intravenously over 15 minutes every 12 to 24 hours and acepromazine 0.05 to 0.10 mg/kg intravenously every 6 to 12 hours. Oxygen therapy and respiratory support may be necessary for severely affected cases. Dogs are susceptible to repeat bouts of tick paralysis. Even though an immune response develops against *Ixodes* neurotoxin, it has only a limited duration. Vaccines are currently unavailable, so minimizing tick infestation is the best method of prevention.

194.2.2.5 Miscellaneous Toxins

The nervous system is the target of a tremendous number of toxic compounds. The list of drugs, metals, and other environmental chemicals that have been associated with peripheral neuropathy in humans is lengthy.[1] Unfortunately the clinical significance of most of these agents in veterinary medicine is uncertain. Far fewer documented toxic peripheral neuropathies exist in dogs and cats than in human beings. Potential explanations for this observation include difficulty in identifying toxin exposure without critical historical information and difficulty in identifying subtle signs of sensory deficits, weakness, or both in veterinary patients. Without overt clinical signs, a cause-and-effect relationship between chemical exposure and disease may be difficult to ascertain. Finally, clear differences exist in species susceptibility to recognized toxins. Toxin exposure should be considered for any animal with an undiagnosed peripheral nerve disease. The National Animal Poison Control Center (1-900-680-0000) can provide valuable information regarding any suspicious exposure. Some of the recognized neurotoxicants that affect the peripheral nervous system in dogs and cats are listed in Table 194-4.

194.2.3 Inflammatory and Immune-Mediated Neuropathies

194.2.3.1 Acute Polyradiculoneuritis (Coonhound Paralysis)

Acute polyradiculoneuritis is a common neuropathy affecting primarily dogs and occasionally cats.[1] The syndrome was first described in 1954 as an acute, rapidly progressive paralysis that occurred in dogs 7 to 10 days after contact with a raccoon.[1] An identical syndrome has subsequently been described in dogs and cats with no known exposure to raccoons.[1] The syndrome was originally named *coonhound paralysis* to reflect the association between raccoons and paralysis. However, the recognition of additional cases suggests the broader term *acute polyradiculoneuritis* better reflects the full spectrum of the disease.

Clinical signs of generalized weakness typically begin in the pelvic limbs and progress in an ascending fashion to involve thoracic limbs. In severe cases, cranial nerves and respiratory muscles may be affected as well. Even animals severely affected often retain voluntary tail movement and voluntary control of urination and defecation. Sensory function is likewise preserved, and many animals seem unusually sensitive to mild stimulation indicating generalized hyperpathia. In rare cases, the thoracic limbs may be affected first or preferentially. Clinical signs may progressively worsen for up to 10 days after the onset of signs and then plateau. The severity of motor deficits once the plateau is reached varies from mild weakness to complete flaccid paralysis, areflexia, and respiratory paralysis. Remission may begin as early as 1 week after the onset of clinical signs or may be delayed for several months. Complete recovery may take several months and is often incomplete. Some animals do not improve within the period that supportive care is tenable. Unfortunately no reliable prognostic criteria exist by which clinicians can gauge the probable speed or degree of functional recovery of individual cases.

Despite the fact that polyradiculoneuritis is a well-recognized syndrome, definitive diagnosis is not always straightforward. History of raccoon exposure shortly before the onset of clinical signs is helpful, but as previously mentioned, not present in all cases. Abnormal spontaneous activity is usually detected with needle EMG 5 to 7 days after the onset of clinical signs. Motor nerve conduction is typically slowed at about the same time that EMG changes are present, and the muscle action potential is often dispersed, indicating both demyelination and axonal injury. Small motor potentials produced by orthodromic conduction of evoked motor action potentials to the cell body and then back to the muscle (F wave) are often delayed or absent, reflecting injury to ventral nerve roots.[1] Increased protein without an increase in white blood cells (WBCs) (albuminocytologic dissociation) is typically found in lumbar cerebrospinal fluid (CSF) but not fluid collected from the cisterna magna. This protein appears to be albumin rather than immunoglobulins and probably arises from transudation across the blood-brain barrier.[30]

Histologically, all regions of peripheral nerves have signs of injury, but lesions are usually concentrated in ventral roots. Demyelination and inflammatory cell infiltration is the predominant finding, with more variable degrees of axonal degeneration accompanying the inflammation. The pathogenesis of the diseases is uncertain. However, an antigenic stimulus in raccoon saliva is thought to stimulate an immune reaction against peripheral nerve myelin. The source of antigenic stimulation in animals without raccoon exposure is unknown but may be viral, toxic, or infections in origin. In an attempt to find potential triggers, serum from affected dogs was evaluated for antibody titers to a number of infectious agents. Affected dogs did have significantly higher titers to *Toxoplasma gondii* than controls, but a causal relationship is not clear.[31] Similarly, antibody titers to *Campylobacter jejuni* were not significantly different between affected and control animals. Therefore the inciting agent in cases without raccoon exposure remains to be identified. An

immune basis for this syndrome is supported by several factors. Epidemiologic evidence indicates that not all dogs bitten by the same raccoon are affected. Once affected, repeated episodes can be precipitated in the same animal by raccoon exposure or injections of raccoon saliva. These two observations indicate that disease is associated with an idiosyncratic response in some dogs. Dogs with an acute onset of clinical signs shortly after a known raccoon exposure have antibodies against an antigen in raccoon saliva.[1] Histologically, demyelination can occur in regions without inflammatory cells suggesting antibody-mediated damage in some instances. Finally, the disease shares many clinical and histopathologic features with human Guillain-Barre syndrome, an immune-mediated radicuoneuropathy.

Therapy for this disease is largely supportive. Despite the probable immune-mediated cause, immunosuppressive therapy usually increases the incidence of secondary infections and muscle atrophy. Plasmapheresis has become standard in human beings with Guillain-Barré syndrome. Unfortunately, this is not widely available for animals.

194.2.3.2 Chronic (Relapsing) Demyelinating Neuropathy and Acquired Demyelinating Neuropathy

A generalized polyneuropathy that follows a remitting and relapsing clinical course has been identified in male and female dogs and cats of various breeds.[1] Clinical signs may be acute or chronic in onset and are often asymmetrical in distribution. In most cases, an overall progressive course of generalized weakness, areflexia, and diffuse muscle atrophy is interrupted by spontaneous periods of partial remission. Cranial nerves may be affected as well.

Electrophysiologic changes consist of variable degrees of spontaneous activity in limb muscles and marked slowing of nerve conduction velocities with more variable degrees of attenuation of the evoked response. These findings are most suggestive of a demyelinating neuropathy. Cerebrospinal analysis reveals increased protein concentrations without concomitant pleocytosis (albuminocytologic dissociation). Muscle biopsies contain changes characteristic of denervation, whereas primary demyelination with remyelination is seen in peripheral nerves. Variable degrees of mononuclear cell infiltrates are found in both peripheral nerves and nerve roots. The inflammatory response varies markedly between nerves and probably varies with stage of the disease process. Macrophages, monocytes, and lymphocytes are associated with prominent primary demyelination and remyelination. Redundant Schwann cell membranes form concentric layers around nerve fibers (onion bulbs are prominent in some cases, indicating repetitive cycles of demyelination and remyelination). Lesser degrees of axonal necrosis are also present in peripheral nerves, suggesting that axonal injury occurred as a consequence of the inflammatory reaction against peripheral nerve myelin. Immunosuppressive doses of prednisolone (2 mg/kg orally every 12 hours) resulted in reversal of clinical signs in some cases within weeks of therapy.[1,32] Prednisolone may be tapered after 6 or 8 months, but some cases require additional cycles of therapy. Rare cases are resistant to therapy and follow a progressive course.[1] The pathogenesis of the neuropathy in all cases remains unknown. Based on histologic appearance of an inflammatory response against peripheral nerve myelin and the response to immunosuppressive therapy, an immune-mediated cause is likely.

194.2.3.3 Brachial Plexus Neuritis

Brachial plexus neuritis is an inflammatory neuritis involving primarily the ventral branches of spinal nerves that give rise to the brachial plexus. This rare condition has been reported in two unrelated dogs and a single cat.[1] Clinical signs consisted of an acute onset of flaccid paralysis in the thoracic limbs only, with

diminished or absent spinal reflexes. Sensory nerves may be affected as well, causing anesthesia of the distal limb. Electrophysiologic changes were confined to the affected limbs. Spontaneous activity suggested denervation in limb muscles, whereas nerve conduction studies were mildly slowed with a reduced or small nerve action potential. CSF was evaluated only in the dogs and was normal. Clinical recovery occurred in the cat and one dog between 4 days and 4 months respectively.[1] No improvement was noted in the remaining dog 45 days after the onset of clinical signs.[1] In the dog that was euthanized, axonal degeneration appeared concentrated in ventral branches of spinal nerves with wallerian degeneration and mast cell infiltration present in most peripheral nerves in the thoracic limbs. More proximal portions of axons in ventral nerve roots were spared, and the disease process appeared mildly asymmetrical between left and right brachial plexi. Retrograde sensory degeneration and chromatolysis in motor and sensory neurons was the only change noted in the CNS. The cause of the condition is unknown.

194.2.3.4 Sensory Ganglioneuritis

Sensory ganglioneuritis is a poorly defined sensory neuropathy that has been reported in young adult dogs of various breeds.[1,33] The onset of clinical signs maybe subacute, acute, or chronic, with an equally variable rate of progression. Initial signs consist of rear limb ataxia that progresses over weeks or months to generalized ataxia. Facial hypalgesia, dysphagia, and regurgitation secondary to megaesophagus have been seen in some cases. A characteristic feature of the syndrome is preservation of limb muscle mass, strength, and tone, but diminished to absent proprioception and tendon reflexes. Withdrawal reflex is usually intact and most have some preservation of nocioception. Less frequent findings in some of these dogs include self-mutilation and masticatory muscle atrophy.

Electrophysiologically, needle EMG and motor conduction velocity is either normal or only mildly abnormal. However, sensory nerve conduction is usually not recordable. CSF is typically normal or may show mild increases in protein and WBC count. Axonal atrophy of large-diameter fibers is found in biopsy material from a mixed or sensory nerve.

The pathology of this syndrome is characterized by a nonsuppurative inflammation of dorsal root ganglia and cranial sensory ganglia with loss of sensory neuronal cell bodies. A concomitant loss occurs of larger-diameter fibers corresponding to sensory axons involved in proprioception and stretch reflexes in both peripheral nerves and sensory tracts in the spinal cord. The masticatory muscle atrophy reported in a few dogs was attributed to the loss of motor fibers as they coursed through the trigeminal ganglion. The cause is unknown, but immune-mediated, toxic, and viral causes have been considered. Similar clinical and pathologic changes can be produced by number of toxins including mercury intoxication, pyridoxine (vitamin B_6) excess, and doxorubicin. No treatment exists for the condition, and recovery has not been reported.

194.2.3.5 Myasthenia Gravis

MG is a disorder characterized by inefficient neuromuscular transmission secondary to a reduction in acetylcholine receptors on the postsynaptic muscle membrane. Two forms of the disease are recognized in dogs and cats: (1) congenital and (2) acquired. In congenital MG, the deficiency in acetylcholine receptors has been attributed to reduced or imperfect synthesis, probably secondary to a genetic defect. In acquired myasthenia, antibodies, usually immunoglobulin G (IgG), are generated against acetylcholine receptors. These autoantibodies block neuromuscular transmission either by directly interfering with the actions of

acetylcholine on receptors, accelerating the normal turnover rate of receptors, or activation of compliment-mediated lysis of the postsynaptic membrane.[1]

Acquired MG is the most common form of the disease. An increased risk has been identified in Akitas, various terriers, German shorthaired pointers, and Chihuahuas, whereas rottweilers, Doberman pinschers, dalmatians, and Jack Russell terriers have lower relative risks compared with mixed-breed dogs. Despite these statistics, German shepherds, and Labrador and golden retrievers are the breeds most commonly diagnosed with the disease.[1] Abyssinians and Somalis appear over-represented in cats.[34] Two age groups appear most susceptible in dogs (2 to 3 years of age; >9 years of age). Cats can be affected at any age.

Myasthenia involves a spectrum of clinical signs that vary in both distribution and severity of muscle involvement. Three major categories have been identified in dogs: (1) focal, (2) chronic generalized, and (3) acute fulminant generalized.[1] The focal form occurs in approximately 36% of recognized cases and consists of variable degrees of facial, pharyngeal, laryngeal, and esophageal dysfunction. Subclinical evidence of appendicular muscle involvement has been demonstrated in some focal myasthenics. The two generalized forms are distinguished primarily by the rate with which clinical signs develop. Twenty-five percent of dogs with generalized neuromuscular weakness have acute, fulminate clinical signs that result in nonambulatory tetraparesis and severe dyspnea within 72 hours, whereas the remaining 39% will exhibit a more chronic onset and gradual progression of clinical signs. Studies indicate that not all dogs with generalized weakness worsen with exercise, and weakness may appear concentrated in pelvic limbs. It is important to note that about 90% of dogs with generalized myasthenia also have megaesophagus.[1] Chronic regurgitation and aspiration pneumonia is a common complication. The incidence of megaesophagus is lower in cats, most likely because of the different distributions of skeletal muscle in the feline versus the canine esophagus. However, both generalized and focal forms are present in cats.[34] Thymomas are much more common in feline myasthenics, and methimazole treatment appears to be a predisposing factor.

Currently the primary criteria for diagnosis of all forms of acquired myasthenia in both dogs and cats is demonstrating serum antibodies that react with α-bungarotoxin extracted acetylcholine receptors.[35] This test is readily available and appears to be specific for MG. Sensitivity of this test is difficult to evaluate; however, approximately 15% of suspected myasthenics are seronegative for acetylcholine receptor antibodies, yet they have immune complexes localized to endplates in their muscle biopsy samples or antibodies in the serum that bind the postsynaptic membrane of normal muscle.[1] Explanations for these apparent false-negative serum tests are speculative but may be caused by the production of high-affinity antibodies that are largely bound and not free in serum. Alternatively, antibodies may be directed to additional antigens on muscle membranes other than those recognized by α-bungarotoxin. Antibodies to the muscle protein titin and a calcium channel receptor ryanodine (RyR) have recently been identified in myasthenic dogs, and these may also play a significant role in the severity of muscle weakness seen in some cases.[36]

Additional supportive evidence for the diagnosis of myasthenia can be made by the demonstration of increased muscle strength after administration of the short-acting acetylcholinesterase agent edrophonium chloride (Tensilon) or by finding a decrementing evoked muscle response after repetitive nerve stimulation. Recommended doses of Tensilon are 0.1 to 0.2 mg/kg intravenously and should cause temporary improvement in clinical signs within minutes. Esophageal musculature does not respond to Tensilon, limiting the usefulness of this test in focal myasthenics. Similarly, a large percentage of myasthenics will have a decrementing response after repetitive motor nerve stimulation that will be blocked by Tensilon administration. Both false-positive and false-negative results occur with both of these tests, so they should be

used for supportive evidence only. Recently the canine nicotinic acetylcholine receptor alpha subunit gene has been cloned and an ELISA developed to identify dogs with circulating antibodies to this receptor.[37] Sensitivity and specificity of this test is not yet known.

Treatment is directed toward amelioration of generalized muscle weakness with longer-acting anticholinesterase agents that prolong the interaction of acetylcholine with any available receptors. Pyridostigmine bromide (Mesthinon, Roche Laboratories) may be given at 1 to 3 mg/kg every 8 to 12 hours in dogs and cats. Therapy should begin at the low end of the scale and gradually increase to desired effect. Alternatively, injectable neostigmine (Prostigmin, Roche Laboratories) has been recommended at a dose of 0.04 mg/kg every 6 hours intramuscularly to bypass the problem of oral administration of medication in regurgitating pets. Esophageal motility is minimally affected by anticholinesterase therapy. Immunosuppressive therapy is controversial. Many animals can be adequately controlled with anticholinesterases, lessening potential complications of immunosuppression in pets with aspiration pneumonia. In a recent review, 47 of 53 dogs treated only with anticholinesterase therapy developed spontaneous remissions within an average of 6.4 months.[38] However, immunosuppressive therapy increased the probability of patient survival in one study and has been used successfully to shorten the course of disease in others.[1] The best advice is to tailor drug therapy to each individual patient while providing supportive care. If corticosteroids are used, current recommendations are to begin with an anti-inflammatory dose and gradually increase to an immunosuppressive dose over 3 to 4 weeks.

Most myasthenics die from aspiration pneumonia. Clinicians and owners can reduce the risk of aspiration pneumonia by feeding in an upright position and holding the animals in an elevated position for 5 to 10 minutes after feeding. Percutaneous gastrostomy has been recommended for alimentary support but will not prevent the occurrence of aspiration pneumonia. Pneumonia may require additional therapy such as antibiotics and oxygen supplementation. Several drugs (e.g., aminoglycoside antibiotics, antiarrhythmic agents, phenothiazines, methoxyflurane, and magnesium) may reduce the efficiency of neuromuscular transmission and worsen clinical signs in myasthenics. Therefore additional drugs should be used with caution.

A simple correlation between acetylcholine receptor antibody and severity and distribution of clinical signs does not exist in dogs with MG. However, clinicians can monitor the course of the disease by evaluating serum acetylcholine receptor antibodies. Spontaneous remission occurs and the antibody titer will decrease as the animal goes into remission. Duration of the disease varies from months to years, and recurrence is possible.[35] One of the most important, yet unanswered questions about myasthenia is what initiates the immune response to acetylcholine receptors. An association has been made between the occurrence of thymomas and myasthenia in both dogs and cats.[1] This is probably related to antigenic similarity between neoplastic thymocytes and acetylcholine receptors. A less direct association has been made between myasthenia and other forms of neoplasia.[1] More recent association with immune-mediated endocrinopathies such as hypothyroidism and hypoadrenocorticism, myocarditis with third-degree atrioventicular (AV) block, myositis, and other immune-mediated diseases suggests that a generalized immune dysfunction may occur in many patients.[1]

A congenital form of MG has been reported as an autosomal recessive condition in Jack Russell terriers, smooth-haired fox terriers, and English Springer spaniels.[1] It has also been reported in Siamese and domestic shorthaired cats.[1] Clinical signs are similar to generalized acquired MG, with the exception that megaesophagus has only been infrequently reported in smooth-haired fox terriers. Remissions have not been reported. Instead, clinical signs are chronically progressive usually resulting in paralysis despite treatment

with pyridostigmine bromide. Circulating autoantibodies are not present in congenital MG. Instead the diagnosis is based on response to anticholinesterase agents, decrementing response on repetitive stimulation, and demonstration of reduced concentrations of acetylcholine receptors in skeletal muscle.

194.2.3.6 Neoplastic Neuropathies

Neoplastic processes can affect the peripheral nervous system in at least three different ways. The most common clinical manifestation is the development of primary neural tumors that arise from the neoplastic transformation of cells intrinsic to the peripheral nervous system. Less commonly, secondary peripheral nerve tumors develop as peripheral nerves are invaded by neoplastic hemolymphatic cells or entrapped by nearby carcinomas or sarcomas. Finally, the peripheral nervous system can be the target of paraneoplastic processes. Both clinical and subclinical neuropathies have been attributed to the remote effects of a wide number of neoplastic process.

194.2.4 Primary Peripheral Nerve Tumors

The peripheral nervous system is composed of neurons and their cell processes surrounded by fibroblasts, Schwann cells, and perineural cells. Each of these cell types is capable of becoming neoplastically transformed.

Neuroblastomas, ganglioneuroblastomas, and ganglioneuromas are primary neural tumors that develop in the peripheral nervous system. These are rare tumors that arise from neural crest cells, usually in adrenal medulla or sympathetic ganglia, and are distinguished primarily by the degree of differentiation of the neoplastic cells. These tumors typically occur in young dogs in retroperitoneal or mediastinal locations.[1] Occasionally, tumors are reported in the GI tract, olfactory mucosa, and peripheral sympathetic ganglia.[1] A single case of a kitten with an intestinal ganglioneuroma has been reported.[1] Clinical signs vary with location of the tumor, with vomiting, diarrhea, and dyspnea being most common. Neurologic signs occur after metastasis to the brain or spinal cord.[1]

Primary tumors that develop from the neoplastic transformation of supporting cells in the peripheral nervous system are more common. Considerable controversy exists over the nomenclature of these tumors. They have been referred to as *schwannomas*, *neurinomas*, *neurilemmomas*, *neurofibromas*, and *neurofibrosarcomas*. Much of the controversy stems from difficulty in determining the primary cell of origin. Most canine primary nerve sheath tumors are poorly differentiated, pleomorphic neoplasms in which the cell of origin is difficult to identify.[1] Therefore the term *malignant nerve sheath tumor* is preferred by most authors. Malignant nerve sheath tumors may arise along the course of any peripheral nerve, including cranial nerves and spinal nerve roots. They typically are slow-growing tumors that extend by local invasion along the peripheral nerve and its branches. They rarely invade surrounding tissue, and metastasis is rare.[1] Neurologic signs are created by compression of peripheral axons, spinal cord, or brain stem by the expanding neoplastic mass. Although any peripheral nerve may be affected, over 80% of the reported cases have occurred in the brachial plexus or its nerve roots. The remaining 20% of cases occur in the pelvic plexus, thoracolumbar nerve roots, and cranial nerves.[1] Of the cranial nerves, the trigeminal nerve is most commonly affected.

Clinical signs typically begin in mature dogs with only rare examples of the disease in cats. No breed or sex predisposition has been identified. Clinical signs vary with area affected, but they begin as a chronic, progressive forelimb lameness. Muscle atrophy, pain in the axillary area, and a palpable mass may be present. Horner's syndrome and loss of the ipsilateral panniculus response reflects loss of the first two thoracic nerve roots that contain preganglionic sympathetic fibers that supply the face and give rise to the lateral thoracic

nerve. Ipsilateral hemiparesis that progresses to paraparesis occurs with extension of neoplastic tissue and secondary spinal cord compression. In cases that involve the cranial nerves, multiple cranial nerve deficits are accompanied by ipsilateral hemiparesis secondary to brain stem compression.

Diagnostically, EMG reveals denervation in muscles innervated by affected nerves. Survey radiographs may show enlarged intervertebral foramen, and myelography may show an intradural extramedullary mass if neoplastic cells have invaded nerve roots. Computed tomography (CT) has been helpful at identifying tumors in peripheral nerves.[1] Surgical exploration and biopsy of nerve or plexus may be necessary to confirm the diagnosis.

Surgical excision has been curative in a few cases.[1] Unfortunately, inability to completely resect all neoplastic tissue usually results in tumor recurrence. In one study, median survival interval after diagnosis in dogs with tumors of the brachial plexus or nerve roots was 12 and 5 months respectively.[1] Radiation therapy has been proposed as a potential treatment for malignant nerve sheath tumors, but results have not been reported.

194.2.5 Secondary Peripheral Nerve Tumors

Peripheral nerve involvement by non-neural tumors is rare. However, infiltration of cranial and spinal nerves by neoplastic lymphocytes has been reported in cats and dogs with lymphosarcoma.[1,39] More recently, two dogs with myelomonocytic neoplasia and infiltration of multiple cranial nerves and spinal nerve roots has been reported.[1] Both dogs had an acute onset of “dropped jaw” and facial hyperesthesia secondary to bilateral trigeminal neuropathy. One dog also had Horner's syndrome, whereas the other had clinical signs of optic nerve and hypoglossal nerve involvement. Antemortem diagnosis was made in one dog by identification of blast cells in lymph nodes and peripheral blood. In both cases neoplastic myeloid cells were found infiltrating cranial nerves and spinal nerve roots on postmortem examination.

194.2.6 Paraneoplastic Neuropathies

Although paraneoplastic diseases can affect a variety of tissues, neurologic involvement can be quite disabling. The incidence of paraneoplastic peripheral neuropathy in veterinary patients is uncertain but probably varies with tumor type. Most cases with clinically significant neuropathies have been associated with insulinomas.[1,40] A total of 6 dogs with histologically confirmed insulinomas have been described that had tetraparesis. All had generalized muscle atrophy, diminished spinal reflexes, and electrophysiologic changes compatible with diffuse axonal degeneration. Angular atrophy of both type I and type II myofibers seen in muscle biopsy suggested denervation and axonal degeneration was apparent in peripheral nerve sections. The association between clinically significant neuropathies and other tumor types in animals is more tenuous.

In an effort to identify the subclinical incidence of peripheral nerve changes in dogs with cancer, Braund and colleagues evaluated peripheral nerves from a series of 21 dogs with malignant tumors.[1] All of the dogs examined with bronchogenic carcinoma, insulinoma, malignant melanoma, osteosarcoma, thyroid adenocarcinoma, mammary adenocarcinoma, and one dog with a mast cell tumor had significantly more degenerative changes than age-matched controls. A combination of demyelination, remyelination, and axonal necrosis was present in every case. The number of dogs with each tumor type was relatively small, and no correlation between duration of the tumor and degree of neuropathic change was attempted. Additional studies are needed to better define the true incidence of peripheral nerve changes in animals with cancer.

Several hypotheses have been proposed regarding the pathogenesis of paraneoplastic diseases. The most widely investigated include elaboration of a neurotoxic substance by the neoplastic cells, secondary nutritional deficiencies caused by competition between the tumor and the host for an essential metabolite, cancer-associated immunosuppression may predispose affected individuals to opportunistic infections, and finally an immune-mediated disorder in which autoantibodies are produced against antigens shared by the tumor and the nervous system. To date, most evidence supports an immune-mediated disorder. Antibodies that recognize specific neuronal populations have been found in humans with a variety of paraneoplastic neurologic syndromes including Eaton-Lambert myasthenic syndrome, cerebellar degeneration, subacute sensory neuropathy, retinal degeneration, and others.[1] Although probably responsible for the neurologic signs, identification of these antibodies has also proven useful as a serologic marker for neoplasia. In many instances neurologic signs may antedate the diagnosis of cancer, and identification of these specific antibodies in serum provides presumptive evidence of occult neoplasia.

Treatment for paraneoplastic neuropathies has been unrewarding in animals. A single case with insulinoma-associated neuropathy improved with corticosteroid therapy, whereas another case regained motor function after removal of mammary carcinomas.[1,40]

194.2.7 Traumatic Neuropathies

Research into peripheral nerve trauma suggests that at least five different classifications exist for the types of injury that can occur.[1] Class 1 is referred to as *neurapraxia* and describes the response to mild or moderated focal compression. Nerve conduction is reversibly blocked. Histologically, either no lesions or mild segmental demyelination occurs. Complete recovery may occur within hours; however, with more severe compression, it may be delayed for up to 6 weeks. Class 2 injuries or axonotmesis usually occur with crush or percussion injuries. Axons are interrupted, but the supporting connective tissue remains intact. Wallerian degeneration usually occurs distal to the site of injury, but regeneration is usually effective because regenerating axons can be guided back to the appropriate targets. Class 3, 4, and 5 injuries refer to varying degrees of neurotmesis. Class 3 injuries result in disruption of axons and endoneurium, but fascicular orientation is preserved by an intact perineurium. Class 4 injuries also disrupt the perineurium, whereas the entire peripheral nerve is severed in class 5 injuries. With increasing degrees of damage to supporting structures, the ability of regenerating axons to successfully bridge the gap and reinnervate original structures is lessened.

All five classes of injury exist in animals, and more than one class can occur simultaneously. Unless the peripheral nerve is completely severed, most surgeons wait several weeks before attempting repair to assess how much functional return will occur. Surgical repair of transected nerves has been attempted either using direct end-to-end anastomosis or using a nerve graft to bridge the defect. Autologous sensory nerves may be harvested to be used as a graft, or a non-neural conduit can be used. Experimentally, application of nerve growth factors to synthetic conduits has aided peripheral nerve regeneration after complete resection and may be clinically useful in the future.[1] Axonal regrowth occurs at a rate of approximately 1 to 2 mm/day. Therefore the prognosis for functional return depends not only on class of injury or precision of surgical repair but also on the distance the axon must travel to reach its end organ.

Individual peripheral nerves can be injured in a number of ways. Injection injuries, trauma from bone fracture and repair, lacerations from dog fights, and automobile accidents are some of the more common sources in dogs and cats. Motor and sensory deficits associated with individual peripheral and cranial nerves are outlined in Tables 194-1 and 194-2. Diagnosis is usually based on clinical signs of motor and sensory deficits. EMG will

reveal denervation, and peripheral nerve conduction should fail 5 to 7 days after the injury. Recently, ultrasonography has shown promise at imaging transected nerve stumps.[1]

194.2.7.1 Brachial Plexus Avulsion

The brachial plexus is typically formed from the sixth cervical through the second thoracic spinal nerve roots. Because nerve roots lack a perineurium, traction of the forelimb or severe abduction of the scapula frequently results in avulsion of these nerve roots, usually within the dura. Depending on the direction and extent of forelimb traction, all or only part of the brachial plexus may be involved. The caudal portion of the plexus is more commonly involved in partial injuries.[1]

Clinical signs are characterized by an acute, nonprogressive monoparesis usually precipitated by an automobile accident or a fall. The resulting motor and sensory dysfunction in the limb varies with the extent of the avulsion. Avulsion of C8, T1, and T2 nerve roots injures the radial, median, and ulnar nerves. The limb may be carried in a flexed position because the musculocutaneous, axillary, and suprascapular nerves are intact, but weight bearing is impossible without the ability to extend the elbow and carpus. Injury to C8, T1, and T2 spinal nerve roots also results in Horner's syndrome and loss of the ipsilateral cutaneous trunci (panniculus) reflex due to damage to the origins of the presynaptic sympathetic innervation to the face and lateral thoracic nerve respectively. More rostral nerve root injuries also involve the musculocutaneous nerve and prevent flexion of the elbow. Limb movement is generated by advancement of the shoulder. Injury of only proximal portions of the brachial plexus is rare. Useful limb function depends on the radial nerve; in a review of 30 cases, the radial nerve was involved in 92% of dogs with brachial plexus avulsion.[1] Like motor function, sensory deficits depend on the number and distribution of nerve roots avulsed. In some instances, dorsal roots may be spared, resulting in some preservation of sensation even though motor function was lost with avulsion of the ventral roots. Despite the potential variability in sensory deficits, most cases are analgesic distal to the elbow.[1]

Diagnosis of brachial plexus avulsion depends on history, clinical signs, and electrophysiologic evidence of denervation in limb muscles. Motor nerve conduction is usually abolished in affected nerves. A sensory nerve evoked potential may be present even in the absence of conscious perception of pain, if the dorsal nerve root is avulsed proximal to the dorsal root ganglion. Somatosensory evoked potentials produced by stimulation of a peripheral nerve and measuring the response of afferent neurons in the spinal cord and brain will be abolished if all nerve roots are avulsed. Unfortunately, somatosensory evoked potentials are less useful with partial lesions.[1]

Prognosis for functional return is hopeless if the radial nerve has been avulsed. Several salvage procedures have been described for distal radial nerve deficits, but triceps innervation is required for any useful limb movement. Neurapraxia is certainly a feature of any traumatic peripheral nerve injury. Therefore a hopeless prognosis should not be given before a minimum of 4 to 6 weeks after the injury. Unfortunately less than 12% of reported cases regained radial nerve function.[1] Limb amputation should be considered if self-mutilation or other continuous trauma occurs in desensitized areas.

194.2.8 Vascular Neuropathies

Acute obstruction of blood vessels supplying peripheral nerves is rare except in cats with aortic thromboembolism. Reports in dogs usually involve heartworm disease. Although thromboembolism of any major artery could produce clinical signs, the most common site is the terminal aorta obstructing the internal

and external iliac arteries and the median sacral artery. Both physical restriction of blood flow by the embolus and the production of vasoactive substances, including serotonin and thromboxane that limit collateral blood flow, combine to produce ischemia of the sciatic nerve and adjacent muscles. Axonal necrosis occurs in the center of nerve fascicles in the distal sciatic nerve and its branches, whereas paranodal demyelination is evident in peripheral areas.[1] Muscle damage consists of focal necrosis, with inflammatory cell infiltrates and myophagia.

Clinical signs typically consist of an acute onset of pelvic limb paralysis. The femoral pulse is usually weak or absent, the rear limbs are cold, and nail beds are ischemic and fail to bleed if cut. Rear limb musculature often feels stiff because of ischemic muscle contracture, and the cats often are painful on muscle palpation. Evidence of cardiac disease is usually present either in physical examination findings, thoracic radiographs, or echocardiography. Most cats have hypertrophic cardiomyopathy; however, other forms of cardiac disease are possible. Therapeutically, in addition to specific treatment for the cardiac disease, most cats benefit from warming the limbs and administering acepromazine 0.2 to 0.4 mg/kg subcutaneously every 8 hours to encourage vasodilatation and collateral blood flow. Heparin sodium (100 to 200 IU/kg intravenously initially, followed by 50 to 100 IU/kg every 6 to 8 hours) is recommended to prevent further thrombus formation, and analgesics such as butorphanol (02. to 0.4 mg/kg every 6 to 12 hours) should be used to control pain. Specific therapy to remove the clot has been attempted both surgically and medically using thrombolytic agents.

194.2.9 Idiopathic Neuropathies

194.2.9.1 Distal Denervating Disease

Distal denervating disease is considered the most common neuropathy in dogs in the United Kingdom.[1] Dogs of all ages, breeds, and both sexes are affected. The onset of clinical signs is variable, ranging from days to a month or more. Quadriparesis to quadriplegia is accompanied by neck weakness, loss of bark, diminished spinal reflexes, and muscle atrophy (especially prominent in proximal limb muscles). Voluntary control of tail movement, urination, and defecation is maintained, and pain sensation is preserved. EMG reveals diffuse spontaneous activity in all muscles. Motor nerve conduction velocity is modestly reduced, but the evoked muscle action potential is usually small and dispersed. These electrophysiologic changes are most compatible with primary axonal loss with little demyelination. Sensory nerve conduction is normal. Muscle and nerve biopsy confirms a distal axonopathy with denervation atrophy of muscle. Most cases spontaneously resolve without treatment, with complete recovery occurring 4 to 6 weeks after clinical signs plateau.[1] Pathologic changes are restricted to the distal motor axon. No changes have been reported in the CNS, nerve roots, or main portions of peripheral nerves. Intramuscular branches are reported to show extensive collateral axonal sprouting, with early cases also exhibiting modest degrees of terminal axonal degeneration. The cause is unknown, but an unidentified toxin is considered likely.

194.2.9.2 Distal Symmetrical Polyneuropathy

Numerous adult, large breeds of dogs have been described with a distal sensorimotor polyneuropathy, which have been collectively referred to as *distal symmetrical polyneuropathy*.[1] A remarkable similarity exists to the developmental and congenital axonopathy "polyneuropathy in rottweiler dogs." Clinical signs are insidious in onset and gradually progressive over 1 to 2 months. Pelvic limb paresis is the initial presenting sign, but tetraparesis with atrophy of distal limb muscles and muscles of mastication eventually develops. Diffuse spontaneous activity is prominent with needle EMG. Motor nerve conduction velocities are usually normal or slightly slowed, but the amplitude and duration of the evoked muscle action potential is small and

prolonged, suggesting axonal injury. Muscle and nerve biopsy confirms a distal axonopathy with denervation atrophy of skeletal muscles. No other abnormalities have been reported in peripheral blood or CSF. Histologically, lesions are confined to the distal regions of motor nerves. Degeneration of large-diameter motor axons is prominent in distal limb nerves and the recurrent laryngeal nerve. Variable degrees of demyelination are present as well but appear secondary to axonal loss. Sensory and autonomic nerves may be affected as well but to a lesser degree. No lesions are found in the CNS. The cause is obscure, but metabolic, toxic, and paraneoplastic neuropathies may appear similarly. Prognosis is poor because the disease is chronic and progressive in nature and has not previously responded to treatment. However, preliminary results from a multicenter trial involving the use of Prosaptide™ TX14(A), a neurotropic peptide, in large breed dogs with idiopathic distal symmetrical peripheral neuropathy showed promising results.[41] Of the seven dogs that completed the trial, three showed improvement in neurologic function.

194.2.9.3 Dancing Doberman Disease

Dancing Doberman disease is an unusual neuromuscular disorder that presently appears restricted to adult Doberman pinschers of both sexes.[1] Clinical signs begin between 6 months and 7 years of age and are gradually progressive over several years. Affected dogs have a characteristic habit of holding one or both pelvic limbs flexed while standing. The condition may begin in one limb and then spread to the alternate limb within 3 to 6 months. When both pelvic limbs are affected, the condition may appear as shifting rear limb lameness with an increased tendency for the dogs to sit rather than stand. Conscious proprioceptive deficits have been reported in two dogs 5 and 6 years respectively after the disease was diagnosed. Exaggerated pelvic limb reflexes and atrophy of the gastrocnemius muscle are also common.

Electrophysiologic abnormalities suggest a mixture of mild myopathic and neuropathic changes. EMG shows spontaneous activity in affected muscles, but motor and sensory nerve conduction velocities are usually normal. Pathologic changes are confusing. Some dogs have multifocal pelvic limb muscular atrophy and hypertrophy, fibertype grouping, focal necrosis, and endomysial and perimysial fibrosis suggestive of a form of myotonic myopathy.[1] Other dogs have peripheral nerve changes suggestive of a primary axonopathy. Evidence of axonal degeneration in sensory and autonomic fibers has been reported, suggesting that dysesthesias caused by pressure on the feet may be responsible for the unusual clinical signs.[42]

No treatment has proven beneficial to date. Although the syndrome is slowly progressive, affected animals remain functional pets for many years. Without definitive diagnostic criteria, the syndrome can only be diagnosed by ruling out other diseases such as lumbosacral stenosis, intervertebral disk disease, or nerve root tumors that might initially appear with rear limb paraesthesias without obvious motor impairment.

194.2.9.4 Dysautonomia

Dysautonomia is a general term for dysfunction of the autonomic nervous system. A syndrome characterized by diffuse autonomic dysfunction was first reported in cats in 1982 by Key and Gaskell.[1] Over the next 2 years this previously undiagnosed disease was reported in epidemic proportions throughout the United Kingdom and later in Europe and the United States. The incidence of the disease has since markedly declined in cats. The first case of dysautonomia was reported in dogs in 1983, again in the United Kingdom.[1] Only sporadic reports of canine cases appeared until recently when 11 dogs were identified in Missouri over a 7-year period.[1] Although additional dogs have subsequently been described, all cases appear confined to the Midwest.[43,44]

Animals between 6 weeks and 11 years have developed dysautonomia, but both dogs and cats less than 3 years of age appear to be more susceptible. Both males and females are equally affected. The onset is acute in most cases, with clinical signs developing over 2 to 3 days. Rarely the onset is more insidious, lasting a week or more. Initial clinical signs are usually nonspecific and consist of lethargy, anorexia, and depression. GI signs including regurgitation and vomiting, constipation or diarrhea follow. Dysuria with a distended urinary bladder, myasis with depressed PLRs, dry mucus membranes, prolapsed third eyelids, dysphagia, and weight loss are also commonly seen. More inconsistent features include loss of anal tone and mild postural reaction deficits. Many pets also have bradycardia with heart rates less than 120 beats per minute that do not change with stress or exercise.

No consistent abnormalities have been detected in peripheral blood or CSF. Radiographically most animals have evidence of decreased peristaltic activity throughout the GI tract including megaesophagus, delayed gastric emptying, and generalized ileus. Electrodiagnostic testing is usually normal, with the exception of occasional spontaneous activity in limb muscles. Pharmacologic testing has been used to confirm parasympathetic and sympathetic nervous system dysfunction. Specifically, denervation of the iris muscle results in supersensitivity to cholinergic drugs. Instillation of 0.05% pilocarpine ophthalmic solution should cause rapid constriction of the pupils. It usually takes at least 30 minutes for miosis to occur in normal dogs, and no effect should be seen in cases where parasympathetic signs are due to atropine or a similar toxin.[44]

Histologically, sympathetic and parasympathetic ganglia are affected. Because the degree of involvement of any one ganglia can be quite variable, multiple samples are recommended. Depletion of neuronal cell bodies is the more prominent change, with many remaining neurons containing atypical homogenous cytoplasm, dissolution of Nissl substance, and an eccentric pyknotic nucleus. Axonal degeneration is present in autonomic nerves. Peripheral nerves are relatively spared, although occasionally smaller neurons in dorsal root ganglia and cranial nerve ganglia may show chromatoylitic changes. A percentage of neurons in cranial nerve nuclei, ventral horn cells, and cells in the intermediolateral gray matter of the spinal cord may also show characteristic changes. Unusual ultrastructural changes consist of derangement of rough endoplasmic reticulum with existing cisternae denuded of ribosomes and distended with electron-dense flocculent material.[1] No normal Golgi bodies are found, but instead stacks of smooth membranous profiles are seen. Membranous dense bodies and autophagic vacuoles are common in some neurons.

Treatment is largely supportive. Pilocarpine (1%) eye drops may improve mydriasis and stimulate lacrimation and salivation. Bethanechol (2.5 to 7.5 mg every 8 hours) should facilitate evacuation of the bladder at least temporarily. Metoclopramide will enhance the actions of any available acetylcholine on muscarinic receptors in the GI tract and enhance gastric emptying. Unfortunately the prognosis is poor. Less than 25% of affected cats survive, and recovery often takes over a year. The cause of the disease remains a mystery, despite numerous efforts identify an infectious or toxic agent. The clustering of cases in the United Kingdom and more recently Missouri suggests an environmental agent; however, none have been identified. Recently, autoantibodies against ganglionic acetylcholine receptors were demonstrated in dogs with dysautonomia.[45] It is not yet clear whether this represents a cause or an effect of the disease process.

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194.2.9.5 Idiopathic Trigeminal Neuritis

The trigeminal nerve is most commonly injured by inflammatory or neoplastic intracranial diseases. Rarely, the trigeminal nerve is directly infiltrated by neoplastic cells (as previously described with peripheral nerve neoplasia). The trigeminal nerves are also the target of an idiopathic, inflammatory condition referred to as *trigeminal neuritis*. Clinical signs are characterized by an acute onset of bilateral trigeminal motor paralysis

causing inability to close the mouth ("jaw drop").[1,46] Facial sensation is usually preserved. Occasionally, Horner's syndrome may accompany trigeminal neuritis, presumably because the postganglionic sympathetic axons course with the ophthalmic branch of the trigeminal nerve.[46,47]

Biopsy of the muscles of mastication reveals denervation atrophy. CSF may be normal or may have mild increases in protein concentration. Rarely, a lymphocytic pleocytosis is described.[46] Histology has been limited, but nonsuppurative neuritis in all portions of the trigeminal nerve and ganglion has been described.[1,47] The brain stem is spared. Spontaneous recovery usually occurs within 2 to 3 weeks but may take months to completely resolve. Steroid therapy does not appear to alter the course of the disease.[46] Maintenance of hydration and alimentation is critical during this time. Percutaneous gastrostomy has been helpful in this regard.

194.2.9.6 Idiopathic Facial Neuritis

Because of its anatomic proximity to the inner and middle ear, the facial nerve is commonly injured in otitis media and interna. The facial nerve also has a superficial location after emerging from the stylomastoid foramen and is therefore easily susceptible to traumatic injury. The facial nerve is often affected in generalized peripheral nerve diseases including polyradiculoneuritis, tick paralysis, and botulism. Less frequently, facial nerve paralysis results from no identifiable cause and has been referred to as *idiopathic facial neuritis*.[1]

Clinical signs of facial paralysis are characterized by inability to move the lip, ear, and eyelids. Ptyalism and inability to blink are the most common admitting complaints. The facial nerve also provides parasympathetic innervation to lacrimal glands, and proximal injury may result in keratoconjunctivitis sicca. Xerostomia, focal hypalgesia to the pinna, and partial loss of taste may also occur with facial nerve paralysis, but these are difficult to appreciate clinically. Both dogs and cats have been reported with idiopathic facial neuritis.[1] The syndrome tends to occur in mature animals, and Cocker Spaniels have been identified in two studies as being predisposed.[1] Clinical signs typically appear acutely and in the absence of any other systemic illness. One or both facial nerves may be initially affected. In cases with unilateral facial neuritis, the other side may become affected later. Electrophysiologically, spontaneous activity suggestive of denervation appears in superficial facial muscles. Stimulation of the facial nerve failed to evoke an action potential in one report.[1] Fascicular biopsy of the ventral buccal branch of the facial nerve in two dogs showed axonal degeneration.[1]

The cause of this condition is unknown. A casual link has been made, with hypothyroidism. Statistically the relationship with hypothyroidism has been difficult to prove.[1] However, numerous cases have concurrent hypothyroidism and clinically improve with thyroid supplementation.[1] Other theories that are also unproved include herpes viral neuritis or swelling of the facial nerve causing compression in the bony facial canal traversing the petrous temporal bone.

The prognosis for idiopathic facial neuritis is poor. Steroid therapy has been recommended, but its efficacy is uncertain. Cases may improve within weeks or months. However, the facial nerve remains permanently paralyzed in a significant number of cases. Exposure keratitis, especially if compounded by decreased lacrimation, is the most significant complication.

194.2.9.7 Idiopathic Peripheral Vestibular Disease

An idiopathic vestibular dysfunction has been identified in old dogs and cats of all ages.[1] Clinical signs are acute in onset and consist of head tilt, nystagmus, falling, rolling, and ataxia. Postural reactions remain intact, and spinal reflexes are normal. Facial nerve deficits and Horner's syndrome are common features of otitis media and interna are conspicuously absent in idiopathic vestibular disease. In cats an unusually high frequency of cases occurs in July and August.[1] The reason for this seasonal incidence is unknown. The diagnosis is based on clinical signs and failure to identify other causes of vestibular dysfunction including trauma, otitis media and interna, or toxins. Aminoglycoside antibiotics, especially streptomycin in cats, can damage vestibular and auditory receptors and result in vestibular dysfunction. The prognosis for idiopathic vestibular dysfunction is excellent. Most cases spontaneously improve within weeks. Some cases have a residual head tilt. An association between idiopathic peripheral vestibular disease and hypothyroidism has been noted.[1] Other inner and middle ear diseases are covered more thoroughly in Chapter 209.

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195 CHAPTER • 195 Disorders of the Skeletal Muscles—Canine*

Stéphane Blot

Striated muscle, which accounts for approximately 50% of the body mass, is an intricate machine designed to convert chemical energy into mechanical energy. The component processes include excitation-contraction coupling, the contractile mechanism itself, various structural components, and the energy system that supports the activity and integrity of the other systems. Proper function of striated muscle, therefore, depends on the integrity of all organs of the body. This chapter focuses on primary defects involved in skeletal muscle diseases (primary myopathies), but numerous secondary myopathies are encountered as a result of defects in other organs. Disorders of the neuromuscular junction are discussed elsewhere.

195.1 ANATOMY AND PHYSIOLOGY

Skeletal muscles are composed of fusiform, multinucleated cells, called *myofibers,* as well as connective tissue, vessels, and nerves.[1–3] During myogenesis, myofibers are produced by the fusion of *myogenic cells,* the myoblasts that stem from the same mesodermal embryonic tissue that provides bone, cartilage, and connective tissue. However, all muscles do not derive from the same origin, which explains the immunologic differences between groups of muscles and therefore may account for specific topographic muscle lesions. Some multinucleated myogenic cells, called *satellite cells,* do not merge, but rather lie beneath the basement membrane of mature muscle fibers. When a muscle is damaged and necrosis occurs, the satellite cells develop and merge to form new muscle fibers.

On transverse section of normal muscle, myofibers are all polygonal, roughly of equal size with peripheral nuclei; however, different types of myofibers are identified based on physiologic and histochemical criteria (Table 195-1). *Slow contraction fibers (type 1)* withstand fatigue and use oxidative metabolism, whereas *fast contraction fibers* extract energy from the glycolytic pathway. Most skeletal muscles are made up of a mixture of these functional types, the proportion of each type being stable for a given muscle in each species.[4] In specific muscles, one type appears largely predominant. The functional type of each myofiber is actually determined by the neuronal cell body innervating the cell.[5,6] All myofibers innervated by the same motor neuron define a motor unit, the size of which varies; muscles with fine movement are composed of small motor units (e.g., extraocular muscles), and antigravity muscles are composed of large units.

Perimysial connective tissue defines fascicles that enclose several motor units. All motor units are closely intermingled, producing a particular mosaic-like or checkerboard pattern. Each muscle fiber is surrounded by a thin layer of connective tissue (the *endomysium*), and the entire muscle is encased in epimysial connective tissue. Each myofiber is composed of hundreds of myofibrils made of thin and thick contractile filaments separated by an intermyofibrillar network containing aqueous sarcoplasm, mitochondria, glycogen, and the sarcoplasmic reticulum (calcium reservoir) with the associated transverse tubular system. The protein myosin is the main component of the thick filaments, and actin, troponin, and tropomyosin constitute the thin contractile filaments.

Ultrastructurally, the regular spatial distribution of the contractile filaments presents a characteristic striated appearance that is the result of the repetition of a transverse pattern. This repetitive pattern, called the *sarcomere,* contains an electron-dense area (the *A band*), which is produced by the overlapping of thick and thin filaments, and an electron-lucent area (the *I band*), which contains thin filaments alone. In the middle of the A band is an area in which the absence of thin filament produces an additional electron-lucent band, the *H zone*. The *transverse*

M line in the H zone is composed of cross-linked thick filaments, and the *transverse Z line* in the I band is made up of protein-anchoring adjacent thin filament. The sarcomere thus is the structural unit defined by two successive Z lines.

Molecular studies yield constant enlightenment about the components of the cytoskeletal, sarcolemmal, or contractile apparatus, leading to the discovery of molecular defects involved in degenerative myopathies. The muscle fiber converts a biochemical signal (i.e., the release of acetylcholine from the nerve terminal after arrival of a nerve action potential at the neuromuscular junction) into a mechanical force produced by the coordinated contraction of several thousand sarcomeric units. To achieve this complex process, known as *excitation-contraction coupling,* several elementary phases are required, comprising depolarization of the sarcolemma, transverse tubules, and sarcoplasmic reticulum. Depolarization leads to the release of calcium into the sarcoplasm. At rest, tropomyosin (a regulating protein) blocks the active site of actin and prevents the myosin-actin interaction. Binding of the calcium to troponin moves tropomyosin, which then promotes formation of several cross-bridges between actin and myosin molecules. With the availability of energy (adenosine triphosphatase [ATPase] from myosin catalyzes hydrolysis of adenosine triphosphate [ATP], which comes from the phosphocreatine stock—the myofiber's battery—or from oxidative phosphorylation metabolism or glycogenolysis), the thin filaments move on the thick myofilaments, leading to the shortening of the myofibrils. Dissociation of the cross-bridges, which produces relaxation time, also requires energy.

* At the author's request, this chapter (with feline referencing deleted) has been reprinted from the last edition.

195.2 GENERAL CLINICAL FEATURES

The main sign of a disease affecting the appendicular musculature is weakness. Weakness induced by skeletal muscle disorders usually is persistent but may become more pronounced after exercise (increased fatigability). In rare cases weakness disappears with exercise, and the signs are exacerbated by rest (myotonia). Weakness may be discrete, manifesting as a stiff gait; tremors; an abnormal posture, such as neck ventroflexion (more pronounced in cats owing to the absence of a nuchal ligament); palmigrade or plantigrade stance; splaying of digits; bunny hopping gait; or difficulty negotiating simple motions, such as jumping over steps or climbing into the car. Weakness may also be extreme, mimicking a neurogenic disease. Muscle atrophy is common; however, hypertrophy can occur in some instances. In most cases hypotony with normal tendon reflexes is encountered, although hypertonic muscles are also observed (polymyositis, myotonia). Absent tendon reflexes are sometimes observed in congenital myopathies or later in the course of degenerative myopathies. Muscular fibrosis and contracture, causing reduced range of articular movement, is a frequent feature in severe inflammatory or degenerative myopathies. Muscle pain *(myalgia)* occasionally may be identified in inflammatory conditions. The normal muscular response to percussion is a barely visible transient contraction of the myofibers. It disappears prematurely in primary muscle diseases, in contrast to the conservation of tendon reflexes. However, mechanical excitability is exaggerated in neurogenic muscular atrophies. In the myotonic syndrome, the myotonic dimple persists for several seconds. Signs affect the appendicular musculature and several other striated muscles, such as the masticatory, extraocular, cardiac, digestive, and respiratory musculature. Therefore disorders of striated muscle should be suspected as one cause of the condition in dogs with regurgitation, vomiting, dysphagia, dysphonia, or ophthalmoplegia.

Table • 195-1 Characteristics of Mammalian Myofiber Types

PROPERTIES	TYPE 1	TYPE 2m*	TYPE 2a	TYPE 2b†	TYPE 2c‡
Histochemistry Staining Intensity					
ATPases pH 10,4/9,4	Low	Low	High	High	High
ATPases pH 4,63/4,53	High	Moderate	Low	Moderate	Moderate
ATPases pH 4,35 Oxidative	High	Low	Low	Low	Moderate
NADH-TR, SDH	High		Moderate	Low	Moderate
Menadione	Low		Moderate	High	
Phosphorylase	Low		Moderate	High	
Periodic acid–Schiff	Low		High	Moderate	High
Physiologic/Morphologic Features					
Contraction speed	Slow		Intermediate/fast	Fast	—
Fatigue resistance	High		Intermediate	Low	—
Size	Small	—	Intermediate	Large	—
Myoglobin	High	—	High	Low	—
Energy metabolism	Oxidative	—	Oxidative/glycolytic	Glycolytic	—
Mitochondria	Many	—	Many	Few	—
Glycogen content	Low	—	High	Intermediate	—
Lipid content	High	—	Intermediate	Low	—

From Guy PS, Snow DH: Skeletal muscle fibre composition in the dog and its relationship to athletic ability. *Res Vet Sci* 31:244, 1981.

* Masticatory myofiber type.

† Type 2B myofiber does not exist in the canine.82

‡ Type 2C myofiber is a primitive myofiber that may be a precursor of types 2A and 2B.

Because weakness is a nonspecific sign frequently encountered in other nonmuscular diseases, ancillary tools must be used to confirm the presence of a myopathy.

195.3 GENERAL DIAGNOSTIC FEATURES

Several serum enzymes, such as creatine kinase (CK), lactate dehydrogenase, aldolase, and aspartate aminotransferase, may be elevated in muscle diseases.[3] In particular, owing to the short half-life of creatine kinase (about 6 hours), the level of serum CK is the best indication of a recent muscle lesion.[7] However, tremendous variability occurs, based on age (the younger the animal, the higher the value), breed (the smaller the dog, the higher the value), motor activity (exercise produces a higher value), recent intramuscular injections, and sampling methods. Although some myopathies are associated with dramatic persistent elevations (i.e., muscular dystrophies, polymyositis), numerous myopathies cause little, transient, or no elevation at all. Therefore a normal CK level should not exclude a muscle disease from the differential diagnosis.

Electrophysiologic tests (electromyography, nerve conduction studies, and repetitive stimulation) are more valuable in the evaluation of peripheral neuropathies than in myopathies.[8] If contractile activity is recorded, myopathies are classically associated with smaller, shorter, and sometimes polyphasic motor unit potentials. Spontaneous abnormal activity (fibrillation potentials, positive waves, high-frequency discharges, and complex repetitive discharges) may be recorded in numerous myopathies, but no activities are specific for certain myopathies except the myotonic burst that is pathognomonic for myotonia. If a muscle biopsy is planned, that muscle site should not be electrophysiologically tested, to avoid iatrogenic changes.

When muscle disease is suspected, a muscle biopsy is indicated to confirm the diagnosis. The sampling is a relatively innocuous procedure, but certain guidelines must be followed if maximum information is to be gained.[9] Blood for serum muscle enzyme analysis should be collected before the biopsy is performed. Selection of the muscle for biopsy is guided by electromyography or, failing that, atrophic or hypertrophic muscles are chosen. Although a single muscle biopsy is usually satisfactory, the chances of identifying characteristic lesions are considerably enhanced if several muscles are sampled (generally at least one muscle biopsy each from the pelvic and thoracic limbs). The biopsy specimen is taken at the center of the muscle belly by parallel incisions along the longitudinal axis of the myofibers. A section 4 to 5 mm wide and 2 cm long is satisfactory for routine light microscopic evaluation. Tools for reducing the shortening of the muscle sample may be used (muscle biopsy clamp or a sterile applicator stick). 902 903

The muscle sample should be divided into two fragments; one is fixed in 10% buffered formalin, and the other is submitted prior to fixation, in a refrigerated gauze sponge, within 24 hours, so that histochemical stains can be applied. Such stains are the only satisfactory method for analyzing degenerative myopathies. When muscle atrophy is of nervous origin, it is characterized by variability in fiber diameter, the presence of angular, atrophied fibers, and alteration of the normal checkerboard pattern.

Myopathies can be categorized as inflammatory or degenerative (Box 195-1). The inflammatory conditions are either infectious or immune mediated, whereas degenerative myopathies are acquired or inherited. This discussion focuses on the main myopathies in dogs.

195.3.1 Box • 195-1 Classification of Myopathies

195.3.1.1 Inflammatory

Infectious

Bacterial

Leptospirosis

Toxoplasmosis/neosporosis

Parasitic

Immune mediated

Masticatory muscle myositis

Polymyositis

Dermatomyositis

195.3.1.2 Degenerative

Acquired

Endocrine

Hyperadrenocorticism

Hypothyroidism

Hypokalemic polymyopathy (cats)

Fibrotic/ossifying myopathies

Ischemic

Nutritional

Neoplastic

Toxic

Inherited

Muscular dystrophy

X-linked muscular dystrophy (dystrophin deficient)

Other muscular dystrophies (dystrophin positive)

Myotonia

Metabolic

Glycogen storage disease

Mitochondrial myopathy

Lipidic myopathy

Malignant hyperthermia

Centronuclear myopathy (Labrador retriever)

195.4 INFLAMMATORY MYOPATHIES

A classic distinction is made between infectious myositis conditions and those that are immune mediated. In cases of infectious myositis, bacteria (*Leptospira* or *Clostridium* spp.) or parasites (*Toxoplasma* or *Neospora* spp.) are

directly responsible. Some agents are capable of triggering noninfectious myositis by modifying muscle immunogenicity (leishmaniasis or ehrlichiosis).

195.4.1 Infectious Bacterial Myositis

Bacterial myositis is a rare disorder in carnivores; it occurs more frequently in food animals.[10] A distinction can be made between polymyositis and focal myositis. The manifestation of the latter disorder is lameness accompanied by pain and muscle enlargement. This type of myopathy occurs with bacterial spread from a distant site of infection via the blood or after bacterial inoculation through external trauma, such as a bite, a sting, or contamination of surgical wounds.[11–14] Staphylococci and streptococci are often involved in canine traumatic infectious myositis. Clostridial myositis (caused by *Clostridium perfringens*) is rarely found in domestic carnivores. *Leptospira icterohaemorrhagiae* is responsible for serious myositis. However, the severe nature of the general signs masks the muscle damage. The treatment consists of lancing the wounds and draining any abscesses. In the case of secondary bacterial myositis, the first step consists of identifying the primary site. The antibiotic is selected by the results of sensitivity testing. Clindamycin (5 mg/lb given orally twice a day) is the anti-biotic of choice for anaerobic bacterial myositis.[12,15,16]

195.4.2 Parasitic Myositis

195.4.2.1 Toxoplasmosis (Toxoplasma gondii)

Toxoplasmosis develops clinically only in young animals (less than 1 year old) and often arises when another disease occurs. The muscular signs are characterized by abnormal gait, muscle pain, and muscle atrophy. In some cases myositis with subsequent fibrosis evolves quickly.[17]

195.4.2.2 Neosporosis (Neospora caninum)

Neurologic damage dominates the clinical presentation of neosporosis, and pups that are affected rapidly show hyper-extension of the hindlimbs. Transplacental transmission mimics a hereditary disease. Clindamycin (5 mg/lb twice daily) or trimethoprim combined with sulfadiazine (7 mg/lb twice per day) is the drug of choice; however, pelvic limb extensor rigidity does not respond to therapy.[18–20]

195.4.2.3 Other Parasites

Trichinella spiralis, Ancylostoma caninum, and *Sarcocystis* spp. may infect the muscle and only rarely produce clinical signs. Generally, they are discovered purely by chance.[17,18,21,22]

195.4.3 Immune-Mediated Myositis

195.4.3.1 Myositis of the Masticatory Muscles

The muscle fibers of the masticator muscles have a distinct embryologic origin, which explains the presence of a particular type of fiber called *type 2M*. These fibers enclose a specific myosin, which is specifically involved in this immune-mediated reaction. Type 1 fibers are spared. This myopathy affects all dogs regardless of age, gender, or breed, but the German shepherd seems to have a predisposition.[23–26]

In the acute form, hypertrophy of the temporal and masseter muscles is observed with myalgia. The animal is reluctant to open its mouth. It has difficulty eating and may dribble saliva. Sometimes the jaws remain open because complete closing is impossible. Fever, inflammation of the tonsils, and local adenitis may also be found. In most cases myositis of the masticatory muscles is a chronic condition with severe, progressive muscular atrophy accompanied by fibrosis, resulting in a reduced ability to open the mouth and trismus (lockjaw).

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The disorder generally is bilateral. Exophthalmos linked to enlargement of the temporal muscles sometimes can be the cause of an optic neuritis and can result in vision disorders. Biochemical examinations are not specific, but the serum CK level may be increased, and leukocytosis is sometimes found. Electromyography (EMG) reveals abnormal spontaneous activity. Muscle biopsy shows sites of necrosis and phagocytosis of type 2M fibers, with perivascular infiltration of mononucleate cells. In the serum of affected dogs, type 2M antitype antibodies are identified.

Administration of immunosuppressive doses of cortico-steroids is the only advisable therapy. Clinical recovery is usually rapid and complete if treatment is begun early. A dosage of 0.5 to 1 mg/lb twice a day is maintained for 15 days, after which the dose is gradually reduced. Should a relapse occur, the maximum dose should be administered again. Sometimes a prolonged course of treatment is required, with small doses administered on alternate days. Therapy is ineffective if administered to an animal that has already experienced several inflammatory episodes that have resulted in extensive fibrosis.

195.4.3.2 Polymyositis

Polymyositis is an inflammatory polymyopathy with an immune-mediated etiology. It is sometimes associated with other immune-mediated diseases, such as systemic lupus erythematosus. Polymyositis may also be caused by parasitic disorders (toxoplasmosis and ehrlichiosis) or various forms of cancer (paraneoplastic syndrome).[26] In most cases the etiology is unknown. Polymyositis affects all skeletal muscles of the limbs, although occasionally there are reports of focal damage, such as the extraocular muscles.[27]

Large adult dogs are most commonly affected. Signs include muscle weakness, which is sometimes exacerbated by exercise, and myalgia, pyrexia, amyotrophy, and muscle stiffness are sometimes noted. Dysphagia and regurgitation caused by mega-esophagus are less common. Pneumonia is a frequent complication. Generally, an increase in the CK level is observed. EMG abnormalities are similar to those seen in myopathy of the masticator muscles. The muscle biopsy reveals perivascular infiltrations of mononucleate cells, and necrosis and regeneration are also noted. Therapy is based on immunosuppressive doses of corticosteroids. The prognosis is guarded, especially when pneumonias arise. The combination of prednisolone and azathioprine is effective in certain cases that prove refractory to the administration of corticosteroids only.

Dermatomyositis is an inherited disorder in which myositis is associated with dermatitis. It has been reported in the collie, the Shetland sheepdog, and the Welsh corgi.[28–34] The manifestations of the nonpruritic cutaneous disorder are erythema, alopecia, and ulceration. The signs appear in 3-to 11-week-old pups, and the disease appears to wax and wane. The myopathic signs of weakness are usually observed within a few months. Myositis, especially involving the temporal muscles, is seen histologically.

195.5 DEGENERATIVE MYOPATHIES

195.5.1 Endocrine Myopathy

Both myopathy and peripheral neuropathy have been associated with hypothyroidism.[35] These conditions may occur simultaneously. The EMG examination may record high-frequency discharges. In most cases the muscle biopsy result is normal, and if any lesions are present, they are not specific (glycogenic inclusions, type 2 atrophy, necrotic fibers, and centralized nuclei). Moderate signs can be resolved through hormone supplementation. Abnormal serum electrolytes, particularly with regard to potassium, can cause a myopathic syndrome.[35]

Myopathy has been reported in spontaneous and iatrogenic hypercorticism in dogs.[36] Clinical forms vary from muscle weakness to a myotonic form. Myotonia causes limb stiffness and seems to affect the poodle in particular. In some cases, it is even associated with muscular hypertrophy. EMG shows bursts of pseudomyotonic potentials. Muscle biopsy demonstrates disorganized muscle fibers with an abnormal accumulation of mitochondria (ragged red fibers). Treatment of the underlying disease leads to improvement of the neuromuscular signs, except in the pseudomyotonic form.

195.5.2 Hyperkalemia

Hyperkalemic periodic paralysis is an inherited myopathy characterized by frequent episodes of weakness, during which serum potassium is elevated. A myotonic syndrome may often accompany this myopathy, and the fits of weakness can be triggered by oral administration of potassium. Only one report of this has been documented, in a 7-month-old female American pit bull. Administration of acetazolamide and fludrocortisone led to clinical improvement in the patient's condition.

195.6 FIBROTIC AND OSSIFYING MYOPATHIES

Ossifying myopathy is generally described as a progressive ossifying myositis. It may occur in both localized and generalized forms. Clinically, the animal refuses to move. Upon radiographic investigation, intramuscular zones can be seen, and their density is close to that of bone. Histologically, a progressive ossification of the connecting intramuscular tissue is seen in which isolated patches of trabecular bone and cartilage are found, in addition to perivascular lymphocytic infiltrates, which gave rise to the term, myositis, used for this disorder. However, the term *fibrodysplasia* is preferable, because neither the optical microscope nor the electron microscope shows any lesions confirming primary damage to the muscle fibers.[37,38]

The appearance of a permanent focal contracture with muscle fibrosis (infraspinous, femoral quadriceps) causes lameness. The cause is often obscure; congenital malformation, *Neospora caninum* infection, and trauma have been proposed.[18,39,40]

195.7 INHERITED MYOPATHIES

195.7.1 Muscular Dystrophies

Muscular dystrophies are a group of inherited myopathies clinically defined by a muscular weakness and histologically characterized by chronic degeneration and regeneration of muscle fibers accompanied by progressive fibrosis. Among these conditions, the best known is X-linked muscular dystrophy.

195.7.2 X-Linked Muscular Dystrophy

X-linked muscular dystrophy results from an alteration of the gene dystrophin, as is the case in Duchenne muscular dystrophy in humans. The absence of dystrophin or production of abnormal dystrophin leads to degeneration of the muscle fibers. The gene is carried by the X chromosome, and in a natural environment, only males are affected. The canine disease was initially identified in the golden retriever,[41,42] in which the mutation was cloned.[43] Since then, the disease has been detected in the rottweiler, Samoyed,[44] Groenendaeler shepherd,[45] and miniature schnauzer.[46] The clinical signs appear at about 8 weeks of age and manifest as muscular weakness, stiffness in gait, and reduced opening of the mouth. Within a few weeks, exercise intolerance appears and the muscles become atrophic. Hypertrophy of the esophageal muscle, the tongue, and the diaphragm can lead to severe digestive signs. The dog's gait becomes peculiar; abduction of the elbows, adduction of the hocks, and lordosis occurs in older animals. The signs usually stabilize by about 6 months of age, and movement becomes restricted with the onset of muscular fibrosis. There is no neurologic deficiency. Life expectancy depends on the severity of the signs. Death may occur within the first few days, caused by severe diaphragmatic necrosis,[47] or the animal may survive for several years and die after progressive deterioration of its general condition and because of difficulty eating. The onset of dilated cardiomyopathy is gradual, and this condition is considered a major cause of mortality.[48] The CK levels vary (10,000 to 30,000 IU/L). EMG reveals high-frequency and pseudomyotonic discharges.

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Muscle biopsy reveals necrosis with an influx of macrophages and phagocytosis, muscle regeneration, and sites of intracellular calcification.[49] Some muscles, such as the sartorius, the extensor carpi radialis, the deltoid, and the cranial tibial muscle, are affected earlier and more severely. Fiber size varies with the centralized nuclei.

195.8 OTHER MUSCULAR DYSTROPHIES

Several cases of canine muscular dystrophies without dystrophin deficiency have been reported.[50,51]

195.8.1 Labrador Retriever Myopathy

Labrador retriever myopathy is an autosomal recessive myopathy that has been reported in the United States, Australia, Great Britain, and France. It has been initially described as a dystrophic disease affecting type 2 muscle fibers.[28] The cause of the disease remains unknown. Muscle biopsy specimens display a mixture of denervation and primary myopathies.

Clinical signs appear by 8 weeks to 11 months of age, the peak being around 4 months.[52,53] General weakness is seen with muscle atrophy, most visibly in the temporal muscles. Neck ventroflexion and a bunny hopping

gait are also noted. Fatigability is variable. The animal has a very slender profile, in contrast to the muscular stature of a healthy Labrador. Tendon reflexes are absent or reduced. Some dogs have kyphosis or megaesophagus. Clinical signs stabilize after 8 months of age, and the disease is not lethal. The CK level is normal, and EMG reveals early fibrillation potentials, slow positive waves, and repetitive complex discharges that disappear in aged dogs. Muscle biopsy shows a marked diameter difference, with small angular or round fibers and large fibers with centralized nuclei. Later in the course of the disease, most fibers display centrally placed nuclei.[54] Necrosis is visible on rare occasions.[28]

195.8.2 Myotonia

Nondystrophic myotonia is caused by dysfunction of one or several ionic sarcolemmal channels, mainly the chloride and sodium channels. Myotonic or pseudomyotonic syndrome may be continuous or transient and can be drug induced.

In the chow chow, myotonia is inherited with an autosomal recessive trait. Nonetheless, certain descendants may exhibit autosomal dominant transmission with incomplete penetrance. Clinical signs are visible at 10 to 12 weeks of age.[55,56] These dogs have excess muscle mass. Immediately after rest the gait is stiff, and animals may frequently fall forward with the forelimbs spread out. Dyspnea and hypoxia are common because the respiratory muscles are unable to respond to the rise in metabolic requirements. A myotonic dimple persists several seconds after percussion on the surface of a muscle. Myopathy stabilizes after a few months, but because myotonia occurs in young animals, bone or articular deformations may appear. The CK level is normal or only moderately increased, and myotonic discharges are seen on EMG. Muscle biopsy is not specific; it displays mild abnormalities, mainly hypertrophy of the muscle fibers with some centralized nuclei. No satisfactory therapy is available, although the disease itself is not life-threatening. A possible dystrophic myotonia in boxers was recently described.[57]

195.8.3 Metabolic Myopathy

Glycogenoses are storage diseases caused by an enzymatic deficiency in glycolytic metabolism that leads to the accumulation of glycogen in cells. Signs are nonspecific. Muscular weakness, fatigability, syncope, rhabdomyolysis, and convulsions caused by hypoglycemia after a period of fasting or moderate exercise are clinical hallmarks. Seven types have been identified in humans, but only three have been identified in dogs. Type II glycogenosis, or Pompe's disease, is caused by a deficiency in alpha-glucosidase (acid maltase). This disease has been described in the spitz.[41] The mode of transmission is autosomal recessive. Clinical signs are usually observed by 6 months of age, and the animal usually dies in its second year.[58–60] Type III glycogenosis, or Cori's disease, is caused by a deficiency in amylo-1,6-glucosidase. In the German shepherd, clinical signs appear during the second month, and the disease is rapidly fatal.[61] Type VII glycogenosis, which is caused by a phosphofructokinase deficiency, has been identified in a colony of springer spaniels[62] and in an American cocker spaniel.[63] The animals show exercise intolerance and suffer from muscle cramps and hemolytic anemia. Mitochondrial myopathies are characterized by a functional abnormality (an enzymatic deficiency) or a structural abnormality of the mitochondria (membrane transporter deficiency). An enzymatic deficiency in pyruvate dehydrogenase has been identified in the clumber spaniel and the Sussex spaniel.[35] In these dogs, exercise leads to collapse and severe metabolic acidosis. Another mitochondrial myopathy is suspected in the Old English sheepdog, but the biochemical substrate remains unknown.[64]

Lipid storage has been noted in muscle in dogs with myopathies.[35,65] Clinically, once the dogs reach adulthood, they show muscle weakness and muscle pain. Tremors, stiffness, and fatigability may well be encountered.

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196 CHAPTER • 196 Feline Myopathies

Frédéric P. Gaschen

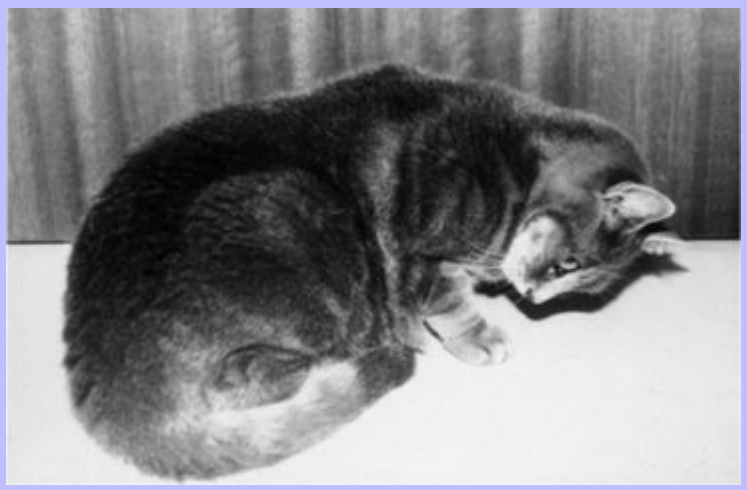
Boyd R. Jones

Although muscle and neuromuscular junction diseases occur relatively rarely in cats, a number of congenital and acquired feline myopathies have been described over the last 20 years.[1] Muscle weakness is a common clinical sign and may cause a stiff, stilted gait. Weak cats are more prone to show cervical ventroflexion than other species with muscle disease because they lack a nuchal ligament (Figure 196-1). Other clinical signs include mild lower motor neuron (LMN) deficits, tiredness, and changes in muscle size (swelling, hypertrophy, atrophy), possibly accompanied by pain in some diseases. Cats with acquired myopathies may additionally show clinical signs involving other organ systems.

The clinical investigation of cats with suspected muscle diseases is similar to that described for muscle disease in the dog. The special techniques for investigation, including electromyography (EMG), muscle biopsy, and histologic and histochemical analysis, are described elsewhere in this text. Specific feline serologic tests such as testing for the retroviruses, feline immunodeficiency virus (FIV) or feline leukemia virus (FeLV), and for the protozoan *Toxoplasma gondii* may be required.

In spite of the relative rarity of muscle diseases in cats, it is important for clinicians who regularly examine feline patients to recognize and identify the specific feline disorders in a timely way. A good knowledge of these diseases and their features is necessary to enable a diagnosis to be made and prognosis to be given. Treatment of individual cats and advice to breeders that may help them to eliminate an hereditary trait from their breeding lines both depend on an accurate diagnosis. The congenital myopathies described in the cat are shown in Table 196-1.

Figure 196-1 Adult cat with severe weakness and cervical ventroflexion.



196.1 CONGENITAL MYOTONIA

Primary congenital myotonia has been reported in a variety of species but only recently in the cat.[2,3] The clinical features of myotonia in cats described by Hickford and colleagues[2] and Toll and colleagues[3] are very similar. The affected cats walk with a stiff, awkward gait. The limbs are abducted when walking due to poor flexion of proximal appendicular joints. Widespread hypertrophy of muscle groups occurs. The stiffness is worse on awakening and in cold weather, but it improves with exercise. When affected kittens are startled, they may stiffen and fall into lateral recumbency with legs extended. Spasm of the eyelids and facial muscles frequently occur when the cats are startled (Figure 196-2). Their jaws cannot be opened fully, and mild dysphagia sometimes occurs. Clinical chemistry, including serum (CK) activity is normal.

The presence of a dimple on percussion of muscle (tongue or skeletal muscle) and the occurrence of spontaneous high-frequency discharges that wax and wane on EMG after insertion of a needle electrode and the "dive bomber" sound are features of all affected cats (Figure 196-3).

Histologic section of muscle shows a variation in fiber size, central nuclei, and proliferation of sarcolemmal nuclei.[2,3] The reports of myotonia in cats neither described treatment nor emphasized that medical treatment was required.

196.2 DYSTROPHIN-DEFICIENT MYOPATHY

Feline dystrophin deficiency, like that in other species, is due to a mutation in the dystrophin gene—a very large gene located on the X chromosome—and is transmitted according to an X-linked recessive inheritance pattern.[4] In cats the most prominent sign is severe hypertrophy of the axial and proximal appendicular skeletal muscles (Figure 196-4). The tongue and diaphragm also show massive hypertrophy in some individuals, and this can result in potentially lethal complications, such as esophageal compression, insufficient water intake, and severe hyperosmolality due to dehydration.[4]

Dystrophin-deficient kittens cannot be differentiated from normal kittens at birth, although they are slow to grow. Appendicular muscular hypertrophy is first seen around 10 weeks of age, followed by axial muscle hypertrophy, especially of the cervical muscles. Dystrophin deficiency causes a disease often called *hypertrophic feline muscular dystrophy* (HFMD). These animals have a stilted gait, and they tend to "bunny hop" when they run. Occasionally, they show marked stiffness and reluctance to move.

Dystrophin-deficient cats develop a subclinical cardiomyopathy with myocardial hypertrophy from 6 to 9 months of age.[5] Fractional shortening of the left ventricle is usually normal, suggesting normal left ventricular contractility. These cats infrequently develop clinical signs of heart failure, but some older cats have died from cardiomyopathy (Gaschen, unpublished observations).

Table • 196-1 Congenital Myopathies

DISEASE	AFFECTED BREEDS AND GEOGRAPHIC PROVENIENCE	MODE OF INHERITANCE	UNDERLYING DEFECT	CLINICAL SIGNS	PROGNOSIS
Congenital myotonia	DSH (NZ, USA)	Autosomal recessive	Probable defect in chloride channels	Stiff gait; hyperactivity of selected muscle groups when startled; percussion dimple	Fair to good (nonprogressive condition, cats enjoy a normal quality of life)
Devon Rex myopathy	Devon Rex (AUS, GB)	Autosomal recessive	Unknown	Cervical ventroflexion; generalized muscle weakness; abnormal gait; megaloesophagus	Poor (many cats die of asphyxiation)
Dystrophin-deficient myopathy	DSH (USA, NL, CH)	X-linked recessive	Dystrophin deficiency	Skeletal muscle hypertrophy with possible complications; sensitivity to stress; stiff gait	Guarded to fair (cats can have almost normal quality of life but may require more frequent veterinary visits)
Glycogen storage disease type IV	Norwegian forest cats (USA, Europe)	Autosomal recessive	Glycogen branching enzyme (GBE) deficiency	Stillbirth; muscle tremor; muscle atrophy; cardiomyopathy	Poor (all cats eventually die)
Hypokalemic myopathy	Burmese (AUS, NZ, GB, NL)	Probably autosomal recessive	Unknown	Transient, paroxysmal clinical signs with generalized muscle weakness, cervical ventroflexion	Good response to potassium supplementation
Malignant hyperthermia	DSH	Unknown	Unknown	Severe hyperthermia during anesthesia (halothane)	Poor (the two reported cats died)
Merosin-deficient myopathy	DSH, Siamese (USA)	Unknown	Merosin (laminin α2) deficiency	Hindlimb weakness from 6 months old, worsening to muscle atrophy and contractures at 1 year old	Poor (both cats were euthanized before 2 years of age)
Myasthenia gravis (MG)	DSH	Unknown	Lack of acetylcholine receptors	Generalized muscle weakness	Fair, generally good response to therapy
Nemaline myopathy	DSH (USA)	Possibly autosomal recessive	Unknown	Progressive weakness (6–18 months); rapid, choppy, hypermetric gait; tremor, exercise intolerance	Poor (all five reported cats died or were euthanized)

AUS, Australia; *CH,* Switzerland; *GB,* Great Britain; *NL,* Netherlands; *NZ,* New Zealand; *USA,* United States of America.
From Gaschen F et al: Congenital diseases of feline muscle and neuromuscular junction, *J Feline Med Surg*, 2003 (in press).

EMG findings include myotonic discharges, fibrillation potentials, prolonged insertional activities, complex repetitive discharges, and positive sharp waves.

In young and adult cats, serum (CK) activity is increased, but serum CK concentrations do not allow a differentiation of dystrophin-deficient kittens from normal littermates at birth. Serum aspartate transaminase (AST) and alanine aminotransferase (ALT) are also increased.

Histopathologic changes in dystrophin-deficient skeletal muscle include variation in myofiber diameter, with large myofibers showing splitting, foci of degeneration and regeneration, with minimal mononuclear infiltration and absence of endomysial or perimysial fibrosis. Severe dystrophic calcification can be present. A definitive diagnosis is made when immunohistochemistry (IHC) staining confirms a lack of dystrophin at the sarcolemma.

The prognosis for HFMD is fair; no specific treatment is available. Many cats enjoy a nearly normal quality of life. However, stress, intense physical activity, and inhalant anesthesia should be avoided if possible because they may elicit acute rhabdomyolysis.[6]

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Figure 196-2 An affected kitten showing flattening of the ears and retraction of the lip after receiving a fright. (From Hickford FH et al: Congenital myotonia in related kittens, *J Small Anim Prac* 39:281, 1998, with permission.)

196.3 MYOPATHY OF DEVON REX CATS

This myopathy has been reported in many countries: Australia, New Zealand, the United Kingdom, and the United States.[7]

The most obvious and consistent clinical sign is passive ventroflexion of the head and neck. Ventroflexion is frequently accentuated when walking, during micturition and defecation. Typically the animal has a high-stepping forelimb gait, head bobbing, and dorsal protrusion of the scapulae. Due to weakness of the shoulder girdle musculature with exertion, they tire easily and eventually collapse in sternal recumbency.

Myopathic Devon Rex cats frequently rest in a characteristic “dog-begging” position, with their front paws on a supporting object (Figure 196-5). One of the significant features of the disease is the difficulty affected cats have prehending food and swallowing. They can choke and asphyxiate due to the accumulation of ingesta in the pharynx. The severity of signs often fluctuate from day to day. Stress, concurrent illness, exertion, and cold all tend to accentuate weakness.

Figure 196-3 Electromyography (EMG) recording from the biceps muscle of an affected kitten showing waxing and waning, high-frequency discharges after needle insertion. (From Hickford FH et al: Congenital myotonia in related kittens, *J Small Anim Prac* 39:281, 1998, with permission.)

Figure 196-4 Adult dystrophin–deficient cat with appendicular muscle hypertrophy and hypertrophy of the tongue.

The age of onset is variable, and less seriously affected kittens may go unnoticed for several months. Breeders normally recognize the affected kittens at about the time they start to walk. The disease is inherited as an autosomal recessive trait.

In the one detailed study by Malik and colleagues[7] of four cats with this muscle disorder, esophageal hypomotility and megaesophagus were identified in all animals. Hematologic and serum biochemistry values including electrolytes and CK are within reference ranges.[7] Sparse fibrillation potentials and positive sharp wave activity may be detected on EMG of the upper limb and cervical muscles.

Skeletal muscles appear grossly normal, but histologic changes are best identified in dorsal cervical and proximal forelimb muscles. The severity of the changes correlates with both the severity of signs and the age of the cat.[7] In muscle biopsies, the significant lesions are variation in cross-sectional area, more rounded fibers, occasional degenerating fibers, some fiber segmentation, and increased subsarcolemmal nuclei. Lesions do not affect one fiber type in particular, and dystrophin is present. No specific treatment is available, but feeding from a raised platform can help ingestion of food and prevent choking.

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Figure 196-5 Young Devon Rex kitten showing the characteristic posture when resting. (Published with permission of Manon publishing.)

196.4 NEMALINE ROD MYOPATHY

Affected cats are normal until 6 to 18 months of age; then they develop muscle atrophy and weakness, and their gait becomes wobbly. They show a fast, jerky, and hypermetric gait and a crouched stance with an exaggerated hip and tarsal flexion. These cats become quickly exhausted and pant after exertion. The clinical course is slowly progressive. CK activity in serum is increased, but no changes are seen on EMG examination. Myofibers contain nemaline rods. The prognosis is poor, and most affected cats are euthanized for humane reasons.[1]

196.5 LAMININ α2 (MEROSIN) DEFICIENCY

Laminin 2, also called *merosin*, is a glycoprotein indirectly anchoring the cell membrane and the basal lamina and is present in skeletal muscle and Schwann cells. O'Brien and colleagues have described two merosin-deficient cats.[8] Hindlimb weakness starts at 6 months of age and is followed by generalized muscle atrophy by 12 months of age. Hindlimb muscle contractures are present. Serum CK is increased, and the motor nerve conduction velocity is markedly decreased. Myofiber necrosis, variation in fiber size, and lipid accumulation are present in muscle, and axonal demyelination is present in peripheral nerves. IHC stains show a lack or decrease of laminin α2 in skeletal muscle.

196.6 GLYCOGEN STORAGE DISEASE TYPE IV

A myopathy associated with glycogen storage disease type IV has been reported in Norwegian forest cats.[9] Many affected cats are stillborn or die within the first few days of life. The surviving cats are often normal until they reach 5 to 7 months of age. They may show clinical signs of persistently increased body temperature, generalized muscle tremors, intermittent listlessness and a “bunny hopping” gait, muscle weakness, atrophy, and contracture. Most affected cats die by 10 to 14 months of age.

The disease is due to a lack of the glycogen branching enzyme (GBE) and is characterized by accumulation of abnormal glycogen in several tissues including skeletal muscle. Hereditary transmission occurs according to an autosomal recessive pattern. Affected cats are homozygous for a deletion in the GBE gene causing instability of mRNA.

Serum CK and ALT are increased. Fibrillation potentials and bizarre high-frequency discharges are present in the EMG. Cytoplasmic inclusions containing periodic acid-Schiff (PAS) and toluidine blue–positive material are present in many organs.

Diagnosis of the disease in an affected kitten unequivocally identifies the parents as carriers of the mutation, which should have direct implications for their use in any breeding program. A DNA-based carrier test is available in selected laboratories to screen problem breeding families.

196.7 MYASTHENIA GRAVIS

Acquired myasthenia gravis (MG) is a rare disease, but sporadic reports and a published series of 20 cases exist.[10] Congenital MG has been described in two cats.[11] Acquired feline MG is an immune-mediated disease as evidenced by the presence of serum acetylcholine receptor antibodies. The main clinical sign is muscle weakness. Ducote and colleagues described three distinct forms.[10] Cats with focal MG have signs isolated to the esophageal, pharyngeal, laryngeal, or facial muscles. Generalized MG is characterized by appendicular muscle weakness with or without esophageal, pharyngeal, laryngeal, or facial muscle involvement. Acute fulminating MG is a severe acute onset form of generalized MG with a rapid progression of muscle weakness often associated with respiratory muscle paresis or paralysis.

The diagnosis of MG in the cat is similar to the dog and includes an increase in muscle strength after intravenous edrophonium hydrochloride administration, decremental evoked muscle action potential response to repetitive nerve stimulation, and an increase in serum ach-receptor antibody concentration. MG in cats may be associated with a thymic mass (thymoma) and concurrent immune-mediated myositis. Thoracic radiography and muscle

biopsy may be indicated in selected cases. Treatment of feline MG patients includes administration of anticholinergics (pyridostigmine 0.25 to 1 mg/kg every 12 hours) with the dose titered to the clinical response. An immunosuppressive dose of prednisone (2 to 4 mg/kg every 24 hours) is indicated if aspiration pneumonia is absent.

196.8 HYPOKALEMIC POLYMYOPATHY

A polymyopathy associated with total body potassium depletion has been recognized in cats of all breeds, ages, and both sexes.[12] Some cats with chronic renal failure and cats eating acidifying diets are affected. Cats with polyuria or polydipsia secondary to hyperthyroidism and cats with anorexia from any cause may also be at risk. Severe total body depletion of potassium occurs secondary to decreased dietary intake or increased urinary excretion of potassium.[12]

Burmese kittens develop hypokalemia associated with disturbances of the intracellular and extracellular balance of potassium.[12] The condition has a familial and inherited basis (putative autosomal recessive), with affected kittens being produced in specific lines of this breed.[12,13]

The significant clinical sign in these cats is weakness characterized by persistent ventroflexion of the neck; a stiff, stilted gait; and reluctance to move. Muscle pain may be elicited on palpation, but the neurologic examination is normal. Clinical signs may have an acute onset and may be episodic. Serum CK activity is often high (>50,000) and the serum potassium concentration is decreased (<3.0 nmol/L), and increased fractional urinary excretion of potassium can be measured (>10% to 15%). No evidence exists for reduced potassium intake or urinary potassium loss in affected Burmese kittens. Many affected cats have renal disease; urea and creatinine concentrations are elevated. Hypokalemia can result in decreased glomerular filtration, which can alter urine-concentrating mechanisms; therefore a low urine specific gravity is not a good guide to renal function.

Mild diffuse EMG changes, including increased insertional activity, positive sharp waves, fibrillation potentials, and high-frequency discharges have been recorded in affected cats. Muscle biopsies show mild myonecrosis or are normal.[13]

Signs of hypokalemic polymyopathy usually resolve after parenteral or oral supplementation of potassium. Oral treatment with potassium gluconate is recommended for mildly affected cats (Kaon Elixir, Adria Laboratories, Columbus, OH; Tumil K, Daniels Pharmaceuticals) at a dose of 2 to 4 nmol/cat twice a day for 2 days, then once daily. The dose administered is adjusted based on the response and the serum potassium concentration. Cats with more dramatic hypokalemia (<2.5 nmol/L) or those with severe muscular weakness will initially require parenteral administration of intravenous saline or lactated ringers with supplemented potassium chloride. Intravenous infusion of potassium should not exceed 0.5 nmol/kg/hour. Oral supplementation with potassium gluconate should be continued and potassium concentration measured at regular intervals.

196.9 HYPERTHYROIDISM

Hyperthyroidism is one of the most common endocrinopathies affecting older cats. Mild muscle weakness is a relatively frequent accompanying sign. However, severe muscle disease only affects a low percentage of hyperthyroid cats.[15] The pathogenesis of hyperthyroid myopathy is unknown. In humans, depletion of energy-rich molecules in the striated muscle and intracellular displacements of potassium have been suspected.[15] In cats, hyperthyroidism may be associated with hypokalemia and hypokalemic myopathy.[16] Increased renal losses of

potassium may occur without evidence of azotemia because hyperthyroidism generally leads to an increase in renal plasma flow and may mask the presence of renal insufficiency. In such cats, renal disease may only become obvious after onset of treatment.

Generalized muscle weakness with abnormal gait and exercise intolerance occur relatively frequently. Sometimes, cervical ventroflexion can occur before hyperthyroidism is diagnosed. In addition to the typical laboratory finding observed in hyperthyroidism, serum activity of CK can be increased. The prognosis is good: signs of muscle weakness usually disappear after hyperthyroidism has been successfully treated. In treated cats developing overt renal failure, regular monitoring of serum potassium concentration and oral potassium supplementation (see previous discussion) are essential for a successful outcome in addition to adequate management of chronic renal failure.

196.10 PARASITIC POLYMYOSITIS

The cat is the definitive host of the protozoal parasite *Toxoplasma gondii*. Although the parasite mainly undergoes an enteroepithelial cycle in this species, it can also occasionally lead to the formation of tissue cysts and cause clinical signs. The prevalence of antibodies against *Toxoplasma* spp. in cats varies from 30% to more than 65%, depending on the geographic area. Prevalence increases with age due to the higher risk of contact with *Toxoplasma*. However, only a small fraction of seropositive cats develop clinical toxoplasmosis.[17]

Typical clinical signs include poor general condition with anorexia, lethargy, and fever. Toxoplasmosis affects different organs such as the lungs, CNS (brain, spinal cord), liver, pancreas, heart, and eyes. In contrast to dogs, myositis is only rarely observed in cats.[17] However, if muscle weakness, exercise intolerance, and myalgia are present, toxoplasmosis should be considered as a differential diagnosis. Positive immunoglobulin M (IgM) titers and increasing immunoglobulin G (IgG) titers can help confirm the diagnosis. Immunodeficiency (e.g., after retroviral infections) can increase the risk of new infections or reactivate chronic *Toxoplasma* infections.[17] (Treatment and prognosis of feline toxoplasmosis are described in detail in the section on infectious diseases.)

196.11 OTHER FORMS OF POLYMYOSITIS

Polymyositis may occur in association with various diseases. Adult cats experimentally infected with FIV show histologic and occasionally EMG changes in skeletal muscle in the absence of clinical signs of muscle disease.[18] Some cats with thymoma can develop a paraneoplastic polymyositis that is sometimes associated with dysphagia.[19] Idiopathic polymyositis is an inflammatory muscle disease for which no specific cause can be found, and an immune-mediated pathogenesis is suspected.[19–21]

The clinical signs are muscle weakness of varying severity; cervical ventroflexion is occasionally observed. Affected cats may show dysphagia, especially with paraneoplastic or idiopathic polymyositis. The serum concentration of CK is significantly increased. Nonspecific EMG changes are present with normal nerve conduction velocities. Multifocal inflammatory infiltrates with mononuclear cells[18,19] are observed histologically.

Idiopathic polymyositis is treated with immunosuppressive doses of glucocorticoids (prednisolone 2 mg/kg twice a day). The prognosis is guarded to good for idiopathic polymyositis, but dysphagia or the presence of megaesophagus are poor prognostic signs.[20,21]

196.12 ISCHEMIC NEUROMYOPATHIES

196.12.1 Arterial Thromboembolism Associated with Cardiomyopathy

Arterial thromboembolism is a significant complication of feline cardiomyopathies and occurs most frequently in the distal aorta. It may also rarely occur secondary to neoplasia in cats without cardiovascular disease.[22] Recently, 271 cats with feline arterial thromboembolism (FATE) were described in three large retrospective studies.[22–24] The main features of these cases are summarized in Table 196-2.

The high proportion of male cats may reflect the high prevalence of hypertrophic cardiomyopathy in male cats.[20] Frequently, cats with FATE have no previous history of cardiac disease. Affected animals most often experience acute to peracute onset of bilateral hind limb paralysis. However, unilateral hind limb or front limb involvement can be observed. Paralysis or paresis is often accompanied by painful swelling of all involved muscles. In the affected hind limbs, the femoral pulse is absent or, with partial embolism, it is weaker. Cyanosis of the unpigmented nail beds and foot pads is observed when compared with the unaffected limbs. The cardiovascular signs of cats with FATE are discussed elsewhere in this text.

In the published case studies, laboratory changes included increases in serum activities of CK, ALT, and AST in most cats and azotemia in up to one half of the cases.[22] Bilateral embolism of the hind limbs and absence of motor function in the affected limbs were negative prognostic factors.[22] Cats that survived the FATE episodes had higher body temperature (mean 99° F [37.7° C] versus 96.5° F [35.8° C] and higher heart rates (median 210 versus 188 beats per minute). The diagnosis of congestive heart failure (CHF) did not appear to significantly influence the prognosis.[22]

Management of FATE includes supportive treatment, including intravenous fluids and oxygen supplementation. Analgesia with opiates (buprenorphine, oxymorphone, or fentanyl) is essential, because most signs of distress are due to pain and abate once the pain is controlled. The use of anti-coagulant and antithrombogenic drugs is controversial. Aspirin is often administered as an antithrombogenic drug, but efficacy data is lacking. No differences in outcome were noticed between cats with FATE receiving anti-inflammatory (81 mg/cat every 72 hours) and low (5 mg/cat every 72 hours) doses of aspirin.[22] Thrombolytic therapy with streptokinase, an activator of fibrinolysis, was studied in 46 cats with FATE. The survival rate did not significantly differ from that of cats receiving no streptokinase in other retrospective studies; however, the authors claim that their study population was more severely affected than cats in other studies.[26] The underlying cardiomyopathy must be treated according to the recommendations given elsewhere in this text.

Table • 196-2 Diagnostic Features of Feline Arterial Thromboembolism

PARAMETER	LASTE ET AL, 1995	SHOEMAN, 1999	SMITH ET AL, 2003
Number of cats	100	44	127
Prevalence in hospital population	N/A	N/A	0.57%
Signalment:			
Mean age (years)	7.7	8.7	8.6
Gender distribution in % (M:F)	67:33	75:25	67:33
History:			
No previous diagnosis of cardiac disease	89%	77%	93.0%
Vomiting shortly before thromboembolic episode	N/A	6.8%	15.7%
Physical examination:			
One limb affected	N/A	N/A	24.8%
Two or more limbs affected	N/A	N/A	75.2%
Partial thromboembolism	20%	31%	N/A
Hypothermia	35%	N/A	65.5%
Tachypnea	26%	N/A	90.8%
Cardiac parameters:			
Cardiac murmur	35%	N/A	30.7%
Gallop rhythm	20%	N/A	24.4%
Arrhythmia	19%	N/A	15.7%
Mod to severe LA enlargement	71.2% (n=63)	66% (n=9)	91.0% (n=78)
Congestive heart failure (CHF)	66.3% (n=80)	51% (n=25)	44% (n=125)
Laboratory parameters:			
Increased CK	N/A	80% (n=5)	100% (n=87)
Increased ALT	88.7% (n=53)	N/A	72.8% (n=87)
Increased AST	84.9% (n=53)	N/A	98.6% (n=87)
Increased BUN	54.7% (n=53)	N/A	41.3% (n=87)
Increased creatinine	56.6% (n=53)	N/A	26.3% (n=87)

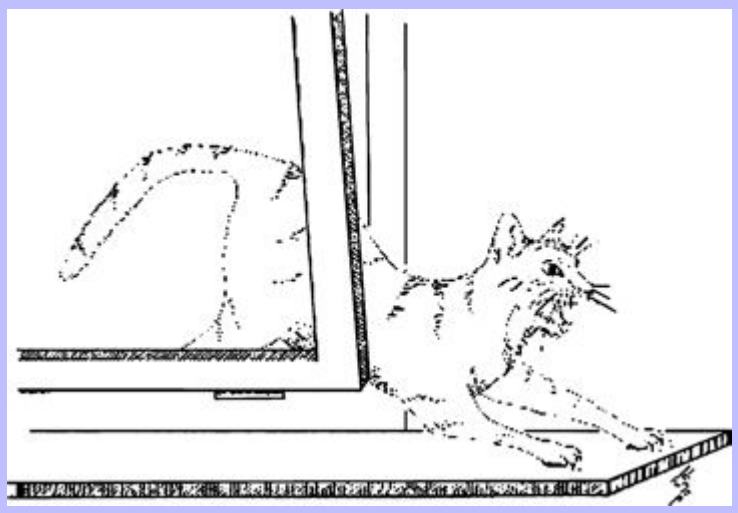
In recent retrospective studies, 35% to 39% of cats survived episodes of FATE, 28% died during the initial hospitalization, and 33% to 35% were euthanized.[22–24] In one study, survival rate was better during the last 10 months of the study (up to 75% survivors) than during the 9 earlier years (less than 30% survivors).[22] Among cats for which treatment was initiated, 45% survived to be discharged.[22] Depending on the study, median survival time (MST) was between 117 days and 6 months. Re-embolization occurred in 24% to 50% of discharged cats. These results confirm that FATE is associated with a poor prognosis. The underlying cardiomyopathy represents a clear risk for new thromboembolic events and contributes to the unfavorable prognosis. Rapid identification of cats with more favorable prognosis is important to allow owners to make an informed decision to treat or not. Cats that recover may have permanent ischemic muscle or nerve damage.

196.12.2 Traumatic Ischemic Neuromyopathy Associated with Bottom-Hung Pivot Windows and Garage Doors

In Europe, bottom-hung pivot windows are common. Cats try to get in or out through these windows and get themselves wedged in between the costal arch and the pelvis (see Figure 196-6). After unsuccessful efforts to free themselves, the cats become wedged with pressure on their abdomen and in a position that can lead to traumatic lesions to muscle, internal organs, blood vessels, spine, and spinal cord. A recent report reviewed the clinical features and outcome of 30 cats trapped in bottom-hung pivot windows.[27]

The signs shown were hypothermia (19 cats); pain in the hind limbs, lumbar area, and abdomen (21 cats); swelling of the hind limb muscles (7 cats); cold hind limbs (6 cats); weak femoral pulse (10 cats); absent femoral pulse (9 cats); and paraparesis or paraplegia (17 cats), often associated with decreased spinal reflexes in the hind limbs (see Figure 196-6). Deep pain perception was decreased in two cats and absent in four.

Figure 196-6 A cat trapped in a bottom-hung pivot window.



Moderate hyperkalemia may be have been due to reperfusion injury after the cats had been freed from the window.

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Serum activities of CK and AST were massively increased, with a moderate increase in ALT. Hematuria was present in some cats. Abdominal radiographs showed soft tissue density underneath the lumbar spine or in the retroperitoneal area, with a loss of contrast in the caudal abdomen. Occasionally, fractured vertebrae were present.

Medical treatment included fluid therapy, management of pain, and administration of antibiotics and high dose of corticosteroids. Physical therapy consisting of massage of the involved muscles and gentle manipulation of the hind limbs was performed once the limbs were less painful.

The prognosis was good. Eighty percent of the cats were discharged, and all but one recovered fully within 1 month.[26] The duration of the hospital stay was between 1 and 12 days.

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197 CHAPTER • 197 Pathophysiology of Heart Failure

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Denise Saretta Schwartz

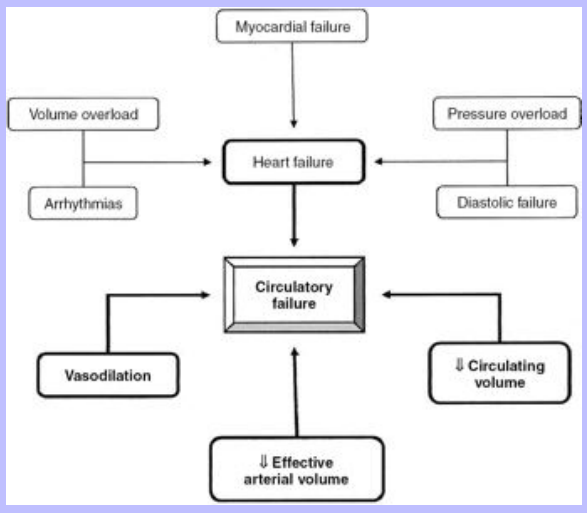
The heart, consequently, is the beginning of life; the sun of the microcosm, even as the sun in his turn might well be designated the heart of the world; for it is the heart by whose virtue and pulse the blood is moved, perfected, and made nutrient, and is preserved from corruption and coagulation; it is the household divinity which, discharging its function, nourishes, cherishes, quickens the whole body, and is indeed the foundation of life, the source of all action.

William Harvey (1628)

197.1 WHAT IS HEART FAILURE?

Heart failure is a clinical syndrome in which impaired pumping decreases ventricular ejection and impedes venous return. During heart failure the heart cannot pump blood at a rate adequate to maintain metabolizing tissue requirements, or it can do so only with elevated filling pressures.[1] However, this definition is not complete because it does not mention that heart failure is a progressive disease.[2] The hemodynamic abnormalities associated with heart failure are in many cases complicated by depressed myocardial contractility and relaxation, caused by biochemical and biophysical disorders in the myocardial cells. These cellular disorders, in turn, are partly the result of molecular abnormalities that not only impair the heart's performance, but also accelerate deterioration of the myocardium and hasten myocardial cell death.[3] *Circulatory failure* is a decrease in cardiac output caused by abnormalities in one or more components of the circulation (i.e., heart, blood volume, oxyhemoglobin concentration, vasculature). Heart failure therefore is one of the many causes of circulatory failure (Figure 197-1).

Figure 197-1 Causes of circulatory and heart failure.



The heart, like any pump, has only two ways to fail: It either cannot pump enough blood into the aorta or pulmonary artery to maintain arterial pressure (low-output heart failure), or it cannot adequately empty the venous reservoirs (congestive heart failure [CHF]). Heart failure therefore can be recognized clinically by signs of low cardiac output (e.g., depression, lethargy, hypotension) or congestion (e.g., ascites, pleural effusion, pulmonary edema). Heart failure can also be classified, based on the side that is failing, as right, left, or bilateral heart failure. Right-sided heart failure is associated with signs of congestion in the systemic circulation (ascites, peripheral edema), whereas left-sided heart failure causes signs of congestion in the pulmonary circulation (pulmonary edema, dyspnea). Bilateral heart failure presents a combination of left-and right-side signs. In small animal practice, pleural effusion is usually associated with bilateral CHF. Both left-and right-sided heart failure can be associated with low-output signs.

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197.2 WHY DO HEARTS FAIL?

Heart failure may result from inability by the heart to eject blood properly (systolic failure), from inadequate ventricular filling (diastolic failure), or both. The final result in all three cases is a reduction in stroke volume, leading to a decrease in cardiac output and a tendency toward decreased arterial pressure. Patients with severe heart failure have reduced or inadequate cardiac output even at rest, whereas patients with mild heart failure or diastolic failure have an inadequate increase in cardiac output with perturbation (e.g., exercise or stress).

197.2.1 Systolic Function and Dysfunction

Systemic arterial blood pressure (ABP) is a result of the interplay between the arterial system and the heart. Any pressure can be estimated as the product of flow × resistance. In the cardiovascular system, cardiac output (CO), or the amount of blood pumped at a given time, is the flow, and the aortic input impedance (Z), the opposition that the vasculature offers to the ejection of blood by the heart, is the resistance factor:

$$ABP \approx CO \times Z$$

Cardiac output (CO) is the product of the left ventricular stroke volume (SV) and the heart rate (HR):

$$CO = SV \times HR$$

The higher the stroke volume, the higher the cardiac output. Increases in the heart rate increase cardiac output linearly until a plateau is reached, at which point further increases in the heart rate do not affect cardiac output. This latter effect occurs because there is less diastolic time for ventricular filling, and increases in the heart rate are balanced by decreases in the stroke volume. With further increases in the heart rate, cardiac output starts to fall. Stroke volume is primarily determined by an intrinsic property of the myocardial cell, contractility, and two coupling factors, preload and afterload. Preload and afterload are considered coupling factors because they depend on vascular changes. Stroke volume increases with increases in preload and contractility and decreases in afterload. *Preload* is the force acting to stretch the ventricular fibers at the end of diastole and to determine the maximal resting length of the sarcomeres.[4] It reflects the degree of ventricular filling just before contraction. Clinically, preload is estimated as being the end-diastolic volume or, less precisely, the end-diastolic pressure. Substitution of pressure for volume in the estimation of preload is not accurate in all clinical situations (e.g., noncompliant or stiff ventricles). *Afterload* is the force opposing ventricular ejection. This opposition is presented by the vasculature to the ejecting ventricle and is best described by the aortic input impedance.[5–7] An increase in afterload communicates itself to the ventricles during systole by increasing wall stress. The end-systolic wall stress, therefore, can be used as an index of the afterload.[7] *Contractility* is a change

in the heart's ability to do work when the preload, afterload, and heart rate are kept constant.[3,7] Stroke volume is also affected by ventricular filling during diastole, ventricular wall motion abnormalities, space-occupying lesions, and arrhythmias. All determinants of cardiac output are intertwined. Therefore as physiologic compensatory and reflex mechanisms affect one component, the other components may also change (Box 197-1).

197.2.1.1

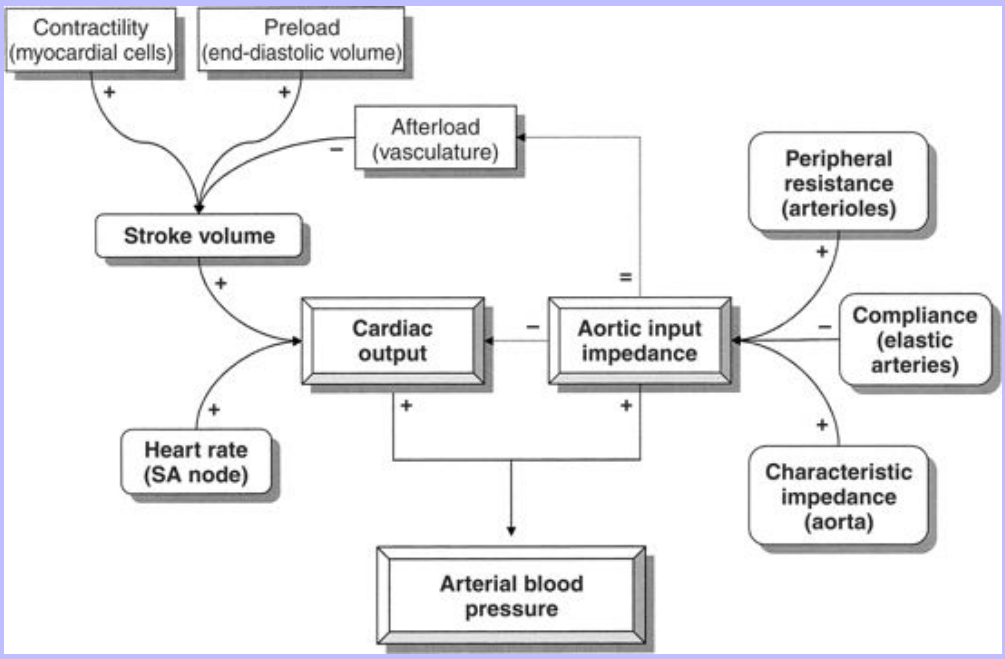
Box • 197-1 Interrelation between Determinants of Cardiac Performance and Properties of the Heart

- **Preload and contractility** → Increases in the preload lead to increases in contractility as a result of optimum myocardial fiber length and greater interaction between actin and myosin.
- **Heart rate and preload** → Ventricular filling depends on the duration of the diastolic period. Decreases in the heart rate may increase preload by lengthening diastole. Excessive increases in the heart rate interfere with ventricular filling, decreasing preload.
- **Heart rate and contractility** → Excessive increases in the heart rate decrease the diastolic period, leading to a decrease in myocardial oxygen delivery, and might negatively affect contractility. Increases in the heart rate can also decrease contractility by decreasing preload.
- **Heart rate and myocardial relaxation (lusitropism)** → Decreased diastolic myocardial oxygen delivery during fast heart rates negatively affects relaxation, an energy-dependent process. Ventricular suction capacity is impaired, and ventricular compliance is decreased because of increased stiffness.
- **Heart rate and automatism** → Increases in the heart rate decrease oxygen offer to myocardial cells, changing membrane potential and favoring the development of arrhythmias.
- **Preload and afterload** → Excessive increases in preload increase wall tension. Increases in wall tension increase afterload, leading to increased myocardial oxygen consumption.

In the estimation of blood pressure, the resistance factor is best represented by the arterial impedance, which is the aortic pressure divided by aortic flow at a given time. The properties of the arterial system can be described by the total arterial compliance, the peripheral resistance, and the characteristic impedance.[8] *Total arterial compliance* is the change in volume that results from a given change in pressure in the elastic arteries. *Peripheral resistance* is largely determined by small arteries and arterioles and represents the resistance to the steady (nonpulsatile) flow. *Aortic characteristic impedance,* the opposition to pulsatile flow, accounts for the elastic wall and blood mass properties in the proximal aorta.[8] Increases in peripheral resistance and characteristic impedance and decreases in compliance increase left ventricular afterload. With a decrease in compliance, the ventricle ejects into a stiff vasculature, increasing both the energetic cost to maintain blood flow and myocardial oxygen consumption (MVO_2). With decreased compliance, ventricles expend more energy to distend less compliant elastic arteries, making less energy available for tissue perfusion.[9,10] Characteristic impedance, a property of the proximal aorta, increases whenever the stiffness of the aorta increases or its radius becomes smaller. Increases in peripheral resistance (caused by decreases in the cross-sectional area of the arterioles) increase the mean aortic pressure and decrease the left ventricular stroke work and stroke volume.[11–13] Peripheral resistance has a greater effect on ventricular performance than does characteristic impedance or compliance.[9] However, it should be remembered that the left ventricle ejects blood into the

proximal aorta and not into the arterioles. The principal factors involved in the determination of arterial pressure are shown in Figure 197-2.

Figure 197-2 Determinants of arterial blood pressure. Arterial blood pressure is a function of cardiac output and arterial impedance. Contractility, preload, and afterload determine the stroke volume, which, multiplied by the heart rate, yields the cardiac output. Changes in arterioles, elastic arteries, and the aorta all influence the aortic input impedance (afterload). Increases in afterload increase arterial blood pressure but decrease cardiac output. (+), Increases in the parameter increase aortic input impedance, stroke volume, cardiac output, or arterial blood pressure; (–), increases in the parameter decrease aortic input impedance or stroke volume; (=), afterload and aortic input impedance are synonymous.



Systolic failure is characterized by normal filling of the ventricle and a decrease in the forward stroke volume. The decrease in SV may stem from a decrease in contractility *(myocardial failure)* or from a primary increase in ventricular pressure *(pressure overload)* or volume *(volume overload)* (Box 197-2). Increases in volume are usually caused by a leaking valve or an abnormal communication between the systemic and pulmonary circulations.

197.2.1.2 Myocardial Failure

Myocardial failure may be primary (e.g., dilated cardiomyopathy) or may occur secondary to chronic volume or pressure overload. In patients with myocardial failure, a decrease in contractility lowers the stroke volume, cardiac output, and arterial blood pressure. Myocardial failure depresses the heart's ability to compensate for the decrease in cardiac output (Figure 197-3).

197.2.1.3 Pressure Overload

The most common reasons for pressure overload in small animal medicine are subaortic stenosis and systemic arterial hypertension on the left side of the heart and heartworm disease and pulmonic stenosis on the right side. In pressure overload states, the ventricles must overcome the increase in resistance to eject blood. The first response is to dilate, increasing the sarcomere length to the point where overlap between myofilaments is optimum (approximately 2.2 μm). Dilatation increases ventricular contractility and pressure through a length-dependent activation of contractility, which helps overcome the increased resistance and maintain stroke volume. However, this adaptation increases ventricular wall stress and consequently MVO_2.

Left ventricular wall stress can be approximated as the product of intraventricular pressure times the left ventricular radius divided by twice the left ventricular wall thickness (Figure 197-4). During the initial dilatation, the ventricular radius increases and wall thickness decreases; both of these factors increase ventricular wall stress. With a sustained pressure overload, the ventricular muscle adapts by undergoing concentric hypertrophy (Figure 197-5). In this type of hypertrophy, an increase in wall thickness occurs at the expense of a decrease in chamber size (decrease in ventricular radius), returning ventricular wall stress toward normal and increasing contractility.

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197.2.1.3.1 197.2.1.3.1 Box • 197-2 Mechanisms Leading to Systolic Heart Failure*

Myocardial failure

- Dilated cardiomyopathy
- Infective myocarditis
- Doxorubicin toxicity
- Cardiomyopathy of overload
- Myocardial infarct
- Right ventricular cardiomyopathy

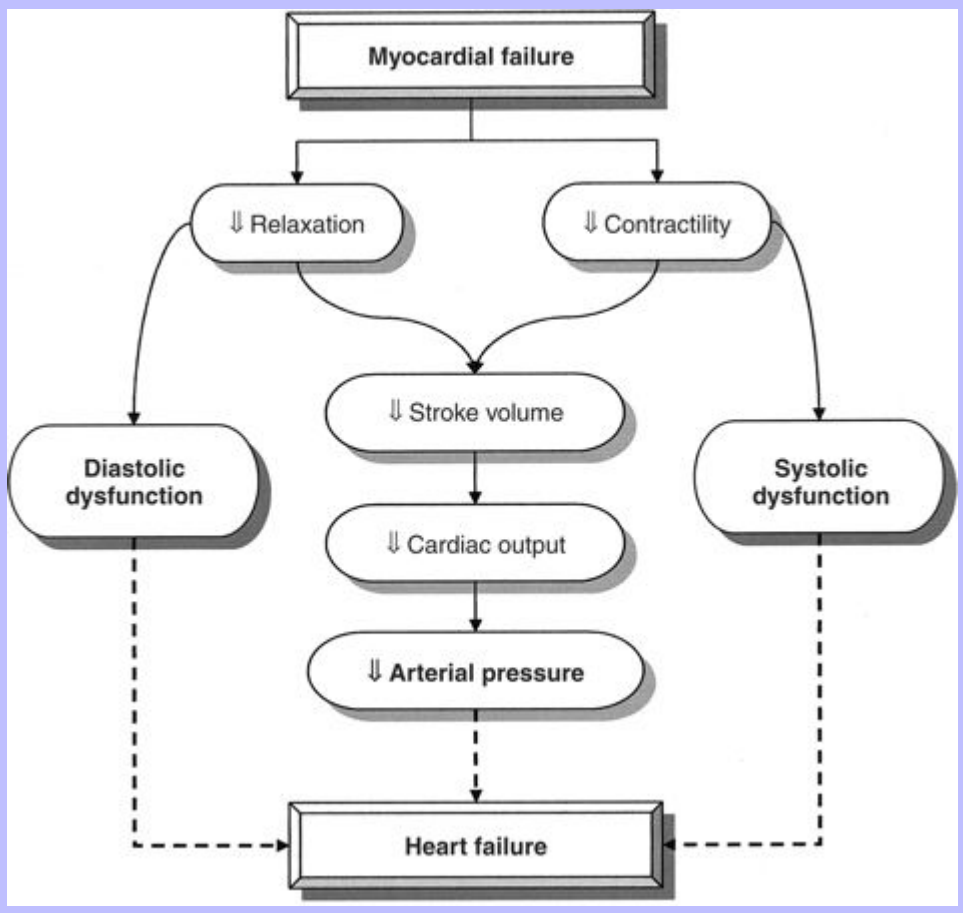
- Volume overload
  - Valvular diseases
    - Endocardiosis
    - Endocarditis
    - Rupture of mitral chordae tendineae
    - Valvular dysplasia
  - Patent ductus arteriosus
  - Ventricular septal defect
  - Atrial septal defect
  - Thyrotoxicosis
  - Chronic anemia
  - Peripheral arteriovenous fistula
- Pressure overload
  - Subaortic stenosis
  - Pulmonic stenosis
  - Systemic hypertension
  - Pulmonary hypertension
    - Primary

Pulmonary embolism

Heartworm disease

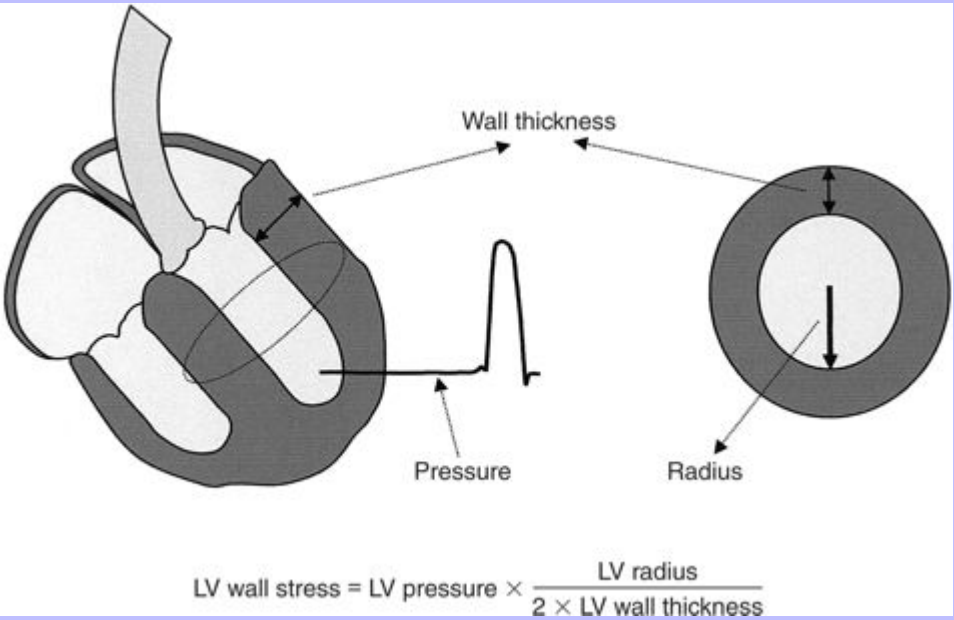
* Many disease are also associated with diastolic dysfunction.

Figure 197-3 Progression from myocardial failure to heart failure.



Myocardium that undergoes hypertrophy secondary to pressure overload is not normal. A close link exists between hypertrophy and systolic dysfunction. The hypertrophied ventricle is also prone to ischemia, which leads to fibrosis and an increase in collagen content. The early increase in collagen helps maintain systolic function, but it interferes with diastolic function. With progression of the myocardial hypertrophy, perimuscular fibrosis impairs both systolic and diastolic function.[1] As secondary myocardial failure settles in, the ventricle again dilates. The sequence of events in heart failure secondary to pressure overload is shown in Figure 197-6.

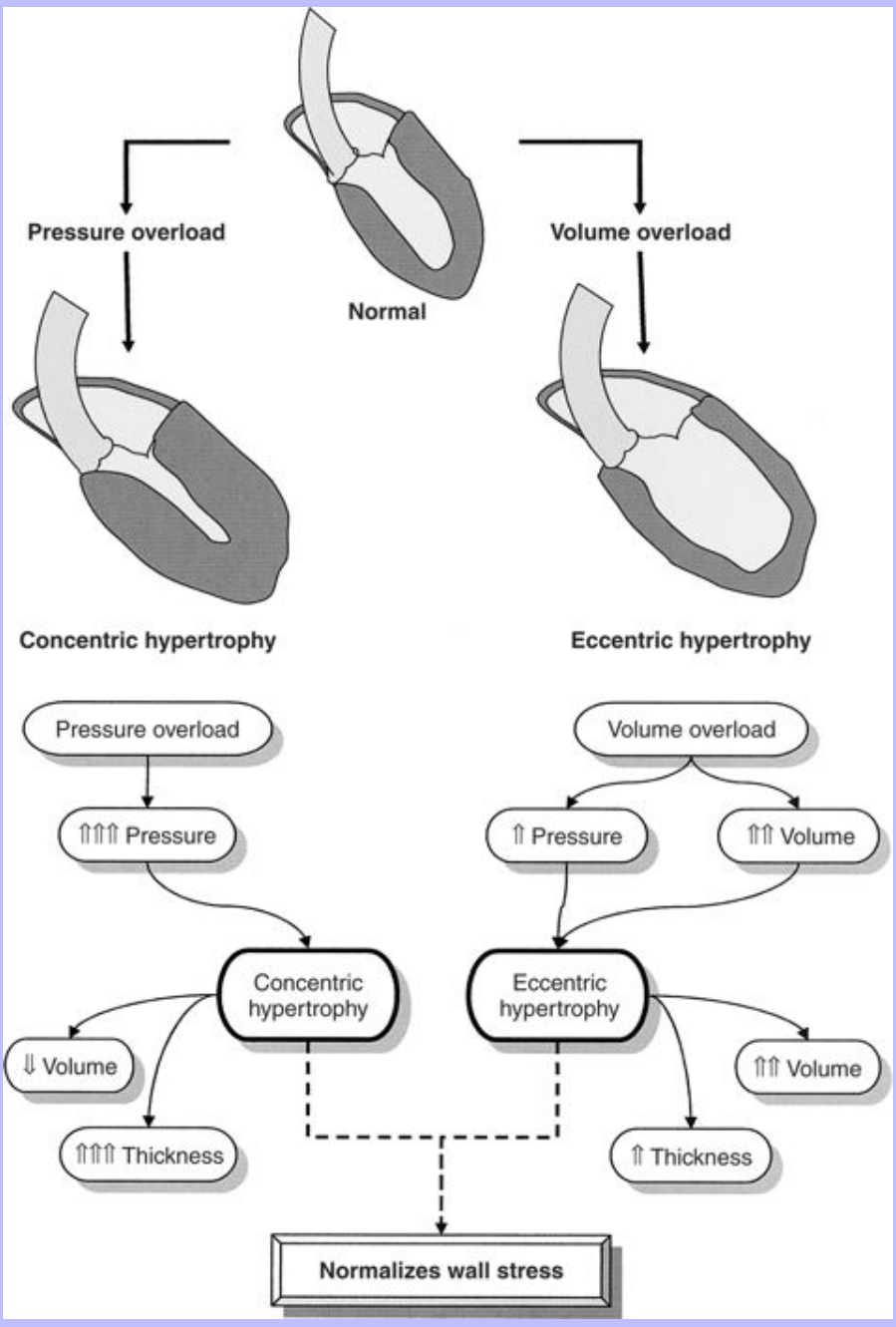
Figure 197-4 Determinants of left ventricular wall stress. *LV*, Left ventricle.



197.2.1.4 Volume Overload

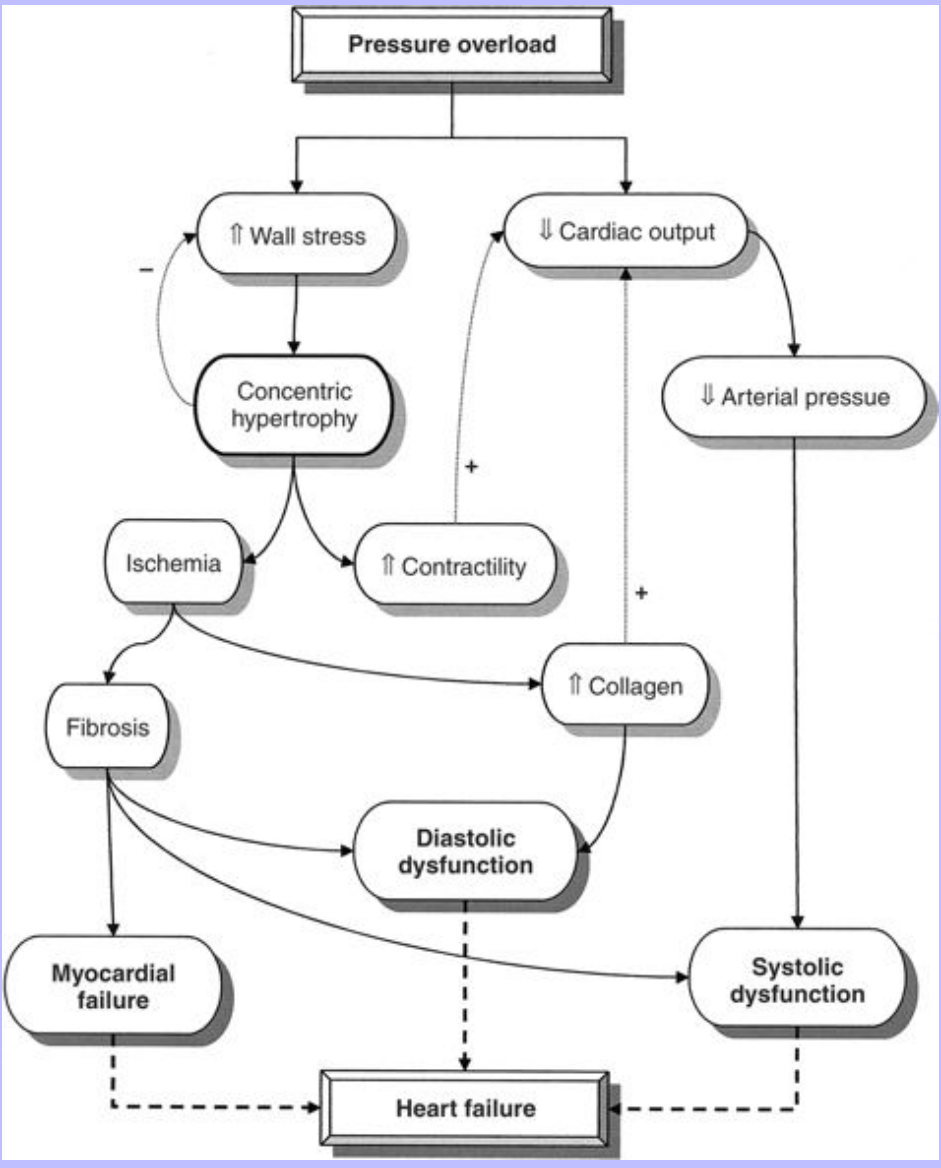
Volume overload may occur with valvular insufficiency, abnormal communications (e.g., patent ductus arteriosus, septal defects), and high-output states (e.g., hyperthyroidism). The initial event, an increase in chamber size, occurs as a result of the need to accommodate a large ventricular end-diastolic volume; this increases the sarcomere length to the optimal 2.2 μm. Again, dilatation leads to an increase in wall stress, which in turn causes ventricular hypertrophy and normalizes wall stress. Volume overload is marked by an eccentric hypertrophy, with a mild increase in wall thickness and an increase in radius (see Figure 197-6). The degree of hypertrophy is not as severe as in pressure overload states because the primary event now is an increase in volume, which causes only a mild increase in ventricular pressure. The performance of each unit of myocardium in a chronically volume-overloaded heart is normal or near normal, allowing a greater than normal stroke volume. The ventricle responds to a volume overload situation by increasing size and also by changing its geometry. Contrary to what happens in the pressure-overloaded myocardium, collagen formation is not a problem in the early stages of volume overload. In fact, a loss of myocardial collagen occurs in volume-overloaded hearts. The loss of collagen causes the ventricle to dilate and increases ventricular compliance. Left ventricular dilatation and increased compliance do not occur in volume-overloaded hearts when collagenase stimulation caused by mast cell degranulation is blocked.[14]

Figure 197-5 Types of ventricular hyper-trophy. Increases in pressure lead to concentric hypertrophy (parallel addition of new sarcomeres), whereas increases in volume lead to eccentric hypertrophy (in-line addition of new sarcomeres).



With progression of the disease, ventricular end-diastolic pressure again rises above the normal range, increasing resting tension and compromising the endocardial perfusion pressure.[15] The increase in tension that occurs in this setting is the result of slippage of fibers, with an excessive increase in chamber size. The mechanism for fiber slippage is poorly understood, but it is probably related to a disruption in normal collagen-myocyte interaction. If collagen fibers fail to support the myocytes, increases in intracavitary pressure may push the myocytes apart by means of fiber slippage.[16] Fiber slippage helps maintain stroke volume by an unknown mechanism, probably by improving diastolic function. The stretched collagen and the longer fiber length act in the diastole in the opposite way that hypertrophied myocardium does, thereby increasing diastolic compliance. Fiber slippage, on the other hand, sets the stage for progressive disease. The increase in chamber size increases wall stress and MVO_2, changes the ventricular geometry, and may cause pressure hypertrophy and fibrosis. Stretch also stimulates the production of tumor necrosis factor alpha (TNF-alpha) in cardiac fibroblasts,[17] increasing protein synthesis and stimulating hypertrophy.[18] With progression of the disease, secondary myocardial failure may ensue, and the ventricle will undergo further dilatation. The sequence of events in heart failure secondary to volume overload is shown in Figure 197-7.

Figure 197-6 Progression from pressure overload to heart failure. Pressure overload states increase wall stress, leading to concentric hypertrophy. Hypertrophy increases contractility and decreases wall stress. Unfortunately, pressure hypertrophy leads to ischemia, fibrosis, and increased collagen formation. The end result is myocardial failure and diastolic dysfunction, leading to heart failure. (–), Decreases wall stress; (+), increases cardiac output.



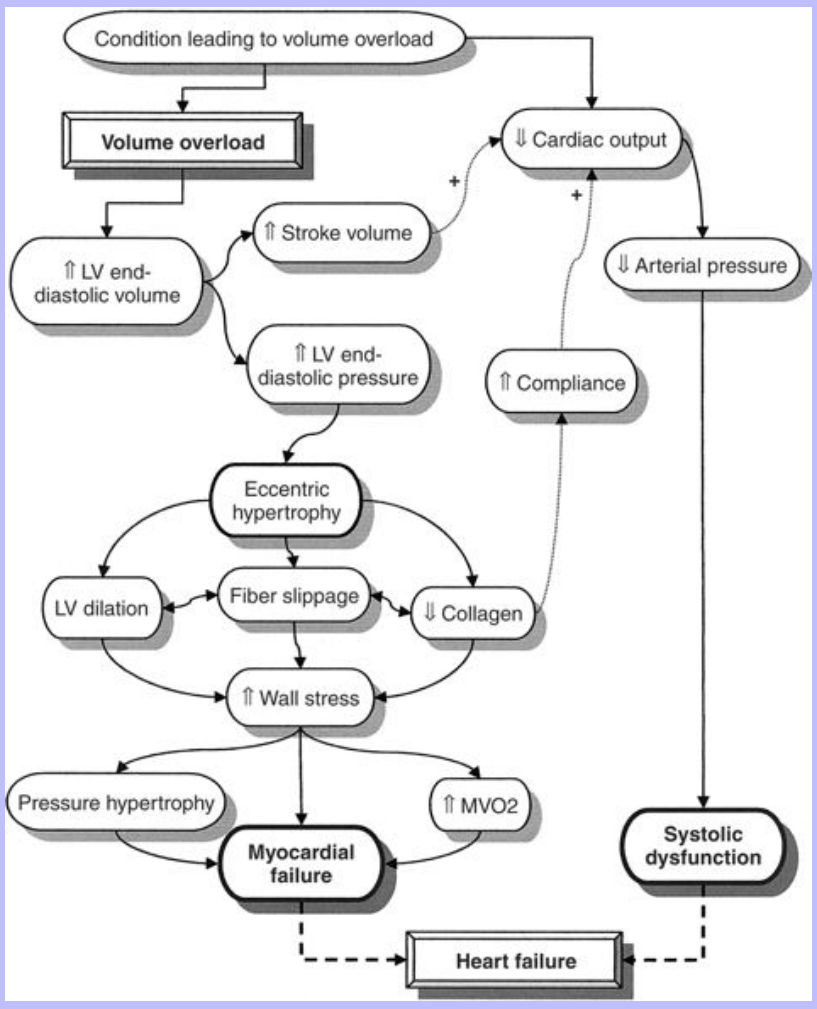
197.2.2 Diastolic Function and Dysfunction

Diastolic dysfunction results from impairment in ventricular filling. Diastolic heart failure exists when pulmonary venous congestion and resultant clinical signs occur in the presence of normal or near normal left ventricular (LV) systolic function.[19] Approximately one third of human patients with heart failure have diastolic failure, another one third have systolic failure, and the remaining one third have impairment of both systolic and diastolic function.[15] Mechanisms that lead to diastolic heart failure are listed in Box 197-3. Diastolic failure may result from abnormal relaxation (early diastole), abnormal compliance (early to late diastole), or external constraint by the pericardium. If diastole is defined as starting at the time of aortic valve closure (there are other definitions), it can be divided into four phases: (1) isovolumic relaxation (aortic valve closure to mitral valve opening); (2) rapid early mitral inflow (or the rapid filling phase, during which most of ventricular filling occurs); (3) diastasis (or the slow filling phase, during which little change occurs in ventricular volume and pressure); and (4) atrial contraction (atrial systole and its contribution to ventricular filling). The second through fourth phases of diastole represent ventricular filling.

Relaxation is a dynamic, energy-dependent process that begins at the end of contraction and lasts throughout isovolumic relaxation and early ventricular filling. Beta-adrenergic stimulation improves relaxation, whereas ischemia, asynchrony of relaxation, an increase in afterload, ventricular hypertrophy, and abnormal calcium fluxes in the myocardial cells delay relaxation. Ventricular *compliance* is the ability of the heart to fill passively, and it is usually measured at the end of diastole, when the heart is relaxed. It is determined by volume, geometry, and the tissue characteristics of the ventricular wall. Compliance is an expression of the distensibility of a fluid-filled organ. The higher the compliance, the lower the pressure at a given volume. Ventricular compliance decreases with increases in filling pressures and intrinsic myocardial stiffness (e.g., infiltrative diseases, fibrosis, ischemia) and with hypertrophy and cardiac tamponade. *Lusitropy*, a measure of the global diastolic performance of the heart, comprises the relaxation and filling phases.[20]

Ventricular filling may be affected by several factors, including the atrioventricular pressure gradient, isovolumic relaxation rate, synchronized atrial kick and ventricular relaxation, and compliance. The driving force for ventricular filling is the pressure gradient between the left atrium and ventricle when the mitral valve opens. This gradient is affected mostly by the intravascular volume and the degree of vasodilatation. The isovolumic relaxation rate is also an important determinant of early ventricular filling. Adrenergic stimulation increases the rate of relaxation, improving relaxation to a greater extent than it improves contractility. This makes evolutionary sense because during faster heart rates, diastole is shortened to a greater extent than is systole. Tachycardia shortens the duration of the diastasis. Incremental increases in the heart rate up to 180 beats/min in dogs progressively increase the rate of relaxation, improve left ventricular contractility, and decrease left ventricular end-diastolic pressure.[21,22] These changes allow increases in early filling when higher heart rates are needed (e.g., during exercise). Patients with ventricular hypertrophy that are ischemic, however, show a decrease in left ventricular distensibility with increases in the heart rate.

Figure 197-7 Progression from volume overload to heart failure. Volume overload states decrease forward stroke volume, leading to systolic dysfunction and an increased end-diastolic volume. The increase in the end-diastolic volume increases the stroke volume but also the end-diastolic pressure, leading to eccentric hypertrophy. Eccentric hypertrophy leads to a decrease in collagen content that helps diastolic function, but it also causes fiber slippage, thereby increasing wall stress and ultimately leading to myocardial failure. Patients with volume-overloaded hearts usually develop congestive heart failure (CHF) secondary to a decrease in forward stroke volume, but in some patients CHF may occur secondary to myocardial failure. (+), Increases cardiac output.



197.2.2.1

Box • 197-3 Mechanisms Leading to Diastolic Heart Failure

- Impaired energy-dependent ventricular relaxation or abnormal ventricular chamber or muscle properties
  - Ventricular hypertrophy
    - Hypertrophic cardiomyopathy
    - Subaortic stenosis
    - Pulmonic stenosis
    - Heartworm disease
    - Systemic hypertension
  - Dilated cardiomyopathy
  - Myocardial infarct
  - Restrictive cardiomyopathy
- Obstruction to ventricular filling at veins, atria, and atrioventricular valves
  - Mitral stenosis
  - Tricuspid stenosis
  - Intracardiac neoplasia causing intracardiac obstruction
  - Cor triatriatum
- Pericardial abnormalities
  - Constrictive disease

Cardiac tamponade

Normal diastolic filling also depends on synchronized contraction between the left ventricle and left atrium.[19] Loss of atrial contraction is one reason why dogs with dilated cardiomyopathy or mitral endocardiosis develop heart failure when the atria start to fibrillate. Asynchronous relaxation of the left ventricle may be observed in cats with restrictive cardiomyopathy. A decrease in the uniformity of relaxation reduces ventricular filling and may contribute to development of heart failure in these patients. Left ventricular compliance also affects ventricular filling. Patients with left ventricular hypertrophy have decreased left ventricular compliance and poor diastolic function as a result of the increases in cardiomyocyte size, collagen formation, and wall thickness.[19] The pericardium may also restrict ventricular filling in constrictive pericardial disease or cardiac tamponade. In these situations ventricular filling is abruptly halted in mid-diastole by the abnormal pericardium, which imposes its mechanical properties on those of the ventricle during the final phases of diastole. The mechanisms that lead to the development of congestive heart failure during diastolic dysfunction are shown schematically in Figure 197-8.

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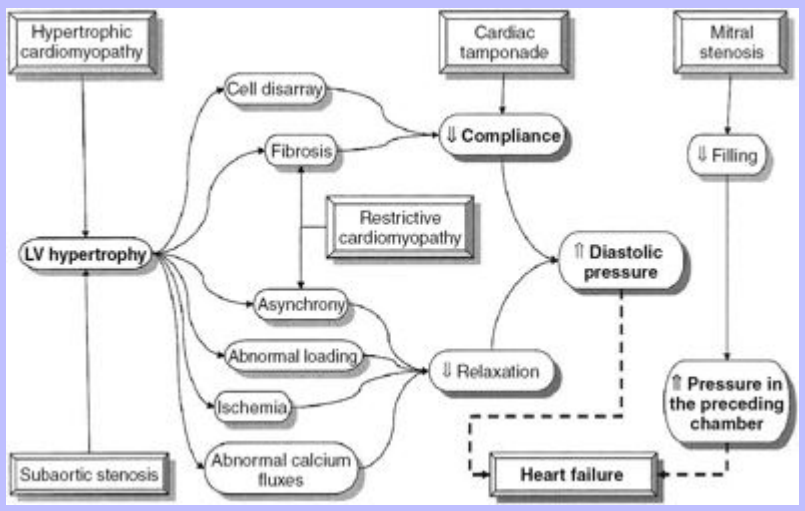
Figure 197-8 Sequence of events leading to diastolic heart failure. Most mechanisms leading to diastolic failure decrease lusitropy by reducing compliance (thus increasing stiffness) or relaxation, or both. Mitral stenosis leads to diastolic heart failure through interference with left ventricular filling.



197.3 HOW DOES THE BODY REACT TO HEART FAILURE?

Many conditions and different heart diseases can progress into heart failure. Regardless of the cause, there is an initial fall in cardiac output that lowers arterial pressure. Clinical signs observed in heart failure are mainly the result of chronic activation of compensatory mechanisms to restore and maintain blood pressure. The cardiovascular system is part of a biologic control system that works in co-operation with the central nervous,

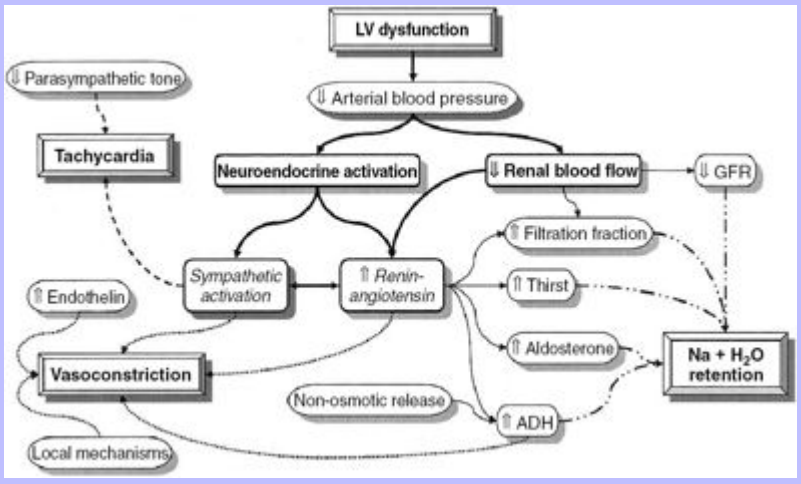
renal, and endocrine systems to keep cardiovascular variables at physiologic levels. Maintenance of arterial blood pressure and effective plasma volume are the main priorities of this integrated system. Changes are sensed by high-pressure baroreceptors in the aortic arch and carotid sinus, by mechanoreceptors in the ventricular myocardium, by volume receptors in the atria and great veins, and by the juxtaglomerular apparatus in the kidneys. During episodes of low blood pressure, a reactive neuroendocrine activation occurs to re-establish normal blood pressure. The immediate response is a decrease in parasympathetic drive and an increase in sympathetic drive, causing vasoconstriction (increasing arterial impedance) and tachycardia (increasing cardiac output). Vagal responses tend to be immediate and short-lived, whereas sympathetic responses are slower but last longer. A decrease in renal blood flow causes the release of renin and activation of the renin-angiotensin-aldosterone system (RAS), contributing to vasoconstriction and causing sodium and water retention, which increases the circulating volume. Compensatory mechanisms are acute responses that evolved to maintain an animal's life during and immediately after an episode of bleeding. During heart failure, however, compensatory mechanisms are chronically activated (Figure 197-9). In an effort to maintain blood pressure, the cardiovascular system allows the venous pressure to increase and redistributes cardiac output, maintaining blood flow mostly to essential organs (Figure 197-10).

Compensation cannot be viewed as an isolated response of the circulation. The heart and the myocardial cells undergo changes to adapt to ventricular dysfunction. A common characteristic of all compensatory responses is that the short-term effects are helpful, but the long-term effects are deleterious. In acute injuries to the heart, cardiac output decreases and acute heart failure may occur; this phase, known as *transient breakdown*, initiates activation of the compensatory mechanisms.[23] In small animals, heart failure is usually a chronic problem, and the transient breakdown phase merges with the following phase. As compensation occurs, cardiac output and clinical signs steadily improve, because the heart and circulation are performing extra work; this compensated phase is known as *stable hyperfunction*. Chronic hyperfunction leads to progression of left ventricular dysfunction, myocardial cell death, the development of clinical signs, and death, the *exhaustion and progressive cardiosclerosis* phase. The chronic effects of the compensatory mechanisms that lead to progression of left ventricular dysfunction are shown in Figure 197-11.

197.3.1 Neuroendocrine Activation

Neuroendocrine activation in CHF is a result of the decrease in cardiac output and atrial hypertension. Neuroendocrine mechanisms include vasoconstrictive/sodium-retaining systems and vasodilator/natriuretic systems (Box 197-4). All neuroendocrine mechanisms are operating fully during severe CHF. The exact point at which each neuroendocrine mechanism is activated is the subject of debate. In a tachycardia-induced heart failure model, increases in neurohormones were detected within 3 weeks of pacing at 180 beats/min during early myocardial dysfunction, when the animals were still asymptomatic.[24] Clinical data are still lacking in small animals with naturally occurring CHF. The underlying cause of the ventricular dysfunction appears to play a role in the determination of when activation of a particular neuroendocrine mechanism starts. The net effect of neuroendocrine activation is vasoconstriction, sodium and water retention, and LV hypertrophy, leading to ventricular and peripheral vessel remodeling.

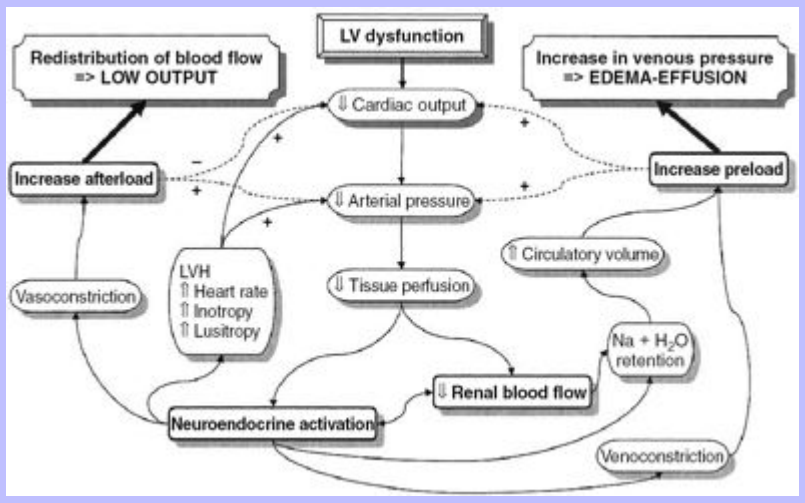
Figure 197-9 Compensation in congestive heart failure. Left ventricular (LV) dysfunction decreases cardiac output and arterial blood pressure. The decrease in renal blood flow and concomitant neuroendocrine activation set in motion compensatory mechanisms designed to restore blood pressure: sodium and water retention *(dash-and-dot line)*; vasoconstriction *(dotted line)*; and tachycardia *(dashed line)*. *ADH*, Vasopressin; *GFR*, glomerular filtration rate.



197.3.1.1 Autonomic Nervous System

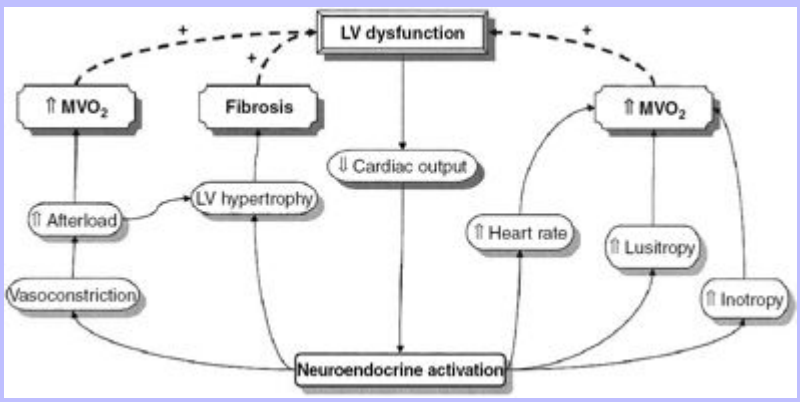
CHF is accompanied by a generalized increase in sympathetic nerve activity and attenuation of parasympathetic tone. Dogs with naturally occurring CHF caused by dilated cardiomyopathy and mitral regurgitation have increased nor-epinephrine concentrations, a finding that correlates positively with the clinical severity of the CHF.[25] The increase in nor-epinephrine, however, does not correlate with the degree of myocardial dysfunction.[25,26] The norepinephrine concentration correlates with cardiac death in human patients with CHF. Increased release of norepinephrine from adrenergic endings and its "spillover" into plasma, as well as decreased uptake by adrenergic nerve endings, are responsible for the observed increase in the norepinephrine concentration during CHF. The decrease in left ventricular function leads to relative hypotension, which stimulates the baroreceptors to activate the sympathetic nervous system.[27] However, the precise mechanisms responsible for the persistent sympathetic overactivity and blunted baroreflex control seen in CHF remain obscure and cannot be explained solely by chronic withdrawal of baroreflex inhibition.[28] Augmented peripheral chemosensitivity also has been demonstrated in CHF.[29] A link between increased peripheral chemosensitivity and impaired autonomic control, including baroreflex inhibition, has been demonstrated in human patients with CHF.[30] Overactivity of muscle metaboreceptors (ergoreceptors) may also contribute to the autonomic imbalance,[31] because ergoreflexes from the ailing skeletal muscle may further promote adrenergic and RAS activation.[32]

Figure 197-10 Compensation and clinical signs of congestive heart failure. The compensatory mechanisms activated to restore arterial blood pressure during heart failure are ultimately responsible for the clinical signs of the disorder. Retention of sodium and water leads to the formation of edema and effusions, and an increased afterload decreases cardiac output. (+), Increases arterial pressure or cardiac output; (–), decreases cardiac output; *ADH,* vasopressin; *LV,* left ventricle; *LVH,* left ventricular hypertrophy.



Despite the increase in the plasma concentration of norepinephrine, patients with CHF have depletion of nor-epinephrine from the atria and ventricles, which blunts the response to sympathetic activation. Increased levels of norepinephrine in the vicinity of beta adrenoreceptors leads to downregulation of these receptors. Downregulation of beta adrenoreceptors occurs in patients with severe cardiomyopathy and correlates with the severity of the heart disease. In normal hearts, the ratio of $beta_1$ to $beta_2$ receptors is approximately 80:20, whereas in failing hearts, it approaches 60:40.[33] In patients with dilated cardiomyopathy, downregulation is consistently shown in $beta_1$ adrenoreceptors but not in $beta_2$ adrenoreceptors, whereas in mitral disease and in ischemic cardiomyopathy, both subsets of beta adrenoreceptors are downregulated. The selective downregulation of $beta_1$ adrenoreceptors may occur because myocardial $beta_1$ adrenoreceptors are innervated and therefore are exposed to the increased norepinephrine released from the nerve endings, whereas myocardial $beta_2$ adrenoreceptors are not innervated. Postadrenoreceptor changes in the beta adrenoreceptor–adenylate cyclase complex can contribute to changes in adrenergic responsiveness.

Figure 197-11 Compensation process and progression of left ventricular dysfunction. The compensatory mechanisms activated to restore arterial blood pressure during heart failure are ultimately responsible for progression of the disease. Increased afterload and increased cardiac activity increase myocardial oxygen consumption (MVO_2); left ventricular (LV) hypertrophy is associated with fibrosis. (+), Causes further left ventricular dysfunction.



197.3.1.1.1

Box • 197-4 Neuroendocrine Factors in Heart Failure

Vasoconstrictive or sodium-retaining factors

- ↑ Sympathetic nervous tone*
- ↑ Renin-angiotensin II-Aldosterone
- ↑ ADH (vasopressin)
- ↑ Endothelin-1
- ↑ Thromboxane
- ↑ Neuropeptide Y
- ↑ Tumor necrosis factor alpha

Vasodilatative or natriuretic factors

↑ Atrial natriuretic factor

↑ Nitric oxide (basal, decreased release upon stimulation)

↑ Prostaglandins (E_2, I_2)

↓ Kallikrein

↑ Dopamine

↓ Calcitonin gene-related peptide

* $Beta_2$-adrenergic stimulation causes vasodilatation and may be antiapoptotic and cardioprotective.

The increase in sympathetic activity is partly responsible for the vasoconstriction and sodium and water retention, whereas the decrease in norepinephrine stores and the changes in adrenoreceptors lead to a decrease in the contractile response of the myocardial cells and in the chronotropic response of the sinoatrial node cells during exercise. Chronic adrenergic stimulation also leads to increases in afterload and MVO_2, as well as to ventricular arrhythmias, and it favors progression of left ventricular dysfunction (Figure 197-12). Remodeling of the heart and peripheral vessels, also stimulated by chronic sympathetic activation, further favors progression of left ventricular dysfunction. It is interesting to note that $beta_2$-adrenergic stimulation leads to vasodilatation and may be antiapoptotic and cardioprotective.[32]

Baroreflex control is altered during CHF, a circumstance that is partly responsible for the increased sympathetic activity and the blunted tachycardic response during exercise or hypotension. Abnormal baroreflexes also contribute to sodium and water retention. Normally, increases in atrial pressure stimulate atrial stretch receptors, inhibiting the release of antidiuretic hormone (ADH), decreasing sympathetic activity, and increasing renal blood flow and the glomerular filtration rate. During CHF atrial and arterial receptors show a decreased response to stimulation, and baroreceptor function is impaired. The mechanisms are not clear but appear to be related to increases in sodium-potassium adenosine triphosphatase (Na^+-K^+ATPase) activity in the baroreceptors. The decrease in parasympathetic activity in CHF decreases the restraint of the sinoatrial (SA) node. The net result is a higher heart rate for a given arterial pressure and a decrease in heart rate variability. Decreases in heart rate variability have been observed in dogs with naturally occurring[34] and experimentally induced [35,36] heart failure (Figure 197-13). Impairment of the heart rate response to postural changes is an early finding in experimental heart failure progression in dogs,[37] which suggests that parasympathetic activity is reduced in the initial phases of heart failure (Figure 197-14). A decrease in parasympathetic tone in CHF carries a poor prognosis.

197.3.1.2 Renin-Angiotensin-Aldosterone System

Low cardiac output during CHF stimulates renin release through direct beta adrenoreceptor stimulation and a decrease in renal flow in the juxtaglomerular apparatus of the kidneys. Renin increases angiotension II concentration. An array of effects of angiotensin II initially brings the blood pressure toward the normal range, but perpetuation of its effects leads to a vicious cycle that contributes to further declines in ventricular function. Angiotensin II is a potent vasoconstrictor. Vasoconstriction increases arteriolar resistance, which helps to normalize blood pressure but also increases afterload. The higher afterload increases MVO_2 and negatively affects cardiac output. On the venous side, angiotensin-induced venoconstriction decreases venous capacity, increasing venous return to the heart and cardiac output. Angiotensin II also stimulates the release of ADH and aldosterone. ADH causes vasoconstriction and stimulates water resorption in the renal distal tubules, whereas aldosterone causes sodium and water retention and contributes to baroreceptor dysfunction. Aldosterone increases total body water and may contribute to increased tissue water content, increasing stiffness and decreasing compliance of the arterial system.[38] Aldosterone also increases potassium and magnesium excretion. Even in the absence of a low serum magnesium level, aldosterone decreases the cytosolic magnesium concentration by decreasing $alpha_1$ antiproteinase activity, a marker of oxidative stress.[39] Increases in plasma aldosterone are associated with an inflammatory response with evidence of oxidative stress and may lead to intramural coronary artery remodeling and fibrosis.[39] Angiotensin II also enhances sympathetic activity, constricts the efferent renal artery, and stimulates thirst.[38] Thus activation of the RAS contributes to vasoconstriction with sodium and water retention during CHF. Sympathetic activation usually precedes RAS activation, although some of the sympathetic activation during CHF is caused by the increased activity of the RAS.

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Figure 197-12 Beneficial and detrimental effects of sympathetic activation. Short-term sympathetic effects are beneficial, whereas chronic activation favors progression of left ventricular dysfunction. Dashed lines indicate long-term effects. (+), Causes further left ventricular dysfunction; *CO,* cardiac output; *ABP,* arterial blood pressure; *HR,* heart rate; *AL,* afterload; *NE,* norepinephrine; *Imp,* arterial impedance; *PL,* preload.

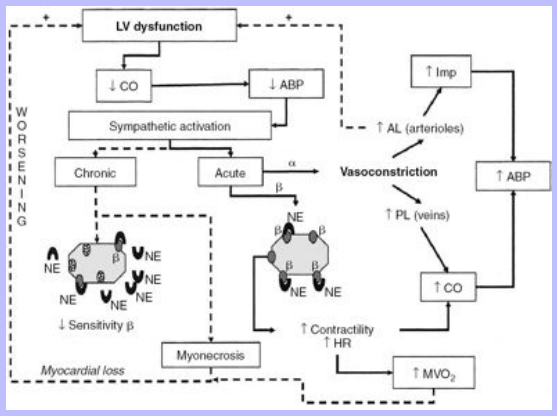


Figure 197-13 Heart rate variability over 1 minute in a dog before and after induction of progressive congestive heart failure. Heart rate variability is shown over time *(x axis)* as heart rate *(y axis)* fluctuation above and below the mean heart rate per minute *(horizontal line)*. With progression of the disease, the heart rate increases and heart rate variability decreases. (From Schwatrz DS: *Studies on baroreceptor function in dogs*, doctoral dissertation, Columbus, Ohio, 2000, Ohio State University.)

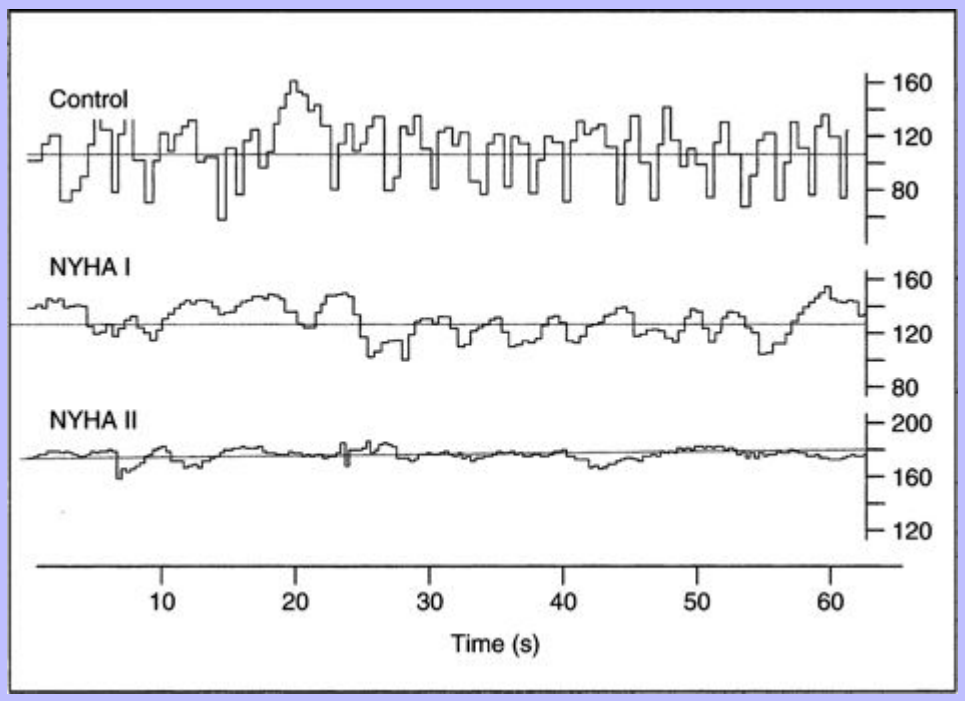
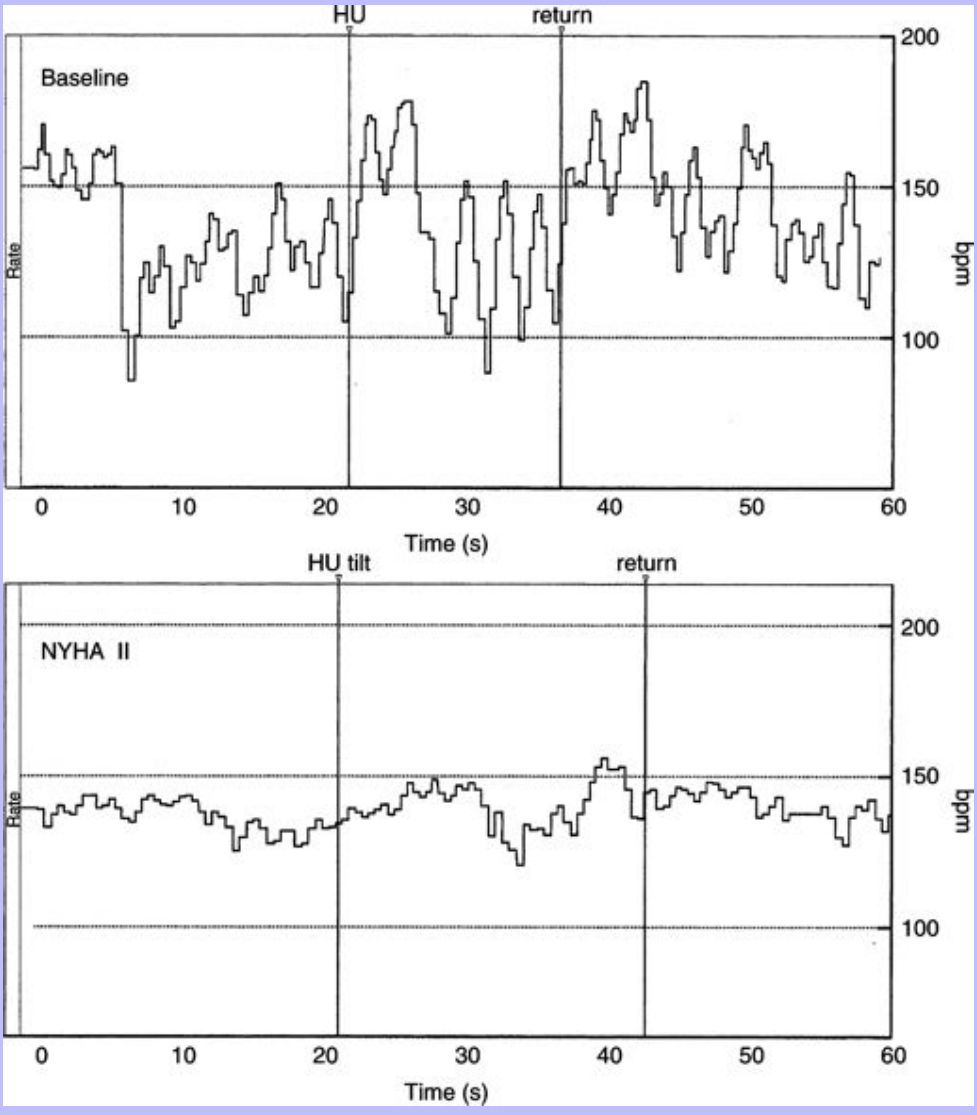


Figure 197-14 Lack of heart rate response to postural change (active head-up tilt, HU) in a dog with rapid pacing-induced heart failure (New York Heart Association [NYHA] class II) *(lower figure)*. Note that before induction of heart failure *(baseline)*, a rapid increase in the heart rate and large heart rate variability immediately after postural change are seen. (From Schwatrz DS: *Studies on baroreceptor function in dogs*, doctoral dissertation, Columbus, Ohio, 2000, Ohio State University.)



Angiotensin II stimulates growth factors, promoting remodeling in the vessels and myocardium. It may also stimulate vessel remodeling by reducing nitric oxide synthesis or by increasing local angiotensin-converting enzyme (ACE) breakdown of bradykinin. Vascular remodeling causes structural changes that further decrease the compliance of the arterial system. Angiotensin II stimulates smooth muscle cell growth, leading to cellular hyperplasia, hypertrophy, and apoptosis (programmed cell death).[38] An increased level of angiotensin II is associated with superoxide formation (oxidative stress), endothelin secretion, plasminogen activation, TNF-alpha production (inflammation), fibroblast hypertrophy, and increased production of collagen. The final result is myocyte and vascular wall fibrosis. Angiotensin II plays a key role in the development of pathologic hypertrophy, exerting cytotoxic effects on the myocardium, causing myocyte necrosis, and contributing to myocardial loss.[40] Stimulation of angiotensin receptors (AT_1) is responsible for altered gene expression and gene reprogramming of cardiac myocytes and fibroblasts, leading to increases in skeletal alpha actin, atrial natriuretic peptide, and beta myosin heavy chain, as well as increases in fibronectin, impairing diastolic and systolic function.[40] The beneficial and detrimental effects of angiotensin II during heart failure are presented in Figure 197-15.

Activation of the RAS contributes to vasoconstriction, increasing afterload and MVO_2 and causing the kidneys to retain sodium and water. Remodeling of the heart and peripheral vessels is also stimulated by the RAAS, conditions that favor progression of left ventricular dysfunction. Angiotensin II induces cardiac myocyte necrosis associated with increased apoptosis and contributes to myocardial loss, perpetuating the progression of left ventricular dysfunction.

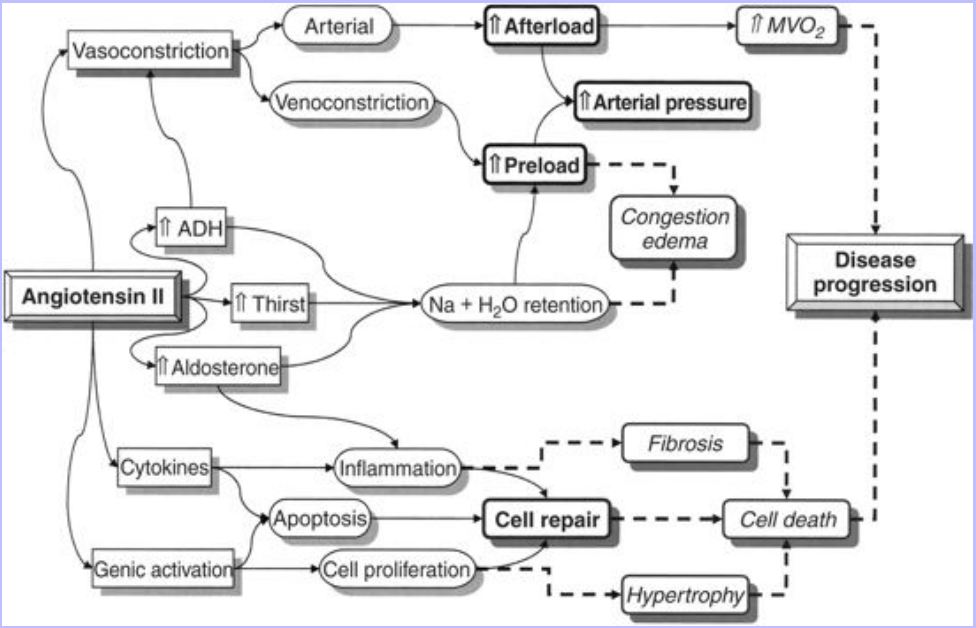
197.3.1.3 Other Vasoconstrictive Agents

ADH levels are increased in patients with heart failure as a result of nonosmotic release, impairment in baroreceptor-mediated inhibition of brain stem centers, and an increase in circulating angiotensin II. ADH synthesis is substantially and chronically elevated in patients with heart failure despite the volume overload and reductions in plasma osmolality often observed in these patients. ADH levels may be increased even in patients with asymptomatic left ventricular dysfunction. The release of ADH leads to vasoconstriction and water resorption and favors the development of hyponatremia. ADH also appears to affect hemodynamics and cardiac remodeling adversely while potentiating the effects of norepinephrine and angiotensin II. Chronic ADH receptor blockade did not attenuate ventricular remodeling in at least one model of left ventricular dysfunction.[41] ADH, therefore, may not play a major role in the structural progression of heart failure.

Endothelin is the most potent vasoconstrictor known for vascular smooth muscle cells. It is elevated in a canine pacing model of heart failure, and the increase correlates well with the right atrial or pulmonary capillary wedge pressure.[42] The increase in endothelin during heart failure is likely due to increased production and not decreased clearance.[43] It has been shown that cardiac overexpression of endothelin-1 (ET-1) is sufficient to increase inflammatory cytokines and cause an inflammatory cardiomyopathy that leads to heart failure and death.[44] Activation of myocardial and plasma ET-1 precedes activation of myocardial and plasma RAS in a canine model of CHF,[45] but angiotensin II further increases the ET-1 concentration. Endothelin plays an important role in the maintenance of blood pressure and blood flow during CHF.[46] Chronic blockage of endothelin receptors may prevent the progression of experimental heart failure in dogs,[47] and an endothelin-converting enzyme prevented vascular remodeling during experimental

heart failure.[48] Unfortunately, clinical trials with chronic ET-receptor antagonism showed worsening of CHF symptoms.

Figure 197-15 Beneficial *(bold)* and detrimental *(italics)* effects of angiotensin II during heart failure. The short-term effects of angiotensin II are beneficial, whereas chronic activation favors the appearance of clinical signs and progression of left ventricular dysfunction. Angiotensin II also participates in sympathetic activation. Dashed lines indicate long-term effects.



197.3.1.4 Vasodilatory Agents

The natriuretic peptides are counter-regulatory hormones involved in volume homeostasis and cardiovascular remodeling. They consist of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), dendroaspis natriuretic peptides (DNP), and urodilatin. The natriuretic peptides promote natriuresis, diuresis, peripheral vasodilatation, and inhibition of the RAS. ANP and BNP are elevated in patients with left ventricular dysfunction; the serum levels correlate with the severity of heart failure and appear to have prognostic value.[49] ANP is stored in the right atrium and released by increases in atrial distending pressures. This peptide causes arterial dilatation, venodilatation, natriuresis, and water diuresis, counteracting the effects of vasoconstrictory agents. It also inhibits renin and aldosterone secretion and reduces sympathetic vasoconstriction.[50] BNP is stored in the ventricular myocardium and also causes vasodilatation and natriuresis. Congestive heart failure is associated with an increase in ANP, and the changes are related to the fall in the ejection fraction and the increase in cardiac filling pressures. Despite the natriuretic peptides' beneficial effects during CHF, their release is over-ridden by the release of agents that cause vasoconstriction and sodium and water retention.

Nitric oxide (NO) is the major physiologic regulator of basal blood vessel tone. NO is produced by virtually all cell types that make up the myocardium, and it regulates cardiac function through both vascular-dependent and vascular-independent effects. Vascular-dependent factors include regulation of coronary vessel tone, thrombogenicity, and proliferative and inflammatory properties, and the cellular cross-talk that supports angiogenesis. Vascular-independent factors constitute the direct effects of NO on several aspects of cardiomyocyte contractility, from the fine regulation of excitation-contraction coupling to modulation of autonomic signaling and mitochondrial respiration.[51] NO also plays a very important role in the maintenance of cardiac architecture and the prevention of pathologic hypertrophy. A dissociation of stimulated and basal release of NO appears to exist in patients with heart failure. The stimulated, endothelial-dependent dilatation exerted by acetylcholine in peripheral resistance vessels is blunted during heart failure, which suggests a reduced release of NO on stimulation. This defective mechanism may be involved in the impaired vasodilator capacity in the peripheral circulation (e.g., during exercise).[52] In contrast, basal release of NO from the endothelium of resistance vessels appears to be preserved and may even be enhanced; also, it may play an important compensatory role in CHF during resting conditions by antagonizing neuroendocrine vasoconstrictive forces.[52]

197.3.2 Peripheral Compensation

Peripheral compensation occurs outside the heart and is directed at normalization of the arterial blood pressure. The main mechanisms involved in peripheral compensation are vasoconstriction in addition to sodium and water retention (see Table 197-1).

197.3.2.1 Blood Vessels and Vasoconstriction

The mechanism responsible for the increased tone of the vascular smooth muscle in CHF is multifactorial but basically results from neuroendocrine activation and the interplay of local mechanisms. Decreased blood flow to muscles causes overactivity of muscle metaboreceptors (afferents sensitive to skeletal muscle work) and peripheral chemoreceptors, which contributes to the autonomic imbalance. An increase in efferent sympathetic neuron discharge causes vasoconstriction. Dogs with paced-induced CHF show an increase in aortic stiffness (characteristic impedance) and a decrease in the compliance of large arteries before vasoconstriction of the small arterioles (increase in peripheral resistance).[53] Sympathetic activation occurs even in patients with asymptomatic left ventricular dysfunction. Further increases in plasma norepinephrine appear to occur in these patients when signs of heart failure develop. The RAS is activated by the decrease in cardiac output, further increasing vascular tone as a direct effect of angiotensin II and indirectly through the facilitative effect of angiotensin II in the alpha-adrenergic neurons. Unlike the sympathetic system, the RAS normalizes as compensation returns cardiac output to normal. Whether dogs with asymptomatic mitral regurgitation or left ventricular dysfunction show activation of the RAS is still the subject of debate.[54–57] ADH may be increased even in patients with asymptomatic left ventricular dysfunction, and this contributes to the increase in peripheral vascular resistance in patients with heart failure.

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Table • 197-1 Peripheral Compensatory Mechanisms in Heart Failure

RESPONSE	MECHANISM	POTENTIAL BENEFIT	POTENTIAL HARM	MANIFESTATIONS	CORRELATES
Sympathetic activation	Decrease in arterial pressure; RAS activation	Inotropic support, tachycardia, RAS activation, vasoconstriction, venoconstriction	Increased MVO_2 and afterload, sympathetic desensitization, excessive preload	Tachycardia, arrhythmias, pale mucous membranes	Norepinephrine concentration correlates with mortality. Beta-adrenoreceptor blockade may improve survival time.
Vasoconstriction	Sympathetic and RAS activation, increase in ADH, local blood vessel mechanisms	Maintenance of arterial pressure and perfusion of "essential" organs	Increased MVO_2 and afterload, stimulation of LVH, decreased cardiac output, redirection of blood flow	Pale mucous membranes	Modulation of excessive arterial tone with vasodila-tors is beneficial during heart failure.
Activation of renin-angiotensin system	Sympathetic activation, decreased renal perfusion	Vasoconstriction, stimulation of thirst, release of ADH and aldosterone, increased sympathetic tone	Increased MVO_2 and afterload, stimulation of LVH and blood vessel remodeling, decreased cardiac output and tissue perfusion, potentiation of mitral regurgitation	Pale mucous membranes	Angiotensin-converting enzyme (ACE) blockade increases survival time in patients with heart failure
Sodium and water retention	Poor renal perfusion, increases in thirst, ADH, and aldosterone	Increased preload, improved LV function	Congestion; excessive preload, which increases wall stress; hypokalemia (aldosterone)	Edema and cavitary effusions, arrhythmias (hypokalemia)	Use of diuretics in CHF decreases sodium and water retention. Aldosterone inhibition reduces risk of hypokalemia. Aldosterone receptor blockade may improve survival time.
Venoconstriction	Sympathetic activation	Increased preload and ventricular function	Congestion; excessive preload, which increases wall stress	Edema and cavitary effusions, venous distention	Venodilators and nitrates can be used in the treatment of heart failure.

ADH, Antidiuretic hormone (vasopressin); *CHF,* congestive heart failure; *LV,* left ventricle; *LVH,* left ventricular hypertrophy; *MVO2,* myocardial oxygen consumption; *RAS,*, renin-angiotensin system.

Local vasoregulatory mechanisms are very important in the modulation of vascular tone during heart failure. In normal dogs, shear stress caused by pulsatile flow prompts the release of NO and prostacyclin and inhibits ET-1, leading to vasodilatation. During CHF, decreased shear stress secondary to decreased peripheral blood

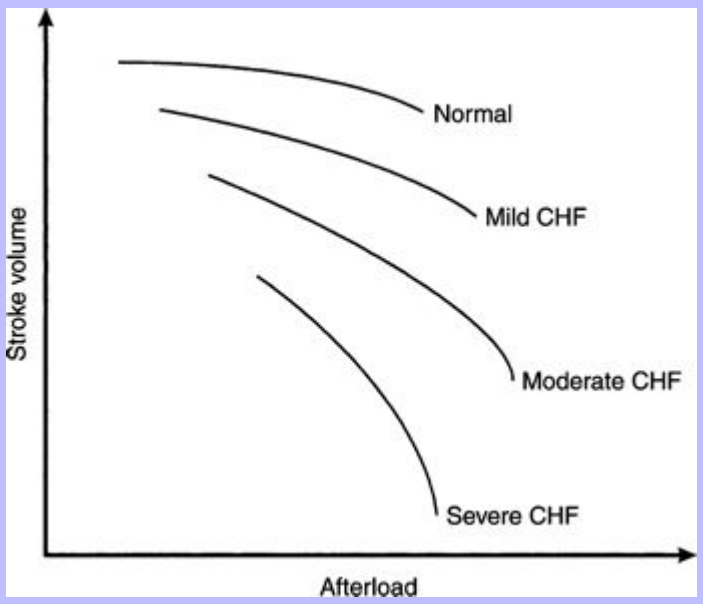
flow and neuroendocrine activation reduces the release of NO and increases ET-1, leading to vasoconstriction.[58] Endothelin is a potent vasoconstrictor that is overexpressed during CHF.

Vasoconstriction is primarily mediated by increased sympathetic tone, RAS activation, and an increased ET-1 concentration.[46,59] ADH becomes an important vasoconstrictive agent only in hyponatremic patients.[59] These mechanisms also lead to venoconstriction, which increases venous pressure and venous return to the heart. Vasoconstriction helps maintain arterial pressure, but the increase in afterload reduces the stroke volume. Failing ventricles are afterload dependent, and the stroke volume falls with any increase in afterload (Figure 197-16). When cardiac output is low, the cardiovascular system redistributes the cardiac output, reducing blood perfusion to "less essential" organs. Increases in afterload also increase MVO_2 by increasing wall stress. In patients with severe mitral regurgitation, the increase in opposition to ventricular ejection increases regurgitation; in patients with a left-to-right shunt, it increases the shunting fraction.

197.3.2.2 Skeletal Muscles

Left ventricular dysfunction leads to a decrease in blood flow to the periphery, causing vasomotor changes and muscle alterations. Mechanisms unrelated to the decrease in blood flow (e.g., decrease in activity, increase in catabolic factors, insulin resistance) also may play a role in muscle changes during CHF. Patients with CHF have substantial skeletal muscle atrophy, and the degree of atrophy correlates with muscle strength and peak oxygen consumption.[60] Skeletal muscles are morphologically and metabolically abnormal in CHF. Muscle apoptosis is observed in a high percentage of heart failure patients but not in normal subjects. The presence of collagen, indicative of fibrosis, is also detected in some heart failure patients and is more pronounced in those with cachexia.[61] Atrophy; changes in muscle fiber type and the mitochondrial ultrastructure; and a decrease in oxidative enzymatic capacity, leading to an increased reliance on anaerobic metabolism and lactate production, all have been demonstrated in patients with CHF. An increase in lactate during exercise stimulates peripheral metaboreceptors (or serves as a marker for the presence of other stimulants). Patients with CHF, therefore, have a higher metaboreceptor stimulation for a given degree of exercise than normal subjects.[28,60] Metaboreceptor stimulation increases sympathetic outflow, which adds to vasoconstriction and reduces blood flow to exercising muscles, because alpha adrenergic–mediated vasoconstriction is not impaired during CHF. In patients with mild heart failure, exercise limitation correlates well with central hemodynamic factors (e.g., cardiac output), whereas in advanced heart failure, peripheral hemodynamic factors become more important (e.g., local blood flow, vascular resistance, and venous tone).[62]

Figure 197-16 Effects of increasing afterload in left ventricular stroke volume in normal animals and in patients with congestive heart failure.



197.3.2.3 Kidneys and Sodium and Water Retention

Several mechanisms are responsible for sodium and water retention in CHF. Competing vasodilator/natriuretic and vasoconstrictive/sodium-retaining mechanisms operate. A decrease in cardiac output decreases renal blood flow and increases sympathetic drive, which causes renal vasoconstriction and further decreases in renal blood flow. Renin is released through activation of the juxtaglomerular apparatus by beta-adrenoreceptor stimulation and decreases in renal blood flow. The end result of renin release is an increase in angiotensin II and aldosterone. Angiotensin II stimulates thirst and release of ADH, leading to water retention. Aldosterone causes sodium and water retention and potassium wasting by the kidneys. Decreases in renal perfusion are countered by the release of prostaglandin E, which dilates the afferent renal arteriole and constricts the efferent renal arteriole, a response mediated by angiotensin II. These alterations combine to increase the glomerular filtration pressure and the filtration fraction (the ratio of glomerular filtration to renal plasma flow) and to maintain the glomerular filtration rate despite the reduction in renal blood flow. Sodium and water retention increases the circulating volume and preload, helping to maintain cardiac filling pressures and increasing cardiac output. Retention of sodium and water, however, leads to an excessive increase in the venous filling pressure, resulting in the development of edema and cavitary effusions. It also increases afterload and favors progression of left ventricular dysfunction.

197.3.3 Central Compensation (the Heart)

The heart participates actively in the compensation for the decrease in cardiac output. Sympathetic activation leads to an increase in the heart rate, inotropy, and lusitropy, all of which increase cardiac output. In addition,

hypertrophy helps normalize cardiac output by increasing the stroke volume. Compensatory mechanisms that act on the heart are shown in Table 197-2.

197.3.3.1 Tachycardia

During heart failure, sympathetic tone increases (increasing the heart rate) and parasympathetic tone decreases, a combination that leads to tachycardia. It is usually believed that sinus rates above 160 beats/min imply not only parasympathetic withdrawal but also sympathetic activation. The end result is an increase in the heart rate and a decrease in heart rate variability. The increase in the heart rate helps normalize arterial pressure, but at a high price: an increase in MVO_2. A decrease in heart rate variability is a negative prognostic factor for overall mortality in human patients with myocardial infarct. In dogs with chronic mitral valve disease, a decrease in heart rate variability correlates with the severity of congestive heart failure.[34] Patients with decreased heart rate variability are also less likely to respond to vasodilator infusion. The increase in the heart rate in patients with heart failure parallels sympathetic activation, which in turn correlates with the severity of the heart failure.

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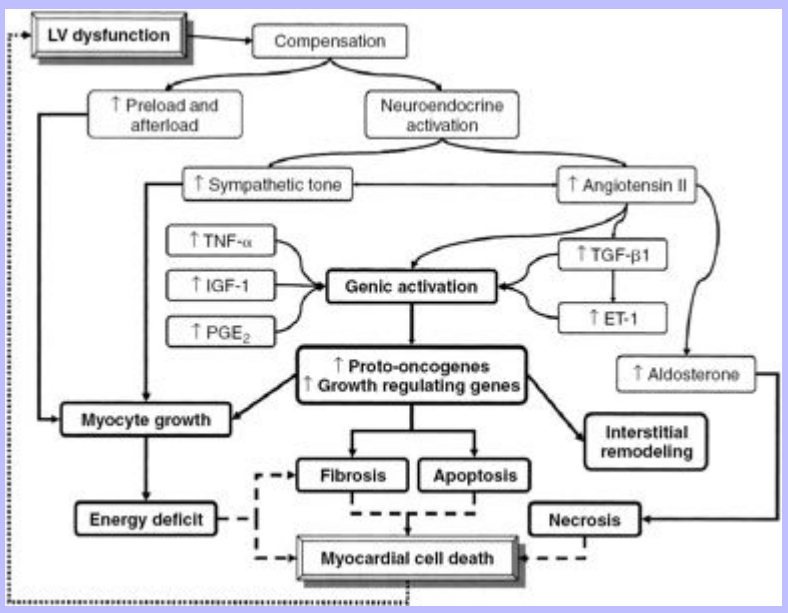
Table • 197-2 Central (Cardiac) Compensatory Mechanisms in Heart Failure

RESPONSE	MECHANISM	POTENTIAL BENEFIT	POTENTIAL HARM	MANIFESTATIONS	CORRELATES
Sympathetic desensitization	Downregulation of $beta_1$ adrenoreceptors, uncoupling of $beta_2$ adrenoreceptors, depletion of myocardial norepinephrine	Energy sparing	Decreased contractility	Low-output signs (e.g., depression, lethargy, hypotension)	Beta-adrenoreceptor blockade may reverse sympathetic desensitization.
Tachycardia	Sympathetic activation, parasympathetic withdrawal	Increased cardiac output	Increased MVO_2	Tachycardia, decreased heart rate variability	Decrease in heart rate variability correlates with mortality. Increase in heart rate correlates with sympathetic activation and severity of CHF.
Increased inotropy	Sympathetic activation	Increased stroke volume	Increased MVO_2	—	—
Increased relaxation	Sympathetic activation	Improved diastolic function (lusitropy)	Increased MVO_2	—	—
Appearance of slow myosin in the atria	Changes in isogene expression	Decreased cost to achieve normal tension, energy sparing, increased atrial kick	Atrial failure	—	Changes do not occur in the ventricles of dogs and cats.
Reduced myocardial ATPase activity	Unknown (altered isoenzymes?)	Facilitation of high-pressure, low-speed work; energy sparing	Slowed contraction rate, decreased contractility	Low-output signs	Myocardial ATPase activity is increased in high-output CHF (e.g., thyrotoxicosis).
Pressure overload (concentric hypertrophy)	Increased afterload, RAS activation, increased levels of TNF-alpha and other cytokines	Unloading of individual muscle fibers, decreased wall stress and MVO_2	Imbalance in energy demand and supply, focal necrosis, fibrosis, increased collagen formation, diastolic dysfunction	Cardiomegaly, increased diastolic dysfunction and venous congestion	Pressure overload induces cardiomy-opathy of overload. Growth-inhibitory drugs (e.g., ACE inhibitors, nitrates) may delay development of cardiomyopathy of overload.
Volume overload (eccentric hypertrophy)	Fiber slippage, increased tension	Increased compliance(?); increased stroke volume with same ejection fraction (dilatation)	Increased wall stress and MVO_2; pressure hypertrophy	Cardiomegaly	Increased wall stress leads to pressure hypertrophy.

ACE, Angiotensin-converting enzyme; *ATPase*, adenosine triphosphatase; *CHF*, congestive heart failure; *MVO_2*, myocardial oxygen consumption; *TNF-alpha*, tumor necrosis factor alpha.

Figure 197-17 Mechanisms that lead to myocardial hypertrophy and remodeling. Increases in the load and activation of proto-oncogenes and growth-regulating genes lead to hypertrophy (myocyte growth) and remodeling. Short-term sympathetic effects are beneficial, but chronic activation favors progression of left ventricular dysfunction. Hypertrophy is beneficial because it decreases left ventricular wall stress and increases cardiac output. Unfortunately, chronic myocardial hypertrophy and remodeling are associated with myocardial cell death. Dashed lines indicate long-term effects. *TNF-alpha*, Tumor necrosis factor alpha; *IGF-1*, insulin-like growth factor-1; *PGE_2*, prostaglandin E_2; *$TGF\text{-}beta_1$*, transforming growth factor $beta_1$; *ET-1*, endothelin-1.



197.3.3.2 Increased Inotropy and Lusitropy

Beta-adrenergic stimulation caused by increased sympathetic tone during heart failure increases calcium entry in the atrial and ventricular cells, calcium release from the sarcoplasmic reticulum, and the interaction between contractile proteins. All these actions increase contractility. Beta-adrenergic stimulation also increases lusitropy by increasing calcium efflux from the cell and calcium uptake by the sarcoplasmic reticulum.[3] The increase in calcium entry is largely responsible for the positive inotropic effect; the facilitated dissociation from troponin and increased calcium uptake by the sarcoplasmic reticulum are the

key factors in causing a positive lusitropic effect.[3] Beta-adrenergic stimulation increases cardiac output, but also increases MVO_2 and contributes to myocardial remodeling.

197.3.3.3 Myocardial Growth

Cardiac mass is increased in patients with heart failure, apparently as a result of a combination of reactive fibrosis and myocyte hypertrophy, along with alterations in the cytoskeletal structure in the myocyte. An increase in afterload and neuro-endocrine activation lead to left ventricular hypertrophy. Hypertrophy reduces the load in individual cells and increases cardiac output. Hypertrophy causes growth of myocyte and nonmyocyte cells in the extracellular matrix of the myocardium. The growth of myocytes and nonmyocyte cells occurs independent of each other. Chronic anemia and thyrotoxicoses cause myocyte growth without the involvement of fibroblasts, whereas hypertrophy secondary to pressure overload is accompanied by reactive fibrosis that is not secondary to myocyte necrosis. Increases in preload, afterload, sympathetic activation, and growth hormone induce myocardial growth, whereas activation of the RAS, prostaglandin E_2, transforming growth factor-$beta_1$ (TGF-$beta_1$), and insulin-like growth factor-1 (IGF-1) induce remodeling of the cardiac interstitium (Figure 197-17).[63] All these substances induce expression of proto-oncogenes and growth-regulating genes that play an important role in the mediation of hypertrophy. Structural remodeling of myocardial collagen matrix contributes to the progression of heart failure.

Hypertrophy in patients with CHF results in a ventricle that is not normal. Morphologic, biochemical, and genetic changes cause ventricular remodeling, leading to progression of the left ventricular dysfunction. The appearance of a “slow” myosin, a more efficient myosin that spares energy in the heart, has been detected in the atria[64] but not the ventricles[65] of dogs with CHF. Pressure-induced hypertrophy unloads the individual myocardial cells and decreases wall stress and MVO_2. However, hypertrophied ventricles have a capillary deficit and a decreased number of mitochondria, leading to a state of energy starvation.[66] The chronic energy starvation leads to necrosis, fibrosis, an increase in the collagen concentration, and diastolic dysfunction. Volume-induced hypertrophy decreases wall stress and MVO_2 and helps maintain stroke volume, probably by increasing compliance. Fiber slippage, however, causes further dilatation of the heart, again increasing wall stress and MVO_2 and favoring progression of the left ventricular dysfunction.

197.4 WHAT IS THE ROLE OF INFLAMMATION IN HEART FAILURE?

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Cytokines are highly potent, endogenous peptides with autocrine and paracrine actions; they are produced by a variety of cell types. Unlike hormones, cytokines are not stored but are secreted in response to specific stimuli. TNF-alpha, interleukin-1-alpha (IL-1α), interleukin-1-beta (IL-1β), and interleukin-6 (IL-6) are classified as proinflammatory cytokines.[2] These cytokines initiate both primary host responses and tissue repair. Interleukin-2 (IL-2) is a potent immunostimulatory polypeptide that amplifies the immune response to antigens. Evidence suggests that proinflammatory cytokines are capable of modulating cardiovascular function through a variety of mechanisms, such as promotion of left ventricular remodeling, induction of contractile dysfunction, and uncoupling of myocardial beta-adrenergic receptors (Table 197-3).[67] Several studies have shown that CHF is associated with increased circulating levels of proinflammatory cytokines. Short-term expression of cytokines in the heart may be an adaptive response to different forms of stress, whereas long-term expression may be maladaptive by producing cardiac decompensation. The cytokine hypothesis for heart failure does not imply that cytokines cause heart failure per se. However, they are potentially involved in the genesis of this pathology, and overexpression of cytokines contributes to the progression of heart failure once ventricular dysfunction ensues.[68]

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Chronic sympathetic activation[69] and increases in angiotensin II[70,71] and aldosterone[72] play a role in the overexpression of cytokines during CHF. Sustained hemodynamic overloading provokes a transient increase in proinflammatory cytokine and cytokine-receptor gene expression.[73]

The main stimulus for cytokine activation in CHF is not known.[74] The heart is primarily involved and could be the main source of proinflammatory cytokines, because the failing myocardium is capable of producing TNF-alpha.[75] It has also been demonstrated that pressure overload stimulates the synthesis of TNF-alpha messenger ribonucleic acid (mRNA). Myocardial stretch induces mRNA production by myocytes.[76] Another potential stimulus for an increase in the production of TNF-alpha by the failing heart is extramyocardial cytokine release caused by tissue hypoxia.[77] Tissue hypoxia and the production of free radicals are potent stimuli for the generation of cytokine release via nuclear factor-kappa-B (NF-kappa-B)–dependent pathways.[78] Cytokines are expressed in the myocardium in end-stage heart failure to a much greater degree than in patients with recent onset of symptoms. Plasma levels of TNF-alpha correlate with mRNA expression in the myocardium and thus may serve as an appropriate marker of myocardial cytokine activation. Whether the production of cytokines in the failing human heart precedes the elevation of cytokines in the plasma remains undefined.[79]

Table • 197-3 Effects of Chronic Proinflammatory Cytokine Activation in Heart Failure

EFFECT	MECHANISM	CLINICAL CORRELATE
Heart		
Myocyte hypertrophy	Generation of reactive oxygen intermediates in cardiac myocytes; activation of fetal gene programs	Cardiac hypertrophy
Left ventricular remodeling	Stimulation of production of extracellular matrix proteins and increased turnover of matrix	Cardiomyopathy of overload
Cardiomyocyte loss	Necrosis, apoptosis	Progression of heart failure
Depression of myocardial function	Nitric oxide dependent; sphingomyelinase pathway; uncoupling of beta adrenoreceptors; abnormal mitochondria energetics	Decreased contractility
Exacerbated inflammatory response	Cytokine cascade	Myocarditis
Skeletal Muscle		
Myopathy	Free radical and nitric oxide overproduction; endothelial dysfunction	Reduced blood flow in muscles, exercise intolerance
Decreased skeletal mass	Apoptosis	Cardiac cachexia
Other Effects		
Anorexia		Cardiac cachexia
Pulmonary edema		Dyspnea

The bowel could also be a source of proinflammatory cytokines during CHF. The intestinal wall edema and ischemia that occur during CHF favor bacterial translocation and may cause the release of endotoxins, with subsequent immune activation.[80] It has been shown that during acute, edematous exacerbation of CHF, endotoxin and cytokine concentrations increase but can be normalized by diuretic therapy.[81]

197.4.1 Tumor Necrosis Factor Alpha

TNF-alpha is a proinflammatory cytokine that exerts negative inotropic effects *in vivo* and *in vitro*. Acute negative inotrope results from disruption of calcium transients, whereas chronic effects are associated with

induction of inducible NO synthase (iNOS) and are due to NO-induced myofilament desensitization to calcium.[82] TNF-alpha also can produce left ventricular remodeling, hypertrophy and apoptosis, pulmonary edema, and cardiomyopathy.[83] It stimulates production of other endogenous pyrogens, such as IL-1β. The main known stimuli that prompt adult mammalian myocardial cells to produce TNF are endotoxins, hypoxia, and increased mechanical stress.[76,84] NF-kappa-B can also participate in the production of TNF-alpha. Oxidative stress activates NF-kappa-B, which binds to a TNF promoter, increasing TNF-alpha transcription.[85] Mild acute increases in TNF-alpha are an adaptive response to stress; they protect the heart during ischemia and favor remodeling during infarcts and adaptive growth during hemodynamic overload. Severe acute increases lead to myocarditis as a result of an exacerbated inflammatory response, and chronic increases are maladaptive, favoring cardiac decompensation and apoptosis.[86]

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Cats with naturally occurring CHF have increased concentrations of TNF-alpha.[87] Increases in the TNF-alpha concentration have been independently associated with a poorer prognosis for CHF. TNF-alpha is produced in the heart by cardiac myocytes and resident macrophages under conditions of cardiac stress. Normal hearts do not produce TNF-alpha, but failing human hearts make abundant quantities.[83] The source of cardiac TNF-alpha appears to be at least partly attributable to production by the cardiac myocyte.[75] TNF-alpha plays an important role in the development of heart failure. Administration of TNF-alpha to experimental animals and transgenic overexpression of TNF-alpha lead to CHF. Mice that overexpress TNF-alpha recapitulate heart failure and a dilated cardiomyopathy state in other species shows (1) four-chamber dilatation, (2) myocyte hypertrophy, (3) interstitial infiltrates, (4) extracellular matrix remodeling with fibrosis, (5) diminished beta-adrenergic responsiveness, and (6) premature death.[86] Attenuation of the biologic activity of TNF-alpha abrogates the development of CHF in experimental model systems. Unfortunately, anti-TNF strategies to date have not demonstrated salutary benefits in large, multicenter, randomized and placebo-controlled clinical trials in patients with symptomatic heart failure.[88]

197.4.2 Interleukins

Interleukin-1 (IL-1) mediates immune response and the production of inflammatory responses through an increase in prostaglandins, and it may be a basal part of the overactivated cytokine cascade during CHF.[2] IL-1 appears capable of modulating myocardial function. It exerts a potent antiproliferative effect on cardiac fibroblasts but induces cardiac myocyte hypertrophy. IL-1β is increased during CHF; it decreases myocardial contractility by stimulating iNOS, and it may uncouple beta adrenoreceptors from adenylate-cyclase, one of the mechanisms of heart failure progression.[89] The negative inotropic effect of IL-1 appears to be mediated, at least partly, by production of NO or by the activation and release of interleukin-18, a member of the IL-1 family.[88] IL-1 induces synthesis by T lymphocytes of interleukin-2 (IL-2), an endogenous T-cell mitogen that enhances T-cell proliferation. IL-2 thus amplifies the immune response and stimulates the production of interferon-gamma and the release of other inflammatory factors (e.g., TNF-alpha). IL-2 levels are increased in human patients with dilated cardiomyopathy and in their relatives, with left ventricular enlargement usually being higher in patients with CHF.[90] Interleukin-6 (IL-6) is a multifunctional cytokine that mediates both immune and inflammatory responses. It is also a promoter of cardiomyocyte hypertrophy and a negative inotrope that is elevated in patients with heart failure, especially those with cardiac cachexia or severe CHF.[91] In human patients with CHF, IL-6 is a predictor of mortality independent of etiology, the sodium concentration, the severity of heart failure, and the ejection fraction.[92]

197.4.3 Nuclear Factor–Kappa-B

During CHF, oxidative stress, increased expression of TNF-alpha, and an increase in the angiotensin II concentration serve to activate NF-kappa-B. NF-kappa-B is a redox-sensitive transcription factor that is critical to initiation of the co-ordinated expression of classic components of the myocardial inflammatory response, including increased expression of proinflammatory cytokines (e.g., TNF-alpha, IL-6), NO, chemokines, and adhesion molecules.[84,88] NF-kappa-B is an important player in inflammation during heart failure. Activation of NF-kappa-B initiates gene transcription of several substances that can lead to cardiovascular injury. NF-kappa-B signaling also plays an important role in myocardial growth, and its inhibition attenuates cardiomyocyte hypertrophy.[93,94] Myocardial cells from patients with heart failure exhibit activation of NF-kappa-B and increased expression of genes it regulates (e.g., TNF-alpha, iNOS). Elevation of NF-kappa-B seems to occur independent of the etiology of heart failure but appears to be related to the severity of CHF. NF-kappa-B can activate cell death pathways, and TNF-alpha–induced apoptosis is associated with an increase in NF-kappa-B. However, blocking of NF-kappa-B in this setting paradoxically exacerbates cell death.[85] It is not known if NF-kappa-B activates antiapoptotic factors. The paradoxical effect of activating detrimental molecules while protecting cells may be related to the inflammatory program mediated by NF-kappa-B; it generates toxic molecules that can kill invading micro-organisms without damaging host cells.[85]

197.4.4 Reactive Oxygen Species

Increases in angiotensin II induce production of reactive oxygen species. An important effect of angiotensin II is activation of the NAD(P)H oxidase, a major source of reac-tive oxygen species (ROS) production by vascular cells. Reactive oxygen species are the end result of univalent reductions in oxygen that produce superoxide anion, hydrogen peroxide, and water.[95] ROS influence both normal and abnormal cellular processes, including cellular growth, hypertrophy, remodeling, lipid oxidation, modulation of vascular tone, and inflammation. The increase in cellular ROS contributes to the pathogenesis of vascular disease by altering endothelial cell function; enhancing smooth muscle cell growth and proliferation; stimulating inflammatory proteins, including macrophage chemoattractant agents, growth factors and cytokines; and modulating matrix remodelling.[96] These ROS can be released from the cardiac myocyte mitochondria, and chronic release of ROS recently was linked to the development of left ventricular hypertrophy and progression of heart failure.[97] The release of ROS is required for the normal physiologic activity of cardiac cells, but abnormal activation of nonphagocytic NAD(P)H oxidase in response to neurohormones and cytokines (angiotensin II, nor-epinephrine, TNF-alpha) has been shown to contribute to cardiac myocyte hypertrophy. The fibrosis, collagen deposition, and metalloproteinase activation involved in the remodeling of a failing myocardium depend on ROS released during the phenotypic transformation of fibroblasts to myofibroblasts that is associated with progression of end-stage heart failure.[97] Studies of genetically altered mice have shown that activation of the NAD(P)H oxidase by angiotensin II contributes to hypertension and left ventricular hypertrophy.[98,99]

The *cytokine hypothesis*[2,100] for heart failure suggests that heart failure progresses because cytokine cascades that are activated after myocardial injury exert deleterious effects on the heart and circulation. This hypothesis does not imply that cytokines cause CHF, but rather that overexpression of cytokines contributes to the progression of heart failure once left ventricular dysfunction ensues.[101] TNF-alpha and IL-6 become activated after left ventricular injury or myocardial stretch. These stress-activated cytokines can exert autocrine and paracrine effects in the myocardium by binding to specific cytokine receptors. If cytokine expression is

excessive, these molecules may produce left ventricular dysfunction and left ventricular dilatation. It is further postulated that cytokines, when overproduced, may spill over into the circulation, leading to secondary activation of the immune system, which is then capable of amplifying the cytokine signal in the periphery.[101] There is an easily recognizable overlap between the neurohormonal and cytokine hypothesis. However, there are likely to be important differences in the mechanisms that initiate overexpression of these molecules, as well as differences in the biologic effects that these molecules exert.

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197.5 WHAT ARE THE CLINICAL MANIFESTATIONS OF HEART FAILURE?

Clinical signs in heart failure may result from accumulation of fluids, low cardiac output, or changes in the skeletal muscles (Box 197-5). Dogs with CHF are usually brought to the veterinarian because of a cough, dyspnea, exercise intolerance, abdominal enlargement, or syncope. Cats, on the other hand, are usually presented because they cannot breathe (pleural effusion or pulmonary edema) or cannot walk (aortic thrombo-embolism) properly.

Sodium and water retention increase the circulating volume and venous pressure, an effect that is potentiated by venous constriction. Venous hypertension and microcirculatory congestion lead to transudation of fluids in body cavities (effusion) or the interstitium (edema). These signs develop preferentially in the capillary beds drained by the failing ventricle. Thus elevated pulmonary venous and capillary hydrostatic pressures in small animals lead to pulmonary edema and can be manifested as dyspnea, cough, pulmonary crackles, and exercise intolerance. Systemic venous hypertension causes jugular distention, hepatic congestion, ascites, and subcutaneous edema. In dogs, ascites always precedes subcutaneous edema in patients with right-sided CHF. Cats rarely develop ascites secondary to right-sided CHF. Biventricular failure shows a combination of left-and right-side signs and is often associated with accumulation of pleural fluid. Although cats may occasionally develop pleural effusion during experimentally induced right-sided CHF,[102] almost all cats with pleural effusion from CHF have bilateral disease or a disease of the left side, with pulmonary hypertension or atrial fibrillation. Pleural effusion in small animals usually accompanies biventricular failure, not isolated right-sided failure.[103] Dogs develop pleural effusion only during experimentally induced right-sided CHF, when large volumes of crystalloid are infused, leading to severe hypoproteinemia.[104] In this setting, pleural effusion correlates better with the pulmonary capillary wedge pressure than with the right atrial pressure, which suggests that right-sided CHF was not the main cause of the development of pleural effusion.

197.5.1 Box • 197-5 Clinical Signs in Congestive Heart Failure

197.5.1.1 Low-Output Signs

Complaints → Exercise intolerance, syncope

Clinical signs → Weak arterial pulses, tachycardia, arrhythmias, cool extremities

197.5.1.2 Signs Related to Poor Skeletal Muscle Function

Complaints → Loss of weight, exercise intolerance, dyspnea*

Clinical signs → Decreased muscle bulk

197.5.1.3 Signs Related to Fluid Retention

Left side (pulmonary edema)

Complaints → Dyspnea, orthopnea, exercise intolerance, cough†

Clinical signs → Pulmonary crackles, tachypnea, gallop rhythm, functional mitral regurgitation, cyanosis caused by ventilation-perfusion inequality

Right side (systemic venous congestion)

Complaints → Abdominal enlargement (ascites), subcutaneous edema

Clinical signs → Jugular distention and pulsation, ascites, hepatomegaly, splenomegaly, hepatojugular reflux, gallop rhythm

Bilateral

Complaints → Left side plus right side complaints, dyspnea caused by pleural effusion

Clinical signs → Left side plus right side clinical signs, muffled heart and lung sounds with fluid line in the chest (pleural effusion)

197.5.1.4 Other Signs

Arrhythmias

Weight loss

Cough

* Activation of metaboreceptors and peripheral chemoreceptors may contribute to dyspnea in patients without congestion.

† Cough may also occur in dogs without congestive heart failure because of left main stem bronchus compression.

A decrease in cardiac output may lead to exercise intolerance, tiring, and fatigue. Because exercise intolerance can occur only in animals that exercise, it is not a prominent complaint of cat owners or of the owners of dogs that spend most of their life on the lap. Syncope may be due to low cardiac output of the failing heart or to concurrent arrhythmia. Low-output signs are nonspecific but, when due to CHF, tend to worsen with exercise.

Dyspnea is usually caused by pulmonary edema or pleural effusion, but it may also occur before the patient develops severe fluid retention. Dyspnea and exercise intolerance may be related to skeletal muscle changes that occur during CHF. Abnormal muscle function and increased fatigability during CHF have been linked to the decrease in muscle bulk, an increased reliance on anaerobic metabolism, decreased muscle blood flow, and metaboreceptor activation.[28] Normal animals become dyspneic during exercise in a manner similar to that which occurs in CHF. The main difference among a normal, fit animal, an untrained animal, and a patient with CHF is the amount of exercise that leads to dyspnea and fatigue. Muscle fatigue is an important determinant of exercise intolerance and dyspnea (fatigue of respiratory muscle) during CHF. In human beings, the same patient may complain of fatigue or dyspnea, depending on the type of exercise performed. It has been proposed that the sensation of fatigue during CHF is generated as a central mechanism to protect against hypoxic damage to essential organs. Ergoreceptors may be responsible for mediating both dyspnea and sensation of fatigue.[105] The muscle hypothesis for CHF states that abnormalities in skeletal muscle blood flow, bulk, and function are major determinants of clinical signs, leading to fatigue and increased ventilatory stimulus. Activation of ergoreceptors leads to persistent sympathetic activation, increasing afterload and reducing blood flow. As cardiac function deteriorates, a catabolic state exacerbates muscle wasting (cardiac cachexia), and patient inactivity leads to further deterioration of muscle function. Such a progression leads to a vicious cycle, in which muscle abnormalities cause clinical signs and favor progression of left ventricular dysfunction, worsening muscle abnormalities and increasing clinical signs.[28]

Cardiac cachexia is a common finding in CHF. It is usually more prominent in right-sided CHF and in giant breeds with dilated cardiomyopathy. In one study, more than half of the dogs with CHF secondary to dilated cardiomyopathy were cachectic.[106] It is very uncommon for an animal with overt CHF to be obese. Obesity is usually associated with respiratory problems. When CHF develops rapidly (e.g., with rupture of a chorda tendineae or the development of atrial fibrillation, or in a few Dobermans with dilated cardiomyopathy), time may not be sufficient for cardiac cachexia to develop, and the animal may show a reasonably normal body condition. The cachectic state is a strong independent risk factor for mortality in patients with CHF.[107] Cachexia is more closely associated with hormonal changes in CHF than are conventional hemodynamic measures of the severity of CHF.[108] Neuroendocrine activation leads to increases in TNF-alpha, IL-1β, norepinephrine, and cortisol and to insulin resistance. All these factors appear to play a major role in the development of cardiac cachexia. An increase in TNF-alpha and its soluble receptors is seen in chronic heart failure. This increase is associated with a rise in the cortisol/dehydroepiandrosterone (catabolic/anabolic) ratio, suggesting that an increase in TNF-alpha is at least partly responsible for the cachexia.[109] In right-sided heart failure, interference with normal absorption of nutrients in the gastrointestinal tract, caused by intestinal and hepatic congestion, may also contribute to cachexia.

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Cough is a common sign of heart disease in dogs but not in cats. Dogs with heart disease may cough because of left-sided CHF, compression of the left main stem bronchus without CHF, or a concurrent respiratory disease (e.g., collapsing trachea, chronic bronchitis). Dogs that cough from pulmonary edema are frequently thin, show severe weight loss, and have a more subtle cough that tends to worsen at night and may be accompanied by a pink nasal discharge or sputum. Dogs that cough because of left main stem bronchus compression or respiratory disease are more likely to be obese or of normal weight and tend to have dry, hacking coughs that are usually worse during the day. Dogs with left-sided CHF usually have fast heart rates caused by sympathetic activation, whereas dogs with left main stem bronchus compression or respiratory disease have normal heart rates with pronounced sinus arrhythmia due to high vagal tone.

Arrhythmias in patients with heart failure may be caused by the underlying disease or by the CHF itself. In addition, chronic, persistent tachycardia may cause left ventricular dysfunction and CHF. The enlargement,

fibrosis, and hypertrophy that occur during left ventricular dysfunction lead to conduction abnormalities that predispose the animal to arrhythmias. A rise in cytosolic calcium, caused by sympathetic activation, may also cause arrhythmias. The presence of arrhythmias is an important negative prognostic factor in patients with CHF.

Clinical signs suggestive of heart disease (although not necessarily CHF) include a diastolic, continuous, or loud systolic murmur; arrhythmias with pulse deficit and gallop rhythms; and ascites with jugular distention and hepatojugular reflux. An aortic thromboembolism (saddle thrombus) in cats also suggests the presence of heart disease. Right-sided CHF is a clinical diagnosis in dogs. It is likely to be present in patients with ascites and jugular vein distention, hepatomegaly, and abnormal cardiac auscultation. Diagnosis of left-sided heart failure, however, requires a chest radiograph. Auscultative pulmonary abnormalities in pulmonary edema are neither sensitive nor specific. A patient with dyspnea, cough, or pulmonary crackles, even with abnormal heart ausculation, may have respiratory signs caused by a primary respiratory disease. In cats, chest radiographs are very useful for diagnosing both right-and left-sided CHF.

197.6 WHY DOES A PATIENT DEVELOP CLINICAL SIGNS OF CONGESTIVE HEART FAILURE?

CHF is a progressive disease, and systolic or diastolic function is eventually compromised to a degree that clinical signs are inevitable. One should not conclude, however, that recent development or worsening of clinical signs is due to disease progression. In many patients a precipitating factor for the CHF can be found, and it may not necessarily be related to the heart itself. Lack of client compliance is a common cause of treatment failure. Clients should be carefully questioned about medications used. Treatment of heart failure usually requires multiple drugs, and confusion about the proper use of the medications is not uncommon. The doses given, the frequency and route of administration, and use of the proper formulation should be verified. Furthermore, the possibility that a person other than the owner (e.g., a pet sitter) may have been temporarily responsible for the dog or cat should be investigated. Inappropriate reduction of therapy is the most common reason for sudden worsening of the clinical condition in human patients with CHF. In small animal practice, inappropriate therapy is more likely when a person who is not completely familiar with the patient's clinical condition is caring for the dog or cat or when the patient goes for a long period without clinical signs and is assumed to be “cured.”

The development of complications is an important precipitating factor for CHF in small animal medicine. Extracardiac complications that impose an extra load on the cardiovascular system may induce CHF in patients with heart disease. Conditions that lead to a hyperdynamic circulation (e.g., anemia, hyperthyroidism, infection, fever) increase MVO_2 and sympathetic tone. Systemic arterial hypertension causes an increase in afterload, which has a devastating effect on a failing myocardium. Systemic hypertension also increases the regurgitant fraction in patients with aortic and mitral regurgitation. In addition, physical, environmental, and emotional stress may lead to CHF, and a second, unrelated disease may affect cardiac function indirectly. Renal failure can potentially cause hypertension and may interfere with sodium excretion, exacerbating the CHF.

A common cause of sudden decompensation of CHF is a cardiac complication. The two most common cardiac complications leading to CHF are the development of mitral regurgitation and arrhythmias. Mitral regurgitation may develop suddenly as a result of dilatation of the annulus valvulus in patients with dilated cardiomyopathy or as a result of the Venturi effect in cats with hypertrophic cardiomyopathy. However, the most devastating cause of acute worsening of mitral regurgitation that leads to CHF is the rupture of chordae tendineae, which occurs in dogs with mitral endocardiosis. The sudden appearance of atrial fibrillation is a common cause of the precipitation of CHF in dogs with dilated cardiomyopathy or mitral endocardiosis. Progression of the cardiacdisease, usually with development of myocardial failure, eventually leads to the appearance of signs of CHF in patients with heart disease.

197.7 HOW CAN WE CLINICALLY EVALUATE HEART FUNCTION?

197.7.1 Is Heart Failure Present?

Heart disease is not synonymous with heart failure. A patient may be presented with a heart murmur or gallop and may even have myocardial failure, yet may not necessarily be in CHF. To facilitate characterization of the severity of heart failure, functional classifications based on clinical signs at rest are used (Box 197-6). The presence of heart failure may be suspected during the physical examination. Right-sided CHF is a clinical diagnosis based on jugular distention and pulsation, the presence of ascites (dogs) and pleural effusion (cats, usually indicating bilateral failure), and peripheral edema. The diagnosis is confirmed by showing elevation of the central venous pressure or, more loosely, by observing a large right heart on radiographs or echocardiography. Left-sided heart failure is a radiographic diagnosis that can be suspected in patients with dyspnea and abnormal respiratory sounds. It can be confirmed by showing elevation of the pulmonary capillary wedge pressure, but identification of pulmonary edema in association with left-heart enlargement would suffice from a clinical standpoint.

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197.7.1.1 Box • 197-6 Functional Classification of Heart Failure

197.7.1.1.1 Modified from the New York Heart Association Classification*

I. Normal activity does not produce undue fatigue, dyspnea, or coughing.

II. The dog or cat is comfortable at rest, but ordinary physical activity causes fatigue, dyspnea, or coughing.

III. The dog or cat is comfortable at rest, but minimal exercise may produce fatigue, dyspnea, or coughing. Signs may also develop while the patient is in a recumbent position (orthopnea).

IV. Congestive heart failure, dyspnea, and coughing are present even when the dog or cat is at rest. Signs are exaggerated by any physical activity.

197.7.1.1.2 International Small Animal Cardiac Health Council†

I. Asymptomatic patient

Ia. Signs of heart disease but no cardiomegaly

Ib. Signs of heart disease and evidence of compensation (cardiomegaly)

II. Mild to moderate heart failure

Clinical signs of heart failure are evident at rest or with mild exercise and adversely affect the quality of life.

III. Advanced heart failure

Clinical signs of congestive heart failure are immediately obvious.

IIIa. Home care is possible.

IIIb. Hospitalization is recommended (cardiogenic shock, life-threatening edema, large pleural effusion, refractory ascites).

* Adapted from Ettinger SJ, Suter PF: The recognition of cardiac disease and congestive heart failure. *In* Ettinger SJ, Suter PF (eds): *Canine cardiology*. Philadelphia, WB Saunders, 1970, p 215.

† Adapted from International Small Animal Cardiac Health Council: Recommendations for the diagnosis of heart disease and the treatment of heart failure in small animals. *In* Miller MS, Tilley LP (eds): *Manual of canine and feline cardiology*, Philadelphia, WB Saunders, 1995, p 473.

Some clinical findings may be helpful, providing indications of cardiovascular function. Gallop rhythms suggest the presence of ventricular dysfunction. The fourth heart sound (S_4 gallop) occurs during late diastole and represents atrial contraction. An S_4 gallop is associated with elevated ventricular end-diastolic pressure related to a decrease in ventricular compliance. An early diastolic filling sound (S_3 gallop) may occur during ventricular dysfunction of any cause and is a very sensitive indicator of ventricular dysfunction. Increased loudness and splitting of the second heart sound suggest the presence of pulmonary hypertension. A distended and sometimes pulsating jugular vein suggests that the right atrial pressure is elevated and the patient is in right-sided heart failure.

197.7.2 What Tests Should Be Performed?

Laboratory tests are used to confirm the presence and cause of the heart disease, the presence and severity of the CHF and ventricular dysfunction, and the presence of complications. Some tests are useful for diagnosing specific conditions and may offer no information about cardiovascular function, whereas others may assess only function or may offer a combination of functional and diagnostic information. In addition to the physical examination, confirmation of the exact cause of CHF usually requires a combination of radiographic, electrocardiographic, echocardiographic, and laboratory assessment techniques. Echocardiography is very helpful in determining the disease leading to the CHF.

Electrocardiography can be used to evaluate the heart rhythm, but it provides only indirect information about cardiovascular function. Arrhythmias may be due to heart disease, but they also can arise from noncardiac causes. The electrocardiogram provides no definitive criteria for diagnosing heart failure. However, it may contribute to the diagnosis (e.g., showing a decrease in QRS voltage and electrical alternans with pericardial effusion). One should bear in mind that a normal electrocardiogram does not rule out CHF or heart disease.

Chest radiographs are very important for patients suspected of having heart disease. Changes in cardiac size and shape may show the compensation effects in the heart (cardiomegaly) and can be very helpful in determining the cause of CHF in dogs. Unfortunately, in cats, chest radiographs do not discriminate among the different

myocardial diseases that may lead to heart failure, and echocardiography is usually necessary. Chest radiographs are of paramount importance in the detection of left-sided CHF (pulmonary venous congestion, pulmonary interstitial or alveolar edema). They are also useful for visualization of pleural effusion in patients with CHF.

Echocardiographic examination is extremely helpful for determining the cause of CHF. There are no echocardiographic criteria for diagnosing CHF, but it is uncommon to see left-sided CHF without echocardiographic abnormalities, such as left atrial enlargement; and right atrial enlargement or pericardial effusion, in right-sided CHF.

Echocardiography, measurement of the arterial blood pressure, and cardiac catheterization may all provide useful information about cardiovascular function. Cardiac catheterization has been used less and less, because most of the information provided by cardiac catheterization can now be obtained noninvasively and without the need to anesthetize the patient. Pressures behind the pumping chambers are useful for estimating ventricular filling pressures. The central venous pressure can be measured with a water-or saline-filled catheter placed in the cranial vena cava or right atrium. The central venous pressure provides an estimation of the right ventricular end-diastolic pressure. The pulmonary capillary wedge pressure is obtained by placing a balloon-tipped (Swan-Ganz) catheter in the pulmonary artery, inflating the balloon to wedge the catheter tip, and then recording the pressure. The pulmonary capillary wedge pressure provides an estimate of the left ventricular end-diastolic pressure. Clinically speaking, congestive heart failure is evidenced by increased ventricular filling (end-diastolic) pressures.[110]

The arterial blood pressure should be measured in all patients with heart disease or CHF. Arterial hypertension can lead to left ventricular hypertrophy and dysfunction and eventually to CHF. CHF secondary to systemic hypertension appears not to be as common in dogs and cats as it is human beings. However, hypertension is a potentially controllable reason for heart disease. In addition, systemic hypertension in a patient with any left ventricular dysfunction increases left ventricular afterload and decreases cardiac output. It also favors progression of left ventricular dysfunction. Hypertension increases valvular regurgitation in patients with mitral or aortic insufficiency and the shunt fraction in dogs and cats with left-to-right shunts.

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Measurement of biochemical markers that are increased during heart disease or CHF can provide information about the disease and in some cases may have prognostic value. The most commonly used markers in small animals are cardiac troponin I, cardiac troponin T, ANP, and BNP. Cardiac troponins are leakage markers that are released into the circulation when cardiac cell membrane integrity has been compromised; they therefore indicate myocardial damage. Any myocardial injury, including CHF, can increase cardiac troponins; a correlation exists between the magnitude of myocardial damage and the degree of elevation of cardiac troponins only in acute states.[111] ANP and BNP are functional markers that increase with an increase in circulating volume (e.g., CHF) or during left ventricular hypertrophy. ANP and BNP tend to increase regardless of the underlying heart disease, but their levels correlate well with the degree of left ventricular dysfunction. They can potentially be used to assess cardiac function, to monitor therapy, and to help determine the prognosis.[49,112] Unfortunately, few clinical studies have highlighted the indications, usefulness, and limitations of different biochemical markers in heart disease in dogs and cats, which limits the use of these markers. As more information becomes available, clinical use of biochemical markers likely will increase.

Several indices are available to aid the evaluation of systolic and diastolic function in intact animals. The large number of indices (Box 197-7 presents a partial list) probably reflects the fact that no single index meets all needs. Only indices that are clinically useful are discussed here.

197.7.2.1

Systolic function

Systolic function is assessed by evaluation of the determinants of stroke volume (preload, afterload, and contractility) and by use of indices of global ventricular systolic performance. For evaluation of cardiac function, many indices require a knowledge of the left ventricular volume or stroke volume. The left ventricular volume can be estimated echocardiographically or by angiography. An echocardiogram provides a good estimation of left ventricular volume non-invasively in dogs and is economically feasible. Two-dimensional echocardiography is superior to M-mode echocardiography in the estimation of left ventricular volume in dogs. The stroke volume can also be obtained by two-dimensional echocardiography (end-diastolic volume/end-systolic volume) or preferentially by Doppler echocardiography. Using Doppler echocardiography, the stroke volume can be determined from the integrated velocity of blood flow across the aorta or pulmonary artery, multiplied by the cross-sectional area of the respective valve orifice.

197.7.2.2

Preload

Left ventricular end-diastolic volume is the best clinical approximation of preload. M-mode–based models for evaluation of the left ventricular volume are associated with unacceptably high variation, especially for the end-diastolic volume. Whenever possible, left ventricular volume should be estimated with two-dimensional echocardiography, using the Simpson's rule or the cylinder-truncated-cone-cone method.[113] Alternatively, preload can be estimated as being equal to the left ventricular end-diastolic pressure based on the relationship between left ventricular pressure and volume. Pressure, rather than volume, cannot be used to estimate preload in stiff or noncompliant ventricles.

197.7.2.3

Afterload

Ideally, afterload should be measured as the aortic input impedance, but this is not clinically feasible. An alternative is to use the effective arterial elastance (Ea). The Ea is a steady-state arterial parameter that incorporates the principal elements of vascular load and is obtained from the ratio of end-systolic pressure to stroke volume.[10] To avoid the need for cardiac catheterization, the mean femoral artery pressure can be used as an estimation of the left ventricular end-systolic pressure.[114] Changes in the Ea show a high correlation with changes in input impedance. Peripheral resistance is another option for estimating left ventricular afterload, but it accounts only for the opposition to steady flow and not for the opposition to pulsatile flow. Peripheral (systemic) vascular resistance (SVR) can be calculated using cardiac output (CO), mean aortic pressure (MAP), and venous pressure (VP) as follows:

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$$SVR = 80 \times (MAP - VP)/CO$$

197.7.2.3.1

Box • 197-7 Some Hemodynamic Indices Used to Evaluate Cardiovascular Function

- Pressure behind the pumping chamber

  Left or right ventricular end-diastolic pressure*

- Pulmonary capillary wedge pressure* (left side)
- Central venous pressure (right side)

- Systolic function
  - Preload
    - Left ventricular (LV) volume
    - LV end-diastolic pressure*
  - Afterload
    - Aortic input impedance*
    - Effective arterial elastance
    - Systemic vascular resistance
    - Arterial blood pressure
  - Contractility
    - Isovolumic indices
      - dP/dt_{max} and derived indices*
    - Pressure-volume indices
      - Preload recruitable stroke work*
      - dP/dt-SdPV*

End-systolic elastance*

Integrated systolic function

Systolic time intervals

Ejection fraction

Fractional shortening

End-systolic volume index

Mean normalized systolic ejection rate

Mean velocity of circumferential fiber shortening

Stroke work*

- Diastolic function

Diastolic time intervals

Isovolumic relaxation time

Flow and volume measurements

Transmitral valve flow profile

Transmitral filling fractions

Pulmonary venous flow systolic fraction

LV flow propagation velocity

Filling fraction

	Peak filling rate
	dV/dt
Other echocardiographically derived indices	
	Rate of change in wall thickness
	Rate of wall relaxation
	Relaxation half-time
Pressure-derived isovolumic relaxation	
	dP/dt_{min}*
	Time constant of relaxation* (τ)
Pressure-volume indices	
	End-diastolic pressure-volume relationship*
	Chamber stiffness*

* Requires cardiac catheterization for proper measurement. dP/dt_{max}, maximum rate of increase in pressure; *dP/dt-SdPV*, end-diastolic volume relation; *dV/dt*, rate of change in volume; dP/dt_{min}, maximum rate of fall in pressure.

The arterial blood pressure can be used as a simple, non-invasive means of assessing the opposition to left ventricular ejection. CHF, however, involves a combination of decreased cardiac output and increased afterload. Because the arterial blood pressure depends on both these factors, it does not provide an adequate evaluation of left ventricular afterload.[115] Nevertheless, it is important to know whether a patient with CHF also has systemic hypertension. The arterial blood pressure may also be important for monitoring vasodilator therapy during CHF.

197.7.2.4 Contractility

Contractility is difficult to define and even more difficult to measure without interference from preload and afterload. Ventricular contraction has an isovolumic phase and an ejection phase. Isovolumic indices evaluate only the isovolumic contraction phase but are less affected by load changes. Ejection phase indices are so affected by changes in afterload and preload that they reflect not the contractility but the integrated systolic function. Indices based on the pressure-volume relationship are relatively load independent and are probably the best indices for evaluating contractility in intact animals. However, they are not routinely used clinically and are beyond the scope of this chapter.

The isovolumic index most commonly used in the evaluation of cardiac contractility is the maximum rate of pressure rise (dP/dt_{max}). dP/dt_{max} is the tangent to the maximum slope of the ascending portion of the left ventricular pressure curve, therefore it can be obtained only with left ventricular catheterization. dP/dt_{max} is influenced by preload (and to a lesser extent by afterload) and cannot be used in presence of valvular regurgitation. It is a sensitive index of contractility but is not specific because of its load dependence. Many other indices based on dP/dt have been developed, but they have roughly the same limitations as the dP/dt_{max}.

197.7.2.5 Integrated left ventricular systolic function

Indices of left ventricular function that evaluate global systolic function can be based on systolic time intervals or on left ventricular volume, diameter, or flow characteristics. The most commonly used systolic time intervals are the left ventricular ejection time (LVET) and the pre-ejection period (PEP). The PEP corresponds to the electric-mechanic interval plus the pressure rise time (onset of QRS to the opening of the aortic valve); it is influenced by changes in afterload, preload, and contractility. The LVET (opening to closing of the aortic valve) is affected by the heart rate and contractility and only mildly by preload and afterload. The information necessary to determine the PEP and LVET can be obtained with an electrocardiogram, a phonocardiogram, and an arterial pressure curve or M-mode echocardiogram of the aortic valve. The PEP/LVET ratio is independent of the heart rate and inversely related to systolic function.[116]

The ejection fraction (stroke volume/end-diastolic volume) and fractional shortening ([end-diastolic dimension – end-systolic dimension]/end-diastolic dimension) are two indices of systolic function expressed as a percentage. They are very sensitive and easy to measure using echocardiography, but they are influenced by changes in load. In addition, the low correlation between M-mode–derived volumes and the true left ventricular end-diastolic volume[113] probably renders an ejection fraction obtained with M-mode echocardiography inaccurate. The left ventricle also must be contracting uniformly, and the ultrasound beam must be parallel to the short axis of the ventricle for an M-mode–derived volume to be representative of global ventricular function.

M-mode imaging of the left ventricle may be performed using short or long axis views of the heart. Left ventricular dimensions obtained from short axis views tend to be higher than those obtained from long axis views, and there may be a lack of agreement between short and long axis views in dogs with heart disease.[117] Fortunately, fractional shortening values obtained from short axis views have shown good agreement with those obtained from long axis images in normal dogs and in dogs with heart disease.[117] When an M-mode of the left ventricle is recorded, it is important to be in the center of the left ventricle, perpendicular to the left ventricular wall, and with the ultrasound beam just below the mitral valve. The short

axis view allows better centering of the beam in the heart, whereas the long axis view is preferred for assuring that the beam is perpendicular to the wall. Either plan can be used to place the beam below the mitral valve. The choice of view (short axis, long axis, or both) for obtaining M-mode measurement of fractional shortening in dogs and cats remains a matter of the examiner's personal preference. Fractional shortening in dogs is also affected by body size, being smaller in giant breed dogs. The end-systolic volume index, left ventricular end-systolic volume obtained by M-mode indexed to body surface. It has been used in dogs,[118] but it is also dependent on afterload and in M-mode estimation of left ventricular volume. The end-systolic volume index may be more accurate than other volume-based indices because only one volume must be estimated, which avoids compounding error from multiple measurements. In addition, measurement of the end-systolic volume improves precision because of the better correlation between M-mode–derived volumes and true ventricular volume at smaller volumes.[113] The time to aortic peak velocity, which can be obtained by Doppler echocardiography, correlates well with global systolic function. Like all ejection indices, it is affected by changes in afterload.

197.7.2.6 Diastolic Function

Diastolic function is harder to evaluate noninvasively than systolic function. Doppler echocardiography remains the primary technique for assessing diastolic function noninvasively. Some indices of diastolic function assess ventricular function during a specific phase, whereas others evaluate global performance during diastole.

Diastolic time intervals can be used to evaluate diastolic properties. The most commonly used diastolic time interval is the isovolumic relaxation time, which is the time from aortic valve closure to mitral valve opening, when the left ventricular volume is constant. It is a relaxation index and can be obtained from phonocardiography (for aortic closure) and M-mode echocardiography (to mitral opening) or from Doppler echocardiography (the time from cessation of aortic flow to commencement of transmitral flow). An isovolumic relaxation time obtained echocardiographically correlated well with the time constant of isovolumic relaxation (τ) in anesthetized cats.[119] Unfortunately, the rate of decline in left ventricular pressure is only one of several factors that determine the isovolumic relaxation period. The aortic diastolic pressure and left atrial pressure affect the length of this period. The isovolumic relaxation time cannot be used in patients with aortic or mitral regurgitation because there is no true isovolumic period.

Doppler echocardiogram–derived changes in blood flow can be used to evaluate diastolic function. Many indices have been proposed, but the ones based on the transmitral valve flow profile (E and A waves) are more commonly used. The E wave represents early ventricular filling and precedes the A wave (atrial filling wave). The E wave is normally larger than the A wave (E/A ratio usually greater than 1). During fast heart rates, especially in cats, E and A waves are often fused, and the E/A ratio cannot be evaluated. An increase in the size of the A wave and a decrease in the E wave occur in patients with relaxation abnormalities. Unfortunately, with progression of the disease and an increase in the left ventricular end-diastolic pressure, the presence of mitral regurgitation, and an increase in the left atrial pressure, pseudonormalization of the E and A waves occurs. Patients with restrictive diseases tend to have smaller A waves and larger E waves.

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M-mode echocardiography can also be used to evaluate diastolic function. The rate of change in wall thickness, the rate of wall relaxation, and the relaxation half time can be obtained with an M-mode echocardiogram (ideally a digitized echocardiogram). The peak rate of posterior wall motion has also been used, but this measurement is susceptible to distortion because of translational motion.

Hemodynamic indices that use pressure rather than volume have been used to evaluate diastolic function. These all require cardiac catheterization. The peak negative dP/dt measures the maximal rate of decline of left ventricular pressure during relaxation and is usually taken as the lowest value of the first derivative of this pressure. It usually occurs around the time of aortic closure. It should be remembered that the peak negative dP/dt occurs at one point in time and does not represent the totality of events, even during relaxation only. In addition, the peak minimum dP/dt is highly dependent on the left ventricular and the aortic systolic pressures.

197.7.2.7 Integrated Function

Cardiac output is considered a measure of integrated cardiovascular performance. Cardiac output is usually measured by thermodilution, a technique based on the indicator-dilution method. Thermodilution offers advantages because it does not require arterial puncture or the withdrawal of blood, and an inert and inexpensive indicator (e.g., cold saline or 5% dextrose in water) is used with virtually no recirculation. However, all indicator techniques require placement of a catheter in the pulmonary artery, which makes these techniques impractical for routine use in clinical veterinary medicine outside critical care units. Doppler echocardiography can also be used to estimate cardiac output. The stroke volume can be determined from the integrated velocity of blood flow across the aorta or pulmonary artery multiplied by the cross-sectional area of the respective valve orifice.[120] Doppler determination of blood flow velocity is a noninvasive method that can be performed in awake, untrained, dogs.[121] It is useful for documenting beat-to-beat variation in the stroke volume in dogs[122] and can be used to determine the cardiac output when the stroke volume is multiplied by the heart rate. As with thermodilution determination of cardiac output, Doppler-derived values for cardiac outputs are variable.[123] Cardiac outputs obtained by Doppler echocardiography and thermodilution show an excellent correlation[124]; however, the technique for obtaining cardiac output by echocardiography appears to be quite operator dependent. It should be remembered that cardiac output at rest is not a sensitive indicator of heart function during CHF because all compensatory mechanisms act to increase cardiac output.

197.7.3 What Tests Should I Use in a Clinical Patient?

Of all the tests available for the evaluation of cardiovascular function, a few are routinely used. Chest radiographs and echocardiography are performed in virtually all patients with CHF. Measurement of the arterial blood pressure and central venous pressure can be easily performed and provides important information about cardiovascular status. Not surprisingly, the most commonly used tests of cardiovascular function are based on echocardiography, whereas chest radiographs are used to confirm left-sided CHF. In the majority of patients, systolic performance is assessed by fractional shortening, the ejection fraction, or the end-systolic volume index. No clinical comparison of these indices has been performed in small animals, therefore the choice of index is a matter of personal preference. In selected patients the aortic velocity, time to peak aortic velocity, and cardiac output can be measured using Doppler echocardiography. Diastolic performance is usually assessed by Doppler evaluation of transmitral flow. In patients undergoing cardiac catheterization, pressure traces, dP/dt_{max}, cardiac output, and estimated systemic vascular resistance, among other measurements, can be obtained.

197.8 HOW DOES HEART FAILURE BECOME A PROGRESSIVE DISEASE?

197.8.1 Vicious Cycles in Congestive Heart Failure

Compensatory mechanisms activated during heart failure paradoxically serve simultaneously as adaptive, compensatory changes and, by causing myocardial cell death, as major contributing elements in the progression of CHF. Cell death in an already overloaded heart adds to the overload on survival myocytes in a vicious cycle. Three primary, interlocked vicious cycles ultimately result in myocardial cell death (Figure 197-18).

197.8.1.1 Increased Left Ventricular Afterload and Myocardial Oxygen Consumption (Cycle 1)

Vasoconstriction and increases in cardiac contractility and the heart rate help maintain blood pressure but also increase MVO_2. Increasing cardiac MVO_2 accelerates myocardial cell death. Wall stress (a function of afterload), contractility, and the heart rate are the main determinants of MVO_2. Myocardial hypertrophy reduces oxygen consumption by decreasing wall stress during ejection. Hypertrophy caused by increases in load, however, does not yield a normal heart. Load-induced hypertrophy sets the stage for myocardial death. An increase in afterload leads to further left ventricular dysfunction, and the patient spirals down until a new, decreased steady-state level is reached, where cardiac output is lower and vasoconstriction is higher than is optimal for the patient.

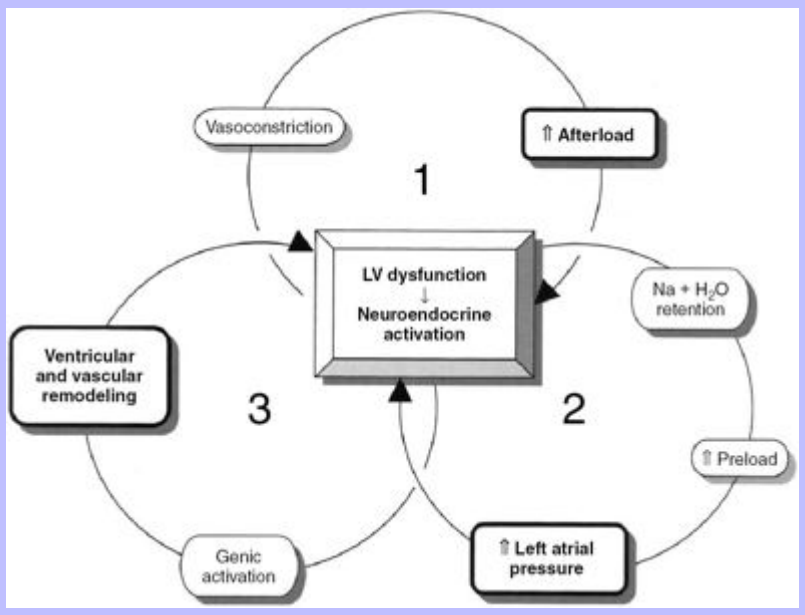
197.8.1.2 Sodium and Water Retention and Increased Left Atrial Pressure (Cycle 2)

Sodium and water retention increase the circulating volume, resulting in increases in preload and the left atrial pressure. An increase in preload increases cardiac output and helps maintain filling pressures but also leads to signs of congestion and edema. An excessive preload increases ventricular pressures, volume, and wall stress, further adding to the deterioration of left ventricular function.

197.8.1.3 Left Ventricular and Vascular Remodeling (Cycle 3)

Stretching of myocardium as a result of overload seems to be the initiating signal for adaptive processes to begin in the myocardium. This leads to hypertrophy as a result of growth factor and proto-oncogene stimulation.[66] Hypertrophy unloads the cells of the failing heart by adding new sarcomeres and also increases contractility and cardiac output. Unfortunately, hypertrophy ultimately leads to cellular abnormalities that result in mitochondrial deoxyribonucleic acid (DNA) abnormalities and apoptosis (programmed cell death), which hasten myocardial cell death.[66] Chronic neuro-endocrine activation, especially increases in angiotensin II and norepinephrine, and increases in afterload lead to left ventricular and vascular remodeling. Globally, the remodeling process in the ventricle is characterized by progressive left ventricular enlargement and increased chamber sphericity. At the cellular level, the remodeling process is associated with myocyte slippage, hypertrophy, and accumulation of collagen in the interstitial compartment. The final result of this process is the so-called cardiomyopathy of overload. Angiotensin II also causes vascular remodeling, which leads to hypertrophy of smooth muscle cells of the vessel walls.[125] Vascular remodeling decreases vessel compliance, thereby increasing ventricular afterload.

Figure 197-18 Interlocked vicious cycles that lead to progression of congestive heart failure: increased afterload (cycle 1), increased left atrial pressure (cycle 2), and ventricular and vascular remodeling (cycle 3). *LV,* Left ventricle.



197.8.1.4 Cardiomyopathy of Overload

Long-term overload-induce hypertrophy in the heart is accompanied by myocardial cell death and cardiac fibrosis. This progressive and eventually lethal growth abnormality has been called cardiomyopathy of overload.[23,66] In embryonic hearts, growth factors induce protein synthesis, leading to normal cell division. Soon after an animal is born, cardiac myocytes withdraw from the cell cycle and are no longer able to divide, and protein synthesis slows to rates appropriate for maintaining and repairing the cells. Stimulation of growth factors by chronic overload leads to an increase in protein synthesis. The cell cycle, however, remains blocked, and the end result is not normal cell division but abnormal hypertrophy. Increases in angiotensin II, a peptide that is not only a vasoconstrictor but also a mitogen, appear to be an important mediator of the reversal of protein synthesis inhibition in the adult heart.

Overload-induced hypertrophy leads to a state of chronic energy starvation in the heart. Because the increase in cardiac mass is not accompanied by an increase in capillary vessels, the hypertrophied ventricle outstrips its blood supply. The cell volume occupied by sarcomeres increases, leading to an increased ratio of mitochondria to myofibrils, which can exacerbate the energy deficit. The net result is a decrease in capillary density and coronary reserve, with the myocardium becoming prone to ischemia, especially in the subendocardium. The relative decrease in oxygen delivery complicates the failing heart's increased need for oxygen, which is already increased by vasoconstriction and sympathetic activation. Hypertrophy and increasing systolic dysfunction are closely linked. The ischemia resulting from hypertrophy leads to the development of focal fibrosis, which increases the myocardial collagen content. The early increase in

collagen helps maintain systolic function, but it also interferes with diastolic function. With progression of the myocardial hypertrophy, the early interstitial fibrosis progresses to perimuscular fibrosis, impairing both systolic and diastolic function. Myocardial cell necrosis occurs in overloaded hearts in the transition to heart failure. Myocyte cell death results not only from necrosis (accidental cell death) but also from apoptosis (programmed cell death). The activation of proto-oncogenes and the increased concentrations of TGF-1α that occur in CHF may induce apoptosis. Regardless of the cause, myocardial cell death occurs in overload-induced hypertrophy, increasing the overload in the surviving myocytes in a vicious cycle. Cardiomyopathy of overload, therefore, represents an unnatural growth of the adult heart that leads to myocardial cell death, progression of myocardial failure, and death.

197.9 SUMMARY

Heart failure is a state in which cardiac output is inadequate to meet the perfusion needs of the metabolizing tissues and exercise capacity is limited. It may be the result of inability of the heart to eject blood properly (systolic failure) or of inadequate ventricular filling (diastolic failure). Correct identification of the cause of heart disease and of the mechanism leading to heart failure allows the clinician to choose the appropriate therapy, thereby improving the prognosis.

Regardless of the mechanism, CHF is associated with a fall in blood pressure and activation of compensatory mechanisms aimed at restoring normal arterial blood pressure. These mechanisms include neuroendocrine activation and renal retention of sodium and water. Vasoconstriction, tachycardia, and volume retention are the initial responses of the circulation to the fall in blood pressure. Excessive compensatory response may lead to overcompensation, and compensatory mechanisms that are beneficial in the beginning become responsible for the development of clinical signs.

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Therapy is aimed at modulating the excessively activated compensatory mechanisms. The inciting cause of the cardiac dysfunction and neuroendocrine activation also stimulates myocardial compensation, leading to increased contractility and relaxation, sympathetic desensitization, and unnatural growth (hypertrophy). Modulation of the unnatural growth response with drugs that have growth-inhibitory as well as vasodilative properties (e.g., ACE inhibitors and nitrates) may delay the appearance of cardiomyopathy of overload and improve the prognosis for patients with CHF. Myocyte changes determined by overload-induced hypertrophy ultimately lead to myocardial cell death, which further compromises myocardial function. Thus once a certain point of myocardial dysfunction is reached, CHF becomes a progressive, irreversible disease.

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198 CHAPTER • 198 Biochemical Markers of Cardiovascular Disease

Karsten E. Schober

During the past decade, considerable research has been conducted into the use of circulating markers of myocardial cell integrity *(leakage markers)* and of specific proteins of cardiac function *(functional markers)*, their diagnostic capability, and their potential to aid therapeutic decisions and allow prognostic risk assessment in patients with cardiovascular abnormalities (Box 198-1). Biochemical screening for heart disease or for definition of the functional status of the heart in certain pet populations based on readily available circulating marker proteins such as cardiac troponins, natriuretic peptides, or endothelin is an attractive hypothesis. Moreover, the prospect of identifying dogs and cats with early asymptomatic or minimally symptomatic congestive heart failure (CHF) or patients at risk for sudden deterioration of ongoing disease processes via biochemical testing is exciting from several perspectives. For example, it would allow individuals without extensive training in cardiology to detect animals with cardiac abnormalities more accurately and at an earlier point in time. This would permit early therapeutic intervention and potentially reduce the morbidity and mortality associated with advanced stages of heart disease, while avoiding unnecessary treatment of unaffected or mildly affected animals. In addition, conditions that currently are still difficult to identify clearly with conventional diagnostic methods (e.g., myocarditis, ischemic heart disease, and pulmonary hypertension) could be detected more specifically.

Biochemical testing might also help clarify the status of animals with equivocal results from other diagnostic modalities, such as for dogs with borderline systolic function on echocardiography, animals with arrhythmias of unknown origin, or dogs with questionable cardiomegaly on thoracic radiographs. Other applications might include monitoring of the effects of potentially cardiotoxic drugs or of extracardiac disease on myocardial integrity and function.

The advent of biochemical markers also opens a category of the pathophysiologic aspect of nonischemic cardiac damage that is not yet fully understood or verified. It likely will provide important prognostic information and may prove useful for monitoring the success of treatment or for determining the need to change treatment protocols. Screening of certain breeding populations for asymptomatic myocardial diseases, such as hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM), may be another possibility.

198.1 LEAKAGE MARKERS

Circulating markers of myocardial integrity provide evidence of cell degradation, supplying the rationale for diagnosis of a disease process using such markers. That is, detection of intracellular constituents released into the blood when a cell either ruptures or loses membrane integrity allows identification of the damaged target tissue. Measurable changes in the serum concentration of these markers are determined primarily by the markers' molecular mass, intracellular compartmentalization, solubility, release kinetics, post-translational modifications, and assay characteristics; by local blood and lymphatic flow; and by the route by which the markers are cleared from the circulation.

Myocardial cell injury is a common event in the pathogenesis of heart failure in dogs and cats.[1,2] Pressure and volume overload, hypoxia and ischemia, abnormal neurohormonal stimulation, toxins, and cytokines all may cause myocardial remodeling, characterized by hypertrophy and dilatation or, at the cellular level, by oxidative and mechanical stress, degeneration, inflammation, fiber slippage, apoptosis, necrosis, and fibrosis of myocardial tissue that finally results in cardiac functional abnormalities.

Analysis of cardiac leakage markers has progressed from measurement of enzymes (e.g., plasma aspartate transaminase) to measurement of structural proteins, including cardiac troponins (see Box 198-1; Table 198-1). Although commonly used diagnostic procedures can serve as the current gold standard for the assessment of cardiac anatomy and function in clinical practice, they most often are inadequate for detecting and quantifying minor myocardial cell injury or active myocardial damage.

198.2 ALPHA-HYDROXYBUTYRATE DEHYDROGENASE (ALPHA-HBDH)

Lactate dehydrogenase (LD) is a tetrameric enzyme with *M* (muscle) and *H* (heart) subunits that is responsible for the interconversion of pyruvate and lactate as the final step in glycolysis. The two subunits are encoded by different genes and give rise to five distinct isoenzymes that provide LD with an element of tissue specificity. LD-1 has four H subunits, and LD-2 has three H subunits and one M subunit. LD-1 and LD-2 form alpha-HBDH, which has some cardiac specificity. However, because other sources of LD-1 and LD-2 exist (i.e., erythrocytes, as well as the brain, kidneys, pancreas, and stomach), tissue specificity for the detection of myocardial injury is rather poor. Reference values for alpha-HBDH in dogs and cats have been published (see Table 198-1),[3,4] but because more specific serum markers of myocardial cell damage are available, analysis of alpha-HBDH is no longer recommended for the diagnosis of myocardial injury in dogs and cats.

198.2.1 Box • 198-1 Biochemical Markers of Cardiac Disease

198.2.1.1 Leakage Markers

Cardiac troponin I*

Cardiac troponin T*

Myoglobin

Creatine kinase isoenzyme MB

Creatine kinase

Lactate dehydrogenase isoenzymes 1 and 2

Aspartate transaminase

Heart fatty acid-binding proteins

Glycogenphosphorylase isoenzyme BB

Myosin light chain

Myosin heavy chain

Plasma oxidase

198.2.1.2 Functional Markers

Brain natriuretic peptide

Atrial natriuretic peptide*

Endothelin-1

Epinephrine

Norepinephrine

Renin

Angiotensin II

Aldosterone

Arginine vasopressin

Tumor necrosis factor-alpha

Adrenomedullin

C-reactive protein

* Currently one of the most commonly used markers in companion animals.

Table • 198-1 Characteristics and Reference Values* of Circulating Myocardial Leakage Markers in Dogs and Cats

MARKER	MOLECULAR WEIGHT(kDa)	SERUM HALF-LIFE (h)	TIME TO INITIAL ELEVATION (h)†	TIME TO PEAK (h)†	TIME TO RETURN TO BASELINE (d)†	CATS (n = 28)	DOGS (n = 40)
AST (U/L)	93	20	6–12	18–36	3–6	20 (12–36)	26 (14–63)
Alpha-HBDH (U/L)	135	10	6–12	24–48	7–10	30 (20–44)	26 (3–52)
Mb (ng/mL)	17,8	0.25	1–4	6–8	1	0 (0–1.86)	0 (0)
CK-MB (ng/mL)	86	2	3–6	12–24	3–4	0 (0–1.30)	0 (0–2.48)
cTnT (ng/mL)	37	2	3–8	12–96	5–14	0 (0–0.01)	0 (0)
cTnI (ng/mL)	22,5	2–4	3–8	12–24	5–10	0 (0)	0 (0–0.93)

AST, Aspartate transaminase; *alpha-HBDH*, alpha-hydroxybutyrate dehydrogenase; *CK*, creatine kinase; *Mb*, myoglobin, *CK-MB*, CK isoenzyme MB (mass determination); *cTnT*, cardiac troponin T; *cTnI*, cardiac troponin I.
Median (2.5th to 97.5th percentile).

* From Kirbach B et al: Diagnostik von Herzmuskelschäden bei Katzen mit stumpfen Thoraxtraumen über biochemische Parameter im Blut. Tierärztl Prax 28 (K):25, 2000; and Schober K et al: Noninvasive assessment of myocardial cell injury in dogs with suspected cardiac contusion. J Vet Cardiol 1:17, 1999.

† After acute ischemic myocardial damage. “0” refers to the lower limit of detection of the assay used (1.0 ng/mL for Mb, 0.5 ng/mL for CK-MB, 0.1 ng/mL for cTnI [OPUS Troponin I; Dade-Behring Diagnostics, Westwood, Massachusetts], and 0.01 ng/mL for cTnT [ELECSYS 1010 Troponin T STAT; Boehringer, Mannheim, Germany]).

198.3 MYOGLOBIN (Mb)

Myoglobin is a low-molecular-weight heme protein that is abundant in cardiac and skeletal muscle but not smooth muscle. It is found predominantly in the cytosol of the cell.[5] Because of its high sensitivity and rapid release after myocardial injury, it has drawn considerable attention in the early diagnosis of acute myocardial infarction (AMI) in humans. It may be less clinically useful in animals, however, because of its low cardiac specificity and rapid clearance after injury, and because, compared with humans, dogs and cats have a low incidence of ischemic heart disease.

198.4 CREATINE KINASE ISOENZYME MB (CK-MB)

Creatine kinase (CK) is a dimeric enzyme with *M* (muscle) and *B* (brain) subunits, each having 381 amino acids.[5] CK catalyzes the transfer of a high-energy phosphate from adenosine triphosphate (ATP) to creatine, producing creatine phosphate. CK isoenzymes consist of CK-MM, CK-MB, or CK-BB. A unique dimeric mitochondrial form not composed of either M or B subunits also exists. Each subunit of CK is regulated by a distinct gene and is expressed in a tissue-specific manner. CK-MB is functionally unbound and cytosolically dissolved and is found predominantly in the myocardium[6] in concentration ranges of 1% to 42% of total CK activity of the heart. There is a significant difference in the concentration of CK-MB between normal and diseased myocardium,[6] depending on the disease state, the patient's age, the chronicity of myocardial stress, and the severity and duration of ischemia. Marked upregulation of CK-MB synthesis in cardiomyocytes may be seen after myocardial injury despite a decrease in absolute CK concentrations. Such dynamic CK-MB alterations may cause a significant elevation of the relative amount of CK-MB in ventricular myocardium within several weeks of the onset of disease. Circulating CK-MB is not 100% specific for cardiac muscle tissue, because a significant portion of CK-MB may be expressed in skeletal muscle, the lungs, intestines, and spleen. Moreover, CK-MB immunoreactivity is not well conserved across species,[7] and species-specific immunoassays for CK-MB are not commercially available for use in dogs and cats. CK-MB is released early after acute myocardial cell damage (see Table 198-1), is inactivated by proteolysis in lymph, and is rapidly cleared by the reticulo-endothelial system. In normal dogs and cats, CK-MB in serum is not detectable.[3,4]

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198.5 CARDIAC TROPONIN (cTn)

Since the descriptions of the measurement of cardiac troponin T (cTnT) in 1989 and cardiac troponin I (cTnI) in 1992, analysis of circulating cTn has revolutionized the noninvasive diagnosis of acute coronary syndromes in human beings. Cardiac troponin levels allow more specific detection of myocardial damage than do traditional “cardiac enzymes” such as LD and CK-MB. A series of landmark clinical studies has defined cTn measurement as the gold standard test for AMI in humans. The advantage of cTn lies in its ability to provide an early, highly cardiac specific diagnosis of even micronecrotic pathology and prognostic risk assessment and to guide therapy. Despite the obvious lack of importance of ischemic heart disease in small animals compared with humans, studies performed in dogs and cats have suggested similar findings indicating superior efficacy of cTnI and cTnT in the diagnosis of myocardial injury in a variety of clinical conditions.[1–17]

198.5.1 Structure and Function

The troponin complex is made up of three structurally and functionally different proteins (TnI, TnT, and TnC), which exist in different isoforms in both skeletal and cardiac muscle but not in smooth muscle. It is located on the thin filament of the contractile apparatus that regulates the calcium-mediated interaction of myosin and actin. Although both TnI and TnT are present in skeletal muscle (in slow-and fast-twitch fibers) and cardiac muscle, they are encoded by individual genes, yielding proteins that are immunologically distinct. Cardiac troponin T has 276 amino acids and is a structural protein that binds the troponin-tropomyosin complex to the actin filament. Cardiac troponin I is a linear protein with five alpha-helices; it has 211 amino acids[18] and is an inhibitory protein that regulates muscle contraction. Its phosphorylation causes a decrease in the affinity of Ca^{2+} for the calcium-binding TnC, leading to inhibition of actomyosin ATPase activity. Cardiac TnI is uniquely specific to the heart, containing an additional 31-amino-acid sequence on its N-terminal region. The remaining amino acid sequence shows approximately 40% dissimilarity from skeletal muscle forms. In the cardiomyocyte, the troponins are compartmentalized into a major, structurally bound pool and a minor, free cytosolic pool, estimated at 6% to 8% for cTnT and 2% to 6% for cTnI. This cellular distribution determines release kinetics, with free cytosolic proteins released earlier. The third protein of the troponin-tropomyosin complex, TnC, has only two isoforms (160 and 161 amino acids) and is an 18 kDa protein with calcium-binding properties. The complete homology between the cardiac and the skeletal muscle isoforms of TnC has limited its diagnostic value.

198.5.2 Release, Degradation, and Clearance

Both loss of membrane integrity and cell necrosis cause the release of cTn from damaged cardiomyocytes. Two basic cTn release patterns have been postulated, depending on the type of underlying disease, the time to peak damage, and the severity of cell injury. In cases of slow disintegration of myofibrils, the release pattern may be biphasic, with the cytosolic pool released first. If the insult is more severe, a more protracted, persistent release from structurally bound stores may occur, representing irreversible cell damage. An important question is whether cTnI and cTnT leaks across the myocardial cell membrane in reversible injury, such as transient ischemia (*reversible injury* concept), as postulated by some investigators. In such cases, only mild cTn elevations and a temporary, monophasic release pattern would be expected.

Early work revealed that cTn first is released as a ternary complex of cTnT-I-C, which subsequently degrades into binary complexes of cTnI-C, free cTnT (with little or no free cTnI), and smaller immunologic fragments. However, more recent data suggest that troponin may already be degraded into small fragments within the myocyte. Once released into circulation, N-and C-terminal regions of cTn are particularly vulnerable to additional, progressive, and highly variable biochemical modifications, including phosphorylation, complex formation, and proteolytic cleavage. The newly formed degradation products may alter their recognition by monoclonal antibodies, affecting assay performance. Furthermore, different pathologic states (e.g., ischemia, inflammation, toxic injury) result in different post-translational profiles of cTn, with cTnI being more susceptible to postrelease modifications and less stable than cTnT.

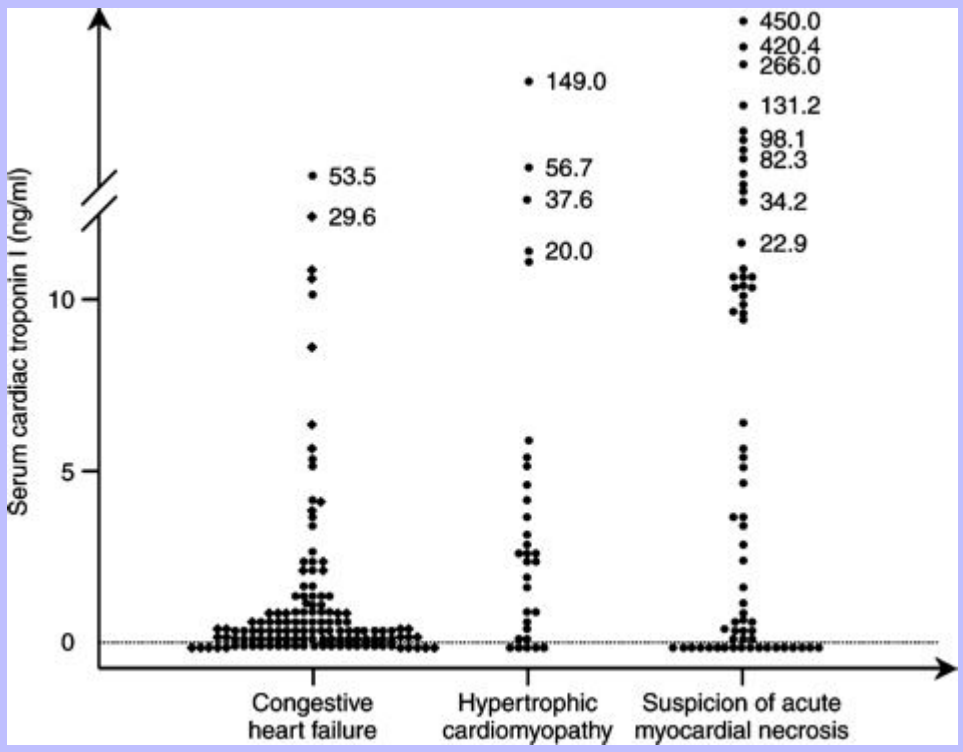
Clearance of cTn is not well documented. As with most marker proteins with molecular weights above 20 kDa, cTn appears to be catabolized in organs with a high metabolic rate, such as the liver and pancreas, and the reticuloendo-thelial system. The serum half-life of cTnT is approximately 120 minutes, with a prolonged window of detection due to continuous release of cTnT from the myofibrillar pool during the myocyte degradation processes.

198.5.3 Analysis

Clinicians must be aware of several analytic issues. Investigations in animals have demonstrated that both cTnI and cTnT immunoassays designed for use in humans can be used reliably and specifically to detect myocardial injury in dogs and cats, because cTn immunoreactivity has been highly conserved across species.[19] The monoclonal antibodies used in second-and third-generation assays for cTn analysis have no known species specificity and no detectable cross-reactivity with skeletal muscle isoforms.

Due to patent restrictions, assays for cTnT are available from only one manufacturer; they therefore are relatively uniform with regard to cutoff concentrations and precision. In contrast, at least 16 different assays for cTnI have been approved by the U.S. Food and Drug Administration (FDA). Because of the lack of standardization in cTnI assays, significant variability exists in the assay methods and cutoff values used. Up to 100-fold differences in absolute concentrations of cTnI for a given patient sample have been observed. With so much variation, attention must be paid to the assay used when the data and results of troponin I measurements are interpreted. Sample requirements for the different assays also may vary. The optimal sample material for most systems seems to be serum clotted adequately. The cTnT molecule is stable at a room temperature of 4° C and when frozen. Cardiac TnI is more susceptible to early epitope degradation; however, serum samples may be stored at room temperature for 4 days without clinically relevant reduction of detectable cTnI concentrations.[2,8,20] In terms of substate stability for analyns, differences between different CTnI assays may, however, exist.

Figure 198-1 Serum cardiac troponin I concentrations in 129 dogs with congestive heart failure (•, dilated cardiomyopathy; ♦, congestive heart failure of other cause), 31 cats with hypertrophic cardiomyopathy, and 67 dogs with the clinical suspicion of acute myocardial necrosis of non-cardiomyopathic origin based on the occurence of venticular arrhythmia. Zero CTnI refers to the lower limit of detection of the immunoassay used (0.1 ng/ml; opus® Troponin I, Dade-Behring Diagnostics Inc., Westwood, MA). From the veterinary medical database of the Department of Small Animal Medicine, University of Leip zig and reference 2 with permission.



198.5.4 Reference Intervals and Clinical Cutoff Values

In healthy dogs and cats, the background level of cTn in the circulation appears to be undetectable (see Table 198-1). Several clinical studies, involving more than 331 dogs[4,9,15–17,21] and 150 cats,[3,10,17,21–23] have shown that both cTnI and cTnT are below the detection limit of the assay used or occur only in trace amounts in the peripheral circulation. However, because of the very high sensitivity of second-and third-generation immunoassays, minimal elevations of cTn may occur in obviously healthy animals as a result of strenuous

exercise or noncardiac disease. This is particularly true for cTnI. To distinguish between minor myocardial cell damage (so-called micronecrosis) and major myocardial injury, two cutoff points were suggested for clinical use in humans: the upper reference limit, defined as the 97.5th percentile of the values measured in the normal control population, and a higher limit, indicating clinically relevant myocardial damage. Given the difficulties in objectively defining the latter value and the currently used, rather liberal thresholds, it is not clear whether the exact magnitude of troponin elevation is indeed essential for clinical decision making. From the clinician's point of view, it appears that characterizing patients as “troponin negative/mildly elevated” or “troponin positive/moderately to severely elevated” and dynamic monitoring of cTn concentrations are most useful for diagnosing and semiquantifying myocardial necrosis and for making a subsequent risk assessment.

198.5.5 Sensitivity and Specificity

When the most current assays are used, cTnI is elevated earlier and more frequently than cTnT in a variety of clinical conditions in dogs and cats, as confirmed by meta-analysis using 500 simultaneously measured serum samples.[2] Circulating cTn is highly specific for myocardial cell injury. Correlation of histopathologic findings with biochemistry results showed that elevated cTn values can be directly related to evidence of cardiac myonecrosis in dogs.[*]

Comparative values for differences in the level of cardiac specificity between cTnI and cTnT have not yet been defined in animals. In humans, however, both markers demonstrated equivalent specificity for myocardial damage. The author believes that cTnI has some advantage in terms of sensitivity, whereas cTnT appears to have a stronger association with the patient's outcome.

* References 2, 5, 7, 8, 12-14, and 16.

198.5.6 Circulating Cardiac Troponin in Disease

The diagnostic benefit of assessing myocardial injury in dogs and cats through cTn analysis has been shown in numerous studies (Figure 198-1).[2–5,7–12,15,16,23] Circulating cTn levels are frequently above normal in different clinical settings (Box 198-2), even in disease states in which acute myocardial necrosis is not a prominent aspect, such as dilated cardiomyopathy, chronic CHF, cardiac contusion, pericardial disease, or cardiac injury in critically ill patients. In general, increased concentrations of cTnI or cTnT in circulation reflect myocardial damage; thus cTn serves as a means to detect both major and minor injury. An association exists between the magnitude of myocardial damage and serum concentrations of cTn in acute situations; this has been verified by histopathologic testing in canine myocardial infarction,[5,7,11,12,16] gastric dilatation-volvulus syndrome (GDV),[8] canine myocarditis,[2,15,16] and dogs with sepsis.[2] In chronic myocardial disease, however, this relationship is not as obvious, for several reasons. Only minor myocardial injury may be present at the time of cTn determination; also, permanent leakage of cTn leads to a significant reduction in the tissue concentration of cTn over time.[13] Therefore absolute levels of circulating cTn do not necessarily represent the amount of irreversibly damaged myocardium in chronic situations.

In symptomatic canine DCM,[2,9,16] circulating cTn is increased in a significant number of patients (see Figure 198-1), with rather minor elevations being the most common finding.[2,9,16,21] Serial monitoring of cTn has revealed different release patterns (Figure 198-2) that not only define the status of the failing heart with regard to acute myocyte damage, but also provide prognostic information. Progressive left ventricular (LV) remodeling, a hallmark of DCM, leads to intermittent or permanent leakage of cTn into the circulation. In addition, the presence of coronary artery disease with small myocardial infarctions, focal myocarditis, and

increased wall strain may contribute to cTn release in heart failure. Elevated concentrations of circulating cTn in such patients reflect ongoing degradation of the contractile apparatus. Presumably, continuous loss of cTn facilitates the process of myocyte dysfunction that accompanies the spontaneous progression of heart failure. In humans, an inverse relationship between peak cTn values and LV function, as assessed by echocardiography, has been reported, and detectable cTn was associated with an adverse prognosis. A similar situation may be expected in animals. Clinical improvement in signs of CHF is associated with normalization of cTn levels, which may serve as a biochemical target in the management of DCM. Therefore dynamic monitoring of serum cTn is recommended in animals with heart failure.

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198.5.6.1 **Box • 198-2 Clinical Conditions Associated with Elevated Circulating Markers of Myocardial Leakage Recently Reported in Dogs and Cats**

198.5.6.1.1 **Primary Myocardial Disease**

Idiopathic dilated cardiomyopathy

Hypertrophic cardiomyopathy

Myocardial contusion

Ischemic myocardial disease

Myocarditis/endomyocarditis/endocarditis

198.5.6.1.2 **Congenital Heart Disease**

Patent ductus arteriosus

Subaortic stenosis

198.5.6.1.3 **Degenerative Cardiac Valve Disease**

Mitral valve endocardiosis

198.5.6.1.4 **Pericardial Disease**

Pericarditis

Pericardial effusion

198.5.6.1.5 **Systemic Disease**

Gastric dilatation-volvulus syndrome

Sepsis

Renal failure/uremia

Babesiosis

Body trauma

Hyperthermia

198.5.6.1.6 Neurologic Disease

Subarachnoid hemorrhage

Steroid responsive meningoencephalitis

Epilepsy

198.5.6.1.7 Endocrine Disease

Hyperthyroidism

198.5.6.1.8 Neoplasia

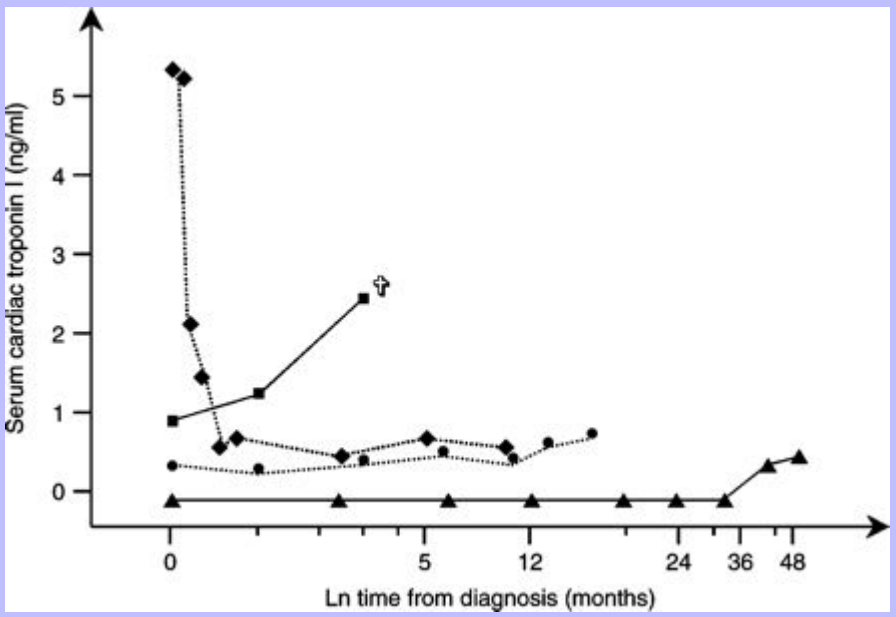
Splenic mass

Lymphosarcoma

Doxorubicin chemotherapy

Detectable cTn concentrations in blood with asymptomatic DCM is a rare event that recently was described in only one of 28 affected dogs.[2,9,16] For this reason, screening of selected populations of dogs for DCM based on cTn analysis does not seem to provide any advantage over commonly used diagnostic methods. However, with further improvement of test sensitivities and with large-scale clinical trials in affected breeds, more promising findings may be anticipated.

Figure 198-2 Different patterns of cardiac troponin I release in 4 dogs with dilated cardiomyopathy (DCM). ♦ Pattern 1: High initial CTnI with fast decrease to mildly, but persistently elevated CTnI (German shephard dog, male, 10 years of age with acute congestive heart failure, prolonged episodes of ventricular tachycardia, and finally complete AV-block); ▪ Pattern 2: Mildly elevated baseline value of CTnI with fast increase despite medical management (German shepherd dog, male, 9 years of age with atrial fibrillation and slow onset of heart failure but fast progression and early death); • Pattern 3: Persistently low serum levels of cTnI (Great Dane, female, 8 years of age with atrial fibrillation); ▲ Pattern 4: Undetectable circulating CTnI for an advanced period of time with fully compensated DCM (Great Dane, male, 6 years of age with persistent atrial fibrillation and late onset of congestive heart failure). Zero CTnI refers to the lower limit of detection of the immunoassay used (0.1 ng/ml; OPUS® Troponin I, Dade-Behring Diagnostics Inc., Westwood, MA). †, died. (Recently unpublished observations).



Analysis of cTn may also be useful in cats with HCM, primarily to identify animals suspected of having inflammatory myocardial lesions or ischemic heart disease as a result of microvessel pathology or intramural coronary artery embolism. Circulating cTn is detectable in almost all cats with HCM, regardless of whether

heart failure is present.[2,10,19,21,23] Cats with CHF have higher cTn levels than cats with no clinical signs or those with a history of heart failure.[10] Further studies are needed to determine whether serum cTn levels may be used to differentiate HCM from other types of cardiomyopathy in cats and to obtain reliable prognostic information.

Monitoring of animals undergoing chemotherapy for signs of cardiotoxicity of antineoplastic drugs may be another promising application of cTn analysis. A small-scale clinical trial in dogs with lymphosarcoma has provided evidence of detectable myocardial injury at cumulative doses of doxorubicin of at least 150 mg/m^2.[6] It has been recommended that serum cTnT levels be analyzed 2 to 3 weeks after each dose of doxorubicin beyond a 90 mg/m^2 cumulative dose. Elevations of cTn may accurately predict the future development of LV systolic dysfunction and ventricular arrhythmias in dogs with anthracycline chemotherapy.

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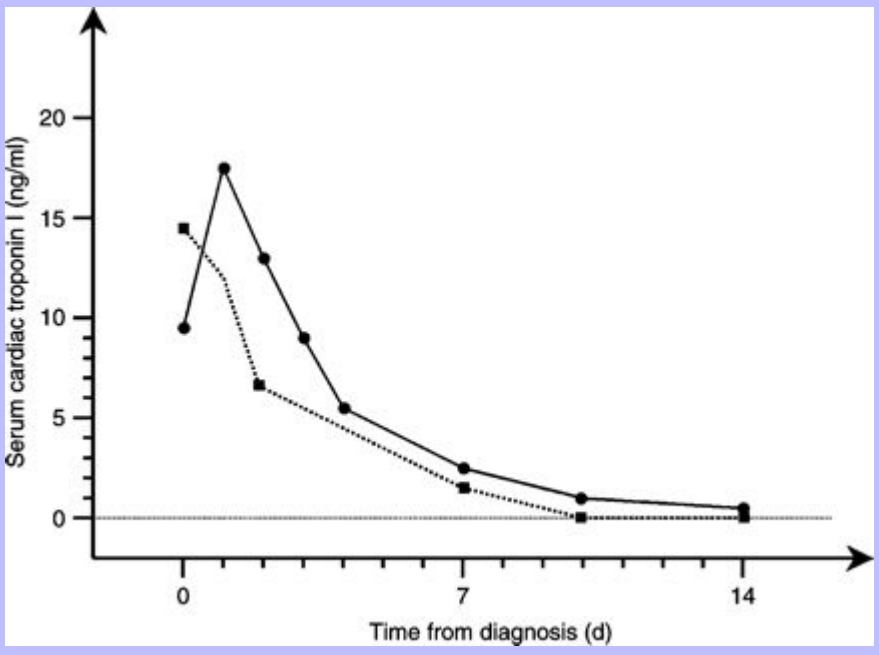
Figure 198-3 Cardiac troponin I release in 2 dogs with suspected acute myocardial necrosis. •, Old English sheepdog, male, 9 years of age with a splenic mass and polymorphic ventricular arrhythmia on days 0, 1, and 2. Splenectomy was done on day 1. ▪, Doberman pinscher, female, 2 years old with acute spinal cord trauma on the day before admission and ventricular arrhythmia prior to and after surgery done on day 0. Zero CTnI refers to the lower limit of detection of the immunoassay used (0.1 ng/ml; OPUS® Troponin I, Dade-Behring Diagnostics Inc., Westwood, MA). (Recently unpublished observations).



Subendocardial injury caused by increased myocardial stress can induce a rise in cTn in patients with arterial hypertension, tachycardia, aortic and pulmonic stenosis,[2] volume overload, or pulmonary embolism. Alternatively, increased serum concentrations of cTn may occur after severe blunt trauma to the thorax that causes myocardial contusion[3,4,9] or in response to severe hypotension or the release of endogenous substances in critically ill patients (e.g., in animals with multiple organ dysfunction syndrome in GDV or after septic shock).[2,8] The clinical usefulness of serial cTn analyses in detecting myocardial cell injury, predicting electrocardiographic abnormalities, and identifying patients at high risk for a fatal outcome has previously been reported in dogs with GDV.[8] In those studies, the predictive abilities of cTnI and cTnT for an adverse outcome were comparable. Furthermore, increased levels of cTn were observed in dogs with pericardial disease,[2,16,24] suggesting involvement of the myocardium in ischemic, degenerative, or inflammatory processes, and in animals with cerebrovascular events and splenic masses (Figure 198-3), most likely due to myocardial necrosis secondary to abnormal catecholamine release.

Monitoring of circulating cTn may also be useful for assessing myocardial cell damage caused by DC cardioversion or interventional cardiac procedures. In addition, cTn analysis has been used to detect myocyte injury in clinically suspected myocarditis and endomyocarditis in dogs[2] and in experimental myocarditis in laboratory animals. However, the diagnosis of myocarditis can be confirmed only by immune histochemical techniques using tissue samples, which makes unambiguous clinical diagnosis based on elevated cTn concentrations difficult. The extent to which knowledge of the troponin status could affect medical care under these conditions deserves further investigation.

198.6 FUNCTIONAL MARKERS

Since the discovery of atrial natriuretic peptide more than 20 years ago, it has been apparent that the heart is not only a simple pump, but also a true endocrine organ that releases specific hormones in response to defined stimuli. Recent studies in humans and preliminary findings in dogs[25–34] and cats[35–37] with heart disease indicate that biochemical markers of cardiovascular function, such as natriuretic peptides (NPs) and endothelin (ET), as well as circulating catecholamines, vasopressin, aldosterone, and cytokines, including tumor necrosis factor-alpha (TNF-alpha), can be used to identify patients with heart disease, to predict disease severity, to monitor therapy, and to obtain prognostic information. In the near future, routine immunoassays for functional marker proteins may provide a preliminary test of cardiac performance and may permit clinicians to more carefully select patients for further investigation and treatment.

198.6.1 Natriuretic Peptides

Natriuretic peptides belong to a unique family of naturally occurring, structurally similar, but genetically distinct hormones that share a central loop containing 17 amino acids closed by a disulfide bond between 2 cysteine residues, with variable carboxy-terminal and amino-terminal tails. The NPs include atrial natriuretic peptides (ANP), brain natriuretic peptides (BNP), C-type natriuretic peptides (CNP), dendroaspis natriuretic peptides (DNP), and urodilatin. The NPs act as key regulators of salt and water homeostasis and blood pressure control. They have potential value as diagnostic and prognostic markers and as therapeutic tools for several clinical conditions associated with expanded fluid volume, such as CHF.

198.6.1.1 Atrial Natriuretic Peptides and Brain Natriuretic Peptides

198.6.1.1.1 Structure

ANP is typically produced by the left and right atrium but may also be expressed in the ventricular myocardium, particularly with ventricular hypertrophy or myocardial ischemia. ANP transcripts also may be present in noncardiac tissues. ANP is synthesized as pre-proANP, which contains 153 amino acids in cats.[38] After cleavage of a 25-amino-acid signal peptide, the precursor proANP, consisting of 128 amino acids, is stored in atrial myocyte granules. In response to an adequate stimulus, proANP is split by a membrane-bound protease into inactive 98-amino-acid N-terminal (NT)-proANP and biologically active 30-amino-acid C-terminal ANP on an equimolar basis and released into the blood. NT-proANP may be further cleaved into smaller, endocrinologically active fragments.[38] The amino acid sequences of ANP and CNP have been highly conserved across species. Canine and human mature ANP are structurally very similar.

Under normal conditions, BNP is produced primarily in the cardiac atria, with very little synthesis in the ventricles. In cardiac pathologies with chronic pressure or volume overload or ventricular hypertrophy, ventricular myocytes become the major source of BNP. Minor extracardiac BNP production has also been reported. Unlike with ANP, regulation of BNP synthesis and excretion occurs mainly at the level of gene expression. Cardiac BNP is stored to a much smaller extent than ANP (coexisting with ANP in granules of atrial and ventricular myocardium), therefore increased BNP release requires increased synthesis. BNP arises from a single precursor pre-proBNP molecule containing 132 amino acids in cats.[39] The signal peptide has 26 amino acid residues, followed by 106 amino acids of proBNP. This peptide is further processed into mature, active BNP that has 35 amino acid residues at the C-terminus, with likely 26 and 29 amino acid isomers. The biologically inactive peptide, NT-proBNP, has 71 amino acids in cats.[39] BNP and NT-proBNP are secreted into the circulation in equimolar quantities. Mature BNP in dogs and humans has only 32 amino acid residues. In contrast to ANP, there is much variability in the length and structure of BNP across species, and the predominant forms differ considerably, resulting in variations in cross-species actions.

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198.6.1.1.2 Physiologic actions

The principal function of NPs is to protect the cardiovascular system from volume overload. The major biologic effects of ANP and BNP are qualitatively similar and include potent natriuresis, diuresis, and balanced vasodilatation. Both NPs antagonize the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS), inhibit the release and action of vasopressin, prevent myocardial fibrosis, and modulate cell growth and myocardial hypertrophy. In addition to the many other important actions of natriuretic peptides, ANP, in particular, enhances vascular permeability, causing redistribution of plasma volume to the extravascular space. The biologic actions of NPs are mediated by two specific receptors, natriuretic peptide receptor type A (NPR-A) and natriuretic peptide receptor type B (NPR-B). A third natriuretic peptide receptor, NPR-C, mainly acts as a clearance receptor. NPRs are widely distributed throughout the body and can be found in the heart, kidneys, vascular endothelium and smooth muscle, adrenals, and central nervous system.

198.6.1.1.3

Release, metabolism, and clearance

ANP secretion is controlled by immediate release from previously synthesized atrial storage granules in direct proportion to atrial stretch,[25,26,29,31,35] which occurs during intravascular volume expansion. Only a minor part is derived from newly synthesized hormone. A second stimulus for ANP secretion is an increase in the heart rate.[26,31,35] The plasma concentration of ANP therefore can change rapidly in response to acute alterations in posture, volume loading, or tachycardia. Thus ANP is a good marker of acute volume overload or of rapid hemodynamic changes. Release of BNP is chiefly controlled at the transcription level, with increased secretion preceded by an increase in messenger ribonucleic acid (mRNA) production. Therefore, in contrast to ANP, a longer term stimulus is required to increase plasma BNP concentrations; this makes BNP blood levels less susceptible to wide fluctuation in response to short-term external stimuli. The production and secretion of BNP are regulated by myocardial stretch and wall tension, primarily that induced by volume load. Circulating BNP is also increased in ventricular dysfunction and in states of ventricular hypertrophy (even in the absence of elevated intraventricular pressure). Atrial production of BNP occurs within 60 minutes of stretch, whereas ventricular production of BNP is stimulated within a few hours. In humans, the plasma half-life of ANP and BNP is approximately 1 to 3 minutes and 20 to 22 minutes, respectively, and that of both N-terminal peptides is 60 to 120 minutes.

Clearance of NPs occurs through two major mechanisms: first, binding to NPR-C, which is followed by endocytosis and subsequent lysosomal degradation, and second, degradation by the nonspecific membrane-bound enzyme neutral endopeptidase 24.11 (NEP), in a competitive fashion. However, enzymatic degradation via NEP does not seem to be as important for N-terminal fragments, resulting in longer half-lives. A small amount of the NPs is accounted for by renal elimination (less than 15%) and other nonspecific degradative enzymes. The liver, lungs, and especially the kidneys are major sites of extraction of the NPs.

198.6.1.1.4

Analysis, storage, and reference intervals

Currently, no consensus exists on the best procedure for measuring NPs in humans and animals, because determination by different immunoassay methods is affected by several analytic problems concerning a lack of sensitivity, specificity, and precision. Commercial assays are not yet standardized, and the results obtained with assays from different manufacturers may differ markedly, affecting reference intervals and decision limits. Commonly used assays for measuring NPs are either competitive immunoassays (radioimmunoassay [RIA] and electroimmuno-assay [EIA]) or noncompetitive sandwich immunoassays (IRMA and EIMA). RIA methods use radiolabeled tracers and usually require a time-consuming extraction step before NPs can be measured. In addition, the detection limit of RIA tends to be higher than that of IRMA. IRMA methods are generally highly sensitive and more specific, and extraction and purification of plasma samples are not required. NT-proANP and NT-proBNP are larger molecules than the C-terminal biologically active peptides, which makes it easier to use immunometric assay design to measure them. In addition, much higher plasma concentrations of the N-terminal fragments (20 to 50 times) and longer plasma half-lives lead to high analytic precision. Unlike the universal nature of ANP antibodies, antibodies for BNP are species specific. Therefore, in contrast to assays for ANP and NT-proANP, C-or N-terminal human BNP assays cannot be used in dogs and cats.

The *in vitro* stability of BNP, NT-proBNP, and proANP in ethylenediamine tetra-acetic acid (EDTA) in whole blood at room temperature is sufficient for routine use. BNP is stable for up to 72 hours, even in the

absence of aprotinin. NT-proBNP and proANP appear to be stable for up to 48 hours, and NT-proANP for 6 hours, in whole blood. ANP is stable only for 2 to 3 hours in blood at room temperature, it is stable for up to several months in plasma frozen at −80° C.

Because of the lack of assay standardization and the differences in methodology, no generally applicable reference intervals for NPs and their N-terminal prohormone fragments can be defined. In addition, normal plasma concentrations of NPs have been shown to increase with age[27] and to be dependent on gender and body weight.[27] Thus reference limits vary, depending on the nature of the control population and the assay used. In general, circulating ANP and BNP concentrations in normal subjects are very low, ranging from 3 to 15 pmol/L* for different assays, with plasma BNP being lower than ANP. Unlike ANP, circulating BNP does not generally show rapid and wide fluctuations in healthy subjects. A cutoff point for BNP (23 pmol/L) for the detection of heart failure in humans more than 55 years of age was recently suggested (BNP-Triage; Biosite Diagnostics, San Diego, California). Small-scale clinical trials in healthy dogs reported similar values for plasma ANP[25,29,31] using a human RIA (means between 10 and 22 pmol/L) and for plasma BNP using a porcine RIA[25,27] (means of 7.0 and 13.6 pmol/L). Preliminary RIA studies in healthy cats revealed a normal BNP range of 1.6 to 8.3 pmol/L (mean, 3.3 pmol/L).[35] As mentioned earlier, the plasma concentrations of N-terminal NPs are much higher than those of ANP[25] and BNP. The NT-proANP concentration has been reported in normal pets (mean, less than 500 pmol/L in dogs[25–27]; and 540 pmol/L in cats),[35] and an optimal cutoff point for cardiac decompensation in Cavalier King Charles spaniels with chronic mitral valve disease (MVD) has been suggested (700 pmol/L).[25]

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* Equivalent units of measurement can be determined as follows: 1 pmol/L of ANP = 3.1 pg/mL; 1 pmol/L of BNP = 3.5 pg/mL; 1 pmol/L of NT-proANP = 10.5 pg/mL; and 1 pmol/L of NT-proBNP = 8.6 pg/mL.

198.6.1.2 Circulating Natriuretic Peptides in Disease

In general, the plasma concentrations of the NPs are increased in disease states characterized by an expanded fluid volume, reduced renal clearance of the peptides, and stimulation of peptide production (e.g., disease states caused by ventricular hypertrophy or myocardial strain, tachycardia, hypoxia, ectopic production from tumor, or excessive circulating glucocorticoid or thyroid hormones). However, the most promising use of NPs may be in their diagnostic potential as functional markers of cardiac disease. As with increased levels of circulating cTn, ANP and BNP are not specific for a particular cardiac pathology. Plasma levels of NPs are increased in many disease states, including chronic MVD, DCM, pacing-induced heart failure, aortic stenosis, congenital heart disease, and dirofilariasis in dogs[25,26,29,31–34] and in different types of cardiomyopathy in cats.[35] In addition, elevated concentrations of NPs have been demonstrated in humans with AMI, hypertension, supraventricular tachycardia, cardiac amyloidosis, myocarditis, right ventricular dysfunction and hypertrophy due to chronic respiratory disease, renal failure, and severe LV diastolic dysfunction.

Considering that ANP originates primarily from the atria and BNP from the ventricles, increased circulating levels of these peptides may reflect different abnormalities. Thus, depending on the underlying disease process in heart failure patients, the secretion pattern of ANP and BNP may vary. ANP and NT-proANP have been shown to be more useful than BNP in the overall assessment of disease severity in chronic MVD[25] and cardiac abnormalities characterized by acute volume overload. In addition, particularly high concentrations of NT-proANP have been reported in patients with DCM and atrial fibrillation compared with

DCM and sinus rhythm.[26] However, BNP is more sensitive than ANP in detecting chronic LV systolic and diastolic dysfunction and ventricular hypertrophy of any cause. BNP secretion increases in proportion to the severity of LV dysfunction.[32] The negative predictive value is the strongest feature of this peptide in humans (more than 90%); however, the reverse is not true, because the positive predictive value is only 30% to 40% in people. BNP analysis may be used as a screening tool, with a value in the normal range virtually excluding LV systolic dysfunction. However, analysis of BNP is not a stand-alone test. An increase in BNP would always warrant follow-up examinations, such as echocardiography, to identify the underlying cardiac pathology. NT-proBNP and BNP appear to be equivalent markers for the detection of LV dysfunction, but the N-terminus has some clinical advantage with respect to plasma concentration, half-life, and stability.

In contrast to humans, there is limited evidence in dogs and cats suggesting that plasma NPs are useful markers for the detection of LV dysfunction in asymptomatic patients.[32] NT-proANP has been found elevated in only a subset of dogs with asymptomatic chronic MVD[25] or DCM[26] despite significant cardiac enlargement. However, in cats with hypertrophic, restrictive, or unclassified cardiomyopathy and no clinical signs, proANP, NT-proANP and, in particular, BNP were raised. If BNP or its N-terminal fragment emerge as a superior diagnostic marker of LV dysfunction in companion animals with asymptomatic heart disease, it may also be used for routine screening for DCM and HCM in selected, high-risk populations; however, this requires further confirmation. In humans, for the time being, analysis of circulating BNP is the most promising biochemical marker for the diagnosis of CHF and has shown the best characteristics for a screening test.

Circulating NP levels have been shown to correlate with the class of heart failure in dogs,[25,26,29,31–33] and their measurement may allow veterinarians to offer pet owners a more accurate long-term prognosis. Elevated concentrations of BNP and NT-proBNP were found to be independent predictors of increased mortality in humans with CHF and both systolic and diastolic dysfunction. In addition, BNP correlates with right and left ventricular mass and may potentially be used as a marker for ventricular remodeling in hypertension and HCM. ANP as well as BNP may also be clinically useful as a biochemical discriminators of cardiogenic and noncardiogenic cough and dyspnea.

As congestion in heart failure is relieved, the levels of ANP and BNP rapidly regress,[29] thus serial analyses of plasma NPs might also prove useful as a guide to therapy in chronic CHF. Moreover, determination of circulating NPs may be used to identify patients that would likely benefit from therapeutic angiotensin-converting enzyme (ACE) inhibition or beta-receptor blockade. In the future, the treatment of patients with CHF may be tailored by neurohormonal profiling.

198.6.1.3 Other Natriuretic Peptides

C-type natriuretic peptide is primarily secreted by vascular endothelial cells and has local vasodilatatory and antiproliferative effects. It is usually undetectable in cardiac tissue. DNP was first isolated from the venom of the green mamba snake but has also been found in human plasma. Its importance in small animal cardiology has not yet been determined. Urodilatin (ANP 95-126) is localized in the kidney and secreted into the urine. It is a paracrine factor involved in the local regulation of body fluid volume and water and electrolyte excretion.

198.7 ENDOTHELIN

Endothelin (ET) belongs to a family of vasoactive peptides, including ET-1, ET-2, ET-3, and ET-4, that are genetically distinct. ET is composed of 21 amino acids in humans, dogs, and cats and is derived from precursors known as pre-proET, which has 212 amino acid residues. The large precursors undergo intermediate cleavage by endopeptidases to form the biologically inactive proET, also called big ET. Big ET is converted to active ET by endothelin-converting enzyme (ECE), which exerts its effects either locally or after release into the circulation. The predominant form of ET produced by endothelial cells and cardiac myocytes is ET-1. It has a wide spectrum of biologic actions, which are mediated by three receptor subtypes: ET_A, ET_B, and ET_C. ET_A is selective for ET-1, but the other receptor types are considered nonselective. ET-1 is a strong, long-lasting, balanced vasoconstrictive agent with inotropic and mitogenic actions; it is a potent stimulus for activation of the RAAS and SNS and plays an important role in the regulation of vascular tone and blood pressure.

Release of ET is regulated at the level of gene expression and peptide synthesis because cells do not store ET. The ET system is activated and synthesis of ET-1 is induced within minutes in response to a variety of factors, including pulsatile stretch, low shear stress, hypoxia, angiotensin II, epinephrine, cytokines, and growth factors. Most ET-1 (about 90%) is released from endothelial cells abluminally, where it acts on endothelial and smooth muscle cells as an autocrine and paracrine mediator. The concentration of ET in vascular tissue is approximately 100 times higher than in plasma. The plasma half-life of ET-1 in healthy humans is only 1 to 4 minutes because it is rapidly cleared from the circulation by ET_B receptors, the kidneys, and NEP. The plasma ET-1 level therefore may not accurately reflect the synthesis of ET-1. The plasma big ET-1 level has been proposed as a more reliable measure of ET-1 synthesis because its removal from the circulation is slower and less variable.

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Plasma ET currently is analyzed either by RIA or by enzyme-linked immunosorbent assay (ELISA). In healthy humans, the plasma ET-1 concentration ranges from 1 to 5 pg/mL. Preliminary results from small scale clinical studies in healthy dogs[40] and cats[37] reported mean (±SD) plasma ET-1 concentrations of 2.07±0.15 pg/mL and 0.805±0.230 fmol/mL, respectively. However, many problems are still associated with the measurement and interpretation of plasma ET-1 concentrations, because the assays available are not yet standardized. In dogs, plasma ET immunoreactivity can be broken down as about 60% big ET-1, 30% ET-1, and 10% ET-3.[30] Because of marked cross-reactivity of the ET antibodies used in current assays, the more realistic term *ET-like immunoreactivity* should be used, rather than “ET-1 concentration.”

There is compelling evidence that the ET system is activated in CHF in people, dogs[33–40], and cats[37] and therefore may be diagnostically useful. Plasma ET–like immunoreactivity is increased twofold to tenfold in CHF compared with controls, regardless of disease etiology, and the magnitude of elevation correlates with hemodynamic compromise and functional class in people and small animals.[37,40] The plasma level of ET appears to be a less powerful discriminator between patients with asymptomatic or mild CHF and control subjects with normal function compared with BNP, NT-proBNP, and NT-proANP but is equally sensitive for predicting short-term mortality. An alternative approach may be measurement of the salivary ET concentration. In addition, ET seems to be important in the pathogenesis of primary and secondary pulmonary hypertension, and a close correlation between plasma ET-1 levels and the extent of pulmonary circulatory abnormalities has been identified in dogs[40] and people. This relationship is unique and deserves further attention with regard to the diagnostic and therapeutic potential of ET-1 and ET-1 antagonists in pulmonary hypertension.

198.8 OTHER MARKERS OF CARDIOVASCULAR FUNCTION

TNF-alpha is a proinflammatory cytokine that seems to be involved in the pathophysiology of CHF. It is produced mainly by activated macrophages but is also expressed in failing cardiac tissue. TNF-alpha has a variety of biologic effects, including induction of cachexia, ventricular systolic dysfunction, pulmonary edema, and direct myocardial cytotoxicity. Moreover, it may play a role in apoptosis, cell dropout, and myocardial fibrosis associated with ventricular remodeling, leading to progression of heart failure. The bioactivity of TNF-alpha and its soluble receptors in serum is likely to be increased in patients with chronic CHF,[36] particularly in association with increased severity of disease. As such, TNF-alpha may be used as a marker of disease progression. In addition, increased circulating concentrations of TNF-alpha may provide a potential target for therapeutic interventions.

Considerable evidence in humans indicates the presence of abnormal endothelial function in patients with CHF, resulting in impaired tissue perfusion, myocardial ischemia, and vascular remodeling. Elevated levels of proinflammatory cytokines, increased vasomotor tone, and reduced vasodilator response to exercise may be responsible for the impairment of endothelium-dependent vasodilatation. Nitric oxide (NO), also called *endothelium-derived relaxing factor (EDRF)*, has important regulatory functions in the cardiovascular system. As with NPs, NO is a functional antagonist of ET and angiotensin II. It is expressed in the vascular endothelium and the myocardium. In heart failure, endothelial release of NO is impaired and myocardial NO synthesis is increased, leading to reduced vasodilatation, negative inotropic and chronotropic effects, and loss of cardiomyocytes. Circulating NO has previously been used as a functional marker of cardiovascular disease in humans. Prospective studies in dogs and cats are needed to determine the exact role of NO as a circulating biomarker of disease.[41,42]

Adrenomedullin is another vasodilating and natriuretic peptide that shows increased plasma concentrations with heart failure. The blood levels of adrenomedullin correlate with the pulmonary artery and pulmonary wedge pressures in patients with CHF and therefore may be used as a marker of pulmonary hypertension. However, its diagnostic importance has not yet been elucidated in companion animals.

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199 CHAPTER • 199 Therapy of Heart Failure

Barret J. Bulmer

D. David Sisson

Heart failure may be recognized as a clinical end-point in nearly all cardiac diseases. Because the underlying cause of the development of heart failure varies significantly between species and disease conditions, it is often difficult to define heart failure accurately and concisely. In 1994, a panel of the National Heart, Lung and Blood Institute concluded:

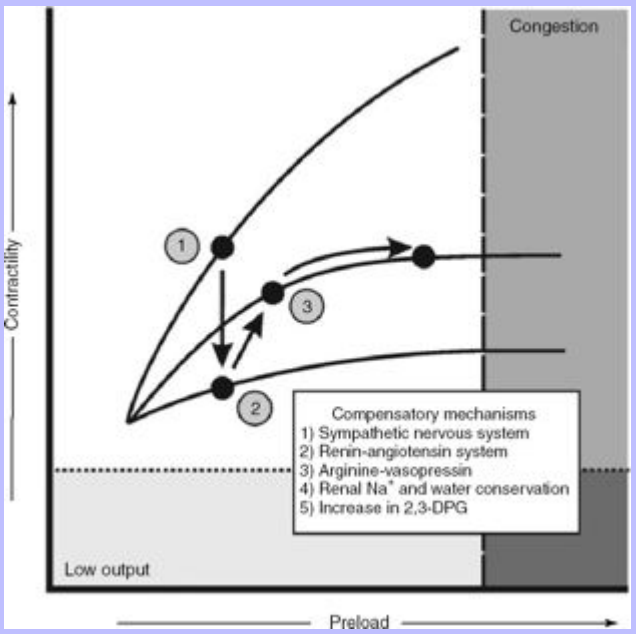
> *Heart failure occurs when an abnormality of cardiac function causes the heart to fail to pump blood at a rate required by the metabolizing tissues or when the heart can do so only with an elevated filling pressure. The heart's inability to pump a sufficient amount of blood to meet the needs of the body tissues may be due to insufficient or defective cardiac filling and/or impaired contraction and emptying. Compensatory mechanisms increase blood volume and raise cardiac filling pressures, heart rate, and cardiac muscle mass to maintain the heart's pumping function and cause redistribution of blood flow. Eventually, however, despite these compensatory mechanisms, the ability of the heart to contract and relax declines progressively, and the heart failure worsens.*[1]

Because all cardiac diseases have the potential to produce heart failure through similar mechanisms, we frequently view their pathophysiology and therapy from a unified perspective. Agents that promote preload and afterload reduction are used to control the clinical signs associated with elevated filling pressures, and neurohormonal modulators are prescribed to blunt the progressive nature of heart disease. This approach allows clinical experience and research to be extrapolated across a wide range of diseases. Although the remainder of this chapter is written primarily from a unified perspective, caution must be exercised to ensure that the variations within cardiovascular diseases are not forgotten.

199.1 PHASES OF HEART FAILURE

Currently, three distinct phases of heart failure are recognized. Phase 1 constitutes the initial cardiac injury. This phase most frequently passes silently, without detectable clinical signs, because compensatory mechanisms (phase 2) are quickly activated (Figure 199-1). Ultimately, myocardial hypertrophy accounts for the long-term stabilization of cardiac output and the normalization of afterload. Unfortunately, the natural history of cardiac disease often is progressive, and the heart's ability to hypertrophy is overwhelmed. The previously beneficial short-term compensatory mechanisms now serve only to increase both preload (contributing to the development of congestion) and afterload (increasing myocardial work and oxygen demand). Often a heart murmur, gallop rhythm, cardiac arrhythmia, or cardiomegaly may be identified during this second phase despite the absence of significant or activity-limiting clinical signs. Phase 3 of heart failure is recognized by the emergence of clinical signs (e.g., exercise intolerance, lethargy, coughing, tachypnea) at rest or with minimal activity. Veterinary patients apparently do not show clinical signs that are recognized by their owners until very late in the disease process. Presumably this may skew our understanding of the natural history of canine and feline cardiovascular disease. This understanding of disease progression is further clouded by the recognition that, depending on the disease process, the first clinical event may be the development of systemic thromboembolism, syncopal episodes, or possibly sudden death.

Figure 199-1 The short-term compensatory mechanisms that help normalize cardiac output during the initial injury often prove detrimental in the face of long-standing cardiac disease.



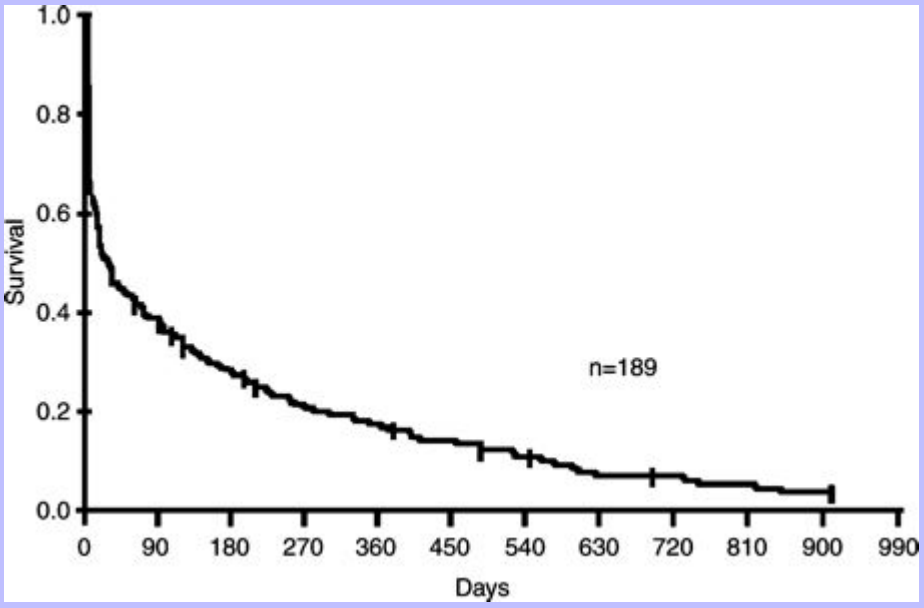
199.2 NATURAL HISTORY OF CARDIOVASCULAR DISEASE

Despite decades of treatment of cardiovascular disease in companion animals, relatively few studies have reported on the survival characteristics of patients afflicted with dilated cardiomyopathy,[2–4] mitral insufficiency,[5] and hypertrophic cardiomyopathy.[6] The spectrum of clinical signs, therapeutic strategies, breed differences, and disease sequelae hampers the formation of any sweeping conclusions regarding the natural history of these cardiovascular diseases; however, some generalities may be recognized. After dilated cardiomyopathy has been diagnosed, the survival curve drops precipitously for the first 3 months, with median survival times from two retrospective studies reported as 27 days and 65 days.[2,3] Months 3 through 6 continue to see a large number of dropouts, although interestingly, the curves appear to flatten markedly at approximately 6 months after the initial diagnosis (Figure 199-2). Whether this represents differences in individual responses to therapy or in the severity of disease at the time of diagnosis is difficult to ascertain.

Analysis of the survival curves for cats with hypertrophic cardiomyopathy presenting with congestive heart failure (CHF) or aortic thromboembolism (ATE) that lived for greater than 24 hours initially showed a steep slope similar to that seen in dogs with dilated cardiomyopathy (Figure 199-3).[6] Approximately 25% of the CHF group and 40% of the ATE group died within 3 months of diagnosis. After 3 months, cats presenting for congestive heart failure began to display a less steep, linear survival curve that concluded in a plateau several years after the diagnosis. The survival curve for cats with ATE also displayed some flattening after the first 3 months, although it ultimately remained linear for the rest of the study period. The median survival times were 563 days and 184 days,

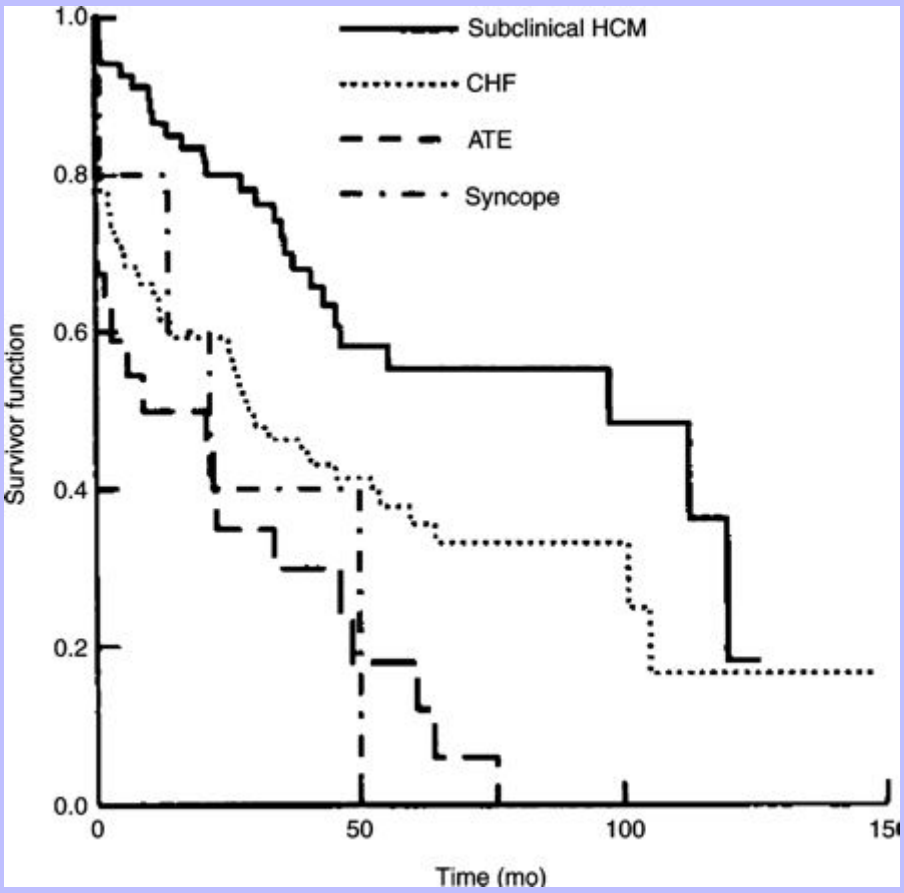
respectively, for cats with congestive heart failure and those with aortic thromboembolism.[6] Cats with subclinical hypertrophic cardiomyopathy were significantly more likely to die of noncardiac disease ($P < 0.001$) and displayed a linear mortality curve for the first 4 years, followed by a prolonged plateau for an additional 4 years.[6]

Figure 199-2 Historically the survival of dogs with dilated cardiomyopathy has been poor, presumably because the disease is significantly advanced at the time of diagnosis. Whether earlier identification of occult DCM, with subsequent administration of neurohormonal antagonists (beta blockers, aldosterone antagonists, ACE inhibitors) or potent positive inotropes (pimobendan), could alter this disease course is uncertain. (From Tidholm A: Survival and prognostic factors in 189 dogs with dilated cardiomyopathy. *J Am Anim Hosp Assoc* 33:4, 1997.)



Interestingly, although mitral insufficiency is the most commonly recognized cardiovascular condition in dogs, the natural history and mortality characteristics after the development of congestive heart failure have received little attention. Investigators for the Long-Term Investigation of Veterinary Enalapril (LIVE) study evaluated the time to treatment failure for dogs with congestive heart failure treated with enalapril and standard medical therapy (furosemide with or without digoxin) versus those treated with placebo and standard medical therapy.[5] In the mitral insufficiency subgroup, the number of dogs remaining in the study randomized to placebo mimicked the survival curve of dogs with dilated cardiomyopathy. A relatively high dropout rate was seen over the first 50 days, followed by a prolonged period of stability. The data for dogs randomized to enalapril did not display this steep dropout rate, but rather formed a linear curve from the time of enrollment until completion of the study.[5]

Figure 199-3 The variable presentation and treatment regimens associated with feline hypertrophic cardiomyopathy make evaluation of survival curves difficult. Not surprisingly, symptomatic cats appear to fare worse than those without clinical signs, many of which eventually died of noncardiac disease. (From Rush JE: Population and survival characteristics of cats with hypertrophic cardiomyopathy: 260 cases [1990–1999]. *J Am Vet Med Assoc* 220:2, 2002.)



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199.3 INFLUENCES ON THE NATURAL HISTORY

Unlike in the management of heart disease in humans, veterinary medicine has the profound ability to influence the natural history of cardiovascular disease in companion animals through the use of euthanasia. The ready access to euthanasia in veterinary medicine not only influences patients' survival times, but also may alter the clinician's responsibilities in treating the heart failure. A study by Mallery et al.[7] evaluated the factors that contributed to clients' decision for euthanasia for 38 dogs with congestive heart failure. The most important factors cited were a perceived poor prognosis (37%), recurrent signs of congestive heart failure (26%), and poor quality of life (13%).[7]

Common contributing factors included weakness (76%), anorexia (68%), recurrent clinical signs of congestive heart failure (55%), and a poor prognosis (42%).[7] These findings suggest that the goals of the practitioner should include careful client education before and after initiation of medical therapy, along with efforts to improve the patient's strength, appetite, and quality of life, possibly at the expense of prolonged survival.

199.4 CLASSIFICATION OF HEART FAILURE

Some measure of subjective criteria must be used to classify the degree of disability in veterinary patients in order to optimize the management and understanding of heart failure. Because the human classification system is based on signs and symptoms evident at rest and during exercise, it does not easily correlate with disease in often sedentary veterinary patients. The International Small Animal Cardiac Health Council has devised a classification scheme based on anatomic diagnosis and the severity of clinical signs at rest.

199.4.1 Asymptomatic Patient

Heart disease is detectable, but the patient is not overtly affected and does not demonstrate clinical signs of heart failure. Diagnostic findings could include a cardiac murmur, arrhythmia, or cardiac chamber enlargement detected by radiography or echocardiography. The subcategories of this stage are:

- No signs of compensation (e.g., volume or pressure overload ventricular hypertrophy) are evident.
- Radiographic or echocardiographic evidence of compensation (e.g., volume or pressure overload ventricular hypertrophy) is present.

199.4.2 Mild to Moderate Heart Failure

Clinical signs of heart failure are evident at rest or with mild exercise and adversely affect the quality of life. Typical signs of heart failure include exercise intolerance, cough, tachypnea, mild respiratory distress (dyspnea), and mild to moderate ascites. Hypoperfusion at rest generally is not present.

199.4.3 Advanced Heart Failure

Clinical signs of advanced congestive heart failure are immediately obvious. These include respiratory distress (dyspnea), marked ascites, profound exercise intolerance, and hypoperfusion at rest. In the most severe cases, the patient is moribund and suffers from cardiogenic shock. Death or severe debilitation is likely without therapy.

Many patients present acutely for respiratory distress despite the absence of significant clinical signs before the “inciting” event. Owners may report one to several days of tachypnea with or without coughing, nocturnal dyspnea, lethargy, weakness, and inappetence. Cats with congestive heart failure may present acutely for severe respiratory distress because they were able to hide successfully for several days before the owner could detect a problem. Astute owners may present patients with mild to moderate heart failure for evaluation of exercise intolerance or subtle changes in the respiratory pattern. Patients with right-sided heart failure may be presented for evaluation of unexplained weight gain. At the far end of the spectrum from acute heart failure are patients that are re-evaluated for refractory congestive heart failure despite aggressive medical management. These patients may be re-evaluated for recurrent signs of congestive heart failure (i.e., pulmonary edema, pleural effusion, or ascites), weight loss and inappetence, or profound exercise intolerance and malaise. Effective

management of acute, chronic, and refractory heart failure requires specific aims and strategies that target the appropriate mechanisms.

199.5 TREATMENT STRATEGIES

199.5.1 Management of Acute Decompensated Congestive Heart Failure

Dogs with dilated cardiomyopathy or mitral regurgitation often present with acute onset of coughing, dyspnea, restlessness, orthopnea, and weakness subsequent to the development of severe pulmonary edema and/or low cardiac output. The immediate priorities in these patients are resolution of the pulmonary edema, maintenance of adequate tissue perfusion pressure, and adequate delivery of blood flow to vital tissues. These goals must be achieved quickly, therefore it is important that the practitioner use drugs with proven hemodynamic benefits and a rapid onset of action.

199.5.1.1 Oxygen Supplementation

As left atrial and pulmonary capillary pressures increase and the lymphatics' capacity to remove fluid is overwhelmed, the interstitial space and alveoli become flooded. Because these flooded alveoli lack ventilation and represent areas of functional shunting, oxygen administration must be combined with agents that effectively lower pulmonary venous pressure. Oxygen can easily be administered to compromised patients by provision of an oxygen-enriched environment (i.e., oxygen cage) or by use of nasal insufflation, achieving maximal inspired oxygen concentrations of 40% to 90%, respectively.

199.5.1.2 Reduction of Pulmonary Venous Pressure

Rapid reduction of pulmonary venous pressure is most readily achieved through use of a combination of intravenous (IV) drugs that lower the circulating plasma volume and redistribute the intravascular volume. Intravenous furosemide (2 to 8 mg/kg) should be administered to dogs with severe pulmonary edema to promote natriuresis and diuresis quickly. These large doses may be repeated (initially every 1 to 2 hours) until the respiratory rate and dyspnea start to decline. After stabilization, the dose should be reduced (2 to 4 mg/kg every 8 to 12 hours), because excessive administration may lead to profound dehydration, electrolyte depletion, renal failure, low cardiac output, and circulatory collapse.

Drugs that decrease preload (to combat congestion) and afterload (to decrease myocardial work) are administered concurrently with furosemide. Intravenous sodium nitroprusside is a potent, ultrarapid, balanced vasodilator that seems to reduce pulmonary venous pressure quickly and effectively. When used in animals with congestive heart failure, nitroprusside decreases right atrial and pulmonary capillary wedge pressures and systemic vascular resistance and increases cardiac output.[8] Although hypotension and tachycardia are reported side effects, the reduction in systemic vascular resistance (SVR) is theoretically associated with an increase in cardiac output (CO) that serves to maintain systemic arterial blood pressure (BP = SVR × CO). Nausea, vomiting, and cyanide toxicity during prolonged administration are other reported side effects. Because of its short half-life, nitroprusside, mixed with 5% dextrose, must be administered by constant-rate infusion (CRI). After institution of an initial dose of 1 μg/kg/min, the rate is slowly titrated upward while the blood pressure is monitored. An infusion rate of 2 to 5 μg/kg/min usually is sufficient to decrease afterload, although rarely doses as high as 10 μg/kg/min may be required. If significant hypotension is encountered after administration of nitroprusside, slowing the infusion rate generally is effective at raising the blood pressure to acceptable levels.

199.5.1.2.1

Sodium nitroprusside

Nitroprusside is an intravenous preparation with potent arteriolar and venous vasodilative properties mediated by the formation of nitric oxide and subsequently the second messenger cyclic guanosine monophosphate (cGMP). To some degree, the combination of nitroprusside and dobutamine can be considered short-term “cardiac life support,” used primarily during an attempt to rescue dogs with severe, life-threatening pulmonary edema subsequent to dilated cardiomyopathy. This drug combination's ability to reduce afterload quickly appears to be beneficial also in patients with chronic degenerative valvular disease and pulmonary edema, although management of these cases often can be accomplished less intensively.

Unfortunately, the beneficial hemodynamic profile of nitroprusside is accompanied by a difficult administration protocol that requires intensive monitoring. Because nitroprusside produces an almost immediate and often profound reduction in systemic vascular resistance, continuous blood pressure monitoring throughout administration is recommended. The drug is light sensitive, is given by constant-rate infusion (typically 2 to 5 μg/kg/min), and should not be infused with another agent, which necessitates placement of a second intravenous catheter for administration of dobutamine. These stringent requirements may provide cause for more frequent use of intravenous bipyridines to combat life-threatening heart failure, at least until studies are able to elucidate whether either method produces better results.

If nitroprusside is unavailable, balanced vasodilatation may be attempted through administration of an arterial vasodilator (hydralazine, 0.5 to 2 mg/kg given orally) in combination with a venodilator (nitroglycerin ointment, $^{1}/_{4}$-to $^{3}/_{4}$-inch applied cutaneously every 8 to 12 hours; or isosorbide dinitrate, 0.5 to 2 mg/kg given orally every 8 hours). Although easier to administer, this therapy seems to be less effective at quickly reducing pulmonary venous pressure compared with nitroprusside.

Potent afterload reduction in patients with severe mitral insufficiency and large regurgitant volumes serves to decrease the left ventricular to left atrial pressure gradient and hence the volume of insufficiency. Nitroprusside, or possibly hydralazine, can effectively decrease the volume of mitral regurgitation and lower left atrial pressure in cases of severe CHF subsequent to rupture of the chordae tendineae or the onset of atrial fibrillation. Despite this obvious theoretical advantage, a recent human study showed that mitral regurgitation worsened in four of nine patients with mitral valve prolapse during nitroprusside infusion.[9] This finding highlights the point that adjustments in the therapeutic regimen may be required and should be based on patient response rather than physiologic principles.

199.5.1.3

Augmentation of Systolic Performance

Preload reducing agents, such as furosemide, cannot enhance systolic function and in fact at high doses serve only to decrease cardiac output. Therefore the use of a rapid-acting, intravenous inotropic agent is vital to the management of acute decompensated congestive heart failure in dogs with dilated cardiomyopathy. Although there is debate over whether dogs with mitral valve insufficiency have systolic dysfunction, acutely positive inotropic agents may serve to decrease the regurgitant orifice area and hence the volume of insufficiency.

The short-acting, positive inotropic agents most commonly used to manage decompensated heart failure increase cyclic adenosine monophosphate (cAMP). Dobutamine and dopamine are sympathomimetic agents that bind to $beta_1$ receptors, thereby stimulating adenylyl cyclase activity and production of cAMP. The

bipyridines amrinone and milrinone increase cAMP by preventing its degradation by phosphodiesterase. Both drug classes are capable of rapidly augmenting systolic function during constant-rate intravenous infusions. By increasing cytosolic cAMP, these agents enhance (1) calcium entry into the cell, promoting ventricular contraction; (2) diastolic calcium uptake by the sarcoplasmic reticulum, promoting ventricular relaxation; and (3) peripheral vasodilatation, reducing afterload. It should be remembered that the sympathomimetics also have alpha-agonistic properties that promote vasoconstriction. Unfortunately, both the sympathomimetics and the bipyridines may promote tachycardia and undesirable ventricular arrhythmias. Therefore careful electrocardiographic (ECG) monitoring is required during administration of these drugs, and significant or worsening ventricular arrhythmias may warrant discontinuation of the infusion and institution of antiarrhythmic therapy.

199.5.1.3.1 Sympathomimetics

The sympathomimetics enhance cardiac contractility by complexing with myocardial beta receptors. After substrate binding to an unoccupied beta receptor, a coupled G-protein stimulates the enzyme cyclase to produce cAMP. This second-messenger "effector" system acts by means of protein kinase A to phosphorylate intracellular proteins, including the L-type calcium channel, phospholamban, and troponin I, thereby enhancing ventricular contraction and relaxation. Despite the sympathomimetics' ability to increase cardiac contractility approximately 100% above baseline, not all drugs in this class are suitable for the management of heart failure. The specificity for beta receptor binding depends on the specific agent and dose administered. Sympathomimetics inappropriate for the management of heart failure include the pure beta agonist isoproterenol and the naturally occurring catecholamines norepinephrine and epinephrine. These agents tend to promote tachycardia, arrhythmias, and untoward alterations in systemic vascular resistance.

Dobutamine and dopamine are more appropriate sympathomimetics for the management of heart failure. Although both drugs can enhance cardiac contractility, several drawbacks discourage long-term use: (1) they must be given intravenously, because successful oral administration is precluded by extensive first-pass hepatic metabolism; (2) because of their extremely short half-lives (approximately 1 to 2 minutes), they must be administered by constant-rate infusion; (3) almost any positive inotropic response tends to increase myocardial work and thus the propensity for ventricular arrhythmias; and (4) after 24 to 48 hours of constant-rate infusion, their positive inotropic response is limited by beta receptor downregulation and uncoupling. The tendency for long-term sympathomimetic administration to increase mortality, as documented in humans, appears to relegate these agents to short-term management of acute, life-threatening heart failure.

199.5.1.3.1.1 Dobutamine

Dobutamine is a synthetic analog of dopamine that displays predominately $beta_1$ receptor binding ($beta_1 > beta_2 >$ alpha). Dobutamine is able to increase cardiac contractility and thus cardiac output without causing a profound, concomitant increase in the heart rate. The mechanism underlying the lack of a positive chronotropic response is not well understood, but this characteristic tends to make dobutamine the most appropriate agent for short-term treatment of heart failure. It appears that complexing with vasodilative beta receptors and vasoconstrictive alpha receptors, combined with an increase in cardiac output, maintains arterial blood pressure at near baseline values. If the systolic blood pressure is normal to elevated, dobutamine infusion (slow titration up to 5 to 15 µg/kg/min in 5% dextrose) can be combined with the potent vasodilator nitroprusside in an attempt to decrease internal cardiac work and further enhance forward blood flow. Continuous ECG and blood pressure monitoring

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is recommended during this treatment regimen, and exacerbation of tachycardia or ventricular arrhythmias may necessitate discontinuation of dobutamine.

199.5.1.3.1.2 Dopamine

A precursor of norepinephrine, dopamine can bind myocardial beta receptors in addition to peripherally located dopaminergic, beta$_2$, and alpha receptors. Within the renal, mesenteric, coronary, and cerebral vascular beds, these dopaminergic DA$_2$ receptors are able to promote vasodilatation at low infusion rates of dopamine (1 to 2 μg/kg/min). However, at higher infusion rates (10 to 20 μg/kg/min), these vasodilative properties are over-ridden by an undesirable, alpha-mediated vasoconstrictive response. Also, high doses are accompanied by increases in the heart rate, the likelihood of arrhythmogenesis, the release of norepinephrine, and the myocardial oxygen demand. Dopamine (slow titration up to 1 to 10 μg/kg/min) may be used in situations similar to those in which dobutamine is appropriate (e.g., profound myocardial failure) and may further enhance renal blood flow. For the authors, an increased propensity for the development of tachycardia relegates dopamine to the role of second-choice drug. As with dobutamine, careful ECG and blood pressure monitoring is indicated during dopamine administration.

199.5.1.3.2 Bipyridines

Similar to the sympathomimetics, the bipyridines promote an increase in cardiac contractility by increasing cytosolic cAMP levels. However, rather than directly enhancing the production of cAMP, they increase circulating levels by inhibiting phosphodiesterase III, the enzyme responsible for cAMP inactivation. Unlike the sympathomimetics, the bipyridines do not rely on beta-adrenergic receptors and therefore are less affected by downregulation and uncoupling. Furthermore, because phosphodiesterase inhibitors increase vascular smooth muscle cAMP without displaying affinity for alpha receptors, they are also vasodilators. Because of the bipyridines' combination of positive inotropic and vasodilative properties, the term *inodilators* has come into use for these agents. Because they increase cytosolic calcium and myocardial work, they inherently carry the caveats of tachycardia and ventricular arrhythmias. In fact, the 28% increase in all-cause mortality identified in humans randomized to oral milrinone versus placebo has severely limited further attempts to evaluate agents that act via cAMP-dependent mechanisms.[10]

199.5.1.3.2.1 Milrinone

The phosphodiesterase inhibitor milrinone is substantially more potent than amrinone and is available in an intravenous preparation. Because of its combined positive inotropic and vasodilative properties, milrinone may be used as a substitute for the dobutamine/nitroprusside combination in the management of acute life-threatening heart failure. Despite milrinone's ability to increase measures of fractional shortening after oral administration in dogs, this formulation is no longer available for prescription.[11]

There are no published reports regarding the hemodynamic effects of intravenous milrinone administered to dogs with acute myocardial failure. When administered to normal dogs at an infusion rate of 1 to 10 μg/kg/min, milrinone increased cardiac contractility 50% to 140%.[12] Whether similar doses are efficacious in dogs with heart failure is uncertain, and dosing recommendations currently are difficult to propose. Because CRI milrinone requires 10 to 30 minutes to reach maximal peak effects in normal dogs, it may be prudent to administer a loading dose, followed by constant-rate infusion.

Theoretical administration guidelines after the bolus would be to titrate the infusion rate upward slowly while monitoring the systemic blood pressure and a continuous electrocardiogram. Efficacy may be monitored clinically (e.g., reduction in the respiratory rate, alleviation of orthopnea) or echocardiographically with periodic measures of systolic function.

199.5.1.3.2.2 Amrinone

The effects of amrinone are almost identical to those of milrinone except that it does not appear to be as potent. Although there are no reports of its large-scale use in the management of acute decompensated congestive heart failure, treatment recommendations have been extrapolated from studies of normal dogs. Constant-rate infusions of 10 to 100 µg/kg/min appear to be capable of increasing cardiac contractility by 10% to 80% in awake, normal dogs.[12] Anesthetized dogs showed a 15% increase in the heart rate at an infusion rate of 30 µg/kg/min and a 20% increase at 100 µg/kg/min.[12] This tachycardia may have been induced either directly, through cAMP stimulation, or indirectly, in response to a decrease in blood pressure. The 30 µg/kg/min infusion rate was associated with a 10% decrease in blood pressure, whereas the 100 µg/kg/min rate reduced blood pressure by 30%.[12] After institution of a CRI, amrinone requires approximately 45 minutes to reach peak effect. Therefore, similar to milrinone, it appears most appropriate to administer a slow IV bolus of 1 to 3 mg/kg, followed by a slowly up-titrated CRI of 10 to 100 µg/kg/min. Continuous ECG monitoring should be instituted to allow evaluation for excessive tachycardia or arrhythmogenesis, and the systemic blood pressure should be monitored to avoid hypotension.

199.5.2 Management of Acute Heart Failure Secondary to Diastolic Dysfunction

Cats with hypertrophic cardiomyopathy (HCM) often present with signs of respiratory distress subsequent to the development of pulmonary edema or pleural effusion. Impaired ventricular relaxation produces elevated atrial and venous pressures, with eventual fluid exudation into the alveoli or pleural space. The treatment goals for cats with HCM and heart failure focus on relieving congestion through preload reduction rather than augmenting systolic function or decreasing afterload.

199.6 PROGRESSION OF HEART FAILURE (THE HUMAN EXPERIENCE)

Traditionally heart failure has been perceived as a hemodynamic disorder that promotes weakness, the development of debilitating congestive signs, deterioration of cardiac function, and ultimately death. Although the initial cardiac insult varies, it was historically rationalized that ventricular remodeling and disease progression occur as consequences of the compensatory mechanisms that promote vasoconstriction and fluid retention. It was recognized that diseased hearts operate on a depressed and flattened Frank-Starling curve, such that volume retention and vasoconstriction, rather than promoting cardiac output, merely exacerbated congestive heart failure. The symptoms of heart failure developed as venous pressures breached the lymphatics' ability to remove edema or as blood flow to exercising muscles was severely limited.

If disease progression were solely mediated by hemodynamic alterations, it was hypothesized, drugs capable of “unloading” the heart (e.g., vasodilators and positive inotropes) would retard this progression and improve survival. In the first Veterans Affairs Heart Failure Trial (V-HeFT) completed in 1985, prazosin or a combination of hydralazine and isosorbide dinitrate was used to decrease preload and afterload.[13] Although prazosin was more effective at reducing blood pressure, only the hydralazine/isosorbide dinitrate combination reduced mortality compared with placebo. The discordance between the hemodynamic and prognostic findings could not be

explained by the traditional perception of heart failure. Support for the hemodynamic hypothesis was further undermined by the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial completed in December of 1994, which found that administration of amlodipine to patients with severe chronic heart failure had no significant effect on mortality.[14]

Similar to the use of vasodilators to decrease ventricular wall stress and increase cardiac output, potent inotropic drugs capable of increasing cAMP levels were developed with the intent to improve survival. If poor pump performance were responsible for the progressive nature of heart failure, it was hypothesized, these positive inotropes should alter the natural course of cardiovascular disease. The phosphodiesterase inhibitor milrinone, which has potent inotropic and vasodilative properties, in fact was found to alter the course of heart failure but in a fashion opposite that expected. In October of 1990, the Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial was stopped 5 months prior to its scheduled completion date because administration of oral milrinone was found to increase all-cause mortality by 28%.[10] Patients with the severest symptoms (i.e., New York Heart Association [NYHA] class IV), who therefore would be the most likely to receive additional medical therapy, showed a 53% increase in mortality. Administration of the partial beta-agonist xamoterol also failed to improve survival in a study of 516 patients.[15]

These drug trial failures were accompanied in the late 1980s and early 1990s by an evolution in the understanding of the traditional hemodynamic model of heart failure. It still was recognized that hemodynamic alterations accounted for the symptomatic manifestations of cardiac disease, but a new understanding of the condition resulted in the conclusion that the body's compensatory neurohormonal mechanisms contributed to the dilemma of disease progression. Activation of the sympathetic nervous system (SNS) and the renin-angiotensin system (RAS) was found to promote both adverse hemodynamic consequences and direct toxic effects on the myocardium. Cultured mammalian cardiomyocytes exposed to norepinephrine displayed a concentration-dependent decrease in viability that was attenuated significantly by beta-receptor blockade.[16] In addition, norepinephrine was implicated in the provocation of ventricular arrhythmias and the impairment of sodium excretion by the kidneys.[17] Pathophysiologic levels of angiotensin II were found to promote myocytolysis with subsequent fibroblast proliferation, and aldosterone was implicated in the process of myocardial extracellular matrix remodeling.[18,19] These findings established a connection between hemodynamic mechanisms and neurohormonal consequences, which mutually promote a cycle of disease progression. The initial cardiac insult is followed by activation of neurohormonal compensatory mechanisms that produce further hemodynamic alterations and myocardial fibrosis. Cardiac output continues to decline, the compensatory mechanisms continue to be activated, and the disease process proceeds unabated.

This more complete understanding of the neurohormonal systems led to the development and use of drugs designed to antagonize the RAS. A breakthrough in the management of cardiovascular disease came with the utilization of angiotensin-converting enzyme (ACE) inhibitors in the mid to late 1980's. Angiotensin-converting enzyme is capable of degrading vasodilative bradykinin and is responsible for cleaving relatively inactive angiotensin I to the potent vasoconstrictor angiotensin II (AT II). Indirectly ACE is responsible for aldosterone production, because AT II is a primary stimulus for adrenal gland production of mineralocorticoids. Given angiotensin-converting enzyme's critical position in the RAS, it was proposed that ACE inhibition may promote beneficial hemodynamic and neurohormonal antagonistic and antifibrotic actions.

The ACE inhibitor enalapril has been extensively studied in humans with varying stages of heart failure. In three studies,[20–22] compared with placebo or the combination of hydralazine and isosorbide dinitrate, enalapril reduced all-cause mortality in humans with a reduced ejection fraction and heart failure. In another study,[23] compared with placebo, enalapril did not reduce the mortality rate in asymptomatic patients with reduced ejection fraction,

although it delayed the onset of heart failure. Because ACE inhibitors have been shown to alleviate symptoms, improve patients' clinical status, and decrease mortality, the current recommendation is that all humans with heart failure due to left ventricular systolic dysfunction receive an ACE inhibitor.[17] The mortality reductions associated with administration of ACE inhibitors lends support to the theory that disease progression is mediated by factors other than hemodynamics alone.

199.6.1 Management of Stable Compensated Congestive Heart Failure

After stabilization of the acute crisis, during which hemodynamic support is the goal, long-term management of heart failure ensues. The goals for this stage are to combat congestion, improve exercise capacity and quality of life, blunt adverse neurohormonal sequelae, and prolong survival time. Drugs can be administered to promote pump function (positive inotropes), to alter hemodynamics (preload and afterload reducers), and to blunt the adverse sequelae mediated by the body's compensatory mechanisms (neurohormonal antagonists). Numerous studies have been performed in humans to evaluate the benefits or limitations of drugs used to combat congestive heart failure, but the cost of well-designed, multi-institutional studies has precluded large-scale investigation in companion animals. For this reason, theoretical benefit often is extrapolated to dogs and cats; however, the practitioner should exercise caution in making these assumptions.

Triple drug therapy using furosemide and an ACE inhibitor, frequently combined with digoxin, serves as the mainstay of treatment for dogs with congestive heart failure secondary to degenerative valve disease and dilated cardiomyopathy.

199.6.1.1 Diuretics

The importance of appropriate administration of diuretics in the management of heart failure should not be underestimated. Diuretics play a pivotal role because they are the most effective agents for promoting rapid symptomatic benefits, and they are the only agents capable of controlling the fluid retention of heart failure. Although no large-scale trials have been done to evaluate the effect of diuretics on morbidity and mortality, there is little debate that they are a vital class of drug in both the acute and the long-term management of patients with congestive heart failure. Trials that would withhold a diuretic in heart failure would be immoral.

The kidney represents a major target organ for the neurohormonal and hemodynamic alterations that occur with a failing heart. Activation of the sympathetic nervous system, stimulation of the RAS, and intrarenal hemodynamic alterations all contribute to an avid state of sodium and water retention. Dogs with severe heart failure have had a 24% increase in plasma volume.[24] Unfortunately, these dogs are existing on the plateau of a depressed Frank-Starling curve, meaning the increased plasma volume is unable to enhance cardiac output. The premise behind administration of a diuretic, therefore, is to control congestion while maintaining optimal cardiac output. The three primary classes of diuretics are the loop, the thiazide, and the potassium-sparing diuretics. Each acts at a different site in the nephron.

199.6.1.1.1 Loop Diuretics

The loop diuretics (furosemide, torsemide, bumetanide, and ethacrynic acid) constitute the drug class most commonly used to treat heart failure. They inhibit the sodium, potassium, chloride ($Na^+/K^+/2Cl^-$) cotransporter on the luminal surface of the ascending limb of the loop of Henle. This inhibition markedly increases the fractional excretion of Na^+ and Cl^- and prevents establishment of the normal medullary concentration gradient, thereby promoting diuresis. In addition to promoting natriuresis and diuresis,

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furosemide, the most frequently used loop diuretic, appears capable of decreasing pulmonary capillary wedge pressure and promoting venodilatation, prior to the onset of diuresis, through local vascular prostaglandin synthesis.[25,26] The loop diuretics are the most effective agents for controlling the fluid retention of heart failure, and their proven safety, combined with their low cost, makes them a crucial therapeutic weapon.

Furosemide is available in formulations for enteral and parenteral administration. When it is administered intravenously, the onset of action is 5 minutes, the peak diuretic effect occurs within 30 minutes, and the duration of effect is 2 hours. After oral administration, the onset of action occurs within 60 minutes and the peak effect and duration of effect are 1 to 2 hours and 6 hours, respectively.

Furosemide's rapid onset of action explains its presence in most emergency crash carts. Severe pulmonary edema requires intravenous furosemide administration (2 to 8 mg/kg in dogs every 1 to 2 hours; 1 to 2 mg/kg in cats every 1 to 4 hours) to reduce preload rapidly. Although mild electrolyte abnormalities and dehydration may result with high doses, these conditions generally resolve when the pet resumes eating and drinking. After alleviation of the acute crisis, it is best to decrease the furosemide dose to the lowest capable of eliminating congestive signs. The authors have found that most dogs with a previous history of heart failure require 1 to 2 mg/kg given orally once or twice daily. Initially some dogs may be managed with as little as every-other-day therapy; however, as the disease process continues, cardiac output declines and diuretic resistance develops, extremely high doses of furosemide may be required to fend off congestive signs (4 mg/kg given orally three times daily). Periodic evaluation of electrolyte and renal parameters should be performed, especially when furosemide is administered concurrently with an ACE inhibitor and digoxin. It is well recognized that hypokalemia may contribute to ventricular arrhythmias and increase the likelihood of digoxin toxicity.

Bumetanide and torsemide have been reported to have more consistent oral bioavailability than furosemide (ranges of 80% to 100% and 10% to 100%, respectively).[27] The diuretic response occurs more slowly with intravenous torsemide than with furosemide, but torsemide promotes diuresis for a longer period.[28] Whether use of bumetanide or torsemide could allow for a more predictable diuretic response has not been evaluated.

199.6.1.1.2

Thiazide diuretics

The thiazides were among the first effective oral diuretic classes that developed widespread use in clinical practice. They block resorption of Na^+ in the distal convoluted tubule by inhibiting the Na^+/Cl^- cotransporter. The increased delivery of Na^+ to the collecting duct enhances potassium (K^+) and hydrogen (H^+) secretion and may promote the development of hypokalemia and metabolic alkalosis. Compared with loop diuretics, the thiazides are relatively weak; they increase renal sodium excretion from a normal value of about 1% to 5% to 8% of the filtered load. Nonetheless, they appear to promote a synergistic effect when administered with a loop diuretic. Although the combination of loop and thiazide diuretics appears effective at combating refractory pulmonary edema, caution must be exercised to avoid hypokalemia. One strategy to prevent excessive potassium loss is to administer the thiazide every second or third day while continuing daily treatment with furosemide. The two most frequently used thiazide diuretics are chlorothiazide and hydrochlorothiazide. Both drugs show good oral absorption and a relatively rapid onset of action. Chlorothiazide (20 to 40 mg/kg given orally twice daily) promotes diuresis within 1 hour, reaches peak activity at 4 hours, and has a duration of effect of 6 to 12 hours. For hydrochlorothiazide

(*dogs:* 2 to 4 mg/kg given orally twice daily; *cats:* 1 to 2 mg/kg given orally twice daily), onset of action occurs within 2 hours, activity peaks at 4 hours, and the effect lasts 12 hours.

199.6.1.1.3 Potassium-sparing diuretics

Potassium-sparing diuretics formerly were allocated solely to the late stages of heart failure or to patients with hypokalemia, but they recently have come to the forefront in the battle against neurohormonally mediated progression of cardiac disease. This class of diuretics (spironolactone, eplerenone, and triamterene) recently has gained prominence because evidence suggests the presence of "aldosterone escape" in approximately one third of humans treated with ACE inhibitors.[29] The precise mechanisms behind this RAS-independent increase in aldosterone are unknown, although increased potassium levels induced by ACE inhibitors and decreased hepatic clearance may be contributing factors. Tissue pathways for the production of aldosterone have also been identified, although their role in the progression of heart failure is uncertain.

Aldosterone promotes the production of Na^+/K^+ exchangers along the luminal surface of the distal tubule and collecting ducts. In addition to its ability to increase sodium resorption, aldosterone now is recognized to contribute to myocardial fibrosis, augmentation of sympathetic tone, and possibly diuretic resistance. It has been postulated that spironolactone's ability to decrease collagen turnover, and presumably myocardial fibrosis, is responsible for the marked mortality benefits recognized in the Randomized Aldactone Evaluation Study (RALES) trial. Whether dogs and cats will benefit similarly has yet to be determined, but more frequent use of spironolactone in companion animals may be warranted.

Spironolactone is well absorbed from the gastrointestinal tract but has a relatively slow onset of action, peaking at 2 to 3 days after administration. It undergoes rapid hepatic metabolism to pharmacologically active canrenone. Spironolactone is administered to dogs and cats at a dosage of 1 to 2 mg/kg given orally every 12 hours, in conjunction with an ACE inhibitor and a loop diuretic, to combat congestive heart failure.

199.6.1.2 Angiotensin-Converting Enzyme (ACE) Inhibitors

Despite their symptomatic benefits, diuretics should not be used as monotherapy in the management of congestive heart failure because they further activate the renin-angiotensin system.[30,31] Drugs designed to inhibit angiotensin-converting enzyme block the formation of AT II, promote an increase in the circulating levels of bradykinin, and may temporarily reduce circulating aldosterone levels. Although ACE inhibitors are frequently categorized as balanced vasodilators, it appears likely that their beneficial effect on mortality is not mediated purely by hemodynamic alterations.[22] They are relatively weak vasodilators compared with direct-acting arterial vasodilators such as hydralazine, and their ability to promote diuresis is much overshadowed by the less expensive loop diuretics. Rather, it is believed that ACE inhibitors reduce mortality through their ability to blunt the detrimental consequences associated with long-standing activation of the RAS. Their early success has helped spearhead the current pharmacologic trend toward neurohormonal antagonism.

Activation of the neurohormonal cascade often begins with detection of arterial underfilling by mechanoreceptors in the carotid sinus and kidney (Figure 199-4). Regardless of whether this relative "hypotension" occurs secondary to low-output heart failure, severe mitral insufficiency, or profound hypovolemia, the common end-point is activation of the sympathetic nervous system and RAS. Additional

activators of the RAS are reduced sodium delivery to the macula densa and sympathetic stimulation. Release of the protease renin from the juxtaglomerular apparatus promotes conversion of angiotensinogen to angiotensin I. Angiotensin-converting enzyme cleaves the C-terminal dipeptide from angiotensin I, thereby forming the octapeptide angiotensin II. In addition to being a potent vasoconstrictor, AT II has several other properties: (1) it is a primary secretagogue for aldosterone; (2) it potentiates presynaptic norepinephrine release; (3) it stimulates the release of antidiuretic hormone (vasopressin); (4) it promotes renal tubular sodium resorption; and (5) it has been linked to cardiomyocyte necrosis, apoptosis, and progression of ventricular fibrosis.[18,32,33] Angiotensin-converting enzyme is also capable of cleaving the C-terminal dipeptide from bradykinin, therefore it appears to be a regulator of vasoconstrictive/sodium retentive and vasodilative/natriuretic mechanisms. Although tissue ACE and additional enzymatic pathways (e.g., chymase, cathepsin G, tonin, and tissue plasminogen activator) capable of producing AT II have been identified, their significance is unknown at this time.[32]

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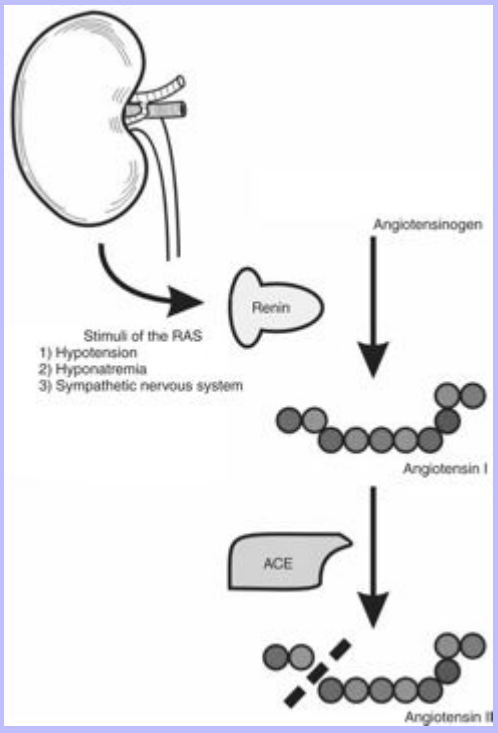
Figure 199-4 After the release of renin, angiotensinogen is cleaved to form angiotensin I, which is subsequently cleaved by angiotensin-converting enzyme (ACE) to form angiotensin II. Angiotensin II promotes numerous physiologic actions, including activation of the sympathetic nervous system and production of aldosterone (see Figure 199-12).



ACE-inhibiting compounds are numerous and vary in their chemical structure, potency, bioavailability, and route of elimination. Most ACE inhibitors, excluding captopril and lisinopril, are administered in the form of

prodrugs that require conversion to their active form by hepatic metabolism. Enalapril requires conversion to enalaprilat, and benazepril is metabolized to benazeprilat. Although claims have been made that some formulations produce more profound ACE inhibition, prolonged periods of efficacy, or superior tissue ACE inhibition, the importance of these characteristics is unclear in naturally occurring heart failure.

The degree of ACE inhibition and the duration of action of several agents, including benazepril, captopril, enalapril, lisinopril, and ramipril, have been evaluated in normal dogs.[34] Hamlin and Nakayama[34] documented that benazepril, enalapril, lisinopril, and ramipril were able to achieve similar degrees of ACE inhibition after drug administration (about 75% inhibition at 1.5 hours and about 50% inhibition through 12 hours). Enalapril, lisinopril, and ramipril continued to display significant activity (about 25% inhibition) beyond 24 hours. These researchers also found that captopril was unable to reduce ACE activity substantially, compared with control, beyond the 1.5-hour sample. Whether captopril's inability to suppress ACE activity was a consequence of sample handling or merely an inability to suppress circulating versus tissue ACE is uncertain.[35] Evaluations of enalapril and benazepril in normal cats have identified maximal ACE inhibition of 48% and 98%, respectively, after single-dose administration.[36,37] Benazepril was reported to show greater than 90% ACE inhibition beyond 24 hours.[37]

Excretion of the ACE inhibitors is primarily via the kidneys, although benazepril appears to undergo significant biliary excretion in companion animals (about 50% in dogs and about 85% in cats).[38] When ACE inhibitors have been prescribed for patients with mild renal insufficiency, the recommendation historically has been to reduce both the dosage and frequency interval by approximately 50%. Administration of enalapril to dogs with experimental mild renal insufficiency is associated with a significant increase in the area under the curve (AUC) for the active metabolite enalaprilat.[39] After benazepril was administered to the same dogs, no significant increase was seen in the AUC for benazeprilat. Whether concurrent cardiac disease, with its relatively depressed cardiac output, would be associated with impaired benazeprilat excretion is unclear. Current trends using “standard” doses of enalapril to treat glomerulonephritis and renal insufficiency are difficult to extrapolate to patients with heart failure and renal insufficiency because of their limited ability to increase cardiac output in the face of a reduced rate of glomerular filtration.[40]

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In summary, the merits and limitations of the different formulations are unknown, and only the ACE inhibitor enalapril has been specifically approved in the United States for the treatment of heart failure in dogs. The hypothesized improved safety of using benazepril rather than enalapril in patients with renal insufficiency has not been clinically evaluated in companion animals with cardiac disease.

199.6.1.2.1

Enalapril

Enalapril is one of the few drugs that has been closely evaluated in dogs with naturally occurring congestive heart failure. The first reported placebo-controlled studies in dogs were short-term investigations, the Invasive Multicenter Prospective Veterinary Evaluation of Enalapril study (IMPROVE; 21 days) and the Cooperative Veterinary Enalapril study (COVE; 28 days), both published in 1995.[41,42] These studies enrolled dogs with mitral valve insufficiency or dilated cardiomyopathy (DCM) to evaluate the hemodynamic (IMPROVE) and clinical (COVE) benefits of enalapril. The drug decreased pulmonary capillary wedge pressures in dogs with DCM and improved the heart failure class, pulmonary edema scores, and overall evaluation for both groups of dogs with heart failure. The benefits of these short-term studies were more pronounced for dogs with DCM than for those with mitral valve insufficiency. The COVE investigators found that twice daily oral administration of enalapril (0.5 mg/kg) appeared to

promote more significant improvements than once daily therapy.[42] The LIVE study group followed a subpopulation of dogs from the two short-term studies to evaluate the long-term effects of enalapril administration.[5] These researchers found that dogs treated with enalapril were able to continue the study for longer than those receiving placebo (157.5 versus 77 days, P = 0.006). In contrast to the results of the short-term studies, the beneficial effect was more prominent in dogs with mitral valve insufficiency (P = 0.041) than in those with dilated cardiomyopathy (P = 0.06). An additional study supporting the benefits of ACE inhibitor administration to dogs with heart failure found that enalapril significantly increased the exercise tolerance of dogs with experimentally created mitral insufficiency.[43]

Despite these symptomatic benefits, the hope that early institution of ACE inhibition will delay the onset of heart failure may go unfulfilled. To date, enalapril has been unable to delay the onset of heart failure in asymptomatic cases of mitral insufficiency.[44] Whether ACE inhibitors can reduce mortality in dogs or cats with heart failure has yet to be determined; even so, preliminary evidence reported in 2003 looks supportive, although not conclusive, for cats with diastolic dysfunction.[45]

199.6.1.2.2

Benazepril

Similar to enalapril, benazepril is a prodrug that must undergo hepatic metabolism to produce the active compound, benazeprilat. Oral administration of benazepril has produced variable and conflicting degrees of ACE inhibition. An initial study reported that peak plasma benazeprilat concentrations were achieved 2 hours after oral administration.[46] The percentage of ACE inhibition after a single dose of 0.5 mg/kg of benazepril administered to normal dogs was 99.7% after 2 hours, 95.2% after 12 hours, and 87.3% after 24 hours. Similar results were found for the same intervals at doses of 0.25 mg/kg (97.8%, 89.2%, and 75.7%) and 1 mg/kg (99.1%, 94.0%, and 83.1%). Maximal ACE inhibition after 15 doses was attained in dogs receiving 0.25 mg/kg of benazepril once daily (96.9% at 2 hours, 92.5% at 12 hours, and 83.6% at 24 hours). A second study, which also evaluated a single dose of 0.5 mg/kg of benazepril in normal dogs, showed ACE inhibition of 81% at 1.5 hours, 37% at 12 hours, and 10.3% at 24 hours.[34] Prolonged administration of benazepril was not evaluated. A final study, in which 0.5 mg/kg of benazepril was administered orally once daily to dogs with mitral insufficiency, showed ACE inhibition to be 33.3% at 1 week, 28% at 2 weeks, and 42.7% at 4 weeks.[47]

Based on these conflicting results, the current dosing recommendations are broad (0.25 to 0.5 mg/kg given orally once or twice daily). Whether benazepril is clinically more effective or safer than enalapril for dogs and cats with congestive heart failure remains unclear.

199.6.1.2.3

Adverse effects

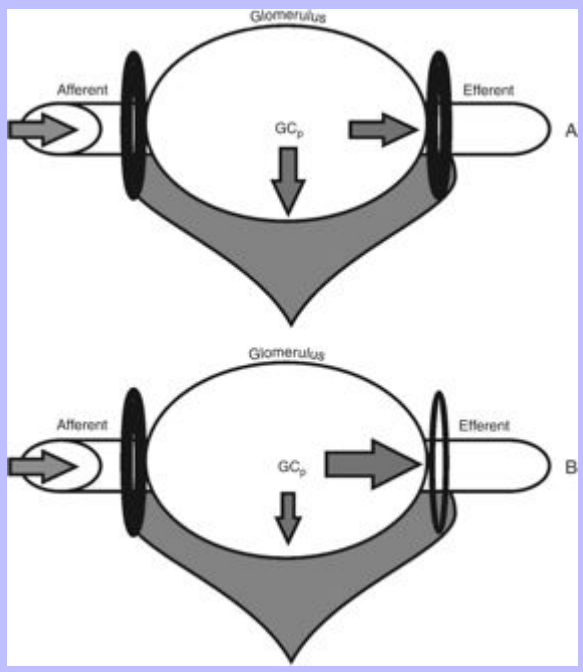
The mechanism by which ACE inhibitors exert their beneficial properties (e.g., inhibition of angiotensin II production) also lends to the potential for adverse consequences. Although infrequently encountered, complications may include systemic hypotension, azotemia, and hyperkalemia.

ACE inhibitors reduce systemic vascular resistance by decreasing circulating levels of angiotensin II and increasing circulating levels of bradykinin. In patients with severe heart failure in which an increase in cardiac output is unable to sustain systemic blood pressure, symptomatic hypotension may develop. Although this complication is infrequent, its likelihood increases with concomitant overzealous use of diuretics. Unfortunately, the clinical signs associated with severe low-output heart failure and systemic

hypotension are very similar (e.g., weakness, exercise intolerance, and possibly stupor), a fact that lends emphasis to an important point: if a patient appears refractory to medical management, the blood pressure should be evaluated before more aggressive measures to combat heart failure are instituted.

A second adverse effect attributed to ACE inhibitors' unique ability to decrease angiotensin II production is a reduction in the glomerular filtration rate (GFR) and the development of azotemia. The GFR is determined by the glomerular capillary pressure (GC_P). Based on the knowledge that pressure is equal to the product of flow and resistance ($P = Q \times R$), it can be ascertained that the GFR ultimately is determined by renal plasma flow and the degree of efferent arteriolar vasoconstriction (Figure 199-5). In cases of heart failure in which renal plasma flow is diminished, the glomerular filtration rate is supported by the ability of ATII to constrict the efferent renal arteriole. ACE inhibitors' ability to depress production of AT II promotes efferent renal arteriolar vasodilatation and hence a reduction in the GFR. The failing heart cannot further increase cardiac output, and an acute bout of azotemia may subsequently develop. A recent study evaluating early institution of enalapril therapy in dogs with compensated mitral valve insufficiency found that dogs allocated to an ACE inhibitor were not at a more significant risk of developing azotemia compared with dogs receiving placebo.[48] In the authors' experience, mild increases in blood urea nitrogen (BUN) and creatinine occur frequently after institution of therapy with an ACE inhibitor and furosemide. However, the development of severe azotemia, necessitating discontinuation of the ACE inhibitor or a reduction in its dosage, occurs infrequently. This complication seems to occur most often in patients with severe heart failure that require aggressive diuretic administration to control congestive signs. Prior to institution of enalapril therapy, the authors evaluate the baseline biochemical parameters and perform a second measurement of the BUN, creatinine, and electrolytes 5 to 7 days after the start of treatment. If patients become anorectic or develop gastrointestinal signs during this time, we instruct the owners to discontinue all drugs and immediately present the animal for veterinary attention.

Figure 199-5 Glomerular capillary pressure (GC_p), and therefore the glomerular filtration rate (GFR), is determined by cardiac output and the relative resistances imparted by the afferent and efferent renal arterioles. Compared with normal **(A)**, ACE inhibitors preferentially dilate the efferent renal arteriole **(B)** and may therefore decrease the GFR and promote the development of azotemia. It appears this consequence is most frequent in patients with low output heart failure that require large doses of diuretics to control their congestive signs.



Hyperkalemia may be encountered during therapy with ACE inhibitors as the result of a reduction in the GFR and a decline in circulating aldosterone levels. In the absence of aldosterone, sodium loss is favored and potassium levels rise. This complication appears to occur infrequently, presumably because most of the potent diuretics have potassium-wasting properties and tend to prevent the development of hyperkalemia. The authors have rarely encountered an increase in potassium that necessitated a dosage reduction for or discontinuation of an ACE inhibitor. There is concern that the addition of spironolactone may potentiate hyperkalemia, therefore periodic electrolyte monitoring is prudent in patients receiving an ACE inhibitor and a potassium-sparing diuretic.

199.6.1.2.4

Drug interactions

Because aspirin inhibits cyclo-oxygenase and decreases prostaglandin formation, some have questioned whether administration of aspirin may negate some of the beneficial vasodilative properties exerted by ACE inhibitors.[49] An additional concern is that aspirin's ability to reduce renal prostaglandin formation may worsen the ACE inhibitor–induced reduction in the GFR.[50] A recent retrospective analysis of six long-term, randomized trials of ACE inhibitors found that aspirin did not significantly alter the beneficial effects of ACE inhibitors in CHF.[50] Whether other commonly prescribed, nonsteroidal anti-inflammatory agents blunt the potentially beneficial vasodilative properties of ACE inhibitors is uncertain.

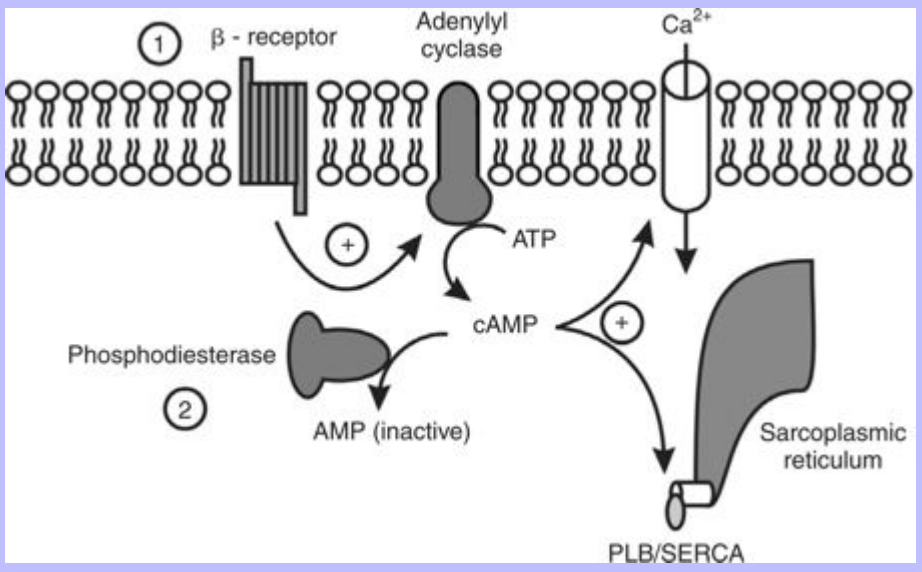
199.6.1.3

Positive Inotropes

Agents capable of increasing cardiac contractility can improve a patient's strength and exercise capacity, thereby potentially enhancing the pet's quality of life. Ideally, these compounds would concurrently promote mortality benefits by improving cardiac efficiency and limiting the activation of endogenous compensatory mechanisms (with their detrimental long-term consequences). Unfortunately, to date most of the potent agents available to augment systolic function act by means of “upstream,” cAMP-dependent mechanisms that have shown negative effects on survival.

Membrane-associated adenylate cyclase is the enzyme responsible for cAMP production, and phosphodiesterase III is responsible for its degradation. Therefore mechanisms to increase cAMP concentrations may take one of two pathways (Figure 199-6): beta agonists increase production of cAMP, and phosphodiesterase inhibitors increase cytosolic cAMP by inhibiting its breakdown. Acting through protein kinase A, cAMP promotes phosphorylation of the L-type calcium channel to increase calcium release from the sarcoplasmic reticulum (SR). The increased systolic Ca^{2+} concentration (1) deinhibits the troponin complex to promote actin and myosin interaction and (2) increases the activity of myosin ATPase.[51] These mechanisms serve to increase both the total force developed and the rate at which the force is developed. Protein kinase A also exerts beneficial lusitropic effects by promoting phosphorylation of (1) the regulatory SR membrane phosphoprotein, phospholamban, to enhance diastolic calcium uptake and (2) troponin I, to increase the rate of cross-bridge detachment and relaxation.[51] Paradoxically, despite these beneficial properties, long-term administration of agents capable of increasing cAMP has been linked to increased mortality rates in patients with heart failure.[10] The increased Ca^{2+} concentrations are believed to contribute to the development of arrhythmias and to increase myocardial energy consumption and oxygen demand, thereby worsening the outcome. These findings lend support to the premise that downregulation and uncoupling of beta receptors, along with upregulation of adenylate cyclase inhibitory proteins, serve as compensatory protective mechanisms rather than primary biochemical abnormalities. Current investigations are evaluating agents capable of enhancing systolic performance “downstream” from cytosolic Ca^{2+} in the hopes of avoiding excessive mortality.

Figure 199-6 The beta-agonists (*1*) dobutamine and dopamine promote their positive inotropic and lusitropic effects through activation of adenylyl cyclase, with a subsequent amplification of cAMP production. The phosphodiesterase inhibitors (*2*) amrinone, milrinone and, to some degree, pimobendan blunt the degradation of cAMP, thereby promoting similar positive inotropic and lusitropic effects that should not be blunted by beta-receptor downregulation. Phosphorylation of the sarcolemmal L-type calcium channel is responsible for the positive inotropic action, whereas phosphorylation of phospholamban (PLB), with ensuing deinhibition of the sarcoplasmic reticulum calcium ATPase (SERCA), accounts for the enhanced diastolic function. Phosphorylation of troponin I (not shown) further enhances diastolic function by altering the cross-bridge kinetics between actin and myosin.



199.6.1.3.1

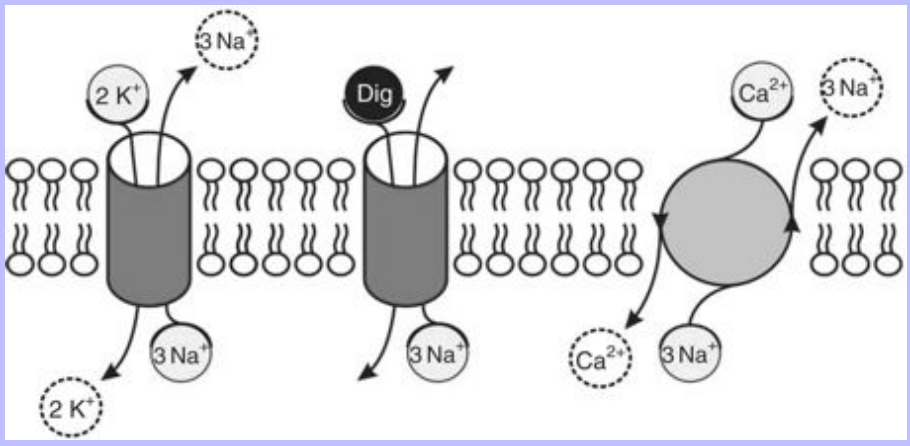
Digitalis glycosides

The digitalis glycosides are the only readily available class of inotropic agents that act independently of the cAMP second-messenger system. This characteristic imparts a degree of safety to the glycosides, with regard to their neutral effect on mortality, but simultaneously limits their inotropic potency.[52] Because of digoxin's potential positive inotropic effects and rate-controlling properties for atrial fibrillation, there is little debate that it is indicated in the treatment of dilated cardiomyopathy; however, there is substantial debate over its role in the management of mitral valve insufficiency. The authors' rationale for the use of

digoxin (0.003 mg/kg given orally twice daily) in dogs with mitral valve insufficiency is primarily its neurohormonal antagonism effect rather than pump support. Inhibition of the Na^+/K^+ ATPase pump in the vagal afferents sensitizes the baroreceptors to the prevailing blood pressure, which may decrease sympathetic outflow and renin-angiotensin activity.[17] Although the findings are purely anecdotal, the authors have had and continue to have cases in which the addition of digoxin to background therapy of furosemide and enalapril has produced clear symptomatic improvement.

The cardiac glycosides inhibit the action of the Na^+/K^+ ATPase pump by competitively binding to the extracellular potassium site (Figure 199-7). This antagonism promotes an increase in the intracellular sodium concentration, with its subsequent exchange for calcium via the reversible Na^+/Ca^{2+} pump. The net result is an increase in cytosolic calcium levels and enhanced cardiac contractility. Inhibition of the Na^+/K^+ ATPase pump further sensitizes the baroreceptors (blunting sympathetic discharge), inhibits renal tubular resorption of sodium (promoting mild diuresis), and increases the delivery of sodium to the distal tubules (inhibiting renin release).[17]

Figure 199-7 The Na^+/K^+ ATPase pump contributes to maintenance of the resting membrane potential by actively pumping three Na^+ ions out across the sarcolemmal membrane and two K^+ ions into the cell. The pump therefore is capable of maintaining both an electrical and a chemical gradient. Digoxin competitively binds the K^+ binding site on the extracellular surface, thereby inhibiting sodium efflux by means of this mechanism. The excessive intracellular Na^+ reverses the Na^+/Ca^{2+} exchanger and ultimately promotes an influx of Ca^{2+} and efflux of Na^+. The increased calcium transport augments calcium-induced calcium release from the sarcoplasmic reticulum, enhancing contractility.



Despite these theoretical benefits, digitalis has been unable to alter the natural course of heart failure.[52] The Digitalis Investigation Group (DIG) enrolled 6800 human patients in a placebo-controlled study to evaluate whether digoxin administration affected mortality or morbidity.[52] Digoxin did not reduce overall mortality but did reduce the rate of hospitalization for worsening heart failure (26.8% versus 34.7%, P <0.001). Subgroup analysis revealed that patients in class III or class IV heart failure showed the greatest benefit from digoxin administration. Compared with results from agents not related to glycosides, including dobutamine and milrinone, the findings of this investigation did not demonstrate excess mortality. It is unlikely that a similar study evaluating the efficacy of digoxin will ever be performed in dogs because of the extreme sample size needed to detect these small differences. One study reported that four of 10 dogs with dilated cardiomyopathy showed echocardiographically identifiable improvements in cardiac contractility after treatment with digoxin.[53] Whether the 7% increase in fractional shortening was a true increase in contractility or merely occurred subsequent to rate control (250 beats per minute [bpm] pretreatment versus 145 bpm post-treatment) is uncertain, but digoxin appears to be a relatively weak inotropic agent in dogs with heart failure. Nonetheless, it is the only oral inotropic agent that is readily available in the United States.

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Therapeutic levels of digitalis increase parasympathetic tone, while blunting sympathetic activation, to promote slowing of the sinus node and increased atrioventricular (AV) node refractoriness with decreased conduction velocity. This property makes them useful in the management of DCM complicated by atrial fibrillation, because the other negative chronotropes (e.g., beta blockers, Ca^{2+} channel blockers) acutely depress systolic function. Digitalis is further indicated for the management of symptomatic DCM with sinus rhythm or left to right shunting lesions complicated by myocardial failure. Although digoxin is not always considered a mainstay of therapy for the management of mitral insufficiency, the authors continue to use it in cases of heart failure subsequent to chronic degenerative valve disease (CDVD). Although some of these mitral insufficiency patients fail to attain symptomatic benefit from digoxin therapy, the drug's low cost and safety when used appropriately continue to make it a useful agent. Digoxin is an inappropriate agent to use for rate control in cases of hypertrophic cardiomyopathy in which the primary abnormality is diastolic rather than systolic dysfunction. Any positive inotropic response predisposes HCM patients to the development or worsening of systolic anterior motion of the mitral valve.

199.6.1.3.1.1

Digoxin

Digoxin is the digitalis glycoside most commonly used in dogs, and it appears to be the most suitable glycoside for cats with systolic dysfunction. The bioavailability of digoxin after oral administration of the tablet form is approximately 60%.[12] The digoxin elixir shows better bioavailability after oral administration (about 75%) and is easier to dose appropriately for small dogs. After absorption, digoxin has a relatively long and variable serum half-life in dogs, with reports ranging from 23 to 39 hours.[12] In cats the duration is even more uncertain, with reports of mean half-lives ranging from 33.5 hours to 57.8 hours, with even longer half-lives during prolonged administration. Because approximately five half-lives are required to attain steady-state concentrations of a drug, digoxin cannot be expected to produce rapid symptomatic or rate-controlling benefits. Digoxin predominately undergoes renal excretion, although a small amount (approximately 15%) is metabolized by the liver. Renal failure significantly reduces the clearance of digoxin and profoundly increases the serum concentration, often to the point of intoxication. Patients with renal failure that require a cardiac glycoside should be given *digitoxin* because it undergoes hepatic elimination.

Determining the appropriate dose of digoxin to attain therapeutic levels yet avoid digitalis intoxication can be a frustrating endeavor. Traditionally, small dogs (less than 20 kg) have been treated with 0.005 to 0.008 mg/kg given orally twice daily, and larger dogs have been treated based on body surface area, with 0.22 mg/m^2 given orally twice daily. The intent with these doses was to attain a therapeutic digoxin level of 1 to 2 ng/mL. The DIG trial found that human mortality varied directly with serum digoxin levels, even within this "therapeutic" range. A new trend has emerged from that data whereby the human medical profession has aimed to keep trough levels of digoxin at 0.5 to 1 ng/ml. Whether these recommendations hold true for dogs is uncertain, but aiming for the low end of the reference range appears to be appropriate. The authors currently institute digoxin therapy at a dosage of 0.003 mg/kg given orally twice daily. If the digoxin level is subtherapeutic 5 to 7 days after initiation of therapy, the dosage is increased by 25%, and the serum level is rechecked a week later. This regimen is continued until therapeutic levels have been attained.

A number of factors may influence the distribution of digoxin, creating a need for special consideration and monitoring. The principal reservoir for digoxin is skeletal muscle, therefore dosing recommendations should be based on lean body mass. Obese dogs require lower doses of digoxin than thin dogs, and the dosing requirement for dogs that experience marked muscle loss tends to decline. Patients with right-sided heart failure and large volumes of ascites need dosage reductions because digoxin does not distribute into free abdominal fluid.[12] After institution of digoxin therapy, it is most appropriate to alter the dosing scheme based on the serum digoxin level, the response to therapy, and evidence of intoxication.

A number of drug interactions also are possible with digoxin. The best recognized interaction is between digoxin and the class Ia antiarrhythmic quinidine. When these drugs are combined, serum digoxin levels increase because quinidine displaces digoxin from the Na^+/K^+ ATPase pump and reduces its renal clearance through inhibition of P-glycoprotein. The binding of digoxin with myocardial Na^+/K^+ ATPase is "tighter" than that with skeletal muscle, therefore the net effect of this drug combination is an increase in the likelihood of digitalis intoxication. It is recommended that these agents not be used together. Fortunately, no interactions have been reported between digoxin and the more frequently used class I anti-arrhythmics procainamide and mexiletine. Most of the other reported drug interactions, with amiodarone, verapamil, nifedipine, propafenone and, to a lesser extent diltiazem, occur because of inhibition of P-glycoprotein. Any agent that alters renal blood flow or hepatic microsomal enzymes has the potential to disturb digoxin's pharmacokinetics.

Similar to quinidine, the extracellular potassium concentration can influence digoxin binding to the Na^+/K^+ ATPase pump. The hypokalemia often associated with anorexia or large doses of a diuretic leaves more receptors exposed for digoxin attachment, thereby increasing the likelihood of digitalis intoxication. With hyperkalemia, more receptors are bound, and digoxin is displaced from the Na^+/K^+ ATPase. Hypercalcemia and hypernatremia promote digoxin's inotropic and toxic properties, whereas decreased calcium and sodium concentrations have the opposite effects.

Since it was recognized that taurine deficiency was responsible for most cases of feline DCM, the number of cats receiving digoxin has declined over the past decade. The authors still encounter an infrequent case of DCM unrelated to taurine deficiency, and some cases of restrictive cardiomyopathy have such poor systolic function that digoxin is indicated. Cats appear to tolerate the tablet form of digoxin better than the alcohol-based elixir. The recommended dose is one fourth of a 0.125 mg tablet given orally. Dosing intervals are as follows: (1) cats weighing 3 kg or less: every 48 hours; (2) cats

weighing 4 to 5 kg: every 24 to 48 hours; (3) cats weighing 6 kg or greater: every 24 hours. Because of the variable half-life of digoxin in cats, the authors typically monitor serum levels 7 to 10 days after initiation of therapy.

199.6.1.3.2 Digitalis toxicity

Without a doubt, digoxin is a toxic substance when excessive amounts accumulate. This narrow therapeutic index highlights the need for careful client and veterinary attention when digoxin is part of a treatment regimen. In the authors' experience, when digoxin therapy is instituted at a dosage of 0.003 mg/kg given orally twice daily, with uptitration based on serum digoxin concentrations, the incidence of digitalis toxicity is low both clinically and biochemically.

Clients should be informed of the most common manifestations of digoxin intoxication and given concise instructions on what to do if clinical signs develop. Continuing drug administration and waiting until the next recheck is not an appropriate step; the authors recommend discontinuation of all drugs followed by an immediate veterinary evaluation. It should be emphasized that the three regions frequently affected by excessive digoxin accumulation are the myocardial, gastrointestinal, and central nervous systems. Gastrointestinal manifestations, which often precede central nervous system (CNS) and myocardial toxicity, commonly include anorexia and vomiting, presumably from a direct chemoreceptor triggering effect exerted by digoxin. The serum concentration at which gastrointestinal signs develop is extremely variable. Some dogs have digoxin-associated anorexia at subtherapeutic drug concentrations, whereas others do not show any evidence of toxicity even with serum concentrations well above the therapeutic range. It can be difficult to determine whether the anorexia is associated with digoxin administration, azotemia secondary to a decreased GFR or renal insufficiency, poor diet palatability, or worsening heart failure. A biochemical profile, serum digoxin determination, and thoracic radiographs should be obtained in any digoxin-treated dog with heart failure that suddenly develops anorexia. In the absence of complicating factors such as azotemia or pulmonary edema, the authors temporarily discontinue digoxin administration even if the serum level is within the therapeutic range. If the pet's appetite returns (suggesting digoxin-associated anorexia), a lower digoxin dose may be instituted or the drug may be discontinued all together. Digoxin does not provide enough mortality benefit or positive inotropic response to warrant administration in the face of profound anorexia or other complications.

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Although the myocardial complications may be more difficult for owners to recognize, they often are the most serious. Digoxin toxicity may induce almost every known cardiac arrhythmia, including both bradyarrhythmias and tachyarrhythmias. First-and second-degree AV block, sinus bradycardia, and sinus arrest are presumably influenced by digoxin's parasympathomimetic properties. Life-threatening ventricular tachyarrhythmias may develop as a consequence of cellular calcium overload. Excessive calcium precipitates late afterdepolarizations, whereby oscillations within the diastolic membrane potential periodically reach threshold and produce a pre-mature complex. The slowed conduction and altered refractory period may then precipitate re-entry, yielding ventricular tachycardia. Obviously, determining whether the ventricular arrhythmia is associated with digoxin administration or is a manifestation of the underlying disease process may be difficult, but in general, discontinuation of digitalis is indicated.

The CNS alterations mediated by digoxin toxicity may include depression, disorientation, or delirium. Again, determining whether such clinical signs are attributable to digitalis intoxication or progression of the underlying disease process often is difficult. These patients should be evaluated for hypotension, in addition to having their serum digoxin levels measured.

199.6.1.3.2.1 Treatment of digitalis toxicity

The aggressiveness with which digoxin toxicity is treated depends on the manifestation of intoxication rather than the serum digoxin level. Gastrointestinal disturbances can frequently be managed by discontinuation of the drug. Dogs with bradyarrhythmias are often asymptomatic, and withdrawal of digoxin is the only therapeutic alteration required. In the rare case of symptomatic patients, short-term administration of atropine may be required while the toxic digoxin concentrations expire. The most aggressively managed complication of digitalis intoxication is ventricular tachyarrhythmias.

The class Ib antiarrhythmic drug lidocaine is the first-choice agent for acute management of digitalis-induced ventricular tachycardia. It is effective at targeting late afterdepolarizations without substantially affecting the sinus rate or AV nodal conduction. An initial bolus of 2 to 4 mg/kg is administered intravenously over 1 to 2 minutes, followed by a constant-rate infusion to suppress the arrhythmias. Lidocaine should be administered conservatively to cats because they are more sensitive to the neurotoxic side effects. Although infrequently used, phenytoin also appears efficacious for the treatment of digoxin-induced arrhythmias.

Because hypokalemia may precipitate digoxin toxicity and limit the efficacy of antiarrhythmic agents, it is important to evaluate the serum potassium concentration and to correct underlying deficits. Because of its ability to bind competitively the Na^+/K^+ ATPase pump, potassium can displace digoxin from the myocardium, thereby decreasing the likelihood of toxicity.

The development of a specific antibody fragment for cardiac glycosides has enabled production of an "antidote" for severe digoxin intoxication. Digibind® (GlaxoSmith Kline, Durham NC) complexes with the digoxin molecule and inhibits binding to the Na^+/K^+ ATPase pump, quickly resolving drug intoxication. Unfortunately, this drug is expensive, and its use in clinical practice therefore is limited.

199.6.2 Deficiencies of the Triple Drug Regimen

199.6.2.1 Early Institution of Therapy

Despite the relative safety and symptomatic benefit of triple drug therapy (i.e., furosemide, enalapril, and digoxin), this regimen has limitations. A possible ineptitude of this combination for the early treatment of cardiac disease is the mechanism by which ACE inhibitors promote their beneficial response. It is logical that, for these drugs to blunt the adverse consequences of the renin-angiotensin system, the system must be activated. In response to RAS activation after cardiac injury, the heart hypertrophies to normalize cardiac output and wall stress. Within physiologic limits, this hypertrophy, possibly combined with the inhibitory effects of circulating atrial natriuretic peptide, may be able to restore the renin-angiotensin system to resting levels.

Studies that have evaluated activation of the RAS in normal dogs, in dogs with asymptomatic dilated cardiomyopathy, and in dogs with symptomatic dilated cardiomyopathy lend support to this hypothesis.[54,55] In a study by Koch et al.,[54] 23 dogs were evaluated; nine dogs had asymptomatic DCM, eight had symptomatic DCM, and six had severe congestive heart failure subsequent to DCM. Sixteen giant breed dogs without evidence of cardiac disease were used to establish the neuroendocrine control values. In dogs with asymptomatic dilated cardiomyopathy, the plasma renin activity and aldosterone concentrations were not

significantly different from those in control dogs (1.48 versus 0.89 and 35 versus 61, respectively). In dogs with symptomatic DCM and congestive heart failure, significant activation of the neurohormonal axis was seen compared with normal dogs and those with asymptomatic DCM. Plasma renin activity and aldosterone concentrations increased substantially between dogs with functional class III and class IV heart failure (3.8 versus 30.8 and 123 versus 600, respectively). Tidholm et al.[55] further evaluated activation of the neurohormonal systems of 45 dogs: 15 dogs with DCM and radiographic evidence of heart failure, 15 dogs with DCM without evidence of heart failure, and 15 age-, breed-, and gender-matched control dogs. They, too, found that in dogs with asymptomatic DCM, plasma renin activity, aldosterone concentrations, and N-terminal (NT)-pro atrial natriuretic peptide levels were not significantly different from those in control dogs. Dogs with DCM and congestive heart failure showed significant differences in all three variables compared with normal dogs and those with asymptomatic DCM.

Investigation of the effects of mitral valve insufficiency on the circulating neurohormonal system has also proved interesting, with some conflicting results. Pedersen et al.[56] evaluated the plasma renin and aldosterone concentrations of 18 Cavalier King Charles spaniels with asymptomatic or mildly symptomatic mitral insufficiency. Compared with 18 Cavalier King Charles spaniels without signs of heart disease, the plasma renin levels (median 3.44 versus 2.51, P = 0.03) and aldosterone concentrations (median 53 versus 27, P = 0.03) were significantly higher in dogs with valvular insufficiency. Haggstrom et al.[57] repeatedly evaluated 11 Cavalier King Charles spaniels with mitral insufficiency at 6-month intervals until signs of decompensation developed. The dogs did not receive cardiac medications during the study, and their diets remained the same throughout. The time of decompensation was considered the end-point of the study (situation 2), and the two most recent study periods (at 4.6 ± 2.2 months [situation 1] and 11.7 ± 1.8 months [situation 0]) prior to decompensation completed the three periods analyzed. The investigators found that N-terminal atrial natriuretic peptide (ANP) concentrations increased significantly from situation 0 to situation 1 and were further increased from situation 1 until the time of decompensation (situation 2). Plasma aldosterone concentrations were not significantly different from situation 0 to situation 1 but were found to decrease significantly at the time of decompensation (P <0.01). Plasma angiotensin II concentrations were not significantly different between situation 0 and situation 1 or between the beginning of the study and the end of the study, but similar to the aldosterone levels, angiotensin II was significantly decreased between situation 1 and situation 2 (P <0.05). The investigators concluded that the reductions in circulating angiotensin II and aldosterone at the onset of decompensation likely occurred subsequent to the elevation in ANP levels. Atrial natriuretic peptide has been reported to directly inhibit the release of renin and aldosterone and to promote a reduction in intravascular volume, thereby limiting RAS activation in the early stages of decompensation.[57] However, significant, long-term elevation of ANP in cases of severe heart failure may promote receptor downregulation, attenuating the inhibitory activity on the renin-angiotensin system.[58] Renal hypoperfusion and enhanced elimination of ANP may further blunt the counterbalancing activity of ANP, possibly allowing the RAS to accelerate the progression of heart failure unabated.[58]

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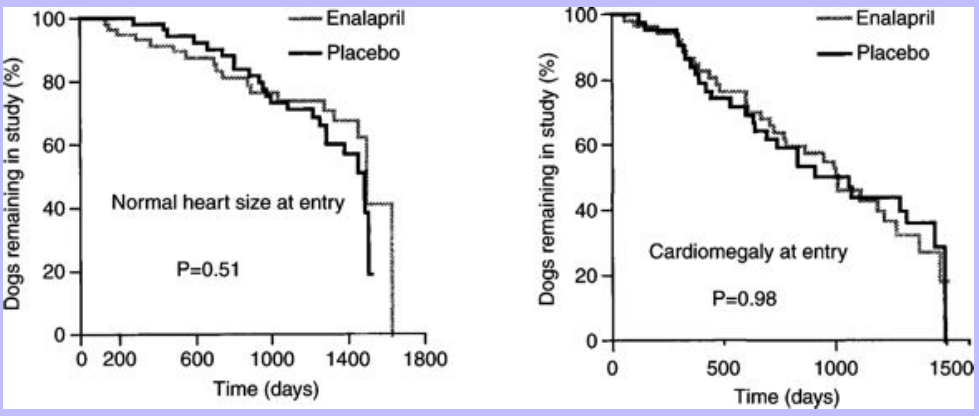
Although it was determined that systemic, circulating RAS is not activated at the onset of heart failure in Cavalier King Charles spaniels or in asymptomatic dogs with DCM, recognition that local tissue pathways exist for the RAS may still support early institution of ACE inhibition. Canine ventricular myocytes have been recognized locally to contain the constituents of the RAS that may promote ventricular remodeling in an autocrine fashion.[59] Dogs subjected to rapid ventricular pacing to induce heart failure were compared with control dogs that were instrumented but not paced. Using reverse-transcriptase polymerase chain reaction (RT-PCR) and Western blot testing, Barlucchi et al.[59] found significant differences in canine myocyte RAS activity between control and failing hearts. Angiotensinogen expression was increased 2.5-fold (P <0.001), renin was increased 3.6-fold (P <0.001), the two forms of ACE identified at 134 and 170

kDa were increased 1.45-fold ($P < 0.005$) and 1.44-fold ($P < 0.002$), respectively, and the AT_1 receptor subtype of angiotensin II was increased 1.7-fold ($P < 0.001$) after 4 weeks of pacing. Angiotensin II levels measured by enzyme-linked immunosorbent assay (ELISA) were increased 2.2-fold ($P < 0.004$) in dogs subjected to pacing, whereas no significant differences were seen in chymase expression ($P = 0.28$) or the expression of the myocyte AT_2 receptor subtype of angiotensin II ($P < 0.06$).[59]

These findings point out one of the most challenging questions in the treatment of cardiac disease in companion animals: when is the appropriate time to initiate therapy? Although ACE inhibitors have proved efficacious at delaying the onset of heart failure in humans with asymptomatic left ventricular dysfunction, no similar published studies exist to support this conclusion in dogs and cats.[23] A double-blind, placebo-controlled study of 229 Cavalier King Charles spaniels with asymptomatic mitral regurgitation found that enalapril was unable to delay the onset of heart failure (Figure 199-8).[44] Although this study has been criticized on some counts (e.g., inadequate dose of ACE inhibitor [0.25 to 0.5 mg/kg daily], use of a single breed with a disease course that may not be representative of all dogs, and insufficient statistical power), it nonetheless was a 4.5-year endeavor that remains the largest published evaluation of therapy aimed at delaying the onset of heart failure in dogs with asymptomatic mitral regurgitation. These findings cannot completely exclude the potential for other ACE inhibitors to delay the onset of heart failure in cases of mitral insufficiency or the possible benefit of early institution of ACE inhibition in dogs with DCM or cats with HCM; however, while awaiting study findings on those questions, the authors will continue to delay institution of ACE inhibitor therapy until cardiac disease has progressed to a point where diuretics are needed to control congestion.

Figure 199-8 Early institution of enalapril therapy was unable to delay the onset of congestive heart failure in a study of 229 asymptomatic Cavalier King Charles spaniels. (From Kvart C: Efficacy of enalapril for prevention of congestive heart failure in a study of 229 cases of asymptomatic myxomatous valve disease and asymptomatic mitral regurgitation. *J Vet Intern Med* 16:1, 2002.)



199.6.2.2 Therapeutic Efficacy in Dilated Cardiomyopathy versus Mitral Insufficiency

Activation of the renin-angiotensin system occurs subsequent to one of three major stimuli: decreased renal perfusion pressure, reduced sodium delivery to the macula densa, or sympathetic activation.[60] Therefore many cardiovascular and systemic disease processes may promote renin release, with eventual production of angiotensin II. Despite the potential for ACE inhibitors to blunt angiotensin II formation, they may have variable efficacy in alleviating the clinical signs of heart failure, depending on the underlying disease process.

The potential for discrepancies in response to ACE inhibitor therapy seemed apparent in the IMPROVE and COVE studies, which evaluated enalapril in the management of heart failure subsequent to dilated cardiomyopathy or mitral regurgitation (MR).[41,42] In both studies, dogs with DCM appeared to show a more dramatic response compared with those that had MR. After 28 days of enalapril therapy, the dogs with DCM showed significant improvement, compared with animals receiving placebo, in the class of heart failure, pulmonary edema scores, overall evaluation, mobility, attitude, activity, demeanor, cough (total, night, normal activity, and exercise), and appetite scores.[42] Dogs with MR allocated to enalapril showed significant improvement only in overall evaluation, mobility, activity, and cough (total).[42] It was noted that a longer study may have identified further significant improvements in patients with mitral regurgitation.

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Subsequently, a longer term study was performed in an effort to determine the effects of enalapril on the survival of dogs with heart failure.[5] Dogs with DCM or MR that had developed congestive heart failure were enrolled and randomly allocated to enalapril or placebo in addition to receiving standard medical therapy. The dogs were followed until death, treatment failure (defined as deterioration of condition requiring additional medications), or termination of the study. In contrast to the short-term investigations, dogs with mitral insufficiency randomized to enalapril remained in this study significantly longer than those randomized to placebo (mean, 159.5 days versus 86.6 days, $P = 0.041$), whereas the DCM subgroup showed no significant differences (mean, 142.8 days versus 56.5 days, $P = 0.06$).[5]

Although no steadfast conclusions can be drawn from the differences between the short-and long-term studies, these findings highlight the difficulty in extrapolating across disease conditions. Furthermore, they should show the pitfalls of extrapolating results from human studies, in which the vast majority of patients have left ventricular dysfunction secondary to coronary artery disease or myocardial infarction. Until further studies can better elucidate the benefits or detriments of current veterinary medical management, practitioners must continue to rely on anecdotal evidence, presumption, and clinical judgment.

199.6.2.3 Failure to Target Other Neurohormonal Pathways

An additional limitation of triple drug therapy is the failure to target two of the neurohormonal modulators that perpetuate cardiomyocyte necrosis and ventricular fibrosis. Studies have shown that adrenergic stimulation decreases cardiomyocyte viability by means of cAMP-mediated calcium overload and that aldosterone promotes myocardial hypertrophy and fibrosis, autonomic imbalance, and electrolyte imbalances that may precipitate arrhythmias.[16,61]

199.6.3 Potential therapeutic strategies

199.6.3.1 Aldosterone antagonists

The neurohormonal hypothesis of heart failure gains further support from the fact that the aldosterone antagonist spironolactone has proved efficacious in the management of severe heart failure in humans. Studies have recognized that small concentrations of aldosterone can stimulate cardiac fibroblast expression of type I and type III collagen, thereby promoting myocardial fibrosis.[19] Although ACE inhibitors are considered effective at reducing aldosterone levels by inhibiting the formation of aldosterone's primary secretagogue, angiotensin II, there is mounting evidence of a phenomenon called *aldosterone escape*.[29] Increased potassium levels induced by ACE inhibitors and decreased hepatic clearance may contribute to this RAS-independent increase in aldosterone.[19] It also has become apparent that local tissue pathways for the production of aldosterone exist in extra-adrenal sites, although the importance of these tissue pathways has not been clarified.[19] Because aldosterone impairs normal vasodilative responses, promotes myocardial fibrosis, potentiates the sympathetic nervous system, and influences electrolyte transport, a recent strategy to target heart failure has been the administration of aldosterone antagonists.[61]

Addition of the aldosterone antagonist spironolactone to the baseline therapy of patients with severe heart failure produced a 30% reduction in mortality and a 35% reduction in the frequency of hospitalization for worsening heart failure.[62] Although identification of the mechanism by which spironolactone exerts its beneficial effects was not the aim of the Randomized Aldactone Evaluation Study (RALES) group, a small substudy of 261 participants suggests that limitation of aldosterone-stimulated collagen synthesis is the major contributor.[63] In a recent model of experimental heart failure created in dogs, the aldosterone antagonist eplerenone was able to attenuate the development of interstitial fibrosis and cardiomyocyte hypertrophy while increasing capillary density.[64] Although the frequency and likelihood of aldosterone escape are unknown in dogs treated with ACE inhibitors, it seems prudent to consider spironolactone administration for patients treated with enalapril. Currently the optimal dosing scheme for dogs is unknown; however, the authors combine spironolactone (2 mg/kg given orally twice daily) with their standard therapy (furosemide and enalapril with or without digoxin) to further combat the detrimental consequences of aldosterone. Whether this is the optimal regimen or whether spironolactone promotes symptomatic or survival benefit in dogs with heart failure is unknown at this time.

199.6.3.2 Beta-blockers

Similar to what happens in humans, in dogs with congestive heart failure the body activates the sympathetic nervous system and RAS in an effort to maintain homeostasis. Unfortunately these short-term compensatory mechanisms promote adverse hemodynamic and biochemical alterations that ultimately contribute to weakness, debilitating congestive signs, deterioration of cardiac function, and ultimately death. The IMPROVE and COVE investigators identified the short-term utility of enalapril in combating dilated cardiomyopathy, and since then ACE inhibition has become routine therapy.[41,42] Although it has not been evaluated in controlled clinical trials, the loop diuretic furosemide appears to have a potent effect in alleviating the congestive clinical signs that frequently accompany heart failure. The efficacy, safety, and affordability of furosemide have made it a mainstay in the management of heart failure. Because systolic dysfunction is the primary phenotypic manifestation of dilated cardiomyopathy, the authors' ideal therapy

would further use an agent that augments systolic performance without promoting adverse events. In humans, long-term administration of beta agonists and phosphodiesterase inhibitors is marred by the resultant increase in mortality and in hospitalizations for heart failure. Whether these findings would also be reflected in large-scale canine trials is unknown, but the historical adverse events have caused pharmaceutical companies to abandon their marketing in the United States. Thus digoxin is the primary positive inotrope available to improve systolic function. Although it has been reported to produce echocardiographically identifiable improvements in fractional shortening in some dogs, it remains a relatively weak positive inotrope.[53]

Just when some investigators had given up on the search for a safe positive inotropic agent, new investigations have identified a drug class that increased measures of systolic performance while decreasing mortality and hospitalizations. Surprisingly, this class of drugs is the beta blockers.

Agents that antagonize beta receptors act by interfering with the endogenous neurohormonal system. The primary integrator of the neurohormonal response to arterial underfilling appears to be the sympathetic nervous system.[19] Excessive catecholamine levels promote a daunting number of detrimental effects: peripheral vasoconstriction, impaired sodium excretion by the kidneys, myocardial hypertrophy with impaired coronary flow, provocation of arrhythmias, apoptosis, and myocytolysis.[17] Some researchers suggested that blockade of this primary integrator may retard the unrelenting nature of heart failure, whereas others were reluctant to blunt the effects (e.g., positive inotropic and chronotropic) of this potentially beneficial system. The proponents of beta blockade contended that these potential benefits are already self-limited by internalization and degradation of beta receptors in response to elevated circulating levels of norepinephrine. To settle the controversy, large-scale, placebo-controlled trials were conducted to identify the potential benefits of antiadrenergic therapy. In these studies, the second-generation beta blockers bisoprolol and metoprolol and the third-generation beta blocker carvedilol were shown to reduce mortality substantially in patients with a reduced ejection fraction.[65–67] Because the study protocols included stringent observation, slow upward drug titration, and recruitment of patients with stable rather than decompensated heart failure, most of the patients enrolled in these trials were able to tolerate the short-term negative inotropic effects associated with beta blocker administration. With long-term administration, at 4 to 12 months of treatment beta blockers were found to induce a time-dependent process of reverse remodeling in which systolic function improved as myocardial hypertrophy regressed and the ventricular geometry normalized.[68] Among the medications used to treat heart failure, this improvement in intrinsic systolic function appears to be unique to beta blockers. Based on these results, beta blocker administration currently is recommended for humans with stable heart failure secondary to systolic dysfunction.[17]

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The primary types of beta blockers evaluated thus far have been those that selectively inhibit the $beta_1$ receptor (metoprolol and bisoprolol) and that antagonize $beta_1$, $beta_2$, and $alpha_1$-adrenergic receptors (carvedilol). Although carvedilol blocks peripheral vasodilative $beta_2$ receptors, it concurrently blocks vasoconstrictive $alpha_1$-adrenergic receptors, thereby enhancing its tolerance in patients afflicted with systolic dysfunction. In patients with mild to moderate heart failure, the reported tolerance for $beta_1$-selective antagonists ranges from 79% to 100%, whereas carvedilol is tolerated by approximately 92% of patients.[68] The most recent carvedilol study was performed in patients with stable NYHA class IV heart failure and an ejection fraction of less than 25%. Despite the severity of their disease, at 4 months 65% of patients assigned to carvedilol were receiving the target dose of their assigned medication.[67]

The safety and efficacy of beta blockers in the management of heart failure have been more critically evaluated in controlled drug trials than has any other class of drugs. A meta-analysis of 18 published double-blind, placebo-controlled trials involving primarily NYHA class II and class III heart failure that were conducted through 1998 revealed persuasive positive effects on mortality, hospitalization, and the ejection fraction. Beta blockers reduced the risk of death by 32% and the risk of hospitalization for heart failure by 41% while increasing the ejection fraction by 29%.[69] Patients assigned to beta blockers were 32% more likely to show improvement in their heart failure class and 30% less likely to experience worsening heart failure.[69] Large-scale trials of bisoprolol, metoprolol, and carvedilol have been reported since 1998, in which mortality reductions of 34%, 34%, and 35%, respectively, were identified.[65–67] These impressive findings have led to small-scale investigations into the management of canine heart failure with carvedilol. While the results of those trials are awaited, new treatment strategies for the management of canine dilated cardiomyopathy and degenerative mitral valve disease can be hypothesized.

199.6.3.3 Beta-Blockers for the management of DCM

The management of canine dilated cardiomyopathy is often frustrating and unrewarding. Two retrospective analyses have shown median survival times of 65 days and 27 days, and 1-year survival probabilities of 37.5% and 17.5% have been reported.[2,3] The prognosis for Doberman pinschers appears even worse, with a reported median survival time of 6.5 weeks and a 1-year survival probability of 3%.[4] Survival times may since have improved with more robust use of ACE inhibitors, but dilated cardiomyopathy seems to progress much more rapidly in dogs than in humans. Approximately 25% of human patients referred to major medical centers with newly diagnosed dilated cardiomyopathy die within 1 year, and the 5-year survival rate is 50%.[70]

This discrepancy between humans and dogs in the rate of disease progression poses a problem for the management of DCM in dogs. As previously described, beta blockers have proved to be one of the most effective agents for combating heart failure, because their antiadrenergic properties offset the toxic and hemodynamic derangements induced by norepinephrine. Unfortunately, therapy for 1 to 3 months appears to be necessary before any improvement in systolic function is recognized, and administration for up to 18 months is needed for reversal of maladaptive remodeling with reduction in left ventricular volumes.[71] It therefore seems that many dogs with dilated cardiomyopathy would not live long enough to reap the beneficial effects of beta blockers. The percentage of dogs that would tolerate the short-term negative inotropic effects induced by beta blockade also is uncertain.

A potential remedy for this situation may be concurrent, low-dose administration of a positive inotropic agent during the uptitration and early target phases of beta blocker therapy. The phosphodiesterase inhibitor and calcium sensitizer pimobendan may satisfactorily fulfill this role. A study evaluating the effectiveness of carvedilol therapy compared with a combination of carvedilol and pimobendan found that withdrawal of therapy because of worsening of heart failure occurred less often in the combination group.[72]

Similar to amrinone and milrinone, pimobendan is able to improve cardiac contractility, promote ventricular relaxation, and induce vasodilatation by increasing cAMP levels. However, pimobendan also has calcium-sensitizing properties that increase contractility by enhancing the interaction between troponin C and the prevailing cytosolic calcium level. Compared with agents that increase cAMP, a calcium sensitizer has several benefits: (1) it lowers the risk of induction of arrhythmias; (2) it reduces cell injury and death caused by calcium overload; (3) it exerts its effects without increasing energy demands; and (4) it has the

potential to reverse systolic dysfunction in the face of acidosis and myocardial stunning.[73] In a study of humans with heart failure, pimobendan was able to increase exercise capacity significantly without increasing oxygen consumption.[74] Proarrhythmic effects were not identified during 24-hour electrocardiography, but a trend toward increased mortality was seen in the patients assigned to pimobendan. Enrollment criteria excluded any patients treated with beta blockers, therefore whether combination therapy may have reduced the trend toward increased mortality is speculative. Nonetheless, the concept of combining a novel positive inotropic agent with a slowly titrated beta blocker may very well deserve attention. Unfortunately, pimobendan currently is not available in the United States, and the use of beta blockers in the management of DCM should be considered purely investigational.

199.6.3.4 Beta-blockers for the management of chronic degenerative valve disease

The authors currently manage CDVD with furosemide, an ACE inhibitor, and digoxin, with the addition of spironolactone in moderate to severe cases. This combination directly targets excessive plasma volume and the renin-angiotensin system while indirectly combating activation of the sympathetic nervous system. A new concept may include the addition of a beta blocker to antagonize directly the detrimental consequences of adrenergic activation. A recent study evaluated the hemodynamic effects of the ACE inhibitor lisinopril versus a combination of lisinopril and the beta blocker atenolol in the treatment of experimental mitral regurgitation.[75] Lisinopril was found to reduce significantly left ventricular end-diastolic pressure, pulmonary capillary wedge pressure, and end-diastolic stress, but it had no marked effect on forward stroke volume or left ventricular contractility. Three months after the addition of atenolol to this regimen, forward stroke volume and left ventricular contractility had returned to normal. Whether this effect occurred subsequent to an additional 3 months of ACE inhibition or was mediated by the beta blockade is uncertain. Regardless, this study suggests that direct adrenergic antagonism may prove beneficial in the management of CDVD, and further studies may be warranted.

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199.6.4 Management of Refractory Congestive Heart Failure

Over time, many patients become refractory to standard medical therapy as disease progression continues or if a concurrent systemic disease process develops that exerts detrimental effects on the cardiovascular system (e.g., hyperadrenocorticism, hypothyroidism, renal failure, systemic hypertension, neoplasia, anemia, pneumonia, or pulmonary thromboembolism). Infrequent causes of an acute bout of decompensation include the development of hemodynamically important arrhythmias, sudden rupture of chordae tendineae, or splitting of the left atrial wall subsequent to severe mitral insufficiency and elevated left atrial pressure. For these reasons, any patient that continues to show clinical signs of congestion or low cardiac output despite appropriate medical therapy should be closely re-evaluated. After determining whether the owner is administering the prescribed drugs at the appropriate intervals, the practitioner should obtain an ECG, thoracic radiographs, complete blood count, biochemical profile, and blood pressure measurement. Echocardiography often is warranted to characterize the severity of valvular insufficiency, the extent of chamber enlargement, and the degree of systolic dysfunction.

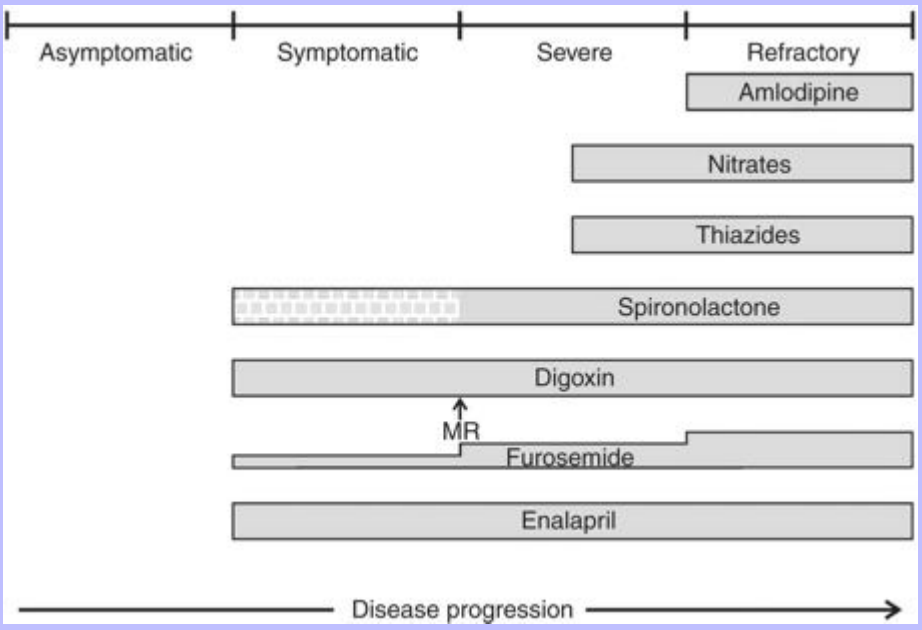
If an underlying disease process is identified, it should be managed appropriately before institution of therapy with new cardiac drugs. Attempts should be made to suppress significant ventricular arrhythmias; agents capable of slowing conduction through the atrioventricular node (e.g., calcium channel blockers or beta blockers) may be required to help control the ventricular response rate in the face of atrial fibrillation. Potent afterload reduction with nitroprusside or hydralazine often is required to combat the effects of ruptured chordae tendineae. Left atrial tears are difficult to manage.

If no underlying disease process is identified, several strategies may be used to manage these refractory patients (Figure 199-9). Afterload reduction using arterial vasodilators, preload reduction using additional diuretics or venodilators, or additional neurohormonal blockade using beta blockers or spironolactone may be warranted. The route of diuretic administration may be modified, or positive inotropic agents periodically may be given intravenously. The inherent risks and complications of treatment are greatest in patients with refractory heart failure, and referral to a specialist is wiser than embarking on an unconventional treatment protocol.

199.6.4.1 Vasodilators

Vasodilators promote smooth muscle relaxation of the arterioles (arterial vasodilators), veins (venodilators), or arteries and veins (balanced vasodilators). Although these drug classes promote a similar therapeutic end-point, vasodilatation, a variety of mechanisms are involved in achieving their effect.

Figure 199-9 Although therapy must be tailored on a case-by-case basis, the authors traditionally do not start medical therapy in asymptomatic patients. As the disease progresses over time and compensatory mechanisms overwhelm traditional ACE inhibitor, diuretic, and digoxin therapy, other strategies must be used to combat congestive and low-output signs. Currently the optimal time for institution of therapy with aldosterone antagonists is uncertain.



Heart failure is associated with activation of the sympathetic nervous system and renin-angiotensin system. In the face of decreased cardiac output, these systems promote arteriolar vasoconstriction to maintain

adequate perfusion pressure and venoconstriction to enhance venous return to the heart. Unfortunately, the arteriolar vasoconstriction further increases the workload of the failing heart; more energy must be expended to overcome high systemic vascular resistance, and less energy is available to expel blood into the aorta. Stroke volume (and hence cardiac output [CO]) decreases, but systemic vascular resistance (SVR) continues to increase in an effort to maintain blood pressure (BP = CO × SVR). The increase in preload promoted by venoconstriction also proves detrimental because the diseased heart, operating on the plateau of the Frank-Starling curve, is unable to further hypertrophy or increase its contractility. Ventricular end-diastolic pressures begin to rise, leading to the eventual formation of edema.

Based on these hemodynamic sequelae, it seemed apparent that a reduction in afterload and/or preload ultimately would reduce mortality. Interestingly, the first V-HeFT study found that prazosin, the agent most capable of reducing blood pressure, was unable to reduce mortality compared with placebo.[13] The combination of hydralazine and isosorbide dinitrate reduced mortality, but in the V-HeFT II trial, enalapril was more effective than the combined vasodilators at preventing death.[22] This beneficial effect was seen despite the inability of the ACE inhibitor to reduce blood pressure. Obviously blood pressure and systemic vascular resistance are not synonymous, but these findings have detracted from the use of potent afterload reducers in the routine management of heart failure. Venodilators may still be effective at reducing the development of edema, but the problem of drug tolerance has limited their use to animals with refractory heart failure.

199.6.4.1.1

Amlodipine

Amlodipine is a second-generation, dihydropyridine (DHP) calcium channel blocker that primarily produces arteriolar vasodilatation and is used in the treatment of systemic hypertension. Unlike the non-DHPs diltiazem and verapamil, amlodipine has little effect on conduction through the atrioventricular node, and its negative inotropic properties appear to be offset by a reduction in afterload. Although amlodipine was unable to reduce mortality in an evaluation of 1153 patients with left ventricular dysfunction and severe heart failure (P = 0.07), it did reduce the mortality rate by 31% (P = 0.04) in the subgroup of patients with nonischemic DCM.[14] Despite this mortality benefit, 14 of the 209 patients with DCM assigned to amlodipine developed pulmonary edema (compared with 2 of 212 patients assigned to placebo). The mechanism involved in this development was uncertain.

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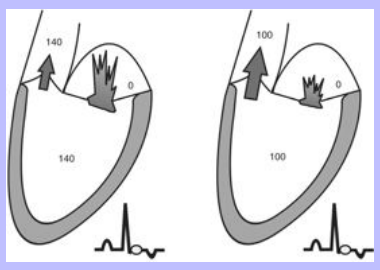
Figure 199-10 Left ventricular systolic pressure is influenced by the systemic vascular resistance, therefore agents capable of reducing afterload have the potential to decrease the volume of mitral insufficiency while increasing the effective forward stroke volume.



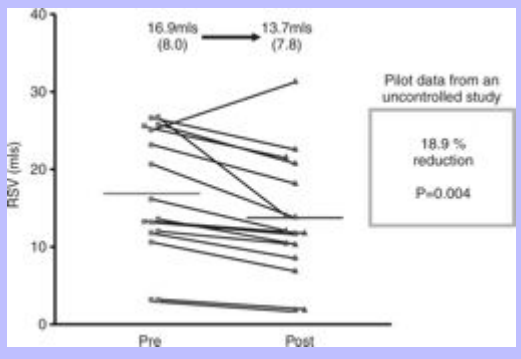
An interesting application of amlodipine therapy may be for severe mitral valve insufficiency. A reduction in systemic vascular resistance (and hence the systolic left ventricular to left atrial pressure gradient) may serve to decrease the volume of mitral valve insufficiency (Figures 199-10 and 199-11). Potential benefits of amlodipine are its 30-hour half-life and peak effect in 4 to 7 days after institution of therapy to dogs. This slow onset of action may give the baroreceptors time to reset, thereby avoiding sympathetic activation and reflex tachycardia. The effective dose of amlodipine seems to vary; a common strategy is to institute therapy at a low dose (0.05 mg/kg given orally once daily), followed by slow titration up to 0.2 mg/kg until a reduction in blood pressure is achieved. Because of the drug's long half-life, the authors typically monitor blood pressure weekly, using uptitration until the target blood pressure is attained.

199.6.4.1.2

Hydralazine

Hydralazine is a direct-acting arterial vasodilator that promotes vasodilatation through an unknown mechanism. It was studied in the 1980s for the management of CDVD in dogs and was found to produce substantial decreases in mean arterial blood pressure, total systemic resistance index, and pulmonary capillary wedge pressure.[76] Since that time, hydralazine appears to have been pushed aside by the ACE inhibitors in the management of uncomplicated heart failure. This trend likely resulted from the commonly encountered side effects of hydralazine (i.e., symptomatic hypotension, anorexia, vomiting, and diarrhea), the presence of elevated aldosterone levels seen after hydralazine therapy compared with captopril, and the significant results of the V-HeFT II trial.[77]

Figure 199-11 After administration of the calcium channel blocker amlodipine, the regurgitant stroke volume in dogs with mitral insufficiency was significantly reduced (by 18.9%). Although these data look promising, it should be noted that this study had no control population, the echocardiographer was not blinded, and no data evaluation of the neurohormonal consequences of afterload reduction was performed. (Courtesy Dr. Mark Oyama, University of Illinois College of Veterinary Medicine, Urbana-Champaign.)



Hydralazine is still used in the acute management of decompensated heart failure when nitroprusside is unavailable (or impractical to use) because of its rapid onset of action. Similar to amlodipine, the reduction in systemic vascular resistance may reduce the volume of mitral insufficiency and promote an increase in the forward stroke volume. In contrast to amlodipine, the peak vasodilative effect of hydralazine occurs within 3 hours and subsides within 12 hours. Unfortunately, this same characteristic may result in reflex tachycardia and further stimulation of the sympathetic nervous system and RAS. A study by Haggstrom et al.[31] identified significant increases in heart rate and plasma aldosterone and angiotensin II concentrations, as well as evidence of fluid retention, in Cavalier King Charles spaniels with mitral insufficiency that were treated with hydralazine monotherapy for 3 weeks. These findings suggest that ACE inhibitors should be used concurrently with hydralazine if chronic afterload reduction is warranted.

For the management of fulminant congestive heart failure, hydralazine may be administered at a dosage of 2 mg/kg given orally twice daily to dogs with a systolic blood pressure above 100 mm Hg. The authors recommend blood pressure monitoring, with the twin goals of avoiding hypotension and monitoring therapeutic efficacy. Ideally the increase in effective cardiac output will counterbalance the hydralazine-mediated reduction in systemic vascular resistance, preventing the development of symptomatic hypotension.

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199.6.4.1.3 Nitrates

The nitrates, which include nitroglycerin, isosorbide dinitrate and isosorbide mononitrate, and nitroprusside, are a class of vasodilators that promote the formation of nitric oxide. Although nitroprusside administered intravenously is a potent balanced vasodilator, topical and oral administration of nitroglycerin and oral administration of isosorbide dinitrate and isosorbide mononitrate appear to promote primarily venodilatation. The premise behind venodilatation is to promote redistribution of the circulating blood volume from the heart and pulmonary vasculature to the systemic venous circulation. This reduction in preload should decrease ventricular end-diastolic, atrial, and pulmonary capillary pressures, shifting the Frank-Starling curve to the left and alleviating pulmonary edema. Currently the efficacy of nitrates in the management of chronic heart failure is uncertain and may be limited by *nitrate tolerance*, the phenomenon in which continued drug exposure reduces the agent's effectiveness.

199.6.4.1.3.1 Nitroglycerin

A 2% topical formulation of nitroglycerin combined with furosemide and oxygen (with or without hydralazine) is frequently used in the management of acute heart failure. Anecdotal recommendations have called for application of nitroglycerin cream to a clipped or hairless region ($^1/_2$ to 2 inches every 6 to 8 hours for dogs; $^1/_4$-inch every 6 to 8 hours for cats) to promote continuous transdermal absorption and venodilatation. Studies evaluating the absorption of cutaneously applied nitroglycerin, the optimal site for topical administration, and the efficacy of this therapy for dogs or cats with heart failure have not been reported. There is a report that nitroglycerin applied to the auricular pinna promotes splenic vasodilatation in normal anesthetized dogs, but by no means should nitroglycerin replace furosemide as the primary agent for reducing preload and alleviating pulmonary edema.[78]

199.6.4.1.3.2 Isosorbide dinitrate and isosorbide mononitrate

Isosorbide dinitrate and its major metabolite, mononitrate, are orally administered venodilators that may help reduce preload and hence pulmonary edema. Similar to nitroglycerin, the orally administered nitrates have not been extensively studied in naturally occurring heart failure. However, Adin et al.[79] were unable to document circulatory redistribution after a single dose of isosorbide mononitrate in normal dogs or in those with heart failure. Whether nitrates can regress cardiac remodeling in naturally occurring heart failure remains to be investigated.[80]

Although their efficacy is unknown, isosorbide dinitrate (0.5 to 2 mg/kg given orally twice daily) and isosorbide mononitrate (0.25 to 2 mg/kg given orally twice daily) occasionally are used in the management of refractory heart failure or in combination with hydralazine or amlodipine for patients unable to tolerate ACE inhibitors. Whether dosing-free intervals are required to combat the development of nitrate tolerance for dogs and cats is unknown.

199.6.4.2 Triple Diuretic Therapy

Although twice-daily administration of a loop diuretic appears to be the regimen most frequently used to manage congestive heart failure, there are physiologic benefits to altering the dosing frequency or combining agents from different classes. Although not a true component of diuretic resistance, the activity of the nephron in the absence of therapeutic diuretic concentrations must be kept in mind. The loop diuretics currently available are not long-acting formulations. Therefore the original diuretic effects have dissipated well before the administration of a second daily dose. During this time, when it is not inhibited, the $Na^+/K^+/2Cl^-$ pump promotes avid sodium resorption, possibly to a degree that negates any previous natriuretic effect.[27] This highlights the point that, in cases of worsening heart failure, three times daily dosing of furosemide may be more beneficial than merely increasing the twice daily dose. In cases of right-sided heart failure, in which oral drug absorption may be impaired, changing the type of administration to the subcutaneous or intramuscular route may prove beneficial. Administration of a diuretic by means of a constant-rate infusion may prove the most beneficial during emergency treatment of heart failure, although frequent, moderate doses likely achieve a similar end-point.

No matter the dosing interval or the route of administration, the segments of the nephron distal to the loop of Henle are capable of producing diuretic resistance. Increased solute exposure to the distal nephron promotes hypertrophy and increased resorptive capacity of the early distal tubule, the connecting tubule, and the cortical collecting duct.[81] Although the exact mechanisms are unclear, aldosterone has been implicated as promoting this process.[81] Strategies to combat diuretic resistance associated with long-standing administration of a loop diuretic include (1) addition of a thiazide diuretic to encourage diuresis in the hypertrophied region and/or (2) addition of an aldosterone antagonist to target the proposed hypertrophic mechanism. This synergistic nephron blockade, using multiple agents with activity in different regions of the nephron, may allow a reduction in the dose of furosemide required to control the patient's congestive signs. In the authors' experience, furosemide and spironolactone, combined with conservative doses of hydrochlorothiazide, have palliated the congestive signs of many heart failure patients. However, this more aggressive diuretic management predisposes the patient to the development of electrolyte abnormalities and a reduction in cardiac output and the GFR unless care is taken to avoid overzealous volume contraction. Outpatients should be carefully and periodically evaluated through biochemical profiles to make sure that adverse effects are avoided.

Additional factors that can contribute to diuretic resistance include (1) poor cardiac output, which impairs delivery of the diuretic to its site of action; (2) prominent activation of the renin-angiotensin system; and (3) hypokalemia, which may impair the efficacy of the diuretic. If concern exists about diuretic resistance, care should be taken to optimize the ACE inhibitor dose, to correct electrolyte imbalances, and to combat low-output conditions.

199.6.4.3 Dietary Sodium Restriction

Historically, sodium restriction has been recommended for patients with cardiovascular disease to decrease the delivery of sodium to and its resorption in the distal tubule.[82] This recommendation was in place well before any of the current understanding of the renin-angiotensin system developed, and it therefore may need to be reevaluated.

It currently is recognized that reduced sodium concentrations at the macula densa serve as a stimulus for renin release and subsequent production of angiotensin. A study of Cavalier King Charles spaniels with mild asymptomatic mitral valve insufficiency showed that a low-sodium diet (17 mg/kg/day) was associated with higher plasma renin activity and aldosterone concentrations than a control diet (96 mg/kg/day).[83] In light of the concern that activation of neurohormonal pathways promotes the progressive nature of cardiovascular disease, the authors currently do not use sodium restriction in asymptomatic patients. Whether symptomatic patients receive clinical benefit from sodium restriction is uncertain, but one study found that dogs with mitral valve insufficiency that were fed a low-sodium diet (24 mg/kg/day) had significantly smaller left atrial and left ventricular dimensions than they did when fed a moderate-sodium diet (42 mg/kg/day).[84] Only a small number of dogs with dilated cardiomyopathy were enrolled in the study, but no significant differences in their echocardiographic parameters were seen between the two diets. Despite ACE inhibitor therapy, greater than 70% of the dogs enrolled in the study had increased baseline concentrations of ANP and increased plasma renin activity and aldosterone concentrations; however, the dietary modifications were not associated with significant alterations from baseline.[84]

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Whether exclusively feeding a low-sodium diet to patients with heart failure is feasible often hinges on the palatability of the diet and the willingness of the owner to abandon treats and table scraps. Although uncertain of its clinical benefit or potential detriment, the authors often recommend a low to moderate-sodium diet for patients with refractory heart failure. As evidenced by the study by Mallery et al.,[7] anorexia is a large contributing factor (68%) in the decision for euthanasia; therefore caution, education, and a willingness to abandon the regimen must accompany the prescription of a potentially less palatable, sodium-restricted diet.

199.6.5 Management of Heart Failure Secondary to Diastolic Dysfunction

199.6.5.1 Maintenance Therapy

After stabilization, furosemide is switched to oral administration and the dose is decreased (6.25 mg given twice daily) to prevent excessive preload reduction, dehydration, and hypokalemia. In cases of hypertrophic cardiomyopathy, additional drugs may be instituted to reduce the heart rate and improve diastolic filling. Drugs frequently used in the management of HCM include the beta blocker atenolol and the calcium channel blocker diltiazem. Calcium channel blockers theoretically can exert a beneficial effect in the management of HCM by modestly reducing the heart rate and contractility, thereby diminishing myocardial oxygen demand.

Diltiazem may promote a direct positive lusitropic effect, and verapamil may partially reduce coronary endothelial dysfunction compared with propranolol.[85,86] Atenolol (6.25 to 12.5 mg given orally every 12 to 24 hours) appears to exert better rate control and more consistently alleviates left ventricular outflow tract obstruction compared with diltiazem. Beta-adrenergic blockade may also prevent myocardial fibrosis by inhibiting catecholamine-induced cardiotoxicity and may combat ventricular arrhythmias by decreasing myocardial oxygen consumption. One theoretical disadvantage of the use of beta blockers in the management of diastolic dysfunction is that phospholamban is an inhibitory protein that controls the rate of diastolic calcium uptake into the sarcoplasmic reticulum. Beta-adrenergic stimulation phosphorylates phospholamban and removes this inhibitory effect. Beta blockade may prevent this phosphorylation (and therefore decrease diastolic calcium uptake) and further impair the active process of ventricular relaxation.

Similar to beta blockers, with their proposed neurohormonal benefits, ACE inhibitors likely are beneficial in the management of feline HCM. The authors have seen cats with symptomatic cardiomyopathy show marked neurohormonal activation.[87] With this finding, and with the frequent requirement for furosemide to control pulmonary edema, it appears prudent to use enalapril (1.25 to 2.5 mg given orally every 12 to 24 hours) in the management of diastolic dysfunction. Although there is concern that afterload reduction may precipitate dynamic left ventricular outflow tract obstruction, recent data suggest that ACE inhibitors can be used safely in cats with systolic anterior motion of the mitral valve.[88]

199.7 FUTURE PROSPECTS CURRENTLY UNDER INVESTIGATION

199.7.1 Medical Therapy

199.7.1.1 Search for a Safe Positive Inotropic Agent

A class of drugs currently receiving attention in the management of congestive heart failure is the calcium sensitizers. These agents can augment systolic performance by enhancing calcium binding to troponin C or by affecting the cross-bridge turnover kinetics without increasing cytosolic calcium levels.[89] A potential drawback to clinical use of pure calcium sensitizers would be the enhanced reactivity of troponin C with diastolic cytosolic calcium levels, which would slow the process of myocardial relaxation.[73] In an attempt to avoid this potential diastolic dysfunction, most of the agents under investigation today use a combination of phosphodiesterase (PDE) inhibition and calcium sensitization. Because these drugs produce both calcium sensitization and PDE inhibition, it becomes difficult to determine whether the positive inotropic action stems from enhanced reactivity of troponin C and Ca^{2+} or cAMP-mediated phosphorylation of phospho-proteins, or a combination of the two.

In an effort to elucidate the mechanisms of the positive inotropic effects of pimobendan, EMD 53998, levosimendan, and OR-1896, a group of investigators sought to determine whether these drugs were capable of increasing left ventricular contractility (+dP/dt) without altering the myoplasmic Ca^{2+} transient.[90] Each agent was administered at variable concentrations, and subsequently +dP/dt, myocardial calcium transients, phosphorylation of key intracellular phosphoproteins, and myocardial cAMP levels were measured. The investigators found that low concentrations of levosimendan and OR-1896 were capable of increasing left ventricular contractility without affecting Ca^{2+} transients or myocardial cAMP levels and without promoting significant phosphorylation of troponin I and C proteins.[90] Administration of low concentrations of pimobendan or EMD 53998 produced more pronounced increases in Ca^{2+} transients compared with

increases in left ventricular contractility. As the administration dose increased, all of the agents caused an increase in +dP/dt that was associated with further increases in myocardial cAMP levels and phosphorylation of intracellular phosphoproteins.[90] The investigators therefore concluded that pimobendan, EMD 53998, and higher doses of levosimendan and OR-1896 exerted positive inotropic properties through PDE inhibition–mediated responses rather than through calcium sensitization.[90] These researchers felt that their results lent support to the premise that low-dose levosimendan and OR-1896 were capable of augmenting left ventricular contractility by increasing the response of the myofilaments to the prevailing calcium concentrations.[90]

It should be noted that these conclusions are far from universally accepted. Other investigators, including Endoh,[73] have found that pimobendan can elicit a positive inotropic effect even in the presence of carbachol, a muscarinic receptor agonist that is useful for differentiating cAMP-mediated effects from those classified as calcium sensitization. Endoh's report[73] found that although levosimendan appears to have calcium-sensitizing properties, it must rely on simultaneous activation of cAMP-mediated signaling processes.[73]

The varying results of these studies show that the precise mechanisms by which the calcium sensitizers exert a positive inotropic effect is uncertain and that long-term controlled studies are required to evaluate the effects of these drugs on the heart rate, arrhythmogenesis, and sudden death.

199.7.1.1.1 Pimobendan

Despite its questionable calcium-sensitizing properties, pimobendan currently is the most investigated agent in this drug class. Similar to other agents in this class, pimobendan combines calcium sensitization and PDE inhibition to circumvent any diastolic dysfunction. However, this same property carries the potential for cAMP-dependent increases in arrhythmogenesis. Despite its predominantly cAMP-mediated inotropic effect, pimobendan can increase cardiac contractility to a degree similar to that of dobutamine but at a lower oxygen cost for contractility.[91] Although pimobendan appears to lower myocardial oxygen consumption, the stigma associated with positive inotropic agents, especially those that increase cAMP concentrations, may have doused early enthusiasm for pimobendan in the United States. Although not available in the United States, pimobendan currently is available in Canada, Europe, and Japan and has undergone several small to medium-sized investigations in humans and dogs.

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Multiple pimobendan trials have been completed in humans with heart failure.[74,92] The results of these trials have been variable, pointing out both apparent beneficial effects and questionable, undesirable side effects.

A recent placebo-controlled study has been published that evaluated pimobendan therapy (0.3 to 0.6 mg/kg/day) in a small number of Doberman pinschers and cocker spaniels with dilated cardiomyopathy.[93] The addition of pimobendan to standard therapy with digoxin, enalapril, and furosemide was associated with a significant improvement in the heart failure class. The cocker spaniels allocated to placebo and to pimobendan showed statistically similar median survival times (537 days versus 1037 days, $P = 0.77$), whereas the Doberman pinschers allocated to placebo had significantly shorter median survival times than those given pimobendan (50 days versus 329 days, $P < 0.02$).[93]

This small study highlighted several findings. The first interesting finding is that cocker spaniels with dilated cardiomyopathy appear to have the potential for long-term survival. At the conclusion of the

4-year study, six of the 10 cocker spaniels were still alive (two in the pimobendan group and four in the placebo group). Three of the four dogs that had died (one in the placebo group and two in the pimobendan group) were euthanized for noncardiac disease; the fourth dog, allocated to pimobendan, died suddenly within 1 month of diagnosis. The study was too small to allow assessment of the propensity of pimobendan to exacerbate arrhythmias, but the drug may have contributed to the cocker spaniel's sudden death.

Another interesting aspect of this study is that although positive inotropic therapy may prolong survival in Doberman pinschers with DCM, it may be prudent to randomize patients with atrial fibrillation (AF) separately from those without this condition. Historically Doberman pinschers with atrial fibrillation have had an abysmal 2.9-week median survival time.[4] The pimobendan randomization happened to allocate three Doberman pinschers with AF into the placebo group and only one into the pimobendan group. This may have negatively affected survival in the placebo group, but it should be noted that the Doberman with atrial fibrillation that was treated with pimobendan survived for 37 weeks.[93]

The observed reduction in heart failure class associated with pimobendan therapy likely will prompt further investigations into this agent. Whether pimobendan administration to dogs produces a trend toward increased mortality, as identified in the Pimobendan in Congestive Heart Failure (PICO) trial, is uncertain.[74] Whether the combination of low-dose pimobendan and a beta blocker would have synergistic properties in dogs with dilated cardiomyopathy is uncertain but is an interesting concept. The study by Mallery et al.[7] continues to pose the question of whether a small but significantly increased incidence of sudden death in dogs should preclude the availability of an agent with the potential to enhance their quality of life.

199.7.1.2 Angiotensin II Receptor Antagonists

The beneficial effects of ACE inhibitors have largely been attributed to these drugs' ability to decrease the formation of angiotensin II and increase circulating levels of bradykinin. However, alternative, ACE-independent pathways for the production of angiotensin II, including tissue plasminogen activator, cathepsin G, tonin, and chymase, may enable AT II "escape" even with administration of ACE inhibitors.[32] A study of patients treated with a variety of ACE inhibitors identified angiotensin II "reactivation" in 15% of patients.[29] This process occurred in the face of both high and low levels of ACE activity, which suggests that alternate pathways were responsible for the production of angiotensin II. As a potential strategy for offsetting these alternate angiotensin II–generating pathways, agents capable of directly antagonizing the AT II receptors were developed.

Two subtypes of angiotensin II receptors have been identified in humans: angiotensin II type 1 (AT_1) and angiotensin II type 2 (AT_2). Although these receptors belong to the same family, some researchers have suggested that their biologic activities differ markedly (Figure 199-12).[32] AT_1 receptors are found primarily in the adrenal glands, vascular smooth muscle cells, kidney, and heart, where they mediate almost exclusively all the known actions of angiotensin II on blood pressure and osmoregulation.[32] AT_2 receptors are expressed in high density during fetal development; in adults they are found less abundantly in the adrenal medulla, uterus, ovary, and vascular endothelium and in areas of the brain. AT_2 receptors appear to mediate biologic processes that counteract the trophic, AT_1-mediated responses.[32] Agents capable of blocking the AT_1 receptor subtype were developed with the aim of achieving more complete angiotensin II

antagonism than is obtained with ACE inhibitors. Also, selectively targeting the AT_1 receptor subtype would still allow for the potentially beneficial actions mediated by the AT_2 receptors and avoid common side effects, predominantly coughing, associated with ACE inhibitor therapy in humans. It is believed that the increased circulating levels of bradykinin promoted by ACE inhibitors contribute to these drugs' side effects, but it must be noted that this same property, which is lacking in AT II receptor antagonists, may contribute to the ACE inhibitors' success in the management of heart failure.

Efforts to determine whether ACE inhibitors or angiotensin II receptor antagonists were superior or noninferior quickly followed the development of the latter agents. An early study, the Evaluation of Losartan in the Elderly (ELITE) trial, lent support to the premise that ATII receptor blockade may yield mortality benefits compared with ACE inhibitors.[94] Other studies that examined various subgroups followed. Mortality and morbidity end-points were examined to determine whether AT II inhibitors are preferable to ACE inhibitors.[94–96]

The results of ELITE II and the Valsartan Heart Failure Trial (Val-HeFT) suggest better tolerability of AT II inhibitors compared with ACE inhibitors, but these studies provide no data to support the superiority of AT II inhibitors in the management of heart failure subsequent to systolic dysfunction. The proposed significant benefit behind combination therapy with AT II inhibitors and ACE inhibitors identified in Val-HeFT is limited after the ACE inhibitor–naïve subgroup is removed from the analysis.[97] Of additional concern was the fact that valsartan, compared to placebo, had an adverse effect on mortality (P = 0.009) in patients previously treated with ACE inhibitors and beta blockers.[96] Although these results cannot be extrapolated to veterinary medicine and because clinical trials have not been performed in dogs or cats with naturally occurring heart failure, the current utility of angiotensin II receptor antagonists appears limited.

199.7.1.3

Neutral Endopeptidase Inhibitors

With the success of the ACE inhibitors established, research interests quickly shifted to additional, potentially beneficial neurohormonal pathways. Based on the recognition that ANP can promote natriuresis and diuresis and can directly inhibit the release of renin and aldosterone, new agents were developed in an effort to increase ANP's circulating concentration. Neutral endopeptidase (NEP) is an enzyme that inactivates several substrates, including natriuretic peptides, angiotensins, and bradykinins.[98] It was hypothesized that drugs capable of inhibiting NEP may prove beneficial in the management of congestive heart failure as single agents or in combination therapy. Early studies of the NEP inhibitor ecadotril given to dogs with pacing-induced heart failure showed increased urine output, sodium clearance, and renal sodium excretion compared with dogs given placebo.[98] Another short-term study of ecadotril identified a dose and time-dependent reduction in left ventricular end-diastolic pressures in dogs with experimental heart failure produced by repeated coronary embolization.[99] Long-term administration of ecadotril (3 months) in dogs with left ventricular dysfunction produced by sequential intracoronary microembolizations was recently reported to attenuate left ventricular remodeling and progressive left ventricular dysfunction compared with dogs receiving placebo.[100]

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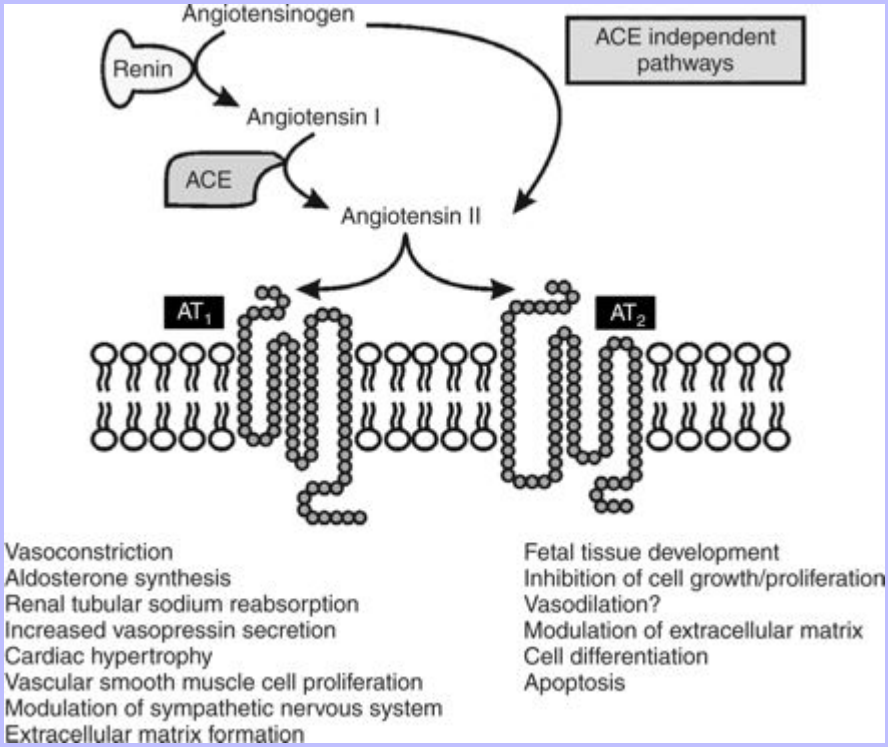
Figure 199-12 The formation of angiotensin II may follow ACE-dependent or ACE-independent pathways. Despite the potential for angiotensin II receptor blockers to promote more complete antagonism, current studies in humans have found them no better than traditional ACE inhibitors at combating heart failure.



Despite these findings, NEP inhibitors administered as single agents appear to have fallen out of the research arena. A communication on behalf of the International Ecadotril Multi-Centre Dose-Ranging Study reported findings from a study of 279 patients with chronic heart failure randomized to placebo or one of four doses of ecadotril.[101] The study's primary aim was to evaluate the safety and tolerability of ecadotril at doses of 50–400 mg twice daily. Two patients randomized to the highest dose of ecadotril developed pancytopenia at 47 and 53 days, and died rapidly of sepsis. The presence of a thioester group within the compound suggested an idiosyncratic ecadotril-induced aplastic anemia that was potentially dose related.[101] Lower doses of ecadotril were not associated with adverse reactions. Although the study was not powered to exclude symptomatic benefit, patient-reported symptoms and quality of life-scores were unable to reveal any overall symptomatic benefit during the administration of ecadotril.[101] A similar, smaller pilot study from the United States evaluating 50 patients randomized to placebo or ecadotril, 50 to 400 mg twice daily, did not identify any adverse sequela but again there were no changes identified in signs and symptoms of heart failure, NYHA class, or patient self-assessment of symptoms.[102]

199.7.1.4 Vasopeptidase Inhibitors

Although it is difficult to determine the reasons for the relative lack of efficacy seen in the small pilot studies of ecadotril, the problem may have been that the drug increased not only natriuretic peptide levels but also the levels of circulating angiotensin II. More recently a group of drugs that can inhibit NEP and ACE, the so-called *vasopeptidase inhibitors*, has been developed.

Omapatrilat has been the most rigorously evaluated vasopeptidase inhibitor in several trials for the management of congestive heart failure. No significant difference was seen in the primary end-point of combined risk of death or hospitalization for heart failure requiring intravenous treatment (P = 0.187) between omapatrilat and ACE inhibitors.[104] To date, the inability of vasopeptidase inhibitors to provide substantial benefit compared with the proven efficacy of ACE inhibitors may limit their clinical utility.

199.7.1.5 Endothelin Antagonists

Endothelin, a peptide released from endothelial cells, has powerful vasoconstrictive activity. Currently three peptides, endothelin-1, endothelin-2, and endothelin-3, and two receptor subtypes, ET_A and ET_B, have been identified. In principle, endothelin-1 promotes vasoconstriction by complexing with the ET_A receptor and vasodilatation by binding to the ET_B receptor, but this is somewhat species dependent. In addition to its vasodilative properties, the ET_B receptor may promote vasoconstriction in some regional blood vessels, including the mesenteric and coronary vasculature.[105]

Although endothelin's name suggests that it is produced only in vascular endothelial cells, the genes that encode the three peptides have been identified in varying patterns in vascular smooth muscle cells, cardiac myocytes, renal tubular epithelial cells, bronchial epithelial cells, glial cells, pituitary cells, macrophages, and mast cells.[105] Therefore the importance of endothelin may extend well beyond simple vasoconstriction and include additional pleiotropic effects on many nonvascular tissues. Although endothelin is suspected of being linked to systemic hypertension, pulmonary hypertension, vascular remodeling, and acute renal failure, the emphasis of this discussion is on potential applications of endothelin to the progression of heart failure.[105]

Heart failure, through increased filling pressures and decreased peripheral perfusion, promotes activation of numerous neurohormonal reflexes to maintain cardiac output and circulatory homeostasis. Activation of the RAS and SNS and the release of arginine vasopressin are recognized to increase the concentration of circulating vasoconstrictors (i.e., angiotensin II, norepinephrine, and vasopressin) and to promote maladaptive remodeling. Furthermore, it has been shown that these compensatory mechanisms enhance the production of endothelin.[105] Increased endothelin binding to the ET_A receptors promotes vasoconstriction and smooth muscle cell proliferation, thereby further diminishing cardiac performance through afterload mismatch. Studies have also shown that the ET_B receptors become upregulated and can promote vasoconstriction and cardiac fibrosis in the presence of heart failure.[106] These findings have raised the possibility of administration of ET_A receptor antagonists or a combination of ET_A/ET_B receptor antagonists to combat heart failure.

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Chronic administration of endothelin antagonists to laboratory animals with experimental heart failure and acute administration to humans with heart failure resulted in beneficial hemodynamic profiles. In rats with heart failure induced by coronary artery ligation, the combination of an ACE inhibitor and an endothelin

(ET_A) antagonist lowered the systolic blood pressure and the left ventricular end-systolic and left ventricular end-diastolic pressures significantly more than the ACE inhibitor or endothelin antagonist alone.[107] However, the drug combination did not significantly improve survival or reduce left ventricular weight and collagen density compared with rats randomized to an ACE inhibitor alone. Endothelin antagonism without the benefit of ACE inhibition did not result in a survival benefit compared with untreated rats with heart failure.

Despite these promising hemodynamic profiles, early evidence suggests that chronic nonselective and ET_A-selective antagonism of endothelin receptors is of limited benefit in patients with severe heart failure. The Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure (ENABLE) trial evaluated the nonselective endothelin antagonist bosentan, which has proved beneficial in pulmonary hypertension, for the management of humans with NYHA class IIIb-IV heart failure and an ejection fraction of less than 35%. The patients randomized to Bosentan appeared to have an increased early risk of worsening heart failure requiring hospitalization.[108]

These studies appear to highlight the fact that hemodynamic benefit may not equate with clinical benefit. Whether lower doses of the endothelin antagonists and slow uptitration might prove beneficial is unresolved at this time; however, the results of studies to date may have curtailed the momentum for the use of endothelin antagonists in the management of chronic heart failure.

199.7.2 Interventional Therapy

199.7.2.1 Passive Ventricular Constraint

In the early 1990s an experimental “ventricular assist” technique was developed in which a patient's native skeletal muscle was wrapped around the failing ventricles to provide cardiac support. The latissimus dorsi, connected to a synchronizable burst stimulator, was used in an effort to increase cardiac contractility and hence functional status.[110] The utility of dynamic cardiomyoplasty held promise because it alleviated the need for cardiac bypass, donor organs, and immunosuppression, which are required for cardiac transplantation. The feasibility of dynamic cardiomyoplasty in dogs was subsequently documented, and researchers found a potential for improved contractile function even during contractions that were not assisted by myostimulation of the latissimus dorsi.[111]

Although dynamic cardiomyoplasty has failed to gain prominence in the management of heart failure, the potential for limiting ventricular dilatation by means of passive constraint has prompted further study. The premise is that passive ventricular constraint may significantly slow or stabilize the remodeling process that accompanies heart failure. Because the constraint is passive and does not require myostimulation, a synthetic wrap could be used, simplifying the surgical procedure.[112,113]

Despite the potential benefit of passive ventricular constraint in these models, the fact remains that veterinary patients tend to be presented for evaluation after severe cardiac dysfunction has already developed. New diagnostic modalities may allow for earlier detection of occult cardiac disease, but the variable nature of disease progression could still complicate the determination of which patients should be fitted with a cardiac support device. At this time, further studies are required to evaluate the efficacy of passive ventricular constraint in severe cardiac dysfunction, and diagnostic tests allowing early detection of cardiac disease must be developed.

199.7.2.2 Ventricular Resynchronization

Although systolic dysfunction classically is believed to be a myocardial phenomenon, the important role the cardiac conduction system plays in maintaining optimal cardiac performance is often forgotten. The normal conduction pathway modulates the contraction rate, the mechanical efficacy of atrial systole, and the co-ordination of the ventricular chambers.[114] In humans the presence of an intraventricular conduction delay, typically in a left bundle branch block pattern, promotes disco-ordinate contraction, with early activation of the septal wall followed by delayed lateral contraction at higher stress.[114] The presence of this conduction defect has been associated with a 60% to 70% higher risk of all-cause mortality and has remained an independent risk factor after adjustment for age, underlying cardiac disease, severity of heart failure, and treatment with ACE inhibitors or beta blockers.[115] The problem of ventricular discordance has long been recognized in patients with artificial ventricular pacemakers, and efforts to approximate the ventricular activation sequence more closely (i.e., by pacing the right ventricular outflow tract rather than the apex) have been shown to increase cardiac output.[116–118]

Recently a similar approach, called *cardiac resynchronization therapy* (*CRT*), has been used in patients with congestive heart failure and intraventricular conduction delay. Biventricular pacing or univentricular pacing of the left ventricular free wall has improved the contractile index $+dP/dT_{max}$ and arterial pulse pressure within a single beat of commencement of pacing.[114] The proposed benefits of CRT include a reduction in end-systolic and end-diastolic volumes and the ability to promote reverse remodeling. Ventricular resynchronization has been associated with increased systolic function despite a decline in myocardial oxygen consumption.[114] This contrasts with traditional cAMP-dependent inotropic therapy and may explain the ability of biventricular pacing to improve functional patient status while promoting mortality benefits. Unfortunately, the ability of CRT to improve heart failure class and reduce mortality in veterinary medicine may be limited by the low prevalence of intraventricular conduction disturbances in dogs with dilated cardiomyopathy.

199.7.2.3 Stem Cells and Cellular Transplantation

Historically it has been recognized that cardiac and neural tissues lack the large postnatal regenerative capacity seen in the epithelial layers of the skin, intestinal and pulmonary mucosal linings, and connective tissues. Therefore the ability to repopulate areas of ischemic myocardium with cells capable of promoting angiogenesis or areas of fibrosis with cells that contribute to contractile function could prove curative.

Numerous cell types have been identified that may serve as potential sources for tissue grafting, including skeletal myoblasts, fetal cardiomyocytes, smooth muscle cells, embryonic stem cells and bone marrow–derived stromal and hematopoietic stem cells.[120] Because of the complex electrophysiologic, structural, and contractile properties of myocardial cells, cardiomyocytes appear to be the ideal donor cells. The difficulty lies in harvesting and transplanting enough cells to mitigate the degree of cardiac dysfunction. The isolation of pluripotent stem cells from mouse blastocysts in 1981 may have provided the key to an endless vault of viable, transplantable cardiomyocytes.[120]

The promise of stem cells lies in their capacity for prolonged self-renewal and their potential to differentiate into one or more cell types. Embryonic stem (ES) cells display wide-ranging plasticity, which allows them to form derivatives of all three germ layers. Their ability to undergo near endless cell doublings while retaining

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the capacity to differentiate into various cell types further advances their therapeutic potential. However, beyond the ethical considerations involved in the use of human embryonic stem cells (which veterinary practitioners may not face), many other hurdles must be overcome. One of the most important obstacles is defining a methodology to generate reproducible, spontaneous cardiomyocyte-differentiating stem cells with sufficient purity for clinical purposes.[120] Emerging evidence suggests that an unknown combination of growth factors, transcription factors, feeder layers, and physical properties is involved in early cardiomyocyte differentiation.[120] Delivery systems such as intracoronary catheterization techniques, intramyocardial injection, transendocardial delivery by means of catheter-based systems, and intravenous administration are currently being evaluated and refined to optimize the long-term survival of the grafted cells, to ensure the delivery of a critical mass of viable cells, and to promote the appropriate alignment with the host cells.[120] These steps are vital to the functional and structural integration of stem cells in the host tissue.[120] The immunogenicity of embryonic stem cells poses yet another challenge.

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Stem cells are not confined to embryos; rather, small numbers of stem cells can be harvested from adult bone marrow. These adult mesenchymal stem (MS) cells maintain an undifferentiated phenotype in culture and appear to have the capacity for multilineage differentiation.[121] The potential benefits of autologous adult MS cells, including ease of attainability, lack of immunogenicity, and absence of ethical objections, have prompted widespread research into their use in the management of cardiovascular disease. It remains to be seen whether repopulation of the myocardium with these cells is feasible in veterinary medicine and whether a sufficient number of viable cells to enhance systolic function can be delivered.

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200 CHAPTER • 200 Congenital Heart Disease

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200.1 DEFINITION

The term *congenital heart disease* includes morphologic and functional abnormalities of the heart and adjacent great vessels that are present at birth. These abnormalities are defined as congenital even if they are not discovered until much later in life. Congenital heart disease arises from altered or arrested embryonic development of the rudimentary heart. The eventual consequences of such a failure can include gross anatomic alterations and/or inability of the heart to perform its normal functions of maintaining normal venous and arterial pressures and providing adequate perfusion of the tissues with oxygenated blood.

200.2 CLINICAL APPROACH TO CONGENITAL HEART DISEASE

Malformations of the heart and great vessels constitute a relatively small but clinically important percentage of cardiovascular disorders in dogs and cats.[1a,14a*] The types of defects, pathogenesis, and etiology of disease that afflict animals and humans are remarkably similar, and most of the diagnostic and therapeutic methods used in veterinary cardiology have been adapted from those used in the management of children and adults with congenital heart disease. Although absolute diagnosis and evaluation of congenital heart disease may require echocardiography or cardiac catheterization, a complete physical examination, electrocardiography, and chest radiographs provide a wealth of information that can be used to make a provisional diagnosis and to guide the formulation of an appropriate treatment plan. To this end, every veterinarian should be familiar with the most common congenital diseases and should be able to counsel owners regarding the prognosis, the treatment options, and the impact on breeding programs.

* References with a superscript (a) correspond to the reference from the third edition with the same number; those with a superscript (b) correspond to the reference from the fourth edition with the same number; and those with a superscript (c) correspond to the reference from the fifth edition with the same number.

200.3 HISTORY AND PHYSICAL EXAMINATION

The diagnostic approach for animals with congenital heart disease is similar to that used to evaluate animals with acquired disease. In this regard, the evaluation should always include a careful history and complete physical examination. When assembling the history, the clinician should take care to note the breed of the patient, because many congenital diseases have a suspected or proven genetic basis, and most have breed predilections. Whenever possible, the health records of the sire, dam, and any siblings should be reviewed. Additional testing (e.g., electrocardiography, radiography, and echocardiography) usually is advisable, depending on the client's expectations, the nature and severity of the disease, and the medical or surgical treatment options available.

200.3.1 History

The breed and age should always be considered in the evaluation of animals suspected of having congenital heart disease. Table 200-1 shows the breed predilections reported for canine cardiac defects in North America and Europe.[1c-6c] These associations support the suspected genetic basis of many malformations. Gender predispositions to congenital heart disease are weak or poorly established in dogs except for the higher prevalence of patent ductus arteriosus in females.[1a,4a,8a] In cats, Siamese, Burmese, and Asian shorthair breeds may be predisposed to some defects, and male kittens seem to be affected more often than females.[2c,36a]

Consideration of gender predilection, however, has little influence on the evaluation of individual patients. Age may be an important factor in the interpretation of the results of initial examinations. Most defects are detectable shortly after birth, but the severity of the hemodynamic abnormalities may change significantly during the first 6 to 12 months of life. For example, the lesion of congenital subaortic stenosis may not be present at birth, but it can develop during the first 2 months of life and can increase in severity during the first year of life.[2a,9a] Similarly, the consequences of left-to-right shunting defects may not be fully manifested until pulmonary vascular resistance and right heart pressures decrease to the low levels of a normal adult, several weeks after birth. Some defects appear to be severe in the very young but have relatively modest consequences in adulthood.

Table • 200-1 Canine Breed Predilections for Congenital Heart Disease

BREED	DEFECTS
Basset hound	PS
Beagle	PS
Bichon fries	PDA
Boxer	SAS, PS, ASD
Boykin spaniel	PS
Bull terrier	MVD, AS
Chihuahua	PDA, PS
Chow chow	PS, CTD
Cocker spaniel	PDA, PS
Collie	PDA
Doberman pinscher	ASD
English bulldog	PS, VSD, TOF
English springer spaniel	PDA, VSD
German shepherd	SAS, PDA, TVD, MVD
German shorthair pointer	SAS
Golden retriever	SAS, TVD, MVD
Great Dane	TVD, MVD, SAS
Keeshond	TOF, PDA
Labrador retriever	TVD, PDA, PS
Maltese	PDA
Mastiff	PS, MVD
Newfoundland	SAS, MVD, PS
Pomeranian	PDA
Poodle	PDA
Rottweiler	SAS
Samoyed	PS, SAS, ASD
Schnauzer	PS
Shetland sheepdog	PDA
Terrier breeds	PS
Weimaraner	TVD, PPDH
Welsh corgi	PDA
West Highland white terrier	PS, VSD
Yorkshire terrier	PDA

AS, Aortic stenosis; *ASD,* atrial septal defect; *CTD,* cor triatriatum dexter; *MVD,* mitral valve dysplasia; *PDA,* patent ductus arteriosus; *PPDH,* peritoneopericardial diaphragmatic hernia; *PS,* pulmonic stenosis; *SAS,* subaortic stenosis; *TOF,* tetralogy of Fallot; *TVD,* tricuspid valve dysplasia; *VSD,* ventral septal defect.

Most animals with congenital heart defects are asymptomatic when first examined; these patients are recognized when a heart murmur is detected during a routine examination. Dogs and cats with hemodynamically severe regurgitant, obstructive, or shunting defects may appear completely normal to the owner during the first 6 to 12 months of life, therefore it should not necessarily be concluded from an unremarkable history that the underlying defect is mild. For instance, dogs with severe subaortic stenosis may not demonstrate any clinical signs prior to sudden and unexpected death. Similarly, young animals with patent ductus arteriosus and imminent cardiac failure often appear normal to the owner until pulmonary edema becomes life-threatening and causes dyspnea. Additional clinical signs that may develop with severe defects include failure to grow at a normal rate or to a normal size, exertional fatigue, abdominal distention (ascites), episodic weakness or syncope, or cyanosis.

200.3.2 Physical Examination

The ability to detect and decipher heart murmurs and abnormal transient heart sounds is an invaluable skill that cannot be overemphasized in the evaluation of patients with congenital heart disease. The typical characteristics of the heart murmurs associated with the most common congenital defects are listed in Table 200-2. Descriptions of the acoustic properties of the various murmurs and an algorithm for differentiating their causes are presented in Chapter 55. When a heart murmur is first detected, the examiner must determine whether it is pathologic or innocent, because normal puppies and kittens often have benign heart murmurs. Innocent murmurs are usually of low intensity (grade I-II/VI), protosystolic or midsystolic in timing, and best heard at the left heart base. They often vary in intensity according to changes in the heart rate or body position. Innocent murmurs usually but not invariably diminish or resolve by 6 months of age; however, soft systolic innocent murmurs can persist well into adulthood, especially in large-breed dogs.

Cardiac murmurs caused by congenital disease are typically louder (grade III-VI/VI) and of longer duration than innocent murmurs, often obscuring the normal heart sounds. Murmurs of this description are unlikely to be innocent, and additional diagnostics are warranted; however, the examiner is cautioned not to correlate the intensity of the murmur with the severity of the suspected underlying defect. The murmur associated with patent ductus arteriosus or a small ventral septal defect is often very intense, even when the volume of the shunted blood is relatively modest. The murmurs of some lesions, notably atrial septal defects and mild subvalvular aortic stenosis, are easily misinterpreted as innocent. In animals with large septal defects, including severe atrioventricular valve dysplasia and some forms of serious cyanotic heart disease, the heart murmur may be soft or even inaudible. Although a cardiac murmur of any grade indicates the possibility of congenital heart disease, common sense, guided by the patient's clinical circumstances and the owner's wishes, should dictate the vigor of the diagnostic evaluation.

Abnormalities of the arterial pulse, mucous membranes, jugular veins, or precordial impulse may support a suspicion of congenital heart disease. Hyperkinetic and bounding (“waterhammer”) arterial pulses are characteristic of lesions that cause abnormal diastolic runoff of aortic blood and low arterial diastolic pressure, such as patent ductus arteriosus or severe aortic regurgitation. Hypokinetic pulses are typical of moderate to severe left ventricular outflow obstruction (i.e., subaortic stenosis) or of other severe defects accompanied by low left ventricular output. Visible cyanosis develops when the partial pressure of arterial oxygen falls below 45 mm Hg and reduced (unoxygenated) arterial hemoglobin reaches 5 g/dL. Cyanosis in animals with congenital heart disease is usually caused by a systemic to pulmonary (right-to-left) shunt at the level of the heart or great vessels. Distended jugular veins indicate elevated central venous pressure, which is usually caused by an abnormality of the right side of the heart, such as tricuspid valve dysplasia or pulmonic stenosis. A precordial impulse of increased strength or area often indicates enlargement of the underlying ventricle or ventricles. The presence of a precordial thrill defines the most intense cardiac murmurs (grade V-VI/VI). The focus of this vibration is synonymous with the point of maximal acoustical intensity and is characteristic of the associated underlying defect.

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Table • 200-2 Auscultatory Findings in Congenital Heart Disease

LESION	TIMING	FEATURES	POINT OF MAXIMUM INTENSITY	COMMENTS
Atrial septal defect	Systolic (diastolic)	Ejection (diastolic rumble)	Left base	Systolic murmur ends prior to S_2, which is usually split; murmur (or murmurs) due to relative pulmonic (tricuspid) stenosis
(Sub)aortic stenosis	Systolic*	Ejection (crescendo-decrescendo)	Left base	Often nearly as loud at the right base; diastolic murmur of aortic regurgitation may also occur
Mitral valve dysplasia†	Systolic	Regurgitant (holosystolic)	Left apex	May radiate widely
Patent ductus arteriosus	Continuous	Machinery	Left base	Murmur peaks at S_2, often radiates to right base and thoracic inlet
Pulmonary hypertension (Eisenmenger's syndrome)	None (systolic)	Split S_2 (ejection)	Left base	Accentuated and split S_2; systolic murmur of tricuspid regurgitation or blowing, decrescendo diastolic murmur of pulmonic regurgitation may also occur
Pulmonic stenosis	Systolic	Ejection (crescendo-decrescendo)	Left base	Occasional systolic ejection sound; blowing, decrescendo diastolic murmur of pulmonic regurgitation may occur
Tetralogy of Fallot	Systolic	Ejection (crescendo-decrescendo)	Left base	Murmur due to pulmonic stenosis; may be soft or absent with pulmonary artery hypoplasia
Tricuspid valve dysplasia†	Systolic	Regurgitant (holosystolic)	Right midprecordium	Often low pitched and rumbling
Ventricular septal defect	Systolic*	Regurgitant (holosystolic)	Right base	Often higher pitched and more cranially located than tricuspid regurgitation; may also be loud at left base

PMI, Point of maximum intensity.

* At time a diastolic murmur of aortic regurgitation may also be present.

† Mitral stenosis and tricuspid stenosis are rare but may cause diastolic murmurs over the affected valve and ventricle.

200.4 LABORATORY TESTS

Even though a strong clinical suspicion of congenital heart disease may arise based on the history and physical examination, definitive diagnosis of an animal with a cardiac murmur usually requires additional studies. In this regard, an electrocardiogram, thoracic radiographs, and echocardiography are usually required. The results of these studies often dictate the performance of subsequent diagnostic procedures, such as blood gas determinations, cardiac catheterization, and angiography. Distinctive laboratory abnormalities may occur in animals with cyanotic heart disease (i.e., tetralogy of Fallot, reversed patent ductus arteriosus) and may include

arterial hypoxemia, hypocarbia, metabolic acidosis, and erythrocytosis. However, in most cases hematologic testing is not an important part of the evaluation for congenital heart disease. Although serum biochemical test results may be abnormal in the presence of congestive heart failure or concurrent organ disease, the biochemical profile and urinalysis results typically are normal.

200.5 ELECTROCARDIOGRAPHY

In most animals with congenital heart disease, an electrocardiogram (ECG) can provide helpful information, mainly through its ability to detect cardiac chamber enlargement. Although a normal ECG does not rule out heart disease, an abnormal ECG indicating left-or right-sided enlargement in a young animal can strongly suggest a short list of likely cardiac defects. For instance, an ECG indicating a rightward shift in the mean electrical axis and right ventricular hypertrophy immediately suggests the possibilities of pulmonic stenosis, tetralogy of Fallot, or tricuspid valve dysplasia. Such an ECG would be rare in dogs with predominantly left-sided disease, such as mitral dysplasia or subaortic stenosis. Conduction delay with right mean electrical axis deviation and widening of the QRS complex (partial or complete right bundle branch block) can indicate pronounced right ventricular enlargement, congenital right bundle branch block, or the presence of both abnormalities. An ECG should be recorded whenever a rhythm disorder is suspected. Serious congenital heart defects often result in cardiac arrhythmias, some of which require specific treatment or some modification of diagnostic or therapeutic plans. Supraventricular arrhythmias, such as atrial tachycardia and atrial fibrillation, are prone to occur in animals with congenital defects that cause marked atrial enlargement, such as mitral or tricuspid valve dysplasia. Ventricular arrhythmias are common in disorders resulting in arterial hypoxemia, extreme hypertrophy of the ventricular myocardium, or reduced myocardial perfusion. Relevant examples include pups with tetralogy of Fallot or subvalvular aortic stenosis. Rhythm disorders with a genetic basis are being recognized with increasing frequency in juvenile and adult cats and dogs (see Chapter 202).

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200.6 CARDIAC IMAGING

200.6.1 Radiography

Radiographs of the thorax assist in the determination of cardiac size, identification of chamber or great vessel enlargement, assessment of the pulmonary circulation, and detection of congestive heart failure. Much of radiographic interpretation is subjective in nature, and distinguishing left heart, right heart, or bilateral enlargement in young animals is relatively difficult.[1] There is a general tendency to overinterpret the size of the right heart in neonates because of normal right ventricular prominence. This can lead to the erroneous diagnosis of pulmonic stenosis in a young animal with an innocent heart murmur. Further confusing the examiner, the ventricular apex can be shifted rightward on the dorsoventral or ventrodorsal view, contributing to the illusion of right heart enlargement in a normal animal. Despite these pitfalls, thoracic radiographs provide a reasonably sensitive and specific indication of heart size and the severity of disease, especially when the underlying disease is one of volume overload (i.e., patent ductus arteriosus, tricuspid dysplasia). This is not the case for congenital diseases characterized by pressure overload (i.e., pulmonic stenosis, subvalvular aortic stenosis), in which concentric hypertrophy is better appreciated with echocardiography. Measurement of the radiographic cardiac silhouette, using a vertebral heart scoring system similar to that used in adult dogs, provides objective criteria for the interpretation of heart size. In one study, using the lateral radiographic projection, the sum of the long and short axis cardiac dimensions averaged 10 ± 0.5 vertebrae (as measured caudally from the fourth thoracic vertebra) in healthy 3-month-old pups and did not change significantly as the dogs reached 6, 12, and 36 months of age.[2]

Inspection of the great vessels often provides additional information about the underlying cardiac defect. Aneurysmal dilatation of the proximal ascending aorta is typical for subvalvular aortic stenosis and aortic insufficiency, whereas dilatation of the proximal descending aorta is typical of patent ductus arteriosus. Dilatation of the main pulmonary artery can develop as a consequence of pulmonic stenosis or insufficiency, increased pulmonary blood flow caused by a left-to-right shunt, or pulmonary hypertension. Assessment of the size and symmetry of more peripheral pulmonary arteries and veins can help identify pulmonary overcirculation or undercirculation, as well as pulmonary venous congestion. Left-to-right shunts potentiate pulmonary blood flow, increasing the number, diameter, and prominence of the pulmonary arteries and veins, whereas right-to-left shunts reduce pulmonary flow, resulting in diminished prominence and reduced diameters of the pulmonary arteries and veins. Animals with decompensated or impending congestive heart failure may show selective widening of the caudal vena cava (right heart failure) or pulmonary veins (left heart failure). The typical radiographic findings of the common congenital heart defects are specifically addressed in their respective sections of this chapter.

200.6.2 Echocardiography

Echocardiography is an extremely powerful noninvasive diagnostic tool and has reduced the need for invasive cardiac catheterization and angiography to establish a definitive diagnosis of congenital heart disease. The various congenital heart diseases exert excessive pressure or volume loads (or both) on specific chambers of the heart, resulting in concentric or eccentric hypertrophy, respectively (or both). These patterns of hypertrophy can be easily recognized and quantified by two-dimensional and M-mode echocardiography.[3] Doppler echocardiography can be used to examine cardiac blood flow, which is often disturbed by the presence of congenital disease.[3] By relying on the shift of ultrasound frequencies reflected by moving objects (e.g., red blood cells), Doppler ultrasound allows the examiner to measure the velocity and direction of blood flow and to distinguish turbulent from laminar flow. Doppler ultrasound information can be viewed as a spectral display or can be superimposed on two-dimensional images as a color flow map. Spectral Doppler is used primarily to quantify the velocity of blood flow. An electronic cursor is positioned parallel to the direction of flow, and the resulting Doppler study displays blood flow velocity in a graphic format. Blood flow toward or away from the transducer location is displayed above and below the baseline, respectively. Maximal velocity of flow is measured from the peak of the Doppler signal and can be converted to units of pressure (mm Hg) using the modified Bernoulli equation:

$$\text{Pressure gradient between two cardiac chambers (mm Hg)} = 4 \times \text{Maximal velocity (m/s)}^2$$

The Bernoulli equation allows the examiner to estimate the hydrostatic (blood) pressure difference between individual cardiac chambers. This information is particularly important for quantifying the severity of disease with obstructive lesions (e.g., subaortic stenosis). As the severity of a lesion worsens, pressure in the ventricle increases to produce the required cardiac output. This increase in pressure translates into a higher blood flow velocity across the area of obstruction. Proper alignment of the cursor with respect to the direction of flow is crucial to the accuracy of spectral Doppler studies. The cursor must be positioned within 20 degrees of parallel along the main direction of blood flow to ensure accurate measurements.[4]

Range-gated or *pulsed wave Doppler* allows interrogation of blood cell velocities in specific locations by having the operator direct a depth-range "gate" (which is superimposed over a two-dimensional image) to the region of interest. This mode provides accurate information about the exact anatomic site of the abnormal flow and the relative direction of flow. It is limited to the measurement of relatively low velocities because of a sampling phenomenon called *aliasing* (related mainly to the sampling rate), in which velocities greater than a

known limit (the *Nyquist limit*) appear to reverse direction and cause an ambiguous display. *Continuous wave Doppler* uses two crystals (a constant transmitter and a constant receiver) to achieve very high sampling rates and to allow recording and measurement of very high velocities along the directed ultrasound beam. The velocities of all cells along the beam line are recorded and displayed, a technique that allows the high flow velocities across stenotic or insufficient valves to be displayed and measured but prevents precise localization of the abnormal flow. Pulsed wave and continuous wave Doppler are therefore complementary; the pulsed wave mode is used to identify and localize a lesion, and the continuous wave mode is used to measure any high velocities.

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Color flow Doppler images consist of range-gaited, color-encoded velocity data that are superimposed on two-dimensional images. Laminar flow toward or away from the transducer is displayed as red or blue, respectively, with lighter hues of each color representing higher velocities. Turbulent flow is often displayed as a mosaic pattern of green, light blue, or yellow, but different color patterns can be selected by the user as a matter of personal preference. Color flow Doppler is conveniently used to identify and localize areas of high velocity and turbulent blood flow, which allows the operator to survey the heart quickly and identify regional flow disturbances. When areas of high velocity or turbulent flow are discovered, the examiner can focus attention on the two-dimensional anatomy of that region and perform more detailed, quantitative Doppler interrogations of blood flow in that area.

Echocardiographic contrast agents, composed of highly reflective air-agitated saline or other gas-containing microbubbles, can be used to enhance Doppler studies by amplifying weak signals from small jets that are otherwise difficult to interrogate. When Doppler technology is not available, contrast agents are used as sonographic targets to improve the detection of shunting lesions (especially right-to-left shunts) and other cardiac defects. Contrast echocardiography is a useful tool when Doppler technology is not available, and it can also enhance Doppler studies.

Experienced examiners have found that evaluation of patients suspected of having congenital disease is facilitated if the echocardiographic study is performed in a stepwise fashion, with particular attention paid to the pattern of cardiac hypertrophy, the identification and quantification of high-velocity and turbulent blood flow, and the detection of anatomic lesions particular to each type of congenital disease.[3]

200.7 OTHER IMAGING MODALITIES

Single-pass or blood pool radionuclide scanning studies can also be used to detect and quantify congenital shunts, but such methods are generally limited to university teaching hospitals. Computed tomography (CT) and magnetic resonance imaging (MRI) offer particular advantages in the evaluation of specific congenital heart diseases. MRI, for example, is an effective method of evaluating the aortic arch and related vascular anomalies in humans. However, because of their expense and limited availability to veterinarians, these modalities are infrequently used to evaluate animals with congenital heart disease.

200.8 CARDIAC CATHETERIZATION AND ANGIOGRAPHY

Cardiac catheterization is an invasive hemodynamic and angiographic procedure performed for diagnostic or therapeutic reasons. Prior to the widespread use of echocardiography, cardiac catheterization was considered the gold standard for diagnosis and evaluation of congenital heart disease. Much of the anatomic and hemodynamic information gathered during cardiac catheterization can now be obtained noninvasively with two-dimensional and Doppler echocardiography. For this reason, cardiac catheterization is reserved mainly for attempts to repair certain congenital defects (e.g., balloon valvuloplasty for pulmonic stenosis and device occlusion of patent

ductus arteriosus) or to clarify ambiguous anatomic lesions when surgery is contemplated. In selected cases, diagnostic cardiac catheterization is warranted to verify pressure estimates derived from Doppler echocardiographic studies, to collect blood for oximetry, to measure cardiac output, or to examine structures not accessible to echocardiographic interrogation, such as the peripheral pulmonary or systemic vasculature.

200.8.1 Hemodynamic Measurements

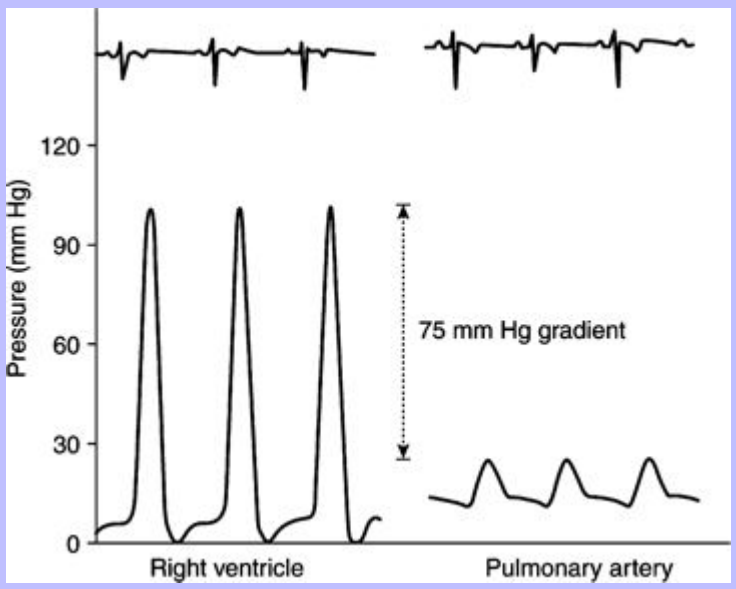
For selective catheterization of the heart, the operator introduces specially designed catheters into a peripheral vessel and guides them into specific cardiac chambers or great vessels to measure intracardiac and vascular pressures, cardiac output, and oxygen content (oximetry). Such studies are performed before angiographic imaging, because all radiopaque contrast agents can alter vascular tone and cardiac performance. Vascular and intra-cardiac pressures are measured either by attaching the proximal end of fluid-filled catheters to a pressure-sensing transducer or by using specially designed catheters with microtransducers incorporated into the distal end. Pressures are displayed and saved with a digital or an analog physiologic recorder.

The peak systolic pressure in the left ventricle and aorta is approximately four times that in the right ventricle and pulmonary artery. Because the systemic and pulmonary circulations are connected in series and cardiac output from the left and right ventricles is balanced, it can be appreciated that pulmonary vascular resistance is much lower than systemic vascular resistance. Blood flowing through the heart moves from areas of high to low resistance and therefore from areas of high to low pressure. For instance, left ventricular systole produces a small, instantaneous pressure gradient between the left ventricle and the aorta, causing opening of the aortic valve and commencement of left ventricular outflow. It is important to note, however, that once the aortic valve is open, the pressures in the ventricle and aorta quickly equalize. In contrast, a pressure gradient during systole is maintained between the left ventricle and left atrium because of the intervening and closed mitral valve. Should the aortic valve not open completely, pressure between the left ventricle and the aorta does not equalize, and a pressure gradient (increased pressure proximal to the obstruction, relative to the pressure distal to the obstruction) is maintained during the entirety of systole. This pressure gradient is needed to maintain normal flow through the stenotic aortic valve. Thus an intracardiac pressure gradient is indicative of an obstructive lesion, and its severity correlates with the magnitude of the obstruction. A systolic pressure gradient between the right ventricle and main pulmonary artery, consistent with pulmonic stenosis, is shown in Figure 200-1. Pressure, resistance, and flow (cardiac output) are interrelated so that the magnitude of a pressure gradient across obstruction varies with flow; it can be diminished by heart failure, anesthesia, or hypovolemia and can be increased by exercise, anemia, or excitement. The configuration of the pressure waveforms is also altered in predictable ways by congenital heart defects. In dogs with severe subvalvular aortic stenosis, the slope of the aortic pressure rise and the peak systolic pressure are decreased. In cases of patent ductus arteriosus, diastolic runoff of aortic blood into the pulmonary artery reduces the systemic diastolic pressure, and the pulse pressure (the difference between the peak systolic and diastolic pressures) increases.

Elevation of end-diastolic pressure is a subtle but important abnormality that can be identified by a ventricular pressure recording. This important abnormality may be caused by volume overloading from regurgitant valvular lesions or left-to-right shunts, by increased diastolic ventricular stiffness associated with ventricular concentric hypertrophy or myocardial fibrosis, or by pericardial disease. Substantial increases in ventricular end-diastolic pressures (i.e., greater than 15 to 20 mm Hg) herald the development of overt congestive heart failure (i.e., edema, effusion, ascites). Pressures in the right atrium (measured directly) and left atrium (estimated by measuring pulmonary wedge pressure) increase as an unavoidable consequence of high ventricular end-diastolic pressure. Stenosis of the atrio-ventricular (AV) valves is characterized by elevated atrial and normal ventricular diastolic pressure, which produces a measurable diastolic pressure gradient

across the affected valve. Transmission of ventricular systolic pressure to the atria across an incompetent AV valve results in ventricularization of the atrial pressure tracing and elevated mean atrial pressure.

Figure 200-1 Intracardiac pressure tracing from a 1-year-old mixed breed dog made during catheterization of the right heart and pulmonary artery. The pulmonary artery pressures are normal. A systolic pressure gradient of 75 mm Hg exists between the right ventricle and pulmonary artery, indicating the presence of an obstruction to right ventricular outflow (in this case, valvular pulmonic stenosis). A small diastolic pressure gradient also exists between the pulmonary artery and right ventricle; this is caused by diastolic closure of the pulmonic valve and is a normal finding. The ECG displays a deep S wave, which is often found in animals with pulmonic stenosis and secondary right ventricular hypertrophy.



Flow through the heart (cardiac output) can be measured by means of cardiac catheterization using a variety of indicator-dilution techniques or by combining measurements of the oxygen content of arterial and mixed-venous blood (oximetry) and oxygen consumption in respiratory gases. The most commonly performed technique, thermodilution, involves injection of an indicator (temperature, in the form of cold saline solution) and subsequent downstream measurement of its dilution over time (the change in the temperature of the blood). Cardiac output measurements are used to quantify cardiac performance, to calculate the pulmonary or systemic vascular resistance (R = Pressure/Flow), and to help define the severity of obstructing lesions. *Oximetry*, the measurement of blood oxygen content or saturation, is used mainly to detect and quantify cardiac shunts. Blood samples are sequentially drawn from the great vessels and right and left cardiac chambers and processed through a blood gas analyzer. The oxygen content in chambers and vessels on the

ipsilateral sides of the heart should be roughly equivalent. A substantial change in oxygen content indicates mixing of blood from the two sides of the heart and the presence of a shunt. For instance, when oxygen saturations are recorded from the right atrium, ventricle, and pulmonary artery, a significant increase between chambers (usually greater than 5%) indicates the presence of a left-to-right shunt just proximal to the site of the step-up. Conversely, when oxygen saturations are recorded from the left side of the heart, a significant decrease indicates the presence of a right-to-left shunt. The magnitude of change in oxygen saturation directly correlates with the degree of cardiac shunting, and the severity of the shunt lesion can be calculated.

200.8.2 Angiography

For selective angiographic studies of animals with congenital heart disease, a bolus of radiopaque contrast solution is injected into a specific location in the heart or vessels, and its transit through the circulation is visualized by fluoroscopy. This allows identification of any anatomic abnormalities and alterations in the normal pattern of blood flow. Multiple injection sites are often used to define a lesion completely. In some instances angiograms are performed with the patient in both lateral and sternal or dorsal recumbence to provide images from multiple orientations. For shunts and obstructive lesions, contrast is injected into the chamber just proximal to (upstream from) the site of the suspected defect, whereas for valvular insufficiency lesions, the contrast is injected into the chamber just distal to (downstream from) the lesion. Commonly performed injections include those made into (1) the right ventricle, to identify pulmonic stenosis, tricuspid dysplasia, right-to-left shunting ventricular septal defects, tetralogy of Fallot, transposition of the great vessels, (pseudo)truncus arteriosus, right-to-left shunting patent ductus arteriosus, and abnormalities of the pulmonary vascular tree; (2) the left ventricle, to identify subaortic stenosis, mitral dysplasia, left-to-right shunting ventricular septal defects, transposition of the great vessels, aorticopulmonary windows, and left-to-right shunting patent ductus arteriosus; (3) the main pulmonary artery, to identify anomalous pulmonary venous drainage, aorticopulmonary windows, left-to-right shunting atrial septal defects, and mitral valve stenosis; and (4) the aortic root, to identify aortic insufficiency, aorticopulmonary windows, anomalous coronary arteries, aortic coarctation, left-to-right shunting patent ductus arteriosus, and bronchoeso-phageal or other collateral pulmonary vessels. Angiograms can be recorded on videotape or multiple radiographic plates, or they can be stored digitally to optical or magnetic media.

200.8.3 Therapeutic Procedures

In the current era, cardiac catheterization plays an important role in the treatment of several types of congenital heart disease. Specialized catheters with inflatable balloons on the distal tip can be used to dilate stenotic valves or narrowed vessels. Catheters can also be used to deliver embolization devices to close shunting defects, such as patent ductus arteriosus. The electrical activity of the heart can be mapped and arrhythmias can be abolished using radiofrequency waves generated from an appropriately positioned catheter (see Treatment of Arrhythmias.)

A primary advantage of catheter-based therapy over traditional surgical approaches (thoracotomy) is the minimally invasive nature of cardiac catheterization. The evolution and clinical application of specific therapies are discussed further in later sections of this chapter.

200.9 ETIOLOGY AND PREVALENCE OF CONGENITAL HEART DISEASE

200.9.1 Etiology

Congenital cardiac malformations may be caused by a large number of genetic and environmental factors, and in most cases a single causative agent cannot be conclusively proven. The possible interaction of the potential toxicologic, nutritional, infectious, and genetic factors makes it difficult to answer the question posed by many clients, "Why did my pet get this congenital disease?" The observation that certain congenital defects display a species and/or breed predilection suggests that many defects have a heritable basis (see Table 200-1). This hypothesis has been unequivocally demonstrated for several specific defects in certain dog breeds.[5–7] Most of these studies indicate a simple mendelian basis for transmission, indicating that identifiable genetic factors contribute to malformations during development of the embryonic heart, giving rise to each specific type of congenital heart disease. Additional genes with additive effects may produce a discrete phenotype once a mendelian trait has been inherited.[8–11] Regrettably, the complexity and uncertainty surrounding the exact mode of inheritance of many defects makes it difficult to counsel breeders about the breeding of individual dogs. Although recent attempts have been made to identify dogs with congenital heart disease before breeding, these efforts are often confounded by the limited sensitivity and specificity of currently available screening methods. A normal physical examination does not equate with genetic normalcy, soft murmurs are difficult to interpret, and echocardiographic screenings often yield similarly equivocal findings. Even with careful attention to pedigree and the results of breeding trials, it can be very difficult to affect the overall prevalence of a specific defect in a large population. Progress in this regard hinges on the development of economical tests that can detect the genes responsible for the congenital defect.

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200.9.2 Prevalence

Surveys in North America indicate that the overall prevalence of congenital heart disease in dogs is 0.46% to 0.85% of hospital admissions. For 40 years, patent ductus arteriosus (PDA), subvalvular aortic stenosis (SAS), and pulmonic stenosis (PS) have topped the list of most commonly reported congenital defects in dogs. Hospital surveys of congenital heart defects in the United States have been reported by Patterson and Detweiler in dogs and by Liu and by Harpster in cats.[2a,12a,14a,36a] In the largest survey of dogs from the 1960s, 325 malformations were detected in 290 dogs, and the overall prevalence in a university hospital population was 6.8 per 1000 dogs.[1a,2a,14a] The frequency of diagnosis was approximately 28% for PDA, 20% for PS, 14% for aortic stenosis, 8% for persistent right aortic arch, 7% for ventricular septal defect, and less than 5% for tetralogy of Fallot, persistent left cranial vena cava, and atrial septal defects. In a 1989 survey of 339 cases of congenital cardiac defects in dogs in the United Kingdom, the most common diagnoses were subaortic stenosis (32%), PDA (20%), mitral valve dysplasia (14%), PS (12%), and ventricular septal defect (8%). A more recent report by Buchanan[1c,9b] that includes prevalence information from a North American database of more than 1300 cases indicates that patent ductus arteriosus is still most frequently reported (31.7% of cases), but subaortic stenosis (22.1%) now exceeds pulmonic stenosis (18.3%) in prevalence.

The shifting popularity of some dog breeds over time influences the regional or global prevalence of a particular defect. For example, the growing popularity of golden retrievers may increase the number of dogs diagnosed with subvalvular aortic stenosis. Harpster's review of congenital heart disease in cats summarizes data from the literature, from Angell Memorial Animal Hospital (Boston), and from the Animal Medical Center (New York City). The prevalence of congenital heart defects in cats was 0.2% to 1% of hospital

admissions. Of the reported diagnoses, the most commonly diagnosed defects included atrio-ventricular septal defects (24%, including ventricular septal defect, atrial septal defect, and endocardial cushion defect), atrioventricular valve dysplasia (17%), endocardial fibroelastosis (11.5%), PDA (11%), aortic stenosis (6%), and tetralogy of Fallot (6%). Males were affected nearly twice as often as females.[36a]

200.10 CLASSIFICATION OF CONGENITAL HEART DISEASE

A number of schemes have been devised for classifying congenital heart defects. The system presented in Box 200-1 emphasizes the nature of the cardiac overload and the physiologic consequences rather than the embryologic basis for maldevelopment. It should be apparent that some lesions fit into more than one category. Some of the lesions listed are very rare, and some have been reported only in conjunction with other defects.

200.11 DEFECTS THAT CAUSE PRIMARILY VOLUME OVERLOAD

200.11.1 Systemic to Pulmonary (Left-to-Right) Shunts

200.11.1.1 Patent Ductus Arteriosus

The circulation in the fetus differs from that in the adult. In fetal animals the ductus arteriosus develops from the left sixth embryonic arch and extends from the pulmonary artery to the descending aorta, where it diverts blood from the nonfunctional fetal lungs back into the systemic circulation. Prior to birth, the ductus diverts approximately 80% to 90% of the right ventricular output back to the left side of the circulation. After parturition and the onset of breathing, pulmonary vascular resistance falls, flow in the ductus reverses, and the resulting rise in arterial oxygen tension inhibits local prostaglandin release, causing constriction of the vascular smooth muscle in the vessel wall and functional closure of the ductus arteriosus. Although the ductus may be probe patent in puppies less than 4 days of age, it usually is closed securely 7 to 10 days after birth.[4a,41a,42a] Persistence of a PDA beyond the early neonatal period is the first or second most commonly diagnosed congenital cardiac defect in dogs.[37a,61a] Cats are also affected but much less commonly than dogs.

200.11.1.1.1 Pathogenesis

Failed ductal closure in dogs is characterized by distinct histologic abnormalities in the ductal wall. The normal fetal ductal wall contains a loose, branching pattern of circumferential smooth muscle throughout its length. In prenatal puppies bred to have a high probability of PDA, varying portions of the ductal wall are comprised of elastic fibers rather than contractile smooth muscle fibers. According to the work of Patterson et al., increasing genetic liability to PDA results in "extension of the noncontractile wall structure of the aorta to an increasing segment of the ductus arteriosus, progressively impairing its capacity to undergo physiologic closure."[4a] It is tempting to speculate that some defect prevents one or more of the series of processes that permits smooth muscle cells to proliferate in the wall of the ductus prior to birth. In the defect's mildest form, the ductus closes at the pulmonary arterial end only and a blind, funnel-shaped outpouching of the ventral aspect of the aorta, called a *ductus diverticulum*, results. This hidden form *(forme fruste)* of incomplete ductal closure can be diagnosed only by angiography or necropsy, but it indicates that the dog possesses genes for this defect.[4a,39a,40a] Increasing genetic liability results in a tapering, funnel-shaped ductus arteriosus that remains patent after the early natal period and

that allows blood to flow from the high-pressure aorta to the low-pressure pulmonary artery (Figure 200-2), thereby creating varying amounts of left-to-right shunting. The most severe but least common form is the cylindrical, nontapering ductus with persistent, postnatal pulmonary hypertension (Eisenmenger's syndrome) and bidirectional or right-to-left shunting (see Figure 200-2). Based on the breeding studies of poodle-type dogs, Patterson et al. concluded that the mode of transmission of PDA in dogs is most likely polygenic, but other mechanisms of inheritance are possible. For additional information on the morphology and pathogenesis of PDA, the reader is referred to several outstanding reviews of the subject.[12–14]

200.11.1.1.2 Pathophysiology

The direction of flow through the PDA is determined by the relative resistances of the pulmonary and systemic vascular beds; in the vast majority of cases, it is directed from left to right (from the aorta to pulmonary artery). This results in a continuous cardiac murmur, increased pulmonary blood flow, and volume overloading of the left atrium and left ventricle. Because of the relatively high resistance of the systemic circulation after birth, aortic blood pressure is greater than pulmonary pressure, and blood shunts continuously across the PDA during both systole and diastole. For a given pressure gradient, the magnitude of shunting is determined by the morphology (effective resistance) of the ductus arteriosus. In most cases the ductus is widest at the aortic end and tapers to its narrowest (flow limiting) region at the point of attachment to the pulmonary artery. Increased left ventricular stroke volume and rapid runoff of blood from the aorta to the low pressure pulmonary circulation via the PDA causes increased aortic systolic and decreased aortic diastolic pressures. The resulting widened arterial pulse pressure offers a hemodynamic explanation for the bounding or hyperkinetic (waterhammer, Corrigan's) arterial pulse detected in dogs with substantial shunts.

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200.11.1.1.2.1

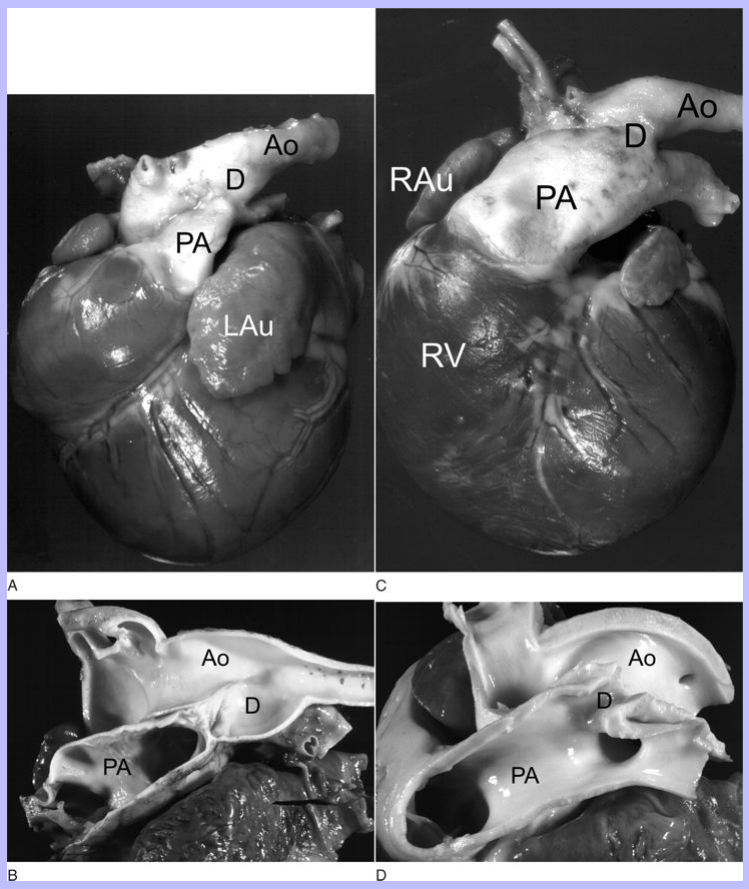
Box • 200-1 Classification of Congenital Defects According to Pathophysiology

Canine	Feline
Defects primarily causing volume overload	
Systemic to pulmonary (left-to-right) shunting	
Common	Common
Patent ductus arteriosus	Ventricular septal defect
Ventricular septal defect	Patent ductus arteriosus
Uncommon	Atrial septal defect
Atrial septal defect	Endocardial cushion defect
Endocardial cushion defect	Uncommon
(Pseudo) truncus arteriosus	Truncus arteriosus
Valvular regurgitation	Valvular regurgitation
Common	Common
Mitral dysplasia	Mitral dysplasia
Tricuspid dysplasia	Tricuspid dysplasia
Uncommon	
Pulmonic insufficiency	
Aortic insufficiency	
Defects primarily causing pressure overload	
Common	Common
Pulmonic stenosis	Dynamic subaortic stenosis
Subaortic stenosis	Uncommon
Uncommon	Pulmonic stenosis
Valvular aortic stenosis	Pulmonary artery branch stenosis
Coarctation and interruption of the aorta	Fixed subaortic stenosis
Cor triatriatum dexter	Valvular aortic stenosis
	Cor triatriatum dexter
	Cor triatriatum sinister
Defects primarily causing cyanosis	
Common	Common
Tetralogy of Fallot	Tetralogy of Fallot
Uncommon	Endocardial cushion defect
Pulmonary to systemic shunting (ventral septal defect [VSD])	Uncommon
Pulmonary to systemic shunting (patent ductus arteriosus [PDA])	Pulmonary to systemic shunting (VSD)
Tricuspid atresia/right ventricular hypoplasia	Pulmonary to systemic shunting (PDA)
Double outlet right ventricle	Double outlet right ventricle
Transposition of the great vessels	Truncus arteriosus
Truncus arteriosus	
Aorticopulmonary window	
Miscellaneous cardiac and vascular defects	
Common	Common
Peritoneopericardial diaphragmatic hernia	Peritoneopericardial diaphragmatic hernia
Persistent right aortic arch	Endocardial fibroelastosis
Persistent left cranial vena cava	Uncommon
Uncommon	Persistent right aortic arch
Endocardial fibroelastosis	Anomalous right atrium
Pericardial defects	
Anomalous pulmonary venous return	
Double aortic arch	

Retroesophageal left subclavian artery
Situs inversus

All vascular structures involved in the transport of the shunted blood enlarge to accommodate the extra volume flow. Increased volume flow causes dilatation of the proximal aorta and main pulmonary artery and overcirculation of the pulmonary vascular bed. Dilatation of the left atrium and eccentric hypertrophy of the left ventricle develop in proportion to the volume flow of the shunt. This mechanism permits compensation for a variable period, but if the shunt is large, myocardial failure (cardiomyopathy of volume overload) develops, together with progressive elevation of left ventricular end-diastolic pressure and overt pulmonary edema. Because the left-to-right shunt occurs at the level of the great vessels, the right ventricle and atrium never handle the shunted blood, and these structures remain normal unless pulmonary vascular resistance and pulmonary arterial pressure increase.

Figure 200-2 Gross pathology of patent ductus arteriosus (PDA). **A,** Left-sided view of the heart of a 9-week-old Australian shepherd with a left-to-right PDA, demonstrating the anatomic location of the ductus *(D)* between the descending aorta *(Ao)* and the main pulmonary artery *(PA)*. The left auricle (*LAu*) is enlarged. **B,** Cutaway view of a left-to-right PDA in a dog. The ductus is funnel shaped, tapering toward the PA end. **C,** Left-sided view of the heart of a dog with a right-to-left shunting PDA. Note the enlargement of the right ventricle *(RV)* and right auricle *(RAu)*. The pulmonary artery *(PA)* is enlarged. **D,** Cutaway view of a right-to-left shunting PDA in a dog. Note the cylindrical nature of the ductus *(D)* and the fact that the anatomic location of the ductus is distal to the aortic branches that supply the cranial portion of the body.



In a small percentage of cases, the lumen of the PDA remains wide open after birth. The absence of a restrictive ductal orifice allows aortic pressure to be transmitted to the pulmonary circulation, precluding the normal postnatal decline in pulmonary vascular resistance. In this circumstance the aortic and pulmonary artery pressures equilibrate, and the right ventricle remains concentrically hypertrophied after birth. In Patterson's colony of dogs, this pattern of pulmonary hypertension and reversed (right-to-left) shunting developed within the first few weeks of life.[39a] These observations fit the usual clinical presentation of most dogs diagnosed with a *reversed PDA*, in which the animal usually has no history of a continuous murmur and no evidence of left ventricular enlargement or a large left-to-right shunt earlier in life. Most dogs with reversed PDA flow have diminished pulmonary blood flow, a normal to small left ventricle, and marked concentric hypertrophy of the right ventricle. On rare occasions, dogs with a moderate to large left-to-right shunting PDA experience a gradual increase in pulmonary resistance and gradual reversal of the direction of shunting, typically at several months to several years of age. These dogs often have a history of prior left heart failure. Substantial residual left ventricular (LV) enlargement is evident on thoracic radiographs and by echocardiography. Pulmonary blood flow is reduced, but right ventricular hypertrophy is less pronounced than in dogs in which the direction of shunting is reversed at an early age. The precise pathogenesis of pulmonary hypertension is not completely understood, but anatomic descriptions of the pulmonary vasculature are similar in humans and animals. Histologic changes within small pulmonary arteries include hypertrophy of the media, thickening of the intima and reduction of lumen dimensions, and development of plexiform lesions of the vessel wall.[60a,61a,15] Most of these changes are considered to be irreversible, precluding surgical correction of the reversed PDA.

200.11.1.1.3

Clinical findings

The clinical features of PDA have been thoroughly characterized in both a breeding colony and in clinic populations.[1a,4a,10c,16,37a-53a] Compared with male dogs, female dogs have a substantially greater risk of developing a PDA (2.49 per 1000 versus 1.45 per 1000).[2a] The Chihuahua, collie, Maltese, poodle, Pomeranian, English springer spaniel, keeshond, bichon frise, and Shetland sheepdog are most frequently affected, although other breeds, such as the Cavalier King Charles spaniel, may also be predisposed. Many other breeds, including larger dogs, such as the German shepherd, Newfoundland, and Labrador retriever, may also be prone to PDA in some regions. Although severely affected pups and kittens may appear stunted, thin, or tachypneic from left heart failure, most are reported to be asymptomatic and developing normally at the time the condition is discovered. Clinical signs are rarely recognized within the first few weeks of life, and most dogs are not diagnosed until the initial examination at 6 to 8 weeks of age.

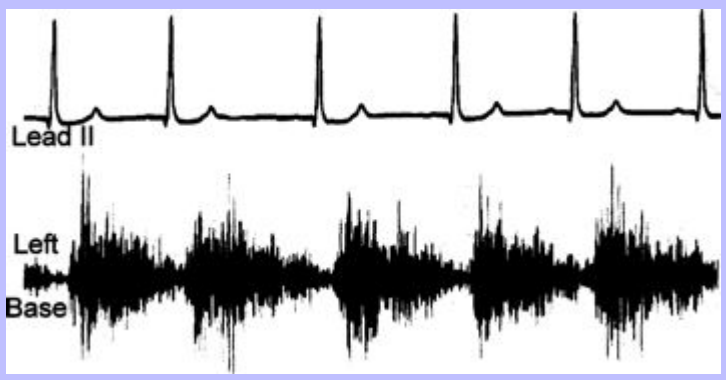
200.11.1.1.4

Left-to-right shunting patent ductus arteriosus

A thorough physical examination and chest radiographs usually suffice to suggest the diagnosis. Mucous membranes are pink in the absence of heart failure. The precordial impulse is often exaggerated and more diffuse than normal as a result of left ventricular enlargement. A thrill may be palpated at the heart base, and a continuous murmur is best heard in the same location (Figure 200-3). The murmur's point of maximum intensity is located over the main pulmonary artery at the dorsocranial left heart base and may radiate cranially to the thoracic inlet and to the right base, where it is almost always softer.[5a,16,39a,47a] Often only a systolic murmur is audible over the mitral area. This murmur may simply represent radiation of the loudest portion of the continuous murmur from the heart base to this location, or it may indicate that secondary mitral regurgitation has developed as a consequence of severe left ventricular

dilatation. In cats, the continuous murmur of a PDA may be heard best somewhat more caudoventrally than in affected dogs. Increased LV stroke volume and rapid diastolic runoff through the PDA combine to produce peripheral arterial pulses that are hyperkinetic (bounding).

Figure 200-3 Phonocardiogram recorded at the left heart base from a dog with left-to-right patent ductus arteriosus. The lead II ECG is recorded simultaneously for timing purposes (ventricular mechanical systole is approximately the period from the middle of the QRS complex to the end of the T wave; the remainder of the time is diastole). The recorded murmur is continuous, increasing in intensity during systole, peaking near the end of systole, and decreasing in intensity during diastole.



Electrocardiography typically indicates left ventricular enlargement (increased R-wave voltages in leads II, III, and aVF and in the left chest leads, V_2 and V_4) and normal mean electrical axis (Figure 200-4). 981

Widened P waves may also be found, indicating left atrial enlargement. Chest radiographs indicate left atrial and left ventricular enlargement and pulmonary hypervascularity in proportion to the magnitude of the left-to-right shunt (Figure 200-5). On the dorsoventral (DV) projection, the aortic arch, left auricle, and main pulmonary artery may be abnormally prominent. The most specific radiographic finding is the appearance of an aortic bulge ("ductus bump") near the origin of the ductus, which is caused by abrupt narrowing of the descending aorta just caudal to the origin of the ductus (see Figure 200-5). Moderate to severe LV enlargement sometimes causes the cardiac apex to shift to the right (common in cats). 982

Figure 200-4 Electrocardiogram from a dog with left-to-right patent ductus arteriosus. The mean QRS axis is normal (+80%), but the QRS voltage (amplitude) is increased in several leads, including leads II, III, aVF, and V_4, consistent with left ventricular enlargement. (The square waves in each lead are 1 mV standardization impulses). Paper speed = 50 mm/s.

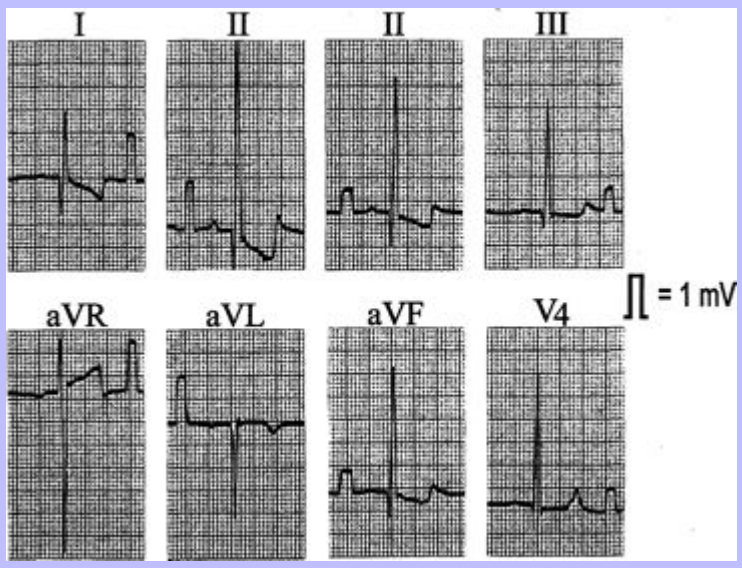
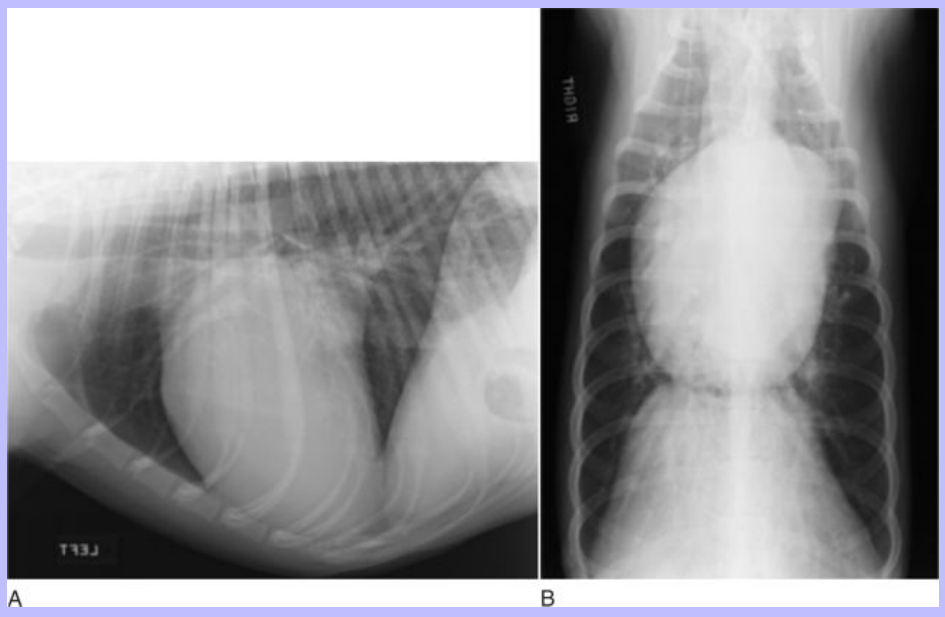


Figure 200-5 Thoracic radiographs from a dog with a left-to-right shunting PDA. **A,** Lateral projection shows left atrial enlargement and enlarged cranial pulmonary arteries and veins. **B,** Dorsoventral projection shows moderate cardiomegaly, a characteristic bulge in the descending aorta, dilatation of the main pulmonary artery, and left auricular enlargement. The pulmonary vasculature is prominent.



The diagnosis of a PDA can be confirmed by echocardiography in almost all cases. Two-dimensional and M-mode echocardiography demonstrate eccentric LV hypertrophy and dilatation of the left atrium, ascending aorta, and pulmonary artery (Figure 200-6).[11c] Reduced myocardial contractility is often observed and is reflected by reduced fractional shortening and/or increased LV end-systolic dimension and e-point to septal separation (EPSS) measurements. The ductus usually can be imaged from the left cranial parasternal window (see Figure 200-6). Doppler interrogation of the pulmonary artery consistently demonstrates high-velocity continuous ductal flow directed toward the pulmonic valve (see Figure 200-6). In the typical case, the peak velocity of this jet is about 4.5 to 5 m/s and occurs at end-systole. Other common echocardiographic findings include a mildly increased LV outflow velocity (1.8 to 2.3 m/s) and modest secondary mitral and pulmonary valve insufficiency. In dogs with PDA, associated cardiac defects are uncommon; nonetheless, a careful echocardiographic examination is worthwhile to exclude the concurrent presence of other common congenital defects, such as subaortic stenosis.[4a,44a] Cardiac catheterization and angiocardiography are usually not needed to confirm a diagnosis of PDA and are not advised unless the Doppler echocardiographic evaluation is ambiguous or additional congenital malformations are suspected.[12c,13c]

200.11.1.1.5 Patent ductus arteriosus with pulmonary hypertension (right-to-left shunting PDA)

High pulmonary vascular resistance that causes right-to-left shunting through a PDA defines the clinical syndrome commonly referred to as a reversed PDA.* Right-to-left shunting is observed in a very small minority of dogs with a PDA, but the prevalence of this phenomenon is probably underestimated and may be greater in dogs living at altitudes higher than 5000 feet above sea level.[16c] Obvious clinical signs are usually evident during the first year of life, but many owners do not recognize clinical signs in their pet during the first 6 to 12 months of life, and some animals are not diagnosed until 3 to 4 years of age or later. Reported signs include exertional fatigue, hindlimb weakness, shortness of breath, hyperpnea, differential cyanosis and, more rarely, seizures.

The clinical examination findings are very different from those in the more common left-to-right PDA. Right-to-left flow through a widely patent ductus arteriosus exhibits little turbulence, and the physical examination reveals either no murmur or only a soft, systolic murmur at the left base. The most common auscultatory finding is an accentuated and split second heart sound. Differential cyanosis (cyanosis of the caudal mucous membranes with pink cranial membranes) may be observed, but recognition may require examination after exercise. Differential cyanosis is caused by the location of the PDA, which shunts right to left from the pulmonary artery into the descending aorta (see Figure 200-2) but spares the proximal branches of the aorta, which provide normal oxygen delivery to the cranial portion of the body. Perfusion of the kidneys with hypoxemic blood triggers elaboration of erythropoietin and secondary polycythemia and hypervis-cosity as the packed cell volume (PCV) gradually increases to 65% or greater.[59a] Polycythemia may occur during the first year of life, but it often does not become severe until 18 to 24 months of age.

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Figure 200-6 Echocardiography of left-to-right PDA. **A,** Right short axis view shows eccentric dilatation of the left ventricular cavity *(LV)* compared with the right ventricle *(RV)*. **B,** Right long axis view from the same dog reveals eccentric dilatation of the left ventricle *(LV)* and left atrium *(LA)*. The interventricular septum *(1)* and left ventricular posterior wall *(2)* appear relatively thin compared with the dilated left ventricle. The mitral valve *(3)* is in the closed position. The right ventricle *(RV)* and right atrium *(RA)* are normal. **C,** Continuous wave Doppler tracing of the PDA jet obtained from the left heart base, demonstrating continuous flow and a peak velocity of 5.2 m/s, which is converted to units of pressure (108 mm Hg) using the modified Bernoulli equation. **D,** View of the ductus *(D)* imaged from the left heart base. The typical left-to-right ductus is widest at the aortic *(Ao)* end *(1)* and tapers near the main pulmonary artery *(MPA) (2)*. **E,** Close-up view of the ductus *(D)*, pulmonary artery *(PA)*, and aorta *(Ao)*. **F,** Color flow Doppler imaging applied to the echocardiographic view in **E,** demonstrating turbulent left-to-right blood flow through the ductus.

The electrocardiogram of dogs with a reversed PDA almost always reveals evidence of right ventricular hypertrophy (i.e., right axis deviation and increased S-wave amplitude in leads I, II, and III and in the left precordial chest leads V_2, and V_4) (see Chapter 202). Thoracic radiographs indicate right heart enlargement, dilatation of the main pulmonary artery, a visible ductus bump, and variable appearance of the lobar and peripheral arteries. Echocardiography demonstrates right ventricular concentric hypertrophy and a dilated main pulmonary artery. In some cases a wide, cylindrical ductus may be imaged (Figure 200-7). Pulmonary hypertension can be verified in some cases by Doppler interrogation of tricuspid or pulmonic insufficiency jets. Contrast echocardiography, nuclear scintigraphy, oximetry, or angiography can be used to demonstrate the presence of right-to-left shunting should Doppler interrogation prove inadequate. Contrast echocardiography is performed by injecting air-agitated saline into a cephalic or saphenous vein, thereby opacifying the right heart, pulmonary artery, and descending aorta (best observed by imaging of the abdominal aorta dorsal to the bladder). Cardiac catheterization can demonstrate pulmonary artery hypertension with equilibration of right and left ventricular and aortic systolic pressures. Oximetry verifies decreased oxygen saturation distal to the entrance of the PDA in the descending aorta. Right ventricular angiography demonstrates right ventricular hypertrophy and usually outlines a wide PDA that appears to continue distally as the descending aorta (Figure 200-8). The lobar pulmonary arteries may appear normal, especially during the first year of life, or may show increased tortuosity. Aortic or left ventricular contrast injections permit visualization of an often extensive bronchoesophageal collateral circulation (see Figure 200-8).

* References 5a, 8a, 9a, 16c, 39a, 46a, 59a, and 61a.

200.11.1.1.6 Natural history of patent ductus arteriosus

Eyster[53a] reported that approximately 64% of dogs diagnosed with a left-to-right shunting PDA die of complications within 1 year of diagnosis if the condition is not surgically corrected. Complications include left heart failure with pulmonary edema, atrial fibrillation, pulmonary hypertension secondary to left heart failure, and mitral regurgitation secondary to left ventricular dilatation.[53a,58a] Dogs and cats with PDA and more modest shunts often survive to maturity, and some live beyond 10 years of age.[10c] In humans with an uncorrected PDA, the gradual development of pulmonary hypertension and shunt reversal is a significant risk, but this gradual transition to right-to-left shunting is uncommon in dogs. When persistent pulmonary hypertension in the neonate leads to reversed shunting, clinical signs result from hypoxemia, polycythemia, hyperviscosity, and cardiac arrhythmias. Congestive heart failure almost never develops, but sudden death and complications from hyperviscosity are common. Animals with reversed PDA often live 3 to 5 years, and some survive beyond 7 years if the PCV is kept below 65%.

200.11.1.1.7 Clinical management

Surgical correction is recommended in virtually all young dogs and cats with a left-to-right shunting PDA. Correction may not be warranted in older pets if the shunt volume is small and cardiomegaly is minimal or absent. Consultation with a specialist may be helpful in borderline circumstances. Recommended preoperative studies include ECG and chest radiographs to help assess the severity of the shunt and to determine whether congestive heart failure is present. An echocardiogram should always be performed to verify the diagnosis and to rule out additional defects. The timing of surgery is debatable, but PDA correction is typically recommended at an early age or as soon as the diagnosis is made, especially if congestive heart failure appears imminent. If pulmonary edema is found on the chest radiograph, the patient should be treated medically for heart failure (furosemide, angiotensin-converting

enzyme [ACE] inhibitors) prior to surgery. Positive inotropic support should also be considered. Treatment with prostaglandin inhibitors such as indomethacin (often used in premature human infants to assist closure of a structurally normal but functionally immature PDA) is not effective in dogs and cats, most likely because of the absence of smooth muscle in the ductal wall.

Two approaches to PDA correction are currently available. For many years, left thoracotomy and surgical closure, typically by ligation, was the only available treatment.[15c] Other surgical methods of repair include suture occlusion with metallic clips and surgical division. These techniques and their results have been described in detail in several reports, indicating high surgical success rates and an excellent prognosis after repair.[10b-12b,48a-54a] Complications of surgical PDA repair in dogs most often include hemorrhage, infection, pneumo-thorax, cardiac arrhythmias, cardiac arrest, and heart failure. Surgical mortality should be less than 3% in uncomplicated cases.[10b-12b,53a] Pre-existing congestive heart failure (CHF) dramatically increases the risk of anesthetic or operative death and the rate of serious complications, underscoring the necessity of resolving pulmonary congestion prior to surgery. Positive inotropic support provided through a dobutamine infusion should also be considered for patients in this circumstance. Most dogs experience an uneventful recovery after surgery, and overall cardiac size gradually decreases toward normal, although the heart and great vessels often retain an abnormal shape.[44a] Postoperative Doppler examination may indicate a small residual shunt, although the continuous murmur is usually absent and the clinical outcomes are good. A soft left apical systolic murmur, usually from residual secondary mitral regurgitation, is often heard for a variable period after ductus ligation.[47a] Echocardiographic LV fractional shortening declines sharply immediately after surgery as a result of diminished preload and increased afterload. Medical therapy is not usually needed if signs of heart failure were not evident preoperatively. Medical therapies required prior to surgery for CHF are often required for several months after repair. Postoperative ductal recanalization has been reported but is uncommon, occurring in less than 2% of cases, and it most commonly is associated with infection.[15c] Postoperative fever and pulmonary infiltrates may indicate infection at the surgical site and hematogenous pneumonia.[57a] The owner should be informed of the suspected heritable nature of the defect and should be advised not to use the animal for breeding.

Less invasive alternative techniques for PDA occlusion are gaining popularity.[17–20,17c-21c] Percutaneous embolization of the ductus using expandable metal devices imbedded with thrombogenic Dacron strands can be accomplished in most small animals with a PDA, avoiding the morbidity of surgical thoracotomy (see Fig. 200-9 *A* and *B*). The most commonly used embolization device is a helical metal coil that is delivered through a small catheter via the femoral artery or other peripheral vessel. After the device has been deployed in the ductus arteriosus, the attached Dacron feathers induce thrombus formation, thereby occluding the PDA. The purported advantages of PDA coil embolization over thoracotomy and surgical ligation include lower morbidity, shorter hospitalization, and faster recovery. To date the success rate of this technique has been promising and the major complication rate has been acceptably low, consisting mainly of residual shunting and pulmonary embolization of a coil.[17,19,17c-21c] Coils that embolize to the lungs can be ignored, pushed to a peripheral location, or removed. The authors prefer to remove dislodged coils, which can be quite easily accomplished using heartworm extraction forceps or other retrieval devices. Because device retention within the PDA is required for successful closure, the ideal candidates for coil occlusion should have a relatively small, funnel-shaped PDA that tapers to a diameter of 2 or 3 mm at the pulmonary artery end.[20]

Figure 200-7 Echocardiography in right-to-left PDA. **A,** Right long axis view from an American Eskimo dog shows enlargement of the right ventricle *(RV)* and atrium *(RA)*. **B**, Right short axis view shows enlargement of the right ventricle and flattening of the interventricular septum toward the left ventricle. This finding is highly suspicious for pressure overload of the right ventricle. **C,** Transesophageal echocardiogram of a dog with a right-to-left PDA. The ductus *(D)* connects the aorta *(Ao)* with the pulmonary artery *(PA)* and is wide and cylindrical in shape. Both the pulmonary artery and the left pulmonary artery *(LPA)* are enlarged. **D**, Continuous wave Doppler study of the dog in **A** showing bidirectional flow through the ductus. Right-to-left flow (below the baseline) occurs during systole, and left-to-right flow (above the baseline) occurs during diastole. **E**, Simultaneous two-dimensional and color flow Doppler study of the dog in **A**. Flow from the pulmonary artery *(PA)* can be seen moving right-to-left into the large ductus *(D)*. **F**, Continuous wave Doppler study of pulmonic insufficiency in the dog in **A.** The peak velocity of insufficiency is 4.5 m/s, indicating a pulmonary artery diastolic pressure of approximately 80 mm Hg. This finding is consistent with a diagnosis of pulmonary arterial hypertension and the presence of a right-to-left shunt.

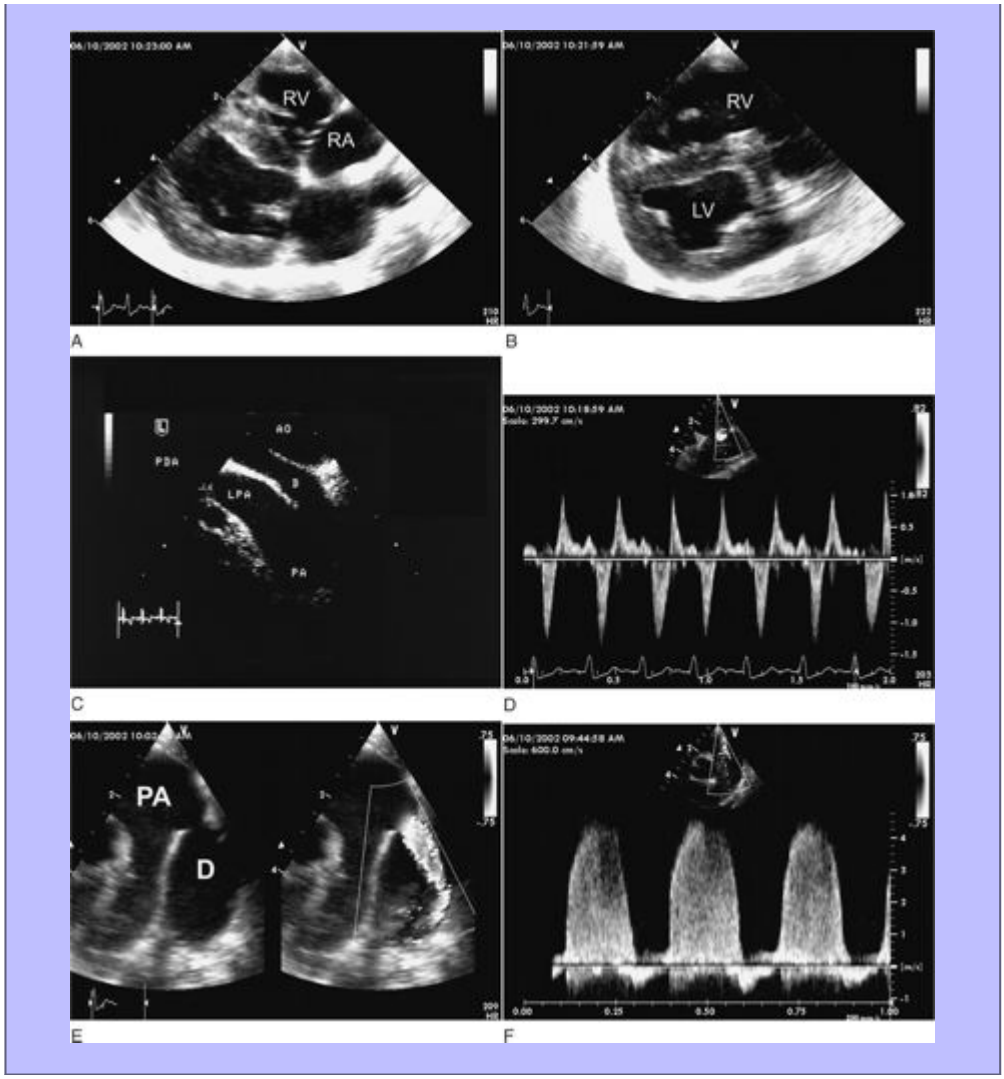
RV
RA
A
RV
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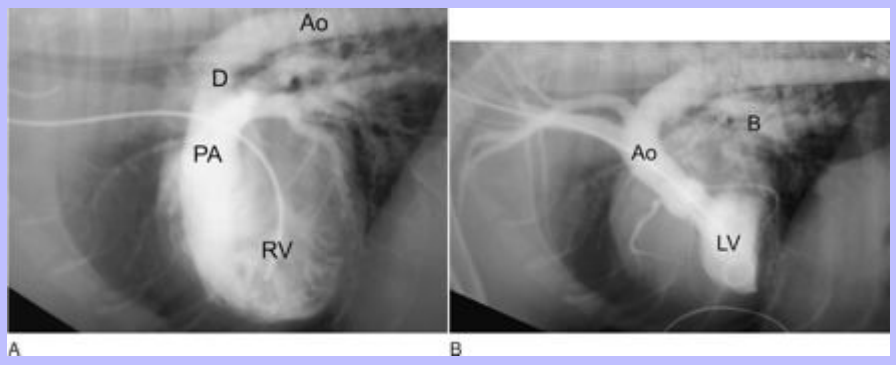
Figure 200-8 Angiographic diagnosis of right-to-left PDA in a dog. **A,** Right ventricular injection opacifies the right ventricle *(RV),* pulmonary artery *(PA),* ductus *(D),* and descending aorta *(Ao)*. Note that the systemic arteries to the cranial portion of the dog are not opacified. **B,** Left ventricular injection of the same dog opacifies the left ventricle *(LV),* the aorta *(Ao),* and prominent collateral bronchoesophageal circulation *(B)*.



Occlusion of large-diameter PDAs (4 mm or greater) can be attempted by deploying multiple coils into the ductal ampulla, but coil dislodgment and residual shunting are more problematic in this circumstance (Figure 200-9).[19] Mushroom-shaped, self-expanding, occluding stents (Amplatzer) developed for human use have been successfully used to accomplish PDA closure in dogs (Figure 200-10).[18] Advantages of this technique include secure retention of the device in the ductus with a correspondingly low rate of dislodgment, ease of delivery through the femoral vein, and suitability for closing large-diameter PDAs with a single implant. The need for specialized equipment (i.e., coils, occluding stents, catheters, fluoroscopy) and an operator experienced in performing cardiac catheterization limits the application of transcatheter PDA closure techniques to university teaching hospitals and large specialty referral centers. The historical success of the traditional PDA surgery makes thoracotomy and ligation a perfectly acceptable and, in some circumstances, a preferable alternative to transcatheter closure.

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Figure 200-9 Thoracic radiographs from a dog after coil embolization of a left-to-right PDA. **A,** Lateral view shows multiple coils in the ductus. **B,** Dorsoventral view shows multiple coils in the ductus near the bulge in the descending aorta.

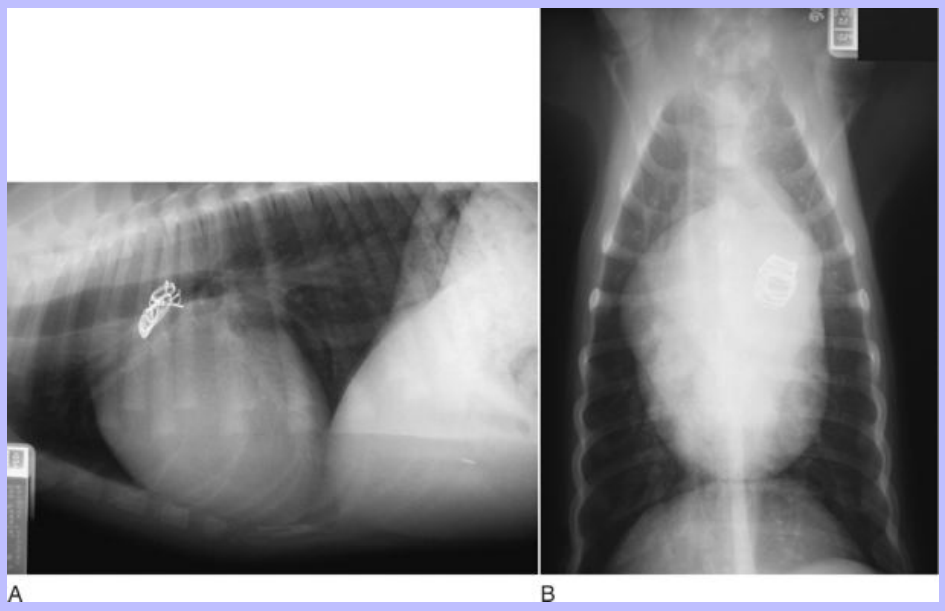
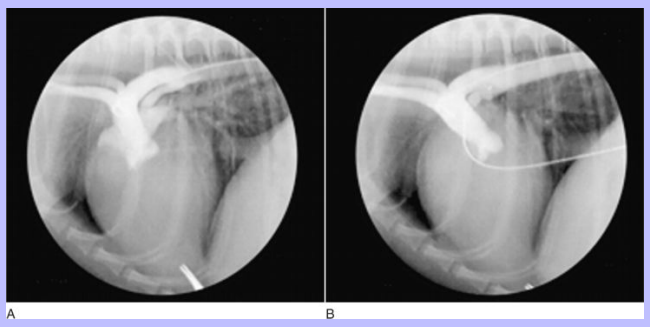


Figure 200-10 Aortic angiograms prior to and 15 minutes after deployment of an Amplatzer duct occluder into a patent ductus arteriosus (PDA). **A,** Contrast agent injected into the aorta before deployment of the duct occluder is seen flowing through the PDA into the pulmonary circulation. **B,** Contrast agent stops in the proximal PDA at the level of the Amplatzer occluder because of thrombus formation in the device.



Animals with reversed PDA have irreversible obstructive pulmonary vascular disease. Morbidity and mortality is usually due to complications related to polycythemia and chronic hypoxemia rather than congestive heart failure. Treatment of these patients consists of exercise restriction, avoidance of stress, and maintenance of the PCV between 58% and 65% by periodic phlebotomy.[14] Long-term management by these techniques is possible.[21] Phlebotomy should be performed cautiously to avoid weakness or collapse, and intravascular volume may be supported during phlebotomy by administration of crystalloid solutions. Attempts to reduce the red cell volume of reversed PDA cases using drug therapy (e.g., hydroxyurea) have been reported and may be an alternative to repeated phlebotomy.[22] Activity restriction is usually advised, because exercise-induced systemic vasodilatation increases the degree of right-to-left shunting and predisposes to posterior paresis or collapse and cyanosis. Closure of reversed PDA is strongly contraindicated, because it invariably leads to late operative or early postoperative acute right heart failure and death.

200.11.1.2 Atrial and Ventricular Septal Defects

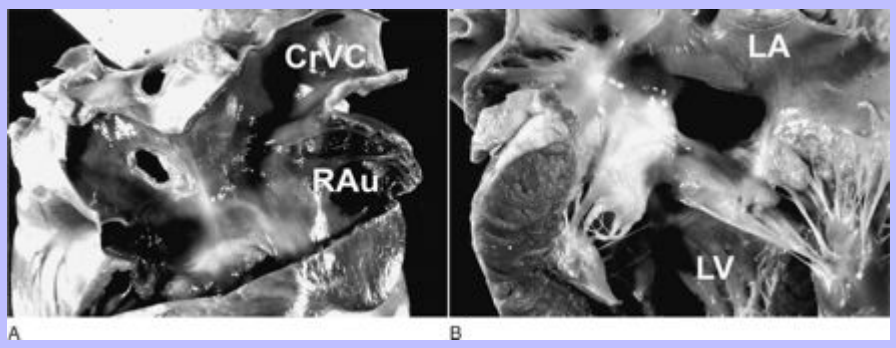
During cardiac embryonic development, the atria and ventricles begin as a common chamber. The heart is subsequently partitioned into the normal four-chambered heart by the growth of cardiac septa.[15a] The atria are partitioned by a wall formed mainly from two septa, the septum primum, which forms first, and the septum secundum, which develops to the right of the septum primum. The foramen ovale, a slitlike passageway that persists between these septa, permits right-to-left atrial shunting in the fetus, but functionally and anatomically closes in the neonate when left atrial pressure rises. The major portion of the ventricular septum forms by inward growth from the ventricular walls. The area of atrioventricular confluence, including the upper ventricular septum, lower atrial septum, and atrioventricular valves, is formed primarily by growth and differentiation of the endocardial cushions. Defects in the development of the embryonic ventricular septum, the primum or secundum atrial septa, or the endocardial cushions may result in atrial or ventricular septal defects, or both. Congenital septal defects are common in both dogs and cats as isolated lesions and as components of more complex lesions, such as tetralogy of Fallot.[4a,13a,62a-79a]

200.11.1.2.1 Pathogenesis

Except for the proven genetic basis of ventricular septal defect in keeshonden with conotruncal malformation,[124a] no data are available on the cause or causes of spontaneous septal defects in dogs or cats.[4a] Atrial septal defects (ASDs) are usually classified based on the anatomic region of the malformation.[15a,16a] Defects at or near the foramen ovale are referred to as *ostium* (or *septum*) *secundum defects*, and defects of the lower atrial septum are called *ostium primum defects* (Figure 200-11). Rarely observed sinus venosus atrial septal defects are found dorsocranial to the fossa ovalis near the entrance of the cranial vena cava.[65a] Because the endocardial cushions are responsible for partitioning the lowermost atrial septum, defects in the region immediately adjacent to the AV valves (septum primum) are often included in the term *endocardial cushion defects*. A defect in this area may also include anomalous development of the atrioventricular valves, such as a “cleft” in the septal leaflet of the mitral valve. A complete endocardial cushion defect is a large defect of the lower atrial septum and upper ventricular septum with fusion of the septal leaflets of both AV valves. This is also referred to as an *AV canal defect*, because the embryonic atrioventricular canal area never partitions, and communication exists between all four cardiac chambers. Patent foramen ovale is not a true ASD inasmuch as the atrial septum forms normally but the walls of the foramen are pushed apart, usually by conditions that increase

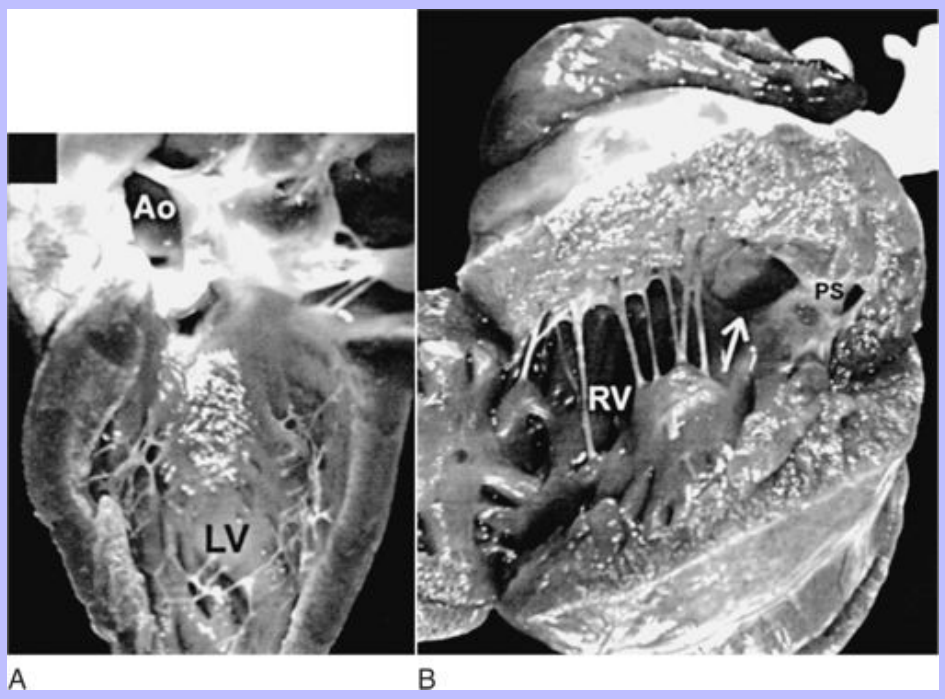
right atrial pressure.[62a] A patent foramen ovale achieves clinical significance when it allows right-to-left shunting, as may occur with severe pulmonic stenosis or tricuspid valve dysplasia.

Figure 200-11 Gross pathology of atrial septal defects (ASDs). **A,** Right atrial view in an 18-year-old dachshund with a secundum ASD. Location of the ASD at the site of the fetal foramen ovale and relative to the cranial vena cava *(CrVC)* and right auricle *(RAu)* is shown. **B,** Left-sided view in a 12-year-old Brittany spaniel with a primum ASD. Location of the ASD, low in the left atrium *(LA)* and near the mitral valve, can be appreciated. A prominent cleft in the mitral valve just below the ASD is also present. *LV,* Left ventricle.



Most ventricular septal defects (VSDs) are located in the upper ventricular septum (Figure 200-12).[68a] Muscular apical or midventricular septal defects are uncommon in small animals. On the left side, the typical location of a VSD is just below the aortic valve, most often centered between the right coronary and non-coronary cusps. On the right side, the opening is often described by its position relative to the crista supraventricularis muscular ridge.[15a] A subcristal (infracristal) VSD is located proximal to the crista supraventricularis near the cranial aspect of the septal leaflet of the tricuspid valve, which may partially cover it. A supracristal VSD is located distal to the crista supraventricularis just below the pulmonic valve. Large defects may obliterate the crista and are usually associated with additional defects, as in tetralogy of Fallot (see Figure 200-12).[2a,4a] The right side of the root of the aorta, including the right coronary and noncoronary cusps, may be displaced to the right so that the aorta straddles the defect. The altered geometry of the aortic root that accompanies many VSDs sometimes results in substantial aortic valve regurgitation.[17b]

Figure 200-12 Pathology of ventricular septal defect (VSD). **A,** Small, restrictive VSD in a young cat, viewed from the left ventricle *(LV)*. The defect is located in the upper septum, just beneath the aortic valve *(Ao)*. **B,** Large, unrestricted VSD in a young dog with tetralogy of Fallot, viewed from the right ventricle. The large defect is located just cranial to the tricuspid valve *(arrow)*. The right ventricle *(RV)* is markedly thickened, and a narrow, fibrous ring of subvalvular pulmonic stenosis *(PS)* is present where the pulmonic valve should be seen.



200.11.1.2.2 Pathophysiology

Shunting across small (resistive) defects depends primarily on the size of the communication and the pressure difference between the two chambers, whereas shunting across large (nonresistive) defects depends primarily on the relative resistances of the systemic and pulmonary circulations.[15a,62a,68a,72a,73a] In the absence of other abnormalities, left heart pressures exceed those on the right, and the direction of shunting is left to right. Cardiac chambers in the circuit of the shunt enlarge to accommodate the excess blood volume, and the pulmonary vasculature is overcirculated. Large-volume left-to-right shunts eventually result in myocardial failure, elevated filling pressures, and the development of overt congestive heart failure. Right-to-left shunting occurs via a septal defect when pulmonic stenosis,

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tricuspid dysplasia, or pulmonary arterial hypertension raise pressures on the right side of the heart. The consequences of reversed shunting include cyanosis from arterial hypoxemia, polycythemia, hyperviscosity, and sudden death.

200.11.1.2.3

Atrial septal defect

Flow across an atrial septal defect occurs primarily during diastole. The pressure difference across the defect is low, and the direction and magnitude of the shunt are determined mainly by the relative diastolic resistance to inflow for each ventricle.[15a,65a] Normally, the right ventricle is more compliant than the left and offers little resistance to filling, causing blood preferentially to shunt from the left atrium into the right atrium and ventricle. The result is dilatation of the right atrium, eccentric hypertrophy of the right ventricle, and pulmonary overcirculation. Oxygen saturation in the right heart and pulmonary arteries is increased. The left atrium receives the shunted blood, but most of the increased pulmonary venous return is shunted immediately into the right atrium, resulting in minimal left atrial dilatation. If considerable left atrial enlargement is observed in an animal with an ASD, an additional defect, such as an endocardial cushion defect with mitral regurgitation, should be suspected. Endocardial cushion defects are more commonly detected in cats and may cause left-sided or bilateral congestive heart failure. Endocardial cushion defects are reported in dogs but are rare.[23]

The flow across an ASD does not usually generate an audible heart murmur because the pressure gradient and flow velocity across the defect are low. When the shunted blood joins blood entering from the vena cava, the volume and velocity of flow through the right heart are increased, resulting a murmur of relative pulmonic stenosis (common) or tricuspid stenosis (uncommon). Delayed closure of the pulmonic valve (and early closure of the aortic valve) causes splitting of the second heart sound.[62a,63a] Because the volume overload affects the right ventricle and not the left, large shunts culminate in the development of right heart failure.

200.11.1.2.4

Ventricular septal defect

Flow across ventricular septal defects occurs primarily during ventricular systole. In the absence of other cardiovascular defects, LV systolic pressure is four to five times that of the right ventricle, and flow proceeds from the left to the right ventricle. The magnitude of left-to-right shunting with small (resistive) defects is mainly determined by the diameter of the defect and the systolic pressure difference (gradient) between the ventricles. The peak pressure difference across the defect can be estimated noninvasively by Doppler echocardiography. Using the peak flow velocity (in meters per second) of the blood flow passing through the defect, the pressure gradient is calculated using the simplified Bernoulli equation ($\Delta P = 4V^2$). A resistive defect with normal right and left ventricular pressures (approximately 20 mm Hg and 100 mm Hg, respectively) would be expected to have a peak jet velocity equal to or greater than 4.5 m/s, corresponding with a peak pressure gradient across the defect equal to or greater than 80 mm Hg. If the peak velocity is lower than predicted, right ventricular systolic pressure is most likely increased, due either to the presence of pulmonic stenosis or to increased pulmonary vascular resistance (pulmonary arterial hypertension).

When a small VSD is located high in the membranous septum, blood is ejected by the left ventricle directly into the right ventricular (RV) outflow tract and out the main pulmonary artery; the right heart experiences only a very modest volume load, and right heart enlargement is minimal. Right heart enlargement is more prominent when the VSD is large or located in the muscular region of the

interventricular septum. With a typical, small, high VSD, oxygen saturation in the right ventricular outflow tract and pulmonary artery is higher than in the right atrium or apex of the right ventricle. Large shunts (those with a pulmonary to systemic flow ratio greater than 3:1) may overload the left and/or right heart enough to increase ventricular diastolic pressures and cause signs of left, right, or biventricular failure. Very large, non-resistive VSDs cause the pressures in both ventricles to equilibrate, and the two ventricles behave as a common pumping chamber. Unless the pulmonary circulation is protected by a stenotic pulmonic valve, the development of pulmonary hypertension is unavoidable.

200.11.1.2.5

Eisenmenger's syndrome

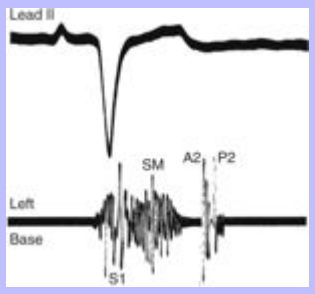
In newborn animals with a large VSD, pulmonary vascular resistance may not decline after birth, resulting in sustained pulmonary arterial hypertension.[13b,14b] If right ventricular systolic and diastolic pressures equilibrate at or above systemic (left ventricular) levels, bidirectional or right-to-left shunting may occur. The development of pulmonary hypertension associated with a shunting cardiac defect is known as *Eisenmenger's physiology* (or *syndrome*). When the defect is a VSD, the term *Eisenmenger's complex* often is used. Sustained pulmonary hypertension is characterized by progressive and irreversible changes in the pulmonary arteries similar to those mentioned in the section on reversed PDA. As in dogs with a PDA, reversed (right to left) shunting through a ventral septal defect is usually established prior to 6 months of age. In contrast to human patients, gradual development of pulmonary vascular disease and progressive pulmonary hypertension is relatively common in dogs and cats.

200.11.1.2.6

Clinical findings

Breed predispositions for atrial and ventricular septal defects are presented in Table 200-1. Clinical findings of the typical left-to-right ASD include a soft, grade II-III/VI, systolic ejection murmur over the left heart base and splitting of the second heart sound (Figure 200-13).[23c-25c,24] The murmur is often misinterpreted as mild pulmonic stenosis or as an innocent murmur. A low-pitched, right-sided diastolic murmur of relative tricuspid stenosis may occur, but it is usually not audible, especially in smaller patients. Cyanosis is absent unless an additional defect (e.g., pulmonic stenosis or tricuspid valve dysplasia)[15b] or the infrequent complication of pulmonary hypertension is present.[26c] Signs of right heart failure develop in dogs or cats with large defects. The differential diagnosis is anomalous pulmonary venous return, which is an extremely rare anomaly in dogs and cats.[80a]

Figure 200-13 Phonocardiogram recorded at the left heart base from a dog with a primum atrial septal defect. The lead II ECG has a negative, slightly prolonged QRS complex, which is indicative of a right ventricular conduction disorder (partial or incomplete right bundle branch block). The phonocardiogram shows a systolic ejection murmur *(SM)* that ends well before the second heart sound, which is widely split. S_1, First heart sound; A_2, aortic component of the second heart sound; P_2, pulmonic component of the second heart sound.



The main cardiac structural changes caused by an ASD include dilatation of the right atrium and eccentric hypertrophy of the right ventricle. The electrocardiogram may indicate right ventricular enlargement (i.e., right axis shift, increased S-wave depth in leads I, II, and III). Intraventricular conduction disturbances, especially partial or complete right bundle branch block (Figure 200-14), are also common, especially with atrial ostium primum or atrioventricular septal defects.[4a,64a,66a] Thoracic radiographs show enlargement of the right heart and main pulmonary artery, as well as pulmonary hypervascularity proportional to the magnitude of the shunt (Figure 200-15). The left atrium is only modestly enlarged unless concurrent mitral regurgitation from a cleft mitral valve or a more extensive endocardial cushion defect is present. Echocardiography permits direct imaging of atrial septal defects, but false-positive impressions of an ASD are common due to imaging artifacts caused by beam orientation and the thinness of some portions of the normal interatrial septum. Doppler evidence of transatrial shunting is more reliable and typically shows laminar or mildly turbulent diastolic flow through the ASD (Figure 200-16) and increased RV outflow and pulmonary artery velocities. Doppler studies are also helpful for demonstrating associated problems such as mitral regurgitation or other associated defects.[16b,24] Contrast echocardiography is helpful, particularly when the defect is large or when elevated right heart pressures cause reversed flow across the defect (see Figure 200-16).

Figure 200-14 Electrocardiogram from a dog with a primum atrial septal defect. The QRS axis is shifted to the right and cranially (+265 degrees), and the last two thirds of the complex is prolonged, as shown by widened and notched S waves in leads III and aVF. A prominent S wave is also present in lead V4. These changes are consistent with a right ventricular conduction disorder, often referred to as a partial or incomplete right bundle branch block. Paper speed = 50 mm/s, 10 mm = 1 mV.

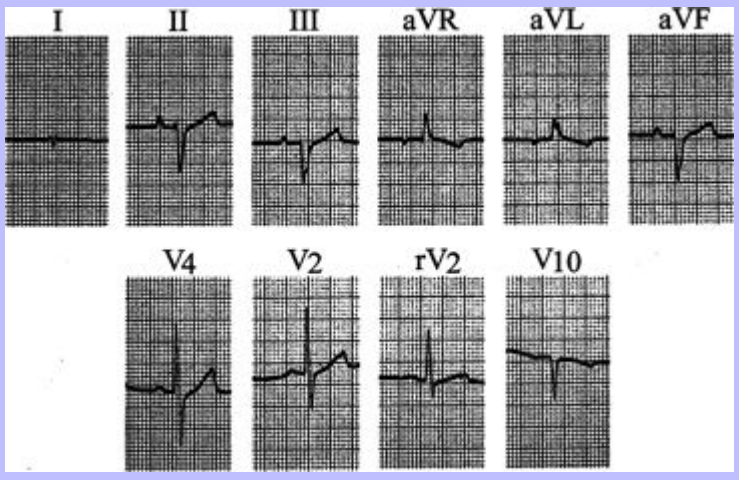
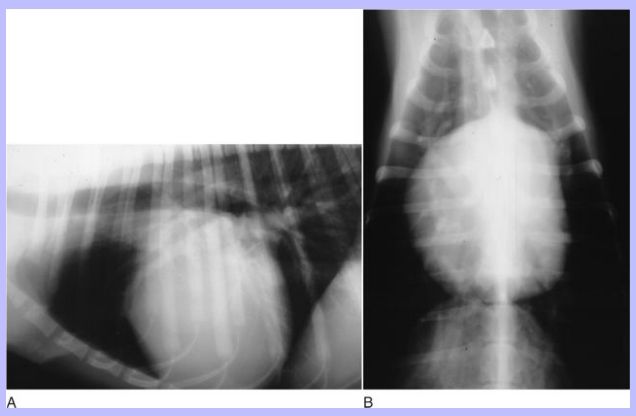


Figure 200-15 Lateral **(A)** and dorsoventral **(B)** radiographs from a standard poodle with an atrial septal defect. The cardiac silhouette is enlarged, with prominence of the right atrium, right ventricle, and pulmonary vessels.



Cardiac catheterization of animals with an ASD is helpful in the evaluation of the magnitude and direction of shunting. In cases of left-to-right shunting, oximetry samples from the venae cavae, right atrium, and right ventricle indicate an increase in oxygen saturation between the venae cavae and the atrium and/or ventricle, and the magnitude of systemic to pulmonary shunting can be estimated.[25] Central venous and right ventricular diastolic pressures are elevated when congestive heart failure is present or imminent. Increased systolic flow across the pulmonic valve may result in "relative" pulmonic stenosis, identified by a mild systolic pressure gradient (5 to 15 mm Hg) between the right ventricle and pulmonary artery.[63a] Flow through the atrial septal defect can be demonstrated by angiocardiography. When introduced via a femoral vein, a catheter often can be easily passed from the right atrium through an ASD or patent foramen ovale into the left atrium, allowing injection of a contrast medium and visualization of the left-to-right shunting. Alternatively, injection of the contrast material into the pulmonary artery outlines left-to-right shunting defects during the left-sided phase of the study. After pulmonary venous return, the atrial septum usually can be seen between the left atrium and the aorta on the lateral projection. Passage of dye from the left atrium into the right atrium and vena cavae confirms the presence of the defect. With more extensive endocardial cushion defects, a left ventricular injection can be performed to demonstrate the VSD, mitral regurgitation, and occasionally left ventricular-to-right atrial shunting.

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Figure 200-16 Echocardiography of atrial septal defect (ASD) and endocardial cushion defect. **A,** Right long axis view from a standard poodle with a secundum ASD. Color flow Doppler **(B)** and contrast echocardiography **(C)** studies indicate left-to-right flow through the ASD. **D,** Right long axis view from a dog with an endocardial cushion defect. A large ASD, a ventricular septal defect, and a single atrioventricular valve override the interventricular septum. Both the left and right atria are enlarged. *RA*, Right atrium; *RV*, right ventricle; *LA*, left atrium; *LV*, left ventricle.

The clinical features of a VSD depend on the magnitude of the shunt and whether complications or other defects are present. In animals with a typical small, subcristal VSD, a harsh, holosystolic murmur is heard best over the right midprecordium to cranial precordium.* In rare cases of supracristal VSD, the defect opens just under the pulmonic valve, and the systolic murmur may be heard best at the left base. Splitting of the second heart sound can occur, but it often is not recognized because of the imposition of the murmur on the second heart sound. If distortion of the aortic root causes significant aortic regurgitation, a blowing, decrescendo diastolic murmur is audible over the left ventricular outflow area. These combined systolic and diastolic murmurs are sometimes described as a *to-and-fro murmur*. Aortic regurgitation flow into the right ventricle can produce a diastolic murmur best heard on the right hemithorax.[17b] Systolic murmurs over the atrioventricular valves may also be detected if the defect is part of a more extensive endocardial cushion defect.

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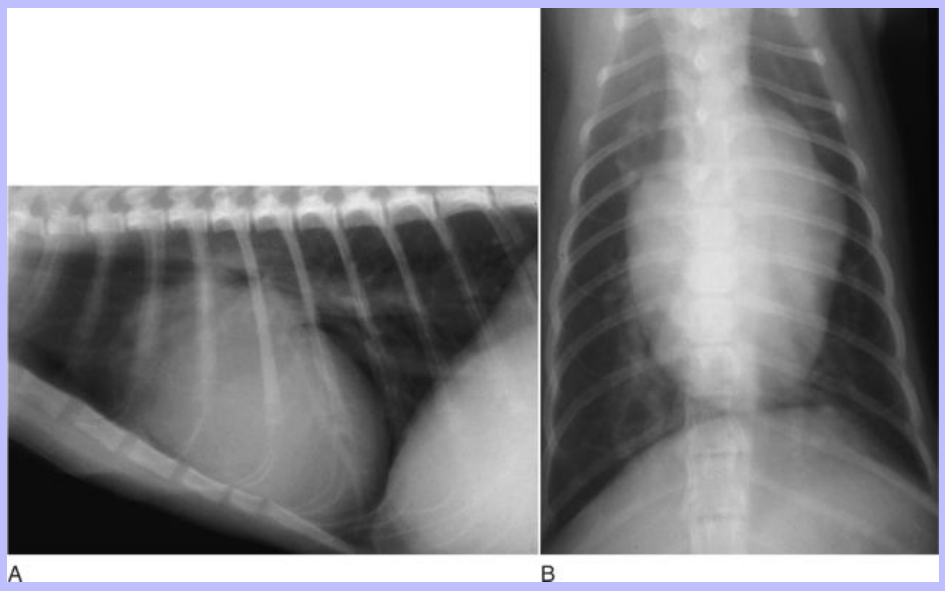
Figure 200-17 Lateral **(A)** and dorsoventral **(B)** thoracic radiographs of a cat with a ventricular septal defect and a large left-to-right shunt. Cardiac silhouette is enlarged, and rounding of the cranial border of the heart can be seen on the lateral view. The main pulmonary artery and left atrium are enlarged on the dorsoventral view. The pulmonary vasculature is prominent.



Electrocardiographic findings in animals with a VSD are variable. With moderate or large left-to-right shunts, there is often evidence of left atrial or ventricular enlargement, but right ventricular conduction defects also occur. Frontal plane leads may demonstrate a subtle abnormality in early ventricular septal activation, characterized by a Q wave that is wide or contains high-frequency notching.[69a] Right axis deviation and a narrow QRS complex in a dog with VSD usually indicates right ventricular hypertrophy

and a more complex lesion, such as VSD with pulmonic stenosis or pulmonary hypertension. Thoracic radiographs are very useful in assessing the magnitude of left-to-right shunting VSDs. Pulmonary hypervascularity and left atrial and ventricular enlargement are observed in proportion to the magnitude of the shunt (Figure 200-17).[22a,24a] The main, lobar, and peripheral pulmonary arteries are usually prominent. In animals with small defects, thoracic radiographs may appear entirely normal. With large defects, the right ventricle may also enlarge. A large pulmonary artery segment, underperfused lungs, and small peripheral pulmonary vasculature suggest the possibility of pulmonic stenosis or pulmonary hypertension and right-to-left shunting. Two-dimensional color flow Doppler echocardiography usually identifies all but the smallest VSDs (Figure 200-18). Spectral Doppler studies are useful for quantifying the high-velocity jet through small, resistive VSDs, as previously mentioned. Contrast echocardiography may also be used to identify flow through the defect, but it is usually not necessary if a careful echocardiographic examination is performed.

Cardiac catheterization in animals with a VSD allows identification of the anatomic defect and estimation of the degree of shunting.[27c] Oximetry samples demonstrate a “step-up” in oxygen content between the right ventricle and pulmonary artery. Intracardiac pressures are usually normal in dogs and cats with a small VSD. Right ventricular pressures are often elevated 5 to 15 mm Hg above the pressure in the pulmonary artery, a reflection of increased transvalvular flow and relative pulmonic stenosis. More dramatic increases in right ventricular systolic pressure indicate pulmonary hypertension or concurrent pulmonic stenosis, and the development of elevated end-diastolic ventricular pressures and central venous pressure herald the onset of heart failure. In uncomplicated cases, left ventricular angiocardiography can outline the VSD (Figure 200-19). Bidirectional or right-to-left shunting is observed when RV systolic pressure reaches and exceeds LV systolic pressure. Anatomic changes of the semilunar valves or great vessels, especially of the aortic root, are best visualized by injection of contrast in the proximal aorta, which is also the preferred location for determining the presence and severity of aortic regurgitation.[17b]

* References 5a, 10a, 23c, 27c, 28c, and 68a.

200.11.1.2.7

Natural history

The morbidity and mortality associated with atrioventricular septal defects depend on the size and location of the defect, the magnitude and direction of shunt flow, and whether additional lesions are present. Spontaneous closure of small VSDs often occurs in children, but this is an uncommon occurrence in cats and dogs.[71a] Animals with uncomplicated small defects (ASDs and VSDs) and modest shunts usually live a normal life span without ever developing recognizable clinical signs. Large shunts that cause moderate to severe cardiomegaly often lead to intractable congestive heart failure. 992

Moderate to severe aortic regurgitation, an uncommon complication of VSD, presents a very substantial 993 risk of left heart failure and shortened survival.[17b] It is often difficult to predict the outcome in very young animals with a VSD; this is more easily done when they grow closer to adult size at 6 to 12 months of age. Animals that develop pulmonary hypertension (Eisenmenger's syndrome) have a guarded short-term prognosis and a very guarded to poor long-term prognosis, although survival beyond 7 years is possible. Cats with severe endocardial cushion defects often develop marked cardiomegaly and biventricular congestive heart failure at an early age (less than 2 years), warranting a very guarded to poor prognosis.

Figure 200-18 Echocardiography of a Siamese cat with a ventricular septal defect (VSD). **A,** Right long axis view shows the VSD (*) between the left ventricular outflow tract *(LVOT)* and aorta *(Ao)* and opening into the right ventricle *(RV)*. Note the proximity of the VSD to the root of the aorta and the origin of the aortic valve *(arrowhead)*. **B,** Right long axis color flow Doppler study reveals systolic left-to-right shunting across the VSD into the right ventricle.

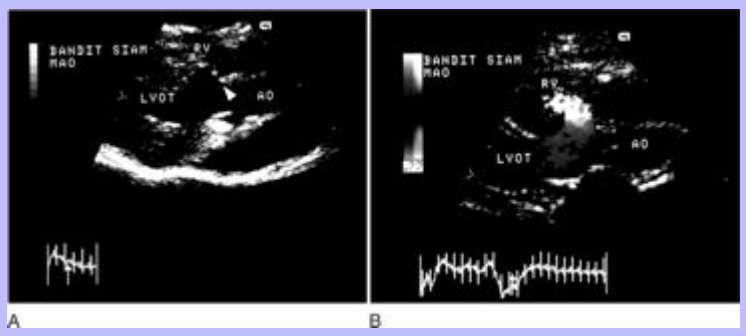
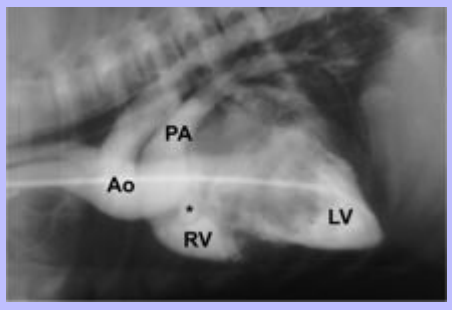


Figure 200-19 Angiogram of a 6-month-old Welsh corgi with a ventricular septal defect (VSD). An injection into the left ventricle *(LV)* outlines the aorta *(Ao)*. Contrast can be seen shunting across the VSD into the right ventricle *(RV)* and the pulmonary artery *(PA)*. The left ventricle is mildly enlarged. A portion of an aortic valve leaflet (*) appears to prolapse into the VSD.



200.11.1.2.8 Clinical management

Surgical closure is the definitive treatment for all atrioventricular septal defects, but open-heart correction is uncommonly attempted in animals because of the usual requirement for cardiopulmonary

bypass or other techniques to arrest the heart.[29c-31c,76a,77a] Palliative treatment of a VSD may be accomplished without bypass by applying a constrictive band around the main pulmonary artery. This technique creates supravalvular pulmonic stenosis and increases the right ventricular systolic pressure, thereby reducing the magnitude of left-to-right shunting.[75a] This procedure is recommended for dogs and cats showing signs of rapidly progressive cardiomegaly and overt or impending congestive heart failure. Overaggressive banding should be avoided, because it can result in pressure overload, acute right heart failure or, in surviving animals, right-to-left shunting. Alternatively, systemic arterial vasodilators can be administered to reduce systemic vascular resistance and the magnitude of left-to-right shunting.[79a] As noted for reversed PDA, surgical correction should not be attempted in animals with Eisenmenger's syndrome. Restricted physical activity is probably the most prudent and effective strategy, and periodic phlebotomy may be useful in some patients that develop extreme polycythemia. The PCV should be maintained at 58% to 65%.

200.11.2 Valvular Regurgitation

200.11.2.1 Pulmonic and Aortic Valve Insufficiency

200.11.2.1.1 Pulmonic insufficiency

Primary congenital pulmonic insufficiency (PI) is an uncommon abnormality that results from abnormal development of valve leaflets or dilatation of the pulmonary artery annulus.[95a,96a] Pulmonic valve insufficiency causes volume overload and eccentric hypertrophy of the right ventricle. The main and proximal branches of the right and left pulmonary arteries enlarge to accommodate the concomitant increase in RV stroke volume. Isolated pulmonic valve insufficiency is often well tolerated, but heart failure can develop when severe PI is induced experimentally in dogs. Congenital pulmonic insufficiency is more likely to cause heart failure if pulmonary vascular resistance subsequently increases as a result of severe pulmonary parenchymal or vascular disease. Trivial pulmonic insufficiency is often observed in dogs with a PDA, presumably from dilatation of the main pulmonary artery. Most dogs with pulmonic valve stenosis have mild valvular insufficiency, but severe concurrent PI is sometimes seen. Pulmonic insufficiency of varying degrees of severity may also develop as a result of surgery or balloon dilatation to relieve PS. Pulmonic insufficiency is a potential consequence of any disorder that prompts the development of pulmonary hypertension.

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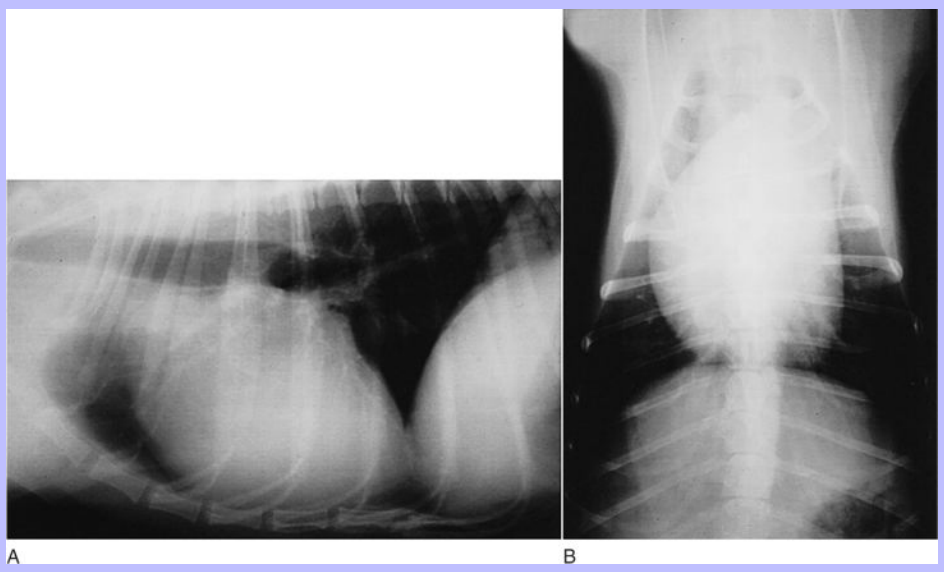
Clinical features of PI include variable systolic (due to increased flow) and diastolic murmurs best heard at the left heart base. This to-and-fro murmur should not be confused with the continuous murmur of PDA. Electrocardiograms from dogs with congenital PI may be normal or may reflect right ventricular enlargement. Thoracic radiographs show enlargement of the main pulmonary artery and right ventricle, giving the erroneous impression of PS to the unaware (Figure 200-20). Injection of a contrast medium into the main pulmonary artery using a small-diameter catheter documents valvular insufficiency (Figure 200-21). Slow clearance of contrast from the dilated and thin-walled right ventricle also supports a diagnosis of PI. Color flow Doppler echocardiography elegantly demonstrates these same features and permits visualization of the rudimentary or misshapen valve leaflets (see Figure 200-21). Doppler studies also aid the recognition of pulmonary arterial hypertension. When the velocity of the pulmonary regurgitant jet exceeds 3 m/s, pulmonary hypertension is the likely cause of the pulmonary artery dilatation and valvular insufficiency. Treatment for congenital PI has not been described in companion

animals. In dogs suffering from heart failure, conventional medical therapy with diuretics and ACE inhibitors is a reasonable palliative approach.

Figure 200-20 Radiographs from a Cavalier King Charles spaniel with congenital pulmonic valve insufficiency, showing convincing evidence of right ventricular enlargement in the lateral **(A)** and dorsoventral **(B)** projections. The pulmonary artery segment is markedly enlarged (see text for discussion).



200.11.2.1.2 Aortic insufficiency

Isolated congenital aortic insufficiency (AI) is a rare disorder. It occasionally is detected in young or older dogs with idiopathic dilatation of the aorta *(annuloaortic ectasia)*. Mild to moderate aortic insufficiency has also been reported in a boxer and a hound with quadricuspid aortic valves.[26] With the increasing application of Doppler echocardiography, aortic regurgitation is recognized with increasing frequency as a complication of other cardiac malformations.[108a,109a] Aortic insufficiency often accompanies subvalvular aortic stenosis and has been observed with ventricular septal defects and tetralogy of Fallot and after balloon catheter dilatation for SAS. The potential mechanisms for aortic valvular insufficiency in these conditions have been reviewed.[108a] As in congenital pulmonic insufficiency, the murmur resulting from AI can be both systolic and diastolic (to-and-fro murmur) and is best heard over the left hemithorax. Many dogs with mild AI do not evidence an audible murmur. The diagnosis of AI is supported by palpation of a hyperkinetic arterial pulse resulting from the increased stroke volume and diastolic runoff of aortic blood back into the left ventricle. Left ventricular eccentric hypertrophy develops in proportion to the severity of the insufficiency. Severe AI commonly results in left-sided congestive heart failure. Documentation of AI and estimation of its severity requires angiocardiography or Doppler echocardiography. Definitive repair requires cardiac bypass surgery and valve replacement, an unlikely proposition. Use of arterial vasodilators can reduce the regurgitant

volume and may delay the onset of heart failure. Treatment with diuretics, ACE inhibitors, and positive inotropic drugs are indicated if heart failure is present.

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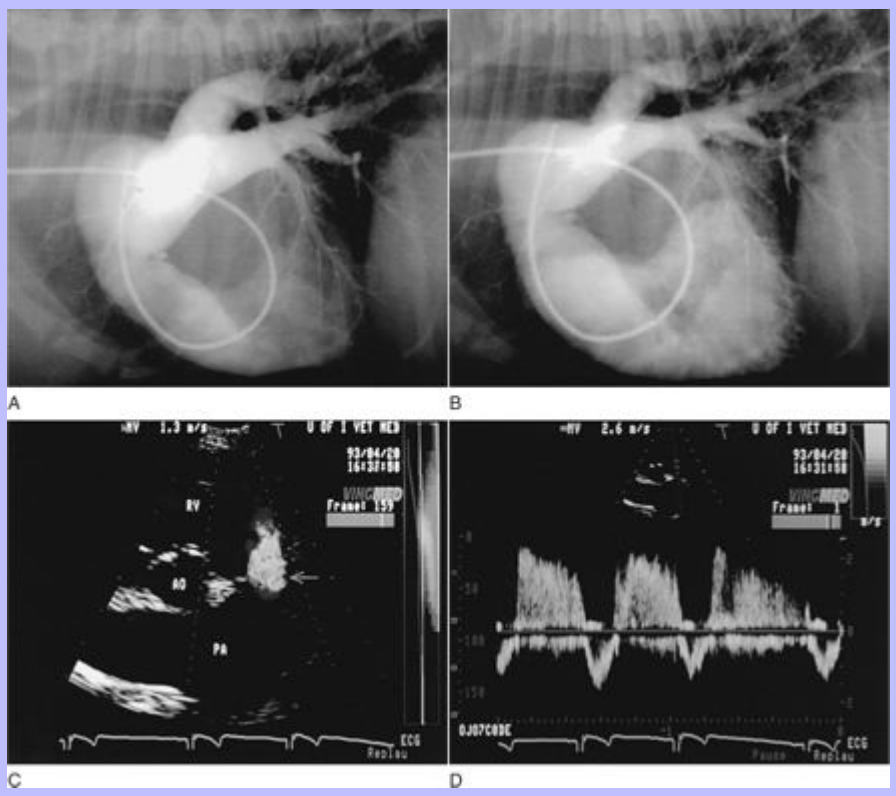
Figure 200-21 Angiocardiogram recorded from the same dog as in Figure 200-20. **A,** Contrast material injected into the pulmonary artery leaks immediately back into the right ventricle through the incompetent pulmonic valve. **B,** Several frames later, the right ventricle has filled with contrast, establishing substantial pulmonic valve incompetence. A dysplastic valve remnant is also visible. **C,** A color flow Doppler study was performed several years later in the same dog. Disturbed flow entering the right ventricle *(RV)* from the pulmonary artery is shown on this black and white rendition of a color study. Note the very dilated main pulmonary artery. *Ao*, aorta. **D,** Pulsed wave Doppler study shows that the diastolic flow is moving at a relatively low velocity (just over 2 m/s), excluding the possibility of pulmonary hypertension.



200.11.2.2 Atrioventricular Valve Dysplasia

Congenital malformations of the mitral and tricuspid valves are reported in both cats and dogs.[1–5c,12a,58–62c,110a-121a] Consequences of these malformations include mitral and tricuspid regurgitation, inflow obstruction (i.e., mitral or tricuspid valve stenosis), and dynamic obstruction of the left ventricular outflow tract. The most common physiologic consequence of atrioventricular valve malformation is valvular insufficiency. The pathophysiology and clinical course of congenital mitral regurgitation are similar to acquired degenerative valvular disease in the dog. For this reason, only the salient features of these conditions are reviewed, and the reader is directed to Chapter 201 for greater detail. Congenital stenoses of the atrioventricular valves, as well as other interatrial obstructs, are recognized more frequently in dogs and cats, presumably because of the increased use of Doppler echocardiography. Systolic anterior motion (SAM) of the mitral valve apparatus and dynamic LV outflow obstruction in cats and dogs, long regarded solely as a manifestation of hypertrophic cardiomyopathy (see Chapter 203; 204), may be caused solely by architectural changes in the mitral valve apparatus in some animals. When the primary disorder is valve dysplasia, concentric left ventricular hypertrophy resolves if the obstruction is abolished by treatment (beta-receptor blocking drugs).

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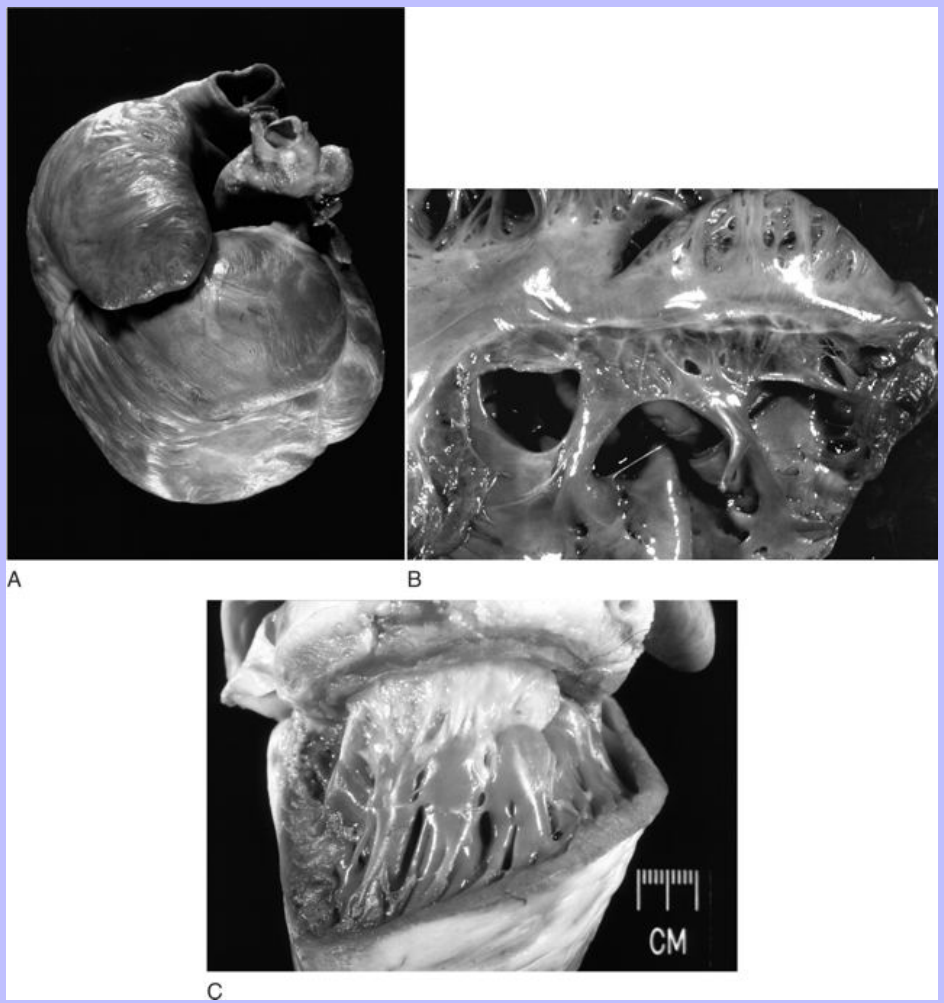
200.11.2.2.1 Pathology and pathogenesis

Tricuspid valve dysplasia has been shown to have a genetic basis in the most commonly afflicted breed, Labrador retrievers.[6,7] A heritable basis for mitral valve dysplasia in cats and some breeds of dogs is suspected, but convincing evidence has not yet been reported. A wide spectrum of morphologic abnormalities of the mitral and tricuspid valves have been described, including shortening, rolling, notching, and thickening of the valve leaflets; incomplete separation of valve components from the ventricular wall; elongation, shortening, fusion, and thickening of the chordae tendineae; direct insertion of the valve edge into a papillary muscle; and atrophy, hypertrophy, fusion, and malpositioning of the papillary muscles and chordae tendineae.[27,113a,120a] The usual consequence of these changes is valvular insufficiency. Examples of tricuspid and mitral valve dysplasia are shown in Figures 200-22 and 200-23. In dogs, mitral valve stenosis is common only in bull terriers, often occurring along with valvular aortic stenosis.[40b] Some dogs and cats with mitral or tricuspid dysplasia evidence a patent foramen ovale or a concurrent ASD, resulting in left-to-right or right-to-left shunting. Supravalvular mitral stenosis is discussed in a later section of this chapter, together with cor triatriatum.

Figure 200-22 Gross pathology of tricuspid dysplasia (TD). **A,** Cranial view of the heart from a patient with severe right atrial, auricular, and ventricular enlargement caused by TD. **B,** Tricuspid valve from a 2-year-old Labrador with severe TD. The edges of the valve leaflets insert directly into the papillary muscles, and conspicuous absence and shortening of the chordae tendineae are seen. The right atrium and ventricle are dilated. **C,** Curtainlike deformity of the tricuspid valve from a 2-year-old Samoyed with TD and tricuspid stenosis. The tricuspid valve is thickened and opaque. Multiple large, fused papillary muscles with short chordae tendineae are present.



200.11.2.2.2 Pathophysiology

The fundamental pathophysiologic abnormalities of atrioventricular valve malformations are briefly presented. Valvular insufficiency produces volume overloading, manifested as atrial dilatation and eccentric hypertrophy of the affected ventricle. Congestive heart failure often develops at a young age but occasionally does not develop until adulthood. In some dogs and cats with tricuspid dysplasia, cyanosis can be observed as a consequence of right-to-left shunting across a patent foramen ovale or ASD. Malformations that cause valve stenosis obstruct ventricular filling, resulting in increased atrial pressures and signs of congestive heart failure. Severe stenosis limits cardiac output such that hypotension, syncope, or collapse with exertion may be observed. Pulmonary hypertension and right heart failure frequently develop secondary to severe mitral stenosis as a consequence of chronically elevated left atrial pressure. As a result, some dogs that initially present with signs of pulmonary congestion from mitral stenosis can present again months later with signs of right heart failure. Dogs and cats with severe congenital valvular stenosis or regurgitation are predisposed to atrial fibrillation and paroxysmal or sustained supraventricular tachycardia; these conditions typically result in sudden clinical deterioration.

Figure 200-23 Gross pathology of mitral valve dysplasia. **A,** Marked left atrial dilatation in a cat with mitral valve dysplasia. **B,** Mitral valve in this cat shows a bizarre malformation of the anterior (cranioventral) leaflet. Also, the posterior (caudodorsal) papillary muscle is abnormally located, and it attaches directly to the leaflet with no intervening chordae. **C,** Marked dilatation of the left atrium is seen as a result of obstructed flow into the left ventricle. **D,** Grossly distorted mitral valve from a bull terrier with concurrent stenosis and insufficiency of the mitral valve. A thickened aortic valve, which caused mild aortic stenosis, is just visible on the left side of the picture. *LA*, left atrium.

200.11.2.2.3 Clinical findings

Cats of all breeds, Great Danes, German shepherds, bull terriers, golden retrievers, Newfoundland retrievers, Dalmatians, and mastiffs are predisposed to mitral dysplasia.[30b,111a,114a] Tricuspid dysplasia occurs in cats but seems to be most common in large male dogs, particularly Labrador retrievers.[9a,28] Clinical signs are referable to exertional fatigue or to right ventricular, left ventricular, or biventricular congestive heart failure. The hallmark of valvular insufficiency is a holosystolic murmur heard best over the affected valve area. A loud gallop may also be detected.[111a] A soft, late diastolic murmur and opening snap are sometimes auscultated in dogs or cats with valvular stenosis, but these findings are often absent or missed (Figure 200-24). In severe cases of tricuspid dysplasia, a murmur may not be present because the valve offers no resistance to regurgitant blood flow (Figure 200-25). Jugular venous distension and pulses are common findings in cases of tricuspid dysplasia.

Splintered QRS complexes (Rr′, RR′, rR′, rr′) are a distinctive and common ECG finding in dogs and cats with tricuspid dysplasia.[64c] Right heart enlargement patterns are also manifest. Tall or wide P waves are observed with all types of valvular dysplasia, but ventricular enlargement patterns are mainly limited to animals with regurgitant physiology and are not observed with isolated valve stenosis except when pulmonary hypertension develops secondary to mitral stenosis. Atrial arrhythmias, especially atrial fibrillation, are often recorded. The pattern of chamber enlargement on the thoracic radiographs generally reflects the involvement of the affected valve and resulting physiologic consequences (Figure 200-26). In cases of tricuspid dysplasia the degree of cardiomegaly is often impressive, and the heart may have a globoid appearance resembling that produced by pericardial effusion. The possibility of valvular stenosis should be considered whenever the atrium is markedly dilated without enlargement of the ipsilateral ventricle.

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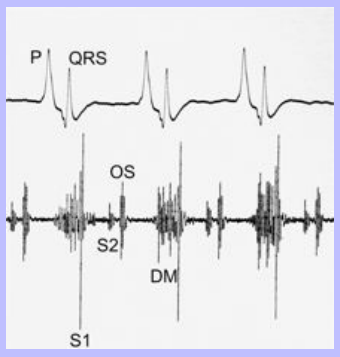
Figure 200-24 Phonocardiogram from the right apex in a 2-year-old Samoyed with tricuspid dysplasia and tricuspid stenosis. The ECG shows markedly elevated P waves consistent with right atrial enlargement. An early diastolic opening snap (OS) is present, followed by a late diastolic (presystolic) murmur (DM) that coincides with the P wave and atrial systole. S_1, First heart sound; S_2, second heart sound.



Definitive diagnosis of atrioventricular valve malformation requires echocardiography or cardiac catheterization and angiocardiography. Abnormal location, shape, motion, or attachment of the valve apparatus is easily observed by echocardiography (see Figure 200-25). With valve stenosis, color flow Doppler studies show a prolonged high-velocity jet (often greater than 2 m/s) entering the left or right ventricle during diastole, indicating the presence of a diastolic pressure gradient. With valve insufficiency, Doppler studies demonstrate regurgitant jets streaming from the ventricle into the atrium through the incompetent valve. Diastolic pressure gradients (valve stenosis) and varying degrees of ventricularization of atrial wave forms (valve insufficiency) can be recorded during cardiac catheterization. Angiographic visualization of valvular insufficiency is best appreciated by ventricular injections of contrast material, whereas valve stenosis is best demonstrated after an atrial injection (transseptal catheterization is required to accomplish left atrial injection).

200.11.2.2.4 Clinical management

Repair of the affected valve can be attempted, and surgical replacement of dysplastic atrioventricular valves has been successfully accomplished in a small number of animals.[65c-67c] Cardiac bypass is required for these infrequently performed procedures. Balloon valvuloplasty, with limited success, has been described in dogs with tricuspid stenosis.[68c,29] In most affected animals, medical treatment is instituted only if heart failure develops. Treatment of valvular insufficiency largely consists of diuretics, ACE inhibitors, and digoxin.[28] In dogs with tricuspid dysplasia and refractory heart failure, periodic thoracocentesis or abdominocentesis is often needed. In patients with valve stenosis, diuretics are used to control congestion. Inasmuch as tachycardia is poorly tolerated in patients with stenosis, every effort should be made to prevent stress and to restrict exercise. Administration of beta blockers, calcium channel blockers, and/or digoxin is helpful in some cases for the management of atrial fibrillation or other supraventricular tachyarrhythmias. Some patients tolerate serious defects surprisingly well for many years. In other cases, rapid progression to heart failure and death occur.

200.12 DEFECTS THAT CAUSE PRIMARILY PRESSURE OVERLOAD

200.12.1 Ventricular Outflow Obstructions

200.12.1.1 Pulmonic Stenosis

Pulmonic stenosis (PS) is the third most common congenital heart defect in dogs,[5c,30] and it is occasionally recognized in cats.[2c,32c,89a] In most cases pulmonic stenosis occurs as an isolated heart defect, but it frequently is accompanied by other cardiac anomalies, such as tricuspid dysplasia. Congenital outflow tract obstructions of the right heart can develop in the subvalvular and supravalvular regions, but primary malformation of the pulmonary valve (dysplasia) is the most frequently observed defect in dogs. Patterson et al.,[86a] who studied the heritability and pathology of pulmonic valve dysplasia in the beagle, initially suggested a polygenic mode of transmission for this defect. However, these breeding studies did not exclude the possibility of a single-gene mechanism with variable penetrance. The pattern of inheritance of PS has not been studied in other predisposed dog breeds or in cats.

200.12.1.1.1 Pathology

Valvular lesions consist of varying degrees of valve thickening, leaflet fusion, and/or hypoplasia of the valve annulus. Although some dogs manifest a thin, dome-shaped valve with a central orifice (Figure 200-27), many dogs have more complicated lesions that resemble atypical PS in children.[15a,86a,88a] The valve leaflets are often thickened, misshapen, and/or fused (see Figure 200-27). The annulus of the pulmonic valve is hypoplastic in some dogs, which further narrows the area available for right ventricular ejection. Histologic abnormalities include thickening of the valve spongiosa and the presence of bands of fusiform cells in a dense collagen network. These changes are thought to represent overproduction of normal valve elements or failure of conversion of the cushionlike embryonic valve primordia. Some dogs with valve dysplasia have a fibrous ring just below the valve leaflets in addition to the valvular changes. In other dogs, the obstructive lesion occurs in the infundibular region of the right ventricular outflow tract (RVOT). On occasion the RVOT is partitioned from the body (inflow region) of the right ventricle by a well-developed, fibromuscular ridge, resulting in an anomaly referred to as double-or dual-chambered right ventricle.[31] Supravalvular PS is uncommon and in the authors' experience has been most often observed in giant schnauzers. A unique form of subvalvular PS caused by anomalous development of the coronary arteries has been described in English bulldogs and in boxers.[32,33] In this condition, the left and right coronary arteries branch from a single large coronary artery, which originates from the right aortic sinus of Valsalva (Figure 200-28). From this location the anomalous left coronary artery encircles the RVOT just below the pulmonary valve, contributing to the subvalvular component of this complex malformation (see Figure 200-28).

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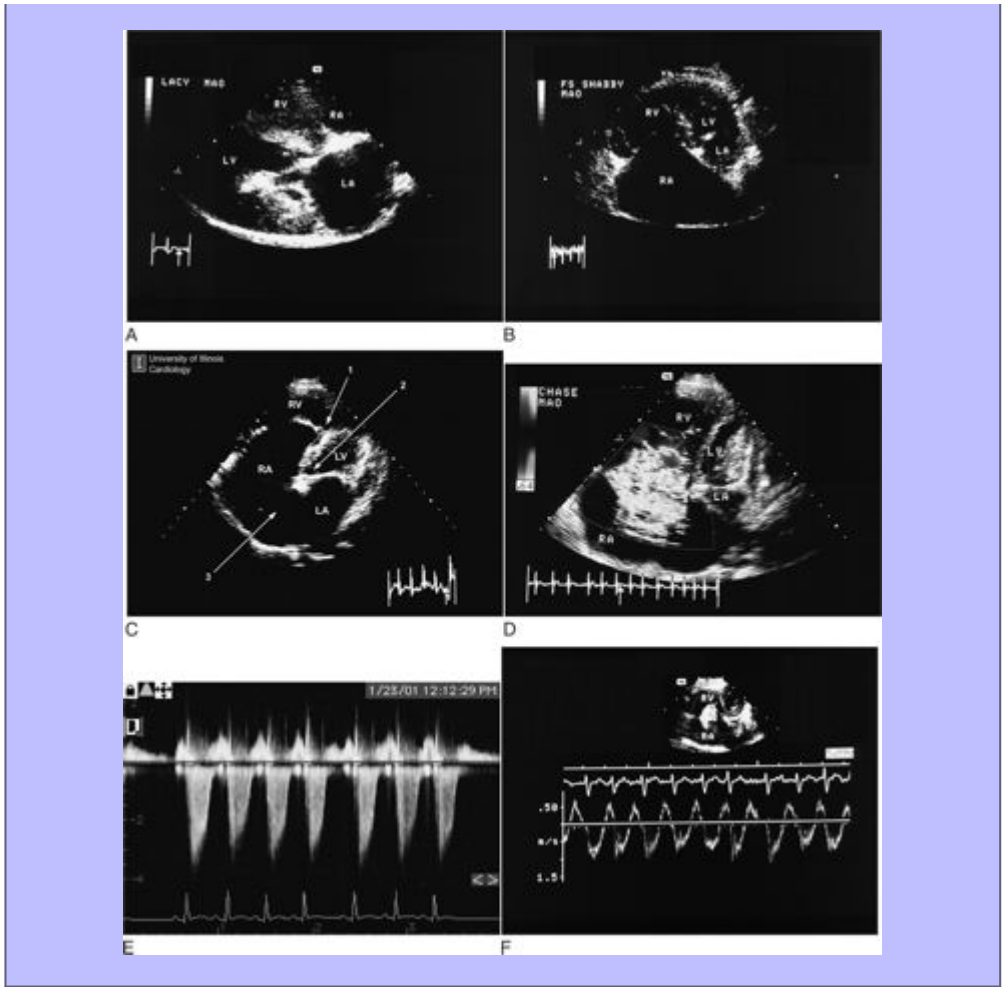
Figure 200-25 Echocardiography of mitral dysplasia (MD) and tricuspid dysplasia (TD). **A,** Right axis view from a 4-month-old pit bull with MD and aortic stenosis. The mitral valve leaflets are markedly thickened, and the chordae tendineae are shortened. The left atrium *(LA)* is enlarged, and the left ventricle *(LV)* is hypertrophied. **B,** Left apical view from a cat with TD, showing severe right atrial (*RA*) and right ventricular *(RV)* enlargement. **C,** Left apical view from a dog with an Ebstein-like abnormality. The origin of the tricuspid valve is displaced apically, and the septal leaflet is fused to the interventricular septum *(1)*. The origin of the mitral valve leaflet *(2)* is shown for comparison. The near-parallel orientation of the ultrasound beam gives the false impression of a large atrial septal defect *(3)*. **D,** Left apical color flow Doppler study from a 2-year-old Labrador retriever with severe tricuspid regurgitation caused by TD. **E,** Continuous wave Doppler tracing of tricuspid regurgitation from a dog with TD. The maximal velocity of the regurgitant jet is 3.5 m/s, suggesting a moderate increase in right ventricular systolic pressure. **F,** Pulsed wave Doppler study from a 7-year-old cat with severe TD demonstrates low velocity and laminar tricuspid regurgitation, indicating that the defect is very large and offers little resistance to regurgitant flow. No murmur was ausculted in this patient.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B
C
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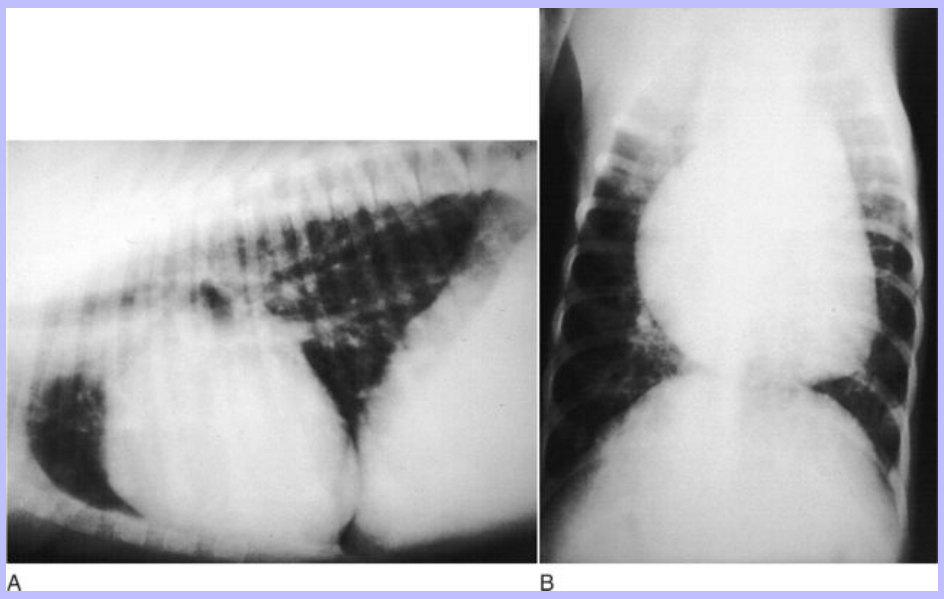
Figure 200-26 Lateral **(A)** and dorsoventral **(B)** thoracic radiographs from a dog with tricuspid dysplasia (TD). Right atrial and ventricular enlargement is seen in both views. The lateral film demonstrates a bulge in the cranial waist, most likely due to right auricular enlargement.



Increased resistance to systolic ejection results in concentric right ventricular hypertrophy, which generally develops in proportion to the severity of the obstructing defect. Although this compensatory response serves to normalize wall stress, it can have deleterious effects. In some dogs with PS, secondary hypertrophy of the infundibular region of the RVOT contributes to outflow tract obstruction, particularly during exercise or stress. The existence of this additional mechanism of obstruction can complicate the clinical outcome of surgical valvotomy or interventional balloon valvuloplasty. Other cardiac defects can complicate the physiology and alter the clinical presentation and prognosis of patients with PS. Pulmonic stenosis and tricuspid valve dysplasia can be a particularly injurious combination. Insofar as the volume of tricuspid regurgitation is a function of the size of the regurgitant orifice (the severity of dysplasia) and the systolic pressure gradient (the severity of PS), severe tricuspid regurgitation tends to develop in affected dogs, leading to intractable right-sided heart failure.

Meticulous ultrasonic examination, often using contrast echocardiography, reveals that patent connections between the right and left heart occur in a substantial percentage of dogs with PS, and some dogs with severe PS become cyanotic as a result of right-to-left shunting through an ASD, patent foramen ovale, or VSD. Many of these abnormalities have a common origin in the maldevelopment of the embryonic conotruncal septum. These types of defects are discussed more thoroughly in the section on tetralogy of Fallot.

200.12.1.1.2 Pathophysiology

Obstruction to right ventricular outflow increases resistance to ejection, causing a proportional increase in ventricular systolic pressure. Concentric hypertrophy of the right ventricle develops in an attempt to normalize wall stress. During systole, blood ejected from the right ventricle accelerates as it traverses the obstructive orifice. Blood flow velocity increases and becomes turbulent distal to the obstruction. A poststenotic dilatation develops in the main pulmonary artery as the turbulent jet of blood decelerates and expends some of its kinetic energy against the vessel wall.

Concentric hypertrophy reduces right ventricular diastolic compliance, impairs ventricular filling, and often results in elevated right atrial pressure. Tricuspid regurgitation from progressive ventricular dilatation, valvular dysplasia, or a combination of these factors can contribute to further increases in atrial pressure. As right atrial pressure approaches 15 mm Hg, jugular distension, ascites, pleural effusion, and other signs of right-sided congestive heart failure develop. Syncope and sudden death are uncommon in dogs with PS. The physiologic mechanisms responsible have not been elucidated. Hypotension is presumed to develop as a consequence of reduced cardiac output (secondary to bradycardia or worsening of a dynamic infundibular obstruction) and in combination with peripheral arteriolar vasodilatation (with or in anticipation of exercise). Stimulation of mechanoreceptors in the pressure overloaded right ventricle may trigger the reflex bradycardia and vaso-dilatation. Reduced right coronary blood flow has been documented in some dogs with pulmonic stenosis and may contribute to the development of syncope, exercise intolerance, and myocardial failure. On rare occasion, severe septal hypertrophy due to PS results in dynamic left ventricular outflow tract (LVOT) obstruction.

200.12.1.1.3 Clinical findings

Pulmonic stenosis is common in certain breeds, including beagles, Samoyeds, Chihuahuas, English bulldogs, miniature schnauzers, cocker spaniels, Boykin spaniels, Labrador retrievers, mastiffs, chow chows, Newfoundland retrievers, basset hounds, and other terrier and spaniel breeds.[8a,9a,9b,19b] Miniature Doberman pinschers also seem predisposed. Most dogs with PS are asymptomatic in the first year of life, during which the condition usually is discovered through detection of a heart murmur. Approximately 35% of dogs with severe disease demonstrate clinical signs, which can include exertional fatigue, syncope, or ascites.[34] Signs of congestive right heart failure (e.g., ascites) are most often reported in older dogs.[88a] Cyanosis may be noted when PS is complicated by right-to-left shunting across a patent foramen ovale or coexisting atrial or ventricular septal defect.

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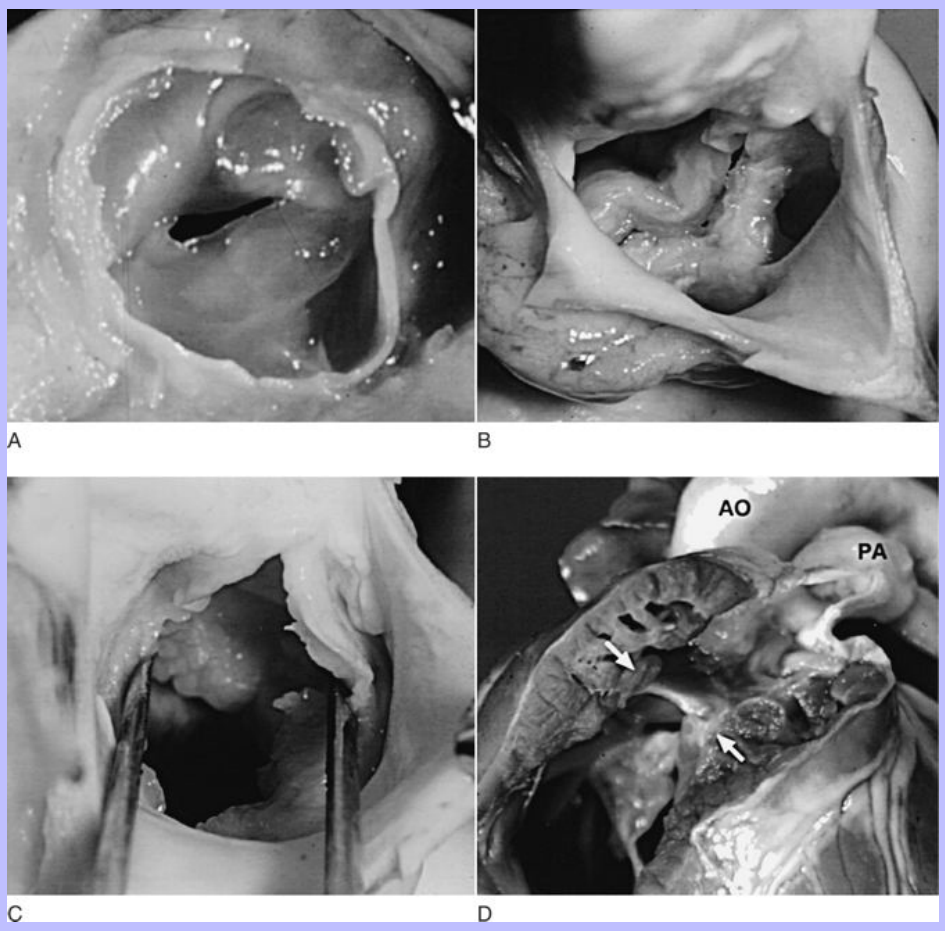
Figure 200-27 Pathology specimens from dogs with pulmonic stenosis (PS). **A,** Pulmonic valve leaflets are thin but fused with a central orifice in this 1-year-old Labrador retriever; they are similar to the domed valves of children with PS. **B,** Very thick (dysplastic) and bicuspid pulmonic valve from a Staffordshire terrier. **C,** Same dog as in **B;** the leaflets have been distracted to show a small subvalvular ridge. **D,** Fibromuscular ring *(arrows)* in the right ventricular infundibulum several centimeters below the pulmonic valve.



The most prominent physical examination finding is a systolic ejection murmur that is best heard over the left heart base and that often radiates dorsally. In some cases the murmur is heard equally well on the right cranial thorax. In dogs with concurrent severe pulmonic valvular insufficiency, the systolic ejection murmur is accompanied by a soft decrescendo diastolic murmur, which is heard best just ventral to the pulmonic valve region. A holosystolic murmur of tricuspid regurgitation may be noted over the right

hemithorax as well. Large-amplitude jugular pulses may result either from a giant *a wave* caused by atrial contraction into the stiff right ventricle or from *cv waves*, which indicate significant tricuspid regurgitation. Jugular venous distension and prominent jugular pulses are evident in most dogs with right heart failure and ascites. Peripheral arterial pulses are usually normal.

Right ventricular enlargement is usually present on the electrocardiogram unless the lesion is very mild.[31a,32a,90a] Right axis deviation and deep S waves in leads I, II, and III and in the left precordial chest leads (V_2 and V_4) are common indicators of right heart enlargement (Figure 200-29). Thoracic radiographs typically show a prominent right heart and poststenotic dilatation of the main pulmonary artery (Figure 200-30).[8a,22a,24a,88a] These changes are usually most evident on the dorsoventral view. Additional and more variable findings include dilatation of the proximal left pulmonary artery, diminished size of the pulmonary vasculature, and enlargement of the caudal vena cava.

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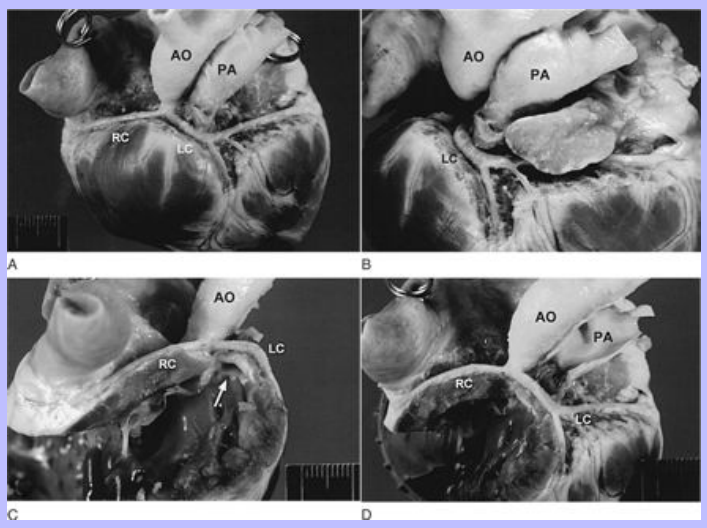
Figure 200-28 Coronary artery anomaly seen in some English bulldogs with pulmonic stenosis. **A,** Left and right coronary arteries are seen to branch from a single large coronary artery that originates from the right aortic sinus of Valsalva. From this location, the left coronary artery encircles the right ventricular outflow tract just below the pulmonary valve **(B),** thereby contributing to the subvalvular component of this complex malformation **(C** and **D). C,** Left coronary artery courses over the right ventricular outflow tract just below the annulus of the pulmonic valve *(arrow)*. **D,** Anterior wall of the pulmonary artery *(PA)* has been removed to show the hypoplastic pulmonic annulus, the diminutive proximal PA, and the crowded and thickened valve leaflets.



Echocardiography is the technique most commonly used to confirm a diagnosis of PS. M-mode and two-dimensional imaging typically show concentric hypertrophy of the right ventricle, increased prominence of the papillary muscles, deformity in the region of the obstruction or obstructions, narrowing of the RVOT, varying degrees of right atrial enlargement, and poststenotic dilatation of the main pulmonary artery (Figure 200-31).[3,35] Of the four cardiac valves, the pulmonic valve is often the most difficult to visualize clearly by transthoracic echocardiography. Thus it is impossible to visualize the exact location and nature of the obstruction in some dogs. It is often particularly difficult to identify a discrete subvalvular obstruction close to the pulmonary valve. The pulmonic valve leaflets are typically thickened and often fused, and they appear to dome upwards into the pulmonary artery during systole (see Figure 200-31). Hypoplasia of the pulmonic valve annulus further obscures the valve anatomy and confounds consideration of treatment. Color flow Doppler echocardiography is useful for establishing the anatomic location of the obstruction, because the turbulent, high-velocity jet can usually be seen emerging just distal to the obstructive orifice (see Figure 200-31). Mild to moderate pulmonic valve insufficiency is also apparent in many dogs with valvular PS.

For accurate quantification of the severity of the obstruction, the peak velocity of the blood flow jet must be recorded on a spectral Doppler tracing acquired with the continuous wave Doppler beam in parallel alignment with the direction of flow (see Figure 200-31). This usually is accomplished from either the right or left cranial parasternal windows. The modified Bernoulli equation ($\Delta P = 4V^2$) is applied to relate the instantaneous pressure gradient across an obstruction (ΔP, in mm Hg) to the peak velocity of the jet distal to the obstruction (V, in m/s). As a general rule, Doppler-derived gradients are 40% to 50% higher than the gradient measured during cardiac catheterization in an individual dog.[20b] Such discrepancies are attributed in part to the fact that Doppler studies are performed in awake animals, and transvalvular flow is considerably higher under these circumstances than in dogs that have been anesthetized for cardiac catheterization. In addition, hemodynamic studies typically indicate the severity of obstruction as a peak-to-peak pressure gradient, and such measures are almost always lower than the instantaneous peak pressure gradient calculated from Doppler measures of peak flow velocity.[36] Doppler interrogation of the right heart is also particularly helpful for identifying and assessing the severity of coexisting tricuspid valve insufficiency. Measurement of the velocity of this regurgitant jet is particularly helpful for assessing the severity of the PS obstruction when proper alignment with flow through the outflow tract cannot be obtained. In dogs with both dynamic (infundibular) and fixed (valvular) stenosis, Doppler interrogation of the outflow tract and pulmonary artery can produce a tracing that displays the temporal and velocity relationship between the two components of the stenosis.

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Figure 200-29 Electrocardiogram from a dog with pulmonic stenosis, showing a typical right ventricular enlargement pattern. The mean electrical axis is shifted to the right (–100 degrees), and prominent S waves are seen in leads II, III, aVF, V_2, and V_4.

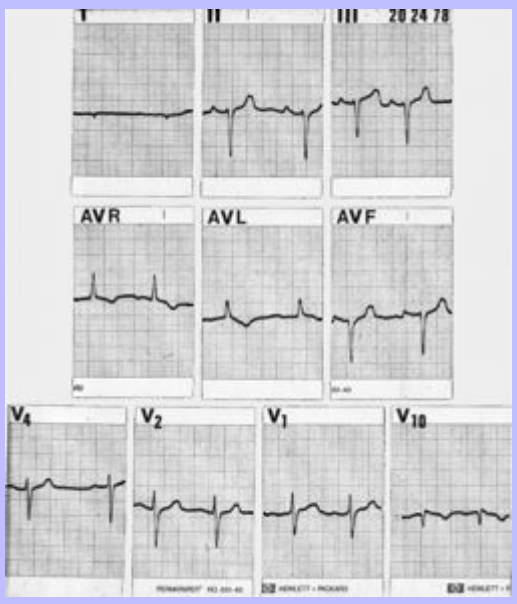


Figure 200-30 Lateral **(A)** and dorsoventral **(B)** thoracic radiographs from a dog with pulmonic stenosis. Rounding of the sternal border and a bulge in the cranial waist of the heart can be seen in the lateral view. Right heart enlargement and a bulge in the main pulmonary artery segment are seen in the dorsoventral view. Pulmonary vessels are diminished even in the absence of a right-to-left shunt.

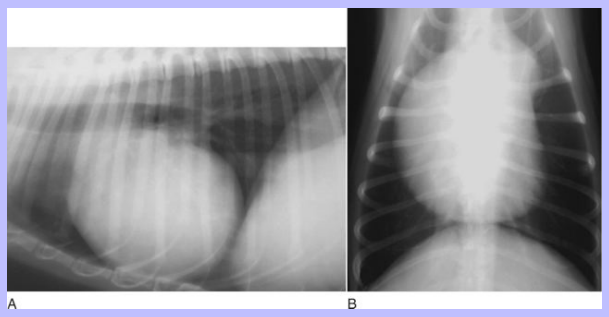


Figure 200-31 Echocardiography of pulmonic stenosis (PS). **A,** Right long axis view from a dog reveals severe concentric hypertrophy of the right ventricle *(RV)*. Right atrium *(RA)* is dilated. **B,** Right short axis view from a dog shows flattening of the interventricular septum and right ventricular concentric hypertrophy caused by pressure overload. **C,** Right short axis view of the heart base from a dog with valvular PS shows thickened pulmonic valves. Poststenotic dilatation of the PA can be seen (PA, pulmonary artery). **D,** Transesophageal ultrasound study of a young rottweiler with valvular PS. The pulmonic valve leaflets can be seen doming into the pulmonary artery *(PA)* during systole. **E,** Color flow Doppler study in a dog shows high velocity and turbulent blood flow moving from the right ventricle *(RV)* through the stenosis *(arrow)* and into the main pulmonary artery *(MPA)*. **F,** Continuous wave Doppler tracing obtained from a view similar to **E** shows high-velocity systolic flow (5 m/s) through the obstruction. Pulmonic insufficiency is also noted during diastole. *LA,* Left atrium; *LV,* left ventricle; *RVOT,* right ventricular outflow tract.

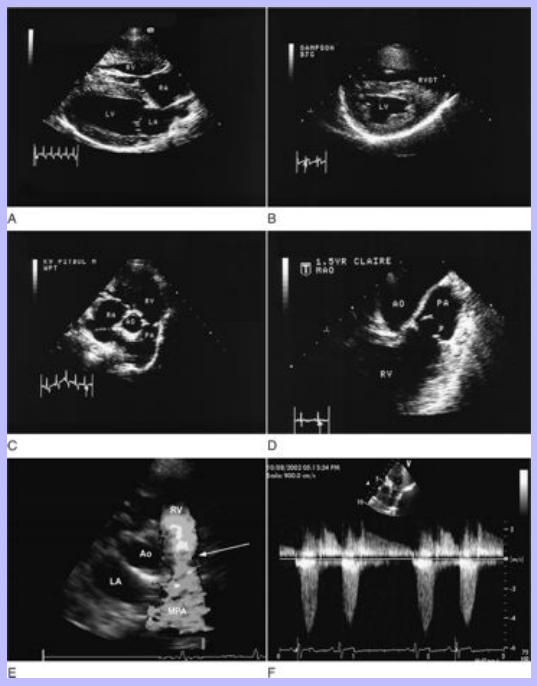
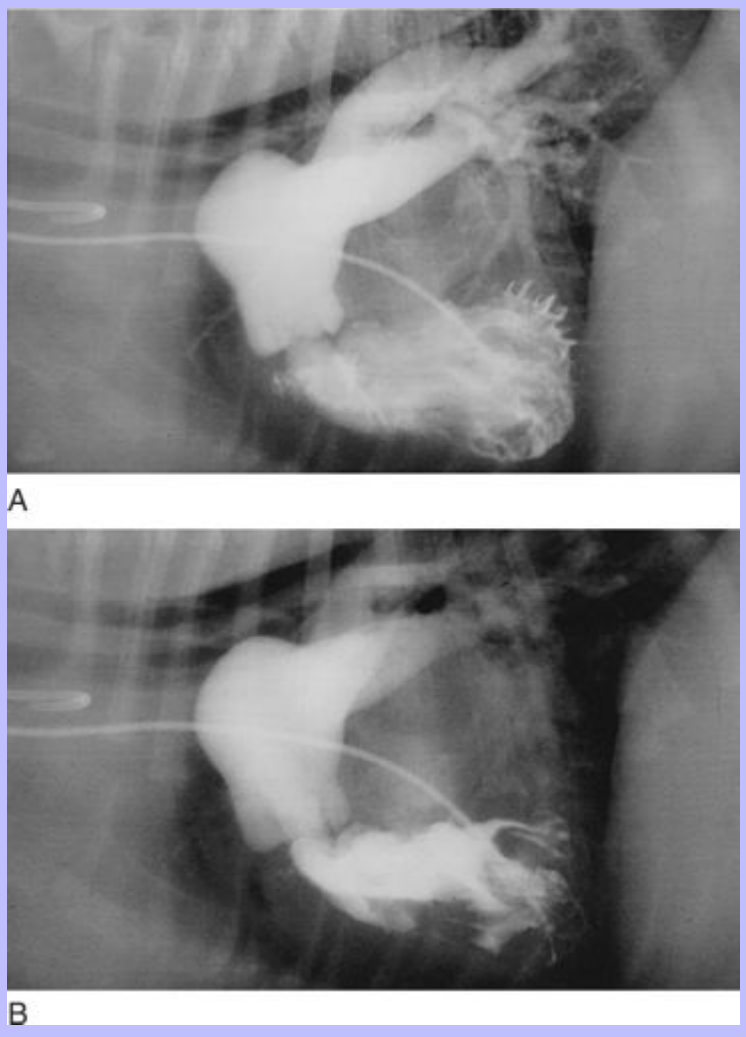


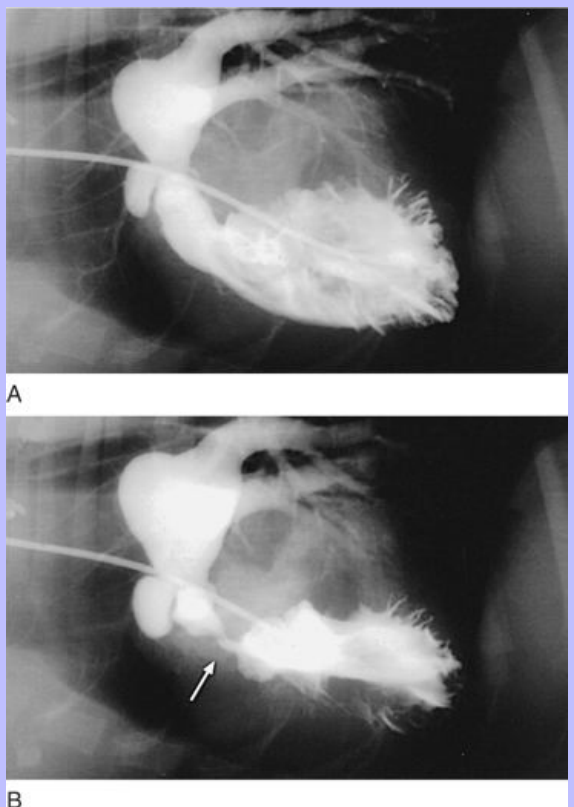
Figure 200-32 Diastolic **(A)** and systolic **(B)** frames of a right ventricular angiogram in a dog with pulmonic stenosis. Note the narrow jet of contrast as it passes through the pulmonic orifice. Poststenotic dilatation of the pulmonary artery is visible in both frames, as is hypertrophy of the RV wall and papillary muscles.



Angiocardiography is often performed just prior to balloon valvuloplasty or to clarify right heart anatomy in anticipation of surgery. Such studies clearly demonstrate the anatomic location of the obstruction or obstructions, the degree of right ventricular hypertrophy, whether tricuspid regurgitation is present, and poststenotic dilatation of the pulmonary artery. The angiographic features of valvular stenosis consist of any combination of the following: narrowing at the immediate base of the valve

sinuses; asymmetric valve sinuses; hypoplasia of the annulus or of a valve sinus; thickening of individual valve leaflets, producing a lucent filling defect; narrowing of the dye column, with a central or asymmetric jet of contrast medium observed within a narrowed valve orifice; or systolic doming of the valve (indicating fusion of the commissures) (Figure 200-32).[86a,88a] Dynamic muscular obstruction of the right ventricular infundibulum is often visible in dogs with PS (Figure 200-33). The term *double-chambered right ventricle* is used when the right ventricle is divided into a low-pressure region (the infundibulum) and a high-pressure region (the apex and inlet portion of the RV) by a muscular or fibromuscular ridge deep in the infundibulum (Figure 200-34). Left ventricular angiography or coronary arteriography should be performed when abnormalities of the left heart or coronary circulation are suspected. Such studies must be performed whenever surgery or balloon valvuloplasty is contemplated in an English bulldog or a boxer. Enlargement of the right coronary artery is an expected finding in all dogs with PS, as is well-developed right ventricular hypertrophy.

Figure 200-33 Right ventricular angiocardiogram from a dog with severe pulmonic stenosis. Comparison of the diastolic **(A)** and systolic **(B)** frames shows complete obliteration of the outflow tract due to vigorous contraction of the hypertrophied infundibulum. Compare with Figure 200-32. Also note the distortion of the pulmonic valve sinuses *(arrow)*.

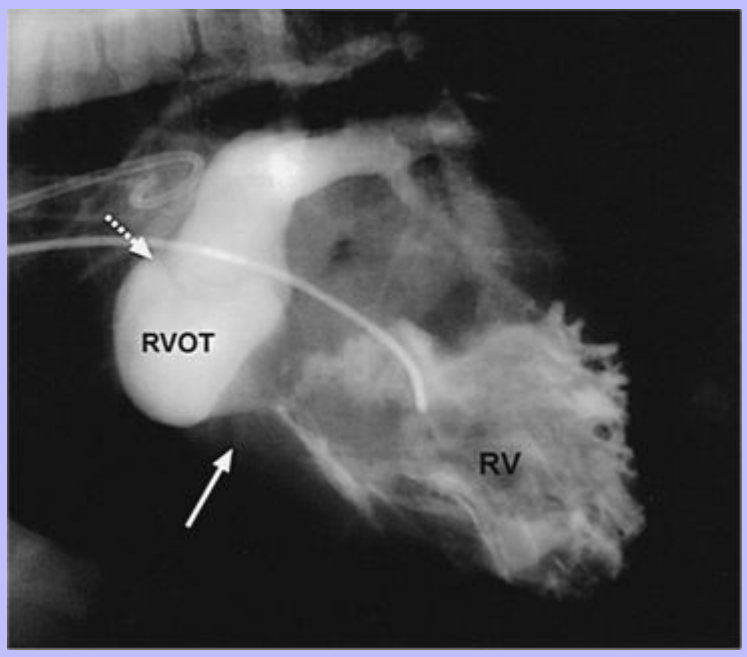


Hemodynamic confirmation of outflow tract obstruction is accomplished by measurement of a systolic pressure gradient across the lesion (see Figure 200-1). The severity of the obstruction usually is defined as the difference in peak systolic pressures measured above and below the obstruction (peak-to-peak pressure gradient). Inasmuch as the recorded gradient varies with the rate of flow across the obstruction, this measurement is greatly affected by myocardial contractility and the anesthetic regimen selected. Despite these limitations, the systolic pressure gradient has been used to categorize patients with pulmonic stenosis as having mild (less than 50 mm Hg), moderate (50 to 80 mm Hg), or severe (greater than 80 mm Hg) disease.[87a,88a,93a] A more accurate approach requires the measurement of cardiac output and calculation of the functional area of the constricted orifice.

200.12.1.1.4 Natural history

Precise criteria for establishing an accurate prognosis have not been developed for dogs and cats with PS. 1005
Clinical experience indicates that most dogs with mild and even moderate PS (Doppler-derived gradient 1006
less than 80 mm Hg) usually live normal or nearly normal lives. This generalization does not include dogs with other complicating defects. The problem of concurrent tricuspid valve dysplasia and its relation to developing heart failure has already been discussed. Although systolic pressure gradients are not always predictive of clinical outcome, a general correlation between pressure gradient and survival appears to exist. Dogs with Doppler-derived gradients greater than 125 mm Hg frequently develop secondary tricuspid regurgitation, heart failure, exertional syncope, or a serious cardiac arrhythmia (e.g., atrial fibrillation). When an ASD, patent foramen ovale, or VSD coexists with PS, the potential for right-to-left shunting exists. If the right-to-left shunting is pronounced, the consequences include arterial hypoxemia, polycythemia, and serious debilitation. Sudden death occurs in some dogs with severe PS, but this is uncommon.

Figure 200-34 Right ventricular angiocardiogram recorded from a rottweiler with an unusual form of subvalvular muscular pulmonic stenosis. Some refer to this lesion as a "double-chambered right ventricle" to distinguish it from dynamic collapse of the hypertrophied infundibulum (see Figure 200-32). Others use the term only when the lesion is deeper within the right ventricle, and some avoid the term altogether. Solid arrow indicates the muscular obstructing lesion in the right ventricular outflow tract. Dashed arrow indicates the location of the pulmonic valve.



200.12.1.1.5 Clinical management

Patients with uncomplicated PS of mild or moderate severity usually do not require treatment. Serial echocardiographic examinations can be performed to monitor the degree of ventricular hypertrophy and to determine whether secondary infundibular stenosis or tricuspid regurgitation has developed. Exercise restriction is usually unnecessary. Some dogs develop more severe obstruction over time. Dogs with severe or symptomatic disease are candidates for surgery or balloon valvuloplasty. The exact pressure gradient warranting intervention cannot be stated with certainty. Dogs with a Doppler gradient exceeding 100 to 125 mm Hg should be considered candidates for balloon valvuloplasty or surgery. Dogs with lesser gradients are also candidates for these procedures if they are symptomatic or have a large amount of tricuspid regurgitation. Intervention at a young age should be encouraged, because the development of

overt congestive heart failure substantially lessens the chance for a successful outcome, regardless of the method of repair. Due to a high likelihood of heritability, even mildly affected dogs should not be bred.

The goals of intervention in dogs with severe PS are to abolish or reduce the systolic pressure gradient to the mild range and to provide symptomatic relief in dogs experiencing clinical signs. The effect of intervention on survival time in dogs or cats is not known. For many years surgery was the only available option for treating PS, and a number of surgical techniques have been advocated, including valve dilatation, patch grafting, or the placement of a conduit from the right ventricle to the pulmonary artery.[*] The open patch-graft technique is a particularly versatile and cost-effective method of treating dogs with PS, particularly cases involving a substantial subvalvular obstruction.[22b,34c,35c] The technique is well-suited to the treatment of some defects not amenable to balloon valvuloplasty (e.g., muscular RVOT obstruction, double-chambered right ventricle, or severe hypoplasia of the pulmonic annulus). The patch-graft technique should not be performed in dogs with subvalvular PS caused by anomalous coronary artery development, because severing of the artery and death will result.

Catheter-based percutaneous balloon valvuloplasty is a preferred alternative to surgery in many dogs with valvular PS.[*,†] A dilatation catheter tipped with an inflatable balloon is placed across the obstructing orifice and repeatedly inflated (Figure 200-35). Successful reduction of the obstructive gradient by 50% or more has been reported in 75% to 80% of dogs treated with this technique.[34,38–40] Improvements in the design of the balloon catheter and refinements in the technique have expanded the application of this procedure to dogs weighing as little as 2 kg.[40c] Balloon valvuloplasty is most successful when the pulmonary annulus is normally developed and the valves are relatively thin and fused. More variable results are obtained in dogs with complex lesions and hypoplasia of the pulmonary annulus.[38c,41c] In the authors' experience, balloon dilatation has been of dubious value in dogs with severe muscular RVOT obstruction or double-chamber-type defects. Although balloon valvuloplasty is generally regarded as a safe procedure with a low complication rate, life-threatening problems such as hemorrhage, cardiac puncture, and arrhythmias do occur. Dogs with hypoplasia of the pulmonary annulus or anomalous development of the coronary arteries are at particular risk for serious complications, including avulsion of the coronary artery or rupture of the pulmonary annulus.[36c] Delayed restenosis can occur, but this is not thought to be an important problem.[39] When CHF or atrial fibrillation develops secondary to PS, the prognosis is poor. If medical stabilization can be achieved, balloon valvuloplasty or surgery can be attempted.

* References 21b, 22b, 34c, 35c, 37, 87a, 91a, and 94a.

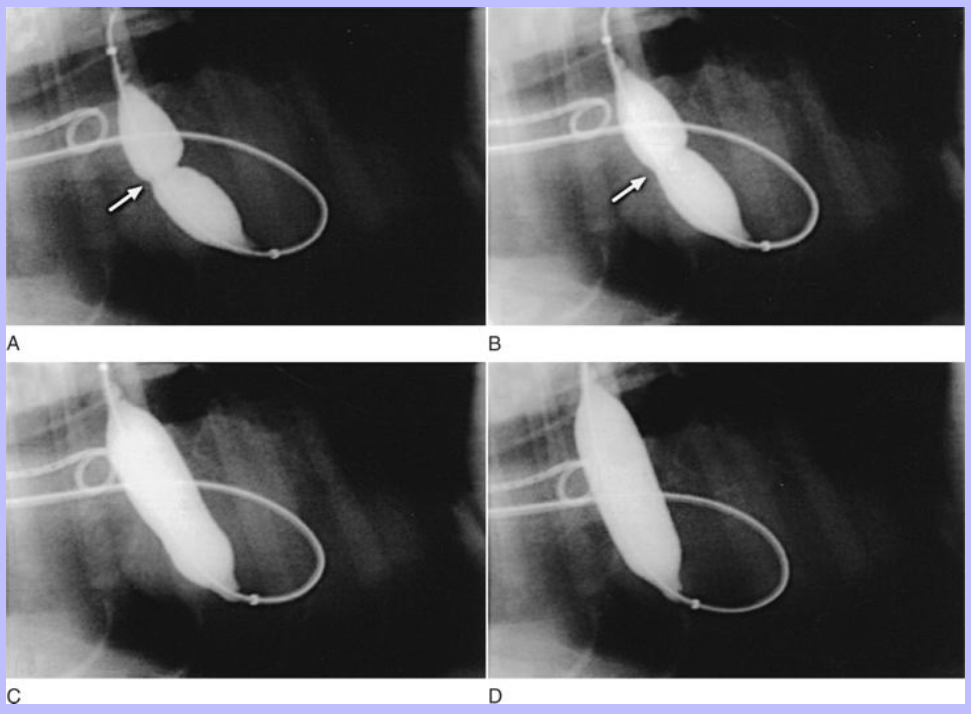
† References 20b, 23b, 24b, 35c-39c, 38, and 94a.

200.12.1.2 Aortic Stenosis

Subvalvular aortic stenosis is the most common congenital cardiac malformation in large-breed dogs.[1c-5c,42c,97a,109a] Most cases of SAS result from a fixed ridge or ring of fibrous tissue located in the left ventricular outflow tract just below the aortic valve. Subvalvular aortic stenosis is a problematic disorder for several reasons. It is very difficult to diagnose in mildly affected dogs, and when the condition is severe, it is difficult to treat. The phenomenon of dynamic SAS is also being recognized with increasing frequency in dogs and cats with a variety of cardiac disorders, including fixed SAS, mitral valve dysplasia, hypertrophic cardiomyopathy, and other conditions that cause hypertrophy of the interventricular septum (i.e., PS, tetralogy of Fallot).[26b] Bull terriers are predisposed to valvular aortic stenosis in which the leaflets

are thickened and the aortic valve annulus is mildly hypoplastic. Mild aortic stenosis (AS) caused by a bicuspid valve occurs on rare occasion. Fixed aortic stenosis has been described in a small number of cats,[12a,13a,25b,36a] including one case of supravalvular stenosis.[101a]

Figure 200-35 Sequence of radiographs taken during balloon dilatation in a dog with valvular pulmonic stenosis. The balloon catheter is seen to traverse the cranial vena cava, right atrium and ventricle, and pulmonary artery. Radiopaque markers on the catheter are used to help position the balloon across the valve. Prominent stenotic lesion *(arrow)* is seen on inflation of the balloon **(A)**; it becomes less obvious as the lesion is stretched or torn open **(B)** and **(C)**; and it is no longer evident when the balloon is fully inflated **(D)**.



200.12.1.2.1 Pathology and pathogenesis

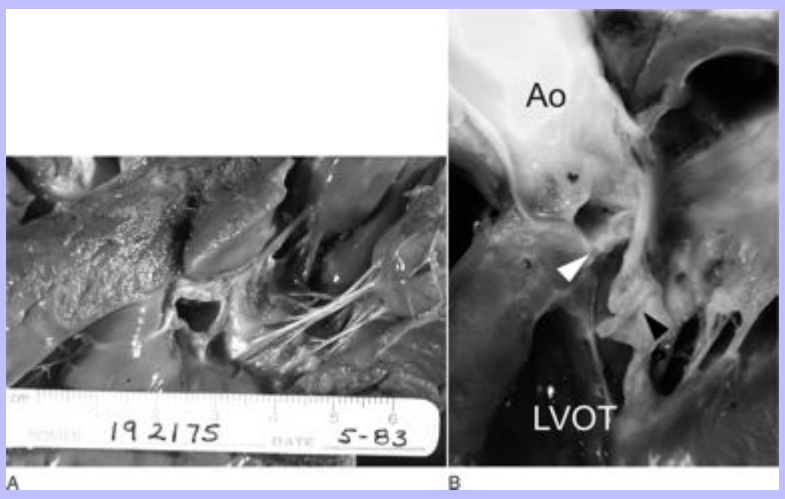
Subvalvular aortic stenosis has been extensively studied in Newfoundlands, for which breeding studies have established a genetic basis for the perpetuation of SAS.[4a,100a] The pattern of inheritance is most compatible with an autosomal dominant mode of transmission with modifying genes; however, a polygenic mechanism cannot be excluded. The breeding colony studies of Pyle and Patterson further indicate that the obstruction may not be present at birth but rather may develop during the first 4 to 8

weeks of life.[4a,99a,100a,103a,104a] This progression is particularly significant with regard to identification of cardiac murmurs in pups of breeds known to be at risk for SAS.

The lesions of SAS in Newfoundlands have been described in postmortem studies as mild (grade 1), consisting of "small, whitish, slightly raised nodules on the endocardial surface of the ventricular septum immediately below the aortic valve"; moderate (grade 2), consisting of a "narrow ridge of whitish, thickened endocardium" extending partly about the LVOT; and severe (grade 3), consisting of "a fibrous band, ridge, or collar completely encircling the left ventricular outflow tract just below the aortic valve".[4a,100a] This ring is raised above the endocardium, extends to, and may involve the cranioventral leaflet of the mitral valve and the base of the aortic valves (Figure 200-36). The stenotic ring consists of loosely arranged reticular fibers, mucopolysaccharide ground substance, and elastic fibers. Discrete bundles of collagen and even cartilage are found in advanced lesions.[100a] Cardiac catheterization of dogs with grade 1 lesions failed to reliably detect the postmortem lesion, whereas grade 2 lesions often were associated with soft cardiac murmurs and minimal systolic pressure gradients. As evidenced by these studies, clinical detection of mild SAS can be quite difficult and genetic counseling can be fraught with error. A variety of cardiac abnormalities can accompany SAS, most notably mitral valve dysplasia, PDA, and a host of aortic arch abnormalities. The valvular lesions seen in bull terriers, including myxomatous degeneration and cartilaginous metaplasia of the valve leaflets, resemble those in humans with calcific valvular stenosis.[41]

In some affected dogs, the pathologic findings diverge from the classical description. The anterior mitral valve leaflet is thickened in apposition to a septal plaque of endocardial fibrosis where the mitral leaflets impact the interventricular septum as a consequence of dynamic obstruction. Instead of a fibrous collar, the septum is uniformly hypertrophied, or a broad, fibromuscular ridge that arises from the base of the interventricular septum protrudes into the LVOT. Malformed, malpositioned, or malaligned papillary muscles, thickened chordae tendineae, and elongated or distorted mitral leaflets contribute to the development of obstruction.[42,43]

Figure 200-36 Gross pathology of subaortic stenosis (SAS). **A,** Left ventricular outflow tract in a dog, as viewed from the apex of the left ventricle, shows a circumferential ring of fibrous tissue. The anterior mitral valve leaflet and associated chordae tendineae are seen to the right of the lesion. **B,** Cutaway view of the left ventricular outflow tract *(LVOT)* and aorta *(Ao)* in a dog with fixed, dynamic SAS. A ridge of thick, fibrous tissue *(white arrowhead)* is seen just below the aortic valve. The anterior leaflet of the mitral valve *(black arrowhead)* is thickened and elongated.



Concentric hypertrophy of the left ventricle develops in dogs with valvular, fixed, or dynamic SAS more or less in proportion to the severity of the outflow obstruction, although the correlation between wall thickness and the magnitude of the measured gradient is often poor.[44] Structural and functional abnormalities of the left ventricle[45] and coronary circulation are well documented in dogs with SAS.[103a,104a] Abnormal coronary flow has also been measured in the larger, extramural arteries, with diminished baseline diastolic flow and reversal of coronary flow during systole.[8a,104a] Focal areas of myocardial infarction and fibrosis are commonly observed in the papillary muscles and subendocardium of dogs with severe SAS, often in association with abnormal intramural coronary arteries. Histologic changes of the intramural coronary arteries in these locations include intimal proliferation of connective tissue and smooth muscle, and medial degeneration. These changes are presumably related to the high wall tension found in this condition, and their genesis may be related to the elaboration of angiotensin II or other biochemical mediators of hypertrophy and remodeling.[46–48] Moreover, these arterial lesions may be important in the genesis of malignant ventricular arrhythmias and sudden death.

200.12.1.2.2

Pathophysiology

Obstruction to left ventricular outflow causes an increase in left ventricular systolic pressure and concentric hypertrophy. Consequent to fixed obstruction, left ventricular ejection is delayed, causing a diminished and late rising arterial pulse (*parvus et tardus*). High-velocity and turbulent flow across the stenotic area produces the systolic ejection murmur and results in poststenotic dilatation of the ascending aorta, aortic arch, and brachiocephalic trunk. Left atrial hypertrophy develops as a consequence of the reduced compliance of the hypertrophied left ventricle. Mild aortic regurgitation is commonly present, presumably due to thickening of the valve leaflets or dilatation of the ascending aorta. Damage to the aortic valvular endothelium (jet lesions) predisposes dogs with SAS to bacterial endocarditis. Dogs with severe SAS can develop left-sided congestive heart failure from myocardial failure, diastolic pump failure due to increased ventricular stiffness, mitral regurgitation, atrial fibrillation, or a combination of these factors. More often, exertional syncope or sudden death is reported, presumably as a result of myocardial ischemia and the development of malignant ventricular arrhythmias. In some dogs, exertional collapse may be due to hypotension precipitated by exercise-induced increases in left ventricular pressure, activation of ventricular mechanoreceptors, and inappropriate bradycardia or vasodilatation.[49]

200.12.1.2.3

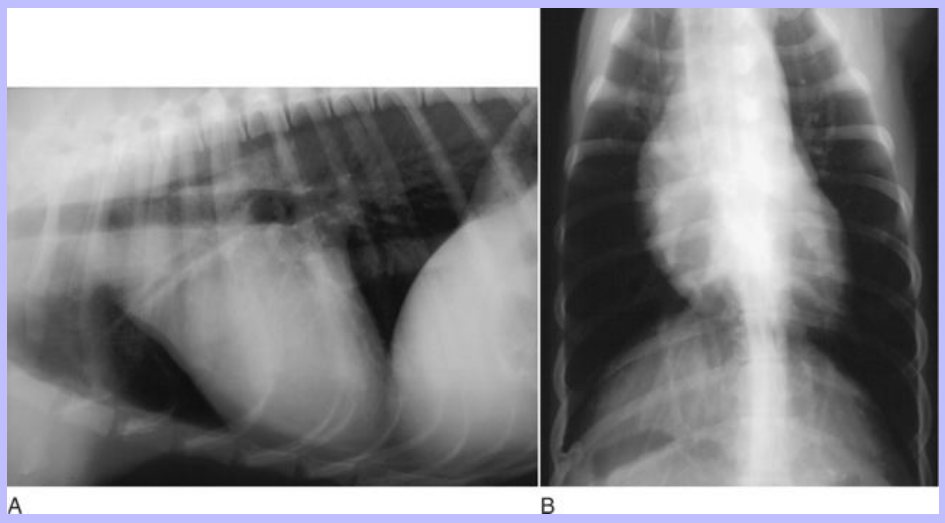
Clinical findings

Congenital SAS is most common in Newfoundland retrievers, boxers, rottweilers, golden retrievers, and German shepherds.[30,50] Valvular AS is common only in bull terriers. The clinical findings of SAS vary with the severity of the obstruction and the presence of concurrent cardiac defects. Clinical findings in pups with mild SAS are often subtle and easily overlooked.[5a,9a,98a,100a] Asymptomatic dogs have a soft to moderately intense ejection murmur that can easily be confused with an innocent or functional heart murmur.[51] Insofar as the lesions of SAS can develop during the postnatal period, the murmur may become increasingly prominent during the first 6 months of life. Severely affected dogs may present with exertional fatigue, syncope, or left-sided congestive heart failure, but the vast majority of dogs are asymptomatic. In dogs with severe disease, a common client observation is that the affected dog is smaller than healthy littermates. Sudden death, without premonitory signs, is common in dogs 1 to 3 years of age.[50c]

Figure 200-37 Electrocardiograms demonstrating ST segment depression **(A** and **B)** and elevation **(C)** in three dogs with severe SAS. These results are suggestive of myocardial ischemia. (Sensitivity =10 mm/mV.) **A,** Tracing from a 1-year-old golden retriever (25 mm/s). **B,** Tracing from a 6-month-old Newfoundland retriever that collapsed and died suddenly 1 hour after the ECG was performed (25 mm/s). **C,** Tracing from a 1-year-old golden retriever (50 mm/s).

Recognition of severe SAS is not difficult, because the murmur generally becomes louder and longer when the obstruction is more severe.[46c] The murmur of severe SAS is usually best heard at the left heart base, recognizing that in some dogs, the systolic murmur is equally loud or louder at the right cardiac base, presumably from radiation into the ascending aorta. The murmur of aortic stenosis often radiates up the carotid arteries and can be ausculted over the ventral cervical region. In some affected dogs, a soft diastolic murmur secondary to aortic valve insufficiency is also detected. A substantial percentage of dogs with SAS have mitral regurgitation, but these murmurs are usually difficult to separate, given their similar timing and overlapping areas of maximal intensity. Other physical abnormalities detected in moderate to severely affected dogs include a diminished and late-rising arterial pulse and a prominent left ventricular heave arising from the hypertrophied left ventricle.

Figure 200-38 Lateral **(A)** and dorsoventral **(B)** radiographs from a young dog with subaortic stenosis. Prominent bulge in the cranial waist on the lateral view and widening of the cranial mediastinum on the dorsoventral view are consistent with poststenotic dilatation of the ascending aorta.



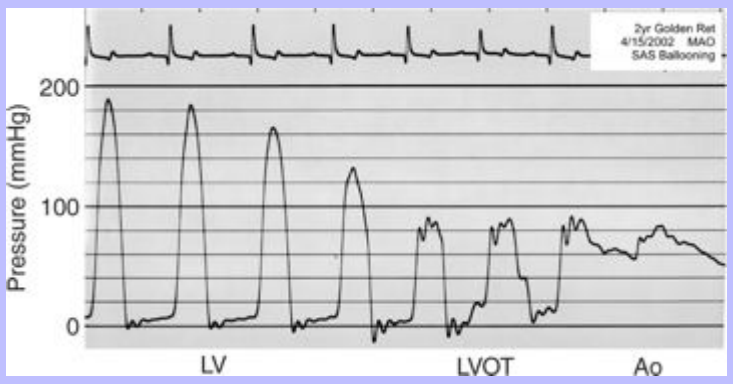
The electrocardiogram is often normal but in severe cases may indicate left ventricular hypertrophy (increased R wave amplitude in leads II, III, aVF, V_2, and V_4). Depression of the ST segment and T-wave changes suggest myocardial ischemia, particularly when these alterations are precipitated by exercise or occur in the company of ventricular ectopia (Figure 200-37). Compared with the resting electrocardiogram, 24-hour ambulatory (Holter) ECG recordings offer a more sensitive method of detecting ventricular arrhythmia and ST-segment changes, particularly when such changes are precipitated only by exercise. The severity of arrhythmias detected in this fashion often corresponds to the severity of disease.[52]

Thoracic radiographs may be normal or may indicate left ventricular hypertrophy.[8a,22a-24a] Poststenotic dilatation of the horizontally inclined ascending aorta causes loss of the cranial waist on the lateral radiograph and widening of the mediastinum on the dorsoventral radiograph (Figure 200-38). Mild left atrial enlargement is common in dogs with moderate or severe SAS, but marked left atrial enlargement suggests concurrent mitral regurgitation. Angiocardiography is useful for delineating the site and geometry of obstruction, which is usually most evident in the ventral aspect of the outflow tract when viewed on the lateral projection (Figure 200-39). Other angiographic findings include poststenotic dilatation of the ascending aorta, enlargement of the left coronary artery and its extramural branches, a small left ventricular cavity, and hypertrophy of the papillary muscles and left ventricular wall. Supravalvular aortic injections can be performed to identify insufficiency of the aortic valve, but Doppler echocardiography is a more sensitive technique. Hemodynamic recordings are made to document the presence and severity of a systolic pressure gradient across the obstruction (Figure 200-40). Such recordings are also useful for detecting elevated left ventricular end-diastolic pressure and

impending congestive heart failure.[8a,105a] As a result of diminished flow (cardiac output), pressure gradients recorded from dogs with SAS are depressed by general anesthesia to approximately 40% to 50% of those measured in the unanesthetized state.[47c]

Figure 200-39 Angiogram from a dog with subaortic stenosis. Left ventricular injection opacifies the left ventricle and aorta. Tunnel-like narrowing of the contrast column is seen in the left ventricular outflow tract; a prominent left circumflex coronary artery is also seen.

Figure 200-40 Intracardiac and aortic pressures from a 2-year-old golden retriever with subaortic stenosis obtained through cardiac catheterization. The catheter is withdrawn from the left ventricle (LV) into the left ventricular outflow tract (LVOT) and the ascending aorta (Ao). A 100 mm Hg systolic pressure gradient is demonstrated between the LV and LVOT, indicating the subvalvular location of the obstruction.



Moderate to severe SAS is easily confirmed by two-dimensional and Doppler echocardiography. Typical findings include concentric left ventricular hypertrophy, a subvalvular obstructing lesion, and poststenotic dilatation of the aorta (Figure 200-41).[3,27a,35,106a] The papillary muscles and endocardial surface of the ventricular myocardium often appear hyperechoic, presumably as a result of myocardial ischemia and replacement fibrosis or calcification. Structural changes in the mitral valve can often be appreciated and abnormal motion of the mitral valve (systolic anterior motion) can be detected in dogs with coexisting mitral valve dysplasia and dynamic obstruction.[43] Spectral Doppler interrogation of the left ventricular outflow tract is used to assess the severity of disease through measurement of the peak velocity of flow in the LVOT.[48c] Such measurements show excellent correlation with invasive measurements (see Figure 200-41).[49c] Doppler measurements can be made from a variety of parasternal or subcostal imaging windows, although velocities obtained from the subcostal position generally display the highest values.[27b] Doppler-estimated pressure gradients between 80 and 100 mm Hg (peak flow velocities ranging from 4.5 to 5 m/s) are used to indicate moderate LVOT obstruction, and higher velocities are used to indicate severe obstruction, but these designations are somewhat arbitrary. Doppler-derived pressure gradients are affected by the amount of flow (cardiac output) through the obstructive orifice and may either overestimate the severity of obstruction if cardiac output is high (e.g., in dogs that are stressed or excited) or underestimate severity if flow is subnormal (e.g., in dogs with concurrent myocardial failure). In these cases, indexing the gradient to stroke volume or some related measure or simple estimation of the two-dimensional orifice area may provide a better estimate of disease severity.[44,53] Color flow Doppler recordings are valuable for detecting and estimating the severity of coexisting aortic or mitral valve insufficiency.

Antemortem detection of the mildest forms of SAS by echocardiography is often not possible. Dogs with subtle abnormalities (i.e., grade 1 lesions as described previously) escape detection by even the most accomplished examiners. Even with dogs that have grade 2 lesions, segregation from normal dogs on the basis of left ventricular velocities is problematic. An upper limit for aortic velocity in normal dogs has been reported but is not well established for differing breeds and examination conditions.[54] The maximum normal aortic velocity in the authors' laboratory is 1.7 m/s (upper limit of the 95% confidence interval); however, velocities in excess of this value are sometimes recorded in completely normal dogs or in dogs with no evidence of a discrete outflow obstruction but that have slightly diminished outflow tract dimensions (boxers, bull terriers, golden retrievers). A diagnosis of mild SAS is more secure when mildly elevated velocity measurements are accompanied by disturbed flow, when an anatomic lesion is visible, and when velocity flow suddenly accelerates over a discrete region in the LVOT. Inability to reliably detect mild SAS is a great source of frustration with regard to efforts to provide genetic counseling to breeders, who are interested in reducing the incidence of disease.

200.12.1.2.4

Natural history

Severe SAS is a discouraging condition, because many affected dogs die prematurely. In a retrospective survey of 96 dogs with SAS, 21 died suddenly, most often during the first 3 years of life.[50c] Eleven dogs developed endocarditis or left heart failure and 32 dogs showed evidence of exercise intolerance or syncope. Dogs with minimal ventricular hypertrophy, mild ventricular outflow obstruction, and a maximal Doppler pressure gradient of less than 50 mm Hg are more likely to live normal lives, whereas dogs with pressure gradients in excess of 125 mm Hg are very likely to develop serious complications or to experience sudden death. Complicating factors that contribute to an adverse outcome include: mitral regurgitation, aortic regurgitation, aortic valve endocarditis, and atrial fibrillation.[51c-53c] Sudden death is most likely to occur during or shortly after vigorous activity.

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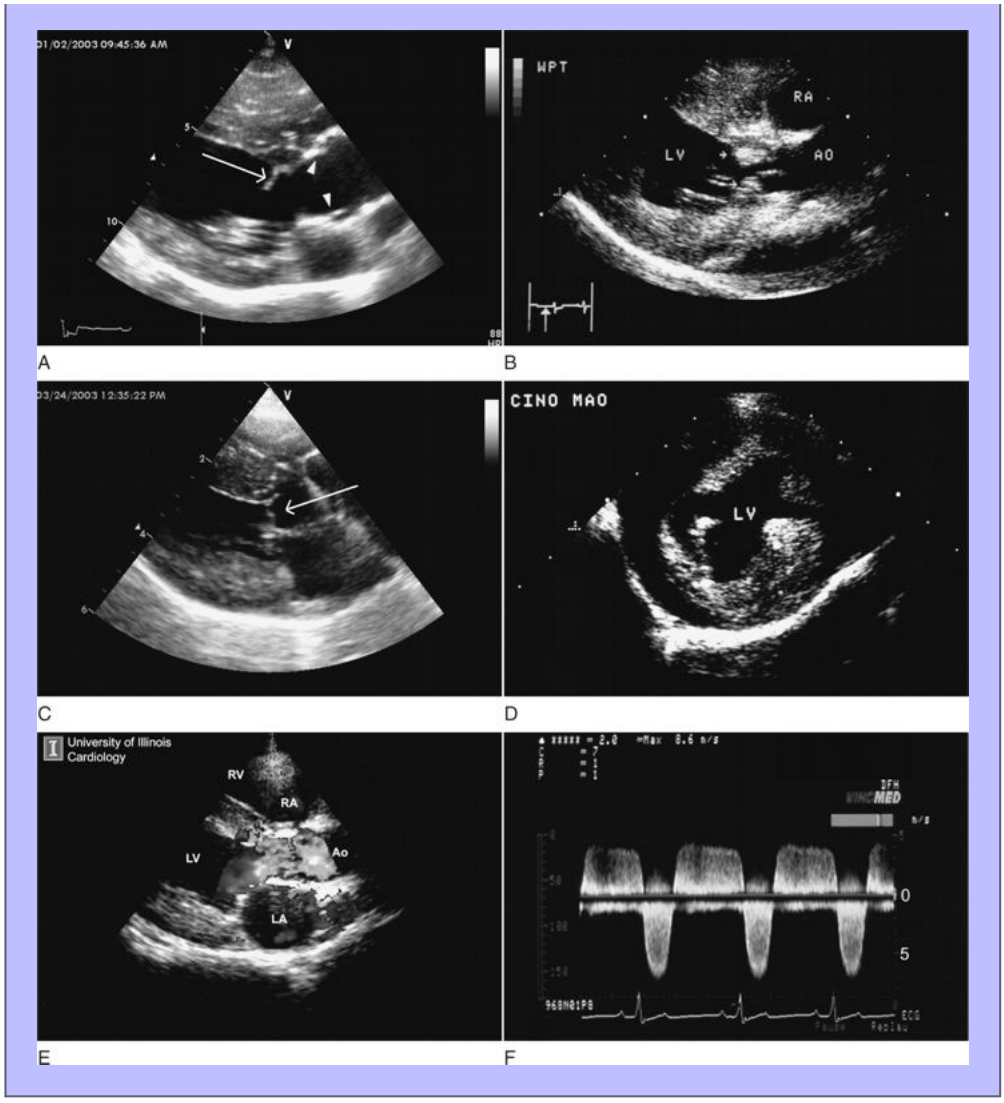
Figure 200-41 Echocardiography of subaortic stenosis (SAS). **A, B,** and **C** are right long axis views showing the various morphologic forms of obstruction in the left ventricular outflow tract in dogs with SAS. **A,** Mild membranous SAS in a 5-year-old rottweiler. A thin, membranous flap of tissue extends from the interventricular septum. No appreciable left ventricular concentric hypertrophy is noted. The open aortic valve leaflets are indicated by the arrowheads. **B,** Severe, tunnel-like SAS in a 4-year-old golden retriever. Two ridges of hyperechoic tissue are present at the base of the aortic valve *(arrows)*. The left ventricle is hypertrophied and has a hyperechoic endocardial surface. **C,** Dynamic SAS in a poodle. Systolic anterior motion of the mitral valve is seen projecting into the left ventricular outflow tract *(arrow)*. The left ventricle shows concentric hypertrophy. The blood flow velocity across the obstruction exceeded 5.5 m/s, indicating a severe degree of pressure overload to the left ventricle. **D,** Right short axis view from a 3-month-old mixed breed dog shows left ventricular concentric hypertrophy and marked hyperechogenicity of the subendocardial tissue and papillary muscles. This finding is thought to represent areas of myocardial ischemia and replacement fibrosis. **E,** Right long axis color flow Doppler study from a dog with SAS shows high-velocity, turbulent blood flow in the left ventricular outflow tract and aorta. **F,** Continuous wave Doppler tracing from the left apical view in a dog with severe SAS shows a peak systolic velocity of 6.5 m/s, indicating a pressure gradient of 169 mm Hg across the obstruction. Aortic insufficiency is also detected.



200.12.1.2.5 Clinical management

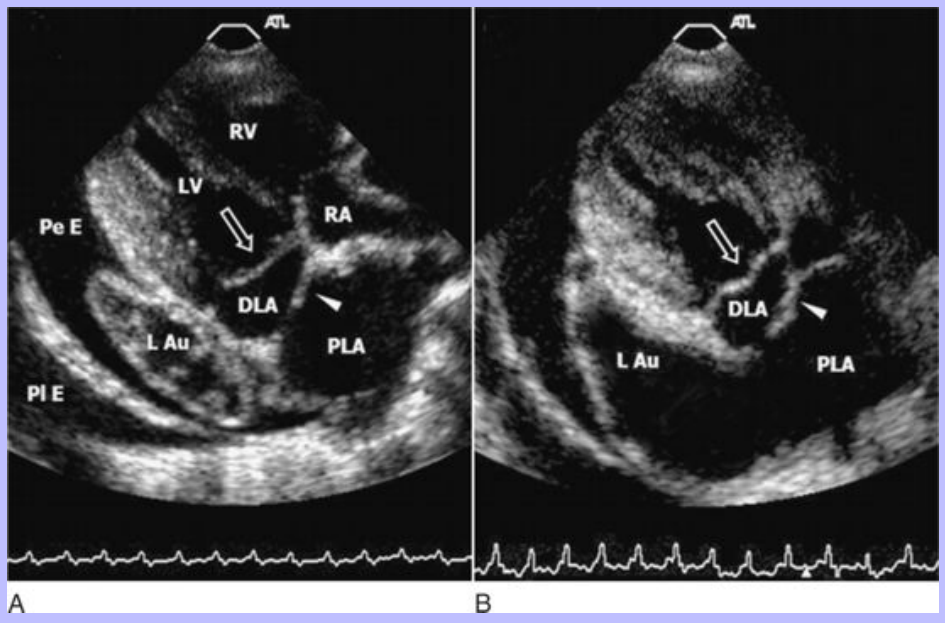
Dogs with mild SAS are not treated other than with administration of prophylactic antibiotics during periods of anticipated bacteremia, such as during dental procedures, surgery, or whenever a concurrent infectious disease is suspected. This practice remains common despite the fact that the efficacy of prophylactic antibiotics for reducing the risk of bacterial endocarditis in dogs with SAS has not been definitively established.[53c] A number of treatment options can be considered for dogs with moderate to severe SAS, but most are of uncertain value. Open resection of the obstructing lesion during cardiopulmonary bypass clearly offers the best opportunity to reduce the systolic pressure gradient substantially and permanently[54c,55c]; however, an otherwise successful procedure does appear to alter the prevalence of sudden death significantly.[55c] Other surgical procedures for dilating or bypassing the obstruction have either failed to achieve sustained reduction of the systolic pressure gradient or have

entailed an unacceptable risk of complications.[56c,57c] Moreover, these remedies are usually limited in their availability and are prohibitively expensive.

Balloon dilatation of SAS has been attempted in dogs as an alternative to surgery. On average, catheter-based balloon dilatation can reduce the severity of SAS obstruction in dogs by 50%.[29b] This benefit is attenuated in some (and perhaps a majority) of dogs over time.[48c] Balloon dilatation of SAS is more challenging than balloon valvuloplasty of pulmonic stenosis. Life-threatening complications of SAS include fatal arrhythmia, the development of aortic valve endocarditis, rupture of the aortic annulus, and avulsion of the brachiocephalic artery during balloon withdrawal. Moreover, the inability of surgical resection to prevent sudden death suggests that effective treatment requires more than reduction of the pressure gradient.

The authors typically recommend avoidance of prolonged, vigorous exercise, recognizing that in young and otherwise healthy dogs, even this conservative recommendation is not always practical. Based on clinical and pathologic evidence of myocardial ischemia, the authors also advise administration of beta-adrenergic receptor blockers to dogs with high gradients or a history of syncope. Beta blockers (e.g., atenolol) reduce the maximal heart rate, decrease myocardial oxygen consumption, and improve diastolic coronary artery flow, thereby exerting a protective effect on the myocardium against ischemia and the development of arrhythmias. Moreover, dogs on high doses of beta blockers seem less willing (or are less able) to indulge in prolonged, vigorous exercise. In theory, treatment with calcium channel blockers or ACE inhibitors may also be of value in dogs with SAS; however, none of the medical strategies have been evaluated in placebo-controlled clinical trials.

Figure 200-42 Long-axis, four-chamber, two-dimensional echocardiograms of a cat with supravalvular mitral stenosis. **A,** Clearly visible membrane *(solid arrow)* is located above the mitral valve *(open arrow)* that partitions the left atrium into proximal (PLA) and distal (DLA) compartments. **B,** Left auricle (LAu) communicates with the proximal left atrial compartment, and the membrane is located distally. This feature distinguishes supraventricular mitral stenosis from cor triatriatum (sinister), in which the partitioning membrane is proximal to the auricle. *RV,* Right ventricle; *RA,* right atrium; *Pe E,* pericardial effusion; *Pl E,* pleural effusion. (Fine DM, Tobias AH, Jacob KA: Supravalvular mitral stenosis in a cat. *J Am Anim Hosp Assoc* 38:403–406, 2002.)



200.12.2 Anomalous Development of the Atria and Cor Triatriatum

Cor triatriatum (sinister and/or dexter) has been reported in both cats and dogs.[33b,69c-72c,156a,158a] With these defects, the atrium is partitioned into an accessory atrial chamber, which receives venous return, and is separated from the true atrium by a perforate membrane. The suffix, *sinister* or *dexter*, is used to indicate whether the left or right atrium is abnormally partitioned; the term *cor triatriatum* alone usually refers to a left-sided lesion. If the partitioning membrane causes obstruction, dilatation of the venous chamber and the entering veins is evident and congestion develops. In contrast to mitral or tricuspid valve stenosis, blood flows through the stenotic orifice during both systole and diastole; however, the functional consequences of these

defects are very similar. From a clinical perspective, supravalvular mitral stenosis (SMS) often closely resembles cor triatriatum (sinister); however, SMS is frequently accompanied by additional mitral valve abnormalities. The primary distinction between SMS and cor triatriatum (sinister) relates to the location of the obstructing membrane. In animals with SMS, the obstructing membrane is located ventral (distal) to the foramen ovale, and the left auricle is functionally part of the proximal chamber and dilates as pressure in this chamber rises (Figure 200-42).[55] In animals with true cor triatriatum (sinister), the obstructing membrane is located dorsal (proximal) to the foramen ovale; the left auricle lies downstream from the obstruction and is not enlarged. If the foramen ovale is closed, there is little difference between these defects. Affected cats typically present with signs of pulmonary congestion, but pulmonary hypertension and right heart failure are also seen.

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Cor triatriatum dexter results from persistence of the embryologic right sinus venosus valve.[71c] In dogs with this malformation, the right atrium is partitioned by a diaphragm located caudal to the tricuspid valve and foramen ovale. Affected dogs usually evidence congestion in the caudal half of the body (ascites) but fail to demonstrate jugular distension or an audible murmur. Other clinical findings include prominence of the cutaneous abdominal veins, hepatomegaly, and diarrhea from malabsorption. Dogs with congenital or acquired obstruction of the caudal vena cava (Budd-Chiari syndrome) present with similar clinical findings. In most affected dogs, the electrocardiogram and thoracic radiographs, with the notable exception of caudal vena cava enlargement, are unremarkable. Diagnosis can be accomplished by echocardiography or angiography.[56] Treatment for cor triatriatum generally requires surgical resection or bypass of the obstruction,[57,73c,74c] Balloon dilatation of the obstructing membrane can also be attempted.[58,59]

200.12 LESIONS THAT CAUSE RIGHT-TO-LEFT SHUNTING: CYANOTIC HEART DISEASE

The term *cyanotic congenital heart disease* is used to categorize congenital defects that cause admixture of venous and arterial blood, such as tetralogy of Fallot. Because the pathophysiology and clinical signs of these conditions are similar, they are considered as a group. Only the most important defects are discussed to illustrate the clinical syndrome common to these conditions. The reader is also directed to the previous sections on PDA and VSD, which comment on the complicating conditions promoting right-to-left shunting.

200.13.1 Pathophysiology

200.13.1.1 Mechanisms of Right-to-Left Shunting

For desaturated blood to shunt into the systemic arteries, a defect must exist that allows admixture of unsaturated and saturated blood, as occurs with transposition of the great vessels, or a communicating defect that connects the two sides of the circulation and some mechanism elevating pressures on the right. Reversed shunting has been observed with PDA, aorticopulmonary window, ventricular septal defect, and atrial septal defect. The term *Eisenmenger's syndrome* is invoked to describe circumstances in which increased pulmonary vascular resistance causes reversal of a left-to-right shunt and cyanotic heart disease.[148a-150a] The factors underlying the development Eisenmenger's syndrome are incompletely understood but are most likely related to shear stresses caused by the high flow rates in the pulmonary vasculature and proliferative changes in the vessel wall.[15a,49a,60a,148a,150a] Eisenmenger's syndrome usually develops rapidly in small animals and almost always before 6 months of age.

Intimal thickening, medial hypertrophy, and plexiform lesions of dogs and cats with Eisenmenger's physiology are similar to those of humans as described by Edwards and Heath and amended by Roberts.[15]

These plexiform lesions are considered irreversible; consequently, neither medical therapy nor closure of the shunt effectively improves the condition once these changes have developed. In fact, surgical closure of the shunt pathway forces the right ventricle to work solely against a tremendous resistance, resulting in right ventricular failure, circulatory collapse, and death.

200.13.1.2 Effects of Hypoxemia

Systemic response to arterial hypoxemia includes an increase in red blood cell mass in an attempt to improve systemic oxygen transport. Hypoxia of the renal tissue incites erythropoietin release and induces secondary polycythemia. When the PCV exceeds 65% to 68%, the high viscosity of the blood predisposes the patient to thrombosis and microvascular complications.[15a,148a] This hyperviscosity syndrome is the primary cause of morbidity and mortality in affected animals. Clinical manifestations include weakness, hemostatic deficiencies, renal dysfunction, metabolic acidosis, iron deficiency, cerebrovascular events, syncope, and seizures.[59a,60,137a,139a]

200.13.1.3 Ratio of Systemic to Pulmonary Resistance

The magnitude of right-to-left shunting fluctuates with the relative resistances of the systemic and pulmonary circulations. Exercise promotes systemic arteriolar vasodilatation and decreases systemic resistance, thereby increasing the magnitude of right-to-left shunting. In cases of right ventricular hypertrophy and VSD, tachycardia or elevated sympathetic tone can increase the magnitude of right-to-left shunting by exacerbating dynamic infundibular obstruction and increasing resistance to right ventricular ejection.[60] Beta-adrenergic blocking drugs are sometimes used to blunt or prevent this phenomenon, particularly in patients with tetralogy of Fallot.[139a,140a] Beta blockers also tend to limit exercise, offering another explanation for their efficacy in some patients. Anemia, absolute or relative, reduces the ratio of systemic to pulmonary resistance when pulmonary resistance is fixed.[138a] By this mechanism, overzealous phlebotomy can increase the severity of arterial hypoxemia as it decreases the oxygen-carrying capacity of blood.

200.13.1.4 Additional Circulatory Factors

Right-to-left shunting leads to compensatory increases in nutritive blood flow to the lung via the bronchial arteries. These systemic collateral vessels are easily recognized at angiography. Although the phenomenon is uncommon, these vessels can rupture, leading to hemoptysis. Paradoxical embolization is another potential complication of right-to-left shunting defects. Normally, the pulmonary vasculature filters systemic venous emboli before they can reach the left side of the circulation. With reversed shunting, the possibility of a venous embolus reaching the coronary, cerebral, or other systemic arteries must be considered, particularly when intravenous catheters are used. By this mechanism, a thrombus, infectious agents, or air may gain access to vital systemic organs. Animals with cyanotic heart disease sometimes experience adverse reactions (particularly bradycardia) to sedatives and tranquilizers.

200.13.2 Clinical Evaluation of the Patient with Cyanotic Heart Disease

Common causes of cyanotic heart disease in companion animals include septal defects in association with tricuspid valve disease (ASD + TVD) or pulmonic stenosis (ASD or VSD + PS); and patent ductus arteriosus or septal defects complicated by pulmonary hypertension (PHT + ASD or VSD or PDA). Presenting signs

include failure to grow, shortness of breath, exertional fatigue, weakness, syncope, and seizures. Affected animals evidence dyspnea when stressed. Systemic hypoxemia is best confirmed by measurement of the oxygen content of an arterial blood sample obtained while the animal breathes room air. It is important to realize that providing 100% oxygen does not significantly improve the hypoxemia caused by right-to-left shunting.[61] Administration of 100% oxygen raises the concentration of dissolved oxygen but does not substantially raise the amount of oxygen bound to hemoglobin, which represents the primary reservoir of oxygen in the blood. Animals with cyanotic heart disease are usually polycythemic. This phenomenon is most obvious when the hemoglobin concentration of young animals with cyanotic heart disease is compared to age-matched normal animals.[128a]

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Clinically detectable peripheral cyanosis of the mucous membranes or skin occurs when the amount of reduced (unoxygenated) hemoglobin is greater than 3 g/dL. If this condition is suspected, the mucous membranes of both the cranial and caudal portions of the patient should be examined and compared, preferably both before and after exercise. A finding of cyanosis limited to the caudal tissues is known as *differential cyanosis* and suggests the presence of a right-to-left shunting PDA.

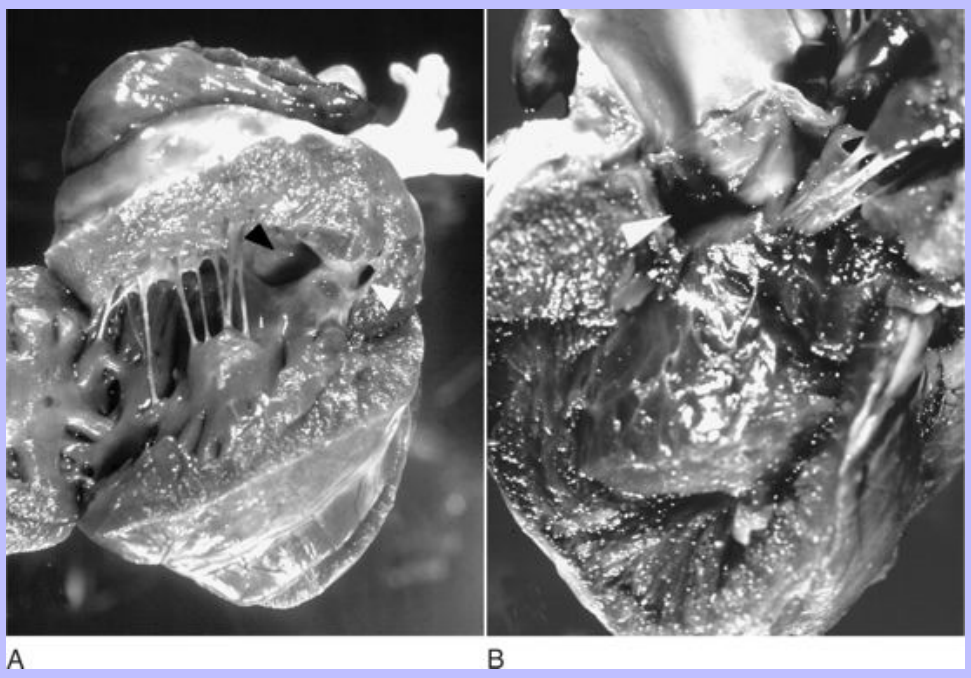
Cardiac auscultation of cyanotic patients varies in accordance with the underlying defects. Dogs and cats with tetralogy of Fallot usually evidence the typical systolic murmur of pulmonic stenosis. In contrast, most animals with Eisenmenger's physiology lack a prominent murmur but often display a loud or split second heart sound due to pulmonary hypertension and asynchronous semilunar valve closure.[8a,9a,128a] On occasion, an ejection sound with a soft, short, systolic murmur may be evident at the left heart base.

Cyanotic heart disease, with rare exceptions (i.e., tricuspid atresia and anomalous systemic venous return), is characterized by right ventricular hypertrophy, which is usually evident on ECG recordings, thoracic radiographs, and echocardiograms. As a general rule, the pulmonary arteries and veins are diminished in size and the lungs appear underperfused (hyperlucent) on survey chest films.[24a] The main pulmonary artery and proximal lobar arteries are usually visibly dilated when Eisenmenger's syndrome is the basis for reversed shunting, but these structures are not enlarged with pulmonary or tricuspid atresia. In dogs with classic tetralogy of Fallot with a muscular infundibular obstruction, the pulmonary artery is hypoplastic, and poststenotic dilatation of the main pulmonary artery is not prominent on the dorsoventral radiograph. Dogs and cats with valvular pulmonic stenosis and a restrictive VSD demonstrate more prominent enlargement of the pulmonary artery segment and proximal lobar arteries. These seemingly trivial distinctions often become important when surgical repair is contemplated.

200.13.2.1 Echocardiography

The echocardiogram is particularly helpful in the assessment of the cyanotic patient, because most defects can be easily visualized. Careful evaluation of the right ventricular inflow and outflow tracts usually reveals the site of shunting, and the direction of blood flow can be easily ascertained by Doppler or contrast imaging.[3] Detailed ultrasound studies often render cardiac catheterization unnecessary unless surgery is contemplated and pulmonary hypertension (as opposed to pulmonic stenosis) cannot be otherwise ruled out. The pulmonary vascular and right ventricular pressures can often be estimated noninvasively by measuring the peak velocity of even a small jet of pulmonic or tricuspid valve insufficiency and applying the Bernoulli equation (see Cardiac Imaging). Echocardiographic contrast agents can be used to amplify weak signals from small jets, permitting more accurate assessment of jet peak velocity and cardiac pressures.

Figure 200-43 Gross pathology of tetralogy of Fallot. **A,** Right-sided view of a dog with tetralogy of Fallot shows concentric hypertrophy of the right ventricular wall, a markedly narrowed and hypoplastic right ventricular outflow tract *(white arrowhead),* and a large ventricular septal defect (VSD) *(black arrowhead)*. **B,** Left-sided view of a large, nonresistive VSD *(white arrowhead)* in a patient with tetralogy of Fallot. Note the proximity to the root of the aorta and the possibility for prolapse of an aortic valve leaflet into the VSD.



200.13.2.2 Cardiac Catheterization

Cardiac catheterization and angiocardiography are advisable whenever uncommon or complex defects are suspected or when surgical repair is contemplated. In addition to showing the location and severity of the shunt, angiography outlines the anatomy of the defect (e.g., pulmonic, tricuspid dysplasia) and permits visualization of the pulmonary vasculature. Direct measurements of intravascular pressure are useful for assessing the severity of pulmonary hypertension and for confirming the presence of unusual or easily overlooked defects, such as tricuspid valve stenosis. The measurement of pulmonary artery pressure is essential when cardiac or vascular surgery is contemplated for a patient with cyanotic heart disease. If pulmonary vascular resistance is normal, pulmonary flow can be augmented and systemic hypoxemia improved by the creation of an artificial left-to-right shunt between a systemic and a pulmonary artery distal to the site of the cyanotic defect (e.g., Blalock-Taussig shunt).[61,128a,136a,141a]

200.13.3 Tetralogy of Fallot

The defining anatomic features of tetralogy of Fallot include right ventricular outflow obstruction (pulmonic stenosis), secondary right ventricular hypertrophy, a subaortic ventricular septal defect, and a rightward-positioned aorta (Figure 200-43). Pulmonic stenosis that occurs in combination with an isolated VSD produces similar findings, but the infundibular septum is not malaligned, the aorta is normal in size, and the infundibulum of the right ventricle is not narrowed.[75c] These distinctions are commonly ignored in veterinary patients because corrective surgery is rarely performed.

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200.13.3.1 Pathogenesis

Tetralogy of Fallot has been extensively studied in keeshond breeding colonies, and a spectrum of lesions ranging from the subclinical to the clinically complicated has been identified.[31b,124a,127a] Patterson et al.[124a] graded the conotruncal defects as follows:

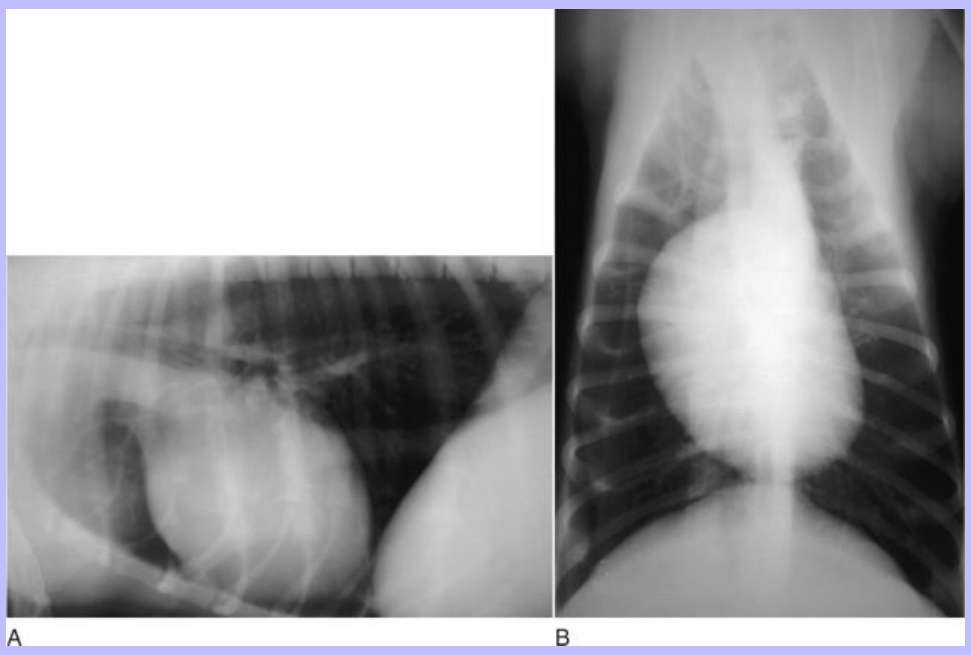
- *Grade 1:* Subclinical malformations involving persistence of the conus septum fusion line, aneurysm of the ventricular septum, and absence of the papillary muscle of the conus.
- *Grade 2:* Pulmonic stenosis or ventricular septal defect in addition to the grade 1 lesions.
- *Grade 3:* Tetralogy of Fallot—pulmonic stenosis, ventricular septal defect, and dextropositioned aorta (with secondary right ventricular hypertrophy.

Additional abnormalities found in some dogs included a dilated and tortuous ascending aorta, pulmonary atresia, hypoplasia of the supraventricular crest, and anomalies of the aortic arch system. Based on extensive breeding studies and sophisticated genetic analysis, conotruncal defects have been shown to be an inherited autosomal recessive trait with variable expression.[76c]

200.13.3.2 Pathophysiology

The essential components of tetralogy of Fallot are severe right ventricular outflow tract obstruction and a ventricular septal defect. As a result of the outflow obstruction and elevated right ventricular pressure, desaturated blood shunts from the right heart through the septal defect to mix with oxygenated blood coming from the left ventricle.[122a-123a] Pulmonary arterial blood flow and pulmonary venous return are scant, and the left atrium and left ventricle are small (underdeveloped). The addition of unoxygenated blood from the right ventricle to the systemic side of the circulation causes arterial hypoxemia, decreased hemoglobin oxygen saturation, cyanosis, and secondary polycythemia. Systemic collateral circulation to the lung increases via the bronchial arterial system. These vessels supply blood to the capillaries of the pulmonary parenchyma either directly or via anastomosing connections with a larger pulmonary artery. A substantial portion of this blood can participate in pulmonary gas exchange. Other aspects of clinical pathophysiology have been previously described (see Clinical Evaluation of the Patient with Cyanotic Heart Disease, above).

Figure 200-44 Lateral **(A)** and dorsoventral **(B)** radiographs of a dog with tetralogy of Fallot. Right heart enlargement is suggested by the rounding of the sternal border on the lateral view and the reverse D appearance on the dorsoventral view. The main pulmonary artery and peripheral pulmonary vessels are diminished. The appearance of the heart on the dorsoventral view is classically described as "boot shaped" *(coeur en sabot)* but is often difficult to reconcile.



200.13.3.3 Clinical Findings

Tetralogy of Fallot is common in the keeshond and English bulldog and in some families of other breeds.[30] It has also been recognized in the cat.[9a] Presenting complaints and clinical signs are as previously described for cyanotic heart disease. In most cases, the murmur of tetralogy of Fallot is produced by blood flowing through the stenotic pulmonic valve.[75c] A right-sided murmur, resulting from blood flow through the VSD, may predominate when PS is mild and left-to-right shunting occurs across a restrictive VSD (i.e., an acyanotic defect). The absence of an obvious murmur suggests pulmonary atresia and/or polycythemia with hyperviscosity (which reduces blood flow turbulence) and ejection across a large, nonrestrictive VSD. Exercise or excitement may induce or enhance detection of peripheral cyanosis by accentuating right-to-left shunting by mechanisms previously described.

Radiography usually reveals a small or normal-sized heart with rounding of the right ventricular border (Figure 200-44). The main pulmonary artery is not always visibly enlarged, in contrast to the usual case of

pulmonic stenosis with intact ventricular septum. The pulmonary vasculature is diminished, and the left auricle may be inconspicuous as a consequence of decreased venous return. The ECG typically exhibits criteria for right heart enlargement, including right axis deviation, although left or cranially directed vectors may be found in some cats.[129a] Echocardiographic findings include right ventricular hypertrophy, increased right ventricular chamber dimensions, reduced left atrial (LA) and LV dimensions, a large subaortic VSD, and right ventricular outflow obstruction (Figure 200-45). Doppler or contrast studies can be used to document right-to-left shunting at the ventricular outflow level (Figure 200-46).[3,130a]

Figure 200-45 Echocardiography of tetralogy of Fallot in a keeshond puppy. **A,** Right long axis view shows severe right ventricular (RV) concentric hypertrophy and right atrial enlargement. **B,** Right short axis view shows severe RV concentric hypertrophy, flattening of the interventricular septum, a small, underloaded left ventricle (LV), and hyperechogenicity of the RV subendocardium. **C,** M-mode study shows enlargement of the RV compared with the LV. The tricuspid and mitral valves are seen moving in the center of their respective ventricles. Paradoxical septal motion toward the RV during systole appears to occur. **D,** Right long axis view shows the ventricular septal defect (VSD) and rightward (dextropositioned) displacement of the aortic root and aorta (Ao). **E,** Color flow Doppler study of an image similar to that in **D** shows right-to-left shunting of blood from the right ventricle, across the VSD, and into the aorta. **F,** Continuous wave Doppler study from the left heart base across the pulmonic valve indicates the presence of high-velocity blood flow and pulmonic stenosis.

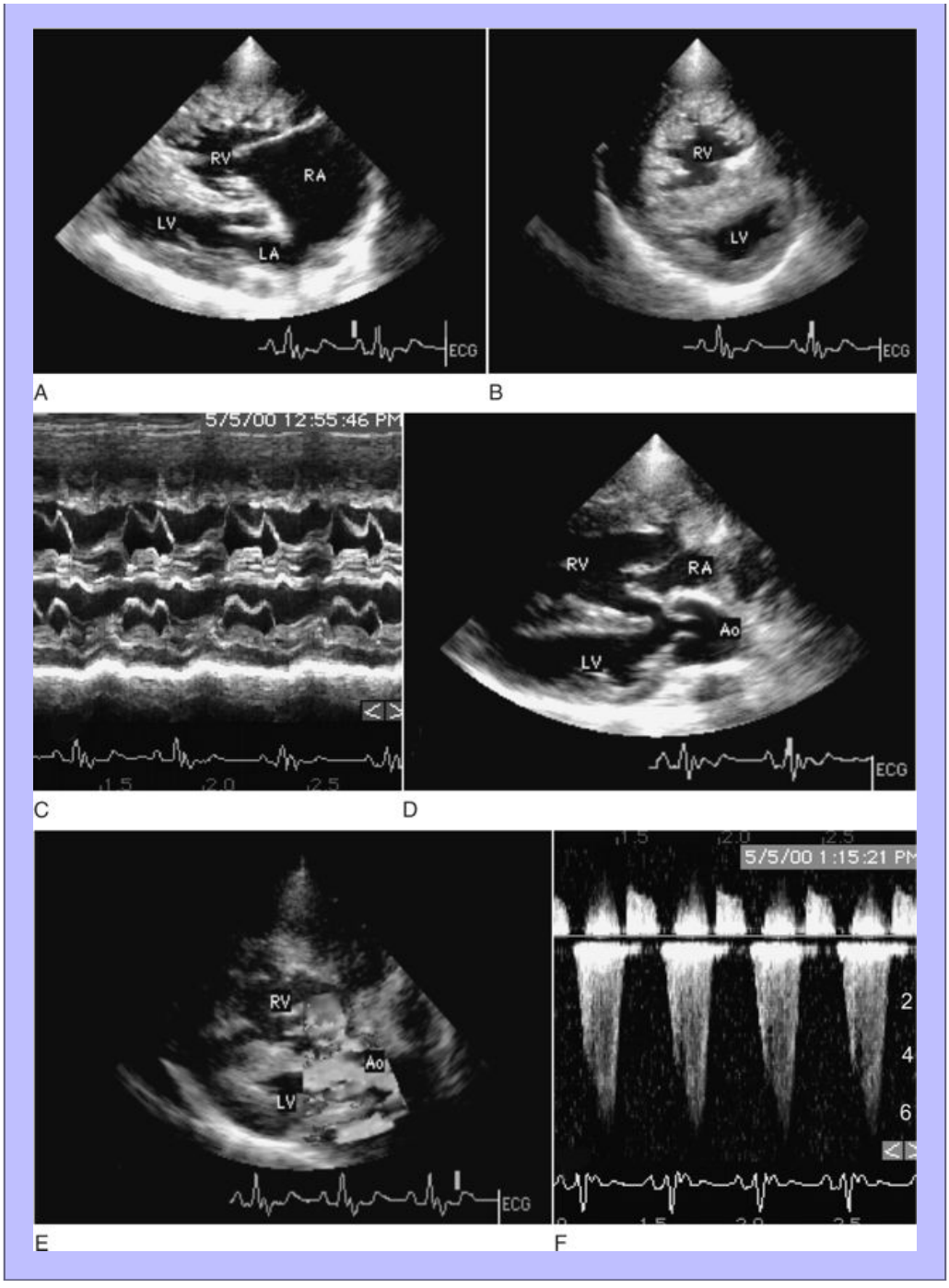

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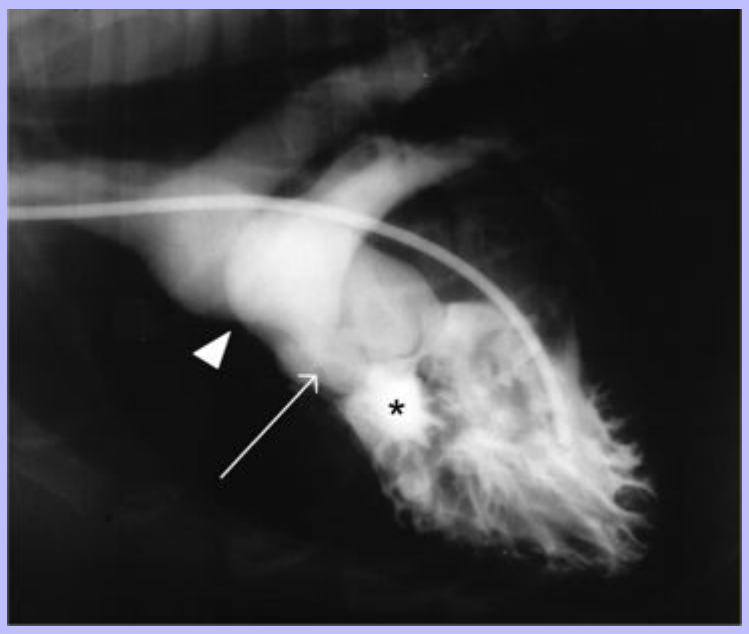
Figure 200-46 Angiogram from a keeshond with tetralogy of Fallot. The right ventricular injection opacifies the right ventricle, pulmonary artery, and aorta. Contrast can be seen in the region of the suspected ventral septal defect (*). The contrast column narrows in the right ventricular outflow tract and the region of the pulmonic valve (*arrow*). A large, poststenotic dilatation of the main pulmonary artery (*arrowhead*) is present. A wide, rightward-positioned aorta can be appreciated.



Cardiac catheterization demonstrates equilibration of left and right ventricular systolic pressures, compatible with a large, nonrestrictive VSD.[128a] Oximetry samples reveal a step-down at the left ventricular outflow level, and the aortic blood is relatively desaturated. Angiocardiography reveals right ventricular hypertrophy, narrowing of the right ventricular infundibulum, pulmonic stenosis with minimal poststenotic dilatation, varying degrees of pulmonary artery hypoplasia, a large subaortic VSD, a small, dorsally displaced left ventricle, an enlarged and rightward-positioned aorta, and prominent bronchial circulation (Figure 200-46).[124a,128a] Bidirectional shunting across the VSD is common in anesthetized animals. Anticoagulation therapy (e.g., heparin) should be considered to prevent cerebral embolization during and immediately after cardiac catheterization.

200.13.3.4 Clinical Management

The natural history and survival times of dogs and cats with tetralogy of Fallot are not well characterized. Like other cyanotic heart diseases, tetralogy of Fallot can be tolerated for years if pulmonary blood flow is

maintained and hyperviscosity is controlled.[21] Most affected animals have severely limited exercise capacity. In cases of pulmonary atresia, pulmonary blood flow must be derived from a patent ductus arteriosus, the bronchial artery, or an elaborate network of systemic collaterals. Sudden death is common due to the combined consequences of hypoxia, hyperviscosity, or cardiac arrhythmia. Unlike with pulmonic stenosis with intact ventricular septum, congestive heart failure is an unusual outcome.

Options for treating animals with tetralogy of Fallot include medical and surgical approaches. Definitive correction of the defect (i.e., closure of the VSD and removal or bypass of the stenosis) can be done under cardiopulmonary bypass, but such surgery is rarely performed in animals.[62,77c] As a general rule, the stenosis should not be relieved if the VSD cannot be closed because the loss of right ventricular pressure results in marked left-to-right shunting with subsequent left-sided congestive heart failure.[63,128a] As an alternative to definitive correction, surgical palliation through the creation of a systemic to pulmonary shunt can be quite rewarding.[64,78c,128a,141a] Subclavian to pulmonary artery (Blalock-Taussig), ascending aorta to pulmonary artery (Potts), and aorta to right pulmonary artery (Waterston-Cooley) connections have been made in dogs and cats. Creation of a left-to-right shunt distal to the cyanotic defect increases pulmonary perfusion and allows a greater contribution of oxygenated blood to the systemic circulation. The size of the accessory shunt must be controlled to prevent overloading of the diminutive left ventricle and subsequent pulmonary edema. The extent to which these shunts remain patent over long periods in veterinary patients has not been reported.

Periodic phlebotomy, performed to maintain the PCV between 62% and 68%, produces a satisfactory result in many cases.[21] Excessive bleeding should be avoided, and the blood that is withdrawn is replaced with crystalloid fluids to maintain cardiac output and tissue oxygen delivery.[138a] Some children with tetralogy of Fallot benefit from beta blockade with propranolol; however, controlled studies of the clinical efficacy of this treatment in animals are lacking.[139a,140a] Severe hypoxic spells should be treated with cage rest, oxygen, and sodium bicarbonate (if metabolic acidosis is evident). Treatment with vasoconstrictive agents such as phenylephrine can also help reduce the amount of right-to-left shunting. Drugs with marked systemic vasodilating properties should be avoided.

200.13.4 Other Causes of Cyanotic Congenital Heart Disease

200.13.4.1 Valvular Atresia

Pulmonary atresia with a ventricular septal defect is essentially an exaggerated form of tetralogy of Fallot (Figure 200-47). All the blood ejected from the right heart is shunted right-to-left across a large VSD and into an enlarged aorta. The tricuspid valve is usually normal. The term *pseudotruncus arteriosus* has been used to describe this defect, which differs from a true truncus arteriosus because careful dissection reveals an imperforate pulmonic valve and a vestigial cord representing the main pulmonary trunk. On occasion, both the pulmonic and tricuspid valves are atretic (see Figure 200-47). The right ventricle is small or hypoplastic, and blood returning to the right atrium shunts through a patent foramen ovale or ASD to produce cyanosis. The lungs are supplied via a PDA or an extensive bronchoesophageal collateral circulation.

Aortic atresia with a hypoplastic left heart is a rare form of cyanotic heart disease in dogs. The aortic orifice is often imperforate, the ascending aorta is hypoplastic, and the mitral valve is usually atretic or hypoplastic. In the absence of a VSD, the left ventricle is very small; when a VSD is present, the left

ventricle is better developed. The right heart supplies the entire pulmonary and systemic circulations, resulting in profound cyanosis and, in most cases, early death.

200.13.4.1.1 Double outlet right ventricle

Double outlet right ventricle (DORV), in which both great vessels exit from the right ventricle, has been reported in dogs and cats (Figure 200-48).[146a,147a] A VSD provides the left ventricle with an avenue for outflow into the great vessels. Depending on the location of the VSD in relation to the origin of the great vessels, DORV can manifest as either pulmonary overcirculation or cyanosis. Concurrent abnormalities such as pulmonic stenosis, pulmonary hypertension, and coarctation of the aorta can also affect the development of clinical signs. Cyanosis is likely if the VSD lies under the pulmonary artery. Surgical correction of this condition in dogs has been reported.[31]

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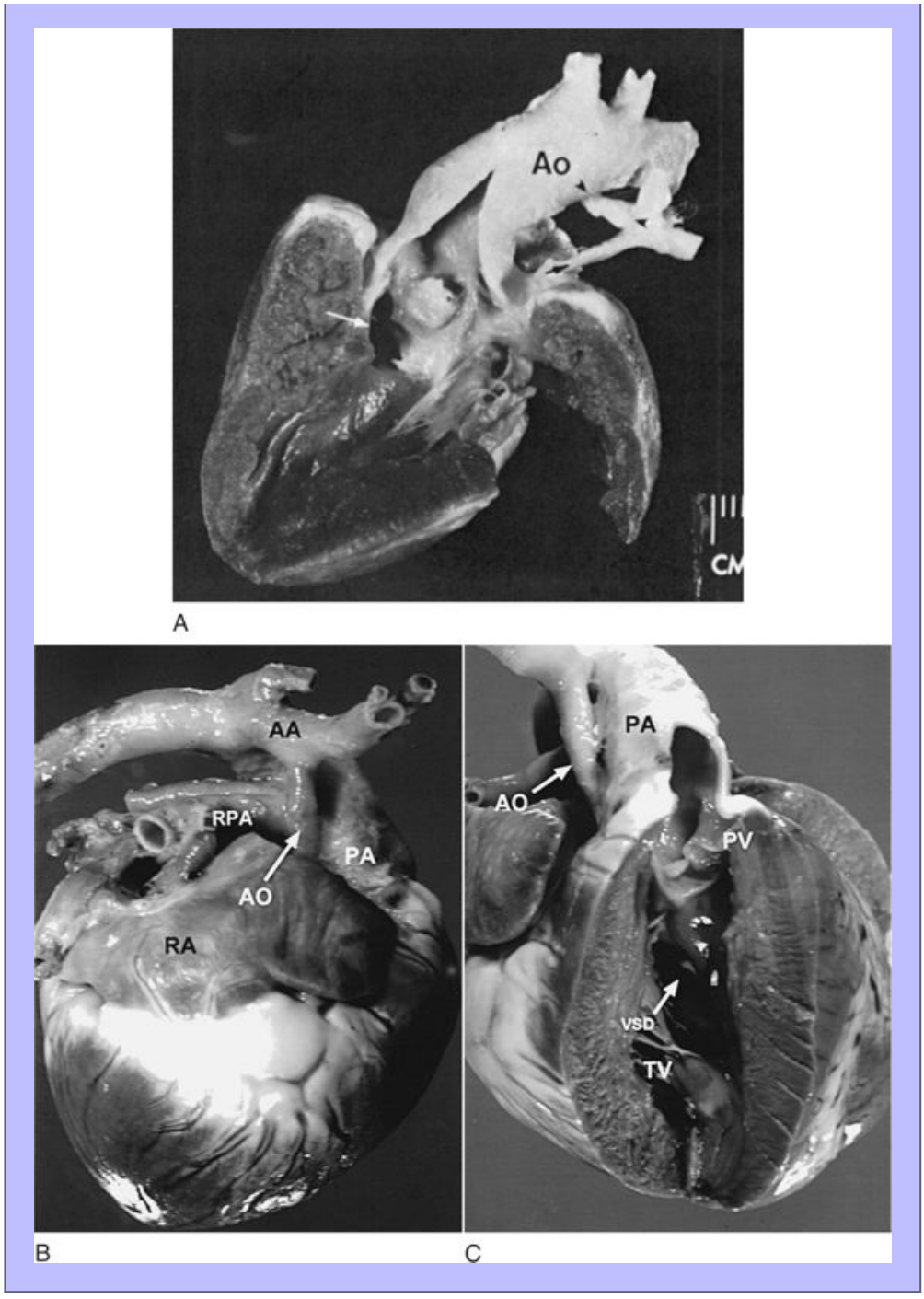
Figure 200-47 **A,** Specimen from a cat with tetralogy of Fallot and pulmonary artery atresia (pseudotruncus arteriosus). The left ventricle has been opened to expose the large ventricular septal defect *(white arrow)*, the hypoplastic pulmonary artery *(small arrow)*, and the dilated aorta *(Ao)*. Pulmonary flow was through the ductus arteriosus, the origin and termination of which are shown by arrowheads. Although the lobar pulmonary arteries were patent, almost no blood was found in the main pulmonary artery. **B,** Specimen from a dog that exhibited severe cyanosis from birth. The proximal aorta is hypoplastic, and an aortic opening (valve) could not be identified. A huge pulmonary artery gives origin to the right and left pulmonary branches, and a large patent ductal segment connects to the aortic arch, supplying the brachiocephalic vessels, the descending aorta, and the hypoplastic aorta. **C,** Same dog as in **B**. Note the marked hypertrophy of the opened right ventricle, as well as the ventricular septal defect, which received blood from the underdeveloped left heart.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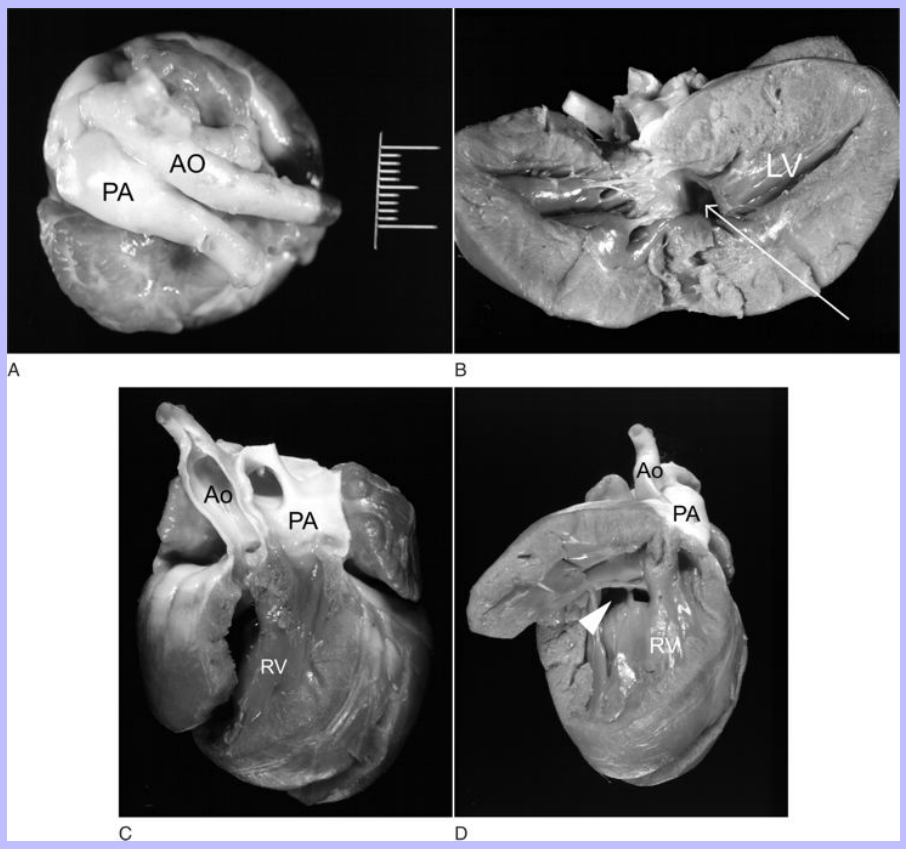
200.13.4.1.2 Transposition of the great arteries

In D-transposition of the great arteries, the aorta originates from the right ventricle and the pulmonary trunk from the left ventricle.[15a,145a] In the pure and fatal case, two independent circulations exist, and the systemic arteries never receive oxygenated blood. Survival of an animal with D-transposition depends on the presence (or production) of shunts between the two circulations to allow for mixing of blood to prevent fatal hypoxemia. These defects are complex, generally lethal, and most likely underdiagnosed in animals, relative to children, because most animals probably die at a very young age undiagnosed.

200.13.4.2 Miscellaneous Cardiac Defects

The potential for anatomic and physiologic variants of congenital heart disease is tremendous, and it is beyond the scope of this chapter to discuss the entire spectrum of malformations. The following descriptions summarize clinically relevant aspects of rarely encountered cardiac and pericardial defects.

Figure 200-48 Pathology of a double outlet right ventricle (DORV) in a 6-month-old domestic shorthair cat. **A,** Dorsal view of the heart showing the side-by-side positioning of the aorta *(Ao)* and pulmonary artery *(PA)* at the cranial right edge of the heart. **B,** View of the ventricular septal defect *(arrow)* from the left ventricular *(LV)* side. Note the absence of a left ventricular outflow tract and aorta originating from the LV and the discontinuity between the mitral valve apparatus and the missing aorta. **C,** View from the right cranial aspect showing the origin of the aorta and pulmonary artery from the right ventricle. The opening of the VSD into the right ventricle is below the crista supraventricularis and is not easily seen in this view. **D,** View of the right side of the interventricular septum reveals the location of the VSD *(arrowhead)* near the origin of the aorta (aortic-committed DORV) (Courtesy Dr. Richard Kienle, Gilroy, CA.)



Endocardial fibroelastosis has been reported in dogs[65,151a,154a,155a] and cats and is probably familial in some lines of Burmese and Siamese cats.[12a,79c,151a-153a] The gross anatomic findings include left ventricular and left atrial dilatation with severe endocardial thickening, characterized grossly by diffuse, white, opaque thickening of the luminal surface (Figure 200-49). Histologic lesions in the cat include diffuse hypocellular, fibroelastic thickening of the endocardium with layering of thin, randomly organized collagen and elastic fibers.[151a,153a] Edema of the endocardium with dilatation of lymphatics is prominent, and there is no evidence of myocardial inflammation or necrosis. The clinical features of endocardial fibroelastosis include early development of left or biventricular failure, generally before 6 months of age. Mitral regurgitation may be detected. Left ventricular and atrial dilatation are evident on radiographs and on the ECG. The limited echocardiographic studies performed to date suggest reduction of left ventricular myocardial function as opposed to pure valvular disease in which shortening fraction tends to be normal or increased.[155a] The diagnosis of primary endocardial fibroelastosis is at times tenuous, inasmuch as chronic left ventricular dilatation may lead to similar changes, particularly in the setting of mitral dysplasia, aortic stenosis, restrictive and dilated cardiomyopathy, or myocarditis. Dogs with endocardial fibroelastosis often have thickening of the mitral valve leaflets and mitral regurgitation.[154a,155a] Affected animals fail to thrive. Medical treatment of congestive heart failure may be effective in prolonging life, but recovery is unlikely.

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Figure 200-49 Gross pathology of a cat with endomyocardial fibrosis. Cutaway views of the left ventricular inflow tract **(A)** and the left ventricular outflow tract **(B)** show diffuse fibrosis of the endomyocardial surface of both the atrium and ventricle.

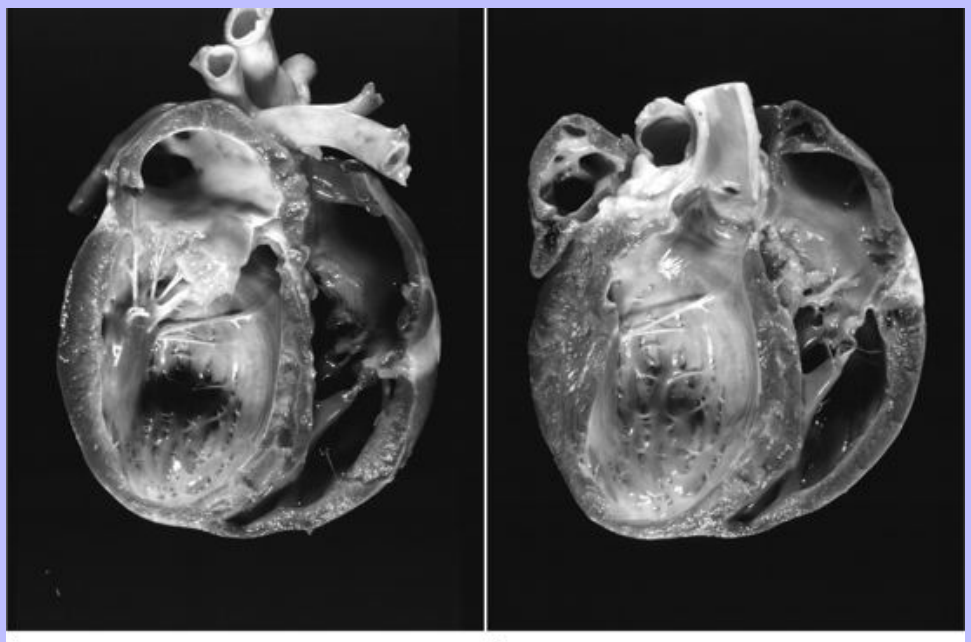
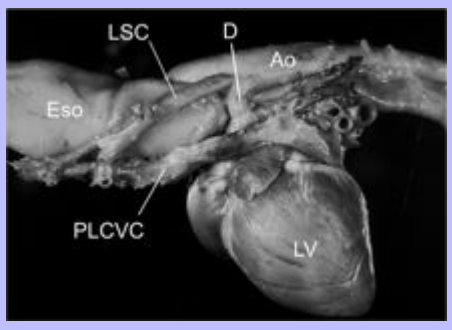


Figure 200-50 Gross pathology from a dog with persistent right aortic arch, patent ductus arteriosus *(D),* anomalous origin of the left subclavian artery *(LSC),* and persistent left cranial vena cava *(PLCVC)*. The left-sided view of the heart, great vessels, and esophagus *(Eso)* shows the entrapment and cranial dilatation of the esophagus by the patent ductus arteriosus. The origin of the left subclavian artery is moved distal from its usual location and is behind the esophagus. The persistent left cranial vena cava can be seen extending laterally alongside the esophagus and left heart base and coursing around the caudal waist of the heart.



Peritoneal-pericardial diaphragmatic hernia (*PPDH*) is a relatively common developmental anomaly of dogs and cats.[163a,170a] This condition is not a true cardiac anomaly, but it can be confused with other congenital and acquired conditions. For further information, the reader is referred to Chapter 205.

200.13.4.3 Vascular Anomalies

Vascular anomalies can be classified based on their location in the vascular system. A number of vascular malformations have been reported.[49a,50a,66–68,171a-196a] Patent ductus arteriosus, discussed previously, is the most important of the vascular malformations. Peripheral vascular disorders, including abnormal abdominal and hepatic venous drainage and arteriovenous fistulas,[37b] are detailed in their respective chapters. Unilateral atresia of a pulmonary artery has been described in a cat with respiratory difficulty.[185a] Coronary arteries can develop anomalously but rarely cause documented clinical disease except when associated with pulmonic stenosis.[33] Other major vascular defects center about the aorta and the systemic venous drainage, and the salient features of these disorders are briefly addressed.

200.13.4.4 Aortic Anomalies

Persistence of the right aortic arch, as opposed to the left fourth aortic arch, causes regurgitation in weanlings due to constriction of the esophagus.[49a,50a,171a-183a] Vascular ring anomalies include this

common malformation and other total or partial ring anomalies, such as those formed by retroesophageal subclavian arteries, double aortic arch, or left aortic arch with right-sided ligamentum arteriosum.[177a,179a,180a,184a] The condition is quite common in German shepherds and has been recognized in many other canine breeds, including Irish setters and Great Danes. The condition is uncommon in cats. Occasionally, other cardiac defects are present, including PDA (Figure 200-50 and Figure 200-51). This condition is described more fully in Chapter 208.

Aorticopulmonary septal defect (window) is caused by failure of the truncus arteriosus to differentiate; this results in a common opening between the aorta and the pulmonary artery, and shunting develops between the left and right sides of the circulation. Although a clinical condition similar to PDA can develop, some reports suggest that in most cases, pulmonary hypertension develops during the first year of life and that clinical signs are similar to those in dogs that develop Eisenmenger's syndrome due to other defects.[68,188a,191a] Management is similar to that for a reversed PDA. Surgery is difficult without cardiopulmonary bypass and should not be attempted if pulmonary vascular resistance is markedly elevated.

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Figure 200-51 Surgeon's view of a persistent left cranial vena cava. This venous anomaly is often encountered during the approach to a patent ductus arteriosus. No hemodynamic consequences result from this anomaly.

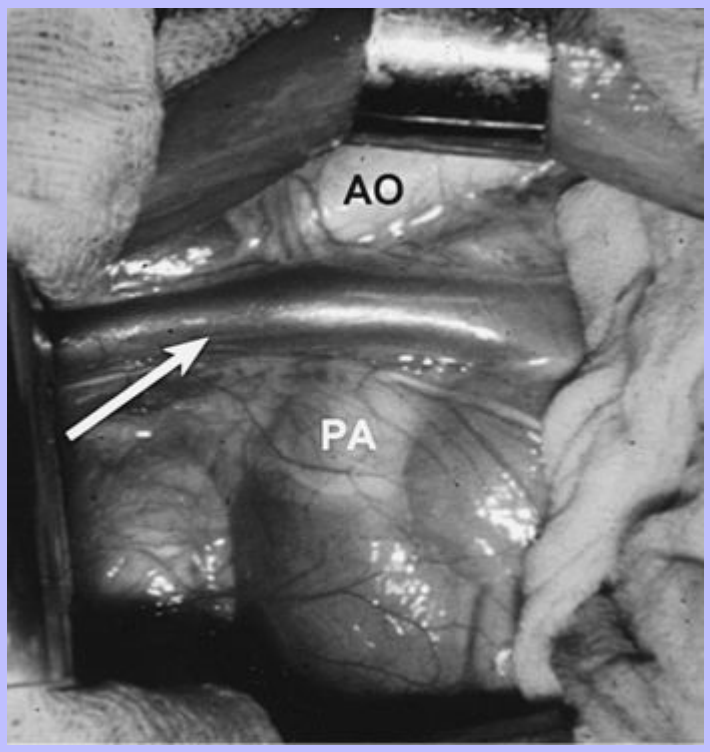
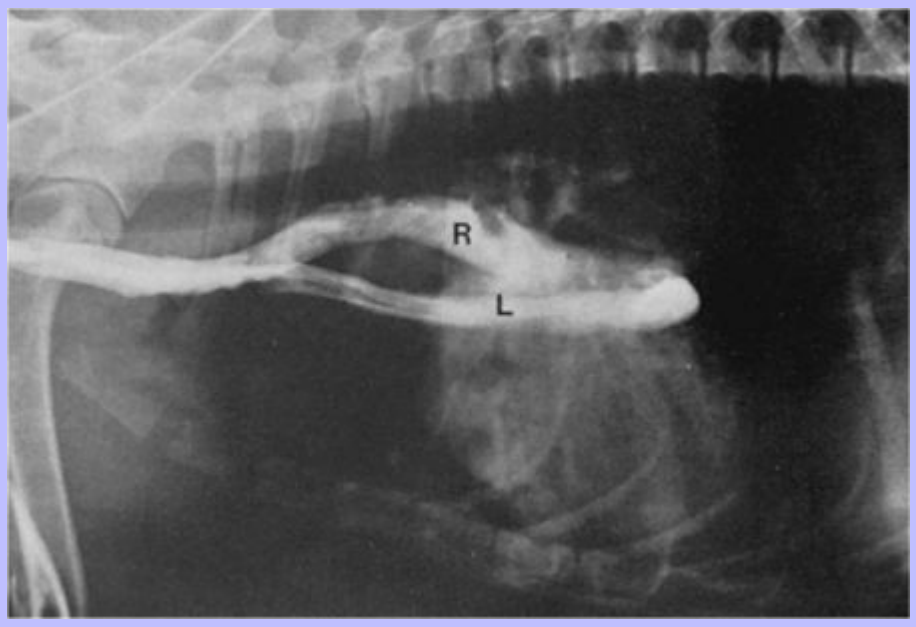


Figure 200-52 Persistent left cranial vena cava in a dog. Contrast was injected simultaneously into the right and left jugular veins. The normal right cranial vena cava is evident (*R*), as is the persistent left vena cava (*L*). Note that the left vena cava enters the caudal portion of the right atrium and empties into the coronary sinus.



Coarctation and interruption of the aorta is a rare defect in dogs that is characterized by narrowing of the aorta distal to the subclavian artery, adjacent to the ductus arteriosus. A case reported by Eyster[193a] demonstrated systolic and diastolic murmurs and left ventricular failure. The clinical features of coarctation in children are well described and in many ways are similar to this case.[15a] Aortic interruption has been reported in two dogs,[80c,193a] and a case of tubular hypoplasia of the ascending aorta in a dog has also been described.[194a] Although these lesions differ from coarctation, they are additional examples of malformation of the aorta in small animals. Definitive diagnosis usually requires angiography, although MRI and CT are effective methods of evaluating lesions of the aortic arch. Surgical correction has been successful in affected dogs.

200.13.4.5 Venous Anomalies

Thoracic venous anomalies rarely cause cardiac problems in small animals. Total or partial anomalous pulmonary venous return, which has been reported in a dog, behaves functionally as a left-to-right shunt at the atrial level.[80a] Abnormalities of abdominal venous drainage, such as patent ductus venosus, can induce hepatic encephalopathy. A relatively common venous abnormality of clinical significance during thoracic

surgery or cardiac catheterization is the persistent left cranial vena cava.[69,81c,195a] This structure, normally present in the fetus as part of the left cardinal venous system, may persist and drain into the embryologically related coronary sinus in the caudal aspect of the right atrium. Persistent left cranial vena cava may interfere with surgical exposure, particularly during surgical treatment of persistent right fourth aortic arch, or may confound cardiac catheterization, but otherwise it is of no known functional significance. As with persistence of the right fourth aortic arch, this vascular anomaly is common in German shepherds and has been reported in other canine breeds and in cats.[133a,195a] Division of this vessel generally poses no clinical problem provided the normal right cranial vena cava is also present. Venous aneurysms or related anomalies are extremely rare.[38b]

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201 CHAPTER • 201 Acquired Valvular Heart Disease

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201.1 CHRONIC MITRAL VALVE INSUFFICIENCY

Chronic mitral valve insufficiency (CMVI) in dogs is usually caused by a progressive myxomatous degeneration of the atrio-ventricular valves. The disease has been given many names in the veterinary literature, including endocardiosis and chronic valvular disease. Similar changes of the mitral valve are also seen in humans, horses, and pigs.[1–3]

201.1.1 Occurrence

CMVI is common in the dog and has been estimated to account for 75% to 80% of canine cardiac diseases.[4–7] The prevalence of CMVI is strongly age dependent: from only a few percent in young dogs to approximately 75% in dogs older than 16 years.[4,5,7,8] CMVI is encountered in all breeds, but the prevalence of the disease varies greatly: dogs of small-to medium-size breeds, such as the Papillon, Poodle, Chihuahua, Dachshund, and Cavalier King Charles spaniel, are most commonly affected.[9–12] The prevalence of CMVI in cats without primary myocardial disease is unknown but seems to be low.

201.1.2 Significance and Progression

CMVI is characterized by slow progression. Risk factors for progression of CMVI from mild to severe in small dogs include severity of valve lesion, age, and gender.[13–17] The disease progresses into moderate and severe CMVI at a lower age in males than in females.[13,14,18,19] Whether or not these risk factors apply in large dogs is unknown. Typically, it takes several years for the disease to evolve from mild, clinically silent CMVI to severe disease with signs of heart failure.[14,15,19] Many affected dogs will therefore not develop clinical signs from the disease during their lifetime. The most severely affected dogs, however, will end up needing therapy for heart failure, and, in the end, die or be euthanized due to refractory cardiac failure (Figure 201-1). CMVI has been reported to account for 75% of the cases of congestive heart failure in dogs[7,20], a proportion which is considerably higher in affected breeds.[10,13,21] Furthermore, the presence of CMVI and ongoing medical treatment for heart failure may complicate medical treatment for other conditons and decisions for surgical procedures or anesthesia.

201.1.3 Pathology

Macroscopic appearance of myxomatous degeneration depends on at which stage of disease the valve is examined. Macroscopic findings in cases of mild myxomatous degeneration may not be apparent and may be overlooked, especially in dogs without evidence of valvular insufficiency. Common findings at early stages include elongated chordae tendineae and enlarged, thickened leaflets with areas showing

bulging/ballooning/prolapse towards the atrial side (Figure 201-2, *A*).[6,22,23] The changes begin in the area of apposition of the leaflets and are usually most pronounced in sections where chordae tendineae inserts. The bulging of such areas towards the atrial side of the leaflets has been described as rolling of the edges. With progression, the bulging becomes worse and the free edge becomes thickened and irregular and the lesions spread into other parts of the leaflets. Within the same valve leaflet one section may look relatively normal while another, neighboring section is moderately or severely diseased. In late stages, secondary fibrosis can cause marked thickening and contraction of leaflets and chordae tendineae. The chordae tendineae may rupture[23], which leads to an unattached free edge, that is, a flail leaflet.[24] Ultrastructurally, there is myxomatous proliferation of the valve, in which the spongiosa component of the valve is unusually prominent and the quantity of acid-staining glucosamino-glycans (GAGs) is increased (Figure 201-2, *B*).[6,22,23] The valvular interstitial cells in affected areas often have morphologic changes of the nucleus, a localized concentration of abnormally shaped mitochondria and rough endoplasmic reticulum, disorganized cytoskeleton, and lack of secretory vesicles.[25] There is haphazard arrangement, disruption and fragmentation of the collagen fibrils surrounding the interstitial cells (see Figure 201-2, *B*). The endothelial cells covering affected areas become polymorphic and some areas completely loose the endothelium, exposing the underlying extracellular matrix (Figure 201-2, *C*, and 201-2, *D*).[25] Exposure of collagen and other matrix components to the blood is expected to promote thrombosis. Although thrombosis may develop as a complication in CMVI dogs, thrombus formation on the mitral valve is uncommon. Why it is absent in the presence of endothelial damage is currently not known. Inflammation is not an apparent part of the degenerative changes.

Figure 201-1 Proposed model for progression of CMVI in the Cavalier King Charles Spaniel population. The effect of age on the annual percentage of new cases of heart murmurs attributable to CMVI out of the total population in male (thin black line) and female dogs (thin gray line), and on the annual percentage deaths/euthanasias caused by heart failure (thick black or gray lines). Note that both curves resemble a distribution of a random variable with a means of approximately 6 to 7 years (heart murmurs) and 9 to 10 years (deaths/euthanasias), respectively. The male and female populations differ in their epidemiology concerning age of onset of MR and mortality attributable to CMVI. Initiated breeding programs aim at pushing the curve of new cases of CMVI to higher age to reduce the number of cases of congestive heart failure. (From Häggström J: Chronic valvular disease in Cavalier King Charles Spaniels—epidemiology, inheritance and pathophysiology. Thesis, Swedish University of Agricultural Sciences, Uppsala, 1996.)

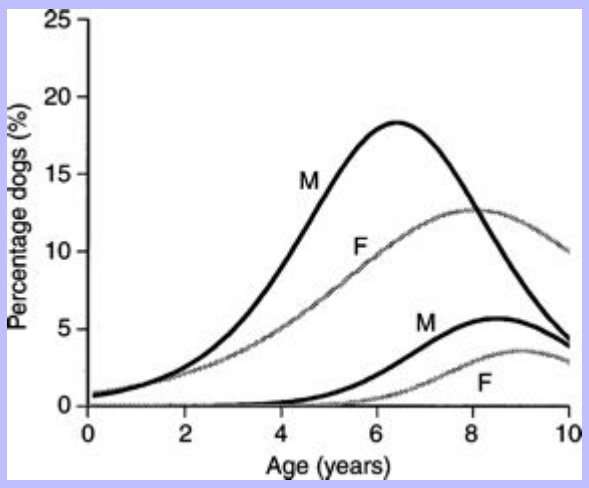
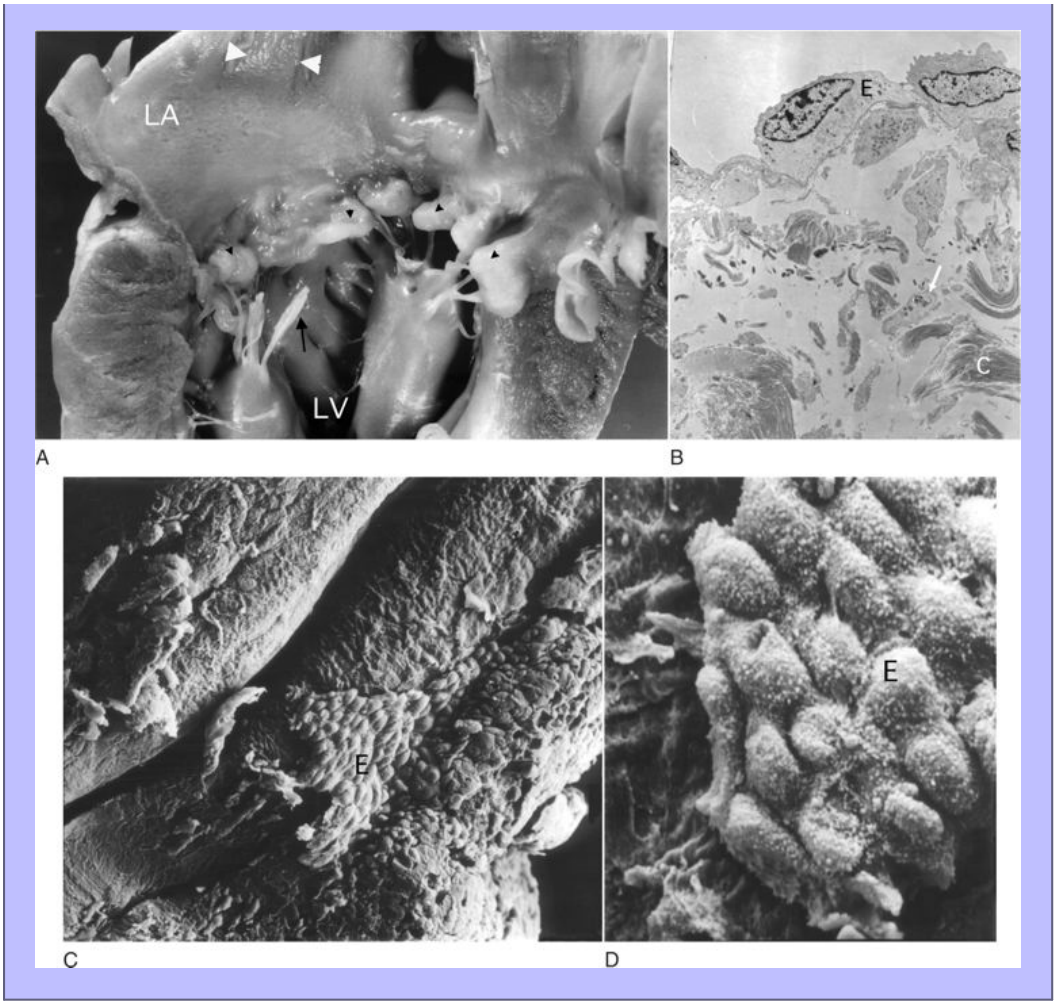


Figure 201-2 **A,** Postmortem specimen of an opened left ventricle (LV) and left atrium (LA) from a dog that suffered from CMVI. The left ventricle and atrium are dilated, and the mitral valve leaflets are thickened and contracted, with nodules rolling in the free edges *(arrowheads)*. Evidence of chordal involvement present in the form of ruptured chordae tendinae *(arrow)*. Jet lesion is present on the atrial wall *(between white arrowheads)* result when the regurgitant streams of blood from the left ventricle strike the atrial wall. **B,** Transmission electron micrograph demonstrating loss of collagen in the subendothelial layer of the mitral valve of a dog with CMVI due to myxomatous degeneration. Fragments of valvular interstitial cells *(white arrow)* are visible interspersed between disrupted bundles of collagen (C). There is obvious variation in the appearance of the endothelial cells (E). **C**, Scanning electron micrograph of the surface of the distal zone of a diseased mitral valve. The triangular area of endothelium in the middle of the picture (E) is the only endothelium left in this area; the remaining area is completely denuded. Underlying collagen has been revealed, which indicates the absence of basement membrane remnants. **D,** Higher magnification of the triangular "endothelial island *(E)*" in Figure **C,** shows that these cells are somewhat clumped, with a very dense microappendage population, considerably more dense than is seen in the normal state with the entire cell surface covered. (**A,** From Pedersen HD, Häggström J: Mitral valve prolapse in the dog: a model of mitral valve prolapse in man, *J Cardiovasc Res* 47:234, 2000. **B, C,** and **D,** Courtesy Brendan Corcoran, Alexander Black, Joanna Dukes-McEwan, Anne French, University of Edinburgh, Scotland and University College Galway, Ireland.)



The valvular regurgitation leads to secondary changes including dilation of the left atrium, mitral annulus, and left ventricle (eccentric hypertrophy), atrial endocardial lesions (fibrosis) opposite the mitral orifice (i.e., “jet lesions”), and, in severe cases, varying degrees of atrial rupture, such as endomyocardial splits, ruptured pectinate muscles in the atrial appendage, acquired atrial septal defect, and hemopericardium.[6] Myxomatous degeneration is not restricted to the mitral valve and it may be detected in any of the four intra-cardiac valves. The incidence of valve involvement in dogs was reported as follows: mitral valve alone 62%; mitral and tricuspid valve 32.5%; tricuspid valve alone 1.3%.[6] The pulmonary and aortic valves are less commonly affected. Interstingly, lesions similar to myxomatous degeneration of the atrioventricular valves have been described in the main pulmonary artery in Cavalier King Charles spaniels.[26] Other findings in dogs with advanced stages of CMVI include intramural arteriosclerosis and multiple small myocardial infarcts.[27–29] In contrast to humans with mitral valve prolapse, infectious endocarditis affecting the damaged leaflet is a rare complication in dogs.[1]

201.1.4 Inheritance and Breeding

The etiology of CMVI has not been ascertained but heredity has long been suspected to play a major role, owing to the strong association of this disease with certain small to medium-sized breeds. Two recent studies of families of Cavalier King Charles spaniels and families of Dachshunds provide evidence that genetic factors play a large role in the etiology.[17,18] The disease seems to have a polygenic inheritance; that is, multiple genes influence the trait and a certain threshold has to be reached before CMVI develops.[17,18] Males have a lower threshold than females, which means that males will develop the disease at younger age than females within a family of dogs in which the offspring on average have the same genotype. The polygenic mode of inheritance means that a combination of a sire and a dam that both have an early onset of CMVI will give offspring that have, on average, an early onset of CMVI (and heart failure). A combination of dogs with late onset will give offspring that manifest the disease at old age or never. The major role played by genetic factors implies that other factors, such as level of exercise, degree of obesity, and diet, play a relatively minor role in the etiology. Likely because of this, very little is known about the influence of such factors on the disease. Breeding programs aimed at reducing the prevalence of CMVI have been launched in Europe and North America and elsewhere for Cavalier King Charles spaniels and Dachshunds. These breeding programs use auscultation to identify the presence of a heart murmur or echocardiography to detect and quantify mitral valve prolapse or regurgitation. Dogs that are under a specific age and have developed a heart murmur or echocardiographic findings consistent with CMVI are not allowed to breed. Likewise, offspring from parents that have developed a heart murmur or echocardiographic evidence of early CMVI under a certain age limit are excuded from breeding in some programs. The age limit for potential breeding dogs and parents is very important. It should be set at an age at which dogs with an early onset of CMVI are excluded, but not too high because this may impoverish the breeding population to unacceptable low numbers.[13]

201.1.5 Etiology and Pathogenesis

Little is known about the pathogenesis of the progressive thickening and degeneration of the leaflets. An old theory is that the changes are response-to-injury type lesions, such as that repeated impact to the leaflets (especially the areas of apposition) results in slowly progressing changes.[30] Probably, one or more primary inciting factors increase the risk of disease in predisposed animals as not all dogs develop atrioventricular valve myxomatous degeneration. The nature of these primary initiating factors are currently not known, although certain abnormalities of collagen and other extracellular matrix components have been suggested.[13] It has been suggested that a primary defect leads to abnormal valve motion, that is, prolapse of the leaflets, which in turn increase the shear stress imposed on them, both directly through the abnormal leaflet apposition and indirectly through the increased regurgitant flow.[15,19] It likely plays an important role for the progression of the disease that the endothelium is damaged or even missing in diseased areas[25,31], because endothelial cells are known to communicate extensively with subendothelial cells (e.g., valvular interstitial cells). Specifically, endothelial damage may lead to an imbalance in local concentrations of growth-promoting and growth-inhibiting substances produced by endothelial cells. For instance, associations have been found between disease severity and the expression of endothelin receptors and nitric oxide synthase.[32,33] Future research into local disease mechanisms may suggest ways of treating the actual disease rather than merely the resulting circulatory disturbances.

201.1.6 Pathophysiology

Proper mitral valve closure requires an anatomically and functionally intact valve apparatus. Mitral regurgitation (MR) can be due to alterations of the valve leaflets, dilatation of the atrio-ventricular annulus, rupture of chordae tendineae, or inappropriate contraction of the papillary muscles. More than one of these factors can usually be identified when CMVI is present. The consequences of CMVI depend on several factors[34]: the reduction in forward flow, the regurgitant volume, the size and compliance of the left atrium and the pulmonary vascular bed, the development of tachyarrhythmias (atrial or ventricular) or thromboembolism, and rupture of the left atrial wall.

Primary MR of lesser degree does not induce any apparent change in indices of cardiac size or function. The forward stroke volume is maintained, and the small regurgitant volume is easily accepted by the left atrium. With progression of the valve lesions, the regurgitant part of the total left ventricular stroke volume increases, but several cardiac and non-cardiac (e.g., renal, neurohumoral, and vascular) compensatory mechanisms contribute to maintain the forward stroke volume.[13,34] The left ventricle compensates for the loss of forward stroke volume by increasing the end diastolic volume (preload) and, to some extent by increased heart rate.[35,36] However, the heart rate is usually not significantly changed until advanced stages of CMVI, when it increases.[34,36] The increased preload causes an increased force of contraction according to the Frank-Starling mechanism.[37] The resistance to ventricular emptying is reduced in the first stages of ejection because the regurgitant volume is ejected into the left atrium at low pressure, before sufficient pressure is generated at lower volume to open the aortic valve and cause forward ejection into the aorta. These mechanisms lead to exaggerated motion of the left ventricle (hyperkinesia). Myocardial systolic function is relatively well preserved because the ejection into the left atrium at low pressure require relatively little work by the left ventricle. Patients may tolerate even severe CMVI for years.[7,34] Nevertheless, because of chronic volume overload and the fact that the hypertrophy, while necessary, is a pathologic remodeling, myocardial contractility decreases slowly, even in clinically compensated dogs, but progressively and inexorably.[7,35,38] Arteriosclerosis may complicate the condition by being the cause for multiple small myocardial infarctions, further decreases in contractility, and increased risk of congestive heart failure or sudden death.[28,29]

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The left atrium has an important function by allowing the regurgitant volume to be absorbed within the atrial cavity, and it protects the pulmonary vascular bed from hypertension.[39] Increased left atrial pressure results in pulmonary venous congestion and edema. The effect of regurgitant volume on left atrial pressure and volume and consequently pulmonary capillary pressure, depends on the left atrial size, as well as on the compliance of the left atrial wall. Consequently, left atrial compliance is determined by the rate of increase in regurgitant volume, which itself is determined by the rate of progression of CMVI, and by remodeling in response to the volume overload. Maintained left ventricular compliance allows filling at low pressures with the large volume overload of MR, and is a result of the remodeling that is inherent in eccentric hypertrophy. In cases with slowly progressing CMVI, there is often a drastic enlargement of the left atrium, whereas pulmonary congestion and pulmonary edema develop late. The edema is also delayed by the development of a more effective lymphatic drainage of the pulmonary interstitium in chronic pulmonary venous hypertension.[40] The enlarged left atrium may induce coughing by compression of the left main stem bronchus that lies dorsal to the left atrium. In cases with acutely increased MR, as in rupture of a tendinous cord, the left atrium is unable to adapt, which results in a rapid elevation of left atrial pressure. Pulmonary capillary pressure subsequently increases, which leads to pulmonary congestion and edema.

Advanced cases of CMVI may be complicated by processes that are related to increased left atrial size and pressure.[7,41] The left atrium may rupture and cause cardiac tamponade; right-sided heart failure may develop as a consequence of concurrent tricuspid valve insufficiency and/or pulmonary artery hypertension; and tachyarrhythmias may develop as a consequence of ultrastructural changes in the myocardium. These complications are discussed later.

201.1.7 Clinical Signs

The progress of CMVI from the detection of a soft heart murmur to end-stage is often a matter of years in small dogs. Some large dogs appear to be less tolerant to CMVI. In these dogs, the disease has a more drastic progression with more severe clinical signs than in small dogs. The first clinical signs of decompensation are usually mild but may be aggravated within days or sometimes weeks. Since these signs are vague and not specific for decompensated heart failure, the differential diagnostic challenge in CMVI is often not if the disease is present, but whether or not CMVI is responsible for the clinical signs. The signs relate to the presence and degree of one or several of the following pathophysiologic events, listed in order of their relative importance: (1) elevated left atrial and pulmonary venous pressure, which results in respiratory distress and cough due to pulmonary edema and main-stem bronchial compression; (2) reduced left ventricular or right ventricular forward flow, which results in weakness and reduced stamina; (3) right-sided heart failure, which results in pleural effusion and ascites; (4) acute decompensation with fulminant pulmonary edema or ventricular fibrillation, which causes sudden death.

Mild to moderate CMVI is usually not associated with any signs of disease. Most dogs with CMVI are free of clinical signs for most of the time they have a murmur, although exercise intolerance might be noted. Cough is the most common presenting complaint in CMVI. Although this sign is not specific for heart disease or heart failure, it should merit further evaluation. In the case of advanced CMVI, the cough may be caused by pressure of the left atrium on the left mainstem bronchus, by pulmonary congestion and edema or, most commonly, a combination.[20] With pulmonary edema present, other common clinical signs are tachypnea and dyspnea. The dogs are often anxious and restless during the night while they lie in lateral recumbency (orthopnea) and prefer sternal positioning. In more advanced cases respiratory sounds, often wheezes, may be audible. These dogs are often inactive and have varying degrees of inappetence. Cardiac cachexia may develop, although loss of body weight may be masked by concurrent fluid retention and edema. Dogs with left mainstem bronchial compression but without pulmonary congestion or edema may have coughing spells at any time during the day, especially during physical exercise or excitement. Otherwise they do not demonstrate clinical signs.

Syncope is encountered in some dogs with CMVI. Syncope may be associated with a tachyarrhythmia, but the course of events often resembles that which is described in vasovagal syncope.[42] The frequency of the syncope vary from occasional spells to several attacks per day. Other causes of syncope include tussive fainting that may occur in conjunction with paroxysm of coughing or exercise in the presence of pulmonary hypertension.[20]

201.1.8 Physical Examination

A mid-systolic click is frequently encountered in early stages of CMVI (Figure 201-3, *A*),[43,44] although it may be difficult to detect by auscultation. The presence of this sound is dependent on heart rate and body position.[43] A systolic click may be accompanied by a low-intensity systolic murmur. The murmur is most

frequently early systolic but may be late systolic or may in some dogs vary between the two. With progression, the most prominent clinical finding is a holosystolic heart murmur. The sound begins as a soft apical systolic murmur on the left side of the thorax and may be intermittent and sometimes audible only during inspiration (Figure 201-3, *B*). In the early stages of CMVI, the murmur can often be augmented by physical maneuvers, such as a short run.[43] With further progression, the sound becomes holosystolic and more intense (Figures 201-3, *C*, and 201-3, *D*)[13,15,43–45] and may radiate over to the right side of the thorax. A thrill may be palpated over the left thoracic wall (cardiac apical area) and the apical beat may be pronounced. Musical murmurs (whoop sounds) of high intensity occur less frequently. This murmur does not indicate the severity of CMVI (Figure 201-3, *E*).[44] There is usually a shift in the relative intensity of S1 and S2 (see Figure 201-3, *D*).[45] In the absence of significant myocardial failure, the first heart sound is usually enhanced, whereas the second heart sound becomes less intense.[20,44,45] A low-intensity third heart sound is often present, but this sound is often difficult to detect by auscultation (see Figure 201-3, *D*).[44,45] The presence of a clearly audible third (gallop) sound is a strong indicator for myocardial failure.[44] In cases of severe heart failure, the heart sounds and murmurs may be muffled by pleural effusion or cardiac tamponade. Thus even though auscultatory findings may be suggestive, the clinician must rely on the supporting historical, clinical, echocardiographic, and radiographic data to determine the hemodynamic significance of the insufficiency.

The presence of sinus arrhythmia in advanced CMVI indicates that decompensated heart failure is absent.[36] The heart rate increases in response to decreased forward cardiac output as decompensation develops, and the heart rate becomes more regular. A rapid and irregular heart rate is indicative of arrhythmia. The most common form of ectopy is atrial premature contractions. In more advanced CMVI, supraventricular tachycardia, atrial fibrillation, and ventricular premature contractions may be encountered.

Figure 201-3 ECG lead II (upper registration) and phonocardiograms (middle and lower registrations) in dogs with different stages of CMVI. Recordings were obtained from the following dogs: **(A)** a dog with a systolic click (C) and an intermittent early systolic murmur (M), **(B)** a dog with an interrmittent systolic murmur (M), **(C)** a dog with a continuous holosystolic murmur (M), **(D)** a dog in end-stage MR with a loud first heart sound (S1), a dampened second heart sound (S2), a systolic murmur (M) and a prominent third heart sound (S3), **(E)** a dog with a comparably uncommon high intensity musical murmur (M) where the intensity of the murmur does not reflect the severity of MR. (**A**, **B**, **C**, and **D** From Häggström J: Chronic valvular disease in Cavalier King Charles spaniels—epidemiology, inheritance and pathophysiology, thesis, Swedish University of Agricultural Sciences, Uppsala, 1996. **E** from Kvart C, Häggström J: Cardiac auscultation and phonocardiography in dogs, horses and cats, Uppsala, 2002.)

With sinus rhythm the femoral arterial pulse is usually normal. Weak pulses may be noted in heart failure. Weak and variable pulses with deficits can also be observed with rhythm disturbances. If tamponade occurs, owing to a tear in the left atrium and pericardial hemorrhage, the femoral pulse will be weak. Jugular venous distention may be present in severe heart failure, pulmonary hypertension, or pericardial effusion.

In cases of CMVI without signs of heart failure, the lung sounds are expected to be normal. Crackles, snaps, and popping sounds, best heard at end of inspiration, may be detected in advanced CMVI with pulmonary interstitial edema. Similar findings are common in dogs with small airway disease,[46] and if concurrent it may be a diagnostic challenge to determine the cause of the clinical signs. In more severe cases with alveolar edema, the pulmonary sounds are usually more pronounced and they may be auscultated even without a stethoscope.

Mucous membranes are usually normal, even in cases with pulmonary edema but may be cyanotic, grayish, or ashen in advanced cases of heart failure. Ascites in isolated CMVI is uncommon, but progressed CMVI often

tends to involve the right side of the heart as a consequence of pulmonary hypertension or development of a tachyarrhythmia. In these dogs, ascites, hepatic, and splenic enlargement are common.

201.1.9 Electrocardiographic Findings

Electrocardiographic findings in CMVI vary from normal tracings to marked abnormalities in rate, rhythm, or configuration of complexes. With the exception to document and classify a certain arrhythmia, the ECG is of limited use in the diagnosis or management of CMVI. ECG is an insensitive indicator of cardiac enlargement and cannot detect heart failure or pulmonary edema.

Sinus arrhythmia is usually preserved during the early course of CMVI. In heart failure, sinus tachycardia and a loss of sinus arrhythmia are common.[36] Decompensated heart failure from CMVI should be questioned in a coughing patient with sinus arrhythmia. Cats with MR usually maintain sinus rhythm, although atrial fibrillation and/or ventricular ectopy may develop.

Most ECG abnormalities associated with CMVI are the result of accentuations of the normal ECG. The mean electrical axis in the frontal plane often remains within the normal range throughout the progression of the disease. In cases with significant left atrial enlargement, the P-wave may be prolonged. In cases of significant left ventricular enlargement, the QRS complex may be prolonged and the R wave amplitude in lead II increased,[47] but the former is generally a more reliable criteria to detect left ventricular enlargement.

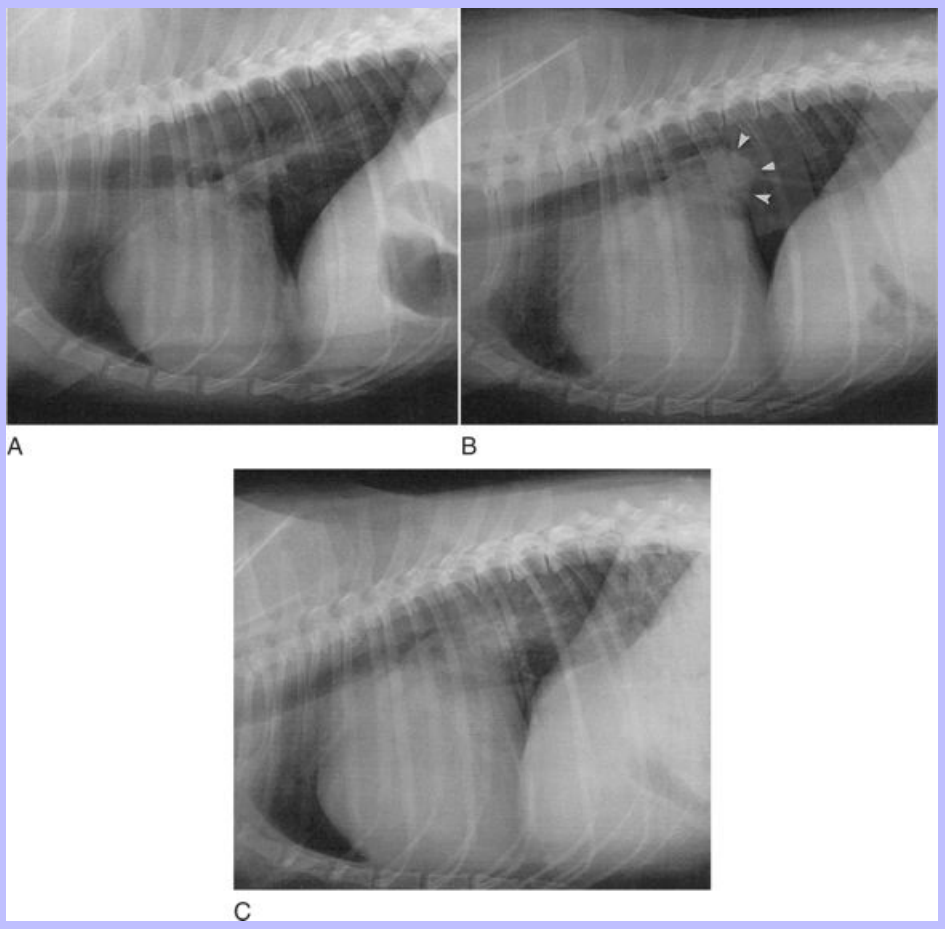
Supraventricular premature beats are common in CMVI. In most cases, this finding is of little hemodynamic significance. Atrial fibrillation, paroxysmal supraventricular tachycardia, atrioventricular dissociation, ventricular premature beats, and ventricular tachycardia are less common. These arrhythmias are most often encountered in progressed cases and hence often indicate a poor prognosis.

201.1.10 Radiographic Findings

The value of radiography is in assessment of the hemodynamic consequences of CMVI (global cardiac size and presence of pulmomary congestion and edema). It helps to exclude other possible causes for the clinical signs: presence of pulmonary congestion and edema is of particular interest in geriatric dogs. Two orthogonal projections should be obtained: lateral and dorsoventral or ventrodorsal. Absolute straight positioning is essential for accurate evaluation of heart size and shape and position of the main bronchi. In dogs with CMVI, important structures to evaluate are the left atrium, the left ventricle, the mainstem bronchi, the pulmonary vessels, and the lungfield. Dogs with a low degree of CMVI usually have a normal heart size, normal lung fields, and normal vascular markings.

Left atrial enlargement is one of the earliest and most consistent radiologic features of CMVI. The left atrium and left ventricle continue to enlarge with progression of the disease. Signs of left atrial and left ventricular enlargement in lateral projection include dorsal elevation of the caudal portion of the trachea and carina; dorsal displacement of the left mainstem bronchus; visible prominence of the left atrium causing the caudal border of the heart to appear straight or bulge dorsocaudally (Figure 201-4). In the dorsoventral (or ventrodorsal) projection, the enlarged left atrial appendage may be identified as a bulge in the left cranial part of the cardiac border (between the 2 and 3 o'clock positions). The border of the enlarged left ventricle appears rounded and there may be a shift of the cardiac apex to the left or right. In advanced cases of decompensated CMVI, pleural effusion, ascites, and enlargement of the liver and spleen are commonly identified as signs of associated right heart failure.

Figure 201-4 Radiographs in left lateral projection of a dog with CMVI: **(A)** The dog was at this time asymptomatic, and the radiograph shows a slight left atrial enlargement and normal vascular perfusion. **B,** Radiograph of the same dog 4 years later. The dog had developed exercise intolerance and persistent cough. Visible are marked left atrial *(white arrows)* and left ventricular enlargement and elevation and slight compression of the left mainstem bronchus, whereas the vascular markings are within normal limits. **C,** Six months later the dog had also developed dyspnea and had suffered episodes of syncope. In addition to the findings in previous radiograph **(B)**, there is a more obvious compression of the left mainstem bronchus and evidence of pulmonary congestion and interstitial edema. (Courtesy Kerstin Hansson, Uppsala, Sweden.)



During the progression of CMVI, radiographic signs of pulmonary congestion and edema usually develop. Pulmonary edema and congestion is more likely to be present in a dog with significant heart enlargement (indicating advanced CMVI) than in a dog with normal or slightly increased heart size. However, the degree of cardiac enlargement is poorly related to the severity of pulmonary congestion and edema (see Pathophysiology). Because many dogs with significant CMVI and enlarged hearts have not developed decompensated heart failure, therapy should be based primarily on clinical signs and the presence of pulmonary edema and congestion, not the degree of cardiac enlargement. Pulmonary venous distension, when present, is an early indication of pulmonary congestion; the diameter of the veins is greater than that of the corresponding pulmonary arteries and they often become tortuous (especially in cats). However, venous distention is not a consistent finding even in dogs with pulmonary edema, and in some dogs, the outlining of the distended vein is indistinct as interstitial edema partially obscures the pulmonary vessels. With progression, interstitial and alveolar edema develop. In dogs, alveolar edema is often first detected in the perihilar region and the dorsal parts of the caudal lung lobes, sometimes more prominent on the right side, but acute edema may involve the cranial lobes. In cats, the location of a cardiogenic pulmonary edema is not as predictable as in dogs. It commonly has an ill-defined, patchy appearance.

Pulmonary findings may be inconclusive, since early radiographic changes of pulmonary interstitial edema and bronchial pattern resemble the radiographic appearance of chronic airway disease. The tendency is to overdiagnose pulmonary edema of heart failure. It is therefore important, if possible, to have series of radiographs and evaluate other evidence of left-sided heart failure that should be present by the time pulmonary edema has developed, such as venous distention, before diagnosis is determined.

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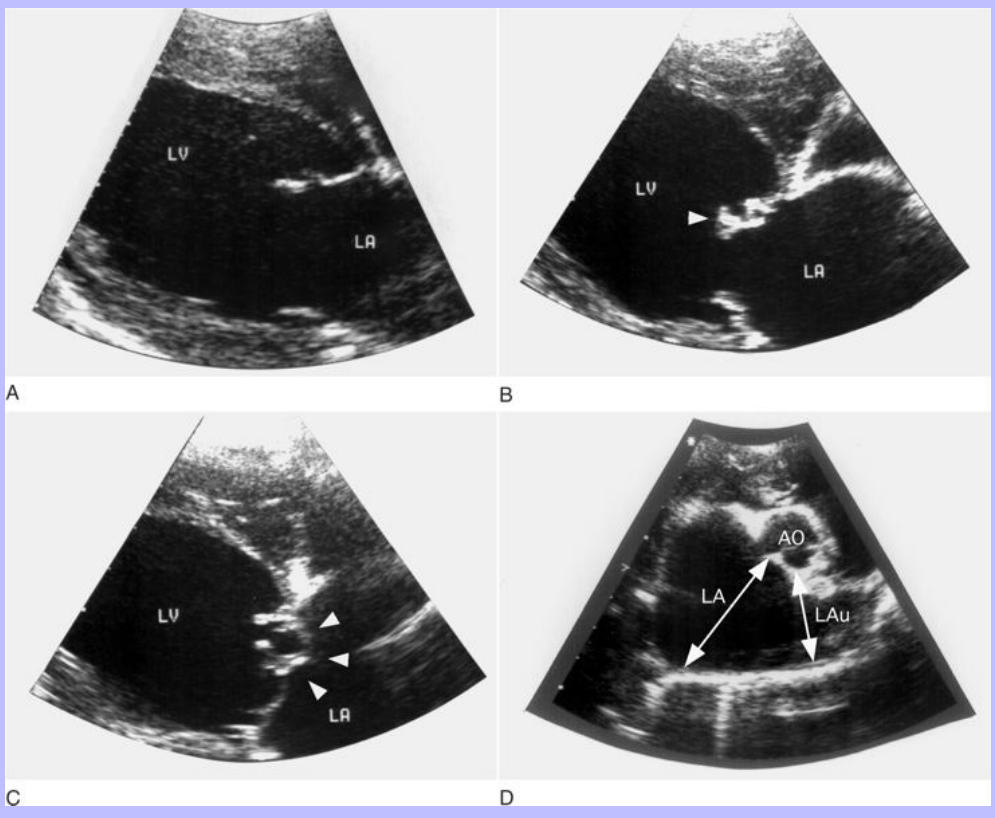
201.1.1.1 Echocardiographic Findings

Echocardiography is useful for obtaining a diagnosis of CMVI, and thereafter to monitor the condition, although it cannot diagnose the presence of heart failure. Two-dimensional echocardiography allows the ultrasonographer to evaluate the anatomy of the mitral valve and to identify leaflet thickening and leaflet protrusion into the left atrium. A systolic bulging of one or both leaflets to the atrial side of the mitral annulus is an early indication of affected valves and it may be present in dogs with or without mitral regurgitation (MR).[15,48] The presence and severity of protrusion of the leaflets may be measured in the right parasternal long axis view.[16,48]

In cases with insufficient valves, the degree of displacement is reported to relate well with the severity of MR.[15,16,48] With progression, the degenerative changes become more prominent and the leaflets often have an irregular “club-like” appearance with greatest thickening at the tip (Figure 201-5, *B*). The gross pathologic changes of the two leaflets (anterior and posterior) are often equally severe at postmortem examination, but the degenerative changes commonly appear more prominent on the anterior leaflet in the right parasternal long axis view on the echocardiogram.

Figure 201-5 Echocardiographic right parasternal long-axis views of the left atrium *(LA)* and left ventricle *(LV)* during diastole **(A** and **B)** and systole **(C),** in a normal dog **(A),** and in the same dog with CMVI **(B** and **C)**. The mitral valve appears thickened **(B)** *(arrowhead)*, and there is systolic displacement of both leaflets to the atrial side of the mitral annulus **(C)**. Figure **D** shows the left atrium in a right parasternal short axis view at the aortic valve *(AO)* level of a dog with severely enlarged left atrium. The *arrows* demonstrate the difference in LA diameter obtained by measuring the greatest diameter and the diameter often used in M-mode. *Lau*, Left auricle.



It is important to examine the entire valve as the lesions are often quite unevenly distributed. Chordal thickening may be identified and systolic displacement (prolapse) of the leaflets or a valve flail may be evident (Figure 201-5, *C*). Valve flail is when the edge of a leaflet or, in severe cases, a complete leaflet moves into the left atrium in systole. The finding of a valve flail leads to the suspicion of chordal rupture, which may occasionally be identified in the left atrium or in the left ventricle.[24]

The left atrium is an important structure to evaluate with MR because its size reflects disease severity. The general "rule of thumb" is that the larger the left atrium, the greater is the degree of MR present, but there are exceptions (see Pathophysiology). Although the left atrium may be examined from a right parasternal long axis view and a left apical four chamber view, the best view is the the right parasternal short axis view with the aortic root, the left atrial body and the auricle in view (Figure 201-5, *D*). The most useful information from this view is the left atrial size because it can be compared with the size of the aortic root, which is relatively constant for a given dog size. The normal ratio of the left atrial diameter to the aortic root (LA/Ao) in M-mode is reported to be between 0.8 to 1.2.[49] With the more traditional M-mode method, however, the left atrial dimension measured is not the largest that can be obtained, as it measures the diameter of the left atrial appendage or underestimates the diameter of the left atrial body. In dogs with MR, the diameter of the left atrial body may be considerably greater than that of the left atrial appendage (see Figure 201-5, *D*).[50] The normal range for 2D La/Ao values is reported to be 0.84 to 1.27 in Cavalier King Charles spaniels and 0.86 to 1.59 in a mixture of breeds.[50,51] In the authors' experience, a 2D La/Ao greater than 1.5 represents an enlarged left atrium in all breeds. This limit is presumably lower in specific breeds. Early cases of CMVI with a small degree of MR have no echocardiographic signs of left atrial enlargement. With progression of CMVI the left atrial dimension increases and dogs in congestive heart failure often have a left atrial to aortic root ratio of 2 or greater.[52]

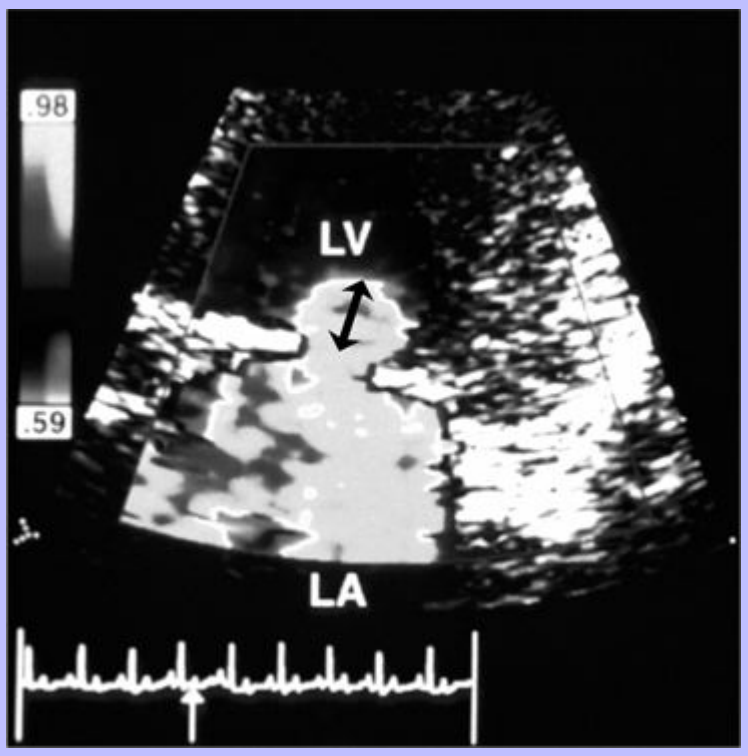
Evaluation of left ventricular size and motion is important in MR and measurements are often obtained in the M-mode. Mild MR usually does not lead to abnormal dimensions. With progression, the left ventricular-end-diastolic short axis dimension increases, whereas the end-systolic dimension does not increase at the same rate. The left ventricular wall thickness is usually within normal limits. The increased size of the left ventricle combined with a normal wall thickness indicates that volume overload and eccentric hypertrophy are present. An increase in left ventricular end-diastolic dimension in the presence of normal or minimally increased left ventricular end-systolic dimension is a consequence of increased preload and rapid left ventricular emptying into the low-pressure left atrium.[7,53] In MR, values of ejection phase indices (e.g., left ventricular fractional shortening, ejection fraction, and mean velocity of circumferential shortening) are often normal (mild MR) or greater than normal (moderate to severe MR). Therefore in the setting of moderate or severe MR, a normal fractional shortening represents a significant reduction of myocardial contractility. End-systolic volume indices (e.g., left ventricular end-systolic short axis dimension or end-systolic volume index) more accurately estimate myocardial contractility in MR.[7,53] However, when heart failure is present and the sympathetic nervous system is activated to increase apparent contractility, even these measurements overestimate intrinsic myocardial contractility.[38]

End-systolic dimension may increase in small dogs with end-stage CMVI, but increase appears to be more common in large dogs that present with heart failure and severe MR but with a fractional shortening in the normal range or slightly increased. In these dogs, the mitral valve leaflets may or may not look as severely affected as in small dogs. Often, they look less affected, and it is currently an enigma why these dogs present with severe MR and prominent myocardial failure. The large dogs with MR and myocardial failure may be confused with DCM, but DCM may be questioned in a dog with normal or slightly depressed fractional shortening. It has been suggested that these dogs may actually suffer from congenital mitral dysplasia rather than myxomatous degeneration.[54] Mild pericardial effusion may be present in dogs with heart failure, whereas significant pericardial effusion should raise the suspicion of another disease or of a complication of CMVI such as left atrial rupture. Mild pleural effusion may also be evident in dogs with heart failure.

It is rare, even in severe cases of CMVI, to detect incomplete closure of the leaflets as means of confirmation of the presence of MR. Instead, the valvular insufficiency may be detected and quantified by spectral or color-flow Doppler.[43] Ideally, the regurgitant flow should be aligned with the ultrasound beam and this is most often acheived in the left apical four-chamber view. As the flow direction depends on the orientation of the regurgitant orifice which, in turn depends on the leaflet morphology, other views may also give good alignment. Spectral Doppler may be used to identify the regurgitant jet when color-Doppler mapping is not available. Furthermore, spectral Doppler gives information of the velocity of the regurgitant jet and velocity time tracings may help in estimating regurgitant volume (see below). Typically, dogs with CMVI without myocardial failure have a velocity of the regurgitant jet of 5 to 6 m/sec.[54] However, the velocity may be increased in individuals with systemic hypertension and decreased in individuals with hypotension, significantly increased left atrial pressure or myocardial failure.

Color-flow echocardiography confirms the presence of a regurgitant jet and the size of the jet can be compared with the size of the left atrium. This measurement is semiquantitative in dogs and cats. A small jet rules out moderate to severe MR, but it is difficult to discriminate between moderate and severe regurgitation from the jet size. Small jets in the vicinity of the mitral valve should not be overinterpreted in dogs without any other valve abnormality, as trivial regurgitation may often be detected in normal dogs.[55] Recently, it was demonstrated that the regurgitant fraction may be quantified with use of the proximal isovelocity surface area (PISA) color-flow method in dogs with MR (Figure 201-6).[56,57] In MR, blood flow converges on the ventricular side of the mitral valve orifice before it passes the regurgitant orifice, and this area is characterized on the color-Doppler echocardiogram as a hemisphere. Based on the values of the radius of this hemisphere, the aliasing velocity, the maximal velocity of the regurgitant jet, and the velocity time integral of the regurgitant flow (the latter two are obtained from spectral Doppler measurements), the regurgitant stroke volume may be calculated. The regurgitant fraction is obtained by dividing the regurgitant volume with the sum of the forward and regurgitant stroke volumes. Although this method has significant advantages compared to other methods of measuring regurgitant fraction, it has several practical limitations and may not be readily applicable in all cases of MR.

Figure 201-6 Zoomed color-flow Doppler image of the mitral valve in a left apical 4-chamber view showing the hemicircle of the flow convergence on the ventricular side of the mitral valve. The radius of the proximal isovelocity region is measured from the ventricular side of the mitral valve leaflets to the edge of the hemisphere (*double-sided arrow*). The radius of the hemisphere is used to calculate the regurgitant fraction of the total stroke volume. There is also evidence of significant regurgitation into the left atrium. *LV*, left ventricular chamber; *LA*, left atrial chamber. (From Kittleson MD, Brown WA: Regurgitant fraction measured by using the proximal isovelocity surface area in dogs with chronic myxomatous mitral valve disease, *J Vet Intern Med* 17:84, 2003.)



The mitral regurgitant stroke volume may also be estimated indirectly using the difference between total stroke volume and forward stroke volume into the aorta. The total stroke volume may be estimated using M-mode measurements of left ventricular size, and the forward stroke volume may be estimated by multiplying the aortic cross sectional area with the velocity time integral obtained from the spectral Doppler tracing of the aortic flow. Alternatively, the total stroke volume may be estimated by multiplying the annular

cross-sectional area of the mitral valve obtained from the two-dimensional mode with the velocity time integral obtained from the spectral Doppler tracing of the diastolic flow over the valve. Both these methods involve multiple measurements, each with its own errors, which means that they will only provide estimates of regurgitant volume. Measurements of regurgitant fraction in dogs with moderate to severe MR indicate that they can eject more than 75% of the total stroke volume into the left atrium, which is remarkable.

At present, none of the Doppler methods (subjective estimation of jet size, spectral Doppler methods, and the PISA method) have been shown to be more reliable indicators of disease severity than left atrial size in dogs and cats with MR. Spectral Doppler may be used to study the transmitral flow during diastole. Significant mitral regurgitation is usually associated with increased diastolic filling velocities as a consequence of increased diastolic transmitral flow.[58] Furthermore, abnormal diastolic ventricular function as a consequence of severe volume overload may be detected. It is important to time the events when evaluating the transmitral flow to separate systolic regurgitation from diastolic to avoid a false-positive diagnosis of clinically significant mitral regurgitation. Diastolic regurgitation is common in cases with bradycardia or arrhythmias and probably indicates small reverse pressure gradients during cardiac filling.[59]

201.1.12 Differential Diagnosis

The signalment, clinical signs, and physical examination findings are often such that they strongly suggest CMVI. Although the usual cause for MR is myxomatous degeneration, other causes are noteworthy: dilated and hypertrophic cardiomyopathy; widespread arteriosclerosis with myocardial infarcts; bacterial endocarditis of the mitral valve; undiscovered congenital heart disease, such as mitral valve dysplasia and patent ductus arteriosus (PDA). Early cases of CMVI may have an early systolic heart murmur that may be confused with slight aortic or pulmonic stenosis or physiologic flow murmur. Often the early or late systolic murmur due to MR is accompanied by a systolic click, which is an indicator for early myxomatous degeneration and mitral valve prolapse. The signalment, point of maximal intensity of the murmur, and echocardiography are distinctions between slight MR and slight aortic or pulmonic stenosis and physiologic flow murmurs. Furthermore, dogs with slight MR are usually old and the murmur has maximal intensity over the mitral area, whereas dogs with physiologic flow murmurs or aortic or pulmonic stenosis are usually young and have a murmur with maximal intensity over the heart base. The exclusion of dilated cardiomyopathy and hypertrophic cardiomyopathy requires echocardiographic examination. However, it may not be possible to discriminate CMVI from DCM in some medium-and large-sized dogs, such as Cocker spaniels, which present with valvular abnormalities, significant MR, left ventricular and left atrial enlargement and a normal to subnormal fractional shortening. Measurement of biochemical markers of myocardial damage, such as Troponins, may aid in diagnosing myocardial infarcts, provided that the myocardial damage was recent and significant.[60]

The echocardiographic appearance of a mitral valve affected with endocarditis may appear very similar to nodular thickening of valve leaflets characteristic for myxomatous degeneration. However, lesions of endocarditis may be more echogenic and more isolated. The signalment usually helps to distinguish between these two diseases. Bacterial endocarditis occurs most frequently in large dogs; CMVI is more common in small dogs; dogs with bacterial endocarditis often have a history of fever, arthritis, systemic disease, a recently developed heart murmur, and clinical signs that may indicate thromboembolic disease. Dogs with CMVI are usually older, often have had a heart murmur for years, and do not have fever or signs of systemic disease. Bilateral regurgitation is commonly encountered, but isolated tricuspid regurgitation does occur. In these cases, the heart murmur may radiate to the left side of the thorax.

Although CMVI may readily be diagnosed in a patient with clinical signs, the true diagnostic challenge lies in determining if decompensated heart failure is the underlying cause. Most dogs with CMVI are older, small to medium-sized dogs, and many of these dogs exercise little. Thus exercise intolerance may be difficult to identify and, if present, difficult to attribute to the heart condition as obesity, chronic joint disease, and other disease may be present. Furthermore, the hallmark of left side heart failure, coughing and dyspnea, may be caused by several conditions, such as small airway disease, tracheal instability, pulmonary fibrosis, neoplasia, heartworm disease, and pneumonia. Many of these differential diagnoses can be excluded by different clinical tests, particularly radiography, but in some cases, the results may be inclusive. In these cases, a 48-to 72-hour trial diuretic therapy with repeat radiographs may help to identify the underlying etiology. In addition, "bedside" assays of natriuretic peptides (ANP and BNP) will soon be available to aid in diagnosis of such cases.

201.1.13 Management

Ideally, therapy of CMVI would halt the progression of the valvular degeneration. Improvement of valvular function by surgical repair or valve replacement would likewise stop further deterioration. However, no therapy is currently known to inhibit or prevent the valvular degeneration, and surgery is usually not technically, economically, or ethically possible in canine and feline patients. The management of CMVI is therefore concerned with improving quality of life, by ameliorating the clinical signs and improving survival. This usually means that therapy is tailored for the individual patient, owner, and practitioner and often involves concurrent treatment with two or more drugs once signs of heart failure are evident. Management of CMVI will be discussed in five groups of patients: those without overt signs of heart failure (asymptomatic), those with left mainstem bronchial compression, those with syncope, those with mild to moderate heart failure, those with recurrent heart failure, and those with severe and fulminant heart failure. Possible complications are discussed separately. It is unusual to treat cases of isolated CMVI in cats and details of drug dosages for cats are therefore not included in this section.

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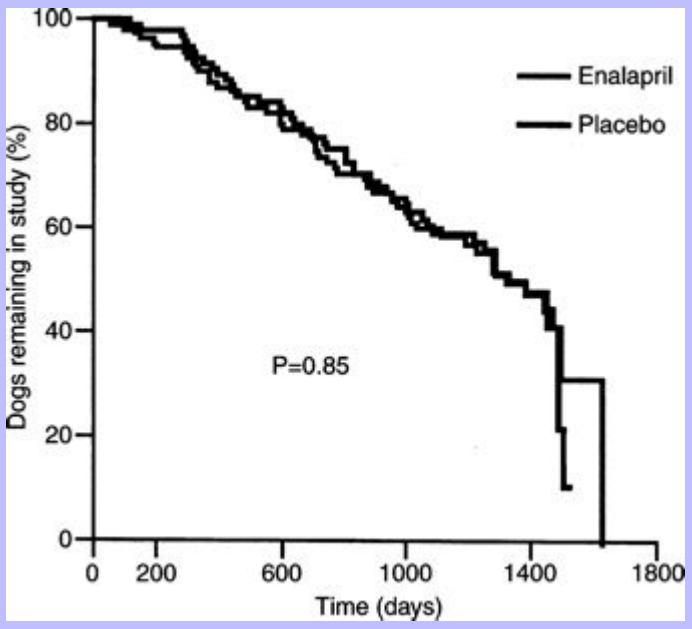
201.1.13.1 Asymptomatic Disease

The stage when a patient starts to show clinical signs of CMVI, that is, have developed decompensated heart failure, is the end of a process started much earlier with the onset of valve leakage. The valvular leakage was compensated through a variety of mechanisms but as the leakage increases the valves eventually became incapable of preventing pulmonary capillary pressures from exceeding the threshold for pulmonary edema, and of maintaining forward cardiac output. It is likely that minor signs of reduced activity and mobility are present even before overt signs of heart failure develop. However, it is very difficult to objectively evaluate the presence of slight to moderately reduced exercise capacity in most dogs with CMVI, as they are often old small companion dogs, which if obese, have little, if any, demand on their exercise capacity. Furthermore, other concurrent diseases in the locomotor system or elsewhere are common and restrict exercise. Thus vague clinical signs such as slightly reduced exercise capacity in a typical dog with progressed CMVI may or may not be attributable to CMVI.

This dilemma leads to the questions of when to start therapy, and if therapy before the onset of decompensated heart failure is beneficial, ineffective, or harmful. ACE-inhibitors are frequently prescribed to dogs with CMVI before the onset on heart failure. At present, however, there is no evidence that administration of any medication to a patient with asymptomatic CMVI has a preventive effect on development and progression of clinical signs of heart failure or improves survival. Two large placebo-controlled multicenter trials, the SVEP and the VetProof trials,[14,61] have been conducted to study

the effect of monotherapy of the ACE-inhibitor enalapril on the progression of clinical signs in asymptomatic CMVI in dogs. Both failed to show a significant difference between the placebo and the treatment groups in time from onset of therapy to confirmed congestive heart failure (Figure 201-7).[14,61] The two trials differ in the following features: the SVEP trial included only dogs of one breed (Cavalier King Charles spaniels) whereas the VetProof trial included a variety of breeds. The dogs in the VetProof trial were more frequently progressed cases of CMVI than the dogs in the SVEP trial, and the SVEP trial comprised more dogs than the VetProof trial (229 versus 139 dogs). Suggested reasons for the non-significant findings in these trials include lack of activation of circulating RAAS activity in asymptomatic animals,[62] low concentration of angiotensin II receptors in the canine mitral valve,[63] or lack of effect of ACE-inhibitors on myocardial remodeling and progressive ventricular dilatation in MR.[64]

Figure 201-7 The SVEP study investigated the effect of enalapril on preventing decompensated heart failure in dogs with asymptomatic CMVI. The graph shows the percentage of dogs included in the enalapril and the placebo groups, respectively, versus time. The difference in number of days in the study between placebo-and enalapril treated dogs was not significant. (From Kvart C et al: Efficacy of enalapril for prevention of congestive heart failure in dogs with myxomatous valve disease and asymptomatic mitral regurgitation, *J Vet Intern Med* 16:80, 2002.)



Owners of dogs with progressed asymptomatic CMVI should be instructed about signs of developing heart failure and, in case of breeding, about the fact that the disease is significantly influenced by genetic factors.

The disease may be monitored at regular intervals of 3 to 12 months if significant cardiomegaly is present. Milder cases do not warrant frequent monitoring (see Significance and Progression). Frequently asked questions from owners of dogs with asymptomatic CMVI are if exercise should be restricted and if dietary measures should be instituted. At present there is little evidence-based information concerning the effects of exercise or diet on the progression of CMVI in dogs. Dogs with mild CMVI do not need any dietary or exercise restriction. However, from the pathophysiologic standpoint, strenuous exercise or diets with high sodium content should be avoided in progressed CMVI as this may promote pulmonary edema. Furthermore, it is the authors' experience that dogs with advanced asymptomatic CMVI usually tolerate comparably long walks at their own pace and do better if obesity is avoided.

201.1.13.2

Patients with Left Mainstem Bronchial Compression Without Pulmonary Congestion and Edema

Severe left atrial enlargement may produce coughing even in the absence of pulmonary congestion and edema by compression of the left mainstem bronchi, which may be identified on the lateral radiograph. With significant coughing, therapy is aimed at suppression of the cough reflex or reduction of the influence of the underlying cause for the compression, the left atrial enlargement. Cough suppressants such as butorphanol (0.55 to 1.1 mg/kg q6-12h PO), hydrocodone bitartrate (0.22 mg/kg q4-8h PO), or dextromethorphan (0.5 to 2 mg/kg q6-8h PO) may alleviate the coughing in some cases. Dogs with evidence of concurrent tracheal instability or chronic small airway disease may improve with a bronchodilator, or a brief course of glucocorticoids. Different xanthine derivatives, such as aminophylline (8 to 11 mg/kg q6-8h) and theophylline (Theo-Dur (sustained duration) 20 mg/kg q12h PO, Detriphylline (Choledyl) (sustained action) 25 to 30 mg/kg q12h PO), are commonly used bronchodilators, although the efficacy of these drugs varies considerably between individuals. Beta 2-receptor agonists such as terbutaline and albuterol should be used with caution in CMVI dogs, as these drugs may produce unwanted elevation in heart rate and contractility as a consequence of myocardial beta 2-receptor stimulation. A reduction of left atrial size may be obtained either by reduction of the regurgitation or by reduction of pulmonary venous pressure. Regurgitation can be decreased by reducing aortic impedance with an arterial dilator or by contracting blood volume with a diuretic.

ACE-inhibitors or a directly acting arterial vasodilator, such as hydralazine, may reduce systemic arterial resistance.[65] The ACE-inhibitors are substantially weaker arterial vasodilators than hydralazine.[65] Side effects of ACE-inhibitors are infrequent, but monitoring of renal function and serum electrolytes, particularly potassium, may be indicated.

Hydralazine has been widely used in patients with CMVI at an initial dosage of 0.5 mg/kg every 12 hours PO. The dosage is increased at daily to weekly intervals to an appropriate maintenance dose of 1 to 2 mg/kg every 12 hours PO, or until hypotension develops, detected either by blood pressure measurements or by clinical signs. Clinical hypotension is defined as a mean arterial blood pressure of less than 50 to 60 mm Hg or a systolic blood pressure below 90 mm Hg.[54] Reflex tachycardia may develop in response to hypotension, and gastrointestinal problems are sometimes observed. In tachycardia, digoxin may be considered in order to limit the resting heart rate. As a consequence of hypotension, hydralazine may induce fluid retention and thereby is needed in the form of a diuretic.[66] Patients that receive hydralazine should routinely be monitored, including having the owner check the heart rate at home and having renal function assessed periodically. Diuretic mono-therapy may be considered to decrease the MR by contracting the blood volume and thereby the left ventricular size. However, diuretics activate the renin-angiotensin-aldosterone system (RAAS),[66] and in the long term may cause electrolyte disturbances.

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Accordingly, these drugs are often reserved for patients with signs of pulmonary congestion and edema or patients in which cough suppressants, glucocortocoids, and vasodilators have failed to alleviate clinical signs.

201.1.13.3 Patients with Syncopes but Without Pulmonary Congestion and Edema

With advancing CMVI it is not uncommon that episodes of syncope develop in otherwise asymptomatic dogs (see Clinical Signs). These episodes vary in frequency from isolated to multiple events every day. In dogs with CMVI with syncope, it is important to ascertain that the patient is actually fainting and not suffering from neurologic or metabolic disease. Furthermore, it is important to rule out the presence of congestive heart failure or a bradyarrhythmia such as third degree AV-block or a tachyarrhythmia such as atrial fibrillation. Although ventricular tachyarrhythmias do occur in dogs with advanced CMVI, supraventricular tachyarrhythmia is far more common. Typically, the 24-hour (Holter) ECG shows episodes of a rapid supraventricular rhythm immediately followed by a bradycardia during which the dog faints. Management of these dogs often includes digoxin to control the supraventricular tachyarrhythmia. In fact, the frequency of syncopes may often be controlled at lower doses, such as 50%, of digoxin than the recommended dose (which is 0.22 mg/m2 q12h PO). The place for beta-blockers in controlling episodes of fainting in CMVI dogs is not clear. Reports indicate positive results of carvedilol in some dogs.[67] However, beta-blockers may reduce myocardial performance and some CMVI dogs do not tolerate this type of therapy.

201.1.13.4 Patients with Pulmonary Edema Secondary to CMVI

Considering the pathophysiology of CMVI, therapy should be directed toward (1) reduction of the venous pressures to alleviate edema and effusions, (2) maintainance of adequate cardiac output to prevent signs of weakness, lethargy and prerenal azotemia, (3) reduction of the cardiac workload and regurgitation, and (4) protection of the heart from negative long-term effects of neurohormones. Cases with mild pulmonary edema may be managed on an outpatient basis with regular re-examinations. Cases with moderate to severe pulmonary edema may need intensive care, including cage-rest and sometimes oxygen supplementation.

201.1.13.5 Mild to Moderate Heart Failure

Patients with mild to moderate heart failure usually present with cough, tachypnea, and dyspnea. It is not common for an untreated dog in congestive heart failure to present initially with isolated significant ascites. Signs of congestive heart failure are usually present on thoracic radiographs as pulmonary venous congestion and increased pulmonary opacity. In some cases, it may be difficult to appreciate mild edema owing to obesity, chest conformation, underinflated lungs, or presence of age-related changes. Radiographs from the patient obtained before the onset of clinical signs may be helpful for comparison. Dogs with mild to moderate heart failure should be treated. Treatment can often be managed on an outpatient basis and should include a diuretic, such as furosemide, and an ACE-inhibitor. The place of digoxin and other positive inotropes are more controversial for treating dogs with mild to moderate heart failure (see below). The dosage of furosemide should preferably be based on clinical signs rather than radiographic findings. A patient may breathe with ease even in the presence of radiologic signs of interstitial edema, or vice versa. The usual course of treatment of a case with mild to moderate heart failure is an initial intensive treatment with furosemide (2 to 4 mg/kg q8-12h) for 2 to 3 days, after which the dosage of the diuretic is decreased to a maintenance level, such as 1 to 2 mg/kg every 12 to 48 hours or lower. More severe cases of heart failure may require higher dosages. It is important to use an appropriate dosage of diuretic to relieve clinical signs

but to avoid an unnecessarily high maintenance dosage. Overzealous use of diuretics may lead to weakness, hypotension, syncope, aggravation of prerenal azotemia, and acid-base and electrolyte imbalances. Often the owner can be instructed to vary the dosage, within a fixed dose range, according to the need of the dog.

The dosage of ACE-inhibitor (e.g., enalapril, benazepril, lisinopril, ramipril, and imidapril) is usually fixed and depends on the specific ACE-inhibitor used. ACE-inhibitors are indicated in advanced CMVI with heart failure in combination with diuretics, because dogs in large placebo-controlled clinical trials receiving an ACE-inhibitor have been shown to have less severe clinical signs of disease, better exercise tolerance,[68–70] and live longer than those not receiving an ACE-inhibitor.[68–70] In the dose range that is recommended for use in dogs and cats, the vasodilating actions of the drugs are not prominent and side effects associated with hypotension, such as fainting and syncope, are rare.[14,65,69,70] A reason for this may be that the short-term effects of ACE-inhibitors on the circulation are dependent on the activity of the RAAS prior to administration of the drug, the higher activity the more pronounced effect of the drug.[62] In combination with diuretics, such as furosemide, the ACE-inhibitors have synergistic effect with the diuretic by counteracting the reflectory stimulation of RAAS that occurs in diuretic therapy. Thus they decrease the tendency for fluid retention and counteract a peripheral vasoconstriction and other negative effects on the heart.

Digoxin is controversial in treating dogs with CMVI. There is generally a lack of scientific evidence supporting the use of digoxin. Many cardiologists, however, initiate digoxin therapy when signs of heart failure first appear. Although digoxin is a comparably weak positive inotrope and myocardial failure may not be a prominent feature of CMVI until progressed stages, digoxin has a place in heart failure therapy by reducing reflex tachycardia, by normalizing baroreceptor activity and by reducing central sympathetic activity.[71] Thus digoxin may be useful to reduce the heart rate, such as when hydralazine is administered, or in supraventricular tachycardia such as atrial fibrillation, and to abolish or limit the frequency of syncope (see above).

The place for a positive inotrope in the management of CMVI is controversial, since in small dogs signs of left-side heart failure usually precede overt myocardial failure. Nevertheless, the combined calcium sensitizer/PDE III inhibitor pimobendan is now approved for veterinary use in dogs with DCM and CMVI in many European countries, Canada, and Australia at a dose of 0.25 mg/kg every 12 hours PO. Data from controlled clinical trials of pimobendan in veterinary patients is available, although its efficacy is less documented in CMVI than in DCM. Recently, two controlled clinical trials (the PITCH trial and a recently completed study from UK) were presented (unpublished).[72,73] The results indicate that dogs with CMVI receiving pimobendan as adjunct therapy to diuretics show less severe signs of heart failure and are less likely to die or reach the treatment failure end-point than those receiving an ACE-inhibitor and diuretics. Many practitioners using pimobendan have experienced a dramatic improvement in overall clinical status in some CVMI dogs, even in dogs without overt myocardial failure. The reason for this may be that pimobendan, in addition to being a positive inotrope, has arterial vasodilating properties and differs from the pure PDE III antagonists (such as milrinone) in that it increases myocardial contractility with minimal increase in myocardial energy consumption. Furthermore, positive inotropes may theoretically reduce the MR by decreasing the size of the left ventricle and the mitral valve annulus through a more complete emptying of the left ventricle. However, the increased contractility may also theoretically lead to an increased systolic pressure gradient across the mitral valve and thereby generate increased regurgitation in some cases with high peripheral vascular resistance and increase the risk for chordal rupture in affected dogs. Therefore some cardiologists initiate pimobendan as adjunct therapy to other heart failure treatment in CMVI dogs only when echocardiographic evidence of reduced myocardial performance (increased left ventricular end-systolic dimension) is evident. Whether or not this treatment strategy is the optimal use of

calcium sensitizers has not been evaluated. Some cases of CMVI with evidence of myocardial failure have evidence of disseminated myocardial micro-infarctions, most commonly as a consequence of widespread arteriosclerosis.[28,29] Some of these patients might benefit from prophylactic antithrombotic and antiplatelelet therapy, although this has not been evaluated in veterinary medicine.

The way dogs with mild to moderate heart failure are managed after initiation of therapy varies. Typically, the dog is re-examined after 1 to 2 weeks of therapy, if the dog is managed on an outpatient basis, to monitor therapeutic outcome and to establish a suitable maintenance dosage of diuretic. Should the treatment response be satisfactory after this visit, dogs may often be managed by phone contacts and re-examinations every 3 to 6 months. More severe cases may require more frequent monitoring of the disease. In areas with a seasonal climate it may be valuable to re-examine the dog before the temperature increases and instruct the owner to avoid high ambient temperatures. The use of low-sodium diets as complementary therapy in heart failure is controversial. Currently, there are no clinical studies to support that they are beneficial in managing heart failure in dogs and cats. However, dogs with symptomatic CMVI should avoid excessive intake of sodium. Dogs that are stable on their heart failure therapy usually tolerate walks at their own pace, but strenuous exercise should be avoided.

201.1.13.6 Recurrent Heart Failure

Once an appropriate maintenance dosage of furosemide has been set in a CMVI patient with decompensated heart failure, the dosage has to be gradually increased, often over weeks or years. Reasons for increasing the dosage often include recurrent dyspnea caused by pulmonary edema or the development of ascites. Severe ascites, which compromises respiration, may require abdominocentesis. Many CMVI cases with less severe ascites respond to an increased dose of diuretics. Even in case of abdominocentesis, the diuretic dosage should be increased as the ascites will re-occur without changed medication after evacuation. When the dosage of furosemide has reached a level of approximately 4 to 5 mg/kg every 8 to 12 hours, sequential blocking of the nephron should be considered by adding another diuretic. The drug of choice is spironolactone (1 to 3 mg q12-24h PO) which is an aldosterone antagonist and a potassium-sparing diuretic. A thiazide, such as hydrochloro-thiazide (2 to 4 mg/kg q12h PO), or triamterene (1 to 2 mg/kg q12h PO) or amiloride (0.1 to 0.3 mg/kg q24h PO), may also be considered. The documentation of triamterene and amiloride in veterinary medicine is limited.

Because the furosemide treatment precedes and is used concomitantly with these drugs, the risk of hyperkalemia is low, even when they are added to a patient that is currently treated with an ACE-inhibitor. The risk of inducing prerenal azotemia, hypotension, and acid-base and electrolyte imbalances increases with the intensity of the diuretic treatment. However, the practitioner usually has to accept some degree of these disturbances when treating a patient with heart failure and, although common, they seldom result in clinical problems. A calcium senzitizer (pimobendan) is often introduced in cases with recurrent heart failure, as echocardiographic evidence of systolic dysfunction often has developed (see above).

201.1.13.7 Severe and Life-Threatening (Fulminant) Heart Failure

The causes of acute severe heart failure are often a ruptured major tendinous chord, development of atrial fibrillation, undertreatment of existing heart failure, or intense physical activity, such as chasing birds or cats, in the presence of significant CMVI. Patients with severe heart failure have radiographic evidence of severe interstitial or alveolar edema and have significant clinical signs of heart failure at rest. They are often severely dyspneic and tachypneic and have respiratory rates in the range of 40 to 90. They may cough white or pink froth, which is edema fluid. These dogs require immediate hospitalization and aggressive

treatment. However, euthanasia should also be considered, if the dog is already on high doses of diuretics and other heart failure therapy, owing to the poor long-term prognosis. It is important not to stress dogs with severe or fulminant heart failure as stress may lead to death. Therefore thoracic radiographs and other diagnostic procedures may have to wait until the dog has been stabilized.

Dogs with significant dyspnea benefit from intravenous injections of furosemide at a relatively high dose (4 to 6 mg/kg q2-6h IV). The furosemide may be administered intramuscularly should placement of an intravenous catheter not be possible. Dogs with fulminant pulmonary edema may require Herculean furosemide doses at 6 to 8 mg/kg every 2 to 8 hours IV over the first 24 hours. The exact dosage of furosemide depends not only on severity of clinical signs but also on whether or not the dog is already on oral furosemide treatment. Oxygen therapy is always beneficial in hypoxemic patients and it can preferably be administered using an oxygen cage provided that the temperature can be controlled inside the cage. Nasal inflation or a facial mask may also be used provided that the animal accepts them without struggle. Once the dog has received furosemide and oxygen treatment, an arterial vasodilator and a positive inotrope may be considered to stabilize the patient.

Commonly used vasodilating agents are hydralazine per os or intravenous nitroprusside (2.0–10 mg/kg/min). Of these two vasodilators, hydralazine is most commonly used. Owing to the severity of heart failure, dogs without previous vasodilating therapy may receive an initial dose of hydralazine of 1 to 2 mg/kg PO. Titration of the hydralazine dosage as described above is indicated in dogs already on an ACE-inhibitor and blood pressure should be monitored to detect hypotension. Nitroprusside can only be administered as an intravenous infusion, which requires an intravenous catheter. This potent vasodilator has actions on both the venous and arterial circulation. However, it is not easy to control the effects of nitroprusside and the dosage has to be titrated under careful blood-pressure monitoring to avoid serious hypotension and to ensure efficacy. These disadvantages have prevented nitroprusside from being a commonly used arterial vasodilator.

A positive inotrope such as dobutamine, or more commonly the calcium-sensitizer pimobendan (0.25 mg/kg q12h PO), may be considered to stabilize the patient with fulminant heart failure. Pimobendan may be administered together with furosemide without any arterial vasodilator as the drug has vasodilating properties itself. The dose of any concurrently administered arterial vasodilator has to be adjusted. Dobutamine is administered as a constant infusion usually in combination with nitroprusside. One problem with dobutamine that limits its use is that the patient needs to be weaned from IV to oral therapy within 1 to 2 days.

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Patients with severe or fulminant heart failure need frequent initial monitoring of the respiratory rate because it reflects the clinical response to the furosemide treatment. Significantly decreased respiratory rate within the first hours indicates successful therapy, whereas absence of change indicate that furosemide is required at a higher dose or more frequently. Once the respiratory rate has decreased, the dose of furosemide may be reduced according to the status of the animal and clinical judgment. Abnormal laboratory findings such as pre-renal azotemia, electrolyte imbalances and dehydration are common after high doses of furosemide. Again, these abnormalities are seldom a clinical problem and the laboratory values often tend to shift towards normal with clinical improvement and as the dog starts to eat and drink. Dehydration is usually not severe even after intensive furosemide treatment and intravenous rehydration should be performed slowly and with caution in cases where it is needed, as the volume challenge may produce pulmonary edema.

201.1.14 Complications

201.1.14.1 Acute Exacerbation of Pulmonary Congestion and Edema due to Ruptured Chordae Tendineae

Ruptured chordae tendineae (RCT) may be suspected in all dogs that suffer from CMVI with drastic aggravation of pulmonary congestion and edema, whereas RCT is a rare finding in cats. It is not unusual for the RCT to be a result of extra-ordinary stress or exercise (e.g., chasing cats or birds). The most important ruptures involve those of first order chordae that are attached to the septal leaflet, and these patients are expected to die rapidly from acute volume overload and fulminant pulmonary edema. Ruptures of lesser order chordae or perhaps first order chordae that are attached to the free wall leaflet may result in minor clinical signs or none at all. Significant RCT causes acutely increased MR, and the clinical findings may differ from those encountered in chronic MR. Due to the acute increase in MR, there may be a marked increase in left atrial and pulmonary venous pressures leading to acute pulmonary edema, pulmonary artery hypertension and right heart failure.[34,39,41]

The physical examination of these patients often reveals a heart murmur of lower intensity than that of chronic MR, an S3 gallop is more likely to be present, and jugular venous distention is more likely to be present with pulsations. The radiographic and echocardiographic findings of cardiac size vary, depending on how far the CMVI had progressed before the onset of RCT. Doppler echocardiography shows severe MR, and a flail segment of the mitral valve leaflet may be detected using two-dimensional views. Thoracic radiographs show a markedly increased interstitial and alveolar pattern with distention of the pulmonary veins. These patients require intensive care to stabilize the condition, and thereafter maintainance therapy for CMVI (see under Management section). As long as a first order chordae attaching to the septal leaflet has not occurred, many of these cases may sustain with the aid of appropriate medication.

201.1.14.2 Right-Sided Heart Failure due to Pulmonary Hypertension

Many patients with long-standing history of CMVI develop right-sided heart failure. It is presumed that this condition develops as a consequence of concurrent chronic tricuspid insufficiency attributable to myxomatous degeneration, or the development pulmonary hypertension, or a combination of both. In CMVI, the pulmonary hypertension is believed to develop secondary to the persistent elevation of the left atrial and pulmonary venous pressures, but concurrent chronic airway disease may also contribute. Because the right ventricle is thinner and more compliant than the left ventricle, it can accept relatively large increases in volume but not in pressure.[74] Even small increases in pulmonary artery pressure cause sharp decreases in right ventricular stroke volume.[74] Individuals with pulmonary hypertension are sensitive to exercise, with signs of weakness or collapse, even at mild exercise. A physical examination may reveal evidence of right heart failure, such as ascites, pleural effusion, hepatic and splenic congestion, and distention of the jugular veins with abnormal pulsations. The presence and degree of pulmonary hypertension may be indirectly quantitated by Doppler echocardiography (see later section on TVI).

Individuals with pulmonary hypertension may be difficult to manage. The goal of therapy is to eliminate contributing factors and restrict even mild exercise. Oxygen supplementation is indicated in cases of acute collapse. Since persistently increased left atrial and pulmonary vein pressures are in large part responsible for the condition, therapy should be directed as for CMVI with pulmonary congestion (see Management). At present, there is no vasodilator available that specifically acts on the pulmonary artery, but it appears

that hydralazine may be one of the better drugs in this aspect.[41] In humans, several endothelin-receptor antagonists are either launched or in Phase II or III clinical trials for treatment of pulmonary hypertension. So far, the experiences with these drugs in dogs are limited. Bronchodilator therapy may also be indicated, and methylxanthines and beta 2-selective agonists may be considered in these cases. Aggressive diuretic treatment may be required to resolve ascites, if present.

201.1.14.3 Acute Exacerbation of Pulmonary Congestion due to Tachyarrhythmia

An enlarged left atrium predisposes to supraventricular premature beats, atrial fibrillation, and supraventricular tachycardia. Ventricular arrhythmias are less common but may occur in progressed cases. A tachycardia with a ventricular rate greater than 180 bpm is of hemodynamic significance. These patients often have a long-standing history of CMVI, with an acute onset of pulmonary edema. In addition to other findings characteristic of CMVI, these cases have a change in cardiac rhythm. The goal of therapy is to relieve the pulmonary edema, as described earlier under management, and to reduce heart rate to an acceptable rate for improving cardiac output. Digoxin is the drug of choice in cases with supraventricular tachycardia. Should this fail to control heart rate, diltiazem (0.5 to 1.5 mg/kg q8h PO) or a beta1-receptor antagonist such as, atenolol (6.25 to 12.5 mg/kg q12h PO) or metoprolol (0.5 to 1 mg/kg q8-12h PO), could be added. It should be noted that some individuals with CMVI are highly dependent on sympathetic drive so that these drugs may not be well tolerated in the recommended dose range. Therefore both types of drugs should be initiated at the lowest possible dose and then gradually increased with careful monitoring.

201.1.14.4 Left Atrial Rupture and Cardiac Tamponade

As a consequence of the left atrial dilatation in CMVI the left atrium becomes thin walled and more vulnerable to increases in pressure, such as in the case of a ruptured tendinous chord or trauma. Endocardial splitting is a frequent postmortem finding in dogs with a history of long-standing CMVI.[7] The significance of this finding is that it may progress to rupture of the left atrium with the sudden development of hemopericardium, cardiac tamponade, and sudden death. Most cases with atrial rupture and cardiac tamponade are expected to die suddenly. There is often a history of trauma, excitement, or physical exercise, preceding the atrial rupture and sudden death. For those dogs that survive the initial event, clinical signs of cardiac tamponade together with signs of CMVI can be found. Thus acute development of ascites, collapse, or marked exercise intolerance are to be expected. The physical examination may reveal signs of pericardial effusion (see separate chapter) together with evidence of CMVI. Echocardiography is often required for definite diagnosis by identifying the presence of significant pericardial effusion, whereas the left atrial tear is often difficult to detect. Treatment of atrial rupture with hemopericardium and cardiac tamponade is usually futile. Immediate pericardiocentesis is indicated, and pericardial fluid should be removed to alleviate the tamponade without removing so much that further bleeding is stimulated. If the bleeding continues after pericardiocentesis, the final option is emergency thoracotomy with pericardiectomy and closure of the tear, but the prognosis for this procedure is poor to grave.

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201.2 TRICUSPID VALVE INSUFFICIENCY

Since the advent of Doppler echocardiography, tricuspid valve insufficiency (TVI) has been recognized as a common incidental finding in dogs and cats.[75] TVI of clinical significance most often occurs concomitantly with chronic CMVI as a consequence of primary valvular changes, secondary right ventricular enlargement, or both.[7] In these circumstances, the degenerative changes of the tricuspid valve apparatus are identical to those found in

CMVI (see Pathology section).[7] Other conditions that may affect the tricuspid valve apparatus itself include infective endocarditis and, more seldom, chordal rupture.[7,44,54] Secondary or functional TVI may occur as a consequence of right ventricular dilatation in all conditions associated with an acquired increase in right ventricular pressure. These include heartworm disease, pulmonary thromboembolism, pulmonary hypertension secondary to left heart disease, and idiopathic pulmonary hypertension. In addition, secondary TVI occurs in biventricular or right ventricular dilated cardiomyopathy and in congenital pulmonic stenosis. TVI occurs in cats with cardiomyopathy and hyperthyroidism.[76]

201.2.1 Consequences (Pathophysiology)

TVI, in the absence of concurrent obstruction of the pulmonary valve or pulmonary artery hypertension, is comparably well tolerated.[77] However, because the right ventricle is designed to contract against a low-pressure artery, it is vulnerable to increases in pressure. It responds poorly to the increased work; even relatively small acute increases in pulmonary artery pressure cause sharp decreases in right ventricular stroke volume.[74] Thus TVI is of significance if pulmonary hypertension is present. In addition to the right ventricular dilatation, right atrial enlargement develops and adds to the tricuspid annular dilatation and TVI. Enlargement of this chamber may result in atrial tachyarrhythmias, such as atrial fibrillation and supraventricular tachycardia. As a consequence of increased right atrial pressure, ascites, pleural effusion (especially in cats), pericardial effusion, hepatomegaly, and splenomegaly may develop.

201.2.2 Clinical Signs

Isolated TVI does not commonly result in clinical signs of disease.[7,41,54] Evidence of reduced exercise tolerance, weakness, or syncope occur mainly in instances with pulmonary hypertension, such as secondary to CMVI or tachyarrhythmia. It is common for these animals to show signs of right heart failure that may include respiratory distress due to pleural effusion; abdominal distention due to ascites, hepatomegaly, or splenomegaly; or gastrointestinal signs such as diarrhea, vomiting, and anorexia.

201.2.3 Physical Examination

Significant TVI is characterized by a holosystolic murmur with varying intensity and with the point of maximal intensity over the tricuspid area, and, in some cases, by the presence of venous distention and pulsations in the jugular veins. The heart sounds may be muffled by pleural effusion. Abdominal distention may be present with ascites, hepatomegaly, or splenomegaly. A rapid irregular heart rhythm and femoral artery pulse are observed in the presence of tachyarrhythmia, and pulse deficits may be detected. A weak femoral artery pulse may be found in cases with pulmonary hypertension or left-side heart failure.

201.2.4 Electrocardiographic Findings

ECG has a low sensitivity in detecting right atrial and right ventricular enlargement secondary to primary TVI.[7] In significant TVI with pulmonary hypertension, the ECG changes may include evidence of right atrial enlargement (tall P wave), a right ventricular enlargement pattern, and a right deviation of the mean electrical axis.[47] However, even in severe cases of TVI and pulmonary hypertension secondary to CMVI, these signs may not be obvious because of the concurrent changes to the left cardiac side. In these cases, the recording

may only show evidence of left side involvement.[7,41] Arrhythmias, such as supraventricular premature beats, atrial fibrillation, and ventricular premature beats, may be noted.

201.2.5 Radiographic Findings

Mild right atrial and ventricular enlargement are usually not associated with detectable radiologic signs. Signs of moderate to severe right atrial enlargement in lateral projection include bulging of the right atrium in the craniodorsal direction. This causes the cranial border of the heart to appear straight rather than convex and elevates the trachea as it courses dorsally over the right atrium. In addition to elevations of the trachea and caudal vena cava, signs of right ventricular enlargement include increased sternal contact and rounding of the right heart border. In the dorsoventral (or ventrodorsal) projection, the enlarged right atrium may be identified as a bulge in the right cranial part of the cardiac border (in the 9 to 12 o'clock position). The border of the enlarged right ventricle appears rounded and, in severe enlargement, it may resemble an inverted “D” sign. There is a shift of the cardiac apex to the left. Signs of right heart failure may be observed including pleural effusion, abdominal effusion, hepatomegaly, and splenomegaly. If biventricular failure occurs, the global cardiac size will be increased and signs of left heart failure may be present.

201.2.6 Echocardiographic Findings

Echocardiography is useful to detect increased right atrial and right ventricular size and for evaluation of tricuspid valve morphology. Thus it is an important tool to rule out differential diagnoses, such as an undiscovered congenital heart defect. The echocardiographic appearance of the tricuspid valve with myxomatous degeneration is similar in two-dimensional mode to myxomatous lesions on the mitral valve already described (see CMVI Echocardiography section). With the use of color-flow Doppler, TVI may be detected and semiquantified. The right atrium is, however, not as easily accessible as the left atrium owing to the anatomy, and the orientation of TVI jets is not consistent. The Doppler echocardiographic findings in TVI are similar to those of MR with a few exceptions. Trivial, physiologic TVI is common in dogs and this regurgitation is usually silent to auscultation. Spectral Doppler may be used to estimate right ventricular stroke volume and to identify pulmonary hypertension by estimation of right ventricular systolic pressure and pulmonary arterial systolic and diastolic pressures.[54] The right ventricular pressure is estimated by finding a tricuspid regurgitant jet and measure its peak velocity by continuous-wave Doppler. TVI jet velocities generally peaks at approximately 2.6 m/sec, unless there is elevation of right ventricular pressure that forces blood at a higher velocity, usually above 3 m/sec.[58] The pressure gradient between the right atrium and ventricle may be calculated with use of the peak velocity of the regurgitant jet and the modified Bernouilli equation.[78] The right ventricular pressure is obtained by adding an estimate of the right atrial pressure to the pressure gradient over the AV-valve. It has been suggested that appropriate estimates of right atrial pressure is 5 mm Hg in patients without right heart failure and 10 to 15 mm Hg in patients with right heart failure.[54] Similarly, the peak velocity of a pulmonic valve regurgitation and an estimate of right ventricular diastolic pressure may be used to predict pulmonary artery diastolic pressure.[79]

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201.2.7 Management

Because primary TVI is usually relatively benign, patients with clinical signs of right-sided heart failure with suspected TVI must be thoroughly evaluated for concurrent conditions that may mimic or exaggerate TVI. Examples of these include congenital heart defects, heartworm disease, CMVI, pulmonary hypertension, pericardial effusion, restrictive pericarditis, and mitral valve stenosis. The signs of right heart failure, that is,

abdominal and pleural effusions, may be alleviated with diuretic treatment and often involves two or more drugs to obtain sequential blocking of the nephron (see CMVI under Management), but abdominocentesis may be required. If tachyarrhythmia is present, successful management depends on controlling the increased heart rate or preferably abolishing the tachyarrhythmia.

201.3 SEMILUNAR VALVE INSUFFICIENCY

With the advent of color flow echocardiography, a low degree of aortic and, more commonly, pulmonic valve insufficiency are frequently detected.[75] This finding may be of no clinical significance but in others it occurs with different types of congenital heart disease. Aortic valve insufficiency (AVI) occurs most often in dogs as a consequence of subaortic stenosis and pulmonic valve insufficiency (PVI) of pulmonic valve stenosis.[7,41,54] Acquired AVI of clinical significance, except in association with bacterial endocarditis (see Infective Endocarditis), is a rare disorder in dogs and cats. PVI is observed in the majority of cases with pulmonary artery hypertension, and secondary to pulmonary artery dilatation, such as in PDA and severe heartworm disease. Isolated PVI as cause of clinical signs is extremely rare. Although myxomatous degeneration is sometimes evident at postmortem on one or both semilunar valves,[7,41,54] it is not expected to have caused significant insufficiency associated with clinical signs.

201.4 INFECTIVE ENDOCARDITIS

Infective endocarditis (IE) is a life-threatening disorder that results from microorganisms that colonize the cardiac endocardium, which commonly causes destruction of valves or other structures within the heart. Bacteremia is by far the most common etiology, with the mitral and aortic valve most frequently affected.[80] Vegetation may cause thromboembolism or metastatic infections, which involve multiple body organs and produce a large variety of clinical signs which makes diagnosis difficult. The incidence of infective endocarditis in necropsied dogs has been reported to range from 0.06% to 6.6%.[41,81] Evaluation of clinical data from university animal hospitals points to IE as a comparably rare condition with incidences ranging from 0.04% to 0.13%.[82] Medium to large breed, mainly purebred, middle-aged male dogs are reported to be predisposed.[80] The incidence in cats, based on clinical experience, is considered to be 7 to 10 times lower than in dogs.[82,23] Animals with congenital heart disease have a low incidence of IE[41,80], but associations have been reported with subaortic stenosis[84] and occasionally with PDA.[85] IE has not been found to have any association with CMVI in dogs.[13,41,81]

201.4.1 Pathology

Vegetation associated with by IE mainly affects the left heart with the highest incidence involving the mitral valve.[86] Involvement of the right heart or mural endocardium is uncommon.[86] Pathologic findings vary and depend on the virulence of the infecting organism, the duration of infection, and the immunologic response. Intracardiac vegetation consists of different layers of fibrin, platelets, bacteria, red and white cells, and is often covered by an intact endothelium. Bacteria may continue to grow despite antibiotic therapy owing to the location deep within the vegetation and a slow metabolic rate (Figure 201-8).[87] Necrosis and destruction of the valve stroma or chordae tendineae proceed rapidly in peracute or acute IE, which causes valvular insufficiency and cardiac failure.

201.4.2 Etiology and Pathogenesis

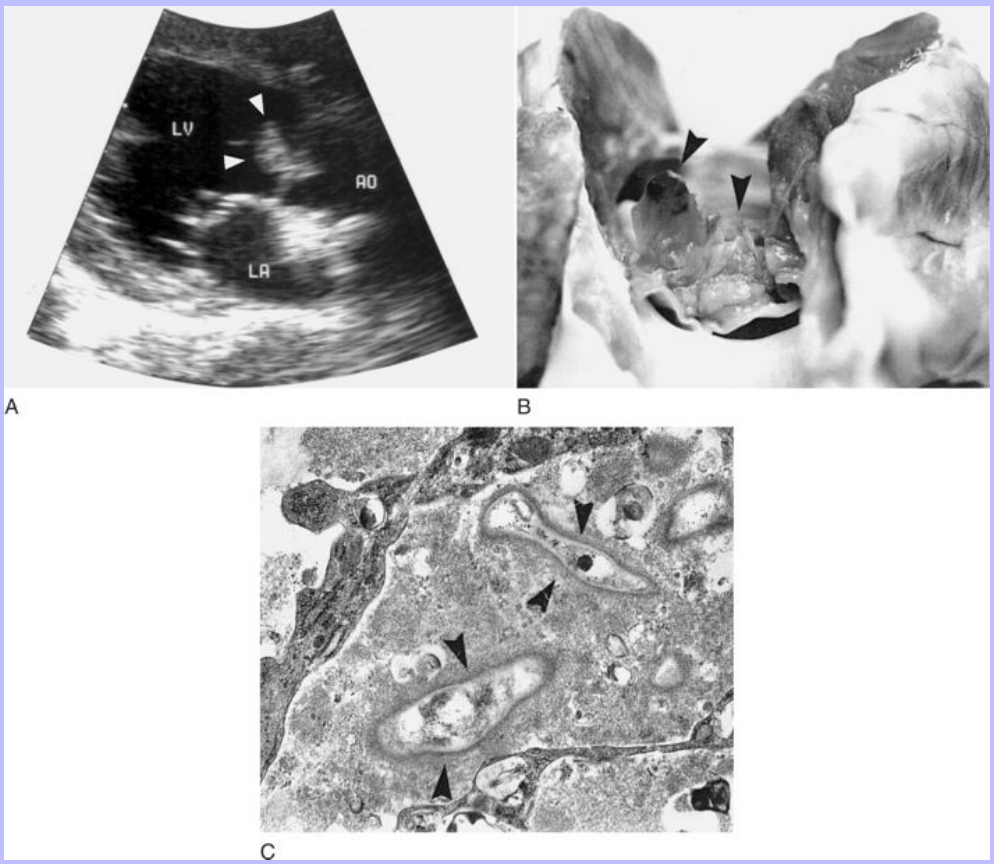
Transient or persistent bacteremia is a prerequisite for the development of IE. A large number of bacteria have been associated with bacteremia[88] (see section on Blood Culture below) and some are known to cause IE.[86,88] Most bacteria require predisposing factors to cause IE, such as depression of the immunosystem or endothelial damage, sometimes with depositions of platelet-fibrin complexes, to adhere to the valve and create IE.[87] The origin of the bacteremia may be active infection localized somewhere within the body.[88] A proportion of cases with IE has no clinically detectable source of infection.[86,88] Possible routes for bacteria to reach and infect the endocardium are by direct contact with the surface endothelium via the bloodstream or from capillaries within the valve (vasculitis).[89]

The consequences of IE depend on several factors: virulence of the infective agent; site of infection; degree of valvular destruction; influence of vegetation on valvular function; production of exo-or endotoxins; interaction with the immunosystem with the formation of immunocomplexes[90]; and development of thromboembolism and metastatic infections. Gram-negative bacteremia results often in a peracute or acute clinical manifestation, whereas gram-positive bacteremia typically results in a subacute or chronic condition. The vegetation may cause valvular insufficiency or obstruction. The destruction of valvular tissue is caused by the action of bacteria or the cellular response from the immunologic system. Deposition of immunocomplexes in different organs may cause glomerulonephritis, myositis, or polyarthritis.[90] Septic embolization that produces clinical signs is uncommon but 84% of affected dogs had evidence of systemic embolization at necropsy and glomerulonephritis was reported in 16% of 44 dogs with IE.[80]

201.4.3 Case History and Clinical Signs

The diagnosis of IE can easily be overlooked because the case history and clinical signs are not specific and there may be an absence of predisposing factors to raise the suspicion of IE. Clinical signs are variable and occur in different combinations. Commonly reported signs include lethargy, weakness, fever (sometimes recurrent), anorexia, weight loss, GI disturbances, and lameness.[80,90] Stiffness and pain originating from joints or muscles may be caused by immunomediated responses and abdominal pain may be caused by secondary renal or splenic infarction, septic embolization, or abscess formation. If the condition leads to severe valvular damage, especially of the aortic valve, signs of cardiac failure and syncope from arrhythmias may occur. Predisposing factors that in combination with the clinical signs above, should raise the suspicion of IE are immunosuppressive drug therapy, such as corticosteroids[88,91]; aortic stenosis[84]; recent surgery, especially in conjunction with trauma to mucosal surfaces in the oral or genital tract and infections in these body regions, especially prostatitis; indwelling catheters, infected wounds, abscesses, or pyoderma.[88]

Figure 201-8 **A,** Echocardiographic long axis view from a 3-year-old male boxer. The dog had previously been diagnosed with slight aortic stenosis but had recently suffered recurrent episodes of fewer and lethargy. An irregular-shaped echogenic mass was attached to the aortic valve *(white arrowheads)*. **B,** A valvular vegetation *(arrowheads)* localized to the base of the aortic valve leaflet was evident at postmortem examination. **C,** Electron micrograph showing two rod-shaped bacteria *(arrowheads)* about 1μ in diameter located intracellularly in a phagocytic cell found within the vegetation (original magnification × 35000). (Courtesy L. Jönsson and T. Nikkile, Upsala, Sweden.)



201.4.4 Physical Examination

Most clinical signs lack specificity for IE. However, fever, heart murmur (particularly if newly developed), and lameness are considered classical signs. Fever is reported to occur in 80% to 90% in dogs with IE.[80]

Absence of fever is reported to be more common in cases with aortic valve involvement[86] but may also be attributed to treatment with antibiotics or corticosteroids. Since aortic insufficiency is otherwise uncommon in dogs, the finding of a diastolic murmur (Figure 201-9) and bounding peripheral pulse should raise the suspicion of IE of the aortic valve. Systolic murmurs may be caused by destruction of the mitral valve, which results in MR or vegetations that obstruct the aortic outflow tract, which leads to stenosis.[80] These murmurs are, in contrast to diastolic murmurs, poor indicators of IE since they frequently occur in dogs with other conditions, such as CMVI and aortic stenosis. It should be noted that 26% of dogs with IE are reported to lack audible murmurs.[80] Lameness is also an inconsistent finding in IE with an incidence of 34% in one study.[81] A range of other physical findings may be present, depending on which organs are affected by circulating immunocomplexes or septic embolization. Possible findings are pain reactions from muscles or abdomen (spleen, intestines, or kidneys), cold extremities, cyanosis, and skin necrosis from severe embolization and a variety of neurologic disturbances if the central nervous system is affected.

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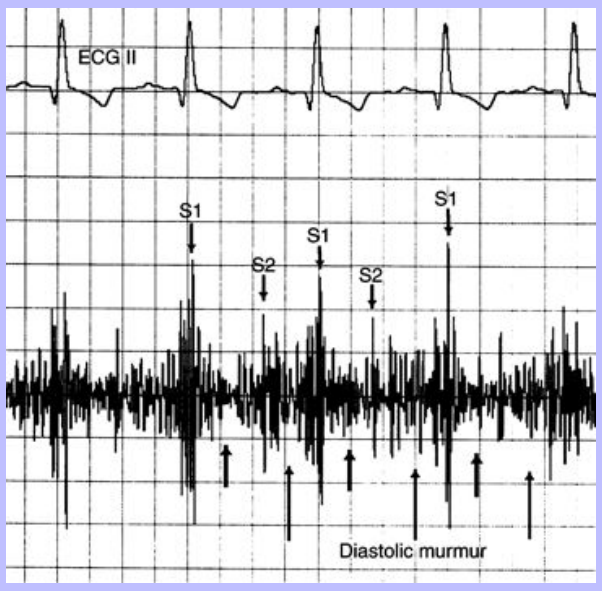
Figure 201-9 Phonocardiogram (PCG) and ECG lead II recorded from a dog with a diastolic murmur from aortic regurgitation caused by IE. A systolic murmur from mitral regurgitation is also present *(thick arrows)*, which in combination with the diastolic murmur from aortic regurgitation causes the auscultatory finding of a continuous murmur easily be misinterpreted to be caused by PDA. The PCG rules out the diagnosis of PDA as the lowest murmur intensity recorded is around the second heart sound (S2). Continous murmurs caused by PDA usually has maximal intensity at the location for S2.[44] The PCG is filtered with a nominal frequency of 100 Hz. *S1*, First heart sound; *S2*, second heart sound.



201.4.5 Blood Culture

Positive blood cultures are crucial evidence of IE. The theory that bacteremia from IE is intermittent has changed in recent years to the opinion that, if existent, it is continuous.[87] Thus negative or intermittent positive cultures are unusual when collection and handling of samples is conducted properly.[87] The time for sampling is probably not critical, but a constant finding through repeat samplings is valuable to exclude sample contamination. The technique for obtaining samples aseptically and anaerobically is important and described in detail below. In cases of positive blood culture, it is important to evaluate if the microorganism is consistent with the diagnosis of IE.

Microorganisms known to cause IE in dogs are, in order of reported incidence, *Staphylococcus aureus, E. coli*, betahemolytic streptococci, *Pseudomonas aeroginosa*, *Corynebacterium* spp., *Erysipelothrix rhusiopathiae (tonsillarium)*[86], and *Bartonella vinsonii*.[92] *B. vinsonii* and related proteobacteria has recently been recognized as a potential cause for endocarditis in dogs. They have been found in dogs with cardiac arrhythmias, endocarditis, or myocarditis.[93] *Bartonella* spp. are also a potential cause for IE in cats.[94] Furthermore, *Bartonella* spp. have been reported to occasionally cause IE in immunocompromised (but also immunocompetent) humans, with the cat serving as the major reservoir (cat scratch disease). The recommended antibiotic therapy when the resistance is unknown is erythromycin or doxycycline. Immediate antibiotic therapy of humans after significant dog or cat bites may furthermore be motivated as commensals, such as *Capnocytophaga canimorsus*, in the saliva of dogs and cats have been reported to occasionally cause septicemia with a mortality as high as 30%.[95,96] Negative blood cultures are fairly common and may be due to antibiotic therapy, chronic situations with “incapsulated” infections, noninfective IE (only platelets and fibrin in vegetation), or failure to grow organisms from samples. Some bacteria may grow slowly and samples should not be regarded as definitely negative until they have been incubated for 10 days. More common is a rapid growth of microorganisms with 90% of cultures positive within 72 hours of incubation.[97]

201.4.5.1 Obtaining Blood Cultures

The referral laboratory should be contacted concerning the preferred type of preprepared vials before obtaining a sample; special additives are available if the patient has been on antibiotics. Pediatric vials are useful because less blood is required but volumes in the range of 20 to 30 mL increase the chance for growth. To avoid contamination, strictly aseptic sampling should be observed which includes thorough shaving and disinfection of the sampling site and strict use of sterile gloves. Three samples with adequately filled vials from different puncture sites should be collected. If samples are collected with a syringe, suction should cease before withdrawal of the needle from the patient to avoid contamination with skin bacteria and a new sterile needle should be used for the transfer of blood into the bottles. The bottles should be prewarmed to 37° C and, after sampling, incubated at the same temperature. Sampling through indwelling catheters should be avoided but may be used as a second choice. The former recommendation to draw samples over 24-hour periods has changed, since multiple simultaneously drawn samples in humans have been shown to be equally sensitive.[87]

201.4.6 Electrocardiographic Findings

Arrhythmia is reported to occur in 50% to 75% of dogs with IE.[80,86] Ventricular premature beats and tachyarrhythmias are the most commonly encountered arrhythmias, but they are usually not life threatening.

Deviation in the ST-segment suggests myocardial hypoxia and may indicate coronary artery embolism or ischemia from heart failure. Evidence of chamber enlargement may occur in chronic IE. All the mentioned ECG abnormalities are, however, nonspecific.

201.4.7 Radiographic Findings

Radiography often does not add any information specific for IE. In cases of chronic IE with aortic or mitral insufficiency, left-sided cardiac enlargement may be detected. Calcified deposits on the valve leaflets are occasionally observed in chronic cases.

201.4.8 Echocardiographic Findings

Echocardiography has significantly improved the possibility of diagnosis and monitoring of animals with IE.[88] Valvular vegetations may be detected using two-dimensional echocardiography, although minor lesions may be difficult to distinguish from myxomatous lesions. M-mode can be used to measure secondary changes in cardiac size and to detect abnormal mitral valve motion such as fluttering from aortic regurgitation. Mitral or aortic regurgitation may be detected using continous or color-flow Doppler echocardiography.

201.4.9 Other Laboratory Findings

Mild anemia is found in 50% to 60% of cases with IE.[80,86] The anemia is similar to those from other infections, usually being normocytic and normochromic. Leukocytosis is found in about 80% of dogs with IE, usually due to neutrophilia and monocytosis (left shift). Other findings that may be encountered include elevated blood urea nitrogen (BUN) due to embolization, metastatic infection, heart failure, or immune-mediated disease. Urine analysis may reveal pyuria, bacteriuria, or proteinuria. Elevated serum alkaline phosphatase may be found, probably caused by circulating endotoxins[88] and reduced hepatic function, which may cause hypoalbuminemia.[81] The serum glucose concentration may be decreased and serologic tests for immuno-mediated disease, such as Coombs test, may be positive.[88]

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201.4.10 Diagnosis

Since the clinical signs of IE are often a result of complications, rather than reflecting the intracardiac infection, the diagnosis may easily be overlooked. Major criteria for IE are positive blood cultures with typical microorganisms for IE from two separate samples plus evidence of cardiac involvement.[87] The localization and severity of cardiac lesions is confirmed by echocardiographic visualization of vegetations. In the absence of positive cultures, a tentative diagnosis of IE can be made if there is clinical and laboratory evidence of systemic infection, such as fever and leukocytosis plus cardiac involvement and possibly signs of embolization.

201.4.11 Management

The goal of therapy is to eradicate the infective microorganism and to treat all secondary complications. A successful outcome of the therapy is based on early diagnosis and immediate and aggressive treatment. Only bactericidal antibiotics capable of penetrating fibrin should be considered. The antibiotic concentration in serum and deep within vegetations should exceed the organisms minimal inhibitory concentration (MIC), but

preferably also the minimum bactericidal concentration (MBC), continuously or throughout most of the interval between doses. Treatment should continue for at least 6 weeks to eradicate dormant microorganisms.[87]

201.4.11.1 Management of Cases with Tentative Diagnosis of IE

A blood culture (see section above) and an antibiotic sensitivity profile should be obtained. While results from cultures and sensitivity tests are awaited, intravenous treatment with a high dosage of bactericidal antibiotic IV, such as cephalosporins (second generation), should be initiated. Alternatives to cephalosporins are combinations of ampicillin or amoxicillin for gram-positive organisms and gentamicin or amikacin for gram-negative organisms. An alternative to gentamicin and amikacin, which are potentially toxic and only recommended to be used for at most one week, is enrofloxacin for suspected gram-negative IE. Enrofloxacin is bactericidal and may penetrate myocardium and heart valves and is also indicated for treating *Bartonella* infections. Choice of anti-biotic should preferably depend on the suspected source of infection and the estimated resistance pattern for the primary infection. Practitioners should try to identify the source of infection and treat it as aggressively as possible, such as use of surgical drainage or debridement.[98] Possible secondary problems should be identified, such as heart or renal failure that need therapy or may impair the prognosis.

For dogs with heart failure from aortic regurgitation, hydralazine titered to an adequate reduction of arterial blood pressure is effective and should be considered as a part of medical therapy. When results are available from blood cultures, appropriate antibiotics are selected and aggressive IV treatment continued for 5 to 10 days while renal function is monitored. If results from cultures are negative, the decision to continue antibiotic therapy should be based on clinical improvement. Depending on the early outcome of therapy, subcutaneous administration may substitute a 5 to 10 days IV treatment, and later be superseded by oral preparations. The duration of therapy should be at least 6 weeks on the effective antibiotic. Frequent clinical examinations, blood screening, and urine analyses should be performed during that period.

201.4.12 Prognosis

Factors that indicate a poor prognosis include late diagnosis and late start of therapy; vegetations on valves (especially the aortic)[86]; gram-negative infections, heart or renal failure that do not respond to therapy; septic embolization or metastatic infection; elevation of serum alkaline phosphatase and hypo-albuminemia (70% mortality is reported if this is found in cases with IE)[81]; concurrent treatment with corticosteroids, regardless if antibiotics are given simultaneously[80,91]; treatment with bacteriostatic antibiotics or premature termination of anti-biotic therapy. Factors that indicate a more favorable prognosis include only mitral valve involvement (47% of dogs are reported to survive)[80]; gram-positive infections, origin of infection being the skin, abscesses, cellulitis, or wound infections.[88]

201.4.13 Prevention

Prophylactic antibiotics may be indicated 1 to 2 hours before and 12 to 24 hours after diagnostic or surgical procedures when turbulent blood flow is suspected to have damaged the endocardium, such as aortic stenosis, PDA, or VSD. In these cases, early treatment of all manifest infections is important to avoid bacteremia and reduce the risk for IE, and caution should be observed when bleeding or infection is anticipated or evident in the oral, urogenital, intestinal, or respiratory tract. Amoxicillin may be the first choice, but other antibio-tics,

such as clindamycin or cephalosporins, may also be considered depending on the organ system involved and site of infection.[87]

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202 # CHAPTER • 202 Electrocardiography and Cardiac Arrhythmias

Etienne Côté

Stephen J. Ettinger

The diagnostic test of choice for clinical evaluation of cardiac arrhythmias is the electrocardiogram (ECG).[1–5] The ECG also has invaluable applications in monitoring patients with systemic abnormalities, including electrolyte disturbances and hypoxia. Additionally, abnormalities in the dimensions of various components of the ECG may serve as a rough guide for evaluating structural heart disease. These ECG morphologic criteria are rarely based on controlled studies identifying specificity and sensitivity, however, and ECG parameters for dogs or cats by breed, body type, age, and sex are not comprehensively established. An abnormal heart may have a normal ECG and vice versa. Therefore the ECG, like a blood count, is not an absolute indicator of normalcy or disease, and deviations from normal suggest but do not identify structural cardiac abnormalities (Boxes 202-1 and 202-2).

202.1 ## CARDIAC CONDUCTION SYSTEM AND ELECTROCARDIOGRAPHY

Each component of an ECG tracing reflects an electrical event occurring in a specific part of the heart.[1,2,5,6] The sequence of electrical events follows specific anatomic pathways within the heart, and in health, does so precisely and consistently (Figure 202-1).

202.1.1 202.1.1 ### Box • 202-1 Criteria for the Normal Canine Electrocardiogram (ECG)* (Note: Patient in right lateral recumbency; no ECG filtering†)

Heart rate: 70 to 160 beats per minute (bpm) in adult dogs; 60 to 140 bpm in giant breeds; up to 180 bpm in toy breeds; up to 220 bpm in puppies

Heart rhythm: normal sinus rhythm (NSR); respiratory sinus arrhythmia (RSA); wandering SA pacemaker common (cyclic changes in the R-R interval can be associated with cyclic alterations in P-wave amplitude)

P wave: up to 0.4 mV in amplitude; up to 0.04 sec duration (0.05 sec in large breeds); positive in leads II and aVF; positive or isoelectric in lead I

P-R interval: 0.06 to 0.13 sec (inversely related to heart rate)

QRS complex: ‡positive in leads II and aVF, negative in lead V_{10}; mean electrical axis (MEA), frontal plane: +40° to+100°

Amplitude: maximum R wave 2.5 to 3.0 mV in leads II, III, and aVF (dogs > 2 years of age); R in rV_2 or V_{10} < 3 mV; V_2 and V_4 < 5.0 mV; minimum amplitude R wave leads II, III, and aVF is 0.5 mV;

duration: up to 0.05 sec (0.06 sec in large breeds) S in V_4 not deeper than 0.7 mV; QRS negative in V_{10}

Q-T segment: 0.15 to 0.25 sec; varies with heart rate

S-T segment and T wave: S-T segment free of marked coving (repolarization changes); S-T segment depression not > 0.2 mV in limb leads and not > 0.25 mV in chest leads; S-T segment elevation not > 0.15 mV in leads II and III; T wave positive in lead V_1 (rV_2) and negative in V_{10} (except in the Chihuahua); T wave amplitude not > 25% of amplitude of the R wave; T waves may be positive, negative, or biphasic

* Represents commonly encountered values for dogs and cats. The ECG is extremely variable; serial ECGs are recommended. Measurements outside these ranges suggest but do not identify cardiac disease. Values from references 1, 2, 5, and personal experience.

† Dvir E, Lobetti R: Effect of electrocardiographic filters on the R-amplitude of canine electrocardiograms. *Vet Rec* 150:171-176, 2002.

‡ Detweiler DK: The dog electrocardiogram: a critical review. *In* MacFarlane PW, Veitch Lawrie TD (eds): Comprehensive Electrocardiology: Theory and Practice in Health and Disease. Oxford, UK, Pergamon Press, 1989, pp 1267–1329; Hurst JW: Naming of the waves in the ECG, with a brief account of their genesis. *Circulation* 98:1937–1942, 1998.

Initiation of the normal heartbeat occurs in the *sinoatrial (SA) node*, located in the dorsolateral right atrium (RA), and spreads through both atria, forming the *P wave* on the ECG (Figure 202-2). Specifically, part of the electrical spread from the SA node travels along three sets of specialized fibers in the atria, the internodal pathways,[7] which converge on the *atrioventricular (AV) node* in the floor of the RA. Thus the outward movement of electrical activity from the SA node both activates the muscular contraction of the atria and carries a sequence of electrical impulses to be transmitted to the ventricles.

At the level of the AV node, the electrical impulse depolarizing the heart is purposefully delayed, allowing the atria to finish contracting. The period of relative electrical quiescence during which the impulse slowly passes through the AV node is reflected on the ECG as a flat segment between the P wave and QRS complex. In addition to transmitting impulses from the atria to the ventricles, the healthy AV node acts as a *gatekeeper*, blocking unwanted atrial impulses from crossing to and activating the ventricles, such as when these impulses are premature or excessive (e.g., atrial fibrillation [AFib]). In normal individuals, the unidirectionally conducting fibers of the AV node-His bundle complex make up the only electrical connection between the atria and the ventricles.

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202.1.3
202.1.2 Box • 202-2 Criteria for the Normal Feline Electrocardiogram (ECG)* (Note: Patient in right lateral recumbency; no ECG filtering†)

Heart rate: up to 240 beats per minute (bpm) (usually 140–180 bpm)

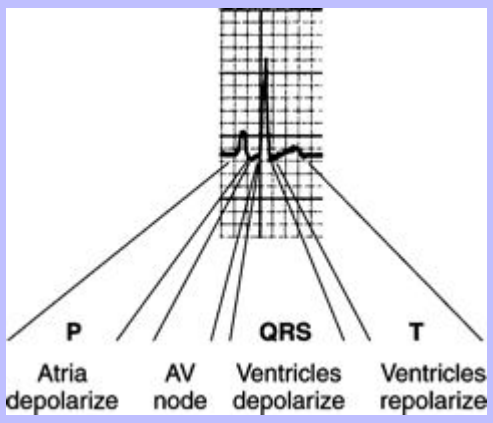
Heart rhythm: normal sinus rhythm (NSR) or physiologic sinus tachycardia (STach)
P wave: positive and up to 0.2 mV in leads II and aVF; may be positive or isoelectric in lead I; should not exceed 0.04 sec (rate dependent) in duration
P-R interval: 0.04 to 0.09 sec duration (inversely related to heart rate)
QRS complex: † more variable than in the canine; the mean electrical axis (MEA) in the frontal plane is often irrelevant and may be isoelectric in all frontal plane limb leads; MEA most commonly from 0° to +160° (frontal plane); amplitude of the R wave is usually low; maximum is 0.9 mV; duration: under 0.04 sec
Q-T segment: 0.12–0.18 sec duration; varies inversely with heart rate
S-T segment and T wave: S-T segment and T wave should be small and free of repolarization changes, marked depression, or elevation; T waves usually positive, occasionally negative or biphasic; up to 0.3 mV height
Precordial leads: few established rules exist for the V leads in cats; R in V_4 should not exceed 1.0 mV

* Represents commonly encountered numbers for dogs and cats. The ECG is extremely variable; serial ECGs are recommended. Measurements outside these ranges suggest but do not identify cardiac disease. Values from references 3, 5, 10, 14, and personal experience.

† Schrope DP et al: Effects of electrocardiograph frequency filters on P-QRS-T amplitudes of the feline electrocardiogram. *Am J Vet Res* 56:1534–1540, 1995.

Having crossed through the AV node, the electrical impulse of a normal heartbeat travels rapidly and uniformly through the ventricles via the *His-Purkinje* system.[8] This network of conductive fibers ensures that the impulse is carried quickly and distributed uniformly, such that the ventricles depolarize in a synchronized fashion. The fibers begin as a thick shaft, the *His bundle*, that accepts transmission from the AV node and crosses through the endocardial cushion to the ventricles. The His bundle quickly divides into *right and left bundle branches* (RBB and LBB), directed to their respective ventricles, and the left bundle in turn divides into *left anterior, left posterior, and septal fascicles*. The clinical relevance of this division relates to interruptions of electrical conduction through these bundles, which can occur under various pathologic, and occasionally normal, conditions (see Bundle Branch Blocks, following). Overall, depolarization of the ventricles is apparent on the ECG as the *QRS complex*. When the ventricles have completely finished depolarizing, a sequence of repolarization returns the myocardial cells to their resting state. This repolarization sequence, which follows in the wake of the depolarization sequence, is seen as the *T wave* on the ECG.

Figure 202-1 A heartbeat on the electrocardiogram (ECG). Correlation with electrical activity in anatomic regions of the heart.



202.2 CLINICAL USE OF ELECTROCARDIOGRAPHIC LEADS AND MEAN ELECTRICAL AXIS

202.2.1 Electrocardiographic Leads

In practical terms, an ECG lead is nothing more than one perspective on the electrical activity of the heart. That is, different leads offer different vantage points on the same electrical events that take place during a heartbeat.[9] Therefore an ECG showing multiple leads can be thought of as an ECG with multiple observers reporting the electrical activity of the heart from different positions (Figures 202-3 to 202-5).

Having multiple observation points (multiple leads) is important because all cardiac electrical events are not always apparent in all leads. Indeed, important information about the heartbeat is often visible in some ECG leads but not in others. This is because any ECG lead is characterized by the ability to sense only electrical activity traveling toward or away from it. The drawback of this characteristic is that electrical activity coursing through a three-dimensional structure like the heart often occurs in a direction that is neither toward nor away from a particular lead and therefore is perceived partially, or suboptimally, in any one lead alone. At an extreme, electrical activity that occurs exactly perpendicular to a lead (i.e., the electrical activity moves in a direction that is in no way toward or away from the lead) registers nothing (isoelectric ECG) for that lead, regardless of how normal or strong the electrical activity.

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Figure 202-2 Electrocardiogram (ECG) dimensions and nomenclature for a normal heartbeat.

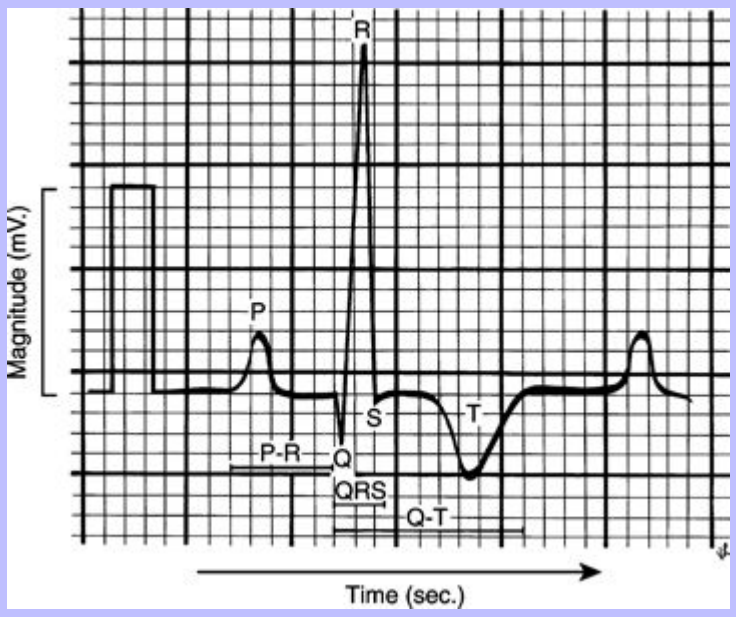


Figure 202-3 The positive pole of an electrocardiogram (ECG) lead as observer. The overall thrust of electrical energy for one beat of the ventricles is oriented caudally and slightly leftward (i.e., directly toward the positive pole of lead II [eye]) in the normal dog. Therefore a large, positive QRS complex is registered in that lead.

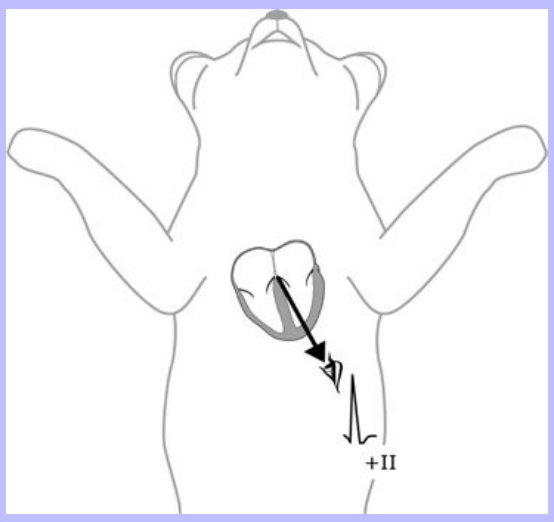


Figure 202-4 Same normal heart as in Figure 202-3. The observer at the positive pole of lead aVR registers an overall thrust of electrical energy directed away from it. Therefore lead aVR displays a large (deep) negative QRS complex.

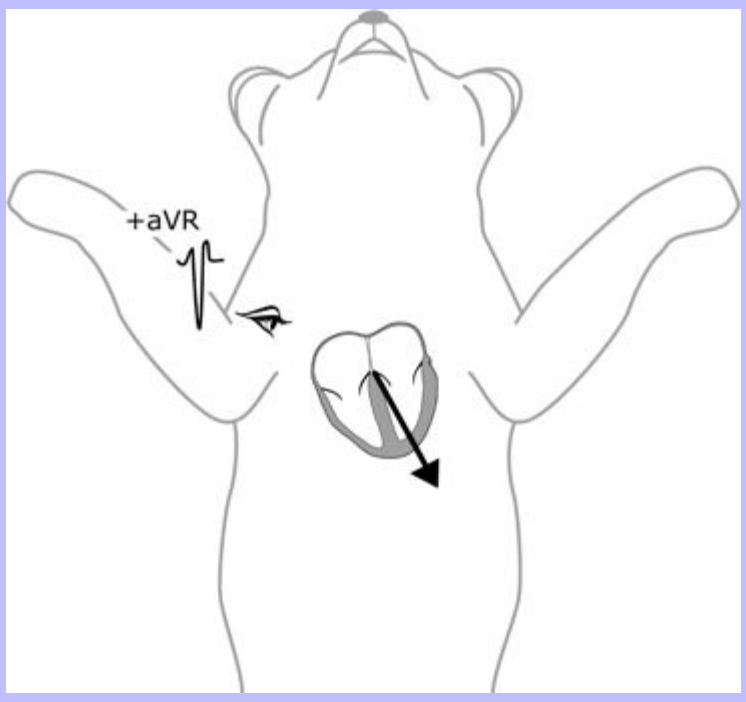
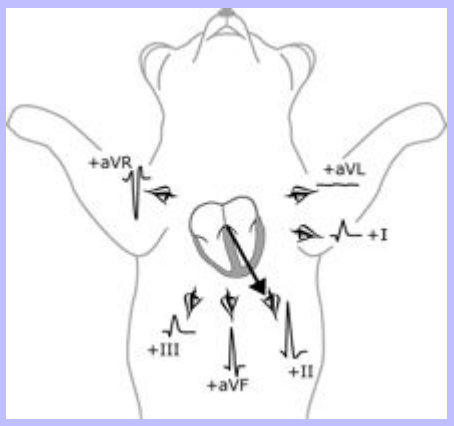


Figure 202-5 Typical appearance of QRS complexes in the six limb leads when the mean electrical axis (MEA) is in the normal range for dogs (here: +60 degrees). The reader should note that the overall size and polarity of each QRS reflects the amount and direction of electrical energy detected by the positive pole (observer) of each lead. This is the basic principle that allows the clinician to understand the overall direction of electrical thrust (MEA) based on observing QRS complexes in all leads of a patient's electrocardiogram (ECG).[9]

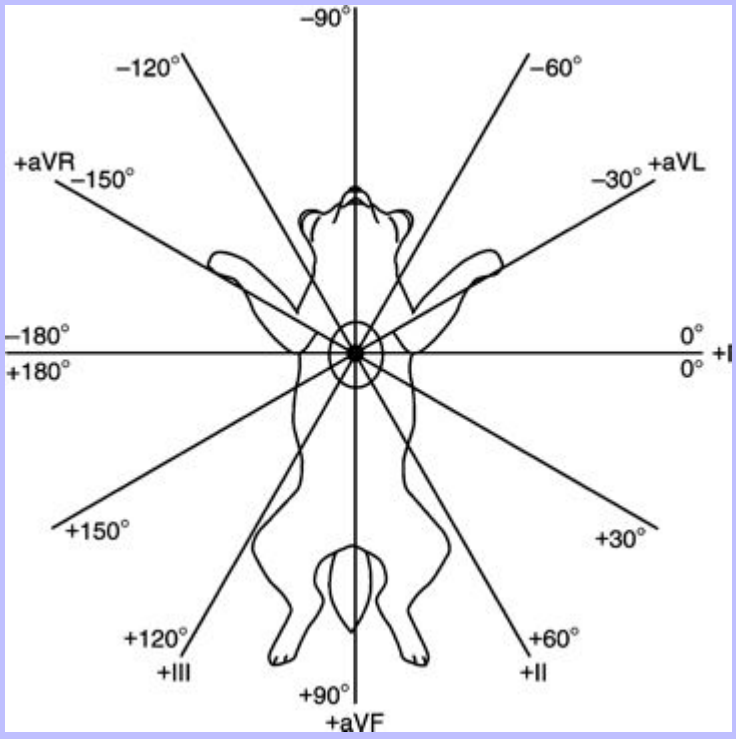


Electrical activity that travels directly toward the positive pole of a lead creates a strong positive deflection (wave) above the baseline on the ECG for that lead (see Figure 202-3). Similarly, electrical activity that travels directly away from the positive pole of a lead registers a strong negative ECG wave, below the baseline (see Figure 202-4). Intermediate orientations of electrical activity create waves that are of intermediate degrees of positivity or negativity, depending on the magnitude of the positive or negative component of the electrical activity that is detectable on that lead. For example, an impulse traveling *almost* directly toward the positive pole of a lead will create a large positive wave (see Figure 202-5, lead aVF) but not quite as tall as when the energy is traveling fully toward the positive pole of the lead (see Figure 202-5, lead II). All leads register the amount of positivity or negativity generated by that impulse relative to their positive pole and record a wave in proportion to that. The lead that is almost 90 degrees away from the direction of the electrical activity will record little to no activity (i.e., almost isoelectric line; see Figure 202-5, lead [aVL]), and the positive pole of the lead that is closest to 180 degrees away from the direction of electrical activity will register a very large, negative complex (see Figure 202-5, lead [aVR]).

Therefore it can be seen that using multiple leads for an ECG has two major advantages (Figure 202-6). First, the leads directly and proportionally perceive the amount of energy (i.e., number of cells depolarizing, the smoothness of conduction) involved in depolarization. Thus left ventricular (LV) hypertrophy may be suspected when QRS complexes are abnormally tall in lead II, for example, because the amount of energy transmitted in the normal direction (toward the LV) is greater due to the increased myocardial mass. Right ventricular (RV) hypertrophy can be suspected when the bulk of ventricular electrical activity is directed

abnormally toward the right heart (see discussion of right axis deviation, following). Second, having multiple leads solves the problem of any single lead's "blindness" to perpendicularity. Posting numerous observers at regular stations around the heart (i.e., having multiple leads) ensures that some leads inevitably will perceive the heart's electrical energy better than others and therefore will show larger, more easily interpreted waves and complexes (see Figure 202-5). Therefore on any ECG that shows multiple leads, the clinician will usually find it easiest to interpret the rhythm by first scanning the different leads to see which ones offer the clearest (i.e., largest and with the least artifact) P waves, QRS complexes, and T waves.

Figure 202-6 Location and names of electrocardiogram (ECG) limb leads in the standard hexaxial system (frontal plane).



It is worth noting that by convention the diagram that shows the position of the 6 standard ECG limb leads is visualized in a ventral-dorsal orientation—or seen from above when the patient is in dorsal recumbency (see Figure 202-6). Each lead is named according to the location of its positive pole. The points around the circumference of the map, unfortunately, are named in a confusing manner. The change from +180 degrees to −180 degrees at the 9 o'clock position is a meaningless designation that has no implication regarding the positivity or negativity of the electrical energy or leads in the upper (cranial) half of the circle, and a much less confusing approach would have been simply to continue numbering the points from +180 degrees to +359 degrees. A more detailed description of this basic series of concepts may be found in most comprehensive books on electrocardiography.[2,4,5,9,10]

202.2.2 Mean Electrical Axis

As the ventricles depolarize, the sequential activation of the cardiomyocytes creates an overall direction or thrust of electrical activity in the ventricles. This electrical activity is best detected by an ECG lead most closely oriented with the direction of the electrical activity, as described previously. The sum total of electrical energy for all the depolarizations in one beat of the ventricles represents the final tally of individual depolarizations, with impulses headed in the same direction adding to each other and impulses headed away from each other canceling each other out. Therefore in a normal heart, the sum total of electrical energy expended for one beat of the ventricles has an overall thrust that is leftward (because the left ventricle [LV] is larger than the right) and caudal (because more energy is directed toward the apex of the heart during initial activation than travels back toward the base at the end of ventricular activation). This sum total, or overall thrust, of electrical energy, is also called the *mean electrical axis* (MEA) (see Figures 202-3 to 202-6).

The direction and thrust of electrical energy (MEA) is characteristic for an individual and, barring an intermittent intraventricular conduction abnormality, is constant from beat to beat on an ECG tracing. In normal individuals, the MEA, as just mentioned, points leftward and caudally because that is the overall direction in which the normal ventricles point (see Figure 202-5). However, the sum total of electrical energy for one beat of the ventricles (the MEA) may change if the heart changes in shape. For example, if a patient's RV becomes pathologically enlarged to a sufficient degree, the bulk of electrical energy for ventricular depolarization may be directed move towards the right instead of the left. This is called a *right axis shift* or *right-axis deviation*. In such a case an ECG with multiple leads in a clinical patient could show QRS complexes that were more positive than usual in the right-sided lead (aVR) and QRS complexes that were more negative than usual in the left-sided leads (aVL, I, and II) (Figures 202-7 and 202-8). This simple ECG finding would increase the suspicion of disorders that cause RV enlargement. As a second example, conduction through the RV involves passage of the electrical impulse along the right bundle branch (RBB) for rapid spread through the RV. Hampered conduction through the RBB, a phenomenon called *RBB block*, redirects the electrical impulse, a variation that is visible on the ECG (see Bundle Branch Blocks, following; see Figure 202-45).[11] As a result of RBB block, the incompletely depolarized RV is depolarized late, and slightly less efficiently, by impulses redirected from the LV. This “swing” of electrical energy reorients the overall thrust of electrical energy for that beat of the ventricles toward the right, creating a right axis deviation. Therefore the two main differential diagnoses for right axis deviation in a patient with sinus rhythm are (1) RV hypertrophy and (2) RBB block. Left axis deviations occur uncommonly because the bulk of electrical activity already is directed toward the left in the normal heart. LV hypertrophy does not alter the direction of thrust of overall electrical activity from the left-caudal direction but often will increase its magnitude (e.g., taller R waves in lead II). Left anterior fascicular (LAF) block is an example of a conduction abnormality within the ventricles that is compensated for with a thrust of energy in the left dorsal direction, which can cause a left axis shift (see Figure 202-46 for an example).[12]

Figure 202-7 In this heart, marked right ventricular (RV) hypertrophy is present. The greater myocardial mass directs the overall thrust of ventricular activity rightward. This physiologic phenomenon is revealed on a standard electrocardiogram (ECG): the positive pole of a lead aVR registers more electrical energy directed toward it, and its QRS complex is markedly more positive than normal, whereas leads aVL, I, II, and aVF are more negative than normal because the thrust of energy travels away from them. These findings represent a right-axis deviation.

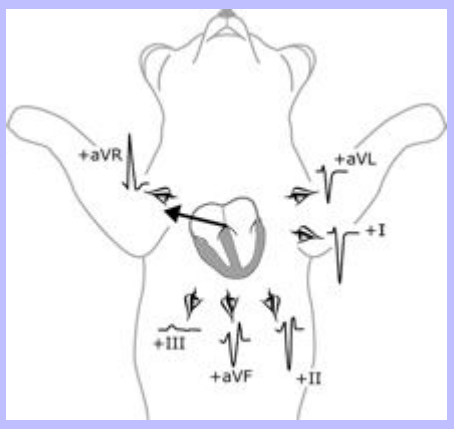
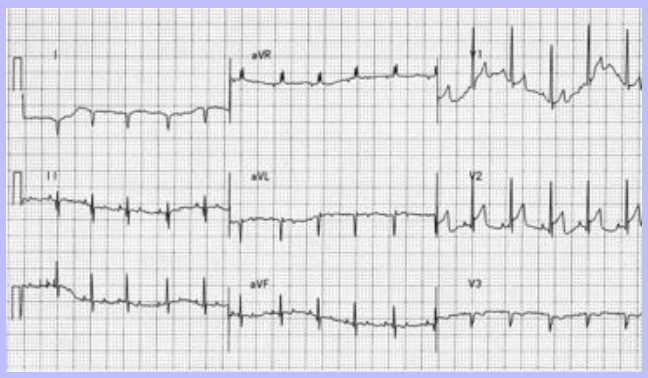


Figure 202-8 Right axis deviation. The mean electrical axis (MEA) is +150 degrees. Precordial leads also indicate a predominance of electrical activity to the right (rV2, marked "V1"; V_4 marked "V3"). Right ventricular (RV) hypertrophy was confirmed echocardiographically in this young miniature Schnauzer dog with severe pulmonic stenosis (25 mm/sec, 1 cm = 1 mV).



The concept of using the polarity and size of ECG deflections to infer the orientation of electrical thrust applies to the atria (P waves) and to the ventricles. Variations in atrial MEA have been associated with atrial enlargement or intra-atrial conduction abnormalities, yet as with the ventricles, MEA is at best a rough index, and its accuracy for assessing morphology appears to have been widely surpassed by that of other diagnostic modalities such as echocardiography.

Using vectorial enhancement, the ECG machine uses the three electrode wires connected to patients undergoing an ECG (the fourth is an electrical ground) to assess electrical activity from three additional perspectives (aVR, aVL, and aVF) in addition to I, II, and III, for a total of six different perspectives. The six positions, or leads, are evenly spaced 30 degrees apart and are called the *limb leads* (see Figure 202-6).

MEA can be calculated on an ECG in several ways, allowing the clinician to understand the overall direction of electrical thrust in the ventricles. Probably the simplest is to look for the lead with the most positive QRS complex. This represents the lead toward which the bulk of electrical activity is most directly oriented (i.e., the MEA). An equally effective, converse approach is to find the most isoelectric lead, namely the lead that perceives the least electrical energy. Because the isoelectric lead is the lead that is least aligned with the thrust of electrical activity, then the lead 90 degrees to it must be the lead with the most electrical activity. The MEA is therefore the positive pole of the lead perpendicular to the isoelectric lead, in the direction that corresponds to positive QRS complexes. Finally, the classic way of determining MEA consists of calculating the surface area of the QRS complexes of two ECG leads (as the number of small boxes within the complexes). On the ECG axis map (see Figure 202-6), one then places a marker on the lines of each of the two leads examined. The distance of the two markers away from the center of the diagram is the number of small boxes that made up the surface area of each of the two examined leads. From the markers on each of these two leads' lines, a perpendicular line is drawn such that the two perpendiculars meet. A line from the center of the axis map to the point where the perpendiculars cross indicates the MEA. When MEA is correctly determined by any technique, all leads “agree” and are consistent with one direction of thrust of electrical activity, because the leads are only offering different perspectives on the same cardiac electrical activity. Any contradictory, nonsensical information in this regard is usually explained by erroneous connection of the electrode wires (ECG lead-patient limb mismatch).

Determining which is the “most positive QRS complex” or “most isoelectric lead” must take into account that the negative elements of a QRS complex cancel out an equivalent amount of the positive elements on the ECG tracing. Therefore it is a QRS complex's net positivity or negativity that is assessed. For instance, if lead II shows the tallest R wave and no Q or S wave, and lead aVF shows an identically tall R wave but some small Q and/or S waves as well, then the QRS is considered to be smaller in lead aVF; therefore the MEA is closer to +60 degrees than to +90 degrees (see Figure 202-5). By the same principle, a QRS complex that is wide is considered “bigger” (greater surface area) than a narrow QRS complex of the same height.

On an ECG, the cardiac rhythm is not affected by a patient's posture. However, the MEA is markedly altered by the position of the limbs, and a consistent approach to patient restraint is essential (by convention: right lateral recumbency, with limbs held perpendicular to the long axis of the patient's body). Changes in recumbency or in limb position can markedly and misleadingly alter the MEA.[6,14,15] This artifact was nicely illustrated in an experiment in which dogs in right lateral recumbency had an ECG done with one forelimb held forward and the other drawn back, and then the leg positions were reversed. A marked, but artifactual, change in MEA was observed.[15] Therefore in the ambulatory patient, no information can be inferred regarding MEA (see Ambulatory Electrocardiogram, following).

202.2.3 Precordial Leads

The concept of designing ECG leads to "survey" the electrical activity of the heart from multiple angles is a sound one, but even with a lead at every 30 degrees, a major shortcoming still exists. The six limb leads (I, II, III, aVR, aVL, aVF) may cover the entire frontal plane of the body (see Figure 202-6), but electrical energy traveling through a three-dimensional structure like the heart may travel "outward" or "inward" (i.e., in a dorsal or ventral direction). In such a situation, none of the six leads perceives the electrical activity as going clearly toward or away from any positive pole; electrical activity is perpendicular to all of them and therefore is invisible to all. The solution to this problem is the precordial leads (chest leads, thoracic leads, V leads). With precordial leads the ability to perceive electrical activity of the heart extends to three dimensions, because the ECG clips for precordial leads are placed circumferentially around the chest. Thus the precordial leads (rV_2, V_2, V_4, and V_{10}) assess electrical activity in the transverse (lateral and ventral-dorsal) plane (Figure 202-9). Precordial leads provide essential information that may not be apparent in the limb leads (frontal plane) (Figure 202-10) but they are more susceptible to artifact caused by chest wall motion (Figure 202-11).

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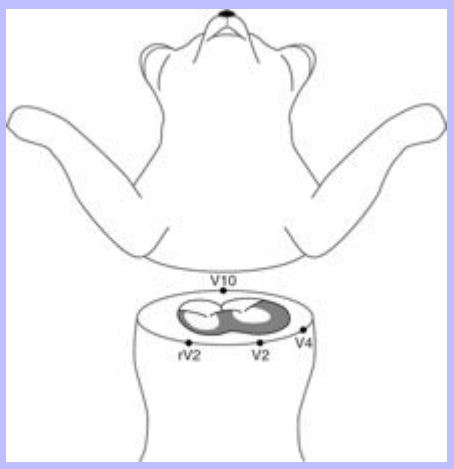
Figure 202-9 Precordial leads. Using the summation of limb leads as one "virtual" pole in the center of the chest, the positive poles of precordial leads are positioned to register electrical energy in the transverse plane as follows: right fifth intercostal space, just lateral to the sternum (rV2, or CV5RL), left sixth intercostal space, just lateral to the sternum (V2, or CV6LL), left sixth costochondral junction (V4, or CV6LU), and dorsal midline directly dorsal to lead V4 (V10), approximately over the seventh thoracic vertebra.[9]



202.2.4 Combining Mean Electrical Axis and Electrocardiographic Leads: Understanding the Direction and Force of Electrical Activity in a Heartbeat

From the explanations given previously, it should be seen as logical that lead II is routinely used for evaluating the ECG in small animals. This is because the positive pole of lead II (i.e., the point from which a lead II "observer" detects electrical activity) is at + 60 degrees, or in the left caudal region (see Figures 202-5 and 202-6). This is in the middle of the normal range of MEA for healthy dogs and cats.[2,5] The LV receives more energy than the right, and the overall thrust of electrical energy is caudal, so the positive pole of lead II is likely to perceive a large thrust of electrical energy toward it in normal small animals and thus display a clear ECG with large, visible QRS complexes (see Figure 202-3). The same can be said for atrial activity and the P waves. However, interindividual variation reveals the limitation of using only lead II. Certain patients may fail to provide the desired information in a specific lead (see Figure 202-10).

Deviation of the QRS MEA denotes an abnormal orientation of the sum total of ventricular electrical energy.[1,2,5] Normal MEA is +30 degrees clockwise to +110 degrees for the dog, and zero degrees clockwise to +160 degrees for the cat. The most common causes of right axis deviation (MEA to the right of normal [from +110 degrees clockwise to −90 degrees in the dog]) are RV hypertrophy and enlargement (see Figure 202-7 and 202-8), RBB block (see Figure 202-45), and ventricular ectopy of LV origin (see Figure 202-32)—all conditions in which the bulk of ventricular electrical activity travels toward the RV. Left axis deviation (MEA to the left of normal [from +30 degrees clockwise to −90 degrees in the dog]) is rare and can be caused by LAF block (see Figure 202-46) or experimental transection of the left bundle branch. In cats the wide range of normal for MEA and the substantial overlap between normal and abnormal limits the usefulness of MEA, and some cardiologists omit it altogether. It can also be seen that a premature ventricular complex (PVC, VPC) originating from the LV, for example, will spread outward (i.e., toward the right) and thus presents a thrust of energy that is directed rightward. This radical difference in orientation of electrical thrust explains why classic PVCs of LV origin are commonly *bizarre looking*: they are oriented away from the positive pole of lead II, so are predominantly negative in that lead (i.e., bizarre in shape). PVCs also are usually wider than sinus beats because they spread from an ectopic focus through ventricular myocardium, not along the rapidly conductive fibers of the His-Purkinje system as normal beats would. This slower conduction means the QRS complex will be wider on the ECG (takes longer to be traced). Because the His-Purkinje system is more widely developed in the LV, PVCs of RV origin are more apt to propagate along on it and thus RV PVCs often are only slightly different from normal sinus QRS complexes.

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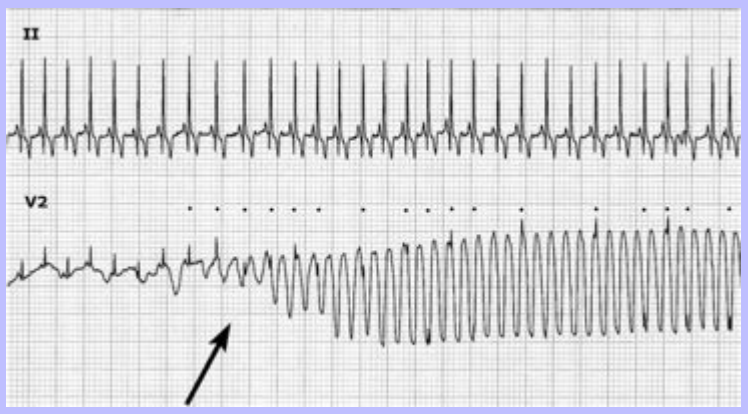
Figure 202-10 Deficiencies of limb leads and utility of precordial leads. **A,** This electrocardiogram (ECG) from an adult male Doberman dog with a chief complaint of dyspnea could be misinterpreted as indicating atrial fibrillation (AFib) because no P waves are seen in the limb leads and a fine, undulating baseline is present. However, P waves are clearly present, as seen in lead V2. This ECG shows normal sinus rhythm (NSR), not AFib. The P waves are isoelectric to the limb leads, indicating that the overall thrust of atrial electrical activity was oriented ventrally, toward lead V2 (Figure 202-9). The fine baseline undulations are motion artifact. The erroneous suspicion of AFib also was at odds with the regular rhythm and pulse noted on physical examination. Mild variation in R wave amplitude, as seen toward the end of the lead II rhythm strip at bottom, can occur with aberrant ventricular conduction or as an artifact of ECG filtration. Simultaneously recorded nine-lead tracing and rhythm strip (25 mm/sec, 1 cm = 1 mV). **b**, Sinus rhythm with motion artifact mimicking atrial flutter or fibrillation. Unlike true atrial flutter or fibrillation, the QRS complexes occur at regular intervals. P waves *(dots)* are seen, especially when the dog stops shivering at the end of the tracing (lead I, 25 mm/sec, 1 cm = 1 mV). (*B*, tracing courtesy of Sophia David, AHT.)

Figure 202-11 Artifact affecting a ventricular (precordial) lead; leads II and V_2 recorded simultaneously. In this dog, the cyclical chest excursions of panting *(onset: arrow)* can disrupt the ECG similar to ventricular arrhythmias. A closer inspection of lead V_2 reveals the persistence of superimposed, normally timed QRS complexes *(dots)*, many of which can be seen and none of which would occur if the rhythm were VT. This artifact is absent in the limb leads, which do not move with panting as does the chest wall. Speed: 5 mm/sec; scale: 10 mm/mV.



Despite the incontestable superiority of echocardiography over ECG for assessing cardiac size and structure, the ECG continues to provide clues about abnormal heart size or shape. It can increase the index of suspicion for cardiac disease or can help to refine the differential diagnosis before an echocardiogram is performed. For example, heart diseases causing RV enlargement continue to be noted as causing a right axis deviation in many or most affected patients, including those with pulmonic stenosis (right axis deviation in 19 of 21 patients [90%][16]), right-to-left patent ductus arteriosus (right axis deviation in eight of eight patients [100%][17,18]), and cor pulmonale.[19]

202.2.5 Confounding Factors

Sources of error may alter the apparent MEA and result in an erroneous diagnosis. Changes in position of the limbs[14,15] and of the position of the heart within the chest (e.g., pericardial effusion [see Figure 202-17], peritoneopericardial diaphragmatic hernia, intrapericardial mass, or body motion in ambulatory ECG) change the perspective from which ECG leads perceive the heart's electrical activity, often causing the false appearance of changes in the MEA.

202.3 NORMAL ELECTROCARDIOGRAM

Extremely fit dogs with athletic hearts, such as Alaskan sled dogs, deviate substantially from the "normal" ranges listed at the beginning of the chapter (see Box 202-1).[20] In most normal dogs, heart rates range between 60 and 160/min. Rates above these limits are classified as *tachycardias*, and below 70 beats per minute (bpm) are *bradycardias*. Bursts of sinus tachycardia (STach) of up to 300 bpm have been identified for brief periods in normal dogs.[1] In healthy cats in the hospital setting, the normal heart rate extends up to 260 bpm, with a median of 180 bpm.[21] The low limit of normal varies, depending on whether the patient is at home or in the hospital. Generally 130 to 150 bpm would be considered low-normal for a healthy cat in a clinical environment.[21] Ambulatory electrocardiographic testing provides an excellent opportunity to evaluate the real heart rate across the species and identifies a higher prevalence of arrhythmias than conventional monitoring.[22–25]

Figure 202-12 Respiratory sinus arrhythmia (RSA) and wandering pacemaker (WP). Lead II, 25 mm/sec, 1 cm = 1 mV.

The *P wave* is the first deflection on the ECG after isoelectric diastole (baseline after T wave) (see Figures 202-1 and 202-2).[13] It should be positive in leads II and aVF, and isoelectric or positive in lead I. It may be negative in leads III, aVR, aVL, V_2, and V_{10}. The first half of the P wave represents RA activation, and the second half represents left atrial (LA) activation. The spread of atrial excitation begins in the upper portion of the RA at the SA node and spreads across the atrium, depolarizing the LA. The maximum normal amplitude of the P wave in any limb lead is 0.4 mV in the dog and 0.2 mV in the cat. The amplitude of the P wave may increase during inspiration and with increased heart rate. High vagal tone also allows the exact pacemaking site within the SA node to change. Higher centers are responsible for early activation, and lower centers closer to the AV node produce lower rates and lower amplitude P waves.[1] This vagally mediated change in the origin of the pacemaking site in the SA node is a normal feature of canine ECGs and is called a *wandering pacemaker* (WP) (Figure 202-12). The amplitude of the P wave may also vary between tracings due to changes in the position of the heart and of the ECG clips.

The duration of the P wave should not exceed 0.04 second in the dog (0.05 second in larger breeds) and 0.04 second in the cat. Notching of the P wave is not significant unless the duration of the wave exceeds stated limits, in which case it may indicate LA enlargement *(P mitrale)* (Figure 202-13). Conversely, P waves of increased amplitude, especially with a peaked shape, have been associated with enlargement or hypoxia of the RA *(P pulmonale)* (see Figure 202-13).

The morphology and amplitude of the canine P wave are more variable than in other animals, especially in the limb leads. The mean P wave MEA in normal dogs is within 90 degrees of the ventricular MEA in the frontal plane.

The *P-R segment* is the isoelectric period that follows the P wave on the ECG (see Figures 202-1 and 202-2). It is measured from the end of the P wave to the beginning of the first deflection away from the baseline, indicating

ventricular activity. During the P-R segment, the electrical impulse is being conducted slowly through the AV node. Atrial repolarization occurs during this period and into the QRS; atrial repolarization generally is too low in amplitude (or occurs too far into the QRS complex) to be detected on surface recordings, except in rare cases in which an atrial repolarization wave, or T_a wave, is seen within the PR segment (see Figure 202-13).[26] T_a waves distort the baseline of the PR segment and usually are indicative of atrial enlargement, hypoxia, or electrolyte changes.

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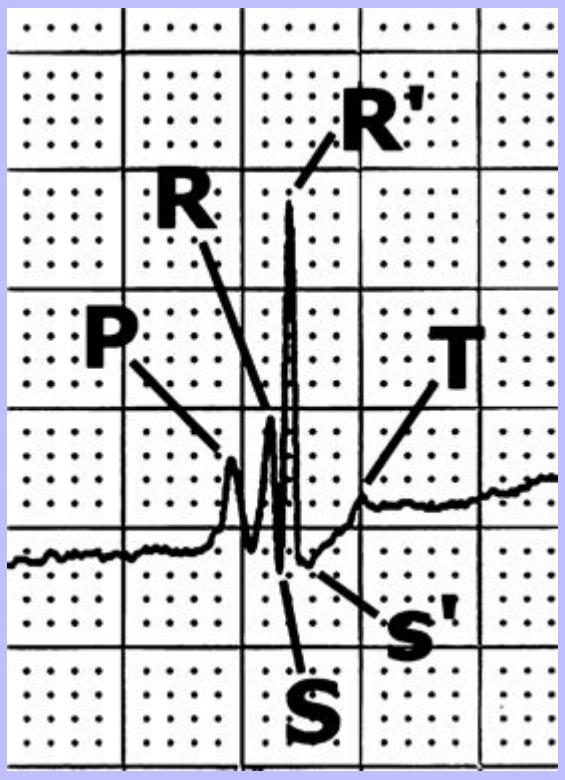
Figure 202-13 P wave abnormalities. Lead II, 25 mm/sec, 1 cm = 1 mV.

The period from the onset of the P wave to the onset of the QRS complex is the *P-R interval* (see Figure 202-2). The duration of the P-R interval varies inversely with the heart rate. With rapid heart rates it may be 0.04 second but usually varies from 0.06 second to 0.14 second (dog) and from 0.04 to 0.09 second (cat). Normal dogs vary considerably. Prolongation of the PR interval is first-degree heart block, an electrocardiographic—but not hemodynamically important—term (see Atrioventricular Block, following). Short P-R intervals suggest rapid heart rates or accessory pathways that bypass normal A-V conduction (see Pre-Excitation Syndromes, following).

The *QRS complex* is the ECG representation of ventricular depolarization (see Figures 202-1 and 202-2).[13] It occurs immediately after the P-R interval. The components of the QRS complex are named for their sequence of occurrence, not for correlations with activation of specific parts of the ventricles. The Q wave is the first negative deflection occurring before a positive wave after the isoelectric P-R segment. The R wave is the first positive deflection after the P-R segment, regardless of whether or not a Q wave precedes it. The S wave is a negative deflection occurring after a (Q) or (R) deflection (or both). If no positive waves are present, the negative deflection is called a *QS complex* (e.g., lead I in Figure 202-8). Additional positive or negative deflections that occur in the QRS complex after the R or S wave has returned to the baseline (producing "splintered" QRS complexes) are called *prime* (R′; S′) *waves* (Figure 202-14).[13] Any of the following ventricular patterns may arise: QR, QS, RS, R, QRS, plus prime deflections. If the wave amplitude is small (i.e., < 0.5 mV), it is written as a small letter (e.g., *q*); if it is greater than 0.5 mV, a capital letter is used (e.g., *Q*).[1,13] These types of complexes occur under various conditions. For example, an association with congenital tricuspid valve malformations in Labrador retrievers is known to exist.[27]

Figure 202-14 Example of a splintered QRS complex. The exact description is an RSR's' complex. The short P-R interval also suggests pre-excitation. Lead II, 25 mm/sec, 1 cm = 1 mV.



The size of QRS complexes (and P waves) is significantly affected by the presence or absence of filters on the ECG machine. Use of routine ECG filtration in one canine study produced a median 51% reduction in QRS amplitude,[28] with the greatest amount of artifactual attenuation noted in smaller dogs and in tracings with narrower QRS complexes. Marked filtration effects also have been noted in feline ECGs.[29] Therefore the presence or absence of filtration should be recorded on ECG tracings whenever possible.

LV muscle mass normally exceeds RV mass. Depolarization of the LV overwhelmingly controls the magnitude and direction of the forces of the QRS complex in the dog and the cat. Ventricular activation occurs in three smooth, transitional phases: (1) initial, (2) main, and (3) terminal. The interventricular septum, except for the basilar region, is depolarized first, followed by bilateral apical and central endocardial to epicardial activation until a single cone of depolarized muscle surrounds each cavity. Terminal electrical activity proceeds from apex to base, exciting the basal septum and basal and lateral LV. The electrical thrust (vector) is directed from left to right in the interventricular septum, then endocardium to the epicardium, depolarizing the free (lateral) ventricular walls, and finally basally in the upper walls and septum (ventricular outflow tracts).[1,2,5,30] The durations of these phases are normally 0.01 second, 0.025 to 0.035 second, and 0.01 second, respectively, in the

dog.[30,31] They are proportionate but shorter in the cat, where the entire QRS complex duration is usually between 0.02 and 0.03 second.

Prolongation of the QRS complex beyond 0.05 second (0.06 second in large breeds) indicates delayed ventricular depolarization. In cats, durations exceeding 0.04 second are unusual. Ventricular hypertrophy, bundle branch block (BBB), electrolyte disorders, formation of ventricular ectopic beats (either premature or escape rhythms; see discussion of premature ventricular complexes and conduction disorders, following), and aberrantly conducted beats (e.g., RBB block) can result in prolonged complexes.

More specifically, the initial ventricular electrical thrust, or vector, when the impulse first emerges from the AV node and begins to travel in the His bundle, is oriented rightward, craniad, and ventrad. Leads I and V_{10} should therefore each have a Q wave, indicating an initial rightward (lead I) and ventrad (lead V_{10}) force. The Q wave in canine leads II and aVF represent cranially directed initial forces (duration under 0.01 second). The initial vector is directed cranially for only a short period prior to turning caudad. If a Q wave is present in older dogs in leads I, II, III, and aVF, and if its amplitude is greater than −0.5 mV in lead II, it is probably abnormal and specifically suggests the possibilities of RV enlargement or RBB block.

The main portion of the QRS complex reflects depolarization of the LV and RV free walls. The main ECG deflection is formed by depolarization of the LV wall directed to the left, caudad, and ventrad, producing an R wave in leads I, II, III, and aVF (leftward and caudad) and a Q wave in lead V_{10} (ventrad).

The terminal force of the QRS complex represents dorsal basal (apicobasilar) depolarization. The force is either rightward or leftward, depending on the extent to which the basal region of the LV lies to one side of the midline. If part of the dorsal basal region lies electrically to the right side of the thorax, then the terminal electrical forces will be directed cranially and to the right, producing a small S wave in leads I, II, III, and aVF. This $S_1S_2S_3$ pattern sometimes is noted with severe heartworm disease and other causes of marked RV hypertrophy (Figure 202-15). Normally no S wave occurs in lead I and it may also be absent in lead II. Lead V_{10} should always have a Qr complex, the small *r* wave representing the terminal dorsal basal depolarization of the ventricles. 1047 1048

Figure 202-15 S waves *(arrows)* seen in leads I, II, and III ($S_1S_2S_3$ pattern). This is a manifestation of the final forces of ventricular depolarization being directed cranially (S waves in leads II and III) and to the right (S waves in leads I and II). Classically it has been associated with right ventricular (RV) hypertrophy, as in this 6-year-old Husky dog with severe heartworm disease (25 mm/sec, 1 cm = 1 mV).

The upper-normal limit of amplitude of the canine R wave is 2.5 mV; above 3.0 mV is virtually always abnormal except in some young dogs. Abnormally tall R waves in lead II suggest LV enlargement. R waves of amplitude less than 0.5 mV in leads I, II, and III are small.[1] Consistently diminished R wave amplitude suggests pericardial or pleural effusion (or both), intrathoracic mass, severe pulmonary disease, hypovolemia, hypothyroidism, hypothermia, acute hemorrhage,[32] or obesity. These associations are true only if QRS complexes are diminished in all leads, including the V leads. Otherwise, QRS complexes may simply be small in one lead because they are larger in other leads (i.e., the MEA is directed elsewhere; see Mean Electrical Axis). Cyclic changes in heart rate may cause cyclic variations in QRS complex size. A pattern of alternating change in R-wave height from beat to beat is seen in some dogs with pericardial effusion (Figure 202-17). This finding, called *electrical alternans*, results from the swinging motion of the beating heart within a distended, fluid-filled pericardial sac.

Figure 202-16 Normal sinus rhythm (NSR) in a cat. Heart rate: 140 beats per minute (bpm). Mean electrical axis (MEA): +85 degrees. Left ventricular (LV) hypertrophy is also suspected based on the tall R Waves in lead II and was confirmed echocardiographically. The fifth precordial lead is inserted between V_2 and V_4 as described by Harpster[10] (25 mm/sec, 1 cm = 1 mV).

Figure 202-17 Electrical alternans. Lead II, 25 mm/sec, 1 cm = 1 mV.

Occasionally the QRS complex is nearly isoelectric in all six limb leads, a variation of normal referred to as a *horizontal heart*. The MEA is indeterminate in the frontal plane, and normal MEA parameters cannot be used; however, the precordial leads often still give useful information regarding left-right and dorsal-ventral orientation of the electrical thrust. The rhythm durations of waves, complexes, and intervals are not altered by the horizontal heart situation.

The Q-T interval begins with the onset of the QRS complex, ends when the T wave returns to baseline, and denotes the entire period of ventricular electrical activity (see Figure 202-2).[2,13] The duration of the Q-T interval varies directly with the preceding RR interval. Nevertheless, and despite wide variations in heart rate in the dog, the Q-T interval does not vary during respiratory sinus arrhythmia (RSA).[33] Measurements of the Q-T interval have traditionally been corrected ($Q\text{-}T_c$) for the effect of heart rate using the Bazett formula:

$$Q\text{-}T_c = \text{Q-T interval/square root of R-R interval}$$

This formula may overcorrect at rapid heart rates and undercorrect at lower heart rates and is dependent on identification of the exact duration of the T wave, which may be challenging in some ECGs. Clinically the Q-T interval may be assessed routinely without correction and, when that is required, the formula is the simplest adequate method. In small animal practice, Q-T interval prolongation is usually associated with certain medications[34] specific medical conditions[34,35] but not the arrhythmogenic cardiomyopathy of boxer dogs.[36] Amiodarone, a class III antiarrhythmic agent (see Therapy of Arrhythmias, following) is known in human beings and in dogs to prolong the Q-T interval when administered over long periods of time.[37] This effect is due to its effect on potassium ion channels (I_{to} transient outward K+ current and others). Such electrocardiographic changes have been linked to proarrhythmia in humans, although this association has not been clearly demonstrated clinically in dogs or cats. Some veterinarians are called upon to evaluate Q-T intervals critically because their work involves research laboratory studies that test the effects of drugs on such ECG changes as Q-T interval prolongation. In this instance the reader may wish to pursue specific information on Q-T interval corrections and nonclinical electrocardiology.[1,34,38,39] Regardless of context, marked prolongation of the Q-T interval can be an issue of concern; it raises the possibility of such acute, “malignant” arrhythmias as torsades de pointes (TdP, see Figure 202-38) and ventricular fibrillation (VF, see Figure 202-37).

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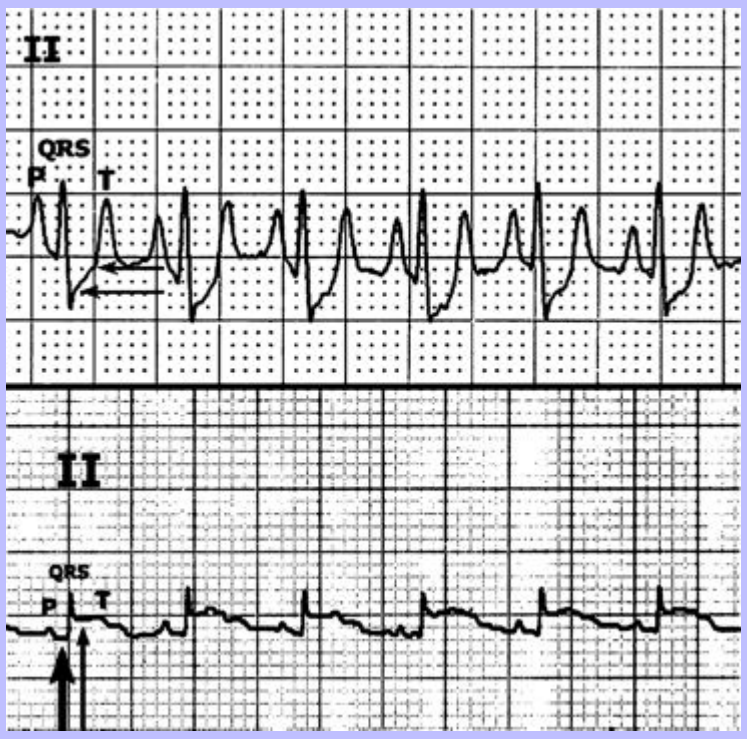
The S-T segment and T wave represent ventricular repolarization (see Figures 202-1 and 202-2).[13] The S-T segment, which represents the slower phase of repolarization and its predominance of slow calcium channel activity, begins with the end of the QRS complex (i.e., the J or junctional point or wave) and ends with the first deflection of the T wave.[2,34] The T wave represents the most rapid period of ventricular repolarization, during which potassium briskly leaks out of the cell. It ends when the wave returns to the isoelectric baseline. The S-T segment and T wave should be examined for depression or elevation from the baseline, either of which may be associated with myocardial hypoxia, nonspecific electrolyte changes, or cardiac hypertrophy (Figure 202-18). The degree of ST deviation appears to vary cyclically with the R-R interval, and deviation increases with shorter preceding R-R intervals.[1] Abnormal deviations of the S-T segment are defined as a depression of 0.2 mV or elevation of 0.15 mV in leads II and III, or they are defined as a depression or elevation of 0.3 mV in lead V_4. A subjective appearance of a delayed return to baseline in the S-T segment (i.e., an S wave that has an oblique or curved terminal upstroke) is referred to as *S-T segment slurring* or *coving* (see Figure 202-18). Like S-T elevation or depression, S-T slurring most often suggests myocardial hypoxia, particularly when it is new (e.g., intraoperative ECG demonstrating its sudden onset). In a study comparing normal and sick cats, S-T changes were frequently reported in cats with identifiable cardiac disease. Abnormal S-T segments occurred in 70% of cats with congenital heart disease, in 43% to 47% of cats with cardiomyopathy, and only in 10% of normal cats.[40,41]

The T wave may be concordant or discordant in normal dogs, meaning that its polarity may be in the same direction or in the opposite direction, respectively, compared with the QRS complex. The polarity of the T wave depends on the direction of repolarization within the ventricular wall (from epicardium to endocardium, or vice versa) and is of no known clinical importance in small animals at this time. In healthy human beings, the QRS complex and T wave are usually concordant, and this important interspecies difference has led physicians and nurses to misinterpret canine ECGs with QRS-T discordance as abnormal (because QRS-T discordance is sometimes a feature of myocardial infarction in people). Normally the T wave is positive in lead V_2 and negative in V_{10} or else RV hypertrophy is suggested (exception: Chihuahua). If the amplitude of the T wave is greater than 25% of that of the R wave (Q wave if it is deeper), LV enlargement may be suspected. These links between T wave morphology and cardiac structure appear to be fairly insensitive and nonspecific, and their utility has been essentially replaced by echocardiography.

Figure 202-18 ST segment changes in two cats. *Upper panel*, ST segment depression. The two arrows should completely overlap. ST segment coving, or slurring, also is present (50 mm/sec, 2 cm = 1 mV). *Lower panel*, ST segment elevation. The height of the ST segment *(small arrow)* should be the same as the baseline *(large arrow)*. Lead II, 25 mm/sec, 1 cm = 0.5 mV.



202.3.1 Technical Aspects of the Electrocardiograph

Techniques for obtaining the ECG are discussed in Chapter 90. By convention, paper speed is 50 mm/sec in small animals, although the paper speed commonly used in human cardiology, 25 mm/sec, may be used in veterinary medicine if the heart rate is 120 bpm or lower. The usual amplitude setting is 1 cm = 1 mV, and this is halved or doubled if the patient's tracing shows unusually large or small deflections, respectively.

202.3.2 Evolution of the Electrocardiograph

At birth the MEA of the normal canine ECG is directed rightward, cranially, and ventrally. Over the first 3 months of life this orientation slowly changes in the normal dog to leftward, caudal, and ventrad. A similar pattern of evolution exists for kittens.[42] The criteria used for establishing a “normal” ECG are not the same for a dog less than 12 weeks of age as they are for an older dog.[43] In a study of normal dogs raised on regular or

calorie-restricted diets from adulthood until death, no changes were observed with advancing age on the annual ECGs of dogs in either group during the dogs' lifetimes.[44]

202.4 DIAGNOSTIC MANIPULATIONS WITH ELECTROCARDIOGRAPHY

202.4.1 Vagal Maneuver

Artificially increasing a patient's vagal tone has potential value both diagnostically and therapeutically. Diagnostically, slowing the heart rate and increasing AV nodal refractoriness through vagal maneuvers may slow a rapid tachycardia, allowing some of its features to be more apparent and facilitating the ECG diagnosis (Figure 202-19). Therapeutically, an increase in vagal tone that interrupts macro re-entrant circuits can briefly reduce an excessively high ventricular rate through AV block (as described for atrial flutter later in the chapter) or can terminate such arrhythmias as AV nodal re-entrant tachycardia and orthodromic AV reciprocating tachycardia (see Pre-Excitation Syndromes, following).

Carotid sinus massage (gentle, sustained compression of the carotid sinuses, located just caudal to the dorsal aspect of the larynx, often to the point of eliciting a gag reflex) can be applied for 5 to 10 seconds and should be tolerated by the patient (signs of discomfort, resentment, or a marked change in heart rate warrant immediate termination of the vagal maneuver). Because dogs and cats very rarely suffer from carotid artery atherosclerosis, concern for thromboembolic consequences of carotid sinus massage as expressed in human cardiology is unlikely to be relevant to small animal practice. Ocular pressure over closed eyelids is another form of vagal maneuver, but it is contraindicated in patients with ocular problems and subjectively appears to be less effective than carotid sinus massage.

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Figure 202-19 Atrial flutter. The diagnosis of atrial flutter is made easier by the initiation of carotid sinus massage *(arrow)*. This vagal maneuver was applied because this dog had a persistently high heart rate in the absence of an identifiable cause (320 beats per minute [bpm], first part of tracing). Carotid sinus massage induces second-degree AV block beginning after the ninth QRS complex *(small asterisk)*. As a result the flutter waves *(F)* are seen more distinctly as separate from the T waves and QRS complexes. Two premature ventricular complexes (PVCs) also are seen in the middle of the tracing. After the AV node has increased in refractoriness, the flutter waves *(F)* are much more clearly seen as distinct from the QRS complexes and T waves and are always evenly spaced, even when buried in a QRS complex *(small arrow)*. Lead aVF, 25 mm/sec, 1 cm = 1 mV.

202.4.2 Atropine Response Test

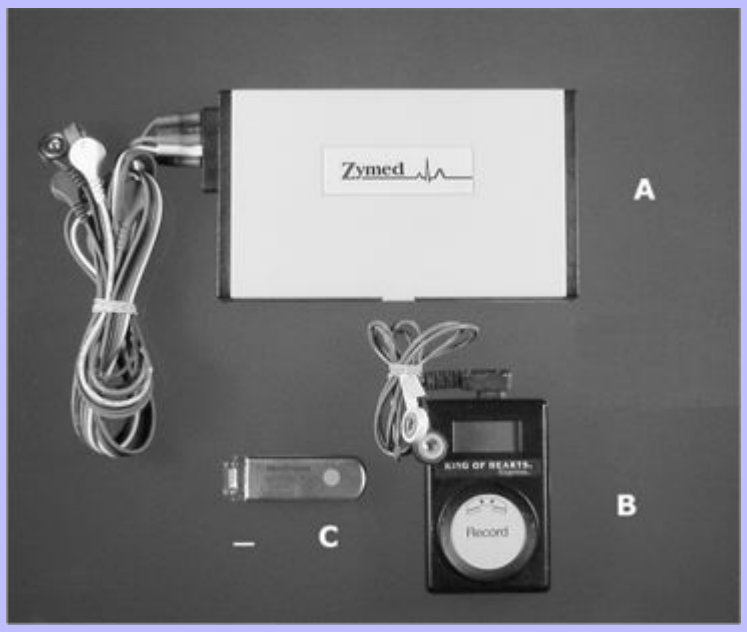
Administration of atropine sulfate 0.02 mg/lb (0.04 mg/kg) intravenously can be used diagnostically to evaluate bradycardias.[3] It allows the differentiation between bradycardias purely of vagal origin (atropine increases the heart rate) and bradycardias caused by intrinsic disturbances of impulse formation or conduction (atropine has no effect). The response occurs within seconds to minutes (always within 15 minutes) after injection.[3] Unfortunately, a positive response to atropine is poorly predictive of response to oral vagolytic drugs such as propantheline bromide in dogs with sick sinus syndrome (SSS).

202.5 AMBULATORY ELECTROCARDIOGRAPHY

In a patient with clinical signs caused by an intermittent cardiac arrhythmia, an ECG performed in the veterinary hospital may or may not be abnormal. Ambulatory ECG offers the possibility of correlating the ECG to the overt clinical manifestations observed by the owner. As a result, ambulatory ECG is valuable for evaluation of patients with episodic clinical signs because it can either rule in an arrhythmic problem (arrhythmia is diagnosed) or rule it out (normal rhythm occurs throughout the episode).[23–25,45–48]

Three types of ambulatory ECG monitors are available (Figure 202-20). Dr. Norman Holter developed the continuous monitor that now bears his name in the 1950s, when the earliest models weighed some 80 lbs (36 kg). Currently, Holter monitors are approximately the size and weight of a VHS videocassette, and they record the ECG continuously for 24 or 48 hours, usually on multiple leads simultaneously.[49,50] An audiocassette inside the monitor typically is used for storing the information during the recording period and must be decoded afterwards in an analyzer machine. Veterinarians can rent Holter monitors from various suppliers, including such on-line sources as www.labcorp.com, www.vetheart.com, www.idexx.com, and www.pdsheart.com. Holter monitor leads are placed on dogs as shown in Figure 202-21. Owners need to maintain a diary of the patient's activities—and lack thereof—during the entire monitoring period to provide a context for analysis of the tracing. For example, a heart rate of 40 bpm may not be unusual for a sleeping dog, but it would be an important finding if it occurred during brisk exercise. A veterinary patient's Holter report, if produced through human cardiology software, should be reviewed carefully.[49] Over-and underinterpretation are common, because software for automated Holter analysis is designed only for human ECGs at this time. Common sources of error from human Holter interpretation programs include inaccurate heart rate counting (undercounting QRS complexes that are too small during body movement or overcounting such as interpreting T waves as QRS complexes) and inaccurate arrhythmia diagnosis (over-or underinterpretation). It remains the veterinarian's obligation to assess the abnormal ECG segments shown in the Holter report and to decide whether the interpretation correlates well with the rest of the patient's information. Continuous in-hospital monitoring systems similarly allow long-term cardiac rhythm monitoring and manual analysis of tracings, and they offer the advantage of immediately displaying ECG information during patient observation and treatment.

Figure 202-20 Ambulatory heart monitors. **A,** 24-hour (Holter) monitor. **B,** External event monitor. **C,** Implantable event monitor. Scale: white bar = 1 cm.



The second and third types of ambulatory ECG monitors are event monitors (see Figure 202-20). They continuously receive ECG information into a loop memory system, which can usually only retain the information temporarily. When an episode of clinical signs is observed, however, the owner needs to trigger the event monitor. Doing so saves an exact segment of ECG information in the monitor's permanent memory. Several episodes can thus be recorded over a number of days and then decoded either at the veterinary hospital or transtelephonically. Event monitors usually record only one lead, although newer models may record two leads. The difference between the two types of event monitors is that one is external, whereas the other is implanted subcutaneously. External event monitors are approximately the size of a deck of cards and require standard commercial (e.g., AA) batteries that provide 5 to 7 days of monitoring time.[47,48] If the batteries run out, all acquired episodes are deleted. External event monitors are connected to patients using two or three wires attached to cutaneous ECG patches, one on each side of the chest over the heart (modified precordial lead). The memory capacity of external event monitors ranges from 5 to 18 minutes, and the monitors are programmed beforehand to save a selected amount of ECG information (e.g., 45 seconds preceding the push of the button and 15 seconds after it for each triggered episode). They are available for use from various sources, including many of those listed previously for Holter monitors. Internal event monitors are implanted subcutaneously.[51,52] They measure 0.5×2×7 cm, about the size of a man's thumb, have a battery life of 1 year or more, and have a memory capacity of about 1 hour of ECG recording. The information they capture is retrieved after the episode is over, using a handheld unit placed over the area of skin where the monitor is located. The use of both types of event monitors is of proven diagnostic value in humans; both external, and to a much lesser extent so far, internal, monitors are in use in small animal patients.[23–25,47,48,51–53]

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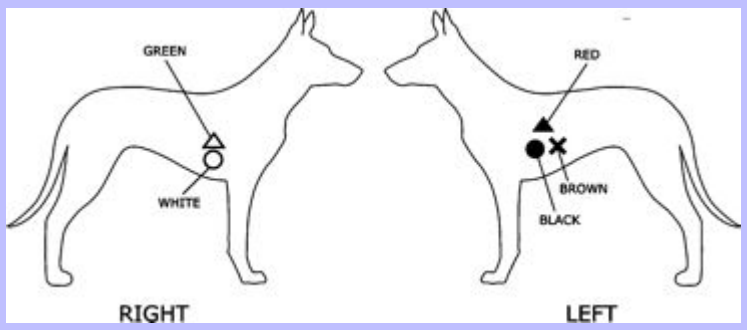
Figure 202-21 Electrode patch placement for Holter monitor. Colors correspond to the colors of the connecting tips on the ends of the Holter monitor wires.



Each form of ambulatory ECG monitoring has its relative merits.[47] Holter monitors are superior for screening the number of abnormal heartbeats on the ECG in a fixed 24-or 48-hour period, such as for assessing boxers for familial arrhythmic heart disease or for the evaluation of animals receiving systemic experimental drugs.[23,25,39,45,54] Holter monitors are also superior for therapeutic monitoring of antiarrhythmic drug effects[46] and recently have been shown to provide predictive information regarding the future development of dilated cardiomyopathy in Doberman pinschers, often before the earliest echocardiographic changes.[55,56] Conversely, external event monitors also have a number of advantages: they are smaller and lighter (3.5 oz [100 g], compared with 14 oz [400 g] for a Holter monitor), making them practical for cats and small dogs; they have a longer memory (up to 1 week), which is useful for episodes occurring less frequently; they eliminate some uncertainty of interpretation by directly associating the ECG information with an observed event; and they can transmit information transtelephonically, allowing the monitor to be reset and a new monitoring period to begin without a return visit to the hospital. Both Holter and external event monitors are costly electronic devices carried by patients that can damage them, and owners must be instructed to avoid their pets' exposure to moisture, extremes of temperature, and rough handling of the monitors.

202.6 CLASSIFICATION OF CARDIAC RHYTHM DISTURBANCES

A useful and practical classification scheme is one that separates cardiac arrhythmias into three groups: (1) disturbances of impulse formation (cardiac excitability), (2) disturbances of impulse transmission (cardiac conduction), and (3) complex disturbances involving abnormalities both of excitation and conduction. Some rhythm disturbances fit poorly into any category. Some disturbances of cardiac excitability are secondary to conduction disturbances (e.g., junctional or ventricular escape rhythms). Disturbances are listed according to the anatomic level of their origin (i.e., atrial, junctional, or ventricular).

Excitation disturbances can cause either excessive or inadequate contraction of the heart or its parts. Increased excitability produces extrasystoles (if intermittent) and tachycardia (if sustained). *Ectopy* is the term that describes spontaneous production of impulses anywhere in the heart. Decreased excitability leads to loss of impulse formation with electrical quiescence, resulting in bradycardia or asystole.

Conduction disturbances within the heart are all called *blocks*. Their categorization depends on the anatomic location of the block and its extent or degree. *First-degree block* refers to a slowing of conduction, *second-degree block* implies complete but intermittent interruption, and *third-degree block* involves complete and sustained interruption of conduction. Block can occur at the SA node (rarely identified), the AV node, or in branches of the His bundle (BBBs).

Finally, two disturbances combining excitability and conduction abnormalities are discussed. In pre-excitation, accessory conduction pathways bypass part of the normal A-V conduction pathway. Sick sinus syndrome (SSS) generally involves periods of bradycardia and tachycardia caused by dysfunction of the sinus node and supraventricular and ventricular conductive tissues.

202.6.1 Clinical Impact of Rhythm Disturbances

The rhythm disturbances mentioned previously do not all carry the same clinical importance. Furthermore, interspecies differences are marked. Some are commonly encountered, whereas others are extremely rare. Their clinical impact may range from harmless (some are benign variations of normal) to severely detrimental (potentially life-threatening arrhythmias). In cats, pre-excitation and isorhythmic AV dissociation have been associated with feline cardiomyopathies. In the dog, disturbances of excitability, especially extrasystoles and AFib, are more common than are disturbances of conduction, the majority of which are AV blocks.[1,2,57]

The hemodynamic consequences of cardiac arrhythmias depend on at least eight factors: (1) the ventricular rate, (2) the duration of the abnormal rhythm, (3) the temporal relationship between the atria and ventricles, (4) the sequence of ventricular activation, (5) inherent myocardial and valvular function, (6) cycle length irregularity, (7) drug therapy, and (8) extracardiac influences.[1–3] Ultimately, the sum of these factors—not just the appearance of the ECG—determines the impact of the arrhythmia on the patient. This is the reason that some animals with ventricular tachycardia (VT) are asymptomatic, whereas others are moribund.

202.6.2 Identification of Rhythm Disturbances

Today most clinical electrocardiography in veterinary medicine relies on single-lead, in-hospital ECGs. Multilead ECGs provide an additional level of information that is sometimes indispensable (see Figure 202-10). Ambulatory ECG is an effective and increasingly popular method for detecting intermittent rhythm disturbances or identifying the frequency of arrhythmias over a period of time (see previous discussion).

Rhythm disturbances are identified on the ECG using a methodical four-point examination. First, a rapid, cursory evaluation from left to right of the entire tracing gives a general idea of the cardiac rhythm and an initial diagnostic orientation. This step reveals whether a single rhythm or many rhythms exist. (Are all QRS complexes of the same morphology? Are the R-R intervals the same, or do they vary? If so, does the variation occur in a predictable manner?) One grossly assesses the heart rate (slow, normal, or fast), whether the rhythm is regular or irregular, and detects premature or delayed complexes.

Second, the R-R intervals are evaluated in representative sections of the entire tracing (Figure 202-22). In cats, variability of the R-R interval is not normally seen and is considered pathologic.[58] In dogs, a cyclical (i.e., rhythmic, patterned) variation of the R-R interval, respiratory sinus arrhythmia (RSA), is normal (see Figures 202-12 and 202-22). Irregularly irregular R-R variations are always abnormal in both species (see Figure 202-22).

Figure 202-22 Approach to the recognition of cardiac rhythm disturbances.

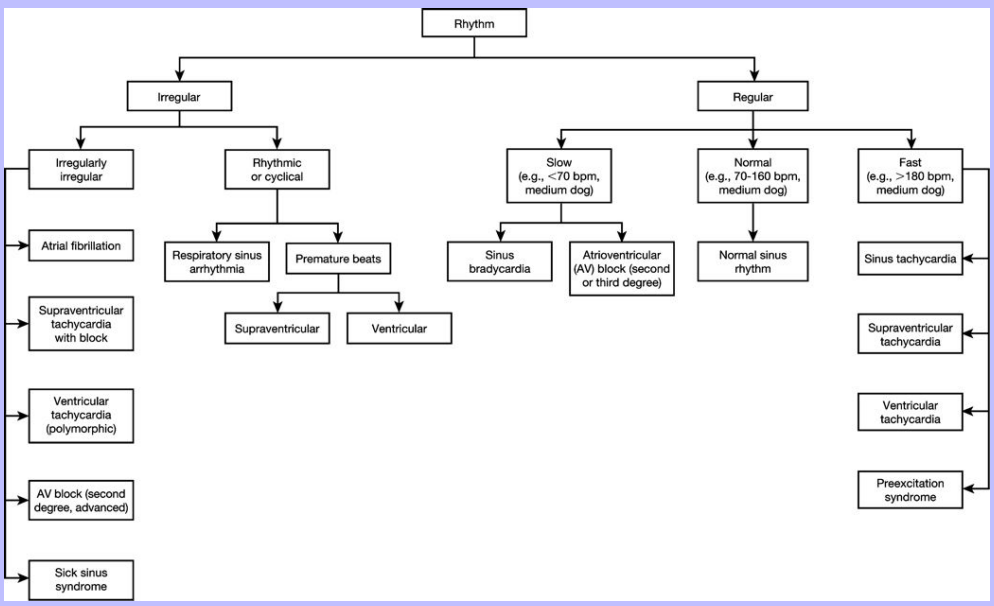


Figure 202-23 Artifact producing a wide, bizarre deflection in a dog. This is not an abnormal depolarization of the ventricles because the T wave is normal. Abnormal depolarization would invariably be followed by different or "abnormal" waves of repolarization (see Figures 202-32, 202-33, 202-35, and 202-36). Lead V_2, 25 mm/sec, 1 cm = 1 mV.

Third, the examination of individual QRS complexes consists of determining whether they are narrow or wide. Narrow QRSs generally identify ventricular depolarization of supraventricular origin (e.g., Figure 202-16). Wide QRSs represent the asynchronous depolarization of the two ventricles, which may be due to the ventricular origin of a depolarization, to BBB, or to pre-excitation (see following). Because repolarization follows directly in the wake of the wave of depolarization, then a QRS complex of abnormal shape should also have a T wave of abnormal or different shape. If the T wave is normal, the possibility of artifact, rather than a truly abnormal QRS, should be considered (Figure 202-23).

Fourth, examination of the P waves (present, absent; positive, negative; see Figure 202-13) provides information on the depolarization of the atria. Examination of the PR interval (1) determines if a P wave exists for every QRS complex and a QRS complex for every P wave (to assess A-V synchrony) and (2) assesses AV nodal conduction (PR interval duration) (see Figure 202-2).

Finally, the basic underlying rhythm and any additional or secondary rhythms that are superimposed are identified. Normally a P wave exists for every QRS complex (an atrial depolarization for every ventricular depolarization). Abnormalities causing more than one P wave for each QRS complex include second-and third-degree AV blocks, and abnormalities producing QRS complexes without P waves include ventricular arrhythmias, AFib, and atrial standstill.

202.6.3 Disturbances of Excitability

An important subdivision involves classifying disturbances of excitability broadly as disturbances of supraventricular excitability,[59,60] including STach, atrial extrasystoles (premature atrial complexes [PACs]), atrial tachycardias, atrial flutter, and AFib; or as disturbances of ventricular excitability, including ventricular extrasystoles (PVCs, VPCs), VT, TdP, ventricular flutter, and VF. The inciting factors that produce the arrhythmias in these two subgroups are often specific to the subgroup, and antiarrhythmic treatment is also sharply different between the two subgroups.

202.6.3.1 Disturbances and Alterations of Sinus Excitability

These arrhythmias are variations of sinus rhythm (see Figure 202-16), and are most commonly linked to normal, autonomic inputs. They may sometimes be abnormal and then are potentially detrimental. For example, STach is a normal and appropriate physiologic phenomenon during exercise, but it is commonly encountered in heart failure where, pathologically, it occurs even at rest.

202.6.3.1.1 Respiratory (normal) sinus arrhythmia (RSA)

In the dog the balance between the sympathetic and parasympathetic inputs to the heart generally tilts in favor of the parasympathetic system. This characteristic is in contrast to the average adult human or cat. This vagal predominance in the dog produces two particular features of sinus rhythm on the canine ECG: (1) RSA and (2) wandering pacemaker (WP).

RSA is the result of vagal effects that occur within the thorax during each respiratory cycle (see Figure 202-12). In dogs it is a normal physiologic phenomenon requiring no treatment. The result is a correlation between heart rate and respiratory rate, with slowing of the heart rate during expiration and acceleration of the heart rate during inspiration. The repeating cyclic nature of this arrhythmia is its hallmark. RSA is first noted in the puppy after 4 weeks of age,[1] generally disappears when the heart rate exceeds 150 bpm,[1,2] and often is enhanced when severe dyspnea is present (pneumothorax, fibrosis, emphysema) due to exaggerated changes in intrathoracic pressure.[1] Interestingly, the presence of RSA may constitute a valuable diagnostic clue in a common clinical situation, namely in the coughing, small-to medium-breed adult dog. It is common for these dogs to have concurrent mitral valvular heart disease (typical murmur is auscultated) and a primary respiratory disorder such as collapsing trachea or chronic bronchitis. It may be difficult to pinpoint whether congestive heart failure (CHF) or a primary respiratory problem is responsible for the animal's cough, yet the need for immediate and long-term

treatment and the prognosis both depend on knowing which disease process is the cause of the cough. The presence of RSA makes decompensated mitral valvular disease as the sole cause of the cough highly unlikely, because the cardiogenic pulmonary edema of CHF would almost invariably bring on increased sympathetic tone and loss of RSA. In cats in the hospital setting, RSA generally is considered pathologic.[58]

In the treatment of CHF with tachycardia (sinus or other supraventricular), successful digitalization may bring about the reappearance of RSA. This return of RSA is due to the reactivation of baroreceptors, which had been downregulated ("exhausted") by the ongoing sympathetic stimulation of heart failure.

202.6.3.1.2

Wandering pacemaker

WP is a normal, physiologic phenomenon in dogs that is not associated with pathologic conditions and requires no treatment (see Figure 202-12). In the dog the origin of depolarization in the heart is not fixed but may move within the RA, between the SA node and the AV node. On the ECG the result is variation in the P wave amplitude, with QRS complexes that retain a normal, supraventricular appearance. This variability in the P wave is often cyclic and often associated with RSA (see Figure 202-12). In this situation the amplitude of the P wave increases with an increased heart rate (inspiration) and decreases with decreased heart rate (expiration), sometimes to the point of disappearance (isoelectric P wave) or, rarely, negativity in leads II, III, and aVF.[1,2] The ECG differential diagnosis for WP includes morphologic abnormalities (e.g., P pulmonale) and supraventricular extrasystoles. In some individuals with marked resting vagal tone (e.g., brachycephalic dogs), an exaggerated but normal RSA and WP may be difficult to distinguish from a pathologic arrhythmia, namely PACs (supraventricular extrasystoles). Both PACs and the combination of WP and RSA produce a P wave of different morphology, a shorter R-R interval, and QRS complexes of normal morphology. Differentiation rests on the degree of prematurity (WP and RSA should not occur so prematurely as to produce a P wave inside the preceding T wave), and the appearance of a series or "paroxysm" of such beats closely coupled to each other (corresponding to multiple supraventricular extrasystoles [i.e., supraventricular tachycardia], not RSA). If neither characteristic is apparent, a Holter monitor can be used for assessing a large number of heartbeats (see previous discussion), or an atropine response test (see previous discussion) can be performed to abolish the vagal effect and seek out persistently premature heartbeats with a different P wave morphology and normal QRS complexes (i.e., PACs, in the absence of vagal tone).

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Figure 202-24 Sinus bradycardia (SB) in a dog. The heart rate is 50/min. Lead II, 25 mm/sec, 1 cm = 1 mV.

202.6.3.1.3

Sinus bradycardia

Sinus bradycardia (SB) is a sinus rhythm in which the heart rate is abnormally low (see Boxes 202-1 and 202-2; Figure 202-24). A 1:1 ratio of normal-appearing QRS complexes and P waves exists. Although some approximate normal ranges of heart rate exist for dogs and cats (see Boxes 202-1 and 202-2), the notion of bradycardia varies according to species, body weight, age, and breed, with larger, older, or brachycephalic dogs tending to have slower heart rates than average, and cats having normal heart rates that are markedly influenced by environmental stimuli.

SB generally indicates the physiologic (e.g., brachycephalic, athletic individual) or pathologic (e.g., systemic intoxication) predominance of the parasympathetic system. A diagnostic aid is the response to an intravenous injection of atropine (see previous discussion).[61] In general, only severe bradycardias directly linked to overt clinical signs (syncope, malaise, seizures) warrant specific treatment with drugs or pacemaker implantation, and SB is rarely the primary cause of such clinical manifestations. One exception is the instantaneous transition from a tachycardia to SB (or other bradycardia [e.g., ventricular escape rhythm]; see following) in a debilitated, unstable, often unconscious patient. Such a rapid change may herald an upcoming cardiac arrest and should be addressed with assessment of the patient for underlying causes and preparation for cardiopulmonary resuscitation.[62] (Antiarrhythmic drugs to consider: none; parasympatholytics; sympathomimetics; rarely pacemaker.)

202.6.3.1.4

Sinus tachycardia

STach is a sinus rhythm that occurs at an elevated rate (see Boxes 202-1 and 202-2; Figure 202-25). The wide range of resting heart rates in normal cats and dogs makes the cut-off between NSR and STach an approximate one. In dogs, STach exists when the increase in heart rate (P-QRS-T complexes of normal sinus origin) gives rise to the loss of RSA, the latter being a normal physiologic phenomenon in the dog (see previous discussion; see also Figure 202-12). Diagnosing this arrhythmia on the ECG can be difficult when the heart rate is extremely elevated, causing T and P waves to blend together. Carotid sinus massage, which temporarily slows the heart rate, separates the P and T waves, and clarifies that the tachycardia is of sinus origin (see previous discussion).

Figure 202-25 Sinus tachycardia (STach). The heart rate is 200/min in this dog with chocolate (theobromine) toxicity. Lead II, 25 mm/sec, 1 cm = 1 mV.

The causes of STach are diverse and are all marked by sympathetic predominance over parasympathetic inputs. Treatment of this arrhythmia is therefore aimed at the underlying cause when one exists. To slow a STach is only indicated if the tachycardia itself is producing clinical signs and is poorly controlled with treatment of the underlying disorder. For example, in hyperthyroidism, a beta-blocker may be given concurrently with antithyroid treatment. (Antiarrhythmic drugs to consider: class II.)

202.6.3.2 Disturbances of Atrial Excitability

Disturbances of atrial excitability are common, especially in the dog. Indeed, in the most common forms of heart disease in dogs (endocardiosis, cardiomyopathy, many congenital malformations), atrial distension leads to pathologic disorganization of the atrial tissue, which can then generate atrial hyperexcitability (and possibly conduction disturbances as well).

202.6.3.2.1 Atrial extrasystoles

Atrial extrasystoles (synonyms: PACs or premature atrial contractions, atrial premature complexes or contractions (APCs), atrial premature depolarizations) are premature depolarizations that originate in an ectopic atrial focus (Figure 202-26). Identification of atrial extrasystoles is based on a combination of two or more of the following five abnormalities but always must include the first two points: (1) prematurity of the P-QRS-T sequence; (2) QRS complexes that have a supraventricular appearance, in that they are narrow and comparable in shape to the sinus QRS complexes (rarely, QRS complexes may be absent or widened in cases of atrial extrasystoles that are exceptionally early and thus occur during the total or partial refractory period, respectively); (3) a P wave of different amplitude than sinus P waves, including negative, biphasic, or positive P waves, but always preceding the QRS complexes; (4) a P-R interval that is often different from the sinus PR interval, be it shorter or longer,[2] and (5) a postextrasystolic pause that most often is noncompensatory (Figure 202-27). The pathogenesis of atrial extrasystoles is most commonly related to a structural cardiac (atrial) lesion. Distension of the atria is the main cause of these ectopic foci, but atrial tumors (hemangiosarcoma), hyperthyroidism in the cat, digitalis toxicity, and other systemic disturbances also are recognized causes.[3] Clinical repercussions of atrial extrasystoles are minor, except in cases of multiple repeated bursts (Atrial Tachycardias, following), and the main interest in identifying atrial extrasystoles on an ECG is to add weight to a suspicion of atrial disease. Treatment for atrial extrasystoles is therefore first aimed at addressing the underlying cause rather than resorting to antiarrhythmic drugs specifically.

202.6.3.2.2 Atrial tachycardias

An atrial tachycardia (supraventricular tachycardia) is a series of atrial extrasystoles occurring at a rate greater than sinus rhythm (Figure 202-28). It may be intermittent or continuous, and the impulses may all be transmitted to the ventricles or AV block may be noted in some instances. The exact mechanism of atrial tachycardias can involve micro re-entry (intra-atrial re-entrant tachycardia) or spontaneous automaticity of an ectopic atrial focus (automatic atrial tachycardia).[59,63] Identifying intermittent atrial tachycardias is usually straightforward: the ECG shows a burst of atrial extrasystoles. Establishing a diagnosis of sustained atrial tachycardia may be difficult, however, because P waves may not be clearly evident, each one potentially being buried within the previous QRS complex. Differentiation between sustained atrial tachycardia and “high” ventricular (i.e., originating near the AV node) tachycardia can therefore be helped by exteriorizing the P waves, which can be elicited with a vagal maneuver (see

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previous discussion) and subsequent slowing of the tachycardia or even sinus capture (resumption of sinus rhythm). The same goal may also be reached pharmacologically using graded doses of such intravenous agents as propranolol, esmolol, edrophonium, or phenylephrine (Table 202-1). Intravenous adenosine used for this purpose subjectively appears to be much less effective in dogs than in humans. Causes for atrial tachycardias are the same as those listed for atrial extrasystoles (see previous discussion). The clinical impact of an atrial tachycardia depends on its duration, rate, and underlying cardiac lesions. Intermittent AV block can limit the ventricular rate and may lessen clinical impact in cases of rapid atrial tachycardias. Atrial tachycardias often precede the development of AFib. Treatment of the underlying disease is an essential part of managing these arrhythmias. (Antiarrhythmic drugs to consider: digoxin, class II, IV.)

Figure 202-26 Premature atrial complexes (PACs) in a dog. Two PACs are seen in the middle of this lead II strip; the first is more premature than the second one (25 mm/sec; 1 cm = 1 mV). Premature P waves *(arrows)* of a different morphology than the sinus P waves and QRS complexes of the same shape as sinus QRS complexes are noted.

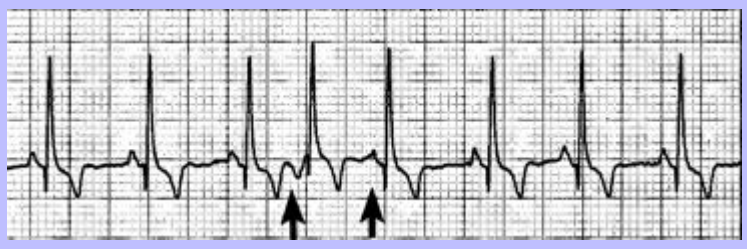

Figure 202-27 Schematic representations of normal sinus rhythm (NSR) and premature complexes. *NSR:* The heart rate remains constant, and the interval from P to P or from R to R does not change. *Resetting:* A premature atrial complex (PAC; beat 3) resets the sinus rhythm so that the period from the beginning of the premature P waves to the next normal P wave is equal to exactly one P-P interval. *Resetting with pause:* The PAC (beat 3) is followed by a pause greater than one P-P interval but less than two P-P intervals. Both resetting and resetting with pause are examples of noncompensatory pauses (the rhythm of the *SA* node is affected by the premature beat, which alters the SA node's ability to provide a normally-timed, “compensatory” beat after the premature beat). *Compensatory pause:* The premature ventricular complex (PVC, beat 3) is followed by a compensatory pause; that is, the period from the normal P wave in the beat preceding the PVC to the normal P wave of the beat after the PVC is equivalent to exactly two P-P intervals. The sinus P wave occurs on time, but it is not conducted through the atrioventricular (AV) node to the ventricles, which are in a refractory state due to the PVC. *Interpolation:* A PVC (beat 3) occurs between two normal sinus complexes without disrupting normal rhythm. Because of concealed conduction into the AV node, interpolated PVCs commonly delay AV nodal transmission of the next beat, which manifests as prolongation of the PR interval for the heartbeat that follows the interpolated PVC (see also Figure 202-32). This characteristic is useful for differentiating interpolated PVCs from motion artifact.

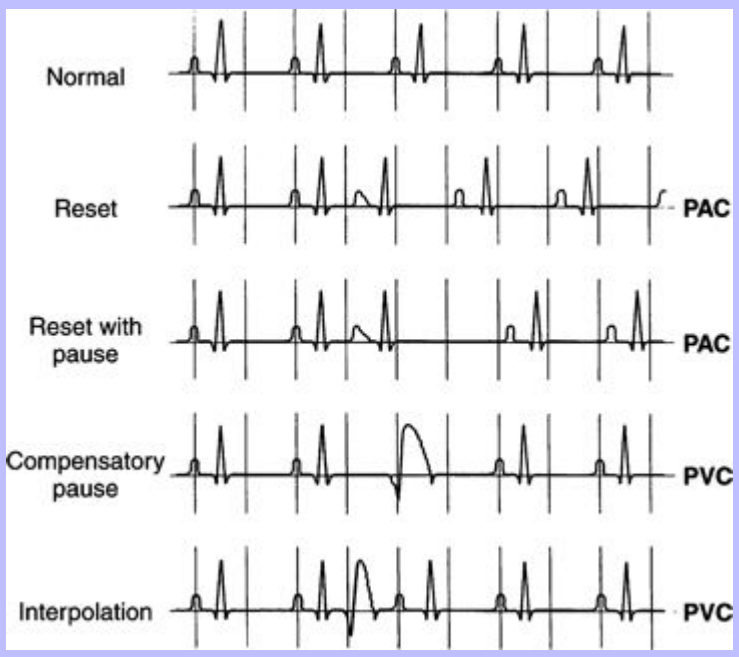

Figure 202-28 Supraventricular tachycardia. A burst of premature (rapid) QRS complexes is seen in the middle of the tracing. The QRS complexes are of the same shape as sinus QRS complexes. No clinical signs were present in this older Golden retriever dog, either at admission or during follow-up, and an echocardiogram was unremarkable. Lead II, 25 mm/sec, 1 cm = 1 mV.

202.6.3.2.3 Atrial flutter

Atrial flutter is characterized by a rapid and regular series of atrial depolarizations, without a rest phase between atrial depolarizations (see Figure 202-19). Identification of this arrhythmia is therefore based on the occurrence of (1) rapid, rhythmic waves of atrial electrical activity referred to as *flutter (F) waves*, usually occurring at a very high rate (often > 300/min); (2) absence of a return to baseline of the F waves (giving a "saw tooth" baseline appearance); (3) QRS complexes of a supraventricular appearance; and (4) a variable, irregularly irregular R-R interval. Atrial flutter is different from other atrial tachycardias in that no return to the isoelectric baseline occurs after each atrial depolarization in atrial flutter. This diagnosis may be very challenging when each flutter wave is transmitted through the AV node to the

ventricles. Such 1:1 conduction leaves the F waves buried in the preceding QRS complexes, which complicates the diagnosis (see Figure 202-19). Atrial flutter occurs as a result of a macro re-entrant circuit within one atrium—an abnormal, self-perpetuating cyclical electrical loop in the atrium in which an endless circle of electrical conduction can be initiated through atrial stretch, for example. Termination of atrial flutter can occur spontaneously, but treatment is necessary when a persistently high ventricular rate occurs. Treatment most commonly aims to control ventricular rate (see Atrial Fibrillation, following). Permanent abolition of atrial flutter is achieved with radiofrequency catheter-based interruption of the flutter circuit (see Radiofrequency Ablation, following).[59]

202.6.3.2.4

Atrial fibrillation

AFib is a common and important arrhythmia. It represents 14% of all canine arrhythmias, including a 50% incidence in cases of dilated cardiomyopathy in dogs, and it can bring on clinically overt hemodynamic changes requiring specific treatment.[64] A prevalence of AFib in up to 2% of the human population is estimated,[59,65,66] but a similar statistic is not available in veterinary medicine. AFib is characterized by complete electrical disorganization at the atrial level, leading to a chaotic, rapid series of atrial depolarizations (400 to 1200 per minute) (Figure 202-29). In AFib, the AV node acts as a "gatekeeper" for this chaotic electrical activity, allowing only those electrical depolarizations with optimal intensity, timing, and orientation to pass through to the ventricles and thus controlling the ventricular rate to some extent.

The three ECG characteristics of AFib are (1) supraventricular-appearing QRS complexes (narrow, upright, and of only slightly variable amplitude in lead II, unless ventricular aberrancy/BBBs are concurrent); (2) an irregularly irregular rhythm, with ventricular rates that may be low, normal, or most commonly without treatment, high; and (3) no visible P waves (replaced by a fine undulation of the isoelectric line, termed *f waves*). The absence of organized atrial depolarizations can have hemodynamic, and therefore clinical, consequences during physical activity or in patients with advanced stages of structural heart disease. During diastole, active filling is associated with the P wave (i.e., atrial contraction), which can account for up to 30% of total ventricular filling. Its absence therefore can reduce ventricular volume to suboptimal levels, producing overt clinical signs during exertion. Furthermore, the rapid overall ventricular rate, as well as the premature occurrence of some individual QRS complexes, bring about poor diastolic filling. For these reasons, some contractions may be ineffective intermittenly and one or more ausculted heartbeat, may be without a corresponding palpable arterial pulse (i.e., pulse deficit). AFib is one of the few arrhythmias that may be suspected from the moment of auscultation and palpation during the physical examination, based on the chaotic irregularity of the cardiac rhythm on auscultation and palpation of the chest, together with pulse deficits. Polymorphic VT and frequent PVCs, however, should be included in the differential diagnosis of this physical exam finding (see following). Counterintuitively, high vagal tone (e.g., from concurrent gastrointestinal [GI] disease) predisposes to AFib, because parasympathetic stimulation of atrial myocytes accelerates their repolarization in a heterogeneous fashion, which increases the likelihood of the initiation of arrhythmia.

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Table • 202-1 Drugs Used for the Treatment of Cardiac Arrhythmias

GENERIC NAME	TRADE NAME	ADMINISTRATION ROUTE	COMMON INDICATIONS	DOSE	COMMENTS
Adenosine	Adenocard	IV	Terminates acute paroxysmal supraventricular tachycardia	1.5–3.0 mg/dose; repeat in 1 min to maximum of 6–12 mg	Side effects: sinus arrest, sinus bradycardia (SB), and atrioventricular (AV) block; often ineffective in dogs and cats
Amiodarone	Cordarone	Oral	Recurrent ventricular fibrillation; recurrent hemodynamically unstable or malignant ventricular tachycardia (VT); atrial fibrillation (AFib)	4.5 mg/lb bid PO × 1 week, then 2.2–3.8 mg/lb PO sid; if IV, give in graded dose to 5 mg/lb; in sick dogs dose is unknown; serum levels is 1–2 µg/mL	Side effects include proarrhythmia, Coombs' positive test result, pulmonary fibrosis, hypothyroidism, liver necrosis, photosensitivity, and gastrointestinal (GI) toxicity
Atenolol	Tenormin	Oral	Same as propranolol	0.15–0.5 mg/lb bid in the dog; 0.5–1.4 mg/lb sid to bid in the cat	Weakness, depression, hypotension, bradycardia, inappetence
Atropine			1. Test responsiveness of sinus node	0.01–0.03 mg/lb IV	1. Do not use in states of heart failure
Tablets		Oral	2. Hyperactive carotid sinus reflex (SA arrest)		2. Do not administer when bronchial tree secretions a problem
Injectable		IV, IM, SQ	3. AV block (second and third degree)		

Digoxin	Lanoxin		1. Supraventricular premature contractions and tachyarrhythmias 2. Right heart failure 3. Pump dysfunction	0.22 mg/m2 bid PO as maintenance dose; doubledose initially first 24 h forrapid effect; lower dose in large (>30 lb) and giant breeds of dogs	1. Digitalize cautiously 2. Monitor with ECG3. All doses approximate and must be titrated based on patient response
Tablets	Cardoxin	Oral			
Elixir		Oral			
Injectable		IV		0.0312 mg per cat eod PO in cats—not for use in restrictive disease states	4. Side effects: malaise, anorexia, vomiting, diarrhea
Diltiazem	Cardizem (not sustained-release form)	Oral IV	Supraventricular tachyarrhythmias; feline hypertrophic cardiomyopathy used orally and chronically	0.2–0.7 mg/lb q8h PO in dogs 0.7 mg/lb q8h PO in cats IV: 0.02–0.03 mg/lb; repeat every 2 min to effect—max dose 2 mg/lb IV	Side effects include bradycardia, hypoten-sion, collapse, and severe weakness; if SUT is physiologic response to systemic problem, correct the problem first (or risk of cardiac arrest)
Esmolol	Brevibloc	IV	Supraventricular tachycardia	0.025–0.1 mg/lb/min (25–100 µg/lb/min) 0.05–0.22 mg/lb IV Effects occur within 2 min	Short-term IV agent; used to control ventricular rate while agents are given for long-term effects; used for AFib, atrial flutter, supraventricular tachycardia; side effect is rapid, severe hypotension; do not use in congestive heart failure (CHF) -compromised patient

Isoproterenol Injectable	Isuprel Injectable	IM, IV, SC	1. Advanced second-degree and third-degree heart block 2. SA arrest 3. SB (?)	For bradyarrhythmias: one 1-ml vial (0.2 mg) in 250 D5W IV to increase heart rate, use to effect (0.5–1 mL/min) 0.1–0.2 mg SQ or IM q4h for heart block (variable efficacy by these routes)	May be used on temporary basis parentally until conduction improves or pacemaker is implanted
Lidocaine 2% without epinephrine	Xylocaine	IV only	Ventricular tachyarrhythmias causing hemodynamic disturbances or malignant arrhythmias; do not use for occasional VPC or hemodynamically stable multiform beats	1. 1–2 mg/lb IV slow bolus over 2 min or until arrhythmia controlled 2. 1 mg/lb IV slowly, then 10–40 µ/lb/min continuous infusion or 1 mg up to 4 times over 5 minutes to effect 3. For cats, 0.25–0.5 mg/lbIV bolus, then 5–20 µ/lb/min (0.005–0.02 mg/lb/min) CRI	1. Reserve for serious arrhythmias 2. Toxicity includes convulsions and respiratory arrest 3. Single IV dose lasts 15–20 min only 4. Excretion is hepatic
Metoprolol	Lopressor Toprol XL	Oral	Hypertension, beta-blockade	0.2–0.5 mg/lb sid or divided in multiple doses bid-tid depending on product used	Used for hypertension, beta-blockade, CHF arrhythmias (both supraventricular and ventricular)
Mexiletine	Mexitil	Oral	Ventricular tachyarrhythmias	2–5 mg/lb q8-12h (dogs)	Few side effects; may be used with digoxin and class I and II antiarrhythmic agents; hepatic excretion

Phenytoin	Dilantin		1. Some ventricular tachyarrhythmias	7–14 mg/lb q8h orally 2.24–4.5 mg/lb IV	Infrequently used as an antiarrhythmic drug; hepatic excretion
Capsules		Oral	2. May be useful in treating arrhythmiascaused by digitalis overdose		
Injectable		IV			
Procainamide	Pronestyl		1. Ventricular premature contractions	1.3–10 mg/lb q2-6h (to 8hsustained release form)	1. IV effect is brief, and oral maintenance dose must be given q4h
Capsules	Pronestyl-SR		2. VT	2. Dogs: 1–10 mg/lb IV over 30 min, then infuse 10–20 µg/lb/min (0.01–0.02 mg/lb/min) CRI	2. Oral forms available in sustained release tablets may not be absorbed
Tablets	Procan SR	Oral		3. Cats: 0.5–1.0 mg/lb IV bolus, then 5–10 µg/lb/min CRI	3. Hepatic excretion
	Injectable	IV			
Propafenone	Rhythmol	Oral	(a) Supraventricular tachyarrhythmias	Unknown; begin in medium-to large-size dogs with 75–125 mg orally tid	May be proarrhythmic with structural heart disease; do not use if Q-T is prolonged
		IV (?)	(b) Accessory conduction arrhythmias		
			(c) VT		
Propranolol	Inderal		1. Supraventricular tachyarrhythmias	Oral: general 0.2–0.5 mg/lb q8h: 2.5–20 mg q8-12h small dogs; 10–40 mg q8-12h medium and large dogs; 40–80 mg q8-12h large and giant dogs; 2.5 mg q12-24h cats; 0.1–0.5 mg IV no more frequently than q1-3 min to 5 mg maximum; administer until rate slows or toxicity occurs Cats: 0.1-0.5 mg IV boluses, 2.5–5 mg/cat PO sid-bid	1. Use with caution: as a negative inotropic agent, it may induce CHF
Tablets		Oral	2. To slow ventricular rate in atrial fibrillation or to distinguish the latter from VT		2. Excessive dose causes reduction in cardiac rate and prolongation of PR and QT intervals
Injectable		IV	3. Arrhythmias of digitalis intoxication		
			4. Pre-excitation syndromes		
			5. Some ventricular arrhythmias, when other agents fail		

1. Quinidine sulfate (tablets)	Quinidinesulfate	Oral	1. Ventricular premature contractions 2. VT	3–10 mg/lb (of base) IM or PO q6-8h; may be given q2h until loading dose controls arrhythmia or induces toxicity	1. Do not use in presence of CHF unless this is being treated simultaneously
2. Gluconate (long-acting tablets)		Oral	Sustained release forms given 8.8–12h PO		2. Toxicity results in increased heart rate and prolongation of the PR, QRS, and QT intervals
3. Gluconate (injection)		IM		3–10 mg/lb (of base) q2-4h IM, PO; sustained-release forms: 4–10 mg/lb PO q8h	3. Often effective in lower doses when used with procainamide, mexiletine, or a beta-blocking agent 4. Hepatic excretion 5. IV use may cause hypotension 6. Injectable product is not used IV—only IM (epaxial) 7. Competitive with digoxin; do not use together
Sotalol	Betapace	Oral	Class II and III for ventricular arrhythmias	Canine: 0.44–2.8 mg/lb bid-tid Feline: 10–20 mg/cat bid	GI disturbances; hepatotoxicity; decreased HR; P-R prolongation
Tocainide	Tonocard	Oral	Ventricular tachyarrhythmias	7–11 mg/lb q8-12h (dogs)	May need to use with other class Ia antiarrhythmic agents for better effect; hepatic excretion

Verapamil	Isoptin	Oral IV	Supraventricular tachycardia	Oral: 0.2–1.0 mg/lb bid-tid IV: 0.01 mg/lb IV to maximum of 0.07 mg/lb	Side effects: weakness, collapse, bradycardia; contraindicated in shock, heart block, sick sinus syndrome (SSS), CHF, VT

Figure 202-29 Atrial fibrillation (AFib). The irregularity of the rhythm is less apparent when the ventricular rate is fast, as when this dog with dilated cardiomyopathy and congestive heart failure (CHF) was first evaluated (*left panel,* ventricular rate = 280/min). Diuretics, digoxin, and eventually beta-blocking therapy led to good rate control and a clearer electrocardiogram (ECG) diagnosis (*right panel,* ventricular rate = 135/min). Lead II, 25 mm/sec, 1 cm = 1 mV.

A major diagnostic impostor on ECG is the combination of AFib and BBB (Figure 202-30), which produces wide QRS complexes and therefore can appear to mimic VT, but without P waves to conclusively indicate AV association (BBB) or dissociation (VT). In such a situation, a vagal maneuver can be performed, and its effect on the AV node could reduce the ventricular rate with AFib + right bundle branch block (RBBB) but not with VT. In addition, sustained, monomorphic VT is generally characterized by regular R-R intervals, whereas AFib with BBB is not.

Table • 202-2 Comparison of Ectopic Beats of Supraventricular or Ventricular Origin

FEATURE	SUPRAVENTRICULAR	VENTRICULAR
Wide, bizarre QRS complexes	Very rare	Common
QRS complex shape	Same as sinus QRS	>10% different from sinus QRS
P wave for every QRS	Yes; often of different shape	No; Ps occur regularly throughout tracing, but independently of QRSs
T wave	Same as sinus T wave	Different from sinus T wave
Postextrasystolic pause (see Figure 202-27)	Usually noncompensatory	Usually compensatory
QRS fusion beats as hallmark	No	Yes
Positive response to vagal maneuver	Possible	Virtually never

Figure 202-30 Atrial fibrillation (AFib) with right bundle branch block (RBBB). This impostor for ventricular arrhythmia is distinctive in its irregular R-R interval and its response to vagal maneuvers. Lead II, 25 mm/sec, 1 cm = 1 mV.

AFib in dogs most often is caused by primary, underlying cardiac disease. However, AFib may also occur in individuals with structurally normal hearts (e.g., anesthesia, hypothyroidism, rapid, large-volume pericardiocentesis, GI disease, volume overload causing atrial stretch) if those hearts contain sufficient atrial myocardial mass to permit fibrillation (i.e., medium to large breed dogs).[67] In giant breed dogs, particularly the Irish wolfhound, AFib commonly occurs in otherwise healthy dogs with grossly normal atria (i.e., lone AFib).[67,68] It remains to be determined whether those patients with AFib and structurally normal hearts that progress to dilated cardiomyopathy do so because of their arrhythmia, or whether, conversely, AFib is only the arrhythmic prelude to a disease that later causes dilation and systolic dysfunction.

In cats, AFib occurs uncommonly and is virtually always associated with structural heart disease causing atrial enlargement.[69] Most cats have clinical signs suggesting heart failure (e.g., dyspnea) or thromboembolism at the time of diagnosis of AFib, but 20% to 25% of cases of AFib in cats are discovered incidentally (e.g., during a routine annual examination) and as such, this arrhythmia may be an early manifestation of heart disease in some cats. AFib does not clearly influence survival negatively in cats compared with the prognosis associated with the underlying heart diseases proper. In a subgroup of 24 cats with AFib and known survival statistics, 21% lived between 6 and 12 months after the diagnosis of AFib and 33% survived 1 year or more.[69]

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AFib usually is a persistent, permanent arrhythmia. It does occur paroxysmally in the dog[70] and very rarely so in the cat. Paroxysmal AFib usually is of short duration and in most cases progresses to persistent AFib because of severe underlying cardiac disease (usually atrial enlargement).

In most cases of AFib, two goals of treatment exist: (1) managing the underlying heart disease and (2) maximizing cardiac output by controlling (slowing) the rate of conduction through the AV node if needed (see Figures 202-29 and 202-31). The approach of letting the atria fibrillate and concentrating on ventricular rate control, rather than attempting to convert the AFib to sinus rhythm, was recently supported by the results of a prospective study of 4000 human AFib patients. It was found that converting the AFib back to sinus rhythm brought no significant benefit in terms of survival, and that conversion carried a higher risk of adverse effects.[71] As a rule, beta-blockers, calcium channel blockers, or both are given in low initial doses and up-titrated to effect, typically over a period of days to a few weeks, based on heart rate. Subsequently, even once an acceptable range of heart rates has been reached, periodic drug dose adjustments (e.g., re-evaluation every 3 to 6 months, sooner if problems occur) are usually necessary to maintain good rate control.

In small animal medicine, the ideal ventricular rate varies for each patient depending on many factors, including stage of CHF and body weight. One substantiated guideline suggests a target ventricular rate for dogs with AFib weighing 20 to 25 kg of approximately 130 to 145 bpm.[72] A recent study compared ventricular rates in canine AFib obtained on careful physical examination by trained persons including cardiologists to the rate obtained simultaneously by ECG. The level of accuracy ranged from 64% to as low as 12% for veterinary students and some veterinarians.[73] Follow-up monitoring of ventricular rate control relies on repeated ECGs rather than physical exams alone. (Antiarrhythmic drugs to consider: digoxin; class II or class IV agents; combination therapy is often most successful and produces fewer adverse effects than high doses of a single drug.)

202.6.3.3 Disturbances of Ventricular Excitability

Disturbances of ventricular excitability are important because they involve the main element in the cardiac pump, and may therefore have very severe hemodynamic and clinical repercussions. However, it must be recognized that ventricular arrhythmias have very diverse mechanisms and causes (especially noncardiac), such that severity, treatment, and prognosis depend on more than ECG findings alone.

202.6.3.4 Ventricular Ectopy: Premature Ventricular Complexes, Accelerated Idioventricular Rhythm, and Ventricular Tachycardia

202.6.3.4.1 Ventricular extrasystoles or premature ventricular complexes

Ventricular extrasystoles (synonyms: premature ventricular contractions, beats, or depolarizations [PVC; VPB, VPC, VPD, ventricular ectopy]) are premature depolarizations generated by an ectopic focus located in the ventricular tissue.[1,2,23,45,74] These arrhythmias are the most common of all rhythm disturbances.[64] Their identification often is simplified by the wide QRS complexes they generate, which have a different morphology (shape) than normal sinus QRS complexes. Most ventricular extrasystoles have a wide, often bizarre-appearing QRS complex (>0.07 second in dogs), without an associated P wave, and a different (often very large) associated T wave (Figures 202-32 and 202-33). Single PVCs are usually followed by a compensatory pause (see Figures 202-27 and 202-33) but may be interpolated instead (see Figures 202-27 and 202-32). Multiples of two PVCs are referred to as *a pair*; 1:1 alternation between sinus beats and PVCs is referred to as *bigeminy;* and three or more PVCs in a row constitutes

ventricular tachycardia (VT; see following). *Trigeminy* describes a repeating pattern of either 2:1 PVCs: sinus beat, or 2:1 sinus beats: PVC.

For purposes of identifying an underlying cause and for accurate therapy, it is important to differentiate ventricular extrasystoles from PACs (see Table 202-1). It is also essential to differentiate ventricular extrasystoles from the other major causes of widened QRS complexes: (1) morphologic changes due to cardiomegaly and axis shift (see Figure 202-8); (2) intraventricular conduction disturbances within the bundle branches (see Figures 202-44 and 202-45); (3) abrupt motion or other artifact (see Figure 202-23); and (4) the wide but nonpre-mature QRS complexes of ventricular escape beats (see Figure 202-42, *a*). These four causes for wide QRSs are not ventricular arrhythmias, do not involve a pathologic focus in the ventricle, are not associated with a disproportionately high occurrence of VT/VF, and therefore are not treated with anti-arrhythmic drugs.

Causes of ventricular extrasystoles include virtually any cardiac or systemic disorder,[75] with the most common of these including such primary cardiac diseases as cardiomyopathy,[55,56,76] valvular heart disease, congenital heart disease, and endocarditis[77] and such systemic problems as hypokalemia, anemia, hypoxia, blunt trauma,[78] gastric dilatation-volvulus,[79,80] abdominal masses (commonly splenic or hepatic)[81–83] intoxication, and acidosis. Normal dogs will commonly have up to 24 PVCs daily as recorded on Holter studies.[22,23] In cats, ventricular extrasystoles seem to be associated predominantly with cardiomyopathy rather than extracardiac causes. The most challenging aspect of managing ventricular extrasystoles remains the evaluation of their severity and the assessment of the need for treatment (see Ventricular Tachycardia and treatment discussions, following). Evaluation of causes and whether to treat ventricular ectopy are discussed under Ventricular Tachycardia, following.

Two specific diseases of dogs are almost exclusively arrhythmogenic, producing PVCs and VT, and often overt clinical manifestations of acute arrhythmia (malaise, syncope, Stokes-Adams seizures, or sudden death) as the chief abnormality. Familial ventricular arrhythmia of Boxer dogs (Boxer cardiomyopathy, arrhythmogenic RV cardiomyopathy and dysplasia) causes ventricular extrasystoles and VT.[84,85] Initially no thoracic radiographic or echocardiographic changes are seen, although individuals with disease that is more advanced may have dilated cardiomyopathy (see Chapter 203, Canine Myocardial Diseases). No sex predilection has been found, and it is suspected that the syndrome is inherited as an autosomal dominant trait (no carriers).[45] The causative lesion is a degeneration of myocytes in the outflow tract region of the RV, as supported by histopathologic studies[84] and the typical, left BBB-like appearance of the PVCs indicating their RV origin.[74] In many cases the ventricular arrhythmia is an incidental finding in Boxer dogs that otherwise appear normal. These occult, latent cases are predisposed to developing clinical signs later in life, having offspring with the disease, or both. Also commonly, familial ventricular arrhythmia of Boxers produces overt clinical signs that are the patient's chief complaint. Overt arrhythmic manifestations range from aborted syncope (episodes of stumbling or “drunken” appearance) to true syncope, sudden cardiac death, or both.[46,84] These events may be triggered in some cases by intense sympathetic activity, including excitement and physical exertion, and thus are managed by avoiding circumstances that trigger such behavior. Since its original description,[84] the disease seems to coexist less commonly with grossly dilated ventricles, poor contractility, or both, whereas overt manifestations due to severe ventricular extrasystoles are now a common problem in the breed. This change may simply reflect increased awareness of the problem and early screening. Clinical confirmation of the diagnosis begins with identification of the signalment and chief complaints as described previously and ultimately rests on the demonstration of ventricular

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extrasystoles on ECG in the absence of any other inciting cause (diagnosis of exclusion). Frequently, serial Holter monitoring is necessary to evaluate potential breeding individuals, because affected dogs may have only a few PVCs per hour. The presence of PVC pairs, or of VT, strongly supports the diagnosis.[24,85] Treatment involves management of arrhythmias (see Ventricular Tachycardia, following) and prevention of transmission of the disease through screening and not breeding affected individuals.

Figure 202-31 Therapeutic approach to atrial fibrillation (AFib).

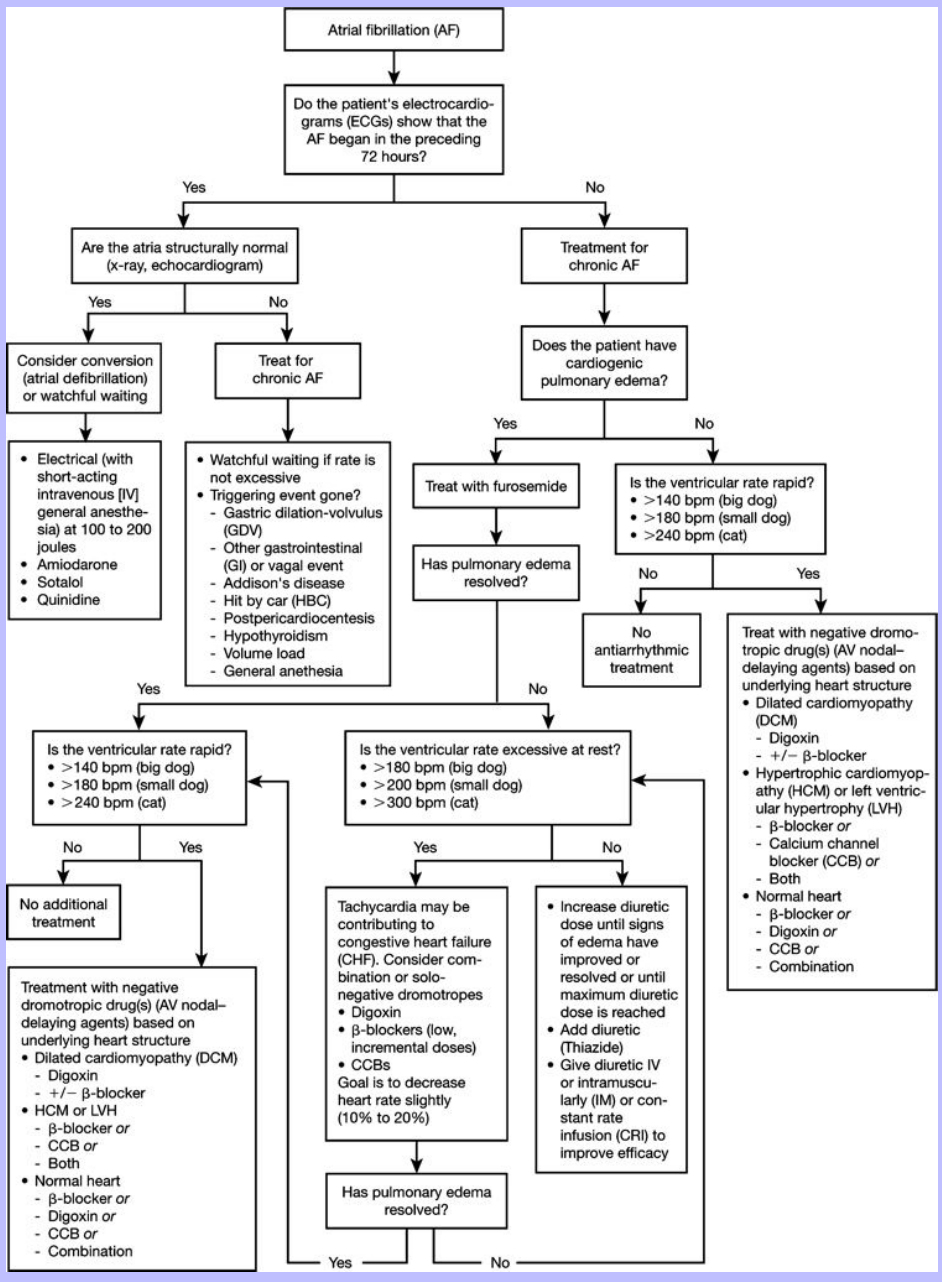
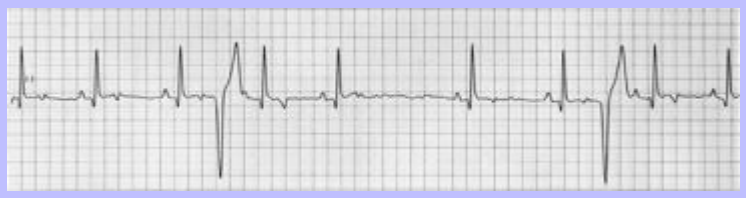


Figure 202-32 Premature ventricular complex (PVC). The classic, wide and bizarre appearance of a prematurely occurring heartbeat is seen. These PVCs are interpolated between normal QRS complexes (see also Figure 202-27). Lead II, 50 mm/sec, 1 cm = 1 mV.



Inherited sudden cardiac death of German shepherd dogs may similarly exist in a latent state or may produce overt clinical signs.[86,87] The disease occurs rarely but is international in distribution and has affected several generations.[87] The predominant abnormality is paroxysmal, rapid VT. Dogs with this disease often develop clinical signs early in life, and these include both syncope and a high prevalence of sudden death. Therefore the disease causes clinical manifestations mainly in puppies or young adult dogs (mean age: approximately 1 year; age range: 4 to 30 months). As a rule the arrhythmia does not coexist with structural cardiac changes, such that thoracic radiographs and echocardiograms generally are normal. A myocardial repolarization defect appears to be the cause of the arrhythmia.[88] Although treatments that limit bradycardia (e.g., vagolytic drugs, ventricular pacing) reduce the occurrence of arrhythmia, no definitive treatment exists for the disorder at this time.

202.6.3.4.2

Accelerated idioventricular rhythm

Accelerated idioventricular rhythm (AIVRs) has been identified as a specific subset of ventricular tachycardia (VT) for the last 30 years (and was given the clear but oxymoronic name *slow VT* at first). AIVRs have the same ECG characteristics as VT, except rate. AV dissociation, wide and bizarre QRS complexes, and the possibility of capture beats and fusion beats are seen. In medium-sized dogs, the rate of AIVRs is between 70 and 160 bpm, which places it between idioventricular (i.e., escape) rhythms (<70 bpm) and true VT in terms of rate. The causes of AIVRs are similar to those of ventricular extrasystoles, but the lower ventricular rate is less compromising of diastolic ventricular filling time; as a result, AIVRs generally are well-tolerated.[89] Treatment therefore is directed at the underlying cause; antiarrhythmic medications are not considered unless management of the underlying cause is ineffective at abolishing the arrhythmia and the rate increases to the point that the criteria for VT are met (Figure 202-34).

Figure 202-33 Three premature ventricular complexes (PVCs). This cat with hypertrophic cardiomyopathy developed PVCs both of the classic wide and bizarre appearance *(arrows)* and of a more subtly different morphology *(arrowhead)*. In all cases, PVCs are premature, not associated with a P wave, different in morphology from sinus QRS complexes, and have a T wave that is different from sinus T waves. Lead II, 50 mm/sec, 1 cm = 1 mV.

202.6.3.4.3

Ventricular tachycardia

VT is a series of three or more ventricular extrasystoles occurring at a high rate (Figures 202-35 and 202-36). It may be continuous (sustained) or intermittent (paroxysmal). Causes are the same as those listed for ventricular premature complexes (see previous discussion). Clinical manifestations are frequent (weakness, syncope, Stokes-Adams-type seizures) but their occurrence depends directly on the hemodynamic consequences of the rhythm (see Clinical Impact of Rhythm Disturbances). An increasingly rapid tachycardia, for example, will cross a threshold of ventricular rate beyond which a greater number of beats will not translate into greater cardiac output. This "point of diminishing returns," which is highly individual and varies according to the variables described previously, exists because diastolic filling time is most compromised at high heart rates. Thus very rapid VT, like any other very rapid tachycardia, can produce overt clinical signs of reduced cardiac output. At a lesser extreme, Doppler echocardiography has shown that VT may be asymptomatic because VT has been demonstrated in conjunction with an adequate cardiac output. This situation is particularly true in cases of VT at slower rates (approaching AIVR; see previous discussion).

The identification of VT is easier when it is paroxysmal. The typical appearance is one or several series of QRS complexes that are widened (>0.07 second in the dog), do not resemble the sinus QRS complexes, are associated with giant T waves, are not linked to P waves, and may include capture beats (sinus P-QRS complexes after the paroxysm of VT) and fusion beats (QRS complexes with a morphology that is intermediate, between sinus QRS complexes and ectopic QRS complexes) (see Figure 202-35). Capture beats and fusion beats are pathognomonic for VT. In VT, P waves are present (the atria depolarize, but the impulse is blocked at [or just after] the AV node because the more rapid rhythm [VT] dominates the ventricles) but are often masked by QRS complexes. Thus the presence of P waves at regular intervals but not fixedly associated with QRS complexes is consistent with VT (see Figure 202-36). The ECG diagnosis can become more challenging when VT is continuous, particularly if it is of septal or RV origin and thus produces QRS complexes that are fairly narrow and that may resemble supraventricular complexes. Wide QRS complexes caused by other factors (see previous discussion of ventricular extrasystoles) must not be mistaken for VT.

The goals of treatment of VT are, in order: (1) to accurately identify the arrhythmia, (2) to eliminate or palliate predisposing factors that may be responsible for the arrhythmia, (3) to control the rhythm and rate so as to optimize cardiac output, and (4) to avoid detrimental side effects of antiarrhythmic treatment (see Figure 202-34). The desire to suppress VT to reduce the risk of progression to lethal arrhythmias is not sound. Although it is known that ventricular arrhythmias can degenerate into increasingly unstable rhythms, no drug has ever been shown to delay this progression (see Therapy of Arrhythmias, following). Prophylactic treatment of asymptomatic ventricular arrhythmias is detrimental in human medicine and therefore is not recommended in human or veterinary medicine. (Antiarrhythmics drugs to consider for VT: none or class I, II, or III antiarrhythmics.)

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Figure 202-34 Approach to patients with a rhythm consisting entirely of wide, bizarre QRS complexes.

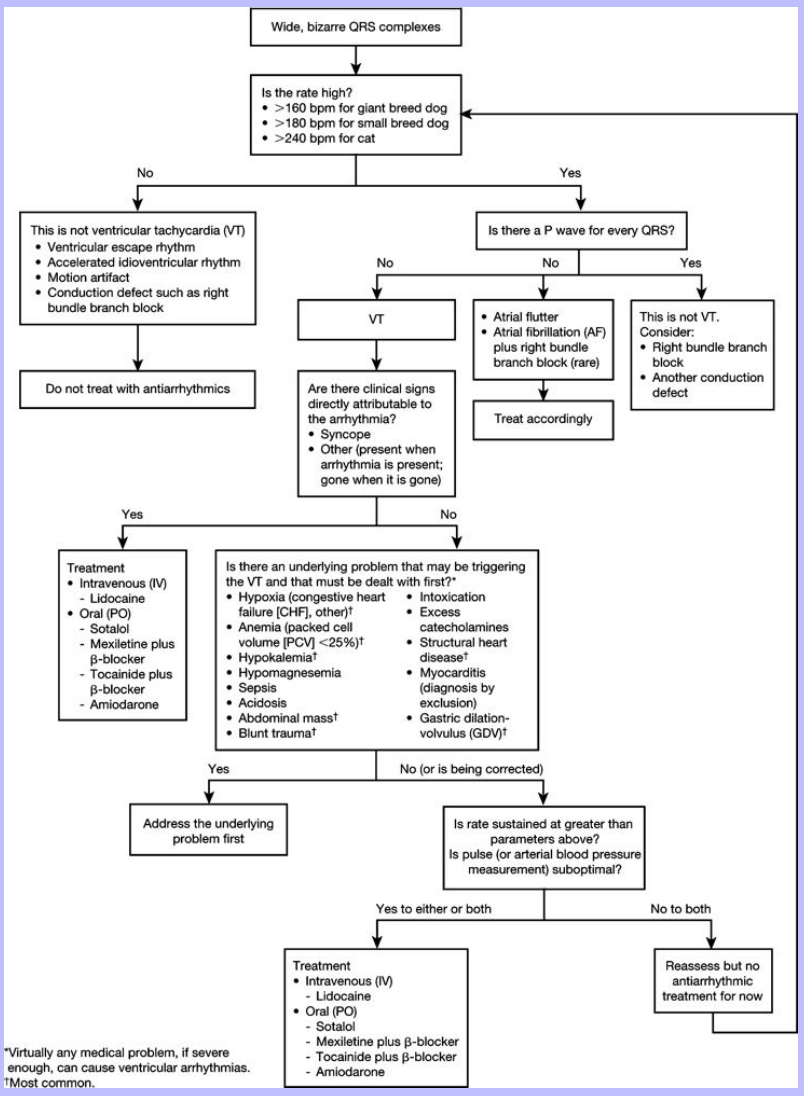

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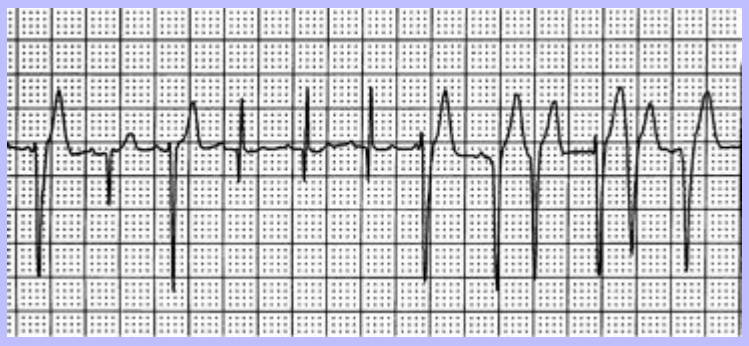
Figure 202-35 Ventricular ectopy in a dog. Premature ventricular complexes (PVCs) (first and third beats) and ventricular tachycardia (VT) (from seventh beat to end of tracing). This tracing presents many hallmark findings of ventricular ectopy. A *fusion beat* (beat 2) is an electrical hybrid formed by the collision of a PVC and a sinus beat. The reader should note its characteristically normal PR interval and QRS morphology that is intermediate between a PVC and a sinus beat. A *capture beat* is the term given to the sinus beat that resumes normal sinus rhythm (NSR) after ventricular ectopy (beat 4). In this case the sinus rhythm lasts for only three beats. The next-to-last beat occurs very prematurely and thus demonstrates the R-on-T phenomenon. Lead II, 25 mm/sec, 1 cm = 1 mV.



202.6.3.4.4 Ventricular flutter

Ventricular flutter is a rapid and prefibrillatory stage of VT. The ECG appearance of this rhythm is a tight, tall sinusoidal wave in which it is impossible to separate QRS complexes and T waves and in which neither capture nor fusion beats are seen. This intermediate stage between VT and VF is rare, brief, and precedes cardiac arrest. It must be differentiated from motion artifact. Artifact masquerading as ventricular flutter still shows evidence of coordinated ventricular activity (normal QRS complexes within the “flutter” impostors) on close inspection (see Figure 202-11). Ventricular flutter is considered a severe ventricular arrhythmia and warrants immediate correction of predisposing causes, intravenous antiarrhythmic treatment, and possibly electrical defibrillation.

202.6.3.4.5 Ventricular fibrillation

VF is a disorganized, chaotic pattern of ventricular depolarizations involving complete desynchronization of ventricular electrical activity. Hemodynamically, it produces circulatory collapse and arrest. Therefore it is a preagonal state leading to death within minutes. Indeed, the cardiac rhythms

that are defined as producing cardiac arrest include VF, asystole, and pulseless electrical activity (pulseless VT, electromechanical dissociation [EMD]).[90] The ECG appearance of VF consists of erratic, patternless waves of variable morphology, amplitude, and frequency (Figure 202-37). The underlying cause is generally a severe disorder, such as myocardial trauma, anoxia, severe electrolyte disturbance, and advanced states of shock. If VF is suspected on ECG, artifact must immediately be ruled out; poor electrical connection between the patient and the ECG leads can mimic VF. Rapid confirmation of VF consists of (1) applying isopropyl alcohol to the skin-ECG lead interface to improve conductivity; (2) assessing that the arrhythmia is present in multiple leads, not just lead II; and (3) noting that the patient is unconscious, because VF is inconsistent with adequate cerebral perfusion. VF is often preceded, and therefore heralded, by ventricular extrasystoles (possibly demonstrating the R on T phenomenon), then sustained VT, then ventricular flutter.[2] When the rhythm has reached VF, treatment (cardiopulmonary resuscitation), though often unrewarding, must be instituted immediately and generally involves electrical defibrillation if available. (Antiarrhythmic treatments to consider: electrical defibrillation, precordial thump, KCl and $CaCl_2$, Class III).

Figure 202-36 Ventricular tachycardia (VT) in a dog. With ventricular arrhythmias, the sinus node and atria continue to function, as evidenced by P waves *(dots)*. Atrial activity occurs regularly but independently of the QRS complexes (AV dissociation). Lead II, 25 mm/sec, 1 cm = 1 mV.

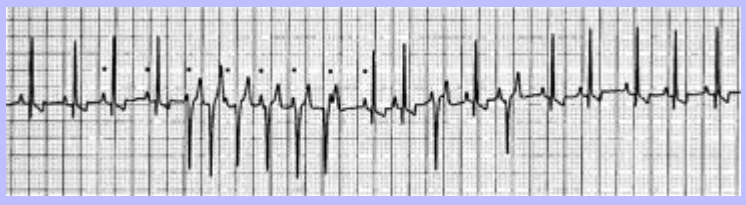
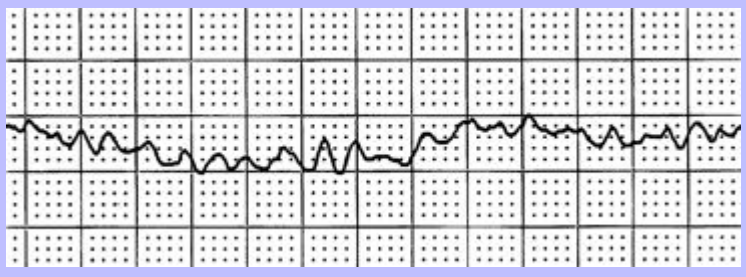


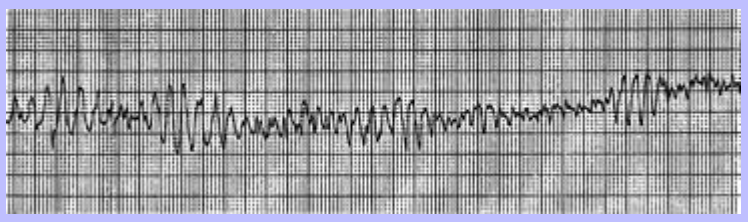
Figure 202-37 Ventricular fibrillation (VF) in a dog. An important differential diagnosis is technical error (poor electrical connection between patient and ECG machine). Lead I, 25 mm/sec, 1 cm = 1 mV.



202.6.3.4.6 Torsade de pointes

TdP is a ventricular arrhythmia that arises from prolongation of the QT interval.[91,92] The rotation of the peaks of the QRS complexes on the horizontal axis of the ECG is due to the ever-changing geometry of the re-entry circuit, which oscillates within the ventricles. The diagnosis of TdP is based on the following criteria: (1) the rhythm immediately prior to onset of TdP is slow, and the QT interval is prolonged (>0.25 second in the dog); (2) the onset of TdP involves an R on T ventricular extrasystole (e.g., depolarization [R wave] occurs during the vulnerable part of the T wave); (3) the ensuing rapid (>180 bpm) ventricular rhythm has QRS complexes that are more regular than in VF but that are continuously changing in amplitude and polarity (Figure 202-38). The total duration of a self-resolving paroxysm of TdP is usually very brief (5 to 10 seconds), but it may persist for longer; in those instances it often evolves lethally into VF. TdP is not commonly recognized in the dog but may be caused by any disorder that prolongs the QT interval:[92] congenital long QT syndrome (Dalmatian), hypokalemia, hypocalcemia, and overdose or toxicity due to antiarrhythmic drugs, particularly class 1A antiarrhythmics such as quinidine. The treatment is highly specific and requires discontinuation of all antiarrhythmic drugs and institution of intravenous magnesium sulfate (10 to 30 mg/lb slow intravenous administration).[92]

Figure 202-38 Torsade de pointes (TdP) in a dog. Lead II, 25 mm/sec, 1 cm = 1 mV. (Tracing courtesy of Dr. Michael B. Lesser, Lawndale, Calif.)



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202.6.3.4.7 Ventricular parasystole

Ventricular parasystole ("one heart beats as two") is a complex arrhythmia that results from the concurrent and independent activity of two pacemakers, one being a normal supraventricular pacemaker and the other existing in a protected site in a ventricle.[93] By definition, parasystole has (1) a ventricular focus with independent, abnormal automaticity and that has a rate that is greater than an escape focus and (2) a unidirectional (entry) block that shields this focus from sinus depolarizations. Parasystole is most often benign, does not warrant antiarrhythmic treatment, and regardless is usually refractory to antiarrhythmic therapy.

202.6.4 Disorders of Conduction

Disorders arising from faulty intracardiac electrical conduction are simply referred to as *blocks*. Blocks are grouped according to anatomic and functional criteria. Anatomic criteria separate them depending on their level of physical location: SA blocks, AV blocks, BBBs, and fascicular blocks.

Functional criteria characterize blocks according to their degree of severity. First-degree block produces a delay in conduction; second-degree block causes complete but intermittent block; and third-degree block causes complete, sustained block.

202.6.4.1 Atrioventricular Block

AV blocks are defined as delays or stoppages of conduction between the atria and the ventricles (specifically, between the upper part of the AV node and the His bundle prior to its trifurcation). First-degree AV block simply is a delay in AV conduction. Conduction through the AV node is slower than normal, but every impulse crosses the node successfully (Figure 202-39). It may be permanent or transient and may arise from a structural lesion or simply be functional. The ECG diagnosis is based on normal, sinus-appearing QRS complexes and a prolonged PR interval. The clinical manifestations are nil; first-degree AV block is an ECG finding only and does not warrant treatment. Its importance is at best diagnostic, drawing the clinician's attention to possible causes of delayed conduction, which include AV nodal damage in the major forms of heart disease and iatrogenic problems including excessive administration of such cardiac glycosides as digitalis or other antiarrhythmic therapy. Most commonly it is normal and is due only to high vagal tone. First-degree AV block does not progress to second-or third-degree AV block except in cases of drug toxicity.

Second-degree AV blocks involve the complete (but transient) interruption of AV conduction. Therefore a P wave exists for every QRS complex, but a QRS complex does not exist for every P wave. Two important subtypes of second-degree AV block exist. The first, Mobitz type I second-degree AV block, is characterized by a progressive lengthening of the PR interval until ultimately a P wave is blocked (P wave without QRS complex), known as the *Wenckebach phenomenon*. Anatomically, Mobitz type I second-degree AV block originates high in the AV node and is said to carry a good prognosis because it is closely related to first-degree AV block, and virtually never causes clinical signs (Figure 202-40). The second, Mobitz type II second-degree AV block, by contrast, demonstrates perfectly regular PR intervals for all QRS complexes, but one or more P wave or waves is or are blocked (Figure 202-41). Mobitz type II second-degree AV block arises from the AV bundle and is said to carry a more guarded to poor prognosis because it more closely resembles third-degree AV block; however, objective evidence to support this extrapolation from human cardiology in veterinary patients is lacking. In *simple* Mobitz type II second-degree AV block, more conducted P waves occur than blocked P waves, whereas in *advanced* Mobitz type II second-degree AV block (as in Figure 202-41), more blocked P waves occur than conducted P waves. The presence or absence of clinical signs appears to be related to the overall ventricular rate. Therefore simple Mobitz type II second-degree AV blocks rarely produce clinical manifestations such as exercise intolerance, whereas the more advanced Mobitz type II second-degree AV blocks commonly produce clinical signs that are similar to third-degree AV block: weakness, lethargy, syncope, and Stokes-Adams seizures (true convulsions caused by critical, arrhythmia-induced cerebral hypoperfusion) even with minimal exertion.

Figure 202-39 First-degree AV block. The interval between each P wave and the following QRS complex is markedly prolonged in this extreme example (PR interval = 0.18 second). Lead II, 50 mm/sec, 1 cm = 1 mV.

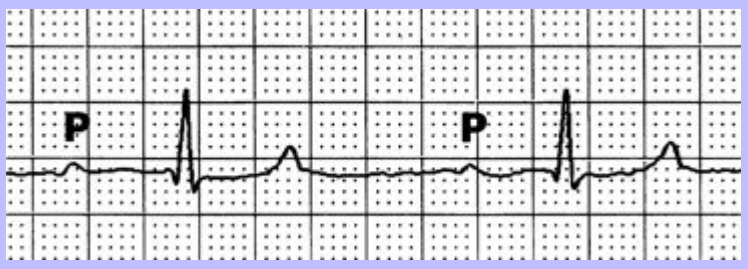


Figure 202-40 Second-degree AV block, Mobitz type I (Wenckebach phenomenon). Gradual prolongation of the PR interval occurs until a P wave is completely blocked *(arrow)*. Lead II, 25 mm/sec, 1 cm = 1 mV.

Third-degree AV block is a complete and sustained interruption of AV conduction. The ventricles depolarize according to a slow, regular, autonomic rhythm, called an *escape rhythm* (junctional or ventricular; see following) (Figure 202-42). It is essential to recognize the lifesaving *salvage* function of a ventricular escape rhythm, because it prevents asystole. Therefore even though ventricular escape QRS complexes are wide and bizarre, ventricular antiarrhythmic therapy is absolutely contraindicated.

In third-degree AV block, communication between the atria and ventricles is nonexistent (complete AV dissociation). Therefore the ECG diagnosis is based on the complete absence of P wave conduction (P waves without QRS complexes; no consistent PR interval) and on slow ventricular QRS complexes, which are usually of a uniform, but wide, bizarre morphology (shape) and that usually occur with near-perfect regularity. Third-degree AV blocks typically produce marked exercise intolerance, weakness, and syncope. 1065
Even so, it is possible to encounter older animals, not very active by nature, who have "asymptomatic" 1066
third-degree AV blocks, or individuals (especially cats) with third-degree AV block and a rapid escape rhythm in which the block is an incidental finding (see Figure 202-42).[1,3] The asymptomatic situation also is likely in cases of *isorhythmic AV dissociation*, a situation in which third-degree AV block occurs but the atrial rate and ventricular rate are nearly identical (see Figure 202-42).

Figure 202-41 Second-degree AV block, Mobitz type II. P waves are blocked without a gradual lengthening of the preceding P-R interval, in contrast to Mobitz type I second-degree AV block. For most of the tracing, only every third atrial impulse crosses the AV node and activates the ventricles, as evidenced by the fixed P-R interval for every third P wave (3:1 block). Lead II, 25 mm/sec, 1 cm = 1 mV.

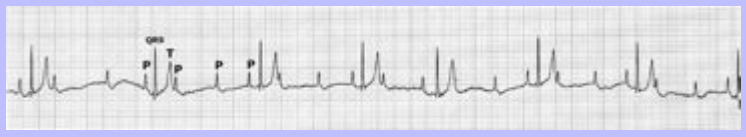
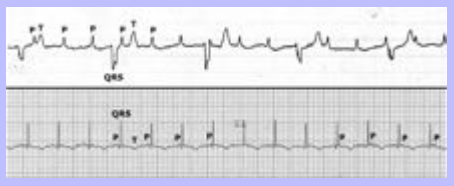


Figure 202-42 Third-degree AV block. No connection occurs between P waves and QRS complexes. Lead II, 25 mm/sec, 1 cm = 1 mV. In the upper panel, the escape rhythm is clearly ventricular because the QRS complexes are wide and bizarre in lead II and are slow to occur (rate = 55/min). This cat had clinical signs caused by the arrhythmia (lethargy) and required implantation of a pacemaker. In the lower panel, the escape rhythm is likely junctional (supraventricular), because the QRS complexes are narrow and upright in lead II, and they occur at a near-normal (near-sinus) rate (150/minute). That is, AV block is present in the proximal part of the AV nodal-His complex, and the escape rhythm originates in the distal part. This arrhythmia was an incidental finding in an otherwise normal cat.



The causes of AV blocks are diverse. First-degree AV and Mobitz type I second-degree AV blocks often are functional (high vagal tone in healthy individuals, negative dromotropic effects of digitalis, antiarrhythmics, or alpha 2-stimulating anesthetics). Less commonly, cardiac disease with atrial dilation and AV nodal lesions may be present. Mobitz type II second-degree AV block and third-degree AV block are sometimes functional (hyperkalemia, digitalis toxicity, alpha 2-stimulating anesthetics), but are commonly associated with a structural lesion, be it inflammatory (endocarditis, Lyme myocarditis,

traumatic myocarditis) or degenerative (physical disruption arising from cardiomyopathy, endocardiosis, or fibrosis).[94,95] Treatment is therefore aimed at the underlying cause when possible. In clinically overt, advanced, Mobitz type II second-degree AV blocks or third-degree AV blocks, response to parasympatholytic or sympathomimetic drugs tends to be fairly disappointing and potentially dangerous. Pacemaker implantation is a better choice (Figure 202-43).

Figure 202-43 Normal pacemaker function. Electrical activity generated by pacemakers appears as spikes on the electrocardiogram (ECG) *(arrowheads)*. The spikes are larger for unipolar pacemakers (left panel) than for bipolar pacemakers (right panel). No atrial activity was present in the dog in the left panel. No association exists between atrial activity (P waves) and paced activity in the right panel because the pacemaker activates only the ventricles (VVI mode). Lead II, 25 mm/sec, 1 cm = 1 mV.

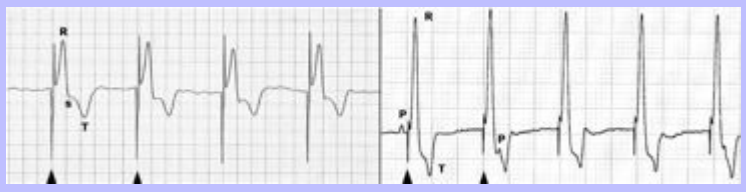


Figure 202-44 Left bundle branch block (LBBB) in a dog. The QRS complexes are very wide (0.10 second, *small double arrow*) but of otherwise normal configuration. Normal sinus rhythm. Simultaneous leads I, II, and III, 50 mm/sec, 1 cm = 1 mV.

202.6.4.2 Bundle Branch Blocks

BBBs are slowings or interruptions of conduction involving one or more of the ventricular branches of the His bundle. Blocks may be functional (transient interruptions due to the depolarizations occurring during the refractory period) or structural (permanent interruptions due to a physical disturbance). The ECG diagnosis of BBBs is based on the abnormal shape of the QRS complexes, which become widened due to the desynchronization of the two ventricles. The duration of the QRS complexes is greater than 0.07 second in dogs with BBB, and the polarity is positive in lead II for left BBBs and negative in lead II for RBB blocks (Figure 202-44 and 202-45). If BBBs occur during sinus rhythm, the ECG diagnosis is straightforward, because other than the very abnormal appearance of the QRS complexes, the P-QRS-T sequence throughout the ECG is normal: a P wave occurs before each QRS and the PR interval is fixed and normal. If the block occurs concurrently with a nonsinus rhythm, such as AFib, however, establishing a diagnosis in BBB can be much more challenging (see Figure 202-30). A BBB together with AFib mimics ventricular extrasystoles or VT, which may misdirect therapeutic decisions, (see previous discussion of atrial fibrillation). Cats with heart disease (especially cardiomyopathy) are classically described as being prone to developing block in a subdivision of the LBB known as the *left anterior fascicle* (or LAF).[5] LAF block produces a tall R wave in leads I and aVL, and a deep S wave in leads II, III, and aVF, and therefore a left-axis deviation (see Figure 202-6; Figure 202-46).[12]

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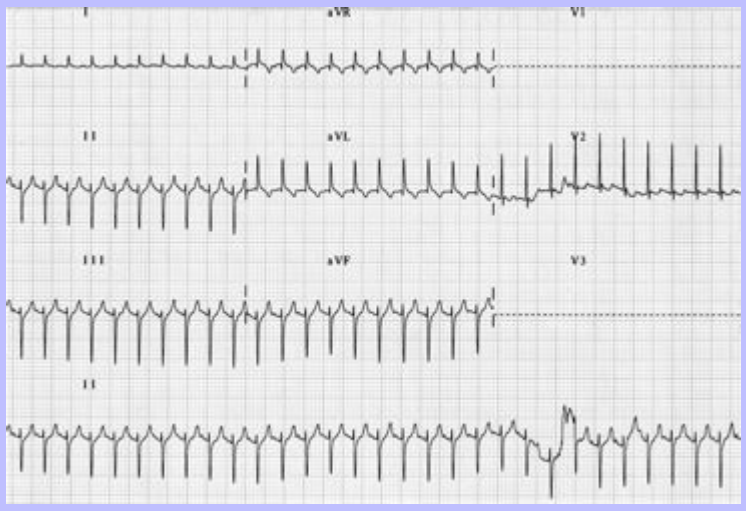
Figure 202-45 Intermittent right bundle branch block (RBBB) in a dog. Each QRS complex is preceded by a P wave. This important finding indicates that this is a supraventricular rhythm and not a ventricular arrhythmia. The cyclical increasing-decreasing heart rate, constant PR interval, and similar appearance of all P waves indicate that this rhythm is respiratory sinus arrhythmia (RSA). The wide, bizarre QRS complexes occur when the sinus rhythm is slightly faster (shorter R-R intervals), indicating a rate-dependent form of intraventricular conduction disturbance. The wide, bizarre appearance of QRS complexes in this lead II tracing indicates that this disturbance is a block of the RBB. RBB block generally is a normal or inconsequential finding in dogs and has no hemodynamic repercussions in the patient. The main significance of RBB block lies in how easily it can be mistaken for a ventricular arrhythmia. Lead II, 25 mm/sec, 1 cm = 1 mV.

Figure 202-46 Left anterior fascicular (LAF) block. Prominent S waves occur in leads II, III, and aVF, indicating a leftward mean electrical axis (MEA) deviation (−75 degrees). Motion artifact is noted in the last quarter of the rhythm strip *(lower-right corner)*. This adult cat had moderate left ventricular (LV) hypertrophy echocardiographically, as suspected from the large (deep) QRS complexes. Seven-lead electrocardiogram (ECG) and simultaneous rhythm strip; 25 mm/sec, 1 cm = 1 mV.



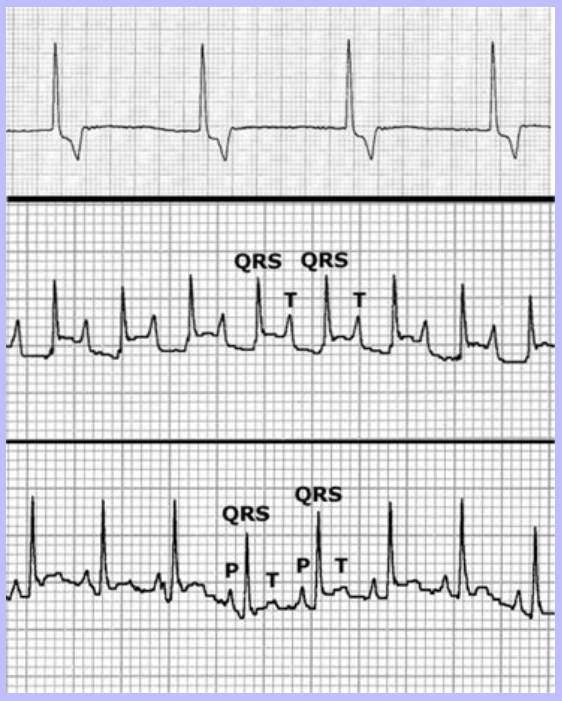
The causes of BBB are many, because they may be due to a variety of pathologic changes including hypertrophy (as in feline hypertrophic cardiomyopathy), dilation (as seen in dilated cardiomyopathy), and inflammation (endocarditis, traumatic myocarditis). In the dog, RBB block is often a completely normal, unnecessarily worrisome ECG finding (see Figures 202-30, 202-45). Clinical manifestations of BBBs alone generally do not occur.[11,12] These disturbances therefore do not warrant specific treatment beyond that of their underlying cause. The importance of recognizing BBB lies in the fact that they could be the first indicators of underlying cardiac disease, which itself warrants further diagnosis and treatment, and that they can be misinterpreted as ventricular arrhythmias.

202.6.4.3 Atrial Standstill (Silent Atrium)

This rhythm disturbance does not truly fall into the category of blocks. It is an arrhythmia characterized by the total absence of atrial depolarization (Figure 202-47). A sinus impulse may nevertheless be properly formed and conducted to the AV node if the internodal pathways remain functional. In this situation, common with hyperkalemia, the rhythm is referred to as *sinoventricular*. Otherwise, if no sinus impulse arises and the atria are electrically silent, then a junctional or ventricular escape rhythm must emerge to avoid asystole. The three differential diagnoses for atrial standstill are (1) moderate to marked hyperkalemia ($K^+ > 7.5$ mEq/L), (2) atrial myopathy, and (3) ECG artifact (P waves too small, or

isoelectric, preventing them from being seen properly on a chosen ECG lead). Perhaps the most easily identified initial change of moderate hyperkalemia on ECG is disappearance of the P waves; this change follows mild tenting of the T waves (often imperceptible) and precedes ventricular flutter and cardiac arrest. Alternatively, atrial standstill may occur due to marked atrial stretch,[96] as occurs particularly in cats with various forms of cardiomyopathy, or atrial parenchymal hypoplasia, as is seen in association with a dystrophic form of neuromyopathy, particularly in the Springer spaniel. Either way, the ECG appearance is therefore of a regular rhythm, usually with QRS complexes that are of a supraventricular appearance, and with a normal rate but without detectable P waves in any lead on the ECG. Differentiating between the two main causes of this rhythm using the ECG alone is difficult, and immediate measurement of serum electrolytes is warranted.

Figure 202-47 Atrial standstill. In the upper panel, a primary atrial myopathy was responsible for the lack of atrial activity seen in this dog's tracing. Serum [K^+] = 4.3 mEq/L (within normal limits). Lead II, 25 mm/sec, 1 cm = 1 mV. In the middle and lower panels, presence (middle) and absence (lower) of atrial standstill in a cat with urinary obstruction before and after correction of severe hyperkalemia, respectively. The reader should note the rapid ventricular rate in the middle panel (220/min) despite an elevated serum [K^+] (8.4 mEq/L). In contrast to dogs, severely hyperkalemic cats often are tachycardic. Lead II, 25 mm/sec, 1 cm = 0.5 mV.



202.6.4.4 Electromechanical Dissociation

EMD is not, strictly speaking, an abnormality of cardiac rhythm. *EMD* refers to the absence of conversion of an electrical rhythm into a mechanical force of contractility.[97,98] The ECG therefore may show virtually any rhythm, and the diagnosis rests on the combination of a hemodynamically collapsed patient with an ECG that shows any rhythm but asystole. The pulse is usually barely perceptible or absent, the patient typically is unconscious, and EMD most commonly is a prearrest or terminal condition (Figure 202-48). Treatment requires correction of underlying causes if possible and then is aimed at increasing circulation to improve myocardial perfusion. Because EMD generally indicates profound myocardial hypoxia, the prognosis is poor even with treatment.

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Figure 202-48 Electromechanical dissociation (EMD). By definition, pulselessness was present during this ECG. Lead II, 25 mm/sec, 1 cm = 1 mV.

202.6.5 Complex Disorders Involving Abnormalities of Both Excitability and Conduction

Of the multiple rhythm disturbances described previously, many can occur jointly on the same ECG tracing, producing mixed disturbances of excitability and of conduction. This next section will discuss examples of disturbances of excitability and of conduction that produce specific clinical syndromes.

202.6.5.1 Pre-Excitation Syndromes

In pre-excitation, the normal impulse originating from the SA node is split at the end of atrial depolarization, with part of the impulse traveling normally through the AV node and another part of the impulse traveling simultaneously through an abnormal shaft of rapidly conductive fibers that links the atria and the ventricles, (also called an *accessory pathway* or *bypass tract*) thus bypassing the AV node. The result is partial, premature, immediate activation of the ventricles through the bypass tract, without the benefit of a pause in the AV node; hence the term *pre-excitation*. With one major exception (see following), the effect of this abnormal pattern of activation is minimal, because only a part of the atrial contribution to ventricular filling is lost. The ECG demonstrates that the normal delay through the AV node was pre-empted by conduction through the bypass tract (i.e., no segment separates the P wave from the QRS complex) and that conduction through the bypass tract caused asynchronous activation of the ventricles (the bypass tract and the normal AV nodal conduction ultimately each activate their share of the ventricles), resulting in a notched QRS complex. The size and location of the QRS complex's notch, the *delta wave*, depends on the distance that separates the bypass tract and the AV node in the individual's heart (i.e., on the amount of myocardium that the His bundle and the bypass tract can each depolarize before the impulses collide with each other; Figure 202-49).

Under usual circumstances, pre-excitation is an incidental, clinically silent finding. However, in individuals with pre-excitation, a premature atrial depolarization may initiate a type of re-entry cycle that can produce extreme tachycardias. Although bypass tracts conduct impulses rapidly, their refractory period typically is longer than that of the AV node. Therefore the timing of a premature supraventricular depolarization may fail to conduct through the bypass tract but be able to conduct through the AV node, depolarizing the ventricles normally. As the impulse completes the depolarization of the ventricles, the bypass tract has repolarized and is able to conduct. Bypass tracts can often conduct impulses in either direction, such that the ventricular impulse conducts retrograde through the bypass tract to the atria, initiating an endless loop of conduction. This type of self-perpetuating circuit is a type of *macrore-entry circuit*, and it may produce a potentially very rapid and clinically overt (apparent discomfort, exercise intolerance, lethargy, syncope) tachycardia called *orthodromic* [the impulse travels in a normal direction through the AV node] *AV re-entrant tachycardia*, or the *Wolff-Parkinson-White* (WPW) syndrome.[59,63,99] Dogs with this syndrome may have unrelenting heart rates above 300 bpm. Initial treatment can involve vagal maneuvers that, through slowing of AV conduction (i.e., negative dromotropic action), break the cycle of re-entry. Amiodarone or procainamide may be used in the management of such tachyarrhythmias in dogs. Conversely, digoxin is contraindicated because it decreases the refractory period of the bypass tract. Many drug therapies or combinations thereof have been used to reduce the occurrence of WPW episodes in pets with *symptomatic* re-entrant tachycardias caused by pre-excitation. Frequently in these cases, no drug therapy is entirely successful, and the clearest and most successful form of treatment involves referral to a specialized center for intracardiac catheter-based radiofrequency interruption (ablation) of the re-entrant pathway, which permanently abolishes pre-excitation and all future risk of recurrence of the WPW syndrome.[63,100]

Figure 202-49 Pre-excitation. The P-R interval is the same as the duration of the P wave (i.e., no P-R segment is seen). This finding indicates pre-excitation of the ventricles through an accessory bypass tract. The asynchronous activation of the ventricles is demonstrated through the presence of a subtle notch in the QRS complex, the delta wave *(arrow)*. Lead I, 25 mm/sec, 1 cm = 1 mV.

202.6.5.2 Sick Sinus Syndrome

SSS (bradycardia-tachycardia syndrome, sinus node dysfunction) involves a complex disturbance of the cardiac conductive tissues, producing simultaneous defects in sinus activity (SB and sinus arrest), AV conduction disturbances (first-degree and second-degree AV blocks) and disturbances in supraventricular and ventricular excitability (Figure 202-50). Therefore the disturbance is not a problem involving only the SA node, as the name *SSS* suggests, but rather is an illness that affects cardiac tissue at all levels.

The cause of SSS is unknown. Some human beings with SSS have autoantibodies directed at SA nodal tissue or at cholinergic receptors,[101,102] but these mechanisms have not been described in dogs with SSS. Certain epidemiologic features stand out from cases reported in the veterinary literature. The disease is recognized almost exclusively in dogs, and the stereotypical breed predilection for female miniature Schnauzers is far from exclusive, many other breeds, notably Cocker spaniels,[103,104] West Highland white terriers,[103,105] and mixed breed dogs represent an ever-increasing proportion of patients with this disorder. The spectrum of disease described as SSS likely regroups more than one distinct disorder that future research will categorize into separate entities.

The age of onset typically is mid to late adulthood (6 to 10 years), and the association with chronic mitral valvular disease is common but not obligatory. Histopathologically, nodal tissue fibrosis is seen, associated with vascular disturbances (microcoronary arteritis). The ECG diagnosis often requires repeated and sufficiently long (2 to 3 minute) tracings, to convincingly demonstrate some or all of the aspects of SSS: SB (often with first-or second-degree AV block), prolonged sinus pauses with variable escape beats and bursts of supraventricular tachycardia or ventricular extrasystoles at various rates (see Figure 202-50). In some cases only SB occurs. Because these features occur intermittently, the diagnosis often is only made by obtaining an ECG during an episode of syncope, stumbling, or ataxia (near syncope), which are the most common overt clinical manifestations of this arrhythmia. Ambulatory ECG, especially cardiac event recording, is ideally suited for establishing the diagnosis of SSS when the in-hospital ECG is unhelpful (see Ambulatory Electrocardiography). Such technology has identified that episodes occur during bradycardia rather than tachycardia. Vagolytic drugs may acutely improve the situation by reducing the impact of bradycardia episodes and pauses, but definitive treatment when episodes are recurrent generally requires the implantation of a pacemaker (see following). Digitalis glycosides are usually contraindicated, including in the CHF patient, because of the risk of furthering AV block and thus decreasing ventricular rate. If CHF is present, diuretics (e.g., furosemide) and angiotensin-converting enzyme (ACE) inhibitors are typically used, with or without spironolactone. Correction of bradycardia through pacemaker implantation occasionally improves cardiac output sufficiently to eliminate CHF and allow the gradual reduction, and possibly discontinuation, of diuretics.

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Figure 202-50 Sick sinus syndrome (SSS). Second-degree AV block followed by an extremely long sinus pause, an escape beat, sinus bradycardia or a supraventricular escape rhythm, and one premature ventricular complex, are seen. Lead II, 25 mm/sec, 1 cm = 1 mV.

202.7 THERAPY OF ARRHYTHMIAS (Table 202-1)

First and foremost, any underlying or predisposing factors involved in the precipitation of arrhythmias need to be identified and resolved when possible (see Figure 202-34). For example, attempting to treat VT with antiarrhythmic drugs when a patient is hypokalemic is counterproductive and probably dangerous. Hypokalemia can both make ventricular arrhythmias more likely to occur and, through effects on myocardial sodium channels, hypokalemia makes the arrhythmia refractory to the more commonly used intravenous antiarrhythmics including lidocaine.

Overall, a practical approach to choosing antiarrhythmic therapy incorporates known clinical efficacy, adverse drug reactions, pharmacokinetic effects, and results of administration. Substantial changes in the approach to antiarrhythmic therapy have evolved since the publication of the 1991 Cardiac Arrhythmia Suppression Trial (CAST) in human beings with myocardial infarction. In this multigroup, placebo-controlled, double-blinded study, researchers unexpectedly found an increased rather than decreased risk of death when certain type IC antiarrhythmic agents were administered. Although ambient ventricular arrhythmias are still regarded as a risk factor for adverse cardiovascular events, these arrhythmias are increasingly perceived as *messengers* of myocardial disturbance rather than primary problems needing to be quelled. Accordingly, the rush to treat asymptomatic ventricular arrhythmias has been markedly reduced.[106,107] By contrast, the general approach to the treatment of supraventricular tachyarrhythmias, whether latent or responsible for clinical signs, has remained the same or become more aggressive in small animal medicine (Figure 202-51).[63,100]

The decision to treat ventricular arrhythmias in veterinary medicine should be based on the functional effects of the rhythm, not the frequency ("more than *x* PVCs/min") or morphologic complexity (monomorphic versus polymorphic) of the abnormal beats.[89,106] Expressions of the functional effects of arrhythmias that can be assessed clinically include the presence of clinical signs (e.g., lethargy, syncope, Stokes-Adams seizures) and perfusion during the arrhythmia (pulse quality, mentation, and if available, short-term trends in blood pressure parameters).

Ventricular tachyarrhythmias may be progressive and can compromise cardiac output. However, even complex ventricular arrhythmias, when they are asymptomatic, do not necessarily represent a target for attempting to reduce the risk of sudden death.[107] In human medicine, from which the overwhelming majority of veterinary clinical cardiac arrhythmia information is extrapolated, "rendering treatment to suppress a risk factor because of the temptation to equate causality with association between the risk factor and a putative clinical outcome has never been more misguided than with nonsustained ventricular tachycardia."[107]

"When to treat?" probably remains the single most important and unresolved question in veterinary cardiology. The veterinary experience may or may not be substantively different from the human. Therapy based on human medical recommendations may be inappropriate considering the principal differences in causes of disease between the species (e.g., coronary versus noncoronary heart diseases). Clinicians do not know what happens to dogs or cats with arrhythmias of differing causes, nor are we generally able to compare arrhythmias of different causes regarding outcome or specific drug therapies. Survival and efficacy studies for complex arrhythmias in veterinary medicine are few, and, with one exception, none has been double-blinded or controlled. The exception is a prospective study of 49 Boxer dogs with familial ventricular arrhythmia *(Boxer cardiomyopathy)* that were randomized to receive one of four antiarrhythmic medication strategies. Results of the study showed that some antiarrhythmics were better than others for reducing the occurrence of arrhythmia, but none of the four significantly decreased the extent of clinical manifestations of the arrhythmias (syncope).[46] Otherwise,

experience-based generalizations may be made, including the observation that dogs with mitral endocardiosis are not likely to die suddenly of arrhythmic causes, whereas cardiomyopathic Doberman pinschers and dogs with advanced subaortic stenosis have a greater risk of sudden death when they reach a stage of disease associated with ventricular ectopy. When overt clinical signs such as syncope or aborted syncope are present, it is difficult to argue with therapeutic efforts to contain the arrhythmia. When clinical signs are absent, however, it is relevant to compare the potential side effects of therapy, including proarrhythmia, to the potential and difficult-to-prove benefit of a stabilized or normalized rhythm. Proarrhythmic effects of cardiac drugs aside, Calvert[108] has shown the adverse effects of routine anesthesia and surgery in Doberman pinschers with occult cardiomyopathy, thereby reminding the clinician to consider the dangers of medical procedures that may exacerbate uncontrolled arrhythmias.

202.7.1 Classification Systems for Antiarrhythmic Agents

Antiarrhythmic drugs have traditionally been classified into one of four groups according to their predominant effect on the action potential. Dissatisfaction with the shortcomings of the Vaughn-Williams (V-W) classification scheme for antiarrhythmic drugs resulted in the creation of a competing classification system[109] correlating antiarrhythmic drugs with the mechanism of the arrhythmia and vulnerable parameters, as well as actions of the drug.[110] The scheme, known as the *Sicilian gambit* (SG), is based on the actions of drugs on arrhythmogenic mechanisms and was another attempt to provide a rational basis for therapy. Regrettably, although academically reasonable, it has not improved the clinical approach to arrhythmia therapy in human or veterinary medicine.

Limitations of the traditional V-W system include its incomplete classification, crossover within the system among specific drugs, and its discussion principally of blocking mechanisms, whereas activation of channels, receptors, or both are downplayed. Antiarrhythmic agents may be effective in a number of ways: slowing tachycardias, terminating arrhythmias, making them tolerable, or preventing their initiation.[109] The V-W classification is based only on the electrophysiologic drug effects of isolated, normal cardiac tissue (except for class II agents), which is different from the diseased state. The classification excludes compounds such as digitalis, adenosine, and alpha-adrenergic-blocking agents. The V-W classification system assumes that we know more than we really do. Not all drugs within a class have the same physiologic or clinical effects. The danger in using only the V-W scheme is that most drugs have more than one mode of action, and all the drugs within a category clearly are not always the same.

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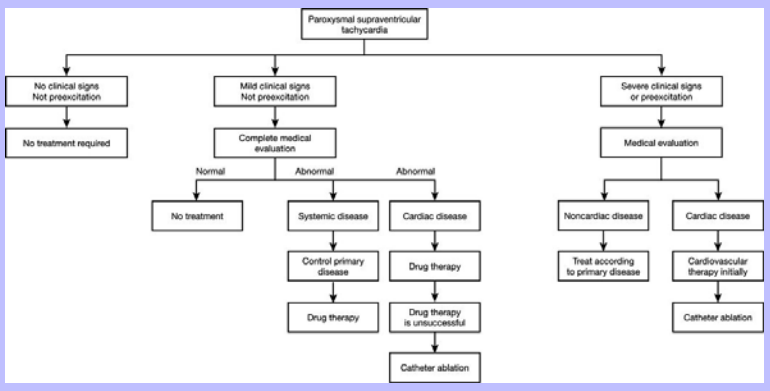
Figure 202-51 Approach to management of supraventricular arrhythmias.



Antiarrhythmic therapy for the practicing veterinarian with access to ECG monitoring, ambulatory ECG (available at most referral veterinary centers or via on-line rental [see previous discussion]), and echocardiography (available at many referral facilities) is described later in this chapter. Electrophysiologic testing and terminology, although desirable, are (with few exceptions) not practiced. Therefore the discussion of these techniques is limited to what is required to make knowledgeable medical decisions in practice. Only commonly used drugs or those likely to be useful in canine or feline heart disease are discussed. New drugs are identified, as are new uses for older drugs.

202.8 CLASS I ANTIARRHYTHMICS (Table 202-1)

Class I drugs selectively block the fast sodium channels, decreasing sodium influx during phase zero of depolarization. A reduced slope of phase zero is the manifestation of decreased conduction velocity. Slowed conduction velocity can interrupt a reentrant pattern.[3] These drugs work best in cells dependent on the fast sodium channel for their action potential, such as normal and ischemic Purkinje cells and ventricular myocardial cells. Within this class are three subgroups, distinguished by their electrophysiologic and antiarrhythmic differences. Most of the compounds within this class fail to perform adequately in the presence of hypokalemia.

202.8.1 Class IA Drugs

Class IA antiarrhythmic drugs are intermediate sodium channel blockers that markedly depress phase zero action potential, depress conduction of electrical impulses through the heart, and slow cardiac repolarization by lengthening the effective refractory period.[3] By depressing the conduction velocity and prolonging the refractory period, arrhythmias dependent on re-entry may be interrupted. Drugs in this class include quinidine (prototype IA drug), procainamide, and disopyramide (Table 202-1). Quinidine decreases the rate of spontaneous depolarization in pacemaker fibers, prolongs anterograde refractoriness accessory pathways, and can suppress or trigger delayed afterdepolarizations. Quinidine may prolong the PR interval, widen the QRS complex, and lengthen the QT interval, and it was originally indicated for the control of supraventricular and ventricular arrhythmias. Today it and the other class IA drugs have very limited usefulness in clinical antiarrhythmic therapy of small animals. Proarrhythmic and other side effects make quinidine an agent that is now rarely used.

Procainamide has cardiac effects similar to those of quinidine. However, its propensity for inducing hypotension with intravenous use or increasing ventricular rates from enhanced AV conduction is less than that of quinidine. Procainamide specifically has been demonstrated to prolong the effective refractory period and slow conduction in the accessory pathway of dogs with orthodromic AV reciprocating tachycardia.[111]

Procainamide is metabolized by the liver and eliminated by the kidneys. The sustained release formulations may be poorly absorbed and even eliminated as intact tablets in the feces of dogs. Procainamide may be used in conjunction with other class I agents and beta-blockers for refractory arrhythmias. Oral administration of the drug at higher than usually recommended doses to achieve trough serum concentrations of 10 to 12 μg/mL were successful in controlling some supraventricular tachyarrhythmias.[111,112] Side effects are infrequent and include anorexia, nausea, vomiting, fever, proarrhythmia, and agranulocytosis. In a four-way trial of antiarrhythmic drugs in boxer dogs with ventricular arrhythmias, procainamide (10 to 12 mg/lb orally, three times a day) successfully reduced the frequency of ventricular ectopy. However, the frequency of syncope was unaffected, and there were substantial side effects.[46]

202.8.2 Class IB Drugs

Class IB agents block fast sodium channels, which decreases the slope of phase zero, depresses automaticity, and increases the threshold for VF. These drugs have an affinity for binding with inactivated sodium channels, thereby acting selectively on diseased or ischemic tissue. Minimal effects are seen on the sinus node, AV node, and atrial muscle or on inotropy. Lidocaine, phenytoin, tocainide, and mexiletine are examples of drugs in this class (Table 202-1).

Lidocaine is used for acute control of life-threatening ventricular arrhythmias. In usual doses it is not likely to affect myocardial contractility, systemic arterial blood pressure, the QRS complex, or AV conduction time,[3] although extremely high doses have been shown to decrease ventricular contractility. Lidocaine suppresses automaticity and conduction velocity and prolongs refractoriness in ischemic cardiac cells.

Lidocaine is most effective when used intravenously, owing to first-pass hepatic metabolism. It is less than 10% protein bound. Hepatic disease, chloramphenicol, propranolol, halothane, cimetidine, and norepinephrine may all delay hepatic metabolism of lidocaine. Hepatic microenzyme inducers enhance degradation.

Lidocaine intoxication results in ataxia, mental depression, and seizures. These signs usually subside within minutes after lidocaine infusion is discontinued. Diazepam or a short-acting barbiturate may be necessary to control seizures. Lidocaine may be administered by slow (2 to 5 minute) intravenous loading bolus (1 to 2 mg/lb) followed by a continuous rate infusion (CRI) of 10 to 30 µg/lb/min in dogs. Alternatively, after the initial bolus, an additional amount can be given at half the dose every 10 minutes to maintain the rhythm. Caution is recommended when using lidocaine in cats because of historical reports of bradyarrhythmias and sudden death. Lower bolus doses of 0.25 to 0.5 mg/lb slowly followed by 5 to 10 µg/lb/min CRI are recommended for cats. Intramuscular lidocaine is less efficacious and is rarely used.

Tocainide and mexiletine are structurally analogous to lidocaine but have oral bioavailability. Response to lidocaine may not be a predictor of response to these oral agents, however.

Tocainide is orally absorbed and undergoes hepatic metabolism and renal excretion. It may be used after lidocaine or as initial treatment in a hemodynamically stable patient. At 6.8 to 11.4 mg/lb orally every 8 hours, peak levels were reached in cardiomyopathic Doberman pinscher dogs after 2 hours and began to diminish by 8 hours. Fifteen of 23 (70%) dogs experienced a 90% diminution of VT, and there was a 70% reduction of all PVCs in 80% of the cardiomyopathic dogs. Although there was no relationship between dose and serum concentration, dogs without signs of toxicity had serum levels under 11 mg/L and all those with toxic signs exceeded 14 mg/L.[113] Side effects observed within 8 days are weakness, head tremor, ataxia, and head bobbing. Long-term side effects, including corneal dystrophy, corneal edema, and renal failure, were observed in more than 50% of dogs.[113,114]

Mexiletine is absorbed orally and undergoes less than 10% first-pass hepatic elimination. It is 70% protein bound. The drug is eliminated by renal excretion, and its half-life varies depending on urine pH. Side effects are infrequent in the dog but can include nausea, inappetence, and tremor.[115] Sinus bradycardia, ataxia, dizziness, and thrombocytopenia are other potential problems. No data exist regarding its use in cats. In a group of Boxers with familial arrhythmia, mexiletine was given jointly with the beta-blocker atenolol as one of four forms of therapy being tested. This antiarrhythmic therapy reduced the frequency and “grade” of ventricular arrhythmia, and there was a reduction in peak heart rate. However, the frequency of syncope was not reduced with this form of treatment or with any other in the study.[46] Mexiletine is only available in the

oral formulation in North America. Both mexiletine and tocainide appear to have synergistic properties when combined with class IA or class II agents.[46]

202.8.3 Class IC Drugs

Class IC drugs are blockers of slow sodium channels and are strong depressants of phase zero and conduction velocity. They exert a minimal effect on refractoriness or action potential duration. They are indicated for supraventricular and some ventricular arrhythmias and arrhythmias involving accessory pathways. They are notorious in humans for their proarrhythmic tendencies when given in patients with coronary artery disease. They depress contractility, cardiac output, and systemic blood pressure. These drugs are contraindicated in the presence of AV block, BBB, and myocardial depression. Flecainide and propafenone are class IC agents.

Flecainide is indicated for paroxysmal supraventricular tachycardia (SVT) and paroxysmal AFib but not for chronic AFib or in patients with ventricular dysfunction, ventricular hypertrophy, ischemic heart disease, or valvular heart disease. It has not been studied in clinical small animal medicine. This drug may induce or aggravate congestive heart failure.

Propafenone has local anesthetic effects and a direct stabilizing action on myocardial tissue, as well as weak beta-adrenergic–blocking activity. It prolongs A-V nodal conduction (A-H and H-V) and has negative inotropic action. It is effective against many SVT and accessory pathway arrhythmias but has not performed as well as had been hoped in the context of treating ventricular arrhythmias.[116] In structurally normal hearts, proarrhythmia is unlikely in humans. Propafenone is only available in the oral form in North America.

202.9 CLASS II ANTIARRHYTHMICS

Class II antiarrhythmics (beta-blockers) decrease or nullify the electrophysiologic and arrhythmogenic effects of beta-adrenergic sympathetic stimulation.[117–119] The magnitude of the beta-blockade effect is dependent on the prevailing level of sympathetic tone. Sympathetic stimulation increases the likelihood of slow calcium channels opening and increases the rate of pacemaker discharge. Overall, beta-blockers depress the slope of phase 4 depolarization and minimally raise the threshold for activation in sinus and AV nodal cells, thereby suppressing automaticity. The effect of beta-blockers on normal cell refractoriness and conduction is modest, and it is unlikely that they influence cardiac repolarization. As a result of the negative inotropic (contractility), chronotropic (rate), and dromotropic (AV node clearance time) effects, cardiac output is reduced and myocardial oxygen requirements and LV work are decreased in normal tissue. In the past several years the beneficial effects of beta-blockers have become increasingly recognized in the setting of severe myocardial disease, where initiation of treatment at extremely low doses and careful up-titration appear to provide a long-term cardioprotective effect.

Beta-blockade is indicated for supraventricular tachycardias, including atrial flutter, AFib, and pre-excitation tachyarrhythmias. It is more effective in controlling the ventricular rate response to AFib when combined with digitalis. Beta-blockade should be helpful in ventricular arrhythmias induced by sympathetic stimulation.[120] It may be used in combination with a class I agent for refractory ventricular tachyarrhythmias in the dog[46] or alone as the primary agent in the cat. Beta-blockade traditionally has been useful in the treatment of systemic hypertension, obstructive heart disease,[121] thyrotoxicosis, and digitalis toxicity. Elimination of propranolol paradoxically is longer in hyperthyroid cats than in euthyroid cats. Additional roles in the management of pheochromocytoma, theobromine intoxication (see Figure 202-25), dilated cardiomyopathy, and portal hypertension are possible.[119]

Contraindications include AV block and SSS (unless a functional artificial pacemaker is in place). Many beta-blockers are not cardioselective (i.e., they exert their effects on both $beta_1$ and $beta_2$ receptors), resulting in bronchial smooth muscle constriction. Nonselective beta-blockers are contraindicated in patients with dynamic bronchial disease. Beta-blockers, especially nonselective types, may interfere with the compensatory response to hypoglycemia and exercise.[119]

Since the publication of the last edition of this textbook, a number of clinical studies involving thousands of human patients have been conducted, and they have demonstrated conclusively that when properly initiated and titrated, some specific beta-blockers are of benefit in patients being treated for CHF (see Chapter 199).[117,122–125] Of specific interest in CHF, carvedilol has both beta-adrenergic and $alpha_1$-blocking activity, which provides additional vasodilation. These effects appear to be unrelated to the drug's antiarrhythmic action. However, other beta-blockers that do not also possess $alpha_1$-blocking properties are also similarly effective in treating heart failure patients.[124] When administered correctly, beta-blocking drugs improve long-term myocardial function through a number of mechanisms.[117,118,125,126] Because of the potential for adverse effects from excess beta-blockade, the dose rate must be individually titrated.[127] Side effects of beta-blockade therapy include lethargy, fatigue, depression, anorexia, vomiting, and diarrhea. Adverse reactions might include hypotension, onset or recurrence of CHF, AV block, bronchospasm, or hypoglycemia. Myocardial depression may be addressed with carefully titrated isoproterenol or dobutamine infusions, and sinus bradycardia with atropine or glycopyrrolate administration, but prevention of these effects through slow, meticulous up-titration and regular monitoring is the preferred course. After chronic oral use, drug withdrawal should be gradual to prevent acute arrhythmia induction or systemic hypertension.

When a beta-blocker is given to patients with CHF, they must be euvolemic. That is, patients receiving beta-blockers under any circumstance should not have pulmonary edema or other form of critical fluid retention. The slight decrease in heart rate and ventricular contractility that may occur with even small doses of these agents may mean the difference between survival and decompensation in a patient with fulminant pulmonary edema, for example. Other contraindications for beta-blockers include systemic hypotension and peripheral vascular disease.

Cardioselective ($beta_1$-blocking) agents exert their primary effect on cardiac $beta_1$ receptors, especially at lower doses. This property is helpful in patients with asthma, chronic bronchial disease, hypoglycemia, peripheral vascular disease, or thrombosis. Atenolol, esmolol, and metoprolol are examples of $beta_1$-selective blockers. Other beta-blockers possess mild intrinsic sympathomimetic activity (ISA) that provides some protection for patients with underlying myocardial failure or those dependent on high sympathetic tone to maintain cardiac output.

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As with all beta-blockers, dose must be titrated individually. Published doses are target doses, and initiation of therapy often begins at one eighth, one quarter, or one half of these doses, with the lowest fraction used when the myocardium is most dyskinetic (hypocontractile).[127] For example, in healthy dogs, acute carvedilol doses of 1.5 mg/kg orally, twice a day are tolerated and effective at preventing STach.[128] However, in dogs with experimentally induced mitral regurgitation, a target dose of 0.4 mg/kg once daily of carvedilol should be reached via initiating the drug at a dose of 0.2 mg/kg or less, because a small but significant, acute decrease in systemic blood pressure is seen with the 0.4 mg/kg dose.[127] In general with beta-blockers, careful up-titration from small initial doses is the rule, especially with a history of CHF. Retitration is also required when switching

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to sustained release formulations. Intravenous therapy is reserved for acute arrhythmias, especially anesthetic-or pre-excitation related supraventricular tachycardias (see Class IV Antiarrhythmics, following).

Propranolol was the standard beta-blocker used in veterinary medicine for years, and it remains the drug against which newer agents are compared. It blocks both $beta_1$ and $beta_2$ receptors. It is well absorbed orally, experiences large and variable first-pass hepatic and portal elimination, and has variable plasma protein binding. The half-life is 3 to 6 hours in dogs, but effects may persist long enough to require only twice-daily dosing after prolonged use. Lethargy in cats is a prominent side effect. Beta-blocking agents with longer durations of action are often used in place of propranolol.

Atenolol is a $beta_1$-selective agent with the advantage of requiring once or twice daily dosing in cats. In nine normal cats, atenolol reduced heart rates for 12 hours or more; β-blockade was not evident at 24 hours using an oral dose of 1.4 mg/lb.[129] A practical approach for determining whether once daily or twice daily atenolol dosing is best for a particular cat consists of initiating the medication to be given once daily in the evening. A daytime recheck visit is scheduled for 7 to 14 days after initiation of treatment, and if an exam room heart rate is superior to the desired maximum with beta-blockade (e.g., maximum 180 bpm in a chronic heart failure patient; maximum 160/min in a compensated patient never having been in heart failure), then the dose is increased to twice a day. In a four-way drug study involving boxer dogs with familial arrhythmia, atenolol alone at 0.17 to 0.27 mg/lb did not change the frequency or "grade" of ventricular ectopy or the heart rate, and there was no reduction in the frequency of syncope.[46] When atenolol was combined with mexiletine, results were slightly more positive (see previous discussion).

Another longer-acting drug, metoprolol, is effective in dogs requiring beta-blockade and in those with CHF associated with MVD or DCM. Studies of induced CHF in dogs indicate efficacy of a sustained release human formulation for the dog, and suggest a possible beneficial increase in ejection fraction when beta-blocking agents are added.[130]

Esmolol is an ultrashort-acting (9 minutes), rapid onset (2 minutes), cardioselective beta-blocker. It has been used as a trial agent (initial dose of 0.05 mg/lb intravenously; may increase to dose of 0.22 mg/lb [0.5 mg/kg] given intravenously over 1 minute) to transiently block AV nodal conduction in supraventricular arrhythmias[63] and at a similar dose over a period of 6 minutes to reduce LV outflow tract gradients in cats with obstructive hypertrophic cardiomyopathy.[131] It may also be given at the lower dose to temporarily slow a supraventricular tachycardia, which can assist in identifying its ECG features for an accurate diagnosis or may terminate the arrhythmia.

202.10 CLASS III ANTIARRHYTHMICS

Class III drugs specifically prolong the action potential duration and the refractory period, principally by inhibiting the repolarizing potassium channel (I_K). This class of drugs reduces the myocardium's ability to generate a new action potential before repolarizing, and thus these drugs slow or terminate tachycardia. These effects are most pronounced at higher heart rates. These drugs lengthen the action potential duration in a tachycardia,[132] but they should have few effects at normal heart rates. They are noted for increasing the threshold for AFib and VF. Each drug in this class also frequently displays properties of other antiarrhythmic classes. This drug group includes amiodarone, sotalol, bretylium, ibutilide, and dofetilide (Table 202-1). Only the first three agents are used in small animal medicine, and bretylium is expected soon to be unavailable because of the exhaustion of the world supply of bretylium.[90]

Amiodarone is one of the drugs of choice for many supraventricular and malignant ventricular tachyarrhythmias in humans. It exhibits properties of all four classes of antiarrhythmic agents and thus is considered a "broad-spectrum" antiarrhythmic. Unlike many antiarrhythmics, amiodarone has not been linked to increased mortality in large clinical trials in human cardiology, and it is second only to automated internal defibrillators in terms of beneficial outcomes in human patients with severe ventricular arrhythmia.[116] It may be useful in dogs with LV systolic dysfunction and to offer rate control, as well as for converting acute AFib to sinus rhythm. Amiodarone relaxes vascular smooth muscle, resulting in a decreased afterload that also may be beneficial. Amiodarone increases serum digoxin levels so that the dose of digoxin should be halved. Quinidine and procainamide levels are also elevated.[133] Side effects reported in humans include liver damage, photosensitization, thyroid derangements, ocular lesions, and irreversible pulmonary fibrosis. In dogs, neutropenia and hepatopathy have been reported with amiodarone treatment,[134] as have anorexia, GI disturbances, hepatopathy, and positive Coombs' testing.[135] These signs resolved with discontinuation of treatment. Anecdotal reports of acute hypersensitivity, hyper-or hypothyroidism, likewise have surfaced but are not conclusively attributable to the drug. In an experimental study, normal dogs given amiodarone 12 mg/lb orally, twice a day for 3.5 weeks, followed by 12 to 14 mg/lb orally, once a day as maintenance, had serum amiodarone concentrations considered to be therapeutic (1 to 2.5 μg/mL) within 4 days, but these levels only reached a steady state after 11 weeks of treatment.[37] However, several anecdotal reports have surfaced indicating that adverse effects occur at this dose and that a lower dose may be preferable, such as 4.5 mg/lb orally, twice a day for 1 week and 2.2 to 3.8 mg/lb orally, once a day subsequently for maintenance.[136] No clinical reports exist in veterinary medicine that address hemodynamic or electrophysiologic effects that could indicate proarrhythmia—a major concern in humans with the long QT syndrome. Despite the clear benefits of amiodarone in human cardiology, acceptance in veterinary medicine is compromised by these descriptions of adverse effects and the lack of reports indicating a benefit of amiodarone therapy over other antiarrhythmic agents. Amiodarone use has not been described in cats.

Sotalol provides both class III (higher dose) and class II (l-isomer, lower dose) effects. It is not a negative inotrope and thus does not decrease LV contractility. It induces systolic and diastolic hypotension and is considered to have ~30% beta-blocking potency compared with propranolol. It is considered to be protective against proarrhythmia, particularly life-threatening ventricular arrhythmias. Currently, only *dl*-sotalol, which combines the class III and class II effects, is used (*d*-sotalol caused increased mortality in human clinical trials and is not advocated).

In the first reported veterinary study using sotalol, three classes of Boxer dogs with familial ventricular arrhythmia were identified: asymptomatic, syncopal, and CHF. Slowing of the heart rate and first-degree AV block were the only side effects observed, although proarrhythmic effects have been suspected in other cardiomyopathic dogs with sotalol. The dose of sotalol administered to these dogs was 0.44 to 2.8 mg/lb/day twice a day orally, titrated to effect. The heart failure dogs received less medication, up to 104 mg/day average versus the syncopal group at 183 mg/day. Syncopal signs were diminished on sotalol therapy, and dogs with markedly diminished shortening fraction did not appear to exhibit untoward drug effects.[139] In a second study comparing four types of treatment for familial ventricular arrhythmia of Boxers, sotalol 0.68 mg/lb to 1.6 mg/lb orally twice a day significantly reduced the number of PVCs, arrhythmia grade, and maximum and minimum heart rates. However, there was no significant change in the occurrence of syncope for sotalol or for any of the other three treatments studied.[46] Sotalol has been effectively administered to cats with severe ventricular arrhythmias at 10 to 20 mg orally every 8 to 12 hours.[138] It is thought that class II effects are predominant at lower doses and class III effects are predominant only at higher doses (>160 mg in humans).

Sotalol's good oral absorption is reduced when given with food. Steady state is reached within 2 to 3 days. It is indicated for life-threatening ventricular arrhythmias, may be used with caution in CHF, and should not be abruptly discontinued. Sotalol is used cautiously with other drugs that decrease blood pressure, as well as other antiarrhythmics, specifically those that prolong the Q-T interval. The authors of this chapter have observed prolongation of the P-R interval with sotalol treatment in dogs, as has been reported anecdotally. No overt problems or progression occurred, and it was not necessary to discontinue the drug concurrent with this finding.

202.11 CLASS IV ANTIARRHYTHMICS

Class IV drugs, known as the *calcium channel blockers*, selectively inhibit slow inward calcium current channels (L-type) during the action potential. Calcium channel blockers interrupt arrhythmias resulting from abnormal automaticity and triggered mechanisms and inhibit re-entry. They slow the sinus rate and, more profoundly, AV conduction by blocking the inward calcium current carried by the L-(and probably T-) type channels.[140] By decreasing sarcoplasmic reticulum release of Ca^{++}, they also decrease the force of contraction. Decreasing the amount of calcium into the myocyte may help to decrease myocardial protein synthesis and thus attenuate the pathologic process of hypertrophy. They have indications for the control of most supraventricular tachycardias. Contraindications include SB, AV block, myocardial failure, SSS, and digoxin toxicity. Calcium channel blockers are classified as either dihydropyridines, which do not affect conduction and act principally on the vasculature (e.g., nifedipine, amlodipine), or nondihydropyridines, which have SA and AV nodal (but minimum vascular) effects (e.g., verapamil, diltiazem) (see Table 202-1).

Verapamil has potent negative inotropic effects, offers moderate rate control, and has minimal peripheral vascular effects. In dogs it may slow the sinus rate, increase AV conduction time, or decrease the ventricular response. In acute supraventricular tachycardias, it is given in 0.01 mg/lb intravenously in increments to a maximum of 0.07 mg/lb. Acute hypotension, AV block, collapse, or hypocalcemia may result from overly zealous up-titration. Judicious calcium chloride administration may correct iatrogenic disturbances.

Diltiazem's effective antiarrhythmic properties, combined with minimal inotropic depressive actions, have caused it to be used widely in cats with hypertrophic cardiomyopathy. Its frequency-dependent channel blockade in the AV node makes it effective in slowing supraventricular arrhythmias as has been shown in experimental dogs.[141] It is usually used in combination with digoxin to effectively slow the ventricular rate in AFib, except if LV thickening is present. Comparison studies in dogs between diltiazem and beta-blockade, with or without digoxin, are not available. Diltiazem-induced vasodilation may create a reduction in afterload that is of chronic benefit to the patient with systolic heart failure.[140] Regular (not sustained release) diltiazem has been administered to cats with hypertrophic cardiomyopathy in a nonplacebo-controlled study. Over 6 months there was a reduction in LV and septal wall thickness and a reduction in LA size.[142] The dose of diltiazem for dogs and cats is 0.2 to 0.7 mg/lb three times a day. However, because three-times-daily dosing of a lifelong drug can be extremely challenging for many cat owners, sustained release formulations of diltiazem (e.g., Dilacor®, Cardizem-CD®), which carry the advantage of once daily administration, have been used extensively. Evidence has shown that cats receiving 4.4 mg/lb oral sustained release diltiazem CD have plasma concentrations of the drug that are similar to cats receiving 0.44 mg/lb regular diltiazem orally, three times a day.[143] However, sustained release diltiazem is hampered by its apparently lower efficacy at preventing STach when compared with the beta-blocker atenolol, as well as a significant occurrence of reversible but severe adverse effects including anorexia, vomiting, lethargy, and evidence of hepatopathy in a substantial proportion of treated cats in one large prospective, placebo-controlled study.[144] For these reasons, sustained release diltiazem is used cautiously or not at all in cats with hypertrophic cardiomyopathy.

For intravenous treatment of supraventricular tachycardias, diltiazem has been recommended at 0.2 to 0.44 mg/lb[141] or 0.12 mg/lb over 2 minutes and repeating until conversion or a maximal dose of 2.2 mg/lb has been reached. These high doses are reserved for patients with tachycardia and a structurally normal heart. Patients with a structurally compromised heart (e.g., cardiomyopathy) should be given one-sixth to one-quarter of the starting dose (i.e., 0.02 to 0.03 mg/lb) initially, and then the dose should be titrated upwards to effect. If the tachycardia is a physiologic response to a systemic problem (e.g., hypovolemia, CHF), it is essential to treat the underlying problem first. Administration of intravenous drugs to suppress an appropriate physiologic tachycardic response can be fatal. Intravenous rate-suppressing drugs such as the calcium channel blockers are given when, despite treating systemic problems that could trigger high heart rates (e.g., CHF), an extreme tachycardia persists and is felt to compromise cardiac output. An example is a dog with dyspnea and weakness caused by dilated cardiomyopathy, cardiogenic pulmonary edema, and AFib with a ventricular rate of 310 bpm. If vigorous diuretic treatment, oxygen therapy, thoracentesis (if necessary), calming, and possibly mild sedation do not reduce the ventricular rate, the tachycardia itself may be compromising cardiac output and intravenous calcium channel–blocking (or beta-blocking) treatment meant to acutely and *slightly* lower the ventricular rate (e.g., to 260 bpm initally) should be considered. Continuous ECG and blood pressure monitoring are essential with all IV calcium channel–blocking agents.

Amlodipine and nifedipine are potent vasodilators that produce a marked decline in arterial blood pressure through calcium channel blockade. They have minimal effect on AV nodal tissue and are not used as antiarrhythmic agents. Instead they are used for treating systemic hypertension (see Chapter 130).

202.11.1 Digitalis Glycosides

Digitalis glycosides (digoxin) have multiple effects on cardiac muscle and conductive tissues. Their predominant antiarrhythmic properties result from neuroendocrine and baroreceptor effects and parasympathomimetic action on the SA and AV nodes and atrial muscle.[145] AV nodal conduction is slowed, AV nodal refractoriness is increased, and vagal tone to ventricular muscle is increased. Digitalis glycosides 1074
are the only antiarrhythmic agents that produce a positive inotropic effect, although this effect may be limited 1075
in degree and real benefit. Their primary indications for use are treatment of supraventricular tachycardias, which they accomplish by slowing the ventricular rate response. Often a second agent in combination, such as a beta-blocker or calcium channel blocker, is needed to attain adequate rate control. Combination therapy of this sort is particularly beneficial because both products are then administered at lower doses and thus are less likely to induce toxic reactions. A recent, intriguing finding is an endogenous cardiac glycoside deficiency that appears to exist in some dogs with naturally occurring CHF and AFib.[146]

They are contraindicated in pre-excitation, because they may speed conduction through the accessory pathway and thus promote VF. Caution should be exercised with the use of digoxin in the face of existing ventricular arrhythmias. Dosing and pharmacokinetics are discussed in Chapter 199.

Digitalis intoxication is a serious, potentially life-threatening event. GI signs may be the first symptoms observed. Myocardial poisoning may take one of several forms, all of which culminate in cardiac arrhythmias. Increased sympathetic tone may result in increased automaticity. Slowed conduction and altered refractoriness may precipitate re-entry. Increased intracellular calcium levels predispose the cell to delayed after depolarizations. Any of these changes can be the source of arrhythmogenesis. Electrocardiographically, VT, supraventricular tachycardia, junctional escape complexes, SA arrest, Wenckebach or other forms of AV block, and tachycardias with aberrant conduction may be seen. The cornerstone of treatment is to stop the drug immediately and completely. Supportive fluid and electrolyte therapy should be provided as necessary.

Hypokalemia exacerbates digitalis intoxication. Specific treatment for VTs may be needed. Lidocaine and beta-blockers may be considered, as well as many other drugs, depending on the predominant arrhythmia. Atropine may help patients that are symptomatic from bradyarrhythmias. Acute ingestion may be treated with cholestyramine or activated charcoal to reduce absorption. Soluble, intravenously administered digitalis neutralizing antibodies (Fab fragments) bind serum digitalis molecules and are the treatment of choice for life-threatening digitalis (or oleander) poisoning,[147] although high cost limits the use of this treatment. After resolution of clinical signs of intoxication and a minimum of 48 hours without receiving a dose, the digoxin may be restarted at half the dose.

One must be aware of numerous potential drug interactions when using digitalis glycosides. Kaolin-pectin, metoclopramide, neomycin, antacids, and bran decrease oral absorption, and quinidine and verapamil may increase serum digoxin levels substantially. Decreased excretion may result with captopril, verapamil, and spironolactone,[3] although newer protocols incorporating spironolactone therapy in the standardized treatment of CHF have not demonstrated this interaction to be a problem.

202.11.2 Adenosine, Edrophonium, Phenylephrine

Adenosine is an endogenous nucleoside occurring in all cells of the body. Therapeutically, when given intravenously, it slows AV nodal conduction and restores sinus rhythm in patients with paroxysmal supraventricular tachycardia. Adenosine is indicated as the drug of choice in human patients with acute paroxysmal supraventricular tachycardia, including those caused by the WPW syndrome (see previous discussion). Suggested total doses for a human adult are 1.5 to 3.0 mg initially, repeated to a maximum of 6 to 12 mg.[120] In dogs, doses corresponding to two or more times this amount on a body weight basis have been ineffective in abolishing supraventricular tachycardias,[63] and adenosine is considered much less effective in veterinary patients. In small animal medicine, adenosine's lack of a convincing advantage over intravenous diltiazem or esmolol and its high cost make it a second-or third-line treatment agent.

Edrophonium is an anticholinesterase agent with both nicotinic and muscarinic side effects. This drug classically has been used for the diagnosis of myasthenia gravis (MG) and may be useful to treat SVT acutely. The dose is 0.05 mg/lb intravenously. Side effects include vomiting and muscular twitching.[3,120]

Phenylephrine, an alpha-adrenergic agonist, slows AV nodal conduction and induces vasoconstriction and hypertension. A baroreceptor-mediated reflex is thought to be the mode of slowing SVT. It is given at 0.002 to 0.004 mg/lb intravenously.[120]

202.11.3 Radiofrequency Ablation

In human medicine, cardiac catheter-based electrophysiologic testing followed by radiofrequency ablation of re-entrant circuits has become the treatment of choice for intra-atrial re-entry (e.g., atrial flutter) and AV reciprocating tachycardias such as WPW. This type of treatment can permanently interrupt the pathways and terminate the arrhythmia. Radiofrequency ablation thus offers the possibility of a permanent cure for certain arrhythmias including WPW and atrial flutter.

The high rate of success, low morbidity and mortality, and cost-effectiveness of this technique have resulted in an entirely new subspecialty of human medicine dedicated to the study and treatment of specific electrophysiologic dysfunctions of the heart. In veterinary medicine, radiofrequency ablation has received limited attention.[100,111,148] In addition to eliminating the subsequent need for antiarrhythmic medications,

radiofrequency ablation of arrhythmia pathways prevents, and can even reverse and eliminate, structural changes such as ventricular dilation caused by a persistent arrhythmia *(tachycardiomyopathy)*.[100] Although radiofrequency ablation therapy has clear indications and applications in small animal medicine, the cost, need for specialized equipment, required skills, and limited demand restrict its use to a small number of highly specialized cardiac institutions at this time.

202.11.4 Pacemaker Therapy

Implantable cardiac pacemakers were first placed in human beings in 1958.[149] During the intervening period there has been a revolution in the understanding and treatment of bradyarrhythmias, as well as pacemaker and electrode technology.[149] Whereas over one-half million pacemakers are now placed annually by physicians, only several thousand have been implanted clinically in dogs and cats during the past four decades.[95] Internal cardioverter-defibrillator-pacemaker implants increasingly are the treatment of choice for ventricular arrhythmias in humans.[116] Their clinical use in dogs previously has met with problems, and such treatment remains under development.[150]

In small animal medicine, pacemakers are used predominantly for bradyarrhythmia therapy, including sinus node dysfunction (SSS), AV block, and atrial standstill.[103,104,151,152] In human beings, implantable electrical devices are used for pacing and cardioversion, defibrillation, and specific forms of heart failure.[149]

Costs, availability of pacemaker generators and pacing leads, the age and debilitated state of some candidate dogs or cats, and concerns regarding complications, aftercare, and general philosophy continue to restrict the availability of this technique to a limited number of patients. Whereas the human literature is replete with articles and current recommendations, such as dual-chamber versus single-chamber ventricular pacing, the balance of this section identifies current veterinary techniques and experiences with pacemaker implantation in North America. Although veterinary pacemaker techniques are not up to those used in humans, current treatment options for animals are discussed.

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Reported methodology, problems, side effects, and expectations are addressed in three large cases series totaling some 300 dogs[3,103,104] and reports of fewer than 10 cats.[3,94,153] Pacemakers were originally implanted transdiaphragmatically using epicardial leads,[95] but now most are implanted in the dog transvenously through the jugular vein and attached internally to the RV wall. This is accomplished either with a “tined” lead or a lead that is screwed into the ventricular endocardium and myocardium.[151,152] In cats such adverse reactions to transvenous leads as chylothorax have been observed anecdotally and in at least one report.[94] The trend today is to implant epicardial leads in cats requiring pacemaker treatment. The permanent pacemaker generator is usually buried in a subcutaneous pocket of the neck, lateral thorax under the cutaneous trunci muscle,[104] or cranial abdomen and is connected to the pacing lead through a subcutaneous tunnel. Anesthesia has used a balanced formula avoiding barbiturates,[151] and temporary pacing during the initial part of pacemaker implantation is recommended. Traditionally, temporary pacing was achieved transvenously,[151] but a recent evaluation of transthoracic pacing, a function found in many modern defibrillators in veterinary intensive care units, has demonstrated that this completely noninvasive form of temporary cardiac pacing is effective and safe in canine patients.[154]

Pacemakers are usually identified via a three-letter code.[3,149,152] The first letters identify the chamber or chambers paced, sensed, and the response to sensing. Whereas the DDD mode is the preferred pacemaker for

most humans, the VVI mode is used most often in dogs and cats. It is essential to ensure that the pacemaker generator's polarity and the pacing lead polarity are compatible. Unipolar generators may be used with any pacing lead that fits, but bipolar generators must only be used with bipolar pacing leads.[151] The pacemaker's program, the fit between generator and pacing lead, and the length of the lead must all be confirmed prior to beginning implantation.

Most veterinary cardiologists and internists secure their pacemakers from private sources, morgues, or from the ACVIM Cardiology Specialty group. With limited equipment availability, especially pacing lead wires, clinicians must be gracious about the gifts they receive. New pacemakers and wires individually would otherwise cost tens of thousands of dollars for each unit.

Perhaps a perfect pacemaker candidate does not exist. Patients are often older, and the pacemaker does not provide a cardiac panacea. Nevertheless, some stratification of prognosis is possible. Some dogs requiring a pacemaker are in CHF when the need for a pacemaker is identified. These dogs generally experience a marked improvement in, or resolution of, heart failure with pacing, but overall still have a prognosis that is less favorable than dogs without CHF. In one study the 1-year mortality rate after pacemaker implantation was 60% if there was pre-existing CHF and 25% if there was not.[103] Evidence of renal failure (azotemia with isosthenuria) or opportunistic infection (e.g. pneumonia) has resolved with pacing, and such findings at the time of initial diagnosis should not be considered absolute contraindications to pacemaker implantation.

New developments in cardiac pacing include the single-lead AV mode of pacing and alternate sites of generator and lead placement. Using a specific type of single RV pacing lead, it is possible to pace both the atria (through a nexus in the lead that transmits impulses at the level of the RA) and the ventricles (at the distal tip of the lead). This approach offers several advantages, including the use of only one pacing lead to activate both the atria and the ventricles, and preservation of AV synchrony, resulting in superior hemodynamics.[155] In terms of placement of the pacing lead and generator, two reports address the high complication rate (10% overall[103] and up to 35% in large breed dogs[156]) of lead dislodgement. An alternative approach uses thoracotomy and passage of the pacing lead through the costocervical vein instead of the external jugular vein. This approach was successful, with none of six large dogs undergoing pacemaker implantation in this manner sustaining dislodgement of the lead.[156] A drawback is the need for concurrent thoracotomy and fluoroscopic guidance. A second approach consists of routine transvenous jugular implantation but with placement of the generator under the cutaneous trunci muscle instead of between muscles of the lateral neck. This modification was associated with a complication rate of only 6.7% in terms of lead dislodgement.[104]

Overall, pacemaker implantation is an effective form of cardiac therapy in dogs. Prolonged survival routinely is documented, reported complications continue to be addressed via refinements of technique, and in the largest retrospective study of dogs with pacemakers, 80% of owners described a high degree of satisfaction with the procedure.[103]

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203 CHAPTER • 203 Primary Myocardial Disease in the Dog

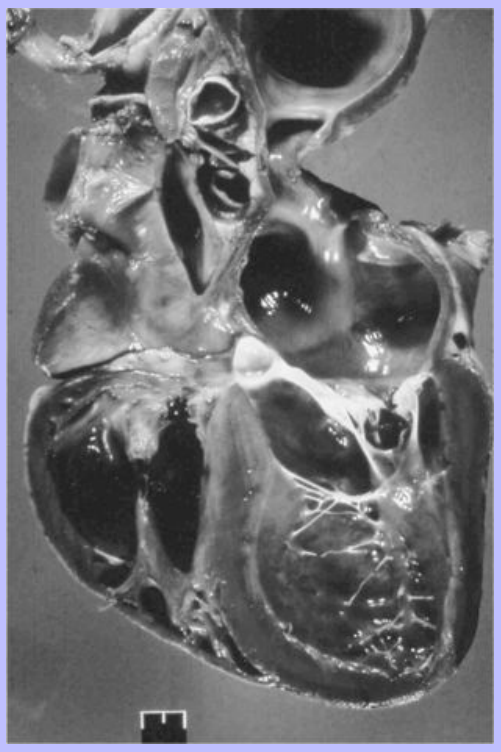
Kathryn M. Meurs

Canine myocardial disease is one of the most common forms of acquired heart disease in the dog.[1] The most common form of myocardial disease in the dog is dilated cardiomyopathy, but arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy and myocarditis, among others, are also reported.

203.1 CANINE DILATED CARDIOMYOPATHY

Dilated cardiomyopathy (DCM) is a primary myocardial disease characterized by cardiac enlargement and impaired systolic function of one or both ventricles (Figure 203-1). Diastolic dysfunction may also be observed.[2] An increased understanding of the etiology of both the human and canine disease has lead to the development of the theory that DCM is the final result of a variety of myocardial insults including viral, nutritional, toxic, and genetic.[3] In human beings, the disease has been shown to be familial in almost 50% of the cases, caused by mutations in nine different genes.[4] The etiology in many cases is never determined and they are considered idiopathic.

Figure 203-1 Heart from a Doberman pinscher with dilated cardiomyopathy. The left ventricle and left atrium are grossly dilated. (Courtesy Bruce Keene.)



Although canine DCM is described as one disease, significant variation in the presenting complaint, clinical evaluation, and rate of progression has been observed depending on the breed of dog.[5–11]

Generally DCM is a disease of large and medium-sized dog breeds. Some breeds are clearly overrepresented, particularly in specific geographic regions. Surveys in North American publications find an increased incidence in the Doberman pinscher, Irish wolfhound, Great Dane, and Cocker spaniels.[12,13] European sources suggest an increased incidence of the Airedale terrier, Doberman pinscher, Newfoundland, and English cocker spaniel.[14] This difference may suggest an influence of environmental factors on the development of DCM, but more likely it is related to the strong genetic influences of certain popular dogs within an area.

203.1.1 Clinical Presentation

Dilated cardiomyopathy is an adult onset disease, with the exception of the Portuguese water dog.[11] The clinical presentation may be subtle and include the gradual development of exercise intolerance and weight loss.[15] However more commonly, early indications of disease may be overlooked. A diagnosis is not made until CHF develops and the patient is presented for coughing, dyspnea, tachypnea, and occasionally, ascites.

203.1.2 Physical Examination

A soft systolic murmur consistent with mitral valve regurgitation and/or a gallop rhythm (S_3) may be ausculted at the left apex. A tachyarrhythmia may be noted. In some cases, these may be the first signs of the disease in an otherwise healthy dog. Since primary valvular disease is relatively uncommon in large breed dogs, and the detection of DCM before the development of CHF may be beneficial in the long-term management of the case, identification of a new murmur, gallop or tachyarrhythmia in suspect breeds may warrant a thorough cardiac work-up. Although canine DCM is predominantly a left ventricular disease, biventricular involvement and heart failure with jugular venous distension and ascites is frequently noted, particularly in the giant breeds.

203.1.3 Electrocardiography

Left atrial and ventricular enlargement and sinus tachycardia, atrial fibrillation, or ventricular tachyarrhythmias are common.

203.1.4 Radiography

Left atrial and ventricular enlargement with or without pulmonary venous distension and pulmonary edema may be observed. In some cases, biatrial and biventricular enlargement may be noted. If the disease is diagnosed in the early stages, radiographic findings may be subtle.

203.1.5 Echocardiography

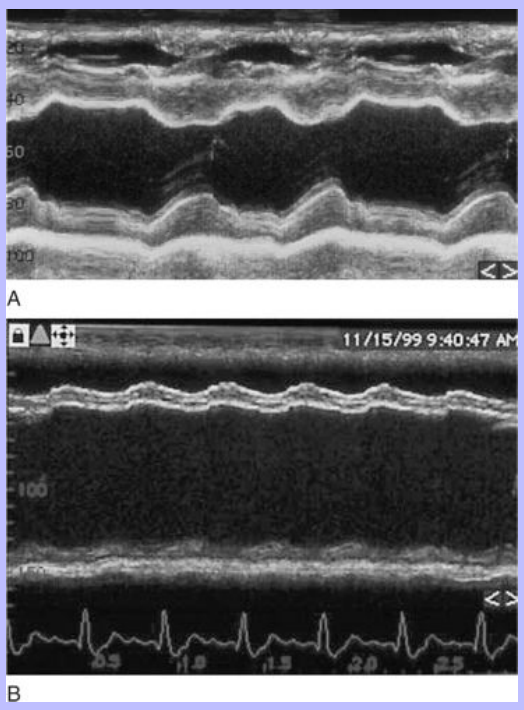
Echocardiography is the diagnostic test of choice for canine DCM and is also an important part of detection of occult disease. Echocardiographic findings in the symptomatic patient should include left and sometimes right atrial and ventricular dilation as quantified by M-mode and two-dimensional measurements (Figure 203-2). The measurements should be compared with the normal values for that particular breed or size (body surface

area) of dog. In some cases, the ventricular wall thickness may appear thin during diastole, but more often it is within normal limits. An important part of the diagnosis is usually concurrent left ventricular systolic dysfunction based upon decreased fractional shortening, ejection fraction, or shortening area and increased end-systolic volume.[16] Doppler echocardiography may be used to document a central jet of mitral regurgitation that may be associated with dilation of the ventricle.

A differential diagnosis for DCM is severe atrioventricular (AV) valve disease since severe ventricular dilation and systolic dysfunction may be observed. Consideration of the breed of dog may be helpful in differentiation between DCM and AV valve disease since it is uncommon for many of the large breed dogs to develop primary valve disease. An exception to this may be the Cocker spaniel, a breed that has a high incidence of primary valve disease and also is at increased risk of DCM.

Unfortunately, the diagnosis of the affected dog in the occult (asymptomatic) stage is much more difficult. In some cases, dilation of the ventricle precedes the development of systolic dysfunction and is an early indicator of DCM.[17] However, this is not always the case and systolic dysfunction may precede dilation. Annual two-dimensional and M-mode echocardiography is recommended for adult dogs of at risk breeds or if early signs (e.g., heart murmur, gallop, tachyarrhythmias) are detected. Suggested additional studies for additive information when evaluation of borderline cases include measurement of the mitral valve annulus motion, systolic time intervals, systolic and diastolic performance index, and stress echocardiography.[18–20]

Figure 203-2 **A,** M-mode echocardiogram from a normal dog with adequate contractility. **B,** M-mode echocardiogram from a Great Dane with a dilated left ventricle with a markedly decreased systolic function.



203.2 BREED VARIATIONS

There is an increasing amount of breed specific information about canine DCM. Because of differences the specific breed should be considered when considering etiology, developing treatment plans, and providing prognostic information.

Occasionally, atypical breeds of dogs develop DCM. The etiology of the disease in these cases is unknown.

203.2.1 Cocker Spaniels

Dilated cardiomyopathy has been reported in both American and English cocker spaniels; however, DCM occurs less commonly in this breed than valvular endocardiosis.[5,21,22]

An association between the development of DCM and low plasma taurine levels has been reported in some American cocker spaniels.[5] Dogs provided taurine and L-carnitine supplementation showed an increase in FS% and a decrease in LVEDD and LVESD over a 4-month period, although myocardial function did not return to normal.[23] This study suggests that at least some Cocker spaniels with DCM may benefit from supplementation with taurine and, perhaps L-carnitine. The current recommendations for American cocker spaniels with DCM are to measure plasma taurine levels (normal >50 ng/ml) and to treat with 500 mg of taurine orally every 12 hours and 1.0 gram of L-carnitine orally every 12 hours.[23] Additional treatment should be given as needed to address such conditions as CHF and arrhythmias. The investigators suggest that supportive cardiovascular medications can be gradually withdrawn after the FS% increases to more than 20% (usually 3 to 4 months of supplementation). Supplementation with taurine, and L-carnitine if possible, should be continued for life. If taurine deficiency is not identified the prognosis is poorer.

English cocker spaniels also get a form of DCM but a relationship to taurine or carnitine levels has not been well studied. Many reported dogs were from the same kennel, which may suggest a heritable component.[24,25] Profound evidence of left ventricular enlargement on the electrocardiogram with R wave amplitudes more than 3.0 mV in lead II was frequently observed.[22,26] Some of the reported dogs died suddenly, but many have had a prolonged, fairly asymptomatic course of disease, or a long survival (years) with medical management.[24–26]

203.2.2 Dalmatians

Male dogs appear to be over represented in Dalmatian DCM, although large studies have not been performed.[6] All dogs had adult onset disease and presented for signs consistent with left heart failure (cough, dyspnea) or syncope. None of the dogs had evidence of biventricular heart failure. Electrocardiography frequently demonstrated sinus rhythm or sinus tachycardia with occasional ventricular ectopy. Atrial fibrillation was not observed in any of the dogs. Duration of survival ranged from 1.5 to 30 months with euthanasia due to refractory CHF. None of the dogs died suddenly. Interestingly, the majority (8/9) of reported dogs had been fed a low protein diet for all or part of their lives for prevention or treatment of urate stones. The cause and effect of these diets on the development of DCM is not known, but Dalmatians that develop DCM that are being fed a low protein diet should be switched to a more balanced diet if possible.

Occasionally Dalmatians develop acquired AV valve disease, so this should be considered as an important differential diagnosis.

203.2.3 Doberman Pinschers

The Doberman pinscher is one of the most commonly reported breeds of dogs to be affected with DCM in North America.[7,13,27] It is characterized as an adult disease that results in the development of left and/or biventricular failure, often with atrial fibrillation. However, about 30% of the dogs develop ventricular tachyarrhythmias and may present for syncope or die of sudden death before the development of heart failure, and in some cases, before the development of ventricular dilation and systolic dysfunction.[28,29]

Dilated cardiomyopathy in this breed is believed to be familial, although the pattern of inheritance is not well documented.[30]

The clinical stage of DCM in the Doberman pinscher appears to be malignant in comparison to the disease in other breeds. The median survival time for dogs once heart failure has developed is 9.6 weeks. Atrial fibrillation and bilateral CHF are poor prognostic signs.[7] However, the occult stage appears to be slowly progressive (2 to 3 years), and some affected dogs die from noncardiac disease before they become symptomatic from DCM. Although there is only a small amount of evidence, there may be some benefit to early diagnosis and initiation of treatment in the occult stage (as discussed below).[31]

Some Doberman pinschers develop syncope or die suddenly before left ventricular dilation or systolic dysfunction ever develops. In most cases, these symptoms are associated with the presence of ventricular tachyarrhythmias. However, bradycardia-associated episodic weakness and syncope has also been observed in cardiomyopathic Doberman pinschers. Therefore Holter monitoring should be performed on the syncopal dog to document the causative arrhythmia before treatment is initiated.[32]

The timing and procedure for treatment of ventricular arrhythmias in the affected dog is not clear cut. Rapid ventricular tachycardia, complex ventricular arrhythmias, or the combination of ventricular arrhythmias, ventricular dilation, and systolic dysfunction is thought to be associated with a higher risk of sudden cardiac death and to be indications for treatment, but this has not been well documented. Additionally, some dogs die suddenly without having any of these arrhythmias documented. If treatment is warranted, consideration might be given to the use of one of several ventricular antiarrhythmics. Sotalol, a combination beta-blocker and potassium channel blocker, may be beneficial in some cases but should be used with caution if systolic dysfunction is present. Amiodarone has been studied in the affected Doberman pinscher at a dose of 10.0 mg/kg orally every 12 hours for 1 week, followed by 8.0 mg/kg every 24 hours.[28] After 6 months the dose may be reduced to 5.0 mg/kg every 24 hours. Careful evaluation of serum concentrations, complete blood counts (neutropenia has been reported), and liver enzymes monthly is suggested.[28] Although the goals of treatment include decreasing the number of VPCs, decreasing symptoms, and decreasing the risk of sudden death. The ability of any antiarrhythmic to reach these goals for these cases has not been proven.

Evidence that the disease is familial and that early intervention may increase survival has lead to significant interest in screening asymptomatic dogs for signs of early disease. Annual echocardiography and ambulatory electrocardiography (Holter monitoring) are believed to be the best predictors of early DCM.[33,34] Criteria that are believed to be indicators of occult disease include an echocardiographically determined LVEDD more than 4.6 cm and a LVESD more than 3.8 cm, even in the absence of systolic dysfunction.[17] These numbers are

based on average sized dogs and may not be valid for very large dogs. Annual Holter monitoring has also been recommended to detect Doberman pinschers that may develop ventricular arrhythmias before ventricular dilation and systolic dysfunction (Figure 203-3). Adult Doberman pinschers with greater than 50 ventricular premature complexes (VPCs) per 24 hours, or with couplets or triplets are suspect for the development of DCM.[34] Owners should be advised that since this is an adult onset disease with variability in the age of onset, screening tests should be performed annually.

Figure 203-3 Adult Doberman pinscher with a Holter monitor used for screening for occult disease.

203.2.4 Great Danes

Dilated cardiomyopathy in the Great Dane appears to be a familial disease.[8] Affected male dogs were overrepresented, which suggests an X-linked pattern of inheritance in at least some families. If this is true, sons of affected females are at high risk of developing the disease; daughters of affected fathers are likely to be silent carriers.

Affected Great Danes presented most commonly for weight loss and/or coughing. Left-sided heart murmurs, gallops, and ascites were frequently observed. The most common electrocardiographic findings included atrial fibrillation with occasional ventricular premature complexes. In some cases, atrial fibrillation may develop before any other evidence of underlying myocardial disease (chamber enlargement or systolic dysfunction). These dogs should be carefully followed for the possible development of DCM.

203.2.5 Irish Wolfhounds

Atrial fibrillation frequently preceded the development of a heart murmur, clinical signs, and CHF in the Irish wolfhound with DCM and was present in the majority of dogs by the time they developed DCM.[9,35] The progression of the disease is not well understood but appears to be slow, with the development of atrial fibrillation preceding the development of CHF by an average of 24 months.[9] Occasionally, additional

electrocardiographic abnormalities have been described, which include ventricular premature complexes and left anterior fascicular block patterns. Echocardiography is useful for separation of normal dogs, dogs with occult disease, and dogs with clinical evidence of heart failure.[36] Affected Irish wolfhounds occasionally died suddenly but more commonly were euthanized due to heart failure, most commonly biventricular and sometimes with chylothorax.[35,36]

203.2.6 Newfoundlands

Adult-onset DCM without a gender predisposition has been reported in the Newfoundland.[10,20] Clinical presentation included dyspnea, cough, inappetance, and ascites with left or biventricular heart failure. Interestingly a heart murmur was auscultable in a very small percentage of the dogs (4 out of 37).[10]

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The most common electrical abnormality was atrial fibrillation, but isolated ventricular premature complexes were also observed.

203.2.7 Portuguese Water Dogs

A juvenile form of familial DCM has been reported in the Portuguese water dog.[11,15] Affected puppies were from apparently unaffected parents. Puppies died from CHF at an average age of 13 weeks after a very rapid course of disease.

203.2.8 Treatment of the Dog with Occult Dilated Cardiomyopathy

Administration of angiotensin converting enzyme (ACE) inhibitors may have some benefit for the dog with early ventricular dilation, with or without systolic dysfunction. Specifically, the use of ACE inhibitors (enalapril, lisinopril, captopril) in the Doberman pinscher with ventricular dilation was found to prolong the amount of time before the onset of CHF.[31] Although this study was limited to evaluation of Doberman pinschers, the use of ACE inhibitors for other breeds of dogs with occult DCM may be considered. This information provides additional support for the practice of screening adult dogs that are at increased risk of developing DCM because of their breed, and perhaps a family history, to allow early medical intervention.

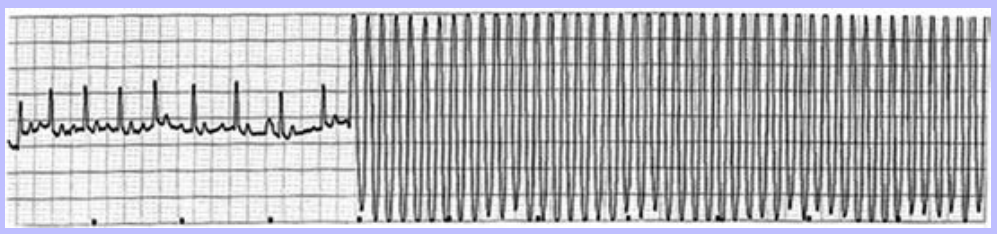
Administration of beta-blockers at this stage is still being evaluated. The addition of low-dose beta-blockers to the treatment of human patients with DCM and stable heart failure has demonstrated a reduction in both mortality and morbidity.[37] However, many human patients with DCM cannot tolerate even very low doses of beta-blockers and demonstrate rapid cardiac decompensation. The use of beta-blockers for the canine patient with DCM has not yet been well studied and a consensus opinion on use of these drugs for patients is not yet available.

Beta-blockers might be considered for the patient with occult disease, but they should be very carefully monitored and should not be given once there is evidence of fluid retention and heart failure until it is very well stabilized. The optimal beta-blocker for this purpose appears to be carvedilol because of its effects on both alpha and beta-receptors. It cannot be overemphasized that the addition of beta-blockers in canine DCM patients should be done very cautiously with gradual increases in dosing after a 2-week period and careful monitoring of heart rate, blood pressure, and symptomology.

203.2.9 Treatment of the Dog with Dilated Cardiomyopathy and CHF

There are no specific therapeutic recommendations for the treatment of DCM other than those mentioned above. Nonspecific treatments, including surgery and nutritional supplementation, have been reported but have not yet been shown to have significant long-term benefits for most dogs.[38–40] As discussed above, early diagnosis and intervention may be of the most benefit. A thorough discussion of treatment of the dog with CHF is provided elsewhere in this textbook.

Figure 203-4 An electrocardiogram from a syncopal Boxer with ARVC. Sinus rhythm with a sudden onset of ventricular tachycardia is present. (Courtesy Alan Spier.)



203.3 ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY IN THE BOXER

Since the early 1980s, the term *boxer cardiomyopathy* has been used to describe adult boxer dogs that present with ventricular arrhythmias, and sometimes, syncope.[41] Recent studies have demonstrated that the disease has many similarities to a human disease called *arrhythmogenic right ventricular cardiomyopathy* (ARVC). The similarities between the diseases include clinical presentation, etiology, and a fairly unique histopathology that includes a fibrous fatty infiltrate of the right ventricular free wall.[42] The disease is most commonly characterized by ventricular arrhythmias, syncope, and sudden death. However, systolic dysfunction and ventricular dilation are seen in a small percentage of cases.

Arrhythmogenic right ventricular cardiomyopathy is a familial disease in the boxer and appears to be inherited as an autosomal dominant trait.[43] Unfortunately, the disease also appears to be a disease of variable genetic penetrance and affected dogs can have many different presentations including asymptomatic, syncope, sudden death, and systolic dysfunction with CHF.

The most common presenting complaint is syncope. Episodes of syncope may be but are not always associated with a period of exercise or excitement. Some dogs present for exercise intolerance or lethargy and others die suddenly without ever developing symptoms. Infrequently (approximately 10% of affected dogs), a dog may present with signs of left or biventricular heart failure.

Most affected Boxers have a completely normal physical examination. However, a tachyarrhythmia may be ausculted. In the small percentage of cases with ventricular dilation and systolic dysfunction, a systolic murmur and/or gallop (S_3) may be ausculted at the left apex. Infrequently, signs of right heart failure (ascites and jugular venous distension) may be observed. The Boxer breed also has a very high incidence of left basilar systolic murmurs. These murmurs may be associated with aortic stenosis, or potentially may be physiologic. Many

boxers with ARVC have these murmurs in addition to their arrhythmic disease, but left basilar systolic heart murmurs are not an indication of boxer ARVC.

A 2-to 5-minute electrocardiogram is frequently normal in the affected Boxer. However, ventricular premature complexes (VPCs) may be present singly, in pairs, and in runs of paroxysmal ventricular tachycardia (Figure 203-4). The VPCs typically have a left bundle branch block morphology in leads I, II, III, and AVF, consistent with the right ventricular origin of this arrhythmia.[44] In some cases, the ventricular arrhythmias that cause syncope may not be observed on the electrocardiogram and a 24-hour Holter monitor should be performed to evaluate for arrhythmias. Interpretation of the Holter results can sometimes be challenging because strict criteria for this diagnosis do not exist. However, since it is unusual for a normal dog to have any VPCs in a 24-hour period, the observation of more than 100 VPCs, or periods of couplets, triplets, or runs of ventricular tachycardia 1080 are abnormal and may be diagnostic in a dog with clinical signs.[45] Supraventricular premature 1081 complexes may also be observed, particularly in boxers with ventricular dilation and systolic dysfunction.

Thoracic radiographs are usually within normal limits. However, in the small number of cases with left ventricular dilation and systolic dysfunction, generalized cardiomegaly with pulmonary edema and/or pleural effusion may be noted.

Echocardiography is an important part of the evaluation because ventricular dilation and systolic dysfunction may occur, but in most cases affected dogs have normal chamber sizes and systolic function. In some cases, careful evaluation will allow the identification of right ventricular enlargement.

The familial etiology of ARVC has led to a widespread interest in screening dogs before selection of them as breeding animals. Since ARVC presents as an electrical abnormality more often than one of myocardial dysfunction, screening efforts should be based on annual Holter monitoring as well as annual echocardiography. Unfortunately, clear criteria for the diagnosis of occult ARVC do not exist. However, dogs that are symptomatic (syncope, heart failure) or have evidence of ventricular tachycardia on a Holter should not be used for breeding. Additionally, dogs that have over 100 left bundle branch block morphology VPCs in 24 hours are probably highly suspicious of being affected. However, not all affected dogs will ever develop clinical signs and many may live a normal lifespan.

It is likely that there are multiple factors that may influence which dogs become symptomatic for the disease. To help decrease the risk of making an error when adding or removing a dog from a breeding program, owners should be encouraged to screen annually rather than putting significant emphasis on a single Holter monitor reading. Since the disease is adult onset and an increase in VPCs has been observed with age in affected animals, an animal that is clear at the age of 2 is not guaranteed to stay clear. Additionally, an animal with a few hundred VPCs at the age of 2 years may have more, less, or the same number the next year. Until a greater understanding of disease inheritance and disease progression exists, caution should be used when advising breeders to remove dogs from breeding programs. Overzealous removal of animals based on the results of a single Holter monitor may have a significant negative impact on the breed.

At this time, there is no evidence that treatment will significantly alter the outcome for affected dogs. However, treatment has been shown to decrease the number of syncopal episodes.[46]

If an arrhythmia is detected on routine examination in an asymptomatic dog a Holter monitor should be performed to evaluate for the frequency and complexity of the arrhythmia. Although a strict relationship between the development of symptoms and the number of VPCs does not exist, treatment is generally started if more than 1000 VPCs occur in 24 hours, runs of ventricular tachycardia occur, or evidence of the R on T phenomenon

exist. Owners should be advised that ventricular antiarrhythmics have the potential for proarrhythmic effects and that treatment is not known to decrease risk of sudden death.

Dogs with syncope and ventricular arrhythmias are generally started on treatment. There are two choices for treatment that are well tolerated and have been shown to decrease VPC number and complexity: sotalol at a dose of 1.5 to 3.5 mg/kg, every 12 hours, orally or the combination of mexiletine at a dose of 5 to 8 mg/kg, every 8 hours, orally and atenolol at a dose of 12.5 mg/DOG, every 12 hours, orally.[46] It is likely that there is individual variation for drug response and if a poor response is observed with one drug, a different one may prove to more effective. Ideally, a Holter monitor would be placed before starting therapy and repeated 2 to 3 weeks after starting therapy to prove that the therapy is helping. Significant day-to-day variation in VPC number exists and a therapeutic effect is likely to exist if at least an 85% reduction in VPC number while on medication is observed.[47]

If echocardiography demonstrates systolic dysfunction and ventricular dilation treatment for DCM (ACE inhibitors, etc.) may be warranted. Additionally, supplementation with L-carnitine might be considered at a dose of 50 mg/kg, every 8 to 12 hours, orally since a small number of affected Boxers have demonstrated improvement in systolic function and prognosis after supplementation.[48]

Dogs with ARVC are always at risk of developing sudden death. However, many dogs may live for years on antiarrhythmics without symptoms, some of these may eventually develop ventricular dilation and systolic dysfunction.

203.4 MYOCARDITIS

Myocarditis is defined by the presence of myocardial necrosis or degeneration and inflammation.[49] A variety of physical, chemical, and infectious agents can damage the myocardial tissue and evoke an inflammatory response. In the dog, protozoal and viral organisms are reported most commonly.

Chagas' disease, caused by the protozoan parasite *Trypanosoma cruzi*, has been reported in the dog, particularly in the southern part of North America. Three stages of infection have been described: acute, latent, and chronic. The acute stage is characterized by lethargy, generalized lymphadenopathy, pale mucous membranes, increased capillary refill time, and hepato-splenomegaly.[50] This stage is associated with a variety of electrocardiographic (ECG) abnormalities, including sinus tachycardia, prolonged PR interval, decreased R wave amplitude, axis shifts, and conduction disturbances.[51] Sudden death may be observed. Dogs that survive the acute stage may enter a prolonged latent period during which the clinical signs appear to regress.[50] The chronic stage of Chagas' disease is associated with signs of progressive right-sided cardiac dysfunction, ascites, pleural effusion, hepatomegaly, and jugular venous distention.[50] Occasional ventricular tachycardias have been reported.[51] Diagnosis is most commonly performed by serology, although the acute form can sometimes be diagnosed by the presence of circulating trypomastigotes on thick blood smears. In general, treatment of Chagas disease is directed at palliation since destruction of the intracellular form of the parasite may result in severe exacerbation of the host inflammatory response.

Additional protozoan parasites that have been associated with the development of myocarditis include *Neopsora caninum* and *Toxoplasmosis gondii*.[52,53]

Parvovirus myocarditis is an uncommon form of myocardial disease. It may present with a peracute form that affects puppies between 3 and 8 weeks of age. Puppies present with acute dyspnea consistent with severe left heart failure and die within hours.[54] At necropsy, the hearts are found to be dilated with multifocal myofiber

necrosis, mononuclear cell infiltrate, and intranuclear inclusion bodies in the myocardial nuclei.[54,55] A second form of the disease in juvenile dogs (generally less than 1 year of age) may be very similar to DCM.[54,56]

Infrequently, infectious organisms including bacteria *Bacillus piliformis, Citrobacter koseri,* and the spirochete *Borrelia burgdorferi* have been associated with the development of myocarditis.[57,58]

203.5 HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is a primary myocardial disease characterized by concentric hypertrophy of the IVS and LV free wall. Hypertrophic cardiomyopathy (HCM) and the variant hypertrophic obstructive cardiomyopathy (HOCM) are infrequent forms of canine myocardial disease. There appear to be significant differences between the canine disease and the disease more commonly observed in cats and human beings with regard to etiology and pathologic findings.[59,60] An inheritable form of hypertrophic obstructive cardiomyopathy has been observed in the Pointer dog, but most canine cases appear to be sporadic.[59–62] Because of the relative infrequency that hypertrophic and hypertrophic obstructive cardiomyopathy is observed in the dog, suspect patients should be carefully evaluated for other reasons that might result in concentric hypertrophy of the LV, including the much more common left ventricular outflow tract obstruction observed with subvalvular and valvular aortic stenosis.

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203.6 HYPOTHYROIDISM

Some dogs with hypothyroidism have been observed to have a reduction in fractional shortening % and an increase in LVESD; however, the values had significant overlap with normal dogs.[63] Thus, although evaluation of thyroid levels might be considered in dogs that have minor echocardiographic changes in addition to other signs of hypothyroidism, it should not be considered a common cause of myocardial dysfunction nor ventricular dilation.[64]

203.7 MYOCARDIAL INFARCTION

Acute myocardial infarctions are an uncommon form of myocardial disease and appear to be most commonly associated with concurrent systemic or cardiac disease that has lead to a thromboembolic state. These conditions might include endocarditis, neoplasia, renal disease, immune mediated hemolytic anemia, and pancreatic disease. Dogs with infarcts were very rarely diagnosed with atherosclerosis as opposed to human beings who have a high incidence of infarcts associated with atherosclerosis.[65]

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204 CHAPTER • 204 Feline Myocardial Disease

Mark D. Kittleson

204.1 CLASSIFICATION

Primary myocardial diseases are generally classified under the general heading of cardiomyopathy. *Primary* indicates the myocardial disease is not secondary to valvular disease, pericardial disease coronary vascular disease, systemic or pulmonary hypertension, congenital abnormalities other than those of the myocardium itself, and myocardial changes due to systemic disease such as hyperthyroidism. The World Health Organization (WHO) has categorized the types of cardiomyopathies and based the categorization scheme primarily on the dominant pathophysiology produced by the myocardial disease.[1] Historically, cardiomyopathy was defined as a myocardial disease of unknown cause, whereas a myocardial disease with a known cause was given a specific name. Over the past 15 years the causes of many of the idiopathic myocardial diseases have been identified in human medicine. Consequently, many of the classic “idiopathic” cardiomyopathies now include groups of patients with a known cause and other groups of patients without a known cause—blurring all lines between idiopathic and specific myocardial diseases. However, the original names of the diseases persist and are useful because they still describe the dominant pathophysiologic process produced by the abnormality in the myocardium.

Cardiomyopathies are the dominant form of cardiac disease in domestic cats. Because there has been only one cause identified for a feline cardiomyopathy (i.e., taurine deficiency in dilated cardiomyopathy [DCM]), no pressure exists to rename the cardiomyopathies from a causative standpoint. Although the WHO classification of cardiomyopathies includes identification of cardiac dysfunction in the definition, this portion of the definition is certainly outdated in human medicine because many patients are now identified as having genetic mutations that produce abnormalities in the myocardium that are not severe enough or are too early to cause cardiac dysfunction.

Therefore feline cardiomyopathy is still defined simply as a primary disease of the myocardium. Cardiomyopathies are classified as (1) DCM, (2) hypertrophic cardiomyopathy (HCM), (3) restrictive cardiomyopathy (RCM), (4) arrhythmogenic right ventricular cardiomyopathy (ARVC) (dysplasia), (5) unclassified cardiomyopathy, and (6) specific cardiomyopathies. Myocarditis is commonly placed in the specific category, although it is also frequently classified separately. In general this classification scheme works reasonably well for cats, and all categories have been identified in cats. However, in individual cats it may be difficult or impossible to comfortably place a cat's myocardial disease into one of these categories. In addition, because cardiomyopathies are so prevalent in cats, it is common for other forms of cardiac disease to be misidentified as one of the forms of cardiomyopathy. For example, mitral valve degeneration is uncommon in cats, and when it is present the cardiac changes are frequently thought to be due to some form of cardiomyopathy.

Is categorization important? In some cases it is extremely important, whereas in other situations the importance is more academic than it is practical. For example, correctly identifying DCM in a cat is essential because DCM may be caused by taurine deficiency, and this form of DCM can be cured using taurine supplementation. HCM is inherited in some cat breeds. Correctly identifying this form of cardiomyopathy is often important to breeding programs.

204.2 DILATED CARDIOMYOPATHY

Myocardial contractility and myocardial contraction are not the same. *Myocardial contractility* is the inherent capability of the myocardium to contract without any forces acting on it. *Myocardial contraction* is how much the myocardium moves and thickens from end-diastole to end-systole (the amount of wall motion and thickening usually observed on an echocardiogram) and is determined by myocardial contractility, preload, afterload, and other variables. It is commonly calculated as the shortening fraction. *Myocardial failure* is defined as a decrease in myocardial contractility and is most commonly manifested as an increase in end-systolic diameter on an echocardiogram. DCM is the name given to diseases in which myocardial failure is present due to primary myocardial disease. Myocardial failure can occur secondary to nonprimary myocardial disease processes.

DCM is characterized on echocardiography by a primary increase in left ventricular (LV) end-systolic diameter and volume (and usually by a compensatory increase in LV end-diastolic diameter and volume). Because end-diastolic diameter and volume do not need to increase as much as end-systolic diameter and volume to maintain a normal stroke volume, shortening fraction (one measure of the amount of wall motion) decreases.

Although most of the cats that are diagnosed with DCM have clinical signs, the diagnosis of DCM may be made in the absence of heart failure, arrhythmia, or sudden death. DCM has a long subclinical phase during which myocardial function, along with cardiac compensatory mechanisms, are adequate to maintain normal hemodynamics.[2] This phase of the disease, during which echocardiographic or electrocardiographic evidence (or both) of the disease is present but clinical signs of the disease are not present, is often termed *occult* in the literature. A patient with DCM may spend most of its life in a subclinical phase and only a short time during which it has clinical signs.

204.2.1 Incidence

Because of the discovery of taurine deficiency as the major cause of feline DCM and the subsequent increase in taurine content in all cat foods, the current incidence of DCM is rare.[3,4] From 1993 to 2003, only 24 cases of feline DCM were diagnosed at the University of California, Davis Veterinary Medical Teaching Hospital (UCD-VMTH). Eight had DCM due to taurine deficiency, whereas 13 were idiopathic. The other three died before a plasma sample could be obtained.

204.2.2 Cause

Taurine deficiency was identified as the primary cause of DCM in cats in 1986 to 1987.[3] Taurine is a sulfur-containing amino acid. One of its functions is to conjugate bile acids.[5] Although some species can also conjugate bile acids with glycine, cats lack this ability and therefore have an obligate loss of taurine through the bile. In addition, they have very limited ability to synthesize taurine in the liver because of the lack of key enzymes. Taurine's definitive role in cellular function is not known, but it is concentrated in the cytoplasm of excitable cells up to 250 times that in plasma.[6] In the heart, taurine has been postulated to help modulate intracellular osmolality, calcium concentration, and transmembrane ion fluxes.[7]

The cause of taurine deficiency in cats is primarily nutritional, although a genetic factor may also be involved.[8] Prior to 1987, dry cat foods contained too little taurine, whereas the taurine in canned foods was not biologically available in adequate amounts, probably because of bacterial overgrowth in the intestinal tract.[9]

Feline DCM due to taurine deficiency has not totally disappeared. It can still occur with the exclusive feeding of one canned food diet. More frequently, taurine deficiency is caused by feeding the cat a home-cooked diet, most commonly one including chicken. One study has documented that cooking meat reduces the taurine content, especially when the meat is constantly surrounded by water during the cooking process.[10] The classic method of producing taurine deficiency is to feed dog food to a cat. Because no taurine is found in vegetables, vegetarian diets also produce taurine deficiency.

Idiopathic feline DCM is now the predominant form of DCM seen in cats. In humans, it is estimated that 30% to 40% of DCM is hereditary, and numerous mutations in a relatively large number of genes have now been identified as causing DCM in people (these include mutations in the genes that encode for cardiac dystrophin, δ-sarcoglycan, actin, α-tropomyosin, β-myosin heavy chain, troponin T, titin, adhalin, lamin A/C, tafazzin, and emerin).[11] It is likely that some cats with idiopathic DCM have a mutational cause for their disease, either because they inherited a mutation from a parent or because they developed a de novo mutation in utero. The latter may be more likely because no cat breeds are known to have feline DCM as a problem.

204.2.3 Pathophysiology

DCM is caused by a myocardial disease that results in a progressive decrease in myocardial contractility, either because of global myocyte dysfunction or because of myocyte death (necrosis or apoptosis). Contractility is mildly decreased initially, which may progress over months to years to a severe decrease in contractility.[12] The decrease in contractility results in an increase in end-systolic diameter and end-systolic volume, which results in a decrease in stroke volume. Chronically the heart compensates for this decreased function by growing larger ventricular chambers through eccentric (volume overload) hypertrophy. This growth is also commonly referred to as *ventricular remodeling* and occurs primarily due to renal sodium and water retention leading to an increase in blood volume that leads to an increase in venous return to the heart. This places stretch on the myocardium that stimulates the myocytes to grow longer and the chambers to grow larger (increased end-diastolic diameter and end-diastolic volume). The increased chamber size allows stroke volume to return to normal when the disease is mild to moderate. At some stage the myocardial failure becomes so severe that the ability of the cardiovascular system to compensate for the disease is overwhelmed. At this stage, LV end-diastolic pressure increases as renal sodium and water retention continues to increase blood volume, resulting in congestive heart failure (CHF).

Myocardial diseases that cause DCM may also cause concurrent diastolic dysfunction, primarily reduced ventricular compliance. A stiffer or less compliant LV results in a higher diastolic pressure for any given diastolic volume, causing pulmonary edema, pleural effusion, or both. Decreased LV compliance has not been documented in cats with DCM but has been in dogs.[13]

Secondary mitral regurgitation is commonly present in DCM. In DCM the atrioventricular (AV) annulus dilates as the LV enlarges, and the papillary muscles are displaced laterally and apically as the ventricular chamber enlarges.[14–16] Both result in the leaflets failing to close completely during systole (incomplete valve closure). The regurgitation is usually mild, however, and so its contribution to the production of heart failure is probably minimal.

204.2.4 Pathology

In cats with severe DCM, the most striking gross pathologic finding is moderate to marked enlargement of all four cardiac chambers. Often the left heart appears more affected. The walls of the LV may appear thin but when measured may be normal or thin. The papillary muscles often appear flattened. Heart weight is greater than normal, indicating the presence of hypertrophy.[17] On cut-section, the LV myocardium often appears remarkably normal, especially in cats with DCM due to taurine deficiency. In other cases, pale regions may be noted. In DCM due to taurine deficiency, histologic findings primarily reveal hypertrophy. In cats with idiopathic DCM, histologically there may be evidence of myocytolysis, myofibril fragmentation, abnormal mitochondria, vacuolization, and fibrosis.

204.2.5 Natural History and Prognosis

Only about 30% of cats that are taurine deficient develop echocardiographic evidence of myocardial failure.[18] 1083
Of the cats with myocardial failure, about 30% develop severe myocardial failure (shortening fraction < 20%). 1084
Some cats have severe myocardial failure for months to years prior to heart failure, yet many cats appear to develop heart failure suddenly.

The short-term prognosis for survival in cats with DCM due to taurine deficiency is guarded. They usually have severe CHF (often with low-output heart failure) and require intensive therapy. Taurine supplementation does not help clinically during this phase. Almost all cats that live longer than 2 to 3 weeks survive. Within 2 to 4 weeks they appear to improve clinically, although no apparent change occurs echocardiographically. Their myocardial function then normalizes over the ensuing 3 to 5 months. Consequently, their long-term prognosis is excellent. In cats with DCM that is not due to taurine deficiency, the long-term prognosis is usually grave (the median survival time [MST] is 2 weeks).[19]

204.2.6 Clinical Manifestations

204.2.6.1 History

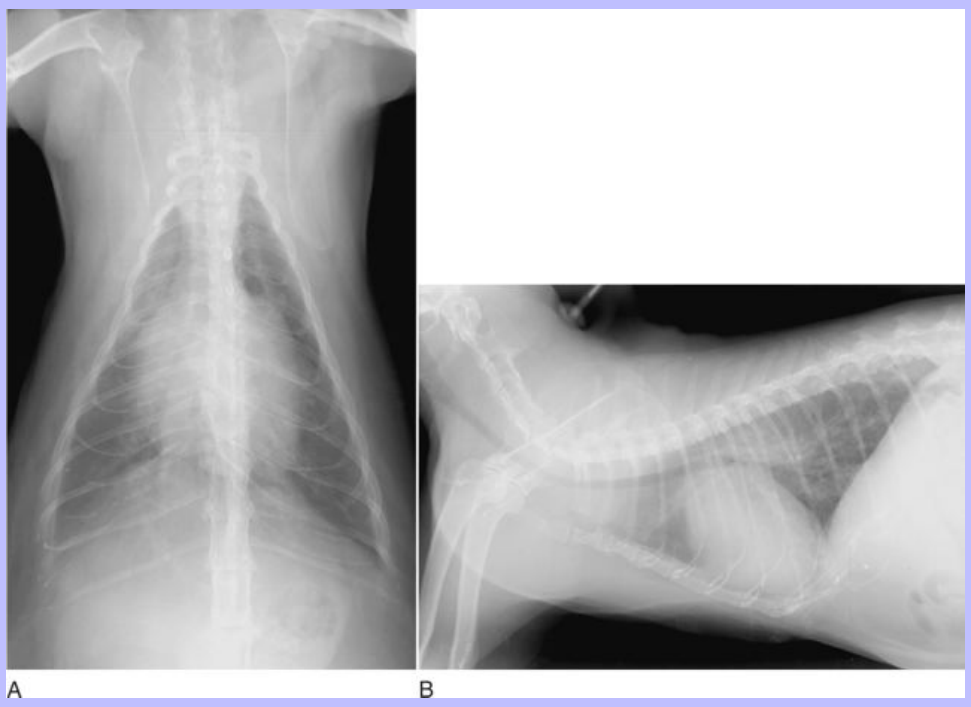
Because cats are relatively sedentary, they often hide the signs of their disease until they are in severe distress. Cats most commonly present in acute respiratory distress from pulmonary edema, pleural effusion, or both. Some cats will cough. This is frequently thought to be vomiting by the owner because vomiting and coughing in cats appear very similar. Distinguishing the two may be possible in the exam room by palpating the trachea vigorously enough to produce a cough while the owners witness the event. A thorough diet history should be obtained on any cat with DCM.

204.2.6.2 Physical Examination

Many cats are tachypneic and dyspneic upon presentation. They may also be lethargic, dehydrated, or hypothermic (or a combination of these symptoms). Auscultation often reveals a soft to moderately loud systolic heart murmur (usually heard best over the sternum, just medial to the left apex beat). A gallop sound may also be heard if the disease is severe. Most cats with DCM have an elevated heart rate so that atrial systole occurs immediately after rapid ventricular filling, making it impossible to distinguish a third from a fourth heart sound. Auscultation of the lungs is often normal except for increased airway sounds due

to hyperpnea. If pleural effusion is present, lung sounds may be absent ventrally when the cat is upright. The ears and feet are commonly cold because of intense peripheral vasoconstriction.

Figure 204-1 **A,** Dorsoventral (DV) radiograph from a cat with dilated cardiomyopathy (DCM) due to taurine deficiency. The cardiac silhouette is grossly enlarged. **B,** Lateral radiograph from the same cat. The cardiac silhouette again is grossly enlarged and pulmonary edema is present.



The retinas should be examined in all cats suspected of having feline DCM for the presence of feline central retinal degeneration (FCRD). If it is present the cat is most likely taurine deficient. However, many cats with taurine deficiency do not have FCRD.[20]

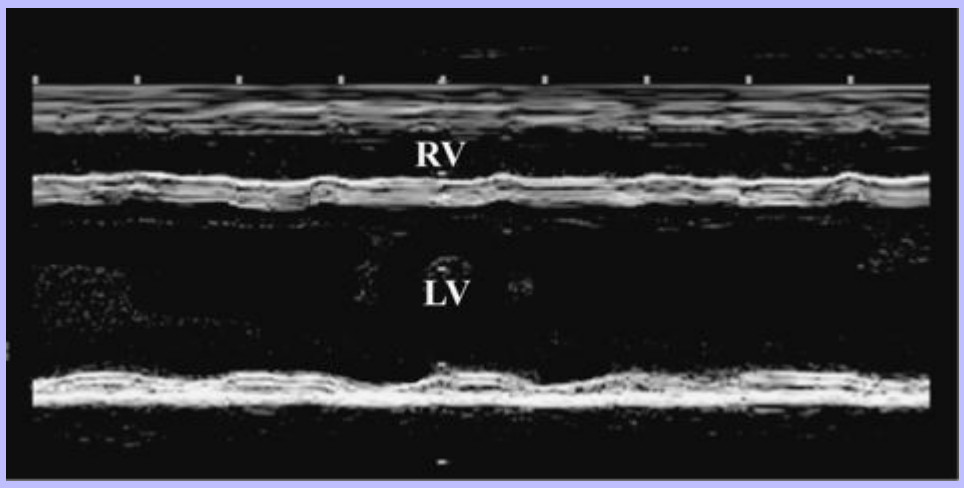
If the cat is severely dyspneic, pleurocentesis using a butterfly catheter should be part of the examination process to determine if pleural effusion is the cause of the dyspnea. If pleural effusion is the cause, one should be able to remove 150 to 250 mL of fluid from the pleural space.

204.2.6.3 Radiography

Radiographs cannot be used to distinguish feline DCM from other forms of feline cardiomyopathy. They should primarily be used initially to determine if a dyspneic cat is in heart failure (cardiomegaly plus pleural effusion, pulmonary edema, or both). Radiographs should not be attempted in a severely dyspneic cat if the process is stressful to the cat because this will often result in death. In cases of severe feline DCM, the cardiac silhouette is markedly enlarged, often especially in the area of the left auricle on the

dorsoventral (DV) or ventrodorsal (VD) view (Figure 204-1). Left atrial enlargement generally cannot be appreciated on the lateral view. If pleural effusion is present, it often becomes impossible to identify pulmonary edema. Pulmonary edema in cats can be caudodorsal in distribution (as in the dog) but is more commonly patchy, is often more ventrally distributed, and may involve the accessory lung lobe.

Figure 204-2 M-mode echocardiogram from a cat with severe dilated cardiomyopathy (DCM). The motion of the interventricular septum (IVS) (between the right ventricle [*RV*] and left ventricle [*LV*]) and the left ventricular free wall (below the LV chamber) are markedly reduced.



204.2.6.4 Echocardiography

Echocardiography is the diagnostic test of choice for identifying DCM. The striking feature of severe DCM is the remarkable lack of LV wall motion (Figure 204-2). The end-systolic diameter is increased to a value over 10 mm (usually over 12 mm and often in the 15 to 20 mm range when severe), whereas the end-diastolic diameter is also increased but to a lesser degree (usually in the 18 to 23 mm range). In cats with severe DCM, the shortening fraction is commonly less than 20%. Both the left ventricular free wall and the interventricular septal motion are reduced, although one may be more reduced than the other. Neither wall is hyperdynamic. Cats that have severely reduced free wall motion and a hyperdynamic interventricular septum (IVS) most commonly have primary mitral valve degeneration or dysplasia rather than DCM. Rarely a cat will have one region of the LV myocardium that is hypokinetic, akinetic, or even dyskinetic and may also be thinner than the rest of the myocardium. Although this may be due to a primary regional myocardial disease, it may also be due to a thrombus or a thromboembolus that has produced an infarct in that region. This pattern of motion may or may not be categorized as DCM, depending on one's viewpoint.

Color flow Doppler echocardiography often reveals the presence of mild mitral regurgitation. Spontaneous echo contrast due to red cell aggregation may be present, especially in the left atrium.

204.2.6.5 Electrocardiography

Electrocardiography Electrocardiography rarely reveals clinically significant information unless an arrhythmia is ausculted. Abnormalities in QRS morphology and an axis deviation may be noted but are nonspecific findings.

204.2.6.6 Clinical Pathology

Any cat with DCM should have a plasma and whole blood taurine concentration measured. The sample must be anticoagulated with heparin, placed on ice, and a portion centrifuged within 15 minutes. Platelets contain a large concentration of taurine, which is released upon platelet activation during the clotting process, so any thrombotic activity in the tube will result in a falsely high plasma taurine concentration. Taurine will also leach out of platelets and white cells into plasma if the sample is left standing, especially at room temperature. Taurine is a very stable compound, but plasma and whole blood samples should generally be frozen to prevent bacterial growth because bacteria will destroy taurine. Normal cats have a plasma taurine concentration greater than 60 nmol and mL and a whole blood taurine concentration greater than 250 nmol/mL. Most, but not all, cats with DCM due to taurine deficiency have a plasma taurine concentration less than 20 nmol/mL and a whole blood taurine concentration less than 100 nmol/mL. Fasting can lower the plasma taurine concentration in cats. Fasting does not alter whole blood taurine concentration.[21] Thromboembolism of skeletal muscle will cause skeletal muscle necrosis and the release of taurine into the circulation, causing a false elevation in a cat that is taurine deficient.

Prerenal azotemia due to low cardiac output is common in cats with severe DCM, cats with dehydration, cats that are not eating or drinking, or cats receiving a high dose of a diuretic. If the azotemia is mild to moderate and the cat feels good enough to eat and drink, the azotemia can safely be ignored. If the azotemia is severe, diuretic therapy must be discontinued and judicious fluid therapy administered. Electrolyte abnormalities occur more frequently in cats on diuretic therapy than in dogs, probably because cats tend to become anorexic more easily when they are dehydrated. Electrolyte levels below the reference range for a laboratory do not mean that this decrease is clinically significant.

204.2.7 Differential Diagnoses

Rarely HCM will progress to severe myocardial failure. Some cases of regional myocardial failure appear to be due to myocardial infarction.[22] Myocardial failure can occur secondary to chronic, severe volume overload, such as primary mitral regurgitation. Sustained tachycardia can also produce myocardial failure, although the rate to produce this phenomenon is not known in cats.

Cats with DCM commonly have pleural effusion. This effusion may be a modified transudate, pseudochylous, or chylous and may change from a modified transudate to a chylous effusion over time. Heart failure is the most common cause of chylous pleural effusion in cats.

204.2.8 Acute Therapy

204.2.8.1 Treatment Goals

The treatment goals depend on the type and severity of the clinical signs. If severely dyspneic the initial goal is to make it easier for the cat to breathe by removing pleural effusion, by reducing pulmonary edema pharmacologically, or by administering oxygen. If the primary problem is a marked reduction in perfusion leading to hypothermia, the goal is to increase cardiac output, if possible, via the administration of an intravenous positive inotropic agent, such as dobutamine, and possibly the judicious use of intravenous fluid administration, especially if the cat is severely dehydrated.

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204.2.8.2 Pleurocentesis

Pleurocentesis is often life saving in the severely dyspneic cat that has a large amount of pleural effusion. Thoracocentesis is described in Chapter 103.

204.2.8.3 Diuretic Therapy

Diuretic administration is the only reliable way to reduce pulmonary edema formation in a cat with severe DCM. Furosemide is used almost exclusively. The dose depends on the severity of the pulmonary edema, on whether the cat is currently on furosemide for heart failure, and whether the situation is acute or chronic. Cats in severe respiratory distress may need an initial dose as high as 2 mg/lb parenterally. Intravenous administration is preferred, but the drug should be administered intramuscularly if restraint for intravenous administration produces stress. Absorption half-life after intramuscular administration is around 5 minutes, so the entire dose is fully absorbed within 20 to 25 minutes. The duration of effect of furosemide after parenteral administration is probably 1 to 2 hours in a cat in heart failure. Consequently, another dose should be administered within that period if the cat is still in respiratory distress and is not severely dehydrated. A cat with a lesser amount of pulmonary edema and less respiratory distress needs a smaller dose of furosemide parenterally in the acute setting. Respiratory rate and character should be monitored carefully after diuretic administration with the cat in an oxygen-enriched environment.

204.2.8.4 Oxygen

Increasing the percent concentration of oxygen delivered to the alveoli is critical in cats in respiratory distress. This can be accomplished using a face mask, standard oxygen cage, a pediatric incubator, or nasal insufflation. Generally the goal is to increase fraction of inspired oxygen (FIO_2) to at least 40% (normal is 21%). If the cat resists a face mask, it should not be used. When placed in a confined space, especially a small space like an incubator, it is mandatory to keep the environmental temperature and the carbon dioxide concentration within reasonable levels. Failure to do so can cause death. A canister containing sodium lime or barium hydroxide lime controls carbon dioxide level in an oxygen cage, and a refrigeration unit controls temperature. Carbon dioxide concentration is usually controlled in an incubator by maximizing the flow rate of oxygen (and therefore flushing out the carbon dioxide).

204.2.8.5 Inotropic Support

Beta-adrenergic agonists, usually dobutamine or dopamine, can be used for acute inotropic support in a cat with severe DCM and severe heart failure. However, conscious cats have more side effects with these drugs than do dogs. They often appear agitated and may even seizure. The half-life of these drugs is around 1 minute, so stopping the drug infusion results in rapid cessation of adverse effects. The infusion rate for dobutamine and dopamine in a cat is less than that used in a dog and is generally in the range of 1 to 2.5 µg/lb/min.

204.2.8.6 Nitroprusside

Nitroprusside is a potent dilator (i.e., smooth muscle relaxant) of systemic arterioles and systemic veins. It can only be used in cats with DCM that are not in cardiogenic shock (systolic systemic arterial blood pressure over 100 mm Hg). If systemic pressure is adequate, the drug can be used in one of two ways: (1) empirically at a dose of 2 µg/lb/min or (2) titrated using blood pressure starting at a dose of 1 µg/lb/min and increased until the systolic pressure has decreased by at least 10 to 15 mm Hg. (See Systolic Blood Pressure Monitoring and Techniques in Chapter 128.)[23]

204.2.8.7 General Supportive Measures

Although dogs commonly start to drink water and eat once they are no longer in respiratory distress, cats may not. Dehydration is a common side effect of aggressive diuretic therapy, and some cats are dehydrated at presentation. Generally cats do better if they are sent home as soon as possible. However, if hospitalization is required after the edema and effusion are controlled, judicious use of fluid therapy may be needed. Electrolyte disturbances, most commonly hyponatremia, hypokalemia, and hypochloremia, are also more frequent in cats than in dogs in this acute setting. Consequently, serum electrolyte concentrations should be monitored.

204.2.9 Chronic Therapy

204.2.9.1 Diuretic Therapy

Diuretics are the only drugs that can routinely control the clinical signs referable to congestion and edema due to heart failure. Consequently, it is mandatory for cats with CHF to be on a diuretic, usually furosemide. The chronic orally administered dose for furosemide in cats is wide and ranges from 0.5 mg/lb a day to 2 mg/lb every 8 hours. The most common doses are 6.25 to 12.5 mg per cat every 8 to 12 hours, orally. In general, cats need a lower dose of furosemide when compared with dogs, although the upper end of the dose range can be similar. The goal of diuretic therapy is to keep pulmonary edema and pleural effusion controlled. This should be done with the lowest possible furosemide dose, although in the author's experience, underdosing appears to be a more frequent problem than does overdosing. Every owner should be instructed to count his or her cat's respiratory rate at home when the cat is sleeping or resting quietly in a cool environment and to keep a written log. The normal respiratory rate for a cat is in the 20 to 40 breaths per minute range. If the rate is greater than 40 breaths per minute or the owner notes that the character of breathing is more labored, these are signals that an increased dose of furosemide, pleurocentesis, or both are needed. Changes in furosemide dose should be done in consultation with a veterinarian during the initial stages of management. Some owners will require continued contact with a veterinarian to manage dose

changes, whereas others will reach a point where they feel comfortable doing this on their own. Cats with severe disease that require a maximum dose of furosemide are often mildly to moderately dehydrated and mildly to moderately azotemic. As long as they continue to eat, drink, and appear comfortable, the dose of furosemide should not be decreased. If the dehydration or azotemia becomes severe enough to cause anorexia, the furosemide administration must be discontinued as long as the cat is not taking in fluid. Owners must be warned that continued use of high-dose furosemide administration in a cat that is not drinking or eating can result in severe, life-threatening dehydration. Judicious use of parenteral fluid administration may be required. These, of course, are poor prognostic signs. Cats that are refractory to the maximum dose of furosemide may need to have another diuretic administered along with the same maximum dose of furosemide. Choices include a thiazide diuretic and possibly spironolactone. (See Therapy in Chapter 199.) Parenteral administration of furosemide may also be beneficial because the oral bioavailability of the drug is only around 50%.

204.2.9.2 Pleurocentesis

Repeated pleurocentesis is often required in cats with pleural effusion. Pleurocentesis may need to be done as infrequently as once a month or as frequently as every 4 or 5 days. As much fluid as possible should be removed at each visit. Ultrasound guidance often helps identify regions where fluid has pocketed. Chylothorax secondary to heart failure can result in chylofibrosis, making it very difficult to remove as much fluid as one would like. Risks of repeated pleurocentesis include infection, pneumothorax, and bleeding, but all are rare.

204.2.9.3 Angiotensin-Converting Enzyme Inhibitors

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Any cat with idiopathic DCM should be on an angiotensin-converting enzyme (ACE) inhibitor for long-term management unless they have an adverse reaction to the drug. Enalapril is most commonly used at a dose of 1.25 to 2.5 mg per cat orally every 24 hours. ACE inhibitors can almost never be used on their own to control signs of heart failure and are not effective for controlling heart failure in the acute care setting. Rather they must be administered in concert with a diuretic and help in the long-term control of the disease. Generally, ACE inhibitor therapy should be started when the cat is reasonably stable and not dehydrated.

204.2.9.4 Digoxin

Digoxin, in theory, may be administered to cats with DCM. However, in the initial trial that identified taurine deficiency as a cause of feline DCM, digoxin was not administered and most of those cats survived; therefore clearly in cats with DCM due to taurine deficiency, no clear mandate exists to administer digoxin.[3]

204.2.9.5 Dietary Modifications

Any cat with DCM should be supplemented with 250 mg taurine orally every 12 hours until the results of the plasma and whole blood taurine concentration analysis are evaluated. Taurine is inexpensive and can be purchased from health food stores or chemical supply houses. Cats that are taurine deficient should be continued on taurine supplementation, whereas those that are not may be taken off or left on at the discretion of the owner. Sodium-restricted diets may be useful, particularly in cats that are refractory to drug therapy. However, it is more important to keep the cat eating than it is to force sodium restriction.

204.3 HYPERTROPHIC CARDIOMYOPATHY

HCM is a disease of the ventricular (primarily LV) myocardium characterized by mild to severe thickening of the papillary muscles and wall (Figure 204-3). The word *primary* means the hypertrophy is due to an inherent myocardial problem, not secondary to a pressure overload or to hormonal stimulation. Concentric hypertrophy (a thickened wall with a normal to small chamber size) of the LV has several possible secondary causes, including aortic stenosis, systemic arterial hypertension, and hyperthyroidism. When any of these diseases are present, the diagnosis of HCM is in doubt and the cardiac abnormality should not be called *HCM* if one is convinced the primary cause of the hypertrophy is the other disease process. Instead it should be called *concentric hypertrophy secondary to the primary abnormality* (e.g., concentric hypertrophy secondary to hyperthyroidism). Besides concentric hypertrophy, the myocardium can also thicken due to infiltration (e.g., with lymphoma).[24]

Figure 204-3 A cross-sectional view of a two-dimensional echocardiogram from a cat with severe hypertrophic cardiomyopathy (HCM). The interventricular septum *(IVS)* is markedly thickened and thicker than the left ventricular free wall *(LVFW)*. The two papillary muscles in the left ventricular chamber *(LV)* are also markedly enlarged.

204.3.1 Incidence

HCM is the most commonly diagnosed cardiac disease in cats, and its prevalence appears to be increasing. However, echocardiographic screening for the disease has also become more prevalent over the past 10 years, so increased awareness and ease of diagnosis may also be major contributing factors to this increase. During a recent 10-year period, the author's cardiology service diagnosed moderate to severe HCM in 447 cats. This is almost twice as many cases as during a previous 10-year period when the incidence was similar to another report in which 46 cats were diagnosed with HCM during a 2-year period at the Animal Medical Center in New York City.[25]

A male predisposition for HCM is commonly reported in clinical studies, although in a study of Maine coon cats the incidence was the same in males and females. However, males often develop the disease at an earlier age and often develop more severe disease. Consequently, it is likely that the male predominance seen clinically is purely because males develop worse disease, not because they are more predisposed to the disease.

204.3.2 Cause

204.3.2.1 Sarcomeric Gene Mutations in Humans with Hypertrophic Cardiomyopathy

The exact cause of feline HCM is unknown, although the disease is known to be heritable in some breeds. In humans the familial nature of the disease was first reported in 1958.[26] It has been demonstrated that approximately 50% of the human cases of HCM are inherited in an autosomal dominant pattern, with the other cases being sporadic (although often still genetic in origin). Since 1989 over 150 mutations in 10 genes that encode for sarcomeric proteins have been identified in human families with HCM.[27–31] They include the β-myosin heavy chain; α-tropomyosin; cardiac troponins I, C, and T; myosin-binding protein C; essential and regulatory light chains; titin; and actin genes.[27,32–36] Several families with HCM have also been shown to have mutations in the gene that codes for LIM protein.[37] Another set of families has been identified with mutations in the gene coding for AMP-activated kinase that produces glycogen accumulation in the myocardium, mimicking HCM.[38] Interestingly, mutations in β-myosin heavy chain, α-tropomyosin, titin, and troponin T genes also cause DCM in humans (although the mutations are at different sites than those that cause HCM) and mutations in the LIM protein gene cause DCM in mice.[39] It is now known that sarcomeric gene mutations actually cause HCM because several mutations that have been identified in human families with HCM have been placed in transgenic mice, and the disease has been reproduced—thus fulfilling Koch's postulates.[40–42]

The pathophysiology of HCM production by sarcomeric mutations is controversial.[43] One theory is that the abnormal protein produced by a mutated gene results in dysfunctional sarcomeres that forces the functional sarcomeres to bear a larger load. The myocardium compensates by replacing the dysfunctional sarcomeres with additional functional and dysfunctional sarcomeres.[33,44–46] The net result is that the heart has twice as many sarcomeres as it should have. Because sarcomeres make up a large part of the heart muscle, the heart muscle ultimately almost doubles in thickness in severe cases.

204.3.2.2 Familial Feline Hypertrophic Cardiomyopathy

The first “family” of cats with an inherited form of HCM was identified in Maine coon cats in 1992 and reported in 1999.[47] The disease is inherited as a simple autosomal dominant trait in this breed and is 100% expressed in experimental cats. However, in nonexperimental Maine coon cats, it appears that the disease is not 100% expressed because both parents of an affected cat may have no echocardiographic evidence of the disease. This phenomenon is common in human families with HCM with a variety of gene mutations.[27] The disease has been reproduced in Maine coon cats by mating affected to unaffected and affected to affected cats, as well as by breeding affected Maine coon male cats to domestic shorthair female cats. The course of the disease is accelerated in affected cats produced by mating affected to affected cats. The disease is progressive. In most affected Maine coon cats, HCM is not apparent during the first year of life but becomes apparent by 2 years of age in males.[48] Females tend to get the disease later, with most manifesting

the disease by 3 years of age but some not showing evidence of the disease until 6 or 7 years of age. When both parents have HCM, an affected Maine coon kitten may have echocardiographic evidence of the disease as early as 6 months of age and have severe disease by 1 year of age, whether male or female.

The most consistent feature of the disease in Maine coon cats and in most cats with HCM is papillary muscle hypertrophy. It is often present before wall thickening is evident. Systolic anterior motion (SAM) of the mitral valve is common. Studies are currently in progress to determine if a specific sarcomeric gene abnormality exists in this family of Maine coon cats.

A family of American shorthair cats, primarily with SAM of the mitral valve but with other evidence of HCM as well, has also been identified.[49] The disease in this breed also appears to be inherited as an autosomal dominant trait. In addition to these breeds, anecdotal evidence exists of HCM being inherited in numerous other breeds, including Persian, British shorthair, Norwegian forest cats, ragdoll, Turkish van, and Scottish fold cats, along with others. HCM is most likely inherited when it is identified in a specific breed. However, HCM is most commonly identified in domestic (mixed breed) cats. Whether the disease is inherited in these cats, is due to a de novo mutation, or is associated with a different disease process is unknown, although suspicion of inheritance has been reported in mixed breed cats.[50–52] Because the disease is inherited as an autosomal dominant trait in some purebred cats, it is not hard to imagine how these mutations could disseminate into the mixed breed population.

Some mutations in humans produce malignant disease in which survival time is short, whereas other mutations produce benign disease with little change in survival.[53,54] Although the Maine coon breed has a malignant disease, the American shorthair usually has a more benign disease. Ragdoll cats, on the other hand, have a particularly malignant form of the disease and often die before reaching 1 year of age.

204.3.2.3 Other Causes of Concentric Left Ventricular Hypertrophy

Congenital valvular or subvalvular aortic stenosis is a rare cause of concentric LV hypertrophy in cats. Certain systemic diseases, especially hyperthyroidism and systemic hypertension, can induce the LV myocardium to thicken.[55] Acromegaly is rare and usually does not produce concentric LV hypertrophy in the author's experience. At least in theory, each of these diseases should be ruled out before making a definitive diagnosis of HCM. However, in general, none of these diseases causes severe LV wall thickening on their own; therefore if severe hypertrophy is present, it is very unlikely that one of these diseases is the sole cause. Rather it is more likely the cat has severe HCM or the cat has had mild to moderate HCM most of its life and then developed one of these complicating diseases at an older age. This event then stimulates further hypertrophy, leading to severe HCM. The primary reasons for this belief are the documentation of this occurrence in a limited number of cases and the logic that HCM and these other diseases are prevalent in the domestic cat population (making it likely that some cats will have HCM in combination with a potentially exacerbating disease, especially when these cats are older). Consequently, cats with significant LV concentric hypertrophy, especially ones that are geriatric or have a disease that causes systemic hypertension, must be screened for hyperthyroidism and systemic hypertension.

204.4 PATHOPHYSIOLOGY

204.4.1 Hypertrophy, Diastolic Dysfunction, and Congestive Heart Failure

Enlarged papillary muscles and a thick LV myocardium with a normal to small LV chamber characterize HCM (see Figure 204-3). HCM may be mild, moderate, or severe. Severe concentric hypertrophy by itself increases chamber stiffness. In addition, blood flow and especially blood flow reserve to severely thickened myocardium is compromised, which causes myocardial ischemia, cell death, and replacement fibrosis.[56] This has been documented in cats by showing that cardiac troponin I concentration, a protein released into the systemic circulation after cell necrosis, is increased in cats with severe HCM.[57] Increased concentrations of circulating neurohormones may also stimulate interstitial fibrosis.[58] Fibrosis increases chamber stiffness (increased pressure for any given volume) further and is probably the primary reason for the marked diastolic dysfunction seen in this disease. The stiff ventricular chamber causes a greater increase in pressure for any given increase in volume when the ventricle fills in diastole. This produces CHF (i.e., pulmonary edema and pleural effusion). The myocardium from cats with HCM also takes a longer time to relax in early diastole, although the clinical significance of this is unknown.[59]

When LV hypertrophy is severe, it is common for the LV wall thickness to be twice the normal thickness. Consequently, LV wall thickness is commonly in the 7 to 10 mm range when HCM is severe in cats. This severe concentric hypertrophy may encroach on the LV cavity in diastole, decreasing its size, although LV diastolic diameter is commonly within the normal range. The end-systolic volume and diameter are almost always reduced, often to zero (end-systolic cavity obliteration; Figure 204-4). Global myocardial contractility is normal in humans with HCM, and the reduction in end-systolic volume is due to a decrease in afterload (wall stress) brought on by the increase in wall thickness.[60]

204.4.1.1 Systolic Anterior Motion of the Mitral Valve

A phenomenon called systolic anterior motion (SAM) of the mitral valve is common in cats with HCM (Figures 204-5 and 204-6). Cats with HCM and SAM are commonly said to have the obstructive type of HCM or hypertrophic obstructive cardiomyopathy (HOCM). In one survey of 46 cats, SAM was present in 67%.[25] SAM of the mitral valve is the process of the septal (anterior) mitral valve leaflet or the chordal structures inserting on this leaflet being pulled into the LV outflow tract during systole. Here it is caught in the blood flow and pushed toward (and often ultimately against) the IVS. The initial pulling of the mitral valve leaflet toward the LV outflow tract in systole can clearly be seen on many echocardiograms from cats with HCM. The grossly enlarged papillary muscles encroach on the LV outflow tract (the region of the LV between the anterior leaflet of the mitral valve and the IVS in diastole) and pull the mitral apparatus structures into the basilar region of the outflow tract. This situation has been reproduced experimentally in dogs by surgically displacing the papillary muscles cranially.[61] SAM of the mitral valve produces a dynamic subaortic stenosis that increases systolic intraventricular pressure in mid-to late systole. The dynamic subaortic stenosis increases the velocity of blood flow through the subaortic region and often produces turbulence (Figure 204-7). Simultaneously, when the septal leaflet is pulled toward the IVS, this produces a gap in the mitral valve, creating mitral regurgitation. These abnormalities are by far the most common cause of the heart murmur heard in cats with HCM. The process of SAM is dynamic—worsening when contractility increases and lessening when contractility decreases. This also makes the murmur dynamic—increasing in intensity with increasing excitement and softening when the cat becomes calmer.

Figure 204-4 The same view as in Figure 204-3 but at the end of systole. End-systolic cavity obliteration occurs.

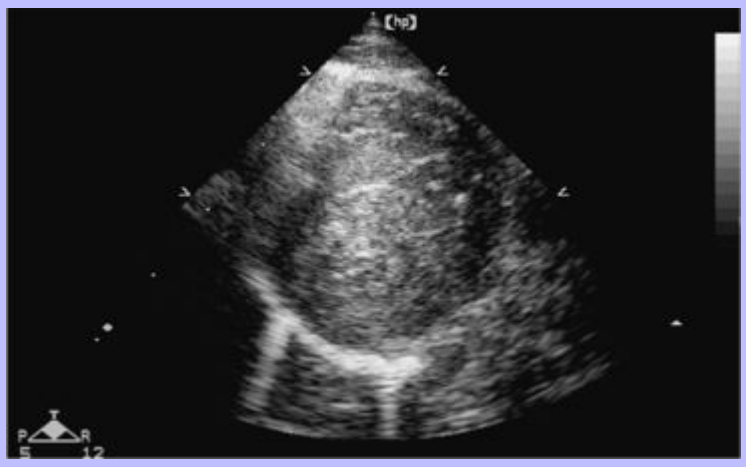


Figure 204-5 A long-axis view of a two-dimensional echocardiogram taken in late systole (same cat as in Figure 204-3). Systolic anterior motion (SAM) of the mitral valve *(arrowhead)*. The enlarged papillary muscle *(P)* is pulling the chordal structures and a portion of the tip of the anterior mitral valve leaflet into the left ventricular (LV) outflow tract, where it is contacting the interventricular septum *(IVS)* and creating an obstruction between the outflow tract and the aorta *(Ao)*. End-systolic cavity obliteration is again present. *LVFW,* Left ventricular free wall; *LA,* left atrium.

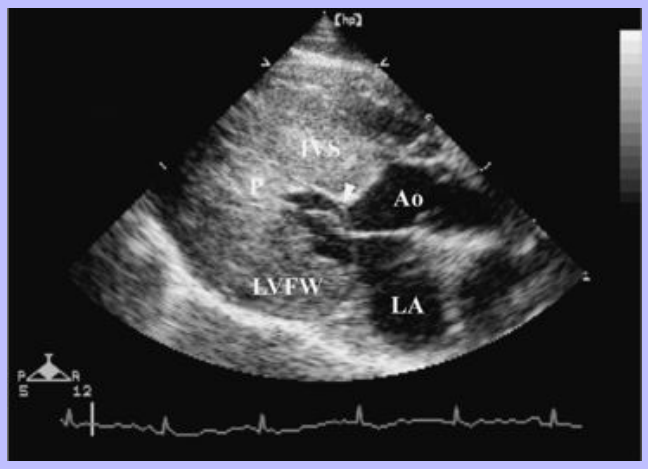


Figure 204-6 A left apical four-chamber view from the cat in Figure 204-4 showing systolic anterior motion (SAM) of the mitral valve. The portion of the mitral valve apparatus causing the dynamic obstruction is aligned with the caudal papillary muscle *(P)*. *LA,* Left atrium; *Ao,* aorta.

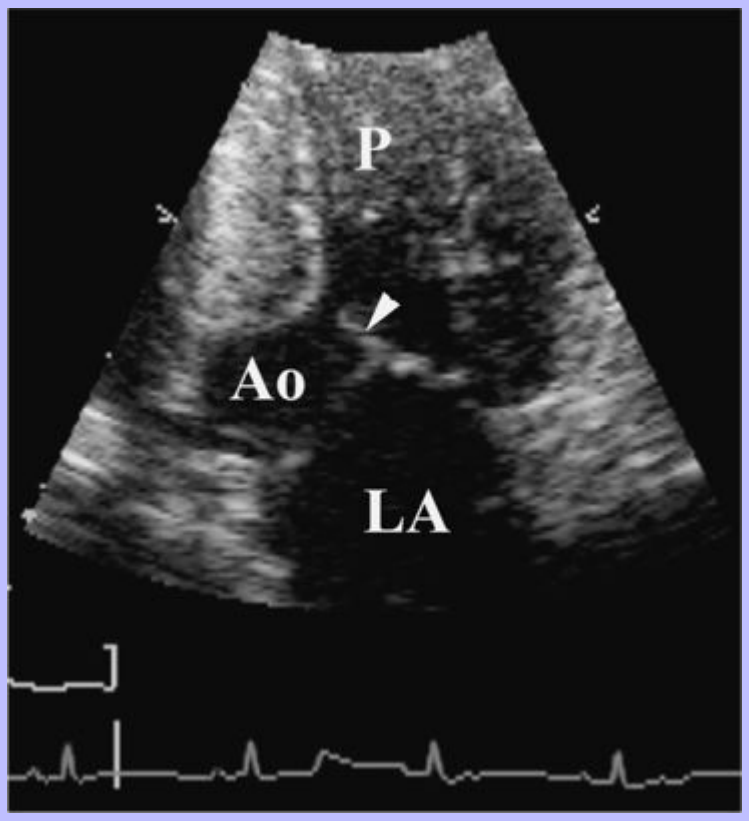
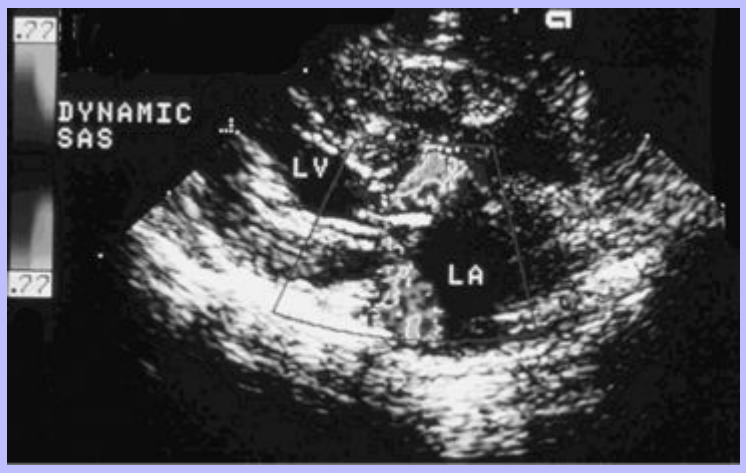


Figure 204-7 A black-and-white rendition of the color flow Doppler signal seen with systolic anterior motion (SAM) of the mitral valve. A bilobed jet—both originating from the left ventricular outflow tract region of the left ventricle *(LV)*. The top jet is created by the dynamic subaortic stenosis (SAS). The lower jet that extends into the left atrium *(LA)* is due to mitral regurgitation, created when the anterior mitral valve leaflet is displaced.



204.4.1.2 Pleural Effusion

Along with pulmonary edema, pleural effusion is common in cats with heart failure. It can be a modified transudate, pseudochylous or true chylous in nature. The most common cause of chylothorax in cats is heart failure.[62] It is unknown exactly why pleural effusion develops in these cats. Two possibilities exist: The first is that left heart failure results in pulmonary hypertension severe enough to cause right heart failure. This does not appear to occur very frequently in cats because it is unusual to identify echocardiographic right heart enlargement, jugular and hepatic vein distension, or ascites in these cases. The second possibility is that feline visceral pleural veins drain into the pulmonary veins such that elevated pulmonary vein pressure (congestive left heart failure) causes the formation of pleural effusion. In the dog the visceral pleura is supplied by pulmonary arteries and drained by pulmonary veins.[63] The dog, the cat, and the monkey have type II lungs.[64] One characteristic of type II lungs is that the visceral pleura is supplied not by bronchial arteries but by pulmonary arteries. Presumably this means that the cat visceral pleura is also drained by pulmonary veins. This means that pulmonary venous hypertension secondary to left heart failure could cause pleural effusion in cats as it does in humans.[65]

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204.4.2 Pathology

204.4.2.1 Gross Pathology

Cats with severe HCM have severe thickening of the LV myocardium (the IVS and free wall), with the LV wall commonly being 7 to 10 mm thick (Figures 204-8 and 204-9). The hypertrophy may be symmetrical, involving the entire circumference of the LV, but it may also be asymmetrical. In some cats the IVS is significantly thicker than the free wall, whereas in others the free wall is thicker (asymmetrical hypertrophy).[25,66,67] In those cats with primarily septal hypertrophy, the hypertrophy may be confined to the basilar region of the septum, and in others may be apical. Isolated free wall hypertrophy most commonly occurs in the region between the papillary muscles. As in many pathologic specimens, hearts from cats with HCM may undergo contraction (rigor) after death, resulting in a wall thickness that is closer to the end-systolic wall thickness in life rather than the end-diastolic thickness. Consequently, heart weight must be combined with subjective or objective evidence of LV wall thickening to make the diagnosis of HCM postmortem. To weigh a cat heart the pericardium should be removed and the aorta and pulmonary artery transected so that no more than 2 to 4 cm are left. Normal heart weight–to–body weight ratio has been reported to be 10.6 +/– 4 g/lb, with cats with HCM having a ratio of 13.2 +/– 3.1 g/lb.[25] This results in a large overlap between the two groups. In the author's experience, most normal-sized cats (6 to 12 lb) have a heart that weighs less than 20 g and most cats in this size range with HCM have a heart that weighs more than 20 g. Cats with severe HCM almost always have a heart that weighs more than 25 g, usually over 30 g, and can be as heavy as 38 g.

The left atrium is often enlarged in cats with severe HCM, often markedly so (Figure 204-10). However, with early, severe disease, the author has identified normal left atrial size in some Maine coon cats. Occasionally a thrombus is present in the body of the left atrium or within the left auricle.

Cats with milder forms of the disease (mild to moderate HCM) have lesser wall thickening and a more normal-sized LV chamber. The left atrium may be normal in size or may be enlarged. Papillary muscle hypertrophy may be the predominant lesion.

Figure 204-8 Gross pathologic cardiac specimen from a cat with severe hypertrophic cardiomyopathy (HCM). The heart has undergone rigor postmortem, causing end-systolic cavity obliteration. Heart weight must be obtained to confirm that the HCM is present (see text).

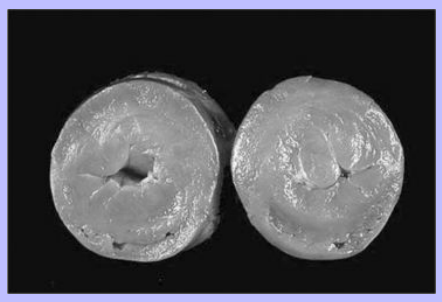
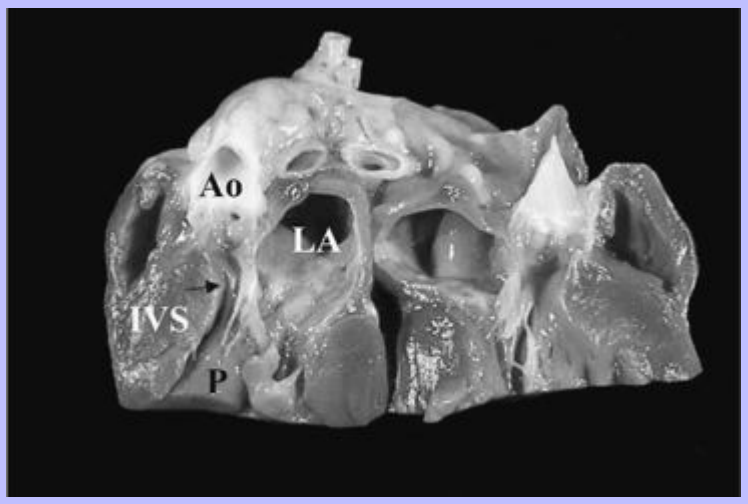


Figure 204-9 Gross pathologic cardiac specimen from a cat with severe hypertrophic cardiomyopathy (HCM). The left ventricular (LV) outflow tract *(arrow)* is narrowed as one papillary is pulling the anterior leaflet of the mitral valve into the outflow tract. *IVS,* Interventricular septum; *LA,* left atrium; *Ao,* aorta.



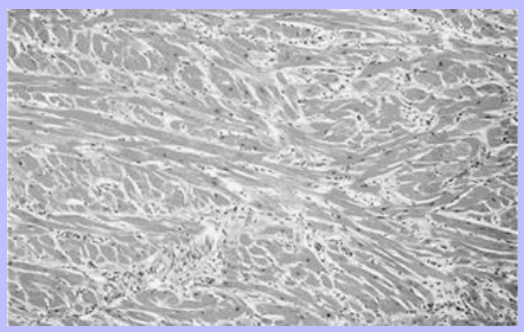
204.4.2.2 Histopathology

Histopathologically, a wide range of abnormalities exist. In some hearts, only myocyte hypertrophy is evident. On the other end of the spectrum, some cats have moderate to severe interstitial and replacement fibrosis and dystrophic mineralization (20% to 40% of cases).[66,68] Intramural coronary arteriosclerosis is present in approximately 75% of cats with HCM.[25,66] Intramyocardial small artery disease is not specific for HCM because it is also identified in cats and dogs with many cardiac diseases.[69]

In humans, myocardial fiber disarray that involves at least 5% of the myocardium in the IVS is found in 90% of patients with familial HCM.[70,71] Other diseases that produce concentric hypertrophy can also cause myocardial fiber disarray, but this almost always involves less than 1% of the myocardium. In cats with HCM, myocardial fiber disarray in the IVS of the same magnitude observed in humans is only identified in 30% to 60% of cases.[66,68,72] However, myocardial fiber disarray is a consistent feature of HCM in Maine coon cats (Figure 204-11).[47] Sarcomeres also have disarray in human patients with HCM. Interestingly, infecting isolated feline cardiocytes with an adenoviral vector containing a full-length mutated human β-myosin heavy chain gene causes sarcomere disruption.[73]

Figure 204-10 A view of the cranial aspect of a heart from a cat with severe hypertrophic cardiomyopathy (HCM). The left auricle *(top, right)* is markedly enlarged.

Figure 204-11 Histopathology from a Maine coon cat with severe hypertrophic cardiomyopathy (HCM) showing myocardial fiber disarray.



204.4.3 Natural History and Prognosis

The prognosis, as with most cardiac diseases, is highly variable for HCM. Some of it is determined by clinical presentation and echocardiographic severity of the disease. Adult cats that are asymptomatic and have mild to moderate disease and no to mild left atrial enlargement have a good short-term (and possibly a good long-term) prognosis. Some, however, may progress to more severe disease and some may die suddenly. Asymptomatic cats with severe wall thickening and mild to moderate left atrial enlargement have a guarded prognosis for developing heart failure in the future. They probably have some risk for developing thromboembolism and may be at risk for sudden death.[74] Cats with no clinical signs but with severe wall thickening and moderate to severe left atrial enlargement are at risk for developing heart failure or often already have mild to moderate heart failure that has gone undetected. These cats are at risk for developing systemic thromboembolic disease and sudden death, although both of these risks appear to be relatively small.[74] Cats presented in heart failure usually have a poor prognosis, but survival time is highly variable. Most die of intractable heart failure. Some develop thromboembolism, and some die suddenly. In one study a MST of 3 months was reported yet some cats (about 20% in one study) in this class stabilize and do well for prolonged periods. The author and colleagues have seen some cats with severe HCM live as long as 2.5 years after the diagnosis of heart failure (see www.vmth.ucdavis.edu/cardio/cases/case5/case5.htm).[75] Some of these cats may develop heart failure when they are stressed and become severely tachycardic and then stabilize after that time. Cats with severe HCM and aortic thromboembolism in the aforementioned study had a very poor prognosis with a MST of 2 months.

204.4.4 Clinical Manifestations

204.4.4.1 Development

In humans, familial HCM develops in most individuals over the first 2 decades of life.[76] HCM is a progressive disease in Maine coon cats and likely in other purebred and mixed breed cats. When a veterinarian examines an older cat with HCM, the disease may have been present for most of the cat's life.

204.4.4.2 History

Cats with HCM may have no clinical signs. Many have a heart murmur; some are brought to a veterinarian with subtle, moderate, or severe heart failure; and some are presented because of thromboembolic disease. Cats with no clinical signs can have mild to severe LV thickening; however, those with severe thickening usually go on to develop heart failure. Cats with severe disease that appear to have no clinical signs may show subtle signs of heart failure (e.g., tachypnea) that may be detected by an observant owner but more often goes undetected. The respiratory rate is often increased in these cats at rest, and they may become more tachypneic or even dyspneic if stressed. Stressed cats with severe HCM may recover quickly after stress or may go on to develop fulminant heart failure. Cats with mild to moderate thickening may never develop clinical signs referable to their disease and may live normal lives. In others, the LV wall may thicken further, and complications may develop when they are older and develop a complicating disease such as systemic hypertension or hyperthyroidism.

Cats with severe HCM and moderate to severe heart failure are usually presented to a veterinarian because of respiratory abnormalities (tachypnea, dyspnea, or both) due to pulmonary edema, pleural effusion, or

both. Because household cats are generally sedentary, owners usually do not notice that they are having respiratory difficulty until the dyspnea is advanced. At that time the onset of the disease commonly appears to be acute or peracute to the owner; however, in reality the disease has been present for years, and the heart failure probably has been gradually worsening over weeks to months.

Cats with HCM may develop systemic thromboembolism (see the last section of this chapter). This markedly worsens their prognosis.

Cats with HCM may die suddenly, often with no prior clinical signs referable to heart disease or failure.[74] The cause of the sudden death in these cats is unknown. In humans, sudden death appears to be either due to arrhythmic or hemodynamic causes.[77] The hemodynamic cause is usually an acutely worsening outflow tract obstruction associated with strenuous exercise (which probably ultimately leads to a terminal arrhythmia). This can, in theory, occur with extreme excitement (e.g., being chased by a dog) in a cat with HCM. A large thrombus occluding flow in the left heart is another possible cause of sudden death. However, in the family of Maine coon cats studied by the author and colleagues, sudden death is usually not associated with physical stress or with thromboembolic disease. These cats likely die of an acute ventricular tachyarrhythmia that degenerates into ventricular fibrillation or of a bradyarrhythmia. The incidence of sudden death in feline HCM is probably under-represented in the veterinary literature because cats that die suddenly are usually not presented or reported to veterinarians.

204.4.4.3 Physical Examination

Cats with severe HCM commonly have auscultatory abnormalities. A systolic murmur, heard best over the midsternum or left apex beat is common and is usually due to SAM of the mitral valve. The murmur is often dynamic, increasing in intensity when the cat becomes excited and heart rate and myocardial contractility, especially contractility of the papillary muscles, increase and decreasing in intensity or disappearing when the cat is calm. A gallop sound may be present in cats with severe HCM. It should be noted that not all three heart sound rhythms are due to gallop sounds. In the author's experience, using an electronic stethoscope, systolic clicks also occur with some frequency in cats. Systolic clicks tend to wax and wane in intensity more than do gallop sounds and are more frequently present in cats with mild or no apparent cardiac disease.

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204.4.4.4 Radiography

HCM cannot be distinguished from the other forms of cardiomyopathy using plain radiography. In a cat in CHF the left atrium is almost always enlarged and usually severely enlarged. Pulmonary edema is commonly present, but its pattern is often different from dogs, being patchy or more ventrally distributed. Pleural effusion is also common. Angiography to diagnose HCM has been supplanted by echocardiography.

204.4.4.5 Echocardiography

The diagnosis of HCM is almost always made using echocardiography. Cats with severe HCM have severe papillary muscle hypertrophy, markedly thickened LV walls (7 to 10 mm), and usually an enlarged left atrium (see Figure 204-3). The hypertrophy can be global, affecting all areas of the LV wall, or it can be regional or segmental.[25] Segmental forms can primarily affect the entire (or one region of) IVS or the free wall, the apex, or the papillary muscles (and often the adjacent free wall). Because of these forms, HCM is a diagnosis that should be made by examining several different two-dimensional echocardiographic views

and measuring wall thickness in diastole from the thickest region or regions on the two-dimensional images. M-mode echocardiography may miss regional thickening unless it is guided by the two-dimensional view. End-systolic cavity obliteration is commonly present in cats with severe HCM, although this phenomenon can occasionally occur in cats without HCM (see Figure 204-4).

204.4.4.5.1 Systolic anterior motion of the mitral valve

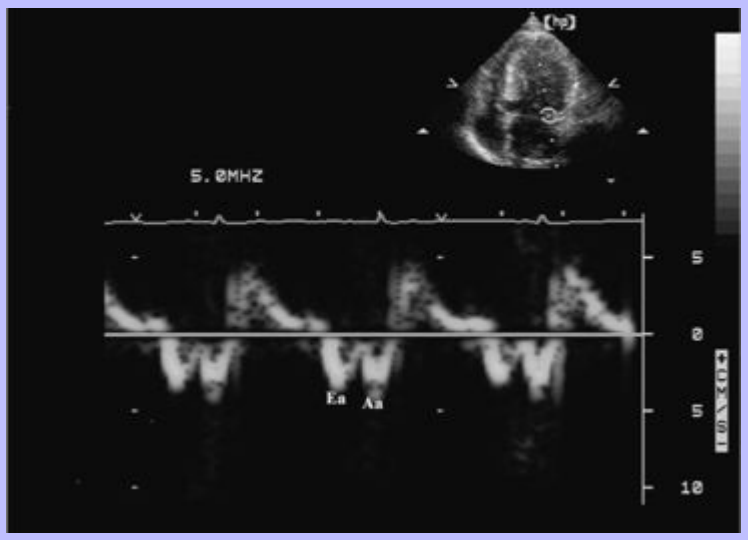
Mitral valve SAM can often be most easily identified using two-dimensional echocardiography, either in real time or in slow motion of a cine loop (see www.vmth.ucdavis.edu/cardio/cases/case5/echodopp.htm and Figures 204-5 and 204-6). Color flow Doppler echocardiography can be used to demonstrate the hemodynamic abnormalities associated with SAM (see Figure 204-7). With this modality, one observes two turbulent jets originating from the LV outflow tract: one regurgitating back into the left atrium and the other projecting into the aorta. Spectral Doppler can be used to determine the pressure gradient across the region of dynamic subaortic stenosis produced by the SAM. The pressure gradient roughly correlates with the severity of the SAM, although it can be quite labile, changing with the cat's level of excitement. Care must be taken not to record the high-velocity mitral regurgitation jet that is positioned close to the dynamic subaortic stenosis jet. Usually, the dynamic subaortic stenosis jet is narrower (shorter period of systole) on spectral Doppler than the mitral regurgitation jet, often becoming even narrower in mid-to late systole. SAM can also be seen with M-mode echocardiography but is usually more difficult to perform because cats' hearts are small.

SAM is not present in all cats with HCM. Although most cats with SAM have severe HCM, some cats develop SAM before they have any evidence of wall thickening, when their papillary muscles are thickened or long. Although the basilar region of the IVS is often thickened during diastole in cats with HCM, the basilar LV outflow tract does not need to be narrowed for SAM to occur.

204.4.4.5.2 Diastolic dysfunction

Diastolic dysfunction in cats with severe HCM has been documented using Doppler tissue imaging (DTI) and measures of transmitral flow and relaxation time. Cats with severe HCM routinely have a decrease in early diastolic wall motion of the left ventricular free wall and mitral valve annulus using DTI (Figure 204-12).[78] In addition, on pulsed wave Doppler echocardiography, peak E wave velocity may be reduced, peak A wave velocity increased, isovolumic relaxation time prolonged, and rate of deceleration of early inflow reduced in cats with severe HCM when the heart rate is slow enough that E and A wave velocities can be identified (Figure 204-13).[79]

Figure 204-12 A Doppler tissue image (DTI) tracing taken from a cat with severe hypertrophic cardiomyopathy (HCM). The DTI is taken from the lateral mitral valve annulus. The early diastolic wave velocity *(Ea)* is markedly reduced to approximately 4 cm/sec. *Aa,* Annular velocity during atrial systole.



204.4.4.5.3 Mild to moderate hypertrophic cardiomyopathy

The diagnosis of HCM is much more difficult and controversial in cats that do not have severe HCM or that only have regional wall thickening on an echocardiogram. In human families with HCM associated with specific gene abnormalities, varying degrees of severity have been noted within the affected family members.[80] Echocardiographic findings in family members with the same mutation range from no abnormalities to severe HCM. This may also be true in cats. Distinguishing mild disease from normal or distinguishing mild to moderate HCM from hypertrophy secondary to other abnormalities is not easy in individual cases. In a clinical situation where one is examining an older cat with what appears to be mild to moderate concentric hypertrophy, one must first decide whether hypertrophy is present or not. Then one must determine if another disease is present and may be causing the hypertrophy before one can really make the diagnosis of feline HCM.

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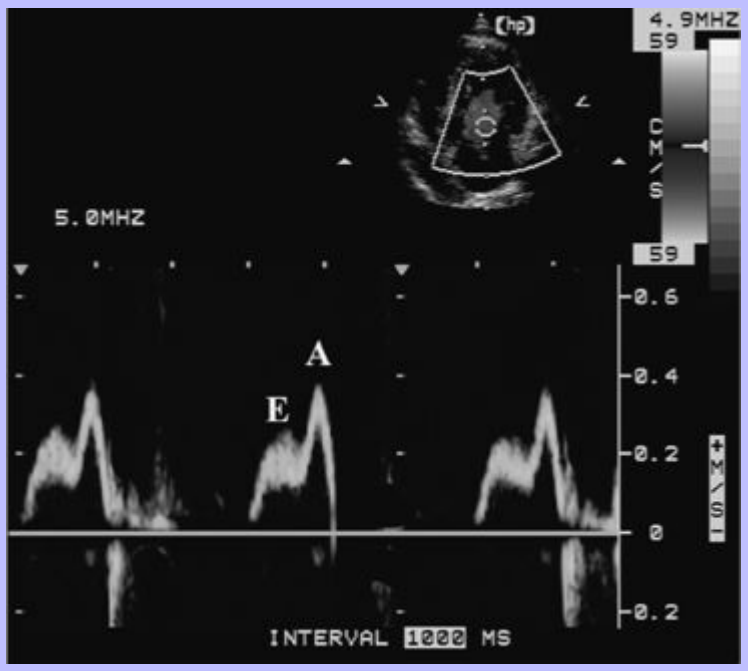
Figure 204-13 A pulsed wave blood flow Doppler tracing taken from just below the mitral valve leaflets during diastole from a cat with severe hypertrophic cardiomyopathy (HCM). Normally the early ventricular diastolic filling velocity *(E)* is faster than the ventricular filling velocity in late diastole, during atrial systole *(A)*. In this cat the relative waveform velocities are reversed.



The upper limit for normal LV wall thickness is generally considered to be 5.0 to 5.5 mm in the cat, although normal ranges that have been generated in cats may be contaminated by cats with mild HCM because of the disease's prevalence. In most normal Maine coon cats the LV wall thickness is in the 3 to 4 mm range. Certainly any cat with a LV wall thickness greater than or equal to 6 mm is abnormal.

204.4.4.6 Magnetic Resonance Imaging

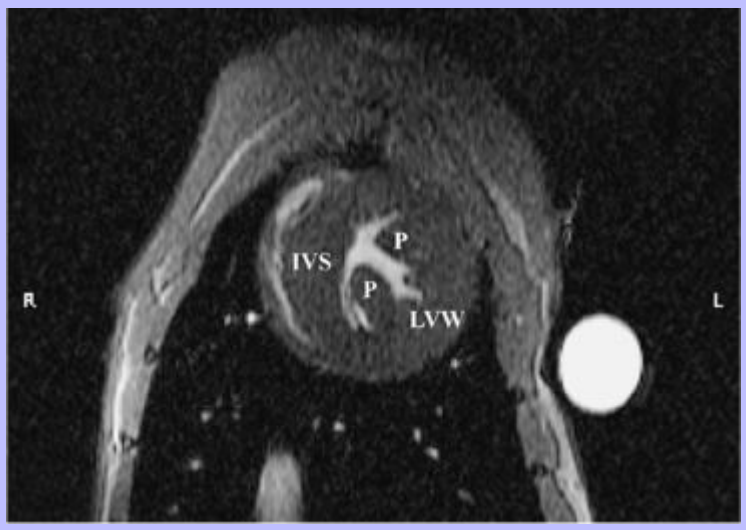
Magnetic resonance imaging (MRI) is a new modality that has been used primarily in humans to assess cardiac anatomy and function. It is more accurate than echocardiography in quantitating LV mass in patients with HCM.[81] It can also be used to quantitate diastolic function.[82] The technique is feasible in cats and may become a useful tool for identifying mild disease and assessing response to therapy (Figure 204-14).

204.4.5 Differential Diagnoses

Hyperthyroidism and systemic hypertension need to be ruled out as either primary or complicating factors. Hyperthyroidism is usually easy to rule out. Devices to measure blood pressure in the cat, however, are not always readily available, and the technique requires some practice to acquire accurate values. In addition, systolic systemic arterial blood pressure may be increased in a normal cat that is stressed, so repeat measurements of increased blood pressure are preferred before a diagnosis of systemic hypertension is made. If systemic arterial blood pressure cannot be measured, one should at least rule out the common causes of systemic hypertension in a cat with LV concentric hypertrophy (i.e., hyperthyroidism, renal failure).

Rarely, infiltrative disease such as lymphoma will produce hypertrophy that is indistinguishable from HCM on an echocardiogram. One such case has been reported.[24] Cats that are homozygous for the dystrophin deficiency seen in hypertrophic feline muscular dystrophy also have thickened but hypoechoic myocardium with hyperechoic foci in the LV myocardium and papillary muscles.[83] The myocardium contains foci of mineralization and no dystrophin.

Figure 204-14 Cross-sectional view of the heart taken using magnetic resonance imaging (MRI) from a cat with severe HCM. The papillary muscles *(P)*, left ventricular free wall *(LVW)*, and interventricular septum *(IVS)* are all markedly thickened. (Picture courtesy of Dr. Kristin MacDonald.)



204.4.6 Precipitating Factors

Certain factors may precipitate heart failure or sudden death in a cat with HCM. Stress (cat fight), anesthesia (especially with ketamine), and surgery appear to be factors.[74] The administration of a long-acting

corticosteroid also appears to be a factor that either produces or worsens heart failure in cats, presumably through the mineralocorticoid effects of these drugs.

204.4.6.1 Therapy of Cats with No Clinical Signs

No evidence exists to show that any drug alters the natural history of HCM in domestic cats until they are in heart failure. Diltiazem, atenolol, or enalapril are commonly administered to cats with mild to severe HCM that are not in heart failure on an empiric basis. Whenever HCM is diagnosed in a cat, the veterinarian should explain the situation to owners and try to let them make informed decisions based on their wishes and life styles. Because no intervention is known to change the course of the disease, treatment at this stage is not mandated.

204.4.6.2 Treatment Goals and General Therapy of Cats in Heart Failure

Cats that present in heart failure have clinical signs referable to pulmonary edema, pleural effusion, or both. Consequently, therapy is generally aimed at decreasing left atrial and pulmonary venous pressures in these cats and physically removing the effusion. In some cats with severe heart failure, clinical evidence of hypoperfusion (low-output heart failure) may be apparent in addition to the signs of CHF. The signs may be manifested primarily as cold extremities.

Pulmonary edema is primarily treated with diuretics (almost exclusively with furosemide) acutely and chronically and an ACE enzyme inhibitor chronically, although recent evidence suggests that ACE inhibition may not be that helpful in prolonging survival in cats with HCM.[84] Diltiazem and beta-adrenergic blockers, usually atenolol, have been commonly used as adjunctive agents. Recent evidence suggests that diltiazem is not helpful in prolonging survival in cats with heart failure due to severe HCM and that atenolol may actually shorten survival time.[84] Pleurocentesis is most effective for treating cats with severe pleural effusion. Furosemide is helpful for preventing or slowing recurrent effusion.

204.4.7 Acute Therapy

Just as with DCM, cats that have respiratory distress suspected of having heart failure secondary to HCM may need to be placed in an oxygen-enriched environment as soon as possible. If possible the cat should be initially evaluated by doing a cursory physical examination, taking care not to stress the patient during this or any other procedure, because stress exacerbates dyspnea and arrhythmias and often leads to death. Most, but not all, cats with severe HCM that are in heart failure will have a heart murmur and gallop rhythm. A butterfly catheter should be used to perform thoracentesis on both sides of the chest to look for pleural effusion as soon as possible. Generally this should be done with the cat in a sternal position so that it does not become stressed during the procedure. Clipping of the hair is not needed. If fluid is identified, it should be removed. Most cats that are dyspneic due to pleural effusion have 150 to 250 mL of fluid in their pleural space. If none is identified, a lateral thoracic radiograph to identify pulmonary edema may be taken with the veterinarian present to ensure that the cat is not stressed (e.g., the clinician should make sure no one stretches the cat out or in any way interferes with its ability to breathe). If the patient struggles or appears to be stressed or fractious during or before radiographic examination, the procedure should be canceled and the patient placed into an oxygen-enriched environment. A preferable alternative to blind tapping is to perform a superficial ultrasonographic examination to identify and locate fluid accumulation.

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204.4.7.1 Furosemide

Furosemide should initially be administered intravenously or intramuscularly to the cat in severe respiratory distress. The route of administration depends on the stress level of the patient. Furosemide should be administered intramuscularly to cats that are very distressed and cannot tolerate restraint for an intravenous injection. Cats that can tolerate an intravenous injection may benefit from the more rapid onset of action (within 5 minutes of an intravenous injection versus 30 minutes for an intramuscular injection). The initial furosemide dose to a cat in distress should generally be in the 1 to 2 mg/lb range, intramuscularly or intravenously. This dose may be repeated within 1 hour to 2 hours (see Chapter 199).

High-dose parenteral furosemide therapy commonly produces electrolyte disturbances and dehydration in cats. Cats with severe heart failure that require intensive therapy are often precarious. They may be presented dehydrated and electrolyte-depleted because of anorexia. They may remain anorexic and consequently dehydrated and depleted of electrolytes once the edema, the effusion, or both are lessened. Judicious intravenous or subcutaneous fluid administration may be required to improve these cats clinically. Overzealous fluid administration will result in the return of CHF. If fluid administration is required, the furosemide administration must be discontinued for that time.

204.4.7.2 Nitroprusside

Anecdotally, nitroprusside may be beneficial in cats with severe pulmonary edema due to HCM. As with DCM, it may be administered empirically at 2 μg/lb/min or titrated, using blood pressure measurement to document efficacy, starting at a dose of 1 to 2 μg/lb/min. Nitroprusside has a very short half-life. Consequently, if clinically significant systemic hypotension is produced (e.g., weakness, collapse, poor capillary refill time) cessation of the infusion will result in the systemic blood pressure returning to normal within several minutes.

204.4.7.3 Nitroglycerin

Nitroglycerin cream may be beneficial in cats with severe edema formation secondary to feline cardiomyopathy. However, no studies have examined effects or efficacy. Nitroglycerin is safe and some benefit may occur with its administration in some cats. Consequently, one-eighth inch to one-fourth inch of a 2% cream may be administered to the inside of an ear every 4 to 6 hours for the first 24 hours as long as furosemide is being administered concomitantly. Nitroglycerin is not a primary drug. Tolerance develops rapidly in other species, and prolonged administration is probably of even lesser benefit.

Once drug administration is complete, the cat should be left to rest quietly in an oxygen-enriched environment. Care should be taken not to distress the cat. A baseline measurement of the respiratory rate and assessment of respiratory character should be taken when the cat is resting. This should be followed at 30-minute intervals and furosemide administration continued until the respiratory rate starts to decrease (a consistent decrease of the respiratory rate from 70 to 90 breaths per minute into the 50 to 60 breaths per minute range is a general guide), the character of the cat's respiratory effort improves, or both occur. When this happens, the furosemide dose and dose frequency should be curtailed sharply.

204.4.7.4 Sedation or Anesthesia

In some cats, sedation with acepromazine (0.02 to 0.5 mg/lb intramuscularly or intravenously) may help by producing anxiolysis. Oxymorphone (0.02 to 0.04 mg/lb every 6 hours intramuscularly, intravenously, or subcutaneously) or butorphanol tartrate (0.04 mg/lb intravenously or 0.18 mg/lb every 4 hours subcutaneously) may also be used but are secondary choices because they can produce respiratory depression. Oxymorphone may produce excitement in some cats.

In some cats with fulminant heart failure, anesthesia, intubation, and ventilation are required to control the respiratory failure. Although this method is not preferred for most severely dyspneic cats, it can be life saving in some. This procedure has the advantage of being able to administer 100% oxygen and to be able to drain or suction fluid from the large airways in a controlled environment. The disadvantage is the administration of anesthetic agents to a cat that has cardiovascular compromise.

204.4.8 Chronic Therapy

Many aspects of chronic therapy of HCM are controversial. All therapy is palliative. Furosemide is the only drug that has a clearly beneficial effect chronically on survival in cats with HCM.[84]

204.4.8.1 Pleurocentesis

Many cats with HCM are dyspneic because of pleural effusion that reaccumulates despite appropriate medical therapy. These cats need periodic pleurocentesis (see Chapter 103).

204.4.8.2 Furosemide

In cats with CHF due to HCM, furosemide administration, once initiated, should usually be maintained for the rest of the cat's life. In a few cases, furosemide can be discontinued gradually once the cat has been stabilized. This usually only occurs in a cat that has had a precipitating stressful event.

As for DCM, the maintenance dose of furosemide in cats usually ranges from 6.25 (one half of a 12.5 mg tablet) once a day to 12.5 mg orally every 8 hours, although the dose may be increased further if the cat is not responding to a conventional dose. The author and colleagues have administered higher doses (up to 37.5 mg every 12 hours) than commonly recommended to a few cats with severe heart failure without identifying severe consequences as long as the cats were eating and drinking. Cats on high-dose furosemide therapy are commonly mildly dehydrated and mildly to moderately azotemic. However, they often continue to maintain a reasonable quality of life.

The furosemide dose needs to be titrated carefully in each patient. The owner should be taught how to count the resting respiratory rate at home and instructed to keep a daily written log of the respiratory rate as outlined previously under DCM. This is highly beneficial for making decisions regarding dose adjustment in individual patients.

204.4.8.3 Angiotensin-Converting Enzyme Inhibitors

Although furosemide has been used to treat heart failure secondary to feline HCM for decades, the use of ACE inhibitors in cats with HCM is relatively recent, because veterinarians, like their colleagues who treat humans, feared that the use of ACE inhibitors would worsen SAM in their patients. Over the past 10 years it has become obvious to most veterinary cardiologists that ACE inhibitors do not worsen the clinical signs referable to HCM, and a recent study has documented that SAM is not worsened by enalapril administration in cats.[85] Many have believed and one study has suggested that ACE inhibitors improve the quality and quantity of life of cats with HCM.[86] Preliminary evidence from a recent placebo-controlled and blinded clinical trial suggests that enalapril produces little to no benefit when compared with furosemide alone in cats with heart failure due to HCM.[84] However, this study also included cats with unclassified (restrictive) cardiomyopathy and both cats with and without SAM. Subgroup analysis failed to change the conclusions of the study but the subgroups were small. Consequently, it is the recommendation of this author to continue to use an ACE inhibitor in cats in heart failure due to HCM at a dose of 1.25 to 2.5 mg orally every 24 hours.

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204.4.8.4 Diltiazem

In cats with severe HCM that have or have had evidence of CHF, diltiazem or a beta-adrenergic blocking agent are often administered. Both provide symptomatic benefit in human patients. Their use in cats with HCM is controversial; however, little doubt exists that neither drugs produces dramatic benefits. Diltiazem, however, appears to produce no harm.[84]

Diltiazem is a calcium channel blocker previously reported to produce beneficial effects in cats with HCM when dosed at 7.5 mg every 8 hours.[87,88] Beneficial effects that have been reported include lessened edema formation and decreased wall thickness in some cats. In the author's experience only a few cats appear to experience a clinically significant decrease in wall thickness, and it is impossible to tell if this is due to drug effect or time. Rarely does it appear clinically that diltiazem controls CHF on its own or helps control pulmonary edema or pleural effusion when added on to furosemide therapy. Diltiazem does improve the early diastolic relaxation abnormalities seen in feline HCM.[59,88] Whether this helps decrease diastolic intraventricular pressure and so decrease edema formation is unknown. Theoretically it should have little benefit in the resting cat with a slow heart rate. Slower myocardial relaxation during rapid heart rates may not allow the myocardium enough time to relax, resulting in increased diastolic intraventricular pressure. Diltiazem may help protect a cat that undergoes a stressful event. Incomplete relaxation and decreased compliance, however, are more plausible explanations for increased diastolic pressure due to diastolic dysfunction in feline HCM. In humans, diltiazem does not change LV chamber stiffness and so does not alter passive diastolic function.[89] In cats it also appears not to alter late diastolic filling properties.[90] Diltiazem decreases SAM, which may decrease the amount of mitral regurgitation, but beta blockers generally produce a greater decrease in the amount of SAM.[91] Recent evidence suggests that diltiazem has no effect on survival time in cats with severe HCM and heart failure.[84]

Dilacor XR is dosed at 30 mg per cat orally every 12 hours and produces a significant decrease in heart rate and blood pressure in cats with HCM for 12 to 14 hours.[92]

204.4.8.5 Beta-Adrenergic Receptor Blockers

Beta blockers are primarily used to reduce SAM and heart rate in cats with HCM. At this stage, beta blockers should probably be reserved for cats with severe SAM at rest or with tachyarrhythmias and not routinely administered to the affected population as a whole, because a recent study has suggested that atenolol shortens the survival of cats with diastolic dysfunction, including cats with HCM.[84] Beta blockade is questionable for SAM and tachycardia observed in a clinical situation. Cats spend 85% of their life asleep, and sleep probably reduces sympathetic activity better than a beta-adrenergic blocking drug. Consequently, many cats with mild to moderate SAM in a veterinary clinic probably have no or milder SAM at home, and the same can be said for tachycardia. Beta blockers are effective for reducing SAM. Two studies have examined the effects of esmolol, a short-acting β_1-adrenergic blocking drug, in cats with HCM and obstruction to LV outflow due to SAM; both showed a reduction in the pressure gradient across the outflow tract.[91,93] In both studies the degree of outflow tract obstruction decreased and the heart rate slowed, and in one esmolol was more effective than diltiazem.[91] If the data on esmolol can be translated to atenolol's effects in cats (which seems reasonable), one would predict that atenolol would decrease SAM.

Atenolol is a specific β_1-adrenergic blocking drug that needs to be administered twice a day, usually at a total dose of 6.25 to 12.5 mg orally every 12 hours.[92,94] In the cat, atenolol has a half-life of 3.5 hours. When administered to cats at a dose of 1.4 mg/lb, atenolol attenuates the increase in heart rate produced by isoproterenol for 12 but not for 24 hours.

204.4.9 Refractory Heart Failure

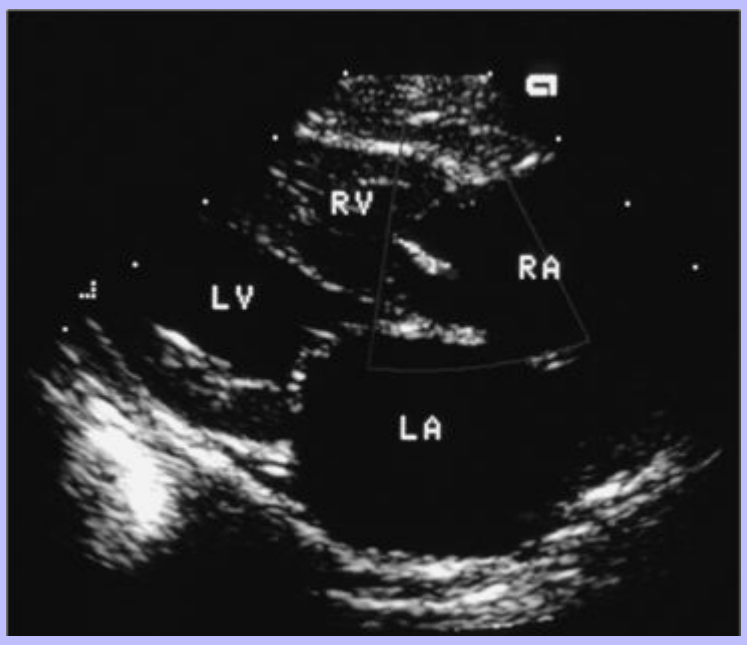
Heart failure that is refractory to furosemide and an ACE inhibitor portends a poor prognosis. Another diuretic may be added to the therapeutic regimen. A thiazide diuretic is generally the most rewarding but is also more likely to cause complications, such as dehydration and electrolyte (sodium, potassium, chloride, magnesium) depletion. Spironolactone, in theory, may have some beneficial effects related to blocking aldosterone's actions; however, clinically it rarely results in noticeable improvement, and its efficacy is unproven. A low sodium diet may be helpful, if palatable. This diet can be a commercial one or one that is devised by a nutritional service. Home-cooked diets formulated by the owner are discouraged unless the owner is counseled. If severe SAM is present and atenolol is not already part of the therapeutic regimen, it may be added at this stage.

204.5 FELINE UNCLASSIFIED CARDIOMYOPATHY

A relatively common echocardiographic finding in cats with heart disease and heart failure is normal to mildly abnormal ventricular chamber size, wall thickness, and wall motion with atrial enlargement (Figure 204-15). The left heart is most commonly affected, but there may also be concurrent right heart changes. It is commonly believed that because no evidence of systolic dysfunction, left-to-right shunting, or obvious valvular regurgitation exists, these cats must have diastolic dysfunction. Consequently, these cats are often assumed to have RCM. One study has suggested that this is not the case.[78] In this study, diastolic function was examined in nine cats with the aforementioned findings using DTI. DTI is a pulsed Doppler technique that measures the velocity of ventricular or annular wall motion and is an accurate means of detecting RCM in humans.[95] Six of the cats in the study had clear evidence of diastolic dysfunction (i.e., lower than normal early diastolic wall velocity). Three cats clearly had normal diastolic function on DTI and therefore did not have RCM. Consequently, not all cats with the

echocardiographic findings described previously have RCM. Therefore the author feels that the more appropriate term for this disease is *unclassified cardiomyopathy* unless it can be documented that diastolic dysfunction exists. In this scheme, RCM then is often a subclassification of unclassified cardiomyopathy, whereas the other subclass is unknown or idiopathic.

Figure 204-15 Two-dimensional echocardiogram from a cat with unclassified cardiomyopathy. The left ventricle *(LV)* appears normal and the left atrium *(LA)* is enlarged. A small color flow Doppler jet of tricuspid regurgitation in the right atrium *(RA)*, which is also enlarged but not to the same degree as the LA. *RV,* Right ventricular chamber.



What could cause this echocardiographic pattern other than RCM? Some form of atrial myopathy is one possibility, and atrial standstill is occasionally identified in these cats (see www.vmth.ucdavis.edu/cardio/cases/case18/case18.htm). Misdiagnosis is another possibility. In the author's clinic, many cats arriving with a diagnosis of primary mitral regurgitation, mitral and tricuspid valve dysplasia, and hyperthyroidism have been placed into this category (called either *unclassified* or *RCM*), probably because it was convenient and gave the clinician a false sense of security of making a “definitive” diagnosis. Significant mitral regurgitation is most often missed when only a high-frequency ultrasound probe is used. A lower-frequency transducer and several views are recommended. Some ultrasound machines do not have a frame rate high enough to adequately detect apparent severe mitral regurgitation in cats.

In some cats, evidence of endocardial scarring can be seen on the echocardiogram, either as a discrete lesion most commonly at the level of the mid-LV or as diffuse scarring of the endocardium. In these cases the diagnosis of RCM may be made echocardiographically.

The terms *intermediate* and *intergrade cardiomyopathy* have been used previously to describe this class of cardiac disease in cats. They are probably inappropriate because they suggest that the characteristic changes seen in these cats share clinical and echocardiographic features of both dilated and HCM.

204.6 FELINE RESTRICTIVE CARDIOMYOPATHY

Although listed as a separate entity in this chapter, in most situations RCM is a subclassification of unclassified cardiomyopathy. Feline RCM is a diverse group of myocardial conditions characterized by abnormal diastolic function, normal to mildly increased LV wall thickness, and normal to mildly reduced systolic function. RCM occurs when ventricular diastolic compliance is impaired (i.e., stiffness is increased) by infiltration of the endocardium, subendocardium, or myocardium by fibrous tissue or another component. In contrast to human medicine where specific causes, such as amyloidosis and eosinophilic infiltration are causes of RCM, specific causes for RCM have not been clearly defined in the cat. Without the use of invasive diagnostic procedures to directly measure LV diastolic function, DTI, other indirect measures of diastolic function, or necropsy examination, it is often impossible to distinguish this disorder from the form or forms of unclassified cardiomyopathy that are idiopathic.

204.6.1 Incidence

The exact incidence of RCM is unknown. Unclassified cardiomyopathy is the second most common feline cardiomyopathy, of which RCM is a component.

204.6.2 Cause

The precise cause of feline RCM is unknown. Some evidence indicates that it may be inflammatory in nature. Endomyocarditis has been recognized in cats at postmortem examination for over 25 years.[96] Endomyocarditis in cats is characterized by focal or diffuse infiltration of the endocardium by lymphocytes, plasma cells, histiocytes, and a lesser number of neutrophils. The inflammatory component of endomyocarditis may be infectious, immune-mediated, or toxic. An interstitial pneumonia may also be common in this group. Within the past 10 years a study documented endomyocarditis in 37 cats at necropsy over a 7-year period.[97] Over this same 7-year span, 25 cats with endocardial fibrosis were identified at the same institution. Four of these 62 cats had features of both diseases. This study and previous findings from Dr. Sam Liu have lead to the speculation that chronic endomyocarditis leads to endocardial fibrosis, a pathologic disease that leads to the physiologic entity termed *RCM*. However, unless an agent that causes endomyocarditis in cats is identified, the theory that endomyocarditis leads to endocardial fibrosis will remain unproven.

In addition to the previous findings and speculation, one study has identified a transmissible myocarditis-diaphragmitis in young cats.[98] The disease is generally self-limiting and causes a transient fever and depression. The investigators were unable to isolate a causative agent in these cats.

Eosinophilic endocardial inflammation is common in humans, more commonly in tropical climates. RCM has been reported in several cats with hypereosinophilic syndrome, although it is impossible to determine if the hypereosinophilia in this small number of cats caused RCM or the two diseases happened to occur together.[99,100]

204.6.3 Pathophysiology

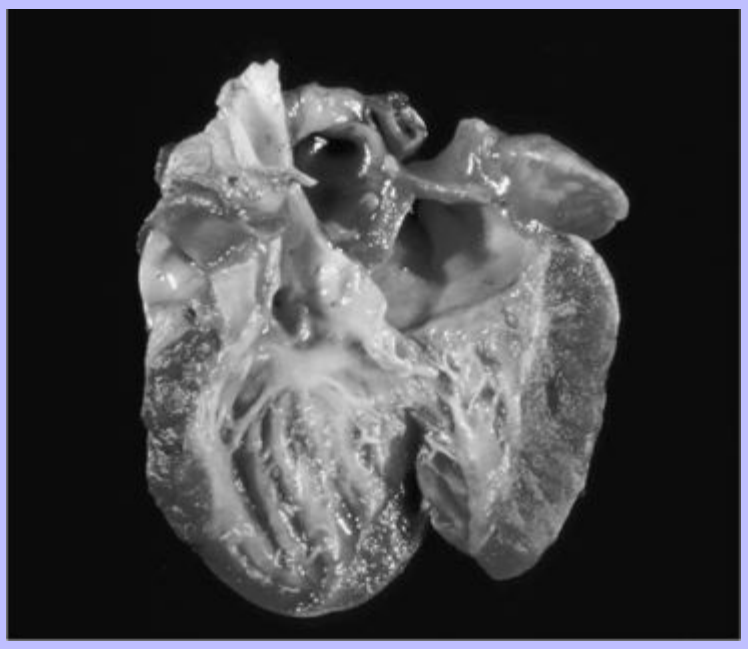
In its classic form, endocardial, subendocardial, or myocardial fibrosis impede ventricular diastolic filling and so impair diastolic function. These disorders are generally and primarily characterized by decreased compliance leading to an elevated LV diastolic pressure with a normal LV filling volume. The elevation in diastolic ventricular pressure results in atrial enlargement and the formation of pulmonary edema and pleural effusion. The lesions are generally confined to the LV in humans and left CHF predominates the clinical presentation.[101] In cats, right atrial enlargement is also common. In some cats the LV is perfectly normal in appearance, whereas in others the LV may be misshapen and may have additional false tendons traversing the ventricle.

204.6.4 Pathology

The postmortem changes are unique to this form of cardiomyopathy and may be used to differentiate it from other disorders. Patchy or diffuse endocardial, subendocardial, or myocardial depositions of fibrous tissue are characteristic necropsy findings. The endocardium may appear whitish-gray, opaque, and thickened when endocardial or endomyocardial fibrosis is present (Figure 204-16). Fibrous adhesions between papillary muscles and the myocardium with distortion and fusion of the chordae tendineae and mitral valve leaflets may also be noted in RCM.[96] In extreme cases a portion of the LV cavity, most commonly the mid-LV, may be obliterated. As with most cardiomyopathies, the LV appears to be most severely affected, although other cardiac chambers may exhibit similar pathologic findings. Extreme left atrial and auricular enlargement is common. Other cats demonstrate apparently earlier stages of the disease in which microscopic evidence of myocarditis is evident without gross pathologic abnormalities. The lesions suggest an inflammatory response; however causative factors have not been identified. Systemic thromboembolism is prevalent.[102]

Histologic features of endocardial fibrosis include extreme endocardial thickening by hyaline, fibrous, and granulation tissue.[96] Chondroid metaplasia is occasionally exhibited by the surface layer of hyaline tissue. A layer of loose fibrous tissue lies beneath this layer with a layer of granulation tissue adjacent to the myocardium. These changes are similar but not identical to those seen in humans with RCM.

Figure 204-16 Postmortem specimen showing the left ventricle *(LV)* and left atrium from a cat with endomyocardial fibrosis producing restrictive cardiomyopathy (RCM). The endocardium of the LV is white and thickened by fibrotic tissue.



204.6.5 Natural History and Prognosis

As with other forms of cardiomyopathy, prognosis is difficult to predict for individual cases, especially prior to observing the initial response to therapy. A high incidence of serious arrhythmias, systemic thromboembolism, and refractory CHF is often present. In the author's experience, cats with RCM, on average, have a poor long-term prognosis. Although an initial response to standard therapy is often possible, progressive and refractory heart failure develops in the majority of cases.

204.6.6 Clinical Manifestations

204.6.6.1 History

Signalment is difficult to accurately report, because little agreement exist among veterinary cardiologists as to which cases fall within this classification. From a series of pathologic studies in cats, Liu reported an age range of 8 months to 19 years.[103] No breed predisposition has been reported. There may be a male predominance, or it may be that males develop more severe disease, as in HCM. Most cats are middle-aged or older. Presenting complaints and clinical signs are similar to other forms of myocardial disease and

include dyspnea and tachypnea, poor general condition, weakness, lethargy or rarely exercise intolerance, and anorexia. In one report, 45% had evidence of systemic thromboembolism at necropsy.[102]

204.6.6.2 Physical Examination

A heart murmur heard best on the sternum, just medial to the left apex beat, is common. An arrhythmia may be ausculted. Many cats are dyspneic.

204.6.6.3 Radiographs

No specific findings exist for unclassified or RCM. Pulmonary edema and pleural effusion are common.

204.6.6.4 Echocardiography

The echocardiographic findings in RCM are variable. Left atrial dilation is the common feature, and the LV internal dimensions are typically normal but may be mildly to moderately reduced or mildly increased. Most commonly the LV looks normal. However, two-dimensional echocardiography may demonstrate loss of normal LV symmetry, distorted or fused papillary muscles, mild LV concentric hypertrophy, mild wall thickening, a mild reduction in shortening fraction, and a mild increase in chamber diameter. Some cats may have evidence of more pronounced endocardial scarring. In these cases the endocardium may be notably thickened and irregular with an increased echogenicity. Others have evidence of cavity obliteration. Mild mitral regurgitation may be detectable with color flow Doppler. A large color flow Doppler jet suggests that the primary problem is primary mitral valve disease rather than unclassified cardiomyopathy. A left atrial thrombus may be identified.

Doppler echocardiography may be abnormal in cats with RCM. However, this remains to be proven. As noted previously, the early diastolic waveform on DTI is reduced in cats with RCM, whereas it is normal in cats with the idiopathic form of unclassified cardiomyopathy.

204.6.6.5 Electrocardiography

No specific findings appear on electrocardiogram (ECG). Supraventricular and ventricular arrhythmias may be present, but sinus tachycardia is most commonly present in the clinic. Shifts in the mean electrical axis and evidence of chamber enlargement may occur.

204.6.6.6 Clinical Pathology

No specific clinical pathologic findings exist. Azotemia due to reduced cardiac output, either from CHF or dehydration caused by diuretic therapy, is the most common abnormality. Elevated liver enzymes may be encountered.

204.6.6.7 Differential Diagnosis

The primary differential diagnoses for RCM are unclassified cardiomyopathy not due to RCM, mitral regurgitation due to primary mitral valve disease, and myocardial infarction. Chronic myocardial infarction usually results in a region of akinetic or hypokinetic myocardium. Often the region of affected myocardium is thinner than normal. With severe mitral regurgitation due to primary mitral valve disease, a large jet is

seen with color flow Doppler (although it may take a lower-frequency transducer and various views, including the left apical four-chamber view, to identify it). The IVS is commonly hyperdynamic, whereas the left ventricular free wall commonly moves less than normal. The LV chamber is usually larger than normal in diastole.

204.6.7 Therapy

Therapy of restrictive and unclassified cardiomyopathy is the same. It is palliative and consists primarily of the administration of furosemide and an ACE inhibitor as outlined in the two previous sections of this chapter. Diltiazem is not indicated because a calcium channel blocker is not able to help to relax scar (i.e., fibrous) tissue. A recent study suggests that atenolol may decrease the survival time in patients with diastolic dysfunction.[84] However, if the cat is persistently tachycardic at home, diltiazem or atenolol may be indicated in an attempt to slow the heart rate.

204.7 ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

ARVC is a recently reported and rare form of feline cardiomyopathy.[104] It has been identified in humans, dogs (boxer dogs), and cats. It is characterized by fibrofatty or fatty infiltration of primarily the right ventricular free wall. The right ventricular wall is commonly thinned in humans and cats with the disease. Ventricular tachyarrhythmias are common in all three species, and sudden death is a common feature of the disease in humans and boxer dogs.[105] The disease is also commonly known as arrhythmogenic right ventricular dysplasia (ARVD).

204.7.1 Cause

The cause of ARVC is unknown in cats. In humans at least six forms of the disease (ARVD 1 to 6) are inherited as an autosomal dominant trait, and one (Naxos syndrome) is inherited as an autosomal recessive trait.[105] The cause of ARVD 2 has been recently identified as several mutations in the gene that encodes for the calcium release channel (also known as the *ryanodine receptor*) on the myocardial sarcoplasmic reticulum.[106] Ryanodine receptor dysfunction has been identified in boxer dogs with ARVC.[107]

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204.7.2 Pathophysiology

In cats, ARVC most commonly (8 of 12 cats in the one study reported to date) produces right heart failure, presumably through the destruction of right ventricular myocardium resulting in right ventricular systolic and, possibly, diastolic dysfunction along with secondary tricuspid regurgitation.[104] The changes in the right ventricular free wall also commonly produce ventricular tachyarrhythmias (9 of 12 cats) and supraventricular tachyarrhythmias (5 of 12 cats). Tumor necrosis factor (TNF) is commonly increased in cats with right heart failure, which may contribute to the systemic effects of the disease.[108]

204.7.3 Pathology

The right ventricular and atrial chambers are markedly enlarged in cats that die of the disease.[104] Thinning of the right ventricular free wall is a consistent feature of the disease and may be focal or diffuse. Aneurysms of the wall may occur, especially at the apex of the right ventricle (RV). The wall is often so thin that light can be

seen through it. Histopathologically either fibrofatty or fatty replacement of myocardium exists. Inflammatory cells are commonly present, especially in regions of fibrofatty replacement. Although most prominent in the right ventricular free wall, these changes are also commonly present in the LV and occasionally identified in the left atrium. Apoptosis is common.

204.7.4 Clinical Manifestations

Evidence of right heart failure, including ascites, pleural and pericardial effusions, and jugular vein distension, is common. The pleural effusion may be severe enough to cause tachypnea and dyspnea. A heart murmur secondary to tricuspid regurgitation is common. Arrhythmias are also commonly heard on auscultation, and ECG evidence of a ventricular arrhythmia may be one clue that one is dealing with ARVC and not tricuspid valve dysplasia. Supraventricular tachyarrhythmias, including atrial fibrillation, may also occur. In the severe stage, echocardiography reveals marked enlargement of the right ventricular and right atrial chambers. The right ventricular chamber enlargement may be segmental. Tricuspid regurgitation is usually present on color flow Doppler. Careful echocardiographic interrogation may reveal localized regions of right ventricular wall thinning or regions of aneurysmal dilation. The right ventricular trabeculae may appear abnormal, especially at the apex. The disease may not be confined to the right heart, which means the left atrial and ventricular chambers may also be enlarged. Syncope due to ventricular tachycardia may be present.

204.7.5 Differential Diagnosis

Cats with severe ARVC are commonly misdiagnosed as having tricuspid valve dysplasia because tricuspid regurgitation is a common sequel to the disease. Cats from 1 to 20 years of age have been diagnosed with the disease.

204.7.6 Therapy

Right heart failure is treated with furosemide and an ACE inhibitor. Digoxin combined with either diltiazem or atenolol may be used to control supraventricular tachycardia or the ventricular rate in cats with atrial fibrillation. Malignant ventricular tachycardia or ventricular tachycardia that causes clinical signs (e.g., syncope) can be managed acutely with lidocaine (5 to 20 μg/lb/min) and chronically with sotalol (1 to 2 mg/lb every 12 hours orally).[109]

204.8 SECONDARY MYOCARDIAL DISEASES

204.8.1 Hyperthyroidism

Hyperthyroidism commonly produces echocardiographic changes, although the changes are usually relatively mild. Changes can include an increase in LV wall thickness, left atrial size, and LV diastolic diameter. Shortening fraction may also be increased.[110,111] Often these changes regress over months once the hyperthyroidism is successfully controlled. These changes are physiologic in response to the direct effects of the excess thyroid hormone on the cardiac myocytes, the increase in metabolic rate, and systemic hypertension. Consequently hyperthyroidism is not a form of cardiomyopathy (i.e., primary myocardial disease). However, some cats with hyperthyroidism will have the classic features of severe HCM, including SAM in some, and a few may experience heart failure. Although unproven, the author theorizes that some of

these cats may have had mild to moderate HCM all their lives and that the hyperthyroidism has exacerbated the hypertrophy.

204.8.2 Systemic Hypertension

Systemic arterial hypertension causes a pressure overload of the LV and leads to concentric hypertrophy. This hypertrophy is generally mild, however, with the average increase in wall thickness being approximately 1 mm.[112] As with hyperthyroidism, the author theorizes that some cats with mild to moderate HCM have an exacerbation of their concentric hypertrophy when they develop systemic arterial hypertension. In addition to the LV wall becoming thicker, the proximal aorta also increases in size with systemic arterial hypertension.

204.8.3 Acromegaly

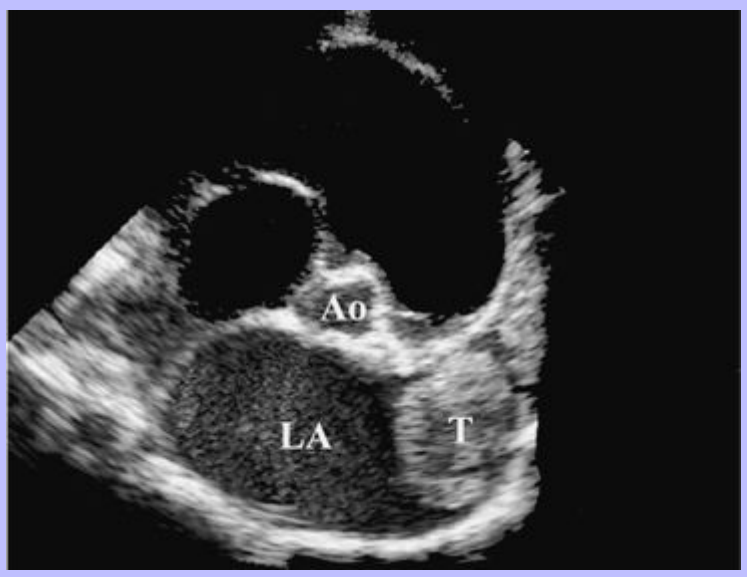
Acromegaly has been reported to increase LV wall thickness severe enough to produce heart failure in cats. In one study, significant wall thickening was identified in seven of 14 cats with acromegaly and six developed heart failure.[55] However, in six cats examined echocardiographically by the author, no evidence of cardiac change was found.

204.9 SYSTEMIC ARTERIAL THROMBOEMBOLISM

A thrombus is a blood clot. Thrombi are usually formed (to prevent hemorrhage) when a blood vessel is traumatized. They can also form spontaneously within the cardiovascular system. A systemic thrombus becomes a systemic thromboembolus when it dislodges from the primary site where it forms in the cardiovascular system and is pushed by blood flow to a distal site where it lodges, partially or completely occluding blood flow distal to the thromboembolus. Most clots that occlude systemic arterial blood vessels are thromboemboli. Spontaneous formation of a clot in a systemic arterial vessel causing occlusion of a systemic artery is an unusual event and requires a predisposing factor (e.g., trauma) to allow it to occur. Most systemic thrombi that form and cause thromboemboli in cats appear to form in the left atrium, most commonly in the left auricle, as they do in humans (Figure 204-17).[113]

Systemic arterial thromboembolism (STE) is most commonly observed in cats with any form of cardiomyopathy, most frequently in those with severe left atrial enlargement, although they also have been reported to occur in cats with hyperthyroidism.[114–116] However, it is unknown if cases of hyperthyroidism have confounding HCM or not. Left atrial chamber enlargement in the absence of mitral regurgitation causes blood flow stasis, especially in the left auricle, allowing red cells to aggregate and thrombus formation to occur. Although STE can occur in cats that do not have cardiac disease, more than 70% of cases seen in veterinary small animal practice are in cats with cardiomyopathy.[115,116]

Figure 204-17 A two-dimensional echocardiogram from a cat with hypertrophic cardiomyopathy (HCM), showing a large thrombus *(T)* in the left atrium *(LA)*, specifically the left auricle, and spontaneous echocardiographic contrast in the left atrium. *Ao,* Aorta.



Most cats (approximately 90%) with STE have the thromboembolus lodge at the terminal abdominal aorta (the aortic trifurcation). The thromboembolus commonly extends down the external iliac arteries, giving it the appearance of a saddle. Consequently, it is commonly called a *saddle thromboembolus*. Thromboembolism of the terminal aorta causes acute cessation of blood flow to the caudal limbs, producing acute caudal limb paresis and paralysis and pain with a loss of the femoral pulses, cold extremities, and pale or cyanotic pads (pain, poikilothermia, paralysis, pulselessness, and pallor). Some cats have a smaller thromboembolus lodge in one femoral artery, a brachial artery, or another smaller artery. Occasionally, a large thromboembolus lodges more proximally in the aorta, above the renal arteries, resulting in acute renal failure. In other cats, a very large thromboembolus lodges in the mitral valve orifice, the LV, or the proximal aorta at the region of the brachiocephalic trunk, causing sudden death.[117]

204.9.1 Pathophysiology

In fast-flowing blood, as occurs with injury to a systemic blood vessel, the principal elements forming a thrombus are platelets, which form a white clot.[118] As blood flow slows due to the clot formation, red cells are incorporated in the clot to form a red thrombus. On the other hand, in slow-flowing blood, coagulation enzymes play the major role in thrombus formation. Here red cells entrapped in a fibrin network result in the formation of a red thrombus. Although no one has examined the composition of left atrial thrombi in cats, in humans they are composed of red cell aggregates within a fibrin meshwork.[118]

The most plausible explanation for thrombus formation in the left atrium of cats with STE is sluggish blood flow. At a postmortem examination, atria from cats with cardiac disease and thromboembolism are often very large and may be fibrotic. In one study the left atrium was severely enlarged in 57%, moderately enlarged in 14%, and mildly enlarged in 22% of cats with STE.[115] Only 5% had a normal left atrial size. The amount of blood that flows through an enlarged left atrium of a cat with cardiomyopathy is normal to low unless significant mitral regurgitation is present, resulting in a lower than normal blood flow velocity within the chamber. When blood flow slows to a certain velocity, red cells and other blood factors clump together (see www.vmth.ucdavis.edu/cardio/cases/case18/echo.htm).[119] In vitro this occurs when blood flow velocity decreases below 10 cm/sec, whereas in humans with atrial fibrillation it occurs when the velocity from the left auricle to the left atrium slows to less than 35 cm/sec.[119,120] Increasing plasma fibrinogen concentration also increases red cell aggregation, whereas red cell aggregation is not altered by the absence of platelets, stimulation of platelet aggregation with ADP, or inhibition of platelet aggregation with aspirin.[119]

Red cell aggregation can be observed with ultrasound and is termed *spontaneous echocardiographic contrast* (SEC), also known euphemistically as “smoke.” SEC is often observed swirling in the enlarged left atrium of a cat with severe cardiomyopathy. In humans, SEC is associated with increased left atrial size and with reduced left atrial blood flow velocity.[120] It is the factor most strongly associated with left auricular thrombus formation and with systemic embolic events. No studies on this subject have been performed in veterinary medicine. However, it is common to see spontaneous contrast in the left atrium of a cat with severe cardiomyopathy and an STE. If low blood flow velocity is such an important factor, one might also expect dogs with DCM to be prone to left atrial thrombus formation. Systemic thromboembolism is rare in dogs with DCM. The reason for this discrepancy may be due to species differences in erythrocyte aggregability. One study has documented that normal cat red cells are more aggregable than those of dogs, rats, rabbits, humans, and gerbils.[121] Although platelets are not necessary for thrombus formation in the left atrium and auricle, cat's platelets are also more reactive than other species. Feline platelets undergo spontaneous aggregation in vitro and are more responsive to serotonin-induced aggregation than are platelets from other species.[122,123] Cats also have a greater volume of platelets per body weight than other species.[122] One study has documented increased platelet aggregability in some cats with cardiomyopathy.[124]

In humans, hyperhomocysteinemia has been associated with venous thrombosis, atherosclerosis, and arterial occlusive disease.[125] Consequently, hyperhomocysteinemia is thought to be associated with atherogenesis and thrombogenesis. Homocysteine is an amino acid metabolically converted from methionine. This conversion is dependent on folic acid and vitamins B_6 and B_{12}, acting as cofactors. The resting plasma concentrations of vitamins B_6 and B_{12} are lower in cats with cardiomyopathy and in cats with STE than control cats, but resting plasma homocysteine concentration is not lower.[126] However, when challenged with methionine, some normal cats show a clear abnormality in their ability to produce homocysteine, showing a marked elevation in plasma homocysteine concentration after oral methionine administration.[127] This may suggest that some cats have an abnormality in their homocysteine metabolic pathway that could make them more susceptible to thrombosis.

204.9.1.1 Thromboembolism

Once a left atrial thrombus has formed, it can do one of four things: (1) it can remain static, especially if it is lodged in the left auricle; (2) it can dislodge and become an STE; (3) it can grow very large and occlude intracardiac blood flow; or (4) it can be dissolved by the body's thrombolytic system. The incidence of the

first and fourth outcomes is unknown, because if a thrombus causes no clinical abnormalities, the thrombus usually goes undetected. If it occludes intracardiac flow, it causes death, and if a postmortem examination is not done, the cause of death is never known. Only the second scenario results in clinical signs for which owners commonly seek medical attention for their pets.

The clinical signs produced depend primarily on the site occluded by the thromboembolus, whether the occlusion is total or partial, and the amount of collateral circulation. Before they dislodge, most left atrial thrombi apparently become larger than any artery exiting off the aorta. Consequently, blood flow pushes them the length of the aorta to lodge at the aortic trifurcation, where the aorta divides into the two external iliac arteries and the common origin of the internal iliac arteries. Here they obstruct blood flow to the caudal limbs.

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Physical obstruction is only a part of the pathophysiology. Experimentally, the terminal aorta has been ligated in an attempt to reproduce the disease.[128,129] Surprisingly, cats with aortic ligation exhibit no pain and walk after surgery, although the femoral pulses are absent and caudal limb blood flow is only 30% of baseline.[130] Slight weakness and hyporeflexia are present, but even these resolve within 72 hours when caudal limb blood flow returns to 90% of baseline. Aortograms in these cats confirm the presence of collateral blood flow through the lumbar vertebral arteries and the cranial and caudal epigastric arteries. The disease can be reproduced, however, if a thrombus is created within the terminal aorta.[129,130] Aortograms from these experimental cats are identical to those from spontaneous clinical cases; both demonstrate very poor collateral flow beyond the region of the thromboembolus. Pretreatment with an antiserotoninergic agent or with indomethacin prevents the loss of collateral circulation, and serotonin or thromboxane A_2 injection reproduces the clinical situation when injected into a caudal aortic segment.[128,131–133] It is hypothesized that thromboemboli release serotonin and thromboxane A_2, agents present in platelets and known to produce intense vasoconstriction, and disrupt collateral flow.[134] Administering antiserotonin agents (e.g., cyproheptadine) and indomethacin after a thromboembolus is present apparently has no effect.

204.9.2 Clinical Manifestations

204.9.2.1 History

The majority of cats seen with STE are mixed breed cats.[115,135] Because more severe HCM is seen in males and HCM is the most common feline cardiomyopathy, more male cats are seen with STE. Most cats with STE have heart disease, but up to 90% have no evidence of heart disease prior to developing STE.[115] Consequently, owners often think that their cat has experienced an acute traumatic event. At the onset of STE, the cat may fall off a structure on which it was lying. Often the cat is found unable to walk and vocalizing because of pain.

204.9.2.2 Physical Examination

Auscultation often reveals a heart murmur or a gallop sound (or both) at presentation.[115] Many cats are in heart failure and so are tachypneic and dyspneic. The rectal temperature is usually reduced.

In cats with a large thromboembolus at the aortic trifurcation, the femoral artery pulses are absent to very weak. Once a thromboembolus lodges in the terminal aorta, ischemic damage to the skeletal muscles and

peripheral nerves occurs. The cranial tibial and gastrocnemius muscles are most severely affected and are commonly swollen, turgid, and painful, especially when palpated and the animal has loss of neural reflexes and motor function to the hind limbs (paresis and paralysis). Initially, the ischemic damage to the muscles of the caudal legs results in intense pain. The pain usually subsides as sensory nervous input is lost. The distal portions of the legs are cool and the nail beds are pale or very dark (purple to black). Femoral artery pulses in most cats with STE (78% in one study) are absent upon presentation.[115] In some cats a smaller thromboembolus may lodge in one external iliac artery, resulting in cessation of blood flow to only one leg. In other cats the femoral artery pulses may be weakly present because of recanalization of the aorta. In some cats it is difficult to determine if a pulse is present or not and a false diagnosis of thromboembolism in a cat with neurologic disease is common.[136] A Doppler blood flow detection device is helpful to identify the presence or absence of blood flow. In cats that have no sensation in their distal limbs, a nail can be cut back to the "quick" to determine if active bleeding occurs.

Most aortic thromboemboli lodge terminally in the aorta where they disrupt blood flow to the spinal canal beyond L_5, meaning blood supply to the spinal cord is not disrupted. Instead, perfusion is lost to the cauda equina and the peripheral nerves that originate from this area. Consequently, loss of motor function is due to lower motor neuron disease. Motor function loss to the caudal body is variable. Many cats retain the ability to move their tails. Some cats lose the ability to move their caudal legs starting at the hip, whereas others only lose the ability to move the limbs distal to the stifles or distal to the hock. These latter cats can extend and flex their hips and so "walk" on their stifles. Loss of cutaneous sensation occurs relatively early and follows the pattern of motor loss. The patellar reflex is lost in many cats but remains intact in others. Anal tone and the anal reflex are usually normal. Bladder function is often normal. Some cats may have urine retention, but the bladder can usually be easily emptied by external manual compression. In cats with experimental thrombosis of the terminal aorta, neurologic function (patellar reflex, withdrawal reflex, thigh adduction, digit extension, caudal limb weight bearing, locomotive ability, and cutaneous sensation) to the caudal limbs is completely lost in 80% of cases.[130] The remaining cats have very little residual neurologic function. Presumably the cats seen clinically with some remaining neurologic function must have some collateral flow to explain their neurologic findings. Acute ligation of the aorta in experimental cats, prior to collateral circulation becoming fully developed, produces cessation of blood flow to the distal portion of the caudal limbs, although proximal flow remains apparently normal.[130] This mimics the situation observed in some feline patients that have function remaining in the proximal portion of their caudal limbs.

After the acute embolic event, thrombolysis starts as plasmin is activated. In some cats with a small thromboembolus, thrombolysis is rapid and complete, allowing function to return within hours. In other cats the thromboembolus is large and the thrombolytic activity of the cat is low, resulting in permanent loss of perfusion to the caudal limbs and permanent paralysis. Regions of necrotic skin and muscle (most commonly dry gangrene) often develop, and muscle contracture takes place over time. Between these two extremes are cats that recover function over time with no untoward events and cats that partially recover function but have skin and muscle necrosis develop. The latter cats may require surgery to débride open wounds or amputate toes or parts of limbs. Cats that have complete and lasting occlusion of blood supply to only one limb do very well after limb amputation.

Coagulopathies can occur in cats with STE, although they are usually not severe enough to produce clinical signs.[137] The platelet count is generally within the normal range, and no evidence of fibrin degradation products is seen. Individual clotting factors, however, may be low in certain cases.

Cats with thromboemboli commonly have severe underlying cardiac disease. Acute terminal aortic blockade by the thromboembolus increases afterload to the LV. This can increase left heart filling pressures

and resultant pulmonary edema and respiratory distress.[116] The heart failure must be treated appropriately. If pulmonary edema is severe, it worsens the short-term prognosis.

204.9.3 Diagnosis

The diagnosis of STE in cats is usually based on the presence of typical clinical signs described previously in this chapter. However 20% to 30% of cases referred for STE have primary neurologic disease, so it does not appear that a diagnosis based only on clinical signs is accurate. Consequently, some effort should be placed into doing more definitive diagnostic tests in these cats. In most cases, simply cutting a nail back to the "quick" is adequate. Cats without blood flow to the caudal limbs will not have any bleeding from a cut nail, or very dark blood will ooze from the site. A Doppler device can also be used to determine if blood flow to affected limbs is present and if flow is returning to a limb. Imaging of the affected regional vessels by intravenous or intraarterial angiography or nuclear tracers is the definitive diagnostic procedure for thromboembolic disease. Risks to the patient must be considered when contemplating angiography. Stabilizing the patient is the primary consideration before attempting invasive diagnostic procedures. Color flow Doppler imaging of the area may demonstrate lack of or severely compromised flow.

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Radiographs reveal cardiomegaly in almost 90% of cats with STE and evidence of heart failure in approximately 50% to 70%.[115,116,135] Most cats (85% in one study) have ECG abnormalities[115] (LV enlargement, conduction system abnormalities, and sinus tachycardia).

Echocardiography is used to identify the underlying cardiac disease. In one study, about 60% of cats had HCM and 25% had unclassified cardiomyopathy, whereas in another study unclassified cardiomyopathy predominated.[115,116]

204.9.3.1 Clinical Pathology

Laboratory abnormalities are common in cats with STE.[115] Most have increases in serum aspartate aminotransferase and alanine aminotransferase concentrations due to muscle necrosis, and serum glucose concentration (stress). Severe increases in serum urea nitrogen and creatinine concentrations may suggest the thromboembolus has lodged in the region of the renal arteries.

204.9.4 Treatment

204.9.4.1 Euthanasia

In cats that are in acute pain that have a poor prognosis due to severe cardiomyopathy, euthanasia is a humane means of dealing with the problem. Systemic thromboembolism is often a horrible complication of cardiomyopathy, the treatment options are all relatively poor, and rethrombosis is common. Consequently, although one should not automatically give up on a patient, one should not give false hope either.

204.9.4.2 Pain Control

Cats that present in pain must be treated appropriately for their pain. Appropriate drugs include a fentanyl patch, oxymorphone (intramuscularly, intravenously, or subcutaneously) and butorphanol tartrate (subcutaneously). Aspirin does not produce adequate pain control. Oxymorphone may produce excitement

in some cats. The analgesic properties of butorphanol are five times that of morphine, and it remains a nonscheduled drug by the Food and Drug Administration. Its respiratory depressant effects equal that of morphine. Consequently, one must be careful when administering this drug to a patient with dyspnea. Acepromazine may be administered intravenously in addition as an anxiolytic agent to cats that still appear distressed after the administration of the analgesic or to cats that become agitated after oxymorphone administration. The pain abates with time (usually hours) as sensory nerves undergo necrosis.

204.9.4.3 Palliative Therapy

Beyond pain control, many cats with STE receive only supportive care or the administration of drugs with no proven benefit. The primary outcome of arterial occlusion depends upon the extent of occlusion and the time to spontaneous reperfusion. Poor prognostic factors for short-term survival include worsening azotemia, moderate to severe pulmonary edema or pleural effusion, malignant arrhythmias, severe hypothermia, disseminated intravascular coagulation, and evidence of multiorgan embolization. Long-term, cats may lose an affected leg because of ischemic necrosis, die of toxemia, remain paralyzed from peripheral nerve damage, or regain full or partial function of their legs. About 50% of cats that are not treated definitively will regain all or most caudal limb motor function within 1 to 6 weeks.[116,138] Return of function presumably is due to the cat's own thrombolytic system (e.g., plasmin) disrupting the thromboembolus. The degree and rapidity of the dissolution depend on the activity of a particular cat's thrombolytic system and the size and quality of the thromboembolus. Usually, cats that have some evidence of caudal limb flow recover more rapidly than do cats with no evidence of flow. Presumably this is because the size of the thromboembolus in cats with some flow is smaller. With total occlusion, some cats recanalize within days (others never recanalize). This extreme variability makes it very difficult to render a prognosis for a particular patient at presentation.

Palliative therapy may be only cage rest and pain control or can include administering drugs such as heparin, aspirin, or arteriolar dilators along with the cage rest. No drugs administered for palliation have any proven benefit over cage rest alone.

Heparin is commonly administered in the hopes of preventing new thrombus formation on top of the existing thromboembolus or in the hope of preventing a new thrombus from forming in the left atrium. However, no evidence indicates that heparin is of benefit in cats with STE. Heparin does not aid in thrombolysis. Heparin can be administered at an initial dose of 100 U/lb intravenously followed by a maintenance dose of 30 to 100 U/lb subcutaneously every 6 hours. The dose should be tailored to each individual cat to increase the activated partial thromboplastin time (aPTT) to at least 1.5 times baseline.

Indomethacin is effective at preventing vasoconstriction distal to the thromboembolus when administered to experimental cats prior to creating an aortic thrombus.[139] Theoretically aspirin could do the same thing. However, no evidence indicates that it improves collateral blood flow.

The administration of drugs that dilate systemic arterioles (e.g., hydralazine, acepromazine) has been advocated. These drugs act by relaxing the smooth muscle in systemic arterioles. The exact anatomy of collateral vessels is not well described, but they are probably larger vessels than arterioles. They contain smooth muscle, because they can open and close. The ability of arteriolar dilators to counteract serotonin and thromboxane A_2-induced vasoconstriction is unknown.

204.9.4.4 Definitive Therapy

Definitive treatments for STE in cats include administration of exogenous fibrinolytic agents, balloon embolectomy, rheolytic thrombectomy, and surgery. All definitive procedures are associated with high mortality and common recurrence of the thromboembolus days to months after the initial removal.

204.9.4.4.1 Surgery

Surgical removal of systemic thromboemboli is generally thought to be associated with high mortality and is not frequently performed. Cats with STE commonly have underlying cardiac disease, and many are in heart failure. They are poor anesthetic risks, and reperfusion syndrome may be produced. In reperfusion syndrome the muscles of the legs prior to removal of the STE undergo necrosis, cellular breakdown, and the release of potassium and hydrogen ions from the cells into the interstitial spaces. Sudden reperfusion carries these ions into the systemic circulation, causing acute and often severe hyperkalemia and metabolic acidosis. Surgical intervention may be a viable option if careful monitoring and treatment for reperfusion syndrome with insulin and glucose, sodium bicarbonate, or calcium (or a combination of these therapies) can be initiated immediately if it occurs.

204.9.4.4.2 Balloon embolectomy

The procedure of choice in human medicine is balloon embolectomy.[140] The author has had limited experience with balloon embolectomy. In this procedure the femoral arteries are isolated and a small balloon embolectomy catheter is passed from one femoral artery into the aorta. The femoral arteries are not extremely difficult to isolate. The catheter is pushed past the thromboembolus, and the balloon is then inflated and the catheter withdrawn, along with thromboembolic material. The catheter is passed sequentially, first in one artery and then in the other. Usually this sequence must be repeated several times. Reperfusion syndrome may occur with balloon embolectomy.

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204.9.4.4.3 Thrombolytic therapy

Thrombolytic therapy is a possible means of dealing with cats with STE using fibrinolytic agents. Thromboemboli in cats are composed of red cells, strands of fibrin, and possibly platelets. Fibrinolytic agents cleave plasminogen to plasmin. Plasmin hydrolyzes fibrin, resulting in thrombolysis. Different agents vary in their ability to bind specifically to fibrin-bound plasminogen and in their half-lives. Efficacy and complication rates appear to be very similar in humans.[141] Complications consist primarily of hemorrhage due to fibrinolysis and rethrombosis. Fibrinolytic agents can be very effective at lysing systemic thromboemboli. However, the author and colleagues currently treat few cats with STE with these agents because reperfusion syndrome and rethrombosis are common.

Tissue plasminogen activator (t-PA) and streptokinase have been used in cats. Tissue plasminogen activator is an intrinsic protein present in all mammals. Numerous reports exist of the use of t-PA for the lysis of thrombi as therapy for acute myocardial infarction, pulmonary thromboembolism, and peripheral vascular obstruction in humans and experimental animals.[141] The activity of genetically engineered t-PA in feline plasma is 90% to 100% of that seen in human plasma. The half-life of t-PA is quite short. Heparin must be administered concomitantly to prevent acute rethrombosis but does not need to be administered with streptokinase because it has a longer half-life. A clinical trial with t-PA in cats with

aortic thromboemboli has shown acute thrombolytic efficacy (shortened time to reperfusion and ambulation) associated with the administration of t-PA at a rate of 0.1 mg to 0.4 mg/lb/hr for a total dose of 0.4 to 4 mg/lb intravenously.[142] Forty three percent of cats treated survived therapy and were walking within 48 hours of presentation. Post-t-PA angiograms demonstrated resolution of the primary vascular occlusion. Thus acutely, t-PA effectively decreases the time to reperfusion and return to function in cats with aortic thromboemboli. However, 50% of the cats died during therapy in this clinical trial, which raises extreme concerns regarding acute thrombolysis. Fatalities resulted from reperfusion syndrome (70%), CHF (15%), and sudden arrhythmic death, presumably the result of embolization of a small thrombus to a coronary artery (15%). Severe hemorrhage into the region distal to the STE causing anemia was also a common complication. The cats that successfully completed t-PA therapy exhibited signs of increasing neuromuscular function and ambulatory ability within 2 days of presentation. This contrasts with 1 to 6 weeks before seeing similar signs of improvement in most cats exhibiting spontaneous resolution.

Mortality due to reperfusion syndrome can be reduced if the patient can be observed continuously by an individual trained to identify clinical and electrocardiographic evidence of hyperkalemia, if intensive monitoring of electrolytes and blood pH can be performed, and if aggressive medical therapy for hyperkalemia and metabolic acidosis can be initiated very quickly. This means dedicated care 24 hours a day until the thromboembolus is lysed. Thrombolysis may occur within 3 hours or take as long as 48 hours.

If reperfusion syndrome was the only major complicating factor in cats treated with thrombolytic agents, continued use in selected patients might be warranted. However, 90% of the cats that were successfully treated in the aforementioned clinical trial had another STE within 1 to 3 months. Rethromboembolism occurred despite aspirin, warfarin, or heparin administration. In addition, t-PA is expensive. Consequently, the author does not currently use t-PA for STE in cats.

Streptokinase has clinical efficacy very similar to t-PA in human patients with coronary artery thrombosis.[143] Streptokinase is less expensive. No controlled clinical trials of streptokinase use for STE in cats are available, and the author's clinical experience with the drug has been generally negative. There has been one small experimental study in which thrombin was injected between two ligatures placed at the terminal aorta to create a soft thrombus, followed by removal of the ligatures.[144] Streptokinase was administered as a loading dose at 90,000 IU followed by 45,000 IU/hr for 3 hours. This dose produced evidence of systemic fibrinolysis in a separate group of normal cats but without evidence of severe fibrinolysis or bleeding. In most cats there was no angiographic change and no improvement in limb temperature. There was a tendency for the thrombus weight to be lower in the treated cats when compared with control cats at postmortem examination. However, lysis of a fresh thrombus created with thrombin is probably much different from trying to lyse an established thromboembolus. Streptokinase is usually unsuccessful, may hasten the death of some cats through bleeding complications, and should not be routinely used.

204.9.4.4.4 Rheolytic thrombectomy

Rheolytic thrombectomy is an experimental catheter-based system used for the dissolution of the thromboembolus using a high-velocity water jet at the end of the catheter that breaks up the thromboembolus and sucks it back into the system using the Venturi effect. Anesthesia is required and blood transfusion is almost always needed. The catheter is passed from the carotid artery to the region of the thromboembolus. The author and colleagues have used it in six cats. The procedure successfully

removed the thromboembolus in five cats but only three left the hospital (Figure 204-18). Time from onset of clinical signs to thrombectomy was several hours to 8 days. The cat that had the procedure 8 days after the event had residual neurologic deficits but was the longest survivor. Interestingly, reperfusion syndrome has not been a common complication.

204.9.4.4.5 Adjunctive therapy

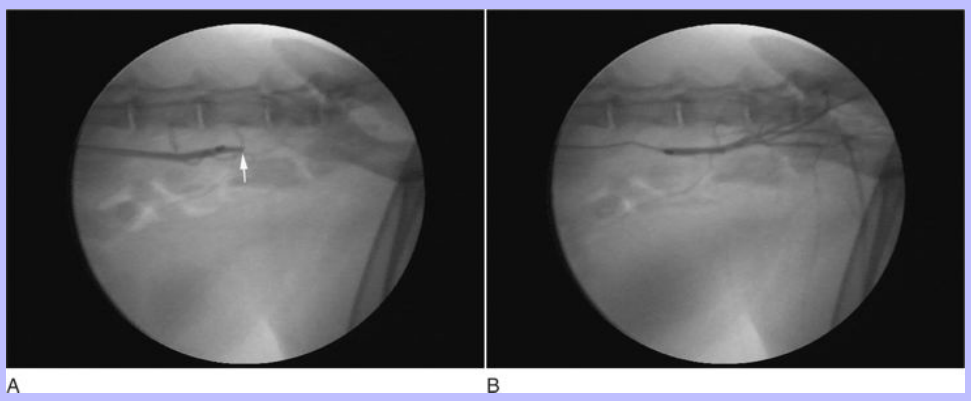
Cats with STE are commonly in heart failure at the time of presentation.[116] Medical therapy with furosemide and an ACE inhibitor is often indicated. Cats that are in pain usually do not eat or drink. Fluid therapy is warranted but must not aggravate or produce heart failure.

Cats that take a long time to recover caudal limb function or that only attain partial function may develop regions of skin and muscle necrosis, especially on the distal limbs. These regions may need to be débrided surgically. Cats that lose the function of only one leg or that do not regain function of one leg benefit from amputating that leg. Cats that have permanently lost muscle function distal to the hock may benefit from arthrodesis.

204.9.4.5 Prognosis

The short-term prognosis for life is guarded in cats without heart failure. Cats with a rectal temperature lower than 98.9° F had a worse prognosis in one study.[116] The long-term prognosis is highly variable and depends on the ability to control the heart failure and the events surrounding the STE. One of the most common causes of death within the first 24 hours is euthanasia.[135] In one study, cats lived between 3 and 30 months after the initial episode.[115] The average survival time was about 10 to 12 months. In another study, MST for cats that recovered and were discharged from the hospital was approximately 4 months but was only about 2.5 months in cats that were also being treated for heart failure.[116] The long-term prognosis for limb function depends on the ability of the cat to lyse its own clot or on the success of intervention. Many biologic variables determine whether or not reperfusion will spontaneously occur. A significant percentage of cats will develop a new thromboembolus, days to months after recovery.

Figure 204-18 **A,** Angiogram of the aorta from a cat with a thromboembolus lodged in its terminal aorta. Contrast can be visualized in the aorta to the level of middle of the sixth lumbar vertebra where it abruptly terminates *(arrow)*. No blood flow is demonstrated past that point. **B,** An angiogram from the same cat after rheolytic thrombectomy. The thromboembolus has been removed. The tip of a catheter can be seen at the junction of the fifth and sixth lumbar vertebrae. Beyond that point the contrast agent outlines the normal blood flow pattern to the caudal limbs.



204.9.4.6 Prophylaxis

Feline patients with myocardial disease, especially those with an enlarged left atrium, should be considered at risk for developing intracardiac thrombi and signs of peripheral arterial thromboembolism, although the incidence appears to be low. Preventing peripheral thrombosis is, in theory, one of the most important therapeutic objectives for the veterinarian managing cats with severe myocardial disease. The ideal means of preventing thrombosis is resolution of the underlying myocardial disease. This is usually only possible in a cat with DCM secondary to taurine deficiency.

At present, the only option available is to manipulate the patient's coagulation system in an attempt to alter the delicate balance between the pathways that promote clotting and those that inhibit thrombus formation to reduce the patient's thrombogenic potential. At this time, antiplatelet and anticoagulant therapies are the only means of preventing thrombus formation in cats with myocardial disease. Unfortunately, they are often ineffective and, in the case of warfarin, can produce serious side effects.[145] Experience is similar in human medicine.[146]

204.9.4.6.1 Antiplatelet therapy

Prostaglandins enhance platelet aggregation via activation of cyclic adenosine monophosphate (cAMP). Aspirin (acetylsalicylic acid) acetylates platelet cyclooxygenase, preventing the formation of thromboxane A_2, a potent prostaglandin-like platelet aggregating substance.[147] The inhibition of platelet cyclooxygenase is irreversible, and bleeding time is restored to normal only after the production of new platelets. The inhibition of endothelial cyclooxygenase is reversible. The dose of aspirin recommended in cats is 10 mg/lb every third day. Whether or not this dose allows endothelial cyclooxygenase to recover or not in cats is undetermined. At this dose, aspirin has a half-life of 45 hours in the cat. In humans, doses as low as 20 to 100 mg/day inhibit platelet cyclooxygenase; however, no evidence suggests that this low dose has any more benefit than conventional daily doses of 625 to 1250 mg. In one study in cats, no difference was seen in thromboembolus recurrence between cats on low dose (5 mg/cat every 72 hours) and high dose (greater than or equal to 40 mg/cat every 72 hours).[116] No evidence indicates that any dose of aspirin is effective at preventing the formation of an intracardiac thrombus in cats with myocardial disease. Clinical impression of aspirin's efficacy varies between clinicians. Cats that have already experienced one STE are the only appropriate population in which to study the efficacy of an agent meant to prevent STE. Aspirin does not prevent recurrence of peripheral thromboembolism in this population.

Glycoprotein IIb and IIIa, an integrin present on platelet surfaces, is a receptor for fibrinogen, fibronectin, and von Willebrand factor. It mediates aggregation, adhesion, and spreading of platelets. The binding of prothrombin to glycoprotein IIb and IIIa also enhances the conversion of prothrombin to thrombin. Glycoprotein IIb and IIIa antagonists have been developed, and one (abciximab) increased mucosal bleeding time and reduced thrombus area when combined with aspirin (when compared with aspirin and placebo).[148]

204.9.4.6.2 Anticoagulant therapy

Available anticoagulants include heparin, the low molecular weight heparins, and warfarin. Heparin binds to a lysine site on AT, producing a conformational change at the arginine-reactive site that converts AT from a slow, progressive thrombin inhibitor to a very rapid inhibitor of thrombin and factor Xa. AT binds covalently to the active serine centers of coagulation enzymes.[150] Factor Xa bound to platelets and thrombin bound to fibrin are protected from activation by the heparin-antithrombin III complex.[147] Heparin may be administered intravenously or subcutaneously. Repeated intramuscular injection is discouraged because local hemorrhage may result. Some owners can administer heparin subcutaneously at home but the method is not ideal. The author and colleagues have noted rethrombosis with heparin therapy in some cats with cardiac disease. The dose of heparin for preventing thrombosis in cats is unknown.

Low molecular weight heparins include nadroparin calcium, enoxaparin sodium, dalteparin, ardeparin, tinzaparin, reviparin, and danaparoid sodium. The low molecular weight heparins have fewer bleeding complications in experimental animals, improved pharmacokinetics over heparin, are administered subcutaneously, and do not require monitoring in most situations.[150] Although heparin does not reduce red cell aggregation in slow-moving blood, heparin and low molecular weight heparins are effective at preventing deep vein thrombosis in humans. Consequently, they may be beneficial in preventing

intracardiac thrombus formation in cats with cardiomyopathy. No controlled studies are available. The author empirically uses enoxaparin sodium at a dose of 2.2 mg/lb every 12 hours subcutaneously in cats that have recovered from an STE or that have a severely enlarged left atrium and SEC.

Warfarin sodium is an oral anticoagulant (see Chapter 199).[147] Warfarin exerts no anticoagulant effect in vitro. In vivo, inhibitory effects on synthesis of clotting factors begin immediately. However, clotting is unaffected until already existing clotting factors decline. Therefore a delay occurs between initial administration and effect on the prothrombin time (PT). Historically, oral warfarin therapy has been monitored with the PT. This test measures the activity of factors II, VII, and X. The factor depressed most quickly and profoundly (usually factor VII) determines the PT during the initial days of therapy. The PT is performed by measuring the clotting time of platelet-poor plasma after the addition of thromboplastin and calcium, a combination of tissue factor and phospholipid.[151] Intra-and interlaboratory variation in the PT was a significant problem for laboratories in the past, when crude extracts of human placenta or rabbit brain were the only source of thromboplastin. The international normalized ratio (INR), developed by the WHO in the early 1980s, is designed to eliminate problems in oral anticoagulant therapy caused by variability in the sensitivity of different commercial sources and different lots of thromboplastin. The INR is used worldwide by most laboratories performing oral anticoagulation monitoring and is routinely incorporated into dose planning for human patients receiving warfarin. When the anticoagulant effect is excessive, it can be counteracted by administering vitamin K_1. However, once synthesis of factors II, VII, IX, and X is reinstituted, time must elapse before factors achieve concentrations in the plasma that will adequately reverse the bleeding tendency. If serious bleeding occurs during therapy with warfarin, it may be stopped immediately by administering fresh blood or plasma that contains the missing clotting factors. Other drugs can modify the anticoagulant actions of warfarin by altering the bioavailability of vitamin K by altering the absorption, distribution, or elimination of the coumarins; by affecting synthesis or degradation of clotting factors; or by altering protein binding of the warfarin.[152] The maintenance dose should be evaluated daily during the initial titration (3 days), then every other day (twice), and then weekly until a safe and stable dose regimen is determined. The therapeutic effect should be reevaluated periodically (at least once per month). The recommended initial dose is 0.1 to 0.2 mg per cat every 24 hours orally to a 6 to 10 lb/cat. The dose may then be increased to maintain an INR of 2.0 to 3.0. It can take up to 1 week for new steady state conditions to be achieved.

The efficacy of warfarin at preventing recurrent thrombosis in cats with cardiac disease has been reported.[114,115] In one report, out of 23 cats examined retrospectively, 10 experienced a new thromboembolic episode while being administered warfarin. Two of these cats had at least two new episodes. In the other report, eight of 18 cats on warfarin experienced a new thromboembolic episode. This may be some improvement over the 75% recurrence rate reported for aspirin alone after t-PA therapy, but these results are still disappointing.[136] In the first report, four cases also died suddenly (which could have been caused by thromboembolism). Three of these cats did not have postmortem examinations. The one cat that did have a postmortem examination had a thrombus present in its left atrium. One cat also died of a renal infarct that produced renal failure. Four cats appeared to have bleeding complications. In the second report, one cat died of a hemoabdomen and one was suspected to have an acute intracranial hemorrhage resulting in death. Consequently, it appears that warfarin therapy can produce fatal complications. However, it should be noted that these studies were performed without using the INR for monitoring.

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205 CHAPTER • 205 Pericardial Disorders

Anthony H. Tobias

Pericardial disorders have previously been reported to account for approximately 1% of cardiac disease in small animals.[1] More recent reports estimate that pericardial disorders comprise approximately 8% of the canine cardiology caseload at referral institutions. Pericardial disorders occur slightly less frequently in cats, but the prevalence remains fairly high at 6% of the feline cardiology caseload. In contrast to dogs, pericardial disorders in cats are usually found as incidental manifestations of underlying disease, rather than as the primary cause for the presenting signs.[2]

Pericardial disorders are emerging as increasingly common and important in small animal practice. The presenting signs associated with pericardial disorders are diverse, and the clinical findings are often subtle. Consequently the prevalence of pericardial disorders may previously have been underestimated, especially before the widespread use of echocardiography. Alternately or coincidentally the increased prevalence may reflect a change in the epidemiology of pericardial disorders over time, possibly associated with increased popularity of breeds that are predisposed to pericardial disorders, such as the golden retriever.

205.1 STRUCTURE AND FUNCTION

The pericardium is the fibroserous envelope of the heart. It is divided into an outer fibrous and inner serous part. The serous pericardium consists of a parietal and visceral layer.[3] The fibrous pericardium is a thin tough sac that contains the heart, serous pericardium, and a small amount of fluid. The base of the fibrous pericardium is continued on the great arteries and veins that leave and enter the heart and blends with the adventitia of these vessels. The apex of the fibrous pericardium is continued to the ventral part of the diaphragm as the phrenico-or sternopericardical ligament.[3]

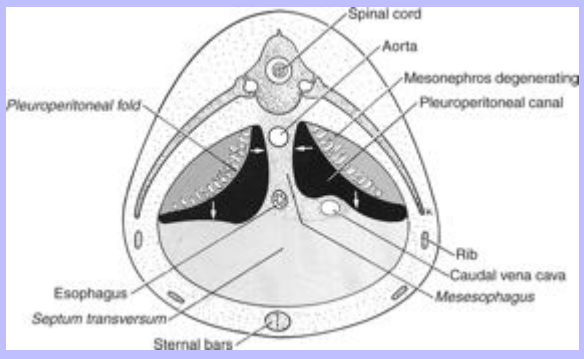
The serous pericardium is a closed sac, approximately half of which is invaginated by the heart. The invaginated portion forms the visceral layer of the serous pericardium or the epicardium. It is firmly attached to the heart muscle, except along the grooves that contain fat and the coronary vessels. The epicardium has a smooth mesothelial surface that is underlaid by a stroma containing elastic fibers. The noninvaginated part or parietal layer of the serous pericardium forms the inner surface of the fibrous pericardium. It is composed of interlacing collagen fibers that blend with the tissue of the fibrous pericardium on one side and a layer of mesothelium on the other. The pericardial space that occurs between the two layers of the serous pericardium contains a small amount of clear light-yellow fluid. The normal amount of pericardial fluid in the dog has been reported as 0.3 to 1.0 mL, and 0.25 ± 0.15 mL per kg.[3,4]

The vagus, recurrent laryngeal, and phrenic nerves pass over the outer surface of the pericardium. The pericardium is innervated by fibers from the vagus, recurrent laryngeal nerve, and various intrathoracic ganglia and plexi. Blood supply is derived from the pericardial branches of the aorta and internal thoracic and musculophrenic arteries.[5] Lymphatic drainage of the pericardial space occurs via the coronary lymphatic ducts to the cardiac and mediastinal lymph nodes and via the left and right parasternal lymphatic ducts to the cranial sternal lymph node.[6]

The physiologic significance of the pericardium remains speculative. Functions attributed to the pericardium include preventing overdilation of the heart, protecting the heart from infection and forming adhesions to

surrounding tissue, maintaining the heart in a fixed position within the chest, regulating the interrelationship between stroke volumes of the two ventricles, and preventing tricuspid regurgitation when ventricular diastolic pressures are increased. In addition, the lubricant effect of pericardial fluid allows the heart to move easily within the pericardial sac during systole and diastole.[5] However, it is clear that the pericardium serves no vital function because it can be removed surgically when diseased without untoward effect.

Figure 205-1 Diagram of the caudal surface of the developing diaphragm. Major structures involved in the formation of the diaphragm are in italics. *Septum transversum* forms the ventral half of the diaphragm and fuses dorsomedially with the *mesesophagus*. *Pleuroperitoneal folds* or membranes extend ventrally and medially *(arrows)* to close pleuroperitoneal canals by fusing with septum transversum and mesesophagus. A pericardioperitoneal diaphragmatic hernia develops as a result of a defect in the ventral portion of the septum transversum. (From King AS: The Cardiorespiratory System. Integration of Normal and Pathological Structure and Function. Oxford, Blackwell Science, 1999, pp 178–217. With permission.)



205.2 CONGENITAL PERICARDIAL DISORDERS

Congenital pericardial disorders include pericardioperitoneal diaphragmatic hernia (PPDH), benign intrapericardial cysts, and pericardial defects. Congenital pericardial disorders are much less common than those that are acquired. However, they represent an important group because they are frequently amendable to surgical correction and, consequently, generally confer an excellent prognosis.

205.2.1 Pericardioperitoneal Diaphragmatic Hernia

A PPDH exists when a defect in the ventral diaphragm and pericardium allows abdominal contents to enter the pericardial space. Herniated structures include liver, gall bladder, spleen, stomach, small intestine, omentum, and falciform ligament. In the dog and cat the defect is congenital, whereas in humans, the diaphragm forms one wall of the pericardial sac and PPDH can be traumatic. The diaphragm does not form part of the pericardium in small animals, and traumatic PPDH has not been reported in either the dog or cat.[7,8]

205.2.1.1 Pathophysiology

In the developing embryo, the diaphragm forms from four structures: (1) the septum transversum, (2) the mesesophagus (or caudal mediastinum), (3) a pair of pleuroperitoneal folds or membranes, and (4) tissue from the body wall (Figure 205-1). The septum transversum, a thick plate of ventrally located mesodermal tissue, partially separates the thoracic and abdominal cavities. It fuses with the mesesophagus, which is located dorsomedially. The aorta, esophagus, and the caudal vena cava pass through the mesesophagus. The pleural and peritoneal cavities communicate on either side of the mesesophagus via the right and left pleuroperitoneal canals. Closure of the pleuroperitoneal canals occurs via formation of the pleuroperitoneal folds or membranes, which expand and fuse with the septum transversum ventrally and with the mesesophagus medially. Finally, as the thoracic cage enlarges during fetal growth, tissue from the body wall becomes incorporated circumferentially into the diaphragm.[9–11]

Several theories for the formation of PPDH have been proposed, including failure of complete fusion of the pleuroperitoneal membranes with the septum transversum or mesesophagus.[12] However, defects in that location result in congenital diaphragmatic hernias or communications between the pleural and peritoneal spaces. Congenital diaphragmatic hernias are among the most common congenital malformations in humans,[11] but they are rare in small animals.[9,10] In small animals with PPDH, communication between the peritoneal and pericardial space occurs via the ventral portion of the diaphragm, and the following pathogenesis has been proposed: the liver arises as a large ventral outgrowth from the foregut ectoderm, and it grows cranioventrally and penetrates the septum transversum.[9–11] Hematopoietic cells, Kupffer cells, and connective tissue of the liver are all derived from the septum transversum.[13] As the liver develops, it distracts from the septum transversum, forming the ventral mesentery that eventually becomes the falciform ligament. If separation between the developing liver and septum transversum is defective, an opening in the ventral part of the diaphragm may occur or the tissue may be so thin that it ruptures, allowing the peritoneal and pericardial cavities to communicate. Abdominal organs may then pass through the defect directly into the pericardial, space resulting in a PPDH.[9,10]

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205.2.1.2 Epidemiology

Whereas PPDH is the most common congenital pericardial anomaly in small animals, it is an uncommon diagnosis. The veterinary medical data base (VMDB) at Purdue University from January 1992 to April 2003 included 62 cats with PPDH among 114,826 new cases, giving a prevalence rate of 0.054%, or one case for every 1852 cats in the data base. Fifty three percent were diagnosed in cats 4 years of age or less, and 16% were first diagnosed in cats 10 years of age or older. The cases in the VMDB disclosed no apparent sex predisposition (35 males:27 females). The majority of affected cases were domestic long-or shorthairs (n = 35). The most commonly affected purebred cats were Himalayans (n = 11). Persians were the second most common purebred cats in the data base (n = 7), and this breed may be predisposed to PPDH.[8] A pattern of inheritance of PPDH in cats has not been established, but congenital agenesis of all or part of the diaphragm in cats is reported to have an autosomal recessive mode of inheritance.[14]

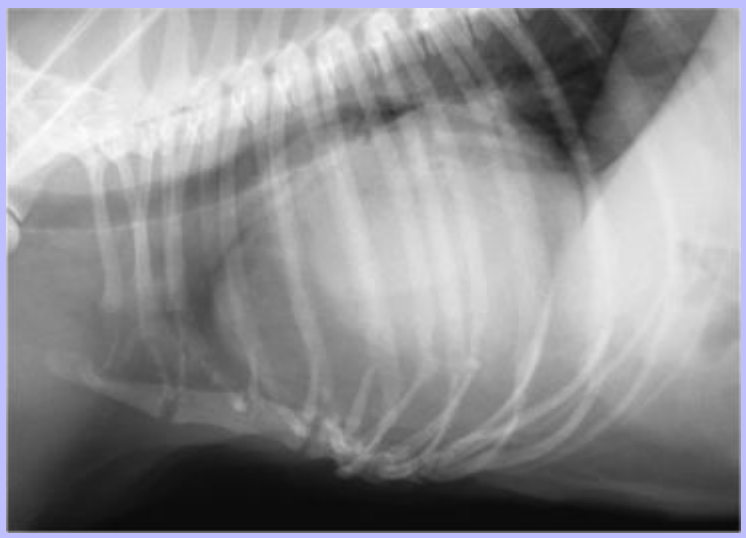
PPDH is less prevalent among dogs than cats. The VMDB from January 1992 to April 2003 included 76 dogs with a PPDH among 399,195 new cases, giving a prevalence rate of 0.019%, or one case for every 5263 dogs in the data base. The diagnosis was most common in younger dogs, with 65% of cases diagnosed in dogs 4 years of age or younger. As in cats, no sex predisposition was apparent (40 males:33 females [the

sex of three dogs was not reported]). Most cases were in mixed breed dogs (n = 12). Among purebred dogs, weimaraners were most commonly affected (n = 7), and this breed appears to be predisposed.[12]

205.2.1.3 Presenting and Clinical Signs

Presenting and clinical signs vary depending on the herniated organ, organs, or tissue. Some affected animals show no clinical signs, and PPDH is an incidental finding. In symptomatic animals, signs referable to the respiratory and gastrointestinal (GI) systems predominate. Tachypnea, respiratory distress, vomiting, and anorexia are common.[8,15] Other presenting complaints include lethargy, weight loss, diarrhea, and coughing. On physical examination, the apex beat may be absent or displaced, and heart sounds are frequently muffled. Some cases have a fever. Additional associated abnormalities in dogs are commonly reported and include sternal malformations (incomplete xiphoid; pectus excavatum; and absent, deformed, and fused sternebrae), ventral abdominal hernias, and other congenital heart defects (pulmonic stenosis, ventricular septal defect).[12,16] Associated abnormalities in cats are less common and are usually limited to sternal malformations and ventral abdominal hernias.[8,12,17] A PPDH should be suspected in any animal with a large umbilical or cranial abdominal hernia, sternal malformation, or history of abdominal hernia repair.[18,19]

Figure 205-2 Lateral thoracic radiograph of a dog with a pericardioperitoneal diaphragmatic hernia showing an enlarged cardiac silhouette that contains differential opacities and missing and deformed sternebrae.



205.2.1.4 Diagnosis

Radiographic findings that support a diagnosis of PPDH include enlargement of the cardiac silhouette with dorsal displacement of trachea, overlapping of the diaphragmatic and caudal cardiac silhouette borders, and

sternal malformations. Signs of left-sided congestive heart failure (CHF) are absent. The cardiac silhouette often contains differential opacities and gas-filled bowel loops (Figure 205-2). A radiographic feature of PPDH that has been described in cats is the presence of a dorsal peritoneopericardial mesothelial remnant. The dorsal peritoneopericardial mesothelial remnant represents the dorsal border of the hernia, and it is recognized in the lateral view as a curvilinear opacity between the cardiac silhouette and the diaphragm ventral to or superimposed over the caudal vena cava. The hepatic silhouette may be smaller than normal or absent in the anterior abdomen (Figure 205-3).[12,17] Positive and negative contrast peritoneography and GI contrast studies are occasionally necessary to confirm the presence of a PPDH.

Electrocardiograms in cases with PPDH may be normal or show low-voltage complexes and abnormal orientation of the mean electrical axis.[8] Echocardiography readily discloses the presence of abdominal viscera within the pericardial sac.[7] Pericardial effusion is present in some cases.[7,8] In cats the liver is the most commonly herniated organ, and focal hyperechoic areas are frequently seen within the herniated liver lobe or lobes (Figure 205-4). Myelolipomas, nodules composed of mature adipose tissue and bone marrow elements, have been reported within herniated liver in cats. These nodules originate as metaplastic change resulting from chronic hypoxia caused by incarceration of liver.[7,20,21] The presence of myelolipomas, or nodular myelomatosis, probably accounts for the focal areas of hyperechogenicity seen within herniated liver lobes.[7]

205.2.1.5 Treatment

Surgical repair is necessary for all cases with PPDH that show clinical signs ascribable to the defect. Repair is also recommended in all young animals with PPDH, whether symptomatic or not. Resection of devitalized herniated tissue is frequently necessary. The prognosis with surgery is generally excellent. In older animals, adhesions between herniated organs and the pericardium that complicate or preclude reduction of the hernia may be present.[15] Consequently, in an asymptomatic older animal in which PPDH is detected as an incidental finding, and especially in those cases where the hernia includes only omentum or falciform fat, it may be prudent to recommend observation rather than surgical repair.

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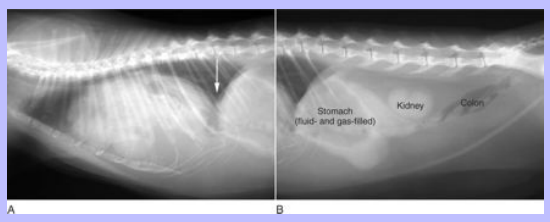
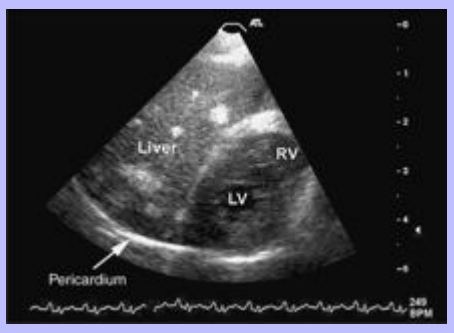
Figure 205-3 Lateral thoracic and abdominal radiographs of a cat with a pericardioperitoneal diaphragmatic hernia. **A,** Markedly enlarged cardiac silhouette that contains differential opacities and gas-filled bowel loops. The curvilinear opacity between the diaphragm and cardiac silhouette *(arrow)* is the dorsal margin of the hernia or the dorsal pericardioperitoneal mesothelial remnant. **B,** Most of the abdominal contents, including the liver and small intestines, are displaced into the pericardial sac.



205.2.2 Benign Intrapericardial Cysts

Large benign intrapericardial cysts occur occasionally in dogs. In virtually all cases, histopathology discloses that the cysts are encapsulated adipose tissue (with extensive hemorrhage and necrosis) or organizing cystic hematomas. True congenital pericardial cysts in humans are endothelium-, epithelium-, or mesothelium-lined, depending on their origin. These are extremely rare in dogs[22,23] and have not been described in cats. Clinical signs in affected dogs include abdominal distention, exercise intolerance, anorexia, and labored breathing. The intrapericardial cysts are demonstrated by echocardiography, and most cases have concomitant pericardial effusion. In some cases, benign intrapericardial cysts are associated with a small PPDH. In others the cyst is attached by a pedicle to the apex of the pericardium. In such cases the cyst is thought to represent prenatal herniation of omentum or falciform fat from the peritoneum into the pericardium and subsequent closure of a PPDH. Cyst formation probably results from vascular obstruction of the herniated tissue or repeated trauma from the beating heart.[19,22] Intrapericardial hepatic cysts have been described in cats with PPDH as a result of incarceration of portions of the liver.[24,25] Benign intrapericardial cysts are treated by surgical removal of the cyst and its associated pedicle, pericardiectomy, and PPDH repair when necessary.

Figure 205-4 Echocardiogram (short axis view from the right parasternal location) from cat with a pericardioperitoneal diaphragmatic hernia. Liver is present within pericardial sac adjacent to caudal aspect and right side of heart. The focal areas of hyperechogenicity within the liver parenchyma are probably due to myelolipomas. *LV,* Left ventricle; *RV,* right ventricle.



205.2.3 Pericardial Defects

Pericardial defects are very rare in dogs and are usually found incidentally on postmortem examination. Some of these defects are thought to be congenital. In a series of eight cases, single defects were present in four dogs, with up to four defects in the remaining dogs. The defects ranged in size from a single 10 × 5 mm hole to total absence of one side of the pericardium. The defects were on the left side in four dogs, on the right side in two, and on both sides in two.[26] Herniation and incarceration of cardiac chambers through pericardial defects has been reported.[26–28]

205.3 ACQUIRED PERICARDIAL DISORDERS

205.3.1 Pericardial Effusion

The most common pericardial disorders in small animals are associated with abnormal accumulations of pericardial fluid or pericardial effusions. At the Veterinary Hospital, University of Pennsylvania from 1990 to 1993, pericardial effusion was present in 7% of dogs with reliable signs of heart disease.[29] At the University of Minnesota Veterinary Medical Center (UMVMC) from January 1999 to December 2001, pericardial effusion was confirmed as the primary cause for clinical signs in 87 of 20,282 new canine cases that were presented to the small animal hospital. This reflects a prevalence rate of 0.43%, or one dog with clinically significant pericardial effusion among every 233 new hospital cases. Thus pericardial effusion is fairly common in the canine patient population at referral hospitals.

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205.3.1.1 Pathophysiology of Pericardial Effusion: Cardiac Tamponade

Cardiac tamponade is defined as significant compression of the heart by accumulating pericardial contents. *Significant compression* depends on whether tamponade is approached from a physiologic or clinical standpoint. Tamponade is a pathophysiologic continuum, not an all-or-none phenomenon. Physiologic abnormalities can be detected with very small amounts of pericardial effusion, although affected cases may show only mild clinical signs (mild tamponade). At the opposite end of the spectrum, acute accumulations of even small amounts of effusion can result in life-threatening hemodynamic compromise (florid tamponade).[30] The classic clinical hemodynamic profile of tamponade includes pulsus paradoxus, elevation and equilibration of right and left ventricular diastolic pressure with pericardial pressure, and depressed cardiac output.[31]

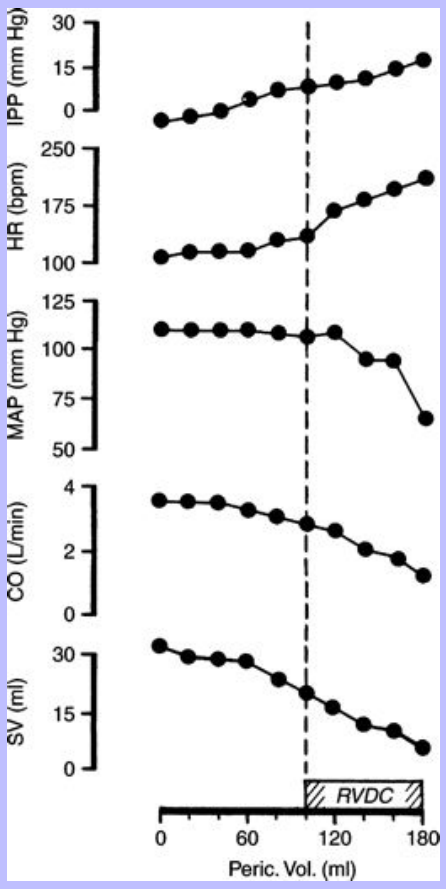
The major pathophysiologic abnormality associated with increased intrapericardial pressure is impaired ventricular filling in diastole, resulting inevitably in diminished stroke volume. For each cardiac chamber, transmural pressure (intracardiac pressure minus intrapericardial pressure) is a principle determinant of its filling. Mean atrial pressure and ventricular diastolic pressure is normally higher than intrapericardial pressure, resulting in positive transmural or filling pressure. In tamponade, rising intrapericardial pressure progressively reduces and can eventually make the transmural pressures of first the right-and then the left-sided cardiac chambers phasically negative. In addition to the deleterious effects on diastolic function, pericardial effusion results in decreased systolic performance because the compressed and underfilled chambers operate at the lower end of their respective Frank-Starling curves.[30]

Figure 205-5 shows the results of an experiment in which intrapericardial volume was increased by infusing 10 mL of warm saline per minute in a dog. Cardiac output and stroke volume steadily decreased with increasing intrapericardial volume and pressure. Mean arterial pressure (MAP) was maintained until intrapericardial volume had increased to approximately 100 mL, and intrapericardial pressure was approximately 10 mm Hg. MAP then dropped sharply as intrapericardial volume was further increased.[32] As illustrated by this experiment, acute accumulations of relatively small amounts of pericardial effusion can result in profound hemodynamic compromise with a clinical picture that is dominated by signs of low cardiac output.

With more chronic accumulations of pericardial effusion, the volume of the pericardial space increases with concomitant expansion of the pericardial sac. The precise mechanisms of pericardial expansion are

uncertain and may include fibroblast proliferation with new connective tissue deposition, remodeling of the pre-existent connective tissue, or both.[33] In addition, a variety of compensatory mechanisms increase preload or filling pressure in an effort to restore cardiac output. The compensatory mechanisms are similar to the various neurohormonal changes that accompany other forms of cardiac disease. Activation of the renin-angiotensin-aldosterone system leads to increased angiotensin II, aldosterone, vasopressin, and sympathetic nervous stimulation, which result in fluid retention and increased heart rate. However, unlike other forms of cardiac disease that result in increased preload, atrial natriuretic peptide does not increase. Despite increased venous pressure, atrial distention, the primary stimulus for secretion of atrial natriuretic peptide, does not occur because of external compression of the heart. Thus tamponade prevents this mechanism for increased renal natriuresis, and this, together with the various other compensatory mechanisms, contributes to increased blood volume and venous pressure.[34,35] Consequently, with chronic pericardial effusion, signs of increased systemic venous pressure predominate and manifest as right-sided CHF.

Figure 205-5 Hemodynamic effects of intrapericardial saline infusion in a dog. Cardiac output *(CO)* and stroke volume *(SV)* decrease as soon as intrapericardial volume begins to increase. Mean arterial pressure *(MAP)* is maintained until intrapericardial volume *(Peric. Vol.)* has increased to 100 mL and intrapericardial pressure *(IPP)* is approximately 10 mm Hg. MAP then drops rapidly with any further increases in intrapericardial volume and pressure. Echocardiography performed during experiment showed that right ventricular diastolic collapse *(RVDC)* first develops when intrapericardial pressure reaches approximately 10 mm Hg. *HR*, Heart rate. (From Leimgruber PP et al: The hemodynamic derangement associated with right ventricular diastolic collapse in cardiac tamponade: an experimental echocardiographic study. *Circulation* 68:612, 1983. With permission.)



Pulsus paradoxus was first described by Kussmaul in 1873 as the apparent paradox of a disappearing pulse during inspiration despite persistence of the heartbeat in patients with pericardial disease.[36] It is defined as a decrease (>10 mm Hg) in systolic arterial blood pressure with inspiration during normal breathing (Figure 205-6).[37] Pulsus paradoxus is an accentuation of the normal small decline of left ventricular stroke volume and systemic arterial blood pressure that occurs with inspiration. During inspiration, intrathoracic pressure decreases and blood flows preferentially into the pulmonary veins, right atrium, and ventricle, because these are the most compliant intrathoracic blood vessels and cardiac chambers. Blood pooling in the pulmonary veins reduces preload to the left heart and consequently reduces left ventricular stroke volume. In humans, left ventricular stroke volume normally decreases by an average of 7% during inspiration, and this is associated with a 3% drop in systolic arterial blood pressure. Right ventricular stroke volume, on the other hand, increases during inspiration due to increased right-sided filling. With a normal pericardium, the phasic variations in right ventricular volume have little effect on the left ventricle, and pooling of blood in the pulmonary veins is the most important contributor to decreased left ventricular stroke volume during inspiration.[38]

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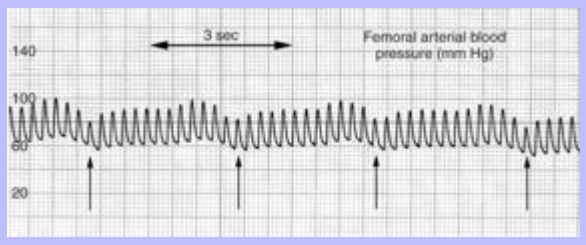
Figure 205-6 Femoral arterial blood pressure showing pulsus paradoxus in a dog with pericardial effusion. At end-inspiration *(arrows)*, systolic blood pressure decreases by more than 10 mm Hg and pulse pressure narrows.



Reciprocal and phasic changes with respiration in left and right ventricular filling and stroke volume are exaggerated in the presence of pericardial effusion. Outward expansion of the ventricles is limited, and any increase in the volume of one ventricle can only occur at the expense of the other. Thus greater right ventricular filling during inspiration increases the pressure within the pericardial sac. This, in turn, further compresses the left ventricle. In addition, increased right ventricular filling causes the interventricular septum to deviate toward the left ventricle, further compromising left ventricular volume.[36] This interaction between the ventricles is superimposed upon the normal decrease in left ventricular stroke volume that occurs during inspiration and leads to pulsus paradoxus. The inspiratory increase in right ventricular filling is indispensable for pulsus paradoxus. When systemic venous return is held constant, tamponade does not result in pulsus paradoxus.[39]

205.3.1.2 Epidemiology

Pericardial disorders resulting in effusion occur primarily in older, large breed dogs. No apparent sex predisposition exists. At the UMVMC from January 1999 to December 2001, the average age among 87 dogs with pericardial effusion was 9.7 years (±2.2 years), average weight was 31.2 kg (±12.6 kg), and

males and females were nearly equally represented (46 males:41 females). Pericardial effusion occurred most frequently in golden retrievers, and its prevalence in this breed was striking. Of the 87 affected dogs, 23 (26%) were golden retrievers. The breed was significantly over-represented when compared with the general hospital population (odds ratio, 4.4; 95% confidence interval, 2.7 to 7.0). Golden retrievers were also the most common breed among dogs with pericardial effusion at the Veterinary Hospital, University of Pennsylvania from 1990 to 1993.[29]

Information regarding the epidemiology of pericardial effusions in cats is limited. One study reported 66 cases with pericardial disease among 2852 feline necropsies. Pericardial effusion was present in 58 cases, and eight had pericardial pathology but no significant effusion. In virtually all cases the pericardial disorder formed part of a more generalized disease, most commonly CHF and feline infectious peritonitis (FIP). Pericardial pathology appears to attend many feline diseases, but symptomatic pericardial effusion in the cat is uncommon.[40]

205.3.1.3 Presenting and Clinical Signs

The presenting signs among dogs with pericardial effusion are remarkably diverse and include lethargy, respiratory distress, reduced appetite, episodic collapse, vomiting, and abdominal distention. Polydipsia, weakness, and coughing are also occasionally reported. Common physical examination findings are muffled heart sounds, weak pulses, pale mucous membranes, and abdominal distention with a fluid wave. Thorough examination reveals jugular distention in most cases. Pulsus paradoxus is usually subtle, but careful pulse palpation may disclose variations in pulse quality associated with phase of respiration.

205.3.1.4 Diagnostic Procedures

205.3.1.4.1 Radiology

Thoracic radiographs in cases with pericardial effusion are frequently described as showing an enlarged and globoid cardiac silhouette, with tracheal elevation and widening of the caudal vena cava. The cardiac silhouette and diaphragm overlap, and in the dorsoventral or ventrodorsal projection, the pericardial sac may touch the costal margins bilaterally. The edge of the distended pericardial sac is often distinct because it undergoes little, if any, motion during systole and diastole. The lung fields are clear of any infiltrate to indicate the presence of left-sided CHF (Figure 205-7).

These radiographic findings, when present, strongly support the presence of a pericardial effusion. *1109*
However, such “typical” findings are only present in more chronic cases with large volume pericardial *1110*
effusions. In cases with accumulations of smaller amounts of pericardial effusion, findings on thoracic radiography are much more subtle. In these cases the cardiac silhouette is enlarged but it is not necessarily globoid, suggesting additional differential diagnoses such as dilated cardiomyopathy. Some pleural effusion is frequently present in dogs with pericardial effusion and may obscure the cardiac silhouette.

Figure 205-7 Lateral thoracic radiograph of a dog with severe, chronic pericardial effusion. Cardiac silhouette is globoid and overlaps diaphragm, and trachea is elevated. A total of 1600 mL of pericardial effusion was removed by pericardiocentesis. Histopathology of the pericardium disclosed pericardial mesothelioma.

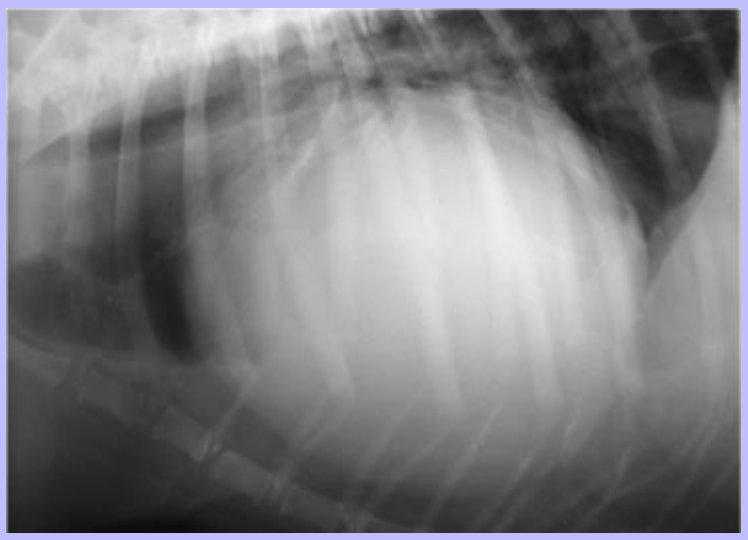
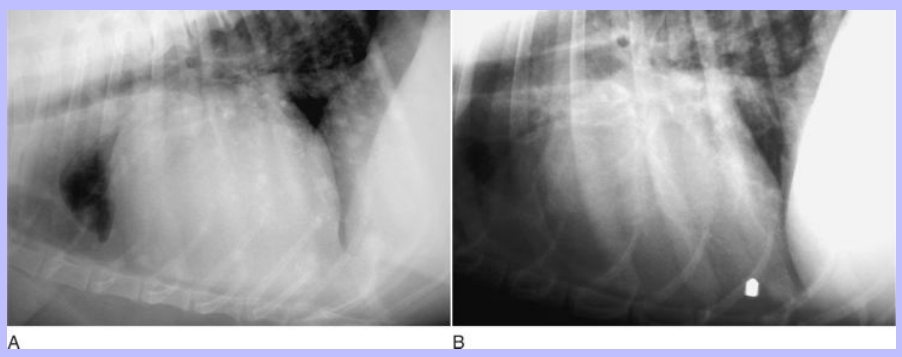


Figure 205-8 Lateral thoracic radiographs of two dogs with pericardial effusions. In both cases, volume of effusion was considerably less than in dog in Figure 205-7, and cardiac silhouettes are consequently much smaller and less globoid. **A,** Focal disseminate pulmonary metastases. The final diagnosis was metastatic cardiac hemangiosarcoma. **B,** A radiopaque foreign body due to an intrapericardial metal pellet.



Despite the various limitations, thoracic radiography is an important component of the diagnostic evaluation of cases with suspected pericardial effusion. In addition to facilitating a diagnosis of pericardial effusion in many cases, thoracic radiographs may demonstrate the presence of other abnormalities, such as pulmonary metastases (Figure 205-8, *A*), or radiopaque intrapericardial foreign bodies (Figure 205-8, *B*).

205.3.1.4.2

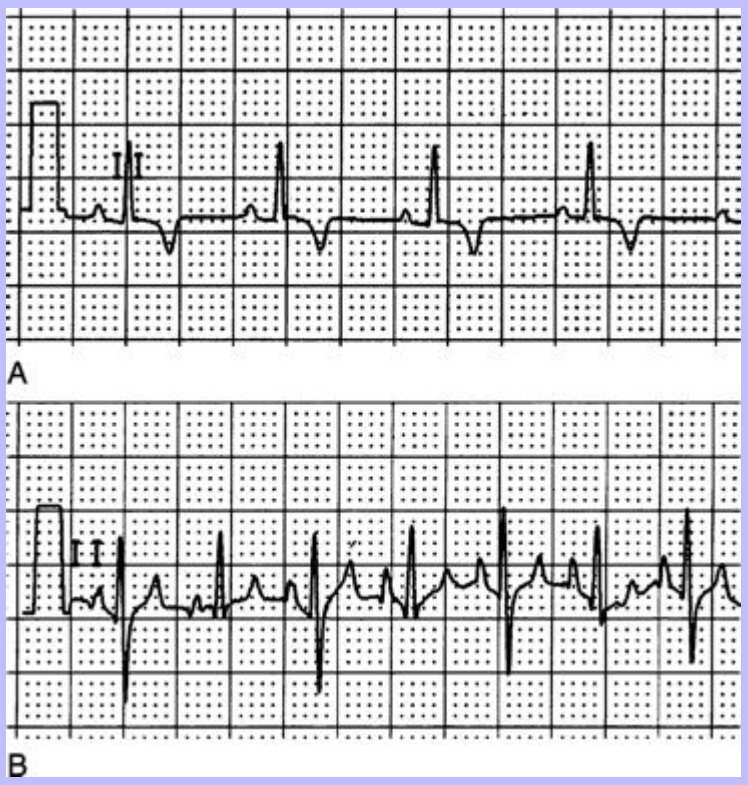
Electrocardiography

In most dogs with pericardial effusion, electrocardiography discloses either a normal sinus rhythm or a sinus tachycardia. Ventricular arrhythmias are fairly common, and supraventricular arrhythmias occasionally occur. Low-voltage QRS complexes (<1 mV in all limb leads) are present in approximately half of the cases with pericardial effusion in which electrocardiography is performed (Figure 205-9, *A*). Other differential diagnoses that result in low-voltage electrocar-diographic complexes include pleural effusion, obesity, and hypothyroidism.

Electrical alternans, a beat-to-beat variation in the contour and amplitude of the QRS and ST-T complexes (Figure 205-9, *B*), is strongly suggestive of a pericardial effusion.[41] Electrical alternans results from 2:1 swinging of the heart, or swinging once every other heartbeat in large pericardial effusions. In humans, clinical data and mathematic modeling show that electrical alternans is a rate-dependant phenomenon that occurs at heart rates of between 90 and 144 beats per minute.[42]

In the original report of electrical alternans in dogs, the electrocardiographic feature was present in seven of 11 dogs (64%) with pericardial effusion, and it was more prone to occur in cases with larger effusions.[41] However, subsequent reports indicate that electrical alternans among dogs with pericardial effusion occurs relatively infrequently. In two studies in dogs with confirmed pericardial effusions, electrical alternans was present in only two of 33 (6.4%) and two of 10 cases (20%).[43,44] Electrical alternans is a similarly insensitive indicator of pericardial effusion in humans, and it occasionally occurs with disorders other than pericardial effusion in both humans and dogs.[41,45,46] Electrical alternans has been reported in cats with pericardial effusion.[40] Electrocardiographic findings are generally too few, subtle, and insensitive to be considered particularly useful as an indicator of the presence of pericardial effusion. However, electrocardiography is indicated in patients with signs of low cardiac output, when arrhythmias are detected on physical examination, and when thoracic radiographs demonstrate enlargement of the cardiac silhouette. Under these circumstances, an electrocardiogram that shows changes consistent with a pericardial effusion will facilitate the diagnosis.

Figure 205-9 Electrocardiograms (lead *II*) from two dogs with pericardial effusions. Calibration square wave is 1 mV in amplitude. **A,** Low-voltage (<1 mV) complexes. **B,** Beat-to-beat variations in amplitude and contour of QRS and ST-T complexes that characterize electrical alternans.



205.3.1.4.3 Pericardial Fluid Analysis

The diagnostic value of pericardial fluid analysis is limited. In dogs, the gross appearance of pericardial effusions is virtually always sanguineous or serosanguineous irrespective of cause, and they are usually classified as hemorrhagic effusions or sterile inflammatory exudates. Total nucleated cell counts, red cell counts, and protein concentrations of pericardial fluid overlap extensively between the various neoplastic and non-neoplastic causes.[47] The pH of pericardial fluid has been reported to distinguish between neoplastic and non-neoplastic effusions.[48] However, considerable overlap in pH values exists between the various causes of pericardial effusion, and pH measurements of pericardial fluid have little clinical use.[49] Hemangiosarcoma and aortic body tumors, the most common tumors associated with pericardial effusions in dogs, are rarely identified on cytologic evaluation of pericardial fluid, presumably because they do not readily exfoliate. Further, pericardial diseases that lead to effusion result in dramatic mesothelial proliferation, and exfoliated mesothelial cells often have characteristics that mimic

malignancy. Consequently, pericardial fluid analysis is associated with a high incidence of false-negative and false-positive cytologic diagnoses of neoplasia.[47,50,51]

Despite these limitations, pericardial effusion cytology does occasionally provide crucial information, and pericardial effusion analysis is especially important for those cases in which no intrapericardial masses suggestive of hemangiosarcoma or aortic body tumor are detected on echocardiography. Some of the less common causes of pericardial effusion, such as infective pericarditis and lymphosarcoma, are diagnosed primarily based on pericardial fluid cytology. Consequently, pericardial fluid analysis is an important component of the evaluation in cases with pericardial effusion, but the results must be interpreted with appropriate care and understanding of the limitations of the test.

205.3.1.4.4

Additional Laboratory Tests

Dogs with hemangiosarcoma are frequently anemic and may have nucleated red blood cells (RBCs), schistocytes, acanthocytes, and thrombocytopenia. Mild to moderate elevations in liver enzymes are frequently present as a result of hepatic congestion. Analysis of ascitic fluid is consistent with a modified transudate. Mild azotemia, which is usually prerenal, may be present. Cats with FIP may have a neutrophilia, lymphocytopenia, and hyperglobulinemia. *Coccidioides immitis* serology should be performed in cases with pericardial disease from endemic areas. Some assessment of coagulation (e.g., activated coagulation time [ACT]) should be performed prior to pericardiocentesis, especially if a coagulopathy is suspected clinically.

205.3.1.4.5

Echocardiography

Echocardiography is the most sensitive and specific noninvasive method to confirm the presence of pericardial effusion, and it has replaced many of the radiographic procedures (fluoroscopy, angiography, and pneumopericardiography) that were previously used to identify the presence and causes of pericardial effusions. With two-dimensional echocardiography, pericardial effusion appears as an anechoic space surrounding the heart. In cases with concurrent pleural effusion, the pericardium is well visualized with anechoic fluid on either side. The heart may show swinging motions within the pericardial fluid. The various heart chambers may appear small, and the walls may show thickening or pseudohypertrophy due to compression.[52]

Pericardial fluid is usually readily distinguishable from pleural effusion, although this is not invariably the case. Pericardial effusion is contained within a circular region around the heart, where it provides contrast for various cardiac chambers, such as the walls of right atrium and auricle and the proximal aorta. Pleural effusion is more diffuse and contains the edges of lung lobes and mediastinum.

The changes in transmural pressure and intracardiac flow with pericardial effusion are reflected in several useful and readily detectable echocardiographic findings. These include inversion or collapse of the right atrial and ventricular free walls resulting from reversal of transmural pressure, as well as exaggerated respiratory variation in blood flow through the right and left heart.

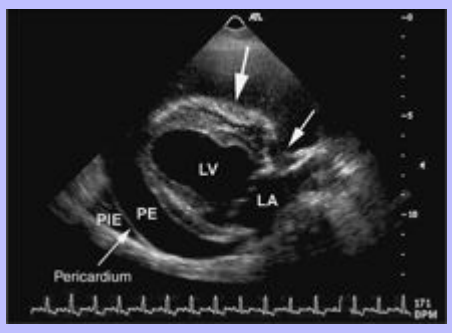
The right atrial free wall is normally rounded throughout the cardiac cycle, reflecting the normal positive right atrial transmural pressure. Any inversion of the right atrial free wall is therefore indirect evidence of elevated intrapericardial pressure and transient reversal of transmural pressure. Right atrial inversion occurs in late diastole and continues into ventricular systole for a variable period before normalizing. Right ventricular diastolic collapse is characterized by inward motion of the right ventricular free wall

during diastole. With mild tamponade, this inward movement produces a localized concavity of the right ventricular free wall. With severe cardiac tamponade, right ventricular diastolic collapse persists throughout diastole, and the right ventricular chamber is almost completely obliterated (Figure 205-10).[53]

Doppler studies of normal hearts demonstrate slightly decreased flow velocity across the mitral valve and slightly increased flow velocity across the tricuspid valve during inspiration. The changes in aortic and pulmonic flow velocity are smaller; however, aortic flow velocity decreases slightly during inspiration, and pulmonic flow velocity increases. In humans, these respiratory changes in flow velocity become markedly accentuated with pericardial effusion, even in the absence of clinical signs of cardiac tamponade.[53] These Doppler indicators are present in dogs with experimentally induced tamponade.[54] 1111

However, the clinical use of Doppler studies in the evaluation of small animals with pericardial effusion has yet to be determined. In addition to confirming the presence of a pericardial effusion and providing evidence of tamponade, echocardiography is the noninvasive procedure of choice to detect intrapericardial masses such as hemangiosarcoma and heart base tumors. Although histopathology is necessary to confirm and definitively identify a tumor, the location and characteristics of an intrapericardial or myocardial mass demonstrated during echocardiography provides important information about the probable tumor type.[55,56] 1112

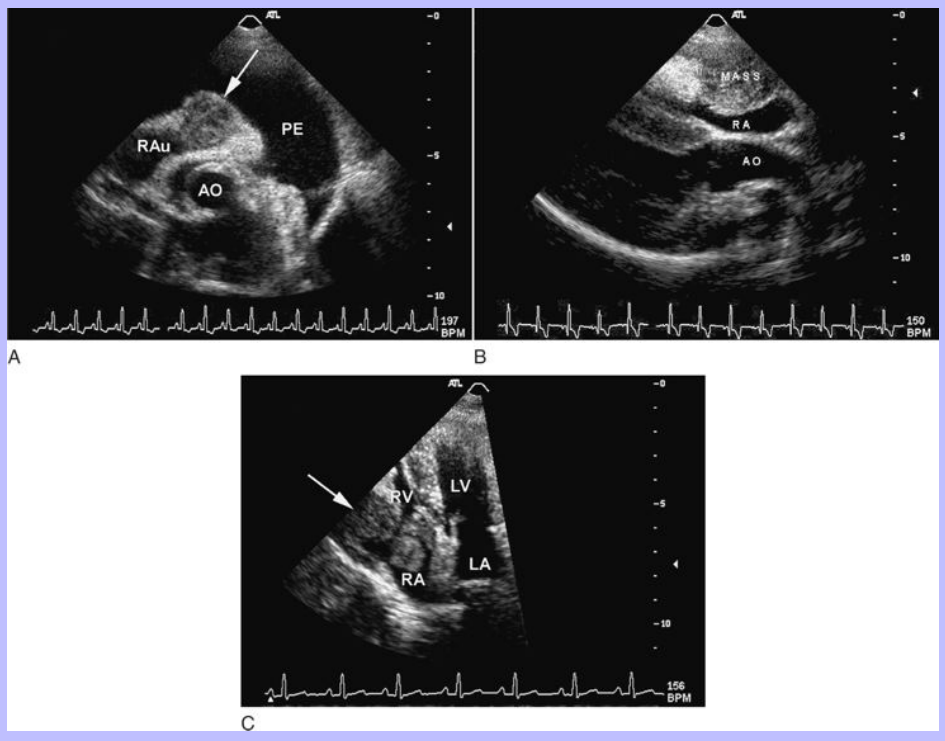
Figure 205-10 Echocardiogram (long axis four-chamber view from the right parasternal location) from dog with pericardial effusion *(PE)* and echocardiographic evidence of tamponade. Right atrial inversion is apparent *(small arrow)*, and right ventricular collapse *(large arrow)* results in virtually complete obliteration of right ventricular chamber. *LA,* Left atrium; *LV,* left ventricle; *PlE,* pleural effusion.



Hemangiosarcoma, a highly malignant neoplasm of vascular endothelium, is the most commonly diagnosed cardiac tumor in dogs. It occurs with an approximately tenfold greater prevalence than the second most common cardiac tumor—aortic body tumors.[57] Primary and metastatic cardiac hemangiosarcoma in the cat has been reported, but it is rare.[58] Hemangiosarcoma most commonly arises from the wall of the right atrium or auricle, protrudes into the pericardial space, and moves with the right auricle or atrium (Figures 205-11, *A* and *B*). These tumors may also protrude into the right atrial chamber, spread to involve other areas of the heart base and pericardium, and involve the right atrioventricular (AV) junction (Figure 205-11, *C*). Hemangiosarcoma involving the wall of the left

ventricle has been described.[59] Hemangiosarcoma typically contains small hypoechoic spaces, giving the tumor a mottled or cavitary appearance, and the tumors are occasionally cystic. Hemangiosarcoma, when present, is usually demonstrated while imaging from the right parasternal long and short axis views. However, these tumors may be small and elusive. Imaging from the left caudal parasternal location to obtain a four-chamber view and from the left cranial parasternal location to provide alternate imaging planes, especially of the right auricle, is necessary to demonstrate the presence of hemangiosarcoma in some cases.

Figure 205-11 Echocardiograms from dogs with cardiac hemangiosarcoma. **A,** Short axis view from right parasternal location, shows a round, cavitary, transmural tumor *(arrow)* near tip of right auricle *(RAu)*. **B,** Long axis left ventricular outflow view from right parasternal location, shows tumor *(MASS)* that involves wall of the right atrium *(RA)*. **C,** Four-chamber (inflow) view from the left caudal parasternal location, shows cavitary tumor *(arrow)* that extensively involves right atrioventricular junction. Part of the tumor protrudes into the right atrium *(RA)* and partially occludes tricuspid valve. *AO,* Aorta; *PE,* pericardial effusion; *RV,* right ventricle; *LA,* left atrium; *LV,* left ventricle.



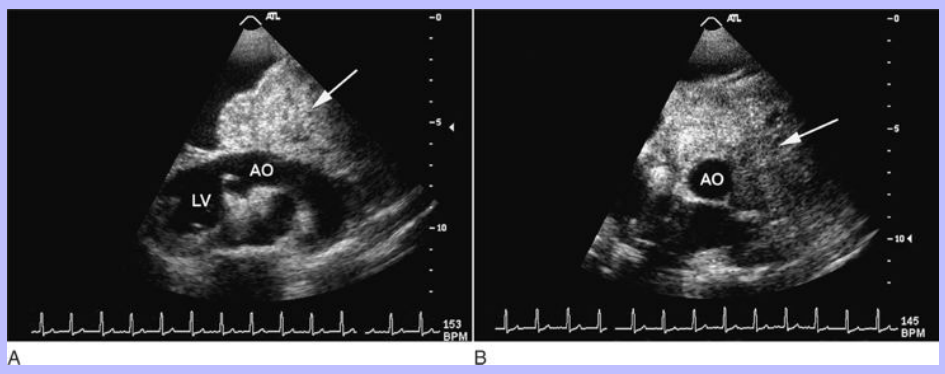
The term *heart base tumor* is used to designate any mass located at the base of the heart in association with the ascending aorta and main pulmonary artery. The most common heart base tumors in dogs are aortic body tumors, which arise from specialized neuroepithelial cells that reside within the adventitia of the aortic arch. The specialized neuroepithelial cells or chemoreceptors serve to detect minute changes in blood oxygen and carbon dioxide tensions, pH, and temperature. Tumors of chemoreceptors are termed *chemodectomas*. They comprise a subgroup of tumors referred to as *paragangliomas*, all of which arise from cells that share a common embryologic origin from the neural crest. Chemoreceptors occur in a variety of locations in the body, including the aortic body, carotid body, nodose ganglion of the vagus nerve, ciliary ganglion in the orbit, pancreas, internal jugular vein below the middle ear, and glomus jugulare along the recurrent branch of the glossopharyngeal nerve.[60,61] Owing to the location of the aortic chemoreceptors, only aortic body chemodectomas are associated with pericardial effusion.[61] In addition to aortic body tumors, between 5% and 10% of heart base tumors in dogs are thyroid tumors (both adenomas and adenocarcinomas) that arise from ectopic thyroid tissue at the base of the heart.[62–66] Aortic body tumors have occasionally been reported in cats.[67–70]

Heart base tumors are usually associated with the ascending aorta. They vary from small ovoid structures attached to the cranial aspect of the ascending aorta to very extensive masses that surround the aorta and main pulmonary artery (Figure 205-12). Tumor indentation or invasion of the atria may be seen. Heart base tumors tend to have a more homogenous appearance than the mottled or cavitary appearance of hemangiosarcoma. They are usually (but not invariably) associated with pericardial effusions.

Echocardiography may also demonstrate other cardiac tumors, the presence of abdominal viscera within the pericardial sac in cases with PPDH, benign intrapericardial cysts, and intrapericardial thrombi associated with left atrial rupture. Left atrial rupture is suspected when signs of acute tamponade develop in smaller breed dogs with significant mitral regurgitation.

Confirming the presence of pericardial effusion with echocardiography is rapid, straightforward, and accurate. However, echocardiography is also crucial for determining the presence or absence of intrapericardial masses, and it provides important information about the size and location of tumors and their accessibility for surgical resection. Identification of intrapericardial tumors is frequently challenging, and transthoracic imaging in multiple planes from both left and right-sided locations may be necessary. The presence of pericardial fluid greatly facilitates the detection of intrapericardial masses, and this is particularly relevant to the diagnosis and delineation of hemangiosarcoma and heart base tumors. Pericardial fluid forms an echolucent zone around the right atrium and auricle and the ascending aorta, the locations at which these tumors most commonly occur. In the absence of pericardial fluid, these locations are obscured by lung interference. Consequently, whenever the clinical condition of the patient permits, pericardiocentesis should be deferred until a thorough echocardiographic examination has been completed.

Figure 205-12 Echocardiogram from dog with a heart base tumor. **A,** Long axis left ventricular outflow view obtained from the right parasternal location, shows a large tumor *(arrow)* attached to cranial aspect of ascending aorta *(AO)*. **B,** Short axis view obtained from right parasternal location, shows that tumor *(arrow)* virtually completely encircles the aorta. Histopathologic diagnosis was ectopic thyroid adenocarcinoma. *LV,* Left ventricle.



205.3.2 Acquired Pericardial Effusions: Specific Causes, Epidemiology, Treatment, and Prognosis

205.3.2.1 Idiopathic Pericardial Effusion

Idiopathic pericardial effusion is a diagnosis of exclusion. It is made in cases with pericardial effusion where no intrapericardial masses are identified after thorough echocardiographic evaluation and the results of ancillary tests, such as pericardial fluid analysis, fail to disclose a cause. Pericardial histopathology and immunohistochemistry from dogs with idiopathic pericardial effusion demonstrate extensive pericardial fibrosis and a mixed inflammatory response of greatest intensity at the cardiac surface of the tissue. Perivascular lymphoplasmacytic aggregates are present at the pleural surface within the fibrosed pericardium. No vascular pathology or deposition of immunoglobulin or complement within the vessel wall exists, suggesting that the pericarditis is not due to a vasculitis. Immunohistochemistry findings are consistent with a predominantly humoral immune response, but they do not support a primary immune-mediated pathogenesis. The factor or factors that initiate idiopathic pericarditis remain unknown.[71]

As with any diagnoses of exclusion, a diagnosis of idiopathic pericardial effusion should be made with appropriate caution. Small intrapericardial tumors may elude detection, especially in cases where echocardiography is performed after pericardiocentesis. In addition, mesothelioma is a diffuse neoplasm of the pericardium and other serosal surfaces, and it does not result in appreciable thickening of the pericardium on echocardiography. Cytology of pericardial effusion cannot distinguish between idiopathic pericardial effusion and mesothelioma.[51] Consequently, mesothelioma should always be considered as an

important differential diagnosis for idiopathic pericardial effusion. Idiopathic pericardial effusion has not been reported in cats.

Idiopathic pericardial effusion was diagnosed in eight of 42 dogs (19%) with pericardial effusion in a retrospective study from the Veterinary Teaching Hospital, Colorado State University.[43] Idiopathic pericardial effusion was provisionally diagnosed in 24 of 87 dogs with pericardial effusion at the UMVMC from January 1999 to December 2001, but mesothelioma was eventually confirmed in four of these cases. Consequently, 20 of 87 cases (23%) with pericardial effusion in the UMVMC study population were finally diagnosed as having idiopathic pericardial effusion, which is similar to the data from Colorado State University. Average age among the cases with idiopathic pericardial effusion in the UMVMC study population was 9.4 years (±2.2 years), average weight was 28.9 kg (±14.5 kg), and there was no apparent sex predisposition (11 males:9 females). Five of the 20 dogs (25%) were golden retrievers, and the breed was over-represented (odds ratio, 4.2; 95% confidence interval, 1.6 to 11.2).

The initial treatment for idiopathic pericardial effusion is pericardiocentesis to remove as much pericardial fluid as possible. The author's preferred approach is to restrain the animal in left lateral recumbency and to approach the pericardium from the right side (See Chapter 103).

The gross appearance of pericardial fluid is usually indistinguishable from blood. To confirm that the catheter is in the pericardial space, an aliquot of fluid is placed in an ACT tube. Blood will normally clot in an ACT tube within 60 to 90 seconds. In contrast, sanguineous effusions in body cavities are rapidly depleted of clotting factors and thrombocytes, and pericardial fluid will consequently not clot. If no clots form within the activated clotting tube after 3 to 5 minutes, all of pericardial fluid is aspirated and samples are collected for fluid analysis and culture. The catheter is then removed.

In virtually all cases with pericardial effusion, pericardiocentesis results in rapid and marked hemodynamic improvement. Clinical signs, pulse quality, and mucous membrane perfusion improve, and heart rate decreases. However, ventricular and supraventricular arrhythmias (including atrial fibrillation) are common after pericardiocentesis. These arrhythmias seldom require therapy and usually resolve spontaneously. The author prefers to hospitalize and monitor cases for 12 to 24 hours after pericardiocentesis.

The author usually treats an initial episode of idiopathic pericardial effusion by pericardiocentesis alone, followed by pericardiectomy in cases that develop recurrent effusions. Recurrent effusions, effusive-constrictive, and constrictive pericarditis are well-recognized complications after pericardiocentesis in cases with idiopathic pericardial effusion.[72–75] Among the 20 cases diagnosed with idiopathic pericardial effusion in the UMVMC study population, six died or were euthanized after developing recurrent effusions with tamponade within 44 days of their initial episode. Cardiac tamponade with pulmonary thromboembolism was the cause of death in one dog. Postmortem examinations were not performed in the remaining five cases, and the possibility that some dogs might have had cardiac tumors that eluded detection during echocardiography cannot be excluded. Among the remaining 14 dogs, four developed recurrent effusions necessitating pericardiectomy, and a further six developed effusive-constrictive pericarditis between 3 months and 3 years after their initial episode. Median survival time (MST) among the 20 cases was 663 days, indicating a generally good prognosis in cases with idiopathic pericardial effusion. However, the complication rate among these cases was high, and this is consistent with the results of others.[73,74]

The complication rate among cases with idiopathic pericardial effusion would probably be lower if pericardiectomy was performed at the time of the initial episode rather than after recurrent effusion. Pericardiectomy would avoid the risk of recurrent life-threatening cardiac tamponade and the potential for

developing effusive-constrictive and constrictive pericarditis. In addition, surgery permits examination of thoracic and intrapericardial structures to rule out other causes of pericardial effusion, including tumors and foreign bodies. Although pericardiectomy is by no means devoid of morbidity and mortality, it is an extremely successful procedure for idiopathic pericardial effusion.[76–79] Consequently, it is likely that pericardiectomy will increasingly form part of the initial treatment for cases with idiopathic pericardial effusion, especially as minimally invasive methods for the procedure become more widespread.[80,81]

Colchicine, nonsteroidal anti-inflammatories, and corticosteroids are prescribed for humans with recurrent idiopathic pericarditis. Colchicine and nonsteroidal anti-inflammatories are recommended in most cases, and the use of corticosteroids is limited to very severe cases. Colchicine for the treatment of recurrent pericarditis in humans is promising, although data from large controlled prospective studies are lacking.[82,83] The safety and efficacy of colchicine, nonsteroidal anti-inflammatories, corticosteroids, and any other medical therapies in the management of idiopathic pericardial effusion in small animals have yet to be established.

205.3.2.2 Mesothelioma

Mesothelioma is emerging as an increasingly important cause of pericardial effusion. Mesothelioma was confirmed in four of 87 dogs (5%) in the UMVMC study population of dogs with pericardial effusion. Average age among the affected cases at time of presentation was 9.5 years (±2.2 years), average weight was 37.5 kg (±11.1 kg), and males and females were equally represented. No breed predisposition has been reported, and affected breeds in the UMVMC population were Akita, golden retriever, Labrador retriever, and springer spaniel. Mesothelioma causing pericardial effusion has been described in a cat,[84] but pericardial mesothelioma is rare in this species.

The clinical course of pericardial effusion due to mesothelioma in the UMVMC study population followed a characteristic pattern. Presenting and clinical signs were no different from other cause of pericardial effusion. In all four cases, a provisional diagnosis of idiopathic pericardial effusion was made after various diagnostic procedures, including echocardiography and pericardial fluid analysis failed to disclose a cause for the pericardial effusion. Pericardiocentesis was performed, and this was repeated at 77 days (± 46 days) when the dogs developed recurrent effusions with tamponade. Pericardiectomies were then performed in all cases; histopathology of the excised pericardia was consistent with idiopathic pericarditis in three cases, and mesothelioma in one. Severe and unremitting pleural effusions requiring repeated thoracocentesis began at 103 days (±44 days) after pericardiectomy. Intracavitary cisplatin was administered in two dogs, but this did not appear to significantly change the course of the disease. Thoracocentesis was necessary every 2 to 3 weeks until death or euthanasia, and MST from the initial episode of pericardial effusion was 312 days (range, 206 to 352). In all cases, mesothelioma that had spread throughout the thoracic cavity was confirmed on postmortem examination.

The signalment and clinical course among cases with pericardial effusion due to mesothelioma in the UMVMC study population are strikingly similar to those described by others.[77,85–87] It is extremely difficult to distinguish between idiopathic pericardial effusion and pericardial effusion due to mesothelioma, even with pericardial histopathology and immunohistochemistry.[87,88] The clinical course of the disease is suggestive, and accumulation of significant amounts of pleural effusion within 120 days of pericardiectomy increases the index of suspicion for mesothelioma.[87] In addition to being a diagnostic challenge, mesothelioma is difficult to treat. However, long-term survival has been reported in a dog in which a histopathologic diagnosis of pericardial mesothelioma was made after pericardiectomy for

recurrent pericardial effusion. Treatment in that case was initiated 48 hours after surgery with intracavitary cisplatin and intravenous doxorubicin, and the dog was free of disease 27 months later.[89] Intracavitary cisplatin has successfully resolved pleural effusions in some dogs with pleural mesothelioma.[90]

205.3.2.3 Cardiac Hemangiosarcoma

In a retrospective study from the Veterinary Teaching Hospital, Colorado State University, cardiac hemangiosarcoma was diagnosed in 14 of 42 dogs (33%) with pericardial effusion.[43] At the UMVMC, cardiac hemangiosarcoma was diagnosed either by echocardiography or echocardiography and histopathology in 53 of 87 dogs (61%) in the study population with pericardial effusion. Cardiac hemangiosarcoma with pericardial effusion was nearly three times more prevalent than the second most common form of pericardial effusion, idiopathic pericardial effusion. Average age among the affected dogs was 9.8 years (±2.1 years), and their average weight was 32.0 kg (±12.2 kg). Males slightly outnumbered females (31 males:22 females), but the difference was not statistically significant when compared with the general hospital population. Sixteen of the 57 dogs (28%) were golden retrievers and the breed was over-represented (odds ratio, 5.3; 95% confidence interval, 2.9 to 9.4).

Two features of these data suggest that important changes have occurred in the epidemiology of cardiac hemangiosarcoma. First, the prevalence of cardiac hemangiosarcoma in the UMVMC study population was nearly twice that of the Colorado State University study population. The reasons for this are not clear; however, regional differences in the epidemiology of cardiac hemangiosarcoma may exist, or the prevalence of the disease may have increased over time. Second, the golden retriever was the only over-represented breed among the cases with cardiac hemangiosarcoma in the UMVMC study population. Cardiac hemangiosarcoma has previously been recognized most frequently in German shepherds.[43,91,92] More recently, cardiac hemangiosarcoma has also been seen commonly in golden retrievers at the Veterinary Hospital, University of Pennsylvania.[93]

Treatment for all forms of hemangiosarcoma is challenging, and a diagnosis of cardiac hemangiosarcoma confers a grave prognosis. By the time of diagnosis, cardiac hemangiosarcoma usually has metastasized and should be considered a systemic disease.[77] At the UMVMC, the majority of owners of dogs with cardiac hemangiosarcoma elect to have their dogs treated by pericardiocentesis alone on one or more occasions. Pericardiocentesis is predictably associated with marked clinical improvement, but clinical signs of tamponade typically recur within a few days, often resulting in death or prompting euthanasia. In the UMVMC study population, MST among dogs with cardiac hemangiosarcoma treated by pericardiocentesis alone (n = 30) was just 11 days (range, 0 to 208). Percutaneous balloon pericardiotomy has been described in the dog,[94,95] and the procedure may provide longer periods of palliation in cases with cardiac hemangiosarcoma.

More aggressive approaches to the treatment of cardiac hemangiosarcoma include various combinations of pericardiectomy, tumor resection, splenectomy in cases with splenic metastases, and chemotherapy.[91,96–100] Survival data for cases managed in this manner are limited. In a case report of right atrial hemangiosarcoma treated with chemotherapy alone, survival time was 20 weeks.[98] In dogs treated by surgery alone (tumor resection and pericardiectomy or creation of a pericardial window, or pericardiectomy alone), reported survival times range from 2 days to 8 months.[91,99,100] No survival data are available that compare surgery alone, with surgery and chemotherapy for dogs with cardiac hemangiosarcoma. Further, no compelling evidence suggests that survival times in dogs with either splenic or cardiac

hemangiosarcoma can be significantly prolonged with adjuvant chemotherapy. Nevertheless, the management of cardiac hemangiosarcoma should always involve consultation with an oncologist to take advantage of continually emerging modalities for the treatment of this highly malignant tumor.[101]

205.3.2.4 Heart Base Tumors

The majority of heart base tumors in dogs are aortic body tumors. English bulldogs, boxers, and Boston terriers are predisposed, although aortic body tumors also occur in nonbrachycephalic breeds. In various studies, brachycephalic breeds have accounted for between 39% and 85% of dogs with aortic body tumors.[70,102,103] Chronic hypoxia induces hyperplasia and neoplasia of chemoreceptors, which may explain the predisposition of brachycephalic breeds to aortic body tumors.[102] Among the predisposed breeds, males may be at increased risk for developing aortic body tumors, but differences in sex predisposition are not statistically significant in all studies.[70,102,103] The age range at time of diagnosis of aortic body tumors is 6 to 15 years with an average of 10 years.[61,70] Between 5% and 10% of tumors at the heart base are ectopic thyroid tumors.[62] Aortic body tumors are reported in cats, but they are rare in this species.[67–70]

Most aortic body tumors are benign and locally expansive, although local invasiveness and metastases occur in both dogs and cats.[61,67–69,104,105] Two studies report metastases mostly to the lungs and liver in approximately 10% to 12% of dogs with aortic body tumors.[102,103] In a third study, 58% (14 of 24) of aortic body tumors were benign, 25% (6 of 24) were locally invasive, and 21% (5 of 24) were metastatic. Sites of metastases included the lungs, left atrium, pericardium, and kidneys.[70] The biologic behavior of ectopic thyroid tumors at the heart base is less well described, and both ectopic thyroid adenomas and adenocarcinomas with metastases have been reported.[63–66]

Heart base tumors were diagnosed either by echocardiography or echocardiography and histopathology in six dogs among the 87 cases (7%) with pericardial effusion in the UMVMC study population. Affected breeds were Great Dane, Labrador retriever, German shorthaired pointer, boxer, English springer spaniel, and Old English sheepdog. Average age was 11.1 years (±2.2 years), and average weight was 31.4 kg (±13.0 kg). One dog was male and five were female. The number of dogs with heart base tumors in the UMVMC study population is small, but the epidemiologic data are reasonably in accord with those of others, with the exception of sex distribution. The prevalence of heart base tumors is consistent with a recent review of the epidemiology of cardiac tumors in dogs. In that study, aortic body tumors were approximately tenfold less common than cardiac hemangiosarcoma.[57]

Complete surgical resection of heart base tumors is seldom possible because the tumors are highly vascular, located close to major blood vessels, and usually extensive by the time of diagnosis. However, palliation with pericardiectomy either alone or in combination with tumor resection often results in prolonged survival with an excellent quality of life.[106,107] No evidence indicates that adjuvant chemotherapy improves the prognosis for dogs with heart base tumors. In a recent retrospective study in dogs with aortic body tumors in which surgery was performed, the following factors were evaluated for effect on survival time: sex; breed; presence or absence of respiratory distress; the presence of an arrhythmia other than respiratory sinus arrhythmia; the presence of pleural, pericardial, or peritoneal effusion; evidence of pulmonary metastases; treatment with pericardiectomy; and treatment with chemotherapy. No attempt was made to achieve tumorfree margins in the dogs in that study. Among the various factors evaluated, only treatment with pericardiectomy had a significant effect on survival, and the survival advantage was remarkable. MST

among dogs after pericardiectomy was 730 days, whereas those that did not have a pericardiectomy had a MST of only 42 days.[106]

205.3.2.5 Other Causes of Acquired Pericardial Effusion

Bacterial, fungal, and viral infections are occasionally associated with pericardial effusions in small animals. Most cases of pericardial effusions due to bacterial infections are thought to arise as a consequence of intrapericardial foreign body penetration, usually by migrating foxtails (*Hordeum* spp.). Foxtail migration is a common and often serious problem in the western United States.[108,109] Bacterial pericarditis has also been described in a puppy after a dog bite and in a young adult dog after thoracic trauma.[110,111] In contrast to most other causes of pericardial effusion, pericardial fluid cytology and culture is crucial in the diagnosis of septic cases. In the largest series of infectious pericardial effusion reported in dogs (five cases), treatment involved pericardiectomy and removal of any foreign bodies, chest drainage, and antibiotic therapy for up to 6 months. All dogs recovered without complications, suggesting that dogs with bacterial pericarditis have a good prognosis when treated aggressively with a combination of surgical and medical therapy.[108]

Systemic coccidioidomycosis in dogs has been associated with pericardial disease. In most cases the fungal infection results in effusive-constrictive or constrictive pericarditis. Coccidioidomycosis should be considered, especially in dogs with pericardial disease that reside in or have a travel history that includes areas where the soil fungus *Coccidioides immitis* is endemic, such as the Southwestern United States.[75,112] Treatment involves pericardiectomy, chest drainage, and antifungal therapy (usually beginning with Amphotericin B). Based on limited published information and experience, the prognosis for cases of coccidioidomycosis with pericardial involvement is poor.[112] A case of effusive-constrictive pericarditis due to *Aspergillus niger* has been reported in a dog.[113]

FIP is one of the more common diseases associated with pericardial effusion in the cat.[40] Pericardial effusions that are occasionally voluminous are present in some cats suffering from this systemic and invariably fatal viral disease.

Left atrial rupture is an uncommon cause of pericardial effusion that occurs in smaller breed dogs with chronic degenerative disease of the mitral valve. Affected cases show clinical signs of acute tamponade, and a loud left apical murmur is usually apparent despite muffling of the heart sounds. Echocardiography discloses intrapericardial fluid, a mass caudal to the left ventricle due to thrombus formation, and substantial mitral regurgitation. Pericardiocentesis is immediately necessary in most cases. Further, the possibility of continued hemorrhage exists, necessitating blood transfusion and emergency thoracotomy to remove larger clots from the pericardial space and to repair the left atrium. The prognosis in such cases is grave.[114,115]

Cardiac lymphosarcoma and rhabdomyosarcoma with pericardial effusion have been reported in both dogs and cats, but these are rare.[40,116–118] Among the various cardiac tumors, cardiac lymphosarcoma is unique because cytology of the pericardial fluid establishes the diagnosis in many cases, and the tumor is amenable to combination chemotherapy.[117,119]

Pericardial effusions secondary to coagulation disorders rarely result in clinically significant tamponade. However, a case of pericardial effusion and cardiac tamponade secondary to anticoagulant rodenticide

toxicity has been reported in a dog.[120] Pericardial effusions secondary to disseminated intravascular coagulation, warfarin toxicity, and other coagulopathies have been reported in cats.[40]

Pericardial effusion is frequently detected in cases with CHF in small animals, but usually not in sufficient quantity to cause significant hemodynamic compromise. Pericardial effusion secondary to uremia has been recognized in both dogs and cats.[40,43]

205.3.3 Constrictive and Effusive-Constrictive Pericarditis

In cases with constrictive and effusive-constrictive pericarditis, cardiac filling is compromised by a nondistensible, thickened, fibrotic pericardium. In human medicine, these diseases are defined as follows: constrictive pericarditis consists of fibrotic fusion of visceral and parietal pericardial layers. Effusive-constrictive pericarditis is an unusual variant of constrictive pericarditis. It describes a condition in which constriction of the heart by the visceral pericardium or epicardium exists, and a tense effusion also occurs within the pericardial space. In cases with effusive-constrictive pericarditis, elevated right atrial pressure persists after pericardiocentesis because of the unyielding epicardium.[121,122]

Several reports exist of tamponade in dogs resulting from relatively small amounts of effusion contained within a fibrotic and nondistensible fibrous and parietal pericardium. The visceral pericardium or epicardium is usually spared or only mildly affected in these cases. Many cases are idiopathic, or develop months or years after an episode of idiopathic pericardial effusion. Other causes include metallic foreign bodies, *Coccidioides immitis*, *Aspergillus niger*, actinomycosis, and osseous metaplasia of the pericardium.[75,113,123,124] Some authors define effusive-constrictive pericarditis more liberally to include this combination of relatively little pericardial effusion with constriction due primarily to an unyielding parietal and fibrous pericardium.[37]

Dogs with effusive-constrictive pericarditis typically present with signs of right-sided CHF. Common complaints are abdominal distention and muscle wasting. Findings on physical examination include abdominal distention with a fluid wave, jugular distention, and muffled heart sounds. These presenting and clinical signs are essentially identical to dogs with chronic tamponade due to pericardial effusion. The similarities extend to electrocardiography where normal sinus rhythm or sinus tachycardia and low-voltage QRS complexes are commonly found. The appearance of the cardiac silhouette on thoracic radiography ranges from normal to moderately enlarged and rounded, and the caudal vena cava may appear wide. The presence of pleural effusion in some cases may complicate evaluation of the size and shape of the cardiac silhouette. Radiopaque intrapericardial foreign bodies may be detected. Echocardiography discloses pericardial effusion that separates the myocardium and fibrous pericardium by just a few millimeters (Figure 205-13, *A*). Echocardiographic signs of tamponade (late diastolic to systolic inversion of the right atrium and diastolic collapse of the right ventricle) are usually present (Figure 205-13, *B*). Pericardial thickness cannot be accurately assessed except in extreme cases.

A diagnosis of effusive-constrictive pericarditis can usually be established with confidence based on the previously mentioned constellation of findings. Treatment involves pericardiectomy, and clinicians at the UMVMC have found that the prognosis after pericardiectomy is excellent for idiopathic cases. Slight epicardial fibrosis and roughness that does not require any surgical intervention is present in most cases. Adhesions between the visceral and parietal pericardium are extremely uncommon. Severe involvement of the epicardium and adhesions between the parietal and visceral pericardium confer a much poorer prognosis. Cases with fungal pericarditis caused by *Coccidioides immitis* appear particularly prone to develop extensive

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involvement of both the visceral and parietal pericardium. Epicardial stripping is necessary in such cases, and the procedure is associated with high perioperative morbidity and mortality.

Figure 205-13 Echocardiogram from a dog with effusive-constrictive pericarditis. Dog had signs of right-sided congestive heart failure 25 months after pericardiocentesis had been performed for idiopathic pericardial effusion. **A,** Long axis four-chamber view from right parasternal location, shows small amount of pericardial effusion *(PE)* that separates fibrous pericardium from myocardium by just a few millimeters (reader should compare with centimeter scale on right side of echocardiogram). **B,** Late diastolic to systolic inversion of right atrium *(arrow)*, confirming the presence of tamponade. *PlE,* Pleural effusion; *RA,* right atrium; *RV,* right ventricle; *LA,* left atrium; *LV,* left ventricle.

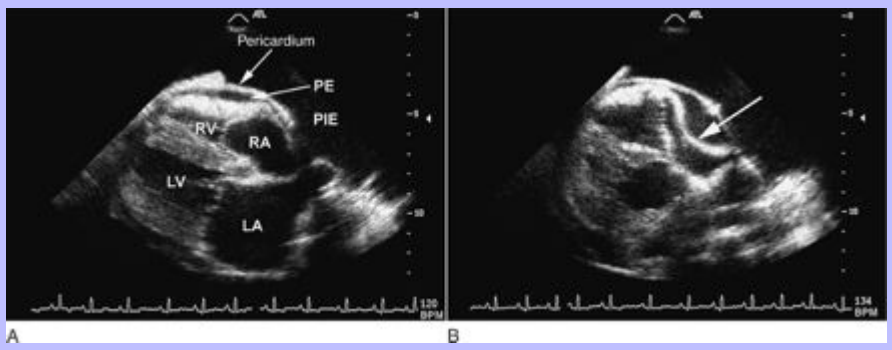
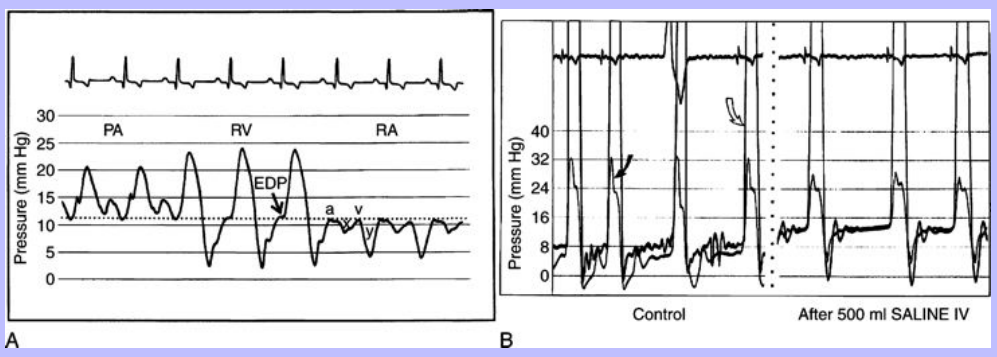


Figure 205-14 Hemodynamic abnormalities associated with constrictive pericarditis. **A,** Elevation and equilibration of end-diastolic pressure *(EDP)* in pulmonary artery *(PA)*, right ventricle *(RV)*, and right atrium *(RA)*. Right atrial pressure waveform has a *M*-shaped pattern due to reduced X descent and a prominent Y descent. **B,** Simultaneous recordings of left ventricular *(open arrow)* and right ventricular *(solid arrow)* pressures before and after saline infusion. Under control conditions, pressure waveforms show slight elevations in end-diastolic pressures. However, true circumstances of the case become apparent with rapid intravenous infusion of 500 mL saline. This procedure results in elevation and equilibration of left and right ventricular diastolic pressure, and a dip-and-plateau pattern in diastole emerges. (From Sisson D, Thomas WP: Pericardial diseases and cardiac tumors. In Fox PR et al (eds): Textbook of Canine and Feline Cardiology, 2nd ed. Philadelphia, WB Saunders Co, 1999, p 679. With permission.)



Constrictive pericarditis is both rare and difficult to diagnose in small animals. In this disease, a stiff fibrotic pericardium encases the heart. Presenting and clinical signs, thoracic radiographs, and electrocardiography are similar to other causes of chronic tamponade and effusive-constrictive pericarditis. However, echocardiography demonstrates neither pericardial effusion nor right atrial and ventricular collapse. Constrictive pericarditis in dogs can develop as a consequence of any form of chronic pericarditis. However, it appears to occur most frequently as a severe complication of systemic coccidioidomycosis. 1117 1118

Certain echocardiographic findings that are suggestive of constrictive pericarditis have been described in humans. M-mode echocardiography may demonstrate abrupt flattening of mid-to-late diastolic movement of the left ventricular posterior wall, reflecting a sudden decline in diastolic filling. Rapid early closure of the mitral valve may be detected, as well as premature pulmonary valve opening because of increased right-sided diastolic pressure. Several other echocardiographic features have been described including a diastolic septal bounce; mild atrial enlargement and vena cava dilation; and alterations in the flow characteristics in

pulmonary veins, vena cava, hepatic vein, and across the mitral valve. Transthoracic echocardiography may demonstrate a thickened pericardium in severe cases. However, transesophageal echocardiography, magnetic resonance imaging, and computer tomography scanning are superior to transthoracic echocardiography to detect pericardial thickening.[125] None of the echocardiographic or other imaging modalities for the diagnosis of constrictive pericarditis have been evaluated in small animals.

Hemodynamic data obtained by cardiac catheterization are generally necessary to establish a diagnosis of constrictive pericarditis in small animals. Usually elevation and equilibration (or near equilibration) of the diastolic pressures of all cardiac chambers occurs. The right atrial pressure trace is often described as having an *M* or *W* pattern. This pattern arises because the A and V waves are separated by a reduced X descent, whereas the Y descent is prominent (Figure 205-14, *A*). The ventricular pressure trace shows a dip-and-plateau pattern (or "square-root" sign) in diastole. A rapid intravenous fluid infusion may be necessary to fully reveal the characteristic hemodynamic features of constrictive pericarditis (Figure 205-14, *B*).[27,75,125]

Treatment for constrictive pericarditis involves surgical stripping of the fibrotic, fused, and adherent pericardium from the underlying myocardium (epicardial decortication). This technically difficult procedure is associated with high perioperative morbidity and mortality.

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206 CHAPTER • 206 Canine Heartworm Disease

Clarke Atkins

Heartworm infection (HWI) (dirofilariasis), caused by *Dirofilaria immitis,* primarily affects members of the family Canidae. Dirofilariasis is widely distributed, being recognized in northern and southern temperate zones, in the tropics, and in the subtropics. Infections are recognized in most of the United States, although the distribution favors the Southeast and Mississippi River Valley (Figure 206-1). In some endemic areas in the United States, infection rates approach 45%, and in some hyperendemic tropical regions, virtually all dogs are infected. Dirofilariasis is generally infrequent in Canada. A recent survey of veterinarians indicated that in 2001 there were approximately 240,000 cases diagnosed in the United States.[1]

Species known to have been infected with *D. immitis* include the domestic dog, wolves, foxes, coyotes, domestic cats, ferrets, muskrats, sea lions, nondomestic cats, coatimundi, and humans. The species of greatest interest to the practicing veterinarian include the dog and domestic cat. Because the consequences, treatment, and prognoses differ between the two species, clinical aspects of canine and feline heartworm disease (HWD) will be discussed separately.

When HWI is severe or prolonged, it may result in the pathologic process, called *HWD*. HWD may vary from asymptomatic (radiographic lesions only) to severe, life-threatening, chronic pulmonary artery, lung, and cardiac disease. In chronic HWI, glomerulonephritis, anemia, and thrombocytopenia may also be recognized. Severe dirofilariasis may, in addition, produce acute and fulminant multisystemic presentations, such as caval syndrome (CS) and disseminated intravascular coagulation (DIC).

206.1 LIFE CYCLE

D. immitis is transmitted by over sixty species of mosquitoes, although important mosquito vectors probably number less than 12. Understanding the complex life cycle of *D. immitis* is imperative for veterinary practitioners in heartworm endemic areas (Figure 206-2). Adult heartworms (L5) reside in the pulmonary arteries and, to a lesser extent in heavy infections, the right ventricle. After mating, microfilariae (L1) are produced by mature adult female heartworms (L5) and are released into the circulation. These L1 are ingested by feeding female mosquitoes and undergo two moults (L1 to L2 to L3) over an 8-to 17-day period. It is important to note that this process is temperature dependent; in times of the year when insufficient numbers of days occur in which the ambient temperature is adequate, moulting in the mosquito does not occur during the lifetime of the female mosquito and transmission cannot occur.[2,3] The resultant L3 is infective and is transmitted by the feeding mosquito to the original or another host, most often a male dog. Another moult occurs in the subcutaneous, adipose, and skeletal muscular tissues shortly after infection (1 to 12 days), with a final moult to L5 3 months (50 to 68 days) after infection. This immature adult (1 to 2 cm in length) soon enters the vascular system, migrating to the heart and lungs, where final maturation (mature male adults range from 15 to 18 cm and females from 25 to 30 cm) and mating occur. Under optimum conditions, completion of the life cycle takes 184 to 210 days. The canine host typically becomes microfilaremic 6 to 7 months after infection. Microfilariae (L1), which are variably present in infected dogs, show both seasonal and diurnal periodicity, with greatest numbers appearing in the peripheral blood during the evening hours and during the summer. Adult heartworms in dogs are known to live up to 5 years and microfilariae up to 30 months. Dillon has recently emphasized that the disease process in HWD begins with the moult to L5 (as soon as 2 to 3 months postinfection), at which time immature adults (L5) enter the vascular system, initiating vascular and possibly lung disease, with eosinophilia and eosinophilic

infiltrates and signs of respiratory disease.[4] It is important to note that this antedates the profession's current ability to diagnose HWI.

Figure 206-1 American Heartworm Society map, demonstrating relative prevalence of heartworm infection (HWI) in the United States and Canada in 1998. (From Seward L [ed]: Proceedings of the American Heartworm Symposium '98. Batavia, Ill., The American Heartworm Society, 1990.)

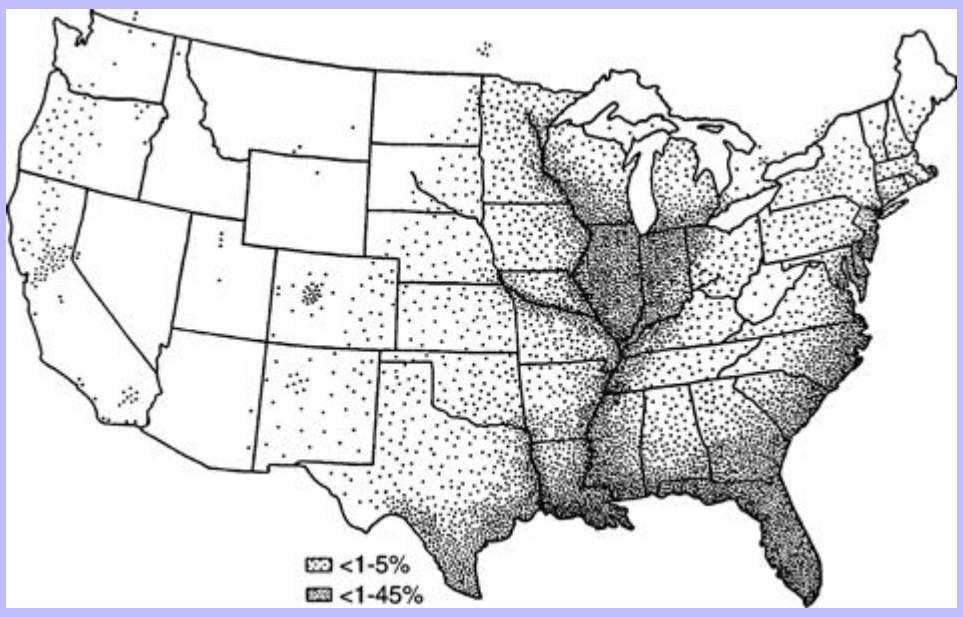
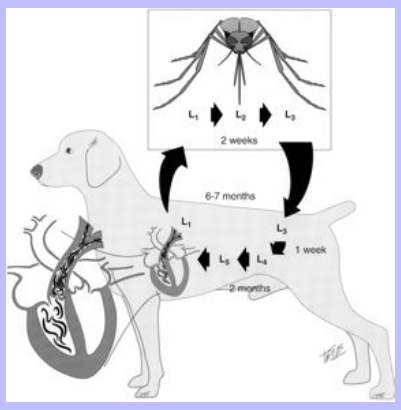


Figure 206-2 Life cycle of *Dirofilaria immitis* in the dog. (From Atkins CE: Heartworm disease. *In* Allen DG [ed]: Small Animal Medicine. Philadelphia, JB Lippincott Co, 1991, pp 341–363.)



206.2 PATHOPHYSIOLOGY

Heartworm is a misnomer because the adult actually resides in the pulmonary arterial system for the most part, and the primary insult to the health of the host is a manifestation of damage to the pulmonary arteries and lung. The severity of the lesions and hence clinical ramifications are related to the relative number of worms (ranging from one to over 250), the duration of infection, and the host and parasite interaction. Immature and mature adult heartworms reside primarily in the caudal pulmonary vascular tree, occasionally migrating into the main pulmonary arteries, the right heart, and even the great veins in heavy infections.

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Obstruction of pulmonary vessels by living worms is of little clinical significance, unless worm burdens are extremely high. The major effect on the pulmonary arteries is produced by worm-induced (toxic substances, immune mechanisms, and trauma) villous myointimal proliferation, inflammation, pulmonary hypertension (PHT), disruption of vascular integrity, and fibrosis. This may be complicated by arterial obstruction and vasoconstriction caused by dead worm thromboemboli and their products. Pulmonary vascular lesions begin to develop within days of worm arrival (as early as 3 months postinfection), with endothelial damage and sloughing, villous proliferation, and activation and attraction of leucocytes and platelets. The immigration of such cells and the release of trophic factors induce smooth muscle cell proliferation and migration with collagen accumulation and eventual fibrosis. Proliferative lesions eventually encroach upon and even occlude vascular lumina. Endothelial swelling with altered intracellular junctions increases the permeability of the pulmonary vasculature. Worms, which have died naturally or have been killed, elicit an even more severe reaction, inciting thrombosis, granulomatous inflammation, and rugous villous inflammation. Grossly, the pulmonary arteries are enlarged, thick-walled, and tortuous, with roughened endothelial surfaces. These changes are only partially reversible.[5]

Although the role of exercise in exacerbation of the signs of thromboembolic HWD is accepted, its role in the development of pulmonary vascular disease and PHT is less clear. Although Rawlings[6] was unable to show an effect of 2.5 months' controlled treadmill exercise on PHT in heavily infected dogs, Dillon[7] showed more severe PHT in lightly infected, mildly exercised dogs than in more heavily infected but unexercised dogs receiving no exercise at 6 months postinfection.

Diseased pulmonary arteries are thrombosed, thickened, dilated, tortuous, noncompliant, and functionally incompetent, thereby resisting recruitment during increased demand; hence exercise capacity is diminished. Vessels to the caudal lung lobes are most severely affected. Pulmonary vasoconstriction results secondary to vasoactive substances released from heartworms. Furthermore, hypoxia (induced by ventilation-perfusion mismatching secondary to eosinophilic pneumonitis, pulmonary consolidation, or both), further contributes to vasoconstriction. The result is PHT and compromised cardiac output.[8] Pulmonary hypertension is exacerbated with exercise or other states of increased cardiac output. The right heart, which is an efficient volume pump but does not withstand pressure overload, first compensates by eccentric hypertrophy *(dilatation and wall thickening)* and, in severe infections, ultimately decompensation (right heart failure). In addition, hemodynamic stresses, geometric changes, and cardiac remodeling may contribute to secondary tricuspid insufficiency, thereby complicating or precipitating cardiac decompensation. Pulmonary infarction is uncommon because of the extensive collateral circulation provided the lung and because of the gradual nature of vascular occlusion. Because of increased pulmonary vascular permeability, perivascular edema may develop. Although, along with an inflammatory infiltrate, this may be evident radiographically as increased interstitial and even alveolar density, in and of itself, it is seemingly of minimal clinical significance and does not indicate left heart failure (in other words, furosemide is not indicated).

Spontaneous or postadulticidal thromboembolization (PTE) with dead worms may precipitate or worsen clinical signs, producing or aggravating PHT, right heart failure or, in rare instances, pulmonary infarction. Dying and disintegrating worms worsen vascular damage and enhance coagulation. Pulmonary blood flow is further compromised and consolidation of affected lung lobes may occur. With acute and massive worm death, this insult may be profound, particularly if associated with exercise. Exacerbation by exercise likely reflects increased pulmonary artery flow with escape of inflammatory mediators into the lung parenchyma through badly damaged and permeable pulmonary arteries (see Figure 207-7). Dillon has suggested that the lung injury is similar to that seen in adult respiratory distress syndrome (ARDS).[4]

Pulmonary parenchymal lesions also result by mechanisms other than post-thromboembolic consolidation. Eosinophilic pneumonitis is most often reported in true occult HWD, when immune-mediated destruction of microfilariae in the pulmonary microcirculation produces amicrofilaremia. This syndrome results when antibody-coated microfilariae, entrapped in the pulmonary circulation, incite an inflammatory reaction (eosinophilic pneumonitis).[9] A more sinister but uncommon form of parenchymal lung disease, termed *pulmonary eosinophilic granulomatosis*, has been associated with HWD. The exact cause and pathogenesis are unknown, but it is felt to be similar to HWD-related allergic pneumonitis.[10] It is postulated that microfilariae trapped in the lungs are surrounded by neutrophils and eosinophils, eventually forming granulomas and associated bronchial lymphadenopathy.

Antigen-antibody complexes, formed in response to heartworm antigens, commonly produce glomerulonephritis in heartworm-infected dogs.[11] The result is proteinuria (albuminuria) but uncommonly renal failure. Heartworms may also produce disease by aberrant migration. This uncommon phenomenon has been associated with neuromuscular and ocular manifestations, because worms have been described in tissues such as muscle, brain, spinal cord, and anterior chamber of the eye. In addition, arterial thrombosis with L5 has been observed when worms migrate aberrantly to the aortic bifurcation or more distally in the digital arteries.[12] Adult heartworms may also migrate in a retrograde manner from the pulmonary arteries to the right heart and venae cavae, producing CS, a devastating process, described following.[13]

206.3 CLINICAL SIGNS

The clinical signs of chronic HWD depend on the severity and duration of infection and, in most chronic cases, reflect the effects of the parasite on the pulmonary arteries and lungs, and secondarily, the heart. It is important to point out that the vast majority of dogs with HWI are asymptomatic. Historical findings in affected dogs variably include weight loss, diminished exercise tolerance, lethargy, poor condition, cough, dyspnea, syncope, and abdominal distension (ascites). Physical examination may reveal evidence of weight loss, split second heart sound (13%), right-sided heart murmur of tricuspid insufficiency (13%), and cardiac gallop.[14] If right heart failure is present, jugular venous distension and pulsation typically accompanies hepatosplenomegaly and ascites. Cardiac arrhythmias and conduction disturbances are uncommon in chronic HWD (<10%). With pulmonary parenchymal manifestations of HWD, cough and pulmonary crackles may be noted and, with granulomatosis (a rare occurrence), muffled lung sounds, dyspnea, and cyanosis are also reported. When massive pulmonary thromboembolization occurs, the additional signs of fever and hemoptysis may be noted.

206.4 DIAGNOSIS

206.4.1 Microfilarial Detection

Ideally the diagnosis is made by routine evaluation prior to the onset of symptoms (i.e., HWD). Dogs in areas in which heartworms are endemic should undergo a heartworm test yearly, particularly if on no heartworm preventative or if diethylcarbamazine is used (see discussion of controversies, following). This was accomplished most commonly in the past by the microscopic identification of microfilariae on a direct blood smear, above the buffy coat in a microhematocrit tube, using the modified Knott test, or after millipore filtration. The accuracy of these tests, typically used for routine screening and for the diagnosis of suspected HWI, is improved by multiple testing. The modified Knott test and millipore filtration are more sensitive because they concentrate microfilariae, improving chances of diagnosis. The direct smear technique allows examination of larval motion, helping in the distinction of *D. immitis* from *Dipetalonema reconditum* (now termed *Acanthocheilonema reconditum*); other useful diagnostic criteria are included in Table 206-1. This distinction is important because the presence of the latter parasite does not require expensive and potentially harmful arsenical therapy, as does *D. immitis*. None of these tests can rule out HWI conclusively because of the potential for amicrofialremic infections (5% to 67%) and the fact that false-negative results may occur, particularly if microfilarial numbers are small, a small amount of blood is collected, or direct smears are relied upon. The number of circulating microfilariae in the peripheral blood do not correlate well with the number of adult heartworms and therefore cannot be used to determine the severity of infection. In the most practices, microfilarial testing has been largely supplanted by (or supplemented with) immunodiagnositic antigen testing (i.e., enzyme-linked immunosorbent assay [ELISA]). The modified Knott test should always be performed, however, in antigen-positive dogs to determine microfilarial status and in instances when owners continue to use diethylcarbamazine as a preventative. Some veterinarians choose to combine the antigen and microfilarial tests. This practice is most useful in dogs receiving diethylcarbamazine or no preventative (macrolides typically render the dog amicrofilaremic). Up to 1% of infected dogs are microfilaria positive and antigen negative.[15]

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Table • 206-1 Differentiating Characteristics of Dipetalonema Reconditum and Dirofilaria Immitis

	NUMBER IN BLOOD	MOTION	SHAPE	LENGTH (MODIFIED KNOTT TEST)
D. reconditum	Usually few	Progressive	Curved body Blunt head Curved or "buttonhook" tail	263 U (250–288 U)
D. immitis	Usually many	Stationary	Straight body and tail Tapered head	308 U (295–325 U)

Table • 206-2 Commercial Antigen and Antibody Test Kits for Heartworm Diagnosis in Dogs and Cats*

MANUFACTURER	PRODUCT	TEST TYPE	FORMAT	SPECIES	SAMPLE	RUN TIME	STEPS
Heska	Solo Step™ CH	M	IMC	P, S, WB	Canine	10 (WB) 5 (S, P)	1
Heska	Solo Step™ CH Test Strips	M	IMC	P, S	Canine	5	1
Heska	Solo Step™ FH (antibody)	M	IMC	P, S, WB	Feline	10 (WB) 5 (S, P)	1
IDEXX	PetCheck® Heartworm Antigen PF	MW	E	P, S, WB	Canine & feline	20	9 or 10
IDEXX	SNAP™ RT Heartworm Antigen Kit	M	E	P, S, WB	Canine	8	4
IDEXX	SNAP™ 3Dx	M	E	P, S, WB	Canine	8	4
IDEXX	SNAP™ Feline Heartworm Antigen Kit	M	E	P, S, WB	Feline	10	4
Synbiotics	Witness® HW	M	IMC	P, S, WB	Canine	10	4
Synbiotics	Witness® FHW (antibody)	M	IMC	P, S, WB	Feline	10	4
Synbiotics	Assure™ FH (antibody)	W (C)	E	P, S	Feline	15	6
Synbiotics	DiroCHEK® HW	MW	E	P, S	Canine & feline	20	8

M, Membrane; *MW,* microwell; *W,* well; *C,* card; *IMC,* immunochromatographic; *E,* ELISA; *P,* plasma; *S,* serum; *WB,* whole blood.

* Tests listed in alphabetic order by manufacturer.

206.4.2 Immunodiagnostic Tests

In dogs not having received macrolide preventative therapies, the prevalence of amicrofilaremic infections is 5% to 67% (typically 10% to 20%).[16] This may be observed in prepatent (young) infections, in single-sex infections, with immune-mediated destruction of microfilaria, and with drug-induced amicrofilaremia. Dogs receiving macrolide preventatives are typically amicrofilaremic. Hence immunodiagnostic tests (heartworm ELISA antigen tests) are now regularly used for both screening and in cases suspected of having HWI. These tests have rapidly gained popularity because of their high sensitivity and specificity and ease of performance (Table 206-2).[17–20] The weakness of these tests is that they detect antigen from adult female heartworms and hence will produce negative results during the first ~6 (5 to 8) months of any infection, in all-male infections and in infections, with low female worm burdens. In fact, a recent study of the performance of three commercial test kits in detecting low worm burden (<4), naturally acquired infections demonstrated an overall (median for three test kits) sensitivity of 79% and a median specificity of 97%.[21] The sensitivity was relatively low (64%) for infections of only one female worm but improved with increasing female worm burden (median of 85%, 88%, and 89% for two, three, and four female worms, respectively for the three test kits evaluated). Of course with higher worm burdens, better sensitivity is experienced. Nevertheless, despite overall excellent results in detection of small worm burdens, false-negative results do occur (Figure 206-3).[21]

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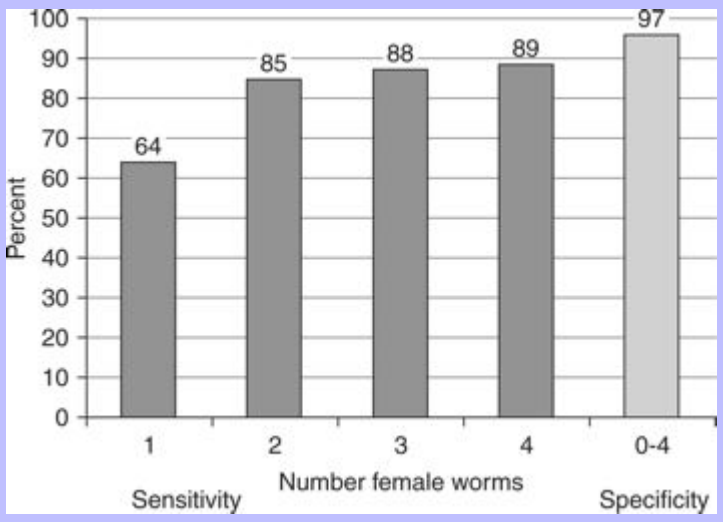
Figure 206-3 Comparison of sensitivity and specificity of three commercial heartworm test kits on known sera from naturally infected dogs with low worm burdens (zero to four adult female heartworms). Black bars represent median sensitivity of the three tests for sera of dogs with one, two, three, and four adult female heartworms. Grey bar represents the median specificity of the three tests for sera from dogs infected with zero to four adult female heartworms. (From Atkins CE: Comparison of results of 3 commercial heartworm antigen tests in dogs with low heartworm burdens. *J Am Vet Med Assoc*, 2003:222, 1221.)



Certain ELISA antigen tests are designed to quantitatively predict worm burdens, based on antigen concentrations. Semiquantitative ELISA (Snap™ Canine Heartworm PF) has been used to successfully predict antigen load and hence approximate worm burden. Rawlings and colleagues[22] have shown this to be useful in predicting thromboembolic complications, with dogs bearing greater worm burdens being more likely to experience such complications after adulticide. This application is most useful, however, in instances of low antigen concentration (suggesting low worm burden), because high antigen concentrations might be recognized when all or most worms are dead, having released a large amount of antigen into the circulation. ELISA technology also allows determination of the efficacy of adulticide therapy. ELISA antigen concentration typically falls to undetectable levels 8 to 12 weeks after successful adulticide therapy, so a positive test persisting beyond 12 weeks post-therapy has been suggested to indicate persistent infection.[23] However, antigen tests may remain positive for longer periods, and this author does not assume a failure in adulticidal therapy unless the antigen test is positive 6 months after adulticidal therapy.

As previously suggested, macrolide therapy with ivermectin, milbemycin oxime, moxidectin, and selamectin results in clearance of microfilaria within 6 to 8 months.[23–25] In addition, embryostasis may be permanent. Thus the use of direct smears, the Knott test, and the millipore filter (microfilarial tests) in dogs receiving

monthly heartworm preventatives (macrolides) is inappropriate. Therefore the only effective testing modality in the ever-increasing number of dogs receiving monthly preventative is the use of antigen assays. A general approach to the diagnosis of HWI is demonstrated in Figure 206-4.

206.4.3 Radiography

Although not an effective screening test for HWI, thoracic radiography offers an excellent method for detecting HWD, for determining its severity, and for evaluating pulmonary parenchymal changes. Radiographic abnormalities, which develop relatively early in the disease course, are present in approximately 85% of cases. According to the study of 200 heartworm-infected dogs by Losonsky and colleagues,[26] radiographic features (Figure 206-5) include right ventricular enlargement (60%), increased prominence of the main pulmonary artery segment (70%), increased size and density of the pulmonary arteries (50%), and pulmonary artery tortuousity and "pruning" (50%). If heart failure is present, enlargement of the caudal vena cava, liver, and spleen, as well as pleural effusion, ascites, or both, may be evident. Thrall and Calvert[27] suggested that pleural effusion is uncommon in heart failure due to HWD, demonstrating that marked enlargement of the cranial lobar pulmonary artery was a more sensitive indicator of HWD-associated heart failure than is enlargement of the caudal vena cava.

Thoracic radiographs obtained in the ventrodorsal projection are preferable for cardiac silhouette evaluation, ease, and often minimizing patient stress. However, the dorsoventral projection is superior for the evaluation of the caudal lobar pulmonary vessels that are considered abnormal if larger than the diameter of the ninth rib where the rib and artery intersect (Figure 206-6). The cranial pulmonary artery is best evaluated in the lateral projection and should normally not be larger than its accompanying vein or the proximal one third of the fourth rib (Figure 206-7).

The pulmonary parenchyma can best be evaluated radiographically. With pneumonitis, the findings include a mixed interstitial to alveolar density, which is typically most severe in the caudal lung lobes (Figure 206-8). In eosinophilic nodular pulmonary granulomatosis, the inflammatory process is arranged into the interstitial nodules, associated with bronchial lymphadenopathy and, occasionally, pleural effusion. With pulmonary thromboembolism, the radiographic findings of coalescing interstitial and alveolar infiltrates, particularly in the caudal lung lobes, reflect the increased pulmonary vascular permeability and inflammation described previously (see Figure 206-13). Consolidation may accompany massive embolization, pulmonary infarction, or both.

206.4.4 Electrocardiography

Electrocardiography is useful in detecting arrhythmias but is generally insensitive in detection of cardiac chamber enlargement in HWD when compared with radiography and echocardiography. If radiography does not suggest HWD, it is unlikely that the electrocardiogram (ECG) will be useful in the absence of arrhythmias. With the exception of CS and heart failure, arrhythmias are rare (2% to 4%).[28] Nevertheless, the finding of a right ventricular enlargement pattern (Chapter 202) is supportive evidence for HWD. Lombard and Ackerman[28] demonstrated that ECG abnormalities were present in 38% to 62% of dogs with moderate and severe echocardiographic changes of HWD, while Calvert and Rawlings[29] found that only 6% of 276 dogs with dirofilariasis had ECG changes of right ventricular enlargement. Calvert and Rawlings[30] also showed that the most sensitive ECG parameters for detection of HWD are lead II S waves deeper than 0.8 mv, mean electrical axis greater than 103 degrees, and greater than three ECG parameters of right heart enlargement.

The latter ECG finding (> three criteria) is considered to be the most accurate. P-pulmonale (tall P waves, indicative of right atrial enlargement) is unusual in HWD.

Figure 206-4 An algorithmic approach to the diagnosis of heartworm infection (HWI) in the dog.

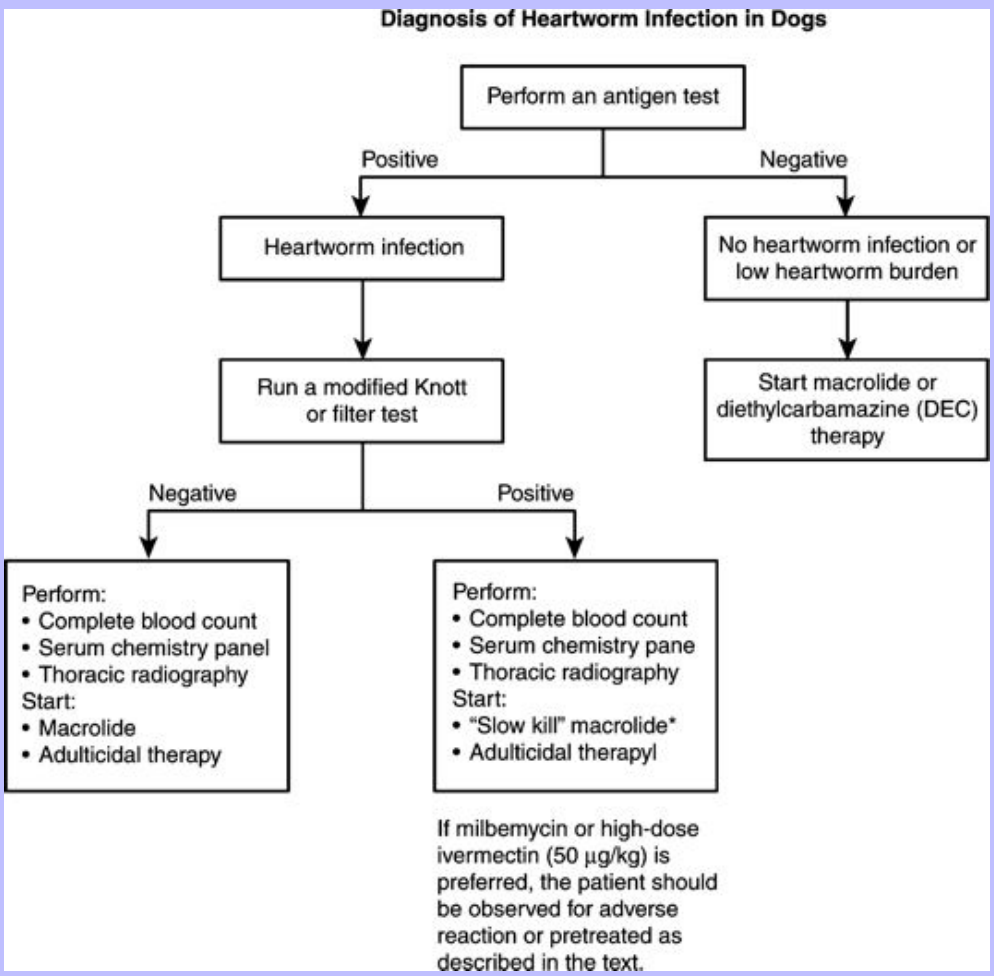


Figure 206-5 The relative frequency of cardiovascular radiographic findings of heartworm disease (HWD). (Losonsky JM, Thrall DE, Lewis RE: Thoracic radiographic abnormalities in 200 dogs with heartworm infestation. *Vet Radiol* 24:120, 1983.)

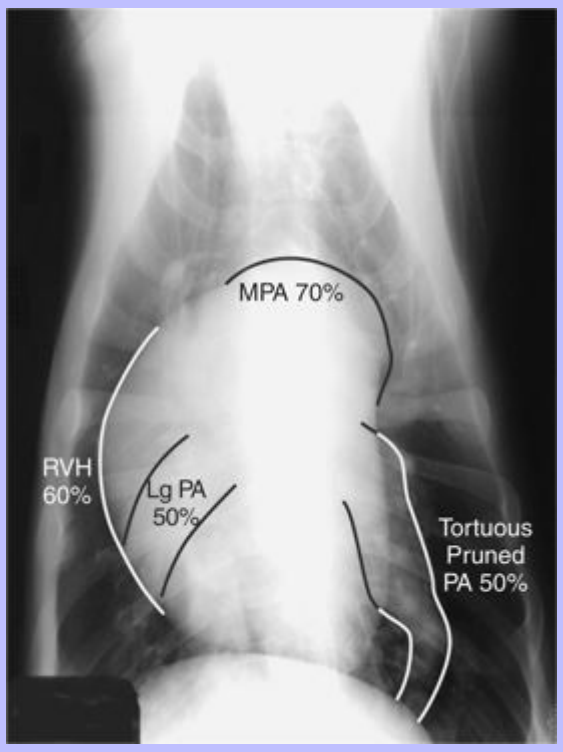


Figure 206-6 Lateral thoracic radiograph obtained from a dog with chronic heartworm disease (HWD). Reader should note right ventricular enlargement (evident in the apex having been lifted from the sternum), enlarged apical pulmonary artery, and an interstitial infiltrate in the caudal lung lobes.

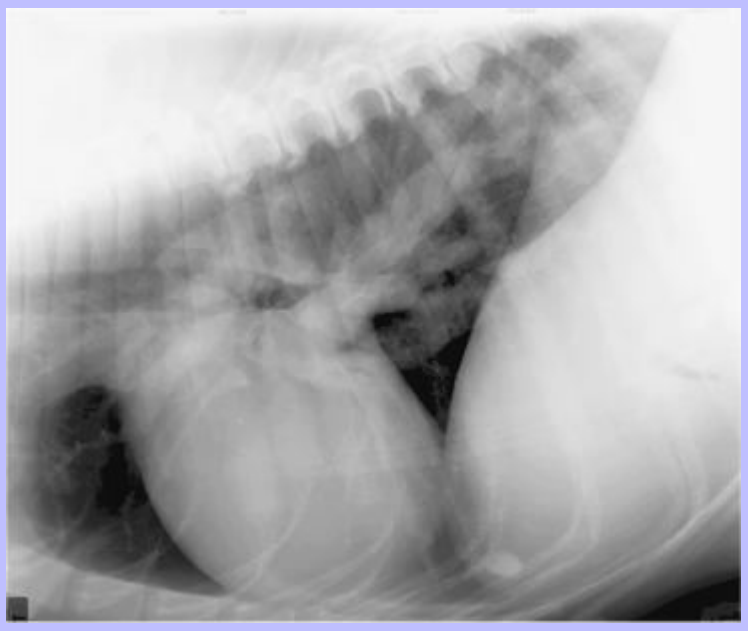


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Figure 206-7 Dorsoventral thoracic radiograph obtained from a dog with chronic heartworm disease (HWD). Reader should note the enlarged main pulmonary artery, right ventricular enlargement, and enlarged, tortuous caudal lobar pulmonary arteries. (See Figure 206-5 for schematic of radiographic abnormalities.)

206.4.5 Echocardiography

Echocardiography is relatively sensitive in the detection of right heart enlargement, because the right ventricular end diastolic dimension and septal and right ventricular free wall thickness are all increased (Figure 206-9). Lombard reported abnormal (paradoxical) septal motion in four of 10 dogs with HWD. The ratio of left to right ventricular internal dimensions is a useful calculation, being reduced from a normal value of 3 to 4 to a mean value of 0.7 in dogs with HWD. In some instances, two-dimensional echocardiography can be used to demonstrate worms in the pulmonary artery (see Chapter 207). Although heartworms can occasionally be demonstrated in the right ventricle, this method is insensitive except in dogs with CS or very heavy worm burdens, because the worms infrequently inhabit this location.[31]

Figure 206-8 Lateral thoracic radiograph obtained from a coughing dog with chronic heartworm disease (HWD). The diffuse interstitial to alveolar infiltrate is severe and represents eosinophilic pneumonitis. Cardiac and pulmonary arterial changes are less severe than seen in Figures 206-6, 206-7, and 206-13.

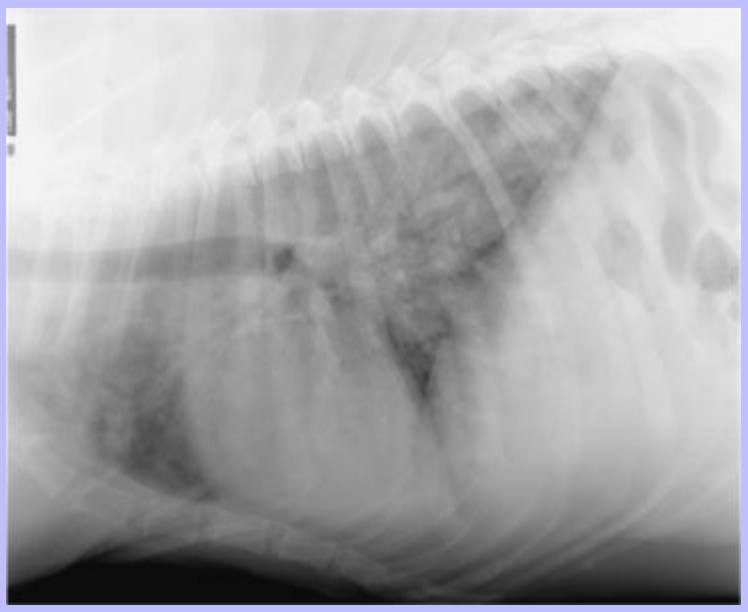
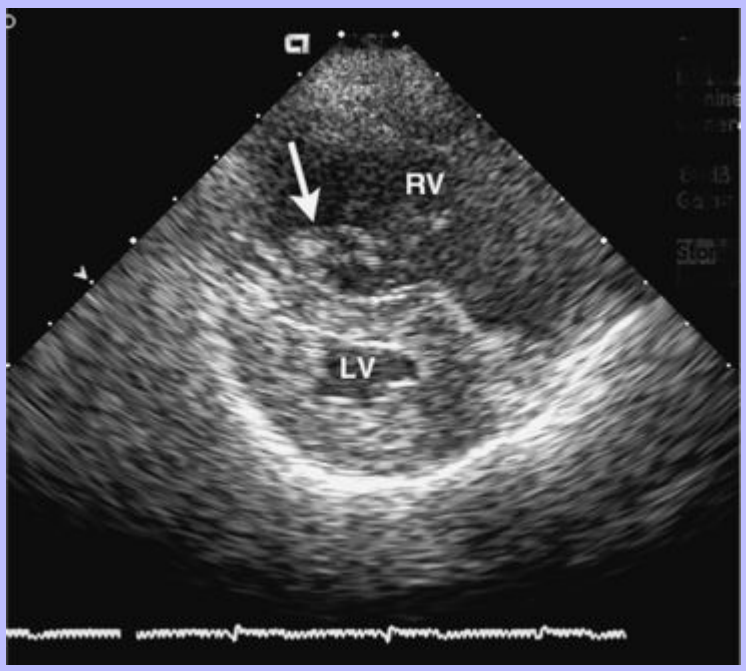


Figure 206-9 A short-axis, two-dimensional echocardiogram obtained from a dog with chronic heartworm disease (HWD). Reader should note the enlarged right ventricular lumen *(RV)* and right ventricular papillary muscle *(arrow)*. The septum is flattened and bows toward the small left ventricle *(LV)*. The electrocardiogram (ECG) at the bottom of the figure demonstrates that this is a diastolic frame.



206.4.6 Clinical Pathology

Hematological and serum chemical abnormalities, although of limited use in making a diagnosis of HWD, are frequently useful in providing supportive evidence and for evaluating concurrent disease processes that may or may not be related to HWD. Calvert and Rawlings[30] report that the dog with HWD in Georgia typically is found to have a low-grade, nonregenerative anemia (present in 10% of mildly to moderately affected dogs and up to 60% of severely affected dogs), neutrophilia (20% to 80% of cases), eosinophilia (~85% of cases), and basophilia (~60% of cases). Thrombocytopenia, which may be noted in chronic HWD, CS, and DIC, is most common 1 to 2 weeks after adulticidal therapy. In severe HWD, especially if heart failure is present, liver enzyme activities may be increased (10% of cases), and occasionally hyperbilirubinemia is noted. Azotemia, seen in only 5% of cases, may be prerenal in origin if dehydration or heart failure are present or may be secondary to glomerulonephritis. In 10% to 30% of cases, albuminuria is noted. If glomerular disease is severe, hypoproteinemia (hypoalbuminemia) has the potential to complicate the clinical picture. Not surprisingly, the most severe clinicopathologic findings are associated with the most severe clinical findings.

Evaluation of tracheobronchial cytology is at times useful, particularly in the coughing dog with eosinophilic pneumonitis, occult HWD, and minimal radiographic evidence of HWD. Microscopic examination reveals evidence of an eosinophilic infiltrate. In microfilaremic dogs, L1 may occasionally be detected in this manner. 1124
Abdominal fluid analysis in cases of congestive heart failure (CHF) typically reveals a modified transudate. 1125
Dogs with HWD and right heart failure have central venous pressure (CVP) that ranges from 12 to more than 20 cm H_2O, but ascites develop at lower CVPs if hypoalbuminemia is present.

206.5 MEDICAL MANAGEMENT

The medical management of HWI is complex because of the complicated parasite life cycle, the marked variability in clinical manifestations and severity of HWD, prophylactic considerations, adulticidal and microfilaricidal considerations, and the relative toxicity and complications associated with adulticidal therapy. For these reasons, the diagnosis, prevention, and treatment of HWI remains a challenge.

206.5.1 Prophylaxis

Prevention of HWI is an obvious and attainable goal for the veterinary profession. Prevention failure results from ignorance on the part of owners as to the presence or potential severity of HWI, lack of owner compliance, or from inadequate instruction on preventative measures by the attending veterinarian.[1,32–34] Studies of owner compliance have revealed that approximately 55% of dog owners that use veterinary care purchase heartworm preventative, and enough medication is dispensed only to meet the needs of approximately 56% of those dogs. Hence the proportion of “cared for” dogs in the population that receive adequate heartworm prophylaxis is less than one third.[33] If one takes into consideration doses purchased but not administered and dogs that are never taken to a veterinarian, the percentage of protected dogs falls drastically. This was emphasized in North Carolina in 1999, when Hurricane Floyd caused extensive flooding and disruption in the poorest part of the state. Of dogs rescued from the floodwaters, 67% were infected with heartworms (personal communication, Dr. Kelli Ferris, North Carolina State University, 2003). In addition, evidence suggests that the veterinary profession is failing in its education of clients. New and colleagues,[35] upon questioning veterinary clients purchasing macrolide preventatives, found that 38% did not realize that their prescribed drug's spectrum was broader than solely preventing HWI.

206.5.2 Diethylcarbamazine

Diethylcarbamazine (DEC), which long enjoyed popularity as the preventative of choice, has now been largely replaced by the safer and more convenient macrolide preventatives. This product is safe (*only* in *amicrofilaremic* dogs) and effective; however, it must be given daily, making owner compliance problematic. Diethylcarbamazine is thought to kill L3 and early L4 tissue migrating larvae but only has a small temporal window of therapeutic efficacy, thus explaining the need for frequent administration. Preventative should be administered daily from the onset of mosquito season, continuously until 1 to 2 months after a killing frost. In some geographic regions, the persistence of mosquitoes dictates yearlong prophylaxis, although this is controversial for much of the United States (see discussion of controversies, following).

Diethylcarbamazine must only be administered to dogs free of microfilariae, thus dictating a yearly heartworm test prior to reinstitution of preventative therapy. Inadvertent administration of diethylcarbamazine to microfilaremic dogs produces an adverse, possibly immune-mediated reaction in approximately 30%.[36] Signs associated with this adverse drug reaction usually occur within 1 hour of medication and include depression,

ptyalism, vomiting, diarrhea, weak pulse, pale mucous membranes with poor capillary refill time, and bradycardia. Subsequently some dogs may become recumbent, dyspneic, and tachycardic, and 18% of reactors succumb. Restated, 6% of microfilaremic dogs to which diethylcarbamazine is administered will die due an adverse reaction.

Not infrequently, owners inadvertently miss one or more doses of DEC preventative. If 1 day of therapy is omitted, no problem exists and drug administration should continue. In the event of a more prolonged lapse in diethylcarbamazine treatment, reinstitution of medication should be advised, with the realization that infection may have occurred during the prophylactic hiatus.

These dogs should be reevaluated in 6 to 7 months to determine if infection has resulted. If a dog is found to be microfilaremic when receiving diethylcarbamazine, prophylaxis should be continued; however, if inadvertently stopped, reinstitution may result in the aforementioned adverse reaction.

206.5.3 Macrolide Antibiotics

The introduction of the macrolide agents (macrocyclic lactones) ivermectin (Heartgard®), milbemycin oxime (Interceptor®), moxidectin (ProHeart® and ProHeart® 6), and selamectin (Revolution™) has provided the veterinary profession with effective heartworm preventatives in a variety of formulations. These agents, because they interrupt larval development during the first 2 months after infection, have a large window of efficacy and are administered monthly or less frequently. Macrolide agents are superior to DEC in convenience. They produce less severe reactions when inadvertently given to microfilaremic dogs, allow a grace period for inadvertent lapses in administration, are more effective with treatment lapses of up to 2 to 3 months when used continuously for the next 12 months,[37] and have a dual role as microfilaricides.[20,37–39] Recently it has been shown that some macrolides have adulticidal activity, if used continuously for prolonged periods.[39–41] (Note: ProHeart® 6 is no longer on the market.)

206.5.4 Ivermectin

Ivermectin, a chemical derivative of avermectin B_1 that is obtained from *Streptomyces* spp., is effective against a range of endo-and ectoparasites and is marketed as a once-monthly heartworm preventative. It is also marketed in a form with pyrantel pamoate to improve efficacy against intestinal parasites (Table 206-3). Macrolides provide a wide window of efficacy and provide some protection when lapses in therapy occur. Ivermectin is effective as a prophylactic with lapses of up to 2 months. Protection is extended, with continuous 12-month administration postexposure, with lapses of 3 months (98% efficacy) and of 4 months (95% efficacy).[37] As stated previously, ivermectin is microfilaricidal at preventative doses (6 to 12 μg/kg/month), resulting in a gradual decline in microfilarial numbers. Despite this gradual microfilarial destruction, generally mild, adverse reactions (transient diarrhea) can occur if administered to microfilaremic dogs.[37] Some breeds (collies and Shetland sheep dogs) are susceptible to ivermectin (and other macrolide) toxicosis at high doses, suffering neurologic signs. This has typically resulted with the use of concentrated livestock preparations, with clinical signs recognized with doses greater than 16 times the recommended dose.[25] For this reason, only preparations designed for pet use should be administered to dogs. When used appropriately, ivermectin is virtually 100% effective in preventing HWI. Additionally, recent studies have shown ivermectin to have partial adulticidal properties when used continuously for 16 months[40] and virtually 100% effective with continuous administration for 30 months.[41] (See discussion of controversies, following.)

206.5.5 Milbemycin

Milbemycin oxime is a member of a family of milbemycin macrolide antibiotics derived from a species of *Streptomyces*. At 500 to 999 µg/kg, it has efficacy against developing filarial larvae, arresting development in the first 6 weeks. It can therefore be given at monthly intervals with a *reachback effect* of 2 months when doses are inadvertently delayed. With 12 months' continuous treatment postexposure, this "safety net" can be extended to 3 months (97% efficacy), falling to 41% with lapses of 4 months.[37] At the preventative dose, milbemycin is a broad-spectrum parasiticide, being also effective against certain hookworms, roundworms, and whipworms (see Table 206-3). In microfilaremic dogs, milbemycin has greater potential for adverse reactions than do other macrolides, because it is a potent microfilaricide at preventative doses.[20] Adverse reactions, similar to those observed with ivermectin at microfilaricidal doses, may be observed in microfilaremic dogs receiving milbemycin at preventative doses.[42] As with microfilaricidal doses (50 µg/kg) of ivermectin, Benadryl (2 mg/kg intramuscularly) and dexamethasone (0.25 mg/kg intravenously) may be administered prior to milbemycin to prevent adverse reactions, particularly in dogs with high microfilarial counts. Milbemycin is also safe for use in collies at the preventative dose. With appropriate use, milbemycin is virtually 100% efficacious as a heartworm prophylactic.

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Table • 206-3 Comparison Clinical Spectrum of Commercially Available Macrolides

DRUG	HW	MICROFILARIAE	ADULTICIDE	HOOKWORMS	WHIPWORMS	ROUNDWORMS	TAPEWORMS	FLEAS & EGGS	TICKS
Ivermectin (chewable)	+	+	+	+*		+*			
Milbemycin (flavored tablet)	+	++		+	+	+		–/+†	
Moxidectin (tablet or injectable)	+	+		+‡					
Selamectin (topical)	+	+	(+)	+				+/+	+

For adulticidal effects, assumes 31 months' continuous therapy for ivermectin and 18 months' continuous therapy for selamectin. *HW*, Heartworm preventative; (), partially effective or incompletely studied.

* Ivermectin/pyrantel pamoate.

† Milbemycin/lufenuron.

‡ Injectable formulation (removed from the market in late 2004).

206.5.6 Moxidectin

The macrolide preventative, moxidectin, has been more recently marketed as a narrow-spectrum heartworm preventative (see Table 206-3) and shown to be safe and virtually 100% effective at 3 µg/kg orally, given monthly or bimonthly up to 2 months postinfection.[43] Moxidectin, at this dose, is gradually microfilaricidal and did not produce adverse reactions in a small number of microfilaremic dogs treated with the prophylactic dose.[38] At 15 µg/kg, 98% reduction in microfilarial numbers was documented 2 months post-treatment.

Lastly, moxidectin appears to be safe in collies.[44] A new liposomal formulation of moxidectin, which provides the potential to improve owner compliance, gives 6 months' protection with one subcutaneous injection. With 12 months' (two injections) continuous treatment, injectable moxidectin is 97% effective at preventing infection after a 4-month lapse in preventative therapy.[45] (This product was removed from the market in late 2004 pending further study.)

206.5.7 Selamectin

Selamectin is a semisynthetic macrolide. It is unique in its broad spectrum and in the fact that it is applied topically once monthly (see Table 206-3). Its efficacy is similar to that of other macrolides (virtually 100%, when used as directed).[46] At 6 to 12 mg/kg topically, this preventative is effective at preventing heartworms infection and kills fleas and flea eggs, sarcoptic mange mites, ticks, and ear mites.[46] Bathing and swimming, as soon as 2 hours after application, does not alter efficacy. Safety has been shown at tenfold topical doses, with oral consumption of single doses and, in ivermectin-sensitive collies, at recommended doses and fivefold overdoses for 3 months.[47] Like other macrolides, selamectin has at least a 2-month *reach-back* effect and with 12 months' continuous administration is 99% protective after 3-month lapses in prophylaxis.[46,48] Selamectin has microfilaricidal activity similar to other macrolides.[48] Chronic, continuous selamectin administration has adulticidal efficacy, although no published data indicate it is as effective in this role as ivermectin.

In summary, the macrolides offer a convenient, effective, and safe method of heartworm prophylaxis with varying spectra and methods of administration (see Table 206-1). They each have microfilaricidal efficacy and render female heartworms sterile. Hence microfilarial tests for HWI cannot be reliably used in dogs receiving these products. Prophylaxis should be commenced at 6 to 8 weeks of age in endemic areas or as soon thereafter as climatic conditions dictate.[19,49] Although safer than DEC in microfilaremic dogs, before first-time administration any dog over 6 months of age and at risk of infection should be tested (antigen test, followed by a microfilaria test, if antigen positive). Additionally, even though protective for at least 8 weeks postexposure, macrolides should be administered precisely as indicated by the manufacturer. If accidental lapses of more than 10 weeks occur, the preventative should be reinstituted at recommended doses and maintained for 12 consecutive months.[25] Macrolides can also be used to “rescue” dogs that have lapsed in their DEC daily therapy for up to 60 to 90 days.[19,49] In the event of a lapse in preventative administration during a time of known exposure risk, an antigen heartworm test should be performed 7 months after the last possible exposure to determine if infection has occurred.

The necessary duration of protection is controversial. The American Heartworm Society indicates that in colder climates, yearlong prevention is not necessary, advocating beginning macrolides within 1 month of the anticipation of transmission season[25] and continuing 1 month beyond the transmission season.[19,49] On the other hand, some experts believe that yearlong prevention should be embraced, regardless of geographic location.[50] This author advocates yearlong prevention, at least below the Mason-Dixon line in North America.

Table • 206-4 Manufacturer's Recommendations for the Use of Melarsomine Dihydrochloride, Based on Patient Status

CLASS 1 HEARTWORM INFECTION (ASYMPTOMATIC, NO RADIOGRAPHIC LESIONS)	CLASS 2 SYMPTOMATIC HEARTWORM DISEASE (MILD TO MODERATE SIGNS)	CLASS 3 SYMPTOMATIC HEARTWORM DISEASE (SEVERE SIGNS)	CLASS 4 CAVAL SYNDROME
Two doses melarsomine 24 hours apart (2.5 mg/kg IM)	Two doses melarsomine 24 hours apart (2.5 mg/kg IM)	One dose melarsomine (2.5 mg/kg IM), followed in approximately 1 month with 2 injections 24 hours apart	Melarsomine not indicated for acute care

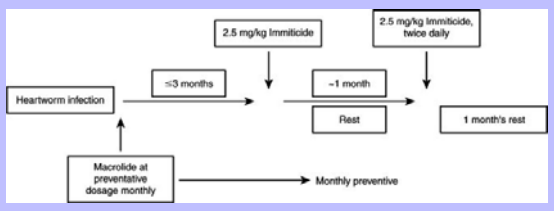
206.6 THERAPY

206.6.1 Melarsomine

In most cases of HWD, it is imperative to rid the patient of the offending parasite. Thiacetarsemide, for decades the only drug approved for this purpose, is no longer available. It has been replaced by melarsomine (Immiticide®), an organoarsenic superior in safety and efficacy to thiacetarsemide.[1] With two doses (2.5 mg/kg intramuscularly every 24 hours), the efficacy is over 96%. Melarsomine has a mean retention time five times longer than thiacetarsemide, and its metabolites are free in the plasma (on which heartworms feed).[51,52] In a study of 382 dogs with HWI receiving melarsomine, none required cessation of therapy due to hepatorenal toxicity (as compared with 15% to 30% with thiacetarsemide), and no case of severe PTE was observed.[53]

Despite the enhanced safety of this product, adverse reactions are still noted.[14,16,54] In fact, successful pharmacologic adulticidal therapy, by definition, dictates thromboembolic events. The clinician can diminish the severity of this complication by restricting exercise after melarsomine administration. Perhaps the drug's biggest asset is the possibility of flexible dosing ("split-dose"—three injections over 1 month or longer), allowing the potential for a safer 50% initial worm kill, followed by subsequent injections to approach 100% efficacy. Studies have shown that patients treated with the split-dose regimen have a higher seroconversion to a negative antigen status than patients treated with either caparsolate or the standard melarsomine dosing regimen.[55,56]

Figure 206-10 An algorithmic approach to the management of heartworm infection (HWI) in the dog. (Atkins CE, Miller M: Is there a better way to administer heartworm adulticidal therapy? *Vet Med*, April 310-317, 2003.)



A split-dose protocol can be used in severely afflicted individuals or in those in which pulmonary thromboembolism is anticipated (Table 206-4). This method allows for destruction of only one half the worms initially (one intramuscular injection of 2.5 mg/kg), thereby lessening the chance for embolic complications. This single dose is followed by a two-dose regimen in 1 to 3 months, if clinical conditions permit. Although the manufacturer recommends this protocol for severely affected dogs, the author uses it for all cases unless financial constraint or underlying concern for arsenic toxicity exists (e.g., pre-existent severe renal or hepatic disease; Figure 206-10).[54] Disadvantages to the split-dose method include additional expense, increased total arsenic dose, and the need for 2 months' exercise restriction.

In 55 dogs with severe HWD that were treated in this manner, 96% had a good or very good outcome with more than 98% negative for antigenemia 90 days post-therapy.[53] Of the 55 severely affected dogs, 31% had "mild or moderate PTE," but no fatalities resulted. The most common sign was fever, cough, and anorexia 5 to 7 days post-treatment. This was associated with mild perivascular caudal lobar pulmonary radiographic densities and subsided spontaneously or after corticosteroid therapy.

206.6.2 Microfilaricidal and Preventative Therapy in Heartworm-Positive Dogs

At the time of diagnosis (usually by a positive heartworm antigen test) a minimum data base is completed. This includes a microfilaria test, chemistry panel, complete blood count (CBC), urinalysis, and thoracic radiographic evaluation. If liver disease is suspected from clinical and laboratory find-ings, serum bile acid evaluation may be useful in evaluating liver function. At this time, monthly macrolide preventative is prescribed (see Figure 206-10). This approach, which differs from the recommendations of the American Heartworm Society, is used to prevent further infection, to eliminate microfilariae (chronic therapy renders the dog of no further risk to infect itself or other dogs and cats), and to destroy developing L4 (not yet susceptible to adulticidal therapy). In microfilaremic dogs, the first macrolide dose is administered in the hospital or at home, with observation, so an adverse reaction might be recognized and treated promptly.

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Corticosteroids with or without antihistamines (dexa-methasone at 0.25 mg/kg intravenously and Benadryl at 2 mg/kg intramuscularly or 1 mg/kg of prednisolone orally 1 hour before +/– 6 hours after administration of the first dose of preventative) may be administered to reduce the potential for adverse reaction in highly microfilaremic patients. It is important to emphasize that adverse reactions are unusual with macrolides at preventative doses.

Depending on the time of year, up to 2 to 3 months might be allowed to lapse before adulticidal therapy is administered. Although monthly macrolide administration prevents further infection, this delay allows larval maturation to adulthood, ensuring that the only stage of the life cycle present is the adult, which is vulnerable to melarsomine therapy. This is more important if the diagnosis is made during or at the end of a mosquito exposure season. If the diagnosis is made in the spring or late winter, when infective larvae have matured, adulticidal therapy may be immediately administered (see Figure 206-10).

206.6.3 Procedure

The first injection of Melarsomine is administered by deep intramuscular injection (2.5 mg/kg) in the lumbar musculature (as described in the package insert) and the injection site recorded. Before injection, the needle is changed and care is taken to inject deep into the muscle and nowhere else. Patients are typically, but not necessarily, hospitalized for the day. The need for exercise restriction for 1 month is emphasized, and sedation is provided if necessary. Owners are also advised as to adverse reactions (fever, local inflammation, lassitude,

inappetence, cough, dyspnea, collapse), to call if they have concerns, and to return for a second series of two injections in approximately 1 month.

If serious systemic reaction results, the second stage of the adulticidal treatment is delayed or, occasionally, even canceled. Typically, however, even with severe reactions, the entire treatment protocol is completed within 2 to 3 months (see Figure 206-10). After a minimum of 1 month, the melarsomine injection procedure is repeated, again with a record of the injection site. If significant local reaction was noted after the first injection, subsequent injections are accompanied by dexamethasone or oral nonsteroidal anti-inflammatory drugs (NSAIDs) to minimize pain at the injection site. The next day (approximately 24 hours after the first injection) the process is repeated with melarsomine injection into the opposite lumbar area. Client instructions are similar to those previously given, with reemphasis of the need for 1 months' strict restriction of exercise. Antigen testing is repeated 6 months after the second series of injections, with a positive test result indicating incomplete adulticidal efficacy. It is emphasized that despite the proven efficacy of melarsomine, not all worms are killed in every patient. The worm burden is typically markedly reduced, but if as few as one to three adult female worms remain, positive antigen tests are likely. Whether to repeat adulticidal therapy, under these circumstances is decided on a case-by-case basis with input from the owners.

206.6.4 Macrolides

It is now known that certain macrolides have adulticidal properties.[39–41] Ivermectin, when administered monthly for 31 consecutive months, has nearly 100% adulticidal efficacy in young HWIs.[41] Selamectin, when administered continuously for 18 months, killed approximately 40% of transplanted worms.[39] Milbemycin and sustained release moxidectin appear to have minimal adulticidal efficacy.[39,40] Although there may be a role for this therapeutic strategy in cases in which financial constraints or concurrent medical problems prohibit melarsomine therapy, the current recommendations are that macrolides not be adapted as the primary adulticidal approach (see discussion of controversies, following).

206.6.5 Exercise Restriction

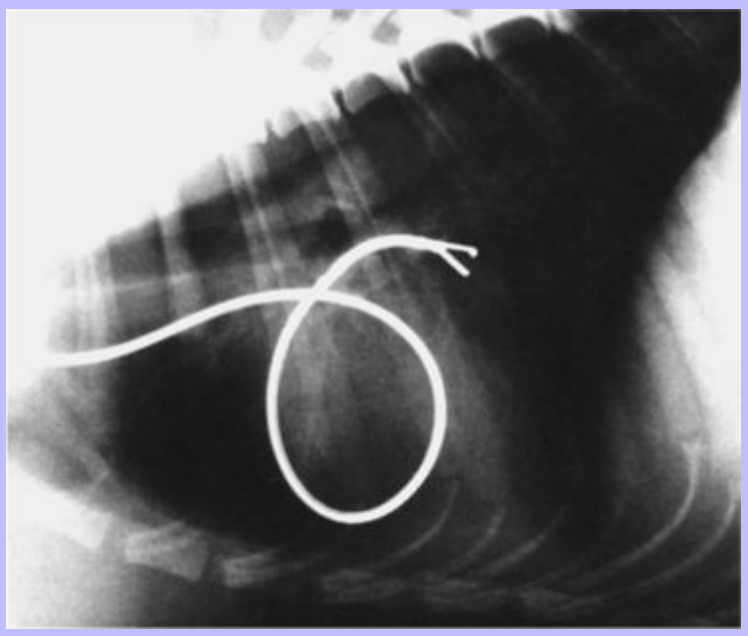
Cage rest is an important aspect of the management of HWD after adulticidal therapy, after PTE, or during therapy of heart failure. This can often be best, or only, accomplished in the veterinary clinic. If financial constraints preclude this, crating or housing in the bathroom or garage at home, tranquilization, or both, with only gentle leash walks are useful alternatives. Nevertheless, some owners do not or cannot restrict exercise, resulting in or worsening thromboembolic complications.

206.6.6 Surgical Therapy

Sasaki, Kitagawa, and Ishihara[57] have described a method of mechanical worm removal using a flexible alligator forceps (Figure 206-11). This method was 90% effective in 36 dogs with mild and severe HWD. Only two of the severely affected dogs (n = 9) died of heart and renal failure over 90 days postoperatively. These data suggest that, in skilled hands, the technique is safe. Subsequent studies by Morini and colleagues[58] demonstrated superior results as compared with melarsomine, producing less PTE and CS. It is important to note that the majority of dogs treated surgically required subsequent melarsomine administration for adequate worm destruction. Advantages to this technique include its diminished potential arsenic toxicity (subsequent adulticidal therapy would be administered to an asymptomatic dog) and relative freedom from thromboembolic complication. Disadvantages include the need for general anesthesia, a degree of operator

skill, fluoroscopy, and subsequent arsenic administration. Nevertheless, it remains a potential alternative for the management of high-risk patients.

Figure 206-11 Heartworm retrieval using the flexible alligator forceps. (From Sasaki Y, Kitagawa H, Ishihara K: Clinical and pathological effects of heartworm removal from the pulmonary arteries using flexible alligator forceps. *In* Otto GF (ed): Proc Amer Heartworm Symposium '89. Batavia, Ill., American Heartworm Society, 1990, p 45.)



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206.7 ANCILLARY THERAPY

206.7.1 Corticosteroids

The anti-inflammatory and immunosuppressive effects inherent to corticosteroids are useful for treatment of some aspects of HWD. Prednisone, the steroid most often advocated, reduces pulmonary arteritis but actually worsens the proliferative vascular lesions of HWD, diminishes pulmonary arterial flow, and reduces the effectiveness of thiacetarsemide. For these reasons, corticosteroids are indicated in HWD only in the face of pulmonary parenchymal complications (eosinophilic pneumonitis, eosinophilic granulomas, and PTE), to treat or prevent adverse reactions to microfilaricides, and possibly to minimize tissue reaction to melarsomine. For allergic pneumonitis, prednisone (1 mg/kg/day) is administered for 3 to 5 days and discontinued or tapered as indicated.[9,16] The response is generally favorable. Prednisone has also been advocated, along with cage rest, for the management of PTE at 1 to 2 mg/kg per day, continued until radiographic and clinical improvement is noted.[16] Because of the potential for steroid-induced fluid retention, such therapy should be used cautiously in the face of heart failure. In addition, caution is warranted because early studies demonstrated that

postadulticidal corticosteroid therapy reduced pulmonary blood flow and worsened intimal disease in a model of HWI[59]; corticosteroids are also procoagulant.[16] As mentioned with adulticidal (previously discussed) and microfilaricidal (discussed following) therapies, corticosteroids may be used to minimize potential adverse reactions to melarsomine and to macrolides given to rapidly kill microfilariae.

206.7.2 Aspirin

Antithrombotic agents have received a good deal of attention in the management of HWD.[59–63] Potential benefits include reduction in severity of vascular lesions, reduction in thromboxane-induced pulmonary arterial vasoconstriction and PHT, and minimization of postadulticidal PTE.[61] Aspirin has shown success in diminishing the vascular damage caused by segments of dead worms,[61] reduced the extent and severity of myointimal proliferation caused by implanted living worms,[62] and improved pulmonary parenchymal disease and intimal proliferation in dogs receiving thiacetarsemide after previous living heartworm implantation.[59] More recent studies, however, have produced controversial results. Four dogs with implanted heartworms, receiving adulticide and administered aspirin, showed no improvement in pulmonary angiographic lesions, and treated dogs had more severe tortuousity than did controls and dogs receiving heparin.[60] Boudreau and colleagues[63] demonstrated that the aspirin dose required to decrease platelet reactivity by at least 50% was increased by nearly 70% with HWI (implantation model) and by nearly 200% with a model (dead worm implantation) of PTE. There were not significant differences in severity of pulmonary vascular lesions in aspirin-treated versus control dogs. For these reasons, the American Heartworm Society does not endorse antithrombotic therapy for routine treatment of HWD.[20] Calvert and colleagues[16] have, however, successfully used the combination of aspirin and strict cage confinement with adulticidal therapy for severe HWD.

If used, aspirin is administered daily beginning 1 to 3 weeks prior to and continued for 4 to 6 weeks after adulticide administration. With protracted aspirin therapy, packed cell volume (PCV) and serum total protein, should be monitored periodically. Aspirin is avoided or discontinued in the face of gastro-intestinal (GI) bleeding (melena or falling PCV), persistent emesis, thrombocytopenia (50,000/mm^3), and hemoptysis.[16]

206.7.3 Heparin Therapy

Low-dose calcium heparin has been studied in canine HWD and shown to reduce the adverse reactions associated with thiacetarsemide in dogs with severe clinical signs, including heart failure.[64] In this study, calcium heparin administered at 50 to 100 IU/kg subcutaneously every 8 to 12 hours for 1 to 2 weeks before and 3 to 6 weeks after adulticidal therapy, reduced thromboembolic complications and improved survival, as compared with aspirin and indobufen. Dogs in both groups also received prednisone at 1 mg/kg/day. It is emphasized that this therapy has not been studied with melarsomine adulticidal therapy. Calvert and colleagues[16] advocate sodium heparin (50 to 70 U/kg) in dogs with thrombocytopenia, DIC, or both, continuing until the platelet count is greater than 150,000/mm^3, for at least 7 days, and possibly for weeks.

206.7.4 Microfilaricidal Therapy

Despite the fact that no agent is approved by the Food and Drug Administration for the elimination of microfilaria, microfilaricidal therapy is traditionally instituted 4 to 6 weeks after adulticide administration.[16] The macrolides offer a safe and effective alternative to levamisole and dithiazanine. Microfilariae are rapidly

cleared with ivermectin at 50 µg/kg (approximately eight times preventative dose) or milbemycin at 500 mg/kg (preventative dose), although this represents an extra-label use of ivermectin. Adverse reactions, the severity of which is likely related to microfilarial numbers, were observed in 6% of 126 dogs receiving ivermectin at the microfilaricidal dose.[65] Signs included shock, depression, hypothermia, and vomiting. With fluid and corticosteroid (dexamethasone at 2 to 4 mg/kg intravenously) therapy, all dogs recovered within 12 hours. One fatality, however, was observed 4 days after microfilaricidal therapy. Similar findings and frequency have been reported with milbemycin at the preventative dose.[38] Dogs so treated should be hospitalized and carefully observed for the day. Dogs less than 16 kg, harboring more than 10,000 microfilaria per milliliter of blood, are more apt to suffer adverse reactions.[61] Benadryl (2 mg/kg intramuscularly) and dexamethasone (0.25 mg/kg intravenously) can be administered prophylactically to prevent adverse reactions to microfilaricidal doses of macrolides.

A slower microfilarial kill rate can also be achieved with ivermectin, moxidectin, and selamectin at preventative doses.[23,38,39,66] Using either the rapid or "slow kill" approach rids the patient of microfilariae and sterilizes the female heartworm.

The American Heartworm Society recommends that macrolide therapy, at preventative doses, be instituted 3 to 4 weeks after adulticidal therapy.[25] Accelerated microfilarial destruction can be achieved using recommended doses of milbemycin or by reducing the dosing interval for the other topical or oral formulations to every 2 weeks. Filter or modified Knott tests are rechecked in 5 months when using a slow kill or after 2 to 3 macrolide doses when using a accelerated dose.[25] This interval for testing can be reduced if milbemycin or high-dose ivermectin (50 µg/kg) is chosen.

This author chooses an alternative approach (see Figures 206-4 and 206-10), beginning the administration of a macrolide preventative at the time of diagnosis, often days to weeks prior to adulticidal therapy. With the slow kill microfilaricides (ivermectin, moxidectin, or selamectin at preventative doses), little chance exists of an adverse reaction; however, the owner is warned of the possibility and advised to administer the medication on a day when he or she will be at home. If milbemycin is used, it is usually administered in the hospital and may be preceded by administration of dexamethasone and Benadryl (as described previously in adulticidal therapy).

206.8 COMPLICATIONS AND SPECIFIC SYNDROMES

206.8.1 Asymptomatic Heartworm Infection

Most dogs with HWI are asymptomatic, even though many of these have HWD (radiographic and pathologic lesions). Treatment is as described previously, using melarsomine in the split-dose regimen, along with a macrolide preventative. 1129 1130

Asymptomatic dogs may, however, become symptomatic after adulticidal therapy due to PTE and lung injury (as described elsewhere). The risk of PTE can be imperfectly predicted by semiquantitation of the worm burden, using certain antigen tests, and by the severity of radiographic lesions.[22] Clearly a dog with severe radiographic lesions will not tolerate thromboembolic complications well, but not all dogs with radiographic signs have heavy worm burdens. For example, a dog with moderate to severe radiographic lesions and high antigenemia may not be at high risk for postadulticidal PTE, because it is quite possible that the worms have died, explaining both the antigenemia (release from dead worms) and radiographic abnormalities (chronic HWD). This conclusion might also be valid in the dogs with severe radiographic lesions and negative or low antigenemia (assumes most or all worms have died, and antigen has been cleared). Alternatively, antigenic

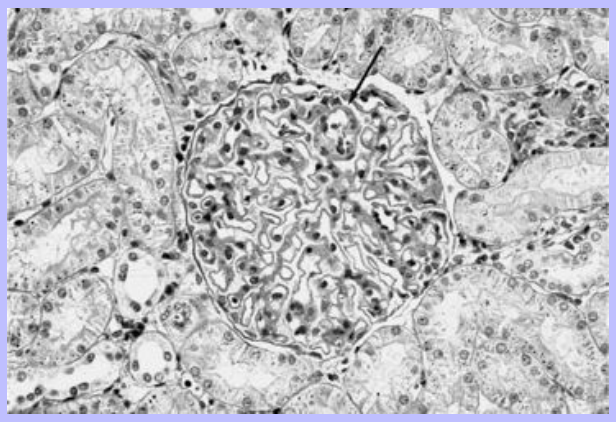
evidence of a heavy worm burden in a dog with minimal radiographic signs might still portend a severe reaction after melarsomine, because the findings suggest large worm numbers but without natural worm attrition (i.e., a relatively young infection with minimal disease). Of course, low worm burden and minimal radiographic lesions would suggest the least risk of an adverse reaction to adulticide.

It bears emphasis that with each scenario, guesswork is involved and precautions should be taken. When the risk is greatest, aspirin (5 to 7 mg/kg daily—begun 3 weeks prior to and continued until 3 weeks after adulticide) or even heparin may be used,[16] and cage confinement is most important. The owners should be educated as to the risk, the suggestive signs, and the importance of prompt veterinary assistance in case of an adverse reaction.

206.8.2 Glomerulonephritis

The majority of dogs suffering from chronic HWI have glomerulonephritis, which can be severe (Figure 206-12).[11] Therefore when a dog demonstrates glomerular disease, HWI should be considered as a differential diagnosis. Although it is generally felt that the glomerular lesions produced by HWI are unlikely to produce renal failure, a therapeutic dilemma results when one is found in a dog with proteinuria, azotemia, and HWI. Logic suggests that adulticidal therapy is indicated because HWI contributes to glomerular disease, but it likewise carries risks. The approach embraced by this author is to hospitalize the patient and to administer intravenous fluids (lactated Ringer's solution at 2 to 3 mL/kg/hr) for 48 hours (beginning 12 hours prior to the first melarsomine dose). The patient is then released, and a recheck appointment for blood urea nitrogen (BUN) and creatinine determination after 48 hours is advised. The second and third injections are tentatively scheduled for 1 to 3 months, with the treatment decision based on renal function and the overall response to initial adulticidal therapy.

Figure 206-12 An H&E stained, 3 µm section of a glomerulus from a dog with chronic heartworm disease (HWD) and resultant membranoproliferative glomerulonephritis. The capillary walls are thickened, and an overall increase in cellularity is seen. The reader should note a thick-walled capillary containing intraluminal microfilariae. (Photograph courtesy Dr. Greg Grauer.)



206.8.3 Allergic Pneumonitis

Allergic pneumonitis, which is reported to affect 14% of dogs with HWD, is a relatively early development in the disease course.[9,16] In fact, the pathogenesis probably involves immunologic reaction to dying microfilariae in the pulmonary capillaries. Clinical signs include cough and sometimes dyspnea and other typical signs of HWD, such as weight loss and exercise intolerance. Specific physical examination findings may be absent or may include dyspnea and audible crackles in more severe cases. Radiographic findings include those typical of HWD but with an infiltrate, usually interstitial, but occasionally with an alveolar component, often worse in the caudal lung lobes (see Figure 206-8). Eosinophils and basophils may be found in excess in peripheral blood and in airway samples.

Corticosteroid therapy (prednisone or prednisolone at 1 to 2 mg/kg per day) results in rapid attenuation of clinical signs, with radiographic clearing in less than a week. The dose can then be stopped in 3 to 5 days if clinical signs subside. Although microfilaricidal therapy is typically not indicated because infections are often occult, macrolide prophylaxis is indicated to avoid further infection. Adulticidal therapy can be used after clinical improvement.

206.8.4 Eosinophilic Granulomatosis

A more serious, but rare, manifestation, pulmonary eosinophilic granulomatosis, responds less favorably. This syndrome is characterized by a more organized, nodular inflammatory process, associated with bronchial lymphadenopathy and, occasionally, pleural effusion. With pulmonary granulomatosis, cough, wheezes, and pulmonary crackles are often audible; when very severe, lung sounds may be muffled and associated with dyspnea and cyanosis. Treatment with prednisone at twice the dose for allergic pneumonitis is reported to induce partial or complete remission in 1 to 2 weeks. The prognosis remains guarded because recurrence within several weeks is common. Prednisone may be combined with cyclophosphamide or azathioprine in an effort to heighten the immunosuppressive effect. The latter combination appears to be the most effective. Adulticide therapy should be delayed until remission is attained. As the prognosis for medical success is guarded; surgical excision of lobar lesions has been advocated.[67]

206.8.5 Pulmonary Embolization

Spontaneous thrombosis or PTE associated with dead and dying worms—the most important heartworm complication—may precipitate or worsen clinical signs, producing or aggravating PHT, right heart failure or, in rare instances, hemoptysis and pulmonary infarction. Acute fatalities may result from fulminant respiratory failure, exsanguination, DIC, or may be unexplained and sudden (arrhythmia or massive pulmonary embolism). The most common presentation, however, is a sudden onset of lethargy, anorexia, and cough 7 to 10 days after adulticidal therapy—often after failure to restrict exercise. Dyspnea, fever, mucous membrane pallor, and adventitial lung sounds (crackles) may be noted on physical examination.

Thoracic radiographs (Figure 206-13) reveal significant pulmonary infiltrates, most severe in the caudal lung lobes. The degree of worsening, as compared with pretreatment radiographs, is typically dramatic. The infiltrate, typically alveolar, is most severe in the caudal lobes, and occasionally areas of consolidation are noted. Laboratory abnormalities vary with the severity of signs but may include leukocytosis, left shift, monocytosis, eosinophilia, and thrombocytopenia. The degree thrombocytopenia may provide prognostic information.

Figure 206-13 Lateral thoracic radiograph obtained from a dog with chronic heartworm disease (HWD), postadulticide. The reader should note right ventricular enlargement, enlarged apical pulmonary arteries partially obscured by pulmonary infiltrate, and an interstitial and alveolar infiltrate, most severe in the caudal lung lobes.

Medical management of thromboembolic lung disease is largely empiric and somewhat controversial. It is generally agreed that strict cage confinement, oxygen administration via oxygen cage or nasal insufflation (50 to 100 mL/kg), and prednisone (1 mg/kg/day for 3 to 7 days) are indicated in the most severe cases.[14,16,68] Some advocate careful fluid therapy (see recommendations for CS), measuring CVP to avoid precipitation of heart failure, to maximize tissue perfusion and combat dehydration.[68] The use of heparin (75 IU/kg subcutaneously three times a day until platelet count has normalized [5 to 7 days]) and aspirin (5 to 7 mg/kg/day) has been advocated by some[30] but remains controversial.[4]

Figure 206-14 Adult male Labrador retriever with congestive heart failure (CHF) due to heartworm disease (HWD). The reader should note the distended abdomen (ascites) and cardiac cachexia.

Other therapeutic strategies might include cough suppressants, antibiotics (if fever is unresponsive), and, although speculative at this time, vasodilators (amlodipine, hydralazine, diltiazem; see discussion of heart failure in Chapter 197).[69,70] If vasodilatory therapy is used, one must monitor blood pressure because hypotension is a potential side effect. Clinical improvement may be rapid and release from the hospital considered after several days' treatment. For less severely affected dogs, careful confinement and prednisone at home are often adequate.

206.8.6 Congestive Heart Failure

Right heart failure results from increased right ventricular afterload (secondary to chronic pulmonary arterial disease and thromboemboli with resultant PHT). When severe and chronic, PHT may be complicated by secondary tricuspid regurgitation and right heart failure. Congestive signs (ascites) are worsened in the face of hypoproteinemia (see Figure 206-14). Calvert suggests that up to 50% of dogs with severe pulmonary vascular complication to HWD will develop heart failure.[16] Clinical signs (see Figure 206-13) variably include weight loss, exercise intolerance, ashen mucous membranes with prolonged capillary refill time, ascites, dyspnea, jugular venous distension and pulsation, arrhythmias with pulse deficits, and adventitial lung sounds (crackles and possibly wheezes). Dyspnea may be due to pulmonary infiltrates (PIE or PTE, but not cardiogenic pulmonary edema), abdominal distension, or pleural effusion.

Treatment aims include reduction of signs of congestion, reducing PHT, and increasing cardiac output. This involves dietary, pharmacologic, and procedural interventions. Moderate salt restriction is logical and probably useful in diminishing diuretic needs. This author chooses a diet designed for senior patients or early heart disease, because salt restriction should only be moderate. Diuretics may be useful in preventing recurrence of ascites but are typically not able to mobilize large fluid accumulations effectively. This then requires periodic abdominal or thoracic paracentesis (or both) when discomfort is apparent. Furosemide is

typically used at 1 to 4 mg/kg daily, depending on severity and patient response. Additional diuretics, which provide a supplemental effect by using differing parts of the nephron, include spironolactone (1 to 2 mg/kg orally twice a day) and chlorothiazide (2 mg/kg orally daily to every other day). The ACE-inhibitors (e.g., enalapril, benazepril, lisinopril, ramipril), by their effect on the renin-angiotensin-aldosterone system, may be of use as mixed vasodilators, in blunting pathologic cardiac remodeling, and in reducing fluid retention, particularly cases of refractory ascites. Adulticide therapy is delayed until clinical improvement is noted. No evidence indicates that digoxin improves survival in HWD. Because of the risk of toxicity and pulmonary vasoconstriction associated with its use, it is not routinely used by is author in the management of HWD-induced heart failure. However, digoxin may be beneficial in the presence of supraventricular tachycardia or refractory heart failure. Aspirin, theoretically useful because of its ability to ameliorate some pulmonary vascular lesions and vasoconstriction, may be used 5 mg/kg/day orally.

The arterial vasodilator, hydralazine, has been shown by Lombard[69] to improve cardiac output in a small number of dogs with HWD and heart failure. It has also been demonstrated to reduce pulmonary artery pressure and vascular resistance, right ventricular work, and aortic pressure without changing cardiac output or heart rate in dogs with experimental HWD (but without heart failure).[70] Clinical experience has shown perceived improvement with the vasodilators diltiazem and amlodipine as well. Research and clinical experience suggest that hydralazine, amlodipine, and diltiazem might have a role in this setting, but further studies are necessary to define their role, if any. In heart failure the author uses hydralazine at 0.5 to 2 mg/kg orally twice a day, diltiazem at 0.5 to 1.5 mg/kg orally three times a day, or amlodipine at 0.1 to 0.25 mg/kg/day orally. The risk of hypotension with these therapies must be realized and blood pressure monitored.

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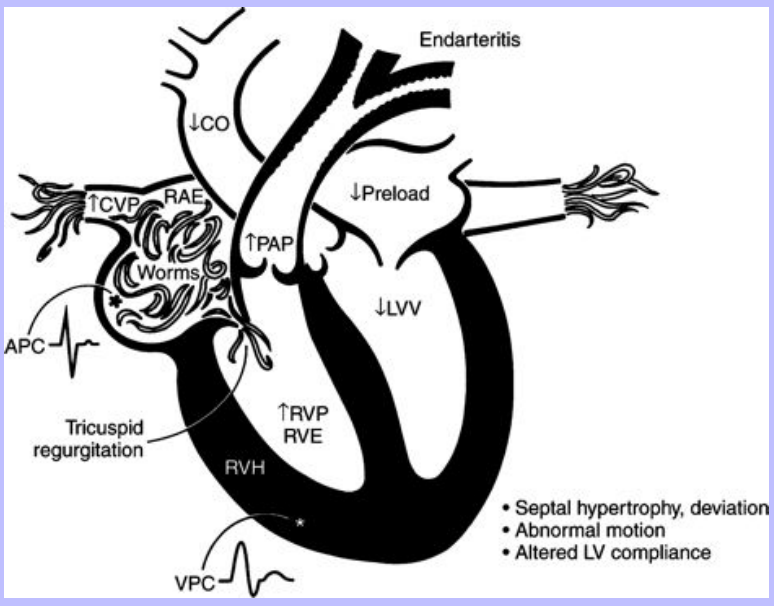
Often heart failure follows adulticidal therapy, but if it is present prior to adulticidal therapy, the difficult question arises as when (or whether) to administer melarsomine. If clinical response to heart failure management is good, adulticidal therapy may be offered in 4 to 12 weeks, as conditions allow. Melarsomine is generally avoided if heart failure is refractory. Antiarrhythmic therapy is seldom necessary, although slowing the ventricular response to atrial fibrillation with digoxin, Diltiazem, or both (see Chapters 197 and 202) may be necessary in some cases.

206.8.7 Caval Syndrome

Heartworm CS is a relatively uncommon but severe variant or complication of HWD. Most studies have shown a marked sex predilection, with 75% to 90% of CS dogs being male. It is characterized by heavy worm burden (usually >60, with the majority of the worms residing in the right atrium and venae cavae) and a poor prognosis.[18]

Studies performed in the author's laboratory indicate that retrograde migration of adult heartworms to the cavae and right atrium, from 5 to 17 months after infection, produces partial inflow obstruction to the right heart and, by interfering with the valve apparatus, tricuspid insufficiency (with resultant systolic murmur, jugular pulse, and CVP increase).[71] Affected dogs also exhibit pre-existent heartworm-induced PHT, which markedly increases the adverse hemodynamic effects of tricuspid regurgitation. These combined effects substantially reduce left ventricular preload and hence cardiac output. Cardiac arrhythmias may further compromise cardiac function (Figure 206-15).

Figure 206-15 Schematic demonstrating pathogenesis of cardiac dysfunction in heartworm caval syndrome (CS). CS complicates chronic heartworm disease (HWD) when retrograde worm migration from the pulmonary arteries occurs, with the majority of worms relocating in the venae cavae and right atrium. Tricuspid valvular function is altered, resulting in incompetence. Tricuspid regurgitation is superimposed on pulmonary hypertension. Left ventricular preload is diminished. Congestive and low-output heart failure ensues. Septal deviation to the left and abnormal, rightward septal motion contributes to preload starvation of the left ventricle. Right ventricular inflow obstruction due to heartworms and cardiac arrhythmias may further contribute to cardiac dysfunction but are probably less important. *CO,* Cardiac output; *PAP,* pulmonary hypertension; *CVP,* central venous pressure; *RAE,* right atrial enlargement; *APC,* atrial premature complex; *VPC,* ventricular premature complex; *RVH,* right ventricular hypertrophy; *RVP,* right ventricular pressure; *RVE,* right ventricular enlargement; *LVV,* left ventricular volume; *Arrows,* increased or decreased. (From Atkins CE: Pathophysiology of heartworm caval syndrome: recent advances. *In* Otto GF: Proc Amer Heartworm Symposium '89. Batavia, Ill., American Heartworm Society, 1990, pp 27–31.)



This constellation of events precipitates a sudden onset of clinical signs, including hemolytic anemia caused by trauma to red blood cells (RBCs) as they pass through a sieve of heartworms occupying the right atrium and venae cavae, as well as through fibrin strands in capillaries if DIC has developed. Intravascular hemolysis, metabolic acidosis, and diminished hepatic function with impaired removal of circulating pro-coagulants contribute to the development of DIC. The effect of this traumatic insult to the erythron is magnified by increased RBC fragility, due to alterations in the RBC membrane in dogs with HWD. Hemoglobinemia, hemoglobinuria, and hepatic and renal dysfunction also are observed in many dogs. The cause of hepatorenal dysfunction is not clear, but it probably results from the combined effects of passive congestion, diminished perfusion, and the deleterious effects of the products of hemolysis. Without treatment, death frequently ensues within 24 to 72 hours due to cardiogenic shock, complicated by anemia, metabolic acidosis, and DIC.

A sudden onset of anorexia, depression, weakness, and occasionally coughing are accompanied in most dogs by dyspnea and hemoglobinuria. Hemoglobinuria has been considered pathognomonic for this syndrome. Physical examination reveals mucous membrane pallor, prolonged capillary refill time, weak pulses, jugular distension and pulsation, hepatosplenomegaly, and dyspnea. Thoracic auscultation may disclose adventitial lung sounds; a systolic heart murmur of tricuspid insufficiency (87% of cases); loud, split S2 (67%); and cardiac gallop (20%). Other reported findings include ascites (29%), jaundice (19%), and hemoptysis (6%). Body temperature varies from subnormal to mildly elevated.[18]

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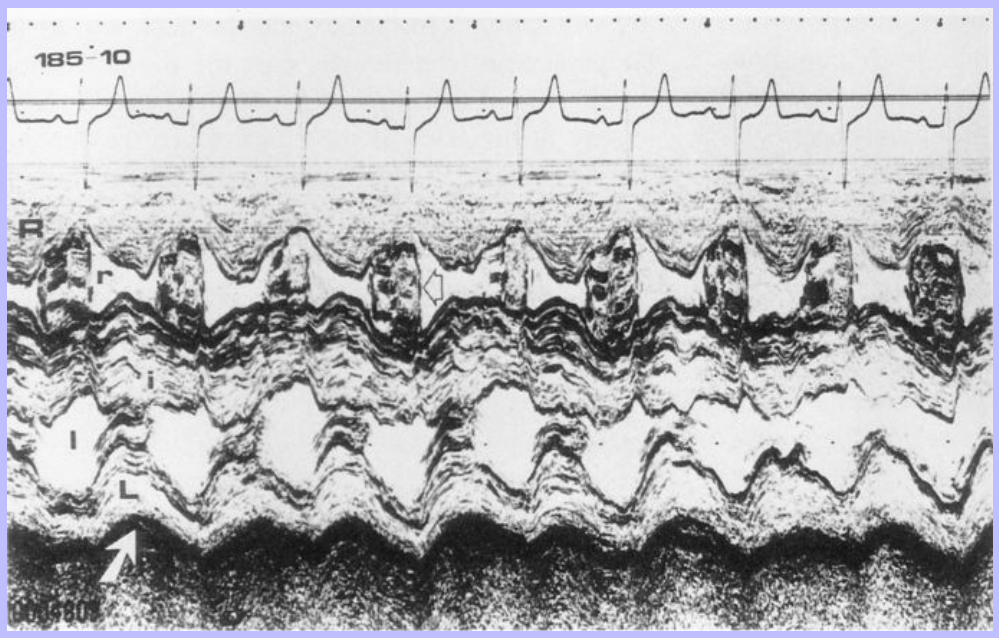
Hemoglobinemia and microfilaremia are present in 85% of dogs suffering from CS.[18] Moderate (mean PCV, 28%) regenerative anemia characterized by the presence of reticulocytes, nucleated RBC, and increased mean corpuscular volume (MCV) is seen in the majority of cases. This normochromic, macrocytic anemia has been associated with the presence of target cells, schistocytes, spur cells, and spherocytes. Leukocytosis (mean white blood cell [WBC] count, approximately 20,000 cells/cm^3) with neutrophilia, eosinophilia, and left shift has been described. Dogs affected with DIC are characterized by the presence of thrombocytopenia and hypofibrinoginemia, as well as prolonged one stage prothrombin time (PT), partial thromboplastin time (PTT), activated coagulation time (ACT), and high fibrin degradation product concentrations. Serum chemistry analysis reveals increases in liver enzymes, bilirubin, and indices of renal function. Urine analysis reveals high bilirubin and protein concentrations in 50% of cases and more frequently, hemoglobinuria.

CVP is high in 80% to 90% of cases (mean, 11.4 cm H_2O). Electrocardiographic abnormalities include sinus tachycardia in 33% of cases and atrial and ventricular premature complexes in 28% and 6%, respectively. The mean electrical axis tends to rotate rightward (mean, +129 degrees), with an S1,2,3 pattern evident in 38% of cases. The S wave depth in CV6LU (V_4) is the most reliable indicator of right ventricular enlargement (>0.8 mv) in 56% of cases. Thoracic radiography reveals signs of severe HWD with cardiomegaly, main pulmonary arterial enlargement, increased pulmonary vascularity, and pulmonary arterial tortuousity recognized in descending order of frequency (see Figures 206-5 to 206-7). Massive worm inhabitation of the right atrium with movement into the right ventricle during diastole is evident echocardiographically. This finding on M-mode and two-dimensional echocardiograms is nearly pathognomonic for CS in the appropriate clinical setting (Figure 206-16). The right ventricular lumen is enlarged and the left diminished in size, suggesting PHT accompanied by reduced left ventricular loading. Paradoxical septal motion, caused by high right ventricular pressure, is commonly observed. No echocardiographic evidence of left ventricular dysfunction exists. Cardiac catheterization documents pulmonary, right atrial, and right ventricular hypertension and reduced cardiac output.

Figure 206-16 An *M*-mode echocardiogram of a dog with recent onset caval syndrome (CS), demonstrating thickening of the right ventricular and intraventricular septal walls, right ventricular eccentric hypertrophy, and a small left ventricle. An echogenic mass *(clear arrow)* of heartworms can be seen "falling" into the right ventricle with each diastole. Paradoxical septal motion is evident. The white arrow denotes the pericardium. *R,* Right ventricular wall; *r,* right ventricular lumen; *i,* intraventricular septum; *l,* left ventricular lumen; *L,* left ventricular posterior wall. (From Atkins CE: Heartworm caval syndrome. Semin Vet Med Surg 2:64–71, 1987.)



Prognosis is poor unless the cause of the crisis—the right atrial and caval heartworms—is removed. Even with this treatment, mortality can approximate 40%.

Fluid therapy is needed to improve cardiac output and tissue perfusion, to prevent or help to reverse DIC, to prevent hemoglobin nephropathy, and to aid in the correction of metabolic acidosis. Overexuberant fluid therapy, however, may worsen or precipitate signs of CHF. In the author's clinic, a left jugular catheter is placed and intravenous fluid therapy instituted with 5% dextrose in water or one-half strength saline and 2.5% dextrose. The catheter should not enter the anterior vena cava because it will interfere with worm embolectomy. A cephalic catheter may be substituted for the somewhat inconvenient jugular catheter, but this does not allow monitoring of CVP. The intravenous infusion rate for fluids is dependent on the condition of the animal. A useful guideline is to infuse as rapidly as possible (up to 1 cardiovascular volume during the first

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hour) without raising the CVP or without raising it above 10 cm H_2O if it was normal or near normal at the outset. Initial therapy should be aggressive (10 to 20 mL/kg/hr for the first hour) if shock is accompanied by a normal CVP (<5 cm H_2O), and it should be curtailed to approximately 1 to 2 mL/kg/hr if CVP is 10 to 20 cm H_2O. Whole blood transfusion is not indicated in most cases because anemia usually is not severe, and transfused coagulation factors may worsen DIC. Sodium bicarbonate is not indicated unless metabolic acidosis is severe (pH, 7.15 to 7.20). Broad-spectrum antibiotics and aspirin (5 mg/kg daily) should be administered. Treatment for DIC is described elsewhere in this text.

The technique for surgical removal of caval and atrial heartworms was developed by Jackson and colleagues.[72] This procedure should be undertaken as early in the course of therapy as is practical. Often, sedation is unnecessary, and the procedure can be accomplished with only local anesthesia. The dog is restrained in left lateral recumbency after surgical clipping and preparation. The jugular vein is isolated distally. A ligature is placed loosely around the cranial aspect of the vein until it is incised, after which the ligature is tied. Alligator forceps (20 to 40 cm, preferably of small diameter) are guided gently down the vein while being held loosely between the thumb and forefinger. The jugular vein can be temporarily occluded with umbilical tape. If difficulty is encountered in passage of the forceps, gentle manipulation of the dog by assistants to further extend the neck will assist in passage of the forceps past the thoracic inlet; medial direction of the forceps may be necessary at the base of the heart. Once the forceps have been placed, the jaws are opened, the forceps are advanced slightly, the jaws are closed, and the worms are removed. One to four worms are usually removed with each pass. This process is repeated until five to six successive attempts are unsuccessful. An effort should be made to remove 35 to 50 worms. Care should be taken not to fracture heartworm during extraction. After worm removal, the jugular vein is ligated distally, and subcutaneous and skin sutures are placed routinely. Other catheters, such as urethral stone basket catheters, horsehair brushes, snares and flexible alligator forceps have also been used.[73] Fluoroscopic guidance, when available, is useful in this procedure.

Successful worm retrieval is associated with a reduction in the intensity of the cardiac murmur and jugular pulsations, rapid clearing of hemoglobinemia and hemoglobinuria, and normalization of serum enzymatic aberrations. Immediate and latent improvement in cardiac function occurs over the next 24 hours. It is important to realize that removal of worms does nothing to reduce right ventricular afterload (PHT), and hence fluid therapy must be monitored carefully before and after surgery to avoid precipitation or worsening of right heart failure. Cage rest should be enforced for a period of time suitable for individual care.

Worm embolectomy through a jugular venotomy is frequently successful in stabilizing the animal, allowing adulticide therapy to be instituted to destroy remaining heartworms in a minimum of 1 month. Careful scrutiny of BUN and serum liver enzyme concentrations should precede the latter treatment. Aspirin therapy is continued for 3 to 4 weeks after adulticide therapy. Substantial improvement in anemia should not be expected for 2 to 4 weeks after worm embolectomy. Macrolide preventative therapy, as described previously, is administered at the time of release from the hospital.

206.8.8 Aberrant Migration

Although heartworms in the dog typically inhabit the pulmonary arteries of the caudal lung lobes, they may find their way to the right ventricle, and rarely (see Caval Syndrome) the right atria and venae cavae. Much less frequently, immature L5 may aberrantly migrate to other sites, including the brain, spinal cord, epidural space, anterior chamber of the eye, the vitreous, the subcutis, and the peritoneal cavity. In addition, the worms may inhabit the systemic circulation, producing systemic thromboembolic disease.[12] Treatment of aberrantly

migrating heartworms requires either nothing (e.g., peritoneal cavity), surgical excision of the offending parasite, adulticidal therapy, or symptomatic treatment (e.g., seizure control with brain migration). The method for surgical removal from internal iliac and femoral arteries has been described.[12]

206.9 PROGNOSIS

The prognosis for asymptomatic HWI is generally good and, although the prognosis for severe HWD has to be guarded, a large percentage of such cases can be successfully managed.[74] Once the initial crisis is past and adulticidal therapy has been successful, resolution of underlying manifestations of chronic HWD begins. The prognosis is poorest with severe DIC, CS, massive embolization, eosinophilic granulomatosis, severe pulmonary artery disease, and heart failure. After adulticidal therapy, intimal lesions regress rapidly.[75–77] Improvement is noted as early as 4 weeks post-treatment in the main pulmonary artery, with all pulmonary arteries having undergone marked resolution within 1 year. Radiographic and arteriographic lesions of HWD begin to resolve within 3 to 4 weeks, and PHT is reduced within months and may be normal within 6 months of adulticide therapy. Pulmonary parenchymal changes are worsened during the 6 months after adulticidal therapy and then begin to lessen in severity, with marked resolution within the next 2 to 3 months. Persistence of such lesions is suggestive of persistent infection. Corticosteroid therapy hastens the resolution of these lesions. Likewise irreversible renal disease is uncommon, with glomerular lesions resolving within months of successful adulticidal therapy. Signs of heart failure are also reversible with symptomatic therapy, cage rest, and successful clearing of infection.

206.10 CONTROVERSIES IN CANINE HEARTWORM DISEASE

206.10.1 Yearly Testing

The remarkable efficacy of macrolide preventatives and the reduced danger of microfilaria-induced reactions with their use (see following section on preventatives), have caused some to question the need for yearly testing.[51] Many experts, however, continue to advocate this practice.[18] The issue of yearly testing is clearly important because it deals with financial and ethical, in addition to medical, issues. The veterinary profession must walk the fine line between adequate testing, by which we protect the public, and excessive testing, by which the public may feel “gouged.” This is difficult because only sparse scientific detail exists to answer this question, and the answer likely differs by geographic region and even within regions, based on socioeconomic strata and client compliance.

Arguments can be put forth both for and against yearly testing.[18] Proponents might argue that this practice gets animals into the clinic yearly (vaccination may not [see Chapters 163 and 164]), thereby ensuring yearly examination and resultant health benefits and income, and provides inexpensive insurance against unrecognized infection caused by poor compliance or dogs that surreptitiously expectorate medications when orally administered. In addition, yearly antigen testing is very specific (i.e., little risk of false-positive results), prevents long-term infections from becoming established during the period between heartworm checks, and would seem to limit liability to the practicing veterinarian. They might well also point out that a recent reports have demonstrated poor compliance for heartworm prophylaxis nationwide,[32–34] and even though macrolide preventatives provide the safety net of the so-called reach-back effect (or retroactive efficacy) discussed elsewhere, that this benefit is realized only with lapses of less than 3 to 4 months, varies between products, and requires continuous administration for 1 year after the lapse.[37] Finally, yearly testing for heartworm

antigen is useful to pick up latent (infections that have progressed too far to be eliminated with preventative but are not patent at the time that preventative was prescribed) or incompletely eradicated infections.

On the other hand, the opponent of yearly testing might point out that if, as a profession, we emphasize the efficacy and importance of preventive agents, we may lose credibility by also promoting yearly testing. Additionally the macrolide preventatives are very efficacious, possessing reach-back potential, in the hands of conscientious clients, and the risk of severe adverse reactions in dogs not known to be infected and receiving macrolides is small. The reason that adverse reactions are less likely is because most dogs will be rendered pharmacologically amicrofilaremic or will have small microfilarial burdens. In addition, the reactions to macrolides in microfilaremic dogs are less severe than to DEC. Furthermore, the argument can be made that the small worm burdens, most likely to result when preventative lapses are brief, will be minimally harmful and might even escape detection by immunologic tests, and that the chances of false-positive tests increase with low prevalence (as would be expected in a population of pets receiving preventative and yearly evaluation).

The American Heartworm Society addressed this question in 1995.[78] It stated "…after the initial retest, if it appears that monthly chemoprophylaxis is being given as prescribed, retesting at intervals greater than 1 year may be sufficient. However, reasonable doubt that administration has been adequate would justify retesting at shorter intervals, perhaps on an annual basis." Unfortunately little data exist on owner compliance with preventatives, and the data that have been generated are alarming. Cummings and colleagues[33] surveyed dispensing records of 50 veterinary practices in heartworm-endemic areas in the United States and found that, based on the practices' own recommendations, only enough medication was dispensed to adequately protect 41% of the canine clients. This was largely due to the fact that medication was dispensed for less than 50% of the dogs in the practices. It is important to add that this study did not identify compliance failure in which dispensed medications were not administered or in which administered medication was not swallowed. These data suggest that the majority of our canine patients should undergo yearly testing. Positive test results in this population should be carefully scrutinized, however.

206.11 YEARLONG PREVENTION

Because of the necessity of the mosquito as an intermediate host for HWI, it has been logical and accepted practice to discontinue preventatives during the winter months in the more northern climates. In warmer climates, where mosquitoes may be encountered 12 months of the year, yearlong prophylaxis has been the practice. With the advent of monthly, very effective prophylactic agents, and with improved understanding of the temperature dependence of heartworm transmission by mosquitoes, this yearlong practice has been called into question.[3] Although no supportive data exist, it might be assumed that the ease of administration of monthly preventatives may improve owner compliance and that the reach-back effect will make up for short lapses in therapy or unexpected exposures at the beginning or end of the transmission season, thereby making the effective period of prevention longer. More importantly, recent studies have shown that transmission, even in heartworm-endemic areas, does not occur during the final quarter of the year.[2] This is because the mosquito, which is generally assumed to live 30 days, requires a minimum average daily ambient temperature to allow larval development to the infectious (L3) stage. This requirement is defined in heartworm development units (HDUs). An HDU is the degree days (in °C) that the average ambient temperature surpasses the developmental threshold of 14° C (57° F).[2] Restated, for each day that the average ambient temperature exceeds the threshold, an HDU is attained; if the average temperature is 16° C for 1 day, for example, then 2 HDUs are attained. For development of infective larvae, 130 HDUs must be attained and, to be effective, these must be attained in the lifetime of the female mosquito (~30 days). If the average temperature is 16° C, for example, it would take 65 days for L3 to develop,

thereby making transmission impossible. On the other hand, a 24° C average temperature would allow the molt to L3 to occur in 13 days, well within the mosquito's life expectancy.

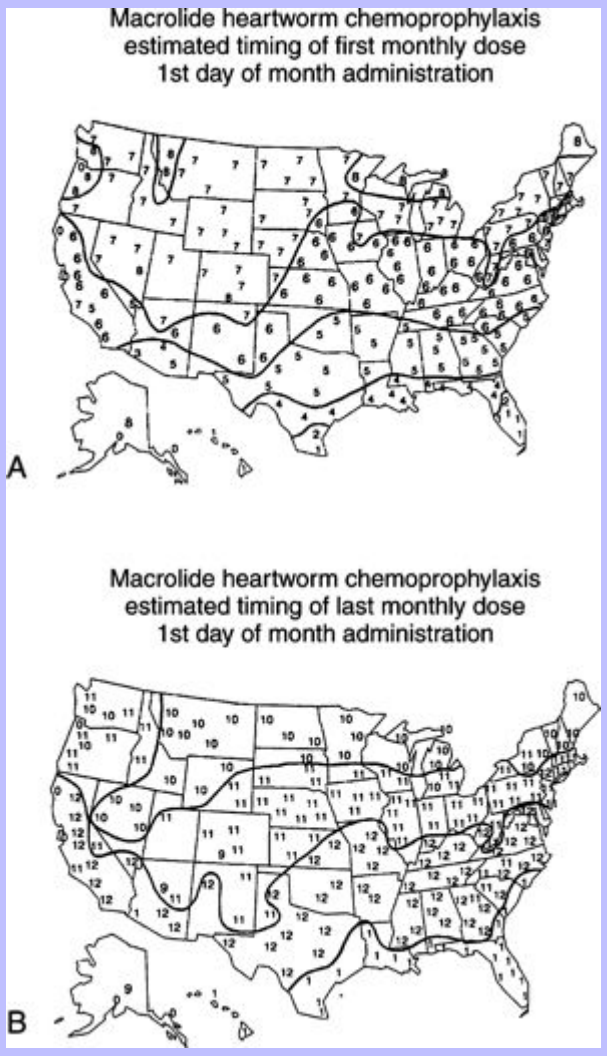
In a very innovative approach to this question, Knight and Lok[3] surveyed temperature extremes in 200 weather stations over a 30-year period and calculated the *worst case scenario* for transmission of heartworms. The resultant isotherm maps (Figure 206-17), constructed from this information indicate the month to begin and to cease heartworm preventative therapy by geographic region. In only Hawaii, Florida, and the southern tips of North Carolina, South Carolina, Georgia, Alabama, Mississippi, and Louisiana is yearlong preventative deemed necessary.

Therefore arguments may be drawn against this theory for yearlong prevention, or at least for a longer prevention season than indicated by the isotherm maps published by Knight and Lok.[3] First, though fascinating and backed by scientific fact, this represents only a theory, and one that can never be proven. It cannot be proven because this would require testing the hypothesis in every locale in the country in an infinite number of years and seasonal variation. Second, some aspects of the HDU model fall under question:

- Do all female mosquitoes really live only 30 days?
- Do some mosquito species live longer than others?
- Are there not other climatic factors such as humidity that play a role in larval development?
- Are there not microclimates within isotherm regions that might allow more HDUs to be attained?
- Might not mosquitoes seek microclimates (indoors perhaps) with temperatures to allow heartworm larval development?

Third, owner compliance has been shown to be less than optimal.[32–34] Fourth, the macrolide reach-back effect, which protects dogs for which compliance is imperfect, is less than 100% after a 4-month lapse in therapy, varies among preventatives, and requires 12 to 14 months of continuous therapy after the lapse.[37] Fifth, sometimes significant differences exist in adjacent isotherm regions, rendering decision making confusing and potentially hazardous. For example, in Florida, adjacent regions exist that require 10 or 12 months of preventative treatment. How does an owner or veterinarian know which protocol to use? Furthermore, in some areas, the change from current recommendations to those based on the isotherm maps is minimal. For example, in Wisconsin, current recommendations would dictate starting heartworm preventative in May and continuing through November, whereas the isotherm map suggests July through October, a difference of two doses. Sixth, animals travel, often to warmer climates during “nontransmission” seasons. Seventh, because some macrolides and macrolide combination drugs have broad spectra, their use in other parasite control might argue for their use for longer than just the projected heartworm transmission season. Lastly, the savings to clients is relatively small. If a client in North Carolina goes from yearlong prevention to the Knight-Lok recommendation (12-month administration to 7-month administration), the savings for a 25 lb dog is about $16.00 per year.

Figure 206-17 Isotherm maps demonstrating the month to begin **(A)** and stop **(B)** heartworm monthly preventative therapy based on data from nearly 200 weather stations (see text for detailed description). A zero (*0*) indicates no preventative necessary. (From Knight DH, Lok JB: Seasonal timing of heartworm chemoprophylaxis in the United States. In Proc Heartworm Sympos '95. Batavia, Ill., American Heartworm Society, 1996, pp 37–42.)



The Knight-Lok model has provided new and useful information, indicating that the risk in other than prime heartworm season is less than previously believed, and that in some instances heartworm prophylaxis is excessive. The Knight-Lok model should stand as a suggestion for the timing of prophylaxis, with practice erring to the conservative. This means extending the isotherm map suggestion 1 month in either direction and taking the

earliest implementation date and the latest cessation date surrounding one's geographic region. As a profession, we are faced with the dilemma of providing the best care with fiscal responsibility. The fact that our previous assumptions have come under some reassessment should be brought to the clients' attention, using the points made previously. It then falls upon the shoulders of the client to determine if the risk of possible, but generally unlikely, infection is worth the savings.

206.12 MACROLIDES AS ADULTICIDES

It is now proven that ivermectin (and possibly selamectin) has adulticidal efficacy that can approach 100% with prolonged, continuous administration.[40,41,48] Ivermectin was demonstrated to be successful as an adulticide in experimental, young infections with 31 months' continuous administration.[41] The exact role of macrolides in the management of HWI, other than as preventatives, is unclear and likely to be a major controversy in upcoming years.

The appeal of macrolides for this use is that it takes the veterinarian out of the *complication loop*. Complications might indeed still occur but would not likely be temporally linked to the macrolide administration (as they are to arsenic use). In addition, reduced cost, patient discomfort, and inconvenience are appealing. Arguments against the use of ivermectin in this way include the following:

- Represents an off-label use of ivermectin
- Requires continuous more than 30 months' compliance from a client that often has allowed HWI to occur—often by poor compliance
- Lack of knowledge about the timing and degree of exercise restriction necessary; safe use might require 31 months of continuous exercise restriction
- Absence of a controlled kill as seen with melarsomine, reducing the ability to effectively monitor for adverse effects
- Lack of knowledge as to the effect of chronic antigen release from slowly dying adult heartworms on the kidneys and lungs
- Knowledge that macrolide “slow adulticidal therapy” does not alleviate the lung disease associated with HWI[79]
- Fact that proven efficacy is only in young (<8 months old) experimental HWIs[41]
- Concern that heartworm resistance to ivermectin might develop in dogs treated in this manner[50]

At the 2001 American Heartworm Symposium, the audience and a panel of experts were polled as to their belief as to the role of ivermectin as an adulticide in their own practices.[80] Five percent of the audience and none of the expert panelists used only ivermectin for adulticidal therapy. Approximately one third of both groups did not or would not use ivermectin as an adulticide under any circumstances. Finally, approximately 70% of the expert panel and 50% of the audience stated that they would use ivermectin for this purpose only under mitigating circumstances of financial or medical constraint.

The author recommends that melarsomine be the primary adulticidal tool and recommends or accepts the use of ivermectin in instances where a preventative is necessary in a heartworm-positive dog and the owner cannot afford arsenic therapy or in which medical conditions preclude its use; in the event of residual infection after appropriate treatment with melarsomine (assumes low worm burden); and, obviously, in unrecognized infections.

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207 CHAPTER • 207 Feline Heartworm Disease

Clarke Atkins

207.1 LIFE CYCLE

The life cycle of *Dirofilaria immitis* is similar in the cat and the dog (see Figure 206-2). Cats differ, however, in that they are not generally the preferred target for feeding mosquitoes, that to be infected the mosquito has to have first fed on a canid, and that, as an unnatural host, cats are inherently resistant to heartworm infection (HWI). Infections in cats therefore tend to be infrequent and small. In addition, the life cycle takes longer in the cat, such that patency (noted in <20% of cats) does not occur until 7 to 8 months postinfection.

207.2 PATHOPHYSIOLOGY

The domestic cat, though an atypical host, can be parasitized by *D. immitis*, with resultant heartworm disease (HWD). The clinical manifestations of the disease are different and often more severe in this species, but the infection rate is only 5% to 20% of that of the dog.[1] Experimental infection of the cat is more difficult than in the dog; less than 25% of L3 reach adulthood. This resistance is also reflected in natural infections, in which feline heartworm burdens are usually less than 10 and typically only 2 to 4 worms.[2] Other indications of the cat's inherent resistance to this parasite are a shortened period of worm patency, high frequency of amicrofilaremia or low microfilaria counts, and shortened life span of adult heartworms (2 to 3 years).[2] Nevertheless, studies have shown a prevalence as high as 14% in shelter cats[1] and a study performed at North Carolina State University (NCSU) revealed HWD in nine of 100 cats had cardiorespiratory signs.[3] Furthermore, antibody testing showed 26% of these cats to had been exposed to HWI.[3] Similar to dogs, the male cat is at higher risk for HWI than is the female. Aberrant worm migration appears to be a greater problem in cats than in dogs.

As in the dog, immature L5 may create pulmonary and pulmonary vascular disease in cats prior to maturation. Uniquely, the disease process develops even in cats that ultimately resist a mature infection, and as in dogs, clinical signs and disease antedate clinicians' ability to diagnose the disease through conventional means. The pulmonary arterial response to adult heartworms is more severe than that of the dog, although pulmonary hypertension has infrequently been reported. Dillon demonstrated pulmonary enlargement within 1 week of transplantation of adults, suggesting an intense host-parasite interaction.[4] A severe myointimal and eosinophilic response produces pulmonary vascular narrowing and tortuosity, thrombosis, and possibly hypertension (Figure 207-1).[5] Because the feline pulmonary artery tree is smaller than that of the dog and has less collateral circulation, embolization, even with small numbers of worms, produces disastrous results with infarction and even death. Although uncommon, cor pulmonale and right heart failure can be associated with chronic feline HWD and is manifested by pleural effusion (hydro-or chylothorax), ascites, or both. The lung per se is also insulted by HWI, with eosinophilic infiltrates in the lung parenchyma (pneumonitis) and pulmonary arteries (Figure 207-2). The pulmonary vessels may leak plasma, producing pulmonary edema (possibly acute respiratory distress syndrome, ARDS), and type II cells proliferate, both potentially altering O_2 diffusion.[4] In addition, radiographic findings suggest air trapping, compatible with bronchoconstriction. The end result to this multifaceted insult is diminished pulmonary function, hypoxemia, dyspnea, cough, and even death.

207.3 CLINICAL SIGNS

Cats with HWI may be asymptomatic and, when present, clinical manifestations may be either peracute, acute, or chronic.[3,4,6–8] Acute or peracute presentation is usually due to worm embolization or aberrant migration, and signs variably include salivation, tachycardia, shock, dyspnea, hemoptysis, vomiting and diarrhea, syncope, dementia, ataxia, circling, head tilt, blindness, seizures, and death. Postmortem examination often reveals pulmonary infarction with congestion and edema. More commonly, the onset of signs is less acute (chronic form). Reported historical findings in chronic feline HWD include anorexia, weight loss, lethargy, exercise intolerance, signs of right heart failure (pleural effusion; rare), cough, dyspnea, and vomiting. The author and colleagues have found dyspnea and cough to be relatively consistent findings and, when present, should cause suspicion of HWD in endemic areas.[8] Chylo-and pneumothorax have also been recognized as unusual manifestations of feline HWD.

In a report of 50 natural cases of feline HWI in North Carolina, presenting signs were most commonly related to the respiratory system (32 cats; 64%), with dyspnea (24 cats; 48%) being most often noted, followed by cough (19 cats; 38%) and wheezing (Figure 207-3).[8] Vomiting was reported in 17 (38%) cats and was noted frequently in 8 (16%). Five (10%) heartworm-infected cats were reported to have exhibited vomiting without concurrent respiratory signs and vomiting was a presenting sign in seven (14%). Neurologic signs (including collapse or syncope [10%]) were reported in seven (14%) cats. Five (10%) of the cats were dead at the time of presentation. Murmurs were infrequently noted in cats that did not have concurrent heart disease, independent of HWI. Heart failure was present in one cat, but it had concurrent hypertrophic cardiomyopathy. HWI was considered to be an incidental finding in 14 (28%) of the cats in this study.

1137
1138

Figure 207-1 H&E stain demonstrating large pulmonary artery with obstruction of lumen due to severe medial smooth muscle hypertrophy and hyperplasia, subintimal and intimal fibrosis, endarteritis, and possibly thrombosis. The reader should also note the periarterial interstitial (probably eosinophilic) pneumonia.

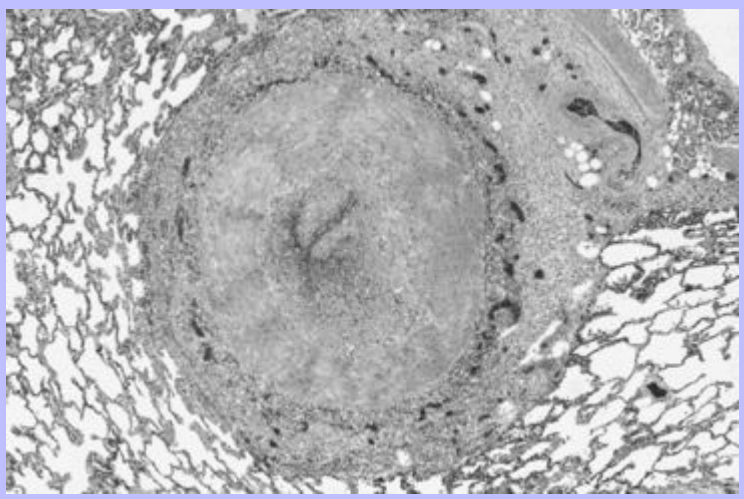
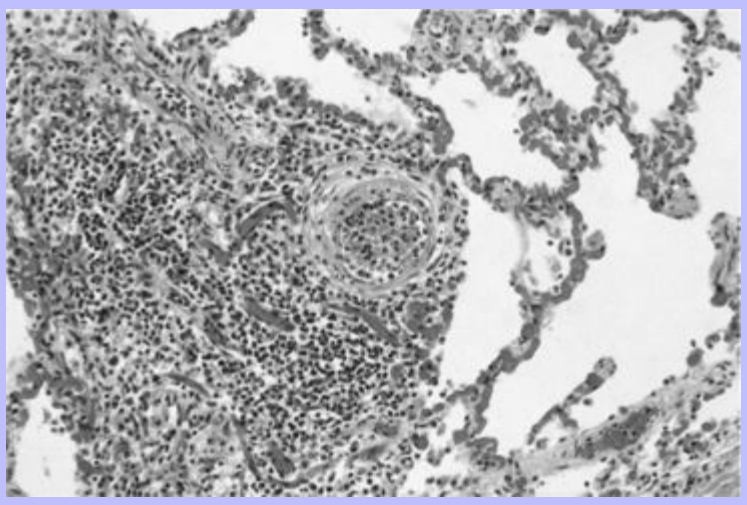
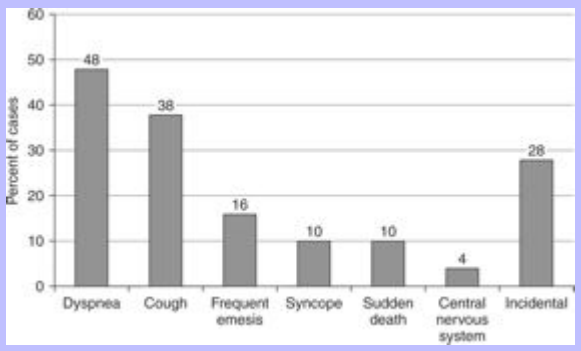


Figure 207-2 Small pulmonary artery from the cat seen in Figure 207-1 showing mild medial hypertrophy. The reader should note the extreme perivascular cuff of inflammatory cells around the vessel, representing an eosinophilic infiltrate.



Physical examination is often unrewarding, although a murmur, gallop, or diminished or adventitial lung sounds (or a combination of these findings) may be noted. In addition, cats may be thin, dyspneic, or both. If heart failure is present, jugular venous distension, dyspnea, and rarely ascites are detected.

Figure 207-3 Clinical signs recorded in 50 cats with proven heartworm infection (HWI). *Freq,* Frequent; *CNS,* central nervous system signs (e.g., seizures, ataxia, circling). (From Atkins CE et al: Heartworm infection in cats: 50 cases [1985–1997]. J Vet Med Assoc 217:355–358, 2000.)



207.4 DIAGNOSIS

The diagnosis of HWI and HWD in cats poses a unique and problematic set of issues.[4] First, the clinical signs are often quite different from those of the dog. In addition, the overall incidence in cats is low, so suspicion is lessened, eosinophilia is transient or absent, electrocardiographic findings are minimal, and most cats are amicrofilaremic.

No compelling medical reasons exist to screen cats for HWI prior to administration of macrolide preventatives because the risk of adverse reactions associated with microfilarial death is small (cats are amicrofilaremic or have small microfilarial numbers, and adverse reactions are minimized with macrolide preventatives). Nevertheless, screening allows the clinician to alert pet owners if their cats have been exposed (antibody positive) so that they might pursue confirmation of the diagnosis, if they wish. It also minimizes public relations problems if the cat develops HWD while on preventative. In addition, routine screening allows the clinician to understand the risk of heartworm exposure in the practice area. The author's approach to routine screening of cats for heartworms differs somewhat from that when suspicion of infection exists (Figure 207-4, *A* and *B*).

Immunodiagnostic methods (Table 206-2) are also imperfect in cats because of the low worm burdens (1 to 12; mean, 3) and hence, antigenic load. In a recent study, enzyme-linked immunosorbent assay (ELISA) antigen tests were positive on sera from 36% to 93% of 31 cats harboring 1 to 7 female heartworms, with sensitivity increasing as female worm burden increased.[9] Cats with male worm or worms were not detected as positive. Therefore false-negative tests occur frequently, depending on test used, maturity and gender of worms, and worm burden. All tests were, however, virtually 100% specific. It is important to realize that infection with signs may be present prior to the presence of detectable antigen (from gravid adult females). McCall and colleagues[10] report that, in natural infections, the antigen test detects less than 50% of cases. Snyder and colleagues[11] present differing data (from natural infections in which blood was obtained as long as 2 hours posteuthanasia) that show that the antigen test is more sensitive than previous reports (74%) indicated. Recently an antigen test (IDEXX's SNAP® Feline Heartworm Antigen Test) has been marketed for cats. This is an adaptation of the canine test, with a reported increase in sensitivity of 15% over conventional antigen tests. Although less specific, heartworm antibody tests may be of use in the detection of feline HWI, even when antigen tests are negative. The antibody test may also be useful as a marker for exposure to HWI, even if the cat never develops a mature infection. Two in-clinic feline heartworm antibody tests are available (HESKA™ SOLO STEP™ FH and Synbiotics' WITNESS® FH).

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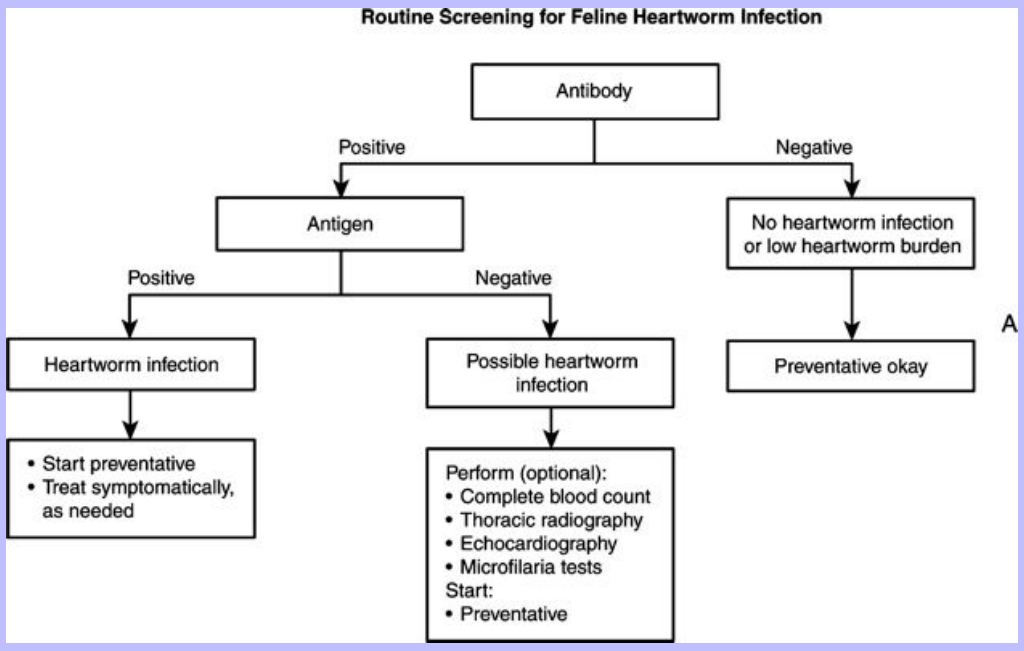
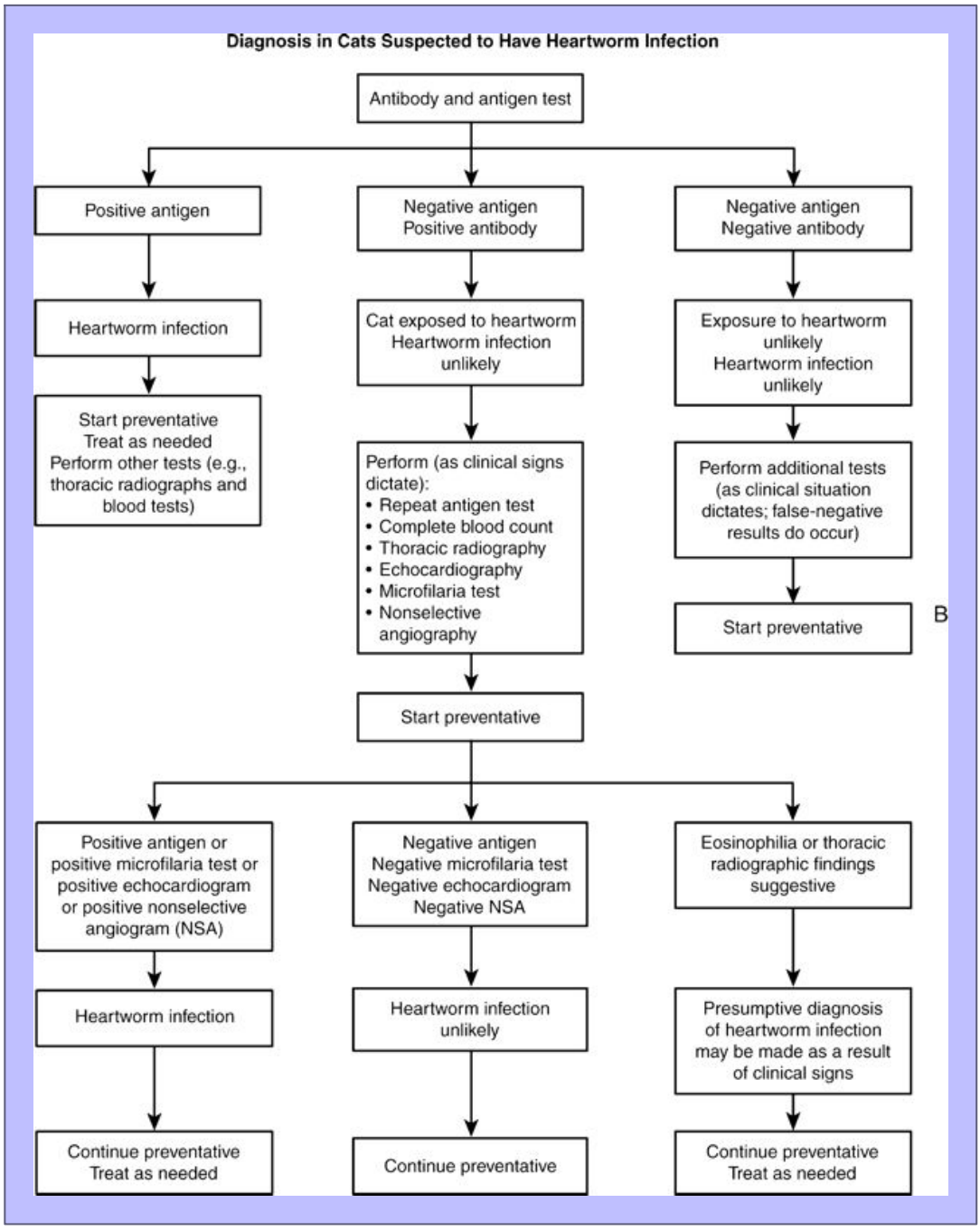
Thoracic radiographs have been suggested as an excellent screening test in cats. However, Schafer and Berry[12] showed that the most sensitive radiographic criterion (left caudal pulmonary artery greater than 1.6 times the ninth rib at the ninth intercostal space on the ventrodorsal projection) was only detected 53% of cases. Furthermore, even though most cats with clinical signs have some radiographic abnormality, the findings are not specific to HWD. In addition, a study by Selcer and colleagues[13] demonstrated that radiographic findings were often transient, and radiographic abnormalities were found in cats that ultimately resisted heartworm maturation and were negative on postmortem. Radiographic findings include enlarged caudal pulmonary arteries (Figure 207-5), often with ill-defined margins, pulmonary parenchymal changes that include focal or diffuse infiltrates (interstitial, bronchointerstitial, or even alveolar), perivascular density, and occasionally, atelectasis (Figures 207-6 and 207-7). Pulmonary hyperinflation may also be evident, and the misdiagnosis of feline bronchial disease can easily be made (see Figures 207-5, *A*, and 207-6, *A*). Pulmonary angiography has also been used to demonstrate radiolucent linear intravascular foreign bodies and enlarged, tortuous, and blunted pulmonary arteries (Figure 207-8).

Figure 207-4 **A,** Algorithm demonstrating the author's approach to screening cats for heartworm infection (HWI). **B,** Algorithm demonstrating the author's approach to the diagnosis of HWI in cats in which infection is suspected.





Echocardiography, in the author's experience, is more sensitive in cats than in dogs.[3,14] Typically, a *double-lined echodensity* is evident in the main pulmonary artery, one of its branches, the right ventricle, or occasionally at the right atrioventricular (AV) junction (Figure 207-9). The author and colleagues found heartworms by echocardiography in 78% of nine cases,[3] as did Selcer and colleagues in 16 experimental infections.[13]

207.5 TREATMENT AND PREVENTION

The question arises as to whether heartworm prophylaxis is warranted for cats because they are not the natural host and because the incidence is low. Necropsy studies of feline HWI in the Southeast have yielded a prevalence of 2.5% to 14%, with a median of 7% (Figure 207-10).[1] When considering the question of institution of prophylaxis, it is worth considering that this prevalence approximates or even exceeds that of feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) infections.[15] A 1998 nationwide antibody survey of over 2000 largely asymptomatic cats revealed an exposure prevalence of nearly 12% (Figure 207-11).[16] It is also noteworthy that, based on owners' information, nearly one third of cats diagnosed with HWD at NCSU were housed solely indoors.[8] Lastly, the consequences of feline HWD are potentially dire, with no clear therapeutic solutions. Therefore the author advocates preventative therapy in cats in endemic areas. Three drugs with FDA approval are marketed for use in cats (Table 207-1). Ivermectin is provided in a chewable formulation, milbemycin as a flavored tablet, and selamectin (a broad-spectrum parasiticide) comes in a topical formulation. The spectrum and the formulation of these products varies; hence the clients' individual needs are easily met in most cases (Table 207-1).

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Because the vast majority of cats are amicrofilaremic, microfilaricidal therapy is unnecessary in this species. The use of arsenical adulticides is problematic. Thiacetarsemide (sodium caparsolate), if available, poses risks even in normal cats. Turner, Lees, and Brown[17] reported death due to pulmonary edema and respiratory failure in 3 of 14 normal cats given thiacetarsemide (2.2 mg/kg twice over 24 hours). Dillon and colleagues[18] could not confirm this acute pulmonary reaction in 12 normal cats receiving thiacetarsemide, but one cat did die after the final injection. More importantly, a significant, though unquantified, percentage of cats with HWI develop pulmonary thromboembolism (PTE) after adulticidal therapy.[4–7] This occurs several days to 1 week after therapy and is often fatal. In 50 cats with HWI, seen at NCSU, 11 received thiacetarsemide. There was no significant difference in survival between those receiving thiacetarsemide and those receiving symptomatic therapy.[8]

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Figure 207-5 **A,** Lateral thoracic radiograph from a cat with heartworm disease (HWD). A fine interstitial pattern is seen in the caudal lung lobes, and the chest is somewhat hyperinflated. This radiographic pattern is similar to and hence confused with that of feline bronchial disease. **B,** Dorsoventral thoracic radiograph from the same cat shown in **A**. Again, the changes are not dramatic, but the right caudal lobar pulmonary artery is enlarged (>1.6 times the ninth rib at the ninth intercostals space; *arrows*). The opposite pulmonary artery can be seen to be somewhat tortuous.

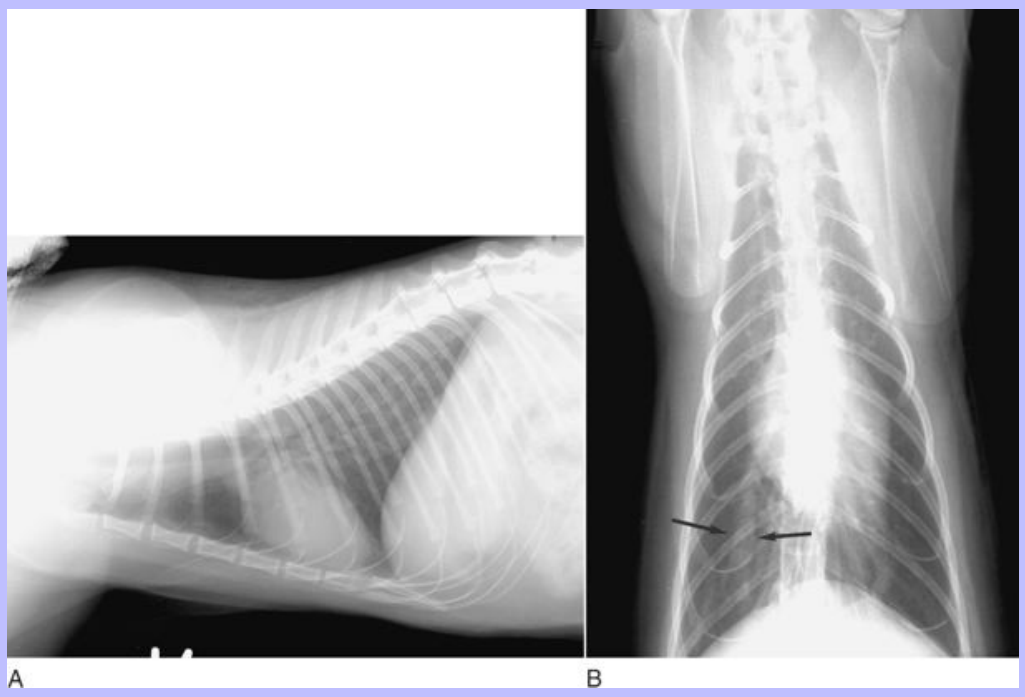


Figure 207-6 **A,** Lateral thoracic radiograph of a cat with heartworm disease (HWD) and cough. The reader should note the hyperinflated chest, flat diaphragm, and moderate interstitial pulmonary infiltrate. The right ventricle is mildly enlarged. **B,** Dorsoventral thoracic radiograph from the same cat shown in **A**. The pulmonary infiltrate is more readily appreciated in this view in the right caudal lung lobe. The reader should note the enlarged right caudal lobar pulmonary artery.

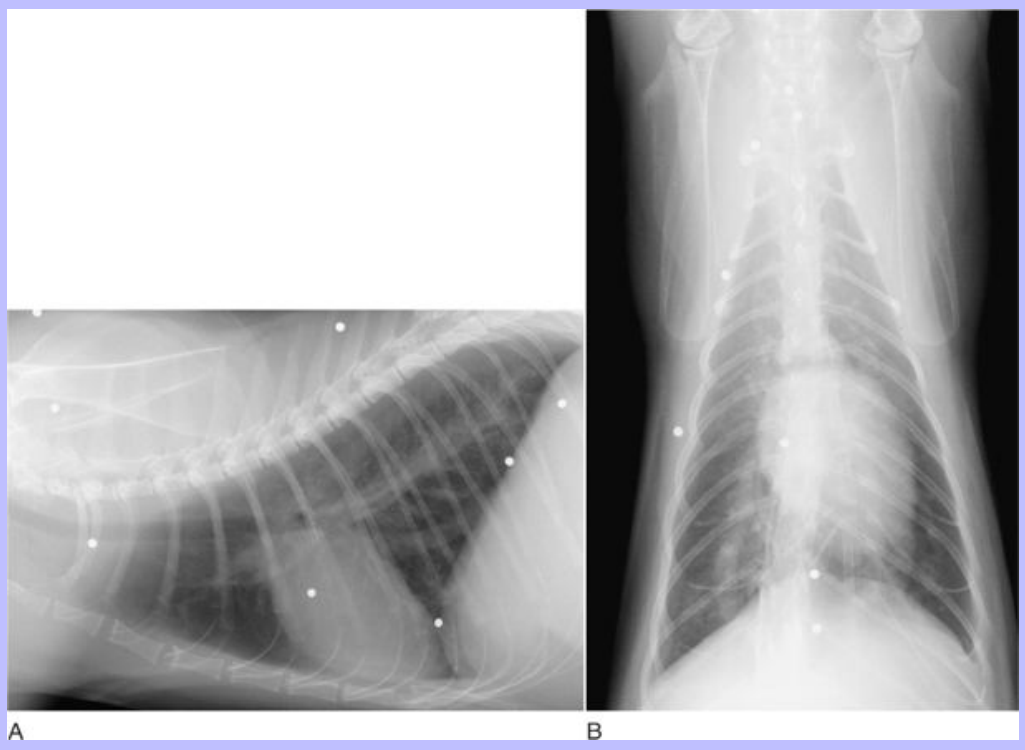


Figure 207-7 Lateral thoracic radiograph of a cat with severe respiratory distress and heartworm disease (HWD). The reader should note the alveolar infiltrate in the ventral thorax and the less severe interstitial infiltrate more dorsally in caudal lung lobes. This severe lung disease is probably due to heartworm death and may represent acute respiratory distress syndrome (ARDS).

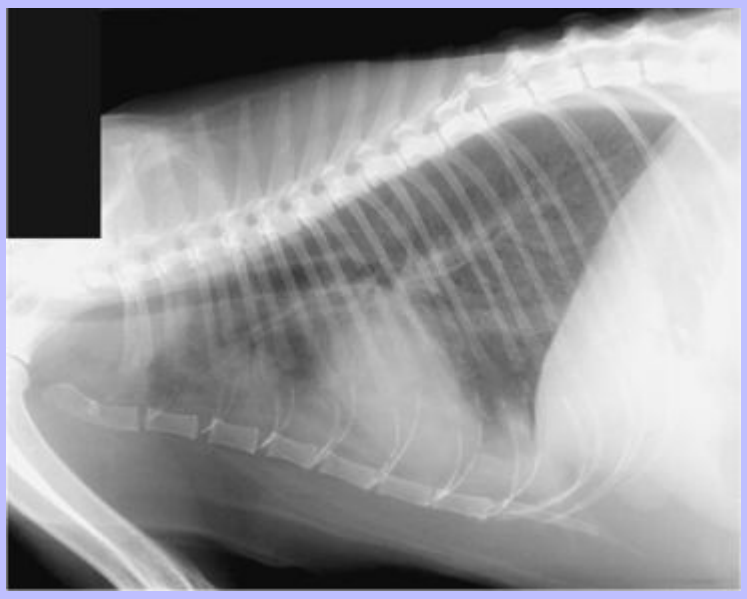


Figure 207-8 Nonselective angiogram obtained from cat with heartworm disease (HWD). The reader should note the enlarged main pulmonary artery *(open arrow)* and the enlarged, tortuous, and blunted caudal pulmonary arteries *(arrows)*. Careful scrutiny reveals linear radiolucencies in the right caudal pulmonary artery. (Photograph courtesy Dr. Kathy Spaulding. From Atkins CE: Heartworm disease. In Allen DG [ed]: Small Animal Medicine. Philadelphia, JB Lippincott Co, 1991, pp 341–363.)

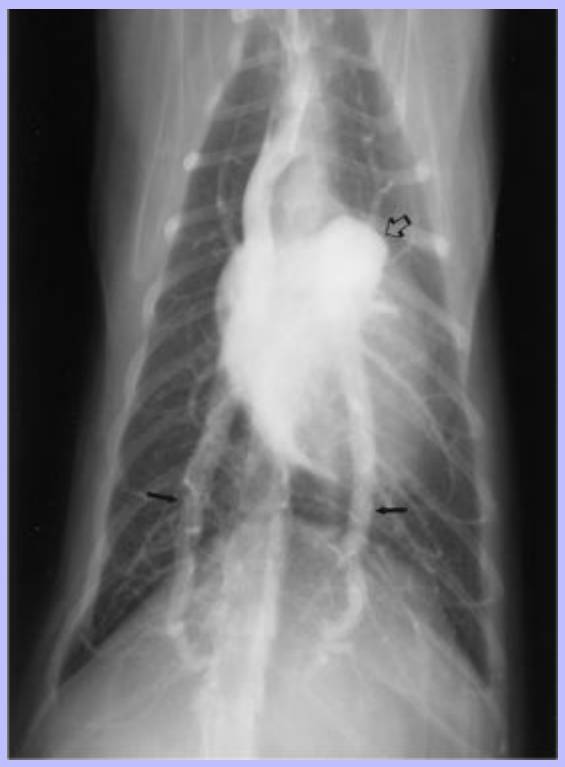
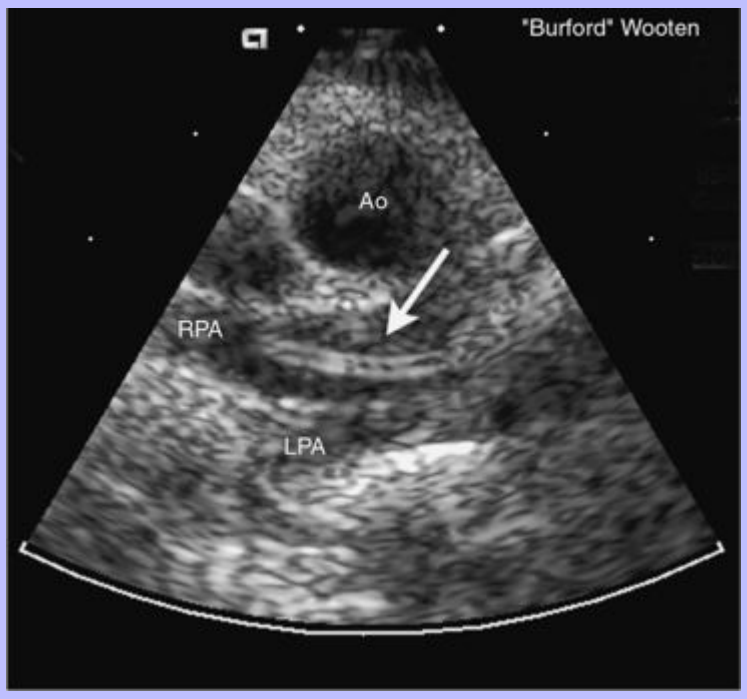


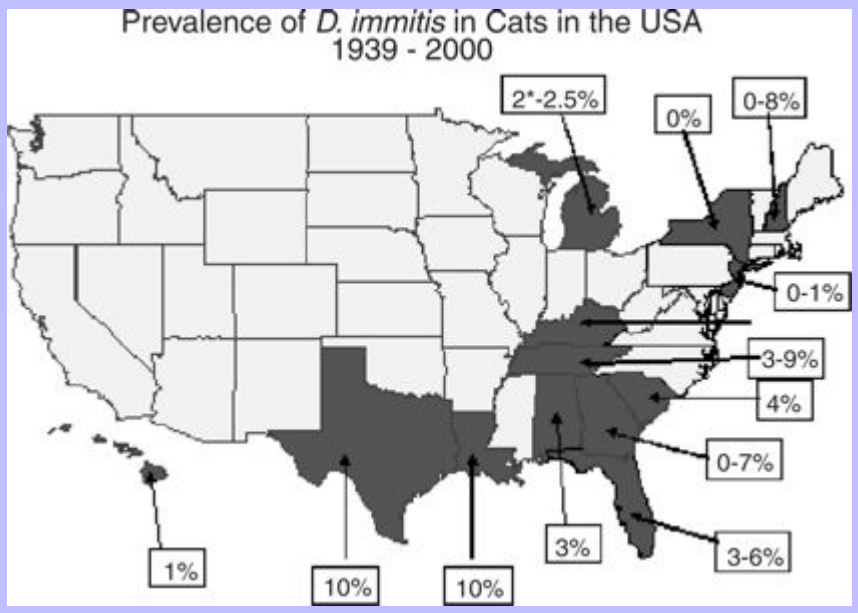
Figure 207-9 A short-axis, two-dimensional echocardiogram obtained from an 18-year-old castrate male, feline cancer patient with an asymptomatic murmur. An adult heartworm can be identified by two echo-dense parallel lines, in the right pulmonary artery *(arrow)*. *Ao,* Aorta; *RPA,* right pulmonary artery; *LPA,* left pulmonary artery.



Data on melarsomine in experimental (transplanted) HWI in cats are limited and contradictory. Although an abstract report exists in which one injection (2.5 mg/kg; one half the recommended canine dose) of melarsomine was used in experimentally infected cats without treatment-related mortality, the worm burdens after treatment were not significantly different from those found in untreated control cats.[19] Diarrhea and heart murmurs were frequently noted in treated cats. A second abstract report, using either the standard canine protocol (2.5 mg/kg twice over 24 hours) or the *split dose* (one injection, followed by two injections, 24 hours apart, in 1 month) described in Chapter 206, gave more favorable results.[20] The standard treatment and split-dose regimens resulted in 79% and 86% reduction in worm burdens, respectively, and there were no adverse reactions. Although promising, these unpublished data need to be interpreted with caution because the transplanted worms were young (<8 months old and more susceptible), and the control cats experienced a 53% worm mortality (average worm burden was reduced by 53% by the act of transplantation). Additionally, the clinical experience in naturally infected cats has been generally unfavorable, with an unacceptable mortality. Because of the inherent risk, lack of clear benefit, and the short life expectancy of heartworms in this species, this author does not advocate adulticidal therapy in cats. Surgical removal of heartworms has been successful and is attractive because it minimizes the risk of thromboemboli. The mortality seen in the only published case series was, unfortunately, unacceptable (two of five cats).[21] This procedure may hold promise for the future, however.

Cats with HWI should be placed on a monthly preventative and short-term corticosteroid therapy (prednisone at 1 to 2 mg/kg every 48 hours, three times a day) used to manage respiratory signs. If signs recur, alternate-day steroid therapy (at the lowest dose that controls signs) can be continued indefinitely. For embolic emergencies, 1142
oxygen, corticosteroids (dexamethasone at 1 mg/kg intravenously or intramuscularly, or prednisolone sodium 1143
succinate at 50 to 100 mg intravenously/cat), and bronchodilators (aminophylline at 6.6 mg/kg intramuscularly every 12 hours, theophylline sustained release at 25 mg/kg orally, or terbutaline at 0.01 mg/kg subcutaneously) may be used. Bronchodilators have logic, based on the ability of agents, such as the xanthines (aminophylline and theophylline), to improve function of fatigued respiratory muscles. In addition, the finding of hyperinflation of lung fields may indicate bronchoconstriction, a condition for which bronchodilation would be indicated. Nevertheless, this author does not routinely use bronchodilators in feline HWD.

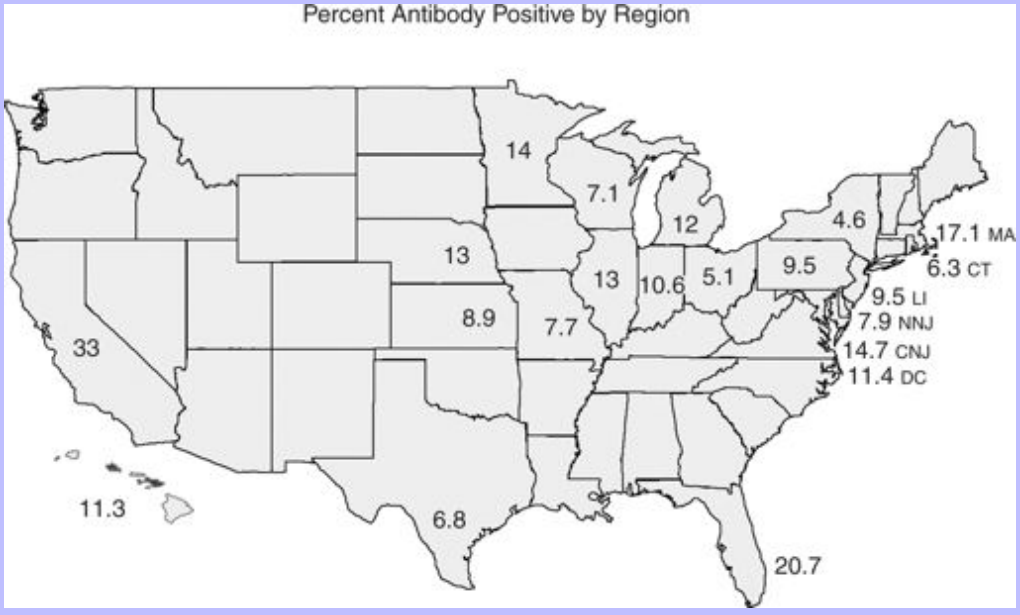
Figure 207-10 Necropsy prevalence of heartworm infection (HWI) in shelter cats. The shaded states are those in which such studies have been completed. One Michigan study, which showed a prevalence of 2%, was an antigen study. (Adapted from Ryan WG, Newcomb KM: Prevalence of feline heartworm disease—a global review. *In* Soll MD, Knight DH [eds]: Proc Heartworm Symposium '95. Batavia, Ill., American Heartworm Society, 1996.)



The use of aspirin has been questioned because vascular changes associated with HWI consume platelets, increasing their turnover rate and effectually diminishing the antithrombotic effects of the drug. Conventional doses of aspirin did not prevent angiographically detected vascular lesions.[22] Doses of aspirin necessary to produce even limited histologic benefit approached the toxic range. Despite this, because therapeutic options are limited, at conventional doses (80 mg orally, every 72 hours), aspirin is generally harmless, inexpensive, and convenient. Because the quoted studies were based on relatively insensitive estimates of platelet function and

pulmonary arterial disease (thereby possibly missing subtle benefits), the author continues to advocate aspirin for cats with HWI. Aspirin is not prescribed with concurrent corticosteroid therapy. Management of other signs of HWD in cats is largely symptomatic.

Figure 207-11 Prevalence (%) of heartworm exposure (positive antibody test) in over 2000 largely asymptomatic cats in 19 states (21 regions). *NNJ,* North New Jersey; *CNJ,* central New Jersey; *LI,* Long Island, NY. (Adapted from Miller MW et al: Prevalence of exposure to *Dirofilaria immitis* in cats from multiple areas of the United States. *In* Soll MD, Knight DH [eds]: Proc Heartworm Symposium '98. Batavia, Ill., American Heartworm Society, 1998; pp 161–166.)



207.6 PROGNOSIS

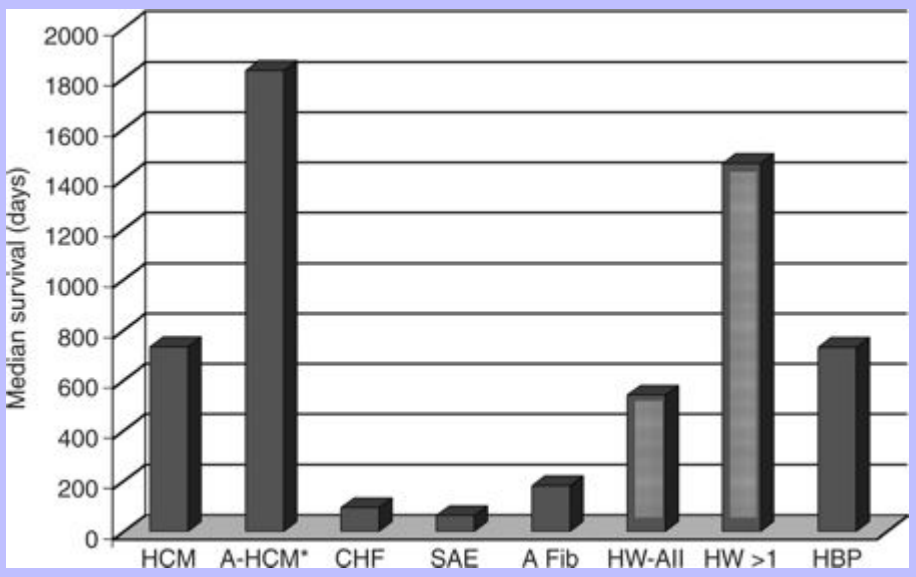
In the aforementioned study of 50 cats with natural HWI, at least 12 cats died of causes other than HWD. Seven of these and two living cats were considered to have survived HWD (lived ≥1000 days).[8] The median survival for all heartworm-infected cats living beyond the day of diagnosis was 1460 days (4 years; range, 2 to 4015 days), whereas the median survival of all cats (n = 48 with adequate follow-up) was 540 days (1.5 years; range, zero to 4015 days). Survival of 11 cats treated with sodium caparsolate (mean, 1669 days) was not significantly different from that of the 30 managed without adulticide (mean, 1107 days). Likewise, youth (<3 years of age), presence of dyspnea, cough, ELISA-positivity for heartworm antigen, presence of echocardiographically identifiably worms, or gender of the cat did not appear to affect survival.[8] The effect of HWI on survival has been compared with that of other cardiovascular diseases (Figure 207-12).[23]

Table • 207-1 Comparison of Spectra of Macrolides Currently in Use in Cats

DRUG	HW	HOOKWORMS	WHIPWORMS	ROUNDWORMS	TAPEWORMS	FLEAS & EGGS	TICKS	SARCOPTES	EAR MITES
Ivermectin (chewable)	+	+							
Milbemycin (flavored tablet)	+	+		+					
Selamectin (topical)	+	+		+		+/+	+	+	+

HW, Heartworm prevention.

Figure 207-12 Median survival from four previous reports for cats with varying cardiovascular diseases. Median survival shown as 5 years was actually more than 5 years. *HCM,* Hypertrophic cardiomyopathy; *A-HCM,* asymptomatic hypertrophic cardiomyopathy; *CHF,* hypertrophic cardiomyopathy with heart failure; *SAE,* hypertrophic cardiomyopathy with systemic embolism; *A Fib,* atrial fibrillation; *HW-All,* heartworm infection, all cases; *HW*>1, heartworm-infection with survival beyond day 1; *HBP,* hypertension. (From Atkins CE et al: Prognosis in feline heartworm infection: comparison to other cardiovascular disease. *In* Seward LR, Knight DH [eds]: Proc Heartworm Symposium '01. Batavia, Ill., American Heartworm Society, pp 41–44.)



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208 CHAPTER • 208 Peripheral Vascular Disease

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Jean-Paul Petrie

Ann E. Hohenhaus

Peripheral vascular disease denotes disorders of peripheral vessels including arteries, arterioles, veins, venules, and lymphatics (Box 208-1). Vascular lesions may result from primary vascular pathology or occur secondary to conditions originating in unrelated tissues or organ systems (Box 208-2). Resultant conditions may remain asymptomatic with little or no effect on morbidity and mortality, or they may progress to become life threatening. The development of newer imaging techniques, including improvements in diagnostic ultrasound, has provided accessible methods to clinically characterize these disorders. Vascular abnormalities have been classified according to the type of vessel affected and functional significance of associated lesions (see Boxes 208-1 and 208-2).

208.1 TECHNIQUES USED TO EVALUATE PERIPHERAL VASCULAR DISEASE

208.1.1 Angiography

Angiography is the gold standard for evaluating peripheral vascular disease owing to its superior ability to characterize and visualize normal and abnormal vascular anatomy.[1]

Diagnostic outcome requires careful attention to three important elements: (1) selection of radiopaque contrast agent, (2) technique for vascular delivery of contrast material, and (3) high-quality radiographic imaging.

Factors to be considered when selecting a contrast agent include patient safety, image quality, and cost. The features of safety and efficacy are somewhat related to the ionic composition of these materials. High osmolar ionic compounds include the diatrizoate and iothalamate salts (Conray, Mallinekrodt) (Renografin, Amersham Health). Low osmolar ionic compounds include iohexol (Omnipaque, Amersham Health), iopamidol (IsoVue), and ioversol (Optiray, Mallinekrodt). Low osmolar nonionic compounds include ioxaglate (Hexabrix, Mallinekrodt). Lower osmolar agents, both ionic and nonionic, are generally tolerated best by patients, particularly those sensitive to an increase in intravascular volume or having advanced cardiac disease (high osmolar compounds can generate a greater osmotic load).[2] Nonionic agents also have reduced risk of contrast-related anaphylactoid reactions such as urticaria, flushing, coughing, dyspnea, peripheral edema, and a sudden drop in blood pressure.[3] Contrast related nephrotoxicity is independent of the contrast agent used but can be reduced by maintaining appropriate patient hydration and minimizing the dose of contrast agent used during the imaging study.[4] Low osmolar agents are generally more expensive than high osmolar agents.

Arterial angiography, often performed using carotid or femoral arterial access, can be performed to evaluate normal or abnormal arterial vascular anatomy preoperatively; to assess vessels for occlusive disease including thromboembolism (TE); and to detect or characterize inherited or acquired lesions including peripheral aneurysms, vascular tumors, traumatic injury, and shunts. The specific catheterization technique to be used is guided by consideration of the anatomic location of interest, anticipated lesion, status of patient health, available equipment, and operator experience. After percutaneous or surgical arterial cutdown, a catheter is directed under fluoroscopic guidance to the desired location and contrast agent is injected by hand or by the

use of a mechanical injecting device. Images are acquired using mechanical rapid film changers or digitally. The advantages of digital angiography include rapid rate of acquisition, postprocessing capabilities, and reduced exposure to radiation.[1] Digital subtraction angiography may be used to cancel out portions of an image and thereby improve visualization of structures of interest.

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208.1.1.1 Box • 208-1 Peripheral Vascular Diseases

208.1.1.1.1 Diseases of Arteries and Arterioles

Occlusive diseases

- Arterial embolism
- Arterial thrombosis
- Angiitis, vasculitis
- Vasospasm, traumatic, toxic
- Diabetic arteriopathy

Nonocclusive diseases

- Arteriovenous (A-V) fistula
- Arterial aneurysm
- Arterial calcification
- Arteriosclerosis, hyalinosis, amyloidosis
- Atherosclerosis
- Vasculitis

208.1.1.1.2 Diseases of Veins

Phlebectasia

Varicosis

Phlebitis and thrombophlebitis

Venous thrombosis

Venous malformations

208.1.1.1.3 Diseases of Lymphatics

Lymphangitis

Lymphedema

Lymphangiectasia

Lymphatic hypoplasia, aplasia, hyperplasia

Lymphangioma, lymphocysts

Lymphangiosarcoma

208.1.1.1.4 Tumors of Peripheral Blood Vessels

Angioma, hemangioma, hemangiosarcoma

208.1.1.2 Box • 208-2 Causes of Peripheral Lymphatic Disorders

208.1.1.2.1 Lymphangitis, Lymphedema, Lymphadenitis, Lymphadenopathy

Infection

Neoplasia

Reactive hyperplasia

Granuloma

208.1.1.2.2 Lymphedema

Primary developmental abnormality of lymphatics

Hypoplasia

Aplasia

Lymphangiectasia

Hyperplasia

Secondary acquired abnormalities of lymphatics

Surgical excision of lymphatics or lymph nodes

Posttraumatic lymphangiopathy

Neoplastic invasion

Extrinsic compression of lymph vessels or tissue

Acute obstructive lymphadenitis

Chronic sclerosing lymphadenitis/lymphangitis

Lymphatic atrophy with interstitial fibrosis

Radiation therapy

208.1.1.2.3 Lymphocysts

Cystic hygroma, lymphoceles, pseudocyst

208.1.1.2.4 Lymphangiomas

Venous angiography is generally less challenging than arterial angiography, owing to easier access and lower pressures of the venous system. A small intravenous line is placed in a superficial vein distal to the site of the vascular lesion and contrast material is injected. Images are obtained similarly to arteriography. This technique is often selected to detect venous clots (appearing as vascular filling defects) or stenosis. The presence of prolific collateral vasculature can indicate chronic obstruction. Contrast venography of the cranial and caudal vena cava can be performed to assess caval patency that may be associated by a variety of neoplastic, compressive, or thrombotic disorders.

Lymphangiography helps to permit local assessment of the lymphatic system. The technique of indirect lymphangiography relies on the contrast agent, which is infused into tissue, to be selectively absorbed and transported through lymphatic channels.[5] Direct lymphangiography is more challenging (unless lymphangiectases have formed) but provides superior results when successfully performed. Selective lymphatic cannulation requires aseptic cutdown over the lymphatic region of interest. (The identification of lymphangiectases may be facilitated by subcutaneous injection of vital dyes [e.g., 3% Evans blue dye or 11% patent blue violet] into the toe web. By selective resorption of these dyes, the main lymphatic channels

proximal to the metacarpus or metatarsus become grossly outlined.) The lymphatic vessel is then cannulated with a 27-or 30-gauge needle or a special lymphatic cannula.[5] An iodine-containing soluble contrast medium such as sodium and meglumine diatrizoate (Renografin, Hypaque) is injected slowly into the vessel. Because water-soluble contrast media rapidly diffuse through lymphatic walls into surrounding tissues, the radiographic detail is blurred unless radiographs are taken shortly after dye injection. Alternatively, oily iodine-containing contrast agents (Lipiodol) are used, reducing leakage of contrast from the lymphatic vessels. The oily contrast agents are sequestered within the lymphatics and lymph nodes along the draining pathways.[1] Patency of the lymphatic channels can be appreciated in addition to the size of regional lymph nodes. Metastatic disease to the lymph nodes (or granulomas) appears as filling defects within the contrast-filled node. Lymphangiography can also be used to identify the location of lymphatic leakage.[1]

208.1.2 Diagnostic Ultrasound

Ultrasound imaging provides a direct, noninvasive technique for assessing anatomic abnormalities, vascular patency, and function.[6,7] Ultrasound can aid in the diagnosis of peripheral arterial occlusion, central and peripheral arteriovenous (A-V) fistulas, venous thrombosis, aneurysms, traumatic vascular disease, and compression of vascular structures from local disease processes.

Duplex ultrasonography incorporates gray-scale two-dimensional imaging, with pulsed wave (PW) and color flow Doppler techniques. Thrombi, foreign bodies, compression, and abnormal vascular anatomy can be identified with two-dimensional imaging. Color Doppler superimposed on the two-dimensional image can further help define anatomy and identify turbulence associated with vascular malformation and stenotic lesions. Normal arterial flow is laminar with the highest velocity recorded centrally, and the respective color Doppler image has a homogenous appearance. Arterial stenosis increases blood flow velocity across the narrowed lumen with corresponding change in color Doppler signal at and distal to the stenosis. PW Doppler velocity measurements are made along the length of the artery in question and at areas or interest indicated from color flow Doppler interrogation. PW Doppler imaging may help assess the degree (severity) of vascular narrowing by estimating the gradient across the stenosis by the modified Bernoulli equation: gradient (mm Hg) = (maximal velocity)^2 × 4. Moreover, arterial blood flow results in characteristic Doppler waveforms (a rapid forward flow component during systole, transient reversal of flow during early diastole, and a prolonged slow forward flow during late diastole). With mild to moderate vascular stenosis, characteristic changes in the PW Doppler waveform include acceleration of peak systolic velocities and loss of diastolic flow reversal distal to the stenosis. Of course, with complete stenosis, blood flow is interrupted.[8]

208.1.3 Magnetic Resonance Imaging

Magnetic resonance angiography (MRA) is a safe, noninvasive imaging technique that may be useful to evaluate the peripheral arterial system. In human medicine, both contrast and noncontrast MRA methods have been applied for planning interventional procedures (e.g., stent placements) in patients with peripheral vascular disease.[9,10] Unlike other vascular imaging techniques, noncontrast MRA displays blood flow and not the blood vessel itself. Limitations of noncontrast MRA include time of acquisition, variation of blood flow characteristics (e.g., diastolic flow reversal) in diseased vessels, and retrograde filling of arteries during complete occlusion resulting in artifacts and reduction of net forward flow on the image. Contrast-enhanced angiography using a non-nephrotoxic contrast material eliminates many of the previously mentioned limitations. Advantages of contrast-enhanced MRA include shorter acquisition times, high spatial resolution, and high signal-to-noise ratios.[10]

208.2 MECHANISMS OF THROMBOSIS

Hemostasis is a complex process that involves blood vessels, platelets, coagulation proteins, naturally occurring anticoagulants, and platelet inhibitors. Thrombosis results when one or more components of the hemostatic cascade are perturbed, tipping the balance between coagulation and fibrinolysis in favor of coagulation. Physiologic alterations leading to the formation of thrombi have frequently been classified into three main categories: (1) alterations in blood flow, (2) damage to vascular endothelium, and (3) changes in coagulation proteins and platelets, resulting in hypercoagulability.

Normal flow of blood through blood vessels is laminar, with the rapidly flowing red blood cells (RBCs) in the center of the vessel. Platelets and white blood cells (WBCs) are suspended in the blood near the vessel wall. Normal laminar flow can be disrupted by changes in the diameter of the vascular lumen and blood velocity, resulting in simultaneous regions of blood stasis and turbulence (e.g., atherosclerosis). When blood stasis occurs, increased contact occurs between platelets, coagulation factors, and the endothelium, thus promoting coagulation. Turbulent flow also causes a denuding endothelial injury that eliminates the anticoagulant function of the endothelium and promotes thrombus formation.[11]

Because under normal conditions the endothelium plays an important role for anticoagulation, factors that cause endothelial injury or dysfunction promote thrombosis. For example, the presence of atherosclerotic plaques is a well-known risk factor for thrombosis in humans and hypothyroid dogs. In addition, elevated levels of homocytseine (a sulfur-containing amino acid produced by the metabolism of methionine) act as a thrombogenic agent by promoting vascular smooth muscle cell proliferation and inhibition of endothelial cell growth. Hyperhomocysteinemia is a risk factor for thromboembolic disease in humans[12] and possibly, cats.[13,14]

Disorders that result in an imbalance of the hemostatic system toward the development of thrombosis are termed *hypercoagulable*, a physiologic alteration linked to the development of thrombosis. Either increased activity of platelets and coagulation factors or decreased activity of naturally occurring anticoagulants such as antithrombin III can result in hypercoagulability.[11]

When a thrombus becomes dislodged from the site of formation, it moves to a distal site (i.e., embolizes). Clinical consequences are generally related to local or systemic effects associated with resultant end-organ ischemia. Arterial TE can result in many organ systems. Venous thrombi may dislodge, resulting in pulmonary TE, or can result in local disruption of blood flow and venous stasis.

208.2.1 Arterial Thromboembolism

Vascular thrombosis is most readily identified when arteries are affected, and the clinical consequences are generally acute and severe. The aortic trifurcation is one of the most common locations for arterial TE in cats[15] and dogs (Figure 208-1). Atherosclerosis leads to the majority of human thromboembolic disease and is most commonly localized to the carotid, coronary, or cerebral arteries.[16] The differences in cholesterol metabolism in dogs and cats may partially explain the low frequency of atherosclerotic-related arterial TE in veterinary patients compared with humans. Most thrombi are formed in the left heart and embolize distally (see Figure 208-1; Figure 208-2). Thrombi formed in the arterial system where the blood flow rate is high consist primarily of platelets and have been termed *white thrombi*.

208.2.2 Venous Thromboembolism

Thrombi formed in the venous circulation under low blood flow conditions are composed of fibrin and erythrocytes (Figure 208-3) and have been termed *red thrombi*. Venous thrombosis frequently causes fewer clinical abnormalities than arterial thrombosis and consequently is frequently undetected. Deep venous thrombosis, a major risk factor for pulmonary TE in over 90% of cases in humans, is not known to be a risk factor for pulmonary TE in animals. Pulmonary TE occurs in several disease states associated with hypercoagulability. These include nephrotic syndrome, hyperadrenocorticism, immune-mediated hemolytic anemia (IMHA), thrombocytosis, cardiac disease, sepsis, disseminated intravascular coagulation (DIC), heartworm disease, and neoplasia.[17–24] Antithrombin III deficiency may be involved in thrombogenesis as part of a number of these diseases. For example, destruction of RBCs in IMHA releases thrombogenic substances.[24] Antithrombin III inactivates thrombin and other clotting factors, and even a mild reduction in antithrombin III can result in thrombosis or TE. A deficiency of antithrombin III can be secondary to decreased synthesis (e.g., congenital), increased consumption (e.g., DIC), loss of antithrombin from the intravascular compartment (e.g., nephrotic syndrome), and increased protein catabolism (e.g., Cushing's disease). Protein C and protein S are vitamin-K dependent protein factors and major inhibitors of the procoagulant system.[11] Deficiencies of both of these proteins have been associated with clinical thrombotic disorders in humans. A single case report of protein C deficiency has been reported in a thoroughbred colt.[25] The presence of multiple concurrent disorders in patients with TE is common. For example, 47% of cats with necropsy confirmed pulmonary TE had multiple concurrent predisposing disorders.[26]

Figure 208-1 **A,** Gross heart dissected to illustrate the left ventricular outflow tract, from a dog that experienced acute posterior paresis. An extensive pedunculated mass (tumor) is present from the sinus of Valsalva and extending through the ascending aorta. **B,** Distal aorta from this dog containing a saddle embolus.

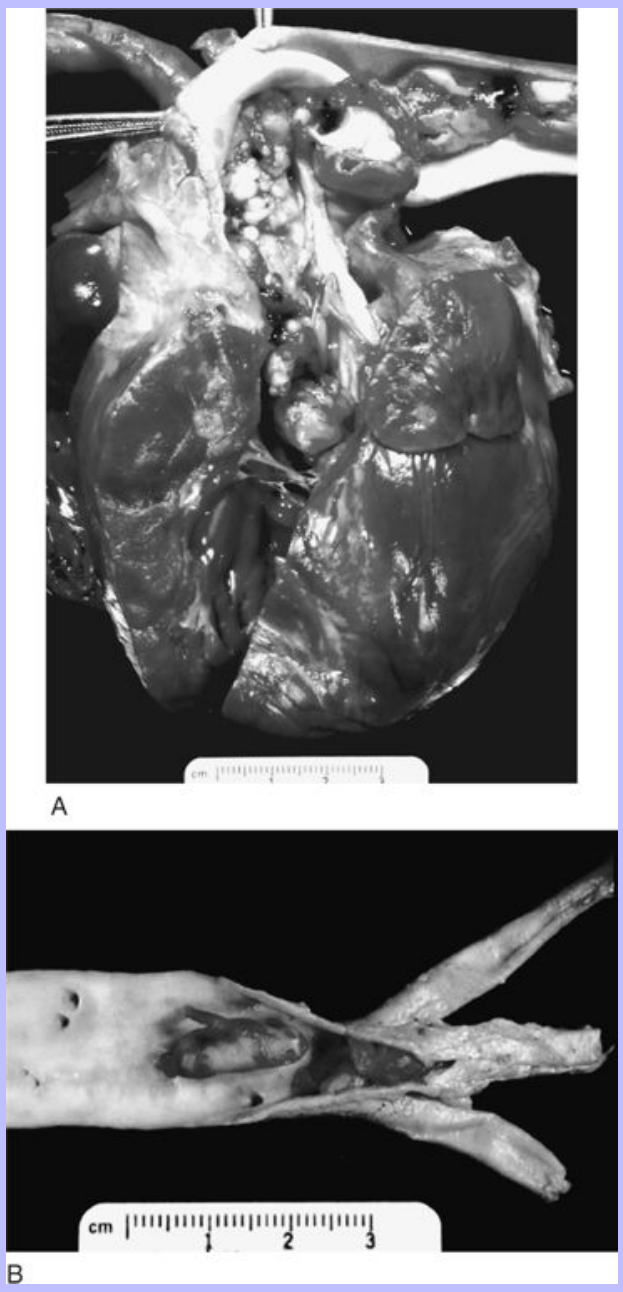


Figure 208-2 Kidney from the dog in Figure 208-1. Extensive, acute hemorrhage is seen that is associated with renal infarction.

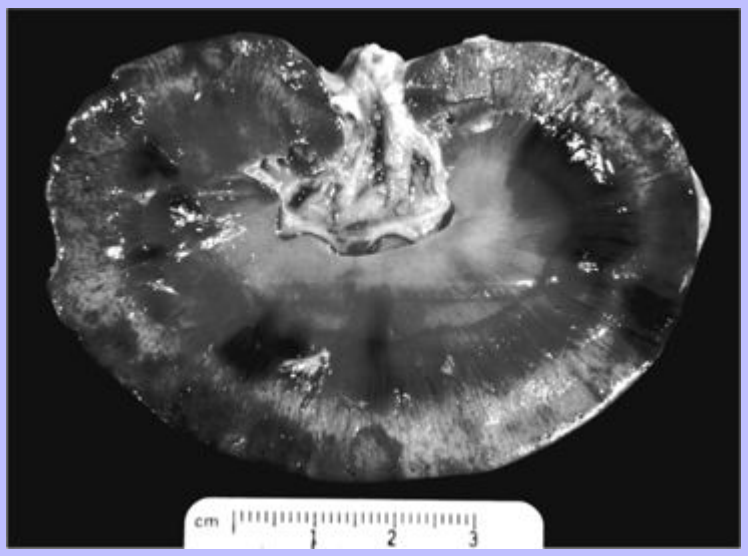
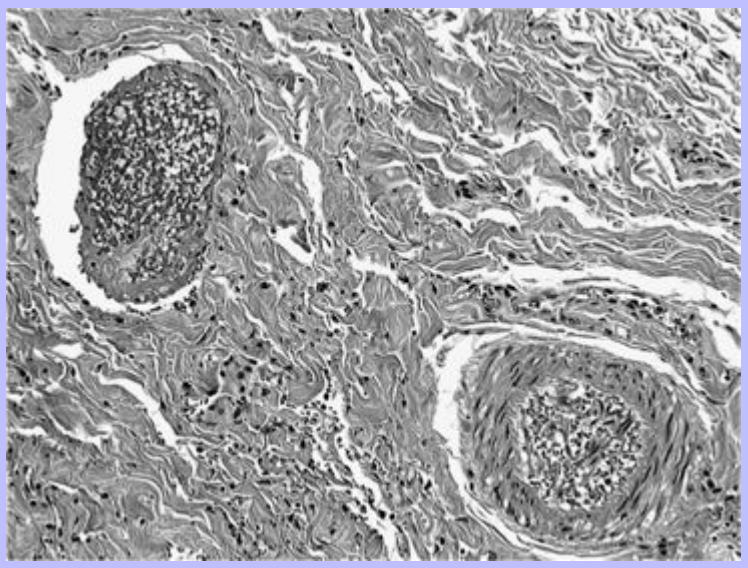


Figure 208-3 Organized thrombus fills the lumen of a vein (*upper left*) in the stomach wall from a dog with disseminated intravascular coagulation (DIC). Gastritis is also evident. A normal artery is present in the lower right.



208.3 CLINICAL DISORDERS FREQUENTLY ASSOCIATED WITH THROMBOEMBOLIC DISEASE

208.3.1 Hypercoagulable States

Many systemic and metabolic diseases are associated with an increased risk of arterial or venous thrombosis and TE. Primary hypercoagulable states refer to congenital abnormalities increasing the risk for thrombosis. Primary hypercoagulable states remain poorly characterized and are infrequently recognized in animals.

Secondary hypercoagulable states refer to risk factors that promote the development of thrombosis.[16] Table 208-1 lists causes and predisposing factors of thrombus and TE. Secondary hypercoagulable states resulting in TE have been described in a variety of systemic and metabolic diseases.

208.3.2 Disseminated Intravascular Coagulation

DIC is a specific pathologic process that involves the development of thrombi in the microvasculature and the generalized consumption of platelets and coagulation factors. This results in simultaneous hemorrhage and thrombosis, ischemia, and multiorgan failure. DIC is characterized by overwhelming thrombin and plasmin activation. Various unrelated diseases associated with DIC are unified by unregulated activation of mononuclear cell cytokines initiating simultaneous coagulation and fibrinolysis. Multiple cytokines are believed to be responsible for the initiation of DIC through induction of tissue factor expression on monocytes and endothelial cells.[16] Tumor necrosis factor (TNF)-alpha and interleukin-6 (IL-6) are two of many cytokines involved in the pathogenesis of DIC. Cytokines also inhibit natural anticoagulants including protein C and S complex, tissue factor pathway inhibitor, and antithrombin III. Cytokines affect endothelial integrity, promoting platelet adhesion and resulting in increased levels of plasminogen activator inhibitor-1 (PAI-1) and promote fibrin deposition.[11]

DIC occurs in patients with a wide variety of clinical disorders. Heatstoke, sepsis, pancreatitis, neoplasia, immune-mediated disease, trauma, and toxin exposure are common inciting causes of DIC. The trigger causing DIC in these seemingly unrelated syndromes may be systemic inflammatory response syndrome and the production of proinflammatory cytokines including but not limited to TNF, IL-1, and IL-8.[27] The most important step in treating DIC is elimination of the underlying pathologic condition or triggering mechanisms and the conditions that promote this hypercoagulable state. Anticoagulants have been advocated, although clinical data regarding efficacy are lacking.

208.3.3 Protein-Losing Nephropathy

Protein-losing nephropathy (PLN) results in loss of plasma proteins into the urine through injured glomeruli. The small molecular weight of antithrombin III (65,000 daltons) allows it to pass through the glomerulus similarly to albumin. The resulting hypercoagulable state is most often associated with venous thrombosis and can result in pulmonary TE.[18–22] Arterial (aortic) TE has also been reported in dogs with PLN.[7]

208.3.4 Hyperadrenocorticism

Both spontaneous hyperadrenocorticism and exogenous administration of glucocorticoids have been associated with the development of thromboemboli.[7] The hypercoagulable state in spontaneous

hyperadrenocorticism is characterized by an increase in coagulation factors II, V, VII, IX, X, XII, and fibrinogen, coupled with a decrease in the natural anticoagulant antithrombin III.[28] Thrombin-antithrombin complexes are also increased in dogs with hyperadrenocorticism but with no clinical signs of thrombosis, suggesting subclinical thrombosis. Long-term exogenous administration of glucocorticoids is associated with proteinuria and glomerular changes.[29] Whether or not this ultimately results in loss of antithrombin III and hypercoagulability is unknown. Both arterial and venous TE have been diagnosed in dogs receiving exogenous glucocorticoids.[30]

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Table • 208-1 Causes and Predisposing Factors of Thrombosis and Thromboembolism

VASCULAR ENDOTHELIAL DAMAGE	HYPERCOAGULABILITY	ABNORMAL BLOOD FLOW
Arteriosclerosis	Infection/sepsis/abscess	Neoplasia
Atherosclerosis	Neoplasia	Cardiomyopathy
Vasculitis	Hyperadrenocorticism	Congestive heart failure (CHF)
Heartworm disease	Protein losing nephropathy (PLN)	Endocarditis
Catheterization	Protein losing enteropathy (PLE)	Hypovolemia
Injection of irritating substances	Disseminated intravascular coagulation (DIC)	Shock
Neoplasia	Thrombocytosis	Anemia
Vascular incarceration/compression	Platelet hyperreactivity	Polycythemia
Hyperhomocysteinemia	Immune-mediated hemolytic anemia (IMHA)	Dehydration
Feline ischemic encephalopathy (FIE)	Parvovirus infection	Hyperviscosity
Fibrocartilaginous embolism		

208.3.5 Feline Cardiomyopathy

The cause of feline TE is multifactorial and principally accompanies myocardial disease with associated injury to left ventricular or left atrial endothelium. Some affected cats with aortic TE have elevated blood levels of homocysteine when compared with cardiomyopathic cats without TE,[13] and homocysteine metabolism may be abnormal in some felines.[14] Several coagulation abnormalities leading to hypercoagulability have been identified in cats with aortic TE.[31] Platelets from some cardiomyopathic cats have also been shown to be hyperaggregable in response to adenosine phosphate (ADP) in vitro.[32]

208.3.6 Immune-Mediated Hemolytic Anemia

Pulmonary TE is a major complicating factor leading to the high rate of mortality in IMHA. Because of the difficulties in antemortem diagnosis of PTE, most estimates of the number of dogs with IMHA and TE are based on necropsy results and range from 15% to 80%.[33] Use of intravenous catheters, elevated bilirubin concentration, elevated alkaline phosphatase concentration, and decreased albumin have all been associated with development of pulmonary TE.[33] Severe leukocytosis, left shift, and neutrophil toxic change may serve as laboratory markers of systemic thrombosis in some cases.[34] Derangements in routine coagulation tests, prothrombin time (PT), partial thromboplastin time (PPT), and fibrinogen concentration are common in IMHA patients.[24] Thrombocytopenia is also common and severe thrombocytopenia (platelets <50,000/μL) occurs in

approximately 25% of IMHA patients. Fibrin (or fibrinogen) degradation products and D dimer are increased in greater than 50% affected of dogs. DIC is also commonly diagnosed in IMHA.[24]

208.4 THERAPY OF THROMBOEMBOLIC DISEASE

The management of primary diseases resulting in the development of TE is discussed in related chapters throughout this textbook. Therapy of TE should be directed toward the underlying disorder whenever possible. Therapeutic strategies for managing TE include short-term systemic anticoagulation and fibrinolysis followed by long-term antiplatelet or anticoagulant therapy to reduce the risk of rethrombosis.

208.4.1 Supportive Care

General patient care is critical for successful management of thrombosis. Analgesic agents should be considered for acute pain management. Fluid therapy should be administered when indicated to correct acid-base abnormalities and dehydration. Dextrose-containing fluids should be avoided whenever possible because they may cause endothelial damage, further promoting thrombosis. A risk of volume overload exists with heart failure or pulmonary hypertension and fluid therapy must be carefully monitored. Strict cage rest and oxygen therapy are indicated in cases of pulmonary TE or thrombosis associated with congestive heart failure (CHF).

208.4.2 Acute Anticoagulation

Heparin is the mainstay of acute anticoagulation. Anticoagulants prevent additional clots from forming but do not dissolve clots (see thrombolysis). Coumadin therapy for the long-term control of thrombosis is initiated after adequate heparinization has been achieved.

Heparin functions as a cofactor with antithrombin III, and together this complex exerts its effect by neutralizing factor X and thrombin. Heparin is inactivated by gastrointestinal (GI) enzymes when given orally and therefore must be administered by injection. Heparin is administered to prolong the baseline activated partial thromboplastin time (aPTT) to 1.5 to 3.0 times the baseline value. Prolongation of the aPTT or activated coagulation time (ACT) does not correlate well with heparin levels in cats and dogs, and measurement of plasma heparin levels may be more useful in monitoring heparin therapy. Although many different heparin doses have been advocated, little clinical data exist concerning efficacy. Doses of heparin required to achieve adequate heparin levels in cats with TE ranged from 175 U/kg every 6 hours to 475 U/kg every 8 hours, subcutaneously.[35] In normal dogs the dose of heparin required to achieve adequate heparin concentrations was 250 U/kg every 6 hours, subcutaneously.[36] The most common side effect of heparin therapy is hemorrhage. In the event of severe hemorrhage, heparin can be neutralized by protamine sulfate administration.[37]

Low molecular weight (LMW) heparin is being increasingly used.[38] Its anticoagulant effect is limited to blocking the activity of factor X. Because LMW heparin has a lower antithrombin effect than unfractionated heparin, LMW heparin does not markedly influence the PT or aPTT. Measurement of factor X activity has been used to assess the effect of LMW heparin. One advantage of LMW heparin is that it has a lower risk of hemorrhage than conventional heparin therapy. The optimal dose of LMW heparin in dogs and cats with thromboembolic disease remains to be determined.

208.4.3 Chronic Anticoagulation

Warfarin (Coumadin) is a vitamin K antagonist inhibiting the synthesis of vitamin K–dependent clotting proteins (prothrombin and factors VII, IX and X). In addition, warfarin reduces efficacy of the vitamin K–dependent regulatory proteins C and S.[11] Proteins C and S are anticoagulant factors, and their function is the first to be inhibited by warfarin administration. Therefore heparin and warfarin administration are generally overlapped for 2 to 4 days to prevent a transient hypercoagulable state. Some animals appear to do well with just warfarin. Starting doses for warfarin are 0.25 to 0.5 mg every 24 hours in the cat and 0.1 to 0.2 mg/kg every 24 hours in the dog. Due to the high individual patient variability, close monitoring of PT is essential. Early recommendations were to maintain PT 1.5 times the baseline value, and more recent recommendations suggest attaining an international normalized ratio (INR) of 2:3.[39] INR is calculated by the formula $(\text{patient PT/control PT})^{ISI}$. The ISI is a value specific to the tissue thromboplastin that is used in measuring the PT. Coumadin is continued on a long-term basis to prevent recurrent TE. Studies documenting the optimal dose, efficacy, and duration of Coumadin therapy for specific thromboembolic diseases in dogs and cats are unknown.

The use of Coumadin is not without risks. The major risk is fatal hemorrhage, which occurs acutely and unexpectedly. Ideally, pets maintained on Coumadin should live indoors and be well supervised to prevent trauma and to monitor for hemorrhage. Periodic measurement of the PT should be done to ensure adequate dosing. Coumadin interacts with many drugs. The addition of medications to the treatment regimen of a pet on Coumadin should be done cautiously because certain drugs will raise the activity of Coumadin and predispose patients to bleeding. Some of these drugs are phenylbutazone, metronidazole, trimethoprim sulfa, and second-and third-generation cephalosporins. Barbiturates will decrease Coumadin anticoagulant effect. If bleeding complications occur, warfarin therapy is discontinued and administration of vitamin K is recommended.[39]

208.4.4 Antiplatelet Therapy

Antiplatelet drugs have been advocated for long-term management to prevent rethrombosis. These drugs inhibit platelet aggregation and adhesion, preventing the formation of the hemostatic platelet plug. Aspirin inhibits cyclooxygenase, leading to decreased thromboxane A_2 synthesis. This renders platelets nonfunctional by preventing their aggregation.[40,41] Cats lack the enzyme needed to metabolize aspirin (glucuronyl transferase), making them sensitive to aspirin-induced platelet dysfunction. Doses of 0.5 mg/kg every 12 hours in the dog and 25 mg/kg twice weekly in the cat may decrease platelet aggregation.[37] However, rethrombosis generally occurs despite aspirin therapy, although it is not known whether aspirin delays recrudescence. Additional antiplatelet drugs include dipyridamole and ticlopidine. Dipyridamole is thought to inhibit platelet aggregation by inhibition of platelet phosphodiesterase, leading to increased levels of cyclic adenosine monophosphate (cAMP) within platelets. Ticlopidine impairs fibrinogen binding and inhibits platelet aggregation induced by ADP and collagen.[37] The use of these newer compounds has been limited thus far in veterinary medicine.

208.4.5 Thrombolysis

Thrombolytic agents such as streptokinase, urokinase, and tissue plasminogen activator (tPA) are potent activators of fibrinolysis. These agents have been used with variable and often limited success in veterinary medicine.[42–45]

Streptokinase binds plasminogen, and the complex transforms other plasminogen molecules into plasmin. Plasmin then binds to fibrin and causes thrombolysis. Streptokinase binds both free and clot-associated plasminogen. It also degrades factors V, VIII, and prothrombin, resulting in a massive systemic coagulation defect.

Streptokinase has been used to treat aortic thromboembolism (ATE) in cats with varying degrees of success. In one study of 46 cats, 15 were discharged from the hospital after streptokinase therapy with a median survival of 51 days.[45] Reperfusion injury occurred in approximately 35% after thrombolysis, with streptokinase often resulting in fatal hyperkalemia and metabolic acidosis. Eleven of the cats developed clinical hemorrhage after streptokinase therapy. In three cats, hemorrhage was significant enough to require transfusion. Others reported conservative management (treatment of heart failure plus Coumadin or aspirin) of ATE with a hospital discharge rate of 28%, which was similar to cats treated with streptokinase.[15] One recommended dose of streptokinase for dogs and cats with TE is 90,000 U, intravenously administered over 20 to 30 minutes, followed by a maintenance infusion of 45,000 U for 7 to 12 hours. Infusions may be repeated over a total of 3 days.[37]

Recombinant DNA technology produces t-PA, a serine protease. A complex forms between t-PA and fibrin, and that complex preferentially activates thrombus-associated plasminogen-resulting in rapid fibrinolysis.[47] Life-threatening hemorrhage is the number one side effect. The half-life of t-PA in dogs is 2 to 3 minutes; consequently, if bleeding occurs, stopping the infusion will result in the drug clearance from the system in 5 to 10 minutes. Because t-PA causes rapid thrombolysis, the risk of reperfusion syndrome and lethal hyperkalemia is substantial. In one report, 50% of cats with ATE died acutely during t-PA therapy, with death attributed to hyperkalemia, severe anemia, and renal hemorrhage.[46]

208.5 VASCULAR DISEASES

208.5.1 Diseases Of Arteries

208.5.1.1 Occlusive Arterial Diseases

Arterial occlusion refers to the interruption of blood flow within an artery and most commonly results from trauma, thrombi, emboli, arteritis, degenerative lesions such as atherosclerosis, and factors associated with endothelial dysfunction or injury. Arterial thrombosis requires one or more inciting local or systemic conditions: (1) vascular endothelial damage, (2) sluggish blood flow, and (3) changes in blood constituents resulting in a hypercoagulable state.[11] Vascular endothelial injury can be induced by infectious agents (e.g., *Dirofilaria immitis*), prolonged hypotension, hypoxia, acidosis, inflammation, trauma, and immune mechanisms. Compressive lesions, such as from tumors, may promote thrombosis by a reduction in local blood flow and endothelial injury. Thromboemboli usually represent blood clots that have broken free from a site of thrombus formation. Emboli can also consist of tissue particles, fat, gas, bacterial vegetations,

parasites (e.g., heartworms), tumors, or foreign bodies.[48] Entrapped emboli may themselves become thrombogenic. Arterial occlusion can be acute or chronic. Chronic gradual occlusion can occur with mural or extramural hematomas, atherosclerosis, arteriosclerosis, vasculitis, or intimal tears forming valvelike structures.

The potential clinical consequences of arterial occlusion (tissue hypoxemia, ischemia, neuropathy, tissue necrosis) are related to extent and duration of vascular obstruction, and the physiologic consequences of the affected organ or organs. Tissues supplied by the endarteries, which have no connections to collateral vascular beds, undergo greater ischemic injury than organs supplied with collateral circulation. Acute, complete arterial occlusion causes rapid ischemic injury. This is largely due to release of vasoactive substances by the clot, which induces vasoconstriction and reduces collateral circulation. In addition to the acute effects, long-term injury (days or weeks) occurs and includes fibrosis and neuromyopathy.[7]

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208.5.1.1.1 Feline systemic thromboembolism

Feline systemic TE is discussed in Chapter 204.

208.5.1.1.2 Canine systemic thrombosis and thromboembolism

Arterial occlusion has been reported in dogs occurring secondary to atherosclerosis, nephrotic syndrome, vegetative endocarditis, neoplastic emboli, dirofilariasis, trauma, and thrombi of left heart origin (see Figure 208-1). The distal aorta, iliac, renal, and femoral arteries are common sites of systemic TE (see Figures 208-1 and 208-2).[7]

208.5.1.1.2.1 History

Acute arterial occlusion is usually indicative of systemic, metabolic, or cardiovascular disease. Clinical recognition and identification of the cause are enhanced by an insightful history, complete physical examination, and appropriate diagnostic tests. Some animals have a history of intermittent claudication, whereas in others, acute paresis or paralysis is the major presenting sign. Acute, complete arterial occlusion may cause posterior paresis, extreme hindlimb pain, and general distress.[49,50] In some cases the animal may have an unsteady gait, lameness, progression to stumbling, weakness, or collapse. Other potential signs include weight loss, exercise intolerance, hindlimb licking or chewing, and hypersensitivity over the lumbosacral region and the hindlimbs. Other signs attributable to systemic or metabolic diseases may sometimes be detected.

208.5.1.1.2.2 Clinical signs and physical examination

The outcome and clinical signs of arterial occlusion depend on (1) size and number of thrombi, (2) degree and duration of vascular occlusion, (3) pathophysiologic consequences of the organ or organs supplied, (4) whether the clot is infected or sterile, (5) whether the event is solitary or repeated, (6) the adequacy of compensatory mechanisms (e.g., collateral vessel recruitment, vasodilatation, clot lysis, restoration of blood flow), (7) the effects of vasoactive chemicals elaborated by the clot on collateral vessels (i.e., vasoconstriction), and (8) related complications (e.g., tissue necrosis, local infection, hyperesthesia). A slowly progressing arteriosclerotic or atherosclerotic stenosis allows time for the development of collateral circulation and may have minimal clinical consequences. A sudden

embolus, however, may not be associated with the development of collateral circulation, and presenting clinical signs may be more severe.[50] Microthrombus formation is common, and rapid clot lysis and abundant collateral circulation usually results in absence of outward clinical signs.

Classic presentation of acute arterial occlusion is described by the seven *P*s: (1) pain, (2) paleness, (3) paresthesia, (4) pulselessness, (5) polar (cold), (6) paresis or paralysis, and (7) prostration.[49] Physical examination may reveal cool distal limbs and swollen muscles. Segmental and pedal reflexes may be depressed. Hypersensitivity over the lumbar spine may exist. A slow onset and progressive peripheral neuropathy after trauma may be associated with ischemia of peripheral nerves. Arterial thrombosis of a front limb may also occur. Clinical signs are usually less severe than those described for posterior limb thrombosis.

In the central nervous system (CNS), arterial occlusion is rarely diagnosed. For signs to be recognizable, several arteries have to be occluded simultaneously, as can occur in severe atherosclerosis or with embolization after arterial catheterization. Cerebrovascular occlusions may lead to sudden disorientation, weakness, anisocoria, and hemiamaurosis. Infarction may follow TE to a localized area of the brain. *Stroke* is a generic term denoting any acute, nonconvulsive, focal neurologic deficit stemming from cerebrovascular disease. The classic presentation includes hemiparesis, but a broad spectrum of neurologic injuries may result. Neurologic signs depend on site, extent, and time course of vascular occlusion. In a series of 17 affected dogs, cerebrovascular disease was associated with coagulopathy, metastatic brain tumor, trauma, sepsis, atherosclerotic thrombus, unknown cause, and vascular malformation.[51] A cerebellar infarction caused by meningeal arterial thrombosis has also been described in a German shepherd dog with acute onset of seizure and neurologic deficits.[52] We have occasionally observed neurologic signs related to stroke in cats associated with severe systemic hypertension. Affected animals usually present acutely blind and show signs of retinal hemorrhage and detachment. Neurovascular disorders may be more common than the literature suggests. Increasing availability of advanced imaging techniques should facilitate the diagnosis of these conditions.

With endocarditis, a heart murmur of mitral or aortic insufficiency may be auscultated. Bacterial embolization from these valves may cause a systemic shower of emboli, which frequently affect abdominal organs, especially the kidneys and small intestines. Complete unilateral or bilateral renal artery occlusion invariably causes severe renal infarction. Affected dogs are depressed and may exhibit an arched back, sublumbar pain, and hematuria.

Acute occlusion of a major mesenteric artery may cause initial gastric hyperactivity, followed by ileus and intestinal infarction. Sudden anorexia, vomiting, bowel evacuation, and abdominal pain may be present. Feces may contain blood. With bowel infarction, bloody diarrhea, severe signs of an acute abdomen, and shock may develop.

208.5.1.1.2.3

Diagnosis

When peripheral arterial thrombosis is suspected, a survey thoracic radiograph is indicated to evaluate cardiac size and shape and to assess for pulmonary changes including edema, thrombosis, or dirofilariasis. Chest and abdominal radiographs should be evaluated for orthopedic lesions, which could result in posterior paresis. In addition, radiographs of the pelvic and hindlimb region may be

indicated to check for masses that could exert pressure on the aorta and for periosteal reactions in the sublumbar area. Doppler echocardiography may be useful for identifying vascular disturbances.[6,7]

Clinical pathology data may help characterize the underlying primary disease. Coagulation profiles are variable. Some cases of glomerulopathies and hypoproteinemia have been associated with reduced levels of antithrombin III.[22] Assessment of protein C and protein S levels should be considered when these tests are available. A clinical pathology data base is also advised to evaluate and detect renal or hepatic disease, dirofilariasis, DIC, and systemic and metabolic disorders. Blood cultures are indicated if endocarditis, bacteremia, or sepsis is suspected.

Confirmation of diagnosis may require proof of a vascular occlusion. This can be accomplished in some cases by physical examination, whereas in others, arteriography or diagnostic ultrasound are required.[1,6,8] The arteriogram can indicate the exact location of the thrombus or illustrate the extent of vascular occlusion and collateral vascular supply (Figures 208-4 and 208-5). Furthermore, radiolucent emboli such as heartworms may be outlined when present as longitudinal filling defects. Contrast angiography and other alternative imaging methods (thermography, perfusion scanning) in human medicine are being replaced by MRA and advanced ultrasound techniques such as intravascular ultrasound.[6,9]

208.5.1.1.2.4

Differential diagnoses

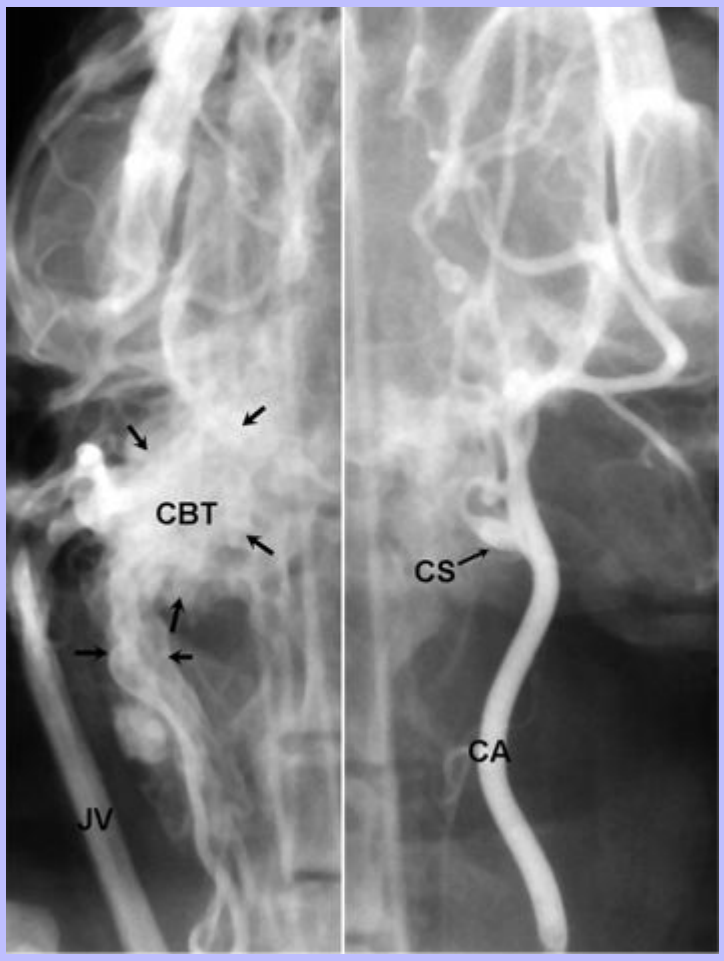
Differential diagnoses include trauma; peripheral neuropathy; spinal, pelvic or vascular tumors; infections; toxoplasmosis; degenerative myelopathy; interventricular disc protrusion; fibrocartilaginous embolic myelopathy; and the cauda equina compression syndrome. Radiographs should be systematically evaluated for signs related to these disorders.

208.5.1.1.2.5

Prognosis

The prognosis depends on the cause, extent, and severity of occlusion, presence or absence of local complications (ischemic neuromyopathy, ulcers), and concurrent embolization to visceral organs. Even in cases with spontaneous recovery, relapses must be expected. Rapid diagnosis and treatment are essential to avoid severe or even irreversible tissue injury.

Figure 208-4 Two ventrodorsal angiograms of a dog with a carotid body tumor. The left panel demonstrates a late arterial-venous phase after injection of contrast medium into the right common carotid artery. A tumor "blush" is seen, with contrast medium opacifying vessels feeding the carotid body tumor (*CBT; arrows*). Venous return is observed via the jugular vein (*JV*). The angiogram in the right panel is a useful comparison and was taken after injection of contrast material into the left common carotid artery (*CA*). Normal flow is observed, and the carotid sinus (*CS*), an area for sensing blood pressure, is evident. (Courtesy of John Bonagura, DVM.)



208.5.2 Feline Ischemic Encephalopathy

Feline ischemic encephalopathy (FIE) results in cerebral ischemic necrosis. FIE occurs in male and female cats of all ages and is more prevalent in the summer months. The cause of FIE is uncertain. Preliminary evidence suggests *Cuterebra* infection as a potential cause in some cases.[53,54]

Clinical pathology is usually unremarkable. Cerebrospinal fluid (CSF) analysis may be normal or have mildly elevated protein levels and a mild to moderate pleocytosis. An increased proportion of large foamy macrophages have been observed in the CSF from 2 to 7 months after the onset of seizures. Suspected diagnosis can be made by T2 weighted MRI. In one study of six cats with FIE, MRI findings included mild to marked asymmetry of the cerebral hemispheres and bilateral asymmetric enlargement of the subarachnoid space.[55]

Gross lesions are usually unilateral and may involve up to 75% of one cerebral or cerebellar hemisphere (or both). Hemispheres may appear atrophic and ridged with wide sulci. Histopathologic findings have included parenchymal atrophy and cystic degeneration, gliosis, and phagocytic macrophage infiltration. Perivascular lymphocytic cuffing of small capillaries and vascular occlusive lesions including thrombosis and vasculitis has been reported. Infarction of the middle cerebral artery represents the most common distribution.

Figure 208-5 Aortogram of a 7-year-old Saint Bernard dog with a saddle thrombus at the aortic trifurcation associated with a chondrosarcoma located near the terminal aorta. The owner had observed four episodes of pain and weakness in the hindlimbs that developed gradually when the dog was taken for a walk. At the beginning of the walk, the dog was normal. If the dog was forced to continue walking after the signs of pain and lameness had appeared, it collapsed. After resting for a few moments, the dog was able to walk again. On clinical examination the femoral pulse was difficult to feel, and the periphery of the hindlimbs was cool. Pain could be elicited when the pelvic area was palpated. Aortography was performed, and a radiograph was taken 4 seconds after the beginning of the injection of contrast medium. On the aortogram the common origin of the internal iliac arteries and the left external iliac artery contain no contrast medium, suggesting that they have been occluded completely. A partial occlusion has reduced the flow of contrast medium into the right external iliac artery. Some collateral blood supply to the hindlimbs probably occurs via the seventh lumbar artery. Anticoagulation therapy was instituted, but it failed to provide relief and the dog underwent euthanasia at the request of the owner.

Clinical signs are typically acute in onset, nonprogressive, and suggestive of unilateral cerebral or brainstem involvement. Seizures are the most common historical or presenting clinical sign. Other clinical signs may include depression, head tilt, anisocoria, circling, seizures, and behavior changes.

Treatment is limited to supportive care, and the prognosis is generally favorable. Clinical improvement typically occurs over several days to weeks. Multiple episodes can occur. Behavior changes and uncontrollable seizures can persist.[54,55]

208.5.3 Fibrocartilagenous Embolization

Fibrocartilaginous embolization (FCE) is associated with ischemic necrosis of the spinal cord parenchyma. The pathogenic mechanism is not resolved. Spinal cord arteries and veins become occluded with fibrocartilage originating from the nucleus pulposus of the intervertebral disc. Trauma may be a predisposing factor in a large percentage of affected cases. FCE can occur at any age but is most common in adult nonchondrodystrophoid breeds. Young Irish wolfhounds and miniature schnauzers are particularly prone to the disease. FCE has been reported less commonly in cats.[55,56]

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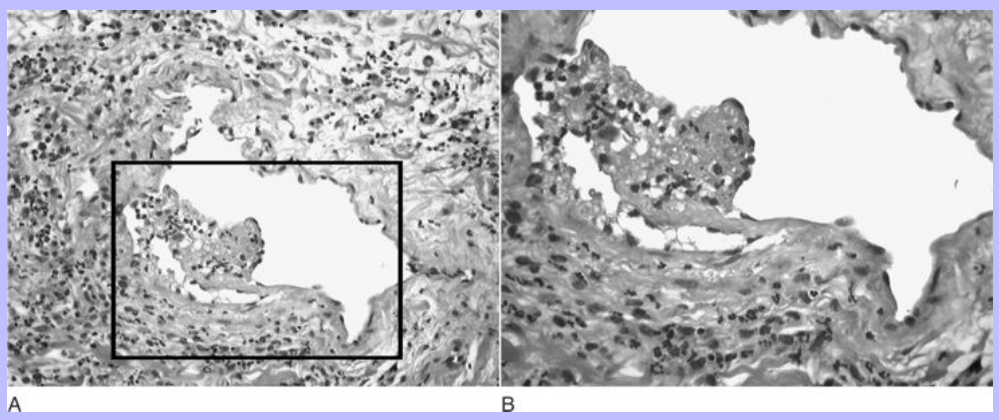
Figure 208-6 Vasculitis is indicated by inflammatory cells present within **(A)** and around **(B)** the venous vessel wall. Vascular injury associated with necrosis, degeneration of endothelial and smooth muscle cells, and fibrin deposition is evident. A small intramural thrombus is also present.



Clinical signs of myelopathy vary depending on the location and severity of the spinal cord ischemic injury. Deficits are often asymmetrical, and the clinical signs are not progressive. Affected animals do not typically show evidence of pain, although brief painful periods have been described just prior to the onset of clinical signs.

Diagnosis of FCE is based on excluding other causes of acute myelopathy. Results of plain radiographs are normal. CSF evaluation may be normal or show nonspecific abnormalities including mild protein elevations,

mild pleocytosis, and xanthochromia. Myelography is typically normal, or mild spinal cord swelling is seen. MRI may reveal spinal cord edema on T2 weight images.[55]

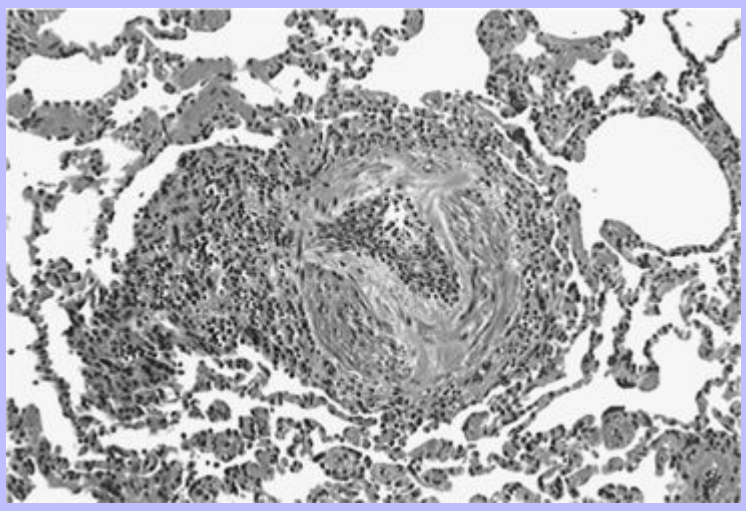
Treatment is primarily supportive care and physical therapy. Evidence for the use of glucocorticoid therapy is lacking. If treatment is attempted, methylprednisolone succinate (MPS) should be given within the first 6 to 8 hours after the onset of neurologic signs. Prognosis for recovery is variable depending on the location and extent of the lesion. Poor prognostic indicators include lower motor neuron (LMN) signs and size of the animal because of the inherent difficulties of performing physical therapy on large breed dogs.[56]

208.5.4 Vasculitis and Angiitis

The terms *vasculitis* and *angiitis* refer to the pathologic syndrome that is characterized by vascular inflammation and necrosis. Although there have been many reported causes of vasculitis, only a few histologic manifestations of the disease have been diagnosed. Vasculitis can occur in toxic, immune-mediated, infectious, inflammatory, and neoplastic disorders. Blood vessels of any type in any organ can be affected, resulting in a wide variety of clinical signs. The nonspecific nature of histologic lesions, coupled with variable clinical presentations, makes the diagnosis of primary vasculitis quite challenging. The clinical consequences of vasculitis depend on the size, number, type, and extent of blood vessels that are affected.[57]

Histologically, vasculitis is characterized by the presence of inflammatory cells within and around blood vessel walls. Vascular injury is associated with necrosis and degeneration of endothelial and smooth muscle cells and fibrin deposition (Figure 208-6). A collection of fibrin, immunoglobulins (Igs), complement, and platelets appears by light microscopy as eosinophilic material within the vessel wall and lumen and is referred to as *fibrinoid*. Eosinophilia secondary to degeneration of collagen and smooth muscle can also be present within the vessel wall.[58] These histopathologic lesions distinguish vasculitis from perivascular inflammation (Figure 208-7). Vasculitides have been classified based on specific inflammatory cell infiltrates that may include neutrophils, lymphocytes, or macrophages.[58,59] As the disease becomes chronic or begins to resolve, predominant cell populations may change. Vasculitis may develop from within a vessel as a result of infectious, immune-mediated or toxic injury or by extension from adjacent areas of inflammation. Infectious agents can injure endothelial cells directly or through the production of endotoxins and exotoxins. The exact mechanism of endothelial injury is not known but involves the formation of oxygen free radicals, local inflammatory mediators, and the recruitment of inflammatory cells.[60] Exposure of subendothelial collagen during endothelial injury results in the activation of Hageman's factor and the subsequent activation of the complement, kinin, and plasmin systems. These lead to increased vascular permeability and inflammation.

Figure 208-7 Section of lung. Perivasculitis is evident as large inflammatory infiltrate surrounding pulmonary arteriole.



Type III hypersensitivity reactions can cause necrotizing vasculitis from the deposition of immune complexes within the vessel walls. Activation of the complement cascade may attract neutrophils, cause immune complex phagocytosis, and result in the release of lysosomal enzymes and oxygen free radicals, thereby leading to further inflammation and necrosis. In the chronic state this reaction becomes diminished, and mononuclear cells replace the neutrophilic inflammation. Immune complex reactions of this type can occur in many disease conditions such as primary immune-mediated disease or be secondary to infectious disease. Emphasis on immune complex activity can only be misleading because immune complexes are rapidly cleared from the circulation.[59,61] In humans the discovery of antineutrophil cytoplasmic autoantibodies (specific for antigens in neutrophil granules and monocyte lysosomes) has allowed further identification of immune-mediated processes in which immune complexes were suspected but not identified. Cell-mediated immunopathogenic mechanisms are initiated in the blood vessel wall. This type of vasculitis is characterized by accumulations of lymphocytes and macrophages within vascular walls. Myocyte necrosis results in fibrinoid degeneration, endothelial hyperplasia, and occasionally thrombosis. A granulomatous type of reaction of the vessel wall can result, particularly in chronic cases. These changes may be accompanied by hemorrhage and ischemic changes in surrounding tissues.[61]

The cause of secondary vasculitides is, by definition, known, and classifications are based accordingly. These conditions usually result from infectious diseases such as feline infectious peritonitis (FIP), canine coronavirus infection, parvovirus infection (rare), Rocky Mountain spotted fever (RMSF), leishmaniasis, and dirofilariasis. They may also occur in drug reactions and in immunopathogenic connective tissue and collagen diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis.[62]

208.5.4.1 Microscopic Necrotizing Vasculitis

Microscopic necrotizing vasculitis (MNV) refers to a large heterogeneous group of clinical syndromes that share similar histologic properties. *Hypersensitivity vasculitis* is often referred to in dermatologic

manifestations and is often clinically distinct from the multisystemic form of necrotizing vasculitis. Termed *juvenile polyarteritis syndrome* (JPS), it has been reported in young beagle dogs.[63,64] Less distinction exists between JPS and those syndromes described as *idiopathic steroid-responsive vasculitides* that can manifest as multisystemic or localized disease.[65,66] Lesions can affect mainly arterioles, capillaries, and venules.

Clinical abnormalities of MNV are often associated with phasic pyrexia, listlessness, and anorexia. In some cases, lymphadenopathy, myalgia, epistaxis, drooling, sneezing, and arthralgia may occur. In addition to the generalized signs, manifestations of specific organ lesions may occur.[67] The most common presenting clinical signs in small animals are dermatologic lesions. Hemorrhagic maculae resembling circular petechiae and ecchymoses are common. Other lesions seen include wheals, urticaria, purpura, nodules, bullae, necrosis, and ulcers. In many cases the skin lesions are associated with pain, pruritus, or both. Less frequently encountered lesions include ulcers at the mucocutaneous junctions or of the mucous membranes, especially located on the head (external ear canal and pinnae, face), bony prominences of the limbs, and the foot pads, as well as pitting edema involving dependent areas such as limbs, ventral trunk, head, and scrotum.[62,63]

Internal organ involvement with MNV frequently goes undiagnosed. This is because clinical signs are vague, simultaneous multiorgan involvement often occurs, or organ manifestations are confused with those of infectious, degenerative, or traumatic conditions (e.g., pneumonia, glomerulonephritis, arthritis, spinal or neuromuscular conditions). The clinicopathologic findings of primary MNV vary according to severity, duration, and specific organ. Lymphopenia, eosinopenia, hypoalbuminemia, hyperglobulinemia, and hyperfibrinogenemia occur commonly. Less consistent findings include leukocytosis with a left shift and toxic neutrophils; leukopenia; neutropenia; monocytosis; a mild normocytic, normochromic anemia; and thrombocytopenia. Serum liver enzymes and triglycerides are often elevated.[57,59]

An idiopathic cutaneous and renal glomerular vasculopathy has been described in kenneled and racing greyhounds, with many characteristics similar to MNV.[68] It is characterized by fibrinoid arteritis, thrombosis, and infarction with deep, slowly healing skin ulcers and peracute renal glomerular necrosis with a predilection for afferent arterioles.

Diagnostic confirmation requires histologic examination of skin, organ, or lymph node biopsies specimen and exclusion of other immune-mediated disease. Special immunologic tests have been recommended to demonstrate a low or high concentration of complement, C3, and elevated levels of circulating immune complexes. The history may be helpful if drug hypersensitivity is suspected.

Primary periarteritis, or polyarteritis, a necrotizing vasculitis affecting small-and medium-sized muscular arteries has been identified in colonies of beagles.[69,70] This polyarteritis occurs in two forms. One form occurs mainly in young beagles, in which arteritis affects major branches of coronary arteries almost exclusively. Clinical signs are usually absent. A second form of polyarteritis is associated with vague multisystemic signs (fever, depression, anorexia, neutrophilia, decreased albumin- to-globulin ratio), a stiff gait, pain on abdominal palpation (beagle pain syndrome), or a combination of these symptoms. The signs are associated with vascular lesions including disseminated, focal, or diffuse intimal thickening and acute fibrinoid necrosis of the media resulting in occlusion and thrombosis.

The differential diagnosis includes pemphigus vulgaris and foliaceus, bullous pemphigoid, SLE; dirofilariasis, specific infectious diseases, chronic neoplasia, and cold hemagglutination disease. The prognosis is usually favorable.

Many therapies have been advocated. Administration of all unnecessary drugs should be discontinued. In many cases immunosuppressive doses of glucocorticoids with or without an antibiotic have been used successfully. Cyclophosphamide may be administered if that fails. Dogs with lesions involving only the skin can be given sulfasalazine (Azulfidine) at an initial dose of 22 mg/lb (49 mg/kg) every 8 hours.[57] Dose frequency can be decreased after lesions improve from three times to twice a day and, later, to once a day. Dogs receiving sulfasalazine should be observed for side effects such as fever, keratoconjunctivitis, and hematologic abnormalities.

208.5.4.2 Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is a rare polysystemic disease associated with a necrotizing vasculitis of unknown cause. The disease affects predominantly segments and bifurcations of small and medium-sized muscular arteries. In humans, PAN is classified among immune-mediated collagen disorders and derives its name from purpural lesions that are palpable in the subcutaneous tissue. In contrast, palpable nodules are not a regular feature of PAN in animals.[71,72] The vascular lesions consist of intimal proliferation, vessel wall degeneration, necrosis, and thrombosis in all stages of development. PAN leads to a loss of vessel wall integrity, petechial and ecchymotic hemorrhages, focal areas of tissue infarction and necrosis, aneurysm formation, nodular swelling, and thickening of the major arteries. Target tissues of canine PAN include the kidneys, skin, mucous membranes, adrenals, meninges, GI tract, connective tissue, and myocardium.[72] The lungs are usually spared.

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The clinical presentation includes systemic signs (pyrexia, lethargy, reluctance to walk, vague pain, or weight loss) and a wide spectrum of organ system abnormalities (linear skin ulceration, ulceration of mucous membranes, nasal discharge, spinal pain, and signs of cardiac or renal failure [or both]).[71,72] Clinicopathologic findings may include leukocytosis with a left shift and proteinuria.

The main differential diagnoses are hypersensitivity angiitis and idiopathic polyarteritis. The diagnosis is confirmed by histologic examination of a skin biopsy specimen, and the prognosis is guarded to poor. Treatment includes glucocorticoids, cyclophosphamide, or both.

208.5.4.3 Lymphomatoid Granulomatosis and Miscellaneous Vasculitides

Lymphomatoid granulomatoses and other unclassified vasculitides are characterized by a polymorpholymphocytoid, plasmacytoid, and histiocytoid granulomatous infiltration around blood vessels. Pulmonary nodular lesions of variable size due to lymphomatosis were first described in dogs.[73] Infarction, necrosis, and cavitation occur in some of the masses. The bronchial lymph nodes can be slightly to greatly enlarged, and pulmonary thrombosis is common. The cause of this rare condition is unknown. Occasionally, similar lesions are associated with eosinophilic pneumonitis in occult dirofilariasis, although they can also occur outside of endemic areas of dirofilariasis. An immune-mediated cause is likely because, in some cases, large amounts of IgG and IgM can be demonstrated in plasma cells and macrophages.[74] The differential diagnosis is primary or secondary neoplasia, with which this condition is often confused. Diagnosis is rarely made clinically and requires histologic examination of biopsy material. The prognosis is usually poor. In some patients, multicentric lymphosarcoma has developed at a later date. Surgery or treatment with glucocorticoids and cytotoxic immunosuppressive drugs is only temporarily effective.

208.5.5 Arterial Aneurysm

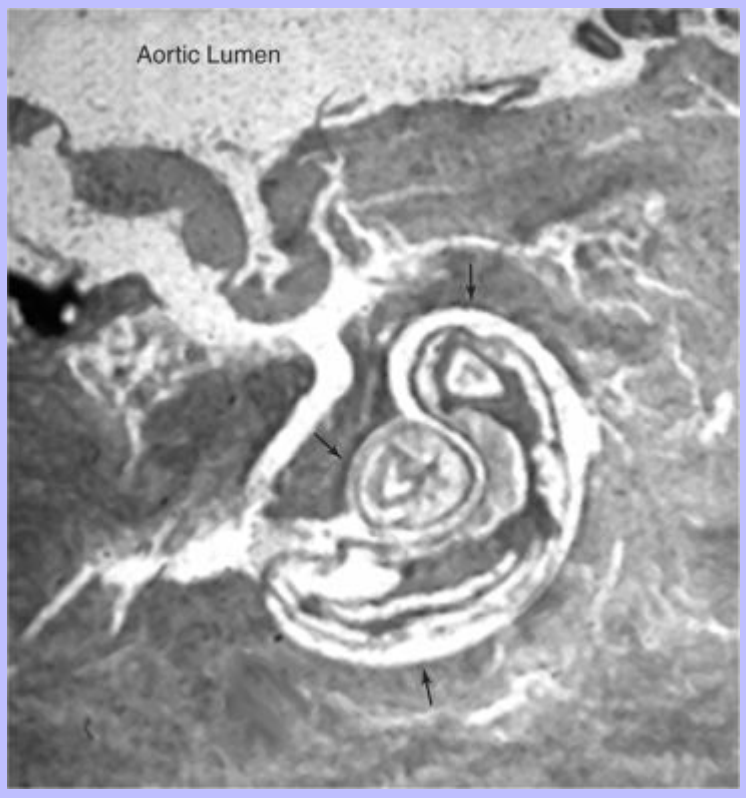
An arterial aneurysm is a circumscribed dilation of an arterial wall or a blood-containing swelling connecting directly with the lumen of an artery. Arterial aneurysms are rare in dogs and cats and only isolated cases have been reported.[75–78] Aneurysms can be categorized based on their shape (saccular or fusiform), cause (atherosclerotic, mycotic, inflammatory, arteritis, traumatic, congenital, dissecting), or their histologic appearance. Two major histologic classes of aneurysms are (1) true aneurysms (aneurysma verum) and (2) false aneurysms (aneurysma spurium).

208.5.5.1 True Aneurysm

A true aneurysm is a vascular dilatation caused by a weakened arterial or venous wall with subsequent widening of the vascular lumen. Histologically, true aneurysms involve the entire arterial wall and contain three microscopic arterial layers. Aneurysms may result from destruction of the media or the elastic fibers of large arteries (or destruction of both) by inflammatory or degenerative processes. Traumatic aneurysms can be true aneurysms or pseudoaneurysms, depending on their cause and histologic appearance. Aneurysms have been found in the aorta of dogs that were caused by migrating larvae of *Spirocerca sanguinolenta* (formerly *S. lupi*)[76] (Figure 208-8). Aneurysms can also result from turbulent blood flow with arteriovenous (AV) fistulas.

Dissecting aneurysm (aortic dissection) involves a hematoma associated with a defect in the aortic intima. Blood within the aortic lumen is forced through the intimal tear into the outer and middle layers of the aortic media, forming a second or false lumen. The dissection can then propagate proximally or distally along the aorta. A report of a dissecting aortic aneurysm was reported in a dog with clinical and histologic findings similar to that reported in humans.[75] Dissecting aortic aneurysm has also been reported in two cats: one with CHF, severe aortic insufficiency and systemic hypertension and a second cat with signs of weakness, lethargy, and cardiogenic shock.[77,78]

Figure 208-8 Photomicrograph of a canine aorta. The intima and media have been disrupted by the presence of the subtropical and tropical parasite *Spirocerca sanguinolenta* (formerly *S. lupi*). The parasite is seen in cross-section (*arrows*). The aortic lumen is at the top of the figure. (Courtesy of John Bonagura, DVM.)



Peripheral aneurysms appear as soft, warm, pulsating bulges. Occasionally, a "machinery" murmur can be auscultated over these areas (see Arteriovenous Fistulas). Clinical signs are frequently absent or vague. If spontaneous vascular rupture occurs, pain, signs of anemia and shock, and pleural or mediastinal effusion may be present. Exsanguination resulting from aneurysmal rupture is possible.

208.5.5.2 Spurious (Pseudo) Aneurysm

Spurious aneurysms, also known as *pseudoaneurysms*, are caused by localized disruption of the native artery. Their histologic appearance includes arterial wall architecture that is formed by fibrous tissue. One cause of spurious aneurysms is a hematoma that communicates with an arterial lumen resulting from venipuncture.[79] Traumatic spurious aneurysms are probably more common than is usually realized. Clinical signs may include lameness, persistent pain, and deep muscular swelling unresponsive to local therapeutic measures, antibiotics, or glucocorticoids. Pitting peripheral edema may be present, and neither blood nor pus can be aspirated from the swelling. The diagnosis of spurious aneurysms may be suspected from

physical examination. Survey radiographs may indicate soft tissue swelling. Diagnostic confirmation has classically relied on arteriography, which illustrates a nodular exudation of contrast medium at the arterial defect. Doppler echocardiography, especially color flow Doppler imaging, aids in identification by depicting blood flow and turbulence. Additional diagnostic tests include computed tomography (CT), radionuclide angiography, and surgical exploration. The differential diagnosis includes chronic infection, obstruction of a deep vein, or abscessation. With a spurious aneurysm, however, pyrexia and neutrophilia are not encountered. The prognosis is favorable if surgical vascular repair can be accomplished.

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208.5.6 Arteriosclerosis

Arteriosclerosis is defined as chronic arterial wall remodeling consisting of hardening, loss of elasticity, and luminal narrowing. These changes result from proliferation of connective tissue and hyaline degeneration of media and intima. Proliferation and thickening of the intima with the deposition of ground substances leads to progressive fibrosis and vascular stenosis. Inflammation is not a feature of arteriosclerosis.[80] Arteriosclerotic lesions are commonly detected in old dogs and cats and may comprise part of the normal aging process.[80–82] These changes are typically mild and usually unimportant to health and survival. Thrombosis is rarely a complication of such microscopic lesions, and their functional significance is not known. In other instances, arteriosclerosis may be severe and associated with substantial reduction in intraluminal diameter (often referred to as *small vessel disease*) (Figure 208-9). Lesions of this nature are also common in feline myocardial diseases, particularly hypertrophic cardiomyopathy, and may be detected in canine aortic stenosis as well.[83,84] Arteriosclerotic changes may also occur in aorta and cerebral, renal, spinal, and sinoatrial node artery.[80] Intramural coronary arterial narrowing commonly occurs in association with chronic degenerative valve disease as well. Arterial lesions may have been associated with small regions of myocardial necrosis and fibrosis. Intramural coronary arteriosclerosis was found in 26.4% of old dogs undergoing necropsy.[80] Extensive nonthrombotic, nonatherogenic stenosis of extramural coronary arteries was described in two adult male Labrador retriever dogs with CHF.[85] Disease of extramural arteries is less common. Endothelial aortic plaque formation associated with arteriosclerosis was detected in 77.8% of 58 dogs brought to a small animal clinic in Helsinki for euthanasia.[86] Spontaneous arteriosclerosis, with a predilection for renal vasculature, has been demonstrated in young (<2 years old) greyhounds.[87] The severity of the lesions was correlated with increased renal vascular tortuosity and high shear stress. Clinical consequences of these lesions have not been determined.

Figure 208-9 Arteriosclerosis in pulmonary arterioles. Severe thickening of the arterial intima and media and dramatic reduction of arteriolar lumen is evident. Inflammatory infiltrates are also diffusely present.

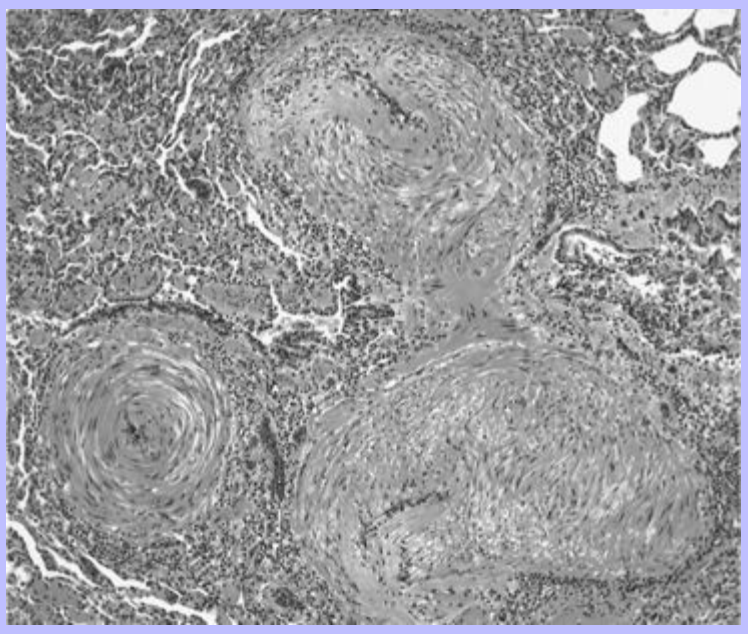
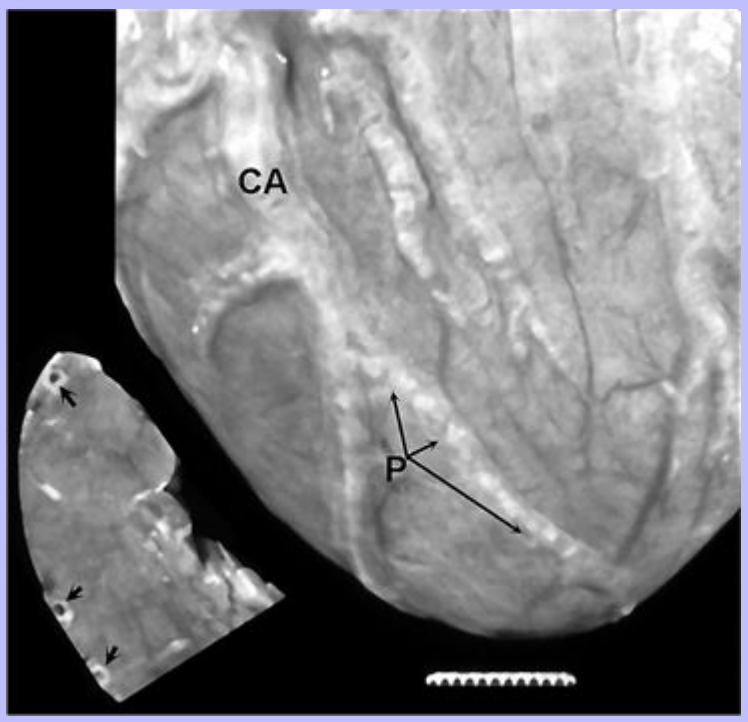


Figure 208-10 Coronary atherosclerosis of extramural coronary arteries in a dog with severe hypercholesterolemia (> 650 mg/dL) caused by hypothyroidism. Epicardial coronary arteries are evident. A larger epicardial branch is labeled *(CA)*. The reader should note numerous light plaques *(P)* within the arteries that represent deposition of lipid. The lower left portion of the figure shows a cut segment of myocardium. The lumina of the subepicardial arteries are also surrounded by a concentric layer of lipid. (Courtesy of John Bonagura, DVM.)



208.6 ATHEROSCLEROSIS

Atherosclerosis denotes inner arterial wall thickening in association with lipid deposition. Affected large coronary arteries often appear grossly thickened, yellow-white, and may have narrowed lumina (Figure 208-10). Histologically, deposits of plaque containing cholesterol, lipoid material, focal calcification, and lipophages thicken the inner sections of arterial wall (intima and inner media; Figure 208-11).[88,89] There can be widespread involvement of arteries from many organs. Unlike the disease in humans, canine atherosclerosis is uncommonly associated with extensive plaque formation, arterial calcification, or thrombosis. Atherosclerosis has not been described in cats.

Atheromas are lipoid arterial plaques and they are rare features of canine atherosclerosis. Atheromas are sometimes referred to as *xanthomatosis*. Atherothrombosis results when a localized atheroma forms on an atherosclerotic plaque, resulting in disruption of blood flow and subsequent ischemia, infarction, or both.[88] Atherothrombosis is most severe in both extramural and intramural coronary arteries, carotid arteries, and renal arteries.

Atherosclerosis has been detected in older dogs as a consequence of the hypercholesterolemia and lipidemia associated with thyroid atrophy. A predisposition for spontaneous atherosclerosis was reported in old, obese dogs with atrophied thyroid glands and hypothyroidism.[88] This observation is in accordance with experiments in which atherosclerosis could be induced in thyroidectomized dogs fed large quantities of cholesterol or cholic acids.[90,91] The spontaneous disease mainly affects male and spayed female dogs. An increased prevalence in miniature schnauzers, Doberman pinchers, and Labrador retrievers has been reported.[88] The distribution and severity of arterial lesions and thyroid atrophy are typically associated with clinical signs of lethargy, anorexia, weakness, dyspnea, collapse, heart failure, vomiting, disorientation, blindness, circling, and coma.[88,92] Recorded ECG abnormalities included atrial fibrillation, notched QRS complexes, and ST segment elevation. Laboratory abnormalities included hypercholesterolemia, lipidemia, low serum triiodothyronine (T_3) and thyroxine (T_4) concentrations, elevated blood urea nitrogen (BUN) (often associated with renal infarction) and liver enzyme concentrations, and high alpha$_2$ and beta fractions in the protein electrophoresis.

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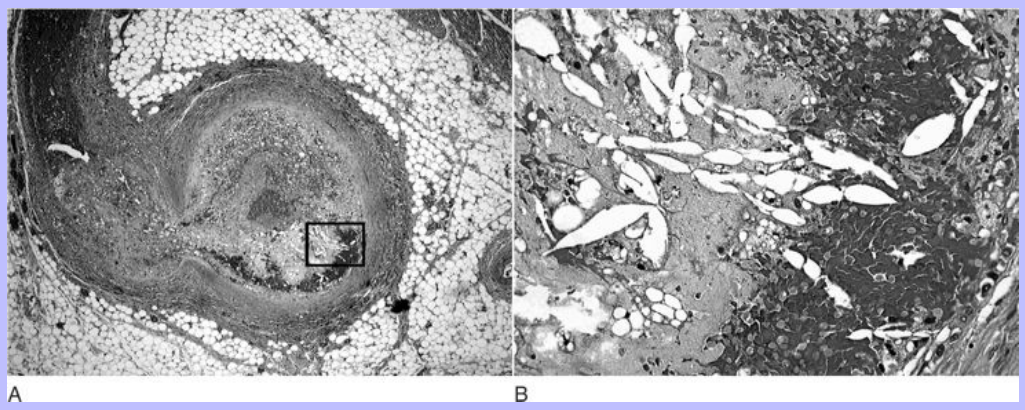
Figure 208-11 Atherosclerosis. **A,** Large coronary artery appears grossly thickened and has a narrowed lumen. The inner sections of arterial wall (intima and inner media) are thickened by deposits of plaque containing cholesterol, lipoid material, focal calcification, and lipophages. **B,** Magnified insert from **A**. Atherosclerotic plaque showing clefts of lipid material (*arrow*).



Clinical diagnosis of atherosclerosis is difficult, and the prognosis for dogs with clinical signs related to stenosing atherosclerosis is poor. Potential treatments include thyroid replacement drugs, antihypertensive medication, blood cholesterol–reducing agents, or a low-cholesterol diet. Treatment strategies have not been tested in dogs, and severe lesions are essentially irreversible. Not all dogs with hypothyroidism develop atherosclerosis. Only those with increased levels of very low–density beta lipoproteins tend to be prone to develop atherosclerosis and

plaques. Blood levels of low-density lipoproteins may be increased in these dogs because lipoprotein receptors are reduced and lipoid removal by the tissues is decreased. The elevated lipoprotein concentrations account for arterial lipoid deposits.[91]

Atherosclerosis is strongly suspected as being an inflammatory disease developing in response to injury in the vessel wall in humans. Infiltration of the mononuclear lymphocytes into the intima, local expansion of vascular smooth muscle cells, and accumulation of extracellular matrix is believed to be the pathogenesis of the inflammation. Previously determined risk factors including hyperlipidemia and hypercholesterolemia are believed to enhance leukocyte adhesion to damaged endothelium and reduce local immune response. The role of inflammation in the development of canine atherosclerosis has yet to be determined.[93]

208.6.1 Arteriovenous Fistulas (Arteriovenous Malformations)

A-V fistula is an abnormal communication between an artery and vein bypassing the capillary network. The true incidence is unknown, although A-V fistulas are reported uncommonly in dogs and rarely in cats. Centrally located anomalies may occur between the cardiac chambers (e.g., ventricular septal defect) or between the great vessels (e.g., aorticopulmonary window, patent ductus arteriosus) and are reviewed in Chapter 200 In this section, only peripheral A-V malformations (A-V fistulas) are discussed.

Congenital A-V fistulas are rare and are caused by arrest or misdirection of embryologic vascular differentiation. The persistence of primitive equipotential capillaries and the subsequent failure of the existing anastomotic embryologic channels to differentiate into arteries or veins are responsible for their abnormal communications. Terminology applied to congenital A-V fistulas has been a source of confusion (e.g., hemangioma racemosum, Park-Weber syndrome, hemangioma cavernosum, strawberry birthmark, nevus angiectasis, cirsoid aneurysm, congenital A-V aneurysm).

The most common cause of an acquired A-V fistula is blunt or penetrating trauma.[94] Iatrogenic trauma is often related to venipuncture and accidental perivascular injection of irritating medicaments.[95] Additional causes include neovascularized tumors (carotid body tumor, thyroid tumor, hemangiosarcoma), ruptured aneurysm, mass ligature of arteries and veins, gunshot wounds, and erosion of contiguous vessel walls by infection or arteriosclerosis. Most A-V fistulas involve the extremities, but they can occur anywhere in the body including the neck, spinal cord, body wall, head, brain, abdomen, liver, and lung. They can also occur as a complication of mass ligation of arteries and veins during closed castration.[96–99]

Irrespective of cause and location, A-V fistulas cause similar altered blood flow dynamics. The basic principle is that blood follows the path of least resistance. The A-V malformation is an abnormal connection between a high-pressure arterial system and a low-pressure venous system with a higher capacity. Due to the difference in resistance, blood flows preferentially through the fistula rather than continuing via the artery to the capillary bed. This shunting results in a reduction of flow in the artery distal to the fistula and increased flow in the venous system. In addition to stealing blood from the distal capillary bed, these changes lead to the development of collateral circulation around the fistula. The communicating shunt increases venous pressure, venous blood oxygen saturation, and the diameter and number of anastomotic arteries and veins. Eventually an ectasia of the feeding artery and aneurysmal sacs in the venous area of the A-V communications may develop. Histologic changes occur in affected vessels so that arteries begin to look more like veins (venification) and veins like arteries (arterialization). The rapid runoff of blood through the A-V fistula into the capacitant venous circulation causes turbulence and, potentially, sound (bruit).[100]

Shunted blood flow through a large fistula can be so great that retrograde flow from a distal artery into the fistula occurs. Arterial blood supply to the tissues distal to the A-V fistula may become compromised from competition with the fistula and secondary venous hypertension, resulting in stagnation of venous blood flow in the dilated veins, or even reversal of blood flow in a distal rather than proximal direction. Local edema and ischemia followed by tissue necrosis, ulceration, or organ dysfunction may ensue. In large and mostly centrally located fistulas, the central blood dynamics also become affected. Large flow volumes across the A-V fistula compromise the blood supply to other regions of the body by shifting blood into the capacitance venous circulation. Compensatory responses to increased blood volume (cardiac preload) include elevated heart rate, cardiac contractility, and eccentric cardiac hypertrophy. Augmented cardiac output and gradual expansion of the blood volume partially restore the blood supply to deprived tissues. Eventually, however, the increased venous return and the elevated cardiac workload may induce high-output heart failure.[101]

Clinical history and signs vary according to the location, size, duration, etiopathology, and topography of the fistula. A-V fistulas of the extremities may appear as painless, easily compressible, warm bulges or varicosities (Figure 208-12). Sometimes they are detected incidentally during routine clinical examination. With medium-sized or large fistulas of the extremities, a continuous palpable thrill and pulsation, along with a machinery murmur, can be detected. The leg or region distal to the fistula may be swollen, warmer, or colder than the proximal area (sometimes with severe local ischemia), painful, and affected by pitting edema. Lameness, cyanosis, therapy-resistant toe ulcers, scab formation, or gangrene can occasionally occur distal to the fistula with severe local ischemia. In the dilated superficial veins, a faint pulsation may be felt. In the feeding arteries a *water-hammer* pulse is often present. Animals with high-output heart failure may develop a cardiac murmur of mitral regurgitation and moist lung sounds, indicating pulmonary edema.

When firm pressure is applied proximal to the A-V fistula, or if the feeding artery is compressed, the thrill and bruit disappear and the pulse, and heart rate may drop as a result of diminished venous return and reduced cardiac output. This is referred to as *Branham's bradycardia sign*, and the maneuver is called *Branham's* or *Nicoladoni-Branham's test.* Together with the local thrill or fremitus and the bruit, the Branham's sign is pathognomonic for A-V fistulas.

Other signs have been reported and vary with respect to location and hemodynamic alterations caused by the A-V fistula. An A-V fistula in the orbit was reported to cause exophthalmos.[102] Recurrent bleeding from the mouth was observed in an A-V fistula of the tongue.[98] Restless behavior and lethargy followed by progressive seizures and hemiparesis were reported in a 10-year-old mixed breed dog with a subcortical cerebral A-V malformation.[103] An A-V fistula of the spinal cord at the thoracolumbar junction in a 10-month-old female Australian shepherd dog caused a deteriorating hindlimb ataxia, difficulty in getting up and down, hypersensitivity over the lumbosacral region, and urinary incontinence.[104] Cardiomegaly and pulmonary overcirculation were detected radiographically in a dog with a postsurgical AV fistula, and these changes regressed after the fistula was surgically closed.[97] An A-V fistula was found surgically in the jejunum of an 8-month-old dog with persistent anemia and melena.[105] A-V fistulas in tumors have been recognized as a strong pulsation and fremitus detectable during palpation of the tumor mass.[94] Auscultation of the tumor mass may reveal a machinery-type murmur or bruit.

Figure 208-12 Coon dog with an arteriovenous (A-V) fistula of the ear. The dog was presented for severe bleeding caused by trauma to large distended veins *(inset, arrows)*. A continuous murmur was ausculted over the ear, and Doppler studies demonstrated continuous arterial-to-venous flow. Venous distention is secondary to direct transmission of arterial pressure and marked increases to flow. (Courtesy of S.E. Johnson, DVM, and J. Bonagura, DVM.)

Congenital hepatic A-V fistulas have been reported in young dogs. The hepatic artery connects to the portal vein and causes portal hypertension or reversal of the blood flow in the portal vein.[106,107] There can be a single fistula or multiple fistulas that can be distinctly visualized by abdominal color Doppler ultrasonography

and coeliac arteriography.[108] Clinical signs include lethargy, vomiting, diarrhea, anorexia, weight loss, ascites, polyuria, and neurologic signs related to hepatic encephalopathy.[109]

Pulmonary A-V fistulas can lead to respiratory distress and cyanosis. Survey thoracic radiographs of animals with large fistulas may indicate cardiomegaly, a prominent aortic arch, a hypervascular lung field, and an increased interstitial or patchy pulmonary radiodensity, indicating pulmonary congestion or edema, respectively.

Diagnostic ultrasonography, especially color Doppler imaging, has been clinically useful for identifying and localizing A-V fistulas (Figure 208-13).[108,110,111] Findings included the presence of focal intra-arterial flow at the fistula site throughout the cardiac cycle, turbulent pulsatile venous flow at the fistula site, and nonpulsatile venous flow proximal to the fistula. Angiography may be used to define fistula anatomy and size more accurately and to plan management strategies. The absence of a normal capillary phase and premature outlining of the veins are typical arteriographic findings in shunting lesions. The differential diagnoses of A-V fistulas include neoplasms, varices, abscesses, cystic skin lesions, aneurysms, lymphedema, and scarring.

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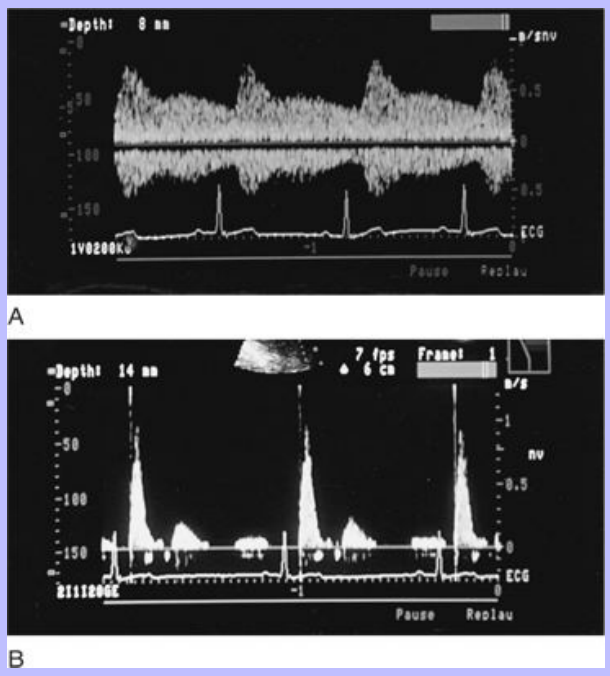
Figure 208-13 Pulsed wave (PW) Doppler recordings from a 5-year-old female golden retriever dog with traumatic A-V fistula. **A,** Doppler interrogation of a large, pulsatile, dilated vessel associated with the right radial artery identified by color flow Doppler at the medial right brachium. The reader should note the continuous flow best seen during diastole. **B,** Pulsed wave (PW) Doppler flows recorded from the normal left radial artery in the same dog.



Management of A-V fistulas has historically required surgical intervention.[112] This usually involves careful ligation of all proximal and distal arteries feeding the fistula, ligation of the draining veins, and complete excision of the A-V collaterals with the venous aneurysmal sacs (so called quadruple ligation). If relapse occurs or if multiple fistulas are present, a wide excision of the involved areas or limb amputation may be the only alternative.

Surgical approaches can often be technically difficult, mutilating, hazardous, and can have a high failure rate with residual clinical symptoms.[113] Consequently, arterial embolization techniques using special embolization wire coils have begun to be used to occlude A-V fistulas, owing to the minimally invasive nature of these procedures.[113,114] In a cat with a forelimb fistula, cyanoacrylate embolization was used to obliterate the fistula followed by en bloc surgical resection of vessels.[115] Transcatheter embolization using vaso-occlusive coils was described in three cats and two dogs with peripheral A-V fistulas.[116]

The prognosis for animals with small A-V fistulas is often good. Morbidity is highest with centrally located A-V fistulas, with fistulas that cause organ dysfunction, with large fistulas that induce a high cardiac output, and with fistulas that cannot be successfully occluded using embolization techniques.

208.6.2 Traumatic and Functional Arterial Disease

Trauma from direct accidental injury or iatrogenic trauma (e.g., surgery or vascular interventional procedures) is a common cause of vascular disease. Direct trauma may result in direct vascular wounds, or it can result in mural contusions leading to delayed thrombosis, necrosis, late hemorrhage, and false aneurysm formation. Vascular wounds can also occur from fractures because adjacent vessels are relatively fixed and vulnerable. Clinical features of traumatic arterial injuries may include diminished or absent pulse, enlarging hematoma, pulsatile arterial bleeding, symptoms of ischemia distal to the wound, injury of anatomically related nerves, and hypotension with major hemorrhage. Compressive forces from local tissue trauma (compartment syndrome) and vascular stenosis may delay or inhibit return to normal function of the affected area. Accurate diagnosis and extent of traumatic vascular injuries can be accomplished by direct examination, arteriography, ultrasound, and magnetic resonance imaging (MRI).[117]

Vasospasm refers to reversible localized or diffuse vasoconstriction of arteries or small blood vessels. If short lived, the ischemia is reversible and permanent damage does not result. However, prolonged vasospasm with ischemia may lead to tissue damage and ulceration. Vasospasm is a common response to blunt and perforating vascular trauma and may also result from perivascular injection of irritating substances. When this occurs, tissue injury and vasospasm can be minimized by local infiltration with procaine hydrochloride or lidocaine. Uncommonly, vasospasm occurs in association with spontaneous arterial rupture (e.g., ruptured cerebral aneurysm, stroke). Angiography is usually required for confirmation. Vasospasm may be elicited by exotoxins. The best-known example is ergotism that produces intense vasospasm of the digits and large vessels by stimulation of the alpha-adrenoceptor. The differential diagnosis of vasospasm includes polycythemia, cold agglutinins, thrombosis, arteriosclerosis, and vasculitis.

208.6.3 Diseases of Veins

Diseases of the venous system frequently cause minor clinical problems, despite the fact that veins are commonly affected by or involved in trauma, TE, edema, local inflammation, and septic processes. Many conditions, however, often go unrecognized. Venous disorders include traumatic injuries, superficial and deep

phlebitis and thrombosis (thrombophlebitis), catheter embolization, aneurysms, venous compression syndromes, varices, and ulcers.

Pulmonary thromboembolism (PTE) is a common and often life-threatening complication associated with a variety of systemic and metabolic diseases. A thrombus formed in the right heart or the peripheral or central venous system can embolize to the pulmonary arterial vasculature. Contributing factors include prolonged immobilization, trauma, surgery, and a range of disorders including IMHA, hyperadrenocorticism, nephrotic syndrome, DIC, sepsis, cardiac disease, amyloidosis, neoplasia, proteins C and S deficiency, and antithrombin III deficiency. PTE is covered in detail in Chapter 218.[21,26]

Varicosis and ulceration are rare in dogs and cats. When detected, they often accompany A-V fistulas. Cutaneous phlebectasia is a benign lesion sometimes erroneously called *telangiectasis*. It is reported almost exclusively in dogs with spontaneous or iatrogenic Cushing's syndrome.[118] Phlebectasia is an abnormal dilatation, extension, or reduplication of veins or capillaries or a combination of these changes.

Venous perforation or *blunt trauma* to veins is usually well tolerated because rapid clotting results in venous occlusion. If when venous occlusion or venous severance is severe, however, resultant edema and cyanosis are usually temporary because of collateral circulation. If all veins draining an area are compromised, marked edema and necrosis can ensue. Blunt trauma has been associated with caudal vena caval obstruction or kinking of the intrathoracic caudal vena cava and ascites.[119]

Venous malformations have been previously referred to as *cavernous hemangiomas*. They can be localized or extensive and appear as cystic dilation of blood vessels. They generally permit only low blood flow, and small lesions are generally asymptomatic. Expansion of the lesion may occur, however, especially after trauma. 1159
Thrombosis may occur due to sluggish blood flow, resulting in local swelling and tenderness. Larger lesions in 1160
dependent areas may enlarge, causing significant vascular dilation. This may result in changes in skin color, ulceration, and hemorrhage. The affected area appears as a warm, soft, compressible mass. No thrills or bruits are present due to the low flow. Pain may result from pressure exerted on deep tissues and nerves.

Figure 208-14 Angiogram of a dog with a cranial vena caval thrombus. The animal developed lymphedema of the neck, face, and front legs 1 week after a transvenous pacemaker lead had been inserted through the jugular vein to facilitate temporary cardiac pacing for complete heart block. Contrast medium was injected into an accessory cephalic vein with the animal positioned in sternal recumbency. Extensive collateral circulation is seen, but filling of the cranial vena cava is not identified. An epicardial electrode is visible in the cardiac apex, and the pulse generator can be seen subcutaneously in the left lateral thorax. (Courtesy of Nancy Morris, DVM.)

Diagnosis is made using history, physical examination, and ultrasound. Venography may be needed to define the lesion. Symptomatic therapy using light, compressive wraps is sometimes helpful for acute management.

Surgical excision of affected vessels is occasionally required, but complete resection is difficult and local recurrence is common.[120]

Thrombosis commonly follows blunt trauma and perforating injuries, particularly with venipuncture or prolonged venous catheterization (Figure 208-14). Phlebitis is a major cause of intimal damage leading to thrombosis. The thrombosis is usually of little local consequence. However, emboli may be carried to the lung and cause PTE. In most animals, blood clots carried to the lung are rapidly lysed and cause no problems. However, when inflammatory diseases, dehydration, or circulatory failure occurs, clot formation may continue in the pulmonary vessels and lead to vascular occlusion, severe dyspnea, pain, and death.[21] In infectious thrombophlebitis, bacterial emboli may be carried to the lungs and cause thromboembolic pneumonia. Spontaneous venous thrombosis is rare, although portal vein thrombosis has been reported. Clinical signs include ascites, peripheral pitting edema, and portosystemic shunting.[121]

Embolization of severed intravascular catheter fragments is an occasional complication of intravenous catheter placement.[122,123] In humans, reported complications of catheter embolization include perforation of cardiac walls, endocarditis, pulmonary embolism, and severe arrhythmias. Therefore it is generally considered prudent to remove catheter fragments. Nonsurgical, transvenous removal of catheter fragments using loop-snare catheters, forceps, and basket catheters have been described. Whenever possible, however, steps should be taken to avoid situations predisposing to catheter fragmentation, including inadequate restraint during catheter placement, withdrawal of catheters through their placement needles during repositioning, failure to properly secure catheter to the patient, and inadvertent severing of catheters during bandage changes.

Phlebitis can occur from a local inflammatory process extending to the veins or can originate from a venous intimal lesion. Common causes of venous intimal lesions are perivenous injection of irritating drugs, infusion of large amounts of fluid, and long-term placement of intravenous catheters. Infusion-related phlebitis occurs in three forms: (1) chemical (injury to vein by irritating drugs), (2) physical (trauma to the intima by catheters, needles, hypertonicity, or particulate matter in infused fluids), and (3) microbial (infected fluids, skin, or catheter tip). Sterile or septic thrombophlebitis may result, usually remains localized, and is characterized by pain, swelling, and exudation (Figure 208-15). Patients with serious illnesses or compromised immune systems, however, may develop sepsis, thromboembolic pneumonia, or endocarditis.

In cases of venous occlusion, clinical signs depend on the anatomic location, extent, and duration of the obstruction. Acute obstruction of centrally located and deep veins causes edema, cyanosis, discomfort, and venous dilatation distal to the obstruction site. Obstruction of the cranial vena cava causes edema in the neck, head, front limbs, and dependent portions of the chest wall (Figure 208-16). Pleural effusion commonly results from central venous obstruction. Clinical disorders of the intrathoracic caudal vena cava have been reported (Figure 208-17).[119] Obstructions of the renal or pelvic area cause edema of the hindlimbs and the scrotum. Clinical signs depend upon collateral vessel reserve and capacity of regional lymphatics. In addition to thrombosis, common causes of venous obstruction include invasive malignant processes and venous compression by abscesses, hematomas, tumors, and lymphadenopathy. A number of tumors have a tendency for venous invasion, including chemodectomas, adrenal tumors, and hemangiosarcomas. Angiography may indicate the occlusive or compressive lesion or highlight increased collateral circulation (or it may do both) (Figure 208-18). Diagnostic ultrasonography can often detect masses or flow disturbances.

The prognosis and therapy of venous obstruction depend on the primary disease. These are discussed in various chapters throughout this book.

208.6.4 Diseases of the Peripheral Lymphatics

The lymphatic system plays a critical role in regulating body fluid volume and immune function. Lymphatics originate within the interstitium as specialized endothelial-lined capillaries transporting fluid, solutes, and macromolecular particles back into the venous system. Fluid, protein, cells, and macromolecular particles from the interstitial space empty into the initial lymphatics composed of a series of small lymphatic capillaries that begin blindly in the tissues. The lymph then flows through a system of lymphatic vessels that progressively increase in diameter. As lymph flows centrally it passes through at least one lymph node before emptying into larger lymphatic trunks.[124] The deep trunks unite to form two major lymphatic vessels: (1) the thoracic and (2) right lymphatic duct. The thoracic duct drains most of the body and returns fluid into the venous system at the brachycephalic vein or the left subclavian vein. The right lymphatic duct drains the right side of the head and neck and right forelimb.

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Figure 208-15 Caudal (left) and lateral (right) views of the right rear limb of a young dog with severe edema caused by thrombophlebitis. The problem developed after placement of saphenous vein catheter. The limb is markedly swollen and edema fluid *(arrows)* is leaking through a small ulcer in the skin. Thrombosis of the vein prevents venous drainage and increases lymphatic fluid formation. (Courtesy of John Bonagura, DVM.)

Lymphatic vessels contain many junctions between individual endothelial cells that are connected to the surrounding extracellular matrix by reticular fibres and collagen. These junctions open when tissue hydrostatic pressure becomes elevated and the anchoring filaments stretch, allowing fluid to move into the vessel. As the fluid is cleared from the interstitium, the connecting fibers contract and the junctions between the endothelial cells close. The opening and closing of these junctions allow them to act as inlet valves, preventing the backflow of lymph into the interstitium. The larger vessels of the lymphatic system have progressively fewer open junctions, increasingly muscular walls, and frequent intralymphatic valves that also prevent backflow of lymph. The action of external muscular contraction along with intrinsic contractility of the lymphatic vessels aid in the movement of lymph through the lymphatic system. Lymph is filtered by at least one lymph node before entering the venous circulation. While in the lymph node, the lymph is in contact with the blood circulation and approximately half of the fluid is drained before leaving into the larger lymphatic ducts.[124]

Figure 208-16 Cranial vena cava syndrome associated with a mediastinal mass and cranial vena caval occlusion. Severe peripheral edema of cranial extremities is present.

In addition to its transport function, the lymph system plays a major role in the immunologic responses to infectious agents. It serves as a filtering system to impede the spread of microorganisms and neoplastic cells. The cellular components, in particular the lymphocytes, are indispensable for immunologic reactions and antibody formation.[125]

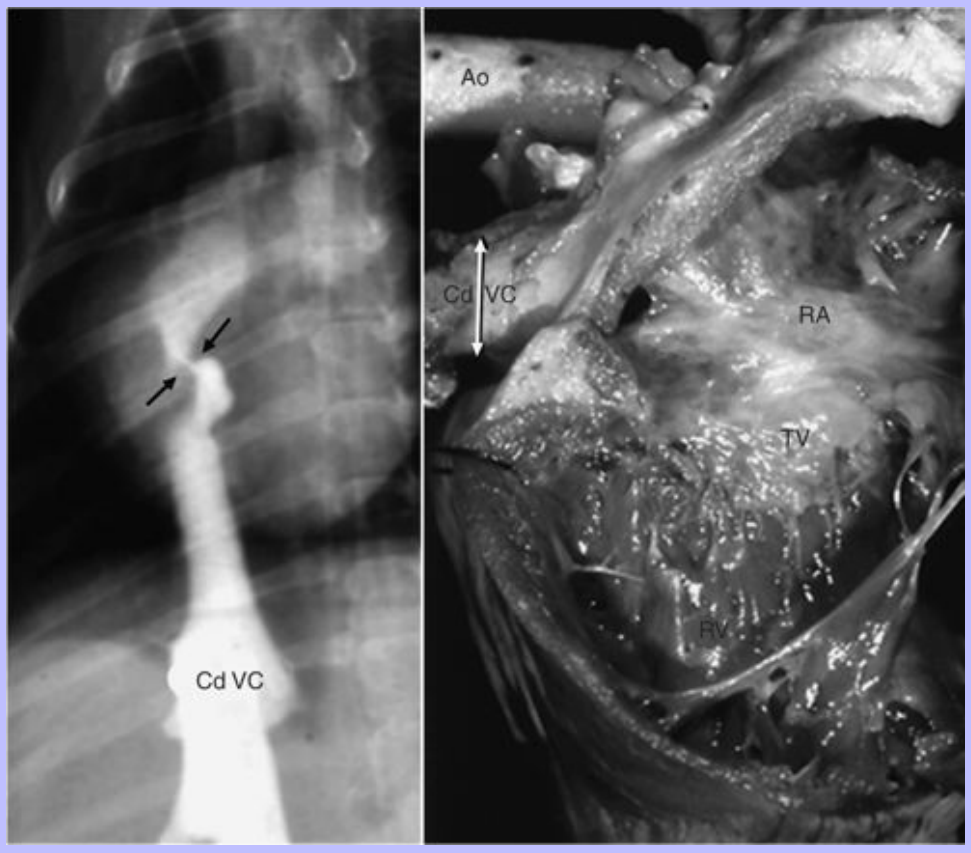
Lymphatic disorders can be subdivided into those of internal organs, such as intestinal lymphangiectasis, and peripheral lymphatic disorders. Several lymphatic diseases have been recognized in animals, including lymphedema, intestinal lymphangiectasia, chylothorax, lymphadenitis, lymphocysts, lymphoma, lymphangioma, and lymphangiosarcoma. Types and causes of peripheral lymphatic disorders are summarized in Box 208-2.

208.6.4.1 Inflammatory Lymphatic Disorders (Lymphangitis and Lymphadenitis)

Lymphangitis and lymphadenitis often occur secondary to local inflammation, particularly involving the skin, mucous membranes, and subcutaneous tissues. Lymphangitis can also result from bacterial or fungal infection or adjacent neoplastic and inflammatory disease. Lymphatics may be affected and occluded as they drain inflammatory agents and their by-products from tissue spaces. In lymph nodes, microorganisms are phagocytized and inactivated or killed by humoral and cellular mechanisms. During this process, lymph nodes may become obstructed, enlarged, warm, and painful. Affected limbs may be locally swollen, and lameness can result. Pyrexia, anorexia, and depression are common, and leukocytosis may be present with acute, severe lymphangitis.

Lymphangitis may become chronic when associated with a granulomatous or static lesion, such as a foreign body, or with unsuccessfully treated acute inflammation. Persistence of inflammatory edema results in mesenchymal cell proliferation, which in turn can cause irreversible thickening of skin and subcutis.

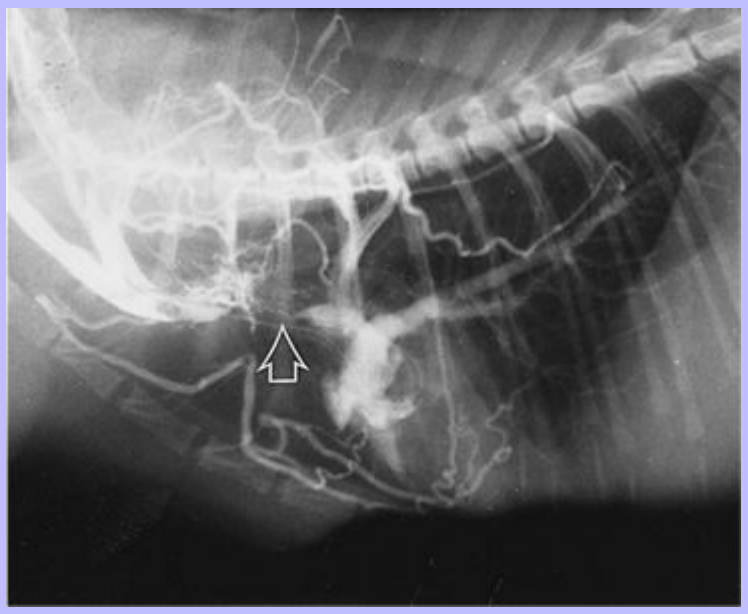
Figure 208-17 Acquired stenosis (fibrosis) of the caudal vena cava in an older dog. The left panel shows an angiogram of the caudal vena cava (*Cd VC*), which demonstrates a severe narrowing of the dye column *(arrows)* at the venous entry into the caudal right atrium. The right panel is a postmortem view of the heart taken from the right lateral perspective. The right atrial and ventricular walls have been retracted to demonstrate the stenotic, caval orifice *(small arrows)*. The reader should compare this opening with the diameter of the caudal vena cava *(to the left, large vertical arrow)*. The right ventricle (*RV*), tricuspid valve (*TV*), right atrium (*RA*), and descending aorta *(Ao)* are shown. (Courtesy of John Bonagura, DVM, and Matthew W. Miller, DVM.)



The prognosis is favorable with early treatment. Therapy consists of moist, warm, local compresses or soaks, which reduce swelling and promote drainage. Aggressive local and systemic antibiotic therapy

usually promotes recovery in animals with fever and anorexia. Bacterial culture and sensitivity testing should be performed if acute lymphangitis fails to respond to treatment and in cases of chronic lymphangitis. Contrast studies and surgical exploration may be indicated if fistulous tracts or abscesses are present or if a foreign body is suspected.

Figure 208-18 Angiogram of a 10-year-old domestic short-haired cat with pleural effusion and edema of the head and neck. Radiocontrast dye was injected into the external jugular vein. Interruption of venous return occurs in the cranial vena cava (*arrow*) caused by compression and obstruction of this vessel by a mediastinal tumor. The reader should note the prominent collateral venous network.



208.6.4.2 Lymphedema

Lymphedema refers to an accumulation of fluid in the interstitial space resulting from abnormal lymphatic drainage.[124] This term should not be used for other forms of edema, such as circulatory edema related to venous obstruction or generalized edema related to hypoproteinemia. Lymphedema may result when capillary filtration exceeds the resorptive capacity of the veins and lymphatics. The protein rich fluid (2 to 5 g/dL) causes a high osmotic gradient and exacerbates fluid accumulation.[125] Numerous classification schemes have been used to categorize lymphedema. Commonly used causative categories of lymphedema include: overload, inadequate collection into lymphatic capillaries, abnormal lymphatic contractility, insufficient lymphatics, lymph node obstruction, and main lymphatic ductal defects.

Traditionally, clinical effort is undertaken to differentiate primary versus secondary lymphedema. *Primary lymphedema* refers to an abnormality of the lymphatic vessels or lymph nodes. *Secondary lymphedema*

refers to disease in the lymphatic vessels or lymph nodes due to a different disease process. Secondary lymphedema can occur as a result of neoplasia, surgery, trauma, parasites, radiation therapy, or infection and is more common than primary lymphedema. Distinguishing between primary and secondary lymphedema is often difficult. A disease process involving a lymph node can result in fibrosis and obstruction with secondary lymphedema developing.

208.6.4.2.1 Primary lymphedema

Primary lymphedema can result from three principle morphologic and functional abnormalities including (1) abnormalities of large vessels including aplasia or hypoplasia of the thoracic duct and cisterna chyli, (2) aplasia of the peripheral lymphatics or congenital valvular incompetence, and (3) lymph node fibrosis or a deficient lymph node size and number.[126]

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Lymphedema caused by aplasia, hypoplasia, or dysplasia of proximal lymph channels or popliteal lymph nodes (or dysplasia of both) occurs most often in the hindlimbs of young dogs (Figures 208-19 and 208-20). The edema can be transient, observed only during the juvenile period, or permanent. Mild cases are restricted to the hindlimbs, whereas severe cases may progress to whole body edema.[127–130] Although the condition is frequently bilateral, one limb is often more swollen than the other. A number of cases of suspected congenital lymphedema have been reported.[129–132] Reported breeds include bulldogs, poodles, Old English sheepdogs, and Labrador retrievers, although it is not clear whether these breeds are at increased risk.

The history may identify chronic limb swelling since birth or edema appearing later in life. The swelling represents a pitting edema of varying magnitude that is neither too warm nor cold. The edema is not usually accompanied by lameness or pain unless massive enlargement or cellulitis occurs. Growth and activity are usually normal, but rest and limb massage do not typically reduce the severity of edema. Total plasma protein, serum protein electrophoresis, hemogram, and blood chemistry are generally unremarkable. The diagnosis of primary lymphedema is based on history (age of onset, disease progression, affected limbs, and distribution of edema), and clinical signs. Previous surgery, trauma, or infections should also be noted. Radiographic lymphography may be needed to confirm the diagnosis in subtle cases and is helpful in determining morphology of anomalous lymphatic systems (see Figure 208-20).

The prognosis for resolution of congenital lymphedema is guarded and depends on the cause. Occasionally, dogs that develop hindlimb edema during the neonatal period may improve spontaneously. More frequently, dogs with severe edema of the limbs and trunk succumb during the first few weeks after birth.[127] Chronic lymphatic vessel dilation leads to loss of contractility and permanent lymphatic valvular dysfunction. Metabolic by-products accumulate and lead to collagen deposition and fibrosis. Complications such as abrasions and infection often develop. Dogs with primary lymphedema should not be used for breeding. Test matings of dogs with congenital lymphedema support the hypothesis of autosomal dominant inheritance with variable expression.

Figure 208-19 Marked, nonpainful edema of the left rear limb in a young dog with congenital lymphatic dysplasia. (Courtesy of John Bonagura, DVM.)

Figure 208-20 Lymphangiogram of a young dog with lymphatic dysplasia. After cannulation of a distal lymphatic vessel, contrast medium was infused into the lymphatic system. The reader should note the dilated, tortuous, lymphatic channels *(L)* that end blindly at the stifle *(arrows)*. *T,* Ttibia; *S,* radiopaque surgical sponges. (Courtesy of C. Wendy Myer, DVM, and John Bonagura, DVM.)

208.6.4.2.2

Secondary lymphedema

Persistent lymphedema occurs only after destruction or blockage of a considerable number of major lymph channels (or several sequential lymph nodes with their afferent or efferent lymphatics).[125] Factors that can delay or prevent edema formation include opening of collateral vessels, rerouting of lymph flow through peripheral lymphaticovenous anastomoses and perilymphatic routes of lymph drainage, and increased venous fluid uptake. Secondary lymphedema is often related to a combination of lymphatic and venous obstruction. Inhibited venous return increases lymphatic flow by altering Starling's forces toward increased tissue fluid accumulation. This overloads the lymphatic capillaries and results in the accumulation of fluid in the interstitial space.[133] Distal lymphatics may become more distended, causing loss of valvular competency, stagnation of lymph flow, mural insufficiency, and further accumulation of proteinaceous fluid in subcutaneous tissues. Other common causes include posttraumatic or postsurgical interruption of lymphatics or lymph node excision and blockage of lymph nodes and lymph vessels by compression or invasive neoplasms. Lymphedema resulting from local neoplasia is usually a sign of a widely disseminated and highly invasive malignant process. Several causes of secondary lymphedema have been summarized in Table 208-2.

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Clinical signs associated with secondary lymphedema vary depending on the underlying systemic causes. Lymphedema may be localized to the periphery of an extremity (Figure 208-21) or extend proximally to the subcutaneous tissues.[134] The location and severity of obstruction determine the extent of edema formation. For example, sublumbar or intrapelvic obstruction induces bilateral hindlimb edema and edema of the thighs and external genitalia. Mediastinal masses and thrombosis of the cranial vena cava induce bilateral edema of the front limbs and tissue of the ventral thorax, neck, and head. The clinician must palpate all lymph nodes carefully for enlargement and pain. With bilateral hindlimb edema, it is important to perform rectal or abdominal palpation to assess sublumbar lymph nodes. The prostate and anal region or mammary glands and vaginal area should be carefully inspected for neoplasms, which can lead to obstructive intrapelvic processes. Intrapelvic masses should be suspected in all dogs with hindlimb edema and vague signs of sublumbar pain, discomfort during ambulation, or difficulties with defecation or urination. Depending on the type and extent of underlying systemic illness, limb edema may be the only detectable abnormality or may be accompanied by fever, anorexia, and weight loss. Clinicopathologic findings depend on the underlying primary disorder.[135]

Figure 208-21 Pitting edema in a dog with a caudal lumbar mass. The edema was caused by either obstruction of venous return in the rear limbs or obstruction of lymphatic drainage. Tissue fluid was deformed by light digital pressure, resulting in a visible subcutaneous pit in the rear limb (*arrows*). (Courtesy of John Bongura, DVM.)

Diagnosis is based largely on history and clinical examination and is facilitated by diagnostic imaging. Survey radiographs should be taken of suspicious areas, which often include the pelvis or cranial thorax. In a substantial number of cases, soft tissue masses or destructive bony lesions can be detected. Abdominal ultrasonography can provide information about soft tissue masses and readily identifies enlarged lymph nodes and other structures. Lymphography or other imaging techniques may be indicated if the diagnosis remains unclear. Lymphography is often relied upon for definitive diagnosis of lymphatic disorders. In some cases the lymphatics are hypoplastic throughout their course. When aplastic, lymphatics suitable for cannulation and injection of radiocontrast agent may not be found. Failure to outline a lymph node after lymphography is not absolute proof of its absence.[127] Lymphographic features of primary lymphedema include lymph node aplasia and small lymphatics that end blindly or anastomose into collateral vessels around (instead of into) lymph nodes where they would be normally found.

Lymphoscintigraphy is an alternative approach for imaging peripheral lymphatics. This technique requires a gamma-camera system and intradermal injection of high molecular weight–radiolabeled colloids.[136–137] Such equipment and specialized training are not widely available. When compared with conventional lymphography, lymph nodes only appear as hot spots, preventing adequate assessment of nodal structure.

Differential diagnoses for dogs with edema confined to one limb include inflammation, trauma, vascular obstruction, hemorrhage, cellulitis, phlebitis, and A-V fistula. Diagnostic considerations for dogs with edema involving both forelimbs include thrombosis or compression or invasion of the cranial cava by a mediastinal mass. With the latter, edema usually involves the head and neck regions and the limbs. Causes of only bilateral hindlimb edema include obstruction of sublumbar lymph nodes by neoplastic infiltration. If all four limbs are involved, the differential diagnoses should include hypoproteinemia, CHF, renal failure, or portal hypertension. The close association of lymphatic and venous structures can make it difficult to distinguish between lymphatic and venous obstruction, and both can occur at the same time. Ulceration, dermatitis, cyanosis, weeping varices, and fat necrosis are signs of venous obstruction rather than lymph stasis.

Therapy is usually unrewarding. In the early stages of lymphedema, medical management is directed to maintaining the patient's comfort and reducing swelling. Infectious disorders require long-term antimicrobial therapy. Some neoplastic conditions may benefit from chemotherapy or radiation therapy. Long-term heavy bandage application (e.g., Robert Jones splint) may encourage lymphatic flow and reduce subcutaneous lymph accumulation. Local topical skin care and intermittent antibiotic therapy are helpful in reducing cellulitis. With the exception of isolated instances, pharmacologic therapies are generally unrewarding. The benzopyrones (e.g., rutin) are a group of drugs that have been advocated to reduce high-protein lymphedema by stimulating macrophages, promoting proteolysis, and enhancing absorption of protein fragments.[138] Long-term diuretic administration may be contraindicated, because after reduction of interstitial fluid, proteins in the residual interstitial space proteins may promote tissue injury.[135] Surgical options may include (1) procedures to facilitate lymph drainage from affected limbs (lymphangioplasty, bridging procedures, shunts, omental transposition), and (2) procedures to excise abnormal tissue. Surgical excision of the subcutaneous edematous tissue should be staged to decrease devascularization.[135] Short-term administration of anti-inflammatory agents or diuretics, bandaging, and physical therapy may be helpful in cases of traumatic and postsurgical induced lymphedemas.

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Figure 208-22 Cat with peripheral edema secondary to lymphatic obstruction by lymphangiosarcoma.

208.7 LYMPHANGIOMA, LYMPHANGIOSARCOMA

Lymphangiomas are benign tumors of lymphatic capillaries and are thought to develop when primitive lymphatic sacs fail to establish venous communication.[139] Lymphangiomas can be classified into three categories based on their histologic appearance: (1) capillary lymphangiomas comprised of a network of capillary-sized lymphatic channels, (2) cavernous lymphangiomas composed of dilated lymphatics that infiltrate the surrounding tissue, and (3) cystic hygromas (unilocular or multilocular, cystic masses lined by a single layer of endothelium supported by a connective tissue stroma and containing a straw-colored, proteinaceous [1.3 to 4.5 gm/dL] fluid).[140] The lesions present as large, fluctuant masses in the subcutaneous, fascial, mediastinal, and retroperitoneal spaces.[141] Lymphangiomas have also been diagnosed on the extremities, metacarpal pads, nasopharynx, axilla, inguinal and mammary region, retroperitoneal space, and skin of dogs.[139,142,143] Clinical signs are related to the size, location, and extent of the lymphangioma. They can exert pressure on surrounding structures and may interfere with muscle function, breathing (compression of the trachea), urination, or intestinal function. Lymph may ooze to the skin surface through single or multiple fistulous tracts. Differential diagnoses include other space-occupying masses such as abscesses, enlarged lymph nodes, neoplasms, and congenital cysts of nonlymphogenic origin. The prognosis can be good after appropriate surgical excision, marsupialization, or radiation therapy.[144] Risk of recurrence is high due to inherent inability to identify distinct boundaries.

Lymphangiosarcoma originates from lymphatic endothelial cells (Figure 208-22).[145] It is a rare malignant tumor in dogs and cats, although it is frequently reported secondary to chronic lymphedema in humans.[146,147] A breed or sex predisposition has not been detected, but medium to large breeds may be at highest risk, and both young and older animals are affected.[145,148] Metastasis occurs commonly in dogs and cats, although an isolated case without metastasis has been reported.[145,149] Clinical signs include pitting edema of the extremities, inguinal region, axilla, and head and neck (see Figure 208-22). In a report of 12 cats with lymphangiosarcoma, nine presented with fast-growing, noncircumscribed subcutaneous masses and the others with a thoracic or abdominal mass. In all cats affected the tumor was invasive, and complete surgical resection was not possible.[149] Associated chylous effusions (pleural, abdominal, subcutaneous) have been reported.[150–153] Pulmonary lymphangiosarcoma was diagnosed in one dog with a chylous effusion.[153] Diagnosis is confirmed by obtaining a biopsy specimen. Histologically, tumors of lymphatic endothelial origin are characterized by a neoplastic proliferation of endothelial cells. Immunocytochemical stains have been used to confirm the diagnosis in dogs. The identification of the factor VIII–related antigen and vimentin indicates the cells are of endothelial origin. The intensity and distribution of the stain has been used to attempt to differentiate lymphangiosarcomas from hemangiosarcomas but is often inaccurate. Newer specific markers to identify lymphatic endothelial cells have been identified in humans and remain to be validated in the canine patient.[153] The prognosis with lymphangiosarcoma is poor, with a high rate of local recurrence and metastasis.

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209 CHAPTER • 209 Diseases of the Ear

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209.1 GENERAL CONCEPTS

Many different disease processes affect otic health and should be considered when evaluating a dog or cat with possible ear disease. Signalment may implicate certain diseases over others. A complete history begins with general questions about the animal's health (e.g., appetite, sneezing, coughing, vomiting, diarrhea, water consumption) and questions pertaining to primary conditions associated with ear disease. Because the ear is a specialized extension of the integumentary system, a complete dermatologic history should be obtained (i.e., appearance of lesions at the onset of the condition; duration, progression, presence of pain or pruritus; past medical therapy and response to therapy; the presence of other dermatologic problems). A complete physical examination should be performed with special attention paid to the skin to evaluate for hypersensitivities, disorders of keratinization, endocrine disorders, and other dermatologic conditions. A complete neurologic examination may reveal abnormalities associated with the middle ear (e.g., abnormalities of cranial nerves VII and VIII, Horner's syndrome, keratoconjunctivitis sicca, head tilt). Involvement of the inner ear results in other neurologic signs (e.g., head tilt, ataxia, strabismus, abnormal nystagmus), and differentiation from central vestibular disease is extremely important.

Specific examination of the ear includes evaluation of the concave and convex pinnal surfaces, palpation of the ear canals, and otoscopic examination. The ear may need to be cleaned before a thorough examination can be completed. Sedation or anesthesia is occasionally necessary to perform a complete otic exam. This is especially true with chronic conditions of the ear. Abnormalities of the otic exam include pain on palpation of the auricular cartilages, nonpliable cartilage, ossified cartilage, epithelial hyperemia, swelling, erosion, ulceration, exudate accumulation, and hyperemia or lack of transparency of the tympanic membrane. Pain upon opening the mouth is not specific to, but can occur with, ear disease. Other diagnostic tests should include cytologic examination of otic exudate and culture and susceptibility testing based on the cytology and clinical signs of the patient. Skull radiographs, computed tomography (CT), and magnetic resonance imaging (MRI) may be indicated for evaluation of the middle and inner ear. Specific diagnostic tests are available to evaluate tympanic membrane integrity, and one should not assume that the tympanic membrane is intact prior to initiation of medical therapy, including ear cleaning, which may cause immediate exposure of the middle ear to ototoxic substances.

209.2 DISEASES OF THE PINNA

Many different disease conditions can affect the pinna—some are specific to the pinna and others represent distribution of part of a systemic condition (Table 209-1). Following are specific diseases that primarily affect the pinnae (or affect the pinnae as an early manifestation of the disease).

209.3 NONPRURITIC PINNAL ALOPECIA

209.3.1 Canine Pinnal Alopecia

Canine pinnal alopecia is most commonly diagnosed in dachshunds but also occurs in Chihuahuas, Boston terriers, whippets, Yorkshire terriers, and Italian greyhounds.[1,2] The condition usually occurs in dogs over 1 year of age and results in slowly progressive, bilateral pinnal alopecia. Small vellus hairs remain, and complete pinnal alopecia, when it occurs, may not be present until 8 to 9 years of age. The pinnae may become chronically hyperpigmented and thickened. The remainder of the haircoat is usually normal. The condition is benign and requires no specific treatment. Differentiation from other alopecic conditions is by exclusion and histopathologic examination. Miniaturized hair follicles are typically seen on histopathology. Minoxidil, pentoxifylline, melatonin, and milbolerone have anecdotally been reported to induce hair growth in some cases.[2]

209.3.2 Pattern Baldness

Symmetrical alopecia or hypotrichosis of the pinnae, ventrum, and caudal or medial thigh has been recognized in the dachshund and Staffordshire bull terrier.[3] Hair loss begins with the pinnae at 6 to 9 months of age and may progress to complete pinnal alopecia. Total body alopecia with pigmentation may occur with age. Treatment with oral melatonin may cause hair regrowth with this and other pattern baldness syndromes.[2]

209.3.3 Periodic Alopecia of Miniature Poodles and Siamese Cats

Hair loss is usually adult-onset and acute with periodic alopecia of miniature poodles and Siamese cats. Progression of the condition may result in complete, bilateral, pinnal alopecia; however, in cats the alopecia may be patchy or complete.[1,2] The skin appears grossly normal. The pathophysiology of the condition is not known, no treatment has been described, and the hair may regrow over a period of several months.

209.3.4 Congenital Hypotrichosis

A lack of pelage or loss of hair within the first month after birth has been diagnosed in the Belgian shepherd, cocker spaniel, toy poodle, miniature poodle, whippet, German shepherd, Yorkshire terrier, bichon frise, Lhasa apso, Labrador retriever, rottweiler, and basset hound. The condition is seen more commonly in males and usually involves the pinna, temporal region, caudal dorsum, and ventrum. Complete hair loss may occur by 12 to 14 weeks of age. Areas of alopecia may be well delineated from normal skin, and the condition can be diagnosed by finding a marked decrease in the density of hair follicles on skin biopsy of the affected area.[2] A similar condition exists in Birman, Burmese, Devon Rex, and Siamese cats but involves the entire coat, whiskers, claws, and tongue. No treatment exists for this condition; it is heritable, and the client should be discouraged from breeding the animal.[2]

Table • 209-1 Disease Conditions Affecting the Pinna

Nonpruritic Alopecia		
Canine		
Periodic alopecia of miniature poodles	Color dilution alopecia	Pattern baldness
Pinnal alopecia of short-coated breeds	Alopecia areata	Demodicosis
Idiopathic follicular dysplasia	Congenital alopecia	Drug eruption
Congenital hypotrichosis	Dermatophytosis	Hypothyroidism
Estrogen-responsive dermatosis	Ectodermal defects	
Feline		
Idiopathic pinnal alopecia	Dermatophytosis	Demodicosis
Iatrogenic hypothyroidism	Congenital hypotrichosis	Alopecia areata
Iatrogenic hyperadrenocorticism	Hyperthyroidism	
Crusting and Scaling Dermatoses		
Canine		
Fly strike dermatitis	Frostbite	Sarcoptic mange
Proliferative thrombovascular necrosis	Demodicosis	Harvest mites
Zinc-responsive dermatosis	Pemphigus complex	Vasculitis
Idiopathic hyperkeratosis of Boston terriers	Ear margin dermatosis	Sebaceous adenitis
Idiopathic lymphocytic/plasmacytic dermatitis	Lupoid dermatosis	Ear fissures
Idiopathic lichenoid keratosis	Superficial necrolytic dermatitis	Hypothyroidism
Lichenoid psoriaform dermatosis	Dermatomyositis	Pediculosis
Cold agglutinin disease	Systemic lupus erythematosus (SLE)	Leishmania
Feline		
Squamous cell carcinoma	Actinic dermatitis	Notoedric mange
Insect bite hypersensitivity	Frostbite	Vasculitis
Pemphigus complex		
Papular and Nodular Dermatoses		
Canine and feline		
Leoproid granuloma (canine)	Neoplasia	Bacterial pyoderma
Sterile nodular histiocytic granuloma (canine)	Deep mycoses	Leishmania
Eosinophilic folliculitis, furunculosis (canine)	Foreign body	Dermatophytosis
Eosinophilic granuloma (canine)	Tick infestation	Xanthoma (feline)
Pustular, Vesicular, and Bullous Dermatoses		
Canine and feline		
Pemphigus foliaceus	Pemphigus erythematosus	SLE
Epidermolysis bullosa	Drug eruption	Contact or irritant dermatitis
Concave Pinnal Disorders		
Canine and feline		
Atopy	Allergic contact dermatitis	Hypothyroidism
Sex hormone aberrations	Seborrhea	Juvenile cellulitis
Food sensitivity	Idiopathic erythema/edema (canine)	
Auricular Cartilage Disorders		
Canine and Feline		
Aural hematoma	Auricular chondritis	

209.4 CRUSTING AND SCALING DERMATOSES

209.4.1 Scabies and Mange

Erythematous, papular dermatitis of the distal pinnae associated with significant pruritus is an early manifestation of *Sarcoptes scabiei* in dogs. Crust and scale will usually first affect the tip of the pinna or ear

margin. The pinnal-pedal reflex (i.e., rubbing the pinna resulting in a pelvic limb scratch reflex) is often associated with sarcoptic mange but is not pathognomonic for the condition. Concurrent lesions often involve the lateral hocks and elbows and may spread to the rest of the body. The diagnosis is usually made with skin scrapings; however, multiple scrapings may be necessary to achieve the diagnosis.[3] The presence of a single mite, egg, or fecal droppings is diagnostic for the disease. All animals in the household should be treated, and the condition is zoonotic, so owners and handlers should be made aware of the condition. Initial treatment consists of removal of crusts and debris, followed by an acaracidal dip such as lime sulfur, permethrin, organophosphate, or amitraz, which may shorten time to resolution of clinical signs and diminish zoonotic potential. Ivermectin administered subcutaneously, twice at 14-day intervals, or orally three times at 7-day intervals, results in cure. A similar dose schedule exists for milbemcyin. Topical application of selamectin or fipronil may also be curative.[1,2]

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Feline mange, caused by *Notoedres cati*, results in alopecia, pruritus, excoriations, and thick crusts of the rostral pinnae and is usually restricted to the ears and head. The extremities and perineum may also be affected due to the sleeping and grooming habits of cats. The parasite may also inhabit dogs, foxes, and rabbits; transient lesions have been reported in humans.[2] The diagnosis is made with skin scrapings, and lime sulfur or amitraz dips are effective treatments. Ivermectin given two or three times subcutaneously is also effective.[2]

209.4.2 Fly Strike Dermatitis

Insect bite dermatitis, primarily caused by the stable fly, *Stomoxys calcitrans*, results in serosanguineous, crusting dermatitis on the ear tips in dogs with erect ears or on the folded edge of the pinna in dogs with pendulous ears. Chronic fly strike dermatitis can become granulomatous in nature. Horse flies (Tabanus species) and deer flies (Chrysops species) may also plague dogs that are housed outdoors, but their bites are usually less reactive than stable flies. The diagnosis is based on an environmental history and response to limiting outdoor exposure. Fly repellents containing permethrin, citronella, or diethyltoluamide (DEET) in petroleum jelly may be used to diminish repeated fly bites. Topical corticosteroid with an antibiotic may hasten the resolution of clinical signs.[1,2] Black flies (Simulium species) may also cause papular dermatitis and alopecia in dogs.

Cats can develop a seasonal hypersensitivity to mosquito bites. Papules, erythema, alopecia, and hypopigmentation occur on the pinnae and face. Pyrexia, lymphadenopathy, and footpad lesions may also occur.

209.4.3 Actinic Dermatitis and Squamous Cell Carcinoma

Damage to the skin by long-term sun exposure occurs most often in white cats, although the condition is also reported in dogs and in cats with pigmented skin. The pinna is most often affected due to its sparse hair covering; the nose, lips, and eyelids may be similarly affected. Waxing and waning ear tip erythema may progress to the development of fine scale and alopecia early in the disease. Erosive, crusted, hemorrhagic lesions and folding of the pinna occur as a precancerous condition, which may ultimately lead to carcinomatous change.[1,2,4] Squamous cell carcinoma is most often diagnosed in older cats (mean age, 12.8 years) with either skin scrapings or biopsy.[5]

Treatment of actinic dermatitis ideally consists of limiting sun exposure between the hours of 10 AM and 4 PM by housing indoors and eliminating sunbathing behavior. Application of sunscreen of SPF 15 or greater may also decrease the effects of solar radiation. β-carotene and canthaxanthin administered orally and the use of

retinoic acids (i.e., isotretinoin, etretinate) have also been reported.[1,2] An initial response to therapy may be seen, but long-term effectiveness has not been thoroughly investigated.[6] Strontium plesiotherapy has been used in the treatment of actinic dermatitis. Failure to respond to medical management is an indication for pinnectomy.

Squamous cell carcinoma is usually locally invasive and slow to metastasize to either local lymph nodes or the lung. Pinnectomy is an effective mode of therapy for severe actinic dermatitis and squamous cell carcinoma. Cryosurgery, radiotherapy, brachytherapy, hyperthermic, and photodynamic therapy have also been used on focal lesions; systemic chemotherapy is not considered effective.

209.4.4 Frostbite

Animals affected by frostbite are usually systemically ill or have recently moved to a cold environment. The ear tips are pale, cyanotic, hypoesthetic, and cool to the touch after exposure. With warming, the tissues become hyperemic and develop scale, crust, and alopecia. The ear tips may curl, necrose, and eventually slough. Initial treatment consists of rewarming with warm water and subsequent symptomatic therapy for scaling and crusting dermatitis. Amputation of necrotic tissue results in improved cosmesis with haired skin and decreases the risk of recurrent freezing, which is more likely in previously frostbitten tissue.

209.4.5 Vasculitis

The underlying cause of vasculitis is often unknown, but the condition occurs subsequent to Type I and Type III hypersensitivity reactions and the deposition of antigen and antibody complex within the vascular wall.[2] The lesions are characterized by erythema, edema, and eventual necrosis and sloughing, leading to a “punched out” or ulcerated appearance to the pinnae. Other affected areas include the lips, tail, pads, and nails. A neutrophilic, eosinophilic, or lymphocytic vasculitis may be evident on histopathology. Proliferative thrombovascular necrosis of the pinnae is a form of vasculitis reported in dogs. Inflammatory vasculitis is not evident in this syndrome and cause is unknown. Conditions such as rickettsial disease, drug eruption, immune-mediated disease, and other underlying systemic conditions should be ruled out. Therapy should be directed at treating the underlying cause. Idiopathic vasculitis cases may respond to immunosuppressive doses of corticosteroids. Other reported treatments include pentoxyphylline, sulfasalazine, or dapsone.[1] Surgical excision of the affected portion of the pinna with wide surgical margins may be indicated if medical management is unsuccessful.[2]

209.4.6 Hyperkeratosis

Crusting and scaling of the pinnae may be caused by idiopathic defects in keratinization, primary disease conditions causing seborrhea, and secondary changes in keratinization due to parasitism. Ear margin dermatosis is common in dachshunds and other breeds with pendulous ears. Seborrheic changes begin at the ear margin and progress to confluence of scale and significant alopecia. Pruritus is variable but may be present in severe cases. The condition is not curable but controllable with keratolytic keratoplastic shampoos (e.g., sulfur-asalicylic acid, benzoyl peroxide or benzoyl peroxide-sulfur, selenium sulfide).[2] Severe cases may require topical or systemic corticosteroid treatment due to inflammation associated with removal of crusts or ear fissure formation.

Sebaceous adenitis is associated with an inflammatory process of the sebaceous glands. Follicular disruption, alopecia, and surface scale initially affect the pinna and may involve the ear canal and trunk.[7] No direct therapy exists for lost sebaceous glands, and supportive care with fatty acids, humectants, and anti-inflammatory corticosteroids can be useful. Retinoids have been used in cases with a granulomatous response to the process.[2]

Other less common disorders can cause hyperkeratosis of the pinna. Idiopathic benign lichenoid keratosis has been diagnosed in four dogs with multiple wartlike papules and hyperkeratotic plaques on the pinnae.[3] Lichenoid psoriaform dermatosis is a rare condition in which erythematous papules and lichenoid plaques appear on the concave surface of the pinna, external ear canal, and ventral head and trunk. Treatment consists of antimicrobial shampoo, systemic antibiotics, and corticosteroids.[2] Lupoid dermatosis is a heritable condition of German shorthaired pointers in which progressive, nonpruritic scale occurs on the pinnae, face, and trunk. No therapy is available for the condition.

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209.4.7 Nutritional Dermatoses

Zinc deficiency caused by dietary insufficiency or inability to absorb dietary zinc results in crusting lesions of the pinna, and perioral, periorbital, perianal, and perivulvar sites of dogs. Food allergy can result in steroid-resistant alopecia, crust, scale, hyperpigmentation, and lichenification of the pinnae. Dietary restriction followed by feeding trials is diagnostic of the condition, which may be associated with lesions and pruritus on other parts of the body.

209.5 DERMATOSES CAUSING PAPULES AND NODULES

209.5.1 Tick Infestation

The following ticks may cause local irritation and secondary granuloma formation of the pinna in dogs: American dog tick (*Dermacentor variabilis*), lone star tick (*Amblyomma americanum*), brown dog tick (*Rhipicephalus sanguineus*), and Ixodes species.[3] Of these ticks, Ixodes spp. is least likely to be identified on the pinna or head. Treatment should be aimed at insect removal and prevention of reinfestation.

209.5.2 Neoplastic Lesions

Auricular tumors are more common and more often malignant in cats than dogs. Commonly diagnosed canine pinnal tumors include squamous cell carcinoma, cutaneous histiocytoma, mast cell tumor, sebaceous adenoma, and papilloma. Squamous cell carcinoma, mast cell tumor, basal cell tumor, and fibrosarcoma are commonly diagnosed in cats.

209.5.3 Granulomatous Lesions

Pinnal granulomas may be associated with bacterial infection (Staphylococcus species, *Nocardia*, *Actinomyces*, mycobacteria, atypical mycobacteria), dermatophytosis, deep mycoses, algae, *Leishmania*, and foreign bodies. Canine leproid granuloma occurs in short haired dogs primarily in cool, moist environments. Two millimeter to 5 cm nodules have been described with superficial alopecia and ulceration occurring on the

dorsal pinna and head. Although acid-fast bacilli have been identified on histopathologic examination, cultures are usually negative. Lesions usually resolve spontaneously or respond to surgical excision.[8]

209.6 DERMATOSES CAUSING PUSTULES, VESICLES, AND BULLAE

Autoimmune disorders commonly affect the concave aspect of the pinnae. Lesions are usually symmetrical; vesicles, erosions, and blisters may appear on the pinna prior to the occurrence of generalized disease. Pemphigus complex, systemic lupus erythematosus (SLE), bullous pemphigoid, and epidermolysis bullosa[9] have been associated with pinnal lesions. The diagnosis may be made with cytology and skin biopsy. Differential diagnoses include bacterial infection, drug eruption, and contact hypersensitivity.[2]

209.7 CONCAVE PINNAL DERMATOSES

209.7.1 Atopy

Erythema and hyperplasia of the pinna and upper external ear canal are early signs of atopy. Hyperpigmentation, lichenification, and erythematous ceruminous otitis may result if the condition is allowed to progress.

209.7.2 Allergic Contact Dermatitis

Allergic contact dermatitis is a rare condition described in middle-aged animals due to the long period of induction required for development of delayed hypersensitivity to the offending substance. The condition is often diagnosed secondary to topical medication used to treat otitis externa and may result in pinnal alopecia.

209.7.3 Defects in Keratinization

Systemic conditions such as hypothyroidism, sex hormone aberrations, and seborrhea may affect the concave surface of the pinna. Grease accumulation and hyperkeratotic dermatosis may result.

209.7.4 Juvenile Cellulitis

Juvenile sterile granulomatous dermatitis and lymphadenitis is a rarely diagnosed condition; predisposed breeds include the golden retriever, dachshund, Labrador retriever, and Lhasa apso. Dogs are usually less than 6 months of age when they develop significant mandibular and prescapular lymphadenopathy and edema, exudate, papules, and pustules of the pinna, muzzle, and periocular skin.[1] The diagnosis is based on clinical presentation, culture and susceptibility testing, and skin biopsy. Treatment consists of immunosuppression with corticosteroids, which are tapered over 3 to 4 weeks after remission of clinical signs. Systemic antimicrobial therapy is indicated for the treatment of secondary bacterial pyoderma.

209.8 AURICULAR CARTILAGE DISORDERS

209.8.1 Aural Hematoma

Aural hematomas occur in both dogs and cats secondary to the self-induced trauma of head shaking or scratching. Blood accumulates within the fractured cartilage of the pinna, although swelling is most visible on the concave aspect. Any animal diagnosed with an aural hematoma should undergo a complete evaluation and treatment for otitis externa, because continued head shaking will predispose the animal to enlargement or recurrence of the hematoma. Small hematomas may resolve without therapy; however, second-intention healing may cause deformation of the pinna with a poor cosmetic result. Treatment of the hematoma may consist of corticosteroid injection, evacuation and bandaging, teat cannula drainage, Penrose drain placement, or closed suction drainage.[10] Surgical incision, drainage, curettage, and closure with mattress sutures is preferred because it provides apposition of the cartilage edges and cosmetic results. Sutures remain in place for 21 days to allow adequate cartilage healing. Treatment of the concurrent otitis externa and its underlying cause are vital to the prevention of recurrence.

209.8.2 Auricular Chondritis

Auricular chondritis (*relapsing polychondritis* in cats) is an inflammation and destruction of auricular cartilage usually classified as an immune-mediated disorder. The pinnae are bilaterally swollen and deformed in most cases, although unilateral involvement is possible. Diagnosis is based on biopsy findings of lymphoplasmacytic inflammation with cartilage necrosis, and treatment may be minimal if no significant systemic signs exist. Attempted treatment with immunosuppressive doses of corticosteroids was not successful in cats; dapsone therapy may induce remission.[2]

209.9 DISEASES OF THE EXTERNAL EAR CANAL: OTITIS EXTERNA

209.9.1 Normal Anatomy and Physiology

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The external ear canal collects and delivers sound to the tympanic membrane. The ear canal is composed of auricular and annular cartilages that roughly approximate with the vertical and horizontal portions of the canal. The normal dog has a 45-degree angle of the horizontal canal; the angle is approximately 90 degrees in cats. Stratified squamous epithelium with sebaceous glands, ceruminous or apocrine glands, and hair follicles line the canal. Sebaceous glands located in the superficial dermis secrete neutral lipids that assist in maintenance of keratinization, in capturing and removing debris, and in decreasing the humidity of the ear canal. Acid mucopolysaccharides and phospholipids are the main secretions of ceruminous glands located deeper in the dermis. The glandular secretions help to maintain proper humidity and pH in the ear canal, and a normal flora of bacteria and yeast have been identified in the external ear canal of normal dogs and cats.[11] Removal of debris from the deeper portion of the ear canal is achieved in many ways. The ratio of apocrine to sebaceous glands decreases from proximal to distal in the ear canal, resulting in more aqueous cerumen deeper in the canal, and the number of glands and hair follicles also decrease deep in the ear canal. The tympanic membrane is composed of three layers, with epithelial cells migrating away from the center of the tympanum, which aids in the removal of debris and secretions from its surface.

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209.9.2 Diagnostic Principles

209.9.2.1 Physical Examination

Complete examination of the pet with otitis includes general physical, dermatologic, otoscopic, and neurologic examinations. An otoscopic examination should be performed slowly and deliberately with dorsal and lateral traction on the pinna, keeping the otoscope centrally located in the canal to avoid placing pressure on the epithelium. Hyperemia, erosions, ulcers, exudate, foreign bodies, stenosis, and masses should be noted. The tympanum should be thin, pale, gray, and translucent, with a visible manubrium of the malleus. The tympanum is usually seen in 75% of dogs with normal ears and in 28% of dogs with otitis.[3] Otoscopy is not sensitive for rupture of the tympanic membrane but can be diagnostic of obvious ruptures.

209.9.2.2 Cytologic Examination

Cytologic examination of exudate within the ear canal is a mandatory part of assessing pets with otitis. Cytology should be done at initial examination and at each re-evaluation, because gross appearance of exudate does not correlate with microscopic character. Material should be collected prior to cleaning the ear canal; specimens collected from the horizontal canal through the otoscope cone may be more representative of the disease process.[3] Mineral oil cytology is the technique most often recommended for identification of parasites. A cerumen sample is mixed with mineral oil on a glass slide prior to microscopic examination. Heat-fixed otic exudate should also be stained with modified Wright's stain (Diff Quik American Scientific McGraw, IL) and Gram stain for evaluation of bacterial pathogens and yeast under oil immersion microscopy (×100). The morphologic type of bacteria, gram-staining characteristics, and presence or absence of inflammatory cells, cerumen, and debris should be noted.

Many clinicians use a scale of 1+ to 4+ in describing numbers of yeast, bacteria, and inflammatory cells to allow evaluation of the progression of the disease process. However, low numbers of bacteria and yeast per high-powered field (hpf) (×40 dry) may be identified in normal ears.[12] Dogs and cats should have two yeast and five bacteria or less per hpf.[12] Yeast numbers 5/hpf or greater in dogs and 12/hpf or greater in cats are abnormal. Bacteria 25/hpf or greater in dogs and 15/hpf in cats are associated with otitis.[12] Persistence of the same pathogens on re-evaluation suggests lack of efficacy or inappropriate therapy, incorrect identification of the primary disease process, or lack of owner compliance with therapy. Any change in the cytologic appearance may suggest reaction to medication or a change in either the type of inflammatory process or secondary pathogens.

209.9.2.3 Culture and Susceptibility Testing

Cultures need not be done if external ear canal cytology is negative for bacteria; it is unlikely that either yeast or bacteria would be present on cultures or would contribute to the disease process in those cases. Culture with susceptibility testing should be considered whenever resistant bacteria may be present or when prolonged or systemic therapy are indicated (e.g., gram-negative bacteria and inflammatory cells identified on cytology, chronic bacterial otitis, suspected otitis media, failure to respond to appropriate medical therapy).[13,14] Cultures should be collected from the tympanic bulla in all suspected cases of otitis media, because horizontal ear canal samples do not correlate with those from the middle ear in over 89% of cases, and cytologic examination of the middle ear may be negative despite the presence of otitis.[15] Because

bacteria may not cross the tympanic membrane, cultures from both sites should provide the highest yield of pathogenic bacteria. Yeast cultures are not routinely performed, because cytology is more sensitive than culture for yeast organisms, which may require specific lipid supplementation of the growth media for some species.[16,17]

209.9.2.4 Radiology, Computed Tomography, and Magnetic Resonance Imaging

Diagnostic imaging may be used to evaluate the patency of the external ear canal and may be necessary to evaluate the integrity of the tympanic bulla. Underlying otitis media should be identified because it perpetuates otitis externa and requires specific therapy separate from that for otitis externa. Evaluating the tympanic membrane to diagnose otitis media, however, can be difficult in cases with significant secondary changes in the external ear canal. Treating otitis externa may decrease secondary changes and allow tympanic visualization at a later date, or imaging may be pursued. Radiographs are not as sensitive as CT or MRI for detecting abnormalities of the tympanic bulla.[18–20] If obstructive external ear disease does not respond to therapy or if the ear canals are palpably fibrotic or ossified, total ear canal excision and bulla osteotomy are required. Imaging of the middle ear is not necessary in those cases, because the middle ear can be evaluated at surgery via bulla osteotomy. Radiographic changes or changes on CT or MRI are valuable in patients with otic neoplasia. Significant changes of the tympanic bulla suggest that complete surgical excision may not be possible. Advanced imaging is also valuable in cases of otitis interna and central vestibular disease.

209.10 PATHOPHYSIOLOGY

Otitis externa describes any inflammatory condition of the external ear canal. The estimated incidence of otitis in dogs and cats ranges from 4% to 20% and 2% to 6.6%, respectively.[1,13] Clinical signs associated with the condition vary, depending on the cause of the otitis. General signs consist of head shaking, scratching, otic pain, and a variable accumulation of cerumen or exudate. The external canal responds to chronic inflammation of the dermis and epidermis with epithelial hyperplasia and hyperkeratosis, sebaceous gland hyperplasia, and ceruminous gland hyperplasia and dilation. These changes are associated with increased cerumen production; however, increased humidity, increased pH, and decreased lipid content of the cerumen predispose the animal to secondary infection. Apocrine gland rupture, sebaceous gland degeneration, ear canal stenosis, and fibrosis or ossification of the canal (or both) usually occur with the end stages of otitis.[21] Because permanent changes of the ear canal can occur with any cause of otitis externa, primary, predisposing, and perpetuating factors should be investigated in all cases of otitis.

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209.10.1 Primary Factors

Primary factors are capable of causing otitis in normal ears. Primary factors may not be cured but often are controlled with appropriate therapy.

209.10.2 Hypersensitivities

209.10.2.1 Atopy and food hypersensitivity

Otitis externa is a clinical sign in 50% to 80% of atopic or food-sensitive dogs and may be the sole clinical sign associated with atopy.[22,23] Erythematous ceruminous otitis is most commonly associated with allergic

skin disease.[24] Early clinical signs of bilateral pruritus, concave pinnal erythema, and mild erythematous and ceruminous otitis of the proximal ear canal may progress to significant otitis externa and pinnal hyperpigmentation. The pet can develop end-stage otitis if the primary cause is not identified and treated. Aural pruritus is common to atopy and food hypersensitivity; however, steroid responsiveness is usually only seen with atopy. Atopic dogs also tend to have a slower progression of disease than food-sensitive dogs. Secondary infection with either *Malassezia pachydermatis* or bacterial cocci is common. A definitive diagnosis is based on biopsy, intradermal skin testing, serologic testing, or dietary restriction and subsequent diet trials.

209.10.2.2 Contact hypersensitivity and irritant reaction

Topical otic preparations may cause a delayed hypersensitivity or irritant reaction to the ear canal. A response to initial therapy is followed by progression of disease or change in the character of the otitis with continued therapy. Worsening of clinical signs can occur if the medication is discontinued then readministered. Neomycin, propylene glycol, and dimethyl sulfoxide have been associated with irritant otitis. Reactions are occasionally noted with alcohol, glycerin, povidone-iodine, and concentrations of acetic acid greater than 2%.[3] Contact hypersensitivity or an irritant reaction should be suspected any time otitis externa is exacerbated by therapy or upon changes in the gross or cytologic appearance of the otitis. Both contact hypersensitivity and irritant reaction act as perpetuating factors of otitis externa despite control of the primary factor.

209.10.3 Ectoparasites

Otodectes cynotis is the cause of otitis externa (otocariasis) in up to 50% of cats and 10% of dogs with otitis externa.[3] The infestation in cats may be classified as one of the following: (1) otitis externa, (2) ectopic infestation, or (3) asymptomatic carrier. Signs of otitis include significant pruritus, pinnal erythema and crusting, and accumulation of cerumen in the external ear canal. Gross character of the cerumen is not correlated to the microscopic findings, but is usually dark brown to black in color. Mites may be observed on otoscopic examination; however, mineral oil cytology is recommended, because few mites are required to cause clinical signs. Mites may concurrently inhabit the skin of the head and neck in animals with otitis. True ectoparasite infestation usually results in miliary dermatitis and patchy alopecia in cats. Treatment can include any of the following: carbamates, pyrethrins, rotenone, ivermectin, thiabendazole, or fipronyl.[25] Selamectin has recently been proven safe and effective for treating otocariasis in both dogs and cats.[26,27] The 3-week cycle of the parasite should be considered in treatment planning.

Demodex canis has been associated with mild otitis and excessive cerumen production in dogs with the generalized form of demodicosis. The diagnosis is made with mineral oil cytology; other diagnostics (e.g., biopsy) are less often required. Other parasites such as harvest mites (*Neotrombicula autumnalis and Euotrombicula alfredugesi*) and ticks (*Otobius megnini*) may cause otitis externa. Reinfestation is a common problem due to environmental exposure to these parasites.

209.10.4 Foreign Bodies

Younger dogs, especially hunting or working breeds, are predisposed to otic foreign bodies. The most common foreign body associated with otitis is the grass awn; however, other foreign bodies include dirt, sand, cerumen, exudate mixed with hair, and conglomerates of dried ear medication. All can incite inflammation.

Dogs are usually acutely painful, bilateral foreign bodies are possible, and approximately 20% of otic foreign bodies penetrate the tympanic membrane, leading to otitis media.[3]

209.10.5 Keratinization Defects

Hypothyroidism, male feminizing syndrome, Sertoli cell tumor, hyperestrogenism, and idiopathic seborrhea may be associated with mild otitis externa. Idiopathic seborrhea in cocker spaniels and hereditary defects in cats leading to seborrhea may cause erythematous ceruminous otitis. Changes in the microenvironment of the ear canal lead to secondary purulent otitis.

209.10.6 Idiopathic Inflammatory or Hyperplastic Otitis

Cocker spaniels may be affected by severe, proliferative otitis externa at a young age. Concurrent dermatologic conditions are not necessarily present but should be ruled out for proper management. The cause of the condition is unknown but may be due to a primary glandular disorder.[2]

209.10.7 Other Primary Factors

Immune-mediated disorders such as pemphigus complex may be associated with both pinnal lesions and otitis externa. Pemphigus foliaceus may involve only the ears in some cases, but lesions on other parts of the body are usually present. Drug eruption from systemically administered drugs may also cause both pinnal lesions and otitis externa. Older animals with chronic or recurrent otitis should be evaluated for benign or malignant neoplasia of the skin or adenexal structures of the ear.

209.10.7.1 Predisposing Factors

Predisposing factors make otitis more likely by altering the environment of the external ear canal, thereby making the ear more susceptible to inflammation and secondary infection.

209.10.8 Anatomic Changes

Increased soft tissue within the ear canal, increased compound hair follicles in the canal, and stenotic canals (e.g., Shar Pei, bulldog, chow chow) or chronic changes associated with previous bouts of otitis may be predisposing factors for otitis externa. Dogs with pendulous ears are predisposed to otitis, and otitis is common in breeds of dogs exhibiting increased ceruminous compared with sebaceous gland area (e.g., cocker spaniel, Labrador retriever, springer spaniel).[28] Hair is normally present in the ear canal, and increased numbers of hairs or presence of compound hair follicles have not been correlated to the incidence of otitis in dogs. Routine hair plucking is therefore not recommended and may incite an inflammatory response within the epithelium, perpetuating otitis externa.

209.10.9 External Environment

Increases in temperature and humidity in the environment may be reflected in the ear canal. The incidence of otitis externa is seasonally related to temperature, humidity, and rainfall. A lag period of 1 to 2 months is associated with cases of canine otitis and may vary with geographic location. Positive cultures of the ear canal are more likely during times of increased environmental temperature and humidity.[3]

209.10.9.1 Perpetuating Factors

Perpetuating factors exacerbate the inflammatory process and can maintain the disease after the primary factor has been eliminated. They can induce permanent pathologic changes to the ear canal and are the main reason for treatment failure in otitis externa.

209.10.10 Secondary Bacterial Colonization and Infection

Normal bacterial flora exist in the ear canal of dogs and cats. Staphylococcus species and Streptococcus species are often cultured, *Pseudomonas* is rarely cultured, and *Proteus* was not cultured from the normal canine ear canal.[13] *Malassezia* has also been identified on cytologic examination in normal dogs and cats, and its numbers are significantly increased in erythematous ceruminous otitis.[13] Bacteria and yeast are opportunistic pathogens but can cause significant secondary changes of the ear canal with chronic infection. Increased numbers of bacteria without an inflammatory response may represent colonization, which often responds to topical therapy. The presence of inflammatory cells suggests true infection, and culture and susceptibility is recommended due to resistance patterns of many bacteria. In colonization and infection, cleaning the external ear canal removes exudate, debris, toxins, free fatty acids, and bacteria that perpetuate inflammation and secondary changes of the ear canal.[29]

Staphylococcus species are common in dogs with otitis as are *Pseudomonas aeruginosa*, Proteus species, *Escherichia coli*, Corynebacterium species, and Streptococcus species.[15,30] Acute purulent otitis externa is less common than chronic, but with chronicity and repeated treatment, gram-negative bacteria, such as *Pseudomonas* and *Proteus*, predominate. The associated otitis may have surface erosions or ulcers and copious exudate. Cats may be secondarily infected with *Pasteurella multocida* and less often *Pseudomonas aeruginosa*, Proteus species, or *E. coli*.[1]

209.10.10.1 Malassezia Pachydermatis

Budding yeast has been identified on ear cytology of normal dogs (up to 50%) and cats (up to 17.6%).[17] *Malassezia* are considered part of the normal flora and an opportunist in cases of otitis externa, particularly in cases of erythematous ceruminous otitis. *Malassezia* are lipid-dependent yeast that overgrow in conditions of increased moisture, increased surface lipids, and compromised barrier function of the stratum corneum.[31,32] Enzymes produced by the yeast may allow depolymerization of the interstitial matrix (e.g., hyaluronidase, chondroitin-sulphatase) and cell membranes (e.g., proteinase, phospholipase), increasing tissue invasion and penetration.[32] Cytologic examination is more valuable than culture, because some species of *Malassezia* require specific media supplemented with long-chain fatty acids.[17,31]

209.10.11 Chronic Anatomic Changes

Increased soft tissue volume within the ear canal associated with chronic otic inflammation leads to ear canal stenosis and alters the otic microenvironment. Chronic changes of the epidermis, adenexa, dermis, and cartilage are described in the previous pathophysiology section. The microenvironmental alterations associated with chronic ear canal stenosis and inflammation favor bacterial and yeast proliferation and the retention of

exudate. The changes also hinder proper cleaning and medication of the deeper portions of the external ear canal.

209.10.12 Otitis Media

Untreated infection of the middle ear serves as a source for perpetuating otitis externa. Failure to identify the bacteria, yeast, or byproducts of inflammation in the middle ear may result in recurrent otitis externa and chronic pathologic changes of the middle and external ear.

209.10.13 Treatment Errors, Undertreatment, and Overtreatment

Incorrect treatment of otitis allows bacterial or yeast overgrowth or infection and denies treatment of the primary factor causing otitis. Overapplication of medication or use of occlusive medications increases the humidity of the ear canal, leading to epithelial maceration and inflammation, perpetuating otitis; accumulation of dried medication acts as a foreign body within the ear canal. Undertreatment allows progression of the disease and the development of resistance in the bacteria causing secondary infection.

209.11 GENERAL PRINCIPLES OF MANAGEMENT

The therapeutic plan for otitis externa requires identification of the primary disease process and perpetuating factors. Ideally management is aimed at thoroughly cleaning and drying the ear canal, removing or managing the primary factors, controlling perpetuating factors, administering appropriate topical or systemic therapy (or both), and evaluating response to therapy.

209.11.1 Ear Cleaning

Ear cleaning serves several functions: (1) it removes material that supports or perpetuates infection; (2) it removes bacterial toxins, white blood cells (WBCs), and free fatty acids that stimulate inflammation; (3) it allows complete evaluation of the external ear canal and tympanum; (4) it allows topical therapy to contact all portions of the ear canal; and (5) it removes material that may inactivate topical medications.[3,13] Significantly painful ears may benefit from initial anti-inflammatory therapy to decrease pain and swelling of the ear canal prior to cleaning. Severe cases of otitis externa often require general anesthesia to facilitate complete cleaning and evaluation of the external and middle ear.

Many different solutions are available for removing cerumen, exudate, and debris from the ear canal (Table 209-2). If the tympanic membrane cannot be visualized, only physiologic saline solution or water should be used, because many topical cleaning agents are ototoxic or incite inflammation of the middle ear. An operating otoscope, ear loops, and alligator forceps facilitate manual removal of large amounts of cerumen or debris. Debris is carefully removed under direct visualization, and care is taken deeper in the ear canal (close to the tympanic membrane). Aggressive hair removal is not advised, because inflammation and damage to the epithelium can result in secondary bacterial colonization and infection. Flushing may be performed after large accumulations of cerumen and debris are mechanically removed from the ear canal.

Flushing and evacuation of solution is done under direct visualization through an operating otoscope. A bulb syringe and red rubber catheter system may be used to both flush and evacuate solutions and accumulations from the ear canal. The operator, avoiding drastic pressure changes within the external ear canal that could damage the tympanum, should carefully control suction and manual evacuation of the contents of the bulb

syringe from the ear canal. Other alternatives include tomcat catheters (3.5 F) or flexible, intravenous catheters (14 gauge, Teflon); stiff, narrow catheters should be used cautiously and under direct visualization deep in the external ear canal. Other reservoir systems for delivery or evacuation of solutions include a 12 mL syringe or suction tubing attached to in-house vacuum systems. In-house vacuum systems should be used cautiously and under direct visualization. Care should be taken to avoid trauma to the tympanic membrane until its integrity can be assessed. Initial flushes should be done with physiologic saline solution or water until the integrity of the tympanic membrane is established.

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Table • 209-2 Otic Cleaning Solutions

TRADE NAME	ACETIC ACID	BORIC ACID	SALICYLIC ACID	ISOPROPYL ALCOHOL	PROPYLENE GLYCOL	DSS	OTHER
Ace-Otic Cleanser	2%		0.1%				Lactic acid 2.7%
Adams Pan-Otic					X	X	Parachlorometaxylenol, tris EDTA, methylparaben, diazolidinyl urea, popylparaben, octoxynol
Alocetic Ear Rinse	X			X			Nonoxynol-12, methylparaben, alovera gel
Cerulytic Ear Ceruminolytic					X		Benzyl alcohol, butylated hydroxytoluene
Cerumene	X	X					25% Isopropyl myristate
DermaPet Ear/Skin Cleanser for Pets							
Docusate Solution					X	X	
Earmed Boracetic Flush	X	X					Aloe
Earmed Cleansing Solution & Wash					X		50A 40B alcohol, cocamidopropyl phosphatidyl and PE dimonium chloride
Earoxide Ear Cleanser							Carbamide peroxide 6.5%
Epi-Otic Ear Cleanser			X		X	X	Lactic acid, chitosanide
Fresh-Ear	X	X	X	X	X		Lidocaine hydrochloride, glycerin, sodium docusate, lanolin oil
OtiCalm			X				Benzoic acid, malic acid, oil of eucalyptus
Otic Clear	X	X	X	X	X		Glycerin, lidocaine hydrochloride
Oticlean-A Ear Cleaning Lotion	X	X	X	35%	X		Lanolin oil, glycerin
Oti-Clens			X		X		Malic acid, benzoic acid
Otipan Cleansing Solution					X		Hydroxypropyl cellulose, octoxynol
Otocetic Solution	2%	2%					
Wax-O-Sol 25%							Hexamethyltetracosane

Other solutions may aid in the removal of wax in the ear canal. Ceruminolytics are emulsifiers and surfactants that break down ceruminocellular aggregates by causing lysis of squamous cells. A ceruminolytic agent in an alkaline pH may more effectively lyse squamous cells via cell surface protein disruption.[3] Oil-based products soften and loosen debris to aid in their removal but do not cause cell lysis. Water-based ceruminolytics are easier to remove and dry more quickly than oil-based solutions, which are occlusive if they remain in the ear canal. Water-based products include dioctyl sodium sulfosuccinate, calcium sulfosuccinate, and carbamate

peroxide, which has a foaming action with the release of urea and oxygen. Oil-based products include squalene, triethanolamine polypeptide, hexamethyltetracosane, oleate condensate, propylene glycol, glycerin, and mineral oil. In a recent study only the combination of squalene and isopropyl myristate in a liquid petrolatum base had no adverse effects on hearing, the vestibular system, and histopathologic examination.[33] Other agents tested contained glycerin, dioctyl sodium sulfosuccinate (2% or 6.5%), parachlorometaxylenol, carbamide peroxide (6%), propylene glycol, triethanolamine polypeptide oleate condensate (10%), and chlorobutanol (0.5%).[33]

Alcohol-based drying agents added to ceruminolytics include boric acid, benzoic acid, and salicylic acid, which decrease the pH of the ear canal, cause keratolysis, and have a mild anti-microbial effect. Drying the ear canal is important to combat increased humidity, which potentiates infection.

If the tympanum is intact, the ear canal is filled with a ceruminolytic agent for at least 2 minutes and the pinna is cleaned at the same time. The solution is flushed twice with warm water, and the canal inspected. The procedure is repeated until cleaning is complete. Other solutions commonly advocated for ear flushing include dilute chlorhexidine solution (0.05%), dilute povidone-iodine, and acetic acid (2.5%). The first two agents are potentially ototoxic or induce inflammation and should not be used if the tympanum is ruptured. A combination of propylene glycol malic, benzoic, or salicylic acid; 2% acetic acid; or dilute povidone-iodine have been suggested for use in dogs with a ruptured tympanum.[3]

Owners may clean the ears at home with mild preparations of ceruminolytics and drying agents if mild otitis is present without severe accumulation of cerumen or exudate. Aqueous solutions are usually recommended because they are less occlusive and easier to clean from the ear, dog, and home environment.

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The ear should be filled with the solution, then massaged for 40 to 60 seconds. The pet should be allowed to shake its head to remove the majority of the solution, and the excess should be wiped from the ear canal and pinna with a tissue. Daily flushing is usually recommended, followed by every other day, weekly, then as needed, depending on the solution. Ear swabs are not recommended for home use, because cerumen and debris may be forced into the horizontal ear canal and impact against the tympanic membrane.

209.11.2 Topical Therapy

Erythematous ceruminous otitis externa is diagnosed 2.7 times more often than acute suppurative otitis according to one report.[24] Yeast ± cocci were identified in those cases, with cocci or rods identified in suppurative otitis.[24] Topical therapy should be based on the cytologic examination to diminish the incidence of inappropriate treatment (Table 209-3). Many preparations combine anti-inflammatories and antimicrobials in an attempt to decrease the inflammation and combat bacterial or yeast overgrowth. All topical medications should be considered supportive, and specific treatment should be aimed at controlling the primary disease process.

Table • 209-3 Topical Medications Used in the Treatment of Ear Disease

GENERIC NAME	TRADE NAME	DOSE	FREQUENCY	DESCRIPTION
Fluocinolone 0.01% DMSO 60%	Synotic	4–6 drops; total dose <17 mL	q12h initially, q48-72h maintenance	Potent corticosteroid anti-inflammatory
Hydrocortisone 1.0%	HB101, Burrows H,	2–12 drops, depending on ear size	q12h initially, q24-48h maintenance	Mild corticosteroid anti-inflammatory
Hydrocortisone 1.0%, lactic acid	Epi-otic HC	5–10 drops	q12h for 5 days	Mild corticosteroid anti-inflammatory, drying agent
Hydrocortisone 0.5%, sulfur 2%, acetic acid 2.5%	Clear X Ear Treatment	2–12 drops, depending on ear size	q12-24h initially, q24-48h maintenance	Mild corticosteroid anti-inflammatory, astringent, germicidal
DSS 6.5%, urea (carbamide peroxide 6%)	Clear X Ear Cleansing Solution	1–2 mL per ear	Once per week to as necessary	Ceruminolytic, lubricating agent
Chlorhexidine 2%	Nolvasan	Dilute 1:40 in water	As necessary	Antibacterial & antifungal activity
Chlorhexidine 1.5%	Nolvasan	Dilute 2% in propylene glycol	q12h	Antibacterial & antifungal activity
Povidone-iodine 10%	Betadine solution	Dilute 1:10–1:50 in water	As necessary	Antibacterial activity
Polyhydroxidine iodine 0.5%	Xenodyne	Dilute 1:1–1:5 in water	As necessary, q12h, once weekly	Antibacterial activity
Acetic acid 5%	White vinegar	Dilute 1:1–1:3 in water	As necessary; q12-24h for *Pseudomonas*	Antibacterial activity, lowers ear canal pH
Neomycin 0.25%, triamcinolone 0.1%, thiabendazole 4%	Tresaderm	2–12 drops depending on ear size	q12h up to 7 days	Antibacterial & antifungal activity, parasiticide (mites), moderate corticosteroid anti-inflammatory
Neomycin 0.25%, triamcinolone 0.1%, nystatin 100,000 U/mL	Panalog	2–12 drops depending on ear size	q12h to once weekly	Antibacterial & antifungal activity, moderate corticosteroid anti-inflammatory
Chloramphenicol 0.42%, prednisone 0.17%, tetracaine 2%, squalene	Liquachlor, Chlora-Otic	2–12 drops depending on ear size	q12h up to 7 days	Antibacterial activity, mild corticosteroid anti-inflammatory
Neomycin 1.75 & polymyxin B 5000 IU/mL, penicillin G procaine 10,000 IU/mL	Forte Topical	2–12 drops depending on ear size	q12h	Antibacterial activity
Gentamicin 0.3%, betamethasone valerate 0.1%	Gentocin Otic Solution, Betagen Otic Solution	2–12 drops depending on ear size	q12h for 7 to 14 days	Antibacterial activity, potent corticosteroid anti-inflammatory
Gentamicin 0.3%, betamethasone 0.1%, clotrimazole 0.1%	Otomax, Obibiotic Ointment	2–12 drops depending on ear size	q12h for 7 days	Antibacterial & antifungal activity, potent corticosteroid anti-inflammatory
Gentamicin 0.3%, betamethasone valerate 0.1%, acetic acid 2.5%	Gentaved Otic Solution	2–12 drops, depending on ear size	q12h for 7 to 14 days	Antibacterial activity, potent corticosteroid anti-inflammatory

Polymixin B 10,000 IU/mL, hydrocortisone 0.5%	Otobiotic	2–12 drops, depending on ear size	q12h	Antibacterial activity, mild corticosteroid anti-inflammatory
Enrofloxacin 0.5%, silver sulfadiazine 1%	Baytril Otic	2–12 drops, depending on ear size	q12h for up to 14 days	Antibacterial activity
Carbaryl 0.5%, neomycin 0.5%, tetracaine	Mitox Liquid	2–12 drops, depending on ear size		Antibacterial activity, parasiticide (mites)
Pyrethrins 0.06%, piperonyl butoxide 0.6%	Ear Mite and Tick Control	5 drops	q12h	Parasiticide (mites)
Pyrethrins 0.05%, squalene 25%	Cerumite	2–12 drops, depending on ear size	q24h for 7 to 10 days	Parasiticide (mites), ceruminolytic
Isopropyl alcohol 90%, boric acid 2%	Panodry	Fill ear canal	As necessary	Drying agent
Acetic acid 2%, aluminum acetate	Otic Domeboro	Fill ear canal	q12-48h	Drying agent, antibacterial activity, lowers ear canal pH
Silver sulfadiazine	Silvadene	Dilute 1:1 with water, 1 g powder in 100 mL water	q12h for 14 days	Antibacterial & antifungal activity
Tris EDTA ±gentamicin 0.03%		2–12 drops, depending on ear size	q12h for 14 days	1 L distilled water, 1.2g Tris EDTA, 1 mL glacial acetic acid; antibacterial activity
Silver nitrate		Use sparingly	As necessary	Cauterization of ulcerative otitis externa
Miconazole 1%; ± topical glucocorticoid (7.5 mL of dexamethasone phosphate [4 mg/mL] to 10 mL of 1% miconazole)	Conofite	2–12 drops, depending on ear size	q12-24h	Antifungal activity
Ivermectin 0.01%	Acarexx	0.5 mL per ear	Once	Parasiticide (mites)
Pyrethrins 0.15%, piperonyl butoxide 1.5%	Many	2–12 drops, depending on ear size	Twice at 7-day interval	Parasiticide (mites)
Pyrethrins 0.05%, piperonyl butoxide 0.5%, squalene 25%	Cerumite	2–12 drops, depending on ear size	q24h for 7 days	Parasiticide (mites), ceruminolytic
Pyrethrins 0.04%, piperonyl butoxide 0.49%, DSS 1.952%, benzocaine 1.952%	Aurimite	10 drops	q12h	
Rotenone 0.12%, cube resins 0.16%	Many	2–12 drops, depending on ear size	Every other day	Parasiticide (mites)

Topical glucocorticoids benefit most cases of otitis externa by decreasing pruritus, exudation, swelling, and proliferative changes of the ear canal. The most potent glucocorticoids available in topical preparations are betamethasone valerate and fluocinolone acetonide. Less potent corticosteroids include triamcinolone acetonide and dexamethasone; the least potent is hydrocortisone. Most dogs benefit from short-term therapy with topical corticosteroids at the initiation of therapy, with concurrent therapy aimed at the primary and other perpetuating factors. Long-term therapy with topical corticosteroids can be deleterious because of systemic absorption of drug. Increased serum liver enzymes and depressed adrenal responsiveness may occur; with prolonged use iatrogenic hyperadrenocorticism is possible. Glucocorticoids alone may be of benefit for short-term therapy in cases of allergic or erythematous ceruminous otitis.

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Antimicrobials are important for controlling secondary bacterial or yeast overgrowth or infection. Antimicrobials are indicated in any case with cytologic evidence of bacterial overgrowth or infection, with attention paid to the morphology and gram-staining characteristics of the bacteria. Otic preparations commonly contain aminoglycoside antibiotics. Neomycin is effective against typical otitis bacteria such as *Staphylococcus intermedium*. Gentamicin and polymyxin B are also appropriate initial topical treatments for gram-negative bacterial otitis externa. The significant risk of bone marrow toxicity in people limits the use of chloramphenicol for treating otitis in dogs and cats despite its antibacterial spectrum and availability.

Due to the frequency of resistant gram-negative bacteria such as *Pseudomonas*, other topical preparations have been developed. Enrofloxacin, ophthalmic tobramycin, and topical application of injectable ticarcillin have been used to treat otitis in dogs.[3,34] Their use should be limited to cases of resistant bacteria, and culture and susceptibility testing should be performed prior to application. Other topical agents may be used to supplement treatment of resistant *Pseudomonas*, such as silver sulfadiazine solution and tris EDTA. Tris EDTA can render *Pseudomonas* susceptible to enrofloxacin or cephalosporins by enhancing membrane permeability and altering ribosome stability. Frequent ear cleaning may also assist in the treatment of resistant bacterial otitis; ceruminolytics have antimicrobial properties, and their use in clinical cases has been evaluated.[33,35] Acetic acid in combination with boric acid is effective against both *Pseudomonas* and *Staphylococcus*, depending on concentration and duration of exposure.[36] Ear cleaning removes proinflammatory products, cells, and substances that diminish the effectiveness of topical antibiotics.

Many topical preparations control yeast organisms, which may complicate erythematous ceruminous otitis and suppurative otitis. Common active ingredients include miconazole, clotrimazole, nystatin, and thiabendazole. Preparations containing climbazole, econazole, and ketoconazole have also been evaluated.[37,38] Eighty percent of yeast were susceptible to miconazole and econazole, intermediately resistant to ketoconazole, and 90% were resistant to nystatin and amphotericin B in one in vitro study.[38] Topical ear cleaning agents have some efficacy against *Malassezia* organisms.[35] Other preparations (e.g., chlorhexidine, povidone-iodine, acetic acid) are also effective in the treatment of secondary yeast overgrowth.

Response to topical therapy should be gauged by re-evaluation of physical, cytologic, and otoscopic examinations every 10 to 14 days after the initiation of therapy. Any changes in the results of these examinations should be recorded. Most cases of otitis can be managed topically; failure to respond to therapy should prompt re-evaluation of the diagnosis and treatment.

209.11.3 Systemic Therapy

Systemic glucocorticoid administration may be beneficial in cases of severe, acute inflammation of the ear canal, chronic proliferative changes of the ear canal, and allergic otitis. Anti-inflammatory doses should be limited to 7 to 10 days. Cases of significant thickening or proliferative changes in the external ear canal benefit from systemic antimicrobial therapy. Systemic therapy should be considered if concurrent dermatologic changes of the surrounding skin, pinna, or other regions of the body are present. Long-term administration of appropriate antimicrobials based on culture and susceptibility is required in all cases of otitis media. Systemic therapy for yeast is rarely recommended in animals with otitis alone. One study evaluated oral itraconazole therapy, and in ear samples evaluated on cytology and culture, no change in cytology score was found.[16]

209.12 THERAPY FOR SPECIFIC DISEASES OF THE EXTERNAL EAR CANAL

209.12.1 Ectoparasites

Thorough cleaning of the external ear canal, treatment of all household pets, and whole-body therapy should be considered in the treatment regimen for ear mites. Pets with no clinical signs may be asymptomatic carriers and a reservoir for reinfestation. Otic parasiticides such as pyrethrins, rotenone, amitraz, and carbaryl must be administered every 24 hours throughout the 20-day mite life cycle because they do not kill mite eggs.[13] Thiabendazole eliminates all mite stages, but it must be applied every 12 hours for 14 days. Ivermectin (0.3 to 0.5 mg/kg) may be applied topically once weekly for 5 weeks.[1] Otic administration of medication does not affect mites on adjacent or distant skin locations, and systemic or other total-body parasiticide may be indicated. Alternatively, ivermectin administered subcutaneously (0.2 to 0.3 mg/kg) 2 to 3 times at 10-to 14-day intervals or orally (0.3 mg/kg) every week for four treatments eliminates otic mites and those found elsewhere on the body.[1] Other topicals proven safe and effective for ear mite treatment include selamectin (6 mg/kg) applied to the skin between the shoulder blades and fipronil spray.[25–27] Selamectin administered once in cats and two times, 30 days apart in dogs gave results similar to topical pyrethrin therapy.[26,27]

209.12.2 Idiopathic Inflammatory or Hyperplastic Otitis in Cocker Spaniels

Treatment is aimed at decreasing the secondary ear canal changes associated with this condition. Anti-inflammatory doses of corticosteroids administered orally may be useful. Topical corticosteroid preparations in combination with antimicrobials decrease the soft tissue mass affecting the ear canal but may not be as effective as oral administration. Maintenance therapy may be required both topically and orally; however, low doses of corticosteroids should be used. Re-evaluation should include attention to the potential side effects of corticosteroid therapy. Intermittent treatment of secondary bacterial or yeast overgrowth and infection may be required. Surgery is often indicated due to the severe secondary changes within the ear canal.

209.12.3 Excessive Moisture (Swimmer's Ear)

Other primary disease conditions such as allergic otitis should be ruled out in any dog with erythematous ceruminous otitis. Dogs with frequent exposure to water, however, may require ear cleaning and drying agents to diminish the humidity of the ear canal. Many cleaning and drying agents also posses antimicrobial effects.[35] Products that combine a drying agent and corticosteroid decrease the ear canal humidity and inflammation associated with allergic otitis complicated by swimming. Care should be taken to control primary disease (i.e., allergic otitis), however, and intermittently manage the predisposing factor (i.e., excessive moisture) as necessary. The dog's ears should be cleaned and dried the day of water exposure and for 2 to 5 days after. For continued frequent exposure, maintenance cleaning may be required every other day to twice weekly.

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209.12.4 Chronic Bacterial Otitis

Resistant bacteria play an important role in the development of chronic otitis externa. Any dog not responding to initial therapy should be re-evaluated for primary and perpetuating conditions such as allergic disease, foreign body, neoplasia, otitis media, and secondary anatomic changes of the ear canal. Primary disease processes identified in one study included hypothyroidism, atopy, food allergy, and immune-mediated

disease.[34] Infection with Pseudomonas species frequently occurs with repeated treatment of otitis externa, and acquired resistance is common. Culture and susceptibility testing is imperative to guide therapy. Oral antimicrobials combined with topical therapy are used in severe cases with secondary changes of the ear canal. Identification of otitis media is vital to remove the middle ear as a source of otitis externa. Otitis media requires long-term treatment.

Ear cleaning prior to the application of topical medication may increase the efficacy of the agent by decreasing exudate in the ear canal that inactivates antimicrobial drugs such as polymyxin.[2] In cases that fail to respond to first-line drug treatments such as polymyxin or gentamicin, other topical antimicrobial agents should be tried. Ophthalmic tobramycin and injectable amikacin have been described for use as topical antimicrobials in ear disease.[2] The integrity of the tympanic membrane should be known prior to use; the clinician should avoid these medications if the tympanic membrane cannot be proven intact. Enrofloxacin or ticarcillin injectable preparations diluted in saline or water may be applied topically for resistant *Pseudomonas*. Parenteral ticarcillin was used in cases with a ruptured tympanic membrane until healing was observed, at which time topical therapy was instituted; clinical response occurred in 11 of 12 cases.[34] Enrofloxacin and silver sulfadiazine combination is also available in an otic preparation (Baytril Otic, Bayer Shawne Mission, KS).

Other topical therapy may assist in eliminating resistant *Pseudomonas* from the ear canal.

Decreasing the pH of the ear canal with 2% acetic acid is lethal to *Pseudomonas*; diluted vinegar in water (1:1 to 1:3) may be used to flush the ear canal. Acetic acid combined with boric acid is lethal to *Pseudomonas* and *Staphylococcus*, depending on the concentration of each agent.[36] Increasing the concentration of acetic acid may broaden its spectrum of activity but causes irritation of the external and middle ear. Silver sulfadiazine in a 1% solution exceeds the minimum inhibitory concentration of *Pseudomonas* and may be instilled into the ear canal. One gram of silver sulfadiazine powder mixed in 100 mL of water may be used for topical therapy and is also effective against Proteus species, enterococci, and *Staphylococcus intermedium*. Dilute acetic acid (2%) and silver sulfadiazine (1%) have not caused adverse effects in cases with a ruptured tympanic membrane.[1,3,13] Tris EDTA may be applied after thorough ear cleaning to increase the susceptibility of *Pseudomonas* to antimicrobial agents. It must be mixed, pH adjusted, and autoclaved prior to use or is available in an otic preparation (TrizEDTA, DermaPet®, Potomac, MD), which is used to clean the ears prior to instillation of topical antibiotic. Topical antiseptics such as chlorhexidine and povidone-iodine solutions may be helpful, but ototoxicity is an issue, particularly in cases in which the tympanum is ruptured or cannot be evaluated.

Re-evaluation of the pet is important for monitoring response to therapy. Evaluation of the ear canal for progressive secondary changes and cytologic examination will allow alterations in therapy as needed. Significant narrowing of the ear canal is an indication for surgical intervention. Yeast overgrowth may occur with aggressive medical management of bacterial otitis and should be identified to maintain proper medical management.

209.12.5 Refractory or Recurrent Yeast Infection

Malassezia infection is a common perpetuating factor with erythematous ceruminous otitis and alterations in the otic microenvironment. Primary causes of the otitis should be identified and treated. Cytologic examination, not culture, should be relied upon for the diagnosis of yeast infection.[17,31] If a case becomes refractory to therapy, reassessment of the primary condition and perpetuating factors should be done. Miconazole, clotrimazole, cuprimyxin, nystatin, and amphotericin B have all been described for treating

Malassezia otitis. Climbazole had better in vitro activity against isolates of *Malassezia pachydermatis* in one study.[37] Yeast were more susceptible to azole antifungals than polyene antifungals; however, oral ketoconazole, itraconazole, or fluconazole have been recommended for refractory cases.[1,38] Long-term therapy may require topical antibacterial and antifungal combinations.

Ear cleaning may aid in the elimination of yeast organisms by removing cerumen, debris, or exudate and altering the microenvironment of the ear canal. Cleaning with antimicrobial agents such as chlorhexidine, povidone-iodine, and acetic acid may be beneficial; but as always the integrity of the tympanum should be established prior to use. Ear cleaning solutions may also have some efficacy against yeast organisms both in vitro and in clinical cases of otitis.[35,39]

209.12.6 Neoplasia

Chronic otitis externa may be the result of otic neoplasia, or otitis may be a predisposing factor in the development of neoplasia. Cocker spaniels are over-represented for benign and malignant neoplasia and otitis externa.[1,40] Tumors of the skin and adenexal structures of the ear predominate. Benign tumors in dogs include sebaceous gland adenoma, basal cell tumor, polyp, ceruminous gland adenoma, and papilloma. Cats are more frequently diagnosed with malignant neoplasms, but benign conditions include inflammatory polyps, ceruminous gland adenomas, ceruminous gland cysts, and basal cell tumors. Malignant neoplasms in both species include ceruminous gland adenocarcinoma, undifferentiated carcinoma, and squamous cell carcinoma. Ceruminous gland adenocarcinomas are the most frequently diagnosed tumors of the ear canal in dogs and cats; however, one report stated that squamous cell carcinoma occurs with equal incidence in the cat.[40,41]

The biologic behavior of otic tumors cannot be judged by their gross appearance; however, benign masses are usually nodular and pedunculated. Ulceration can be secondary to otitis associated with mass lesions, but malignant masses ulcerate more frequently than benign masses. The tympanic bulla is involved in up to 25% of aural neoplasms, and neurologic signs occur in 10% of dogs and 25% of cats with otic neoplasia.[42] The biologic behavior of malignant neoplasms tends to be local invasion with a low metastatic rate (e.g., 10% in dogs) to draining lymph nodes or lung.

Surgery is the mainstay treatment of otic neoplasia. Conservative excision may be possible for benign lesions, depending on the location of the tumor. Malignancies should be removed by total ear canal ablation and lateral bulla osteotomy. Incomplete excision results in recurrence of the mass and secondary otitis externa. Malignant neoplasia is associated with a median survival time (MST) of more than 58 months in dogs and 11.7 months in cats.[40] Extensive tumor involvement and lack of aggressive management are associated with a poor prognosis in dogs.[40,43] In cats a poor prognosis is associated with neurologic signs, squamous cell carcinoma or undifferentiated carcinoma, vascular or lymphatic invasion, and lack of aggressive therapy.[40,44] Ceruminous gland adenocarcinoma has a median disease free interval of more than 36 months and 42 months in dogs and cats, respectively.[43,44] The MST associated with squamous cell carcinoma and undifferentiated carcinoma in cats is 4 to 6 months.[40]

209.13 ROLE OF SURGERY IN THE MANAGEMENT OF OTITIS EXTERNA

The two most common surgical procedures for the treatment of otitis externa are lateral ear resection and total ear canal ablation. Total ear canal ablation is always combined with a bulla osteotomy to allow complete removal

of all secretory epithelium and exudate associated with the external and middle ear. Care must be taken when choosing a surgical technique for otitis externa.

Lateral ear resection is associated with high failure rates (47% to 80%) with inappropriate patient selection.[45] The procedure should be viewed as an adjunct to medical management, not as a cure. The primary and perpetuating factors associated with otitis externa must be identified and managed or controlled even when surgery is elected. Opening the vertical ear canal improves aeration, decreases humidity, facilitates removal of cerumen or exudate, and improves the distribution of topical medication in the ear canal. Lateral ear resection may be used in cases with mild changes of the vertical ear canal but should be avoided with significant secondary changes of the vertical ear canal or horizontal canal stenosis. Owners should be educated to the continuing need for medical therapy after surgery to avoid further progression of secondary changes of the ear canal. Pets can develop end-stage otitis after lateral ear resection.

Total ear canal ablation is used to treat end-stage otitis and malignant otic neoplasia. Severe secondary changes and proliferative disease are surgically removed with the ear canal en toto. A lateral bulla osteotomy of the tympanic bulla allows complete exploration of the middle ear for the removal of secretory epithelium, exudate, and tumor. The surgery removes the site of chronic inflammation and infection to cure the vast majority of cases of otitis externa and otitis media. Complications of the procedure include facial nerve paresis or paralysis, hemorrhage, para-aural abscessation, otitis interna, Horner's syndrome, pinnal necrosis, continued pinnal dermatitis, and hearing loss. Dogs with obstruction of the ear canal from end-stage otitis or neoplasia may be partially deaf, and postoperatively only osseous conduction of sound remains.

Vertical ear canal resection may be performed in cases of tumors confined to the auricular cartilage or traumatic injury. Significant proliferative disease or changes secondary to otitis externa are rarely confined to the vertical ear canal; concurrent stenosis of the horizontal ear canal usually necessitates total ear canal ablation and lateral bulla osteotomy. The anastomosis between the horizontal ear canal and surrounding skin may undergo stenosis after surgery, necessitating reoperation. Progression of the otitis and tumor recurrence are possible after vertical ear canal resection.

209.14 DISEASES OF THE MIDDLE AND INNER EAR

209.14.1 Normal Anatomy and Physiology

The middle ear consists of the tympanic membrane, three cavities (epitympanic, tympanic, and ventral), and the bony ossicles (malleus, incus, and stapes). The tympanic membrane has two parts: (1) the thin pars tensa that attaches to the manubrium of the malleus and (2), above the pars tensa, the thicker, pars flaccida. The main portion of the middle ear, the ventral tympanic bulla, has two compartments in the cat (ventromedial and dorsolateral). The air-filled bulla is lined with modified respiratory epithelium, which is either squamous or cuboidal and may be ciliated. The four openings in the middle ear are the (1) tympanic opening, (2) the vestibular window, (3) the cochlear window, and (4) the ostium of the auditory tube. The auditory tube is the communication between the middle ear and caudal nasopharynx. The normal flora of the middle ear may be due to this pharyngeal communication, but the role of the auditory tube as a source of bacteria in otitis media is unknown. The tympanic opening is a common source of bacterial infection of the middle ear in dogs with otitis externa. The cochlear and vestibular windows are possible ports of entry for progression of otitis media or ototoxic substances into the inner ear.

Cranial nerve VII, or the facial nerve, the sympathetic innervation of the eye, and the parasympathetic innervation of the lacrimal gland are closely associated with the middle ear. The separation of the facial nerve

from the middle ear is minimal along the rostral aspect of its course through the petrosal bone. The nerve supplies motor fibers to the superficial muscles of the head, the muscles of the external ear, the caudal belly of the digastricus, and the ossicular muscles. The nerve also supplies sensation of the vertical ear canal and concave surface of the pinna.

Postganglionic sympathetic nerve fibers course closely with those of the facial nerve to innervate the smooth muscles of the eye. Preganglionic parasympathetic fibers also pass through the middle ear to innervate the salivary and lacrimal glands.

The inner ear is located within the petrosal bone. The cochlea, vestibule (saccule and utricle), and semicircular canals form the membranous labyrinth, which is encased in bone, called the *bony labyrinth*. The vestibular system functions to maintain the position of the eyes, trunk, and limbs relative to the position of the head, responding to linear and rotational acceleration and tilting. The system consists of the saccule, utriculus, and semicircular canals and communicates with the middle ear via the vestibular window. Fluid within the semicircular canals tends to remain stationary during motion, bending the cilia of the cells in the utricle and saccule, causing depolarization. These stereocilia synapse with the dendrites of the vestibular portion of the eighth cranial nerve and the signal is conducted via cranial nerve VIII to vestibular nuclei in the myelencephalon, the spinal cord, centers in the cerebellum and cerebral cortex, and motor nuclei of cranial nerves III, IV, and VI.[46] The result is coordination of the body, head, and eye movement. Projections to the vomiting centers are responsible for nausea and vomiting associated with vestibular disorders and motion. The cochlear system, involved with the translation of sound, consists of the spiral organ, or organ of Corti, cochlear duct, scala vestibule, and scala tympani. Transmission of sound through the tympanic membrane, ossicles, and cochlear window results in undulation of the basilar membrane of the spiral organ. Cilia bend and cause depolarization and transmission of a signal to cochlear nuclei, caudal colliculi, and cerebral cortex.[46] The cochlear nuclei control reflex regulation of sound via projections to cranial nerves V and VII, which control the muscles of the ossicles. Other projections allow for conscious perception of sound.

209.14.2 Otitis Media

Otitis media may result from extension of otitis externa through the tympanic membrane, aspiration of pharyngeal contents up the auditory tube (e.g., a sequela to upper respiratory tract [URT] infection in cats), or from hematogenous spread. Extension from otitis externa is the most common cause of otitis media, but otitis media may serve as a perpetuating factor for otitis externa. Developmental abnormalities of the external ear canal and pharynx may also result in otitis media due to the accumulation of secretions in the middle ear.[47,48] Neoplasia, inflammatory polyps, and middle ear trauma may be associated with secondary otitis media or result in similar clinical signs.

Cholesteatoma is commonly associated with otitis media and chronic otitis externa. A cholesteatoma is a mass of keratinized squamous cells that accumulate within a structure lined with stratified squamous epithelium. 1180
The lesion is presumed to develop when a pocket of tympanic membrane becomes adhered to inflamed middle ear mucosa. 1181
Significant narrowing of the external ear canal is usually present. Radiographic signs of increased density and bony changes of the tympanic bulla predominate with loss of the air-filled lumen of the external ear canal and concurrent calcification. Treatment is usually limited to total ear canal ablation and lateral bulla osteotomy due to the changes of the external ear canal and mass or accumulation of debris in the tympanic bulla.[49]

The clinical signs associated with middle ear disease often reflect concurrent otitis externa (e.g., head shaking, lethargy, exudate, otic malodor). Significant otic pain, lethargy, inappetence, and pain upon opening the

mouth are more suggestive of middle ear involvement. Neurologic signs may be present due to the course of the facial nerve and sympathetic innervation of the eye. Facial nerve paresis or paralysis result in facial asymmetry (i.e., uneven position of the lip commissures, unequal ear carriage, unilateral ptyalism) and abnormal cranial nerve reflexes on neurologic examination (e.g., menace response, palpebral and corneal reflexes, abnormal ear canal, and concave pinnal sensation). Horner's syndrome, or loss of sympathetic innervation to the eye, can also be complete or partial (i.e., ptosis, miosis, enophthalmia, prolapse of the third eyelid). Otitis interna is usually evidenced by head tilt, abnormal nystagmus, and ataxia and should be differentiated from central vestibular disease based on careful neurologic examination. Otitis interna is not usually associated with ipsilateral hemiparesis or abnormalities in level of consciousness.

Cases of para-aural abscessation usually have concurrent otitis media.[3] The primary cause may be trauma to the external ear canal, severe otitis externa, extension of otic neoplasia, or total ear canal ablation. Signs of middle or external ear disease and soft tissue swelling in the parotid area may be accompanied by draining tracts. A head tilt and pain upon palpation of the area are usually present.

The diagnosis of otitis media is based on a thorough history and physical, neurologic, and otoscopic examinations. A ruptured tympanum strongly suggests otitis media. The pharynx should also be evaluated on physical examination; identification of specific conditions may require general anesthesia due to anatomic location (e.g., inflammatory polyps) or pain associated with examination (e.g., otitis media causing temporomandibular joint (TMJ) pain, severe otitis externa). General anesthesia may also be required to perform a complete otoscopic examination in cases of severe otitis externa in which thorough cleaning of the ear is necessary for therapy and diagnosis (i.e., visualization of the tympanum). Significant otitis externa is commonly associated with otitis media; the tympanic membrane is ruptured in up to 50% of dogs with otitis externa, although 70% of dogs with otitis media had an intact tympanic membrane in one study.[15,50] The tympanic membrane in dogs with otitis externa may be difficult to examine due to secondary changes of the external ear canal, pain associated with otoscopic examination, and accumulation of exudate, cerumen, and debris. Treatment to diminish the severity of otitis externa and general anesthesia may increase the ability to evaluate the tympanum in these cases.

Any case that has significant cerumen, exudate, or debris should undergo careful cleaning of the ear canal to allow evaluation of the integrity and character of the tympanic membrane. The presence of a “false middle ear” occurs when large accumulations of debris lodge against the tympanic membrane, causing it to deviate medially into the middle ear. This makes the external ear canal appear elongated and leads to misdiagnosis of a ruptured tympanic membrane.[3]

Gentle probing of the tympanic membrane with a red rubber catheter under direct visualization may assist in the diagnosis of small tears in the membrane. If the catheter tip is consistently visible, rupture is unlikely. Alternatively, an aliquot of 1 mL of physiologic saline placed in the horizontal canal should remain stationary; disappearance suggests an opening in the tympanum, allowing the fluid to drain into the middle ear.[1] Movement of the fluid may be blocked by large amounts of debris in the middle ear, even in the presence of a tear in the tympanum.

If the tympanic membrane is visible, its character should be recorded in the medical record for comparison upon re-evaluation. Bulging, increased opacity, and hyperemia may be present with otitis media. If otitis media is suspected, radiographs of the bullae may be made. Lateral oblique and open-mouth views are most helpful for evaluating the tympanic bulla, but positioning for comparison of left and right sides is difficult and requires general anesthesia. Ventrodorsal or dorsoventral views allow evaluation of the air-filled lumen and calcification of the external ear canal. Abnormalities of the bulla include increased opacity, sclerosis, and

lysis. Fluid cannot be differentiated from increased soft tissue density (e.g., neoplasia), and absence of radiographic changes does not rule out otitis media. Radiographic changes were absent in 33% of the middle ears in one study of dogs with otitis media confirmed by surgical exploration.[18] Otitis media or neoplasia and otitis interna can cause radiographic evidence of lysis of the petrosal bone.

Other diagnostic tools are available to evaluate patients with otitis media interna. Contrast introduced into the external ear canal followed by radiography, termed *canalography*, is used to diagnose tympanic membrane perforations. The method is useful for acute tympanic membrane rupture and increases the frequency of diagnosing tympanic membrane rupture with concurrent otitis externa and media beyond that of otoscope alone.[51] Advanced imaging with CT and MRI have been studied in normal dogs and dogs with otitis media (Figure 209-1).[18,52] CT is considered superior to MRI for bony changes, whereas MRI is better for detection of soft tissue abnormalities in both dogs and cats.[18,20,52,53]

If the tympanic membrane is intact in a dog with otitis media, a myringotomy is performed to obtain samples for culture and susceptibility testing and cytologic examination. Affected dogs are often more comfortable after collection of samples due to decreased pressure in the middle ear after myringotomy. The procedure must be performed with general anesthesia and is usually done after radiography or advanced imaging of the ear. The external ear canal should be thoroughly cleaned and dried prior to myringotomy to avoid contamination with external ear canal debris. Direct otoscopic visualization is used for the procedure. A 20-gauge spinal needle is used to penetrate the tympanic membrane through the caudoventral aspect of the pars tensa. Suction is applied and samples collected—culture and susceptibility takes priority over cytologic examination because cytology is frequently negative, and cultures of the external ear canal do not reflect the middle ear bacteria in the majority of cases.[15] If fluid cannot be aspirated directly from the middle ear, 0.5 to 1 mL of warm, sterile saline can be infused through the needle into the middle ear cavity and aspirated. Alternatively, an open-ended tomcat catheter or small, sterile culture swab may be passed into the middle ear cautiously under otoscopic visualization. Pseudomonas species and *Staphylococcus intermedium* are most commonly isolated, followed by yeast, β-hemolytic *Streptococcus*, Corynebacterium species, Proteus species, and Enterococcus species.[15,54] Surgical exploration is rarely required for the diagnosis of otitis media.

Medical therapy of otitis media should be guided by culture and susceptibility results. The external ear canal is flushed and dried as necessary to treat concurrent otitis externa. Flushing is usually performed under the same general anesthetic episode used for diagnostic testing. If the tympanic membrane is ruptured, the middle ear should be gently lavaged with warm saline. Cytology results, when available, should be used to guide initial therapy. The integrity of the tympanic membrane must be considered when using topical agents to treat concurrent otitis externa: ototoxic medications and vehicles should be avoided if the tympanic membrane is ruptured.

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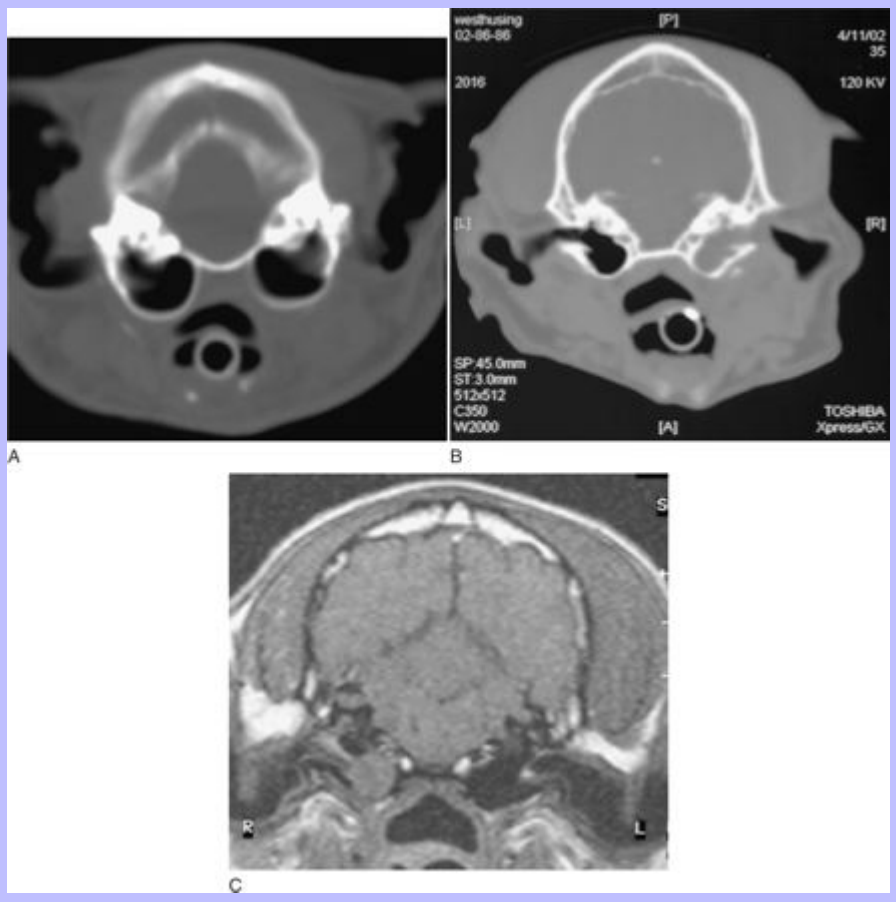
Figure 209-1 Computed tomographic (CT) image of a normal canine ear **(A),** CT image **(B),** and a magnetic resonance image (MRI) **(C)** of a dog with otitis media.



Newly diagnosed cases of otitis media may be started on empiric therapy based on cytology. First-choice antimicrobials include cephalosporins, amoxicillin and clavulonic acid, and fluoroquinolones. Definitive therapy consists of administration of antibiotics based on culture and susceptibility results for a minimum of 4 to 6 weeks. Primary and perpetuating factors of otitis externa should be identified and treated or controlled. Topical medication and flushing of the external ear canal should continue until resolution of clinical signs and normalization of cytology. Gradual improvement of the otitis media is expected within 14 days. The ear canal and tympanic membrane should be evaluated prior to and after discontinuation of therapy. Small tears in the tympanic membrane after myringotomy heal rapidly with appropriate therapy within 2 to 3 weeks.[34,55] However, re-evaluation of the tympanic membrane in dogs with otitis externa media should precede alteration of the topical agents in the therapeutic plan.

Failure to respond to therapy or chronic or recurrent otitis media warrant re-evaluation for surgical intervention. Total ear canal ablation and lateral bulla osteotomy should be considered in cases with severe

secondary changes of the external ear canal and concurrent otitis media. If the external ear canal is not affected, a ventral bulla osteotomy may be performed to remove gross exudate and establish drainage from the middle ear of dogs and cats with chronic or recurrent otitis media. Caution should be taken in considering lateral ear resection and ventral bulla osteotomy in the treatment of concurrent otitis externa and media because lateral ear resection is only an adjunct to medical management of otitis externa.

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209.14.3 Neoplasia of the Middle Ear

Neoplasia of the middle ear is rare; most cases represent extension of tumors originating in the external ear canal.

209.14.4 Inflammatory Polyps

Inflammatory polyps are a non-neoplastic admixture of inflammatory and epithelial cells originating in the tympanic bulla in cats. Other sites of origin include the auditory tube and nasopharynx. Macrophages, neutrophils, lymphocytes, plasma cells, and epithelial cells are usually present on histopathologic examination. The cause is unknown, but ascending infection and congenital causes have been suggested.[56] No age or sex predilection exists for the condition, but younger cats are more commonly affected (1 to 5 years of age). Signs can be unilateral or bilateral and depend on the location of the mass lesion. A single polyp can grow into the external ear canal, down the auditory tube into the nasopharynx, or both. Signs of concurrent otitis externa and media are common with polyps limited to the ear, but respiratory stridor, dyspnea, gagging, and dysphagia occur with growth into the pharynx.

Diagnosis is based on otoscopic and pharyngeal examinations. Radiographs of the bulla, nasal cavity, and pharynx may be considered, and CT or MRI can be used to diagnose the site and side of origin of inflammatory polyps.[53,57] Treatment consists of excision by traction or surgical excision via ventral bulla osteotomy.[8,58] Regrowth is a problem in half of the cats treated by traction extraction alone, and Horner's syndrome is common in cats after ventral bulla osteotomy.[8,58]

209.14.5 Otitis Interna

Otitis interna is usually an extension of otitis media or neoplasia of the middle ear. A careful neurologic examination is imperative to the localization of vestibular signs. Clinical signs associated with otitis interna include head tilt, ataxia, horizontal or rotary nystagmus, circling or falling toward the side of the lesion, or ipsilateral nystagmus. The fast phase of nystagmus is usually away from the side of the lesion. Occasionally, animals will become nauseated or vomit. Horner's syndrome or deficits in cranial nerve VII may accompany otitis media interna, but involvement of other cranial nerves, vertical or changing nystagmus, or the presence of conscious proprioceptive deficits or paresis indicate central rather than peripheral vestibular disease. Bilateral peripheral vestibular disease is rare, but the animal will not have a head tilt, nystagmus, or strabismus and may exhibit wide head excursions and a crouched stance or the inability to stand.

The diagnosis of otitis interna is based on history, clinical signs, and physical, neurological, and otoscopic examinations. Advanced imaging may be helpful in distinguishing the anatomic location of the disease process. Treatment with aggressive medical or surgical intervention appropriate to the localization is important in prevention of adjacent brain stem involvement.

209.14.6 Prognosis for Otitis Media and Interna

A fair prognosis can be given if aggressive surgical and medical therapy are possible. Cases with concurrent severe external ear canal changes require total ear canal ablation and lateral bulla osteotomy. Repeated infections after ventral bulla osteotomy or total ear canal ablation and lateral bulla osteotomy may be operated again with resolution of the condition. Resistant organisms, failure to respond to aggressive surgery, and significant osteomyelitis are associated with a poor prognosis. The neurologic signs associated with otitis media and interna may be permanent, but many animals learn to use visual cues and can compensate for vestibular deficits. Facial nerve deficits, Horner's syndrome, and keratoconjunctivitis sicca are often permanent.

209.14.7 Ototoxicity

Ototoxic substances (Table 209-4) damage the cochlear or vestibular systems or both. Otic application of medication can also cause adverse effects through local inflammation of the tympanic membrane or the meatal window (or both), as well as resultant otitis media. Topical medications also cause adverse effects by systemic absorption. Ototoxic substances reach the inner ear after local application and absorption through the cochlear or vestibular windows or hematogenously. The most frequent cause of ototoxicity is the application of an ototoxic substance to the external ear canal in a pet with a ruptured tympanum, which results in distribution to the middle ear. Absorption by the inner ear is increased when inflammation of the cochlear window occurs with otitis media. Hematogenous distribution of ototoxins to the inner ear is inherent in some medications (e.g., aminoglycosides).

The development of ototoxicity also depends on the vehicle of the preparation, chemical composition, drug concentration, concurrent medications, as well as the route, frequency, and duration of administration.[3] Examples of increased risk of ototoxicity depending on the vehicle (e.g., combination of chlorhexidine and detergents) and concurrent medications (e.g., loop diuretics and aminoglycosides) have been described. Minimization of the risk of toxicity should be considered when any potentially toxic substance is administered either topically or systemically. The integrity of the tympanic membrane should be known prior to topical administration of any potentially ototoxic drug, and consequences of each drug should be considered in light of the animal's health and concurrent therapies.

209.14.8 Idiopathic Vestibular and Facial Nerve Diseases

A complete neurologic examination is key to differentiating peripheral from central vestibular disorders. Head tilt, ataxia, horizontal or rotary nystagmus, and cranial nerve VII deficits may be seen with either condition. Central vestibular disease causes paraparesis, conscious proprioceptive deficits, other cranial nerve abnormalities, and vertical or changing nystagmus. Middle ear neoplasia, otitis media interna, idiopathic vestibular syndrome, and congenital vestibular disorders result in peripheral vestibular signs. Congenital vestibular disorders have been described in the German shepherd, Doberman pinscher, English cocker spaniel, Siamese, and Burmese breeds.[59,60] Bilateral congenital vestibular syndrome has been described in beagles and Akitas.[59,60] Clinical signs of head tilt and ataxia in these dogs and cats may be persistent or may improve; animals can be congenitally deaf.

Table • 209-4 Ototoxic Drugs

Aminoglycoside Antibiotics
Neomycin
Dihydrostreptomycin
Gentamicin
Streptomycin
Kanamycin
Tobramycin
Amikacin
Other Antibiotics
Polymixin B & E
Minocycline
Erythromycin
Chloramphenicol
Vancomycin
Loop Diuretics
Furosemide
Bumetanide
Ethacrynic acid
Antiseptics
Chlorhexidine
Iodine & iodophores
Ethanol
Benzalkonium chloride
Benzethonium chloride
Cantrimide
Antineoplastic Agents
Cisplatin

Nitrogen mustard
Miscellaneous
Quinine
Salicylates
Propylene glycol
Detergents
Arsenic
Lead
Mercury

Otitis media interna may be associated with facial paresis or paralysis if cranial nerve VII is affected by the inflammation. Otitis should be ruled out before diagnosing any animal with idiopathic facial nerve paralysis, because otitis requires aggressive management and the idiopathic condition can only be treated symptomatically or with acupuncture.[61]

209.14.9 Deafness

Deafness is classified as inherited or acquired, conductive or sensorineural, and congenital or late onset. Acquired deafness may be either conductive or sensorineural, depending on the etiologic agent, which also affects the time of onset. Conductive deafness results from a lack of presentation of sound to the inner ear, usually secondary to otitis externa media. Sensorineural deafness occurs with abnormalities of the cochlear system, cranial nerve VIII, or auditory pathways and higher brain centers. Inherited deafness, ototoxicity, cochlear nerve degeneration, and presbycusis (age-related deafness) are forms of sensorineural deafness.

209.14.9.1 Diagnostic Principles

Signalment can help to prioritize possible causes of deafness. Certain breeds have a high incidence of inherited deafness, and clinical signs are usually noticed at an early age if the deafness is bilateral. Most other forms of deafness occur as late-onset disorders. The history is important in establishing the nature of the deafness, because certain conditions or treatments may cause deafness (e.g., otitis externa media, ototoxic medications, head trauma, prior infectious diseases). The owner may note behavioral changes in the pet, and complete, bilateral deafness is usually easily identified. Astute owners may notice behavioral changes in puppies at an early age. Inherited deafness usually results in loss of hearing within 3 to 4 weeks of birth due to a degenerative process of the inner ear.[62] The affected pup is often more aggressive than its littermates, because it cannot hear cries of pain during play. The puppy may also be more difficult to rouse and is more vocal than its littermates, especially when they are out of view of the affected pup.

Unilateral deafness is harder to identify, but the owner may report difficulty rousing the pet when it is sleeping in lateral recumbency or difficulty in the pet's ability to orient to the origin of sounds. The physical, otoscopic, and neurologic examinations are important in differentiating peripheral from central disease and establishing whether conductive deafness is possible. The index of suspicion for conductive

deafness is increased in dogs and cats with abnormalities of the external ear canal, tympanum, cranial nerve VII, or sympathetic innervation of the eye.

Abnormalities suggestive of central disease prompt more aggressive diagnostic testing such as advanced imaging and cerebrospinal fluid (CSF) analysis.

Hearing loss can be evaluated with the pet in the examination room. Different sounds can be used in an attempt to observe behavioral reactions to sound. A Preyer's reflex (i.e., movement of the pinna in response to sound) is the minimal expected response.[62] Care should be taken to avoid visual cues and air movement close to the animal's head, which cause an apparent reaction to sound in an affected dog or cat. Unfortunately, pets may be stressed by the hospital environment and may not react to auditory cues even if hearing is normal.

209.14.9.1.1 Impedance audiometry and tympanometry

Impedance audiometry is based on the concept that the intensity of a sound wave is dependent on the size of the cavity in which it is generated and on the compliance of the cavity's containing walls.[3] The external ear canal is occluded for the test, and a sound wave generated. Changes in the pressure within the canal are measured to evaluate the compliance of the tympanic membrane. Accumulation of fluid in the middle ear canal, rupture of the tympanic membrane, immobility of the ossicles, and other causes of conductive deafness alter the results. Normal results in a deaf animal would be supportive of sensorineural deafness.

The acoustic, or stapedial, reflex test is also known as the *acoustic decay test*. A high amplitude sound is used to cause stapedial muscle contraction that protects the structures of the inner ear. This reflex alters tympanic compliance. The afferent (cranial nerve VII) and efferent limbs (cranial nerves V and VII) must be intact for a normal reflex.[1] A normal dog will maintain this reflex for a known period of time, but decay of the reflex occurs in dogs with lesions of cranial nerve VIII.[3] Tympanometry is not commonly performed because it requires specialized equipment adapted from human kits. Ideally the generated sound affects the tympanic membrane perpendicular to its surface. This is difficult to obtain in the dog or cat due to the angle of the ear canal. The results are not sensitive or specific, but they are reliable for the diagnosis of tympanic membrane rupture.[3,63]

209.14.9.1.2 Brain stem auditory evoked response

The brain stem auditory evoked response (BAER), or brain stem auditory evoked potential (BAEP), is an objective measure of hearing. The test identifies the presence or absence of hearing and progressive changes in hearing. Subjective determination of partial hearing loss is possible.[64] Electrodes placed on standard sites of the head record responses to an auditory stimulus generated in one ear. Sound is generated as a series of clicks, and the contralateral ear is excluded by the presentation of *white noise*. The position of electrodes, stimulus intensity, and body temperature can also alter the waves produced.[3] Electrode position is standardized and the sound generated, or stimulus intensity is presented over a range of decibels; the rate of presentation remains constant. The waves generated are subjectively and objectively evaluated. Wave I corresponds to cranial nerve VIII; wave II represents the cochlear nucleus and intracranial, extramedullary portion of cranial nerve VIII. Wave III corresponds to the dorsal nucleus

of the trapezoid body, and waves IV and V originate in the rostral pons and caudal colliculi, respectively.[3]

Wave latencies and amplitudes are used to assess hearing and conduction of impulses through the brain stem, making BAER testing valuable not only in the diagnosis of hearing loss but also for evaluation of brain stem lesions. Most pets do not require sedation or anesthesia for the procedure, which is beneficial because both cause changes in wave latency. Wave latencies and amplitudes vary with the intensity and rate of delivery of the sound.[3] In general, amplitude increases and latency decreases with increasing sound intensity. Interpeak latencies are used to evaluate conduction in the brain stem, which should not change with stimulus intensity.

Conductive deafness reduces the intensity of sound reaching the inner ear. A lack of air-conducted hearing in the presence of bony-conducted hearing is diagnostic of conductive deafness during BAER. The hearing threshold is usually increased when sound is presented through air conduction, but bony-conducted hearing should remain intact. Increased hearing threshold may be accompanied by decreased wave amplitude and increased wave latency in cases of severe otitis externa.[65] Sensorineural deafness alters the appearance of the BAER, depending on the site of the lesion. Alteration of waveforms, increased hearing threshold, or complete abolition of waveforms may be present in animals with sensorineural deafness.

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209.14.10 Acquired Late-Onset Conductive Deafness

Conductive deafness is due to lack of transmission of sound through the tympanic membrane and ossicles to the inner ear. Conditions that block sound transmission through the external ear canal, tympanic membrane, or middle ear and ossicles, such as otitis externa, otitis media, and otic neoplasia, cause conductive deafness. Less common causes of conductive deafness include trauma-induced fluid accumulation in the middle ear, atresia of the tympanum or ossicles, fused ossicles, or incomplete development of the external ear canal, which results in fluid accumulation in the middle ear.[62,64,66,67] An increase in hearing threshold, absence of air-conducted hearing, and the presence of bone-conducted hearing on BAER suggest conductive deafness.

The application of a bone-anchored hearing aid was described in one dog with conductive deafness after total ear canal ablation.[68] It maintained bone-conducted hearing and tolerated the hearing aid anchored to the parietal bone. Use of a bone-anchored device was required, because the dog did not have an external ear canal in which to place an earpiece. The hearing aid acted as an amplifier, and the dog seemed to respond to its use.

209.14.11 Acquired Late-Onset Sensorineural Deafness

Presbycusis, or decline in hearing associated with aging, may be due to one of the following: loss of hair cells and degeneration in the organ of Corti, degeneration of spiral ganglion cells or neural fibers of the cochlear nerve, atrophy of the stria vascularis, or changes in the basilar membrane. Because this condition occurs in older dogs and cats from 8 to 17 years of age, animals should be evaluated for concurrent causes of conductive deafness such as chronic otitis externa or media and otic neoplasia. BAER testing may demonstrate normal waveforms in response to high-intensity sound.[69] If conduction is intact at an increased hearing threshold, use of an amplifying hearing aid may be beneficial. Pets may not tolerate occlusive types of ear pieces often used in hearing aids, and training to the ear piece should be done prior to application of the hearing aid.

209.14.11.1

Box • 209-1 Canine Breeds Associated with Inherited Deafness

Akita

American-Canadian shepherd

American cocker spaniel

American Eskimo

American Staffordshire terrier

Australian cattle dog

Australian shepherd

Beagle

Bichon frise

Border collie

Borzoi

Boston terrier

Boxer

Bulldog

Bull terrier

Catahoula leopard dog

Chihuahua

Chow chow

Collie

Dachshund

Dalmatian

Doberman pincer

Dogo Argentino

English cocker spaniel

English setter

Foxhound

Fox terrier

French bulldog

German shepherd

Great Dane

Great Pyrenees

Greyhound

Ibizan hound

Italian greyhound

Jack Russell terrier

Kuvasz

Labrador retriever

Maltese

Miniature pincer

Miniature poodle mongrel

Norwegian dunkerhound

Nova Scotia duck tolling retriever

Old English sheepdog

Papillion

Pit bull terrier

Pointer

Poodle (toy & miniature)

Puli

Rhodesian ridgeback

Rottweiler

Saint Bernard

Schnauzer

Scottish terrier

Sealyham terrier

Shetland sheepdog

Shropshire terrier

Soft-coated Wheaton terrier

Springer spaniel

Sussex spaniel

Tibetan spaniel

Tibetan terrier

Walker American foxhound

West Highland white terrier

Yorkshire terrier

Ototoxic substances, chronic exposure to loud noise, hypothyroidism, trauma, and bony neoplasia can also cause acquired late-onset deafness in dogs and cats. Ototoxicity can result in abolition of waveforms or an increase in hearing threshold on BAER.[3] BAER testing can be used to re-evaluate patients for return of function after withdrawal of medication after exposure to ototoxic medication.

209.14.12 Congenital Sensorineural Deafness

Inherited sensorineural deafness usually results in complete loss of hearing in the affected ear by 5 weeks of age. Many breeds can be affected with the condition (Box 209-1). The condition has been linked to coat color in many breeds of dogs and white cats. The condition is common in white cats, and mode of inheritance is thought to be autosomal dominant with incomplete penetrance.[70] The condition is most common in white cats with blue irides. The correlation of white coat, blue eyes, and deafness is not perfect, but cats with two blue irides have a greater risk of deafness than cats with one blue iris, which have a greater risk of deafness than cats without blue irides.[70] Total hearing loss occurs more often in long-haired white cats.[70] The condition is common in certain breeds of dogs, such as dalmatians, which have a nearly 30% incidence of deafness (combining unilateral and bilateral deafness).

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The trait is associated with the dominant merle or dapple gene in collies, Shetland sheepdogs, Great Danes, and dachshunds. The incidence of deafness tends to increase with increasing amount of white in the coat, and dogs homozygous for the merle gene are usually deaf and may be solid white, blind, or sterile.[62] The piebald or extreme piebald gene is associated with deafness in dalmatians, bull terriers, Great Pyrenees, Sealyham

terriers, greyhounds, bulldogs, and beagles. Inheritance is thought to be autosomal recessive, but the trait may be polygenic.[64]

Heterochromia irides and lack of retinal pigment are associated with white color in dogs and cats. Hearing loss may be associated with absence of pigment in the cochlear stria vascularis. Diminished blood supply and disorders of endolymph production, with changes in the chemical or mechanical properties of endolymph, lead to degeneration of the organ of Corti secondary to stria vascularis atrophy. Loss of hair cells and abnormalities of the cochlear duct, Reissner membrane, tectorial membrane, and internal spiral sulcus are typical of cochleosaccular type of end-organ degeneration seen in these cases.[3,64,66,70,71]

Clinical signs of deafness may be recognized in puppies as young as 3 weeks of age by astute owners; definitive diagnosis of uni-or bilateral deafness is usually made by BAER testing at 5 to 6 weeks of age when the auditory system is completely developed and cochlear degeneration, if present, is complete.

209.14.12.1 Congenital Acquired Sensorineural Deafness

Exposure to bacteria, ototoxic drugs, low oxygen tension, and trauma in utero or during the perinatal period rarely causes deafness in young animals.

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210 CHAPTER • 210 Diseases of the Nose and Nasal Sinuses

Anjop J. Venker-van Haagen

210.1 FUNCTIONAL CONSIDERATIONS

210.1.1 Functional Anatomy

The nose has four main functions: (1) to provide a portal through which air can flow to reach the alveoli, (2) to modify or regulate the flow of air, (3) to facilitate water and heat exchange (e.g., to condition the inspired air), and (4) to pass inspired air over the olfactory epithelium—the sheet of neurons and supporting cells that lines the nasal cavities. Speculation exists regarding the functions of the nasal sinuses. It seems plausible that the frontal sinuses protect the rostral portions of the brain from frontal trauma.

The apical portion of the nose, consisting of hairless integument and the nostrils, is called the *nasal plane*. It is supported by cartilage, which also supports the portion of the nose between the nasal plane and the bony portion. The levator nasolabial and levator labii superior muscles can move the cartilaginous parts. Dilation of the nostrils changes the pattern of flow of inspired air. The nostrils are dilated when increased airflow is needed, as in dyspnea, and to aid sampling of interesting odors.

The bony case of the nose is the facial portion of the respiratory passageway. The nasal cavity, comprised of bony and cartilaginous parts, extends from the nostrils to the choanae, being divided into right and left halves by the nasal septum. Each half of the nasal cavity has a respiratory and an olfactory region. The nasal conchae—slightly ossified scrolls covered by nasal mucosa—fill the nasal cavities. Together with the nasal glands, the nasal mucosa has a role in *conditioning* the inspired air. During normal inspiration, the respiratory and olfactory air currents are concurrent. When the dog or cat wants to sample environmental odors, the nostrils are dilated and forced inspiration occurs in which a greater volume of inspired air takes a more dorsal course around the ethmoturbinates, where the olfactory receptors are most numerous.[1]

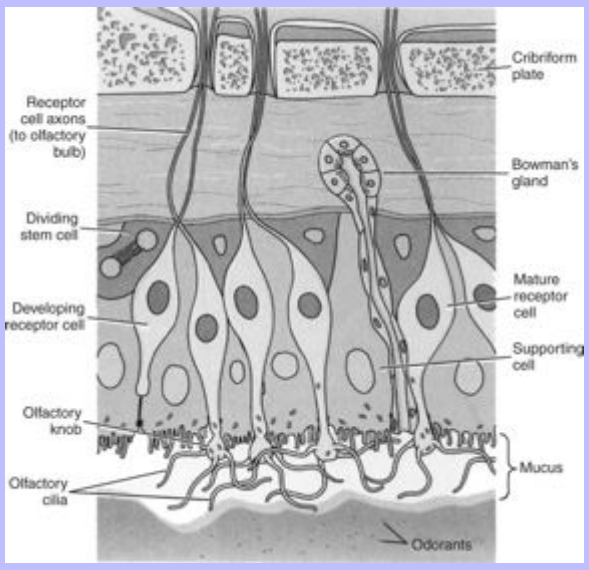
210.1.2 Regulation and Conditioning of the Inspiratory and Expiratory Airflow

The respiratory airflow through the nasal cavity is regulated by the ventilatory control systems. The nose represents an important part of the resistance of the airway and thereby influences gas exchange in the alveoli. The resistance has to be overcome by greater negative pressure in the thorax during inspiration, which leads to better expanding and filling of the alveoli by the inspired air and a greater venous blood flow in the lungs. In humans, a prolonged increase in nasal resistance due to severe obstruction can lead to cor pulmonale, cardiomegaly, and pulmonary edema.[2] In dogs, pulmonary edema is known to develop in laryngeal obstruction. Pulmonary edema may occur by a similar mechanism when severe obstruction of nasal airflow exists. The most common consequence of increased resistance is, however, mouth breathing.

Heating, or cooling of inspired and expired air as it passes through the nose is largely accomplished by radiation from the mucosal blood vessels. The flow of blood is from posterior to anterior, opposite to the flow of the inspired air. Humidification occurs by evaporation from the blanket of mucus covering the mucosa and the serous fluid from the nasal glands. The nasal blood flow and the activity of the nasal glands are regulated by the autonomic nervous system. The autonomic innervation of the nose consists of parasympathetic and sympathetic nerve fibers, joined together in the vidian nerve. The conditioning of the inspired air by the nose

is an important function for protection of the alveoli. Even under extremely dry or cold conditions, the bronchi receive air warmed to body temperature with a humidity of around 98%.

Figure 210-1 Diagram of the olfactory epithelium showing the major cell types and the projection of the olfactory receptor neurons to the bulb (see discussion of Olfaction in text). Bowman's glands produce mucus, and supporting cells help to detoxify chemicals that come in contact with the epithelium. (Courtesy Neuroscience. Sunderland, MA, Sinauer Associates, Inc., 1997, p. 267)



210.1.3 Mucosal Cleaning

The pseudostratified respiratory mucosa in the nose consists of ciliated, intermediate, basal, and goblet cells. They rest on a well-defined basement membrane supported by a deep, loose lamina propria containing small blood vessels, venous plexus, and ducts of mucous and serous glands, sensory nerves, and blood cells. The tall ciliated cell is the predominant type, and it extends from the basement membrane to the luminal surface, where cilia admixed with microvilli are found. The cilia actively move the overlying blanket of mucus by a to-and-fro movement, called the *ciliary beat*. A more forceful forward movement and a less forceful recovery beat occurs. The forward movement transports the mucus blanket toward the pharyngeal end of the esophagus. The two-layer mucous blanket is sticky, tenacious, and adhesive. The outer layer is more viscid than the deeper, periciliary layer. Insoluble particles, allergens, and bacteria caught on the outer layer are thus carried to the esophagus. Soluble material reaches the periciliary layer and is absorbed.[3]

Sneezing starts with a rapid inspiration followed by an involuntary, sudden, violent, and audible expulsion of air through the nose and mouth. The reflex occurs after stimulation of sensory receptors in the nasal mucosa. It is the ultimate cleaning procedure for the nasal cavity in dogs and cats.

210.1.4 Olfaction

Three sensory systems are dedicated to the detection of chemicals in the environment: (1) olfaction, (2) taste, and (3) the trigeminal chemosensory system.[4] Olfactory information can influence feeding behavior, social interaction, and reproduction. A dog's sense of smell, together with its personality and intelligence, functions as a nose for humans in many circumstances.

The transduction of olfactory information occurs in the nasal olfactory epithelium, the sheet of neurons and supporting cells that lines the caudolateral wall, the ethmoidal conchae, and the dorsal part of the nasal septum.[5,6] The olfactory receptor neuron is a bipolar neuron that gives rise on its basal surface to an unmyelinated axon that carries the olfactory information to the brain. At its apex the receptor neuron has a single process that expands into a knoblike protrusion from which several microvilli, or olfactory cilia, extend into the thick layer of mucus that lines the nasal cavity and controls the ionic milieu of the olfactory cilia (Figure 210-1).

Generation of receptor potentials in response to odors takes place in the cilia of receptor neurons. The axons of the olfactory receptor cells form the olfactory nerves that pass through the cribriform plate directly to the olfactory bulb, on the anteroventral aspect of the ipsilateral forebrain. Olfactory information is passed to the amygdala and primary olfactory cortex. Further pathways for processing olfactory information include the thalamus, hypothalamus, entorhinal cortex, and hippocampus.[7]

210.2 HISTORY, CLINICAL SIGNS, AND PHYSICAL EXAMINATION

210.2.1 History and Clinical Signs

The medical history in nasal disease often includes clear statements of specific problems, because the signs of nasal disease—discharge, sneezing, bleeding—are obvious to the owner. Additional questions should be asked about the animal's general condition, appetite, drinking, activity, and endurance, and about changes in its habits. These questions and a general clinical examination are indicated because some systemic diseases cause nasal discharge (distemper, viral rhinotracheitis) or epistaxis (bleeding disorders), whereas some nasal diseases (such as advanced aspergillosis) can cause general malaise, and dyspnea can occur in obstructive nasal disease.

If nasal discharge is the predominant sign, the following questions should help determine whether it is from the left, the right, or both nostrils. If a nasal discharge is present, it should be characterized (watery, mucoid, pus, blood) and its frequency noted. Discharge occurring only during sneezing indicates a less productive mucosal disease than does continuous discharge. Occasional nasal bleeding is less alarming than frequent and profuse nasal bleeding, which can be fatal.

Sneezing, like coughing, is a reflex associated with protection of the mucosa. Particles, foreign bodies, inflammation of the mucosa, or abnormal turbulence in the nasal cavity associated with local drying of the mucosa can stimulate the sensory receptors in the mucosa. Continuous sneezing can cause irritation of the mucosa, leading to more sneezing and sometimes epistaxis.

Pain in the nose may only become obvious when the animal begins to react adversely to the owner's customary petting. A dog with pain in the nose may object to having a collar or the loop of a leash drawn over its head,

even though this is usually associated with the pleasure of a walk. Questions to obtain information about nasal pain should be adapted to the living conditions of the dog or cat.

A nasal stridor is a soft, rustling or sniffing sound that is synchronous with inspiration, expiration, or both. Narrowing of the nasal passageway, which increases the velocity of the airflow, causes the sound.

Dyspnea may be caused by nasal obstruction in cats and dogs, both of which tend to avoid mouth breathing even in this situation, almost to the point of suffocation. Apparently, avoiding the consequent bypassing of the nasal function of air cleansing and conditioning has a high priority.

210.2.2 Physical Examination

After the shape of the nose as a whole is evaluated, the clinician should listen to the animal's respiration for nasal stridor. Under quiet conditions, the clinician should listen close to the dog's (and especially the cat's) nose while gently closing its mouth. If stridor is noted and the clinician suspects it is caused by nostrils that are too narrow, moving the nasal alae laterally can change the tone of the stridor. Symmetry of the airstream can be examined by watching the movement of a small fluff of cotton held in front of each nostril. At the same time, the odor of the expired air can be noted. The area around the nostrils should be inspected for nasal discharge or crusts and the nasal plane for epithelial crusts (which could be caused by pathologic dryness), epithelial lesions, and depigmentation. The ventral wall of the nasal passages, which also forms the roof of the mouth, should be inspected through the opened mouth. The teeth, especially the canine teeth, should be inspected at the same time, because dental abnormalities can cause disorders of the nose.[8] More in-depth inspections belong to special diagnostic procedures and require anesthesia.

210.3 SPECIAL DIAGNOSTIC PROCEDURES

210.3.1 Radiography

The standard radiographic examination of the skull consists of a lateral and a dorsoventral projection. These radiographs may provide all the information that is needed, or they may serve as a part of the *survey* examination. These standard projections are usually of limited value in examination of the nose and nasal sinuses, and special projections, such as craniocaudal radiographs, open-mouth projections, or radiographs with intraoral film, are required.

Radiography of the skull demands the most stringent and careful radiographic technique. Any unintended obliquity in positioning will hinder evaluation of the radiographs. Deep sedation or general anesthesia is mandatory. When the diameter of the skull exceeds 10 to 12 cm, a grid must be used to diminish the unfavorable effect of scattered radiation on radiographic quality. A grid is not used when part of the skull is radiographed in open-mouth projections or when radiographs are made with intraoral film. Both nonscreen film in a lightproof envelope for intraoral application and screen film in a cassette with intensifying screens should be available. Nonscreen films require a much longer exposure time but produce radiographs with greater detail.

Radiographs provide a complete overview of the anatomy, with high spatial resolution. However, superimposition of structures on the film may make it difficult and sometimes impossible to distinguish a particular detail, especially when structures differ only slightly in density.

210.3.2 Computed Tomography

Like conventional radiography, computed tomography (CT) is based on differences in attenuation of an x-ray beam in different parts of the body. With the x-ray beam collimated to a narrow fan shape, the x-ray tube revolves around the object during exposure and the beam is altered as it penetrates the object. An array of sensitive detectors on the opposite side of the object quantitates the x-rays passing through, thereby determining the x-ray attenuation in different parts of the object, in all projections. Computer analysis of this collection of attenuation measurements results in a cross-sectional image of the object. This product is then displayed on a monitor with high spatial resolution and higher contrast resolution than can be provided by conventional radiographs. An intravenously administered radiographic contrast agent should help to define normal from abnormal tissue and facilitate the recognition of blood vessels. Because the images represent "slices" of the object, they do not suffer from superimposition, but they also do not provide a survey view.

Positioning of the animal is just as important in CT as in conventional radiography. The position of the object within the gantry will determine the scan plane. Support is perpendicular to the opening of the gantry and perpendicular to the scan plane. Therefore CT of the body is always axial, perpendicular to the long axis of the body, with some adjustment possible through angulation of the gantry relative to the dog or cat. Other scan planes can be achieved if the object can be positioned differently relative to the gantry opening. This is important, because interfaces between organs or structures can only be imaged satisfactorily when they are perpendicular to the scan plane. The head in particular can be easily examined in different scan planes. Transverse (coronal) scans of the head are made with the animal in prone or supine position and the head extended. Dorsal (axial) scans are made with the animal in supine position and the nose pointing upward. Sagittal scans are made with the animal in lateral recumbency and the head raised on a support.

210.3.3 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is based on the magnetic properties of atomic nuclei that have an odd number of protons. Because protons are in a continuous state of rotation, called the *nuclear spin*, and have an electrical charge, they may be thought of as tiny magnets. The hydrogen nucleus consists of a single proton, and hydrogen is abundant in living tissues; therefore hydrogen is eminently suitable for MRI.

In the body the magnetic forces of protons point in all directions, canceling each other out. When the body is placed in a strong, homogeneous magnetic field (in clinical imaging, usually between 0.15 and 1.5 Tesla [1 Tesla being 10,000 times the strength of the earth's magnetic field]), the protons are forced into positions parallel to the axis of this magnetic field, not only spinning around their own axes but also around the axis of the magnetic field, like a child's spinning top. The frequency of this *precession* is called the Larmour frequency, and it depends on the strength of the external magnetic field.

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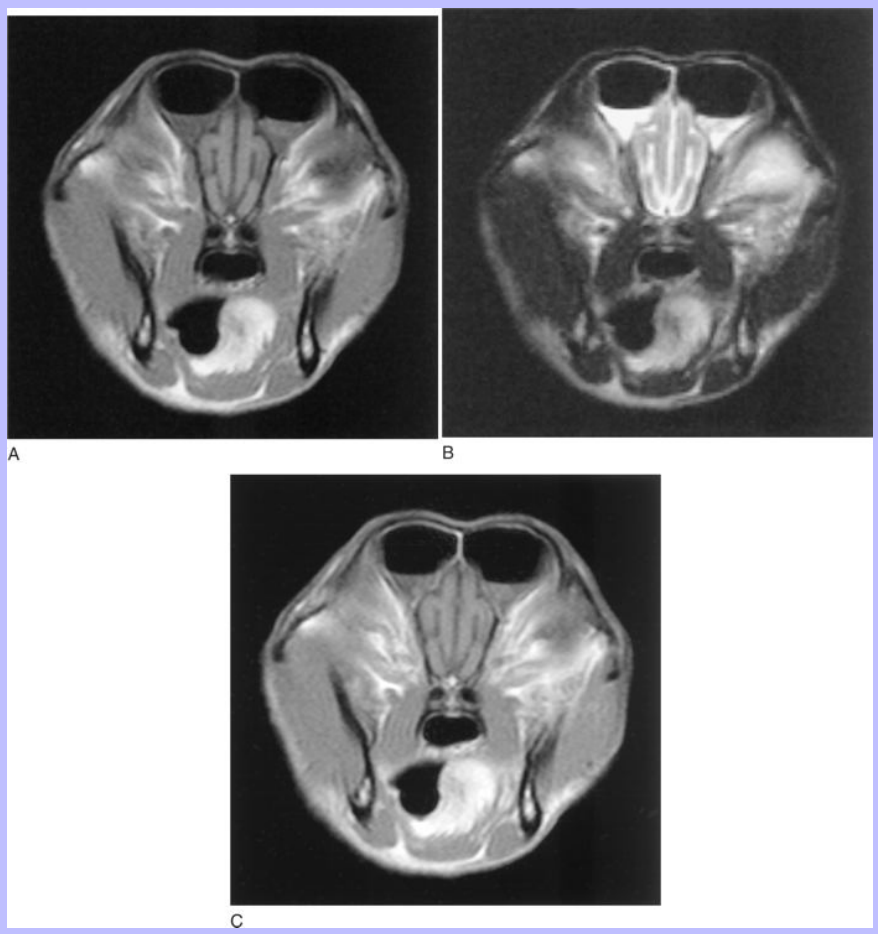
Using radio waves of the same frequency as the precession frequency, the protons can be made to resonate: they will precess around the axis of the external magnetic field at a larger angle, and all protons will be in phase. When the radio frequency wave is switched off, pulse relaxation occurs through two phenomena: (1) the protons realign in the magnetic field (T1 relaxation), and (2) they go out of phase (T2 relaxation). During the process of relaxation, the protons emit weak radio signals; it is these signals that are used to create the images. The images may be dominated by the concentration of protons (proton density), by T1 relaxation (T1-weighted images), or by T2 relaxation (T2-weighted images).

By using gradient coils to create small variations in the x, y, or z direction of the external magnetic field, certain scan planes and slices can be selected in which the precession of protons has exactly the right frequency to be susceptible to the radio wave pulses. Images can then be made in different scan planes without having to reposition the patient. These images are influenced by the concentration of hydrogen nuclei in the part of the body being examined, by the chemical nature of the environment the nuclei are in, and by the interactions between nuclei. MRI provides detailed anatomic images with soft tissue contrast that is superior to that of CT. The soft tissue contrast may be further enhanced by the intravenous administration of a contrast medium that is a paramagnetic substance (usually gadolinium). Its predominant effect is to shorten T1, so the regions that take it up are bright on T1-weighted images (Figure 210-2).

Figure 210-2 Transverse magnetic resonance image (MRI) showing fluid in the frontal sinuses of a dog. The fluid is dark on a T1-weighted image **(A)** and bright on a T2-weighted image **(B)**. After the intravenous administration of contrast medium, the T1-weighted image **(C)** reveals enhancement of the well-vascularized mucosa of the frontal sinus but not of the fluid.



210.3.4 Rhinoscopy

Rhinoscopy is a relatively simple procedure in dogs and cats. It requires anesthesia and tracheal intubation to prevent air circulation through the nasal cavities. Most veterinarians prefer to perform the examination with the dog or cat in sternal recumbency, in a sphinxlike posture. A firm pillow is placed between the head and the front legs so that the head is stabilized but not fixed. The rhinoscopic examination is preceded by a careful inspection of the oral cavity and the pharynx.

A simple otoscope can be used for visualization. It should be of good quality, having a strong light source and dark specula, to illuminate the rostral part of the nasal cavity. The nostril is approached from the lateral side at an angle of 45 degrees to the vertical surface of the nasal plane. The tip of the speculum is placed near the lateral limit of the nostril and is then introduced by slowly turning the otoscope until its line of vision is parallel to the nasal cavity. This movement is necessary to push the nasal ala, which obstructs the opening, into a lateral position.

Once the otoscope is introduced, visibility is often poor. Nasal disease often causes discharge and the tip of the speculum can become blocked by mucus. The lens of the otoscope can be slid slightly to one side, allowing the introduction of a small suction cannula while vision through the lens is maintained. The mucus is removed under visual control, and the rostral part of the nasal cavity is then examined.

The use of an otoscope is often preferable for diagnosis and removal of foreign bodies that have entered the nasal cavity via the nostril. A forceps (called a *foreign body forceps*) developed for use through an otoscope under visual guidance can be found in catalogs for human otoscopic instruments.

An endoscope is needed for complete examination of the nasal cavity. The basic equipment includes a light source, a flexible fiber-optic cable, and a small diameter endoscope. The author and colleagues prefer the 25-degree vision rigid endoscope that is 2.7 mm in diameter and about 15 cm long. The best instruments have a wide-angle lens, which is important for orientation and facilitates the examination. This scope is adequate for most cats and dogs. For small cats, a 1.2 mm diameter rigid scope is needed. In most cats and dogs the 2.7 mm scope can be introduced, and alongside it a suction cannula (size 6) or a foreign body or biopsy forceps can be passed.

The light source for rhinoscopy can be a single-outlet model, but a combined light source and electronic flash generator is necessary to obtain photographic images. The camera should be adapted to the telescope and the timing of the flash. For teaching purposes a chip camera and a video recorder are great assets. Additional equipment for rhinoscopy includes several suction cannulas (size 6), a vacuum source, a selection of biopsy forceps, and a small dropper bottle of 0.1% adrenaline solution to stop profuse bleeding (no more than 1 or 2 drops should be used at a time).

The anatomic borders that guide the inspection of the nasal cavity are the nostril rostrally, the nasal septum medially, the roof of the nasal cavity dorsally, and the bottom of the nasal cavity ventrally. The cribriform plate is part of the caudal boundary, the other part being the ventrally positioned opening to the nasal pharynx, the choanae. The endoscopic procedure aims at bringing the greater part of the nasal cavity into view. The procedure is limited by the choanae, if not by the pathologic process. Careful maneuvering and repositioning of the endoscope should result in a reliable impression of the normal and pathologic structures in the nasal cavity.

The main indications for rhinoscopy are a history of unilateral nasal discharge, the known or probable entrance of a foreign body, obstructive disease indicating tumor with no conclusive radiographic findings, and severe rhinitis with a suspicion of aspergillosis. In all other cases of chronic nasal disease with no significant findings by radiography, rhinoscopy might be helpful but is not always conclusive.

The inspection of the nasopharynx and choanae can be accomplished with a flexible endoscope having a diameter of 4 mm and being capable of 180-degree retrospective vision, introduced via the mouth and then around the soft palate. This instrument not only provides visualization of the lesions but also affords the opportunity to biopsy.

210.3.5 Olfactory Tests

No simple method exists to study olfaction in dogs. The sense of smell should be tested by activation of the olfactory receptor neurons and activation of the brain. The activation of the brain is recorded by electroencephalographic olfactometry analysis. Some authors have reported results in dogs with supposed normal olfactory function and in those that have lost the sense of smell.[9–11]

210.4 CONGENITAL DISEASES

Congenital malformation of the nasal plane is a common finding in brachycephalic breeds. The cartilage supporting the nasal plane is soft; thus the alae collapse, closing the nares. Corrective surgery is a simple procedure and consists of removing a cone-shaped piece of the ala and suturing the sides of the incision together in such a way that the nasal opening is enlarged.[12]

In dogs and cats, variable congenital lesions of the nasal plane or more extensive clefts can be repaired surgically. The success of surgery is largely dependant on the available tissue around the cleft. Oronasal and oropharyngeal clefts cause rhinitis and should be considered for surgical repair. Euthanasia may be justified if repair is not possible and nasal discharge and dysphagia are causing recurrent fever and pain. Nasal dermoid sinus cysts have been reported in dogs.[13] This cyst is recognized as a fistula in the midline of the bridge of the nose, producing intermittent discharge. Exploration of the fistula may reveal skin and hair as far down as the nasal septum. This abnormally located tissue must be completely removed before the skin incision is closed. A congenital cerebrospinal fluid (CSF) fistula, causing rhinorrhea, was reported in a cat. It was closed successfully.[14]

The frontal sinuses are variable in size and sometimes even absent. Their absence is not associated with clinical signs. Congenital ciliary dysfunction has been documented in dogs of various breeds. Primary ciliary dyskinesia is a disorder in which ciliary function is ineffective and uncoordinated, resulting in rhinitis, bronchitis, bronchiectasis, and bronchopneumonia. When associated with situs inversus, the clinical syndrome is known as *Kartagener's syndrome*. The initial signs (nasal discharge and coughing) usually begin at an early age, from days to 5 weeks of age. However, some dogs have remained asymptomatic for months. Complications are caused by colonization of the mucosa and the conchae by *Pasteurella multocida* and *Bordetella bronchiseptica*, which can cause hypoplastic conchae via bone resorption.

Mucociliary clearance in the dog's nasal cavity can be measured by placing a small drop of ^{99m}Tc macroaggregated albumin deep in the cavity, via a catheter, beyond the non-ciliated rostral half. The velocity of mucus clearance ranges from 7 to 20 mm/min.[15] The test is not affected by anesthesia. However, not all normal

dogs have a clearance rate within the reference range, and inflammation can change the velocity of the ciliary beat. To avoid spurious values, the test should be repeated and performed bilaterally.

Functional analysis of cilia in vitro is performed by examining transverse sections in electron micrographs after glutaraldehyde-osmium fixation. Major ultrastructural lesions in cilia of dogs with primary ciliary dyskinesia include lack of outer dynein arms, an abnormal microtubular pattern, and an electron-dense core in the basal body.[15] The prognosis is guarded. Affected dogs that develop severe recurrent bronchopneumonia usually die of sepsis. Continuous treatment with broad-spectrum antibiotics may enable such dogs to survive longer. Therefore cultures should be repeated to maintain correct antibiotic treatment based on sensitivity testing. A worthwhile review of treatment and long-term survival in dogs is available.[15]

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210.5 INFLAMMATORY DISEASES

210.5.1 Viral Rhinitis

Viral rhinitis is a prominent disease in cats. The initial clinical signs are paroxysmal sneezing, conjunctivitis, and serous ocular and nasal discharge. About 5 days after the onset of sneezing, the nasal discharge becomes mucopurulent and there may be ocular complications. The condition usually persists for 2 to 3 weeks. Feline herpesvirus-1 (FHV-1) and feline calicivirus (FCV) are the most prevalent and virulent respiratory pathogens of cats and account for at least 80% to 90% of their infectious upper respiratory tract (URT) infections.[16,17] The introduction of modified-live virus (MLV) vaccine against these two viruses has substantially decreased mortality and morbidity but has not eliminated the diseases. Immunization against these viruses protects the cat from development of severe disease but not from infection.[18]

Because these viruses can spread rapidly among kittens and the prevalence of chronically infected virus carriers is high, elimination of the disease is not feasible. It is estimated that 80% of cats recovering from acute infection become chronic carriers. The predominant route of infection is by direct cat-to-cat contact.[19] The chronic carrier state may develop subsequent to infection with either FHV or FCV and also occurs in vaccinated cats. Although cats carrying FHV do not necessarily shed virulent virus continuously, they should be considered infectious when they are sneezing and have nasal discharge. Calicivirus carriers shed virulent virus continuously from the oropharynx. They may have no clinical signs or mild nasal discharge, gingival ulceration, and periodontitis.

Viral rhinitis is a prominent clinical sign of canine distemper (Figure 210-3). Vaccination has reduced the occurrence of the disease to sporadic cases in countries where stray dogs are limited and veterinary care adequate. Herpes infection in newborn puppies is characterized by profuse mucopurulent nasal discharge. The diagnosis is usually made at autopsy.

Figure 210-3 A 5-month-old Samoyed with distemper and bilateral mucopurulent discharge. Viral rhinitis is a prominent clinical sign of canine distemper.

210.5.2 Bacterial Rhinitis

Primary bacterial rhinitis is uncommon in both dogs and cats. Bacterial rhinitis develops as a sequela to viral rhinitis in cats, can be caused by foreign bodies in both dogs and cats, and occurs secondary to many other disorders due to disruption of normal mucociliary mucosal integrity.

210.5.3 Mycotic Rhinitis

Mycotic diseases involving the nasal cavity, the frontal sinuses, and the nasal plane occur in both dogs and cats. In dogs the most prevalent mycosis in the nasal cavity and frontal sinuses is caused by *Aspergillus* spp. The fungus is also found rarely in the nasal cavity in cats. C*ryptococcus neoformans* is a more common cause of mycotic nasal disease in cats and in certain geographic areas is quite common; nasal infections also occur in dogs. *Alternaria* spp. may infest the nasal plane in cats, causing proliferation of the skin and thereby dyspnea.

Aspergillus spp. are considered to be opportunists, producing infections in man and animals, especially when resistance to infection is reduced or when large numbers of spores are present. Spores of *Aspergillus fumigates* are present on household plants, on furniture made of plant material, around bird cages, and simply in house dust.[20]

In dogs, *Aspergillus* spp. plaques are usually found in the caudal part of the nasal cavity or in the frontal sinus. They are presumed to represent primary infections. The toxins produced by the fungus cause atrophy of the conchae in the areas of the fungus plaques and severe destruction of the mucosa and underlying structures in the entire nasal cavity and frontal sinus. There may be bone resorption and periostitis on the frontal bones, and

atrophy and resorption of the internal surface of the frontal bone may open the way to the brain. The disease may spread bilaterally, destroying all internal and external bony structures, as well as the orbit, the nasal septum, and the nasal plane. *A. fumigatus* was identified in 25 of 27 of dogs (involving the sinus and related structures).[20] Disseminated aspergillosis caused by *A. terreus*, not originating from the airways, has also been reported.[21] *Aspergillus* spp. can be associated with longstanding traumatic changes in the mucosa, caused by persisting foreign bodies in the nasal cavity or oronasal fistulas. These infections are presumed to be secondary to the trauma.

Clinical signs of aspergillosis in the nose and frontal sinus are dominated by profuse mucopurulent nasal discharge and nasal pain. Depigmentation of the nasal plane below the nostril from which discharge appears is a characteristic sign (Figure 210-4). Intermittent hemorrhagic discharge occurs and profuse nasal bleeding is not unusual. When only the frontal sinus is infected, hemorrhagic discharge or profuse bleeding from the nose may be the only sign. The nasal infection is often unilateral initially, becoming bilateral later. Aspergillosis is often not suspected in its initial stage, and histories of nasal discharge present for months are common. No apparent correlation exists between the duration of the initial nasal discharge and the severity or progression of signs by the time of diagnosis. Other factors, such as the number of infecting spores and the resistance of the host, may play a role. Depression is a prominent sign when the frontal sinus is infected.

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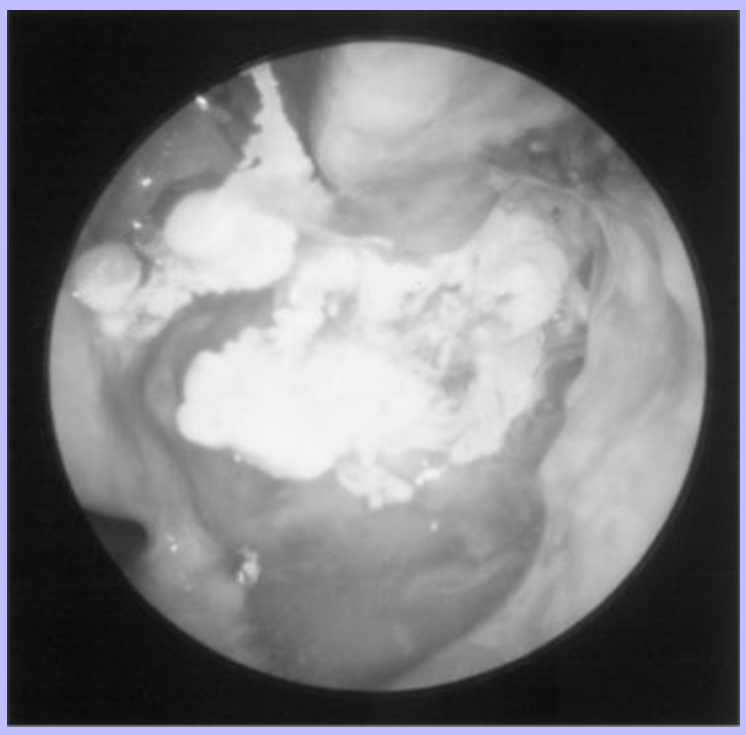
Figure 210-4 Depigmentation of the nasal plane below the nostril from which discharge appears in a dog with nasal aspergillosis in the right nasal cavity.

The diagnosis of aspergillosis as the cause of rhinitis is made by the finding of fungal plaques or positive fungal culture results. Recognition of the fungus plaque is facilitated by the atrophy of the conchae around it, which reduces the normal obstruction to rhinoscopic vision in the caudal part of the nasal cavity (Figure 210-5). The extent of the destruction in the nasal cavities and the frontal sinuses is well demonstrated by radiography, CT, or MRI, but the diagnosis depends on finding the fungus (Figure 210-6). When the fungus is in the frontal sinus alone, radiographs usually demonstrate irregular soft tissue densities in the frontal sinus, thickening of the wall of the sinus, and sometimes reaction of the periosteum. A CT scan may reveal the severity of further bony involvement. A 3 to 4 mm diameter trephined opening in the frontal bone on the side

of the affected sinus can reveal the fungus as thick, grayish-yellow material, sometimes with greenish lumps. This material should be removed and cultured. Cultures from nasal discharge are often negative because the fungus is usually located in the caudal part of the nasal cavity and is not shed in the nasal discharge. A serologic test is available for detecting antibodies to *Aspergillus* spp. in serum.

Treatment of sinonasal aspergillosis is topical or systemic. Topical treatment is usually with enilconazole or clotrimazole. The choice between these two drugs is arbitrary, because there has been no satisfactory clinical trial to compare them. The ongoing discussion is how to apply the suspensions and how long the treatment should be given. The basic idea is to flush the frontal sinus and the nasal cavity (e.g., via tubes introduced through trephine holes). The author's clinical experience (in about 120 cases; an average of 10 per year) indicates that administration of 10 cc of a 10% suspension of enilconazole per tube twice daily for 14 days is sufficient. It is unpleasant for the dog because enilconazole has a bitter taste that most dogs dislike intensely. A retrospective study of cases treated in our clinic (unpublished data) revealed success in about 95% in over 100 cases. Hence 90% success can be expected. A less unpleasant systemic treatment would be much preferred, but the success rates and observed toxicities of other methods are not yet encouraging. Details on clotrimazole therapy have been published.[17]

Figure 210-5 Aspergillus plaque. A rhinoscopic view in the caudal part of the nasal cavity.



Cryptococcosis is found as a cause of rhinitis in dogs and cats. The clinical signs are obstructive rhinitis and mucopurulent discharge. In cats, crusts sometimes occur on the nasal plane and the bridge of the nose. Some cats develop mucopurulent conjunctivitis. In fresh material from the nose placed on a slide and stained with

India ink, *Cryptococcus* spp. organisms are recognized as thick, encapsulated, round to oval yeasts. They can be cultured on Sabouraud's agar.

Ketoconazole, itraconazole, or fluconazole can be used for therapy, which should be continued for 8 weeks. *Alternaria* spp. are found to cause granulomatous infections with crusts on the nasal plane in cats. Antimycotic treatment may be disappointing and removal of the nasal plane, as in nasal plane squamous cell carcinoma, can be a satisfactory solution.[22]

210.5.4 Neurogenic Rhinitis

The clinical signs of neurogenic rhinitis in dogs are dryness of the nasal plane on one or both sides, sometimes with crusts, and slight mucopurulent nasal discharge. The most frequent clinical signs are dryness of one side of the nasal plane together with ipsilateral keratoconjunctivitis sicca and mucopurulent conjunctivitis. The cause of the disorder is loss of parasympathetic innervation and when keratitis sicca is present, the dysfunction also affects the lacrimal, palatine, and nasal glands.[23] In dogs with this disorder, ipsilateral otitis media can be suspected if reddening of the tympanic membrane is noted. The lesion in the parasympathetic nerves may be caused by otitis media, because the parasympathetic nerves are carried in the chorda tympani and pass freely through the middle ear. In all cases, treatment of the otitis media with broad-spectrum antibiotics resolved all problems.

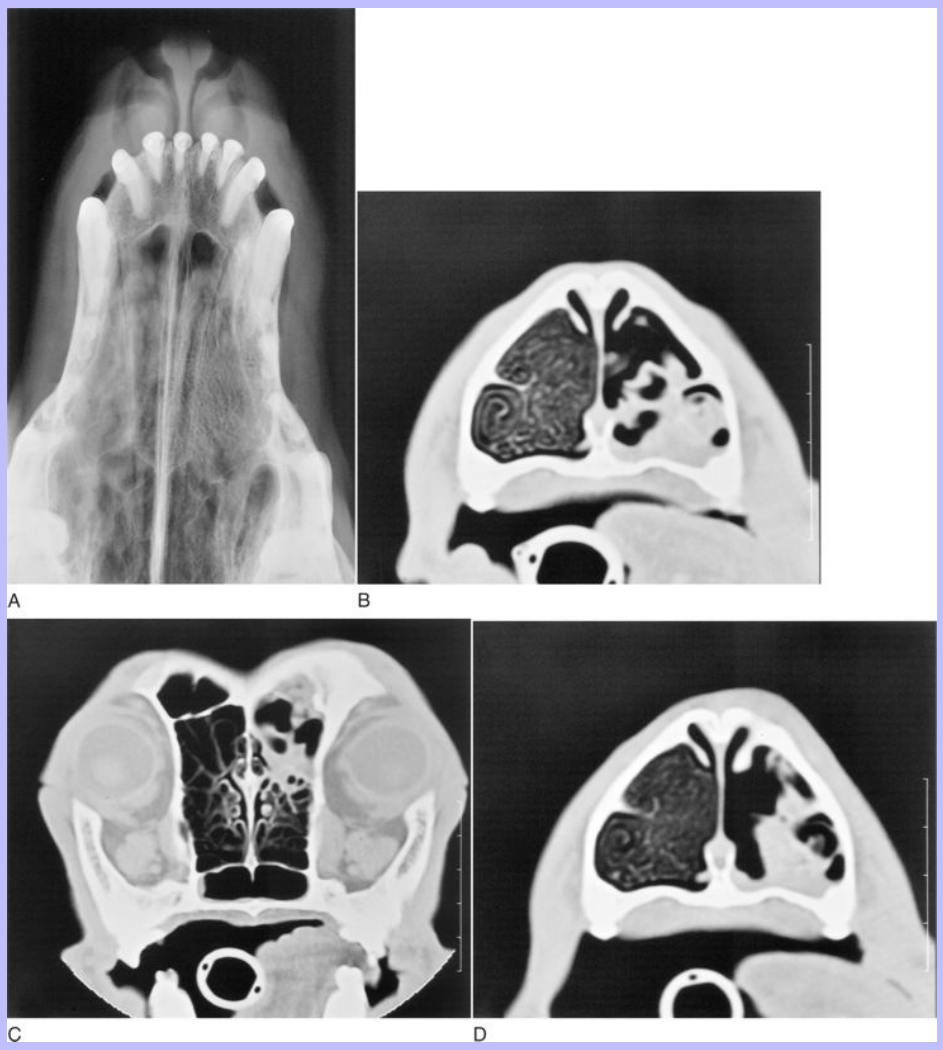
Diagnosis of neurogenic rhinitis is more difficult when it is bilateral. The Schirmer tear test should be helpful, but no values have been reported. Clinical examination and exclusion of other causes may lead to presumption of a possible neurogenic cause. Massaging nonperfumed moistening cream into the nasal plane eight times daily and administering four drops of artificial tears into the nasal cavity four times daily will resolve the clinical signs if the diagnosis is correct. This treatment will be required lifelong, because no known specific treatment for the parasympathetic nerve dysfunction exists.

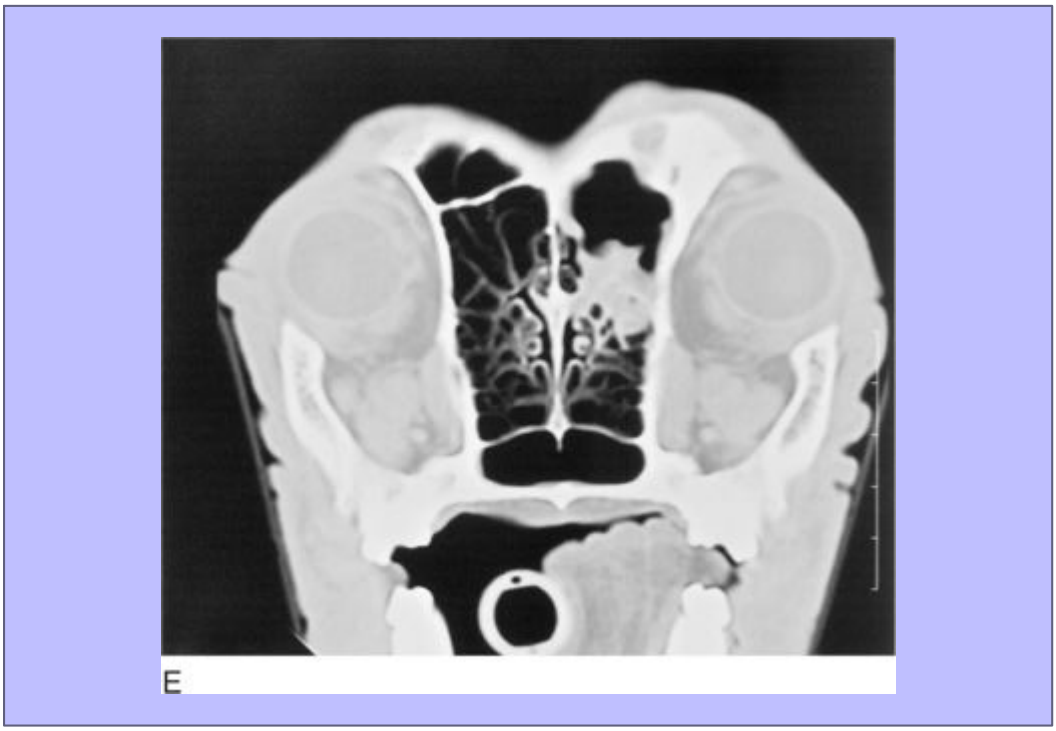
210.5.5 Specific Rhinitis

Polyps occur in the nasal cavity in both dogs and cats. They consist of focal accumulation of edema fluid, hyperplasia of the submucosal connective tissue, and a variable inflammatory infiltrate of eosinophils, plasma cells, and lymphocytes. Hence they are not neoplastic but inflammatory polyps.[24] They are found in the nasal cavity of cats with signs of obstructive rhinitis. Bilateral obstruction may be caused by bilateral polyps or a unilateral polyp that extends into the nasopharynx.

Diagnosis is usually made by rhinoscopy. The polyp is seen as a red mass in the nasal cavity, and biopsy reveals it to be inflammatory tissue. Removal is difficult, usually requiring removal of all structures in the nasal cavity through a small opening in the nasal bone. This damages the olfactory epithelium, and recognition of food is disturbed. When one nasal cavity is freed of polyps, the cat regains its sense of smell with help from the intact side. Bilateral surgery should be avoided and, when necessary, only performed after the cat seems to be fully recovered from the first operation.

Figure 210-6 **A,** Dorsoventral radiograph (intraoral nonscreen film) of the nasal cavity of a Great Dane with aspergillosis of the left nasal cavity and frontal sinus. **B** to **E,** Transverse 5 mm thick computed tomography (CT) images of the nose and frontal sinuses of the same dog before **(B** and **C)** and 6 weeks after **(D** and **E)** successful treatment. The reader should note the remnants of the trephined openings in the nasal and frontal bones. No obvious differences exist between CT images before and after treatment. The extent of the destruction in the nasal cavities and the frontal sinuses is well shown by radiography and CT, but the diagnosis depends on demonstrating the fungus.





Polyps in the nasal cavity are rare in dogs. They are diagnosed by rhinoscopy and biopsy, which reveals inflammatory tissue. They are usually unilateral. Rhinotomy via the nasal bone and removal of all conchae and the polypous tissue relieves the obstruction. Histologic examination will reveal whether the structure is a polyp or an unexpected neoplasm. In dogs, polyps usually recur after 1 or 2 years, but in cats recurrence is rare. 1193 1194

In young dogs and cats, foreign bodies such as grass and other plant material are common. Owners may know when the material entered the nasal cavity, usually via the nostril. Being plant material, the foreign body has the density of soft tissue and is usually not visualized on radiographs. Rhinoscopy in search of a foreign body needs patience and the use of suction, under visual control, to remove mucopurulent exudate before the foreign material is exposed and can be removed. Grass can enter the nasal cavity while a cat is chewing on it, as cats often do. Out of a ball of mucus and grass in the pharynx, a sprig of grass can enter the nasal cavity via the nasopharynx. It can be found by rhinoscopy and removed under visual control via the nostril.

Nasal allergic rhinitis is presumed to occur, but confirmation of the diagnosis has not yet been convincing, partly because IgE-based rhinitis, as occurs in human, has yet to be demonstrated.

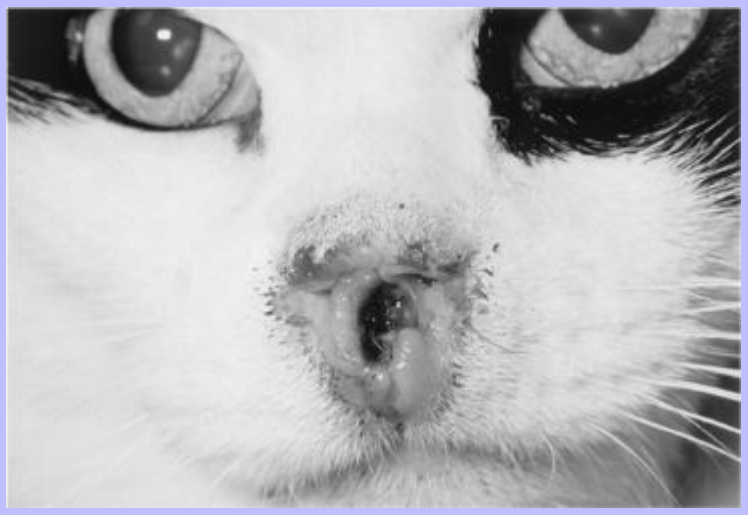
210.6 TUMORS OF THE NASAL PLANE, NASAL CAVITY, AND FRONTAL SINUS

210.6.1 Tumors of the Nasal Plane

Squamous cell carcinoma of the nasal plane is found in cats in most countries of the world (Figure 210-7). The diagnosis should be made by biopsy, but the diagnosis is often delayed because initial biopsies may only reveal inflammation. When the tumor grows and destruction of tissue is in progress, total removal of the process is justified, provided that the removed tissue is submitted for histologic examination. In the

differential diagnosis of processes causing proliferation of the tissue of the nasal plane, with crusts and destruction, infection by *Alternaria* spp. and eosinophilic granuloma should be included. Both are easily identified in biopsy material. Surgical removal of the neoplastic nasal plane in cats has been instructively described.[25] One firm incision will allow histologic confirmation of a tumor-free cut surface. Squamous cell carcinoma of the nasal plane sometimes occurs in dogs. The cosmetic results of removal of the nasal plane are less satisfactory in dogs than in cats. In both, the best results are obtained when tumor growth does not yet extend around the nasal plane. Other tumors of the nasal plane are fibroma and fibrosarcoma, which grow initially beneath the epithelium and do not ulcerate primarily. Surgical removal in an early stage is possible without too much cosmetic damage.

Figure 210-7 Squamous cell carcinoma of the nasal plane of a cat. Biopsy is required to differentiate tumor from inflammatory tissue.



210.6.2 Tumors of the Nasal Cavity

Tumors occur in the nasal cavity of dogs and cats of all ages, but most often in pets over 5 years of age. Almost all are malignant. They invade the surrounding tissue but rarely metastasize before the dog or cat is euthanized. The most frequent tumors are squamous cell carcinoma and adenocarcinoma; less frequent are chondrosarcoma, osteosarcoma, and lymphosarcoma.

The clinical signs include sneezing, hemorrhagic discharge, and mucopurulent discharge. In most cases, unilateral obstruction of the nasal cavity is recognized because of nasal stridor. No evidence of pain is observed, and the dog or cat becomes dyspneic only when the mouth is closed, which means when sleeping. As long as the tumor is unilateral, the dyspnea is moderate. When the tumor obstructs both nasal cavities, dyspnea during sleep becomes a serious hindrance, causing the animal to awaken repeatedly during the night and often be very depressed in the morning. When no therapy is offered beyond permanent tracheostomy, which is rarely accepted by the owner, recurrent nasal bleeding and dyspnea are the usual reasons for euthanasia, in both dogs and cats. Cats, however, often stop eating, which may provide a humane end point and a reason for euthanasia.

Radiographs should be obtained with the dog or cat under anesthesia. Tumor is suspected when increased density is found in one or both nasal cavities, with loss of normal maxillary and ethmoidal conchae.[26] The extension of the tumor should be considered when estimating the animal's life expectancy, but this is usually decided by the owner's interpretation of the quality of the animal's life. In all cases in which the radiographic diagnosis is uncertain, rhinoscopy is the next diagnostic procedure. Under rhinoscopic visualization the tumors vary greatly in shape and firmness, and their color ranges from gray to deep red. Biopsies are always taken for histologic confirmation of the diagnosis. If no therapy is planned, neither CT nor MRI is indicated. Radiation therapy could be considered, and details have been described.[27]

210.6.3 Tumors of the Frontal Sinus

Tumors in the frontal sinus develop within a bony case. The frontal sinus does not have a specific function; therefore development of the tumor will be noticed only when unilateral nasal bleeding is recurrent or when the enlarging tumor causes pressure atrophy of the frontal bone and becomes apparent as a swelling arising in the frontal sinus. 1194 1195

In the diagnostic investigation of recurrent nasal bleeding, radiographs will be made of the nasal cavity and the frontal sinus, and a radiographic density in the frontal sinus will be noticed. The differential diagnosis of such a density in combination with a radiographically normal ipsilateral nasal cavity includes aspergillosis, tumor, and accumulation of mucus associated with obstruction of the nasofrontal duct. Because the frontal sinus is separated from the brain by only a thin layer of bone, additional diagnostic imaging by CT or MRI is valuable. When a swelling arising in the frontal sinus is recognized by physical examination, the same procedure of taking radiographs followed by CT or MRI is indicated. With these imaging tools, extent of the lesion and differentiation of the contents of the frontal sinus may be determined. Tumor in the frontal sinus can be recognized by CT or MRI with an intravenously administered contrast medium. Vital tissue will be enhanced by the contrast medium, whereas debris will not. It must then be determined by CT or MRI whether the bony case of the frontal sinus is intact, especially whether the orbit or the brain is invaded, and whether the contralateral frontal sinus is included in the process.

When these procedures indicate that the tumor can be removed, a surgical approach via the frontal bone is indicated. At the end of the surgical procedure it is important to examine the patency of the nasofrontal duct and to relieve any obstruction. Like tumors in the nasal cavity, most tumors in the frontal sinus are malignant, and complete surgical removal is unlikely. Biopsy of the tumor through a small trephined opening in the frontal bone should be considered as an intermediate step.

210.7 TRAUMA TO THE FRONTAL SINUS AND THE NOSE

210.7.1 Trauma to the Frontal Sinus

Blunt or sharp objects can cause traumatic injury to the frontal sinus. The frontal bone in dogs and cats is relatively thick and provides good protection, so a fracture of it implies that a heavy blow to the head has occurred. The pet should therefore be given a thorough clinical examination for (1) signs of shock such as tachycardia, hypotension (prolonged capillary refill time, weak pulse), rapid respiration, dilation of the pupils, hypothermia, muscle weakness, restlessness, and depression or even coma[28] and (2) other fractures or wounds. Frontal bone fractures do not require immediate attention unless brain damage is suspected. In the absence of signs of brain damage, and when other traumatic injuries have been attended to, the nature and extent of the

frontal bone fracture should be examined by radiography, CT, or both (Figure 210-8). Prolonged anesthesia is needed; thus these procedures are usually delayed for 24 hours or more.

When bone fragments are seen to be present in the frontal sinus they should be removed. Like any foreign body, small bone fragments are likely to become sequestered. Surgery should be performed with full attention to aseptic procedures. Before attempting reconstruction of the frontal bone, it is important to examine the patency of the nasofrontal duct and to relieve any obstruction. Airtight suturing of the subcutis, including periosteum, followed by routine skin closure prevents the development of subcutaneous emphysema. Administration of broad-spectrum antibiotics for 3 weeks and strict limitation of activity during this period (keeping a cat confined to the house) will prevent complications.

Figure 210-8 Transverse 5 mm thick computed tomography (CT) image through the frontal sinuses of a Labrador retriever with fractures of the right frontal sinus caused by being struck by a car. CT allows accurate assessment of the nature and extent of the fractures and identification of loose fragments in the frontal sinus. Bone fragments seen in the frontal sinus should be removed.

210.7.2 Trauma to the Nose

Trauma to the nose is characterized by massive bleeding, which adds to the other effects of the impact in promoting shock. A thorough examination for signs of this is indicated (see Trauma to the Frontal Sinus). Fractures and wounds should be noted, but priority must usually be given to the treatment of hypovolemic shock.

When the dog or cat is sufficiently stable, the larger vessels should be ligated and skin sutures should be placed as needed. Skin sutures, sometimes supported by subcutaneous sutures, may be sufficient to remodel the outer form of the nose. Fractures of the choanae are best left alone, because they are unlikely to ever result in obstruction. Severe traumatic damage to the nose almost always causes temporary obstruction, making tracheotomy necessary. Adequate oxygenation aids in avoiding general malaise and loss of appetite. Liquid or soft food facilitates eating. In dogs the tracheal cannula is often left in place for 10 days or longer. In cats that have difficulties with long-term tracheostomy, a small intranasal catheter may be placed and connected to the oxygen supply. Use of this method, however, depends on the pathway through the wounded nose. In the author's experience, the nose is functionally adequate in 2 to 3 weeks. If needed, more corrective surgery could be attempted after 6 weeks.

210.8 EPISTAXIS

Epistaxis (i.e., nasal bleeding) is often spontaneous and transient, and it is apparently due to a local cause. When it is recurrent or profuse, with considerable loss of blood, diagnostic investigation is indicated. The several causes of epistaxis should be considered in planning diagnostic procedures. Recurring epistaxis occurs in both dogs and cats, but profuse nasal bleeding occurs mostly in dogs. Recurring epistaxis in dogs and cats can be caused by ulcerative rhinitis, mycotic rhinitis, and tumor in the nasal cavity. Profuse nasal bleeding in dogs is most often caused by aspergillosis in the nasal cavity or frontal sinus, or it is caused by tumor in the nasal cavity and frontal sinus. Epistaxis can also be the sole sign of defects in primary hemostasis (platelet plug formation) or secondary hemostasis (coagulation cascade).[29] Lesions in the nasal mucosa leading to epistaxis can also occur with systemic diseases such as leishmaniasis and amyloidosis.

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Epistaxis caused by local disease in the nasal cavity or frontal sinus is approached (as are all nasal diseases) by a general and specific examination for nasal disease, as described earlier in this chapter. When the bleeding has occurred recently, radiographic examination should preferably be delayed for at least 48 hours because clotted blood can be misinterpreted as a mass in the nasal cavity. Rhinoscopy should also be delayed for at least 48 hours after the bleeding has stopped, because the presence of blood clots hinders inspection and could lead to misinterpretation of findings.

In the meantime, profuse nasal bleeding should be stopped. It is best to sedate the animal (phenobarbital [2 mg/kg] is advised, because it does not affect blood pressure). After considerable blood loss, sedation that causes hypotension could lead to shock in association with hypovolemia and should therefore be avoided. Sedation will help stop bleeding.

Nasal tamponade is only acceptable for a short period and under anesthesia. For less profuse bleeding, nasal drops of 0.1% adrenaline are helpful. The use of adrenaline should, however, be restricted. Overdose could cause death due to vasoconstriction of the arteries supplying the brain. The administration of three drops in one of the nasal cavities in dogs and one drop in cats, repeated up to three times per 24 hours, is acceptable and effective when used during the bleeding. It should not be used in an attempt to prevent nasal bleeding. When examination

of the nasal cavity and the frontal sinus reveals no cause for the bleeding, further investigation of primary diseases causing hemostasis is indicated.

210.8.1 Acknowledgement

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211 CHAPTER • 211 Diseases of the Throat

Nolie K. Parnell

211.1 GENERAL ANATOMY AND PHYSIOLOGY

The throat is an important, but mostly ignored, communal area of both the gastrointestinal (GI) and respiratory tracts. Anatomically it is divided into the pharynx and larynx. The pharynx is further divided into the nasopharynx, the oropharynx, and the laryngopharynx. The nasopharynx is located dorsal to the soft palate, between the choanae and the intrapharyngeal opening. It is a functional space that allows the nasal cavity to communicate with the larynx. The oropharynx is ventral to the soft palate and extends from the palatoglossal arches rostrally to the base of the epiglottis caudally. The intrapharyngeal opening and the rostral border of the esophagus create the boundaries of the laryngopharynx, the most caudal part of the pharynx.[1] The laryngopharynx functions as an intersection to both the respiratory and digestive tracts. The larynx consists of three unpaired cartilages (epiglottis, cricoid, and thyroid) and one pair of arytenoid cartilages. The glottis (or cranial opening of the larynx) is composed of the corniculate and cuneiform process of the arytenoid cartilages and the epiglottis. Minor anatomic differences exist between feline and canine larynx.[2] Cats lack the interarytenoid cartilage found in dogs and instead have an interarytenoid ligament in its place. Cats also lack a vestibular ligament. Due to this deficiency the feline arytenoid cartilage is connected to the ventral aspect of the larynx by the vocal ligament. Another important anatomic difference is cats lack the laryngeal ventricles that are found between the vestibular and vocal folds in the dog. No dramatic differences exist between feline and canine innervation and muscles of the larynx.

Swallowing, or deglutition, is a complex reflex action that coordinates many structures. Cranial nerves, the swallowing center in the reticular formation of the brain stem, the muscles of mastication, tongue, soft palate, pharynx, larynx, and esophagus are all involved in what appears to be a simple act of allowing transport of material from the mouth to the stomach.[3] As a lesser recognized function, swallowing also allows saliva and debris to be removed from the pharynx. Deglutition begins as a voluntary act but during its execution becomes a reflex. Deglutition is traditionally described as having three phases: (1) oral, (2) pharyngeal, and (3) esophageal. The oral phase begins when mastication is complete. The tongue then moves the food bolus that is organized at the base of the tongue to a position that is on midline between the tongue and the hard palate. Motor fibers to the tongue are supplied by cranial nerve XII. Sensory fibers from the oral cavity and motor fibers to the masticatory muscles and soft palate originate from cranial nerve V. The oral phase is voluntary, but when the food bolus is pushed into the pharynx, receptors are stimulated that initiate the involuntary, or reflex, component of deglutition. Sensory receptors are found in the pharynx, palate, and epiglottis. Impulses from these receptors are transmitted along the glossopharyngeal nerve, recurrent laryngeal branch of the vagus nerve, and the maxillary branch of the trigeminal nerve to the swallowing center in the medulla (located in the floor of the fourth ventricle). The efferent arm of the reflex involves the motor nuclei of cranial nerves V, VII, IX, X, and XII.[4–6] These nerves supply the muscles of mastication, tongue, palate, pharynx, larynx, and esophagus. During the pharyngeal phase the goal is to pass food from the oropharynx into the esophagus and to prevent food from being aspirated into the trachea or moved into the nasopharynx. This is accomplished by elevation of the soft palate and the palatopharyngeal folds moving inward as the vocal cords are pulled together and the larynx is elevated against the epiglottis. The final act during the pharyngeal stage of swallowing occurs when the cricopharyngeal muscle relaxes, the upper esophageal sphincter opens, the bolus moves into the esophagus, the sphincter closes, and the pharyngeal muscles relax. The cricopharyngeal muscle is innervated by the pharyngoesophageal nerve, which is formed by cranial nerves IX and X.[1] The final stage of deglutition, the esophageal stage, transports the

bolus from the esophagus, through the gastroesophageal sphincter, and into the stomach. The esophagus is innervated by the vagus nerve.

The larynx has three functions: (1) to act as a conduit for air, (2) to protect the lower airway from aspiration during deglutition, and (3) vocalization. The glottis remains partially open when an animal is at rest. When greater airflow is needed, the glottis is widened by abduction of the arytenoid cartilages and vocal folds (via cricoarytenoid muscles) during inspiration (and the same structures adduct during expiration). The cricoarytenoid muscles are innervated by the caudal laryngeal nerves, which are derived from the recurrent laryngeal nerves. The recurrent laryngeal nerve innervates all the muscles of the larynx except the cricothyroid muscles that are supplied by the cranial laryngeal nerves.[7] During deglutition the larynx is pulled cranially by the geniohyoideus and mylohyoideus muscles. This allows the epiglottis to close over the larynx, protecting the lower airways. The adductor muscles close the glottis concurrently. This creates an additional defense against aspiration.

211.2 HISTORY AND PHYSICAL EXAMINATION

Animals with diseases of the throat can have a variety of historical complaints. Pharyngeal diseases can be confusing because historical findings can be related to swallowing difficulties or the upper respiratory tract (URT). Historical findings secondary to laryngeal dysfunction are usually related to either inability to regulate airflow and protect the airway, or they are related to changes in vocalization. Respiratory sounds can be extremely useful in localizing the disease, whether it is pharyngeal or laryngeal, but they are not helpful if one tries to attribute a specific respiratory sound to a specific condition. Coughing, dyspnea, and nasal discharge are common clinical complaints. Stertor, a snoring sound heard on inspiration, is usually due to an intermittent obstruction such as an elongated soft palate. Stridor, an inspiratory high-pitch wheeze, is most commonly associated with laryngeal lesions. Stridor is created by air turbulence through a narrowed laryngeal opening. Any changes in vocalization would suggest a laryngeal disorder. Reverse sneezing, which is described as short periods of forceful inspiratory nasal effort with the head pulled back, indicates irritation to the dorsal nasopharyngeal mucosa.[8] Dysphagia cases can be confusing because ineffective swallowing may not be obvious to the owner and may not be the primary historical complaint. Other signs such as coughing, gagging, regurgitation, and nasal discharge may be reported in animals with either oropharyngeal dysphagia or other diseases of the throat.

A complete physical examination (including a neurologic examination) is important when evaluating animals with pharyngeal or laryngeal disease because dysfunction may be indicative of systemic disease (i.e., myopathy, neuropathy) or there may be secondary complications from the disorder (e.g., aspiration pneumonia). If laryngeal disease is suspected, the larynx should be palpated for pain or structural abnormalities. The area over the larynx should be ausculted for abnormal sounds secondary to turbulence. Part of this complete physical examination may include exercising the patient, because occasionally manifestation of the disease only occurs after physical exertion. Many animals will have dyspnea, and a thorough physical examination may not be possible until the animal is stable. Significant airway compromise may be overlooked. It is important to assess the degree of respiratory compromise by evaluating the patient's attitude, posture, mucous membrane color, and both respiratory rate and pattern. Precluding the emergency situation, once the general examination is complete one may concentrate on examining the oral cavity. It is extremely difficult, if not impossible, to adequately evaluate the larynx and pharyngeal areas without heavy sedation or general anesthesia. In most cases it is easier for the examiner, and safer for the animal, if tracheal intubation is performed. A standard method of evaluating the oral cavity should be established so that one does not miss an important abnormality. The larynx is evaluated both for structural problems and functional abnormalities; the pharynx is evaluated for physical abnormalities. Pharyngeal function cannot be evaluated when the patient is sedated; rather, video fluoroscopy is recommended when critically assessing pharyngeal function.

211.3 DIAGNOSIS

211.3.1 Diagnostic Imaging

Lateral and ventrodorsal radiographic views of both the skull and cervical areas are indicated. Radiopaque foreign bodies can be identified that may be missed on laryngoscopy and pharyngoscopy (e.g., sewing needle embedded in soft tissues). Radiographs are also useful in identifying bony changes associated with chronic inflammation or neoplasia, identifying clues of unreported trauma (e.g., subcutaneous emphysema), and occasionally soft tissue masses. Suggestion of a soft tissue mass is confirmed by direct visualization and histopathology. Thoracic radiographs are also indicated. Symptoms of lower respiratory disease may be masked when a patient has concurrent, and more severe, upper respiratory symptoms. Evaluation for aspiration pneumonia, metastases, or suggestion of a motility disorder (i.e., megaesophagus) is possible.

Ultrasonography and computed tomography (CT) are noninvasive modalities to evaluate the pharynx and larynx. Ultrasonography can identify soft tissue masses, help guide fine needle aspiration, and evaluate laryngeal function.[9,10] The presence of air in these areas can limit the usefulness of this modality in establishing a definitive diagnosis. CT may be used to fully evaluate involvement of neoplasia or middle-ear disease if a nasopharyngeal polyp is suspected.[11]

Videofluoroscopy is essential for any case of dysphagia. A barium swallow allows the act of swallowing to be recorded and studied for abnormalities. The patient should be recorded attempting to swallow barium to mimic liquids and then should be given a meal (canned food mixed with barium) to be recorded. Videofluoroscopy is superior to radiography because it allows all phases of deglutition to be evaluated instead of recording one moment (intermittent moments) of the event. Unfortunately videofluoroscopy is limited to referral centers only.

211.3.2 Pharyngoscopy and Laryngoscopy

Laryngoscopy and pharyngoscopy allow assessment of both structural abnormalities and function of the larynx. A flexible endoscope is used for these procedures because visualization of the nasopharynx requires retroflexion. Occasionally a foreign body will be found just caudal to the larynx and may be retrieved endoscopically. The patient is placed in sternal recumbency and anesthetized with either propofol or sodium thiopental. Once anesthetized, gauze is passed under the maxilla behind the canine teeth. The gauze is used to elevate the head, so external compression of the neck is avoided. Flexible endoscopy is ideal to evaluate the nasopharynx. If that is not possible, the caudal pharynx can be evaluated using a dental mirror and a snook hook. This will be sufficient in evaluating most nasopharyngeal polyps, masses, or caudal foreign bodies. It will not allow diagnosis of more rostral diseases such as nasopharyngeal stenosis. Laryngeal function is usually evaluated first by assessing the motion of the arytenoid cartilages. The traditional approach involves titrating anesthesia that allows both visualization of the arytenoid cartilages and deep spontaneous breaths to occur. In a normal animal the arytenoid cartilages will abduct symmetrically with each inspiration and close on expiration. The frustration with this technique is multiple. Maintaining the correct level of anesthesia is difficult (i.e., the animal is too awake to allow adequate visualization of the arytenoid cartilages or anesthetized so that the patient will not spontaneously breathe); shallow breathing can limit adequate assessment; and concerns about the effect of anesthesia on laryngeal function are legitimate concerns when performing the traditional laryngeal examination. The recently introduced technique attempts to eliminate the effects of anesthesia from the examination. Patients are premedicated with acepromazine maleate and

butorphanol tartrate and induced with propofol. Doxapram hydrochloride (2.2 mg/kg intravenously) is used to increase laryngeal motion and minimize or eliminate the effects of anesthesia.[12]

211.3.3 Miscellaneous

Hematology and biochemical profiles should be performed on patients with pharyngeal and laryngeal dysfunction, but they will rarely confirm the definitive diagnosis. Occasionally virus isolation (feline calicivirus [FCV]) and PCR (feline herpes-1 virus [FHV-1], *Chlamydia* spp., and *Mycoplasma* spp.) are indicated in the diagnostic workup. Culture and sensitivity of tissue or secretions can provide valuable information during the diagnostic workup. Cytology and histopathology are also essential for critically evaluating infiltrative disease or mass lesions.

211.4 DISEASES OF THE PHARYNX

211.4.1 Nasopharyngeal Polyps

Nasopharyngeal polyps are histopathologically benign, pedunculated masses consisting mostly of fibrovascular tissue and variable severity of inflammatory cells.[13] It is the most common nasopharyngeal disease of younger cats and accounts for almost one third of all feline nasopharyngeal diseases.[14] No sex or breed predilection exists; although nasopharyngeal polyps are most commonly found in younger cats (mean range 0.4 months to 6.1 years), this disease should also be included in the differential diagnosis for older cats.[14–17] Nasopharyngeal polyps are believed to originate from the middle ear or auditory tube and then expand into the nasopharynx and external auditory canal.[18] It is unknown why nasopharyngeal polyps occur, but it does not seem likely that the polyps are a manifestation of chronic viral (FCV or FHV) infections.[17] Clinical signs are variable but include nasal discharge, sneeze, stertor, and phonation changes. Definitive diagnosis is made by direct visualization of the nasopharyngeal mass and histopathology. Quite often, nasopharyngeal polyps can be discovered with digital palpation of the soft palate. Diagnostic imaging (skull radiographs and CT) is not necessary for the diagnosis but can provide valuable information toward the extent of the mass and possible middle ear involvement. Treatment depends on clinical presentation and extent of disease. If evidence of concurrent middle ear involvement is seen, a ventral bulla osteotomy is indicated. If the disease appears to be limited to the nasopharynx, then traction avulsion to remove the polyp at its stalk is usually attempted. The high rate of reoccurrence with this disease (33%) has led to the suggestion that ventral bulla osteotomy should be performed on all cats with nasopharyngeal polyps.[16] Nasopharyngeal polyps are considered a disease of cats, but a case of a nasopharyngeal polyp in a dog has been reported.[19]

211.4.2 Nasopharyngeal Stenosis

Nasopharyngeal stenosis is primarily a disease of cats but has been reported in a dog.[20,21] It is a rare disease that is characterized by scar tissue that forms a membrane or “webbing” above the soft palate and obstructs airflow through the nasopharynx. Cats are believed to develop nasopharyngeal stenosis as a consequence of healing from injuries to the area (infectious, traumatic). Cats with the nasopharyngeal stenosis have chronic histories of stertorous breathing and open-mouth breathing.[20,22] Diagnosis is made using flexible endoscopy to evaluate the nasopharynx and visualizing a pinhole-sized orifice where the caudal nares should be seen (Figures 211-1 and 211-2). Treatment of nasopharyngeal stenosis involves surgical resection of the lesion, but

the prognosis should remain guarded because the webbing may reoccur.[21,23] Balloon dilation of the stenotic area has been proposed as a successful alternative to surgery.[22,24]

211.4.3 Pharyngeal Foreign Bodies

Foreign bodies can occur in both dogs and cats and creates both acute and chronic pharyngeal disease.[25–27] Grass awns, fish hooks, and bones are all possible, but wood sticks are the most common penetrating foreign bodies.[25,27] Medium and large breed dogs are affected more often with oropharyngeal penetrating injuries, presumptively because of their stick-chewing or retrieving behavior. Clinical signs of acute disease include pawing at the mouth or face, hypersalivation, oral pain and malodor, dysphagia, and dyspnea. Cervical or facial swellings combined with intermittently draining tracts were more commonly seen with chronic pharyngeal foreign bodies. Pharyngeal and retropharyngeal abscessation is a common complication secondary to bones, grass awns, sticks, pins, or needles. Dogs with pharyngeal or retropharyngeal abscesses will exhibit anorexia, pharyngeal pain, swelling, and will be febrile.[1] Although rare, osteomyelitis and quadriparesis are possible complications to penetrating stick foreign bodies.[28,29] In contrast, nasopharyngeal foreign bodies are more likely to create inflammation and nasal discharge. Migration of nasopharyngeal foreign bodies does not occur. Diagnosis of pharyngeal foreign bodies is difficult and frequently frustrating. Radiographs are helpful if the foreign body is radiopaque; however, if it is radiolucent the foreign body will remain elusive. Endoscopy is helpful in locating a foreign body, and if the foreign body penetrated the pharynx, endoscopy can localize the traumatized area. Aggressive search and retrieval of penetrating pharyngeal foreign bodies is important early in the course of the problem. If the foreign body is not successfully removed in its entirety during the acute stage, the prognosis decreases dramatically.[25]

211.4.4 Pharyngeal Mucoceles

A mucocele is a collection of saliva from a damaged salivary gland or duct. Synonyms include sialocele, ranula, or salivary cyst. Mucoceles are not true cysts because they are lined with granulation tissue and not the characteristic epithelial tissue.[30] The cause of mucoceles is unknown, although traumatic causes such as dog bites and choke collars have been purposed. Pharyngeal mucoceles are the least common type of mucocele, with sublingual and cervical being more common. Regardless, pharyngeal mucoceles are clinically important because most animals with pharyngeal mucoceles present in respiratory distress. Dogs are more affected than cats, and miniature poodles appear to be at increased risk of developing pharyngeal mucoceles.[31,32] Due to the patient's respiratory compromise, it is important to establish a patent airway either via tracheal intubation or tracheostomy prior to examination. Diagnosis requires visualization of soft, nonpainful, fluctuant mass in the pharynx. Fine needle aspirate of the mass will reveal a thick, tenacious fluid that is characteristic of saliva. Drainage of fluid is important in the acute management of pharyngeal mucoceles, but surgical correction via marsupialization and resection of the associated salivary glands will need to be pursued at a later date.[31]

Figure 211-1 Normal nasopharynx.

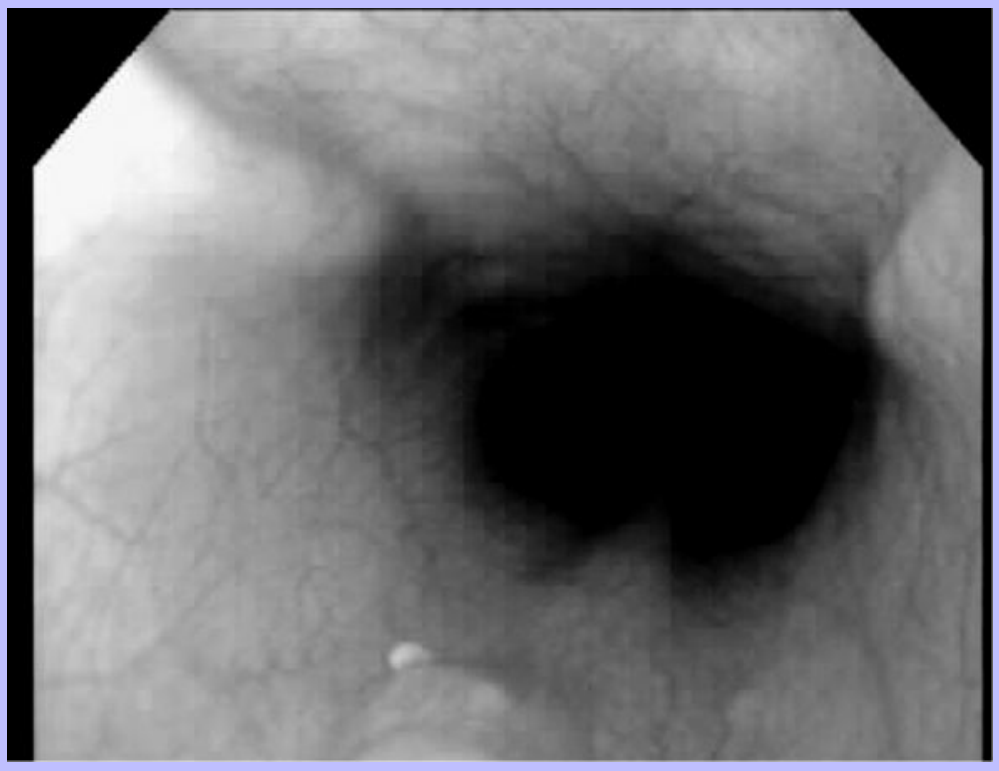
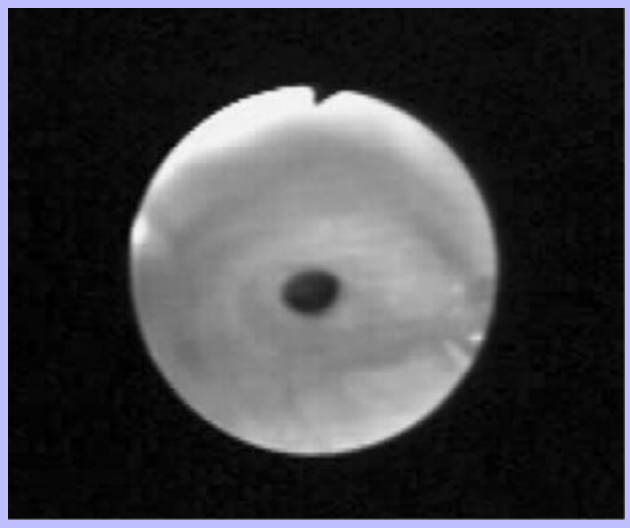


Figure 211-2 Nasopharyngeal stenosis in a young cat with a history of progressive stertor and open-mouth breathing.



211.5 SOFT PALATE ABNORMALITIES

The palate is an important anatomic structure because it divides the oral and nasal cavities. Abnormalities of the palate result from incomplete closure of the primary or secondary palate (or both) during fetal development. The primary palate develops into the lip and incisive bone.[33] The secondary palate becomes the hard and soft palate. Cleft palate and soft palate hypoplasia are two of many palatine defects that have been described. Brachycephalic breeds have a higher incidence of cleft palate. Many factors have been implicated in these abnormalities, but inherited traits seem to be found in Shih Tzus, bulldogs, pointers, Swiss sheepdogs, and Brittany spaniels.[1,34] Teratogens (e.g., vitamin A, griseofulvin) have also been shown to cause palate abnormalities.[35,36] Midline soft palate defects are most common with unilateral or bilateral defects occurring less frequently. Neonates with a cleft palate usually fail to thrive because the defect makes nursing difficult, allows milk to enter the nasal passages, or milk is aspirated into the lower airways. If the neonate is able to survive, chronic rhinitis is the most common clinical sign. Diagnosis is based on oral examination of the soft palate. A cleft palate will have a midline defect usually involving both the hard and soft palate. Soft palate hypoplasia reveals a severely shortened length, with a midline remnant of muscular tissue covered by mucosa (Figure 211-3). Animals with soft palate defects should also be evaluated for middle ear disease because concurrent middle ear disease has been identified as a potential complication.[37] Treatment of both types of soft palate defects involves surgical correction. A variety of techniques have been described to correct midline defects, with good results.[38,39] Correction of soft palate hypoplasia has a poor prognosis due to the absence of adequate tissue for repair. In animals with this problem, it is hoped that addressing the way intake of food and water occurs (i.e., elevation) will decrease the severity of reflux into the nasal cavity.

Figure 211-3 Soft palate hypoplasia in a young adult dog with a history of chronic nasal discharge.

In contrast, brachycephalic breeds can suffer from soft palate excess. Stenotic nares and everted laryngeal saccules are the other components of the upper airway obstructive syndrome known as the brachycephalic syndrome. English bulldogs, pugs, Shih Tzus, Lhasa apsos, and Himalayan cats are all breeds that suffer from brachycephalic syndrome.[40] Hypoplasia of the trachea, especially in the English bulldog, may also be present.[41] Normally the caudal edge of the soft palate should just touch the tip of the epiglottis. Because maxillae are shortened in brachycephalic breeds, the caudal edge extends beyond the tip of the epiglottis. During exercise the soft palate will be sucked into the glottis, reducing the diameter of the airway. Over time this will cause trauma and tissue edema that will further hinder airflow. Clinical signs associated with an obstructing elongated soft palate include stertorous breathing, gagging, coughing, and exercise intolerance or collapse. Diagnosis is based on oral examination and direct visualization of a soft palate that extends beyond the tip of the epiglottis. Treatment involves shortening the length of the soft palate, either with conventional techniques or carbon dioxide laser.[42–44]

211.5.1 Neoplasia

Oral tumors (which include pharyngeal neoplasia) are the fourth most common neoplasia in dogs. Oral neoplasms occur 2.6 times more frequently in dogs than in cats, and males are more likely to develop oropharyngeal neoplasia than females.[45] The three most common oral tumors in the dog are malignant melanoma, squamous cell carcinoma, and fibrosarcoma.[46] Squamous cell carcinoma and fibrosarcoma are the two most common oral tumors in the cat. If the feline nasopharynx is specifically evaluated for neoplasia, lymphosarcoma is the most common tumor diagnosed.[14] Most tumors of the oral cavity are malignant, highly locally invasive, and have a variable degree of metastasis.[45,46] Clinical signs include inappetence or anorexia due to pain, dysphagia, halitosis, ptyalism, and facial deformity (swelling, exophthalmos, or bony thickening). Cats with nasopharyngeal lymphosarcoma will have nasal discharge, sneezing, stertor, or phonation changes. Diagnosis of an oropharyngeal tumor includes a histologic diagnosis and tumor staging. Direct visualization during an oral examination (and endoscopy for nasopharyngeal tumors) is performed prior to obtaining a tissue sample for cytology and histopathology. Thoracic radiographs are part of the staging, as is either skull radiographs or CT. Regional lymph nodes should be aspirated to determine metastasis. Treatment options include surgery, radiation therapy, hyperthermia, chemotherapy, and photodynamic therapy. Treatment protocol depends on tumor type and location, but local control is most effective with surgery and radiation therapy.[47] Prognosis is variable, based on a number of factors.

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211.5.2 Tonsillitis and Pharyngitis

When discussing tonsillitis, one is referring to the palatine tonsil. The palatine tonsil is found within the palatine fossa in the lateral wall of the oropharynx. It is rare for either tonsillitis or pharyngitis to occur as a primary disease. It is much more common for the tonsils and the pharynx to be inflamed secondary to other diseases. Clinical signs are not specific for either the tonsils or pharynx but will support oropharyngeal disease. Inappetence or anorexia, ptyalism, and oral pain are all common clinical findings. Diagnosis is based on history and physical examination findings. Fever is common when infectious agents are involved. Acute tonsillitis will reveal bright-red, friable tonsils on oral examination. It is not unusual for tonsils at this stage to be enlarged and protruding from the palatine fossa. Occasionally the tonsils will have petechiae or small abscesses. The pharynx of acute pharyngitis will be visibly inflamed and can have ulcerations, petechiae, or small abscesses. Bacterial or viral isolation is usually not indicated unless clinical signs are chronic or relapsing. The most common causes of tonsillitis and pharyngitis is upper respiratory infection. FHV-1 and

FCV are the two most common feline viral pathogens. FCV is more likely to cause ulcerations than FHV-1.[48,49] Canine infectious tracheobronchitis (ITB) will occasionally cause problems, although it is more likely to cause laryngitis. *Bordetella bronchiseptica* has caused URT disease in cats as well.[50] Other possibilities include chronic vomiting or regurgitation, periodontitis, and ingestion of caustic or toxic substances (e.g., cleaning detergents, liquid potpourri).[51] Rarely, bacterial infection will be incriminated as the cause. Cats can also develop a progressive, nonspecific inflammatory condition termed gingivitis-stomatitis-pharyngitis complex. Young purebred cats are predisposed to the disease, and the most severely affected cats develop ulceroproliferative lesions in the caudal oropharynx.[52] Treatment of pharyngitis or tonsillitis is directed toward eliminating the underlying cause, if possible, as well as supportive care and antibiotics, if indicated.

211.5.3 Oropharyngeal Dysphagia

Dysphagia refers to abnormal or difficulty swallowing. Oropharyngeal dysphagia indicates an inability to move a bolus from the oral cavity into the proximal esophagus. This symptom can be either secondary to an isolated lesion or manifestation of systemic disease. Clinical signs are variable, depending on severity and location of the problem. Signs include difficulty with prehension, dropping food from mouth, exaggerated head movements during eating, regurgitation with no correlation in time of eating, and repeated attempts to swallow food. Occasionally, respiratory signs such as nasal discharge, coughing, and aspiration pneumonia will occur secondary to nasopharyngeal or laryngotracheal aspiration. Diagnosis of oropharyngeal dysphagia requires multiple areas to be evaluated. Accurate historical information is imperative to differentiate regurgitation from vomiting. It is rare that an owner will recognize the difference until the history and examination occurs. A standardized questionnaire has been evaluated as a sensitive tool to detect oropharyngeal dysphagia.[53] Observing the animal eating and drinking is also extremely helpful. The physical examination should include a thorough oral examination to evaluate for structural abnormalities and foreign bodies. A complete neurologic examination is also critical during the evaluation of oropharyngeal dysphagia. Radiographs of the area can identify radiopaque foreign bodies or masses. Thoracic radiographs can determine if the animal has aspiration pneumonia secondary to the dysphagia. Videofluoroscopy is an excellent diagnostic tool to localize the dysphagia.[54] Other possible diagnostics could include ANA test, evaluation for acetylcholine receptor antibodies, endocrine screening, electromyography, or biopsy for histopathology.

Causes of dysphagia include anatomic abnormalities, neoplasia, foreign bodies, or neuromuscular disorders. Brain stem tumors can also cause dysphagia, but it is usually not the only clinical or physical examination finding. The most common neuromuscular disorder is myasthenia gravis, a disease of altered neuromuscular transmission secondary to autoantibodies against acetylcholine receptors. Akitas, Scottish terriers, German shorthaired pointers, Chihuahuas, and Abyssinians are all breeds identified at increased risk for acquired myasthenia gravis.[55,56] Manifestations of myasthenia gravis may either be focal (pharyngeal or esophageal) or generalized (generalized muscular weakness or collapse). Oropharyngeal dysphagia can be one clinical sign of many that is associated with myopathies. Bouvier des Flanders have been identified with a muscular dystrophy in which oropharyngeal dysphagia is the primary clinical sign.[57] Cricopharyngeal achalasia can be acquired as a polymyopathy, or it can be congenital. Cricopharyngeal achalasia is the failure of the upper esophageal sphincter to relax and allow a food bolus into the proximal esophagus. Cocker spaniels are at increased risk for congenital cricopharyngeal achalasia, but any breed can be affected.[58] It is important to differentiate between congenital and acquired disease, because cricopharyngeal myotomy is indicated in congenital disease but should be avoided with acquired disease. Treatment of oropharyngeal dysphagia should be based on the

underlying disease process. If possible, the underlying cause should be removed; if that is not possible, providing a means of adequate nutrition should be pursued.

211.6 DISEASES OF THE LARYNX

211.6.1 Laryngeal Paralysis

Laryngeal paralysis is a common cause of upper airway obstruction in dogs. Cats can be diagnosed as well, but it is not a common cause of upper airway obstruction for the species.[59] Laryngeal paralysis results when the arytenoid cartilage fails to abduct during inspiration, leading to narrowing of the glottic lumen. Several causes of laryngeal paralysis have been identified, but it is most often idiopathic. Most acquired idiopathic cases are older, large breed dogs. Damage to the recurrent laryngeal nerve from trauma, infiltrative disease, masses, or surgical manipulation (e.g., feline thyroidectomy) can lead to laryngeal paralysis.[59] Polyneuropathies secondary to immune-mediated disease, hypothyroidism, or other systemic disorders can be observed primarily as laryngeal paralysis.[60] Congenital laryngeal paralysis does occur but is uncommon. A hereditary form has been described in Bouvier des Flanders and is presumed in Siberian huskies and husky crossbreeds.[61,62] In Bouvier des Flanders an autosomal-dominant trait causing a loss of motor neurons in the nucleus ambiguus has been identified.[63] A laryngeal paralysis-polyneuropathy complex has been described in young dalmatians and rottweilers.[64,65]

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Clinical signs are usually progressive because the ability of the arytenoid cartilage to abduct fails. Clinical signs of laryngeal paralysis include stridor, exercise intolerance, coughing, gagging, and voice change. Animals with laryngeal paralysis can present in respiratory distress, especially after an episode of excitement, exercising, and when environmental temperatures are elevated. Moderate airway obstruction is worsened by laryngeal edema and inflammation secondary to turbulent airflow in the larynx. Although ultrasound has been described as a diagnostic tool for laryngeal paralysis, most clinicians will use laryngoscopy to definitively diagnose laryngeal paralysis.[9] Laryngeal function is assessed when the animal is under a light plane of anesthesia. Paralysis may be unilateral or bilateral, although most animals with moderate to severe clinical signs have bilateral dysfunction of the arytenoid cartilages. It is important not to be fooled by paradoxic movement of the arytenoid cartilages. Paradoxic movement indicates opposite movement (i.e., medially) by the arytenoid cartilages when negative pressure occurs during inspiration. A thorough oral examination should be performed during the same anesthetic episode to identify any underlying causes. Once laryngeal paralysis has been diagnosed a complete neurologic examination that includes pharyngeal and esophageal function should occur to evaluate for concurrent or underlying problems. Thoracic radiographs are indicated to identify aspiration pneumonia or metastatic disease. When the animal presents in respiratory crisis, stabilization includes sedation and establishing an airway. This is accomplished by either tracheal intubation or tracheotomy. Short-acting corticosteroids are helpful if significant laryngeal edema exists. Once stabilized, surgery is indicated to alleviate the upper airway obstruction caused by laryngeal paralysis. Multiple surgical techniques have been described to palliate the clinical signs associated with laryngeal paralysis. The current surgical technique of choice is unilateral arytenoid lateralization, a technique that attempts to increase the area of the rima glottidis.[66] This procedure has been shown to have the most favorable outcome compared with other possible surgical techniques such as bilateral arytenoid lateralization and partial laryngectomy.[67] Postoperative complications include aspiration pneumonia, laryngeal webbing, surgical failure, and respiratory distress. Postoperative complications are common, and death can occur. In one retrospective study, 34.3% of dogs had postoperative complications and the mortality rate was 19.3%.[67] In the same study, prognosis was

poor if the dog had concurrent neurologic disease. Limited information exists regarding surgical outcome in cats. The surgical technique used was unilateral arytenoid lateralization. Postoperative complications included laryngeal edema that necessitated a temporary tracheotomy tube and an altered ability to vocalize. All cats survived.[68]

211.6.2 Laryngeal Neoplasia

Primary neoplasms of the canine and feline larynx occur uncommonly. The most common canine laryngeal tumors reported are malignant epithelial tumors and rhabdomyoma. The most common laryngeal tumor in the cat is lymphosarcoma, with squamous cell carcinoma the second most common.[10,69,70] Most patients with laryngeal tumors are older, with 8 years as the median age.[69] Other report tumor types are adenocarcinoma, rhabdomyosarcoma, osteosarcoma, chondrosarcoma, mast cell tumor, and melanoma.[10,69–71] Clinical signs are similar regardless of tumor type and include dysphonia, coughing, gagging or choking, and respiratory distress. Occasionally an abnormal larynx can be palpated, but most laryngeal tumors are identified by laryngoscopy (Figure 211-4). Radiographs, CTs, and ultrasound all have diagnostic value in determination of extent of disease and potential metastasis.[10] Definitive diagnosis should be made by histopathology; caution should be used when diagnosis is based on gross appearance alone. This is especially true with feline tumors because granulomatous disease has been reported. Therapy is based on tumor type but, in general, surgical resection and creating an unobstructed airway are goals. Complete laryngectomy and permanent tracheostomy are options with variable success.[72,73] Cats with severe respiratory compromise secondary to laryngeal lymphosarcoma will respond well to radiation therapy. The prognosis of benign tumors is good if complete resection is successful; malignant laryngeal neoplasms have a poor prognosis.

Figure 211-4 Laryngeal neoplasia in a geriatric dog, causing complete obstruction of glottis.

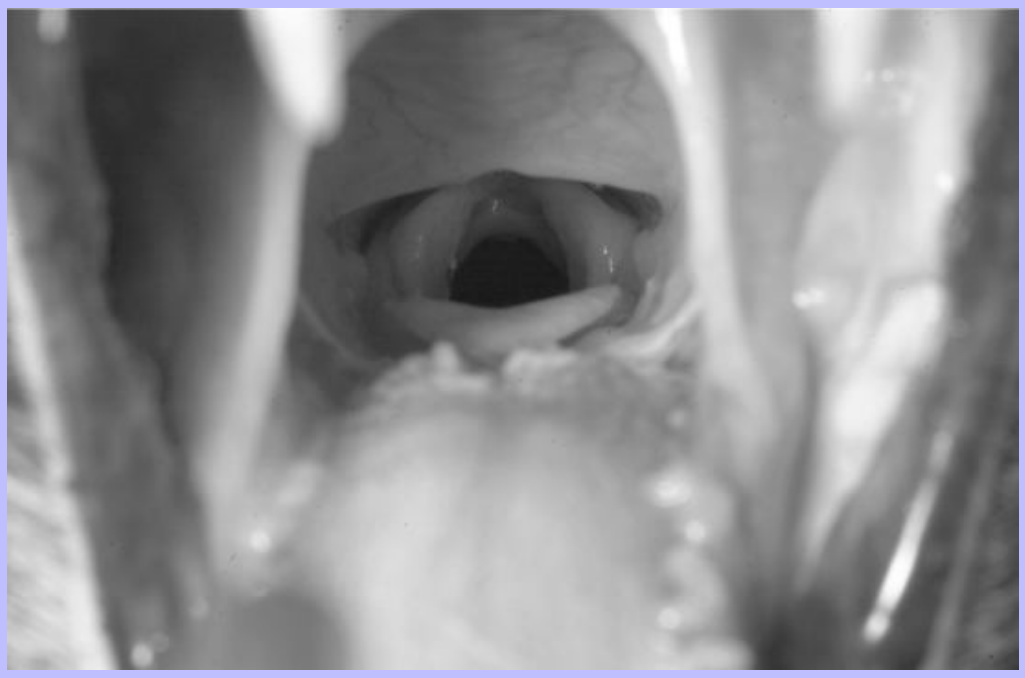
211.6.3 Laryngeal Collapse

Brachycephalic dogs are at increased risk to develop laryngeal collapse secondary to their congenital airway malformations. Stenotic nares, elongated soft palate, and if present, a hypoplastic trachea, create an increased negative pressure during inspiration to move air through the narrowed air passages. It is believed that laryngeal cartilages become deformed from this chronic increased negative pressure and will finally weaken and collapse. Finding that older brachycephalic dogs will often have laryngeal collapse when presenting for upper airway disease support this theory. However young brachycephalic dogs are also diagnosed with laryngeal collapse, which may indicate a defect in cartilage structure.[74] Dogs with laryngeal collapse will experience stridor, episodes of respiratory distress, and a respiratory crisis due to upper airway obstruction. 1202
Determination of laryngeal collapse is possible with laryngoscopy. The corniculate and cuneiform processes 1203
of the arytenoid cartilage will be medially displaced and occasionally will touch. In severe cases these processes will overlap, and the epiglottis will appear to be rolled up or flattened.[74] No specific treatment has been effective for laryngeal collapse. Surgical treatment should be directed toward altering the underlying congenital abnormality (i.e., stenotic nares correction, soft palate resection, everted laryngeal saccule excision) to improve airflow. In cases of severe laryngeal collapse, a permanent tracheostomy is recommended.[44,75] Dogs with severe laryngeal collapse have a poor prognosis.[75]

211.7 LARYNGITIS

Inflammatory laryngeal disease is common in both the dog and the cat. The most common cause of acute inflammation of the larynx is infectious agents such as canine infectious tracheobronchitis (ITB), commonly called kennel cough, or the feline upper respiratory agents (i.e., FHV-1, FCV). ITB is a result of coinfection of *Bordetella bronchiseptica* with either canine parainfluenza virus or canine adenovirus-2 (CAV-2).[76] With most cases of ITB, the only clinical sign is paroxysmal coughing in an otherwise healthy dog. Due to inflammation of the larynx the cough is a loud, high-pitched, “goose honk” cough. Occasionally a dog may be febrile, lethargic, and inappetent. ITB is usually self-limiting, but the severity of the cough, combined with the possibility of pneumonia complicating the disease, warrants treatment. Doxycycline at 5 to 10 mg/kg orally once daily is the antimicrobial of choice for *B. bronchiseptica*. Short-term administration of an anti-inflammatory dose of glucocorticoids can be effective in decreasing laryngeal edema. Antitussives, such as butorphanol tartrate or hydrocodone bitartrate, are effective in minimizing the severity of the cough but should not be used if pneumonia is suspected. Other causes of inflammatory laryngeal disease include endotracheal intubation, insect bites, foreign body penetration, or trauma from bite wounds, leash and choke chain injuries, or being hit by cars. Frequently no cause for acute laryngeal inflammation is found. Acute inflammatory laryngeal disease is usually self-limiting, and no specific treatment is indicated if the animal has only mild signs. However, if moderate to severe signs exist, a short course with an anti-inflammatory dose of glucocorticosteroids can be initiated to decrease laryngeal edema. Respiratory obstruction secondary to laryngeal inflammation is an uncommon clinical presentation but can occur in severe instances such as in laryngeal trauma. A tracheostomy is indicated if the patient is dyspneic, cyanotic, or extremely anxious due to laryngeal inflammation.[7]

Figure 211-5 Normal feline larynx during inspiration.



211.8 OBSTRUCTIVE INFLAMMATORY DISEASE

An obstructive inflammatory laryngeal disease has been described in cats and dogs.[70,77–79,80] Although rare, it is a disease worth noting because the gross appearance can mimic laryngeal neoplasia. The underlying cause of inflammation is unknown. Feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) have not been found to be associated with this disease. In the feline reports, dyspnea secondary to upper airway obstruction was reported in all cats; retching, coughing, and dysphonia were also common. Stridor and dysphonia was reported in dogs. Direct visualization of the larynx reveals a laryngeal mass that cannot be distinguished from neoplasia or severe swelling and edema (Figures 211-5 and 211-6). Histopathology is imperative to distinguish between neoplasia and obstructive inflammatory disease. Histopathology reveals either granulomatous or nongranulomatous laryngitis (neutrophilic and lymphoplasmacytic). Most patients with obstructive inflammatory laryngeal disease need to be stabilized. This is accomplished by establishing an airway through tracheostomy tube placement. Treatment with corticosteroids (dexamethasone, prednisone, or prednisolone) has variable success, and occasionally surgical resection of the proliferative tissue is indicated. The prognosis is guarded, with a high mortality rate during the initial diagnostic and treatment period.

Figure 211-6 Middle-aged cat presented in respiratory distress. Laryngeal examination revealed bilateral arytenoid masses. Biopsy revealed pyogranulomatous inflammation.

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212 CHAPTER • 212 Clinical Evaluation of the Respiratory Tract

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Respiratory diseases can be extremely challenging to manage and diagnose. The respiratory system is one of the four major body systems that require evaluation and treatment on an emergency basis. Respiratory dysfunction can result in severe physiologic compromise and imminent death if not dealt with appropriately. The respiratory workup is often dictated by the patient's condition, rather than the convenience of the clinician and the client. In patients with severe respiratory compromise, a tentative diagnosis and preliminary therapeutic plan must be guided by signalment, history, physical examination findings, and response to therapy pending stabilization for more definitive diagnostics (see Pulmonary Emergencies in Critical Care chapter). It is rare that a definitive diagnosis for the underlying cause of the respiratory problem is found using the signalment, history, physical examination, and response to therapy alone. Ancillary diagnostics are almost always required.

212.1 SIGNALMENT

The animal's signalment can provide direction for the diagnostic workup of the respiratory patient. For example, pediatric or juvenile patients are more likely to contract infectious conditions. Animals with inherited pulmonary disorders tend to manifest signs at an early age and certain breeds are predisposed to specific respiratory abnormalities. Feline asthma is noted more frequently in Siamese cats compared with other breeds. Brachycephalic breeds, particularly bulldogs, may have hypoplastic tracheas and upper airway conditions that result in respiratory difficulties. Respiratory distress due to heart failure is noted more frequently in male than female cats. Signalment provides clues to the underlying disorder but never provides a definitive diagnosis.

212.2 GENERAL MEDICAL HISTORY

A thorough history can provide important clues to the underlying respiratory problem. Questions regarding how long the owners have had the pet are important. For example, have they had the pet since it was a puppy or kitten, or did they obtain the animal when it was an adult? Obviously, owners that obtained their pet as a puppy or kitten will have a more comprehensive life history compared with owners that obtained a pet at a more advanced age. What is the travel history of the pet? This may assist in determining clinical suspicion for infectious or parasitic respiratory disease.

Establishing a clear picture of the pet's environment gives the veterinarian a sense of potential exposure to toxins or infectious diseases that might cause pulmonary problems. Animals that are allowed to run free or are unobserved can potentially be exposed to anything, such as anticoagulant rodenticide, forest fire, or house fire smoke. Was there a recent change in a living environment that is coincident with the development of the respiratory signs? Cats may develop airway hypersensitivity reactions to antigens in a new environment.

It is also important to determine the vaccination status of the animal. Similarly, is the pet in a heartworm endemic area and, if so, is the animal on an appropriate heartworm preventative plan? Are there other pets in the environment that this animal has been exposed to? Multiple animals with similar clinical signs points toward an environmental cause such as an infectious disease or a toxin. Similarly, is the owner or anyone in the family having medical problems that might suggest a zoonotic disease (e.g., trichosporonosis, rickettsial or fungal diseases, leishmania)?

Does the patient have any known hypersensitivities to dietary allergens or medications? Both are diagnostically and therapeutic important. What is the previous medical history of the patient? Has the animal had previous respiratory problems? If so, did the clinical signs improve? Has there ever been a history of trauma suggesting diaphragmatic hernia or pneumothorax?

212.3 PHYSICAL EXAMINATION

A complete physical examination is essential (see Chapter 1). In animals with severe respiratory compromise, the physical examination may point towards a tentative diagnosis from which empirical therapy can be chosen to stabilize the patient (see Approach to Respiratory Distress). Clinical signs combined with physical examination findings provide the initial steps in guiding the diagnostic workup.

Animals with nasal disorders commonly have clinical signs such as sneezing, nasal discharge, loud nasal respiratory sounds and, rarely, open mouth breathing secondary to occlusion of the nasal passages. Pure nasal disorders rarely cause severe respiratory distress, although some cats are reluctant to breathe through the mouth to relieve the obstruction. Palpation over the nasal cavities may reveal pain, asymmetry, or distortion of the nasal cavity due to destructive or proliferative diseases. Examination of the oral cavity may reveal bony abnormalities, severe dental disease, or abnormalities of the hard and soft palate that contribute to, or cause, the nasal disorder. Purulent nasal discharge may be due to primary or, more often, secondary bacterial infections. Unilateral discharge suggests tooth root abscess, cyst or hematoma, oronasal fistula, foreign body, or neoplasia. Bilateral discharge occurs secondarily to neoplasia, infectious agents, or any disease process that is caudal to the nasal septum. Epistaxis is due to any of the aforementioned causes of purulent nasal discharge, although severe bleeding is relatively rare with these conditions. Causes of epistaxis that are not due to primary respiratory abnormalities include thrombocytopenia, thrombocytopathia, coagulopathy, erosive immune-mediated diseases, or, rarely, hypertension. Definitive diagnosis of the underlying nasal disease is rarely derived from clinical signs and physical examination findings alone. Further diagnostics are typically required.

Upper and large airway disease (pharynx, larynx, and trachea) typically manifest as stridor and stertor that is audible without the stethoscope. Localization of the respiratory disease to the upper or large airways does not preclude disease in other parts of the respiratory systems but does warrant specific evaluation of the upper airways and trachea. Extrathoracic dynamic airway disease typically has louder sounds during inspiration, whereas intrathoracic dynamic lesions tend to be louder during exhalation. However, distinguishing the diseased anatomic location in the clinical patient with respiratory distress is often challenging. Auscultation over the specific location of the lesion reveals the most dramatic of sounds. Pharyngeal diseases include abscess, cyst or hematoma, cellulitis, neoplasia, foreign body, nasopharyngeal polyp, and enlarged lymph nodes. Direct visualization during physical examination or under general anesthesia usually localizes the problem. Palpation of the pharyngeal area may reveal swelling, pain, or asymmetry, indicating that the pharyngeal region is at least part of the disease process.

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Laryngeal disease typically manifests as inspiratory stridor, voice change, coughing while drinking water, exercise intolerance, and an exacerbation of the clinical signs during exercise or periods of high environmental temperature. The most common laryngeal diseases include laryngeal paralysis, neoplasia, edema, and inflammation.

Tracheal disease is typically manifested as stridor and coughing, especially with exercise or excitement. A cough is easily elicited upon tracheal palpation when the trachea is inflamed. Respiratory compromise may vary from mild to severe. Distress may be more severe during inspiration, expiration, or both, depending upon whether the

lesion is extrathoracic, intrathoracic, or both, respectively. The most common tracheal abnormalities include infectious tracheobronchitis (kennel cough), tracheal collapse, neoplasia, foreign body, trauma, and parasites.

Small airway and alveolar disease can be particularly challenging to diagnose. Physical manifestations of diseases in this portion of the respiratory tract include varying degrees of respiratory distress, coughing, and increased breath or adventitial sounds such as crackles or wheezes upon auscultation. Location of the increased breath or adventitial sounds may help in identifying the underlying disease process. Adventitial sounds heard loudest over the cranioventral or right middle lung lobe regions are suggestive of aspiration pneumonia. An increase in breath or adventitial sounds over the thorax in dogs with auscultable heart abnormalities is supportive of cardiogenic pulmonary edema. Auscultation abnormalities heard loudest over the caudodorsal regions of the lungs in animals with head trauma, electrocution, seizures, or upper airway obstruction may indicate neurogenic pulmonary edema. Diffuse, fine crackles throughout the thorax in a dog without significant signs of respiratory distress suggests chronic or slow onset of pulmonary parenchymal disease such as pulmonary fibrosis or metastatic neoplasia. Other lower airway and pulmonary parenchymal diseases include pulmonary thromboembolism, pulmonary contusions, pulmonary hemorrhage, acute respiratory distress syndrome (ARDS), heartworm disease, pulmonary infiltrates with eosinophilia, allergic bronchitis, feline bronchial disease, near drowning, smoke inhalation, re-expansion pulmonary edema, and inhalation of toxins.

Pleural space disease is caused by fluid, air, soft tissue, or abdominal organs in the pleural space. Patients with pleural space disorders commonly exhibit a short, shallow breathing pattern, tachypnea, and intermittent attempts at a deep respiration (especially in cats with pleural effusion). Decreased breath sounds of the thorax are ausculted. Diminished breath sounds in the ventral regions of the thorax are suggestive of fluid, whereas a dorsal distribution suggests air accumulation. Most pleural effusions and pneumothoraces are bilateral in dogs and cats, although unilateral fluid or air accumulation may occur. Diaphragmatic rupture often results in an asymmetry of auscultation findings. Diminished breath sounds are typically noted on the side where the abdominal contents are located, and loud heart and lung sounds are commonly heard on the opposite side. Rarely, a diaphragmatic hernia may result in substantial fluid accumulation on both sides of the chest, especially when the liver is present in the pleural space.

A complete, thorough physical examination should be performed even though the primary clinical signs are associated with the respiratory tract. It is rare that primary respiratory problems result in problems elsewhere in the body, but the reverse is not uncommon. Findings in other areas may provide clues as to the underlying cause of the respiratory disease or at least guide the diagnostic evaluation. Weight loss or cachexia suggests more chronic systemic disease, such as neoplasia that has metastasized to the lungs and resulted in respiratory difficulty. Additionally, the presence of masses elsewhere in the body might indicate a primary neoplastic process. Diseases that cause an acute abdomen commonly result in secondary respiratory diseases such as aspiration pneumonia or an acute respiratory distress (ARDS)-like condition subsequent to a severe inflammatory disease process. Petechiation or evidence of an abnormality of hemostasis elsewhere in the body might suggest pulmonary parenchymal hemorrhage or hemorrhagic pleural effusion as the cause of the respiratory distress.

In summary, signalment, previous medical history, clinical signs, and physical examination findings provide a solid foundation to further develop a diagnostic plan. There are numerous diagnostic modalities available to further evaluate respiratory function and identify specific disease processes in order to accurately and most effectively treat these patients.

212.4 DIAGNOSTIC TECHNIQUES

The diagnostic approach to the animal with respiratory disease largely depends on the patient's history, signalment, physical examination findings, cardiopulmonary stability, and the expected diagnostic yield versus

risk of a given diagnostic test. It remains important to take into account the sensitivity and specificity of any test performed when interpreting the results. A general algorithm is displayed in Figure 212-1.

212.5 LABORATORY DIAGNOSTICS

Hematologic and biochemical profiles are important in the assessment of an animal's health status and evaluation of nonrespiratory diseases that may have a substantial effect on the respiratory system, such as acidemia, anemia, or endocrinopathies. Chronic hypoxia stimulates the release of erythropoietin from the kidneys, which results in an increased red blood cell turnover and subsequent polycythemia. Anemia leads to a decrease in total oxygen content, which increases respiratory effort and rate. Leukocytosis with a left shift with moderate to severe airway inflammation, infection, or neoplasia, and leukopenia occurs with acute bacterial bronchopneumonia or sepsis. Parasitic airway disease, asthma, bronchitis, or pulmonary infiltration with eosinophilia (PIE) commonly cause an elevated peripheral eosinophil count, and a basophilia is frequently seen in animals with Dirofilaria immitus or PIE. Hypercalcemia may be associated with a neoplastic or fungal disease process. Hypoalbuminemia may be seen in animals with pleural effusion (cause or effect), and systemic illness or multiple-organ dysfunction can lead to ARDS. Hemorrhagic infiltrates or effusions may occur secondary to severe thrombocytopenia, thrombocytopathia, or coagulopathies.

Animals with no obvious cause of respiratory distress should be examined for other systemic diseases that may predispose to pulmonary thromboembolism (PTE). Underlying diseases might include hyperadrenocorticism, diabetes mellitus, immune-mediated anemia or thrombocytopenia, protein losing nephropathy or enteropathy, or pancreatitis. Coagulation profiles, platelet counts, blood smear analysis, fibrin and fibrinogen degradation products, D-dimer assays, antithrombin III measurements, and/or thromboelastography (TEG) may be useful in the diagnosis of disseminated intravascular coagulation that might lead to PTE or pulmonary hemorrhage.

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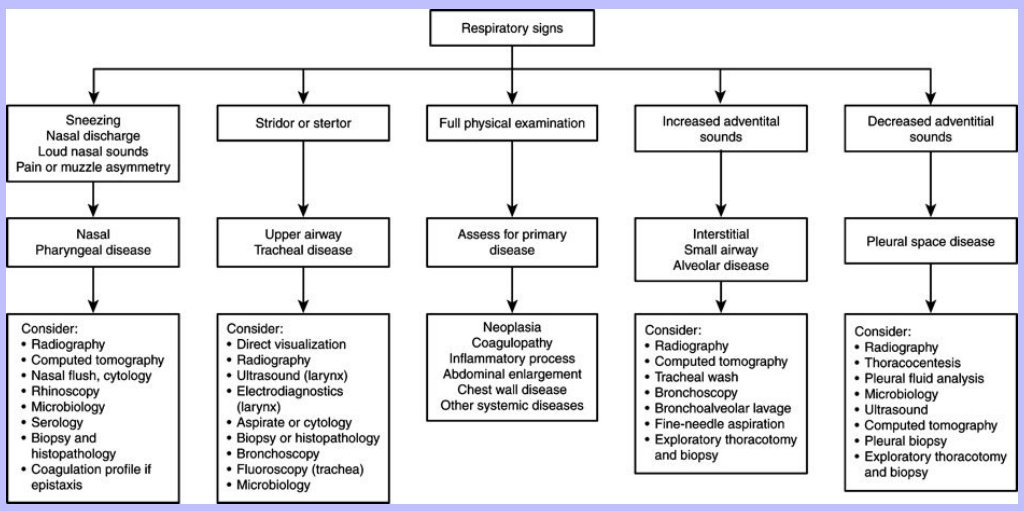
Figure 212-1 General diagnostic algorithm for evaluation of the respiratory tract. As with any algorithm, this provides only guidelines. Numerous exceptions to this algorithmic approach exist.



There are many serologic tests available for the identification of viral diseases, mycoses, and allergens. Specific infectious disease testing will depend on the animal's environment, travel history, and lifestyle. Feline leukemia virus and feline immunodeficiency virus infection commonly leads to secondary opportunistic infections. Additional infectious causes of respiratory disease in the dog or cat that may require further diagnostics include viral diseases (canine distemper, canine parainfluenza, canine adenovirus-2, herpevirus, feline rhinotracheitis, feline calicivirus), bacterial diseases (e.g., *Bordetella bronchiseptica*, streptococci, *Escherichia coli*, *Klebsiella*, *Pasteurella*, eugoic fermenter-4, mycobacteria, *Yersinia* spp., *Pseudomonas mallei*, *Mycoplasma* spp., *Bacteroides* spp., *Clostridium perfringens*, fusobacteria, *Peptostreptococcus* spp.), parasitic or protozoal diseases (e.g., *Dirofilria immitus*, *Paragonimus kellicotti*, *Capillaria aerophila*, *Aelurostrongylus abstrusus*, *Toxoplasma* spp., *Acanthamoeba* spp.), fungal infections (e.g., *Blastomyces*, *Histoplasma*, *Cryptococcus*, *Coccidiodes*, *Aspergillus*, and *Penicillium* spp.), or rickettsial diseases (e.g., *Rickettsia rickettsii*, *Ehrlichia canis*). Bacterial and fungal cultures, serologic testing, cytologic examination, electron microscopy, immunocytology and immunohistochemistry, immunoblotting, and/or polymerase-chain reaction amplification may be required for a definitive diagnosis of infectious diseases.[1] Heartworm disease in the cat may require echocardiography in addition to antibody and antigen testing.[2] Fecal studies should be performed in animals with suspected parasitic pneumonia. A zinc sulfate fecal flotation, including several drops of sediment, is indicated to identify *Paragonimus kellicotti* or *Capillaria aerophila* ova, and a Baermann technique should be used to identify *Aelurostrongylus abstrusus* larvae.

212.6 DIAGNOSTIC IMAGING

212.6.1 Radiography

Radiography remains an essential tool in the diagnostic approach to respiratory tract disease. Serial radiographic studies serve as an important method of monitoring a patient's respiratory disease and response to therapy. Proper radiographic technique is critical when viewing the nasal cavity or chest cavity owing to the nature of the fine nasal turbinates and air-tissue interface in the lungs, respectively.

Nasal radiography is typically used to evaluate animals with clinical signs of sneezing, nasal discharge, or upper airway obstruction. Morphologic changes in the air passages, turbinates, and frontal sinuses may be confirmed and the extent of the lesions defined. Nasal radiography does require anesthesia in order to obtain proper positioning and avoid motion artifact. Three views should be taken to assess the nasal cavity and frontal sinuses: a lateral, frontal, and open-mouth ventrodorsal, or intraoral dorsoventral view. It is important to look for symmetry, obliteration of air spaces between the nasal turbinates or frontal sinuses suggestive of fluid or swelling, destruction of nasal turbinates indicating a neoplastic or severe, chronic inflammatory process, or destruction/deformation of proximal facial structures which is commonly due to neoplasia or *Cryptococcus* spp.[3,4]

Radiography of the neck and extrathoracic airway is indicated in dogs or cats with inspiratory stridor or stertor, gagging, coughing, and/or recent voice change. Lateral radiographs are most useful in assessing these structures; however, tracheal displacement may be more visible on a ventrodorsal view. Both inspiratory and expiratory views are helpful in assessment of dynamic changes in airway diameter. Radiographs may assist in the identification of pharyngeal, laryngeal, or tracheal disease due to radiopaque foreign bodies or soft tissue masses (abscesses, polyps, neoplasms, granulation tissue), anatomic displacement due to mass lesions, tracheal narrowing or hypoplasia, or tracheal collapse.[5] Tracheal displacement secondary to mass lesions, soft tissue masses, hypoplasia, and invagination of the dorsal tracheal membrane are commonly seen in older

symptomatic or asymptomatic dogs with chronic coughing, but rarely in cats. Cervical emphysema or pneumomediastinum following endotracheal intubation or trauma in cats is readily diagnosed with cervical radiography.[4]

Survey thoracic radiographs are commonly used in the diagnostic evaluation of dogs and cats with respiratory disease.[6] There are fewer breed-related and age-related changes seen in the feline thorax compared with the canine thorax.[4,6] A technique chart should be made to avoid over-or under-diagnosis of pulmonary disease when thoracic radiographs are viewed. In addition, a lateral and dorsoventral or ventrodorsal radiograph should comprise the minimum thoracic study. Three views (including both laterals) are commonly taken when looking for metastatic pulmonary disease or unilateral disease, although this practice has been questioned.[7] In cats, the use of high-detail x-ray intensifying screens may help in the identification of small airway disease.

The chest wall, diaphragm, pleural space, mediastinum, airways, and pulmonary parenchyma should be assessed. The thoracic wall should be evaluated for evidence of trauma (rib or sternal fractures), soft tissue masses, lytic, and/or sclerotic processes.[8]

Diaphragmatic abnormalities such as loss of the diaphragmatic silhouette or changes in the shape and position of the diaphragm are assessed in evaluation of thoracic radiographs. The diaphragmatic position and shape varies with the respiratory cycle, species and breed, conformation, coexisting diseases, and body fat content. Changes in the shape of the diaphragm are due to thoracic masses or lung disease adjacent to the diaphragm, diaphragmatic hernias, gastroesophageal intussusception, diaphragmatic masses, and chronic pleural inflammatory conditions. Cranial displacement of the diaphragm occurs secondary to abdominal disease, generalized diaphragmatic paralysis, or muscular dystrophy and caudal displacement occurs secondary to severe respiratory disease or pleural space disease. Decreased visualization of the diaphragmatic line, the presence of abdominal viscera within the thorax, displacement of abdominal or thoracic structures, pleural fluid, and divergence of the diaphragmatic crura or cranial angulation of the diaphragm might indicate a diaphragmatic hernia or diaphragmatic defect. Additional diagnostics that might be performed to confirm a diaphragmatic hernia include an upper gastrointestinal barium contrast study, horizontal beam radiographs, ultrasonography, positive contrast celiography, portography, cholecystography, angiocardiography, angiography, and non-selective cardiography, computed tomography, or magnetic resonance imaging.[9,10] Radiographs of animals with a peritoneopericardial diaphragmatic hernias also display an enlarged, round cardiac silhouette, abdominal organs within the pericardial sac, confluent silhouette between the diaphragm and heart, and an indistinguishable border of the ventral thoracic diaphragmatic surface and the caudal ventral cardiac silhouette. A dorsal mesothelial remnant between the heart and the diaphragm on the lateral view in normal cats is commonly seen.[10]

The presence of fluid, air, or soft tissue within the pleural space should be identified with thoracic radiography. As little as 100 mL of pleural fluid is detectable in a medium-sized dog using standard thoracic radiographic views. A lateral and erect ventrodorsal view enables the detection of as little as 50 mL of fluid in a 15-kg animal.[11] Removal of fluid or air prior to taking radiographs will help stabilize the animal and will improve the radiographic visualization of the lung fields, heart, and mediastinum. Radiographic changes associated with pleural effusion include blurring of the cardiac silhouette, interlobar fissure lines, rounding of the lung margins at the costophrenic angles, widening of the mediastinum, separation of the lung borders from the thoracic wall, and scalloping of the lung margins at the sternal border.[12] Hemothorax, pyothorax, chylothorax, or transudative effusions may be present. Cytology, cultures, and fluid analysis are necessary to classify the effusion (see Pleural and Extrapleural Diseases).

Radiographic changes associated with pneumothorax include dorsal displacement of the heart on the lateral view, retraction of the lung from the chest wall, and an increased density of the collapsed lung lobes. Potential causes might include chest wall trauma, an esophageal perforation leading to severe pneumomediastinum, or rupture of the trachea or lung (commonly secondary to infection, bulla, neoplasia, or positive pressure ventilation).[12]

The mediastinum should be evaluated radiographically for evidence of a mediastinal shift, masses, lymphadenopathy, fluid, or pneumomediastinum. Mediastinal shifts and mediastinal masses are most readily seen on ventrodorsal or dorsoventral radiographs. If mediastinal fluid is suspected, horizontal beam radiographs and ultrasonography may yield further diagnostic information. Pneumomediastinum is best appreciated on lateral films of the chest, and pneumomediastinum may lead to subcutaneous emphysema, pneumoretroperitoneum, and/or pneumothorax in severe cases. Potential causes of pneumomediastinum include alveolar rupture, perforation of the trachea or esophagus, extension of gas in the neck or retroperitoneal space, or a gas-producing organism within the mediastinum.[13] The cardiac silhouette and pulmonary vasculature should also be assessed since left atrial enlargement leading to compression of the left mainstem bronchus, pleural effusion, and/or pulmonary edema commonly leads to respiratory impairment. The pulmonary artery may be prominent in animals with PTE, pulmonary hypertension, or heartworm disease.[14]

Evaluation of the lungs in animals with respiratory disease may reveal an increase in opacity, hyperlucency, and/or pulmonary mass lesions. It is important to assess the distribution of pulmonary abnormalities in conjunction with clinical signs. An increase in opacity of the lung is further separated into three categories of radiographic patterns: bronchiolar, interstitial, and alveolar. Differential diagnoses for the various lung patterns can be found in Box 212-1. Cats may prove more challenging to diagnose since the pattern and distribution of lung abnormalities are often not as reliable as with dogs. For example, the distribution of pulmonary infiltrates in cats with cardiogenic pulmonary edema is often patchy and asymmetric, rather than perihilar, and cats with pneumonia often do not have cranioventral distribution and alveolar patterns, as seen in dogs (Figure 212-2).[4] Pulmonary hyperlucency might be seen secondary to overexposure, hypovolemia, hyperinflation, PTE, cavitary masses, bronchiectasis, or areas of pulmonary parenchymal dissolution (emphysema, pneumatocoele, bulla). Neoplasia is the most common cause of solitary or multifocal mass lesions in the lungs, although abscess, granuloma, or fluid-filled structures cannot be ruled out.[15]

Fluoroscopy allows for real-time imaging of the thoracic structures. The motion studies obtained are often helpful in evaluation of the animal with tracheal collapse. The animal is placed in lateral recumbency and the trachea and bronchi are examined during both quiet respiration and induced coughing. Coughing is induced by gentle digital palpation of the trachea near the thoracic inlet. A videotape of the fluoroscopic study is useful for reviewing the airway changes in slow motion and diagnosing subtle dynamic airway disease.

212.6.1.1 **Box • 212-1 Differential Diagnoses for the Various Lung Patterns Seen on Thoracic Radiographs**

212.6.1.1.1 **Bronchial Pattern**

Chronic bronchitis (irritant, allergic, parasitic)

Calcification

Peribronchial cuffing (edema, bronchopneumonia, pulmonary infiltrates with eosinophilia)

212.6.1.1.2 Interstitial Pattern

Nodular

- Neoplasia
- Granuloma (eosinophilic, fungal, parasitic or heartworm-associated, foreign body)
- Bulla with fluid
- Hematoma, abscess, cyst
- Mucus-filled bronchus
- Bronchiectasis

Hazy and unstructured

- Diffuse
  - Artifact (underexposure, obesity, end-expiratory film)
  - Degenerative changes (“old dog lung”)
  - Neoplasia (lymphosarcoma, metastasis)
  - Pneumonitis (toxic, inhalant, metabolic, viral, parasitic)
  - Acute respiratory distress syndrome
  - Transitional stages of diseases such as edema, hemorrhage, bronchopneumonia
- Localized
  - Hemorrhage

PTE

Foreign body

Partial atelectasis

Transitional stages of disease such as edema, bronchopneumonia, hemorrhage, or parasites

212.6.1.1.3 Alveolar Pattern

Diffuse

Edema (cardiogenic or non-cardiogenic)

Bronchopneumonia

Hemorrhage

Smoke inhalation

Near-drowning

Acute respiratory distress syndrome

Localized

Edema

Bronchopneumonia

Hemorrhage

Primary lung tumor or metastasis

Lobar collapse or atelectasis

Heartworm disease

Infarct

Bronchography creates an outline of the mucosal surfaces of the trachea and bronchi using radiopaque contrast material.[16,17] Since bronchoscopy is now widely available, this diagnostic test is rarely used. The current use of bronchography may be limited to the evaluation of the severity and distribution of severe bronchiectasis prior to considering a lobectomy or pulmonectomy. Bronchography is typically performed under heavy sedation or anesthesia using fluoroscopic guidance to place a catheter through the endotracheal tube and into the pulmonary areas of interest. Contrast material such as Dionosil or sterile barium sulfate is injected and allowed to distribute during patient respiration. Fluoroscopic imaging and/or thoracic radiographs are then obtained. Potential complications (rare) include allergic reactions to the contrast, bronchospasm, retention of contrast in the small airways, or chemical pneumonitis.

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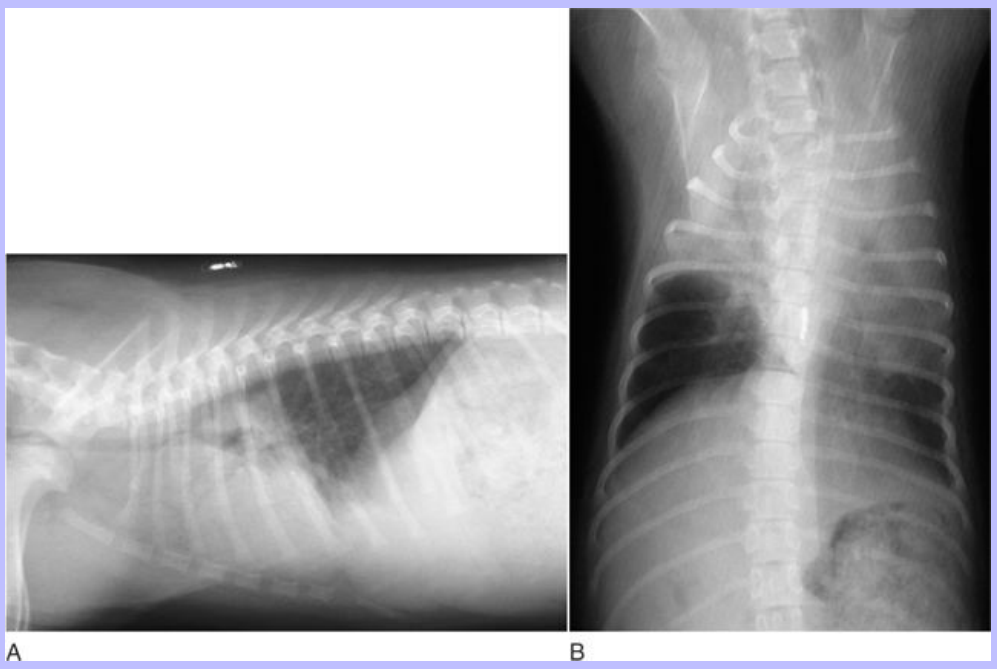
Figure 212-2 A lateral **(A)** and ventrodorsal **(B)** chest radiograph in a puppy with aspiration pneumonia. Cranioventral air bronchograms are evident.



Pulmonary angiography is useful for the detection of vascular anomalies (congenital or acquired) and pulmonary thromboembolism. Pulmonary angiography is performed by injecting iodinated contrast intravascularly in order to opacify the pulmonary arteries and veins. Selective pulmonary angiography is superior to nonselective angiography but does require injection of a medium-density, nonionic contrast material into a catheter in the pulmonary artery or a branch thereof. With nonselective angiography, the

contrast material is injected into the jugular or cephalic vein and films are taken at a speed of 1 to 2 per second or a fluoroscopic recording is made for both procedures (up to 5 to 30 seconds with severe vascular obstruction or cardiac dysfunction).[18] Potential complications include vascular injury, thrombosis secondary to injury, embolization of air, blood clots, or catheter material, infections associated with unsterile techniques, cardiac arrythmias due to endocardial stimulation from the catheter, or immune reactions to the contrast agent (including asystole and death).[19]

212.6.2 Ultrasonography

Ultrasonography can be useful in animals with nasopharyngeal soft tissue or fluid-filled masses.[20] Ultrasound has also been used to assist in the diagnosis of tracheal collapse and laryngeal paralysis in dogs.[21,22] Identification of pulmonary consolidation, masses, atelectasis, or torsion, as well as pleural or mediastinal abnormalities, may be detected using ultrasound. Ultrasound guided aspirates or biopsies are readily obtained using real-time visualization of the needle entering the tissue or fluid lesion.[23–25] Potential risks include bleeding, iatrogenic pneumothorax, or the introduction of infectious agents during the procedure. Using ultrasound, it may be easier to distinguish pleural or pulmonary opacities seen on radiographs or better visualize peripheral, pulmonary lesions that may be obscured by pleural effusion. In dyspneic patients, ultrasound is easily performed with the animal in sternal recumbency and may be better tolerated than radiographs. However, ultrasound is unable to allow visualization of lesions within an aerated lung since air impedes the transmission of sound. Ultrasound is operator-dependant and requires an experienced user for good results.

212.6.3 Nuclear Imaging

Nuclear scintigraphy is performed by the administration of a radioactive nuclide to the patient and detection of the energy from the radionuclides as they decay, with use of a camera that records the results to a computer monitor or photographic film.[26,27] Technetium 99m (^{99m}Tc) is the most common nuclide utilized. If pulmonary mineralization is suspected, bone-seeking radiopharmaceuticals can also be used.[28] (see Chapter 100).

Nuclear scintigraphy is most commonly utilized with lung disease in small animals to evaluate pulmonary perfusion in animals with suspected pulmonary thromboemboli or vascular anomalies.[27,29–31] It is relatively specific and sensitive for this purpose in dogs.[32] The radioactive particles are given intravenously and go through the pulmonary arteries, where they are trapped in the capillary bed. A normal animal shows uniform radioactivity throughout the lung fields. Vascular occlusion secondary to pulmonary emboli appears as deficient radioactive areas or photopenic defects on the perfusion scan. The specificity of diagnosing ventilation/perfusion inequalities is increased if the nuclear scan is combined with a ventilation scan.[33]

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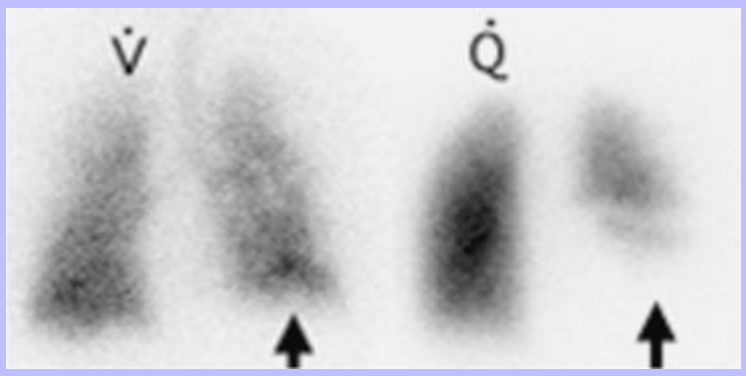
Figure 212-3 A ventilation-perfusion scan in a dog with a pulmonary thromboembolism. Normal ventilation is seen on the left (*V, arrow*), and a perfusion deficit is present on the right (*Q, arrow*).



The ventilation scan is performed using ^{99m}Tc-labeled diethylenetriamine pentaacetic acid, which is delivered via a nebulizer to the patient.[27,33] The radioactive aerosol is distributed in the air spaces, and areas of deficient radioactivity indicate poorly ventilated locations. A simultaneous ventilation and perfusion scan (Figure 212-3) enables the calculation of the ventilation: perfusion ratio (normal is 1:1). However, results are dependent on blood flow and ventilation differences in various parts of the lung and are difficult to interpret in the face of pulmonary interstitial lung disease.

Positron emission tomography (PET) is another noninvasive nuclear imaging technique that uses radioactive positrons to assess the chemical and physiological changes related to metabolism in a specific organ.[34] PET has been used in human medicine to diagnose and stage lung masses, monitor the size and activity of cancerous lesions, diagnose pulmonary thromboembolism, and assess changes in vascular permeability.[35,36] This technology is not often available for use in veterinary medicine but has been used experimentally in dogs to measure lung water, pulmonary vascular permeability, regional pulmonary blood flow, degree of lung injury, and regional pulmonary function.[37–45]

212.6.4 Alternative Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) are useful to detect or monitor nasopharyngeal, tracheal, or thoracic cavity lesions, assess the involvement of surrounding structures, and determine anatomic relationships. This imaging modality requires general anesthesia but may provide more valuable information regarding the pathogenesis, extent, and changes of many disease states.[46–55]

Computed tomography (CT) utilizes a 360-degree x-ray beam to create a three-dimensional, computer-processed cross-sectional image of body tissues or organs. The CT scanner acquires images incrementally, at a rate that varies with the type of machine and settings. The speed of the image acquisition is especially important when viewing the lung, since respiratory and cardiac motion will interfere with image quality. Most conventional CT machines have dynamic modes that acquire 8 to 12 scans per minute, although this rate is still incapable of obtaining suspended respiratory images. CT scans produce images with superior

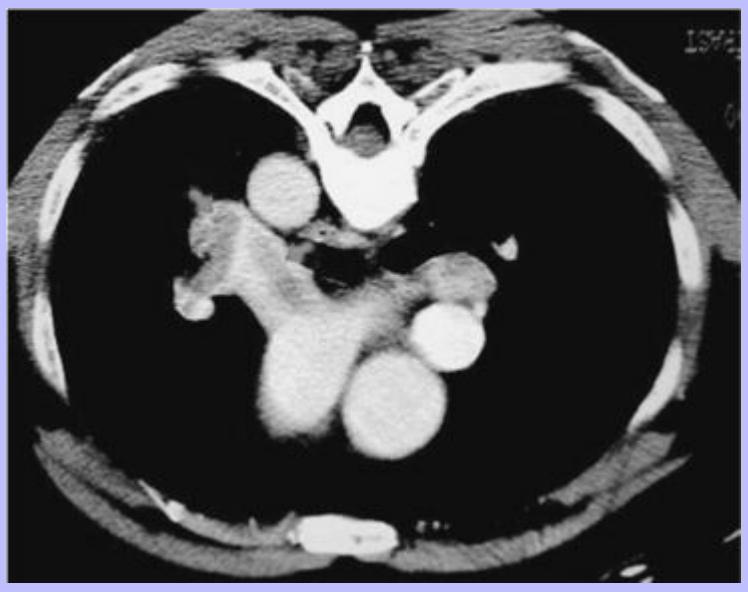
density discrimination that are free of superimposition from overlapping thoracic structures when compared with radiographs.[56] CT scanning is therefore the preferred tool for pulmonary imaging in people and is often used to differentiate pleural, extrapleural, or mediastinal tissues, or to better visualize the lungs when pleural effusion makes radiographic evaluation of the lungs difficult. A CT scan may be indicated to evaluate the lungs when thoracic radiographs are normal, but there is clinical suspicion of pulmonary disease, in animals that have abnormalities present on radiographs that require further clarification (i.e., prior to surgical intervention), or to assist in cancer staging and monitoring changes. Metastatic nodules are more easily detected using CT than radiography, and newer technologies such as spiral CT and high-resolution CT have made CT imaging faster and more diagnostically useful.[47,50,57–60]

High-resolution CT has excellent spatial resolution and is able to demonstrate pulmonary structures that are only 300 μ, as well as monitor changes in airway and vascular diameter in vivo following various stimuli, revealing differences that may not be detectable with spirometry. It has been used in dogs to measure changes in airway diameter and assess the function of pulmonary vessels and airways.[61–63]

Helical or spiral CT utilizes a “slip-ring” technique and high-energy x-ray tubes that allow the tube and detector to continuously circle the patient, taking pictures as the patient is transported through the scanner. It takes approximately 1 second for the scanner to complete a single rotation so that 20-to 30-cm organs can be scanned in under 30 seconds, much more quickly than conventional CT methods.[64] This eliminates the motion and artifacts secondary to inconsistent lung inflation from one slice to the next, a current problem with conventional CT scanners.[65]

Spiral CT angiography enables scanning to occur simultaneously with maximum contrast medium opacification, which obviates the need for selective catheterization. This is especially beneficial in animals since catheterization requires general anesthesia, a potentially risky procedures in dyspneic animals with suspected PTE. Spiral CT angiography has been studied in humans to discover filling defects within the pulmonary arteries secondary to emboli, even in the face of underlying pulmonary disease (Figure 212-4).[66–70] Acute and chronic emboli may be differentiated by their appearance.[71] The clinical usefulness of CT angiography in small animals remains to be determined but may be preferable to nuclear scintigraphy due to its superior diagnostic accuracy and speed.[67,68] The procedure has been used experimentally to effectively diagnose pulmonary thromboembolism in dogs and clinically in dogs with metastatic pulmonary lesions.[72,73] The detection of pulmonary metastases has shown limited success.[73]

Figure 212-4 Spiral CT angiography in a dog with pulmonary thromboemboli. The arrows point to the filling defects within the pulmonary artery. (Courtesy Tobias Schwarz and Steve Cole.)



MRI is based on the principles of nuclear magnetic resonance, a spectroscopic technique that reveals chemical and physical characteristics of the examined tissues using the absorption and emission of energy in the radio frequency range of the electromagnetic spectrum. Conventional MRI is based on the spin magnetism of the hydrogen nucleus and the fact that water is abundant in biologic tissue. However, the air spaces in the lungs are challenging to image since they are porous, which causes large internal magnetic field gradients, and contain primarily air rather than water (which contains the hydrogen proton). The use of hyperpolarized (HP) noble gas (specifically ^{3}He and ^{129}Xe) has emerged over the past decade to circumvent this problem. The polarized or inert gas is inhaled by the patient and subsequently detected with the use of MRI in the airways of the lungs and dissolved in the proximal blood.[74,75] In addition, the use of novel paramagnetic aerosol ventilation and perfusion MRI imaging using gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) has been used experimentally to diagnose airway obstruction and PTE in dogs.[76] More recently, noncontrast, electrocardiography (ECG)-gated fast-spin-echo (FSE) MRI has shown promise experimentally as a means of rapidly assessing dynamically altered regional lung perfusion or airway obstruction in dogs.[77] The MRI technique has also expanded to include three-dimensional reconstruction abilities, so the user can view surface details and internal structures and dissect each layer of tissue in a mock, on-screen approach.
Two-dimensional and three-dimensional techniques have been developed to perform angiographic studies without the need for contrast agents, based on the knowledge that the image intensity of flowing blood is proportional to the velocity of the flow. Although the use HP MRI, vascular MRI (VMRI) or MR angiography (MRA) is limited in veterinary medicine, future studies may prove worthwhile.

212.7 SCOPING PROCEDURES

Laryngoscopy allows visualization of the short cartilaginous lumen between the lower portion of the pharynx and the trachea. It is indicated in patients with suspected upper airway obstruction, palpable or radiographically visible mass lesions in the area of the larynx, or unexplained changes in vocalization. Clinical signs that are commonly related to laryngeal disease include coughing, choking while eating, cyanosis or syncope with exertion, inspiratory dyspnea with stertor or stridor, and changes in vocalization or sound production (meow, purr, or bark). Laryngoscopy is useful in the diagnosis of an elongated soft palate, laryngeal paralysis, laryngeal edema, acute laryngitis, laryngeal collapse, chronic granulomatous or proliferative laryngitis, traumatic lesions, everted laryngeal saccules, laryngeal or pharyngeal foreign bodies, polyps or neoplasms of the larynx, and glosso-epiglottic mucosal displacement.[78,79] In animals with severe clinical signs, stabilization with a tracheostomy or other bypassing maneuver might be necessary prior to examination.[80] The procedure can be performed with use of a standard intubating laryngoscope and mouth speculum to hold the mouth open, although a rigid or flexible bronchoscope may be required if areas distal to the vocal folds or infraglottic region require examination. The tongue is depressed to allow adequate examination of the pharynx, soft palate, lingual and glottal surfaces of the epiglottis, arytenoid cartilages, aryepiglottic folds, and vocal folds. Abnormal shape, color, and/or motility should be noted. The soft palate should be examined and palpated and the nasopharynx is examined by retracting the soft palate rostrally with a spay hook and visualizing the area with a heated dental mirror. Laryngoscopy should be performed with neuroleptanalgesia, if possible, rather than general anesthesia to prevent relaxation of the laryngeal muscles and distortion of the larynx. Propofol or thiobarbiturates are often recommended for examination of laryngeal function. The routine administration of doxapram prior to evaluation has been studied and recommended to increase intrinsic laryngeal function and aid in the diagnosis of laryngeal disease in dogs.[81] The arytenoid cartilage and vocal folds should abduct symmetrically during inspiration and relax during exhalation. The correlation of movement of these structures during the respiratory cycle should be examined.[78]

The pharynx is the crossroads of the respiratory and digestive tracts and consists of the nasopharynx, oropharynx, and laryngopharynx. If a flexible endoscope is used, retroflex nasopharyngoscopy will enable superior visualization, with or without biopsy sampling of the nasopharynx. Respiratory signs that might warrant pharyngoscopy include dyspnea, coughing after swallowing, oronasal reflux of liquid or food, open-mouth breathing, or stertorous breathing. Dysphagia, retching, gagging, and inappetance may also be present in animals with pharyngeal disorders. A standard intubating laryngoscope allows adequate visualization of the pharynx, although an endoscope may be used if further scoping is to follow. Prior to anesthesia in animals with the above clinical signs, cervical and thoracic radiographs, a thorough neurologic examination, and/or a esophagram with fluoroscopy may be indicated. Propofol or thiobarbiturates should be used and examination of the pharynx is performed prior to intubation. The soft palate, tonsils and tonsillar crypts, palatopharyngeal arches, and lateral pharyngeal wall should be carefully examined.[78]

Rhinoscopy is most commonly used in animals with chronic nasal disease, although more emergent cases may benefit as well (nasal foreign body retrieval, nasal parasite detection, and evaluation of epistaxis in animals with normal coagulation parameters).[78] Rhinoscopy has proven to be a useful tool in the animal with nasal disease, having a diagnostic success rate of 83% when performed by an experienced endoscopist and used in conjunction with rhinoscopy-assisted biopsy.[82] Rhinoscopy greatly decreases the morbidity and mortality associated with surgical rhinotomy when used to visualize the nasal passages and obtain biopsy samples. A surgical plane of anesthesia is required for rhinoscopy since the nasal mucosa is extremely sensitive (prior administration of topical anesthetic may be beneficial as well). An otoscopic speculum may be used to visualize the proximal 2 cm

of the nasal passages in most animals. Since a majority of neoplastic and mycotic diseases are in the caudal half of the nasal cavity, this method has limited diagnostic usefulness. In order to perform rhinoscopy, a rigid arthroscope, flexible or rigid cystourethroscope, or flexible pediatric bronchoscope is used. Width, length, and flushing/biopsy port availability makes the various scopes more or less desirable for specific situations.

Bronchoscopy may be useful in animals with suspected lower airway disease. Clinical signs that may indicate the need for a bronchoscopic examination include chronic coughing, hemoptysis, unexplained pulmonary infiltrates on thoracic radiographs, and the suspicion of an airway mass or foreign body. Bronchoscopy allows visual inspection of the airways and the collection of samples from the respiratory tract. Bronchoscopy may be used therapeutically for the removal of foreign bodies, resolution of mucus plugs, and removal of copious secretions or blood.[83,84] Diagnostically, bronchoscopy allows the clinician to visualize, lavage, brush, and/or biopsy the airways. In animals with intraluminal tracheal tumors, bronchoscopically guided biopsies may be obtained.[85] Bronchoscopy is valuable in the diagnosis and staging of tracheal collapse in dogs (Figure 212-5).[86,87] Bronchoscopy must be performed under general anesthesia to prevent coughing and laryngospasm. Intubation may not be possible if the endotracheal tube size is equal to that of the bronchoscope. If the animal must be extubated for a bronchoscopic examination, oxygen should be supplied via a catheter placed in the trachea beside the bronchoscope, through the biopsy channel of the bronchoscope, or by jet ventilation through a catheter. A T-shaped adaptor can be used in larger animals so the scope can be passed through the endotracheal tube while administering inhalant anesthesia.[83,84]

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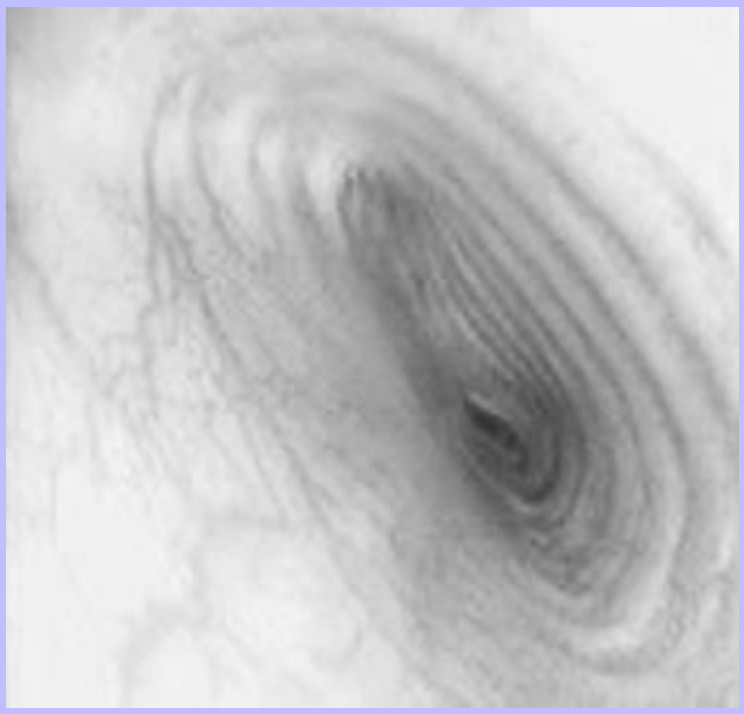
Figure 212-5 Bronchoscopic visualization of tracheal collapse in a dog. (Courtesy Candace Carter.)



212.8 RESPIRATORY SAMPLING TECHNIQUES

It is often necessary to obtain fluid, cells, and/or tissue from the respiratory tract for analysis. There are a variety of techniques that will be discussed in order to obtain specimens from the upper and lower respiratory tract.

Cytologic sampling of the upper respiratory tract can be challenging. Since there is a wide range of normal bacteria in the nasal cavity in small animals,[88] bacterial cultures of nasal swabs are not routinely performed. If a significant nonresponsive bacterial infection is suspected, a surgically obtained sample from the caudal nasal cavity may prove most useful for culture and sensitivity analysis, since cultures from this area are sterile approximately 50% of the time in dogs.[89] Most nasal disease results in inflammation of the mucosal epithelium and secondary bacterial infections, which tends to obscure the underlying disease. In addition, the disease process may be focal or multifocal, rather than diffuse. Nonsurgical techniques for the collection of diagnostic nasal samples include superficial and deep nasal swabs, nasal flushing, traumatic nasal flushing, pinch biopsy, and core biopsy. *Cryptococcus* and *Aspergillus* spp. infection can be diagnosed on examination of a superficial nasal swab; however, these agents may be encountered occasionally as normal flora or colonizers of abnormal sites. Confirmation of the disease typically requires further testing. Serologic testing, tissue biopsy, or fungal isolation should be considered in cats with a chronic nasal discharge.[90,91] Neutrophils commonly predominate in diseases such as trauma, neoplasia, infection, and foreign bodies,[92] whereas eosinophils may predominate in allergic or parasitic diseases.[93]

Biopsy collection techniques should be performed under general anesthesia. The patient should be intubated with a cuffed endotracheal tube and the caudal pharynx packed with gauze to prevent aspiration of blood or discharge. Potential complications include hemorrhage and inadvertent puncture of the cribiform plate.

Transtracheal aspiration may be indicated in dogs with clinical or radiographic evidence of airway disease. It is contraindicated in animals with severe dyspnea or coagulopathies. The procedure is often performed on awake or lightly sedated animals in sternal recumbency or a sitting position with the neck extended. The area over the cricothyroid membrane is clipped and sterilely prepared. A local anesthetic is administered subcutaneously and a relief incision is made in the skin over the cricothyroid membrane. A shielded catheter-through-a-needle or catheter-through-a-catheter (18-to 20-gauge, 8-to 12-inch Intracath with wire stylet jugular catheter by Becton Dickinson, Sandy, UT, works well) system is used to puncture the cricothyroid membrane and the catheter is advanced into the distal trachea.[94] The needle is removed from the airway and covered. A syringe containing 1 to 10 mL of preservative-free 0.9% saline is attached to the end of the catheter. The saline is injected into the trachea and negative pressure is applied to the plunger of the syringe as the animal is gently coupaged. If possible, the catheter is moved up and down the trachea during the syringe aspiration. Fluid injection and aspiration may need to be repeated two to three times. Fluid retrieved is saved for cytologic analysis and microbiologic testing. Potential complications include catheter related trauma to the lower airways, which results in hemoptysis, coughing, and respiratory impairment or needle-related trauma to the laryngeal region that might cause bleeding, subcutaneous emphysema, pneumomediastinum, pneumothorax, or pneumopharynx and airway obstruction.[94] Airway samples from cats or very small dogs should be collected via an endotracheal tube using a long catheter inserted through the tube to infuse and aspirate fluid.[95]

Bronchoalveolar lavage (BAL) may be performed with or without bronchoscopic guidance. BAL cytology has been described in normal cats and dogs.[94,96–101] It is indicated in dogs and cats with alveolar or interstitial lung disease to help identify neoplastic, infectious, or inflammatory diseases.[102] Microbiologic, biochemical, and

immunologic testing of the lavage fluid may be performed. Potential side effects are primarily related to general anesthesia, although transient hypoxemia or exacerbation of respiratory insufficiency may develop during the BAL. In order to obtain a diagnostic sample, the bronchoscope is cleaned and the biopsy port flushed with sterile saline before advancing it into the diseased airway. The scope is wedged into the smallest bronchus possible and 10 to 25 mL of warmed (37° C) nonbacteriostatic saline is instilled (alternatively, polyethylene tubing can be passed through the biopsy channel and wedged into a smaller airway). The fluid is removed by suction into a mucous suction trap or by hand using a 35 mL syringe. Between 40% and 60% of the fluid instilled is typically retrieved, depending on the wedging of the bronchoscope and patency of the airway.

At least two distant segments should be lavaged to increase the likelihood of disease identification.[102] A modified stomach technique has also been described for BAL in dogs.[103] Analysis should include a differential cell count on a cytocentrifuged sample and a culture and sensitivity if indicated. Normal cell counts in the dog and cat are approximately 200 to 400 cells per milliliter, with 65% macrophages in the cat and 83% macrophages in the dog. Neutrophils typically make up 5% of the cells in dogs and cats, lymphocytes 4% to 6%, mast cells 1% to 2%, and eosinophils up to 25% in the cat and 4% in the dog.

Bronchial brushing may be performed through the bronchoscope to obtain samples of focal lesions within the airway. This procedure should be performed after the BAL to prevent blood contamination. A sterile cytology brush with a protective polyethylene tubing is inserted through the instrument channel, placed against the bronchial wall, advanced out of the sheath, and rotated along the lesion site. A smear is made onto a glass slide or the brush is placed in sterile saline solution and swirled to release cells for cytologic analysis and culture/sensitivity testing.[104] Mild bleeding at the site is the most common complication.

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Healthy dogs and cats have a certain percentage of bacteria (*Pasteurella* spp., *Mycoplasma* spp., *Streptococcus* spp., *Staphylococcus* spp., *Acinetobacter* spp., Moraxella spp., *Enterobacter* spp., *Pseudomonas* spp., *Escherichia* coli, *Klebsiella* spp., and *Bordetella bronchiseptica*) isolated from samples taken with a sterile culture swab at the level of the lower trachea or carina.[98,105,106] Therefore the culture results must be interpreted in conjunction with cytologic findings. Intracellular bacteria and suppurative inflammation are supportive of a true bacterial infection.

Biopsies may be obtained using bronchoscopic guidance for histopathologic evaluation of focal abnormalities or for electron microscopic (EM) evaluation in animals with suspected ciliary dyskinesia. Biopsy samples are acquired using the biopsy port of the bronchoscope and samples should be fixed in formalin for histopathology or glutaraldehyde for EM. The animal should be monitored for hemoptysis from biopsy-site hemorrhage following the procedure.[94,107]

Transthoracic fine-needle aspiration (FNA) or biopsy might be indicated in patients with a single or multifocal pulmonary mass lesion greater than 1 cm and easily accessible or animals with diffuse air space or interstitial disease.[108,109] Fluoroscopic or ultrasonographic guidance is useful.[110,111] Contraindications include pulmonary cysts or bullae, unco-operative patients, refractory coagulopathies, or pulmonary hypertension. Animals with respiratory distress, preexisting pneumothorax, or behavior problems are not good candidates. Animals with clinical evidence of an infectious process such as a fever, inflammatory leukogram, and lethargy may be better candidates for endotracheal, transtracheal, or bronchoalveolar lavage.

Potential complications include pneumothorax, empyema, bleeding, implantation of neoplastic cells along the needle or biopsy tract, or death. One study revealed a 12% death rate and 5% incidence of pneumothorax following transthoracic FNA procedures.[112]

212.9 THORACOTOMY AND BIOPSY

An open-chest lung biopsy may be necessary in some cases where other less invasive techniques are nondiagnostic or histopathology is required to confirm a diagnosis. Contraindications include coagulopathy or an unacceptable anesthetic candidate. It requires greater expense, invasiveness, and risk, however it does allow the opportunity to visualize the lung and obtain an adequate sample size for a diagnosis. A standard thoracotomy is typically performed, although a “keyhole” technique is often effective for obtaining a histologic diagnosis of interstitial lung disease in dogs and cats.[113] The tissue sample is cultured, an impression smear analyzed, and the remainder placed in formalin for histopathologic evaluation. Potential complications include hemorrhage, pneumothorax, or secondary infections.

212.10 PULSE OXIMETRY AND ARTERIAL BLOOD GAS ANALYSIS

Pulse oximeters are commonly used to continuously and noninvasively measure the oxygen saturation of hemoglobin. Pulse oximetry measurements can be used to determine the need for oxygen administration and to monitor patients that are receiving oxygen supplementation. A hemoglobin saturation of 95% to 100% is normal in dogs and cats. There are, however, many limitations, especially in critically ill animals, which makes this technology less reliable than direct arterial blood gas analysis.

Arterial blood gases (ABGs) are extremely useful in the assessment of an animal's oxygenation, ventilation, and acid-base balance. ABGs are commonly used to quantitate the severity of respiratory impairment and monitor response to therapy. With the advent of fairly inexpensive, handheld blood gas analyzers, ABGs are routinely used in many private practices. Normal arterial blood gases in the dog and cat are pH=7.36–7.44, PaO_2=90–100 mmHg, $PaCO_2$=36–40 mmHg, HCO_3=20–24 mEq/L, and BE +/– 4 mEq/L.[114]

Arterial blood gas sampling is the most accurate method of evaluating the partial pressure of oxygen in the arterial blood. In dogs, arterial puncture is commonly performed using the dorsal metatarsal or femoral arteries, although the radial artery or digital palmar arteries may also be used. In cats, the femoral artery is typically the only easily accessible artery that is large enough to readily obtain an adequate sample. Preheparinized syringes will help prevent the sample from clotting prior to analysis, and the sample should be capped with material that is not permeable to gas to prevent air contamination and equilibration. Following arterial puncture, direct pressure should be applied to the site for 3 to 5 minutes to prevent bleeding. Hypoxemia is defined as a PaO_2 less than 80 mm Hg and possible causes include a right-to-left shunt (patent ductus arteriosus, ventricular septal defects, intrapulmonary shunts due to atelectasis or consolidation), ventilation perfusion mismatch (due to various types of pulmonary disease), diffusion impairment (relatively uncommon), hypoventilation (secondary to anesthesia, neuromuscular disease, pleural space or chest wall abnormalities), or a decrease in the fraction of inspired oxygen (oxygen tank empty and hooked up to patient, high elevations).[115] The animal's ability to oxygenate is assessed by examining the PaO_2 and determining the difference between the partial pressure of oxygen in the alveolar and the arterial blood, often referred to as the “A-a gradient.” This equation is based on the knowledge that there is almost complete equilibration of gases between the alveolar gas and the pulmonary capillary when alveolar ventilation and pulmonary perfusion (V/Q) are matched. The partial pressure of oxygen in the alveolus (PaO_2) is calculated as follows:

$$PaO_2 = [(PB - PH_2O)FiO_2] - PaCO_2/RQ)$$

where PB = barometric pressure in mm Hg, PH_2O = water vapor pressure in mm Hg, FiO_2 = fraction of inspired oxygen, RQ = respiratory quotient (normally 0.8), and $PaCO_2$ = partial pressure of carbon dioxide in the alveolus in mm Hg.

The normal alveolar to arterial difference is less than 15 mm Hg when the patient is breathing room air. The A-a gradient is increased in animals with a right-to-left shunt, low mixed venous oxygen saturation, ventilation/perfusion mismatching, and diffusion impairment. Another method of assessing the severity of oxygenation impairment is to calculate the PaO_2: FiO_2 ratio. Healthy people and animals have a ratio of 400 to 500, but a value less than 300 is suggestive of acute lung injury and less than 200 indicates acute respiratory distress syndrome in people.[114–116]

Ventilation refers to the movement of gas into and of the alveolus and is measured by the animal's ability to maintain normal arterial CO_2 levels. The carbon dioxide tension in arterial blood represents the balance between the production of CO_2 in the tissues and CO_2 excretion in the alveolus. Carbon dioxide excretion is dependent upon the amount of CO_2 delivered to the alveolus, alveolar ventilation, and the amount of deadspace ventilation that does not contribute to gas exchange. If there is inadequate elimination of CO_2 in the lungs or excessive CO_2 production in body tissues (less common), carbonic acid and hydrogen ions accumulate, resulting in a respiratory acidosis. Potential causes of inadequate ventilation include diseases of the central respiratory center, airways, pulmonary parenchyma, pleural space, pulmonary vasculature, or chest wall. Respiratory fatigue, a primary metabolic alkalosis, or anesthetic drugs may also lead to hypoventilation. If the problem is maintained for 24 to 48 hours, the kidneys respond over hours to days by increasing the excretion of hydrogen ions and retaining bicarbonate.[114–116]

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If alveolar ventilation is increased, a respiratory alkalosis will develop. Potential causes include hypoxemia, primary metabolic acidosis, and central nervous system disease. Anxiety, pain, fear, and excitement may also lead to hyperventilation. If the problem is maintained, the kidneys will again compensate slowly by retaining hydrogen ions and excreting bicarbonate.[114–116]

In order to interpret a blood gas measurement, the pH should first be assessed. Determine whether the pH is normal or if there is a primary respiratory or metabolic cause for the disorder, if there is compensation for the primary disorder, or if there are two primary abnormalities present.

212.11 PULMONARY FUNCTION TESTING

Pulmonary function testing (PFT) is used to objectively assess functional respiratory deficits. It often serves as a valuable tool to provide information regarding the severity of pulmonary dysfunction as well as response to therapy. The information acquired quantifies the degree of dysfunction and is able to localize the site of respiratory dysfunction. There are, however, a few limitations to the use of pulmonary function testing in small animal medicine. Many animals require anesthesia in order to perform the testing, the equipment utilized is expensive and requires operational expertise, and there is a large amount of individual variation that makes isolated measurements in time less valuable in an individual animal.[117]

Since veterinary patients are not able to understand instructions to perform a maximal forced exhalation, it is not possible to perform the noninvasive, rapid spirometric tests that are commonly used in human medicine. Alternatively, the tidal breathing flow-volume loop (TBFVL), which was originally developed for human infants,

can be used in the unanesthetized and untrained veterinary patient to assess and quantify airflow, volume, or respiratory cycle changes.[118]

To measure TBFVL, a pneumotachograph and a differential pressure transducer are used in accordance with the size of the patient.[118–121] The Fleisch pneumotachograph is commonly used in small animals. This device measures the pressure gradient as air follows across a resistance device. The rate of airflow is proportional to the drop in pressure inside the instrument, and is plotted on the x-axis. An electronic integration of the instantaneous flow rate is used to determine flow, which is plotted on the Y-axis, generating a "flow-volume" or "F-V loop."[120] Cats or dogs are allowed to sit or stand during the testing procedure. A tight-fitting mask is placed over the muzzle, including the commisure of the lips. A 1-to 3-minute recording of the TBFVL waveforms is obtained once the animal is calm and free of extraneous movements. Computerized pulmonary mechanics analyzer systems are now available to create the F-V loops (Respiratory Loop Analysis Software, BUXCO Electronics, Sharon, CT) and provide fast, accurate data analysis.[118,122] Information acquired from the flow, volume, and time analysis may be combined to determine time ratios, inspiratory to expiratory flow ratios at indicated lung volumes, flow ratios at different lung volumes, or changes in volume during a selected period of time.[118,121] In order to improve the diagnostic sensitivity and reproducibility of the TBFVL test, application of positive pressure to the external chest wall, negative pressure to the airway, increased concentrations of the inspired CO_2 or doxapram hydrochloride have been used.[123–126] When CO_2 is used adjunctively, an increase in the inspired oxygen concentration may be helpful to prevent hypoxic pulmonary or vascular changes.

TBFVL from normal healthy cats and dogs with differing nasal anatomy have been described.[118,121,127] TBFVL have been used clinically in veterinary medicine to diagnose and/or evaluate treatment modalities in dogs with chronic obstructive lung disease, laryngeal paralysis, tracheal collapse, brachycephalic syndrome, and cats with chronic lower airway disease.[118,121,127–134] Loops are easily obtained in most non-sedated, naïve dogs and cats. It is contraindicated in animals with severe dyspnea since placement of the mask may exacerbate the animal's condition.

The measurement of upper airway pressures can be obtained with use of a transcutaneously placed catheter into the trachea, using the same technique as described for transtracheal aspiration above. Using a pressure transducer, the pressure changes in the upper airways are readily measured. A face mask technique can be used, as described for TBFVL measurements, to obtain the flow and volume measurements and the pressure transducers matched to a defined frequency.[135] The change in pressure is divided by the change in flow to calculate resistance in the upper airway, and this is easily performed using a mechanics analyzer and designated software analysis program. Normal values for upper airway resistance have been established in dolichocephalic and mesaticephalic dogs.[136] Measurements of upper airway resistance might be beneficial in diagnosing and quantifying airway obstruction and changes in response to therapy.

Pulmonary mechanics measurements typically require general anesthesia in small animals in order to pass an esophageal balloon for the measurement of transpulmonary pressure,[137] whereas flow and volume measurements are made via an endotracheal tube. Measurements have therefore been used primarily in the research setting and it is important to recognize the potential effects of the endotracheal tube and anesthetic agents used on measurements obtained.[138–146] Clinical evaluation may be performed using a nasoesophageal canula and a tight-fitting face mask.[147–150] Dynamic pulmonary compliance is calculated as the change in lung volume divided by the change in transpulmonary pressure from the beginning to the end of inspiration. Static compliance

is similarly calculated by measuring changes in volume and pressure during an incremental inflation and deflation of the lungs.

Normal values for dynamic compliance (Cdyn) and pulmonary resistance (RL) have been measured in cats and dogs.[151–154] Due to differences in body conformation, weight, age, and sex, measurements in dogs have considerable variation between studies. In medium-sized dogs, Cdyn may correlate most accurately with trunk length rather than body weight or chest circumference.[154] Measurement of pulmonary mechanics such as tidal volumes, minute ventilation, peak inspiratory pressure, resistance, and compliance may be helpful in the mechanically ventilated patient to assist in identifying pulmonary parenchymal, pleural space or chest wall disorders, deciding when to wean the patient, monitoring changes over time and in response to therapy, identifying, and detecting bronchospasm or mucous plugs during ventilation.[155–159] Clinically, the CO_2SMO (Novametrix Medical Systems Inc., Wallingford, CT) is an extremely useful pulmonary function monitoring device for the ventilated patient. However, positive pressure ventilation may interfere with esophageal pressure measurements.[160] Additional techniques that might be used to assess pulmonary function in dogs or cats include a forced oscillation measurement, forced deflation techniques, whole body plethysmography or dual-chamber plethysmography, and static thoracic compliance using a pediatric spirometer and a water manometer.[157,161–164]

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212.12 ADDITIONAL DIAGNOSTICS

Nitric oxide (NO) has been shown to play a key role in the modulation of airway relaxation and responsiveness in cats.[165–168] Exhaled nitric oxide (ENO) levels might be a noninvasive means of detecting airway inflammation and its response to therapy. Preliminary data have shown that cats with a clinical diagnosis of asthma have increased ENO levels compared with control populations. (Matt Mellema, DVM, Harvard University, unpublished observations, personal communication.)

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213 CHAPTER • 213 Diseases of the Trachea

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213.1 ANATOMY AND PATHOPHYSIOLOGY

The normal trachea is a semi-rigid, flexible tubular passageway connecting the larynx to the bronchi. It is made up of 35 to 45 C-shaped cartilages, each alternating with an elastic annular ligament. The cartilage-free, dorsal portion of the trachea is composed of mucosa, connective tissue, and tracheal muscle (the dorsal tracheal membrane). The trachea bifurcates into the mainstem bronchi at the level of the fourth or fifth thoracic vertebrae.

The cranial and caudal thyroid arteries are the major blood supply to most of the trachea. The recurrent laryngeal and vagus nerves supply parasympathetic innervation to the tracheal mucosa and its smooth muscle, which stimulates muscular contraction and glandular secretion. The inhibitory sympathetic fibers arise from the middle cervical ganglion and sympathetic trunk.

The tracheal mucosal layer is composed of a pseudo-stratified, ciliated columnar epithelium with goblet cells; mucus-secreting tubular glands are found in the submucosa. The ciliated cells of the epithelium act as part of the mucociliary transport system to propel mucous and inspired debris toward the pharynx.

The trachea has a limited number of ways to respond to an insult. Changes seen during examination of the trachea are usually not pathognomonic for a given disease state. The immediate response of the tracheal mucosa to irritation of any cause is increased mucus secretion. With continued insult, epithelial cells desquamate and goblet cell hyperplasia occurs. Squamous metaplasia occurs with continued insults if there is insufficient time for healing between episodes. Superficial defects in the tracheal mucosa begin to heal as early as 2 hours after cessation of an injury. Large areas of damaged epithelium devoid of functional cilia can impair the mucociliary transport system and predispose to infection and delayed healing.

The primary pathophysiologic response to stenotic disease is increased airway resistance that cannot be overcome through mouth breathing and decreased pulmonary compliance. With impaired air flow, hypoventilation and respiratory acidosis occur. Chronic obstruction can result in secondary pulmonary hypertension and right heart failure (cor pulmonale).

213.2 HISTORY AND PHYSICAL EXAMINATION

The most commonly recognized clinical signs of tracheal disease are coughing, stertorous noisy inspiratory sounds, stridulous or wheezing expiratory sounds, pulmonary edema, and occasionally cyanosis. See Chapter 53 for the clinical differentiation of coughing and its most commonly encountered causes and Chapter 54 for dyspnea and tachypnea. A thorough physical examination should follow a record of the history in evaluating patients with suspected tracheal disease. The physical examination should cover all aspects of the animal with particular attention to the entire upper and lower respiratory tracts as well as the cardiovascular system.

The neck should be palpated for evidence of surrounding disease such as subcutaneous emphysema, lymphadenopathies, abscess, cyst, neoplasia, thyroid gland enlargement, or any other mass that may involve the trachea. In most animals, except for the heavy or obese, the trachea can be palpated from the larynx to the thoracic inlet. The trachea is relatively noncollapsible, and obvious borders or angles usually cannot be felt.

Often a cough can be elicited with light tracheal palpation at the thoracic inlet when laryngeal or tracheal irritation or inflammation is present.

Auscultation of the lung sounds as well as respiratory sounds directly over the trachea, larynx, and nose should be compared to help localize the site of the lesion. Sounds are usually most intense near their site of origin. Examination of the oral and pharyngeal cavities is best done with the aid of anesthesia (e.g., Propofol, Thiopental) or light sedation.

213.3 DIAGNOSTIC TESTS

213.3.1 Radiography

Two views of the trachea should be obtained for routine radiographic examination—lateral and ventrodorsal or dorsoventral. Radiographs to evaluate the cervical trachea should be obtained separately from those of the thoracic trachea. The lateral radiographic examination must be performed with careful positioning of the patient to avoid artifactual deviations of the trachea, especially in the caudal cervical and cranial mediastinal regions. Excessive flexion of the occipitoatlantal articulation may cause deviations of the trachea, which may artifactually suggest extra tracheal masses (Figure 213-1). Dorsal deviation of the intra-thoracic trachea can be due to ventroflexion of the neck. Other causes include cardiac enlargement, pleural effusions, and cranial mediastinal masses. Ventral deviation of the thoracic trachea can be seen with a dilated esophagus or with diseases of the dorsal cranial mediastinum. Ventrodorsal (VD) or dorsoventral (DV) views are used to evaluate the course of the trachea. VD oblique views are occasionally needed when the thoracic tracheal lumen is superimposed over the vertebral column and sternum to prevent sufficient radiographic detail. These views are usually not necessary since the intrathoracic trachea normally courses to the right of the vertebral column and reaches the midline only at the tracheal bifurcation (carina).

Figure 213-1 Kinking of the trachea may occur with excessive flexion of the neck in small animals and in those with tracheal malacia. These undesirable causes of narrowing of the trachea must be avoided while the dog is radiographed and, more importantly, while the dog recovers from an anesthetic.

Tracheal radiographs should be surveyed for luminal filling defects, continuity of the mucosal lining, diameter, and placement within the cervical and thoracic regions. Normal aging may result in dystrophic mineralization of tracheal rings. This is not pathologic. The normal tracheal diameter generally decreases slightly from larynx to thoracic inlet but then increases.[9] The normal diameter of the trachea at the third rib should be approximately three times the width of the third rib at the level of the trachea.[1] Another method of determining tracheal diameter uses the ratio of the inner diameter of the trachea at the thoracic inlet to the distance between the ventral edge of the first thoracic vertebra and dorsal edge of the manubrium. The normal ratio is 0.16 or greater.[1] The tracheal lumen is similar to the caudal laryngeal lumen. Measurement of the degree of tracheal luminal stenosis using radiography or tracheoscopy did not correlate with necropsy measurements in one study.[2] Computed tomographic studies in 18 breed dogs determined the correlation coefficient between inner diameters the cross-sectional lumen areas and body weight and found a high correlation between the inner transverse and vertical diameters and the cross-sectional area of the lumen except at the level of the intrathoracic trachea.[48]

Motion studies (fluoroscopy) of the diseased trachea are highly desirable for evaluation of pathodynamics. Image intensification equipment is necessary to safely obtain adequate radiographic detail. These studies are extremely valuable for the evaluation of the collapsed trachea and other coughing syndromes. Patients should be placed in lateral recumbency and the entire trachea visualized. A cough usually can be induced by digital pressure applied at the thoracic inlet. Videotape recordings add to the usefulness of dynamic studies. Playback observations in slow motion can result in the detection of functional features missed during the initial examination.

Fluoroscopic equipment may not be available to the general practitioner. Motion dynamics of the trachea can often be inferred from static images obtained at different phases of respiration. Lateral inspiratory and expiratory projections are used to evaluate changes in the tracheal lumen. A forced expiration can be obtained by inducing a cough with tracheal palpation. Mild physiologic changes in tracheal diameter during respiration are normal. The cervical trachea may narrow slightly with inspiration while the intrathoracic trachea and carina narrow slightly during expiration.

Contrast studies of the trachea and bronchi (bronchography) have been advocated in the past for further evaluation of the trachea and airways. This procedure has generally been eclipsed by bronchoscopy, a more effective and safer technique for evaluation of the lumen and lining of the major airways. Ultrasound examination of the trachea may demonstrate an alteration in the shape of the lumen on ventrodorsal projection.[49]

213.3.2 Tracheoscopy and Bronchoscopy

Endoscopic examination is a useful tool for evaluation of pathologic states of the trachea. It may be performed with a rigid or flexible scope to help localize the site and extent of a lesion. Endoscopy directly visualizes the tracheal mucosa and identifies inflammation, ulceration, and edema. It is used to visualize and to obtain biopsy specimens of tumors and masses; for brush cytology, fluid aspiration, and cultures; for removal of foreign bodies; for demonstration of collapsed, hypoplastic, stenotic, disrupted, or compressed areas; and for evaluation of disease progression or response to therapy.

Small animal respiratory endoscopy requires general anesthesia. The use of atropine sulfate generally is not recommended because of its detrimental effects of thickening and decreasing respiratory epithelial secretions.

There are several options for sedation for tracheoscopy. Short-acting barbiturates (Propofol) permit the rapid and gentle sedation of an animal for intubation and can be given on a continuous basis if the procedure is to be relatively short. Maintenance for a longer period of time is best handled using isoflurane gaseous anesthesia since the animal may quickly awaken after the procedure with few side effects and short duration of the sedation. On occasion, ketamine-diazepam–type sedation proves useful for longer procedures, but the problems associated with waking up are enhanced, especially in difficult-to-manage pets such as those with severe lung disease, obese animals, and brachycephalic breeds. Another option is Numorphan, although its respiratory depressive effects may necessitate manual (bagged) breathing for the patient (see Chapter 104).

213.3.3 Tracheobronchial Culture and Cytology

Examining cytologic specimens can often be an efficient and practical means of helping to support a diagnosis while others are eliminated. There are multiple ways to obtain diagnostically significant samples from the trachea for culture and cytology. In all cases, culture specimens should be obtained before cytology specimens. If tracheal endoscopy is being performed and the equipment has a biopsy port, specimens may be obtained through this instrument with sterile endoscopic brushes. A protected sterile culture swab or cytology brush can also be introduced directly through the mouth and larynx and into the trachea for specimen retrieval.

Bronchoalveolar lavage (BAL) is the preferred method of obtaining cytologic and culture samples from the lower respiratory tract and occasionally from the upper portions of the tract. The endoscope is cleaned externally and the channels flushed with sterile saline. It is then repositioned at the sampling site and gently wedged into position. Multiple aliquots of sterile saline are passed through the channel and immediately suctioned back into the syringe. Multiple samples may be obtained in this manner from one or more positions using BAL.

Another method[1] that works well in smaller animals is to place a sterile endotracheal tube, flush a small amount of sterile saline through the tube and into the trachea, hold the animal upside down, and collect draining fluid in a sterile vial as it runs out of the endotracheal tube. Although this method is not as precise as other methods, it is practical and easy to perform with equipment found in most small animal hospital settings. 1218 1219

An alternative technique that does not usually require general anesthesia is transtracheal aspiration. This usually requires either local anesthesia or mild sedation while a long sterile needle is used to puncture the mid-cervical trachea or cricothyroid membrane. A catheter designed to pass through the needle is threaded into the tracheal lumen and is used for aspiration.

Numerous bacterial culture studies have been made from transtracheal and bronchoscopic aspirations. These samples have principally but not exclusively been taken from the lower tracheal and respiratory tract. In a study evaluating 264 cases of lower respiratory tract specimens, 203 bacterial species were isolated in 116 of 264 dogs. Most (57%) contained a single species of bacteria. Those cultured most commonly were *E. coli* (45.7%), *Pasteurella* spp. (22.4%), obligate anaerobes (21.6%), beta-hemolytic streptococci (12.1%), *Bordetella bronchiseptica* (12.1%), non-hemolytic *Streptococcus* and *Enterococcus* sp. (12.1%), coagulase-positive *Staphylococcus* spp. (9.5%) and *Pseudomonas* spp. (7.8%).

Of these cultures, the most active antimicrobial agents for aerobic micro-organisms, which inhibit more than 90% of the isolates were amikacin, ceftizoxime sodium, enrofloxacin, and gentamicin sulfate.[3] In an earlier study, *Mycoplasma* spp. recovery in normal dogs and those with pulmonary disease was about 25%. Only young dogs under 1 year of age and those with *Bordetella* spp. or streptococci isolations had a significant association between their disease and *Mycoplasma* spp. recovery during tracheobronchial lavage.[4] Following this study, the role of *Mycoplasma* spp. in lower (trachea and lung) respiratory tract disease has been further

elucidated. Half of 224 samples obtained from dogs and cats with lower airway disease were negative for *Mycoplasma* spp. but 49.5% were positive, either alone (15%) or in combination (85%) with aerobic bacteria. *Mycoplasma* spp. are present frequently in patients with lower respiratory tract disease. It remains to be determined whether *Mycoplasma* spp. play a primary or secondary role.[50] *Bordetella bronchiseptica* infection was reported in a series of cats mostly under 8 weeks old with dry nonproductive coughing. Transtracheal washings were positively cultured for *B. bronchiseptica*.[5]

Bronchoalveolar lavage cytology from 33 normal dogs identified alveolar macrophages (79.4%), lymphocytes (13.5%), eosinophils (3.6%), mast cells (2.1%), epithelial cells (0.8%), and neutrophils (0.6%).[6] These numbers vary from earlier reports of limited numbers of macrophages and lymphocytes.[7] Deviations from these numbers, although not usually diagnostic, provide valuable information on the type of response and the type of disease process present. Neutrophilic inflammation most often results from bacterial infection, which can be secondary to a number of other problems including, but not limited to, collapsed trachea, chronic bronchitis, neoplasia, allergic disease, and viral, mycotic, or parasitic infections. Such cytologic findings could include an increased number of neutrophils, degenerative changes within the neutrophils, and phagocytized bacteria.[8]

Eosinophilic inflammation is usually considered significant although it has been noted in clinically normal dogs and cats.[8,9] Eosinophils and mast cells imply an allergic or parasitic tracheobronchitis.[10] A concurrent, nonseptic neutrophilic or chronic inflammatory response is frequently present. Major differential diagnoses include allergic bronchitis, pulmonary parasites, heartworm disease, and hypersensitivity responses secondary to bacterial, protozoal, fungal, or neoplastic diseases. Chronic inflammation is indicated by a mixed inflammatory cell population with a predominant number of activated macrophages.[8] This type of response is nonspecific and has a long list of differentials.

All slides should be carefully examined for organisms or atypical cells. Tight coils of inspissated mucous can be washed out in association with small airway disease.[10] Hemorrhagic inflammation consists of chronic or chronic-active inflammatory cells with erythrophagocytosis and increased numbers of red blood cells.[8] Many diseases of the respiratory tract can cause hemorrhage including systemic clotting disorders. Large numbers of reactive lymphocytes and plasma cells are nonspecific indicators of immune stimulation.[8] Primary ciliary dyskinesis may be suggested when associated with chronic bronchopneumonia, ultrastructural abnormalities, and a lack of sperm motility on testicular aspiration.[11] Neoplastic cells may be identified. Differentiation of criteria of malignancy in epithelial cells is often difficult, especially when accompanied by marked inflammation. Histologic examination may be necessary. Organisms may be found on cytology to make a definitive diagnosis but their absence does not eliminate infectious disease.

213.3.4 Clinicopathologic Studies

Tracheal diseases only rarely have definitive, demonstrable clinicopathologic findings. Hematologic and biochemical analysis of the blood, serology, and a urinalysis should be used as a reflection of the patient's overall health and an indication of systemic or allergic disease. Blood gas analysis is helpful to demonstrate severity of the disease and acid-base status.

213.4 SPECIFIC TRACHEAL DISEASES

213.4.1 Noninfectious Tracheitis

213.4.1.1 Etiology

Tracheitis refers to an inflammation of the epithelial lining of the trachea. This inflammatory response may be infectious or noninfectious; primary or secondary. The noninfectious causes of chronic tracheitis are probably more common and will be discussed as a group. Noninfectious tracheitis is usually a secondary problem to prolonged barking, collapsing trachea, chronic cardiac disease, and disease of the oropharynx. Tracheitis is unusual in cats and when it does occur in the cat it is associated with infectious feline respiratory disease. Allergic lower airway disease may also promote a secondary tracheitis.

213.4.1.2 Clinical Signs and Diagnosis

Since tracheitis may be primary (inhalation of smoke or other noxious gases) or secondary, the history varies with the etiology. Most patients with tracheitis are asymptomatic except for a cough, which is characterized as resonant, harsh, paroxysmal, and often terminated by nonproductive or slightly productive gagging. The physical examination is often normal, and no fever is present. Firm palpation of the trachea near the thoracic inlet elicits the typical tracheal cough. Examination of the oral cavity and oropharynx is unlikely to reveal abnormalities unless the tracheitis is secondary to an oropharyngeal disease process. The tonsils may be enlarged and extend further out of the crypts than normal. Auscultation of the heart is usually normal. If a cardiac murmur or arrhythmia exists, cardiac disease must be eliminated as the primary cause for the coughing (see Chapter 53) or as the cause of chronic tracheitis. A prominent snapping of the second heart sound may be present over the pulmonic valve region. Findings on auscultation of the lungs are normal unless tracheitis is secondary to pulmonary disease (see Chapters 212 and 215), in which case coarse bronchial lung sounds are expected.

Tracheitis as a primary disease often has no specific radiographic features. In acute tracheitis edema of the mucosal lining may result in a reduction of the lumen diameter. Care must be taken not to confuse this for a fixed, hypoplastic trachea. The radiographic features that occur when tracheitis is secondary to other diseases are included in the discussions of those conditions. Hematology and blood chemistries are usually within reference ranges unless a systemic disease state concurrently exists.

Table • 213-1 Drugs Used for Tracheal Diseases

GENERIC NAME (TRADE)	MECHANISM OF ACTION	DOSAGE
Theophylline/aminophylline (IV)	Bronchodilator; specific mechanism unknown	5 mg/lb q6-12h PO/IV
Terbutaline (Brethine, Bricanyl)	Beta-2 adrenergic receptor	0.625–1.25 mg BID PO-Sml 1.25–2.5 mg BID PO-Med 2.5–5.0 mg BID PO-Lg 0.01 mg/kg IV, IM, SQ
Prednisone and trimprazine (Temaril-P)	Antihistamine/cortisone combination	1 tab/20 lb q12h PO
Dextromethorphan (Delsym, Silphen DM)	Antitussive-expectorant	0.5–1 mg/lb q8-12h PO
Dextromethorphan/guaifenesin (Robitussin DM)	Antitussive-expectorant	Dosage similar to dextromethorphan PO
Codeine	Narcotic antitussive	0.5–1 mg/lb q6-12h PO
Hydrocodone with homatropine (Hycodan, Tussigon)	Narcotic like antitussive	1/4-1 tab (or tsp) q6-24h PO Approx 2 mg/kg
Tussionex syrup	Antitussive narcotic syrup-longer acting	Same dosage as hydrocodone
Butorphanol (Torbutrol)	Opioid agonist/antagonist	0.25 mg/lb q6-12h PO

213.4.1.3 Therapy

Therapy should be directed at the primary underlying disease process, and these treatments are discussed in their appropriate sections. The cough associated with secondary tracheitis may act as a continued source of irritation, which perpetuates the tracheitis, and a vicious cycle ensues. Treatment of the underlying disease process may not always be adequate to relieve the cough because of this cycle of "cough-induced tracheitis," which perpetuates the cough as well as the tracheitis. Therefore treatment aimed specifically at the tracheitis is often beneficial, if not mandatory.

Tracheal coughing is often treated with antitussive and bronchodilating preparations (Table 213-1). Many of these preparations also contain expectorants. Occasionally, short-term therapy with corticosteroids is warranted. It is important to emphasize that this provides symptomatic relief only and it could exacerbate the primary condition. With chronic coughing, nebulization four to six times daily may help to soften mucoid material collecting in the trachea. When nebulization is not possible, the dog or cat can be placed in a bathroom filled with steam from a hot shower. This should last 15 to 20 minutes, three times daily. Following either method, gentle couppage of the chest wall helps to loosen secretions and stimulate expectoration.

213.4.2 Infectious Tracheobronchitis

213.4.2.1 Etiology

Infectious canine tracheobronchitis, also known as *canine respiratory disease complex* and *kennel cough*, is not a single disease, but rather a clinical disease syndrome. Involved in this multi-etiology syndrome include infectious agents such as viruses, bacteria, mycoplasma, fungi, and parasites. A combination of *Bordetella bronchiseptica* with canine parainfluenza or canine adenovirus (CAV; CAD-2) is the most frequently encountered cause. Other incriminated agents are, canine herpes virus (CHV), reovirus, *Mycoplasma* spp.,[50] and occasionally canine distemper virus.[12] Most cases of infectious canine

tracheobronchitis involve a primary viral infection. *B. bronchiseptica* infection in cats is unusual but has been described.[5,13] The role of *B. bronchiseptica* has recently been reviewed.[47]

213.4.2.2 Clinical Signs and Diagnosis

Infectious canine tracheobronchitis is highly contagious and most commonly occurs where groups of dogs of different ages and susceptibility are congregated. There is almost always a history of exposure to other animals, as in a kennel, hospital, or dog show. Aerosol or direct contact is considered the main source of exposure. Clinical signs usually develop 3 to 5 days after initial exposure. The clinical signs are generally mild and self-limiting. A dry, hacking, paroxysmal cough is the most consistent sign. A purulent nasal discharge may be noted. Generally, the animal is healthy in other respects.

Diagnosis is made most often on the basis of circumstantial evidence. History of exposure with a dry hacking cough is usually sufficient. Thoracic auscultation, thoracic radiographs, and hemograms are usually unremarkable. Tracheal cytology may reveal increased numbers of neutrophils and bacteria. Bacterial or *Mycoplasma* spp. isolation, as well as virus isolation and serologic evaluation, can be performed but are usually unnecessary. *B. bronchiseptica* commonly associated with this condition may require 3 months for full clearance to occur.

213.4.2.3 Therapy

Uncomplicated cases of tracheobronchitis probably do not require antimicrobials. Even though antibiotics have not been shown to reach significant concentrations in tracheobronchial secretions or to shorten the course of infection, prophylactic therapy has been recommended by some.[14] Antibiotic treatment is indicated if there is deeper respiratory involvement or if the animal is showing signs of systemic illness. Drugs chosen should be based on results of bacterial culture and sensitivity testing. In the absence of culture results, choices of oral antibiotics include chloramphenicol, fluoroquinolones, or cephalosporins. More potent injectable agents such as amikacin, gentamicin, and ceftizoxime should be chosen only after culture results indicate their effectiveness. Doxycycline (5 to 10 mg/kg once daily) is appropriate if mycoplasma are suspected.

Glucocorticoids, administered at anti-inflammatory doses can be effective in suppressing the cough of uncomplicated infectious tracheobronchitis. However, glucocorticoids do not appear to shorten the clinical course of the disease.[14] They may worsen the illness in immunocompromised individuals. If glucocorticoids are used, a bactericidal antibiotic should be chosen over a bacteriostatic one for concurrent use.

Antitussives, either alone or in combination with bronchodilators are recommended. Narcotic cough suppressants seem to be the most effective. These agents can compromise ventilation and should not be used in the presence of concurrent bacterial pneumonia. Methylxanthine bronchodilators may also be of benefit in suppressing the cough through their ability to prevent bronchospasm. Patients with tracheobronchial disease also benefit from nebulization, which can help to loosen excessive accumulations of bronchial and tracheal secretions. Nebulization with sterile saline is as acceptable as mucolytic agents.

213.5 TRACHEAL PARASITES

213.5.1 Lungworm (Oslerus osleri; Filaroides osleri)

213.5.1.1 Etiology

Filaroides osleri renamed *Oslerus osleri* (*O. osleri*) is a worldwide parasitic disease in dogs under 2 years of age. It can be seen in individual situations but is more often a kennel-related problem (especially in greyhounds).[1] Although most often described in young dogs, it does persist in older animals, often without significant pathophysiologic effects.

Although described as a lungworm, this parasite most commonly affects the region proximal to the tracheal carina. It may affect the lumen and lining of the larger bronchi, but only rarely does it extend deeper into the pulmonary system.

Reports of direct transmission through larvae in the stool and saliva suggest that this metastrongyle may not require an intermediate host to complete its life cycle. First-stage larvae are directly transmitted through salivary and airway secretions. These molt in the small bowel followed by migration of the larvae to the lungs and bronchi. Experimental and natural direct transmission have been demonstrated.[1] Transmission to pups has also been reported to occur through parental food regurgitation and licking and cleaning of pups by a nursing bitch.[15]

213.5.1.2 Clinical Signs and Diagnosis

Dogs usually present with chronic, mild to severe inspiratory wheezing sounds, dyspnea, coughing, and/or debilitation. Panting usually is not prominent except in advanced cases. The severity of the clinical signs may be overplayed in the literature. Most dogs experience definite but mild, often nonprogressive respiratory signs. Exercise intolerance does occasionally occur and coughing is typically characterized as a harsh tracheobronchial sound associated with attempts at terminal retching. A small amount of white to blood-tinged mucus is common, but at times larger amounts of exudate are brought up.

Figure 213-2 Lateral thoracic radiograph of an immature male terrier showing multiple nodules in the lumen of the caudal trachea due to *Filaroides osleri*. Note the hyperexpansion of the thoracic cavity, which is probably due to increased resistance within the trachea during expiration.

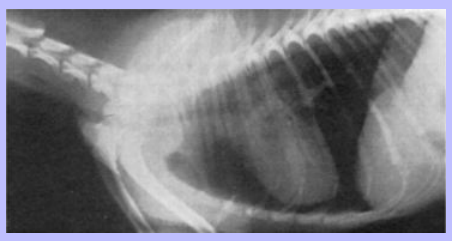
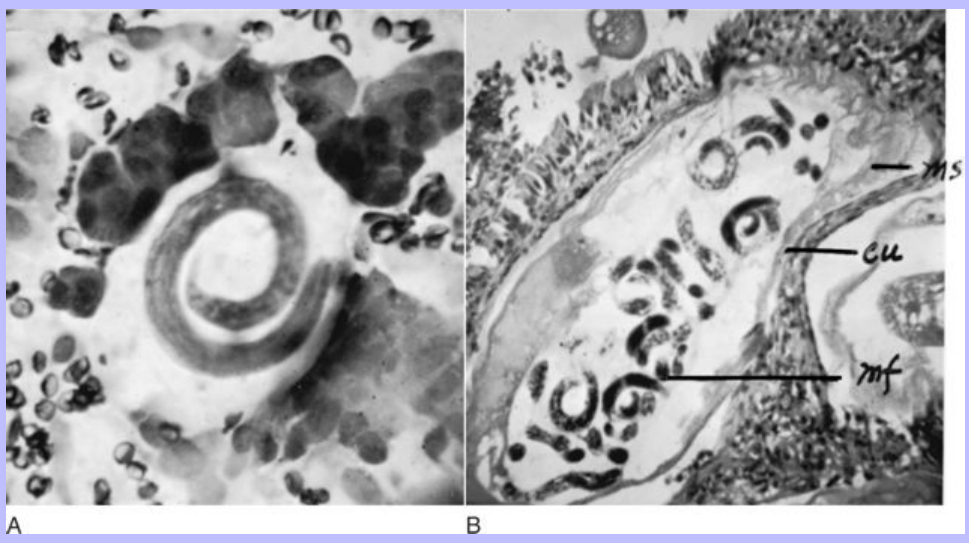


Figure 213-3 **A,** Photomicrograph of a biopsy taken from the trachea just proximal to the carina of the animal in Figure 213-2. The tracheal lining is surrounded by a larval representative of *O. osleri*. Note the kinked tail characteristic of this worm larva. **B,** Parasitic tracheitis that exhibits prominent infestation by adult filarial worms. The worms contain microfilaria (*mf*), which are within the cuticle (*cu*) and are surrounded by mucosal tissue (*ms*) from the host's pulmonary system.



Tracheal sensitivity occurs but physical palpation is normal. Heart sounds are normal. When obvious respiratory embarrassment occurs wheezing, ronchi, or pulmonary edema may be present.

The radiographic examination is helpful if the disease process is extensive and the nodules are large. The tracheal lining may be diffusely thickened, interrupted with indistinct solid masses, or show ill-defined, 2-to 10-mm semicircular lesions protruding into the lumen (Figure 213-2). Endoscopically, cream-colored nodules, 1 to 5 mm high and wide are usually diagnostic. The larvae are often seen peeking into the luminal edge of the growth. Brushings and biopsies of the nodules provide a definitive diagnosis (Figure 213-3).

Larvae are occasionally detected in the feces. Although some flotation methods dehydrate the larvae, zinc sulfate flotation techniques are as diagnostic as is the Baermann technique. Eggs, when seen, are 50 × 80 µm, thin shelled, colorless, and larvated. The larvae are 230 µm long with a distinct kinked tail. Both larvae and eggs may be visualized in the sputum and in washings from the trachea of an affected dog. 1221 1222

213.5.1.3 Therapy

Many drugs have been reported to be effective in treating lungworms, such as thiacetarsamide sodium, diethylcarbamazine, levamisole, fenbendazole, and albendazole.[1] We have treated several dogs with oral

ivermectin at 1000 µg/lb once weekly for 2 months. The nodules were reduced in size but did not resolve entirely. All of these dogs became asymptomatic and continued to thrive. Thiabendazole was administered at 35 mg/kg twice daily for five days and then at 70 mg/kg twice daily for 21 days. Along with thiabendazole, prednisone at 0.5 mg/kg was given twice daily every other day.[16]

Surgical removal is not recommended owing to the large number of nodules. Removal of a large obstructing nodule may potentially be therapeutic in rare situations.

213.5.2 Cuterebrosis

Cuterebra spp. larvae are expected in rabbits and rodents. Several cats have been described with inspiratory dyspnea. Upon tracheoscopy, *Cuterebra* larvae were observed in the trachea, at or just cranial to its bifurcation. Successful treatment consisted of removal of the larva during tracheoscopy in one cat and by thoracotomy and removal through a tracheal incision. The cases were described by the authors as third-stage instar of the *Cuterebra* spp.[51] A fatal case of second stage instar has been reported in another cat.[37]

213.5.3 Tracheal Hypoplasia

213.5.3.1 Etiology

First described in 1972, the hypoplastic tracheal syndrome is a congenital defect resulting from inadequate growth of the tracheal rings.[1] The condition varies from mild to severe. This disease is recognized primarily in young, brachycephalic animals. The first complete report involved a series of dogs, most of which were English bulldogs.[1] In another report, the highest incidence was in English bulldogs (55%), with Boston terriers also being commonly affected (15% of their cases).[17] Other congenital abnormalities, including elongated soft palate, stenotic nares, cardiac defects, and megaesophagus may be associated.

213.5.3.2 Clinical Signs and Diagnosis

Since tracheal hypoplasia is a congenital disease, it can be diagnosed early in life. In one study, the median age at diagnosis was 5 months (range: 2 days to 12 years).[17] Common clinical signs include dyspnea, stridor, and coughing. Occasionally, dogs present with a moist, productive cough, moist rales on auscultation, and a fever associated with bronchopneumonia.

Physical examination may be normal (except for a palpably small trachea) or may reveal a sensitive trachea that, when palpated, evokes coughing. Excitement is likely to exacerbate the coughing episode, which is usually more severe and serious during daytime hours. Heart sounds are normal unless an associated congenital cardiac malformation is present. Clinical pathology reveals a leukocytosis with a left shift if there is a concurrent bronchopneumonia. The radiographic features are most important and usually provide a definitive diagnosis (Figure 213-4). Dorsoventral and lateral radiographs of the thorax and lateral views of the cervical region should be obtained to assess the tracheal diameter and the presence or absence of pulmonary changes. Methods for measurement and determination of normal trachea diameter have been reviewed earlier in the chapter.

The diagnosis of hypoplastic trachea is generally made when the lumen diameter is less than two times the width of the third rib where they cross. The tracheal lumen will also appear smaller than the caudal

laryngeal lumen in these patients. Care must be taken in the young patient, in which the adult proportions of the tracheal lumen may not yet be obtained. *Tracheal edema associated with tracheitis may mimic a hypoplastic trachea on the radiograph*. For this reason it is best to take radiographs when the patient is asymptomatic.

213.5.3.3 Prognosis and Therapy

The prognosis for dogs with a hypoplastic trachea depends on the degree of hypoplasia as well as the presence or absence of concurrent congenital defects. Many patients with slight to moderate hypoplastic tracheas can live normal, satisfactory lives with only an occasional need for bronchodilator therapy and antibiotics. Young dogs with this diagnosis often outgrow the condition. One report suggests that tracheal hypoplasia may be clinically insignificant in the absence of concurrent cardiac or other obstructive upper respiratory disease. Further it supports the idea that the degree of hypoplasia does not correlate with the presence or absence of clinical signs.[17]

Clinical experience has shown that many dogs present with this condition in various states of severity as puppies and young dogs. With effective empirical therapy a significant number of these dogs develop and grow into healthy mature dogs. Because the initial impression is one of a very advanced condition, the veterinarian may wish to advise the client on the potential for the dog to overcome this problem. This is particularly true if there are no associated congenital defects present. Owners who are experienced with these breeds are familiar with the problem and are often quite capable of dealing with the extensive nursing care required. One should be firm on recommending therapy for these patients. Many who have suggested euthanasia have come to regret their haste after seeing some of these dogs as mature adults. The prognosis remains guarded and it is prudent to identify the possibilities to the new pet owner who presents a pet with this condition. Similarly, the veterinarian must carefully evaluate the pet for associated congenital defects (cardiac or other upper airway).

It is important to prevent bronchopneumonia from developing by keeping the affected animal in a draft-free environment and preventing excessive exposure to moisture and cold. Prevention of excessive weight gain also helps the animal by limiting the strain placed on the respiratory system by obesity. When recurrent upper respiratory tract infections do occur, the use of antibiotics is in order, preferably as determined by culture and sensitivity testing.

It is advisable to discourage the breeding of animals affected with this congenital defect, even though at this time there is no absolute evidence indicating a hereditary basis. There are no known surgical corrective procedures.

213.5.4 Segmental Tracheal Stenosis

213.5.4.1 Etiology

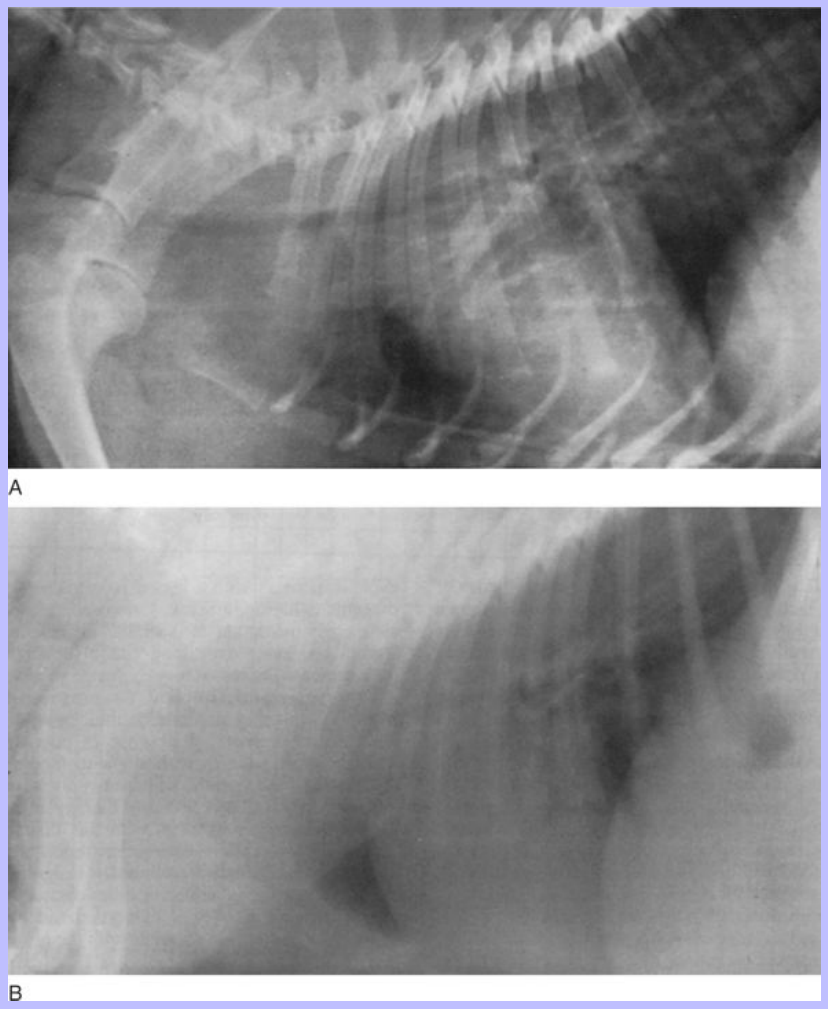
Segmental tracheal stenosis is an unusual condition that affects small animals. It may occur as a congenital lesion or it may result from trauma to the trachea. The congenital absence of tracheal rings that causes a focal stenotic area has been described.[18] Many examples of young cats and dogs with segmental tracheal strictures of unknown cause have been recorded.[1]

Segmental tracheal stenosis can also occur secondary to a tracheotomy procedure, with necrosis and thickening of the tracheal wall from excessive endotracheal cuff pressures, as a complication of thoracic surgery, result of bite wounds to the cervical area, foreign bodies lodged in the trachea and result of massive chest trauma.

213.5.4.2 Clinical Signs and Diagnosis

This syndrome produces stridulous respiratory distress and subsequent cyanosis. Secondary upper airway tract infections may result and develop into overwhelming pulmonary disease.

Figure 213-4 **A,** Lateral cervical and thoracic radiographs of a 1-year-old female bulldog. The radiograph of the thorax clearly demonstrates a markedly hypoplastic trachea in addition to pulmonary changes suggesting bronchitis. The ratio of the tracheal diameter to the height of the thoracic inlet was 0.07. The normal ratio is 0.16 or greater. The indistinct outline of the trachea is due to the accumulation of large amounts of mucous in the trachea. **B,** Hypoplasia of the trachea in a 4-month-old female boxer presented with a productive gagging cough and moderate respiratory distress. Lateral thoracic radiographs show a severely hypoplastic trachea. The ratio of the tracheal diameter to the height of the thoracic inlet was 0.05.



Radiographic studies usually establish the diagnosis. Survey tracheal radiographs often show the stenotic region as an abrupt, segmental reduction in lumen diameter. Inspiratory/expiratory projections or fluoroscopic examination demonstrate little dynamic change in the stenosis during the respiratory cycle. Bronchoscopy identifies the stenotic lesion and its severity and anatomic extent. It is possible that accurate measurement of the degree of tracheal stenosis cannot be made. Percentage of tracheal luminal stenosis as determined by antemortem methods in 15 normal dogs that underwent tracheostomy procedures were determined by radiography, tracheoscopy, and necropsy. The antemortem methods did not correlate well with control planimetric methods.[52]

213.5.4.3 Therapy

The management of segmental tracheal stenosis is similar regardless of cause. The mainstay of treatment is surgical resection of the stenotic region. Several types of procedures have been used and they are well reviewed.[1,18,19] Tracheal resection and anastamosis without excessive tension,[18,19] balloon dilatation[20], placement of polypropylene total ring prostheses applied to the external surface of the trachea and tracheal wall stent placement internally have all been used successfully.[53] The reader is referred to an appropriate surgical textbook for additional information.

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213.5.5 Collapsing Trachea

There are two types of collapsing trachea, the dorsoventral and lateral forms. The lateral form is very unusual. It has been reported without obvious cause but it also has developed after central chondrotomy was performed to treat the dorsoventral form of tracheal collapse. Lateral collapse rarely occurs spontaneously.[21] Dorsoventral flattening (narrowing of the trachea) is a very commonly described lesion that is often associated with a pendulous, redundant dorsal tracheal membrane that prolapses into the tracheal lumen.

The collapsing trachea usually involves the cervical region, but often both the cervical and thoracic areas of the trachea are involved and the collapse may extend into the bronchi. Extension of the tracheal collapse to the bronchi is also described as collapsing of the trachea at the carina. Extension into the cartilage of the lower airways is referred to as bronchomalacia. Regardless of the focal or diffuse nature of the problem, increasing respiratory work leads to dynamic collapse of the dorsal tracheal membrane into the tracheal lumen. This further irritates and inflames the mucous membranes, disrupts the mucociliary apparatus, and increases the risk for associated small airway problems.[22] This condition has been described in cats in association with an intraluminal obstructing lesion[22] and by others but unusually.[23]

213.5.5.1 Etiology

The etiology of the collapsing trachea is unknown. The condition is an acquired disease that usually occurs in middle-aged to aged dogs, although it has been described in young dogs as a congenital lesion.[1] The clinical syndrome and findings in congenital cases are essentially similar to those described in acquired disease. In dogs with an acquired collapsing trachea, there is no loss of potential tracheal ring size, but the rings lose their ability to remain firm and thus subsequently collapse. They become hypocellular and the matrix varies from normal. Glycoprotein and glycosaminoglycan are deficient or totally lacking in dogs with collapsing tracheas.[1] The essential lesion is a deficiency in the organic matrix of the tracheal cartilage. This has led some to associate the condition with tracheal and bronchomalacia. There may be a failure of

chondrogenesis or simple degeneration of hyaline cartilage, decreasing its turgidity. This in time leads to stretching of the dorsal membrane and finally collapsing of the trachea.

Biomechanical and biochemical parameters were similar when comparing cervical to thoracic tracheal rings of young and middle-aged healthy dogs.[24] Tracheal cartilages of normal adult dogs did have significantly higher proteoglycan content and lower water content than an immature group of dogs.

Chronic coughing caused by long-term airway and/or pulmonary parenchymal disease, chronic cardiac disease with tracheal and bronchial compression, tracheal trauma, denervation of the dorsal tracheal membrane, congenital defects, obesity, increased mediastinal fat, and thoracic and extrathoracic masses are likely associated problems rather than primary inciting causes of this anatomical condition. Laryngeal dysfunction and bronchial collapse significantly alter the prognosis negatively.[54]

213.5.5.2 Clinical Signs and Diagnosis

Tracheal collapse produces a “respiratory distress syndrome.” The disease is usually paroxysmal in nature, often with a long history of chronic coughing. The cough may be described as chronic, harsh, or dry. If the owner is asked specifically, the cough often is described as a “goose honk” sound that occurs initially during the day and occasionally into the evening hours. With rare exception, the disease is recognized in toy and miniature breeds, most often Chihuahuas, Pomeranians, toy poodles, Shih Tzus, Lhasa apsos, and Yorkshire terriers. It may occur concurrently with chronic mitral valvular heart disease and must be differentiated from heart failure due to this condition. A slow heart rate helps to distinguish heart failure from primary collapsing trachea. Patients in a compensated cardiac state are presented with a cough due to a collapsed trachea. The pressure of the enlarged left atrium on the left mainstem bronchus may aggravate or precipitate the tracheal cough, even in the absence of heart failure. The characteristic cough is elicited by excitement, tracheal pressure (such as that caused by pulling on a leash), and drinking water or eating food. Often, the owner indicates that the dog begins to cough when it is picked up under the chest or held when excessive pressure is placed on the thoracic inlet.

Physical examination usually reveals a normal dog, which may be obese or thin. Depending on the state of anxiety and the respiratory distress of the moment, the patient's color varies form normal to cyanotic. Most dogs are afebrile but an elevated temperature develops with extreme respiratory distress and agitation. Hyperthermia may result if the distress is not relieved. Perhaps the most significant finding during the physical examination is the elicitation of a “goose honk” cough when the trachea is pressed in the region of the thoracic inlet. In thin patients, dorsoventral compression of the trachea and an angle at the lateral edges of the trachea can be palpated. This is not observed in obese dogs. The cardiac sounds vary from normal to that associated with simultaneous mitral valvular insufficiency. In the normal dog, the second heart sound is less pronounced than the snapping second heart that is often auscultated in dogs with collapsing trachea. The lung sounds vary from normal vesicular sounds to rattling, stridulous sounds associated with sibilant rales and wheezing. Stridor implies inspiratory sounds associated with upper airway obstruction, including laryngeal paresis/paralysis, everted laryngeal saccules, and cervical tracheal collapse. Varying degrees of inspiratory or expiratory dyspnea (respiratory distress), inspiratory noises, and an expiratory grunt (abdominal press) with an abdominal effort are recognized in all cases.

A significant feature of the physical examination is the frequent association of hepatomegaly. Hepatomegaly occurs in a large percentage of patients with this syndrome. It may be associated with fat deposition in the liver (see other rule outs for hepatomegaly, Chapter 225). The relationship of hepatomegaly to the clinical syndrome is unclear.

In most uncomplicated cases, there are usually no electrocardiographic abnormalities other than P-pulmonale resulting from right-sided heart strain. Examination of the oral cavity is usually normal (dental excluded). Culture of the tracheal lining using a protected brush identified aerobic growth in 24 of 29 dogs. Cytologic confirmation of inflammation or infection was not consistent.[55] *Mycoplasma* spp. were identified in patients cultured with lower airway disease. Some of these animals had tracheal diseases[50] and may culture commonly identified bacteria but most have no growth. Tracheoscopy reveals a decreased dorsoventral diameter of the trachea with a pendulous dorsal tracheal membrane. Dynamic changes such as intrathoracic collapse are noted as are other structural abnormalities, such as specific single or multiple flattening or collapse of tracheal rings. In most cases, the tracheal mucous membranes are hyperemic but usually show no exudate. On occasion, a copious, frothy catarrhal exudate may be present.

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In a study of 20 surgically managed cases, 30% of the dogs were observed to have concurrent laryngeal paresis or paralysis.[1] The high figure does not correlate with the authors' experience with large numbers of dogs that cough intermittently with this disease for many years. It may represent an important specific subset of patients, however, and should be looked for when a diagnosis of tracheal collapse is made. Further, laryngeal paresis results in a classic stridulous inspiratory effort in marked contrast to this expiratory wheeze, cough, and grunting syndrome. Upon completion of the visual examination, bronchoalveolar lavage, brush cytology, and/or biopsy samples are taken. The risks of bronchoscopy/tracheoscopy are relevant. Extreme caution is required. Brachycephalic dogs with diminished laryngeal motility or everted saccules are additionally at risk as may be obese patients and those with severe tracheobronchial malacia, concurrent pulmonary disease, small airway collapse, accumulated bronchial secretions, and hypoventilation. Post bronchoscopy recovery requires careful patient attention, minimized stress, occasionally long-term intubation, and on occasion intratracheal administration of 1% lidocaine spray.[25]

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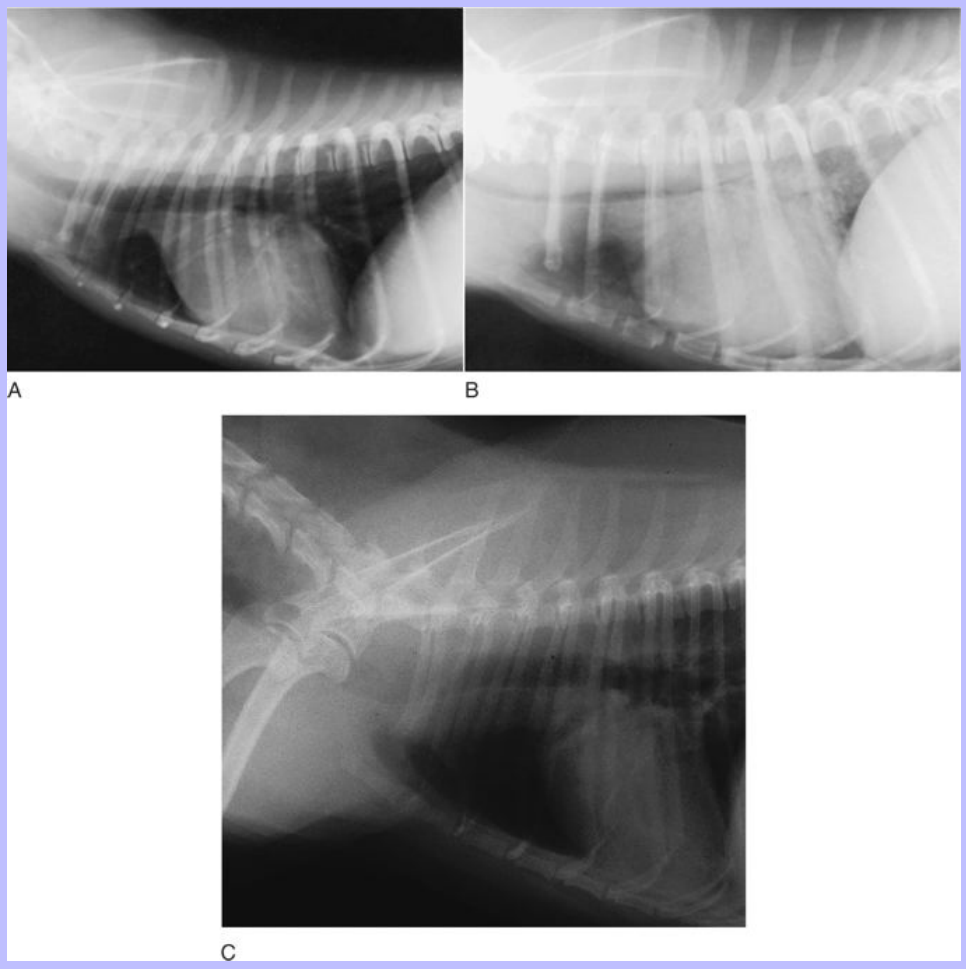
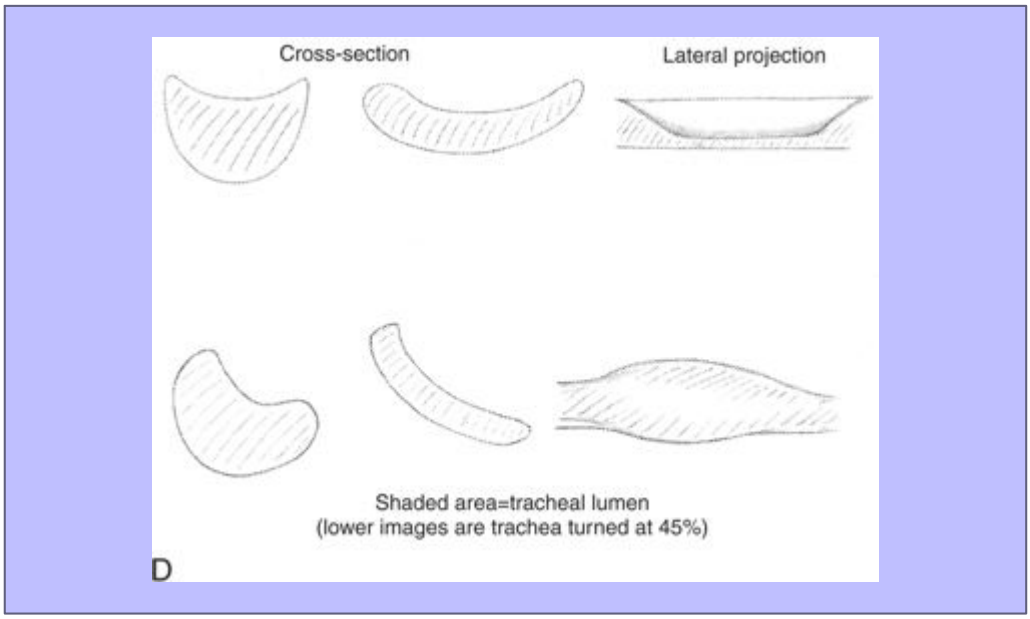
Figure 213-5 Lateral thoracic radiographs of an 8-year-old Yorkshire terrier during **(A)** peak inspiration and **(B)** peak expiration. Note the dramatic change in tracheal diameter that can occur during the respiratory cycle in animals with collapsing trachea and how important it is to obtain inspiratory as well as expiratory views. In severe cases such as this, the expiratory collapse is not limited to the thoracic segment of the trachea but extends into the cervical region as well. **C,** Collapsing trachea observed at the thoracic inlet in a dog with moderate rotation of the trachea. As a result of the rotation, the trachea appears wide rather than collapsed in the lateral view.**D,** Drawing of the actual tracheal position and the line of the x-ray beam explains the appearance of the trachea on the lateral view.





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Radiographic examination of patients with collapsing trachea uses both still and motion studies. The trachea should be examined on dorsoventral and lateral radiographs. Separate lateral radiographs of the cervical and cranial thoracic regions should be obtained to assess the contour of the entire trachea. Lateral radiographs made during both the maximum inspiratory phase and expiratory phase of the respiratory cycle are needed to demonstrate a dynamic collapsing trachea (Figure 213-5). Collapse of the cervical tracheal segment is usually best demonstrated during the inspiratory phase.

Conversely, the study made on expiration usually shows a collapse of the thoracic segment (and occasionally mainstem bronchi) and an unchanged or slightly dilated cervical segment. Care should be taken not to overflex or overextend the occipitoatlantal articulation when obtaining the lateral views, since this may produce pressure on the trachea that can artifactually induce narrowing of the lumen (Figure 213-6) or cause an abnormal tracheal course in the caudal cervical or thoracic region. There can be a subtle loss of radiographic detail at the dorsal luminal margin, which is produced by inversion of the dorsal tracheal membrane. The ventral margin of the tracheal lumen remains well demarcated and is unaffected by the collapsing process. The collapsed region usually involves approximately one third of the tracheal length, and the extremities of the collapse blend into normal lumen size over a distance of 2 to 3 cm. The course of the trachea is usually normal in uncomplicated cases. A redundant dorsal tracheal membrane which invaginates into the tracheal lumen can be seen as soft tissue opacity along the dorsal aspect of the caudal cervical tracheal lumen (Figure 213-5, *E*). This condition is seen in both small and large breed dogs, and can be distinguished from a superimposed esophagus or other structure by the sharp soft tissue-gas interface along the ventral margin. DV or VD views of the thorax do not usually demonstrate changes in the trachea. Concomitant lung disease may be seen.

Ultrasound examination of the trachea may demonstrate an alteration in the shape of the lumen on ventrodorsal projection.[49] Motion studies of normal respiratory function and cough, using fluoroscopy, can be made in order to assess the severity of the lesion. Some cases may show collapse only during the forced expiration of coughing. Slow-motion studies of videotape recordings are often helpful in delineation of the magnitude of the collapse, especially when produced by coughing.

The differential diagnosis of collapsed trachea requires consideration of such common conditions as tonsillitis, laryngeal paralysis or collapse, stenosis of the nares or trachea, eversion of the lateral saccules, elongation of the soft palate, bronchitis or primary tracheitis, foreign body tracheitis, and decompensated chronic mitral valvular disease. The list of causes of coughing that could be confused with collapsed trachea is extensive (see Chapter 53).

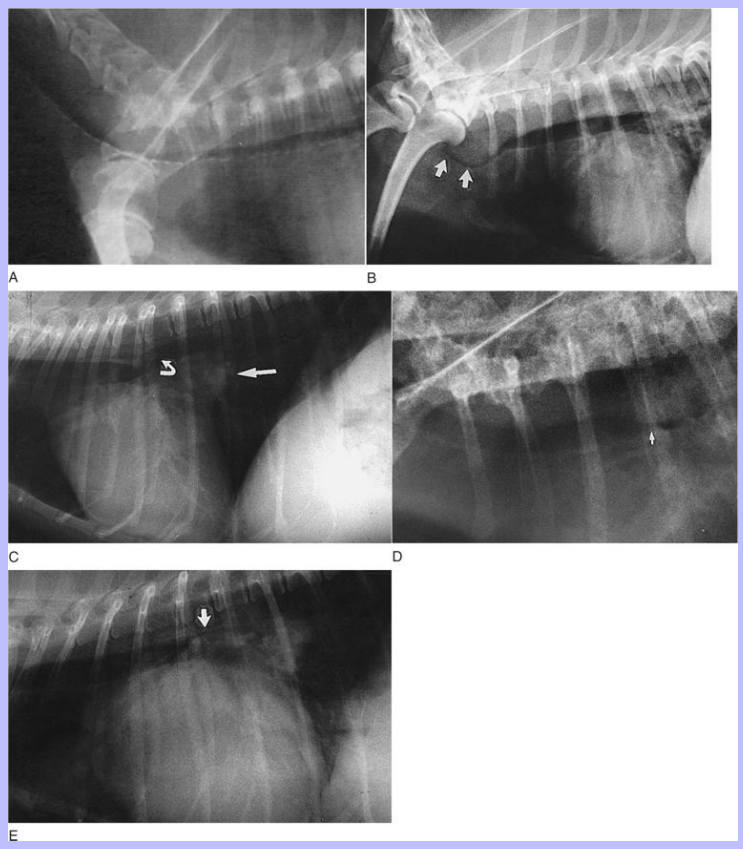
213.5.5.3 Therapy

The therapeutic approach to the collapsing trachea patient covers both the acute and chronic state. Although both conditions use the same common drugs, the need to deal quickly and aggressively with the acute state differs conceptually. Clients are often very anxious and the pet may be equally so, which demands immediate attention and reassurance for the owner.

In the acute state the clinician is concerned with calming the patient as quickly as possible. This may require the use of oral antitussive agents such as butorphanol or dihydrocodeinone. In the event that these products are not rapid or potent enough, injectable butorphanol may be considered. Other agents that are effective in more advanced conditions include dilute acetylpromazine, diazepam intravenously, or morphine by injection. Separating the extremely anxious pet from the client (this can often be very difficult to do) may be very useful and allows the clinician to appropriately sedate the dog and reduce the external stimuli that are continuing to occur. Not infrequently, simply removing the pet from view of the owner acts to calm the dog. In the event of cyanosis, oxygen in a humidified environment such as an oxygen-enriched cage or by nasal catheterization is suggested. The latter is made more difficult by the extreme anxiety of the patient. In such situations any physical manipulation or stress may aggravate the problem and make the cure worse than the disease. The use of short-term corticosteroids has a place in such situations since there likely is tracheal edema present. Injectable steroids initially, followed by oral dosages, tapered slowly is quite helpful during acute treatment. In some cases, pets are sent home with the owner after instructing on the administration of dilute acetylpromazine in the event of an acute exacerbation of the problem.

Throughout treatment, bronchodilators remain effective in treating this condition. The theoretical benefits accrue to reduction in spasm of the smaller airways, which reduces intrathoracic pressures and thus decreases the tendency of the larger airways to collapse. Additionally there is improved mucociliary clearance and reduced diaphragmatic fatigue. In some cases the authors even believe that the alcoholic content of an elixir compound seems to benefit the patient as much as the actual medication. Caution is required concerning the side effects of methyl xanthine drugs, which include vomiting and excitability. Similar results may be obtained by having the owner place a small dab of an alcoholic liquid in the buccal region during acute episodes of coughing at night when at home.

Figure 213-6 **A,** Lateral radiograph of a 13-year-old Chihuahua with a pliable, collapsible trachea showing caudal cervical tracheal collapse due to overextension of the neck. **B,** Lateral thoracic radiograph from a 14-year-old male castrate Pomeranian. Notice the reduced size of the cervical trachea as compared with the thoracic trachea on inspiration *(arrows)*. **C** and **D,** 11-year-old Poodle, female spay, with severe chronic coughing. There is marked left atrial enlargement with bronchial dilatation on inspiration and on expiration there is narrowing and reduction in size of the two mainstem bronchi. Such pathology usually precludes surgical correction of the disease. **E,** Lateral radiograph from a 7-year-old Pomeranian, female spay, with severe coughing. Note the normal tracheal size until the carina at which point the mainstem bronchi shows compression and constriction *(arrow)*. This patient required long-term aggressive medical therapy.



Treating the patient long term on an outpatient basis utilizes the same principles as set above except on a more relaxed level. Usually, medications can be administered on an as required basis and often may not be required throughout every day. The backbone of such therapy remains the bronchodilator agents (usually the methylxanthine derivatives such as aminophylline, theophylline elixir, or another bronchodilator, see Table 213-1). Beta-agonists (terbutaline and albuterol) are reported to be effectively used by some in place of the methylxanthine agents. No clinical studies demonstrating any proof of benefit are available. Antitussive agents butorphanol or dihydrocodeinone (hydrocodone) are quite effective in controlling symptoms. Side effects include oversedation, anorexia, and constipation. Occasionally longer use of low-dose steroids are given, often in combination with a sedative-antihistamine. Some combination products work well here (also see Table 213-1) but many have been removed from the market. Often the clinician will need to change therapies from time to time to find a newer effective agent. The neuroendocrine effect of digitalis may play a role in the effectiveness of this product, although the treatment of the cor pulmonale is considered to be another possible role.

Weight reduction in the obese patient is essential. This is accomplished principally with high-fiber, low-fat diets since exercise modification is unlikely. Weight loss alone can be curative in terms of dealing with the symptoms of this disease. Likewise removal of neck collars and utilizing only a harness when the dog is taken outside can be most effective in reducing clinical signs.

The majority of cases can be successfully treated symptomatically. Bronchodilator preparations containing expectorants and sedatives usually suffice to control this disease (see Table 213-1). Nebulization or vaporization may provide additional relief. Hospitalization with sedation for a period of several days, associated with corticosteroid therapy and nebulization, helps to reduce the degree of associated tracheitis. It is important to recognize that other disease states, specifically chronic lung disease, hepatomegaly, or chronic mitral valvular fibrosis, may be present. Antibiotics are not indicated in treating this disease unless there is concomitant bacterial infection. Removing the dog from respiratory irritants such as noxious gases, smoke, and dust is good common sense.

Several authors have reported on the surgical correction of this condition.[1,25–27] There are no evidence-based studies to link central chondrotomy with effective control of this disease. In one survey evaluating 100 dogs with tracheal collapse, 71% had long-term resolution of clinical signs with conservative care.[29] Of these 100 dogs, 4% required upper airway surgery and 11% were sent for tracheal reconstruction when no other medical conditions were recognized. Only half of this latter group had an asymptomatic recovery. These authors of this study and of this chapter suggest that surgery should be reserved only for younger dogs and those that fail to respond to aggressive medical care.[29]

Surgical methods that have been described include plication of the dorsal tracheal membrane, external tracheal ring prostheses, and intraluminal stent devices. These surgical efforts do not resolve the co-existing problem of mainstem and distal bronchial collapse and may not effectively resolve isolated thoracic inlet disease. Polypropylene C-shaped stent placement has been described with good results.[27,28,30] These authors suggest that surgery involving the thoracic portion of the trachea has been unrewarding because of high morbidity and that dogs with mainstem bronchial collapse are not good surgical candidates. In a group of dogs that did have surgery, 17 of the 90 (19%) required a follow-up tracheostomy and a high percentage of these developed complications due to occlusion with mucous or skin folds. Yet, extraluminal placement of polypropylene C-shaped stents was an effective method of controlling the clinical signs of collapsing trachea in some dogs.

Weight, severity of tracheal collapse, duration of the clinical signs, and the need for a tracheostomy did not affect the long-term outcome. Dogs over 6 years of age had more postoperative complications and a poorer long-term outcome than did dogs under 6.

Twenty-five dogs were treated surgically for tracheal collapse with use of extraluminal polypropylene ring prostheses plus a left arytenoids lateralization.[31] The authors reported a lower complication rate of 4% and a 75% success rate. They felt that this was due to reduced complications as a result of the tie back procedure.[31]

Various intraluminal stenting techniques have been considered and utilized. Varying results have been recorded using Palmaz[56] (negative), Nitinol[57] (no conclusions), Ultraflex, and Smart Stents (manufactured by Boston Scientific) with no strong positive literature to date to support unqualified recommendations. Failure to function well and migration following stent placement are problems that have been identified.

Surgical correction of a 4-year-old Poodle with a lateral collapsing trachea using ring prosthesis provided definitive relief of the symptoms. The authors evaluated the dog postoperatively and found little change anatomically. Since there was so much improvement the authors attributed the improvement to increased airway rigidity, which alleviated the effects of dynamic collapse resulting in improvement of the air flow.[21] Surgical management utilizing polypropylene spiral ring prostheses was identified in two large breed dogs with extra thoracic tracheal collapse.[32]

213.5.6 Obstructive Tracheal Masses

213.5.6.1 Etiology

Obstructive tracheal masses have varied etiologies. Lesions may be intraluminal, as in the case of primary tracheal neoplasia or extraluminally compressive. Tracheal tumors in dogs and cats include squamous cell carcinoma, histiocytic lymphosarcoma, lymphoblastic lymphosarcoma, osteosarcoma, adenocarcinoma, osteoma, chondroma, osteochondroma, chondrosarcoma, and leiomyoma.[1,33,34,58] Also, plasmacytoma, mast cell tumors, seromucinous carcinoma and rhabdomyosarcoma.[59] In dogs and cats, primary tumors of the trachea are uncommon. Other intraluminal masses include tracheal parasites, nodular amyloidosis, eosinophilic granulomas, abscesses, chronic granulomas,[1,35] and inflammatory polyps.[33] A single second-stage instar larval stage of *Cuterebra* spp. was identified in a 7-year-old cat's trachea.[37]

Tracheal foreign bodies can also cause an intraluminal obstruction.[1,38,39] Foreign bodies are not common, but when they do occur, they are usually small enough to pass beyond the tracheal bifurcation, causing subsequent development of inhalation pneumonia. When foreign bodies are relatively large, they are likely to come to rest at the carina.

Tracheal obstruction by external compression has been associated with thyroid and parathyroid tumors; enlargement of the mandibular, retropharyngeal, or prescapular lymph nodes due to infection, mediastinal hemorrhage and abscesses,[60,61] neoplasia, mycotic granuloma; peritracheal abscesses and cysts; extramedulary tracheal masses,[62] cranial mediastinal masses such as thymomas; esophageal tumors; and esophageal granulomas secondary to *Spirocerca lupi*.[1,40,41]

213.5.6.2 Clinical Signs and Diagnosis

Obstructive diseases are associated with a dramatic increase in airway resistance at the point of obstruction, impeding air flow, which causes hypoventilation and respiratory acidosis.[42] Clinical signs depend on the degree of obstruction. Up to one half of the airway diameter may be compromised without obvious clinical signs.[43] Even in these cases, however, close inspection of the patient will reveal an obstructive breathing pattern, which consist of a slow inspiratory phase followed by a more rapid expiratory phase.[43] Most animals present with stridor, loud ronchi (rattling in the throat), and often chronic coughing. Respiratory distress and dyspnea are usually obvious.

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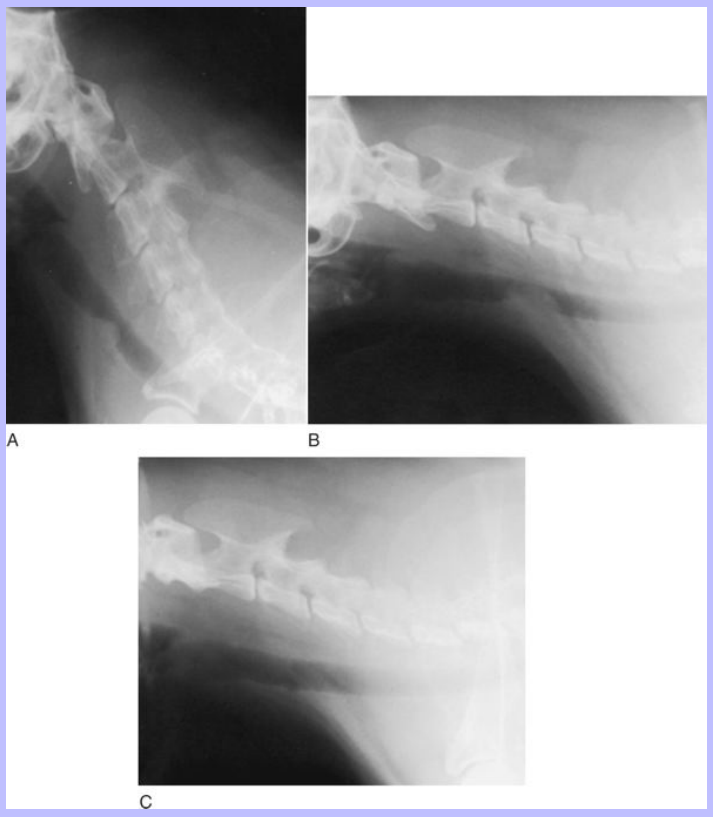
Figure 213-7 **A** and **B,** Lateral cervical radiograph of an 8-year-old cat with inspiratory dyspnea and open-mouth breathing. A tracheal mass can be seen arising from the ventral tracheal wall and growing into the lumen at the level of C4-C5. The air in the trachea provides a natural negative contrast agent. **C,** Cervical radiographs 3 months after surgical resection of the mass. The mass is no longer seen. Histopathologic diagnosis was tracheal adenocarcinoma.

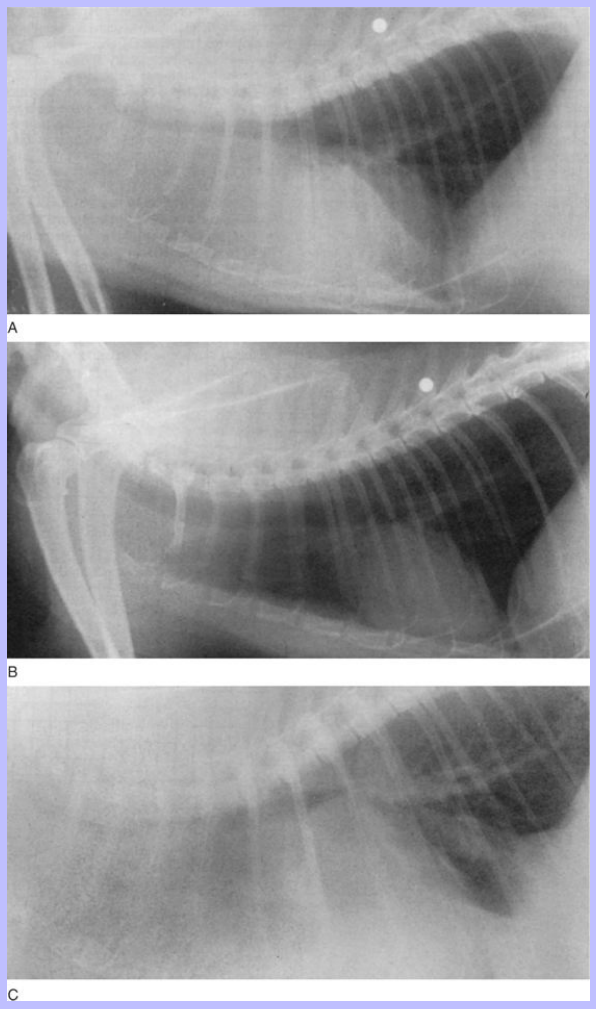


Overzealous examination and performance of laboratory studies may disturb the patient, thereby worsening the condition. Every effort should be made to keep the animal calm, and initial diagnostic tests should be done with as little stress as possible.

The work-up for the patient with suspected tracheal obstructive disease usually begins with radiography. Lateral views should be obtained if the patient can tolerate recumbency without struggling. Ventrodorsal radiographs often put the patient in a stressful position; instead dorsoventral views should be obtained. Tracheal masses may decrease luminal size in a nonlinear manner, resulting in a mass protruding into the lumen. These masses are outlined by tracheal air, which provides a good natural negative contrast medium (Figure 213-7).

Disruption of the mucosal continuity is seen at the base of the mass. This is in contradistinction to the silhouette produced by masses that are extraluminal, in which the line produced by the luminal air-mucosa interface is seen to pass uninterrupted through the mass. Non-radiopaque foreign bodies can be rendered invisible to radiographic examination if they travel distal enough in the bronchi, which results in atelectasis of the obstructed lobe with transudation of serous fluid distal to and around the foreign body. Extraluminal masses that cause tracheal obstruction are generally recognized radiographically as linear decreases in the lumen diameter over a length determined by the size of the mass (Figure 213-8).

Figure 213-8 **A,** Lateral thoracic radiograph of a 5-year-old domestic short-hair cat, presented for dyspnea and emesis, shows elevation and compression of the trachea at the thoracic inlet along with pleural fluid. The cranial lung lobes are displaced caudally. These signs were secondary to lymphosarcoma of the cranial mediastinum. **B,** Same cat as in **A**, 5 weeks after chemotherapy. Notice the re-expansion of the previously compressed trachea. **C,** Lateral thoracic radiograph of an 8-year-old female Burmese cat with pleural fluid secondary to cardiomyopathy. Note that the tracheal elevation is not accompanied by tracheal compression as in the previous case of a mediastinal mass.



In the mediastinal region a mass must be quite large to result in tracheal compression. The trachea is easier to displace then to compress in this location. High-level airway obstruction is most likely to be associated with hypoinflated, small lung fields. Intrathoracic tracheal obstruction may present as a hyperinflated lung due to air trapping as a result of narrowing of the airway during expiration. This creates a ball valve effect and traps air distal to the obstructing lesion. In a cat with an inflammatory polyp partially obstructing the trachea, thoracic radiography suggested increased airway resistance during expiration (hyperinflated lungs and a caudally displaced flattened diaphragm).[36] Contrast esophageal studies are sometimes needed to differentiate the etiology of the tracheal narrowing or displacement in the cranial mediastinal region, particularly in brachycephalic breeds in which cranial mediastinal masses are often difficult to delineate. Concomitant narrowing of the trachea and esophagus in the cranial mediastinum is highly suggestive of an extraluminal mass.

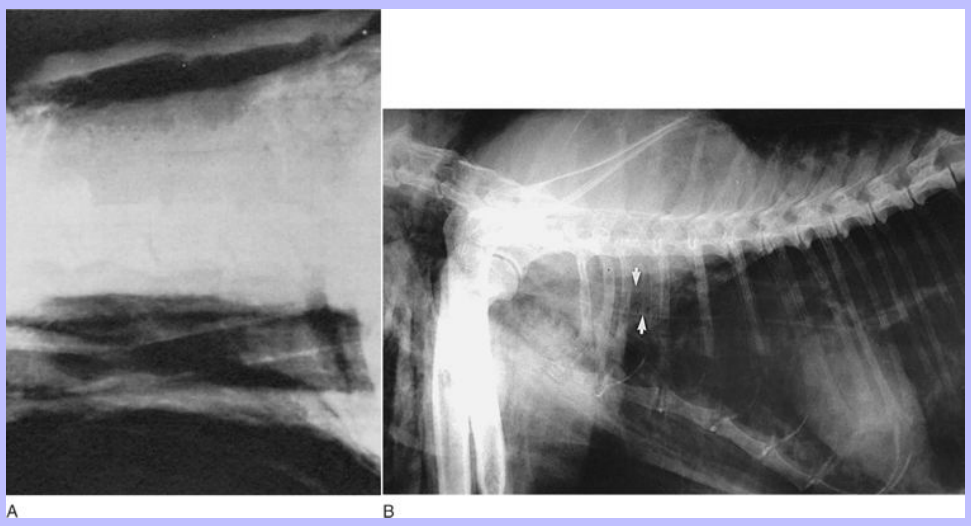
Bronchoscopy allows visualizing tracheal masses and foreign bodies (especially radiolucent foreign bodies), retrieving cytologic specimens of masses, or obtaining biopsies.

213.5.6.3 Therapy

In addition to its diagnostic value, bronchoscopy can be used as part of the treatment. Some foreign bodies can be removed endoscopically, and some tracheal masses may be removed by means of a suction biopsy device attached to the bronchoscope.[34]

For foreign bodies that cannot be retrieved through the bronchoscope and for large or firm tracheal masses, the mainstay of therapy is surgical removal or resection. Surgical procedures of the trachea have been well described. Some foreign bodies may be removed in smaller patients by holding the pet upside down (head down) while under general anesthesia and gently but firmly tapping the thorax. Occasionally the foreign body is actually coughed out and other times it is moved into a more proximal position for easier bronchoscopic retrieval.

Figure 213-9 **A,** Lateral cervical radiograph of a 10-year-old male cocker spaniel with tracheal narrowing and rupture at the level of C3 resulting from a dog fight. There is extensive cervical and subcutaneous emphysema. Not that the outer tracheal wall is visible throughout its length because of the free extraluminal air that provides contrast. **B,** Pneumomediastinum in a cat associated with subcutaneous air collection. Note the prominent tracheal stripes both dorsally and ventrally as a result of the trachea being outlined by air both inside and outside of the trachea lumen.



The prognosis for patients with tracheal obstruction depends on the specific primary disease as well as the present degree of respiratory embarrassment. Stressful diagnostic measures may push the patient into a state of decompensation. With tracheal tumors, the prognosis varies with the amount of trachea involved and with the specific biologic behavior of the tumor type present.

213.5.7 Tracheal Trauma

213.5.7.1 Etiology

Laceration of the tracheal wall causes subcutaneous and mediastinal emphysema. Traumatic injury to the trachea is unusual in small animals. Bite wounds to the neck incurred during a dog or cat fight, transtracheal wash procedure, and inadvertent laceration of the trachea during jugular venous puncture are causes. However, overinflation of endotracheal cuffs, often during dentistry in cats, is another important etiology.[63–65] An uncommon sequela to trauma is a tracheoesophageal fistula.

213.5.7.2 Clinical Signs and Diagnosis

A ventrolateral tear of the annular ligament may produce secondary subcutaneous emphysema over the entire body.[44] This latter condition develops frequently in dogs or cats involved in fights during which a tooth punctures or lacerates the tracheal wall. Air escapes from the tracheal opening and enters the subcutaneous tissue of the neck (Figure 213-9). The subcutaneous emphysema may involve only the peritracheal region or be more extensive and involve the entire subcutaneous area of the body. Such tears may also be responsible for the development of pneumomediastinum in both the dog and the cat (Figure 213-10). Subcutaneous emphysema is recognized by the crackling sensation of the animal's skin. The tissue beneath the skin appears swollen. The presence of such a lesion should immediately indicate the possibility of a tracheal tear.

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Figure 213-10 Lateral thoracic radiograph of a 10-year-old Great Dane with pneumomediastinum. Note how the free air in the mediastinum provides a negative contrast and allows detection of the dorsal tracheal wall *(arrow)*.

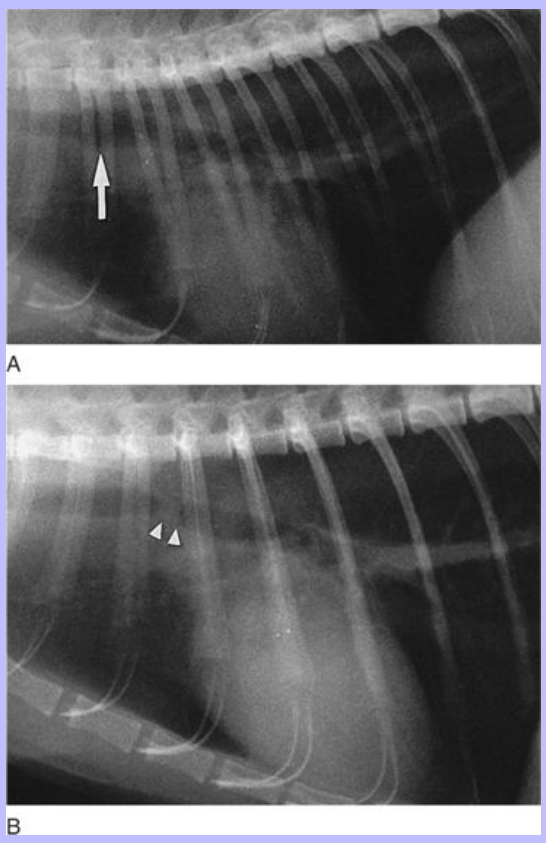
Fractures of the trachea produce radiographic signs of peritracheal, intermuscular, and subcutaneous emphysema. Pneumomediastinum may also be present with a cervical or intrathoracic lesion. Fractures or lacerations of the trachea or tracheobronchial tree should always be considered in cases of persistent, increasing subcutaneous emphysema even when no cutaneous lacerations can be located. Bronchoscopy visualizes the point and extent of tracheal mucosal interruption. Occasionally traumatic injury of the intrathoracic trachea results in a circumferential rupture (*avulsion*), leaving the mucosal or serosal lining intact. This prevents air from dissecting into the mediastinum. Clinical signs develop one to twenty eight days post trauma. Radiographs will reveal the separation of the tracheal rings (Figure 213-11) referred to as

a “pseudo-tracheal” sign.[66–68] A focal widening of the tracheal lumen at the separation during inspiration and narrowing during expiration is often identified.

213.5.7.3 Therapy

If the subcutaneous air collection is regressing and there are no signs of pulmonary distress, it is usually recommended that the patient be cage rested, which allows the emphysema to regress by slow absorption, mild sedation, and occasionally by aspiration through a large-bore needle and wrapping the body with elastic bandages, being careful not to mechanically restrict respiration. Medical treatment alone was effective in 15 of 20 such cases and a sixteenth case died before surgery was attempted.[63] Perhaps of greater importance is the effort to detect other pathologic conditions such as pneumothorax or hemothorax. If another such condition is present, the clinician should consider thoracocentesis.

Figure 213-11 Lateral thoracic radiographs of a cat following thoracic trauma. **A,** Note the focal increased size of the trachea at the level of the fourth rib, which suggests trauma to the tracheal wall. In the lateral view **(B)** taken 1 week later, there is marked diminution in the size of the trachea at the fourth intercostal space due to tracheal stenosis.



Surgical repair of a torn tracheal ligament may be required. Most tears have been found dorsolaterally on the trachea at or near the thoracic inlet.[63] Surgical repair with good results are reported in cats with intrathoracic tracheal avulsion associated with dyspnea, exercise intolerance, and exertional cyanosis.[45]

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214 CHAPTER • 214 Diseases of the Small Airways

Lynelle R. Johnson

The primary role of the small airways is conduction of gases to and from the gas exchange region of the lung at the least energy cost to the animal. Cartilaginous support in large airways and smooth muscle tone in small airways keep airways open to facilitate gas flow. A ciliated, cuboidal epithelial layer that contains mucus-producing goblet cells and submucosal mucus glands lines smaller airways. Production of excessive airway mucus in response to inflammation or infection reduces luminal diameter, increases resistance to airflow, and augments the work of breathing. Activation of the inflammatory cascade and production of inflammatory mediators can cause bronchoconstriction in cats, which further reduces airflow.

214.1 CANINE CHRONIC BRONCHITIS

Chronic bronchitis is an inflammatory airway disease characterized by the presence of a daily cough for greater than 2 months. Neutrophilic or eosinophilic infiltration of bronchial mucosa results in production of proteases, elastases, and oxidizing products. Inflammatory cell products and oxidant injury cause increased epithelial permeability, cellular injury, and mucus hypersecretion. Histologically, chronic bronchitis is characterized by hypertrophy and hyperplasia of mucus glands and goblet cells, smooth muscle hypertrophy, fibrosis of the lamina propria, and epithelial erosion with squamous metaplasia. These changes result in obstruction to airflow and clinical signs of cough and exercise intolerance.

214.1.1 Presentation

Bronchitis affects middle-aged to older dogs. Although classically considered a disease of small breed dogs, bronchitis often affects larger breed dogs.[1] The primary clinical complaint is a harsh productive or nonproductive cough. Many affected dogs have a history of exercise intolerance, and some develop collapse or cough syncope.

On physical examination, dogs with chronic bronchitis appear in good health, are often overweight, and may pant excessively. Tracheal sensitivity is usually present, and auscultation reveals coarse, inspiratory crackles and expiratory wheezes. Dogs with significant bronchitis display prolonged expiration and an expiratory push. Heart rate is normal to low in dogs with respiratory disease, and an exaggerated sinus arrhythmia may be present due to increased vagal tone.

214.1.2 Diagnostic Evaluation

Clinicopathologic abnormalities are typically absent in dogs with bronchitis. Thoracic radiography can establish the likelihood of chronic bronchitis although normal chest radiographs do not rule out chronic airway disease. Thickening of airway walls and increased numbers of visible airway walls are found more commonly in dogs with bronchitis than in age and breed-matched controls.[2] End-on bronchi (doughnuts) and airways seen in longitudinal section (tram lines) represent airway walls thickened by inflammation (Figure 214-1). Right-sided cardiomegaly may be seen in dogs with chronic airway disease that develop pulmonary hypertension and/or cor pulmonale.

Hypoxemia and abnormal distribution of ventilation on radioaerosol scans have been reported in dogs with bronchitis.[1] Tidal breathing flow volume loops in dogs with chronic bronchitis demonstrate reduced expiratory flow and loop shapes similar to those seen in humans with chronic bronchitis.[1]

Collection of airway samples by tracheal wash or bronchoscopy characterizes the cellular infiltrate in the airways and rules out infectious causes of cough. Bronchoscopy is particularly useful in dogs that lack significant radiographic indications of bronchitis since virtually all dogs with chronic bronchitis have rough, hyperemic airway mucosa and mucoid or purulent secretions lining the airways. In animals with long-standing bronchitis, fibrous nodules can be seen protruding into the bronchial lumen. Cytologically, chronic bronchitis is characterized by a preponderance of nondegenerate neutrophils[1] (Figure 214-2), although some dogs have predominantly eosinophils in airway washings. Increased mucus and Curshman's spirals (bronchial casts of airway mucus) are sometimes noted.

Low numbers of bacteria ($<1.7 \times 10^3$ colony forming units per milliliter) can be found in airway samples from bronchitic dogs, and more than one species of bacteria may be isolated[3]; however, significant bacterial infection is not common in dogs with chronic bronchitis.[1,3] Bacteria can also be isolated from airways of healthy dogs (Box 214-1).

214.1.3 Treatment

214.1.3.1 Anti-inflammatories

Short-acting steroids such as prednisone or prednisolone are generally safe and effective in dogs with uncomplicated bronchitis. Remission of clinical signs can usually be achieved with initial doses of glucocorticoids that range from 0.5 to 1.0 mg/kg PO BID. The dosage should be decreased by half every 5 to 10 days, with the goal to achieve alternate day dosing to allow normalization of the pituitary-adrenal axis. If clinical signs recur, a return to the higher dose of glucocorticoid that controlled clinical signs is recommended. Many animals require lifelong therapy, whereas some may be successfully weaned off medication. In dogs with persistent or recurrent signs, concurrent treatment with a bronchodilator or antitussive is indicated.

1233 1234

Figure 214-1 Lateral chest radiograph of a dog with chronic bronchitis. Increased bronchial markings are apparent, primarily in the caudal lung fields.

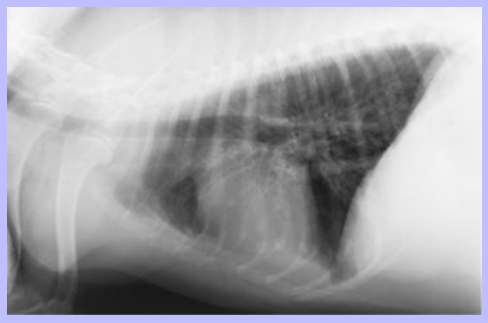
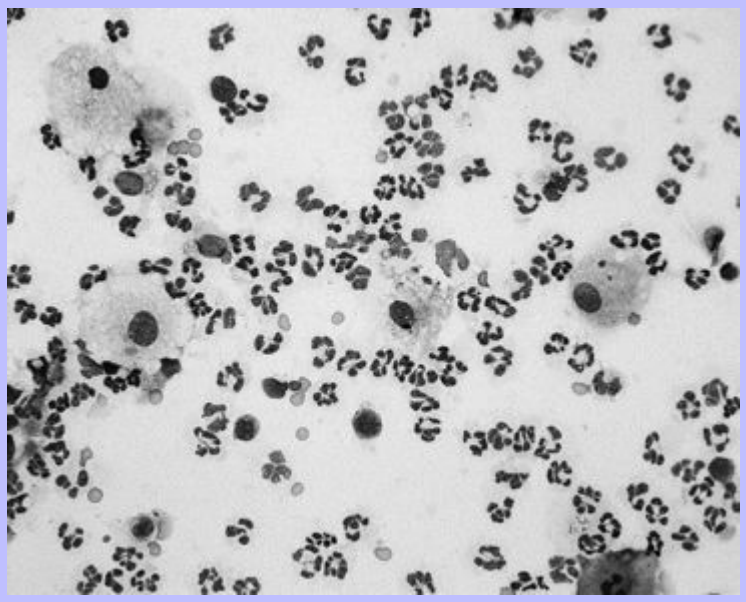


Figure 214-2 Cytology of BALF from a dog with chronic bronchitis demonstrating neutrophilic inflammation (>80% neutrophils on a differential cell count). In healthy dogs, BALF comprises predominantly macrophages (65% to 70%) and low numbers of inflammatory cells (6% to 9% each of neutrophils, eosinophils, and lymphocytes).



214.1.3.2 Bronchodilators

Use of bronchodilators can be associated with clinical improvement due to reduced pulmonary infiltrates or improved expiratory airflow.[1] A trial on a bronchodilator is indicated when a dog exhibits marked expiratory effort and persistent cough despite anti-inflammatory therapy. Bronchodilators can improve diaphragmatic contractility, reduce respiratory muscle fatigue, stimulate mucociliary clearance, and may reduce the dosage of glucocorticoid required.

The bronchodilators used most commonly in veterinary medicine are methylxanthine derivatives and beta-2 agonists. Methylxanthines are believed to act through antagonism of adenosine or effects on intracellular calcium handling, since therapeutic levels do not result in accumulation of cyclic AMP. Long-acting theophylline (Theochron®, Inwood Laboratories) at 10 mg/kg PO BID achieves plasma levels in dogs that approximate the human therapeutic range of 10 to 20 μg/mL.[4] Adverse effects of methylxanthines include gastrointestinal upset, sinus tachycardia, and hyperexcitability. When toxic signs are noted, drug therapy is discontinued and then reinstituted at half the initial dose. If clinical signs improve and the dog tolerates the drug, the dosage may be increased if needed. If no response is seen, an alternate class of bronchodilator is recommended.

214.1.3.2.1
214.1.3.2.1

Box • 214-1 Bacteria Retrieved from the Airways of Healthy Animals[9,17,18]

Pasteurella spp.

Mycoplasma spp.*

Streptococcus spp.

Staphylococcus spp.

Acinetobacter spp.

Moraxella spp.

Enterobacter spp.

Pseudomonas spp.

Escherichia coli

Klebsiella spp.

Bordetella bronchiseptica

* Healthy dogs only, not cats.

Beta-2 adrenergic agonists (terbutaline or albuterol) have been used successfully in management of chronic bronchitis. Dosing of terbutaline is based on animal size, and small dogs receive 0.625 to 1.25 mg PO BID, medium-sized dogs may be given 1.25 to 2.5 mg PO BID, and larger dogs receive 2.5 to 5.0 mg PO BID. Albuterol is dosed at 50 µg/kg PO TID. Beta agonists may result in excitability or tremors during initial therapy but dogs usually become accustomed to the drug.

214.1.3.3

Antitussives

Dogs with bronchitis rely on a potent cough reflex to clear secretions from the airway, and suppression of cough prior to resolution of inflammation could trap mucus in the lower airway, perpetuate airway inflammation, and worsen pulmonary function and clinical signs. When inflammation has been effectively treated but cough persists, use of cough suppressants is warranted since chronic coughing causes repeated airway injury and may lead to syncope. Potent cough suppression can be achieved with narcotic agents such

as hydrocodone (0.2 mg/kg PO BID-QID) or butorphanol (0.05 to 0.12 mg/kg SQ BID-QID and 0.55 mg/kg PO BID-QID). These agents must be given at a frequent interval in order to suppress coughing without inducing excessive sedation.

214.1.3.4 Antibiotics

Airway infection is likely if greater than 3 intracellular bacteria per 50 high-power fields are seen on airway cytology,[3] and appropriate antibiotics are prescribed based on culture and susceptibility results.

214.1.3.5 Ancillary Therapy

Improvements in exercise tolerance and arterial oxygenation can be seen with weight loss alone since obesity decreases thoracic compliance, restricts expansion of the thorax, and worsens both clinical signs and gas exchange in dogs with chronic bronchitis. Exercise should be increased as tolerated. Dogs with concurrent tracheal collapse or marked tracheal sensitivity benefit from use of a harness instead of a collar. When stresses in the environment are encountered, such as cigarette smoke, pollutants, heat, or humidity, the animal should be removed to a cool, clean area.

Some animals may benefit from airway humidification to increase moisture in airway secretions and facilitate clearance. The most significant benefit can be achieved through nebulization with a pneumatic or ultrasonic nebulizer that creates small enough water particles to penetrate the airways. Standard vaporizers create larger water particles and are less effective. Nebulization can be performed two to four times daily for 10 to 30 minutes and should be followed by gentle exercise or coupage therapy to facilitate removal of secretions. Nebulization occasionally results in bronchospasm, overhydration, or distress to the animal. Some patients may benefit from administration of a bronchodilator immediately prior to therapy.

214.1.4 Prognosis

Bronchitis is a chronic disease that can often be controlled but never cured. The majority of patients have residual cough and exhibit clinical signs periodically throughout life. Goals of therapy are to control inflammation thus limiting clinical signs and to prevent worsening airway disease. When inadequately treated, long-standing bronchitis may lead to bronchiectasis or pulmonary hypertension due to chronic hypoxia and/or vascular remodeling. 1234 1235

214.2 BRONCHIECTASIS

Bronchiectasis is a focal or diffuse destructive lung condition characterized by irreversible dilatation of large cartilaginous airways, often with accumulation of pulmonary secretions. Dilatation results from destruction of muscular and elastic support structure of the airways by cytokines and proteolytic enzymes produced by inflammatory cells.[5] It can occur in association with primary ciliary dyskinesia (PCD), as a sequela to long-standing infectious or inflammatory pulmonary disease, secondary to smoke inhalation or airway obstruction, or as a complication of radiation-induced pneumonitis.[5] In cats, bronchiectasis is recognized as a histopathologic response to long-standing airway disease. Cocker spaniels seem predisposed to the disorder.[6]

214.2.1 Presentation

Dogs with bronchiectasis typically have a chronic history of a moist productive cough and frequent bouts of pneumonia that initially respond to antibiotics but then recur.[6,7] Hemoptysis may be present.

Physical examination is remarkable for moist crackles and expiratory wheezing. Loud bronchial sounds can sometimes be heard over dilated airways. Nasal discharge may be related to PCD or associated with pneumonia, when pulmonary secretions are expectorated into the nasal passages.

214.2.2 Diagnostic Evaluation

Nonspecific evidence of chronic infection includes neutrophilia, monocytosis, and hyperglobinemia due to chronic antigenic stimulation. Arterial blood gas analysis typically exhibits hypoxemia and a widened alveolar-arterial oxygen gradient.

Thoracic radiographs can demonstrate mixed bronchial, interstitial, or alveolar patterns with diffuse thickening of bronchial walls.[6] Although central or diffuse bronchial dilatation is classic for bronchiectasis, radiographs are relatively insensitive for the diagnosis. Dilated airways are more readily apparent when a severe pneumonic infiltrate is present. Computed tomography or bronchoscopy can provide evidence of bronchiectasis in dogs and cats. Classic bronchoscopic findings in bronchiectasis include dilatation of the airways with or without trapping of purulent secretions, loss of the cylindrical shape to airway lumens, and mucosal hyperemia and irregularity.

Bronchoalveolar lavage fluid (BALF) typically exhibits suppurative inflammation. Bacterial cultures for both aerobes and anaerobes are indicated since purulent secretions can favor the growth of anaerobic species. In dogs, cultures may fail to reveal bacterial growth[7] yet these cases often respond to antibiotic therapy.

214.2.3 Treatment

Dogs with lobar bronchiectasis or bronchial foreign bodies usually require lung lobectomy for management of disease. Dogs with pneumonia must be treated with broad-spectrum antibiotics that are efficacious against both aerobes and anaerobes. While cultures are pending, intravenous ampicillin (10 to 20 mg/kg IV q6-8h) and gentamicin (2 to 4 mg/kg q8-12h) or enrofloxacin (2.5 mg/kg IM q12h) can be used. Long-term use of antibiotics should be based on culture and susceptibility results. Animals that suffer recurrent infection due to bronchiectasis may be candidates for chronic suppressive antibiotic therapy or treatment with 1 week of antibiotics each month.

Bronchodilators can be beneficial, although animals typically have irreversible airflow limitation. Cough suppressants must be avoided since failure to remove infectious and inflammatory secretions will perpetuate disease. Maintenance of systemic and airway hydration through oral intake, intravenous fluids, and/or nebulization can be a critical factor in resolution of disease. Because dogs with bronchiectasis tend to pool secretions in lower airways, brisk coupage following nebulization is essential to assist in removal of airway secretions.

214.2.4 Prognosis

Owners should be aware of the likelihood of chronic recurrent infection in dogs with bronchiectasis. Resistance to antibiotic treatment may occur. Animals with significant hypoxemia and parenchymal changes may develop pulmonary hypertension or cor pulmonale. Some animals are at risk for sepsis.

214.2.5 Prevention

Bronchiectasis can be limited by use of appropriate antibiotic therapy in infectious lung disease, prompt recognition and removal of foreign bodies, and appropriate management of chronic bronchitis.

214.3 FELINE BRONCHIAL DISEASE

Feline bronchial disease describes a spectrum of inflammatory small airway diseases in the cat characterized by signs that range from chronic or intermittent coughing to life-threatening respiratory distress. Any age can be afflicted with bronchial disease, and Siamese cats seem to have an increased incidence of disease and may suffer from a more chronic form of bronchial disease.[8] Disease results from inflammation within the airways that induces reversible airflow obstruction through smooth muscle constriction and hypertrophy, bronchial wall edema, and hyperplasia of submucosal glands. Hyper-responsive airways and reversible airflow obstruction have been documented in some cases.[9] These conditions lead to a reduction in airway diameter and increased airway resistance, which cause clinical signs of cough and/or respiratory distress.[8,9]

Experimental models of feline bronchial disease that use antigen or allergen induction of airway hyper-reactivity describe generation of inflammatory and immunomodulatory cytokines and mediators within the airways.[10,11,12] Mast cell degranulation likely leads to recruitment and activation of T lymphocytes. Activated eosinophils release granule contents, and expose the epithelium to major basic protein (MBP), which causes ciliostasis and reduces mucociliary clearance. MBP also leads to epithelial cell lysis and desquamation.[13] Sloughing of pneumocytes exposes sensory and nerve endings to increased types and concentrations of allergens or irritants and may also result in a reduction of epithelial derived relaxant factor. Thus inflammatory damage can enhance neural responsiveness. Recent evidence suggests that inflammation can also induce oxidant stress that perpetuates airway injury.[14]

214.3.1 Presentation

The most frequent presenting complaints in cats with bronchial disease are coughing and abnormal respirations, such as wheezing, loud breathing, or respiratory difficulty.[9] Paroxysmal coughing is commonly reported, and the cough is often described as a dry, “hacking” cough or retch. Exercise intolerance or episodes of open-mouth breathing after exertion may be noted in some cats.

Cats with bronchial disease tend toward obesity given an inability to exercise. Bronchitic cats can appear normal at rest and exhibit normal pulmonary auscultation; however, increased tracheal sensitivity is usually present and post-tussive crackles are typically ausculted. Harsh lung sounds, crackles, or expiratory wheezes are evident in some affected cats, and the expiratory phase is prolonged.[9,15] An abdominal component to respiration may also be noted. Air trapping may occur distal to obstructed airways leading to decreased

thoracic compressibility and a barrel-shaped appearance to the chest. Auscultation in this area of the lung is quiet with increased resonance on percussion.

214.3.2 Diagnostic Evaluation

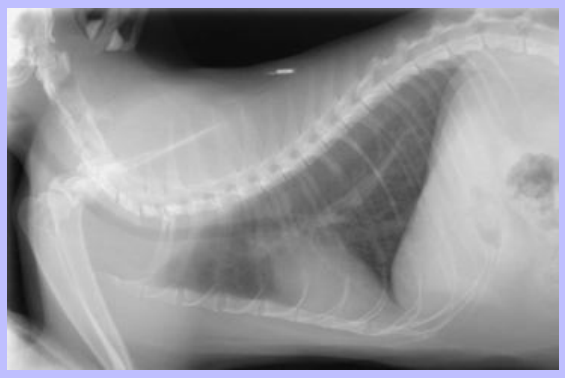
Cats with bronchial disease have nonspecific changes on blood work, and peripheral eosinophilia was reported in only 30% of affected cats.[9] Airway parasites should be ruled out as a cause of airway inflammation and subsequent bronchoconstriction. A sedimentation technique is used to detect the single-operculated egg of *Paragonimus* spp., whereas Baermann flotation is needed to detect *Aelurostrongylus* larvae. A routine fecal flotation can be used to identify *Capillaria* eggs. Heartworm antibody/antigen tests and echocardiography could be considered in cats presenting with cough or respiratory distress.[16]

A variety of interstitial, bronchial, and alveolar infiltrative patterns may be observed in cats with bronchial disease. The severity of the radiographic pattern may not match the degree of respiratory embarrassment in cats with acute bronchoconstriction, and normal chest radiographs do not rule out the diagnosis of bronchial disease. Cats without obvious pulmonary infiltrates may show other radiographic signs compatible with bronchoconstriction, such as air trapping, flattening of the diaphragm, or hyperinflation of the lungs. The hallmark of feline bronchial disease is peribronchial cuffing caused by infiltration of inflammatory cells around the airways (Figure 214-3). Excessive mucus production and obstruction of larger airways can cause alveolar infiltrates, consolidating lesions, or atelectasis.

In the stable cat with airway disease, a transoral tracheal wash or bronchoscopy can be performed to obtain airway specimens for cytology and culture. Substantial elevation of eosinophil and/or neutrophil percentages in airway specimens correlates with the severity of clinical disease[9] and so airway cytology can be used as a guide to therapy. However, normal cats may have up to 25% eosinophils in BALF cells.[17]

Bacterial culture and susceptibility testing should be performed in all cats; however, bacteria can be isolated from a large proportion of healthy cats[9] (Box 214-1). Detection of intracellular bacteria is supportive of a true bacterial infection. *Mycoplasma* species have been isolated from tracheobronchial lavage samples in 21% to 44% of cats with respiratory disease[8,18] but not from bronchoalveolar lavage samples from healthy cats,[17,18] and specific *Mycoplasma* culture on BALF should be considered in cats with respiratory disease.

Figure 214-3 Lateral chest radiograph of a cat with chronic bronchial disease. Airway walls are thickened by peribronchial infiltrates.



Measurement of airway resistance and lung compliance can be performed (in anesthetized cats) at some referral institutions. Cats with bronchial disease can exhibit high lung resistance due to bronchoconstriction. Cats with bronchial disease may also exhibit airway hyper-responsiveness to a nonspecific aerosol stimulant as evidenced by a reduction in the dosage of methacholine required to increase lung resistance.[9] Whole body plethysmography can be used to study airway reactivity in awake, spontaneously breathing cats by measurement of box-pressure signals (expiratory time, peak inspiratory and expiratory flows) and calculation of enhanced pause (PENH), a variable that correlates with airway resistance.[19] Plethysmography is technically challenging, and measured variables are influenced by respiratory rate and the animal's age.

Tidal breathing flow volume loops (TBFVL) have also been evaluated in spontaneously breathing cats with bronchial disease. The cat breathes through a facemask attached to a pneumotachograph and pulmonary mechanics analyzer. Pressure measured at the pneumotachograph is proportional to flow through the mask, and signals are integrated over time to determine volume at each cycle of respiration. Significant findings in cats with bronchial disease include increased expiratory: inspiratory time, decreased peak expiratory flow rate, and decreased tidal breathing expiratory volume.[15]

214.3.3 Treatment

214.3.3.1 Acute Therapy

In the cat with cyanosis and open mouth breathing, diagnostic tests are kept to a minimum initially. Stabilization can be achieved by providing an oxygen enriched environment and using parenteral administration of the beta-2 agonist terbutaline at 0.01 mg/kg IV, IM, or SC.[9] Epinephrine, a sympathomimetic agent, is a potent bronchodilator but should be used only when cardiac disease has been excluded since alpha and beta-1 adrenergic stimulation can result in adverse side effects of cardiac arrhythmias, vasoconstriction, and systemic hypertension. Aminophylline is a weak bronchodilator and its use in an emergency situation may not be justified since terbutaline is more likely to be effective.

Respiratory rate and effort are monitored visually in the first hour of observation to determine therapeutic response. If the cat does not respond to terbutaline initially, use of a short-acting corticosteroid often results in rapid alleviation of airway obstruction. However, use of corticosteroids will affect further diagnostic testing by decreasing migration of inflammatory cells into the airway. Failure to respond to terbutaline and corticosteroids indicates that other causes for respiratory distress should be investigated.

214.3.3.2 Chronic Management

214.3.3.2.1 Anti-inflammatories

Corticosteroids control airway inflammation by inhibition of phospholipase A, the enzyme responsible for initial metabolism of arachidonic acid into inflammatory agents. Corticosteroids also decrease migration of inflammatory cells into the airway, which decreases the concentration of toxic granulocyte products.

The initial dose and duration of corticosteroid therapy depends on the degree and chronicity of respiratory embarrassment, the severity of pulmonary infiltrates, and the level of inflammation detected on cytology. Initially, prednisolone is administered at 1 mg/kg PO BID for 1 to 2 weeks, and the dosage

is decreased to 0.5 mg/kg BID if a good therapeutic response is seen. If the cat remains stable, the dosage can be slowly decreased to once daily and then every other day. Recurrent episodes of coughing or respiratory distress necessitate a return to a higher dosage. Cats are relatively resistant to the side effects of corticosteroids; however, an attempt should be made to achieve the lowest dose of the drug that controls signs. Approximately one half of cats require lifelong medication. 1236 1237

Cats that cannot be orally medicated can be treated with intramuscular injection of a repositol corticosteroid (methylprednisolone acetate at 10 to 20 mg IM every 2 to 8 weeks), or use of inhaled steroids (fluticasone 110 µg) can be considered. Metered dose inhalers of steroid preparations can be attached to a spacer chamber and administered to the cat via facemask. Severely affected cats usually require concurrent oral prednisolone in the initial stages of therapy. Eventually some cats can be maintained with one actuation (and 8 to 10 breaths by the cat) twice daily.

Alternative anti-inflammatory drugs might be beneficial in some cats. In an experimental model of feline asthma, cyproheptadine, a serotonin-receptor blocker, attenuated airway smooth muscle in vitro constriction.[10] Serotonin levels have not been measured in naturally occurring feline bronchial disease; however, some cats may benefit from treatment with cyproheptadine at 1 to 2 mg/cat PO BID. Cyclosporine, an inhibitor of T-lymphocyte activation, may attenuate bronchoconstriction and limit airway remodeling in cats with chronic bronchial disease[11]; however, pharmacokinetics are unpredictable and blood levels must be measured weekly until the desired trough level is achieved. Currently there are no indications for use of anti-mediator drugs such as leukotriene antagonists or 5-lipoxygenase inhibitors in the management of feline bronchial disease.[10,12]

214.3.3.2.2 Bronchodilators

In some cases, bronchodilators may allow a reduction of the dose of steroids required to control clinical signs. Terbutaline can be administered at 0.625 mg PO BID. Inhaled preparations of beta agonists are also available. Theophylline may provide some relief of signs by prevention of acute attacks of bronchoconstriction in predisposed cats or by suppression of inflammation. Sustained-release theophylline can be administered once daily at a dosage of 10 mg/kg PO.

214.3.3.2.3 Antibiotics

Antibiotics should be prescribed based on culture/sensitivity and cytology results if airway infection contributes to bronchial inflammation and hyperresponsiveness. If *Mycoplasma* spp. infection is suspected, a clinical trial of doxycycline can be prescribed while cultures are pending.

214.3.4 Prevention

Because sympathetic tone is particularly important in achieving bronchodilation in the cat, beta-blockers such as propranolol and atenolol should be avoided if bronchial disease is suspected. Cigarette smoke, dusty litters, aerosol spray, and exposure to upper respiratory viruses may trigger clinical signs in susceptible cats.

214.3.5 Prognosis

Therapy with anti-inflammatories and bronchodilators alleviates acute clinical signs in most cases; however, a significant proportion of cats will suffer a recurrence of signs. Continual medical management should be anticipated for many cats diagnosed with bronchial disease.

214.4 PRIMARY CILIARY DYSKINESIA

Clearance of respiratory secretions is dependent on an intact mucociliary elevator. Ciliary ultrastructure is composed of two central microtubules, nine pairs of outer microtubules, dynein arms, and connecting proteins. Primary ciliary dyskinesia (PCD) is an inherited defect in microtubule formation affecting cilia of the respiratory tract, urogenital tract, and auditory canal.[20]

Ciliary dyskinesia can also be an acquired or secondary abnormality caused by chronic respiratory disease in animals with PCD. Clinical signs result from ineffectual movement of cilia and include rhinitis, bronchiectasis, dilatation of renal tubules, infertility, loss of hearing, and hydrocephalus. Kartagener's syndrome is a specific form of PCD characterized by the triad of situs inversus (right to left transposition of thoracic and abdominal organs), chronic rhinitis/sinusitis, and bronchiectasis.

214.4.1 Presentation

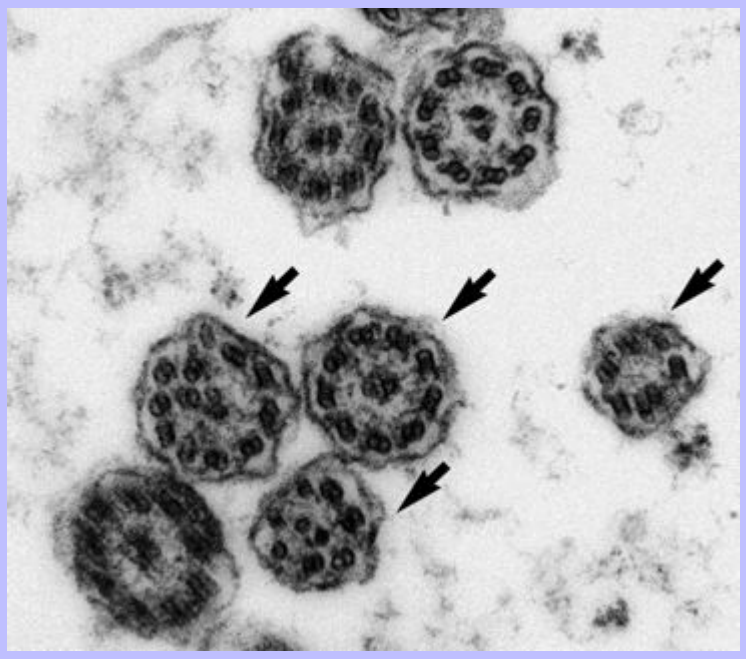
PCD is typically diagnosed in young purebred animals. A higher incidence is reported in the bichon frise, but mix-breed dogs and cats can also be affected. Clinical signs can be observed within the first few weeks of life, but mild clinical signs might not be recognized until later in life.[20] Respiratory findings include chronic serous to mucopurulent nasal discharge, productive cough, exercise intolerance, and respiratory distress. Typically signs do not totally resolve with antibiotic treatment or are recurrent in nature. Physical examination is remarkable for nasal discharge, a moist cough, tracheal sensitivity, or adventitious lung sounds.

214.4.2 Diagnostic Evaluation

Standard diagnostic tests reflect the severity of underlying respiratory infection or inflammation. Radiographic findings are variable and include bronchitis, bronchiectasis, and pneumonia. Consolidating lung lesions can develop in chronic cases. Growth of one or more microorganisms is common in dogs with PCD; therefore airway samples should always be cultured for aerobes, anaerobes, and *Mycoplasma* spp. to provide appropriate antibiotic therapy.

Diagnosis of PCD requires documentation of deficient tracheal mucociliary transport and abnormal ciliary structure. Assessment of functional ciliary transport is typically performed first with nuclear scintigraphy. Because *Mycoplasma* spp. infection, acquired ciliary defects, and exposure to cigarette smoke can delay transport, the diagnosis of PCD is confirmed with transmission electron microscopy of nasal or bronchial respiratory epithelium or seminal samples. Normal animals can have structural abnormalities in 2% to 5% of cilia; therefore both the extent and the quality of ultrastructural abnormalities must be examined (Figure 214-4). Typical findings in PCD include shortening or loss of dynein arms, atypical microtubular orientation, and duplication or deletion of central or outer microtubule doublets.[20,21]

Figure 214-4 Transmission electron micrograph displaying abnormal numbers of microtubules within respiratory cilia (*arrows*).



Culture techniques can be used to differentiate primary from secondary ciliary abnormalities. In cell culture, airway epithelial cells lose cilia as a monolayer develops. With resuspension and reculture, ciliogenesis occurs. In a patient with secondary ciliary defects, the regenerated cilia are normal, however abnormalities persist in the animal with PCD.[21]

214.4.3 Treatment

The primary goal of therapy is to control infection with appropriate antibiotics and to facilitate clearance of respiratory secretions. Use of cough suppressants is contraindicated in PCD since these drugs can enhance trapping of secretions in the lower airway and potentiate airway inflammation.

214.4.4 Prognosis

Control of respiratory infection is essential to prevent debilitating sequellae in dogs with PCD. Some dogs can achieve excellent quality of life despite defective ciliary transport.

214.4.5 Prevention

PCD is suspected to be inherited as an autosomal recessive trait; therefore clinically normal individuals could produce an offspring with PCD. Close relatives of affected animals should not be included in a breeding program.

214.5 BRONCHIAL NARROWING

Larger airways may be compressed by external mass lesions, by an enlarged left atrium, or by loss of cartilaginous support of large intrathoracic airways. Hilar lymphadenopathy due to fungal disease, granulomatous disease, or neoplasia typically causes dorsal compression of the airway at the carina. Left atrial enlargement associated with mitral regurgitation causes dynamic collapse of the left mainstem bronchus and can be a cause of cough in the absence of heart failure. However, the most common cause of airway narrowing appears to be related to failure of the cartilage to maintain the patency of the airways.

214.5.1 Presentation

Bronchial compression or collapse occurs more often in dogs than in cats. This obstructive lesion leads to a chronic, nonproductive cough, respiratory difficulty, or wheezing during inspiration and expiration. An end-expiratory snap may be heard as intrathoracic airways close and open during forced expiration. In dogs with left atrial enlargement and mitral regurgitation, a systolic murmur may be present.

214.5.2 Diagnostic Evaluation

Hilar mass lesions can usually be seen on static thoracic radiographs; however, collapse of the mainstem bronchi or intrathoracic airways often requires fluoroscopic or bronchoscopic examination. Echocardiography assists in the diagnosis of left atrial enlargement.

214.5.3 Treatment

Hilar lymphadenopathy due to active fungal infection usually resolves substantially with antifungal treatment. Rare cases may require steroid therapy or surgical debulking. Collapse of the left mainstem bronchus due to left atrial enlargement may be partially alleviated by therapy directed at reduction of left atrial volume; however, many cases have persistent collapse. Chronic cough associated with deficient cartilaginous support is challenging to control. Cough suppressants are used to alleviate clinical signs when infectious and inflammatory conditions are ruled out.

214.6 AIRWAY FOREIGN BODIES

Aspiration of plant material, sticks, toys, teeth, or stones occurs when the laryngeal reflex fails to prevent access of foreign objects into the trachea. Dogs that are involved in strenuous physical activity in rural environments are especially prone to aspiration. Animals with laryngeal paralysis may be more likely to aspirate due to a combination of poor laryngeal sensation and deficient laryngeal reflexes. Animals should be intubated during dental procedures to prevent aspiration of teeth or dental tartar.

214.6.1 Presentation

Bronchial foreign bodies cause an acute or chronic unrelenting cough, airway obstruction, and marked tracheal sensitivity. Within a variable period of time, consolidating pneumonia develops. A bronchial foreign body should be suspected when an animal has a recurrent cough that partially responds to antibiotic therapy, or when an animal has recurrent airway infection, particularly if anaerobic bacteria are involved.

214.6.2 Diagnostic Evaluation

Thoracic radiography will identify a radiodense foreign object; however, foreign bodies of plant origin are not always visible. Distal atelectasis or consolidation of a lung segment can be suggestive of foreign body obstruction, although a mass lesion, mucus plug, or pneumonic condition would appear similarly. Infection secondary to a foreign body can result in diffuse interstitial or alveolar infiltrates. A pulmonary abscess may be identifiable as a discrete fluid-filled cavity encased by fibrous tissue.

Definitive diagnosis can often be made by bronchoscopic evaluation of the airways. All airway segments must be evaluated in the search for foreign bodies, and objects can often be removed if there is an edge that can be grasped by biopsy or rat tooth forceps. Stones are a challenge to remove bronchoscopically, especially when they are wedged in a bronchus. In chronic cases of plant aspiration, the foreign body is often obscured by purulent exudate, and gentle lavage and suction of the area is required to identify foreign material.

Airway samples are cultured for both aerobes and anaerobes given the high likelihood of bacterial contamination. Animals should be followed closely after removal of the foreign body since bronchiectasis may develop distal to the obstruction.

214.6.3 Treatment

Animals with bronchial foreign bodies are at risk for pulmonary abscess, bronchoesophageal fistula, empyema, and bronchiectasis distal to the obstruction. Lung lobectomy is often required for unretrievable foreign bodies, or when lung abscessation, bronchiectasis, or fistulation has occurred. Pleural infection requires thoracic drainage and usually thoracotomy. Long-term antibiotic therapy is based on culture and sensitivity results.

214.7 BRONCHOESOPHAGEAL FISTULA

Bronchoesophageal fistula may be congenital, or acquired due to trauma, a penetrating esophageal foreign body, or a bronchial foreign body. Affected animals present with chronic cough and recurrent pneumonia related to aspiration of esophageal contents. In some cases, difficulty eating may be the predominant sign. Respiratory signs may be relatively mild, resulting in a marked delay in the diagnosis of a congenital lesion. The diagnosis should be suspected in a young animal with recurrent aspiration pneumonia or a focal, recurrent lung density. The diagnosis is confirmed by a contrast esophagram. Endoscopic examination via the airway or esophagus can occasionally detect a fistula. Surgical resection of the abnormal connection is required, and lung lobectomy is sometimes necessary due to adhesion formation or abscessation.

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214.8 BRONCHIAL MINERALIZATION

Bronchial mineralization can occur secondary to any chronic inflammatory or infectious condition and is seen with bronchitis and bronchiectasis. Prominent mineralization of airways has also been reported in hyperadrenocorticism. The contribution of bronchial mineralization to respiratory dysfunction is unclear.

214.9 BRONCHIAL NEOPLASIA

Animals with bronchial neoplasia can present with cough, an obstructive breathing pattern, or panting. Respirations are typically loud, and harsh wheezing noises are heard over large airways compressed or occluded by mass lesions. Diagnosis and treatment is described under pulmonary neoplasia (see Chapter 127).

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215 CHAPTER • 215 Pulmonary Parenchymal Disease

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Rance K. Sellon

215.1 OVERVIEW OF DIAGNOSTIC CONSIDERATIONS

Dogs and cats are susceptible to a wide variety of inflammatory and noninflammatory diseases of the pulmonary parenchyma. Animals with parenchymal disease may exhibit clinical signs typical of lower respiratory tract disease such as cough and respiratory difficulty, or show no clinical signs despite sometimes extensive pulmonary disease.

When clinical information is suggestive of pulmonary parenchymal disease, a relatively finite number of diagnostic tests become available to the clinician. Thoracic radiography will be the key diagnostic tool in the majority of cases. Collection of respiratory samples by wash techniques, needle aspiration, or biopsy will be appropriate in many cases. Ancillary diagnostic tests that are often employed in patients with respiratory disease include CBC, biochemical profile and urinalysis, fecal examinations, serologic assays, and microbial culture and sensitivity. The diagnostic approach to a given patient will be influenced by the list of likely differentials, costs associated with diagnostic tests, and the patient's status. Many patients will require initial empiric therapy and supportive measures (e.g., oxygen supplementation) for alleviation of respiratory distress and stabilization before proceeding with focused diagnostic tests. A more comprehensive discussion of the diagnostic tools used in the evaluation of the patient with respiratory disease is presented in Chapter 212.

An important diagnostic tool that is underused in small animal practice is blood gas analysis. The availability of portable bedside analyzers makes blood gas measurements accessible to most small animal practitioners. Blood gas analysis provides important information regarding two important functions of the respiratory system, alveolar ventilation and oxygenation of pulmonary arterial blood. Blood gas analysis is the only means to properly assess alveolar ventilation: the capacity of a patient to properly ventilate cannot be assessed by evaluation of respiratory rate or pattern or by thoracic radiographic abnormalities. Although many parenchymal diseases are associated with hyperventilation, some can be associated with hypoventilation, particularly as respiratory fatigue develops. Knowledge of the adequacy of alveolar ventilation has important treatment ramifications. Hypoventilating animals become candidates for ventilatory support depending on the cause of the hypoventilation. Untreated, severe hypoventilation can cause respiratory acidosis, which is associated with cardiac arrhythmias and central nervous system depression.

Blood gas analysis can also help the clinician determine the mechanism that drives the development of arterial hypoxemia. The most common mechanisms that cause arterial hypoxemia in small animal practice are hypoventilation, revealed by increased P_aCO_2, and ventilation-perfusion (V/Q) mismatches. Other mechanisms, such as right-to-left shunts, and diffusion barriers, are less common. Calculation of A-a differences can reveal underlying impairments in oxygenation coexistent with hypoventilation. Hypoxemia caused by V/Q mismatches or diffusion barriers are somewhat responsive to oxygen; hypoxemia caused by right to left shunting is poorly responsive to oxygen. A more complete discussion of blood gas interpretation is presented in Chapter 212.

There are many indications for oxygen supplementation. Animals with parenchymal or other diseases associated with arterial hypoxemia through any of the mechanisms noted above, or patients with diseases that alter hemoglobin affinity for oxygen (e.g., carbon monoxide poisoning) are candidates for oxygen supplementation.

Animals with clinical signs consistent with hypoxemia or tissue hypoxia, such as cyanosis, tachypnea, dyspnea, or central nervous system dysfunction are also potential candidates for oxygen supplementation. Interested readers are referred elsewhere for a more comprehensive review of the indications for oxygen supplementation.[1]

Oxygen may be administered to conscious patients via face masks, nasal oxygen catheters, intratracheal catheters, oxygen cages, or flow-by techniques.[1] The method of delivery selected will reflect availability, patient status, and patient tolerance. Increases in inspired oxygen concentration of 40% or greater can be achieved with these methods depending on flow rates. The risk of oxygen toxicity exists for patients supplemented with inspired oxygen concentrations of 50% for more than 24 hours, or 100% for more than 12 hours. If the patient's PaO_2 cannot be maintained at acceptable levels, generally 60 mm Hg or higher, on inspired oxygen concentrations less than 50% to 100%, ventilatory support may be needed. Humidification of oxygen is advised if oxygen is to be administered for more than a few hours to reduce complications associated with airway drying. Responses to oxygen supplementation can be made subjectively (changes in patient comfort, level of respiratory distress) or more objectively by repeat measurement of PaO_2 or oxygen saturation by pulse oximetry. The reader should be aware that patients monitored by pulse oximetry may still have clinically important hypoventilation and hypercarbia not detected by pulse oximetry when such patients are receiving supplemental oxygen.

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As noted, ventilatory support may be needed in some patients with parenchymal disease. Hypoventilation not readily corrected, as might occur with respiratory paralysis or fatigue, CNS disease, or others, is one indication for ventilatory support. Hypoxemia refractory to supplemental oxygen administration is another. There are many different strategies for providing ventilation, which have been reviewed elsewhere.[2] Short-term ventilatory support can be provided in most practices by use of an ambu bag or the reservoir bag on an anesthetic machine.

215.2 PULMONARY EDEMA

Fluid accumulation in the interstitium and alveoli of the lung is termed *pulmonary edema*. The causes of pulmonary edema are typically divided into four major mechanisms: (1) increased vascular hydrostatic pressure, (2) decreased plasma oncotic pressure, (3) increased vascular permeability, and (4) impaired lymphatic drainage. Occasionally, a fifth miscellaneous or idiopathic category is described if edema develops without any apparent association with the other four mechanisms. When increased pulmonary venous hydrostatic pressure and left-sided congestive heart failure (CHF) are responsible for edema, the term *cardiogenic pulmonary edema* is often used. *Noncardiogenic edema* describes edema from other, non-CHF causes induced by any of the additional mechanisms listed.

The pulmonary parenchyma is somewhat resistant to the development of edema. In general, the hydrostatic pressure in the pulmonary vascular bed is relatively low compared with vascular beds in other regions of the body. Normal pulmonary wedge pressures (an estimate of capillary hydrostatic pressure) are approximately 5 mm Hg. In addition, pulmonary lymphatic drainage is relatively high due to the continual pumping action of the lungs by respiration. The capacitance of the pulmonary lymphatic system is large, and the lymphatic volume can greatly expand to further increase the removal of fluid if necessary. Alveolar surfactant surface tension helps protect against the development of pulmonary edema by decreasing the tendency for fluid to be drawn into the alveoli. Because of these protective mechanisms, acute increases in pulmonary capillary hydrostatic pressures must exceed 20 mm Hg before edema develops.[3, 4] With more slowly developing increases in hydrostatic pressure, pressures in excess of 40 mm Hg have been documented without pulmonary edema.[4,5] In these instances, time allows for stretch and greater capacitance of the pulmonary vessels, as well as an increase in lymphatic drainage to remove interstitial fluid. When fluid translocates into the interstitial space and lymphatic drainage cannot match the rate of fluid influx, interstitial edema occurs. If the pathophysiologic process driving

the movement of fluid continues, the capacitance of the interstitial space is eventually overwhelmed and fluid accumulates in the alveoli. Gas exchange is impaired when airways become "flooded." Atelectasis, decreased lung compliance and airway compression, consequences of pulmonary edema, all increase pulmonary vascular resistance. The combination of impaired gas exchange and increased vascular resistance create ventilation-perfusion mismatches, which results in hypoxemia.

Left-sided CHF is the most common cause of pulmonary edema due to increased hydrostatic pressure (see Chapter 197). However, edema due to excessive fluid administration is not unusual, particularly in the setting of impaired fluid excretion as might be seen with oliguric or anuric renal failure. Pulmonary edema due to decreased plasma oncotic pressure is caused by hypoalbuminemia. Causes of hypoalbuminemia are listed on the inside cover of this book. Pleural effusions (transudative) are more common than pulmonary edema in patients with reduced oncotic pressure as a single driving mechanism. Pulmonary edema formation is not expected from hypoalbuminemia unless serum albumin concentrations are less than 1 g/dL. Even then, subcutaneous edema, pleural effusion or other sites of edema formation typically occur prior to pulmonary edema. Pulmonary edema may be seen in patients with higher serum albumin concentrations if there is vasculitis, or if hydrostatic pressures increase because of impaired ventricular filling or excessive administration of IV fluids.

Pulmonary edema due to increased vascular permeability can occur with a wide variety of pulmonary and systemic disorders. The edema in this case is termed *noncardiogenic* and is usually relatively proteinaceous.[6,7] Capillary wedge pressures are normal. Any septic or nonseptic inflammatory condition or any cause of vasculitis may promote vascular damage and leakage. Other diseases associated with noncardiogenic edema are acute respiratory distress syndrome (ARDS, see later discussion), acute upper airway obstruction, electric shock, neurogenic edema (often secondary to seizures or head trauma), and hepatic disease.[6,8] Although the pulmonary edema that develops in association with many of these conditions is suspected to result from increased capillary permeability, the exact mechanisms driving the formation of edema are for the most part unknown. Primary pulmonary lymphatic obstruction is an uncommon cause of pulmonary edema and when it occurs, is typically the result of a neoplastic process or lymphangitis.

215.2.1 Presentation

Most patients will present with tachypnea and cough, or respiratory distress and hypoxia if alveolar involvement is severe. Symptoms are directly related to the cause and severity of the edema. The character of respiration is usually that of increased effort noted during inspiration and expiration due to increased lung stiffness. Severe edema may cause coughing with expectoration of blood-tinged fluid. Several abnormalities may be heard during thoracic auscultation, classically in the dorsocaudal lung fields. Crackles heard on inspiration and especially end-expiration are common; however, crackles may be absent in early or mild edema. Lungs sounds may seem exceptionally quiet with very severe edema, particularly in cats. Additional changes reflecting underlying disease processes may be noted. Abnormalities of cardiac auscultation (murmurs, transient sounds, arrhythmias) may indicate the presence of heart disease, but their presence does not always indicate an etiology of cardiogenic edema. A patient with a heart murmur and coarse crackles during inspiration without sinus tachycardia should be carefully evaluated for pulmonary diseases other than cardiogenic pulmonary edema. Patients with CHF-induced pulmonary edema would be expected to have tachycardia as a result of increased sympathetic tone. Some patients with congestive heart failure will lack abnormal heart sounds, for example those with certain forms of cardiomyopathy.

215.2.2 Diagnostic Evaluation

Thoracic radiographs, combined with historical and physical findings, are often diagnostic. Cardiogenic edema is characterized radiographically by "fluffy" interstitial opacities that can rapidly progress to an alveolar pattern. In the dog, the opacities are most often distributed in the hilar and caudodorsal perivascular lung regions (see Figure 215-1). In the cat, these opacities are patchy and may be diffuse or focal. Pulmonary venous enlargement suggests pulmonary venous and left atrial hypertension consistent with left-sided CHF. Enlargement of the cardiac silhouette, particularly left chambers, is commonly present in patients with cardiogenic edema. Pulmonary edema caused by increased vascular permeability is also typically most severe in the caudodorsal lung lobes.[7] The absence of cardiac and pulmonary venous changes can, in most cases, distinguish such patients from those with cardiogenic edema. History and laboratory parameters are helpful in identifying underlying causes of noncardiogenic edema such as electrocution, sepsis, pancreatitis, and others. In many cases of noncardiogenic pulmonary edema, the edema is mild and not a part of the primary clinical complaint. Pulmonary edema resulting from decreased plasma oncotic pressure is typically characterized by generalized interstitial or mixed interstitial-alveolar pattern. Pleural effusion may also be present and vascular congestion is absent.

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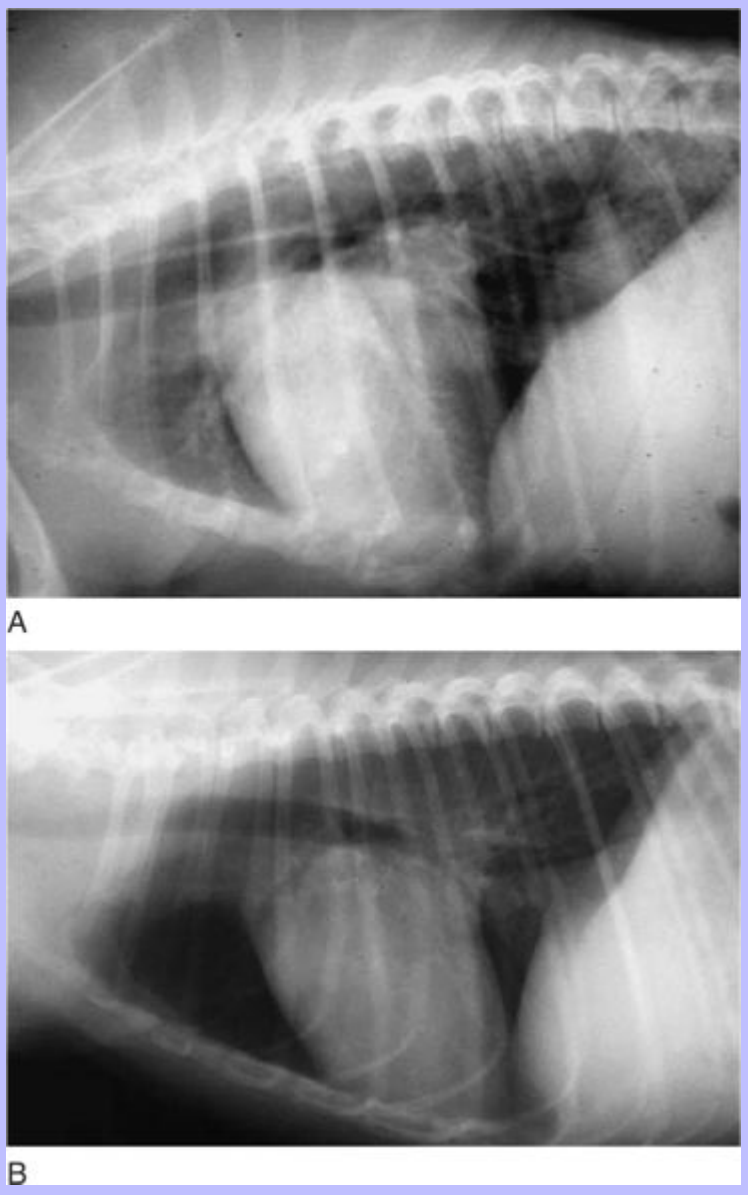
Figure 215-1 Lateral thoracic radiographs of a dog with cardiogenic pulmonary edema before and after treatment. Note the left atrial and ventricular enlargement and the engorged pulmonary veins, especially left cranial lobar vein. **(A)** There is an interstitial and alveolar pattern present in the pretreatment radiograph not evident in the post-treatment film **(B)**.



Arterial blood gas analysis typically documents hypoxemia, hypocapnia, and widened A-a gradient. Results of a CBC, serum biochemistries, and urinalysis may be helpful to determine underlying causes, particularly in noncardiogenic edema. Lung specimens obtained by respiratory washes or biopsy often do not yield a specific diagnosis unless primary pulmonary pathology is demonstrated.

215.2.3 Treatment

The primary therapeutic goal in the management of patients with pulmonary edema is improvement of oxygenation while stress is minimized. Minimizing stress is particularly important in severely distressed animals for which simple manipulations may lead to overt cardiopulmonary arrest. Oxygen may be administered through nasal cannula, face mask, or oxygen cage. Compromised patients may be best treated empirically based upon their initial clinical signs and presumptive diagnosis until deemed stable for additional tests, such as thoracic radiographs. Sedatives can be valuable to relieve anxiety and decrease unnecessary oxygen consumption. Morphine sulfate can be administered IV at a dosage of 0.1 to 1 mg/kg in dogs but is not suggested for use in cats. In addition to sedative benefits, mobilization of pulmonary edema has been attributed to morphine administration. Alternatively, acepromazine can be used in cats and dogs at 0.03 to 1.0 mg/kg IV, IM, or SQ. In critical cases, intubation and positive pressure ventilation may be necessary.

Narcotics and tranquilizers are likely to depress the respiratory center while severe hypoxia initiates significant anxiety. As with many medical states, an appropriate balance is sought.

Diuretic therapy is particularly effective for acute relief of pulmonary edema that develops from volume overload disorders such as CHF. Furosemide, 2 to 4 mg/kg IV every 4 to 12 hours, can be given for clinical pulmonary edema. Diuretics may be less beneficial for edema that develops secondary to increased vascular permeability disorders such as ARDS, and caution is advised when administering diuretics to patients with pre-existing hypovolemia.[9]

Bronchodilators such as the methylxanthines, aminophylline and theophylline may be beneficial to combat bronchospasm, enhance mucociliary function, and diminish diaphragmatic fatigue. Specific therapies should be also be directed at any underlying etiology such as hypoproteinemia (see Chapter 199) or cardiac disease.

215.2.4 Prognosis

Pulmonary function and cardiac disease, if present, are monitored often. Thoracic radiographs should be re-evaluated every 24 to 48 hours; the clinician should remember that radiographic changes often lag behind clinical response. The prognosis with treatment of pulmonary edema is variable and depends on the severity of edema and respiratory dysfunction, the nature of any underlying disorders, and aggressiveness of monitoring and therapy.

215.3 PULMONARY NEOPLASIA

215.3.1 Primary Pulmonary Neoplasia

Primary pulmonary tumors are not considered as common in dogs and cats as are metastatic tumors. Pulmonary neoplasia can be seen in animals of almost any age, although the majority of patients are middle-aged to older reflecting the general increase in prevalence of tumors in the pet population as it ages.

Primary lung neoplasia accounts for approximately 1% of all tumors in dogs, and fewer in cats.[10] Most primary tumors of the lung are carcinomas that arise from bronchial or alveolar epithelium, but occasionally squamous cell carcinomas can be seen.[10,11] Other less common primary lung tumors include osteosarcomas or other mesenchymal tumors.

215.3.1.1 Presentation

The clinical presentation of patients with lung tumors can be variable and may or may not reflect signs referable to the respiratory system. Chronic cough that is unresponsive to antibiotics is seen most often in dogs. Exercise intolerance, tachypnea, or overt respiratory distress can occur. Respiratory distress can result from involvement of the pleural space with development of hemothorax, pneumothorax, or pleural effusion, intraluminal obstruction or extraluminal airway compression, or pulmonary artery obstructions (inflammatory or tumor thrombus) causing ventilation-perfusion mismatches.[13] Cats with primary lung tumors may exhibit lethargy, anorexia, weight loss, dyspnea and tachypnea, wheezes, and non-productive cough. A large proportion of cats with primary pulmonary neoplasia in one study had no clinical signs referable to the presence of the lung tumor.[11] Patients with primary pulmonary neoplasia can exhibit hemoptysis.[13]

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Although primary respiratory signs are expected in most patients with primary pulmonary tumors, some will have clinical signs that reflect metastasis of the lung tumor to extrathoracic organs, such as musculoskeletal structures, including the digits, abdominal organs, or brain. Clinical signs that develop from metastasis of lung tumors to other organs can thus include lameness, abdominal effusion, neurologic abnormalities, or others. Paraneoplastic syndromes that develop in conjunction with either primary or metastatic lung tumors may also be responsible for the development of clinical signs, such as lameness observed in animals with hypertrophic osteopathy (Figure 215-2).

Figure 215-2 Hypertropic osteopathy in a dog with pulmonary metastatic disease. Note the extensive periosteal proliferation along the metatarsal bones.

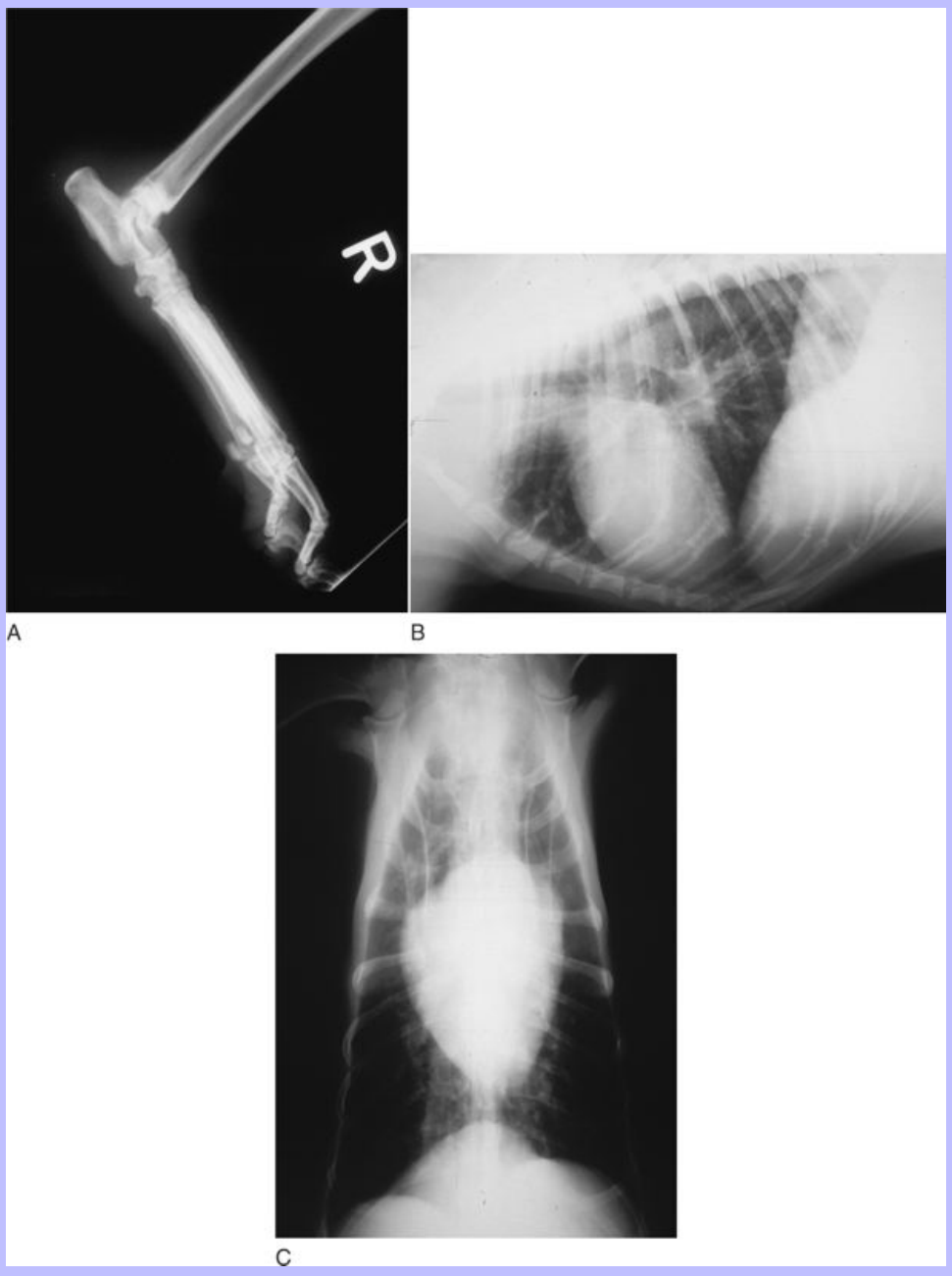

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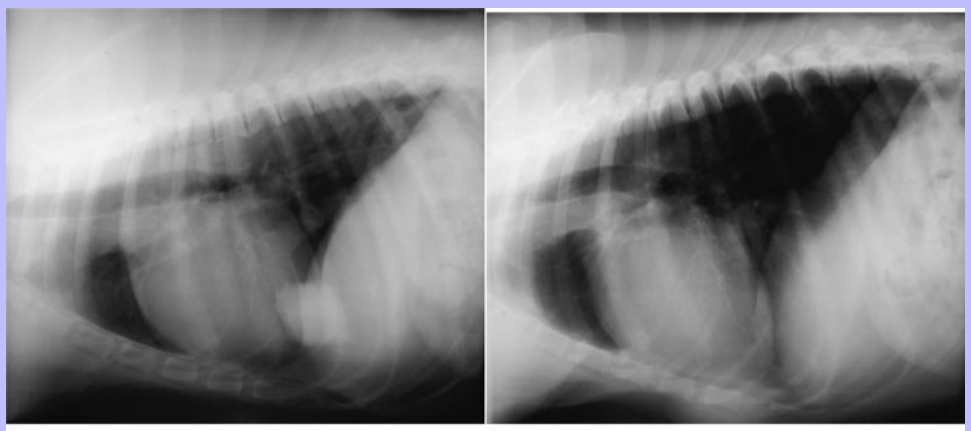
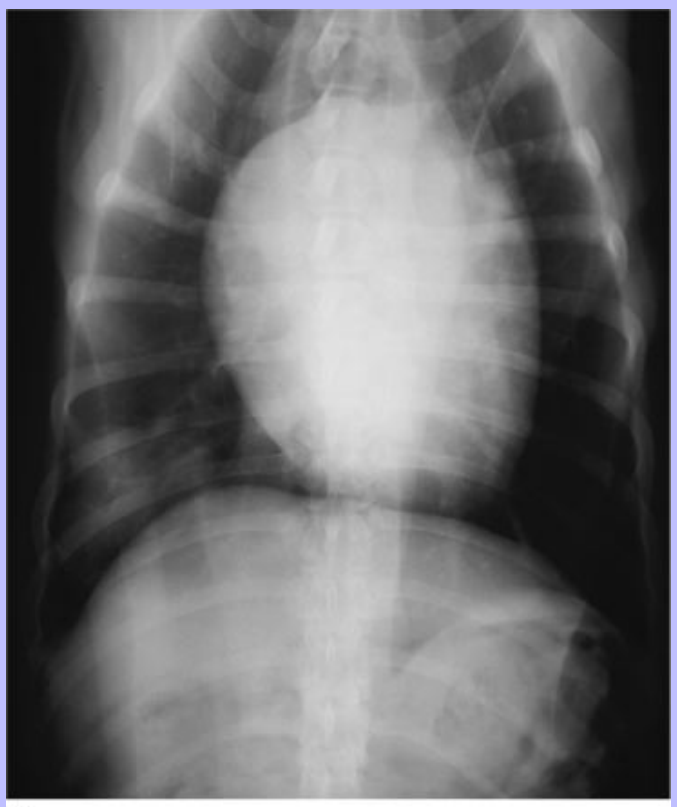
Figure 215-3 Right **(A)** and left **(B)** lateral and ventrodorsal **(C)** thoracic radiographs of a dog with a solitary lung mass best seen in only one radiographic projection.





215.3.1.2 Diagnostic Evaluation

Thoracic radiographs are a key tool in the diagnostic approach to patients with pulmonary neoplasia. The radiographic appearance of primary pulmonary neoplasia varies. Abnormalities observed on thoracic radiographs can range from discrete nodules of varying size and number, to ill-defined interstitial patterns, to consolidated single lung lobes. Radiographic patterns can be focal or diffuse depending on the nature of the neoplasm and whether there has been pulmonary metastasis. Enlargement of hilar lymph nodes may also be seen.

When evaluating animals radiographically for which pulmonary neoplasia or other primary pulmonary disease is suspected, it may be useful to obtain three views of the thorax, right and left laterals, and either a ventrodorsal or dorsoventral image. Three radiographic views maximize the opportunities to see lesions that might be obscured by the heart, or if in caudal lung fields, the liver (Figure 215-3). Computed tomography (CT), available at many referral centers, can provide an extra degree of sensitivity in the characterization and localization of lung lesions, including small metastatic lesions (Figure 215-4).[14–16] The size of lesions detectable with CT is influenced by several factors, including the distance between slices, amount of overlap between slices, and the location of the lesion within the parenchyma, but detection of nodules less than 5 mm in size is possible. As with other imaging modalities, false positive and false negative results are encountered with CT. CT is more expensive as compared to plain thoracic radiographs, and general anesthesia is usually required for diagnostic CT images, which may be of concern in patients with respiratory embarrassment.

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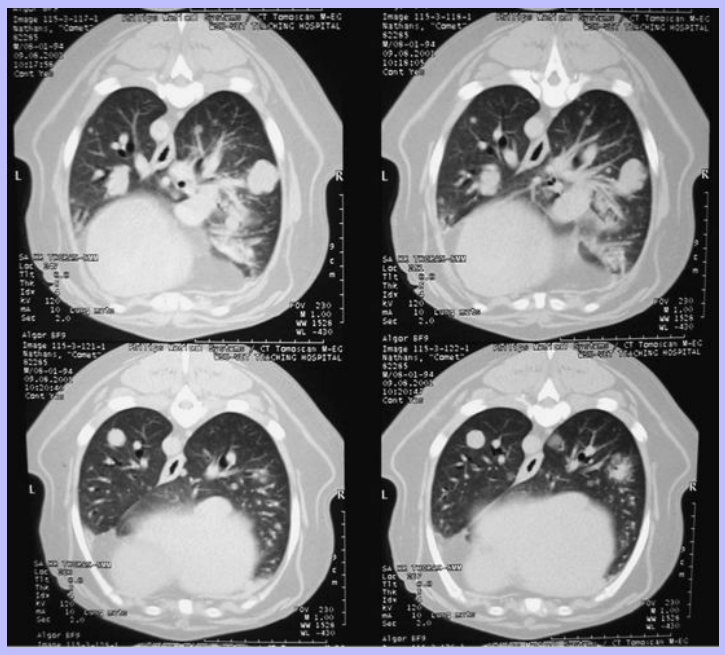
Figure 215-4 Computed tomographic scan of the thorax of a dog with pulmonary metastasis. Note the presence of numerous small densities in the lung periphery.



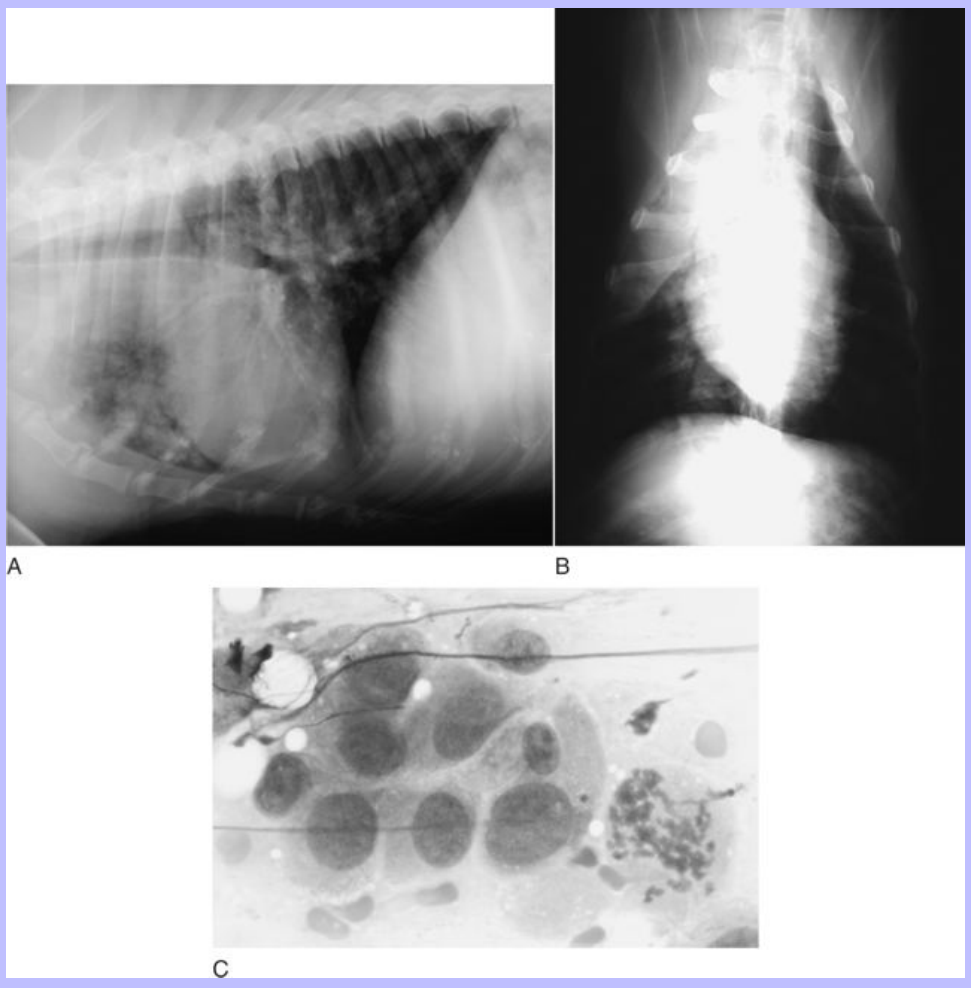
Thoracic radiographs cannot provide cytologic or histologic diagnoses, so the definitive diagnosis of primary pulmonary neoplasia hinges upon demonstration of neoplastic cells either cytologically or histopathologically. The location of lesions observed radiographically can be helpful in guiding the clinician toward appropriate sampling techniques. Some masses, particularly large masses adjacent to the thoracic wall, will be amenable to blind fine needle aspiration using anatomic landmarks observed on radiographs to guide needle placement (Figure 215-5). Smaller masses adjacent to the thoracic wall may be aspirated with ultrasound guidance; the more aerated lung around the mass, the less amenable to ultrasound-guided aspiration it will be. Techniques available at some referral centers for nonsurgical sampling of pulmonary masses include fluoroscopic and CT-guided aspiration (Figure 215-6). Respiratory wash techniques may be considered, but may have poor sensitivity for focal lesions. Bronchoscopy could be valuable to obtain brush cytology or biopsies of lesions extending into the bronchial lumen. Surgical approaches such as thoracotomy or thoracosopy can be both diagnostic and therapeutic.

The decision as to which diagnostic approach will be taken to define the origins of a pulmonary mass will be influenced by the features of the mass and by the client's willingness to tolerate expense, risk of complications, and the status of the patient. Transthoracic needle aspiration and tracheal wash are comparatively inexpensive and widely accessible because minimal equipment is needed to perform these techniques. The most common complication associated with transthoracic aspiration is pneumothorax (see Chapter 103), so the clinician should be prepared to manage the complications of needle aspiration. A key point to be considered when attempting to establish the etiology of a pulmonary mass is that false negative, or even misleading, results with any of the techniques are common. It is possible for samples collected from pulmonary neoplasms to appear as inflammatory or even infectious processes on aspiration cytology or bronchoalveolar lavage.[17] Thus a negative result does not at all exclude neoplasia or other diseases that cause pulmonary masses. A patient may be subjected to various nonsurgical attempts at a diagnosis and still in the end need a thoracotomy or thoracoscopy to establish a definitive diagnosis.[17]

215.3.1.3 Treatment and Prognosis

The treatment for primary pulmonary neoplasia is surgical resection. Patients with small focal lesions can have a good prognosis. The prognosis for dogs is considered better in those patients that have solitary, well-differentiated lesions less then 5 cm in diameter, no metastasis to regional lymph nodes, and no malignant pleural effusion.[10] Cats have been considered in general to have a poorer prognosis in the face of primary lung tumors, with the degree of differentiation of tumors being more predictive of survival.[18] Patients with adenocarcinomas are also considered to have a better prognosis than those with squamous cell carcinomas. Because the prognosis of patients with primary lung tumors is difficult to establish without histologic information (tumor type and degree of differentiation, hilar lymph node metastasis), surgical resection can be advocated early in the course of the diagnostic process as lung lobectomy will be diagnostic, provide prognostic information, and will be the first step in providing definitive therapy.

Figure 215-5 **A** and **B,** Thoracic radiographs (lateral, ventrodorsal) from a dog with primary pulmonary neoplasia. The affected lung lobe was sampled by ultrasound-guided needle aspiration. **C,** Photomicrograph of the carcinoma cells obtained by needle aspiration of the lung mass.



215.3.2 Metastatic Lung Disease

The respiratory system, owing to the key anatomic location of the pulmonary capillary bed, is a frequent site for the development of metastatic tumors of both carcinoma and sarcoma origin. Metastatic pulmonary neoplasia is the most common pulmonary neoplasia in dogs and cats. Although virtually any tumor can metastasize to the lungs, tumors with a high predilection for pulmonary metastasis include canine osteosarcomas, mammary carcinomas in dogs and cats, and oral and nail bed melanomas in dogs.

215.3.2.1 Presentation

Clinical signs observed in patients with pulmonary metastatic disease are widely variable and usually reflect the presence of the primary tumor. Clinical signs referable to the lower respiratory tract such as cough or exercise intolerance are frequently absent even in the face of large metastatic burdens (Figure 215-7). It is not unusual in the authors' experience to see patients with histories of lethargy, anorexia, weight loss, and unremarkable physical examinations that have radiographic lesions consistent with pulmonary metastatic disease. Because of the frequency with which vague clinical signs can be observed in dogs and cats with neoplasia that is not detectable by physical examination, a three-view thoracic radiograph is a recommended component of the initial diagnostic plan for such patients.

215.3.2.2 Diagnostic Evaluation

The diagnosis of metastatic neoplasia is often presumptive based on compatible thoracic radiographic abnormalities in a patient with a history of a histologically confirmed malignancy. Radiographically, pulmonary metastasis can be surprisingly variable in appearance and can run the gamut from multiple, well-defined interstitial nodules, to ill-defined interstitial patterns to alveolar patterns.[19] Many of these patients will not have diagnostic tests performed to confirm that observed lesions are metastatic lesions.

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However, the clinician has to be careful in assuming that observed radiographic lesions are neoplastic lesions, particularly in the patient that has not had a primary tumor identified. Pitfalls in such thinking include the fact that other diseases, such as the systemic fungal infections, occasional bacterial and mycobacterial infections, or hypersensitivity disorders (e.g., eosinophilic granuloma) can mimic the clinical disease and radiographic appearance of metastatic pulmonary disease. In addition, patients with one malignancy can develop other tumors that have no relationship to previously diagnosed tumors, and for which diagnostic and therapeutic intervention would be of benefit. Definitive diagnosis of metastasis can be made using the techniques described above in the diagnostic approach to primary lung tumors.

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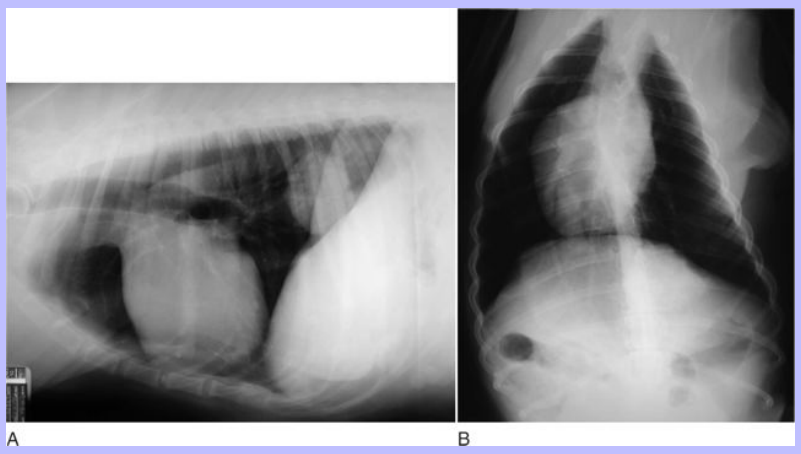
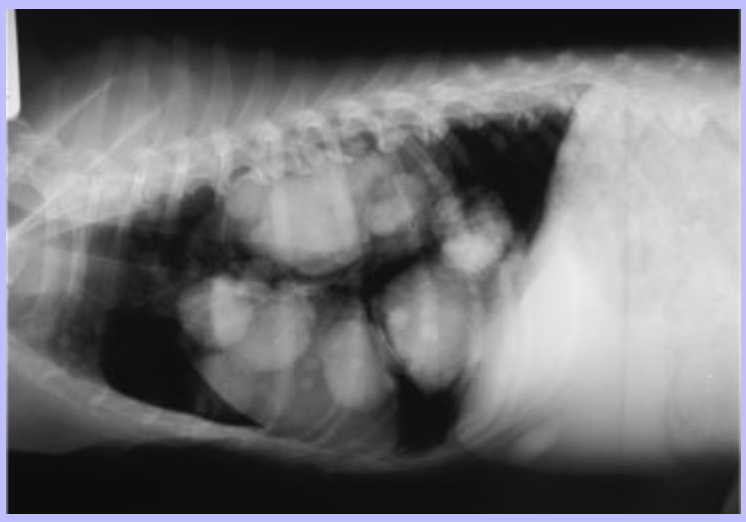
Figure 215-6 Thoracic radiographs (lateral **[A],** ventrodorsal **[B]**) of a dog with a solitary lung mass deep in the thoracic cavity. This mass was successfully aspirated with fluoroscopic guidance.



Treatment of metastatic lung disease is often unrewarding but could be of short-term benefit in patients that exhibit clinical signs referable to their pulmonary lesions. The decision to treat obviously will be weighed against other factors, such as rapidity of disease progression, quality of life concerns, owner wishes, and owner willingness to tolerate expense and complications of treatment. Treatment of metastatic lesions could require surgical resection, best for few lesions, or chemotherapy if not already administered for the patient's primary tumor. Recently, some positive responses have been observed in dogs with metastatic pulmonary disease treated with chemotherapeutic agents or interleukin-2 via inhalation.[20,21] Such an approach offers the potential of treating pulmonary metastatic disease with fewer adverse effects as can occur with systemic administration of such agents.

Figure 215-7 Lateral thoracic radiograph of a dog with extensive pulmonary metastasis. This dog exhibited no clinical signs of respiratory disease. (Courtesy Dan Brown, Moscow, ID.)



215.3.3 Lymphosarcoma

The respiratory tract is frequently affected in dogs with lymphosarcoma, although not all dogs will have clinical signs of respiratory disease. Radiographically, lymphosarcoma can assume a variety of radiographic patters from interstitial to alveolar to mixed patterns (Figure 215-8). The diagnosis of lymphosarcoma is usually made based on assessment of other organs, but the similarities of the radiographic abnormalities to other pulmonary diseases should prompt consideration of other differentials for the respiratory component. Diagnosis of pulmonary lymphosarcoma is often readily accomplished from examination of respiratory wash specimens or needle aspiration. Treatment of lymphosarcoma is addressed in Chapter 181.

215.3.4 Lymphomatoid Granulomatosis

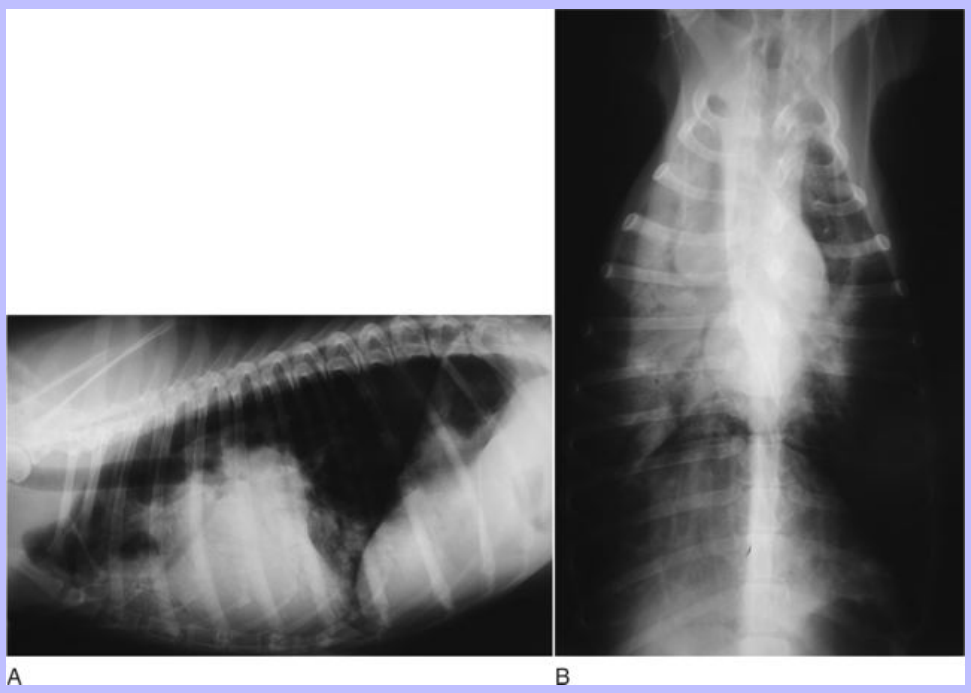
Lymphomatoid granulomatosis is characterized by infiltration around, and invasion of, pulmonary blood vessels with pleomorphic lymphoreticular and plasmacytoid cells. Eosinophils, neutrophils, and small

lymphocytes are also present.[22,23] Lymphomatoid granulomatosis was once considered an immune-mediated vasculitis, but evidence in people and dogs now supports the classification of this disease as a low-grade lymphoma (see Chapter 181).[24,25] Thrombosis, necrosis, and granuloma formation are common. Intrathoracic lymph nodes are also involved.

215.3.4.1 Presentation

This disease has only been described in people and dogs. There is no obvious age or breed predilection.[23] 1246
Patients usually present with respiratory signs such as cough, tachypnea, or respiratory distress, although 1247
fever, anorexia, or weight loss may also be noted. Clinical signs are usually slowly progressive.

Figure 215-8 Thoracic radiographs (lateral **[A],** ventrodorsal **[B]**) of a dog with pulmonary lymphosarcoma. On the lateral view there is a marked alveolar (air bronchogram in cranial lung lobe) and interstitial pattern. On the ventrodorsal projection, note the near consolidation of the right cranial lung lobe and enlarged hilar lymph node that is compressing the mainstem bronchus to the right caudal lung lobe.



215.3.4.2 Diagnostic Evaluation

Thoracic radiographs reveal a mixed nodular interstitial pattern. The pattern is typically generalized and the nodules ill-defined. Hilar and sternal lymph node enlargement may be present.[25] Consolidation of one or more lung lobes has been reported.

Cytology preparations of bronchial wash specimens or transthoracic lung aspirates often show a nonspecific mixed inflammatory response of lymphocytes, plasma cells, eosinophils, and mast cells. The radiographic and cytologic findings can be similar to those found in animals with eosinophilic pulmonary granulomatosis, neoplasia, fungal infection, or atypical mycobacterial infection.[22,26] Heartworm tests, fungal titers, and cultures are indicated to rule out other inflammatory diseases. Definitive diagnosis usually requires surgical biopsy and histopathologic evaluation.

215.3.4.3 Treatment

Chemotherapeutic protocols described for treatment of lymphoma are utilized for lymphomatoid granulomatosis (see Chapter 181). Administration of prednisone alone is often unrewarding.[22,26] Serial thoracic radiography is used to monitor resolution of disease.

215.3.4.4 Prognosis

Prognosis is typically guarded due to the variable individual clinical responses. The small numbers of cases reported hinders comparative assessment of the efficacy of different treatment modalities used in these patients.

215.3.5 Malignant Histiocytosis

Malignant histiocytosis was first recognized in Bernese mountain dogs but has since been recognized in other breeds such as golden retrievers and rottweilers.[23,27,28] In Bernese mountain dogs, malignant histiocytosis has a genetic basis with a polygenic mode of inheritance suspected.[29]

Most dogs are middle-aged and exhibit respiratory signs at the time of presentation. Lethargy, anorexia, and weight loss are also common clinical complaints as most dogs have widespread systemic disease at the time of diagnosis. Thoracic radiographs commonly show multiple pulmonary nodules, lymph node enlargement, and pleural effusion. The disease is characterized by infiltration of multiple visceral organs with atypical histiocytes. The brain and spinal cord may also be affected.[30, 31] Histopathologic examination of tissue is usually necessary for a definitive diagnosis. The prognosis has generally been poor with standard chemotherapy protocols; however, one report documented successful treatment in four dogs administered a human major histocompatibility complex nonrestricted cytotoxic T-cell line.[32]

215.4 INFECTIOUS DISEASES

215.4.1 Bacterial Disease

215.4.1.1 Bacterial Pneumonia

The development of bacterial pneumonia in dogs and cats is often viewed as a complication of a loss of one or more pulmonary defense mechanisms. Important mechanisms that protect the pulmonary parenchyma from infection include normal laryngeal function, cough reflex, the mucociliary escalator apparatus of the airways, an intact respiratory epithelial barrier with surface IgA, and in the alveoli, alveolar macrophages, and IgG. 1247 1248

Bacterial infection of the lung is a common complication of many diseases in dogs but is considered uncommon as a primary pulmonary disorder, which emphasizes the importance of careful assessment of patients with bacterial pneumonia for predisposing causes. Aspiration is considered the most common inciting cause, but other means of infection, such as hematogenous spread of infectious organisms, are also possible. Bacterial pneumonia may complicate viral respiratory infections following injury to the respiratory epithelium and disruption of the epithelial barrier, loss of mucociliary function, and local or systemic immune suppression.

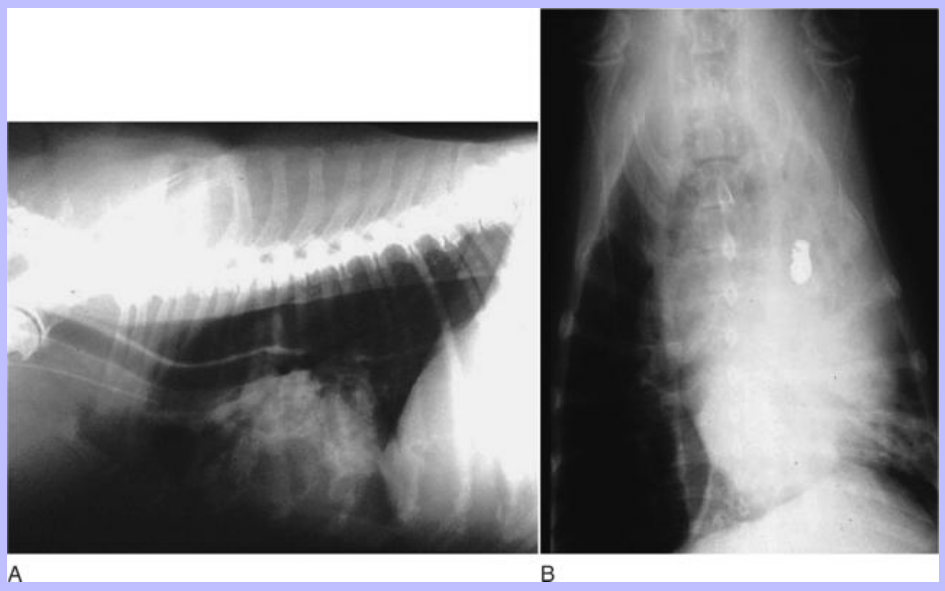
Nosocomial infections become a concern in patients that have been in the hospital for a number of days and have risk factors such as recumbency, regurgitation or vomiting, and prolonged endotracheal tubation as would be needed for patients on ventilators.[33,34] Bacterial pneumonia is considered a less common problem in cats as compared with dogs.

215.4.1.1.1 Presentation

Clinical signs of animals with bacterial pneumonia can be surprisingly variable. One aspect to recognize is that not all animals with pneumonia will exhibit clinical signs referable to the lower respiratory tract. Anorexia and lethargy are common but obviously nonspecific. Cough, which can be acute or chronic, tachypnea, and increased respiratory effort can be seen, with changes in respiratory character commonly reflecting the severity of underlying disease. Cough in cats with pneumonia occurs uncommonly. Some patients with bacterial pneumonia may have hemoptysis.[13] Exercise intolerance is seen in some animals. On physical examination, there may be fever, inducible cough, nasal discharge, increased lung sounds, and crackles or wheezes, but these features are not detected in every patient.

Other clinical signs in animals with pneumonia will reflect the primary diseases that put such patients at risk of bacterial pneumonia. Such patients may exhibit neurologic abnormalities, muscular weakness, gastrointestinal signs such as vomiting or regurgitation, or other signs.

Figure 215-9 Thoracic radiographs (lateral [**A**], ventrodorsal [**B**]) of a dog with focal bacterial pneumonia secondary to aspiration. Note the prominent air bronchogram in the cranioventral lung region on the lateral projection. Note that there is also megaesophagus.



215.4.1.1.2 Diagnostic evaluation

The diagnostic approach to a patient with bacterial pneumonia often involves some hematologic and biochemical assessment, and thoracic radiography, as first-line tests. Abnormalities of the CBC can be variable, and neutrophilia with or without a left shift and toxic changes will be expected in many but not all patients. Thrombocytopenia is associated with systemic inflammatory complications. There are no pathognomonic biochemical and urinalysis abnormalities for bacterial pneumonia, but these tests are often useful for comprehensive assessment of patient status and can give clues to diseases that are risk factors for pneumonia or other respiratory diseases. Abnormalities observed on biochemistries and urinalysis could be as much a reflection of underlying disease as of the pneumonia itself. Hypoalbuminemia reflecting increased pulmonary or systemic capillary permeability is not unusual, and animals that are clinically dehydrated may have azotemia. It is important to understand that animals with bacterial pneumonia may have normal laboratory data base results.

Although changes on arterial blood gas analysis will not be specific for bacterial pneumonia, blood gas results can be useful in the diagnostic assessment of patients with pneumonia. Arterial blood gas results will provide the clinician an indication of the adequacy of oxygenation (PaO_2) and the adequacy of ventilation ($PaCO_2$), which if severely compromised would suggest the need for ventilatory support. Evidence of ventilation-perfusion mismatches (hypoxemia, hypocarbia, widened A-a gradient) is expected in many patients.

Thoracic radiographs are useful in the assessment of patients with bacterial pneumonia. The most common radiographic appearance seen in patients with bacterial pneumonia is an alveolar pattern (Figure 215-9) that may be focal or diffuse depending on the manner in which the respiratory tract was seeded with bacteria. Aspiration pneumonia (see below) is more often associated with radiographic abnormalities in the cranioventral lung regions, although not all patients will have this distribution. Depending on the causative organism, there may be pleural effusion, or soft tissue densities that reflect pulmonary abscesses. In severe cases, lobar consolidation may be apparent. Thoracic radiographs should be carefully scrutinized for other abnormalities that could suggest an underlying disorder that could predispose to bacterial pneumonia such as megaesophagus, bronchiectasis, or neoplasia.[34,35]

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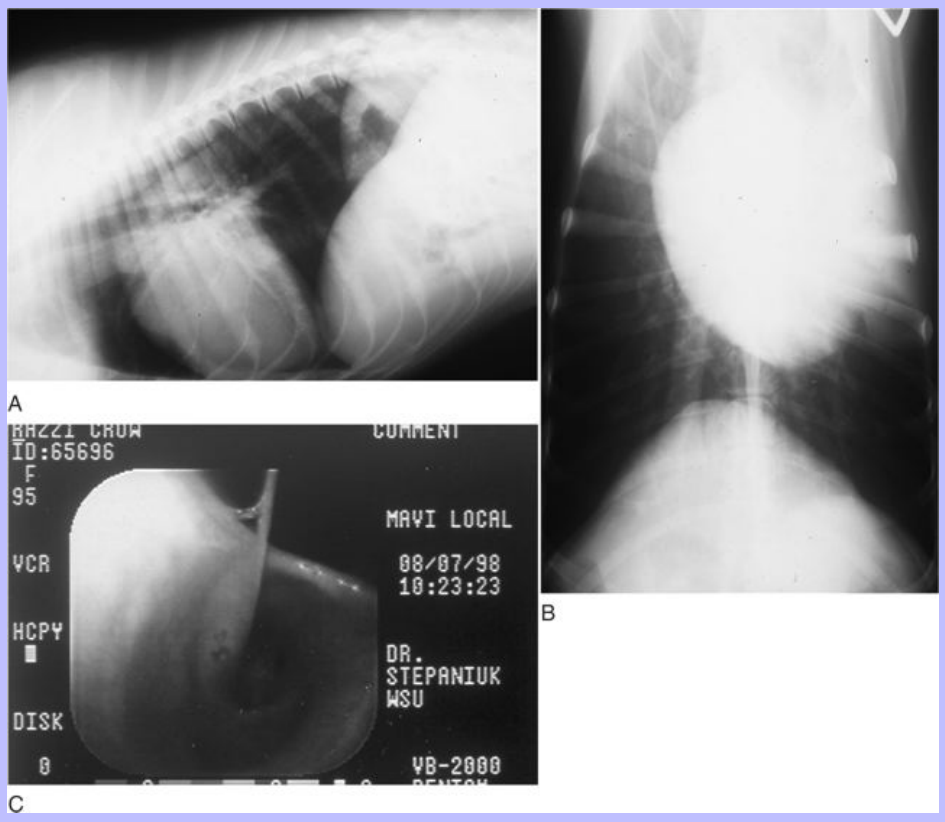
In some patients, extra effort may be required to demonstrate diseases that predispose to pneumonia. In a study of cats with esophageal disease, many were examined for signs of respira-tory disease and required contrast esophagrams to demonstrate abnormalities in esophageal motility.[36] Since bacterial pneumonia can accompany almost any other primary respiratory disease, repeating thoracic radiographs after resolution of pneumonia is important to help uncover other underlying primary diseases. Patients with recurrence of pneumonia confined to a single lung lobe should be suspected of diseases such as endobronchial foreign bodies, airway masses, or other causes of local disruption of pulmonary defense mechanisms (Figure 215-10).

Although a presumptive diagnosis of pneumonia is possible based on history, physical examination, and radiographic findings, definitive diagnosis is established from cytology and culture of material obtained from the respiratory tract by transtracheal washes or bronchoalveolar lavage. Cytologically, suppurative inflammation is expected, with signs of septic inflammation (intracellular bacteria, degenerative neutrophils) present in some, but not all, patients. Because not all patients with bacterial pneumonia have bacteria or septic features evident on cytology, it is important to culture samples for bacteria, including *Mycoplasma* spp. If thoracic radiographs are suggestive of abscessation, anaerobic cultures would also be appropriate. Ideally, samples should be obtained by transtracheal/endotracheal washes, bronchoalveolar lavage, or less commonly, needle aspiration, before administration of antibiotics if the patient's status will allow. Collection of samples by alveolar lavage is especially useful for focal disease, particularly if performed after bronchoscopic examination, which can identify predisposing diseases such as masses or foreign bodies. Fine-needle aspiration for cytology and culture may be considered if respiratory wash techniques do not provide an etiology, if there is lobar consolidation evident radiographically, or if other procedures are cost prohibitive.

Figure 215-10 **A,** Thoracic radiographs (lateral [**A**], ventrodorsal [**B**]) from a dog with recurring focal pneumonia. During bronchoscopy, grass awns **(C)** were found in airways of this lung lobe.



215.4.1.1.3

Treatment and prognosis

Treatment of bacterial pneumonia requires administration of antibiotics. The specific type of antibiotic and route of administration is ideally based upon results of culture and sensitivity of lower respiratory tract secretions or exudates, and in consideration of the clinical status of the patient. Certain situations, such as a patient in severe respiratory distress in which collection of samples by respiratory washes may be dangerous to the patient, may preclude sample collection. Some owners may not wish to incur the financial costs of sample collection and analysis. In such cases, antimicrobial therapy may be needed on an empiric basis.

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Empiric selection of antibiotics for animals suspected of having bacterial pneumonia can be facilitated by knowledge of common bacterial isolates from dogs and cats with bacterial pneumonia. Organisms often isolated from the respiratory tract of dogs with bacterial pneumonia include *Escherichia coli*, *Pasteurella multocida*, *Klebsiella* spp., *Bordetella bronchiseptica*, *Acinetobacter* spp., *Pseudomonas aeruginosa*, *Moraxella* spp., and isolates of *Staphylococcus* and *Streptococcus*.[37,38] In cats, common

isolates include *P. multocida*, *Klebsiella* spp., *Proteus* spp., *Bordetella* spp., *E. coli,* and *Streptococci*.[38,39] *Mycoplasma* spp. are frequently cultured from dogs and cats with pneumonia. The role of *Mycoplasma* spp. as primary respiratory pathogens in both dogs and cats has been suggested, and recent reports are consistent with *Mycoplasma* spp. as a cause of pneumonia.[37,40,41] Less commonly, *Actinomyces* or *Nocardia* spp. can be a cause of pneumonia without pyothorax.

Initial empiric therapy can be further focused by morphologic assessment of observed organisms and gram-staining if available. Good empiric selections for canine and feline bacterial pneumonia are presented in Table 215-1. Good initial combinations would be a beta lactam such as ampicillin or first-generation cephalosporin and an aminoglycoside or fluoroquinolone. An empirically treated patient that shows no clinical improvement, or exhibits clinical deterioration, during the first 24 to 48 hours after initiation of treatment should be thoroughly re-evaluated, and another consideration given to collection of samples for analysis. A change in antimicrobial therapy could be warranted at this point, but selection becomes more difficult in the absence of sensitivity results. The patient exhibiting a positive clinical response should be treated at least 1 week beyond clinical and radiographic resolution of pneumonia as radiographic improvement may lag several days behind clinical improvement.

Table • 215-1 Antibiotic Selections for Empiric Treatment of Bacterial Pneumonia[1]

ANTIBIOTIC	ANTIMICROBIAL SPECTRUM	DOSAGE, ROUTE, FREQUENCY
Ampicillin	Gram-positive aerobes (staphylococci, streptococci), *Pasteurella multocida,* some *E. coli* Anaerobes	10–30 mg/kg IV, IM, PO q8-12h
Cefazolin (or other first-generation cephalosporin)	Gram-positive aerobes (staphylococci, streptococci), *Pasteurella multocida, Bordetella bronchiseptica*, some *E. coli* and *Klebsiella* spp.	10–30 mg/kg IV, IM, PO q8-12h
Gentamicin	Gram-negative aerobes (*E. coli*, *Proteus* spp., *Pasteurella multocida*, *Bordetella bronchiseptica*, some *Klebsiella* and *Pseudomonas* spp.), *Staphylococcus intermedius*	6–10 mg/kg IV q24h
Amikacin	Gram-negative aerobes (*E. coli*, *Pseudomonas* and *Klebsiella* spp., *Bordetella bronchiseptica*); *Staphylococcus intermedius*	10–15 mg/kg IV, IM, SQ q24h
Enrofloxacin	Gram-negative aerobes (*E. coli*, *Proteus* spp., *Pasteurella multocida*, *Bordetella bronchiseptica*, some *Pseudomonas* spp.); *Staphylococcus intermedius*	3–5 mg/kg PO, IV q24h (cat) 5–20 mg/kg PO, IV q24h (dog) 5–10 mg/kg PO, IV q12h
Doxycyline	*Mycoplasma* spp., *Bordetella bronchiseptica*	10–25 mg/kg PO q12h (cat)
Metronidazole	Anaerobes	15 mg/kg IV, PO q12h (dog)

1. Selection of drugs is based ideally on culture and sensitivity. Dosages may need to be altered in the face of concurrent renal or hepatic disease.

The route of administration of antimicrobials will, in most cases, be predicated by the patient's clinical status. Patients that are clinically stable and that have minimal clinical signs of respiratory disease are candidates for oral therapy administered at home. Patients that are clinically unstable will likely require

hospitalization for administration of intravenous antimicrobials, ancillary therapy such as intravenous fluids, and oxygen supplementation. Intravenous antibiotic therapy should be continued until the patient has become stabilized and can be safely discharged on oral medications. Patients with esophageal disease may need prolonged parenteral antimicrobials or gastrostomy tubes to ensure that adequate tissue concentrations of antimicrobials are attained and to provide nutritional support.

Administration of antimicrobials via nebulization may be considered in some patients, but the clinical implementation of this route of administration has some important limitations.[42] The efficacy of nebulized medications reflects a complex set of interactions between the drug administered, the formulation of the drug, the device used to deliver the drug, and patient factors such as the characteristics of the primary disease, breathing patterns, and tolerance of delivery systems. Nebulization of antimicrobials formulated for intravenous use may prove less effective because of an inability to achieve desirable particle size, or could be harmful because of changes in pH or other properties that, when administered as an aerosol, result in respiratory mucosal irritation or injury. The best products for nebulization are those medications that have been specifically formulated for administration via nebulizer. Unfortunately, few antimicrobials, other than aminoglycosides formulated for use in people with cystic fibrosis and *Pseudomonas* infection, are available for specific use in small animal patients.

Administration of bronchodilators to patients with pneumonia has been suggested but is not universally accepted. The most appropriate use of bronchodilators would be for patients with bronchoconstriction, which may be difficult to appreciate in some patients. Bronchoconstriction is not considered an important feature in dogs with pneumonia. In cats, however, inflammation is a potent stimulus for bronchoconstriction, which may contribute to clinical signs in cats. Bronchodilators have the potential to worsen oxygenation by contributing further to ventilation-perfusion mismatchings often present in patients with pneumonia.

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Coupage may help some patients with pneumonia by helping loosen mucus secretions for expectoration to clear airways. Saline nebulization to keep respiratory secretions moist can be beneficial in facilitating clearance of respiratory secretions. Limited periods of exercise in the clinically stable patient that can tolerate activity may accomplish the same purpose.

Occasionally, lung lobectomy may be necessary to treat an animal with bacterial pneumonia. There are no specific criteria that have been established for determination of which patients should receive surgery. Some candidates for lobectomy include patients that have focal disease that has not demonstrated improvement or clinical response to medical therapy, patients that have focally recurring pneumonia, or patients for which less-invasive methods have failed to establish a diagnosis and empiric therapy has failed. Retrospective studies of lobectomies for pneumonia in dogs and cats suggest that the value of surgery may lie as much in its diagnostic value as its therapeutic value. In addition to its therapeutic potential in animals with severe focal pneumonia, surgery may also help rule out other concurrent diseases such as foreign bodies, fungal infection, or neoplasms. The best prognoses reported with lobectomy for pneumonia are associated with foreign body pneumonia, and focal pneumonia, including animals with lobar consolidation, for which no etiology is discovered.[43,44] A poorer prognosis can be expected for dogs with fungal or bacterial pneumonia, or the resection of large amounts of lung tissue.

215.4.1.2 Zoonotic Respiratory Pathogens

215.4.1.2.1 Mycobacteria

Mycobacteria spp. are an important cause of pneumonia in dogs and cats, not necessarily because of the frequency with which they are seen, but because mycobacterial infections can mimic other diseases such as neoplasia, systemic fungal infections, and severe bacterial pneumonia. Additionally, some *Mycobacteria* spp. are potential human health hazards. The clinical presentation of dogs and cats with mycobacterial infection is typically one of chronic cough progressing to more severe signs of respiratory disease such as tachypnea and increased respiratory effort. Radiographically, infected animals can have interstitial nodules of various numbers and sizes, or have prominent interstitial markings. Enlargement of hilar lymph nodes, lung lobe consolidation, and pleural and pericardial effusions may also be seen. As with other pulmonary parenchymal diseases, occasional animals will have hypertrophic osteopathy. Diagnosis of mycobacterial infection is made by demonstration of organisms, which are usually found in the cytoplasm of macrophages in samples collected via tracheal wash, bronchoalveolar lavage, lung aspirate, or biopsy. Mycobacterial nucleic acid can be detected in samples by the polymerase chain reaction[45] and would support a diagnosis in a patient with appropriate clinical signs and radiographic abnormalities.

215.4.1.2.2 Yersinia pestis and Francisella tularensis

Animals in the southwestern and western United States live in areas of endemic plague (*Yersinia pestis*) and tularemia (*Francisella tularensis*). Cats are particularly susceptible to development of clinical plague, with the bubonic form most common. However, pneumonic forms of plague are seen with some regularity in endemic areas and would pose the greatest threat to people.[46] Cats infected with tularemia do not commonly show signs of respiratory disease despite often extensive lesions in the lungs.[47] The diagnosis of these diseases can be established with fluorescent antibody assays performed on aspirates of lymph nodes or bone marrow.

215.4.2 Viral Diseases

215.4.2.1 Canine Distemper Virus

Canine distemper virus (CDV) infection can be associated with parenchymal disease. In CDV-infected dogs, viral infection may lead to secondary bacterial pneumonias. See Chapter 169.

215.4.2.2 Canine Adenovirus (CAV)-2, Parainfluenza (PI)

CAV-2 and canine PI are not typically a cause of parenchymal disease, although severe cases might be associated with secondary bacterial pneumonia. CAV-2 as a sole pathogen has been incriminated as a cause of pneumonia in rare instances.[48]

215.4.2.3 Feline Calicivirus

Feline calicivirus is more often a cause of upper respiratory disease in cats, but has been associated with interstitial pneumonia (see Chapter 173).[49]

215.4.2.4 Feline Infectious Peritonitis

Most cases of respiratory disease caused by feline infectious peritonitis (FIP) are associated with pleural effusion. Although pyogranulomatous pulmonary lesions are often seen in the setting of noneffusive FIP, most cats with non-effusive FIP exhibit signs referable to the eyes, CNS or liver, kidneys, or GI tract and are not commonly examined for respiratory disease.[50] Other clinical features and the diagnostic approach to cats suspected of having FIP are presented in Chapter 172.

215.4.2.5 Feline Immunodeficiency Virus and Feline Leukemia Virus

The feline retroviruses are not considered primary respiratory tract pathogens. Clinically affected cats, however, may develop parenchymal disease as a result of opportunistic infections or development of pulmonary neoplasia. Interstitial inflammation and alveolitis have been described in FIV-infected cats.[51] Diagnosis of underlying causes of respiratory disease in retroviral-infected cats will rely on the principles and techniques presented in Chapter 171, with treatment decisions based on diagnosis as well as the clinical status of the cat. FIV-positive cats may survive for long periods of time with appropriate veterinary care, so treatment decisions for such cats should not necessarily be based solely on the FIV status.

215.4.3 Rickettsial Disease

The primary rickettsial diseases of dogs and cats are infections caused by species in the genus *Ehrlichia* and *Rickettsia rickettsii*, the causative agent of Rocky Mountain Spotted Fever (RMSF) in dogs. RMSF causes a systemic vasculitis, and thus dysfunction of any organ system, including the respiratory tract, may cause clinical signs in affected dogs. Although not a common manifestation of infection, respiratory signs of RMSF that have been described in dogs include cough, tachypnea, and dyspnea.[52,53] Physical examination abnormalities referable to the respiratory tract can include nasal discharge and increased lung sounds. Thoracic radiographs may have an interstitial pattern, or alveolar patterns if vascular leakage secondary to pulmonary vascular inflammation is severe. Diagnosis is based on seroconversion or detection of organisms by immunohistochemical methods, and treatment involves administration of tetracycline family drugs (see Chapter 166). The canine and feline ehrlichioses are uncommon causes of respiratory tract disease despite the systemic nature of the infections.

215.4.4 Protozoal Disease

215.4.4.1 Toxoplasmosis and Neosporosis

Pulmonary disease in cats with *Toxoplasma gondii* infection is common. In a retrospective study of feline toxoplasmosis, fever, dyspnea, and tachypnea were common clinical signs, and pulmonary lesions were identified in approximately 25% of cats necropsied.[54] Pulmonary toxoplasmosis can be an acute, fulminant,

and fatal disease. Physical examination abnormalities can reflect the multisystemic nature of the disease with increases in bronchial sounds or crackles during thoracic auscultation in cats with a respiratory component. Radiographic features of respiratory toxoplasmosis in cats may vary. Patterns reflect diffuse alveolar and interstitial disease, and areas of emphysema can create a patchy appearance to the lungs. There are no pathognomic laboratory abnormalities in affected cats.

Diagnosis is supported by serologic results (increased IgM or increases in IgG in an animal with compatible clinical disease) or established definitively with demonstration of organisms in tissues. *T. gondii* tachyzoites can be detected in bronchoalveolar washings of affected cats and should be a useful technique for cats with respiratory signs and radiographic lesions.[55] Alternatively, lung fine-needle aspiration cytology can be attempted to examine samples for tachyzoites. Toxoplasmosis in cats is discussed in further detail in Chapter 168.

Canine toxoplasmosis is not as common as feline toxoplasmosis and can involve the lungs with similar clinical signs and radiographic features as described in cats. The diagnostic approach would be similar to that for cats.

Pneumonia attributable to *Neospora caninum* infection has been described in a dog that was evaluated for persistent cough, fever, and diffuse interstitial and focal alveolar lung disease.[56] An antemortem diagnosis was established by observation of tachyzoites in a lung fine-needle aspirate and confirmed on necropsy with immunohistochemistry. There were no obvious predisposing factors (concurrent lung disease, immunosuppressive disease) apparent in this dog. Pulmonary neosporosis appears to be an uncommon manifestation of *N. caninum* infection.

215.5 FUNGAL DISEASE

215.5.1 Systemic Fungal Infections

The systemic fungal organisms *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Coccidiodes immitis*, and *Cryptococcus neoformans* are notorious respiratory pathogens. Clinical signs of parenchymal disease are a common reason for infected animals to be evaluated, especially dogs with blastomycosis and cats with histoplasmosis. Clinical signs of cryptococcal pulmonary parenchymal disease are less common as compared with the other systemic fungal organisms. Coccidioidmycosis is rare in cats, and blastomycosis is less common in cats than cryptococcosis or histoplasmosis. Recognition of the contributions of the systemic fungal infections to small animal respiratory disease is important because the clinical signs and radiographic features can be similar to other diseases such as metastatic neoplasia. The systemic fungal infections are easily overlooked if the clinician fails to consider recent travel history of ill patients, particularly those patients that reside in areas where the disease is not endemic. More details of the systemic fungal infections are found in Chapter 174.

Generally, infection with systemic fungi occurs primarily after inhalation of organisms present in the environment. Local infection in the respiratory tract generally precedes systemic spread, although clinical signs of respiratory disease such as tachypnea and dyspnea may not be apparent until after systemic dissemination has occurred. Most affected animals have a history that suggests slowly progressive clinical signs of multisystemic disease; poor response to antibiotic treatment is often a component of the clinical history of animals with systemic fungal infections.

Most animals with clinical signs of respiratory disease will have abnormalities evident on thoracic radiographs, although some animals can have radiographically evident pulmonary disease in the absence of clinical signs of respiratory dysfunction. Although the radiographic appearance of the systemic fungal infections can be quite variable, typical changes on thoracic radiographs include diffuse interstitial patterns that can organize into small nodules (Figure 215-11), or larger, more ill-defined interstitial nodules (Figure 215-12). Some animals will have evidence of alveolar patterns, lobar consolidation (Figure 215-13) or peribronchiolar disease. Hilar lymph node enlargement can be seen in affected animals, and may occur independent of parenchymal lesions, especially with canine histoplasmosis. Hilar lymph node enlargement is also a common feature of canine coccidioidomycosis.[57] Occasionally, calcification of pulmonary nodules can occur with histoplasmosis. Pleural effusion can be a feature of any of these infections.

For all the systemic fungi, definitive diagnosis is often accomplished by demonstration of organisms in exudates, fluid washings, and needle aspirates or tissue biopsies of affected organs. The exception is cryptococcosis, the diagnosis of which can also be made by demonstration of circulating antigen with serologic methods. The cytologic and histologic diagnosis of coccidioidomycosis can be difficult in some cases due to few numbers of organism present in material examined. Most organisms will have to be identified within a cytologic background of inflammation characterized by the presence of neutrophils, macrophages, and depending on the severity of inflammation and the method of sample collection, some evidence of hemorrhage. Samples obtained by tracheal wash, bronchoalveolar lavage, or lung needle aspiration can be negative for organisms necessitating repeating the procedures or choosing an alternative approach, including lung biopsy, to establish a definitive diagnosis. If sufficient material is obtained during sample collection, and the samples do not contain organisms cytologically, consideration can be given to submission of the material for fungal culture. Serologic detection of antibodies, particularly in suspected cases of coccidioidomycosis, can add support to the diagnosis. As with many antibody tests, positive results indicate exposure but do not necessarily confirm clinical disease. Antibody tests can remain positive in animals that have had resolution of clinical disease.

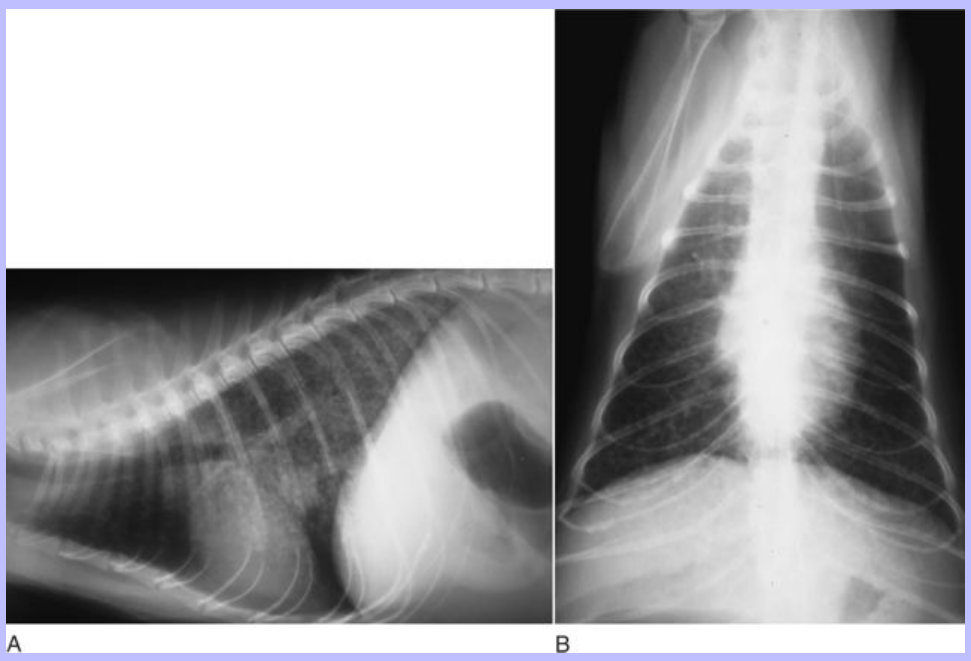
Treatment of the systemic fungal infections centers around administration of antifungal drugs in the azole category (ketoconazole, itraconazole, fluconazole) or amphotericin B. Although not proven in prospective studies, the concurrent administration of anti-inflammatory doses of glucocorticoids to animals with severe disease has been advocated to limit clinical deterioration associated with inflammation secondary to the death of large numbers of fungal organisms. Extension of antifungal therapy for an additional 2 to 4 weeks beyond typical treatment times is suggested if glucocorticoids are used.[58] The prognosis is favorable in animals diagnosed and treated early. The presence of severe respiratory signs worsens the prognosis. The reader is directed to Chapter 174 for additional details regarding the treatment of these infections.

215.5.1.1 Pneumocystosis

Pneumocystis carinii is a fungal organism that can be found in the alveoli of normal animals but can cause clinical disease in animals with immune system dysfunction. Most reported cases in dogs have been in young (<1 year) miniature dachsunds, although dogs of other breeds have also been described with the infection.[59,60] Affected dogs are evaluated for respira-tory difficulty and exercise intolerance, weight loss, and skin diseases (demodicosis, bacterial pyoderma) that also reflect systemic immune system dysfunction.[61] Physical examina-tion abnormalities include poor body condition, tachypnea, dyspnea, increased lung sounds, and skin and hair coat changes that reflect the secondary skin disease. Abnormalities on thoracic radiographs can vary from diffuse, mild, interstitial, or bronchial patterns to more severe interstitial and alveolar patterns. Laboratory assessment is consistent with chronic inflammation

(leukocytosis, thrombocytosis, monocytosis), except affected animals usually have low gamma globulin concentrations.

Figure 215-11 Thoracic radiographs (lateral [**A**], ventrodorsal [**B**]) of a cat with pulmonary histoplasmosis. Note the typical nodular, miliary interstitial pattern that is frequently seen with this infection. (Courtesy Dru Forrester, Blacksburg, Va.)



Definitive diagnosis is made by observation of organisms in respiratory washes, lung needle aspiration cytology, or histologic examination of lung tissue. Additional support for the diagnosis can come from immunohistochemical techniques, or polymerase chain reaction (PCR) performed on tissues from animals with compatible clinical signs. Treatment may be attempted with trimethoprim sulfa combinations (30 mg/kg PO q12h for 3 weeks) or a number of other chemotherapeutic agents including pentamidine isethionate and clindamycin/primaquine, but relapses are common. The long-term prognosis is considered guarded because relapses are common.

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Figure 215-12 Thoracic radiographs (lateral [**A**], ventrodorsal [**B**]) of a dog with pulmonary blastomycosis. Note the larger, more ill-defined interstitial densities.

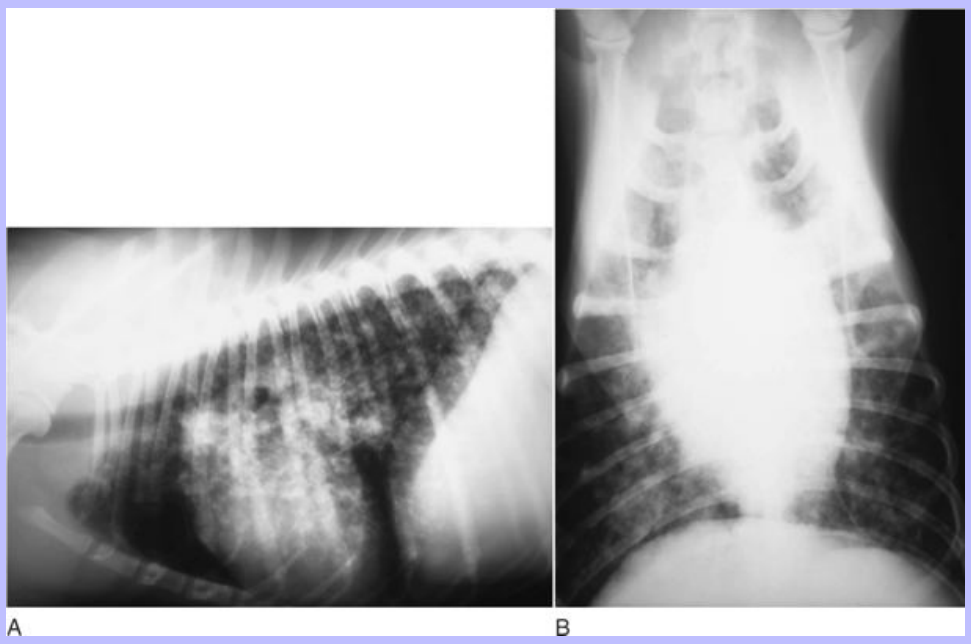
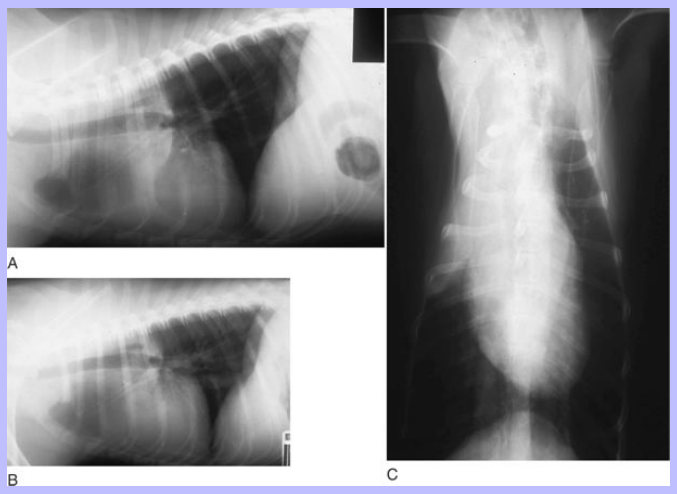


Figure 215-13 Thoracic radiographs (right [**A**] and left [**B**] lateral, ventrodorsal [**C**]) of a dog with *Coccidioides immitis* infection in a single lung lobe. The definitive diagnosis in this dog required lung lobectomy and histology.



215.5.1.2 Aspergillosis

Aspergillus infections are most commonly a cause of nasal cavity disease in dogs. However, systemic aspergillus infection can occasionally be seen, and when it occurs, is usually caused by *Aspergillus terreus*. Rarely *Aspergillus fumigatus*, the cause of nasal aspergillosis, can cause systemic infection.[62] Systemic aspergillosis has been described most often in German shepherds, which commonly present with signs of neurologic disease from diskospondylitis. These dogs may also exhibit cough, dyspnea, and tachypnea as a consequence of pulmonary parenchymal infection. Diagnosis requires demonstration of fungal hyphae in tissues by cytologic examination of needle aspirates, biopsies, or respiratory washes. Treatment requires administration of systemic antifungals as described for the systemic fungal infections. The prognosis is considered poor.

215.6 PARASITIC DISEASES

The respiratory tract is the site of infection with a number of parasitic organisms, both flukes and helminths. As a whole, respiratory parasites are considered an uncommon cause of clinical respiratory disease in dogs and cats. The importance of the respiratory parasites is that they can cause radiographic lesions that can mimic other diseases such as metastatic neoplasia or systemic fungal infections. The eosinophilic pulmonary infiltrates caused by parasitic pneumonia require differentiation from other causes of eosinophilic pulmonary diseases.

When apparent, clinical signs from parasitic infection are usually mild, with some exceptions that can be associated with severe and life-threatening, presentations. The most common clinical sign of respiratory parasitism is cough, which can be acute or chronic. Other clinical signs that can be seen include wheezing, tachypnea, and respiratory distress in severe cases. The pathogenesis of clinical signs can reflect either the direct presence of the parasite or the immunologic response to the parasite.

As with most animals that present with clinical signs of respiratory disease, thoracic radiographs play a role in the diagnosis of respiratory parasites. Radiographic features common to most of the respiratory parasites include peribronchiolar infiltrates, interstitial patterns that can have a nodular appearance, and occasionally alveolar patterns. Other unique radiographic features of parasite infection are discussed below with the specific parasite.

The diagnosis of most of the respiratory parasites is made by detection of eggs or larvae in tracheal wash or bronchoalveolar lavage fluid, or by demonstration of larvae in stool samples, typically by the Baermann technique. Individual exceptions exist as noted below. Cytologic examination of respiratory samples typically reveals a mix of inflammatory cells, with neutrophils and eosinophils present in varying proportions but usually representing the majority of cells present. Peripheral eosinophilia is an inconsistent, although common, hematologic abnormality and its absence should not lessen the consideration of respiratory parasites as a differential diagnosis of respiratory disease if other aspects of the patient are consistent. Unique features of each of the important lower respiratory tract parasites are noted below.

215.6.1 Paragonimus kellicotti

Paragonimus kellicotti is the lung fluke of dogs and cats. Animals at risk of infection live primarily in the southern, midwestern, and Great Lakes regions of the United States, although infections have been seen in other parts of the world. Animals become infected following ingestion of a freshwater snail or crayfish, which serve as intermediate hosts. The fluke leaves the intestine and migrates to the lungs, where it lives in a cyst or bulla within the pulmonary parenchyma. Eggs from adult flukes are coughed, swallowed, and passed in feces

to infect intermediate hosts. Animals with *P. kellicotti* may be clinically normal or be presented for coughing, which results from inflammatory reactions to adult flukes or ova in the parenchyma and airways. Of the respiratory parasites, *P. kellicotti* has potential to cause life-threatening problems to the affected patient if cysts rupture to cause pneumothorax (Figure 215-14). The physical examination can reflect crackles or wheezes, or if a pneumothorax is present, the restrictive breathing pattern and decreased lung sounds typical of pneumothorax. In cats, wheezing may be seen from inflammatory-mediator induced airway constriction.

The suspicion of paragonamiasis is raised by the observation of cystic or bullous lesions on thoracic radiographs, which may or may not be accompanied by pneumothorax. Other radiographic abnormalities that can be seen are common to other respiratory parasites. The diagnosis of paragonamiasis is made by demonstration of fluke ova in feces by sedimentation techniques, which are preferred for examination of feces. Intermittent shedding of ova dictates a need in some patients for multiple fecal examinations to establish a definitive diagnosis. Ova may also be recovered in tracheal wash or bronchoalveolar lavage fluid; the cytologic picture of such samples is characterized by mixed populations of inflammatory cells, including neutrophils, eosinophils, and macrophages.

Drugs recommended for treatment of paragonamiasis are praziquantel (25 mg/kg PO q8h for 3 days) and fenbendazole (25 to 50 mg/kg PO q12h for 14 days); treatment may need to be repeated if fecal examinations remain posi-tive for ova. Animals with pneumothorax may require thoracocentesis, or thoracostomy tubes if repeated thoracocentesis is required.

Figure 215-14 Ova of *Paragonimus kellicotti*. (Courtesy Bill Foreyt, WSU.)

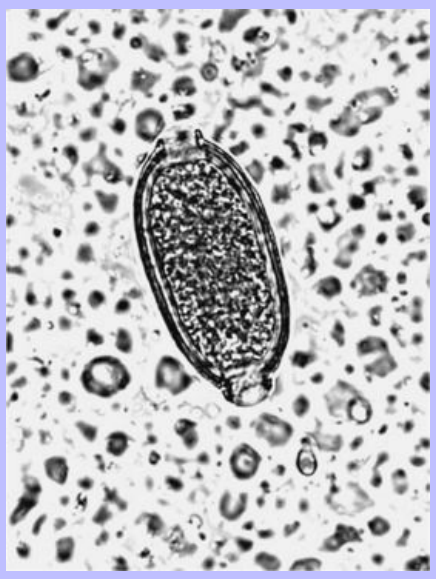
215.6.2 Filaroides hirthi

Filaroides hirthi infects dogs. Adults live in the terminal bronchioles and alveolar spaces. The parasite has a direct life cycle, and larvae can develop within the primary host and contribute to cycles of autoinfection that have the potential to create large worm burdens. Most infected dogs are asymptomatic, and as with other parasitic infections, cough is a common sign. Clinically affected dogs may have conditions associated with immune system compromise. The development of widespread granulomatous inflammation and destruction of respiratory bronchioles and alveolar units is capable of inducing respiratory distress in occasional animals from loss of gas exchange regions of the lung.[63] Interstitial infiltrates, which can appear nodular, as well as alveolar infiltrates, are features of thoracic radiographs that have been described.[63] Definitive diagnosis is made by detection of larvae or larvated eggs in respiratory washes, or in fecal samples by Baermann or zinc sulfate flotation. Administration of fenbendazole (50 mg/kg PO q24h for 14 days) or albendazole (50 mg/kg PO q12h for 5 days, repeat in 3 weeks) can be given to infected dogs, but there is a risk of exacerbation of clinical signs, possibly secondary to reactions to dying worms.[63]

215.6.3 Capillaria aerophila

Capillaria aerophila parasitizes dogs and cats. Adults reside primarily in the trachea and bronchi. Adults deposit eggs, which are coughed, swallowed, and shed in feces. Most parasitized animals are asymptomatic; animals with clinical disease most often cough. Radiographic abnormalities are as described generally above. The diagnosis of *C. aerophila* is made by detection of ova in respiratory washes or fecal flotation. The ova have an operculum at each end and are similar, though smaller, in appearance to the ova of the whipworm *Trichuris vulpis* (Figure 215-15). As with other of the respiratory parasites, intermittent shedding of ova can cause false negative results. Administration of fendbendazole (25 to 50 mg/kg PO q12h for 14 days) is recommended.

Figure 215-15 Ova of *Capillaria aerophila*. (Courtesy Bill Foreyt, WSU.)



215.6.4 Aelurostrongylus abstrusus

Cats are the principle hosts of *Aelurostrongylus abstrusus*. Adult worms live in the bronchioles, where larvae are deposited, coughed, swallowed, and shed in feces to infect a snail or slug intermediate host, which is eaten to complete the transmission cycle. Many cats are parasitized, and most are clinically normal. Clinical signs, when they occur, are attributed to inflammatory reactions to the parasites. Clinical signs can include cough, wheezing, and overt respiratory distress. Because of the overlap in clinical features, cats with a presumptive diagnosis of "asthma" should be considered candidates for *A. abstrusus* infection. Diffuse interstitial nodules are characteristic on thoracic radiographs, and peribronchiolar and alveolar patterns may also be present. Diagnosis is established by detection of larvae in respiratory washes, or in feces by Baermann technique (Figure 215-16).

Clinically symptomatic animals may be treated with fenbendazole (25 to 50 mg/kg PO q24h for 10 to 14 days) or ivermectin (400 ug/kg SC). Administration of bronchodilators and glucocorticoids has been advocated to help address the inflammation-induced bronchoconstriction that can contribute to clinical signs.[64]

215.6.5 Oslerus osleri

Though not a primary lower respiratory tract parasite, *Oslerus osleri* infection has been associated with secondary bacterial pneumonia, likely through disruption of normal pulmonary defenses caused by nodules in the airways. This parasite is discussed more completely in Chapter 213.

215.6.6 Crenosoma vulpis

C. vulpis is a lungworm that infects domestic and wild canids. Dogs acquire the parasite through ingestion of a mollusk like a slug or snail, the intermediate host that contains infective third stage larvae. Adult parasites live in the distal aspects of the bronchial tree where they produce larvated eggs that are coughed, swallowed and passed in feces. Infected dogs are seen primarily in the northeastern United States and eastern provinces of Canada.[65] Baermann techniques are the preferred method of examining feces for larvae, although centrifugal flotation techniques using zinc sulfate may also recover larvae or other parasites. Larvae and larvated eggs are usually readily recovered with airway washings. The preferred treatment is fenbendazole administered at a dosage of 50 mg/kg PO q24h for 3 days. Other anthelmintics such as ivermectin have also been suggested as effective.[65]

Figure 215-16 *Aleurostrongylus* larva. (Courtesy Bill Foreyt, WSU.)

215.6.7 Angiostrongylus vasorum

Sometimes referred to as the heartworm of France,[66] *Angiostrongylus vasorum* parasitizes the pulmonary arteries of dogs primarily in Europe, Africa, and Asia. Historically *A. vasorum* has not been considered a parasite of North American dogs; however, a recent report describes the first known infection of dogs in northeastern Canada.[67] Dogs are infected following ingestion of infected intermediate hosts such as snails and slugs. Adult worms shed eggs that are transported to the pulmonary capillaries where larvae penetrate the capillary wall to migrate into the alveolar spaces. Larvae are coughed, swallowed, and passed in feces.

Adult worms cause a thrombosing pulmonary arteritis, with inflammatory responses contributing to the development of interstitial pneumonia and pulmonary hypertension. Anaphylaxis and consumptive coagulopathies can develop in some infected animals. Clinical signs reflect the pathogenesis, and signs of right-sided heart failure including cough, exercise intolerance, abdominal effusion, and hepatomegaly are possible. Animals with coagulopathies may have evidence of bleeding (anemia, hemoptysis, melena, subcutaneous hemorrhage).

Radiographic abnormalities can include those described above for other respiratory parasites; when alveolar patterns are present, they are usually more prominent in peripheral regions. In addition, dogs with *A. vasorum*

may have right-sided cardiomegaly and pulmonary artery enlargement, ascites and hepatomegaly as can be seen in dogs with *Dirofilaria immitis* infection (see Chapter 206).

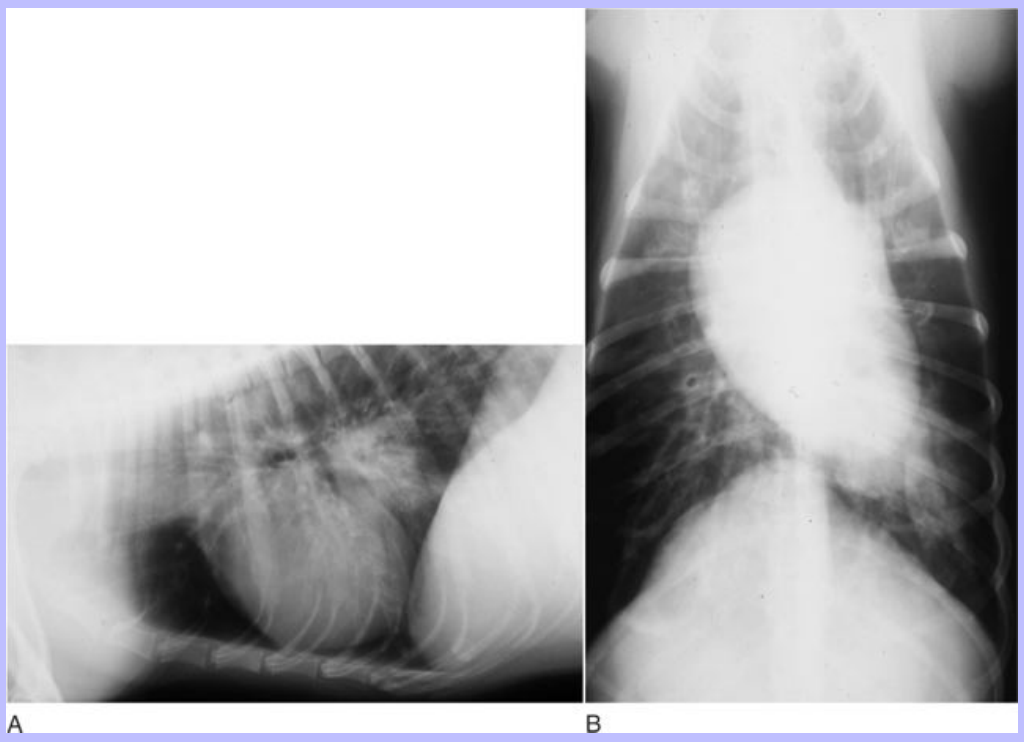
Detection of larvae can be accomplished by Baermann or fecal flotation. False negative results are possible as larvae are not continuously shed. Larvae may also be detected in respiratory washes. Levamisole (7.5 mg/kg PO q24h for 2 days followed by 10 mg/kg PO q24h on the next 2 days) is considered the standard treatment, but other anthelmintics, although known to stop fecal larval shedding, have not yet been adequately investigated for efficacy of killing adult worms.[66]

215.7 HYPERSENSITIVITY DISORDERS

A variety of eosinophilic disorders involving the lungs, either alone or in conjunction with infiltration of other organ systems, have been described in dogs and cats. The clinical spectrum reflects the extent of eosinophilic infiltration and ranges from disease limited to the respiratory tract to multisystemic disease involving not only the lungs, but liver, kidneys, heart, and gastrointestinal tracts. For many affected patients, the diseases are believed to be a manifestation of a hypersensitivity to an environmental or endogenous antigen. Identification of the offending antigen is infrequently accomplished.

Eosinophilic bronchopneumopathy (EB), formerly referred to as *pulmonary infiltrates with eosinophils* (PIE), is an inflammatory disease of unknown etiology that can be seen in dogs of all breeds, although a predisposition in Huskies has been reported.[68] Affected dogs can be of any age, though the majority of cases are seen in young to middle-aged dogs. The primary clinical manifestations of EB are cough, which is often accompanied by gagging, and difficulty breathing; mucopurulent or serous nasal discharge may also be seen. In the authors' experience, EB is frequently associated with coughing that results in expectoration of thick, greenish to greenish-yellow mucus. 1256
Occasionally, dogs may also exhibit lethargy and anorexia. Physical examination abnormalities are typically 1257
confined to the respiratory tract with evidence of nasal discharge, crackles, wheezes or generalized increase in lung sounds heard during thoracic auscultation. Auscultation can be normal in some dogs. Radiographically, EB is characterized by a variety of changes including diffuse bronchointerstitial, alveolar, peribronchio-lar, or some combination of these patterns (Figure 215-17); bronchiectasis may be a feature of some chronically affected dogs. There are no pathognomonic laboratory abnormalities, and peripheral eosinophilia, although common, is not present in all dogs.

Figure 215-17 Thoracic radiographs (lateral [**A**], ventrodorsal [**B**]) of a dog with eosinophilic broncho-pneumopathy. Note the pronounced interstitial and peribronchiolar markings.



The diagnosis of EB is established by ruling out other causes of eosinophilic parenchymal disease such as respiratory or migrating parasites, bacterial or fungal respiratory infections, heartworm, and neoplasia. Thus fecal floats or Baermann examinations, heartworm testing, culture of respiratory washes or lavages, and bronchoscopic and cytologic examination of the respiratory tract all have a role in the diagnostic approach to EB. Bronchoscopic examination often shows evidence of green to green-yellow mucus adhered to airway walls or obstructing small airways (Figure 215-18). Airway mucosa may be thick to polypoid in appearance, and there may be airway collapse. Cytologic examination of material retrieved by transtracheal wash, bronchoalveolar lavage, or mucosal brushing typically reveals large numbers of eosinophils, but neutrophils and macrophages are also common inflammatory cells. Most dogs will have negative cultures for bacteria, but the role of bacteria in the disease in culture-positive dogs is not well defined.

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Administration of glucocorticoids at immunosuppressive dosages is the mainstay of therapy for EB, with treatment lasting weeks to months in most dogs. Many dogs can be maintained on lower doses once the inflammation is controlled, and many can also become steroid-independent. Allergy testing and hyposensitization have been attempted with limited success in reported dogs[68] but could still be a consideration to help lower glucocorticoid doses. The prognosis is generally good with adequate therapy given for appropriate lengths of time.

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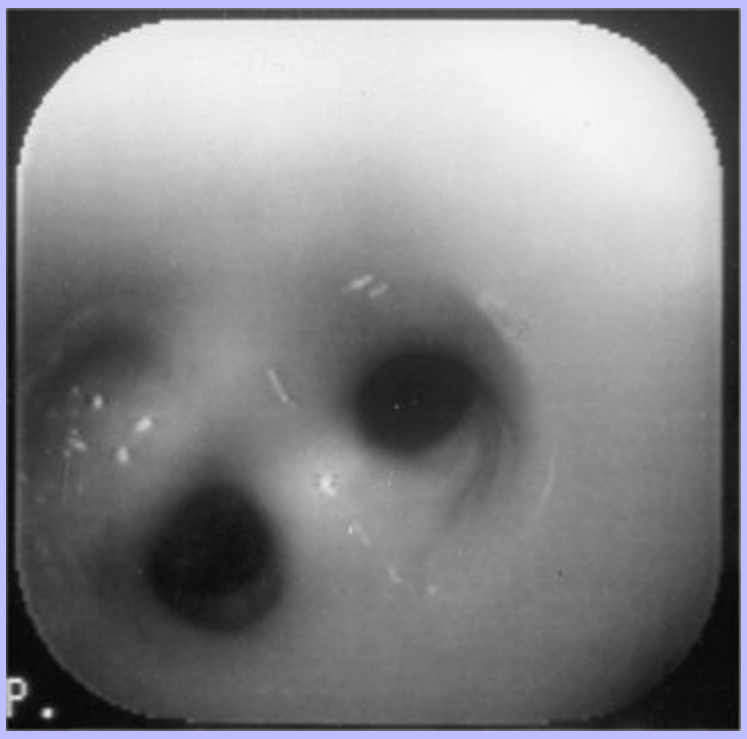
Figure 215-18 Bronchoscopic image obtained during examination of the dog in Figure 215-17 showing airways partially occluded with eosinophilic exudate.



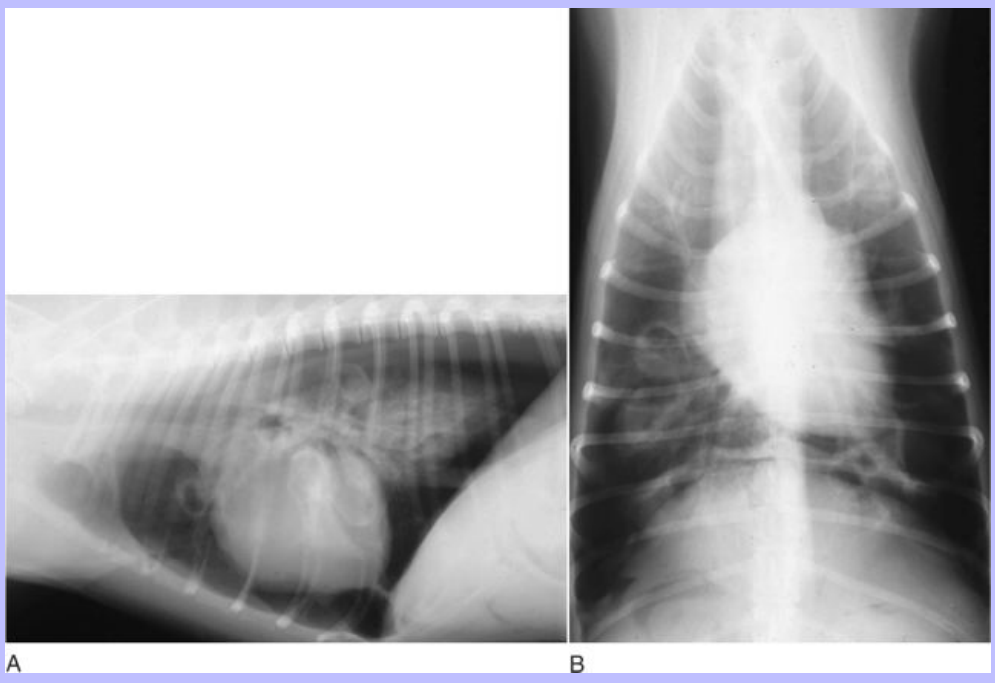
Eosinophilic granulomatosus, primarily a disease of dogs, is characterized by parenchymal infiltration with eosinophils. Unlike EB, the infiltrates of eosinophilic granulomatosis have a tendency to form distinct nodules or mass-like lesions, and the radiographic appearance is thus similar to that seen in patients with systemic fungal infections or pulmonary neoplasia (see above). Clinical signs include dyspnea and cough most commonly; affected patients may also exhibit anorexia, lethargy, and weight loss. Physical examination abnormalities can include abnormal lung sounds and fever. There are no pathognomonic laboratory features, and like EB, eosinophilia is often present, but can be absent in affected dogs. Thoracic radiographic abnormalities include pulmonary nodules of various sizes and numbers, hilar lymph node enlargement, and mixes of other patterns.[69] Some, but not all dogs with EB, will have evidence of heartworm infection.[70]

215.7.1 Vasculitides

Inflammatory vascular diseases of the lung are uncommon in dogs and cats. Reported cases have been associated with lymphoid granulomatosis and systemic-lupus erythematosis. Some patients have presumed pulmonary vasculitis for which a cause is not discovered, but which respond clinically to administration of immunosuppressive doses of glucocorticoids.[64] Clinical features of affected animals have been coughing, interstitial patterns on thoracic radiographs, and granulomatous inflammation on respiratory washes. Other

differentials for such patients include infectious or parasitic diseases that can have a vascular component (Rocky Mountain Spotted fever, FIP, heartworm), systemic fungal infections and neoplasia. Vasculitis has also been incriminated, though not proven, as a cause of thoracic radiograph abnormalities in dogs with leptosporosis.[71] Diagnosis is made by exclusion of other causes of clinical signs and radiographic lesions and by histopathology.

Figure 215-19 Thoracic radiographs (lateral [**A**], ventrodorsal [**B**]) of a dog with pneumothorax likely caused by rupture of a bulla. Multiple bullae remain evident in these projections. This dog had *P. kellicotti* infection.



215.7.2 Cystic-Bullous Lung Disease

Cystic-bullous lung disease is characterized by circumscribed regions of air or fluid occurring in the lung parenchyma. These lesions form as a result of cysts, bullae, or pneumatoceles. Cysts are fluid or air-filled lesions surrounded by respiratory epithelium and may be congenital or acquired.[72,73] Bullae are large areas of air accumulation formed by the loss of alveolar walls.[72,74,75] Pneumatoceles result from air entry into a necrotic lesion such as an abscess, granuloma, or tumor.

Bullae may occur as a result of emphysema (bullous emphysema), inflammation, trauma, or appear idiopathically. Emphysema results from enlargement and destruction of bronchial and alveolar walls due to obstructive pulmonary disease, such as some forms of chronic bronchitis.[76] The loss of radial traction on airway walls provided by alveoli contributes to airway collapse; alveoli may fill with air during inspiration, but negative intrathoracic pressures generated during expiration impair alveolar empyting from airway

collapse. Collagen defects may predispose some animals to the formation of these lesions.[76] *Paragonimus kellicotti* (the lung fluke) can cause bullae and granuloma/pneumatocele formation in dogs and cats (see above).[77] Any of the cystic or bullous lesions may rupture creating a pneumothorax (Figure 215-19). Depending upon the number and severity of lesions, large amounts of functional lung parenchyma may be lost. Large lesions may also compress airways.

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215.7.2.1 Presentation

Symptoms and clinical complaints may relate to the primary disease processes such as chronic bronchitis or traumatic insult. Acute respiratory distress and tachypnea can occur when cysts or bullae rupture, which creates a pneumothorax. Occasionally, cystic-bullous lung disease is an incidental finding on thoracic radiographs in an animal with no clinical signs of respiratory disease.

215.7.2.2 Diagnostic Evaluation

Thoracic radiographs may reveal solitary nodules or the margins of cavitary lesions in the peripheral lung regions. Initially, these lesions may be obscured by soft tissue opacity related to primary disease processes, or by pneumothorax causing collapse of the lung tissue. Pneumothorax is commonly identified if a cavitary lesion has ruptured. Unfortunately, bullous emphysema is rarely as readily apparent per thoracic radiography as it often is during exploratory thoracotomy. Cytology from any specimens obtained via thoracocentesis (for fluid or air) may be helpful as *Paragonimus* ova might be found. Aspiration of a bullous lesion is not recommended due to the risk of inducing pneumothorax. Thoracotomy, excision, and histopathology can be required for definitive diagnosis and may also provide therapeutic benefits.

215.7.2.3 Treatment and Prognosis

Identification and treatment of acute pneumothorax is crucial (see Chapter 217). Surgical exploration and removal of cavitary lesions may be warranted in patients in which leakage of air into the pleural cavity persists in the face of conservative management (thoracocentesis or thoracostomy tubes), or for patients with recurrent episodes of pneumothorax. Removal of localized lesions carries the best long-term prognosis. Bullous emphysematous disease is difficult to correct surgically, as the bulla are numerous and the disorder is typically progressive. Pleurodesis may be considered to reduce episodes of pneumothorax.[75,76] Even though recurrence of lesions is common, survival post-surgery of greater than two years is reported.[76] When identified, successful treatment of underlying diseases, such as chronic bronchial disease or lung flukes, carries the greatest likelihood of resolution. Thoracic radiographs should be monitored frequently for the recurrence of bulla or cysts. If bullae are found radiographically, treatment is generally not advised unless the animal becomes symptomatic, for example develops pneumothorax.

215.8 TRAUMATIC LUNG DISEASE

215.8.1 Pulmonary Contusions

Pulmonary contusions are hemorrhages into the pulmonary parenchyma, most often caused by blunt thoracic trauma. Pulmonary contusions occur frequently in animals struck by motorized vehicles. Pulmonary hemorrhage can occur even when external thoracic damage is not detected. Hemorrhage occurs from traumatic

rupture of parenchymal vessels with bleeding into the interstitium and alveoli in the region of the insult. Flooding of large regions of alveoli with blood impairs normal gas exchange and may result in clinical signs.

215.8.1.1 Presentation

Acute tachypnea and respiratory distress may be noted with severe contusions. Tachypnea may also be the result of pain, pneumothorax, or cardiovascular shock, which are common in acute trauma patients. Crackles may be ausculted over the contused area. Decreased lung sounds are suggestive of lung consolidation or pleural space disease such as effusion or diaphragmatic herniation. Some patients have minimal clinical symptoms if only mild hemorrhage has occurred.

215.8.1.2 Diagnostic Evaluation

History and physical examination abnormalities, such as fractures or abrasions, may suggest a traumatic episode. Thoracic radiographs typically reveal regional, irregular patches of mixed interstitial-alveolar densities. However, radiographic changes may be delayed for up to 24 hours following trauma. Pneumothorax, lung consolidation, or rib fractures can sometimes be identified on thoracic radiographs.[78] Contra-coup radiographic signs may occur as a result of trauma to the opposite side of thoracic wall. The lung is violently moved across the thorax, injuring the lung opposite to the stricken side. Arterial blood gas results will often show hypoxemia, which may be worsened by hypoventilation if there are injuries to the thoracic bellows (ribs, intercostal muscles, diaphragm). Traumatic myocarditis is often concurrently found in thoracic trauma cases.[79] The ECG may reveal occasional to very frequent ventricular premature contractions or sustained ventricular tachycardia.

215.8.1.3 Treatment

When indicated by clinical signs or results of arterial blood gas analysis, oxygen supplementation can be provided with nasal catheters, face mask, oxygen cage, or other strategies. Ventilatory support may be needed if hypoventilation contributes to hypoxemia. Specific treatment for the contusions is not usually necessary. Treatment for the other trauma-related problems, for example, blood loss or circulatory shock, is often more critical. Antibiotics are recommended for patients with penetrating chest wounds but not for rou-tine prophylaxis of animals with contusions only.[80] Serial thoracic radiographs should be evaluated for the resolution of abnormalities.

215.8.1.4 Prognosis

Prognosis is excellent for recovery from pulmonary contusions, provided that other injuries sustained are stabilized and fluid therapy is monitored carefully. Improvement is usually noted within 24 to 48 hours. Secondary complications such as abscesses, lung consolidation, or the formation of cavitary lesions may occur but are unusual.

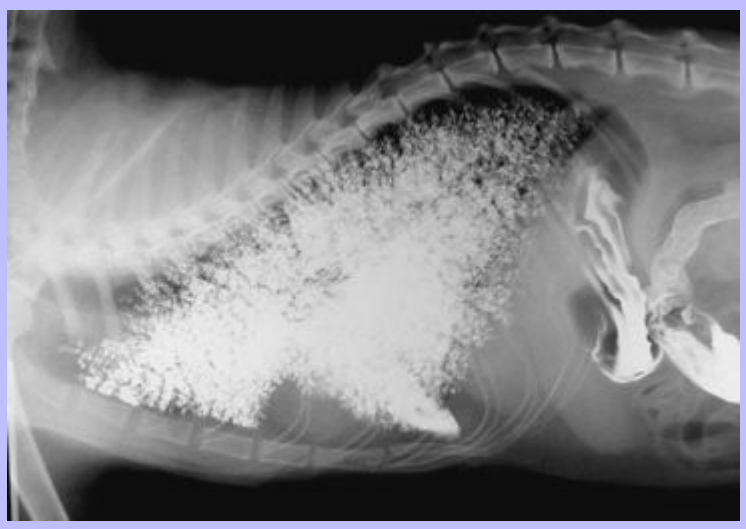
215.8.2 Aspiration Pneumonia

Inhalation of fluid or gastric contents, and bacteria from the oropharynx often results in profound pulmonary inflammation. Aspiration pneumonia can present as an acute fulminant illness, or a chronic and insidious process. The materials usually aspirated are acidic stomach contents and food.

Normal laryngeal and pharyngeal function typically prevent aspiration; however, certain diseases may alter normal laryngeal-pharyngeal function and predispose to aspiration events. Local or systemic neuromuscular disease, irritation and inflammation of the oropharynx secondary to chronic reflux or regurgita-tion (i.e., megaesophagus, esophageal obstruction, esophagitis, chronic vomiting), and anesthesia or depressed mental states resulting in prolonged recumbancy and reflux, are common causes of aspiration pneumonia.[78,81] Impaired oropharyngeal function and secondary aspiration has also been associated with brachycephalic airway conformation.[78,81] Aspiration pneumonia is a frequent complication of surgery for repair of laryngeal paralysis.[82] Accidental introduction of medications, food or contrast agents into the trachea, or lack of patient cooperation during administration of such products, can also result in aspiration pneumonia (Figure 215-20). Administration of mineral oil or similar agents by owners to prevent hair balls in cats is a particularly dangerous cause of inhalation pneumonia.

The severity of lung injury is related to various factors such as the volume of the aspirate, the pH of the aspirate (acidic stomach contents are especially damaging), and toxicity related to any particulate matter. 1259
Aspirated material may cause several reactions. Obstruction and collapse of alveoli, pulmonary hemorrhage and edema, influx of inflammatory cells, necrosis of airway epithelial cells, and reactive bronchoconstriction are common sequels to aspiration. Infection frequently develops due to aspiration of oropharyngeal bacteria or impairment of pulmonary defense mechanisms from lung injury (see Bacterial Pneumonia).[78,81] 1260

Figure 215-20 Lateral thoracic radiograph of a cat with severe barium aspiration.



215.8.2.1 Presentation

Patients are usually evaluated for an acute onset of respiratory distress, tachypnea, and cough, although some animals will die acutely from airway obstruction. There may be a sudden onset of coughing prior to respiratory distress. Some patients are evaluated for chronic, progressive respiratory signs. Systemic signs such as fever, inappetence, lethargy, and shock are common. Inspiratory and expiratory crackles and

wheezes are usually ausculted in the cranioventral lung lobes. Cats are especially prone to wheezes from bronchospasm secondary to airway inflammation.

215.8.2.2 Diagnostic Evaluation

A history of chronic vomiting, regurgitation, or medication administration that precedes the development of respiratory signs allows a presumptive diagnosis. Thoracic radiographs may support the diagnosis. Pulmonary opacities may be diffuse or focal, interstitial to alveolar. Increased alveolar opacities and consolidated regions are more common in the cranioventral and middle lung lobes (dependent areas) but can occur in any lung lobe, depending on the nature of the material aspirated and the position of the patient during the aspiration event. Nodular opacities may be noted in chronic cases or cases in which large solid particles have been aspirated. A miliary nodular pattern may be found in animals that have aspirated mineral oil mimicking neoplastic, fungal or parasitic disease. Depending on the material aspirated, evidence of aspiration may be inapparent initially on thoracic radiographs, but then pulmonary opacities develop over the ensuing 24 hours.

Respiratory secretions obtained by bronchoalveolar lavage or transtracheal wash are warranted in most patients and should be evaluated for cytology and submitted for microbial culture and sensitivity. Transthoracic aspirates may also be helpful, particularly when consolidated lesions are noted on thoracic radiographs. Cytology is typically characterized by a predominance of neutrophils and some hemorrhage. Bacteria may or may not be present. Particulate matter (e.g., food) may found in the wash materials. Bronchoscopy may be performed to examine airways and remove large pieces of foreign material.

A complete blood count often reveals an inflammatory leukogram. Blood gas measurements and electrolytes may be helpful in emergency management. Once the patient is stabilized, investigation for an underlying cause of aspiration should be sought.

215.8.2.3 Treatment

Patients presenting in respiratory distress will need immediate measures to improve pulmonary function. Oxygen may be administered via nasal cannula, face mask, or oxygen cage.

Intubation and positive pressure ventilation may be necessary to overcome severely increased lung compliance, which increases the work of respiration. Fluid therapy is often indicated to treat a shock-like state. Vascular volume, blood pressure, and pulmonary function should be carefully monitored. Respiratory compromise, due to exacerbation of pulmonary edema from increased pulmonary capillary permeability induced by inflammation in response to aspiration, may be worsened by aggressive fluid therapy. Bronchodilators may be beneficial in the acute management of patients with bronchospasm. Methylxanthines such as theophylline may be helpful to relax bronchioles, enhance mucociliary clearance, and decrease respiratory muscle fatigue.[83]

The use of corticosteroids in the management of aspiration pneumonia is controversial. Corticosteroids may be indicated in the deteriorating patient for treatment of shock. Corticosteriods decrease the inflammatory response and stabilize cell membranes but can also inhibit normal lung protective mechanisms. If given, routine use should not be continued for longer than 24 to 48 hours. There is no evidence in people to support prophylactic use of antibiotics in patients with aspiration pneumonia as aspirated gastric contents are typically sterile.[84] Although secondary bacterial infection is common, the development of resistant infections may be encouraged if antibiotics are used initially.[84] The benefits of prophylactic antibiotics

must be weighed against their potential risks. Antibiotic therapy ideally should be administered according to cytology or culture results obtained from wash or aspirate specimens. Attentive monitoring and serial radiographic, cytologic, and microbiologic analysis may be needed for some patients, particularly those with protracted illness or that exhibit clinical deterioration.

Measures should be taken to prevent further aspiration. Endotracheal intubation may be necessary to protect the airway if the patient is anesthetized or has an altered state of consciousness. Feeding tubes may need to be repositioned, or nasogastric or gastric tubes may need to be placed to facilitate removal of large volumes of gastrointestinal secretions. Institution of "upright" feeding for patients with esophageal or pharyngeal disorders may be beneficial, as may feeding through gastrostomy tubes.

215.8.2.4 Prognosis

Prognosis can vary widely depending upon the condition of the animal, the severity of lung injury, and the underlying cause of aspiration. Animals that aspirate a small amount of barium or mineral oil may have an excellent prognosis. Long-term complications may occur with aspiration pneumonia such as lung abscess, granuloma formation, or consolidation of lobes. Lung lobectomy may be indicated in these cases to eliminate sources of persistent or recurrent infections.

215.8.3 Near Drowning

Near drowning occurs with aspiration of water during submersion. Normal reflexes and input from higher neurologic centers cause cessation of ventilation under water; however, increased levels of carbon dioxide in the bloodstream eventually stimulate breathing efforts. Typically, only small volumes of water are typically aspirated resulting in severe pulmonary damage. Many mechanisms contribute to lung injury.[85,86] Aspiration of water dilutes surfactant, collapses alveoli, decreases lung compliance, and severely impairs oxygenation. Near drowning from inhalation of salt water exacerbates fluid flux into alveoli due to the hypertonicity of the solution.[85,86]

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Laryngospasm occurs in about 10% of cases and prevents aspiration of water and "dry drowning" results.[85,86] Aspiration of bacteria or chemicals in the water or vomitus, may contribute further to pulmonary parenchymal injury and predispose to secondary pneumonia. Severe hypoxia may cause profound neurologic disturbances from cerebral edema or herniation. ARDS (see discussion below) can occur up to 24 to 48 hours after a near drowning episode.[85–87]

215.8.3.1 Presentation

Patients are classically presented following a rescue. A loss of consciousness and severe respiratory distress or arrest is typical. Cardiovascular shock and hypothermia are commonly noted and require prompt attention. Auscultation may reveal inspiratory and expiratory crackles and wheezes, or exceptionally quiet lung sounds may be noted. Neurologic abnormalities and altered mentation may signify cerebral edema.

215.8.3.2 Diagnostic Evaluation

Diagnosis is based on the history of rescuing the patient from the water. Thoracic radiographs reveal a generalized, mixed interstitial-alveolar pulmonary pattern. Radiographic changes may not be apparent until 24 to 48 hours after the near-drowning episode. The presence of radio-opaque material in the airways (sand

bronchograms) is a poor prognostic indicator.[86] Bronchial wash and cultures are indicated if there is suspicion of secondary bacterial infection.

215.8.3.3 Treatment

Ventilation is provided as soon as possible. CPR or mouth-to-muzzle resuscitation may be required during initial rescue. The Heimlich maneuver is not recommended due to the possibility of aspiration of stomach contents.[87] As soon as available, oxygen may be provided with a nasal cannula, face mask, or oxygen cage. Positive pressure ventilation is often required due to the profound decrease in lung compliance. If neurologic symptoms are present after metabolic stabi-lization, treatment for cerebral edema may be warranted (see Chapter 191). Animals that have been resuscitated should be observed in the hospital for up to 24 hours for the development of ARDS. Respiratory function and metabolic and neurologic status are followed closely.

215.8.3.4 Prognosis and Prevention

A poor prognosis is associated with coma, blood pH less than 7.0, the need for a CPR episode, and mechanical ventilation.[87] Educating clients as to the risks of allowing young dogs near the water is especially important; one study revealed that half the dogs presented for near drowning were 4 months old or younger.[87] Cold water and rapid currents are particularly exhausting.

215.8.4 Smoke Inhalation

Smoke inhalation causes direct injury to the airways and lung tissue due to heat, particulate matter, and combustion gases. Household fires are the most common cause of smoke inhalation injury in dogs and cats. A compounding factor in the pathogenesis of smoke inhalation is the secondary injury that occurs from the release of pulmonary inflammatory mediators.

In the acute phase (0 to 36 hours) of smoke inhalation, respiratory signs are caused by tissue injury, increased capillary permeability, mucosal edema, and tissue hypoxia. By 2 to 4 days post-injury, tissue edema begins to resolve. During this later phase, there is an increase in mucosal secretions, sloughing of epithelial cells, decreased mucociliary clearance, and secondary bacterial colonization leading to tracheobronchitis and pneumonia.[88] If thermal injury occurs, lesions are usually found rostral to the vocal cords because dry air has low heat carrying capacity. Carbon particulate matter can attach to airway surfaces, which results in impaired mucociliary function and contributes to bronchospasm. Numerous compounds of the gaseous by-products of combustion, when inhaled, are responsible for chemical injury, which contributes more to lung injury than does thermal injury.[88,89] Carbon monoxide inhibits oxygen binding to hemoglobin, reducing oxygen uptake in red blood cells, which results in severe tissue hypoxia. Hydrogen cyanide, hydrogen chloride, and aldehydes are irritants that cause profound airway edema and bronchospasm. In addition, hydrogen cyanide interferes with cellular aerobic metabolism compounding tissue hypoxia. Anaerobic metabolism and the generation of lactate and metabolic acidosis ensues.[90]

215.8.4.1 Presentation

Patients are classically presented following a rescue. Animals may have singed hair, and the presence of soot and smell of smoke on the fur. A loss of consciousness, and severe respiratory distress or arrest is

common. Upper airway stridor may be heard in patients with laryngeal edema. Ocular and nasal discharge, and corneal edema are often present. Mucous membranes may be bright red due to carboxyhemoglobin, or cyanotic. Some patients have minimal signs on presentation but may develop severe respiratory compromise 24 to 36 hours later due to laryngeal edema, release of inflammatory mediators, decreased mucociliary function, infection or ARDS.[90]

215.8.4.2 Diagnostic Evaluation

Thoracic radiographs may be normal initially but can progress to a patchy interstitial pattern and alveolar pattern. These changes correlate with the development of pulmonary edema and pneumonia. Likewise, arterial blood gas analysis may be normal in the acute phase of injury, but PaO_2 levels will drop as pulmonary injury progresses. PaO_2 must be interpreted cautiously in animals with carbon monoxide poisoning, as PaO_2 is a measure of the amount of oxygen dissolved in plasma. In patients with carbon monoxide poisoning, PaO_2 may be normal, but the patient may still manifest severe arterial hypoxemia because carbon monoxide interferes with oxygen saturation of hemoglogin decreasing the total carrying capacity of oxygen. It is important to remember that carboxyhemoglobin is not distinguished from oxyhemoglobin with pulse oximetry, which could give a falsely high impression of the degree of hemoglobin saturation.

Assessment of carbon monoxide toxicity can be accomplished using a co-oximeter, available at most human hospitals, to measure blood carboxyhemoglobin levels.[90] In the early stages of smoke inhalation, cytology from bronchial washings, and hemograms and biochemical profiles are unremarkable. These tests may become useful in chronically managed cases to screen for secondary bacterial infections and metabolic complications. Cardiac and neurologic status should also be carefully monitored in critical patients.

215.8.4.3 Treatment

As stated earlier, animals that are rescued from fire should be observed for at least 24 to 48 hours for progressive pulmonary injury. Patients that present with severe laryngeal edema and obstruction may require tracheostomies. Oxygen supplementation should begin as soon as possible. Carbon monoxide is eliminated by the lungs and elimination is greatly facilitated by 100% oxygen administration. The half-life of carboxy-hemoglobin is 4 hours in room air and 30 minutes in 100% oxygen. Oxygen should be administered until blood carboxyhemoglobin concentrations are less than 10%.[90] Positive pressure ventilation may be required in critical cases. Airway humidification and physiotherapy (chest coupage) may also be warranted.

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Bronchodilators are sometimes used in the management of smoke inhalation. Ideally, antibiotic therapy should be based on documentation of infection by culture and sensitivity testing. Prophylactic therapy is generally not recommended because of predisposition to resistant infections.[90] Corticosteriods may be indicated in cases of acute cardiovascular shock; however, routine administration should be avoided due to their interference with tissue healing and protective mechanisms.

Fluid therapy is often indicated to restore lost circulatory volume and maintain tissue perfusion. Crystalloid or colloid solutions may be necessary to combat shock. If the animal has also suffered surface burns, aggressive fluid therapy will be needed. Fluids are administered with caution to smoke inhalation patients because pulmonary capillary leakage will predispose to pulmonary edema and worsening of respiratory function. Analgesics are indicated particularly if cutaneous burns coexist with smoke inhalation injury.

215.8.4.4 Prognosis

The prognosis ranges from good to grave depending upon the severity of the inhalant injury. In a study of 27 dogs with smoke exposure, 17 out of 17 dogs that had improvement or no change in respiratory signs during the first 24 to 48 hours after exposure were discharged from the hospital.[91] In this same study, dogs with deterioration in signs in the 24-to 48-hour period after hospitalization died or had prolonged stays in the hospital. The prognosis progressively worsens with severe respiratory disease requiring positive-pressure ventilation, the presence of neurologic signs, and cutaneous burns. Infection (pneumonia) and sepsis are common causes of death.

215.9 IDIOPATHIC AND MISCELLANEOUS LUNG DISORDERS

215.9.1 Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) causes acute hypoxemic respiratory failure as a result of lung injury and increased pulmonary capillary permeability. ARDS is not a disease entity by itself, but rather a syndrome that develops secondary to numerous, usually critical, illnesses. Sepsis is the most common cause of ARDS in people, and has been identified as a common cause of ARDS in dogs.[8,92] Other well-described associations include aspiration of acidic substances (e.g., gastric secretions) or inhalation injury, multiple transfusions, shock, pancreatitis, microbial pneumonia, drug reaction or overdose, and major trauma or surgery.[8,92–95]

Although ARDS is a well-described syndrome, particularly in people, the pathogenesis of the syndrome is still poorly understood. Exudation of proteinaceous fluid into the interstitum in the early phase of ARDS occurs as a result of increased capillary permeability from either direct or indirect injury to the alveolar epithelium or pulmonary capillary endothelium.[96] The inflammatory response that accompanies such injuries can involve all lung parenchyma. In the later phases of ARDS (7 to 10 days post insult), increased numbers of inflammatory cells, hyaline membrane formation, and fibrosis with increased dead-space fraction are characteristic.[9,92] Severe hypoxemia that is characteristically refractory to oxygen supplementation is typical due to arteriovenous shunting and ventilation/perfusion irregularities. Pulmonary hypertension occurs as a result of hypoxic vasoconstriction and capillary obstruction from microembolization.[9]

215.9.1.1 Presentation

Most patients present with acute, severe respiratory distress and tachypnea within 24 hours of the precipitating cause, although delays of up to 3 days may occur. Tachycardia and extreme anxiety are commonly noted. Crackles and wheezes, particularly on end-inspiration and throughout expiration, are classically heard in the hilar and dorsocaudal lung fields. Sometimes lung sounds are quieter than normally expected, particularly if the patient is hypovolemic. There may be other physical examination abnormalities, such as fever or evidence of trauma, that reflect underlying causes.

215.9.1.2 Diagnostic Evaluation

ARDS is suspected when the patient demonstrates an onset of respiratory signs hours to days following a precipitating event. Thoracic radiographs usually reveal generalized interstitial or mixed patterns consistent

with noncardiogenic pulmonary edema. Left cardiac and pulmonary venous silhouettes are typically normal unless another (cardiac) disorder is present (Figure 215-21).

Echocardiography is a noninvasive tool that may provide information to help differentiate ARDS from other causes of pulmonary edema. Echocardiography can rule out left atrial and ventricular abnormalities that could be associated with high-pressure (cardiogenic) pulmonary edema, which is a common differential diagnosis. Echocardiographic evidence of acute pulmonary hypertension may support a diagnosis of ARDS. Expected findings include a poorly contracting right ventricle, tricuspid regurgitation (TR), which is often present secondary to acute geometric changes of the right chambers (dilation), and elevations in right ventricular systolic pressures. Tricuspid regurgitation velocities can estimate right ventricular systolic pressure, and thus pulmonary arterial systolic pressure, which is increased in ARDS. Leftward shifting of the interventricular septum is sometimes demonstrated. The main pulmonary artery may appear dilated. Pulmonary capillary wedge pressure, if measured, is low (<18 mm Hg) with ARDS, but elevated with cardiogenic pulmonary edema.

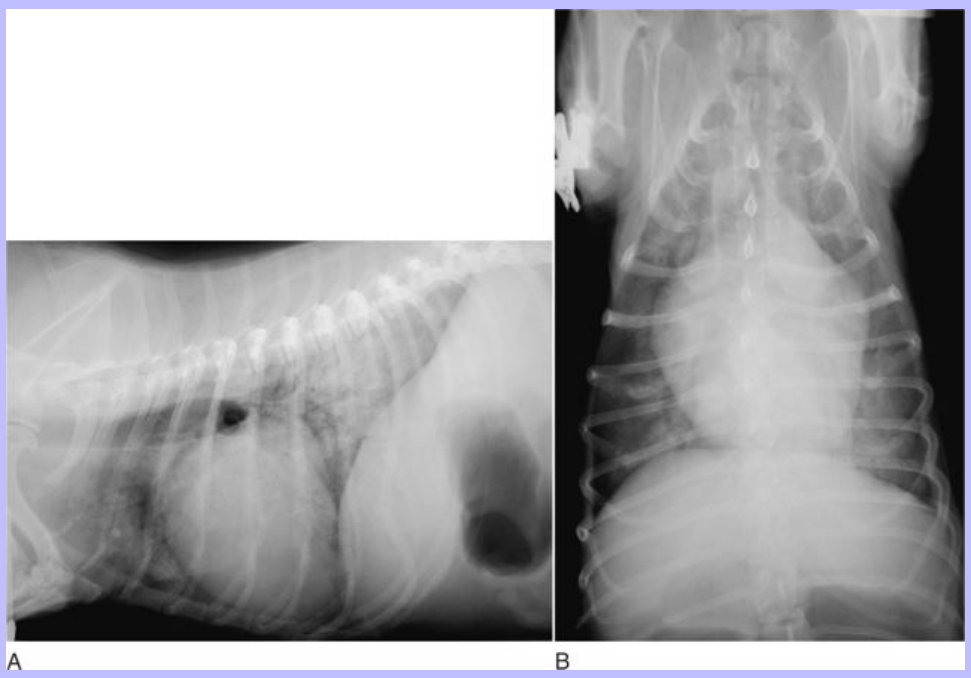
Edema fluid analysis may provide useful information in the early stages of ARDS. Fluid may be suctioned from the airways via tubing passed through an endotracheal tube. The ratio of protein content of the edema fluid (E) to the protein content in plasma (P) in ARDS is 79% to 90%, while the E/P ratio in cardiogenic edema is less than 50%.[97]

215.9.1.3 Treatment

The mainstay of ARDS treatment is addressing the underlying condition if known. Oxygen therapy is essential. Intubation and mechanical ventilation are quite appropriate and often needed for ARDS patients so that positive end-expiratory pressure (PEEP) can be delivered. PEEP can help prevent alveolar collapse in ARDS patient and relieves the patient of the work of respiration in the face of poorly compliant lungs. It also diminishes the need for high inspired oxygen concentrations to maintain acceptable levels of oxygen saturation, thus lowering the risk of oxygen toxicity.

A low-normal circulatory volume should be maintained with cautious fluid therapy. The smallest volume of fluids that maintains cardiac output and arterial blood pressure should be administered. Overzealous fluid therapy may worsen pulmonary edema and hypoxemia. A Swan-Ganz or other hemodynamic measuring catheter may be used to monitor cardiac output, and pulmonary capillary wedge and right heart pressures. Central venous pressures can be misleading as an estimate of volume status if significant pulmonary hypertension exists. Serial measures of arterial blood pressure, packed cell volume, total protein, electrolytes, BUN, and creatinine may be useful to monitor hydration status. Nutritional support and good nursing care, especially of recumbent animals, would also be crucial to successful therapy particularly for patients surviving the initial period of ARDS. Because of the demands these patients place on clinical staff, referral of these patients to tertiary care centers would be appropriate.

Figure 215-21 A left lateral [**A**] and dorsoventral [**B**] radiograph of a 10-year-old dachshund diagnosed with ARDS secondary to trauma. Note the severe, generalized interstitial opacities. This dog had a history of mitral valve endocardiosis, thus left-sided cardiomegaly is seen here. The pulmonary veins are not enlarged as would be expected with left-sided CHF and airway fluid aspiration revealed an E/P ratio of 86% consistent with ARDS. ARDS was confirmed on necropsy.



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Corticosteriods are of unconfirmed benefit in ARDS patients. Diuretics may be helpful in the initial phase, but are of no benefit in the latter phase of ARDS (more than 5 to 7 days).[9,95] Careful attention to hydration status is required with diuretic therapy. Administration of nitric oxide as an endogenous mediator of vascular smooth muscle relaxation is under investigation.[97] Improvements in parameters of serial arterial blood gas analysis and thoracic radiographs may be helpful in the assessment of improving status.

215.9.1.4 Prognosis

ARDS patients typically progress rapidly and are notoriously fragile patients. Death can result from respiratory failure, or complications of ARDS and the underlying disease. The prognosis with severe or chronic ARDS (>3 days) is generally poor.

215.9.2 Lung Lobe Torsion

Lung lobe torsion is the rotation of a lung lobe around its long axis. The exact mechanism that results in increased mobility of a lung lobe is not known. Lung lobe torsion may be idiopathic, particularly in large, deep-chested breeds of dogs; however, toy breeds are sometimes affected.[44–46] Afghan hounds were overrepresented in one study.[98] Torsion can also be associated with several initiating events. Pleural effusion of various causes, thoracic surgery and manipulation of tissues, or trauma causing sudden lung lobe compression may predispose to rotation of a lung lobe.[72,99]

Rotation of the lung lobe at the hilus strangles the bronchus and vascular pedicle, which obstructs ventilation and venous drainage. Because the artery usually remains partially patent, progressive lobar engorgement with blood occurs and the lobe becomes an expansile mass. Increased hydrostatic pressure (venous congestion) causes exudation of bloody fluid into the pleural space. Pleural effusion may further impair tidal volume and respiratory performance. Mild blood loss anemia can be observed. Necrosis, fibrosis, and shrinkage of the lung lobe may eventually occur.

215.9.2.1 Presentation

Clinical signs of pre-existing pulmonary or pleural space disease may be present in the history. Clinical signs caused by the torsion are usually acute and progressive. Respiratory distress, tachypnea and cough, with or without hemoptysis, are common presenting complaints. Other systemic signs, such as hypotension, collapse, or fever and lethargy may be present.

215.9.2.2 Diagnostic Evaluation

Signalment may provide helpful clues, as deep-chested breeds such as sight-hounds appear to have an increased incidence of idiopathic lung lobe torsion. Physical examination abnormalities are compatible with pleural effusion (see Chapters 1, 54, 57). The appearance of thoracic radiographs may vary depending upon the stage of the disease. Pleural effusion usually obscures parenchymal detail. The pleural effusion may be removed and the thorax reradiographed, at which time lobar consolidation is typically noted. Air bronchograms may occur early, but air is reabsorbed with prolonged collapse. Rounding of the lung lobe edges is noted as the lung becomes engorged. The bronchus may lie in an improper anatomic plane. Pleural fluid analysis is consistent with a hemorrhagic modified transudate (see Chapter 57). Underlying conditions may be suggested by other laboratory abnormalities, for example hypoproteinemia associated with protein-losing enteropathy resulting in pleural effusion. Bronchoscopy is sometimes needed to verify rotation of the bronchus. Surgical exploration may be necessary to confirm the diagnosis in some cases. Histopathologic examination of the excised lung lobe should be performed to rule out underlying primary parenchymal disease such as pneumonia or neoplasia.

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215.9.2.3 Treatment

Immediate improvement in tissue oxygenation is usually needed, thus supplemental oxygen is often indicated. Removal of excessive pleural fluid will enhance lung expansion and respiratory performance. Thoracostomy tubes may be warranted in some cases. Circulatory function can be supported with IV fluid therapy as needed to maintain hydration and systemic blood pressure. Surgical resection of the affected lobe is typically curative.

215.9.2.4 Prognosis

Prognosis is typically good with lobectomy, but underlying conditions may require additional therapy and monitoring. It has been suggested that the long-term prognosis may be poor in dogs that develop lung lobe torsions in association with chylothorax.[44]

215.9.3 Pulmonary Mineralization

Mineralization of the airways or pleura can occur in aged dogs of any breed and is often an incidental finding. Chondrodystrophic dogs may demonstrate airway mineralization at an earlier age.[47] Nodular pulmonary parenchymal mineralization of unknown etiology is occasionally misinterpreted as metastatic neoplasia. The nodules may be few or numerous and diffusely distributed (Figure 215-22). They are typically discrete and nonprogressive and are not associated with lung pathology.

Mineral opacities can also occur in areas of intense inflammation, or in necrotic lung lesions. The opacities usually occur in the center of mass lesions resulting from fungal infections, parasites, tuberculosis, or neoplastic disease.[100] Necrotic lymph nodes can also undergo mineralization and mineral-like opacities can be seen in regional lymph nodes from prior barium aspiration. Occasionally, systemic disease such as renal secondary hyperparathyroidism and hyperadrenocorticism can cause mineral deposition in lungs and other organs.

Figure 215-22 A right lateral radiograph of a dog with pulmonary mineralization. Note the multiple discrete opaque nodules, especially prominent over the cardiac silhouette.

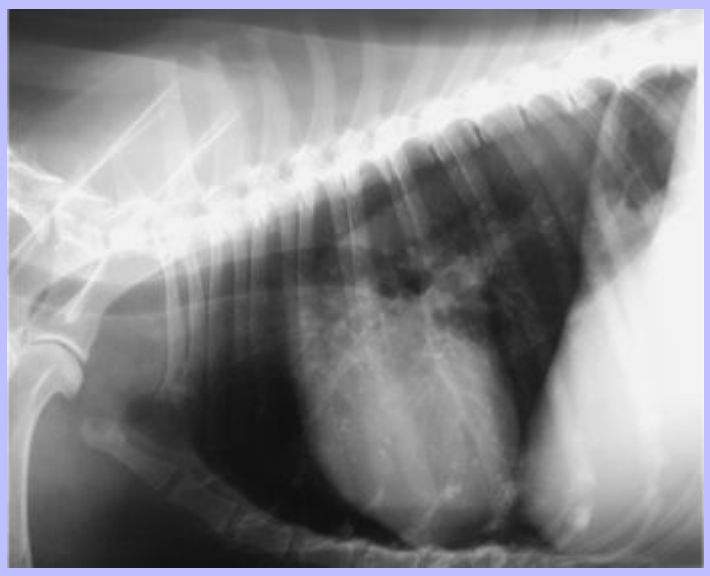
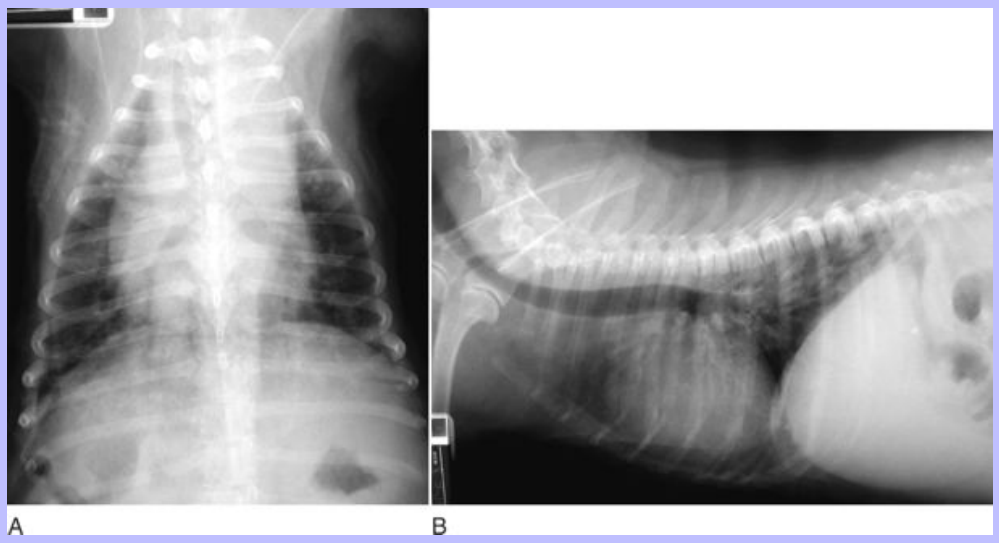


Figure 215-23 Left lateral [**A**] and dorsoventral [**B**] radiographs are shown of a 9-year-old West Highland White Terrier with idiopathic pulmonary fibrosis. Note the generalized bronchointerstitial pattern, especially prominent in the caudal lung regions. There is radiographic evidence of right heart enlargement and an enlarged caudal vena cava consistent with pulmonary hypertension.



215.9.4 Pulmonary Fibrosis

Interstitial lung diseases are poorly characterized in veterinary patients. Pathologically, interstitial fibrosis is characterized by alveolar septal fibrosis, interstitial fibrosis, epithelial hyperplasia, and focal calcification. Inflammation (lymphocytes and macrophages) is a variable finding.[101–103] In humans, these findings can be the result of numerous types of pulmonary injury; however, in over 50% of cases, no cause is identified.[101,102] The term *idiopathic pulmonary fibrosis* is often used to describe this disease in animals.

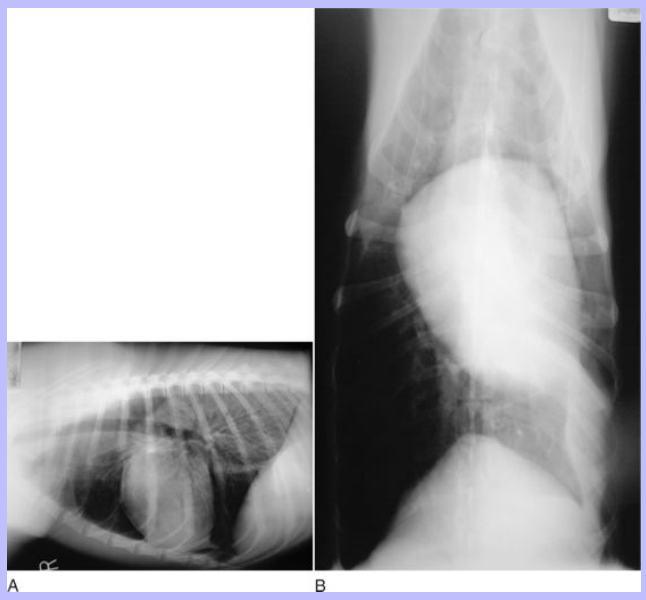
Idiopathic pulmonary fibrosis was first described in West Highland white terriers, but recent reports have suggested that other breeds of dogs may be affected, particularly Staffordshire bull terriers.[104–107] A form of idiopathic pulmonary fibrosis has now also been described in cats.[108] Dogs usually present with chronic and progressive pulmonary signs such as dyspnea and exercise intolerance. Cough is a variable finding.[104–107] Radiographically, there is a diffuse interstitial lung pattern with varying degrees of bronchial involvement (Figure 215-23).[104,106] Echocardiographic findings are usually indicative of moderate to severe pulmonary hypertension. A lung biopsy is generally necessary to confirm the diagnosis. The principal therapy for idiopathic pulmonary fibrosis is corticosteroids. Bronchodilators and azathioprine may be of benefit in some cases.[104,106] The prognosis for pulmonary fibrosis varies but is generally poor owing to the advanced nature of the disease at the time of diagnosis.

215.9.5 Obesity

Specific abnormalities of pulmonary function as a result of obesity have not been well characterized in veterinary patients. Increased oxygen consumption and myocardial work are noted in people with excess body mass with light activity. In humans, Pickwickian syndrome refers to a specific condition of obesity, lethargy, hypoventilation, and erythrocytosis. The syndrome is classically defined as elevations in $PaCO_2$ in the absence of pulmonary disease in patients who are extremely obese. A central neurological condition may be partially responsible for Pickwickian syndrome.[109] In addition, obesity is thought to worsen obstructive sleep apnea syndrome noted in humans and in English Bulldogs.[110, 111]

Excessive intrathoracic and intra-abdominal fat may interfere with lung function in numerous ways. Obese animals may have decreased thoracic wall compliance and thus have more difficulty expanding the thoracic cavity and lungs during inspiration. Hypoxia can result from decreased expansion and hypoventilation of peripheral lung regions.[109] Increased intrathoracic fat has often been suspected to worsen airway collapse in veterinary patients with redundant dorsal tracheal membrane and associated clinical signs. Even though specific obesity-related pulmonary dysfunction has not been reported in dogs and cats, weight reduction in animals with chronic airway or pulmonary disease can dramatically affect clinical signs.

Figure 215-24 A right lateral [**A**] and ventrodorsal [**B**] radiograph of a greyhound revealing consolidation of the left caudal lung lobe. Note the wedge-shaped soft tissue opacity in the left caudal thorax on the VD view and the consolidated caudal lung opacity with air bronchograms on the lateral view. Also notice the enlarged, spherical hilar lymph node dorsal to the heart and airways on the lateral projection. This dog had coccidiomyocosis.



215.9.6 Lobar Consolidation

Lung lobe consolidation can occur as a result of many pulmonary diseases. Lobar consolidation is not a disease entity itself but may occur secondary to processes such as aspiration pneumonia, granulomatous disease, contusions, lung lobe torsion, and neoplasia.[112] Fluid, exudates, or cellular infiltrates fill the alveoli and airways, which creates a wedge-shaped, homogenous soft tissue opacity on radiographs. In the early stages, a regionally diffuse interstitial pattern or an alveolar pattern may be recognized. As the disease process spreads, lesions coalesce, and the entire lung lobe becomes involved. Radiographically, lobar consolidation appears as a soft tissue opacity with visible lung lobe margins (Figure 215-24).[112] Ventilation-perfusion abnormalities occur as blood flow persists through unventilated lung tissue. If treatment of the primary disorder does not resolve the consolidation, surgical excision of the lung lobe may be necessary.

215.9.7 Pulmonary Alveolar Proteinosis

Pulmonary alveolar proteinosis (PAP) is a rare disorder of dogs characterized by the accumulation of protein-and lipid-rich fluid in alveoli.[113] Clinical signs described include chronic exercise intolerance and cough. Thoracic radiographs are characterized by increased interstitial markings. Tracheal or alveolar wash samples contain few cells and moderate amounts of proteinaceous fluid. Histologic examination of lung biopsies shows distension of alveoli with PAS-positive proteinaceous material, mucus granules, and intra-alveolar cholesterol clefts with only occasional inflammatory cells. Treatment requires intermittent lavage of affected lung lobes with 0.9% saline; clinical resolution of the disease has been documented with such an approach.

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215.9.8 Endogenous Lipid Pneumonia

Endogenous lipid pneumonia (EnLP) is an uncommon disease of dogs and cats and is usually secondary to another respiratory or systemic disease process that injures alveolar epithelial cells. In cats, the most common clinical signs are lethargy, anorexia, and weight loss, which could reflect underlying diseases. Common signs referable to the respiratory tract include tachypnea, difficulty breathing, and cough.[114] Thoracic radiographic patterns associated with EnLP include pleural effusion, diffuse interstitial or bronchointerstitial markings, or pulmonary nodules. The cytologic features of the disease have not been well characterized. The most common underlying diseases associated with feline EnLP have been obstructive airway disease of various causes, or systemic diseases such as neoplasia, liver, kidney or heart disease, and pancreatitis. The diagnosis is not typically made antemortem, but is usually an incidental finding during necropsy, during which gross subpleural lesions are commonly found. Histologically, EnLP is characterized by alveoli filled with lipid-laden macrophages.

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216 CHAPTER • 216 Mediastinal Disease

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David S. Biller

216.1 ANATOMY

The mediastinum is a potential space centrally located between the right and left pleural cavities. The mediastinum is lined on each side by parietal pleura and contains and encloses the thymus, heart, aorta, trachea, esophagus, vagus nerves, lymph nodes, thoracic duct, vena cava, and other vessels and nerves that enter or leave the heart.[1] In the dog and cat, the tissue in the mediastinum is incomplete.[1,2] Therefore most unilateral pleural cavity diseases in the dog and cat ultimately become bilateral. The mediastinum is bordered dorsally by the spine, ventrally by the sternum, caudally by the diaphragm, and cranially by the thoracic inlet. The mediastinum also communicates cranially with facial planes of the neck and caudally with the retroperitoneal space through the aortic hiatus. These communications create pathways for spread of disease between the neck, thorax, and retroperitoneal areas.

Anatomic regions of the mediastinum can be subdivided to facilitate radiographic description of mediastinal disease. The mediastinum can be divided by frontal and transverse planes into five regions: craniodorsal, cranioventral, middle, caudodorsal, and caudoventral.

216.2 HISTORY AND CLINICAL SIGNS

The history and clinical signs will vary depending on the area of the mediastinum involved, the rapidity of onset, and the specific etiology of the disease process. Specific events that should prompt a clinician to consider mediastinal disease include trauma to the head, neck and/or thorax; foreign body ingestion; invasive diagnostic and/or therapeutic procedures that involve the trachea, esophagus, or cervical region. Clinical signs may include dysphagia, regurgitation, dyspnea, cough, and Horner's syndrome. Abnormal findings on physical examination that may indicate mediastinal involvement in the disease process include poor compressibility of the cranial thorax, decreased lung sounds, dyspnea, esophageal or thoracic pain, and edema of the head and/or neck. If mediastinal disease is a component of systemic disease, extrathoracic signs of illness may also be present and include, but are not limited to, peripheral lymphadenopathy, weight loss, and polyuria/polydipsia.

216.3 DIAGNOSTIC EVALUATION

The mediastinum is not easily accessible for clinical evaluation due to its location within the thorax. Noninvasive evaluation is therefore dependent upon the utilization of appropriate imaging techniques. Invasive techniques for evaluation of the mediastinum may then be pursued if necessary.

216.3.1 Survey Radiography

The normal mediastinum is difficult to evaluate radiographically due to the lack of contrasting tissue densities. All mediastinal structures, with the exception of the air-filled trachea, demonstrate soft tissue opacity. This results in border effacement, which causes the structures within the mediastinum to appear confluent and

prevents the structures from being visualized distinctly. The craniodorsal region is often more radiopaque than other areas of the mediastinum because of its greater thickness.

On dorsoventral (DV) and ventrodorsal (VD) projection radiographs, the craniodorsal and caudodorsal regions of the mediastinum appear as midline structures that are normally no more than two times the width of the spine. The craniodorsal region may appear wider in obese animals owing to accumulation of fat within in the mediastinum, but the boundaries remain smooth. The craniodorsal and cranioventral regions of the mediastinum are usually incompletely evaluated on DV or VD radiographs because of their superimposition on the sternum and spine. In young animals, the thymus may be visualized as a triangular, sail-shaped soft tissue dense structure in the cranioventral region along midline.

Survey radiography is the imaging modality of choice for localizing mediastinal disease. Survey radiography is used to assess the size, shape, opacity, and position of the mediastinum. Positional radiographs permit free fluid to move away from the mediastinum and may improve visualization of the mediastinum in animals with pleural effusion. Mediastinal disease can be seen radiographically as an abnormal position of the mediastinum (termed *mediastinal shift*), pneumomediastinum, or increased size and/or opacity of the mediastinum.

Abnormal positioning of the mediastinum is usually indicative of disease that originates in the lungs, bronchi, thoracic wall, or pleura. A mediastinal shift may result from the presence of an intrathoracic mass or from uneven inflation of the lungs associated with unilateral changes in lung volume. A mediastinal shift is identified by a difference in size between the right and left hemithoraces as assessed in a VD or DV view. In addition, lateral displacement of major mediastinal structures, such as the trachea or cardiac silhouette, may be apparent. Diaphragmatic asymmetry may also present with mediastinal shift.

Pneumomediastinum is characterized radiographically by visualization of mediastinal structures that are not normally seen, such as the esophagus and aorta, because the presence of air within the mediastinum provides excellent contrast to adjacent soft tissue structures (see Figure 216-1, *A*). Pneumomediastinum is usually not recognized on VD or DV radiographs. Pneumothorax, pulmonary overinflation, and deep-chested conformation in thin dogs can cause a radiographic appearance that may be mistaken for pneumomediastinum. Also, a gas-distended esophagus may drape over the trachea and rarely the great vessels, which creates a false impression of pneumomediastinum.

Increased mediastinal size is usually manifested radiographically as diffuse or focal widening of the mediastinum as assessed on a VD or DV view. Diffuse widening can be caused by mediastinal inflammation, hemorrhage, edema, or the accumulation of fluid within the mediastinum associated with pleural cavity disease. Positional radiography and ultrasonography are helpful in differentiating mediastinal fluid accumulation from other causes of diffuse mediastinal widening. Focal mediastinal widening is usually the result of a mass lesion. Pathologic widening of the mediastinum must be differentiated from diffuse widening caused by an accumulation of fat in obese animals. An accumulation of fat in the mediastinum is common in older dogs, especially brachycephalic breeds.

Contrast radiographic procedures are often helpful in further evaluation of structures within the mediastinum that cannot be adequately visualized on survey films. In the case of suspected esophageal perforation, the contrast medium of choice should be a water-soluble iodinated product.

216.3.2 Ultrasonography

Thoracic ultrasonography provides poor visualization of the normal mediastinum because air in adjacent lung lobes prevents transmission of the sound waves. Sonographic evaluation may provide useful information in

animals with pleural effusion or cranial mediastinal disease.[3,4] Ultrasonography allows visualization of most cranial mediastinal masses. Very large masses can be imaged from almost any location in the craniolateral thoracic wall. Placing the transducer in a parasternal position or using the heart as an acoustic window may be necessary for adequate evaluation of smaller masses. Ultrasonography also helps define the internal architecture of masses as solid or cystic. In addition, ultrasonography allows localization of vascular structures relative to the mass. Although ultrasonography alone usually does not allow identification of the tissue of origin, it can be used to direct needle placement for fine-needle aspirate (FNA) or tissue core biopsy.[3,5,6] Transesophageal ultrasonography provides excellent visualization of the heart base, major cranial mediastinal vessels, descending aorta, and part of the azygous vein.[7] Transesophageal ultrasonography eliminates imaging difficulties due to obesity, poor intercostal windows, and lung air interference.

216.3.3 Computed Tomography

Computed tomography (CT) provides the most detailed anatomic analysis of mediastinal structures.[8,9] It is valuable in defining the margins and size of mass lesions (see Figure 216-4, *C*) and can be used to guide placement of a needle or percutaneous biopsy instrument. Disadvantages of CT include an inability to distinguish mediastinal masses from adjacent collapsed lung lobes, limited availability in veterinary practice, and the need for anesthesia.

216.3.4 Further Diagnostic Evaluation

Thyroid scintigraphy using technetium 99m or iodine 131 can be used to identify ectopic or metastatic functional thyroid tissue within the mediastinum.[10,11] Technetium 99m sestamibi can be used for the detection of parathyroid secreting tissue, although the sensitivity and specificity of this method may be low.[12,13]

In humans, bronchoscopy with transbronchial needle aspiration of perihilar and other pulmonary masses has been shown to be useful in the diagnosis of various cancers.[14] Although not widely used nor reported in veterinary medicine, this technique holds promise in allowing relatively noninvasive needle aspiration of hilar and mediastinal lymph nodes. The author has performed this technique with no apparent complications.

Thoracoscopy is another technique that can be used to examine and biopsy mediastinal diseases and is a proce-dure that is becoming more commonly performed in veterinary medicine at referral practices and institutions.[15,16,17] Thoracoscopy allows examination of the parietal and visceral pleura, lungs, pericardium, and mediastinum. Biopsies and removal of diseased tissue can be performed with this minimally invasive technique.

216.4 DISEASES OF THE MEDIASTINUM

216.4.1 Pneumomediastinum

Pneumomediastinum is the presence of air within the mediastinum and can develop spontaneously, usually in animals with pre-existing respiratory disease, or as a result of damage to the esophagus, trachea, or lungs (Figure 216-1, *A*). This damage can be associated with cervical trauma, mechanical ventilation, transtracheal aspiration, tracheostomy, or central venous catheter placement.[18] Caudal extension of air from cervical fascial planes into the mediastinum and retroperitoneum may occur secondary to external trauma because of the

normal communication between the mediastinum, retroperitoneum, and fascial planes of the neck (Figure 216-1, *B*). Bronchial or alveolar rupture with subsequent dissection of air along perivascular or peribronchial spaces to the pulmonary hilus and into the mediastinum is thought to be the mechanism by which pneumomediastinum occurs secondary to mechanical ventilation and pulmonary trauma.[19] A less common, iatrogenic cause of pneumomediastinum is secondary to tracheal rupture due to overdistention of the endotracheal tube cuff.[20] Severe pulmonary pathology or pre-existing respiratory disease can lead to bronchial or alveolar rupture with subsequent pneumomediastinum.

Pneumomediastinum does not occur secondary to pneumothorax. However, pneumothorax can be secondary to pneumomediastinum and is caused either by rupture of the mediastinal pleura, allowing mediastinal air to leak into the pleural space or by airway or alveolar rupture asso-ciated with underlying pulmonary disease that allows air to extend into the lung interstitium and diffuse into the mediastinum and pleural space. Subcutaneous emphysema and pneumoretroperitoneum may also occur secondary to pneumomediastinum.

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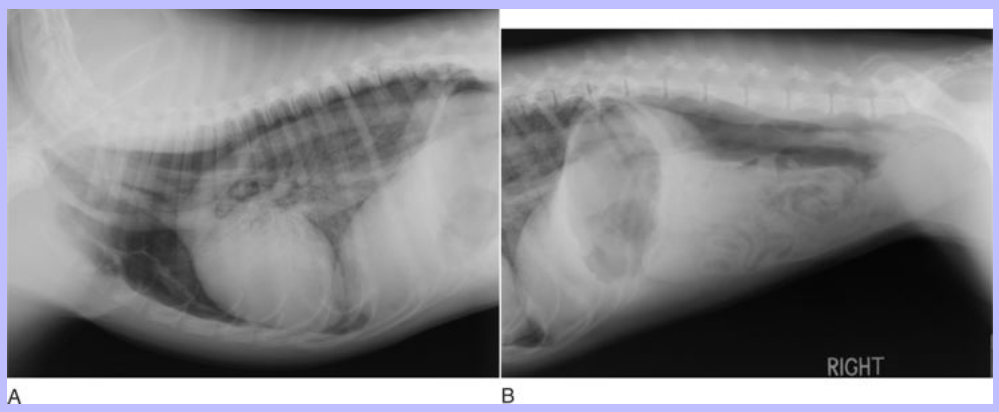
Figure 216-1 **A,** Lateral thoracic radiograph of a 9-month-old female Brittany Spaniel presented after being hit by a car. Numerous mediastinal structures, including the cranial vena cava, aorta, and serosal surface of the trachea, are well visualized as a result of pneumomediastinum. **B,** Lateral abdominal radiograph of the same dog. A large accumulation of air can be seen in the retroperitoneal space.



Pneumomediastinum alone is usually not associated with clinical signs. If the pneumomediastinum progresses to pneumothorax, tachypnea and dyspnea are often seen. The presence of subcutaneous emphysema may be uncomfortable for the animal. Animals with pneumomediastinum associated with esophageal rupture will present with signs associated with esophageal disease, such as regurgitation, pain, and dysphagia. Acute development of severe pneumomediastinum may cause signs of circulatory collapse secondary to decreased venous return resulting from compression of the vena cava and azygous vein.

The air trapped within the mediastinum does not require treatment and will spontaneously resolve within 2 weeks if there is no ongoing source of air leakage. Concurrent subcutaneous emphysema does not usually

require needle aspiration unless the volume is large enough to cause discomfort. Therapy should be aimed at resolution of any underlying disease process present.

216.4.2 Mediastinitis

Mediastinal inflammation is manifested radiographically as either focal or diffuse widening of the mediastinum. This may result from esophageal or tracheal perforation, deep cervical soft tissue infections extending along fascial planes into the mediastinum, or extension of infection from the pericardium, pulmonary parenchyma, or pleural space.[21,22,23,24] Chronic granulomatous mediastinitis may be caused by fungal organisms, such as *Histoplasma* or *Cryptococcus* spp., or bacterial organisms, such as *Actinomyces* or *Nocardia* spp.[24,25,26]

Mediastinitis has been documented secondary to spirocercosis in dogs.[27] Abscessation of the mediastinum may result from progression of chronic infectious or neoplastic mediastinal disorders.[23] Both mediastinal abscesses and granulomas typically appear on radiographs as mediastinal masses and thus may be mistaken for neoplasia.

Clinical signs associated with mediastinitis include tachypnea, likely related to thoracic pain, dyspnea, cough, head and/or neck edema, and regurgitation. Voice changes may occur secondary to recurrent laryngeal nerve involvement. Physical examination may reveal head and/or neck edema, tachypnea, dyspnea, fever, and decreased lung sounds if pneumothorax or pleural effusion are also present. Therapy involves resolving the underlying disorder. Esophageal perforation may require surgical repair and mediastinal masses may require surgical resection and/or drainage, along with appropriate antimicrobial therapy and supportive care.[23,26,28] Mediastinitis without a mass lesion may respond to antimicrobial therapy and supportive care alone. Thoracostomy tube placement may be necessary in animals with concurrent pyothorax or effusive mediastinitis.

216.4.3 Mediastinal Edema

Mediastinal edema can occur secondary to any disease that may result in edema in other areas of the body. The same pathophysiologic mechanisms apply. Although not recognized clinically very often, hypoproteinemia, lymphatic or venous obstruction, vasculitis, and heart failure may result in mediastinal edema. Edema in the mediastinum is often not clinically significant and may be overlooked due to accompanying pleural effusion.

216.4.4 Mediastinal Hemorrhage

Hemorrhage into the mediastinum usually results from either trauma or coagulopathy but also may be associated with neoplastic erosion of mediastinal vessels.[29,30] The clinical signs associated with mediastinal hemorrhage are related to the effects of acute blood loss. Dyspnea may occur if mediastinal hemorrhage progresses to hemothorax. Treatment is aimed at resolution of the underlying cause, such as plasma and Vitamin K_1 therapy for anticoagulant rodenticide intoxication, along with supportive care. If hemothorax due to coagulopathy or trauma is also present, auto-transfusion may be performed. Mild mediastinal hemorrhage usually does not need specific treatment.

216.4.5 Mediastinal Cysts

Benign cysts of pleural, branchial, lymphatic, bronchogenic, or thymic origin occur infrequently in the mediastinum.[31,32,33] Most animals do not have clinical signs referable to the mediastinal cyst. Radiographically, a cyst can appear as a solid mass in the cranial mediastinum due to the fluid within the cyst (Figure 216-2, *A*). A cyst can be differentiated from a solid mass ultrasonographically (Figure 216-2, *B*). Solid neoplasms, abscesses, or granulomas may have cystic components and must be differentiated from a simple cyst. Fine-needle aspiration with ultrasound guidance is the diagnostic test of choice. Cytology and culture can be performed. Mediastinal cysts typically contain a clear, colorless fluid with low cellularity and protein content.[31,32,33]

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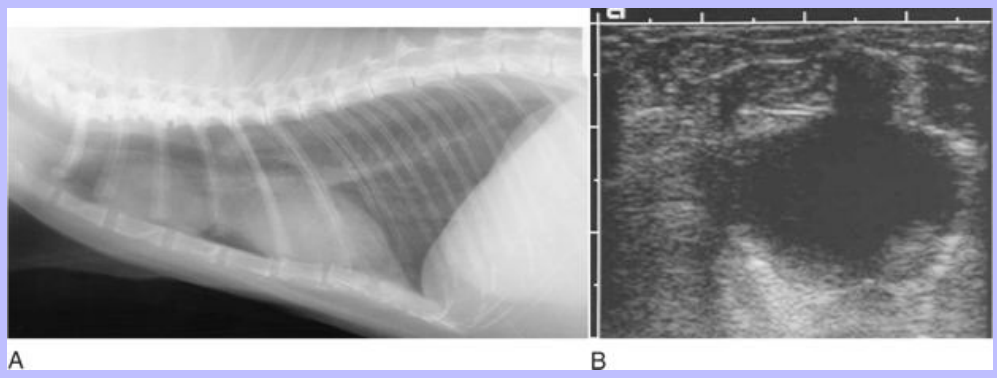
Figure 216-2 **A,** Lateral thoracic radiograph of a 19-year-old castrated male cat who presented for chronic renal failure and a heart murmur. Radiographs demonstrate a smoothly marginated soft tissue mass cranial to the heart, which causes minimal displacement of the trachea dorsally. **B,** Ultrasound of the cranial mediastinal mass. The ultrasonogram demonstrates that the mass is thin walled and cystic. Fluid obtained via ultrasound guided FNA was clear with low cellularity and protein, consistent with a mediastinal cyst.



216.4.6 Non-Neoplastic Mediastinal Masses

Non-neoplastic mediastinal masses in dogs and cats and are usually infectious in origin. Fungal pyogranulomas, abscesses, lymphadenopathy, and hematomas have been described.[23–29] Lymphomatoid granulomatosis is a rare neoplastic/inflammatory disease of unknown etiology that causes hilar lymphadenopathy, pulmonary masses, and pleural effusion.[34] Lymphadenopathy may involve the cranial mediastinal, sternal, and tracheobronchial (hilar) lymph nodes. Cranial mediastinal lymph nodes lie along the major vascular structures and just ventral to the trachea. Sternal lymph nodes are just dorsal to the sternum, medial to the second costal cartilage, and cranioventral to the internal thoracic vessels. Sternal lymph nodes drain the abdomen, so enlargement often indicates intra-abdominal or multicentric disease.[19] The hilar lymph

nodes are found at the bifurcation of the trachea and proximal bronchi. None of these lymph nodes are visible in normal animals on survey radiographs. Other lesions that may appear to be a mass include esophageal foreign bodies, diaphragmatic hernias, and gastroesophageal intussusception.

Radiographically, mediastinal masses appear as thoracic opacities on or near the midline that frequently cause displacement of adjacent mediastinal or thoracic structures, such as the heart, esophagus, and trachea. The carina is normally located at the fifth or sixth intercostal space in the dog and the sixth intercostal space in the cat. It can be displaced caudally by cranial mediastinal masses. Esophageal masses usually cause ventral displacement of the trachea. Most other mediastinal masses displace the trachea dorsally and to the right. Other radiographic changes associated with mediastinal masses include increased opacity in the cranial thorax, widening of the mediastinum, tracheal compression, and loss of distinct, smooth, straight mediastinal borders. Masses that are in contact with a mediastinal structure may not have clearly defined borders. Enlarged sternal or hilar lymph nodes are most easily visualized on a lateral radiograph (Figure 216-3). Cranial mediastinal lymphadenopathy is better appreciated on a VD or DV view. Radiographic findings associated with enlargement of the hilar lymph nodes include separation of the main stem bronchi, elevation of the trachea cranial to the carina, and ventral deviation of the main caudal lobe bronchi caudal to the carina. Left atrial enlargement is the main differential diagnosis for this radiographic appearance. Mediastinal masses are frequently classified by location as cranioventral, craniodorsal, perihilar, caudoventral, or caudodorsal (Box 216-1).

Pleural effusion may imitate a mediastinal mass because of the associated tracheal elevation, which is caused by the dorsal displacement of the lungs.[35] Repeat radiographs obtained after removal of the pleural fluid are often helpful in distinguishing pleural effusion from a mediastinal mass. Other lesions that may be confused with a mediastinal mass include the normal thymus in young animals, mediastinal fat in obese animals, lung masses, especially those involving the accessory lobe or cranial tips of the left and right cranial lung lobes, very large right and left caudal pulmonary arteries, and perihilar edema. The presence of an air bronchogram within a suspected mediastinal mass indicates that it is actually a pulmonary lesion.

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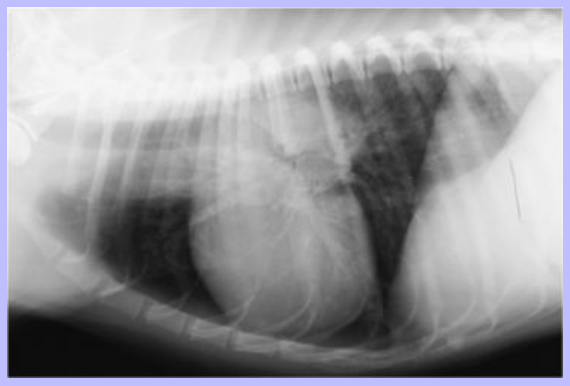
Figure 216-3 Lateral thoracic radiograph of a 3-year-old castrated male German Shorthaired Pointer presented for anorexia, weight loss, and fever. The radiographs demonstrate mass lesions and lymphadenopathy in the craniodorsal and hilar regions with displacement of the main stem bronchi ventrally. The final diagnosis was Nocardiosis.



216.4.6.1

Box • 216-1 Differential Diagnoses for Lesions Associated with Focal Mediastinal Enlargement

Region	Diseases
Cranioventral	Lymphadenopathy; abscess; thymic mass; ectopic thyroid; hematoma; granuloma; obesity; vascular mass (aorta, cranial vena cava); esophageal mass, foreign body, or dilatation; tracheal mass
Craniodorsal	Esophageal mass, foreign body, or dilatation; heart base mass; neurogenic tumor; paraspinal or spinal mass; hematoma; lymphadenopathy; aortic stenosis; patent ductus arteriosus; abscess; tracheal mass
Perihilar	Lymphadenopathy; left atrial enlargement; esophageal mass, foreign body, or dilatation; main pulmonary artery mass (post-stenotic dilatation); heart base or right atrial mass; spinal or paraspinal mass
Caudodorsal	Esophageal mass, foreign body, or dilatation; hiatal hernia; diaphragmatic hernia or mass; spirocercosis; spinal or paraspinal mass; aortic aneurysm; gastroesophageal intussusception
Caudoventral	Diaphragmatic hernia; peritoneopericardial diaphragmatic hernia; abscess; granuloma; hematoma

216.4.7

Mediastinal Neoplasia

Mediastinal tumors can originate from any structure within the mediastinum (lymph nodes, thymus, great vessels, trachea, esophagus, ectopic thyroid or parathyroid tissue) or from extension of neoplastic lesions in adjacent tissues.[36,37] Also, mediastinal neoplasms may be metastatic lesions or components of a multicentric neoplastic process.[38–44] Benign tumors have also been documented.[45]

Clinical signs associated with mediastinal tumors are usually caused by compression or invasion of structures such as the great vessels, thoracic duct, esophagus, and trachea. Signs include coughing, dyspnea, dysphagia, regurgitation, and edema of the head, neck, and/or forelimbs. Signs caused by peripheral nerve entrapment are less common and include laryngeal paralysis, vocalization changes, or Horner's syndrome. Signs associated with multicentric disease may reflect other sites of neoplastic involvement or may be related to paraneoplastic syndromes. These signs include anorexia, weight loss, vomiting, diarrhea, and polyuria/polydipsia.

Mediastinal lymphoma originates from either lymph node or thymic tissue in the cranial mediastinum. Mediastinal lymphoma is often associated with pleural effusion, which may initially obscure radiographic visualization of the mediastinal mass. The diagnosis of mediastinal lymphoma can often be confirmed by cytologic identification of neoplastic lymphocytes in either a sample of pleural fluid or a sample obtained directly from the mediastinal mass via FNA. In dogs, mediastinal lymphoma may be associated with hypercalcemia. The presence of a mediastinal mass is a poor prognostic indicator in dogs with lymphoma.[46] Less common lymphatic based tumors that can cause mediastinal masses include lymphangiosarcoma and lymphangioma.[37,45]

Chemodectomas, which are usually aortic or carotid body tumors, are most often identified as heart base masses.[47] Affected animals may be presented for dysphagia, dyspnea, heart failure, or cervical swelling. Because these tumors often invade and surround roots of the great vessels at the heart base, they result in a mediastinal mass effect.

216.5 DISEASES OF THE THYMUS

The thymus extends from the thoracic inlet caudally to the fifth rib in the dog and the sixth rib in the cat. Dorsally it lies next to the phrenic nerves and cranial lung lobes. Thymic involution in small animals occurs concurrently with the onset of sexual maturity and the loss of deciduous teeth.[48] The thymus atrophies and is gradually replaced by connective tissue and fat, but remnants persist into old age.[48] Thymic branchial cysts arise from remnants of branchial pouch epithelium and may occur in the cranial mediastinum of dogs and cats (also see above).[49]

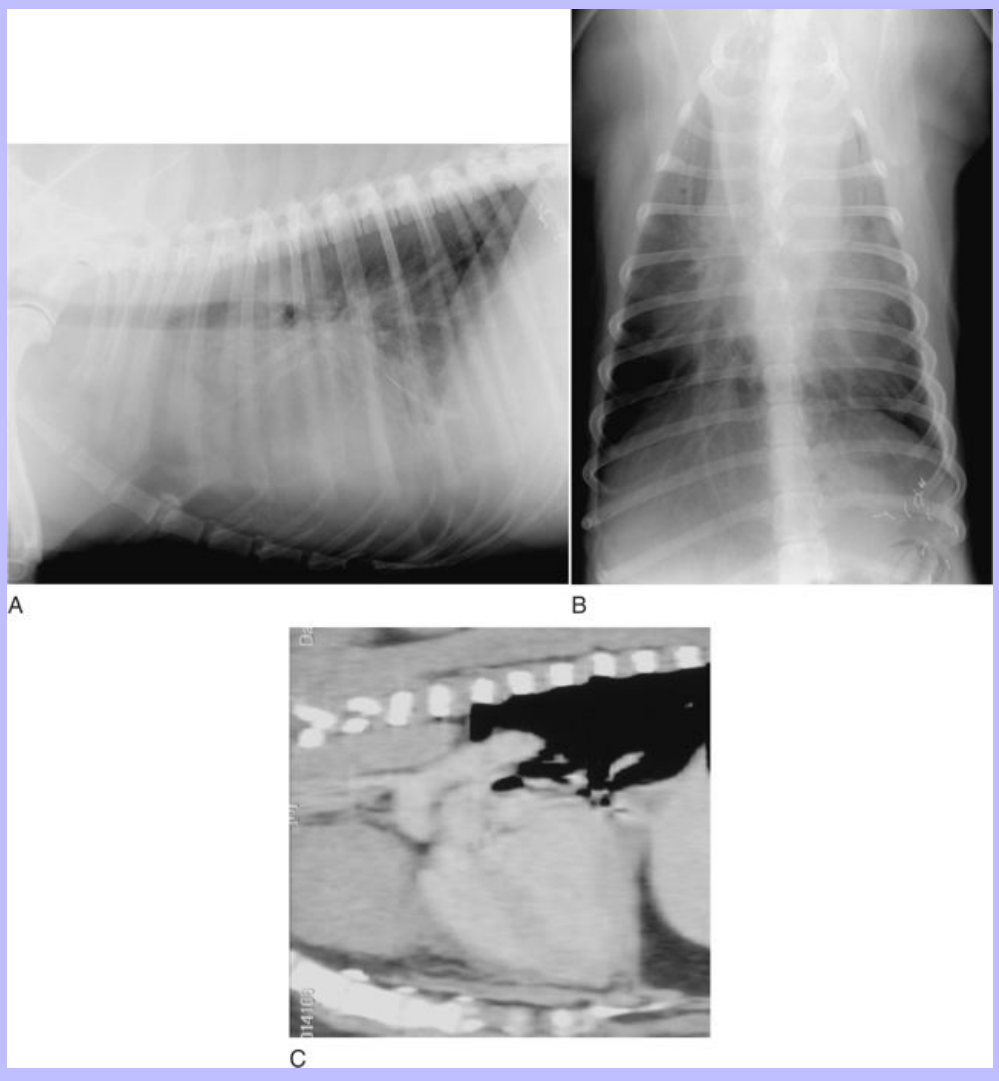
216.5.1 Thymic Hemorrhage

An uncommon disease of spontaneous thymic hemorrhage has been described in dogs and one cat.[49–52] Although not uniformly fatal, most animals documented with this syndrome have died. Most animals affected have been less than 2 years of age, so it appears to be associated with thymic involution. Clinical signs include lethargy, signs of thoracic pain, increased respiratory effort, and dyspnea. Physical examination findings are attributable to acute blood loss/hypovolemia and pleural effusion. Signs include pale mucous membranes, prolonged capillary refill time, tachycardia, tachypnea, and muffled lung sounds. Thoracic radiographs demonstrate a mediastinal mass (hemorrhage, hematoma) usually associated with pleural effusion. Treatment is supportive in nature and involves volume support, blood replacement, and thoracocentesis as needed.

216.5.2 Thymoma

Thymomas are rare tumors in the dog and cat that arise from the epithelial cells of the thymus.[53–56] They appear radiographically as large, poorly defined soft tissue masses in the cranial mediastinum (Figure 216-4, *A* and *B*). Expansion and invasion into adjacent tissues are common, but in some cases the masses are well encapsulated and fairly noninvasive. Metastasis has been reported in dogs and cats.[53,56] Pleural effusion is a variable finding and may hinder visualization of the thymic mass. Sonographically, thymomas can appear as solid, cystic, or a combination. Cytologic examination of FNA samples reveals a variable number of mature lymphocytes, which makes cytologic differentiation of thymoma from mediastinal lymphoma difficult. Mast cells are also frequently identified in cytologic samples from thymomas. Surgical or ultrasound guided percutaneous biopsy is required for definitive diagnosis. Paraneoplastic syndromes are commonly associated with thymoma in both dogs and cats.[53,55] The most well described is myasthenia gravis, which is often associated with megaesophagus in dogs with thymoma.[53] Myasthenia gravis has also been reported in cats with thymoma, but is less common. Surgical resection is the treatment of choice for thymoma, but recurrence and metastasis have been reported.

Figure 216-4 Lateral **(A)** and dorsoventral **(B)** radiographs of a 10-year-old castrated male Labrador Retriever presented for collapse. Radiographs demonstrate deviation of the trachea to the right. The cranial border of the cardiac silhouette is effaced by a cranial mediastinal mass. **C,** Computed tomographic 3D reconstruction of the cranial mediastinal mass in the same dog. The mass was removed surgically. Final diagnosis was thymoma with hemorrhage.



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217 CHAPTER • 217 Pleural and Extrapleural Diseases

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217.1 DISORDERS OF THE DIAPHRAGM

217.1.1 Diaphragmatic Anatomy

The diaphragm is a musculotendinous structure that separates the abdominal and thoracic cavities and is covered by pleura on its convex (thoracic) surface, adjacent to the lungs. It aids in ventilation and movement of lymphatic fluid. The phrenic nerves, which in dogs are derived from C4 to C7, provide innervation.[1] In cats, the phrenic nerves arise from C4 to C6. Prior to reaching the diaphragm, the phrenic nerves traverse the mediastinum and pericardium and are therefore subject to disruption from infiltrative masses or surgical transection (during pericardectomy or mass removal).

217.2 DIAPHRAGMATIC DISPLACEMENT AND DYSFUNCTION

Cranial or caudal displacement of the diaphragm may be associated with certain conditions and can be unilateral or bilateral. Cranial displacement results from enlargement or gas distension of abdominal contents as would be seen with late-term pregnancy or gastric dilatation-volvulus, respectively. It may contribute to respiratory compromise in such circumstances. Removal of a lung lobe or pulmonary atelectasis or consolidation results in unilateral cranial advancement of the diaphragm. Caudal diaphragmatic displacement is associated with pleural cavity disease (e.g., pneumothorax, pleural effusion) or obstructive airway disease that causes air trapping and pulmonary hyperinflation. These displacements are typically bilateral and recognition may be difficult when pleural fluid obscures the diaphragmatic silhouette. Unilateral caudal displacements are uncommon and may occur with either unilateral pneumothorax or pleural effusion, particularly chylothorax or pyothorax.

Paralysis of the diaphragm may also be uni-or bilateral. Unilateral paralysis is unlikely to be associated with clinical evidence of respiratory abnormalities; however, bilateral paralysis can result in substantial impairment of respiration. Bilateral paralysis most commonly results from cervical spinal trauma or fracture. In such cases, cranial displacement of the diaphragm may be radiographically apparent. Lack of movement of the diaphragm during fluoroscopic evaluation increases suspicion of this condition.

217.2.1 Diaphragmatic Hernias

Diaphragmatic hernia (DH) is a term for disorders of the diaphragm that allow abdominal contents to enter the thoracic cavity, either within the pleural space (pleuroperitoneal hernias, hiatal hernias) or pericardial sac (peritoneopericardial diaphragmatic hernias). Diaphragmatic hernias are divided by etiology into traumatic and congenital hernias.

217.2.1.1 Traumatic Diaphragmatic Hernias

Traumatic DHs are more commonly recognized in small animal veterinary patients than are congenital hernias, with studies reporting between 77% and 85% of diaphragmatic hernias being traumatic in origin.[2–4] Traumatic DHs are frequently associated with motor vehicle accidents or other forceful blows to the thorax or abdomen.[3,5] A sudden increase in intra-abdominal pressure, with an open glottis, results in rapid deflation of the lungs. The position of the glottis may be unimportant provided there is the creation of an abrupt, substantial increase in pressure with an abdominal pressure gradient.[2] The large pressure gradient causes the diaphragm to tear at its weakest points (usually in the muscular portions). The location and size of the tear(s) depend on the position of the animal at the time of impact and location of the viscera.

217.2.1.1.1 Signalment and History

Young male dogs between the ages of 1 and 2 years are most commonly diagnosed with traumatic DH because of their propensity to roam and sustain vehicular trauma. Affected animals may present in shock and respiratory distress, depending on the size of the hernia, which viscera have herniated, and severity of other injuries. Concurrent injuries are common. Chronic diaphragmatic hernias are reported and respiratory embarrassment may not be immediately evident. In one study, 20% of animals with traumatic DH were not diagnosed until at least 4 weeks after the injury had occurred.[2] Clinical signs associated with chronic diaphragmatic hernias are generally confined to the respiratory or gastrointestinal system and may include dyspnea, exercise intolerance, anorexia, depression, vomiting, diarrhea, weight loss, and/or pain following ingestion of food.

217.2.1.1.2 Physical Examination

Physical examination findings vary with the acuteness of the trauma, concurrent injuries, and organs herniated. Hypoventilation is often present and is attributable to inadequate lung expansion, voluntary decrease in chest wall motion due to pain, fractures or flail segments causing chest wall dysfunction, or pulmonary atelectasis. Signs consistent with shock include pale or cyanotic mucous membranes, tachypnea, tachycardia with variable pulse pressure, and decreased mentation. Cardiac arrhythmias, attributable to traumatic myocarditis, may be present and if severe, are associated with significant morbidity. The liver is the organ most commonly herniated and is often associated with hydrothorax as a result of venous occlusion and capsular weeping. Extrahepatic biliary obstruction has been reported.[6] Herniation and entrapment of the stomach can lead to gaseous distension, which results in a rapidly declining clinical condition and fatal respiratory impairment. Gastric dilation-volvulus has been reported with DH and should be suspected in dogs and cats presenting with abdominal enlargement and dyspnea.[7]

217.2.1.1.3 Diagnosis

Diagnosis of DH is made either on thoracic radiographs (Figure 217-1) or by ultrasonography of the diaphragm and cranial abdomen. The presence of gas-filled viscera in the thoracic cavity is diagnostic of a DH; however, visualization of thoracic structures and the diaphragmatic silhouette may be obscured by the presence of pleural effusion. In such cases, thoracocentesis may be necessary prior to obtaining diagnostic radiographs. Ultrasound examination is most helpful in cases with herniation of the liver or when large volumes of pleural fluid are present. An upper GI barium study may identify portions of the

intestinal tract that have herniated into the thoracic cavity. Positive contrast celiography with a water-soluble contrast agent is occasionally used as a diagnostic aid but caution must be used when injecting radiographic contrast agents in dehydrated animals. Additionally, omental or fibrous adhesions may obscure diaphragmatic defects and result in false-negative studies.

Figure 217-1 Ventrodorsal thoracic radiograph of a dog with a traumatic diaphragmatic hernia. Notice the gas-filled loops of small intestine in the right hemithorax.

217.2.1.1.4 Management

Initial management should include oxygen therapy in dyspneic animals and treatment for shock, including fluids and administration of a broad-spectrum antibiotic (see Chapter 120, 124). Ventilation may be improved by positioning the animal in sternal recumbency with the front end elevated. Thoracocentesis should be performed if moderate to marked pleural fluid is present. Animals presenting with gastric distension should be considered surgical emergencies and operated on as soon as they can safely be anesthetized. Other animals with diaphragmatic hernias and associated trauma may benefit from stabilization prior to surgical intervention and definitive repair of the DH. However, these animals must be closely monitored for worsening respiratory compromise. Overall mortality rate for dogs and

cats undergoing diaphragmatic herniorrhaphy is cited at approximately 20%.[8–10] Readers are referred to a surgical textbook for details of surgical correction of DH.

217.2.1.2 Congenital Diaphragmatic Hernias

217.2.1.2.1 Signalment and History

Congenital pleuroperitoneal hernias can occur and result from improper development of the left pleuroperitoneal membrane. These hernias are infrequently recognized in dogs and cats as they generally result in death upon or shortly after birth.[11] Hernias involving the esophageal hiatus are typically congenital in nature and are known as *hiatal hernias*. (See Chapter 220.)

Peritoneopericardial diaphragmatic hernias (PPDHs) are the most common congenital pericardial and diaphragmatic anomalies in dogs and cats.[12] Herniation of abdominal viscera into the pericardial sac can result from abnormal development of the septum transversum or from failure of the lateral pleuroperitoneal folds and the ventromedial pars sternalis to unite. This defect likely occurs as a result of a teratogen, genetic defect, or prenatal injury.[13] A high incidence of right-and left-sided DH was induced when the embryotoxic herbicide nitrofen was given to rats during a critical period in gestation.[14] A teratogen was the suspected cause of PPDH and multiple cardiac defects in an entire litter of collies.[15] Unlike in humans, PPDHs are always congenital in dogs and cats because there is no direct communication between the peritoneal and pericardial cavities after birth in these species.

Cardiac abnormalities and sternal deformities often occur concomitantly with PPDHs. Reported concurrent anomalies include umbilical hernias, cranial midline abdominal wall hernias, malformed or absent sternebrae, pectus excavatum or intracardiac defects.[16,17] Polycystic kidneys have been reported in association with PPDH in a cat.[18] Although seldom noted in animals, pulmonary vascular abnormalities may occur in children with congenital DH; persistent pulmonary hypertension is thought to contribute to the morbidity and mortality associated with this condition in affected children.[19] A predisposition for PPDH has been suggested in Persian cats and Weimeraners.[17,20]

217.2.1.2.2 Clinical Signs and Physical Examination

As with other DH, clinical signs of affected animals may vary from none to severe respiratory embarrassment, depending on the organ(s) herniated and degree of compromise of that organ(s). Vomiting and anorexia are often observed. Physical examination may reveal muffled heart sounds and lack of normally palpable organs in the abdomen.

217.2.1.2.3 Diagnosis

Diagnosis of PPDH is usually made from thoracic radiographs and/or ultrasound and is frequently an incidental finding. Radiographic findings include apparent cardiomegaly, dorsal elevation of the trachea, and silhouetting of the heart and diaphragm; gas-filled viscera may be present. As with other diaphragmatic hernias, oral barium administration may be useful if the diagnosis is not readily apparent on radiographs or if ultrasound is unavailable.

217.2.1.2.4 Management

Initial management of the symptomatic animal with PPDH includes oxygen therapy if dyspneic and positioning the animal in sternal recumbency with the chest elevated. Surgical repair of PPDH is recommended in most cases and should be performed at as early an age as possible. Early surgical intervention may decrease the incidence of adhesions and risk of postoperative re-expansion pulmonary edema.

217.3 DISORDERS OF THE THORACIC WALL

217.3.1 Chest Wall Trauma

Damage to the thoracic wall may be due to blunt (motor vehicle accidents, being kicked) or penetrating (bite wounds, gun-shot wounds) injuries. Both blunt and penetrating trauma can cause extensive soft tissue damage of the thoracic wall. Although soft tissue damage is rarely the cause of major morbidity or mortality, it may be the only external evidence of severe thoracic trauma. Pain associated with thoracic wall trauma may lead to hypoventilation because the animal is unwilling to breathe; analgesics may improve ventilation. Similarly, isolated rib fractures, although unlikely to result in significant respiratory impairment, may result in decreased ventilation due to pain. Chest wall trauma alone (without pulmonary parenchymal damage) rarely leads to significant hypoventilation resulting in hypoxia.

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A flail segment (flail chest) is produced when multiple segmental rib fractures produce a free segment of thoracic wall that has lost its continuity with the remainder of the thorax. Intrapleural pressure changes during respiration result in paradoxic segment movement; the segment moves inward during inspiration and outward during expiration. Flail chest segments can initially be stabilized by positioning the animal with the flail side down. Mechanical ventilation is the preferred treatment for people with flail segments. As this may not be practical in veterinary patients, surgical stabilization of the flail segment is thought to help decrease pain, improve ventilation, and prevent further damage to thoracic structures. A recent retrospective study of the medical records from five veterinary teaching hospitals investigating the clinical management of flail chest in dogs and cats reported that the majority of cases were treated without stabilization of the flail segment.[21] The study was not able to demonstrate a difference in outcome between surgically stabilized and conservatively managed cases. It was not possible to determine from the results of the study which animals would benefit from surgery. Readers are referred to a surgical text for more details of the surgical management of flail chest.

Subcutaneous emphysema can occur with both blunt and penetrating trauma and is usually of little clinical significance. It occurs when air dissects along fascial planes under the subcutaneous tissues. Air may enter the subcutaneous tissues from direct communication with an external wound, from disruption of the pleura and intercostals muscles, or as an extension of mediastinal emphysema. The condition is usually self-limiting; treatment should be directed at the underlying cause.

217.3.2 Pectus Excavatum

Pectus excavatum (PE) is a deformity of the costocartilages and sternum that result in a dorsoventral narrowing of the chest. Although the causes are unknown, several theories have been proposed. It has been suggested that there may be both congenital and acquired forms of PE in people.[22] Possible etiologies include shortening of the central tendon of the diaphragm, abnormalities of intrauterine pressure, congenital deficiency

of musculature in the cranial portion of the diaphragm, and abnormal respiratory gradients as may be present with upper airway obstruction.

217.3.2.1 Signalment and History

Sternal depressions are often noted early in the life of the animal and prompt owners to seek veterinary attention. The disease is progressive and the severity of the defect may increase as the animal matures. In humans, males appear to be predisposed, yet a gender predilection has not been clearly identified in animals. PE has been reported in dogs, cats, sheep, and calves. Brachycephalic dogs and Burmese cats are more commonly affected than other breeds.[23,24] PE has occurred in multiple animals of certain litters; therefore affected animals should not be used for breeding. PE can be associated with "swimmer's syndrome," a poorly characterized disease of neonatal dogs in which the legs splay to the sides.

217.3.2.2 Clinical Signs and Physical Examination

Animals with PE may be asymptomatic or may present with clinical signs associated with both respiratory and cardiovascular functional abnormalities. The sternal depression often causes malpositioning of the heart within the thoracic cavity and may result in kinking of the large veins, disturbance of venous return, restriction of ventricular filling, and decreased respiratory reserve. Direct compression of the heart may result in cardiac arrhythmias. Symptoms such as exercise intolerance, weight loss or failure to thrive, hyperpnea or dyspnea, cyanosis, recurrent respiratory infections, and vomiting may occur. A correlation between severity of clinical signs and severity of the abnormality has not been identified. Other abnormalities that may be noted on physical exam include cardiac murmurs and increased or harsh lung sounds. Concurrent cardiac abnormalities such as pulmonic stenosis and atrial septal defects have been reported; care must be taken to distinguish abnormalities caused by the position of the heart from those that result from cardiac disease.

Figure 217-2 A cat with pectus excavatum. Notice the palpable depression of the caudal sternum. (From Fossum TW et al: Pectus excavatum in 8 dogs and 6 cats, J Am Anim Hosp Assoc 25:595, 1989.)

217.3.2.3 Diagnosis

Diagnosis of PE is made on physical examination by palpation of a depression in the sternum (Figure 217-2). Thoracic radiographs show an abnormal elevation of the sternum. The heart is often shifted to one of the hemi-thoraces as insufficient room exists on midline. In this abnormal position, it may appear enlarged on thoracic radiographs. Echocardiography may be necessary to distinguish cardiac disease from this apparent enlargement. Classification of the sternal deformity as mild, moderate, or severe has been described and is based on the frontosaggital and vertebral indices obtained from thoracic radiographs[24] (Figure 217-3).

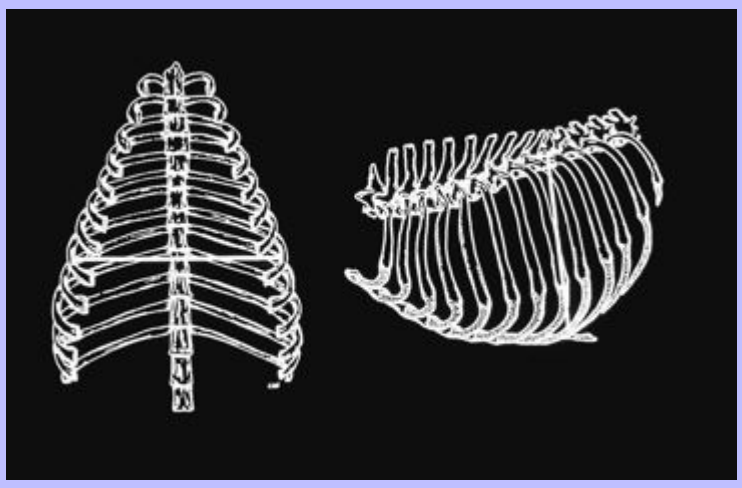
217.3.2.4 Management

Animals with mild PE or those with simply a flattened ventral thorax are unlikely to require surgery. Owners should be instructed to perform medial to lateral chest compressions in such cases. In young animals with moderate to severe disease, or those with clinical signs, application of a splint to the ventral aspect of the thorax is the most commonly used treatment. Older animals with less compliant thoracic and sternal walls may require a partial sternectomy to relieve their clinical signs.

217.3.3 Thoracic Wall and Sternal Neoplasia

Primary tumors of the rib are uncommon in the dog; however, these tumors are usually malignant and have a high metastatic rate. Some reports cite that they generally develop in young dogs, with a mean reported age in one study of 4.5 years[25], whereas others report median ages of between 7 and 9 years.[26,27] Osteosarcomas are the most common neoplasm of the canine rib, followed by chondrosarcoma; the costochondral junction is the usual site of origin of these tumors. Fibrosarcomas and hemangiosarcomas are less frequently reported.[25,28] Most rib tumors cause a localized swelling of the thoracic wall; however, pleural effusion without evidence of a thoracic mass has been reported in two dogs with primary rib tumors and metastatic pulmonary lesions.[29] Other clinical signs noted in two animals with rib tumors included weight loss and dyspnea.

Figure 217-3 The frontosagittal index is the ratio between the width of the chest at the tenth thoracic vertebra (a) and the distance between the center of the ventral surface of the tenth thoracic vertebral body and the nearest point on the sternum (b). The vertebral index is the ratio between the distance from the center of the dorsal surface of the tenth vertebral body to the nearest point on the sternum (b and c) and the dorsalventral diameter of the vertebral body at the same level (c). (From Fossum TW et al: J Am Anim Hosp Assoc 25:595, 1989.)



Neoplasms of the ribs or sternum should be differentiated from bacterial or fungal osteomyelitis. A tentative diagnosis of the tumor cell type can usually be made by fine-needle aspiration of the mass; however, definitive diagnosis requires histologic examination of a biopsy specimen. Although pleural effusion is common in dogs with rib tumors, identification of neoplastic cells in the fluid is very uncommon. Due to the high rate of pulmonary metastasis, the prognosis for dogs with rib tumors is poor. In one study of 15 dogs with primary rib tumors, greater than 90% of the dogs died or were euthanized within 4 months of the diagnosis.[29]

Although also rare, both metastatic and primary tumors of the sternum have been reported in dogs.[30] In humans, metastatic tumors involving the sternum are more frequently recognized than primary tumors. The distant primary site is most commonly in the thyroid, kidney, breast, testicle, lung, stomach, or rectum. Primary neoplasms of the bony chest account for 7% to 8% of all bone tumors in humans, and although primary rib tumors are frequently benign, tumors of the sternum are typically malignant. Similar generalizations are difficult to make in the dog due to the infrequency with which sternal tumors have been reported. However, chondrosarcomas and osteosarcomas involving the sternebrae have been reported in dogs.[31]

When a diagnosis of sternal neoplasia is made, the diseased bone as well as normal surrounding tissue should be removed. Unlike most bones in the body, the sternebrae can be removed with little compromise of

function.[32] Successful treatment of sternal osteomyelitis following resection of large portions of the sternebrae has been reported in dogs and human beings, and the procedure would likely benefit dogs with primary sternal neoplasia.

217.4 PLEURAL EFFUSION

217.4.1 Anatomy of the Pleural Space

The pleura consists of a single sheet of flattened mesothelial cells supported by a layer of elastic connective tissue containing vascular and lymphatic channels. The visceral pleura covers the lung surface; the parietal pleura lines the inner surface of the ribs, diaphragm, and mediastinum. The pleural space normally contains a small amount of fluid that aids in transmission of forces and provides lubrication of the lung surfaces during respiration. Pleural fluid in the normal animal is similar to that of a plasma filtrate with a low protein concentration and a cellular composition of mesothelial cells and monocytes. Differences in electrolyte composition between pleural fluid and blood suggest modification of the plasma filtrate by an active transport or selective diffusion mechanism.[33] Filtration rate and lymphatic drainage increase with animal size and age; larger animals have small pleural fluid volumes.

Theories concerning the regulation of pleural fluid turnover have been expanded greatly over the past few decades. In 1927 Neergard described the balance of fluid formation and resorption as an equilibrium between hydraulic and colloid osmotic pressures.[34] Although these concepts are still valid, additional mechanisms must be in place to explain the stable composition of interstitial and pleural fluids. Given the differential permeability of water and solutes, pleural fluid protein concentration would increase over time if pleural fluid exchange were based solely on the difference between hydrostatic and colloid osmotic pressures. Similarly, if fluid production occurred solely at the arteriolar end of the capillary bed and resorption at the venular end as previously described, then a progressive increase in interstitial protein should occur over time.

The formation of pleural fluid is thought to be the result of filtration of fluid into the pleural space via Starling forces. It is currently thought that the absorption of pleural fluid is controlled by several mechanisms. The pressure differential across the visceral pleura favors liquid absorption; however, this is believed to contribute to only a small amount of fluid absorption.[35,36] Some believe that the pleural lymphatics provide the majority of interstitial fluid drainage[34], including particles, cells, and albumin.[37] There is evidence that stomas that help to transport albumin and water exist between the mesothelial cells of the parietal pleura and endothelial cells of the pleural lymphatics.[34] However, some albumin and liquid are also transported outside of the stomas via transcytosis.[38] A subatmospheric pressure of approximately −10 cm H_2O is generated by pleural lymphatics[39], which allows them to act as a drainage mechanism in pleural fluid accumulation. Lymphatic flow rate can increase dramatically (twentyfold) in response to increased pleural fluid filtration. Lymphatic drainage is greatest in the ventral thoracic cavity, diaphragm, and mediastinum.

More recently, the role of mesothelial cells in active trans-serosal transport (electrolyte coupled liquid absorption) has been investigated[40]; direct and indirect evidence of this function has been provided.[41–43] Mesothelial cell permeability to water and solutes may be equivalent to that of the capillary endothelium and these cells appear to be involved in the active transport of solutes and liquid. Thus the volume and composition of pleural fluid in the normal animal is governed by lymphatic drainage, Starling forces through the mesothelium and capillaries of the connective tissue, and activity of mesothelial cells.

217.4.2 Etiology of Pleural Effusions

Pleural effusions develop when there is an alteration in the balance between fluid formation and fluid resorption. This can result from changes in hydrostatic and osmotic pressures, impaired lymphatic drainage, and increased vascular or lymphatic permeability.[40] Alterations in the pleural fluid protein content and cellularity can give some evidence as to the underlying disease process. Low protein effusions are generally caused by cardiac, renal, or hepatic disease and are known as *transudates*. Effusions with a high protein count (>3.0 g/dL) suggest increased vascular permeability, decreased lymphatic removal, or both and can be caused by inflammatory or neoplastic processes or by diseases of the lymphatic system.

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Alterations in osmotic pressure result in low protein effusions as disruption of Starling forces allows fluid movement out of the vascular space and decreased absorption of fluid by the capillaries of the visceral pleura. Serum albumin concentrations of less than 1.5 g/dL may result in pleural or peritoneal effusions; edema of the extremities may also occur. Hypoalbuminemia can be secondary to decreased production as seen in liver disease or increased loss as in protein-losing enteropathy or nephropathy. Hepatic hydrothorax occurs when a marked pleural effusion occurs in a patient with hepatic cirrhosis in the absence of primary pulmonary or cardiac disease.[44] These effusions often recur and may be associated with diaphragmatic peritoneopleural communications or may occur via transdiaphragmatic lymphatic drainage of the cranial abdomen.

Increased systemic venous hydrostatic pressure is most commonly seen secondarily to congestive heart failure (CHF) and may result in pleural effusion. Left-sided CHF increases visceral capillary hydrostatic pressure and decreases fluid absorption, whereas right-sided CHF increases parietal capillary pressure and tends to favor increased pleural fluid formation.[45] Increased venous pressures also decrease lymphatic drainage within the pleural cavity and can result in a transudative or chylous effusion. Venous or lymphatic obstruction, as might be seen with a lung lobe torsion or incarceration of a liver lobe through a diaphragmatic hernia, can cause transudation of fluid through the organ capsule and result in pleural effusion. Other causes of increased venous pressures include pericardial effusion and cardiac tamponade, heartworm disease, and neoplasia.

Animals with fibrosing pleuritis or severe upper airway obstruction may develop increased negative pressure in the pleural space. In fibrosing pleuritis, the lungs are unable to re-expand despite absorption or removal of pleural fluid, which result in an increase in negative pressure.[33] This negative pressure promotes rapid accumulation of pleural fluid.

Alterations in vascular or lymphatic permeability or decreased lymphatic drainage cause effusions with increasing amounts of protein and fluid accumulation. Increased vascular permeability may be induced by vasculitis, which results from release of mediators such as histamine during inflammatory processes. Diseases that commonly result in vasculitis that may cause pleural effusion include feline infectious peritonitis (FIP), pancreatitis, uremia, and immune-mediated diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. Lymphatic drainage may be altered by neoplastic processes such as lymphangiosarcoma, mesothelioma, or metastatic mammary carcinoma.

217.4.3 Clinical Signs and Physical Examination

Clinical signs associated with pleural effusion can vary according to the etiology of the increased fluid volume, rapidity with which the fluid accumulated, and the volume of fluid present. With increased pleural fluid accumulation, compensatory mechanisms are overcome and clinical evidence of decreased lung

expansion and impaired gas exchange become evident. These signs are likely to have an insidious onset and substantial disease can be present before abnormalities are recognized.

Dyspnea is the most common clinical sign in animals presenting to the veterinarian with pleural effusion. Often the owner reports an acute onset. The dyspnea is usually marked by a forceful inspiration, with delayed expiration. Animals are often reluctant to lie down and may extend their heads and necks in an elevated position. Other clinical signs include tachypnea, open-mouth breathing, and cyanosis. Dogs and cats with chronic pleural effusion may present with coughing as the only clinical sign and should therefore be evaluated for pleural effusion when presenting with a persistent cough that does not respond to routine therapy. Coughing may be a result of irritation caused by the effusion, or related to an underlying disease process (e.g., cardiomyopathy). Other physical exam findings can include muffled heart and lung sounds and dullness on thoracic percussion. Additional findings that are related to the underlying cause of the pleural effusion can include fever, weight-loss, anorexia, depression, pale mucous membranes, heart murmurs or arrhythmias, ascites, pericardial effusion, or Horner's syndrome. Animals that remain dyspneic following pleural fluid removal should be suspected of having underlying pulmonary parenchymal or pleural disease such as pneumonia or fibrosing pleuritis, respectively.

Fibrosing pleuritis is a condition that has been associated with chylothorax in both dogs and cats.[46,47] Although the cause of the fibrosis is unknown, it apparently can develop subsequent to any prolonged exudative or blood-stained effusion. Exudates are characterized by a high rate of fibrin formation.[48] Fibrin formation probably increases because chronic inflammatory exudates, such as chylothorax and pyothorax, induce changes in mesothelial cell morphologic features, resulting in increased permeability, mesothelial cell desquamation, and triggering of both pathways of the coagulation cascade.[49] Desquamated mesothelial cells have also been shown to produce type III collagen in cell culture, and promote fibrosis.[50] Additionally, the chronic presence of pleural fluid might lead to an impairment in the mechanism of fibrin degradation.[51] Fibrinolysis may decrease because direct injury to mesothelial cells may reduce inherent fibrinolytic activity of the cells, and/or the increased fluid volume may dilute local plasminogen activator. Plasminogen activator converts the precursor plasminogen to its active form, plasmin. Fibrinolytic activity in mammals is attributable primarily to this serine protease.[52]

In animals with fibrosing pleuritis, the pleura is thickened by diffuse fibrous tissue that restricts normal pulmonary expansion (Figure 217-4, *A*). Animals with fibrosing pleuritis may be misdiagnosed as having large amounts of pleural effusion, when in fact the pleural effusion is minimal. Diagnosis of fibrosing pleuritis is difficult. The atelectatic lobes may be confused with metastatic or primary pulmonary neoplasia, lung lobe torsion, or hilar lymphadenopathy. Radiographic evidence of pulmonary parenchyma that fails to re-expand after removal of pleural fluid should be considered possible evidence of atelectasis with associated fibrosis (Figure 217-4, *B*). Fibrosing pleuritis should also be considered in animals with persistent dyspnea, yet minimal pleural fluid. In human beings, computerized tomography is occasionally helpful in differentiating pleural fibrosis from other abnormalities, such as neoplasia.[53,54]

217.4.4 Diagnosis

Animals suspected of having pleural effusion should be thoroughly evaluated for underlying cardiac or respiratory disease. Thoracic auscultation may reveal decreased heart and lung sounds ventrally. Thoracic percussion may demonstrate a fluid line with hyporesonant sounds ventrally and normal sounds dorsally. Murmurs may be auscultated in animals with underlying cardiac disease. Animals should be evaluated for the

presence of jugular pulses. In cats with cranial mediastinal masses, the cranial thorax may become less compressible. See below for radiographic and ultrasonographic findings in animals with pleural effusion.

217.4.5 Thoracocentesis

In addition to relieving respiratory difficulty, thoracocentesis also provides samples to aid evaluation and diagnosis. *In the dyspneic animal, thoracocentesis should be performed prior to thoracic radiographs.* Removal of even small amounts of fluid may substantially decrease the animal's ventilatory effort. The animal should be restrained in sternal recumbency with oxygen provided by mask if tolerated. Slight sedation may be required in fractious animals; general anesthetics should be avoided. Caution should be used when sedating dyspneic animals. Typically, the mediastinum in dogs and cats appears to be incomplete and fluid aspiration from either side will permit drainage of the entire thorax. However, due to chronic inflammation and thickening of the mediastinum, unilateral effusions may be noted with certain diseases such as chylothorax and pyothorax. Thoracocentesis techniques are described in Chapter 103.

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Figure 217-4 **A,** Intra-operative photo of a cat with severe fibrosing pleuritis secondary to chronic chylothorax. Notice the small, consolidated lung lobes and the thickened pleura. Decortication of the fibrous pleural was performed in this cat. **B,** Lateral radiograph of the cat from **A**. Note the rounded appearance of the caudal lung lobes. Removal of the pleural fluid did not improve the expansion of the lung lobes.

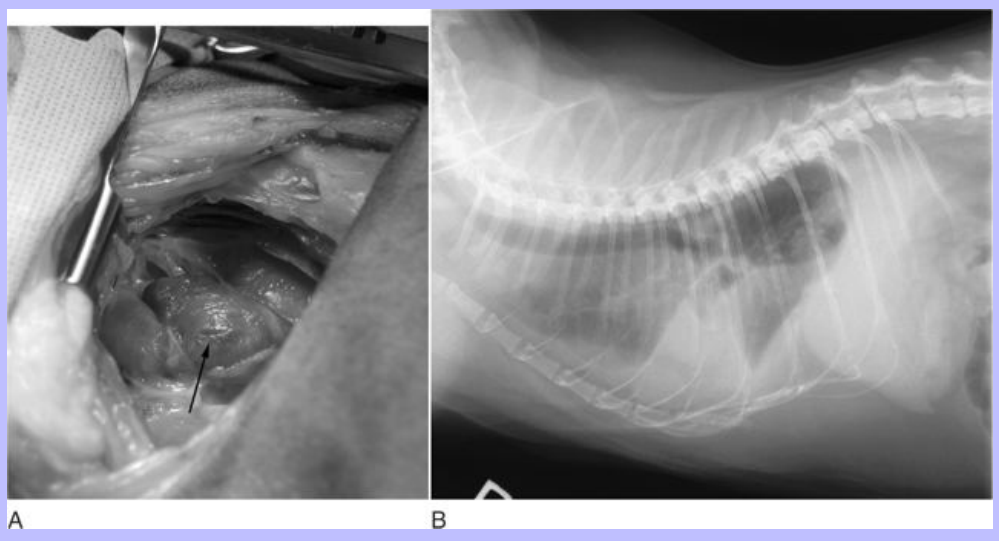
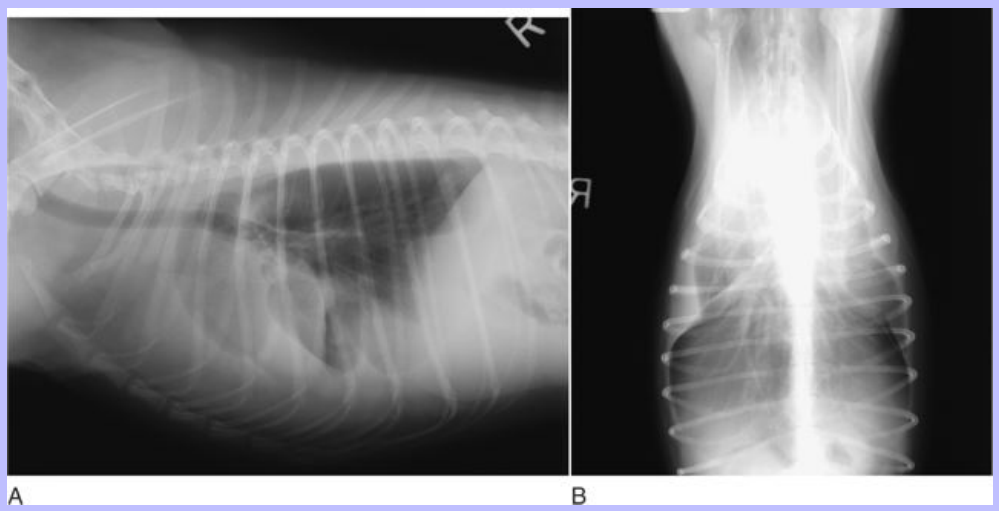


Figure 217-5 Lateral and dorsoventral radiographs of a dog with pleural effusion secondary to chylothorax. Note the loss of the cardiac and diaphragmatic silhouettes, and widened interlobar fissures.



217.4.6 Radiography and Ultrasonography

If the animal is not dyspneic, thoracic radiographs should be obtained to confirm the diagnosis of pleural effusion and allow evaluation of thoracic and intra-thoracic structures (Figure 217-5). Dorsoventral (rather than ventrodorsal) and "standing lateral" views may cause less stress to a compromised animal. Handling should be minimized and supplemental oxygen provided.

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Normal pleura is not generally radiographically visible. With pleural thickening, pleural lines may become visible and may be mistaken for pleural effusion. A horizontal beam radiograph will help differentiate the two. Roentgen signs associated with pleural effusion include widened interlobar fissures, retraction of the lung margins from the thoracic wall, rounding of the lung margins at the costophrenic angles, and obscuring of the diaphragmatic and cardiac silhouettes. Visualization of the cranial aspect of the cardiac silhouette in the presence of pleural effusion is occasionally possible with identification of the "pericardial fat stripe."[55] It is reported that a lucent line is occasionally evident at the cranial edge of the cardiac silhouette and represents the x-ray beam striking fat around the heart at a tangent. To permit more careful evaluation of intra-thoracic structures, radiographs should be repeated once the pleural fluid has been removed.

In the stable animal, ultrasonography should be performed prior to fluid removal as the fluid provides an "acoustic window" and may allow clearer visualization of intra-thoracic structures such as mediastinal masses. Ultrasonography can be used to diagnose cardiac functional and structural abnormalities and identify pericardial effusion. It may aid in location of encapsulated fluid and identification of the appropriate site for thoracocentesis.

217.4.7 Pleural Fluid Evaluation

Cytologic analysis of pleural fluid obtained via thoracocentesis is indicated. Identification of cell types and numbers, protein levels, and other physical characteristics and biochemical markers allow classification of pleural fluids into categories that aid in the identification of the underlying etiology. Fluids are generally divided into three types: transudates, modified transudates, and exudates. Additional sub-classifications include chylous, neoplastic, and hemorrhagic effusions.

Table • 217-1 Characteristics of Fluid Types

	TRANSUDATE	MODIFIED TRANSUDATE	EXUDATE	PYOTHORAX	CHYLOTHORAX	FIP
Protein content (g/dL)	<2.5	2.5–4	>3	>3.5	Variable	>5
TNCC* (cells/μL)	<1500	1000–7000	>7000	>7000	<10,000	<10,000
Color	Clear	Yellow, whitish-pink, red	White, amber, red	Amber to red or white	Usually white or pink	Straw to gold colored
Transparency	Colorless	Hazy to turbid	Opaque (usually) Turbid (rarely)	Turbid or opaque	Opaque	Hazy
Biochemical parameters			LDH >200 U/L	Glucose <10 mg/dL pH <6.9	Triglyceride >serum triglyceride	
Predominant cell types	Mesothelial cells, macrophages	Mesothelial cells, macrophages eosinophils, lymphocytes	Neutrophils (most common) Lymphocytes, macrophages, mesothelial cells, neoplastic cells	Degenerative neutrophils	Lymphocytes or neutrophils	Nondegenerative neutrophils

* *TNCC*, Total nucleated cell count.

217.4.7.1 Transudates and Modified Transudates

Pure transudates are clear, colorless fluids with a low total protein and low cellularity (Table 217-1). The primary cell type is mononuclear, with macrophages, and mesothelial cells most often present in small numbers; occasional lymphocytes or neutrophils can be seen. With chronicity, there is often a small increase in protein and cell numbers as a result of pleural irritation. Because of the low total nucleated cell count (TNCC), cytologic evaluation of a transudative fluid is most efficiently accomplished by concentrating cells with a cytospin preparation. Modified transudates develop from chronic transudates or they may result from increased vascular hydrostatic pressure or lymphatic leakage. In their initial stages, inflammatory processes may cause modified transudates to be produced. In addition to mesothelial cells and macrophages, neutrophils, and lymphocytes may be seen. Mast cells, eosinophils, and neoplastic cells are less commonly observed. A turbid sample may indicate a higher cell count, which allows cytologic evaluation to be performed from direct smears. A cytospin preparation may be used if there are not sufficient cells observed on direct smears. Diseases that may result in transudates and modified transudates include hypoalbuminemia, right-sided heart failure, pericardial disease, diaphragmatic hernia, and neoplasia.

217.4.7.2 Exudates

Exudates have a high protein concentration (see Table 217-1) and higher nucleated cell counts than transudates or modified transudates. They range in color from white to amber or red. The high TNCC of exudates allows accurate cytologic evaluation to be obtained from direct smears. The predominant nucleated cell typed depends on the cause of the exudate. Neutrophils are the most common cell type seen in inflammatory processes. Other nucleated cell types found in exudates include mesothelial cells, macrophages, lymphocytes, and neoplastic cells. A predominance of lymphocytes may indicate a chylous effusion. A mixed cell population, with increased numbers of macrophages and neutrophils may be seen with more chronic chylous effusions. Fungal disease or foreign body reaction should be considered if pyogranulomatous inflammation (equally mixed population of neutrophils and macrophages) is noted. 1278 1279

Mesothelial cells are generally present in all effusions. Reactive mesothelial cells can exhibit characteristics of malignancy and should be interpreted with extreme caution in the presence of inflammation.[56] With the exception of lymphoma, it can be difficult or impossible to definitively identify a neoplastic process on the basis of pleural fluid evaluation. Other neoplastic cells that may exfoliate into pleural fluid include carcinoma cells, mast cells, and cells from malignant melanoma. Degenerative neutrophils indicate a septic process and the presence of bacterial toxin; careful evaluation of the smear for free or intracellular bacteria should follow.

Aerobic and anaerobic bacterial culture and sensitivity should be performed on all samples in which degenerative neutrophils are present, even if bacteria are not evident. Non-degenerative neutrophils suggest a non-septic process or low-grade sepsis. Bacterial culture and sensitivity may be indicated if alternate causes are not identified. Diseases that can result in exudative pleural effusions include neoplasia, chronic diaphragmatic hernia, feline infectious peritonitis, lung lobe torsions, lymphatic obstruction or leakage, and infectious processes.

217.4.8 Biochemical Parameters and Additional Fluid Evaluation

Many biochemical parameters of pleural effusions have been studied in attempts to further classify effusions and determine underlying etiologies. Most of these assays have been validated in people but have not been fully characterized in veterinary medicine. Analyses most frequently used in veterinary medicine include triglyceride, cholesterol, pH, lactate dehydrogenase (LDH), and glucose levels. Serum and fluid triglyceride concentration comparisons are used to definitively diagnose chylothorax (see below). Glucose and pH measurements can be helpful in identifying septic effusions; studies of pleural effusions in cats indicate that a glucose less than 10 mg/dL and a pH less than 6.9 are supportive of a septic effusion.[57] In people, a glucose concentration lower than normal is suggestive of tuberculosis, malignancy, rheumatoid disease, or a parapneumonic effusion. In one study of cats with pleural and peritoneal effusions, adenosine deaminase levels in effusions from cats with FIP were higher than those in unaffected cats.[58]

In humans, much work has concentrated on testing that may help differentiate neoplastic from non-neoplastic effusions. The pH of malignant effusions is typically greater than 7.2.[57] As noted above, decreased glucose concentrations can be supportive of neoplastic disease. Telomerase enzyme activity has been evaluated and was found to be equally as sensitive but less specific than cytology in differentiating fluid of malignant versus benign origin.[59] Vascular endothelial growth factor (VEGF) is expressed by some tumors and is believed to be a causative factor in the pathogenesis of both neoplastic and non-neoplastic effusions[60–62] by increasing

capillary permeability.[63] Receptors for VEGF have been found in mesothelial cells.[64] In mice models, blockage of VEGF activity has led to a marked reduction in the volume of pleural effusion produced.[65] In people, high plasma or serum VEGF concentrations have been associated with a high tumor burden, presence of metastases and a poor prognosis.[66–68] However, elevations in VEGF are not specific for neoplasia and can also be found in inflammatory and infectious effusions. Very high VEGF levels have been noted in exudative effusions.[69] One study in dogs did not detect a difference in VEGF levels between neoplastic and non-neoplastic effusions.[70] In people, immunocytochemistry and chromosome analysis may also be useful in the diagnosis, classification, and prognostication of neoplastic effusions.

217.4.9 Eosinophilic Effusions

Pleural effusions are defined as being eosinophilic when greater than 10% of leukocytes identified are eosinophils.[71] Eosinophilic effusions have been reported in dogs in association with heartworm disease, systemic mastocytosis, interstitial pneumonia, and disseminated eosinophilic granulomatosis.[72–75] In a retrospective study of 14 cases, eosinophilic effusions were associated with diseases such as thoracic wall trauma, pneumothorax, neoplasia, congestive heart failure, and hypersensitivity states.[76] In that study, 43% of cases had neoplastic diseases. Eosinophilic pleural effusion was diagnosed 2 days after pneumothorax developed as a consequence of thoracic tube placement in one cat, and pneumothorax was diagnosed in another cat with eosinophilic peritoneal effusion. Eosinophilic pleural effusion has been associated with pneumothorax in people.[71,77] A report of a dog with pleural effusion secondary to discospondylitis cited cytology of the effusion as an exudate with *Paecilomyces* spp. fungal organisms present.[78] The pleural fluid contained a moderate number of eosinophils. It is believed that eosinophils may accumulate in the pleural space in response to pleural irritation.[79] Some authors suggest that leukotrienes or immune complexes may be chemotactic for eosinophils.[80] Corticosteroid responsive eosinophilic effusions have been reported[73,77]; therefore immune-mediated disease should be considered if alternate causes are not identified.

217.5 PYOTHORAX

Pyothorax is the presence of purulent material in the pleural space; bacterial pleuritis results in accumulation of hemopurulent fluid. The pleural fluid is classified as an exudate. Cytology usually reveals a very high nucleated cell count (often 50,000 to 100,000/uL) and is composed primarily of degenerative neutrophils. Nondegenerate neutrophils can be present if the animal was previously treated with antibiotics or in the presence of certain bacterial agents. Effusions caused by fungi and bacterial organisms such as *Actinomyces* and *Nocardia* spp. may contain nondegenerative neutrophils and macrophages if toxins produced affect only cells in close approximation to the organisms.[81] Multiple intra-and extracellular bacteria can be present; however, the possibility of contamination should be examined if only extracellular bacteria are noted. Macrophages are present in various numbers, depending on the causative organism and chronicity of the effusion. Leukophagocytosis is often seen in chronic infections. Reactive mesothelial cells are frequently present and should be interpreted with caution as they can exhibit criteria of malignancy. Multiple organisms are often cultured. In cats, obligate anaerobes or *Pasteurella* spp. are the most common isolates; in dogs obligate anaerobes or gram-positive filamentous organisms (i.e., *Actinomyces* and *Nocardia* spp.) are frequently cultured (Table 217-2).

The cause of pyothorax is often not identified. It can result from penetrating thoracic wounds, migration of foreign material (e.g., grass awns, particularly in working or hunting dogs), hematogenous spread, extension

from other sites such as discospondylitis or pneumonia, pulmonary neoplasia, pulmonary or thoracic wall trauma, or from a postoperative infection. The underlying disease process should be identified and treated if possible.

Table • 217-2 Bacteria Commonly Associated with Pyothorax in Small Animals

BACTERIA	OXYGEN REQUIREMENTS	GRAM STAIN	MORPHOLOGY	ANTIBIOTIC SENSITIVITY*
Actinomyces spp. (most common in dogs)	Facultative anaerobe to strict anaerobe	Gram-positive	Small rods; may form filaments; often beaded and difficult to discern in clinical specimens; may form sulfur granules	**Ampicillin, amoxicillin plus clavulanic acid, penicillin,** clindamycin, chloramphenicol, erythromycin, minocycline
Bacteroides spp.	Obligate anaerobe	Gram-negative	Bacilli; pleomorphic and may be beaded or cocci, often stain poorly and are difficult to see	Most Bacteroides–**ampicillin, amoxicillin plus clavulanic acid**, clindamycin, chloramphenicol, metronidazole *B. fragilis*–**amoxicillin +clavulanic acid, clindamycin,** chloramphenicol, metronidazole
Clostridium spp.	Obligate anaerobe	Gram-positive	Rods; large, frequently encapsulated, motile, spores uncommon from clinical specimens	Most Clostridium–ampicillin, **amoxicillin plus clavulanic acid,** chloramphenicol, **metronidazole** *C. perfringens*–**ampicillin, amoxicillin plus clavulanic acid,** cefoxitin, clindamycin, chloramphenicol, metronidazole, erythromycin
Escherichia coli	Aerobe, facultative anaerobe	Gram-negative	Rods but shape can vary widely; never forms spores	**Amikacin, enrofloxacin,** ceftizoxime, potentiated sulfa drugs
Fusobacterium spp.	Obligate anaerobe	Gram-negative	Bacilli; often have a cigar-shaped appearance	**Penicillin,** clindamycin, chloramphenicol, metronidazole
Klebsiella *spp.*	Facultative anaerobe	Gram-negative	Rods; mucoid and encapsulated	**Cephalosporin,** gentamicin, tobramycin, ticarcillin
Nocardia spp. (most common in dogs)	Aerobe	Gram-positive (partly acid fast)	Long, filamentous and branching cocci or bacilli; most species produce hyphae; exudates typically have appearance of tomato soup; sulfur granules may be uncommon	**Trimethoprim-sulfa, amikacin,** imipenem, ciprofloxacin, cefotaxime, ceftriaxone
Pasteurella spp. (most common in cats)	Facultative anaerobe	Gram-negative	Coccobacilli; pleomorphic, bipolar staining	**Ampicillin, amoxicillin plus clavulanic acid, cephalosporins,** aminoglycosides
Pseudomonas spp.	Aerobe	Gram-negative	Rods; slender, motile	**Ticarcillin plus clavulanic acid, amikacin, enrofloxacin, gentamicin,** tobramycin, cefotaxime

Modified from Fossum, TW: *Small animal surgery,* ed 2, St Louis, 2002, Mosby, p 813.

* Boldface type denotes typical drugs of choice.

These animals should be managed aggressively as treatment with antibiotics alone is not usually effective. A chest tube should be placed once the diagnosis is made. Bilateral thoracostomy tubes are sometimes necessary with chronic effusions as thickening of the pleura may create a complete mediastinum. Most animals can be successfully managed with intermittent tube aspiration. Thoracic lavage with warm saline or lactated Ringer's

solution should be performed two or three times daily. Twenty mL/kg should be infused slowly into the thoracic cavity and allowed to remain for 1 hour. Animals should be closely monitored for dyspnea and the lavage fluid removed earlier if necessary.

The addition of antibiotics to the lavage fluid offers no advantage over appropriately administered systemic antibiotics. Antibiotics should be chosen based on Gram stain and microbial culture and sensitivity results. Due to the high proportion of anaerobic infections, drugs with a spectrum against obligate anaerobic organisms should be used. Antibiotics should be continued for a minimum of 4 to 6 weeks. Surgery is mandatory in animals with underlying diseases such as foreign bodies, lung abscesses, or lung lobe torsions; and should be considered in animals that do not respond to medical treatment in the first 3 to 4 days. Readers are referred to a surgical text for additional information.

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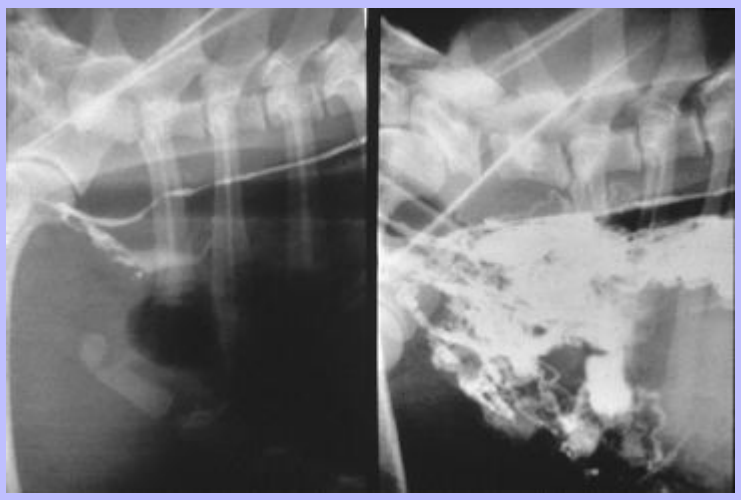
217.6 CHYLOTHORAX

Chyle is the milky fluid absorbed by the lacteals from food in the intestines. It is composed of lymph and triglyceride droplets (chylomicrons). *Chylothorax* refers to the accumulation of chyle in the pleural space. Chylothorax was once believed to be a result of trauma to the thoracic duct. Although this occasionally occurs in veterinary patients, the resulting effusion is usually self-limiting and resolves within 2 weeks. Trauma is, however, still considered a reasonable cause of chylothorax in human patients. Chylothorax may develop from increased lymphatic flow (due to increased hepatic lymph production), from decreased lymphatic drainage into the venous system, or from both. Disease processes that result in increased systemic venous pressures, such as right-sided heart failure, have been shown to cause chylothorax.[82] FeLV and FIV status should be evaluated in affected cats. Chyle is thought to exude from intact but dilated thoracic lymphatics (thoracic lymphangectasia) (Figure 217-6). Chylothorax may also occur in conjunction with diffuse lymphatic disease such as intestinal or generalized lymphangectasia. Chylothorax secondary to pulmonary lymphangiosarcoma has recently been reported in a dog.[83]

The thoracic duct (TD) arises from the cisterna chyli and is the major lymphatic vessel for the return of lymph to the venous system. Thoracic duct anatomy varies between and among species. It usually begins as a single duct, but multiple branches are often present. The convergence with the venous system occurs at the “venous angle” in the cranial vena cava where the external and internal jugular veins meet. In the dog the TD lies to the right of midline in the caudal thorax and crosses to the left side at approximately the fifth intercostal space, whereas in the cat it lies to the left side throughout its course through the diaphragm.

Figure 217-6 Mesenteric lymphangiogram from a normal dog (*left*) and a dog with idiopathic chylothorax (*right*). Notice the entrance of the thoracic duct into the venous system in the normal dog and the marked lymphangiectasia in the dog with chylothorax. Chylothorax is thought to occur as a result of leakage from these dilated, tortuous cranial mediastinal lymphatics.



Animals presenting with chylous pleural effusion should be thoroughly evaluated for underlying diseases that may interfere with lymphatic flow or increase the pressure against which the thoracic duct must empty. These include heart disease (cardiomyopathy, heartworm disease, pericardial effusion, tetralogy of Fallot, tricuspid dysplasia, or cor triatriatum dexter), cranial mediastinal masses (lymphoma, thymoma), fungal granulomas, venous thrombi, or congenital abnormalities of the TD. In those cases with a defined etiology, treatment is aimed at the underlying cause. Intermittent thoracocentesis palliates the clinical signs until a definitive treatment is instituted (if possible). In the majority of animals, however, a cause is not identified (idiopathic chylothorax).

Although any breed of dog or cat may be affected, breed dispositions are suspected in Afghan hounds, Shiba Inus, and Oriental cat breeds (Siamese, Himalayan). A sex predilection has not been identified and the disease has been reported in all ages. Afghans tend to develop the disease in middle age, whereas affected Shiba Inus tend to be less than 1 year of age. In one study that showed older cats more likely to be affected than younger ones, an association with neoplasia was suspected.[84]

Coughing is usually the first and may be the only clinical sign noted in both dogs and cats. Animals with a history of a chronic cough that is unresponsive to general treatment should be evaluated for the presence of thoracic fluid. As noted earlier, coughing may be caused by irritation from the effusion or from the underlying disease process. Many animals present with acute respiratory distress as an emergent situation to the veterinarian, without overt history of previous clinical signs of respiratory disease.

Physical exam findings attributable to the presence of pleural fluid include decreased or muffled heart sounds, decreased ventral lung sounds, and increased bronchovesicular sounds dorsally. Mucous membrane color varies

from normal to cyanotic, depending on the severity of respiratory compromise. Weight loss is often noted with animals with chronic disease due to the loss of fat and protein into the thoracic cavity. Other physical exam findings such as heart murmurs may be present depending on the underlying disease process.

Thoracocentesis revealing milky, opaque fluid permits a tentative diagnosis of chylothorax and should prompt the veterinarian to search for underlying causes. The fluid consistency and color will vary depending on dietary fat content and the presence of concurrent hemorrhage. Fluid samples should be placed in an EDTA tube for cytologic evaluation. Although lymph fluid is resistant to infection due to the presence of fatty acids, samples should be submitted for bacteriologic culture and sensitivity, particularly if repeated thoracocentesis has been performed. Chylous fluid may be classified as an exudate or as a modified transudate, depending on the protein levels and nucleated cell counts which can vary with chronicity and previous treatment. Lymphocytes are typical, but nondegenerate neutrophils are commonly noted with more chronic cases. Protein content is variable and may be inaccurate due to the high lipid content of the fluid. Truly chylous fluids should contain chylomicrons, should clear with the addition of ether, and be positive for the presence of lipid droplets with Sudan III stain. A definitive diagnosis of chylothorax is obtained by comparing fluid and serum triglyceride levels; in chylothorax, fluid triglyceride should be higher than that of simultaneously collected serum.

Differential diagnoses include any other causes of cough or pleural effusion. Once the diagnosis of pleural effusion is made, diseases that cause exudative effusions, such as pyothorax, are considered differentials and should be investigated. Pseudochylous effusion refers to thoracic fluid in which the fluid triglyceride level is less than that of serum and fluid cholesterol level greater. Pseudochylous effusions are rare in veterinary patients and may be associated with tuberculosis.

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As noted earlier, treatment should be directed at the underlying disease process, if identified, and clinical signs palliated by intermittent thoracocentesis. Resolution of the effusion will depend on the underlying cause and may take several months. Surgical treatment should only be considered in animals with idiopathic chylothorax or those that do not respond to medical management.

Medical management of animals with chylothorax involves feeding a low-fat diet, performing needle thoracentesis as needed to relieve dyspnea (not on a regular basis), and supplementing the dog or cat with a benzopyrone such as Rutin (50 to 100 mg/kg, TID, PO). The effusion may spontaneously resolve over a period of weeks or months. If the animal cannot be managed medically, surgical intervention is typically recommended. Thoracic duct ligation is the most widely accepted method for treating animals with chylothorax, yet this intervention has not been reported to be highly successful in alleviating the chylous accumulation. Thoracic duct ligation resulted in complete resolution of pleural effusion in only approximately 50% of dogs operated; in cats, the success rate was even less (<40%).[84–86] A more recent study reported 100% efficacy in dogs and 80% in cats when TD ligation and/or pericardictomy were performed.[88]

Advantages of thoracic duct ligation are that if it is successful it results in complete resolution of pleural fluid (as compared to palliative procedures such as pleuroperitoneal shunting) and thus it may prevent fibrosing pleuritis from developing. Disadvantages include that operative time is long, which is problematic in debilitated animals, there is a high incidence of continued or recurrent chylous or nonchylous (from pulmonary lymphatics) effusion, and mesenteric lymphangiography is often difficult to perform, particularly in cats. Without mesenteric lymphangiography, complete ligation of the thoracic duct is difficult to ensure. Ligation of the thoracic duct using thoracoscopy has been described.[87]

Thoracic duct ligation plus pericardectomy was recently reported as a treatment for chylothorax.[88] In this study, TD ligation plus pericardectomy was performed in 18 animals, and pericardectomy alone was performed in an

additional two animals. Nineteen animals presented for evaluation of chylothorax (9 dogs, 10 cats), whereas one dog presented for serosanguineous pleural fluid after TD ligation that had been performed elsewhere. Echocardiography was normal in all animals with the exception of a subjectively thickened pericardium in six dogs and seven cats. Clinical signs of pleural fluid resolved in ten of ten dogs and eight of 10 cats after surgery. The overall success rate for surgical treatment of chylothorax in this study was 90%.

217.7 NEOPLASTIC PLEURAL EFFUSION

Differentiation of neoplastic and non-neoplastic effusions can be difficult. Neoplastic processes commonly resulting in pleural effusion include mesothelioma, lymphoma, multiple myeloma, carcinoma of the lung, and metastatic mammary neoplasia. Effusions caused by neoplastic processes are often hemorrhagic.

Mesotheliomas can arise from the mesothelial cells of the pleura, pericardium, or peritoneum and can be malignant or benign. Congenital mesotheliomas have been described in calves.[89] In people, mesotheliomas are frequently associated with exposure to asbestos.[90] Histologically, mesotheliomas can be fibrous or epithelial; in humans both are seen but pleural mesotheliomas in dogs are predominantly the epithelial type. Metastasis to other intrathoracic organs such as the myocardium, tracheobronchial lymph nodes, and lung is common. This tumor may also invade the diaphragm and enter the abdomen. A diagnosis is not usually made on fluid evaluation because of the difficulty in differentiating neoplastic versus reactive mesothelial cells (see above); a surgical or thoracoscopic biopsy is generally necessary to obtain a definitive diagnosis. Readers are referred to an oncologic textbook for additional information on diagnosis and treatment of mesotheliomas.

In human medicine, pleurodesis is often used to decrease the incidence of malignant effusions. Attempts at pleurodesis in dogs have been unrewarding[91] and are not recommended by the authors. More recent research has focused on the possible etiologies of the effusions. Vascular endothelial growth factor (VEGF) is thought to play a role in the development of malignant effusions. Studies in mice have demonstrated a reduction in the formation of pleural effusion with treatment directed at VEGF receptor inhibition.[65]

217.8 PNEUMOTHORAX

217.8.1 Traumatic Pneumothorax

Pneumothorax in small animals is most frequently closed (no communication between the pleural space and external environment) and traumatic in origin secondary to motor vehicle accidents or other blunt trauma. Pulmonary or bronchial rupture can occur when a blow to the thorax results in a sudden increase in intrathoracic pressure, theoretically against a closed glottis. Alternatively, shearing forces on the lung may result in subpleural bleb formation, similar to that seen in spontaneous pneumothorax. Pneumothorax secondary to a bronchial tear has been reported following venipuncture in a kitten.[92]

Penetrating injuries such as bite wounds and gunshot wounds can result in an open pneumothorax, where communication exists between the pleural space and external environment. Penetrating wounds may permit influx of air into the pleural space with inspiration and rapid equilibration of intrathoracic and atmospheric pressures. The normal pressure gradient is necessary for mechanical function of the lungs and proper air exchange. Loss of negative intrathoracic pressure also decreases venous return to the heart. Abdominal wounds may result in a pneumothorax if a diaphragmatic hernia is present. A tension pneumothorax develops when the fistula between the pleura and the external environment or the pleura and the lung acts as a one-way valve, which allows air to enter on inspiration but not exit on expiration. Positive pressure develops in the

pleural space causing collapse of the lungs and great veins. Fatal decreases in ventilation and cardiac output rapidly ensue. Iatrogenic tension pneumothorax has been reported secondary to lung or airway rupture in animals that receive positive pressure ventilation.[93] As with diaphragmatic hernias, young male dogs are more likely to incur vehicular or other causes of trauma and are therefore more likely to develop traumatic pneumothorax. Traumatic pneumothorax is less commonly reported in cats.

217.8.2 Spontaneous Pneumothorax

Pneumothorax is classified as spontaneous when no traumatic or iatrogenic cause is identified. Spontaneous pneumothorax is thought to result from rupture of pulmonary blebs or bullae and is considered primary when there is no evidence of underlying pulmonary disease. Subpleural blebs are most commonly located in the apices of the lungs. Primary spontaneous pneumothorax occurs most frequently in large, deep-chested dogs such as hounds. One recent retrospective study reported an over-representation of Siberian Huskies in their case population.[94] Middle-aged dogs are most commonly affected; there does not appear to be a sex predilection.

Secondary spontaneous pneumothorax is more common in dogs than the primary form and occurs when there is underlying pulmonary disease such as pulmonary abscesses, diffuse emphysema, neoplasia, dirofiliarisis, pneumonia or pulmonary parasites such as *Paragonimus* spp. Spontaneous pneumothorax has also been reported in cats with *Dirofilaria immitis* infection.[15] It may also be seen secondary to chronic granulomatous infections or chronic airway obstruction and subsequent overpressurization of abnormal lungs.[95,96] The majority of affected people are cigarette smokers, which suggests that the underlying pulmonary disease could be a result of interference of the normal function of $alpha_1$-antitrypsin in inhibiting elastase. It is believed that $alpha_1$-antitrypsin is inactivated in people who smoke, which allows increased elastase-induced destruction of pulmonary parenchyma.

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217.8.2.1 History and Physical Examination

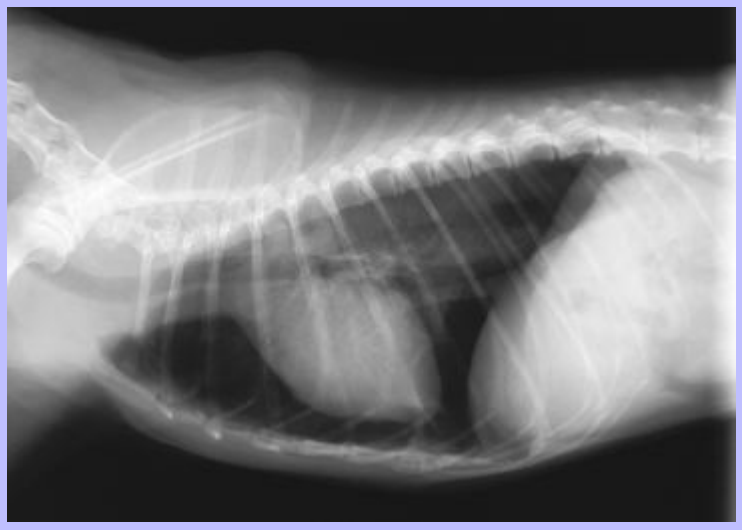
Animals with pneumothorax generally present with acute dyspnea and shallow, rapid respiration. A history of trauma is often vague, which makes it sometimes difficult initially to distinguish between traumatic and spontaneous pneumothorax. In animals with secondary spontaneous pneumothorax, a history attributable to underlying respiratory disease (e.g., chronic cough, fever) may be ascertained. Dogs with pneumothorax are initially able to compensate by increasing their chest wall expansion with inspiration. Animals with hypoxemia will appear cyanotic. Hypoxemia is thought to be a result of impairment of gas exchange, increased pulmonary shunting, and V/Q (ventilation-perfusion) mismatch[97] (increased alveolar-arterial PO_2 difference). In traumatic pneumothorax, concurrent injuries such as rib fractures and pulmonary contusions may exacerbate the clinical signs of respiratory compromise. Auscultation of the thoracic cavity may reveal decreased or muffled heart and lung sounds dorsally. Tension pneumothorax is a rapidly fatal condition. A barrel-shaped chest may be evident as pressure within the thoracic cavity increases. Cyanosis and signs attributable to markedly decreased cardiac output are evident.

217.8.2.2 Diagnosis

Thoracocentesis should be performed to stabilize the dyspneic animal prior to thoracic radiographs being taken. Pneumothorax is most commonly bilateral. Radiographic signs consistent with a pneumothorax include elevation of the heart off the sternum, collapse of the lung lobes and retraction from the chest wall,

and a radiolucent area of free air in which no pulmonary vascular structures are visible, most evident in the caudal thorax (Figure 217-7). In severe cases, the diaphragm may appear flattened or caudally displaced. Apparent elevation of the heart from the sternum is a result of atelectasis of the dependent lung lobes allowing the heart to shift its position with the chest. To identify small volumes of free air, the most sensitive radiographic view is a horizontal beam taken with the animal in lateral recumbency. Although it may be difficult to identify in the presence of collapsed lung lobes, radiographs should be carefully evaluated for underlying pulmonary parenchymal or other thoracic diseases such as trauma or neoplasia. Pulmonary blebs are difficult to identify radiographically. Bullae may be an incidental finding in some cases. Removal of air with thoracocentesis is diagnostic of pneumothorax if radiographs are unclear or unavailable. Pneumomediastinum is characterized by the ability to distinguish thoracic structures (i.e., aorta and great vessels, trachea, vena cava, esophagus) within the mediastinum that are not usually apparent on thoracic radiographs.

Figure 217-7 Lateral radiograph of a dog with pneumothorax. Note the apparent elevation of the heart from the sternum.



217.8.2.3 Treatment

A thoracostomy tube may be required in animals in which air rapidly accumulates. Intermittent or continuous aspiration can be used depending on the volume of air recovered from the thoracic cavity and rate at which it accumulates. Once the animal has been stabilized, the cause of the pneumothorax should be identified. Traumatic pneumothorax is most commonly managed conservatively; surgical intervention is rarely necessary. Thoracocentesis or chest tubes (see Chapter 103) can be used to manage air accumulation and dyspnea while the pulmonary lesions heal, usually within 3 to 5 days. Supplemental oxygen therapy may be beneficial in animals with pulmonary contusions or hemorrhage. Pain management is essential in animals that have experienced trauma; analgesics may help improve ventilation by decreasing the pain associated with thoracic wall movement. Recurrence of traumatic pneumothorax is uncommon. Open chest wounds should be covered immediately. Once the animal has been hospitalized, the wound can be addressed and covered with a sterile, occlusive dressing. Readers are referred to a surgical text for more detailed information on thoracic wound management.

Animals with spontaneous pneumothorax generally require thoracostomy tube placement. As opposed to animals with traumatic pneumothorax, those with spontaneous disease often require surgical intervention. A median sternotomy allows access to both sides of the lungs and permits thorough exploration of the thoracic cavity. If not immediately evident, pulmonary and airway leaks may be identified by filling the pleural space with warm physiologic saline and looking for air bubbles. Animals that undergo surgical treatment of spontaneous pneumothorax are less likely to have recurrence and have lower mortality than those that are managed conservatively.[94] Surgical exploration may permit identification of the underlying etiology that may have not been readily apparent previously. Thoracoscopic evaluation of the thorax has been reported for people and dogs with spontaneous pneumothorax and may obviate the need for surgery if a cause can be identified and treated.[98–100]

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218 CHAPTER • 218 Pulmonary Hypertension and Pulmonary Thromboembolism

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218.1 Pulmonary Hypertension

Pulmonary hypertension (PH) is defined by a systolic pulmonary artery pressure greater than 25 mm Hg. The incidence of PH is difficult to define due to lack of clinical awareness, nonspecific clinical signs, and difficulty in confirming the diagnosis. Unfortunately, many patients with PH are diagnosed late in the course of disease when irreversible vascular pathology has developed. PH results from many diseases and pathophysiologic mechanisms and most commonly occurs secondary to chronic cardiopulmonary disease.

218.1.1 Relevant Pulmonary Physiology

Normal pulmonary vasculature is a low-resistance, low-pressure, high-capacitance circuit. Normal, awake dogs at sea-level have a systolic pulmonary artery (PA) pressure between 15 to 25 mm Hg, end-diastolic PA pressure of 5 to 10 mm Hg, and a mean PA pressure of 10 to 15 mm Hg.[1] When cardiac output increases, such as during exercise, there is recruitment of additional pulmonary arterioles to maintain normal PA pressure. Regional pulmonary perfusion is regulated by pulmonary arteriolar vasoconstriction. Hypoxic vasoconstriction matches pulmonary perfusion to alveolar ventilation and limits the impact of low ventilation on arterial oxygenation. However, with global alveolar hypoxia, the protective effects of hypoxic vasoconstriction are offset by widespread vasoconstriction and development of PH.

The vascular endothelium mediates vascular tone and remodeling through release of several neurohormonal factors, and endothelial injury plays a key role in development of PH. In the normal lung, there is a balance between locally acting vasodilators including prostacyclin (PGI_2) and nitric oxide (NO) versus potent vasoconstricting substances including thromboxane, endothelin-I (ET-1), and angiotensin II (AT-II). Endothelial dysfunction in PH contributes to smooth muscle cell proliferation, increased production of vasoconstrictor mediators including ET-1 and AT-II, and decreased synthesis of vasodilating substances including PGI_2 and NO.[2] Pulmonary artery thrombi are seen histologically in both primary PH (PPH) and secondary PH in people. Pro-coagulant affects may be mediated by increased TXA_2 and tissue factor, as well as reduced anti-coagulant mediators including NO, PGI_2, and thrombomodulin.[3]

218.1.2 Classification of Pulmonary Hypertension

Classification of PH through hemodynamic and pathophysiologic mechanisms helps to guide interventional treatment. Mean pulmonary artery pressure (MPAP) is related to pulmonary blood flow (PBF) and pulmonary vascular resistance (PVR) by the equation

$$\text{MPAP} = (\text{PVR} \times \text{PBF}) + \text{Pulmonary capillary wedge pressure (PCWP)}$$

Abnormalities of any component of this equation can cause PH.

Pre-capillary PH occurs due to abnormalities of the pulmonary arterial vascular bed and is characterized by increased systolic, mean, and diastolic PAP, increased PVR, and normal PCWP. PVR is closely related to total cross-sectional area of the small muscular arteries and arterioles. Given the high capacitance of the pulmonary vasculature, 50% of the pulmonary vasculature must be destroyed before PH develops.[4] Diseases that cause pre-capillary PH include primary pulmonary hypertension (PPH), Eisenmenger's complex, chronic pulmonary disorders, pulmonary thromboembolism (PTE), and peripheral pulmonary artery branch stenosis. PPH has not yet been identified in veterinary medicine. Eisenmenger's syndrome is an irreversible, obliterative vascular disease that results from severe left to right shunting congenital heart disease that reverses to shunt right to left. Chronic respiratory disorders may result in PH in some individuals through hypoxic pulmonary vasoconstriction, extramural compression of the pulmonary arterioles, and destruction of pulmonary microvasculature. In the absence of pulmonary arterial pathologic changes (plexiform lesions, necrotizing arteritis, hyalinizing fibrosis), PH due to hypoxic vasoconstriction may be dynamic and respond to therapeutic intervention.

In post-capillary PH, PAP passively increases due to elevated PCWP. PA diastolic pressure is within 5 mm Hg of the PCWP, and PVR is normal. Left-sided congestive heart failure (CHF) is the most common cause of increased PCWP and may result from severe mitral valve disease, dilated cardiomyopathy, or diastolic heart disease. A mixed hemodynamic response may be seen with chronic elevations in PCWP and consists of a disproportionate elevation in PA pressures in comparison to elevated PCWP. The mechanism for increased PVR in response to elevated PCWP is not entirely clear but likely involves endothelin-1 release, endothelial dysfunction, and abnormal pulmonary vasodilatory reserve.[4] Approximately 30% of human patients with chronic pulmonary venous hypertension develop increased PVR.[4] Based on clinical experience, a low percentage of dogs with severe mitral regurgitation have a mixed hemodynamic response of PH.

Pulmonary blood flow (PBF) can be increased selectively by left to right shunting congenital heart diseases (ASD, VSD, PDA) and some patients are at risk for development of Eisenmenger's physiology. PBF is also increased by high output cardiac disease (arteriovenous fistula, chronic anemia, and hyperthyroidism); however, most patients do not develop recognizable PH. Pneumonectomy leads to selective increases in pulmonary blood flow, but PH is not recognized as a complication in dogs.

Cor pulmonale is defined as heart disease due to PH resulting from chronic pulmonary disease. The most common cause of cor pulmonale in veterinary medicine is heartworm disease in dogs. PH leads to acquired pressure overload of the right ventricle characterized by chamber dilation primarily and also concentric hypertrophy. RV myocardial failure may occur due to inadequate reduction of wall stress and may be worsened by myocardial ischemia from reduced right coronary artery perfusion pressure.[2] The extent of concentric hypertrophy and dilation of the RV ventricle depends on the age of the animal, the severity and duration of pressure overload, and the time course of progression.

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218.1.3 Clinical Features

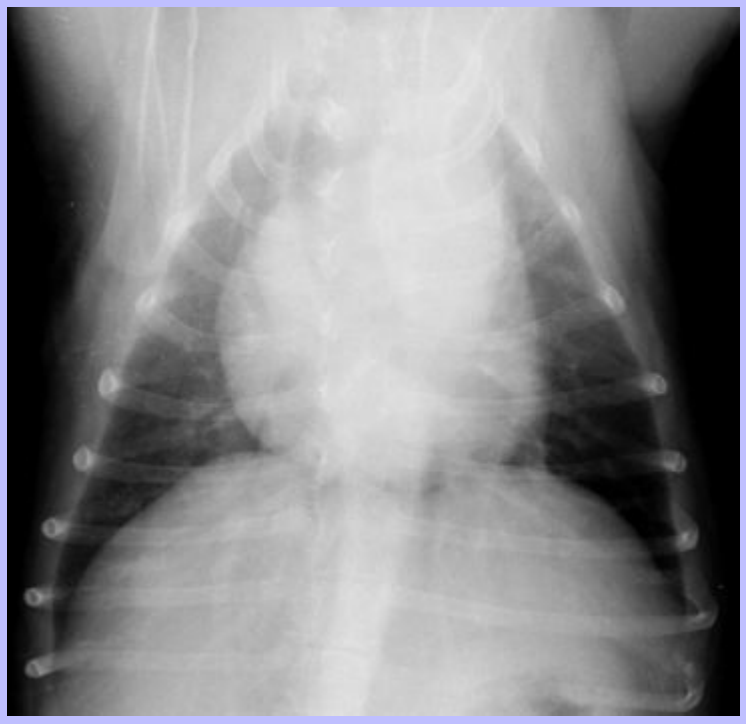
Clinical manifestations of PH are difficult to distinguish from those of underlying cardiopulmonary disease. Ascites may be the most obvious abnormality and is often accompanied by other signs of right heart failure including jugular vein distension or pulsation, subcutaneous edema, and cachexia. The most common clinical signs are nonspecific respiratory abnormalities such as coughing, tachypnea, and respiratory distress. Syncope is relatively common in dogs with PH. Adventitious lung sounds may be ausculted with primary respiratory disease or CHF. Cyanosis can be seen in patients with right-to-left cardiac shunts or severe respiratory disease.

Cardiac auscultation may reveal a split or loud pulmonic component to the second heart sound. Right and left apical systolic murmurs are commonly heard due to tricuspid and mitral regurgitation, respectively.

A minimum database (CBC, chemistry, urinalysis) and heartworm test should be performed to identify underlying diseases that may be associated with PH. Hypoxemia and acidosis should be identified since hypoxemia can cause PH and both may worsen PH.

Thoracic radiographs are necessary to detect respiratory or cardiac diseases that may be associated with PH. Thoracic radiography is almost always abnormal, and cardiomegaly is most commonly seen. Identification of RV enlargement and dilated central pulmonary arteries with rapid tapering towards the periphery should greatly increase clinical suspicion of severe PH (Figure 218-1). Eisenmenger's complex is characterized by pulmonary undercirculation and right heart enlargement. Substantial left atrial enlargement and perihilar to caudo-dorsal pulmonary infiltrates indicate left sided CHF and possible post-capillary PH.

Figure 218-1 Dorsoventral thoracic radiograph of a dog with PH. There is severe right heart enlargement and dilated central portions of the pulmonary arteries.



Electrocardiographic assessment of right heart enlargement is insensitive, and abnormalities are present only with severe PH. Deep S waves and right axis deviation may be seen with severe RV hypertrophy, and tall peaked P waves may indicate right atrial enlargement. Sinus tachycardia is a common rhythm abnormality.

Echocardiography is a useful, noninvasive tool to detect PH and cor pulmonale in veterinary and human medicine.[5,6] Echocardiographic characteristics include RV concentric hypertrophy and dilation, dilation of the

main pulmonary artery and main branches, systolic flattening of the interventricular septum, and paradoxical septal motion (Figure 218-2). In severe PH, the left ventricular dimensions may be reduced due to ventricular underfilling and ventricular interdependence. Pulmonic stenosis (PS) must be ruled out by a normal PA systolic blood flow velocity of less than 1.5 m/s before PH can be documented. In the absence of PS, the RV systolic pressure equals the PA systolic pressure. Using the modified Bernoulli equation (Pressure gradient = 4 × velocity^2), spectral Doppler allows reasonably accurate estimations of RV systolic pressure via measurement of triscuspid regurgitation velocity, and PA diastolic pressure via measurement of pulmonic insufficiency velocity (Figure 218-2). The RV: RA pressure gradient is added to the estimated RA pressure (5 mm Hg is normal, 10 to 15 mm Hg in right heart failure) for the estimated RV systolic pressure, which approximates PA systolic pressure.

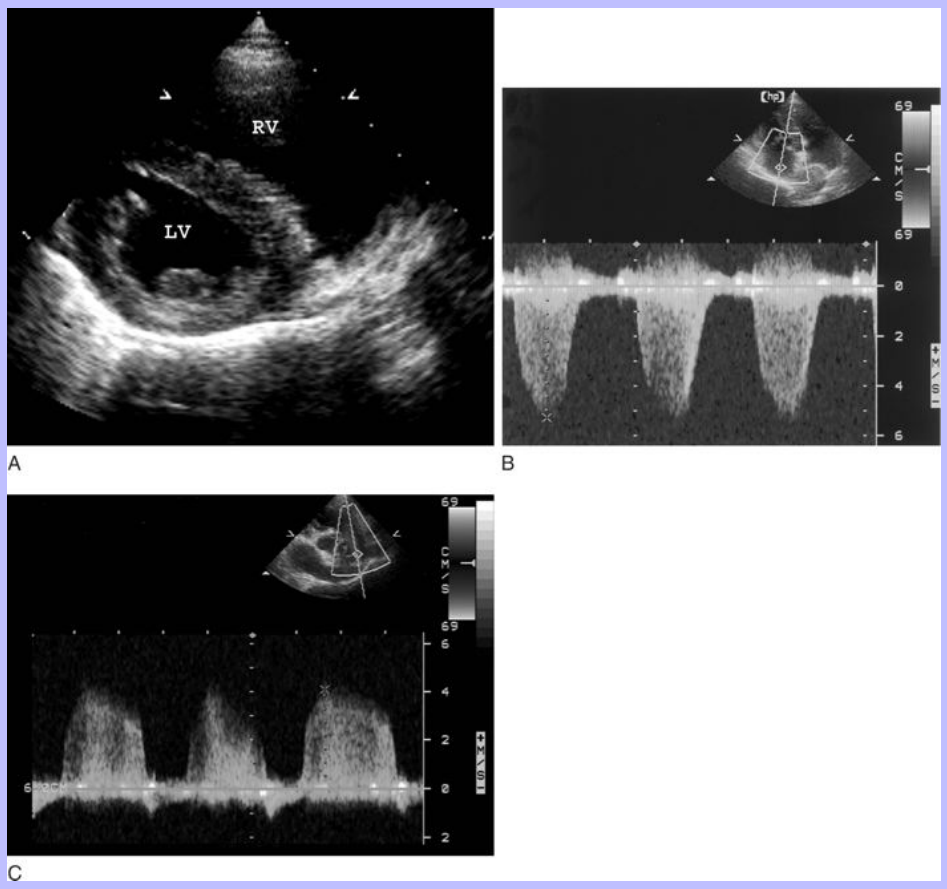
Right heart catheterization is the gold standard for diagnosis of PH and determination of the hemodynamic classification. Unfortunately, catherization requires sedation anesthesia, and these patients are already at increased risk for anesthetic complications. Cardiac output and pressures can be measured, which allows calculation of PVR. Cardiac catheterization allows for pharmacologic tests of vasodilators to identify reversible lesions and evaluate potential pharmacologic treatments.

218.1.4 Treatment

Treatment of PH is aimed at correcting the specific hemodynamic abnormality. Left CHF is treated with diuretics, angiotensin-converting enzyme (ACE) inhibitors, and possibly careful use of afterload reducing agents (amlodipine or hydralazine). Resolution of symptomatic CHF often reduces post-capillary PH and clinical signs of syncope. Surgical or interventional techniques may be used to correct left to right shunting congenital heart diseases but should never be attempted in patients with right to left shunts since it will hasten death. Cautious use of diuretics and ACE-inhibitors are indicated for right heart failure, since patients may develop symptomatic hypotension if they become significantly volume underloaded in the face of fixed PVR. ACE-inhibitors have been shown to delay pulmonary vascular remodeling in experimental animals and have produced beneficial hemodynamic effects in people with cor pulmonale.[7] Digoxin improved cardiac output and reduced circulating norepinephrine concentration in people with primary PH and symptomatic right heart failure[2] and could be considered for treatment of severe PH and right heart failure in veterinary patients.

Treatment of precapillary PH is aimed at reducing PVR and RV pressure overload. Pulmonary vasodilator trials may be performed during cardiac catheterizations to identify responsive patients; however, most veterinary patients likely have fixed PVR at the time of diagnosis. Short-acting vasodilators (adenosine, inhaled nitric oxide, or PGI_2) may be used to identify patients that have reversible vasoconstriction, as evidenced by more than 10 mm Hg decrease in MPAP with no change or an increase in cardiac output, and/or a decrease in PVR by 25%.[4] Only about 20% of humans have a positive pressor response, and these individuals benefit from treatment with high doses of the calcium-channel blocker (diltiazem).[4] No studies have evaluated short-acting pulmonary vasodilator trials and subsequent therapy with calcium channel blockers in veterinary patients with PH.

Figure 218-2 **A,** Two-dimensional echocardiogram of a dog with PH. The right basilar short axis view shows severe right ventricular dilation and concentric hypertrophy that is characteristic of severe acquired pressure overload. The interventricular septum is flattened, which indicates that the right ventricular pressure is greater than the left ventricular pressure. **B,** Continuous wave Doppler measurement of tricuspid regurgitation (TR) velocity in a dog with PH. The TR velocity is 5.2 m/s. Using the modified Bernoulli equation, there is a 110 mm Hg pressure gradient between the RV and RA during systole. Adding 5 mm Hg estimated RA pressure, the estimated RV and PA systolic pressure is 115 mm Hg. **C,** Continuous wave Doppler measurement of pulmonic insufficiency (PI) in a dog with PH. The PI velocity is 4 m/s, and the diastolic pressure gradient between the PA and RV is 64 mm Hg, which closely estimates the PA diastolic pressure.



Intravenous PGI_2 has been shown to improve exercise capacity, hemodynamics, vascular remodeling, and short-and long-term survival in humans.[7] However, lifelong intravenous PGI_2 therapy is not an acceptable treatment modality in veterinary medicine. New oral (beraprost) and subcutaneous (treprostinil) synthetic prostacyclin analogs are under intense investigation in human medicine[7] and may be useful in veterinary medicine. Other promising pulmonary vasodilators being researched for primary and secondary PH include endothelin receptor antagonists (bosentan) and phosphodiesterase inhibitors (sildenafil).[7]

Prognosis for PH is variable and depends on the type and severity of underlying etiology, degree of PH, and reversibility of vascular pathology. In humans with primary PH, mean PA pressure, RA pressure, and PVR are inversely proportional to survival.[2] Earlier identification and treatment of patients with PH may slow the progression, but prognosis remains poor to grave.

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218.2 PULMONARY THROMBOEMBOLISM

218.2.1 Etiology and Pathophysiology

Pulmonary thromboembolism (PTE) is a life-threatening condition that occurs in more than 600,000 human patients a year.[8] Despite increased awareness and sophisticated imaging modalities in human medicine, only 30% of fatal PTE is diagnosed antemortem.[8] Similarly, PTE was suspected antemortem in only 38% of dogs and 14% of cats with postmortem evidence of major PTE.[9,10] PTE comprised 0.9% of all postmortem diagnoses in dogs, which likely underestimates the true incidence in the population.[9]

Pulmonary vascular obstruction can result from thrombus formation, or embolization of thrombi, parasites, fat, or neoplastic cells. Heartworm disease is the most common cause of PTE in dogs. It results in mechanical obstruction of pulmonary blood flow as well as enhanced reactive pulmonary vasoconstriction and reduced endothelium-dependent vasorelaxation.[11] Venous stasis, endothelial injury, and hypercoagulability contribute to thrombus formation within pulmonary arteries/arterioles (in-situ thrombosis) and to thromboembolic disease of the pulmonary capillary bed. PTE is a secondary condition, and immune-mediated hemolytic anemia (IMHA), neoplasia, cardiac disease, protein-losing nephropathy or enteropathy, hyperadrenocorticism, disseminated intravascular coagulation, sepsis, trauma, and recent surgery are associated with PTE in dogs and cats.[9,10,12] A large number of dogs and cats with PTE (47% to 64%, respectively) have multiple underlying disease processes.[9,12] Identification of risk factors and underlying diseases associated with PTE should be used to initiate early prophylactic treatment for PTE and aggressive treatment for the primary disease.

In PTE, PVR is increased due to mechanical obstruction of blood flow and reflex vasoconstriction from release of vasoactive mediators (serotonin, thromboxane) from the thrombus. Low-output cardiac failure and shock may occur with acute, major PTE. Functional status of the cardiopulmonary system plays a role in determination of the hemodynamic consequences of PTE.

Pathophysiologic consequences of PTE include abnormal gas exchange, altered ventilatory control, dysregulated pulmonary mechanics, and potentially pulmonary infarction.[2] Hypoxia results from ventilation/perfusion (V/Q) mismatch, increased alveolar dead space, and intrapulmonary or intracardiac right-to-left shunting. Hypoxia can be worsened by pulmonary edema caused by enhanced blood flow to non-thrombosed regions of the lung. Reduced surfactant function in the region of thrombosis leads to

atelectasis and reduced lung compliance. Release of humoral factors causes bronchoconstriction, increased airway resistance, and tachypnea. All of these factors contribute to hypoxia, increased work of respiration, and respiratory distress.

218.2.2 Clinical Signs and Diagnostic Tests

PTE is seen most often in middle-aged to older animals, with no sex or breed predisposition. PTE, like PH, can mimic and often accompany other cardiopulmonary diseases. Sudden onset respiratory distress and tachypnea are common historical or physical examination abnormalities seen in 58% to 96% of dogs and 55% of cats with PTE.[11,12] The list of differential diagnoses is extensive and includes airway obstruction, pneumonia, acute CHF, ARDS or other noncardiogenic pulmonary edema, pleural space disease, or asthma in cats.

When PTE is suspected, identification of an underlying disease and definition of the degree of cardiopulmonary dysfunction are essential. Definitive documentation of PTE remains difficult in both human and veterinary medicine. CBC, chemistry, and urinalysis should be performed, and a coagulation panel can be used to support the presence of concurrent DIC. Plasma D-dimer is used in the diagnosis of PTE in humans, with 96% sensitivity and 52% specificity.[2] Plasma D-dimer is a breakdown product of cross-linked fibrin, which is produced when fibrin is degraded by plasmin. D-dimer is produced in a number of disease conditions in both human and veterinary medicine. The utility of D-dimer in the diagnosis of PTE in veterinary medicine in unknown, but a negative test might be useful in ruling out PTE. Plasma anti-thrombin III activity should be measured if protein losing nephropathy or enteropathy is diagnosed.

Thoracic radiographic abnormalities are common but are rarely specific for PTE. In fact, 10% to 30% of dogs and 14% of cats had normal thoracic radiographs despite necropsy proven PTE[9,10], which indicates that PTE should be a top differential diagnosis in an animal with marked respiratory distress and normal thoracic radiographs. Pulmonary infiltrates may be interstitial, alveolar, or lobar in dogs and cats. Alveolar infiltrates may represent hemorrhage, edema, or infarction. Pulmonary vascular abnormalities including enlarged central pulmonary arteries, disproportionate vascular tapering, and oligemia were common in retrospective review of thoracic radiographs in cats with PTE.[10] Cardiomegaly and mild to moderate pleural effusion were common in dogs and cats.

Arterial blood gas analysis is often abnormal in dogs with PTE, and common abnormalities include hypoxemia, hypocapnea, and increased alveolar-to-arterial gradient.[9] However, normal arterial oxygenation does not exclude the diagnosis of PTE.[2] Response to supplemental oxygen administration can be variable due to the presence of additional cardiac or pulmonary pathology and pathophysiologic sequelae of embolization.

Echocardiographic abnormalities were present in 94% of people with angiographically confirmed PTE, compared with only 13% of patients with similar clinical signs.[6] Unfortunately in veterinary medicine, echocardiography is rarely utilized in the work-up of animals suspected of PTE, and in one study less than 20% of dogs with PTE were evaluated.[9] Thrombus visualization with trans-thoracic echocardiography is limited to thrombi within the heart, main pulmonary artery, or proximal left or right branches. The majority of dogs (88%) with necropsy proven PTE had thrombi located in the main PA and lobar branches.[9] Since some of these proximal thrombi might be visualized with echocardiography, cardiac ultrasound should be considered in dogs with suspected PTE.

Perfusion scanning with an intravenous injection of technetium magroaggregated albumin, is a safe, noninvasive technique for evaluation of PTE. Perfusion deficits may occur in regions of thrombosis or in nonventilated regions with reflex vasoconstriction. When combined with a ventilation scan using technetium radioaerosol, the ventilation: perfusion (V:Q) scan has enhanced sensitivity for detection of PTE. Definitive positive V:Q scans are defined as multiple segmental or lobar perfusion defects in areas of normal ventilation and no radiographic evidence of pulmonary infiltrates. Although V:Q scans are commonly used in human medicine to increase the likelihood of documenting PTE, fewer than half of patients with PTE have a high probability scan.[2] Since ventilation scans are less practical in veterinary medicine and require specialized facilities to handle radioactive materials, this imaging modality is not commonly used. However, an abnormal perfusion scan can be considered suggestive of PTE.

Pulmonary angiography is the gold standard for diagnosis of PTE in humans but is rarely used in veterinary medicine since anesthesia is usually required, and patients with severe PTE and PH are high-risk anesthetic candidates. Percutaneous right heart catheterization via a jugular sheath under deep sedation may be a safer alternative for veterinary patients. Ionic contrast agents can induce severe hypotension due to reduction in systemic vascular resistance in the face of fixed PVR, and this may worsen RV ischemia and function.[13] 1287

Selective PA angiograms and use of nonionic contrast media reduces risk of serious complications.[13] 1288

Definitive angiographic diagnosis of PTE depends on visualization of an intraluminal filling defect in the pulmonary artery, or abrupt vessel occlusion and visualization of the trailing edge of the thromboembolus.[2]

Spiral computed tomography (CT) and magnetic resonance (MR) angiography are noninvasive imaging modalities that show promise for the future diagnosis and management of PTE. However, requirement for general anesthesia in veterinary patients undergoing CT or MRI makes these modalities less attractive in unstable, high-risk patients.

218.2.3 Treatment

Treatment of PTE must be directed against the primary underlying condition, and efforts must be made to improve gas exchange and cardiopulmonary function. Oxygen administration is indicated to reverse hypoxemia due to V/Q mismatch or diffusion abnormalities; however, pulmonary infarction and dysregulated hypoxic vasoconstriction may result in refractory hypoxemia. Immediate stabilization is necessary for animals in low output cardiac failure. Judicious fluids and inotropic support with dobutamine can be used to improve cardiac output and restore tissue perfusion.

Early and aggressive thrombolytic treatment of PTE is reserved for hemodynamically unstable patients and is uncommonly used in veterinary medicine. The goal of thrombolysis is to reduce PA pressure rapidly, improve RV function, and improve pulmonary perfusion. Although there are reports of successful thrombolytic therapy in experimental canine PTE (in dogs with normal thrombolytic and anticoagulant systems)[14] and in animals with systemic thrombi, there are no published studies evaluating thrombolytic therapy in naturally occurring PTE in veterinary medicine. In experimental canine PTE, tissue plasminogen activator (TPA) caused a rapid, dose-limiting thrombolysis with use of 1 mg/kg intravenously over 45 minutes, and TPA appeared to cause faster and more complete thrombolysis than streptokinase and urokinase.[14] Streptokinase has been effectively used in arterial thromboembolism in dogs and cats (90,000 U IV over 30 minutes, then 45,000 U/hour IV continuous infusion for various time intervals).

Anticoagulant therapy with heparin or warfarin is used to prevent further thrombus formation. Heparin is highly protein bound and has a low bioavailability. Doses ranging from 100 to 300 IU/kg SQ q6-8h can be used to prolong partial thromboplastin time (PTT) to 1.5 to 2 times baseline for adequate anticoagulation. Fresh frozen plasma may be needed to replenish antithrombin III. Low–molecular-weight heparin (LMWH) offers an attractive alternative for anticoagulant therapy, since it is less protein bound than unfractionated heparin, has greater bioavailability, provides a more predictable dose response, and has a longer half-life than heparin. LMWH therapy does not require laboratory monitoring since it does not prolong the APTT, and it is associated with fewer bleeding episodes.[2] In normal dogs, a high dose of 150 U/kg of dalteparin produced adequate anti-Xa activity with no bleeding complications and clinically insignificant changes in APTT and thrombin time.[15] Enoxaparin has been used with anecdotal clinical success for treatment of systemic thromboembolism in veterinary medicine. Long-term anticoagulation may also be achieved with oral warfarin (0.1 to 0.2 mg/kg PO q24h). Before warfarin is given, adequate anticoagulation with heparin is needed to balance the initial hypercoagulable phase of warfarin from reduced proteins C and S.

Although rarely done, large central thrombi may be removed by surgical thrombectomy, and percutaneous removal with a specialized thrombolytic catheter has been used in an experimental canine model of PTE.

Aggressive treatment of underlying diseases that have been associated with PTE is paramount, and prophylactic anticoagulation therapy may prevent PTE in these patients. Heparin can be administered at low doses (10 to 75 units/kg SQ TID) without affecting coagulation parameters. Given its biokinetic properties and ease of monitoring, LMWH is an attractive option for preventative anticoagulant therapy.

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219 CHAPTER • 219 Oral and Salivary Gland Disorders

Mark M. Smith

219.1 ORAL NEOPLASIA

Neoplasia of the oral and pharyngeal cavities is relatively common in the dog and cat, ranking fifth and seventh most common, respectively.[1] Benign and malignant neoplastic disease may be of dental or nondental origin.[2] The annual incidence of oral and pharyngeal neoplasia in dogs is 20 per 100,000, with malignant melanoma and squamous cell carcinoma (SCC) diagnosed most commonly.[1] The annual incidence rate is lower in cats (11 per 100,000), with the predominant neoplastic types being SCC and fibrosarcoma.[1,3]

Predisposing factors in the development of oral neoplasia include the patient's age, gender, breed, and size and the pigmentation of the oral mucosa. Geriatric patients are predisposed in general, although fibrosarcoma has been reported to occur more frequently in young, large breed dogs.[2] Papillary SCC, virus-induced papillomatosis, and undifferentiated malignancies may also be included in the differential diagnosis for young dogs with oral masses.[4,5] Male dogs have been reported to be at risk for malignant melanoma and fibrosarcoma. Breeds with an increased risk for oral neoplasia irrespective of type include the German shepherd and short-haired pointer, weimaraner, golden retriever, boxer, and cocker spaniel.[6] Large breed dogs have a higher incidence of fibrosarcoma and nontonsillar SCC, whereas small breeds have a higher incidence of malignant melanoma and tonsillar SCC.[6] Dogs with heavily pigmented oral mucosa are predisposed to malignant melanoma.

219.1.1 Benign Neoplasms

Papilloma, fibroma, lipoma, chondroma, osteoma, hemangioma, hemangiopericytoma, histiocytoma, and epulides are reported in the oropharyngeal region in the dog.[6] Papilloma and epulis are common benign oral neoplastic conditions in the dog.

Canine oral papillomatosis (COP) are multiple lesions of viral etiology. Grossly, COPs appear on the mucosa as pale, smooth elevations that develop a rough surface early in the disease process (Figure 219-1).[7] Older lesions of 3 to 4 weeks' duration usually have deep, closely packed fronds. Lesions observed during regression appear shriveled and dark gray. Complete regression requires 1 to 2 weeks and leaves no apparent scarring.

Epulides originate from the periodontal stroma and are often located in the gingiva near incisor teeth (Figure 219-2). The epulides are separated into three types based on histologic origin: fibromatous or fibrous epulis, ossifying epulis, and squamous or acanthomatous epulis.[6] The fibromatous and ossifying epulides are pedunculated, nonulcerating, and noninvasive masses. Acanthomatous epulis, although benign, has characteristics of malignancy, including local invasiveness and bone destruction[6]; however, acanthomatous epulis does not metastasize.

Periodontal epulides may be considered odontogenic neoplasms, because they are closely associated with or may contain dental structures. Fibromatous and ossifying epulides have also been described as peripheral odontogenic fibromas, containing varying amounts of bone, osteoid, dentinoid, or cementum-like substances.[7,8] Additionally, acanthomatous epulis, sometimes referred to in the literature as an *adamantinoma,*

may be more properly classified as acanthomatous ameloblastoma or peripheral ameloblastoma.[9] The more common, specific odontogenic neoplasms are ameloblastoma and odontoma. Ameloblastomas arise from vestigial layers of the dental laminae of the mandible, generally in the incisor region. The neoplasm emanates from enamel organ tissue but does not produce dental hard products. These lesions are expansile, slow-growing neoplasms.[6] Odontomas are of odontogenic origin and resemble the embryologic pattern of tooth development. The mass may comprise enamel, dentin, cementum, and sometimes small teeth. Odontomas may form on or near the crown or root of a normal tooth and may resemble displaced or extra teeth. Lesions with characteristics resembling normal teeth are considered compound, whereas complex odontomas have a more disorganized arrangement.[6]

219.1.2 Malignant Neoplasms

Malignant melanomas grow rapidly and are characterized by early invasion of the gingivae and bone. Metastasis to regional lymph nodes occurs early in the disease process, with lung the most common site of visceral metastasis.[6,11] Malignant melanomas are dome shaped or sessile, and they either have varying amounts of pigmentation, ranging from black and brown to mottled, or are nonpigmented (Figure 219-3). A minority of oral melanocytic neoplasms (25%) may be benign, but all suspected melanomas should be considered malignant pending histologic evaluation. Melanomas of the mucocutaneous junction are invariably malignant.

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Figure 219-1 Papillomatosis (*arrow*) of the labial mucosa in a young dog.

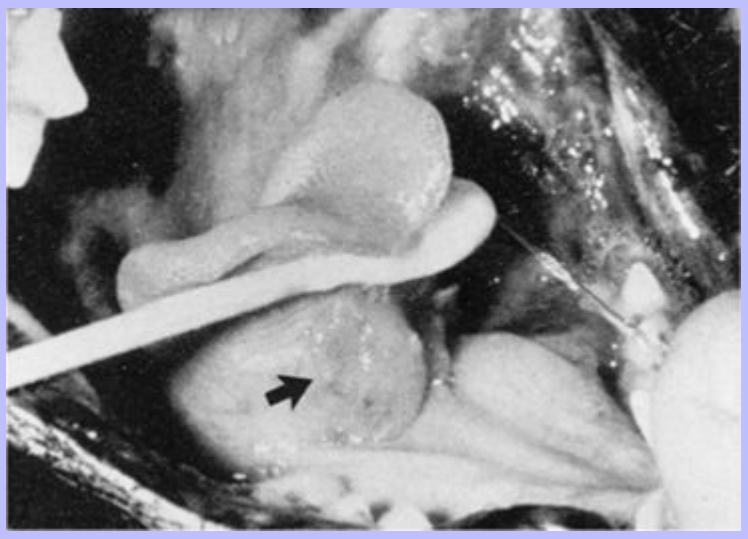
Figure 219-2 Intraoperative view of acanthomatous ameloblastoma of the mandibular incisor area in a dog.

Squamous cell carcinoma may project from the gingival mucosa but more commonly is an ulcerated, erosive lesion. It frequently involves the gingiva mesial to the canine teeth in dogs and ventral to the tongue in cats (Figure 219-4). Other common oral sites include the buccal and labial mucosa, hard palate, and tongue.[3,6,12–15] SCC destroys the mucosa and submucosa and is locally invasive in muscle and bone. Bone involvement is particularly common in dogs, showing a 77% occurrence rate. Metastasis to local and regional lymph nodes is common, whereas visceral metastasis to the lung is rare and occurs late in the disease process.

Fibrosarcoma occurs in oral locations similar to those of SCC but has a greater frequency along the lateral maxillary arcade between the canine and fourth premolar teeth.[6] The neoplasm is firm and smooth and has nodules that may become ulcerated (Figure 219-5). Fibrosarcomas are invasive, and recurrence after local excision is common. Regional lymphatic and visceral metastasis is unusual. Conversely, low-grade fibrosarcomas appear benign clinically and rarely present with ulceration. However, these tumors are biologically malignant and require a high index of suspicion on the part of both the clinician and the pathologist.[16]

Figure 219-3 Malignant melanoma of the mandibular buccal mucosa in a dog.

Figure 219-4 Sublingual squamous cell carcinoma (*arrow*) in a cat. (From Norris AM et al: Oropharyngeal neoplasms. In Harvey CE [ed]: Veterinary Dentistry. Philadelphia, WB Saunders, 1985.)



219.1.3 Clinical Signs, Diagnosis, and Staging

Clinical signs associated with oral neoplasms depend on the lesion's size and location. Food prehension may be abnormal and cause ulceration secondary to trauma in patients with larger neoplasms. Inability to swallow or associated pain may result in the appearance of saliva drooling from the lip commissures at inappropriate times. The saliva is blood tinged when concomitant with ulcerated lesions. Clinical signs associated with dental disease may be related to abnormal mastication. Painful dental structures or partial obstruction of functional dental areas lead to disuse. Subsequent periodontal disease is related to excessive plaque and calculus accumulation in these areas. Severe destructive periodontal disease, halitosis, and tooth loss are potential sequelae. Although severe destructive periodontitis is not associated with a mass lesion, it is often associated with bone lysis and may resemble SCC.

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Figure 219-5 Fibrosarcoma (*arrow*) of the maxillary premolar area in a dog.

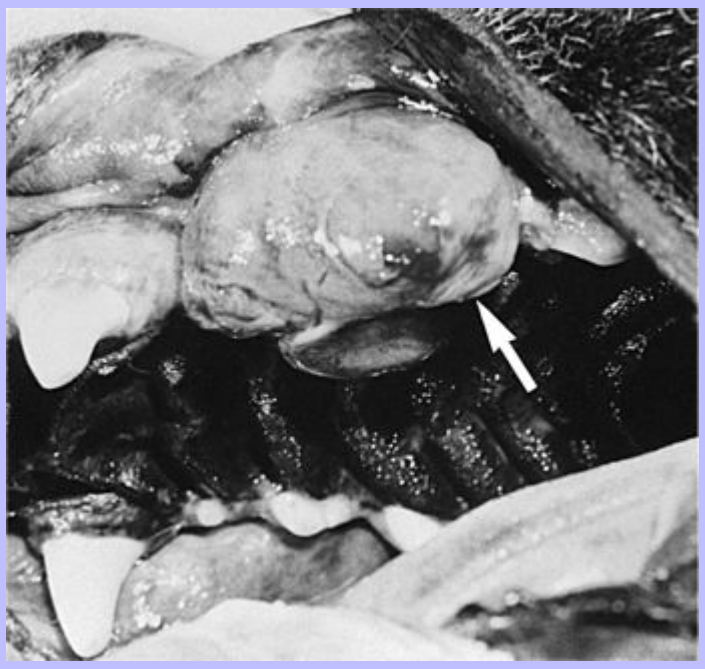
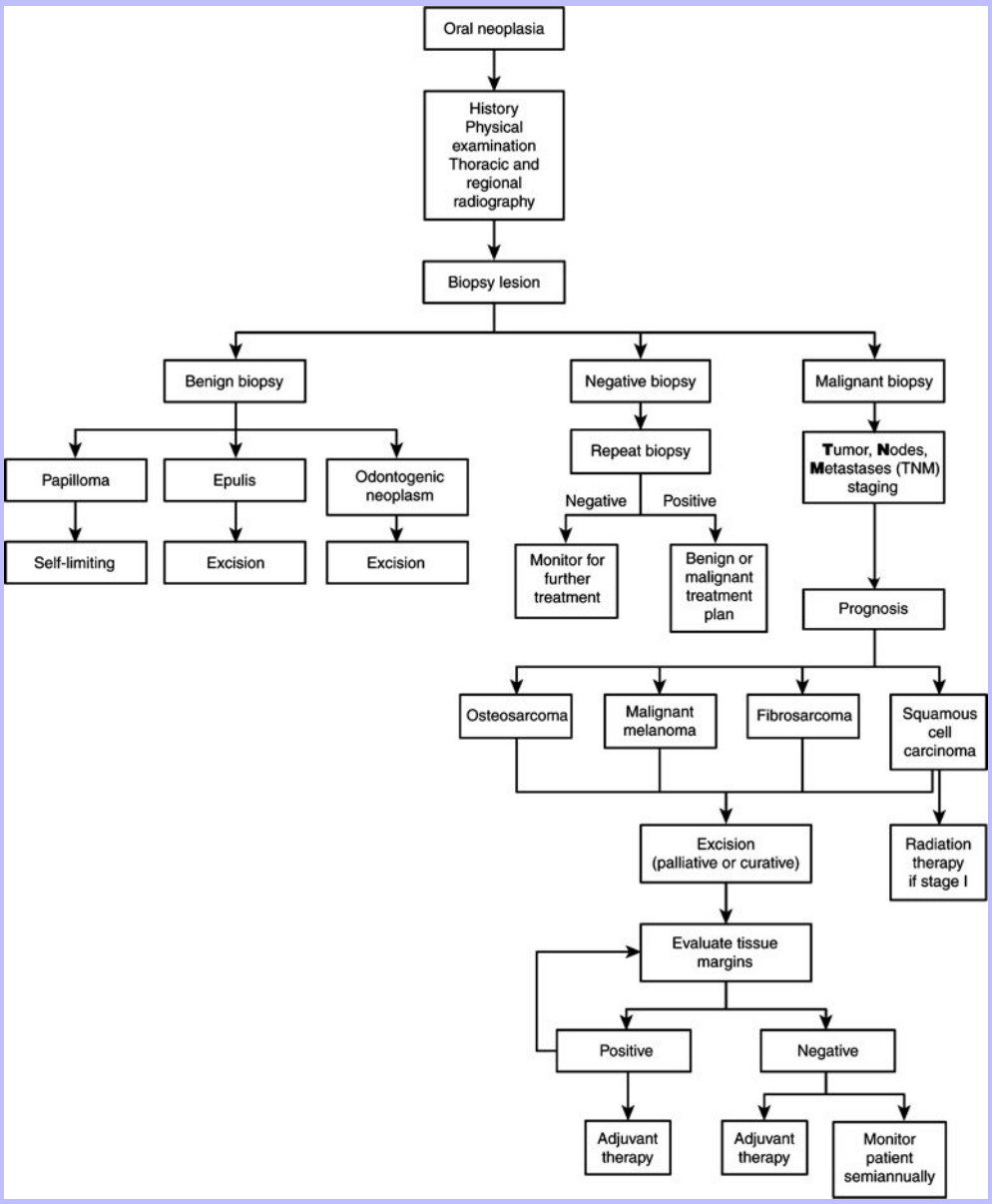


Figure 219-6 Algorithm for the diagnosis and treatment of oral neoplasms.



Diagnosis of oral neoplastic conditions is based on histopathologic examination (Figure 219-6). The differential diagnoses include malignant and benign neoplasms. Recent advances in the development and application of immunohistochemistry techniques in veterinary medicine may provide methods for early detection of malignant neoplasms.[17–20]

Staging of the neoplastic disease should be considered as an active investigative process to be performed in concert with the diagnostic evaluation (Table 219-1).[21] The final result of this process is potentially valuable prognostic information. A complete blood count (CBC), chemistry profile, and urinalysis results should be reviewed to detect organ abnormalities related to metastatic disease or to concurrent disease that would alter the type or preclude the use of general anesthesia.

Thoracic radiographs (right and left lateral, ventrodorsal views) are taken to determine whether visceral metastasis to the lung has occurred. The size of the neoplasm is estimated in the awake patient and may be more accurately assessed after administration of general anesthesia. Skull radiographs or computed tomography (CT) performed during anesthesia can provide information on the presence of bone invasion.

Table • 219-1 Clinical Staging System for Tumors of the Oral Cavity

T: Primary tumor

- T_0 No evidence of tumor
- T_1 Tumor <2 cm maximum diameter
  - T_{1a} Without bone invasion
  - T_{1b} With bone invasion
- T_2 Tumor 2 to 4 cm maximum diameter
  - T_{2a} Without bone invasion
  - T_{2b} With bone invasion
- T_3 Tumor >4 cm maximum diameter
  - T_{3a} Without bone invasion
  - T_{3b} With bone invasion

N: Regional lymph nodes (RLN)

- N_0 No evidence of RLN involvement
- N_1 Movable ipsilateral nodes
  - N_{1a} Nodes histologically negative
  - N_{1b} Nodes histologically positive
- N_2 Movable contralateral or bilateral nodes
  - N_{2a} Nodes histologically negative

N_{2b} Nodes histologically positive

N_3 Fixed nodes

M: Distant metastasis

M_0 No evidence of distant metastasis

M_1 Distant metastasis present

STAGE GROUPINGS

STAGE	T	N	M
I	T_1	N_0, N_{1a}, or N_{2a}	M_0
II	T_2	N_0, N_{1a}, or N_{2a}	M_0
III*	T_3	N_0, N_{1a}, or N_{2a}	M_0
IV	Any T		
	Any T	Any N_{2b} or N_3	M_0
	Any T	Any N	M_1

From World Health Organization: *Report of the Second Consultation on the Biological Behaviour and Therapy of Tumors of Domestic Animals.* WHO, Geneva, 1978.

* Any bone involvement.

The regional lymph nodes should also be evaluated. Enlargement indicates either metastasis or reactivity related to oral inflammation. Regardless of size, the regional lymph nodes should be evaluated by fine needle aspiration (false-negative results are possible) or by incisional or excisional biopsy. Minor surgery to remove a regional lymph node provides worthwhile prognostic information which may influence the owner's decision to pursue definitive treatment.[22,23] The most accessible regional lymph nodes are the submandibular and parotid nodes; the medial retropharyngeal node receives afferent lymphatics from these lymph nodes. Lymph node should be differentiated from salivary tissue, the latter having a tan color with distinct lobulations. A negative lymph node biopsy result does not preclude the possibility of regional metastasis, which may occur along perineural or vascular routes, or metastasis to other, less accessible lymph nodes, such as the medial retropharyngeal node.[23] Unfortunately, oral malignant neoplasms are often detected late in the disease process because their location may not be readily observed by the owner or veterinarian. Consequently, oral neoplasms have usually progressed to at least stage II disease at the time of diagnosis. Higher primary tumor (T)-stage tumors with bone involvement are associated with a poor prognosis.[11]

219.1.4 Treatment

Animals with no radiographic signs of visceral metastasis to the lung should be considered candidates for aggressive therapy. The concept of complete local excision of all visible tumor followed by, or concurrent with, chemotherapy or radiation therapy for treatment of presumed micrometastasis has achieved marked acceptance in human oncologic therapy and is being applied in veterinary medicine.[21,24–26] Surgery is integral

to this multimodality treatment plan, especially for large, aggressive neoplasms.[27–30] Resective surgery plus radiation and/or chemotherapy are usually well tolerated by dogs and cats, leaving conservative management for only the more debilitated or geriatric patients.[31]

The goal of surgery for oral neoplasms in small animals is generally curative resection or palliation.[32] The ideal surgical procedure is one that offers the greatest possibility of cure, restores or maintains function, and has an acceptable cosmetic result. Benign neoplasms that do not involve bone are surgically excised. Malignant neoplasms are also excised; however, an attempt to acquire tumor-free margins is critically important.[33–35] A 2 cm margin of tumor-free tissue is recommended, often necessitating ostectomy as a component of the operative procedure.[36] Neoplasms with radiographic evidence of local bone metastasis require resective procedures, including maxillectomy and mandibulectomy. Hemimaxillectomy and hemimandibulectomy maximize the removal of the entire bony component of the neoplastic process. Segmental bone resective procedures that result in partial maxillectomy or mandibulectomy, without the opportunity for frozen section analysis of tissue margins, risk incomplete resection due to intrabony perineural and microvascular metastatic routes.[37,38] This is particularly important for mandibular lesions, for which hemimandibulectomy may be preferred to partial or segmental mandibulectomy because cosmesis and function are acceptable despite a greater degree of resection.[31,39] Extended dissection from the primary site may improve the incidence of free margins related to surgical resection of direct metastatic pathways, especially for neoplasms of the floor of the mouth. The cranial cervical area may be approached in conjunction with reconstructive surgery. Direct observation of regional lymph nodes allows assessment of gross transcapsular spread of the tumor, which may warrant wider margins for adhered lymph nodes.[40,41]

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Peripheral odontogenic fibromas are treated by aggressive, local surgical resection. Based on the common locations of this neoplasm compared with malignant neoplasms, the operative procedures would be either rostral mandibulectomy or rostral maxillectomy.[42,43]

Odontogenic tumors are treated by local excisional surgery requiring partial or segmental ostectomy.[44–46]

Radiation therapy may be particularly indicated for stage I SCC or after resective surgery for SCC with nonfree margins. This form of treatment is most effective if used in combination with surgical excision of stage II to stage IV SCC or possibly for affected regional lymph nodes.[12] Recent studies report encouraging results from radiation therapy for the treatment of canine SCC, fibrosarcoma, and malignant melanoma.[11,47] This modality should be considered for treatment of oral malignancies with or without surgery. However, as with surgery, larger, more caudally located tumors have a poorer prognosis. Severe, acute radiation reactions may occur approximately 16% of the time; the most common chronic reaction is bone necrosis and fistula formation.[11] Although the latter reaction may be difficult to treat successfully, a relatively low percentage of chronic reactions to radiation therapy may be considered an expected sequela of effective treatment.[11]

Acanthomatous ameloblastomas are sensitive to radiation therapy; however, because malignant neoplastic disease develops at the irradiated site in approximately 18% of dogs, surgical excision may be a more appropriate therapeutic option imorbidity is minimized.[48,49] The type of radiation administered (orthovoltage versus megavoltage) may influence the potential carcinogenic affect of radiation.[50] Smaller acanthomatous ameloblastomas located in the rostral portion of the oral cavity have a more favorable prognosis after radiation therapy than do larger, more caudal lesions.[50] Acute and chronic radiation reactions may occur, as in treatment for oral malignant neoplasms.

Chemotherapy or chemoradiation therapy may provide short-term palliation for oral neoplasia not amenable to surgery, for resections with non-free margins, and for recurrence after surgical excision. Cisplatin has been used in dogs for oral SCC, and doxorubicin and cyclophosphamide have been used for oral fibrosarcoma and SCC in cats.[2] The results of clinical research with radiosensitizing agents (e.g., etanidazole) may show improvement in median survival times for small animals with oral neoplasms.[51–53] Intratumoral administration of carboplatin has proved efficacious in the treatment of SCC of the nasal plane in cats[54] and may have application in the treatment of oral SCC. Systemic carboplatin may be considered as adjunctive treatment for microscopic local or metastatic malignant melanoma.[55] Chemoradiation, including hypofractionated megavoltage irradiation and cisplatin or carboplatin therapy, prolonged survival times in dogs with incompletely resected oral malignant melanoma.[56]

219.1.5 Prognosis

Malignant oral neoplasms have a guarded to poor prognosis regardless of their size or location in the oral cavity. The prognosis may be affected by the size of the lesion and the patient's age and species. Dogs younger than 6 years of age with SCC mesial to the second premolar have a better prognosis than older dogs with neoplasms in other locations. Cats with oral SCC have a shorter tumor-free interval than dogs regardless of the type of treatment.[57,58] The most positive prognosis for oral SCC in dogs is attained with both surgery and radiation therapy. Treatment of oral SCC in cats is strictly palliative, with no improved survival interval.[2,57] Oral malignant melanoma may be resected locally with tumor-free margins, but regional or distant metastasis usually occurs. Tumor-free margins for oral fibrosarcoma are more difficult to achieve, which makes local recurrence likely. A 1-year survival rate of 71% has been reported for dogs with mandibular osteosarcoma treated with surgery only; another study indicated less favorable results with surgery only, reporting a median survival time of 5.5 months.[59,60]

Benign oral neoplasms and odontogenic neoplasms, including epulides, have an excellent prognosis after complete surgical excision.[43–46]

219.2 SELECTED ACQUIRED DISEASES OF THE LIPS, CHEEKS, AND PALATE

Feline eosinophilic granuloma complex (FEGC) comprises an eosinophilic ulcer, plaque, and a linear granuloma. Oral lesions are usually a linear granuloma or an eosinophilic ulcer; the latter has a predisposition for the maxillary lips (80%).[61] Intraoral lesions appear as one or more discrete, firm, raised nodules (Figure 219-7). Clinical signs include dysphagia and/or ptyalism. Although the etiology of this disease is unknown, bacterial and viral infections and immune-mediated and hypersensitivity diseases have been associated with FEGC.[61,62] Biopsy of the lesion, with the aforementioned diseases in mind, should be performed to confirm the diagnosis and to differentiate it from neoplastic disease. Ancillary tests should include a CBC, which usually shows an absolute eosinophilia. Concurrent or potentially causative hypersensitivity diseases should be considered during the diagnostic phase of treatment. The mainstay of FEGC treatment is corticosteroid therapy. Intralesional triamcinolone (3 mg weekly), oral prednisolone (1.0 to 2.0 mg/kg given twice daily), and subcutaneous methylprednisolone acetate (20 mg every 2 weeks), administered until FEGC resolves, are efficacious treatments.[61] Progestational compounds (progesterone or medroxyprogesterone) are often used to treat FEGC. These compounds are not approved for use in cats and have potential side effects that make them undesirable, including adrenocortical suppression, polydipsia, polyuria, polyphagia, obesity, personality change, reproduction

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abnormalities, mammary hypertrophy, neoplasia, and diabetes mellitus. Cats with untreated chronic lesions, responsive previous lesions, and lesions refractory to corticosteroid therapy have a 50% recurrence rate within 5 months.[61] Failure of treatment is usually related to inadequate dosage or premature cessation of therapy. Animals that do not respond to either corticosteroids or progestational compounds have a poor prognosis and are candidates for more aggressive therapy, such as irradiation, cryosurgery, laser therapy, or immunotherapy.[62–64]

Figure 219-7 Oral lesions (*arrows*) of feline eosinophilic granuloma complex. (Courtesy Dr. M. Leib, Blacksburg, VA.)

The term *stomatitis* refers to an inflammation of the oral mucosa. Oral inflammatory lesions in dogs and cats have multiple causes, necessitating a consistent and logical diagnostic approach. A complete history and thorough physical examination are essential. Dogs and cats with no evidence of debilitating systemic disease should receive a short-acting intravenous anesthetic to allow an unimpeded visual and tactile oral examination. Oral ulcerations occur in at least four different immune-mediated diseases, including systemic lupus erythematosus, bullous (pemphigus) disease, idiopathic vasculitis, and toxic epidermal necrosis. The many infectious diseases that are manifested by lesions in the oral cavity include feline leukemia virus, feline immunodeficiency virus, feline syncytium-forming virus, feline calicivirus, feline herpes virus, and feline infectious peritonitis (see Chapters 170-173).[65] Canine distemper and feline panleukopenia virus may cause stomatitis, although other organs are more severely affected. Candidiasis (infection with *Candida albicans*) may cause severe stomatitis in dogs and cats.[61,66] Many cats with stomatitis have immunosuppressive disease or

systemic debilitation or have received chronic immunosuppressive therapy. Although the oral manifestation may appear as a white, pseudomembranous covering of the tongue, the lesions are usually irregular, ulcerated areas in zones of inflamed mucosa.

Feline oral inflammatory disease ranges from simple gingivitis to varying degrees of stomatitis in which inflammation extends beyond the mucogingival junction into the oral mucosa.[67] Cats with chronic gingivitis/stomatitis may have ulceration and extension of granulation tissue involving the palatoglossal folds and fauces. Clinical signs include halitosis, ptyalism, dysphagia, inappetence, and weight loss. Extensive disease is marked by root resorption and possibly bony sequestrae in edentulous areas. Unfortunately, because the causation is usually unknown, treatment is symptomatic, including professional cleaning of the teeth, therapy with antimicrobials or with systemic or local corticosteroid agents similar to those used for FEGC, and laser therapy to stimulate re-epithelialization over inflamed, ulcerated areas. It is not unusual for refractory cases to require extraction of all molars and premolars or all teeth to alleviate the symptoms of this disorder.

Stomatitis may be described as idiopathic despite a thorough diagnostic evaluation. Immunemediated ulcerative gingivitis/stomatitis afflicts Maltese terriers, although the etiology is verified in only 20% of animals.[61] If diagnostic test results are negative in idiopathic stomatitis, it is appropriate to assume a possible immune-mediated component. A prudent treatment plan includes regular cleaning of the teeth, oral preventive medicine at home, and intermittent or chronic provocative corticosteroid therapy. Antimicrobial therapy emphasizing anaerobic pathogens (e.g., metronidazole, amoxicillin, clavulanic acid/amoxicillin) may be administered on an intermittent, chronic basis.

219.3 SELECTED ACQUIRED DISEASES OF THE SALIVARY GLANDS

Neoplasia involving the salivary glands is uncommon. There is evidence that spaniel breeds and poodles, as well as Siamese cats, are predisposed to neoplasia of the salivary glands.[68] In a report of 24 primary salivary tumors in dogs, the parotid gland was involved nearly twice as often as the other major salivary glands; the mean age of the 24 dogs studied was 10 years.[68] Another recent study indicates that the mandibular gland is most commonly affected.[69] Multiple tumor types that affect the salivary glands have been described, including mucoepidermoid tumors, SCC, malignant mixed tumors, adenoid cystic carcinoma, acinic cell carcinoma, adenocarcinoma, undifferentiated carcinoma, and sarcoma. Although primary SCC of the sublingual salivary gland occurs, it should be considered only after an invasive carcinoma involving the oral mucosa or accessory oral salivary glands has been ruled out. The prevalence of salivary gland neoplasms in cats is almost twice that in dogs, with the mandibular salivary gland most commonly affected.[68] Adenocarcinoma is the most common neoplasm affecting the salivary glands in dogs and cats.[68] Adenocarcinoma, regardless of the gland affected, is locally infiltrative, with frequent metastasis to the lung and regional lymph nodes. Cats have more advanced-stage disease at the time of diagnosis than do dogs.[68] Salivary neoplasms should be staged according to the primary tumor–regional lymph node–distant metastasis (TNM) system to allow appropriate prognostication and development of a treatment plan. Thoracic radiographs and incisional biopsy of the neoplasm and nearest regional lymph nodes provide necessary information.

Total surgical excision of salivary malignant neoplasms is difficult because of their invasive characteristics and the intricate neurologic and vascular anatomy of the salivary gland region. Therefore local treatment should include radiotherapy, with or without surgical intervention to debulk the neoplasm.

Mucocele is the most common recognized clinical disease of the salivary glands in dogs. A mucocele comprises an accumulation of saliva in the subcutaneous tissue and the consequent tissue reaction to saliva. The mucocele

has a nonepithelial, nonsecretory lining consisting primarily of fibroblasts and capillaries. The incidence of salivary mucocele reportedly is fewer than 20 in 4000 dogs. Although the condition has been reported in dogs as young as 6 months of age, salivary mucocele occurs most often in dogs 2 to 4 years of age. It occurs more frequently in German shepherds and miniature poodles.

Trauma has been proposed as the cause of salivary mucocele because of the activity of young dogs and the documented damage to the salivary gland-duct complex and the formation of the mucocele. The inability to induce salivary mucocele traumatically in healthy dogs suggests the possibility of a developmental predisposition in affected dogs.

The sublingual gland is the most common salivary gland associated with salivary mucocele. Sialography has shown that the mucocele most often originates in the rostral portion (that portion of the sublingual gland superimposed on the mandible) of the sublingual gland-duct complex. Regardless of the location of origin, the mucocele usually forms near the intermandibular area (cervical mucocele). Other locations associated with the formation of a mucocele caused by a sublingual gland-duct defect are sites under the tongue, which involves the floor of the mouth (sublingual mucocele) and the pharynx (pharyngeal mucocele).

The clinical signs associated with salivary mucocele depend on the location of the mucocele. A cervical mucocele initially is an acute, painful mass resulting from an inflammatory response. Cessation of the inflammatory response results in a marked decrease in size. A decreased inflammatory response allows for the more common presenting history of a slowly enlarging or intermittently large, fluid-filled, painless mass (Figure 219-8). Blood-tinged saliva secondary to trauma caused by eating, abnormal prehension of food, or reluctance to eat are clinical signs that can be associated with sublingual mucocele. The most common clinical signs associated with a mucocele of the pharyngeal wall are respiratory distress and difficulty swallowing secondary to partial obstruction of the pharynx.

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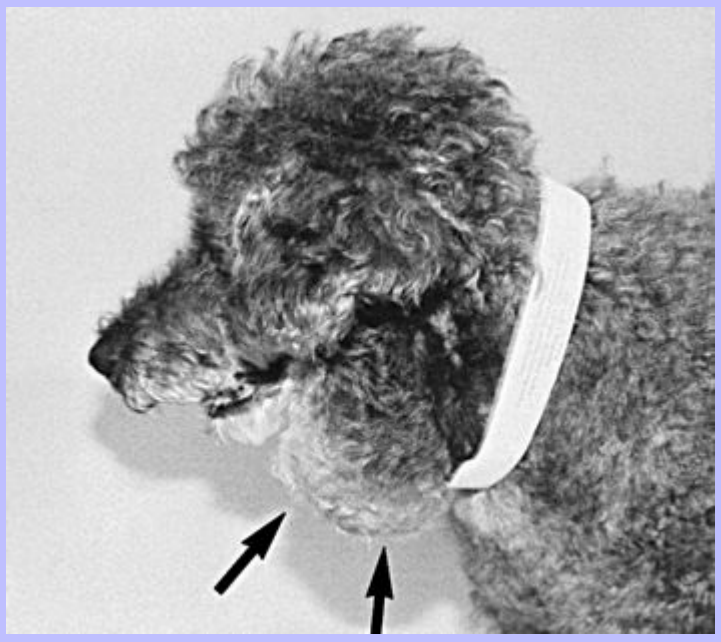
Figure 219-8 Cervical mucocele in a poodle.



Zygomatic salivary mucoceles are infrequently reported in dogs. A visible periorbital mass is usually the presenting clinical sign of zygomatic mucocele. Ophthalmic signs secondary to the mucocele depend on the location and size of the mucocele (e.g., exophthalmos or enophthalmos).

Diagnosis of salivary mucocele is based on the clinical signs, history, and results of paracentesis (Figure 219-9). Mucocele paracentesis reveals a stringy, sometimes blood-tinged fluid with low cell numbers. Mucin and amylase analyses of the fluid are not reliable diagnostic procedures. A chronic cervical mucocele may contain palpable firm nodules that are remnants of sloughed inflammatory tissue previously lining the mucocele. Sialoliths, which are concretions of calcium phosphate or calcium carbonate, may occur with chronic mucocele.

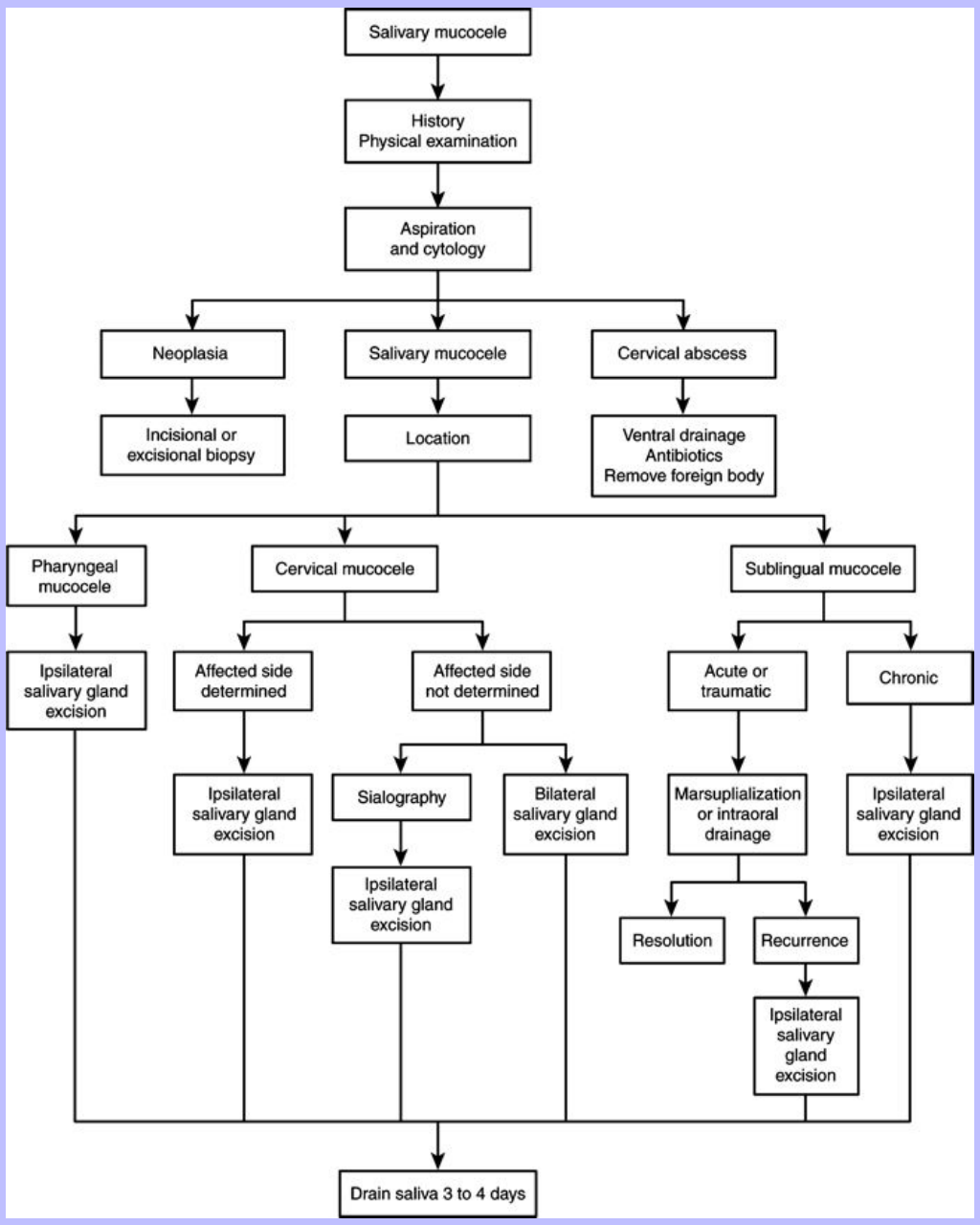
The physical examination and history usually denote the origin of the mucocele. Cervical mucoceles that appear on the midline usually shift to the originating side when the patient is placed in exact dorsal recumbency. Sialography can be used to determine the affected side if careful observation and palpation of the mucocele are unsuccessful. Sialography is also a diagnostic aid when considerations include traumatic injury to one of the salivary glands, salivary neoplasia, a mass or fistulous tract of unknown origin in the head and neck region, or a foreign body in the head or neck. The disadvantages of sialography include the need for general anesthesia and the difficulty associated with locating the duct opening or openings.

Various techniques have been used to treat cervical mucoceles. Mucocele drainage, removal of the mucocele only, and chemical cauterization of the mucocele have been reported. The basis for these therapies was the belief that a mucocele was a true cyst with a secretory lining. The fact that a mucocele is not a cyst but a reactive, encapsulating structure has prompted surgical removal of the affected gland-duct complex. The intimate anatomic association of the sublingual and mandibular glands and their ducts requires resection of both structures. Surgical removal of both the sublingual and mandibular salivary glands, combined with drainage of the mucocele, has been advocated for treatment of cervical mucoceles.

Pharyngeal and sublingual mucocele are treated by removal the mandibular and sublingual salivary glands, based on the common etiology of a sublingual gland-duct defect. Another treatment technique for these mucoceles involves marsupialization. However, resective surgery is preferred for pharyngeal mucoceles, because life-threatening upper airway compromise and morbidity from swallowing dysfunction (e.g., aspiration pneumonia) are potential complications of conservative management or recurrence.

The zygomatic salivary gland can be affected by neoplasia, inflammation, or mucocele. The clinical signs of zygomatic mucocele and neoplasia are similar. Additional signs, such as osteolytic changes of the zygomatic arch and enlargement of the submandibular lymph node, may accompany neoplasia that originate in the zygomatic gland. Surgical removal of the zygomatic gland is indicated either for neoplasia or for mucocele of zygomatic origin.

Figure 219-9 Algorithm for diagnosis and treatment of salivary mucocele in a dog.



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220 CHAPTER • 220 Diseases of the Esophagus

Albert E. Jergens

220.1 NORMAL ANATOMY AND FUNCTION

The esophagus functions to transport ingesta and liquids from the oral cavity to the stomach.[1,2] Its anatomy consists of the striated muscle (cricopharyngeus muscles) of the upper esophageal sphincter (UES), striated and smooth muscle of the body of the esophagus, and the smooth muscle of the lower esophageal sphincter (LES). The entire length of the canine esophagus is composed of striated muscle, whereas the distal one third of the feline esophagus is composed of smooth muscle. The vagus nerve and associated branches (glossopharyngeal, pharyngeal, and recurrent laryngeal nerves) innervate the esophagus. This neural network contains somatic motor nerves from the brain stem nucleus ambiguus to the esophageal striated muscle, autonomic nerves to the esophageal smooth muscle, and general visceral afferent nerves from esophageal sensory receptors.

The high pressure maintained by the UES and LES during fasting ensures unidirectional flow between the oral cavity and the stomach. The LES is also responsive to gut hormones via receptors for gastrin and secretin families. The esophageal phase of swallowing begins with relaxation of the UES, which permits movement of a bolus of food into the proximal esophagus. The peristaltic wave generated in the pharynx is further propagated through the esophagus and carries a bolus aborally to the LES (primary peristalsis). If primary peristalsis fails to propel the bolus to the stomach, then a secondary peristaltic wave is quickly generated by intraluminal distension and completes transport of the bolus to the stomach. Relaxation of the LES in advance of these propagated pressures permits food to empty into the stomach. After the bolus passes, the LES contracts to prevent reflux of gastric contents into the esophagus.

220.2 DIAGNOSIS OF ESOPHAGEAL DISEASES

220.2.1 History

In general, animals with overt esophageal dysfunction are not diagnostic challenges. Clients often report hallmark signs of esophageal disease including regurgitation (liquids or solids), dysphagia (difficult swallowing), odynophagia (painful swallowing), repeated swallowing attempts, and excessive salivation in affected animals. Regurgitation is the most consistent sign of esophageal disease and should be clearly differentiated from oropharyngeal dysphagia and vomiting (Table 220-1). Some animals may also have a mix of signs, such as vomiting and regurgitation, which may occur when chronic vomiting leads to esophagitis.

Other historical clues of esophageal disease may be made based on age and the character of signs. Congenital idiopathic megaesophagus shows distinct canine breed predispositions (see later), and vascular ring anomaly and cricopharyngeal dysphagia may also manifest in very young patients. Acute severe signs in either a young or older animal are suggestive of esophageal foreign body. Conversely, slowly worsening regurgitation is more commonly seen with hiatal defects (causing gastroesophageal reflux), developing stricture, or esophageal tumors. Adult animals showing esophageal dysphagia may have histories of recent anesthesia, ingestion of corrosive chemicals, or pill administration. Concurrent muscle weakness or neurologic signs may implicate extra-esophageal disorders, such as myasthenia gravis (MG) or polyneuropathy, as causes for secondary esophageal disease. Evidence of pain during swallowing is most often due to foreign body ingestion or esophagitis but is uncommonly observed with motility disturbances.

220.2.2 Physical Examination

The physical examination findings in animals with primary esophageal disease are variable. Most animals with acute causes for regurgitation (foreign body or mild esophagitis) show minimal abnormalities with the exception of hyper-salivation and variable dysphagia. Mucopurulent nasal discharge, pulmonary crackles, and fever suggest aspiration pneumonia. Weight loss, malnutrition, and emaciation can be seen with long-standing esophageal disease, such as stricture and idiopathic megaesophagus. Observations in animals with dysautonomia may include dilated pupils and dry mucus membranes. A carefully performed physical examination serves to exclude other gastrointestinal (GI) and systemic diseases.

220.2.3 Diagnostic Tests

Although history provides important clues as to the likelihood of primary esophageal disease, select laboratory tests, radiography, and endoscopy are necessary for definitive diagnosis in most instances (Figure 220-1). Significant alterations in baseline laboratory tests (complete blood count [CBC], serum biochemistry, urinalysis) are uncommonly observed. Exceptions include elevations in CK (associated with myositis), non-regenerative anemia (associated with malnutrition), and proteinuria (suggestive of immune-mediated disease). Specialized serologic assays useful for the diagnosis of regurgitation include an adrenocorticotropic hormone (ACTH) stimulation test (hypoadrenocorticism) and acetylcholine receptor antibody titer (acquired MG).

Survey thoracic and soft-tissue cervical films should be performed in all animals suspected as having esophageal disease. Obvious abnormalities may include radiopaque foreign bodies, hiatal defect, esophageal dilatation (megaesophagus), alveolar opacities (aspiration pneumonia), or evidence of esophageal perforation (pneumomediastinum).

Contrast radiography is a helpful adjunct to survey imaging, being most useful in confirming luminal obstruction (stricture, mass, extraluminal compression), mucosal irregularity (mass, severe esophagitis), and significant alterations in esophageal motility. An esophagram is most often performed using liquid barium suspension followed by a barium meal. Contrast material is rapidly cleared from the normal pharynx and esophagus by a series of brisk, aborally directed peristaltic waves.[2] Persistent pooling of contrast material at any level of the esophagus should be considered abnormal and confirmed on repeat films. If esophageal perforation is suspected, a water-soluble iodinated contrast agent (iohexol, gastrografin) should be used. Dynamic contrast studies (videofluoroscopy) provide more detailed quantitative information regarding esophageal motility.

Table • 220-1 Differentiation of Oropharyngeal Dysphagia, Esophageal Dysphagia, and Vomiting

PARAMETER	OROPHARYNGEAL DYSPHAGIA	ESOPHAGEAL DYSPHAGIA	VOMITING
Abdominal effort	None	None	Marked
Prodromal nausea	None	None	Present
Character of ejected food	Undigested	Undigested	Usually digested
Timing of food ejected	Immediate	Often delayed	Often delayed
Swallow attempts of a single bolus	Multiple	Usually single	Single
Ability to drink	Poor	Variable	Normal
Pain on swallowing	Possible	Possible	Absent
Associated signs	Dyspnea, cough	Dyspnea, cough	+/−Systemic signs

Modified from Guilford WG: Approach to clinical problems in gastroenterology. *In* Guilford WG, Center SA, Strombeck DR (eds): *Strombeck's Small Animal Gastroenterology,* 3rd ed. Philadelphia, WB Saunders Co, 1996, p 55.

Flexible endoscopy (esophagoscopy) provides the clinician the most direct means to quickly and noninvasively assess the esophagus for luminal or mucosal abnormalities. Normal esophageal mucosa is smooth, glistening, and pale pink. Abnormal findings include mass lesions (neoplastic most common), esophagitis (evidenced by mucosal erythema, hemorrhage, erosions), stricture, segmental or generalized dilatation, and perforation. Mucosal biopsy of the esophagus is uncommonly required except for intraluminal mass lesions. Exfoliative brush cytology may be superior to mucosal biopsy (due to technical constraints) for diagnosis of esophageal neoplasia. Interventional procedures allow for esophageal foreign body removal, dilatation of esophageal strictures, and feeding catheter placement via percutaneous gastrostomy or gastro-jejunostomy techniques.

More specialized diagnostic procedures, such as esophageal manometry (for assessment of motility or LES competency) and distal esophageal pH monitoring (for gastroesophageal reflux), are infrequently performed in clinical practice.

220.3 CRICOPHARYNGEAL DYSPHAGIA

Cricopharyngeal dysphagia is a congenital neuromuscular disorder characterized by failure of the UES to relax (achalasia) or a lack of coordination between UES relaxation and pharyngeal contraction (asynchrony). This results in interrupted transport of a bolus through the UES into the cervical esophagus. The cause for this disorder is unknown; however, a dysfunction of the inhibitory neuron mediating UES relaxation has been incriminated.[3]

220.3.1 Clinical Signs

Affected animals demonstrate progressive dysphagia characterized by repeated attempts to swallow, gagging, retching, and regurgitation (often immediately after eating). Clinical signs most often appear at the time of, or shortly after, weaning. A moist, productive cough may develop as a consequence of aspiration pneumonia. Physical examination is generally unremarkable with the exception of moist crackles in animals with pneumonia.

220.3.2 Diagnosis

Videofluoroscopy of the pharynx and UES using liquid barium or paste is the diagnostic test of choice. Intermittent or persistent failure of UES to relax and dilate subsequent to bolus formation and pharyngeal contractions is observed. Static contrast films may demonstrate barium retention in the pharynx or aspiration into the trachea (Figure 220-2). Ancillary tests (serum CK, electromyography [EMG], muscle biopsy) should be performed in animals having more generalized signs of neuromuscular disease (muscle weakness, atrophy, neurologic deficits).

220.3.3 Treatment

Cricopharyngeal dysphagia is best managed by performance of cricopharyngeal myotomy. The failure rate for surgery alone may be high, especially if aspiration pneumonia or malnutrition is present.[4] In these instances, more aggressive medical management (enteral tube feeding) is warranted rather than surgery. Mature animals and those with cricopharyngeal asynchrony respond less favorably to surgical intervention. Medical therapy includes treatment of aspiration pneumonia and enteral nutritional support in emaciated patients.

220.4 ESOPHAGITIS

Esophagitis denotes acute or chronic inflammation of the esophageal mucosa which may extend to the underlying muscularis. It may be caused by chemical injury from ingested substances (corrosives, pill or capsule retention), gastroesophageal reflux (secondary to general anesthesia, hiatal defects, persistent vomiting, malpositioned nasoesophageal or pharyngostomy tubes), or esophageal foreign bodies.[5] Mucosal damage caused by reflux is attributed to prolonged contact with gastric acid, pepsin, bile salts, and trypsin. Reduced esophageal clearance by peristalsis and failure to neutralize acid by bicarbonate-rich saliva contribute to anesthesia-associated reflux esophagitis. Drug-or chemical-induced esophagitis is caused by changes in mucosal pH, hyperosmolarity, and other mechanisms. Disturbances in esophageal motility may accompany esophagitis regardless of the cause. The reported prevalence of acute esophagitis is low; however, this is likely an underestimation due the subtlety of clinical signs and radiographic findings associated with this disorder.[6]

220.4.1 Clinical Signs

The clinical signs vary as to the type of chemical injury, severity of inflammation, and extent of esophageal involvement. Animals with mild esophagitis may be asymptomatic. Moderate-to-severe esophagitis causes anorexia, dysphagia, odynophagia (seen as extension of the head and neck during swallowing), and hypersalivation. Regurgitation is often intermittent, but it may be persistent. Thick, ropey saliva that is blood-tinged is often expelled. The physical examination may be unremarkable in animals with mild esophagitis. Cachexia and weight loss may be seen with prolonged disease.

Figure 220-1 Diagnostic approach to an animal with regurgitation and suspected esophageal disease. (Adapted from Washabau RJ: Diseases of the esophagus. *In* Ettinger SJ, Feldman ED [eds]: *Textbook of Veterinary Internal Medicine*. 5th ed. Philadelphia, WB Saunders Co, 2000, p 1144.)

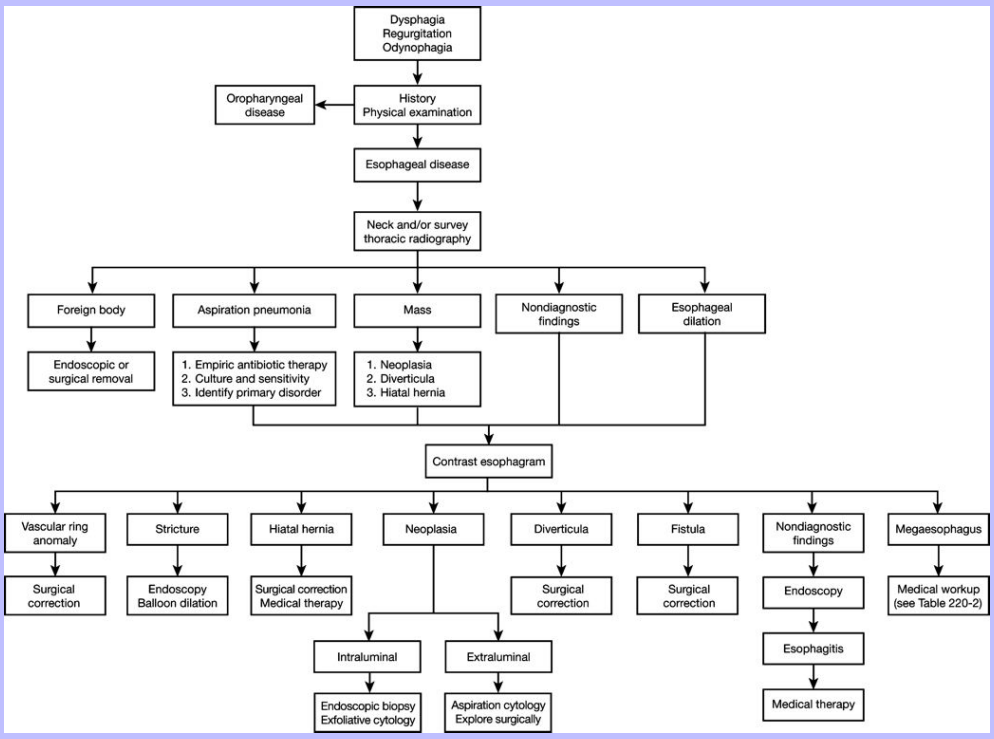
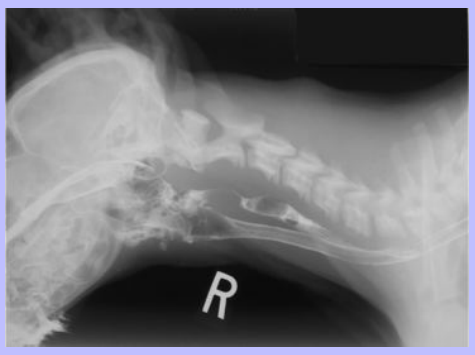


Figure 220-2 Contrast esophagram (static image) performed in a 5-month-old puppy with cricopharyngeal dysphagia. Reader should note the abnormal reflux of liquid barium into the nasopharynx.



220.4.2 Diagnosis

Results of routine hematology, serum biochemistry, urinalysis, and survey thoracic radiographs are usually normal. Segmental or diffuse esophageal dilatation may be seen with severe mucosal inflammation (Figure 220-3). Barium contrast radiography is infrequently performed but may confirm esophageal dilatation, disturbances in motility, and stricture. Esophagitis is an endoscopic diagnosis that does not require mucosal biopsy. A spectrum of mucosal abnormalities may be observed during esophagoscopy including increased erythema, erosions, and alterations in mucosal texture (Figures 220-4 and 220-5). Lesions are usually most evident in the distal esophagus, adjacent to and including the LES. The presence of gastroesophageal reflux with a dilated LES is suggestive of a hiatal disorder.

220.4.3 Treatment

Mild esophagitis frequently resolves with minimal treatment other than dietary management. The clinician should provide frequent, smaller-sized meals of a low-fat, high-protein content to enhance LES tone and to minimize reflux. Animals having more severe esophagitis, especially those with anorexia, weight loss, or the inability to retain food, will require drug therapy and gastrostomy tube feeding. Sulcralfate suspension (0.5 to 1.0 g orally, three times a day) is the most beneficial and specific therapy for reflux esophagitis.[7] It selectively binds to eroded mucosa and provides effective barrier protection against refluxed gastric contents. Metoclopramide should be administered (0.1 to 0.2 mg/lb per os, subcutaneously, three times a day) or cisapride (0.05 to 0.25 mg/lb per os, twice a day) to decrease esophageal reflux (by increasing LES pressure) and to promote gastric emptying. Gastric acid secretory inhibitors (ranitidine 0.5 to 1.0 mg/lb orally or intravenously, twice a day; famotidine 0.25 to 0.5 mg/lb orally, once a day; omeprazole 0.35 mg/lb orally, once a day) should be given to decrease acidity of gastric juice. Broad-spectrum antibiotics are indicated in the occasional animal having concurrent aspiration pneumonia. A water bolus should be routinely administered to cats receiving tablets or capsules per os to prevent medication-associated esophagitis.[5]

Figure 220-3 Contrast esophagram (lateral view) performed with food in a 5-year-old dog. Generalized esophageal dilatation is observed secondary to severe reflux esophagitis. Esophageal function completely normalized after medical therapy for esophagitis.

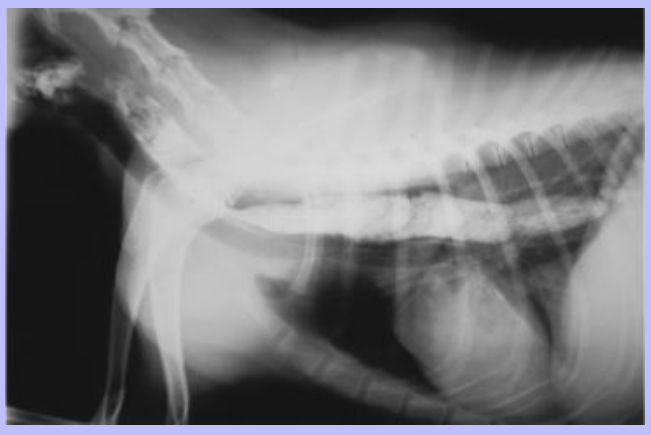
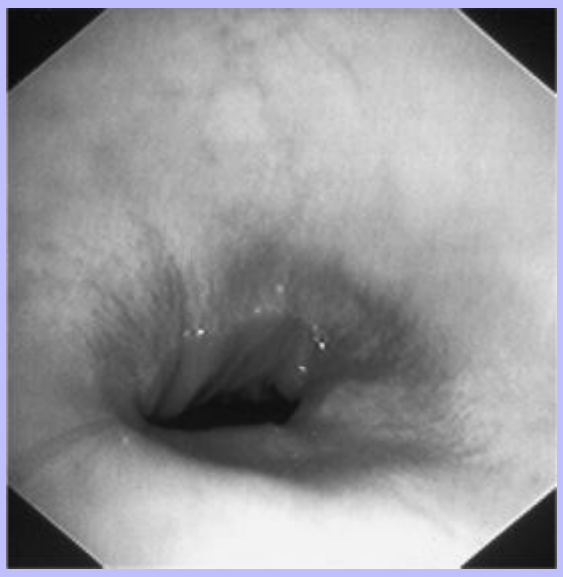


Figure 220-4 Endoscopic appearance of severe esophagitis in the distal canine esophagus. Marked mucosal erythema and dilation of the lower esophageal sphincter (LES) is evident.



The duration of drug therapy is empiric and varies with severity of signs and endoscopic lesions. Mild lesions are treated for 5 to 7 days; moderate-to-severe esophagitis is treated for 2 to 3 weeks. The prognosis in most cases of esophagitis is good with appropriate medical therapy. Animals having severe disease warrant a guarded prognosis because permanent changes in esophageal structure (stricture formation) or function (segmental or generalized hypomotility) may occur.

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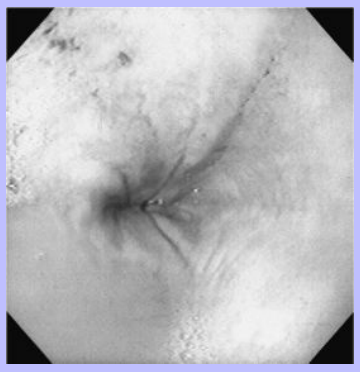
Figure 220-5 Endoscopic appearance of reflux esophagitis in the distal canine esophagus. Pooled liquid reflux and multifocal erosions are seen along the mucosa adjacent to the lower esophageal sphincter (LES).



220.5 ESOPHAGEAL FOREIGN BODIES

The ingestion of foreign bodies is a common cause of esophageal dysphagia in the dog but is less common in cats. Foreign bodies usually lodge at points of minimal esophageal distension including the thoracic inlet, at the base of the heart, or at the diaphragmatic hiatus. The most common objects ingested are bones, fish hooks, needles, sticks, and play toys. Retained foreign bodies cause partial or complete mechanical obstruction. Muscle spasm and tissue edema occur around the foreign body, making passage of the object down the esophagus more difficult. Mucosal abrasion, laceration, and perforation may occur with sharp or angular objects that are lodged intraluminally.

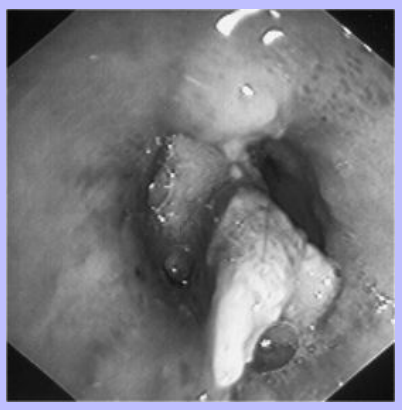
220.5.1 Clinical Signs

The severity of clinical signs is related to the size of the foreign body and duration of esophageal obstruction.[8] Most dogs and cats with large esophageal foreign bodies are presented for evaluation of acute onset of regurgitation, dysphagia, odynophagia, gagging, and excessive salivation. Smaller foreign bodies which are undiagnosed initially may cause identical signs of several days duration.

220.5.2 Diagnosis

Foreign body ingestion may be reported by the owner. Physical examination is variable, ranging from unremarkable to the presence of halitosis seen with tissue necrosis. Cervical esophageal foreign bodies may be palpable. The findings of depression, anorexia, fever, and cough support aspiration pneumonia or esophageal perforation. A hemogram may reveal a leukocytosis with infection. Clinicians should evaluate thoracic radiographs for aspiration pneumonia (alveolar pulmonary opacities) or esophageal perforation (pneumomediastinum, mediastinitis). Contrast radiography is necessary to identify radiolucent objects. A water-soluble positive-contrast agent (iohexol, gastrografin) should be used rather than barium sulfate if esophageal perforation is suspected. Esophagoscopy should be performed to confirm the diagnosis and to assess secondary mucosal damage.

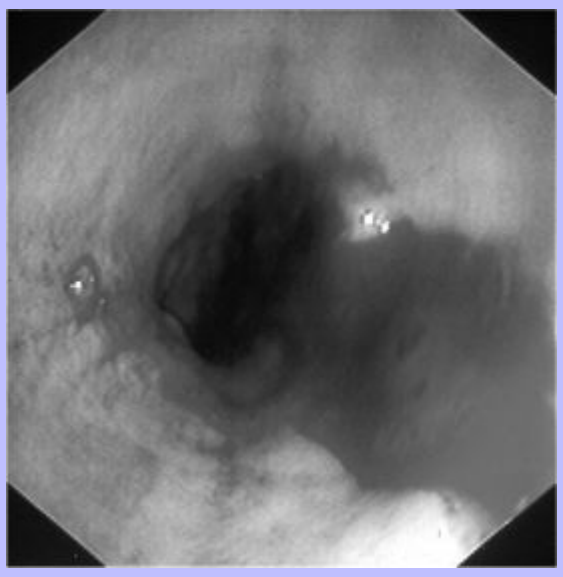
Figure 220-6 Endoscopic appearance of a large angular bone lodged in the thoracic esophagus of a 2-year-old dog. Minor erosive lesions are also present.



220.5.3 Treatment

Esophageal foreign bodies are medical emergencies and should be promptly removed. Endoscopic removal of foreign bodies using a flexible instrument that accommodates a variety of retrieval (grasping) instruments is usually successful. Larger grasping forceps, normally used with rigid endoscopes, may be passed along the side of the flexible endoscope to grasp objects. Distal esophageal foreign bodies may be pushed into the stomach if they cannot be extracted orally. Gastrostomy is not required for most bone foreign bodies, but nondigestible materials retained in the stomach will require surgical removal. The clinician should thoroughly evaluate the esophageal mucosa after foreign body extraction for hemorrhage, lacerations, and perforations (Figures 220-6 and 220-7). Postprocedural thoracic radiographs should be obtained to assess for pneumomediastinum and pneumothorax.

Figure 220-7 Endoscopic appearance of the thoracic esophagus after successful extraction of a bone foreign body (see Figure 220-6). Reader should note the severe trauma and hemorrhage to the esophageal mucosa as a consequence of foreign body retrieval.



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Food or water should be restricted for 24 to 48 hours, depending on the extent of esophageal trauma. Animals with severe mucosal damage will require complete esophageal rest and gastrostomy tube feedings. The clinician should institute medical therapy for esophagitis (see Esophagitis earlier in this chapter). Small esophageal perforations are successfully treated with broad-spectrum antibiotics such as ampicillin (11 mg/lb subcutaneously, intramuscularly, or intravenously, three times a day).[9] Surgery (esophagotomy) is indicated if the foreign body cannot be removed endoscopically.

The prognosis after endoscopic foreign body removal is generally excellent. Significant esophageal trauma or large perforation carries a guarded prognosis. Permanent sequellae may include fistula, diverticulum, or stricture formation, as well as segmental defects in motility.

220.6 ESOPHAGEAL STRICTURE

Esophageal stricture is an abnormal circumferential narrowing of the esophageal lumen that occurs secondary to severe eso-phagitis. After mucosal injury, inflammation extends beyond the mucosa into the muscular layer and heals by fibrosis. Fibrotic changes (maturation with contraction) in the esophageal wall cause luminal narrowing. Strictures may occur at any point along the length of the esophagus. The time period from severe esophagitis to lumenal stenosis is approximately 1 to 3 weeks.[10] The most important causes for stricture are gastro-esophageal reflux (secondary to general anesthesia) and trauma from esophageal foreign bodies.

220.6.1 Clinical Signs

Classical signs for esophageal dysfunction (regurgitation, dysphagia, ptyalism) are observed and tend to be progressive. Animals often are more tolerant of liquid meals rather than solid meals. A ravenous appetite with weight loss is common because of the inability to transport food past the strictured site.

220.6.2 Diagnosis

A diagnosis of stricture is often suggested by clinical history. The physical examination generally reveals no significant abnor-malities other than weight loss. Survey thoracic radiographs are usually normal. Contrast radiography using liquid barium or barium mixed with food demonstrates esophageal lumenal stenosis (Figure 220-8). Contrast studies are useful in assessing the number, location, and length of strictures. Most animals have a single esophageal stricture. Esophagoscopy confirms stricture and permits differentiation of benign from malignant stricture via results obtained from mucosal biopsy and endoscopic exfoliative cytology.

Figure 220-8 Contrast esophagram (lateral view) using liquid barium in a 4-year-old domestic shorthaired (DSH). A 1.5 cm long esophageal stricture is visualized over the base of the heart. Reader should note that the esophagus is dilated cranial to the stricture.

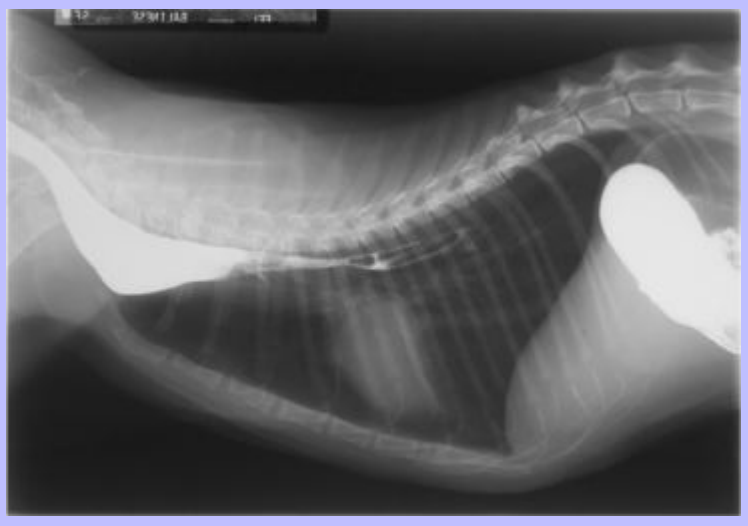
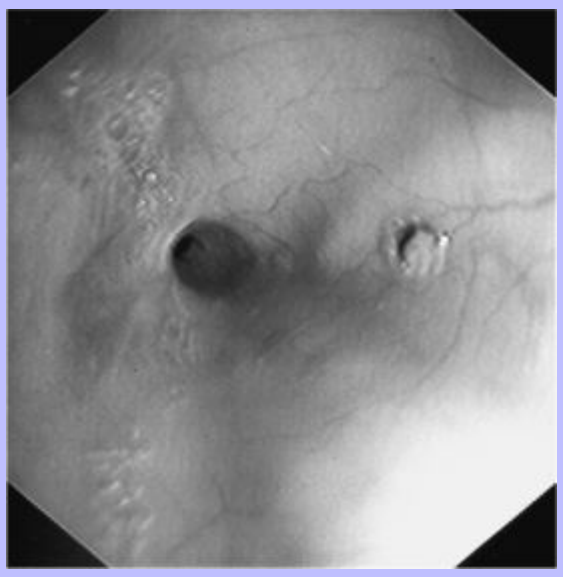


Figure 220-9 Balloon dilatation of an esophageal stricture in a cat using endoscopic guidance (see Figure 220-8). Esophagoscopy demonstrates a 4 mm diameter stricture in the thoracic esophagus.



220.6.3 Treatment

Benign strictures are best treated by mechanical dilatation using a balloon catheter under endoscopic guidance. Balloon catheter dilatation is superior to rigid bougienage because less likelihood of perforation exists, fewer repeated dilatations are required, and a longer clinical response occurs between dilatations.[11] A technique for balloon catheter dilatation in both dogs and cats has been previously described.[11–13] A special polyethylene catheter (Ridgiflex Dilator, Microvasive Inc., Watertown, MA) is carefully advanced adjacent to the endoscope and centered in the lumen of the stricture. The balloon is distended to a desired pressure (not to exceed the maximum pressure recommended by the manufacturer) and held for 2 to 3 minutes. The catheter is then deflated to evaluate lumenal diameter and the extent of iatrogenic trauma. The procedure is immediately repeated using a greater catheter pressure to dilate the stricture further (Figures 220-9 to 220-11). Balloon dilatations are usually performed two to four times (each requiring a separate anesthetic procedures) at intervals of 2 to 3 days because restricture occurs rapidly.[14] Those strictures associated with active esophagitis will require a greater number of dilatation procedures. Complications of balloon dilatation include excessive hemorrhage (common) and esophageal perforation (rare).

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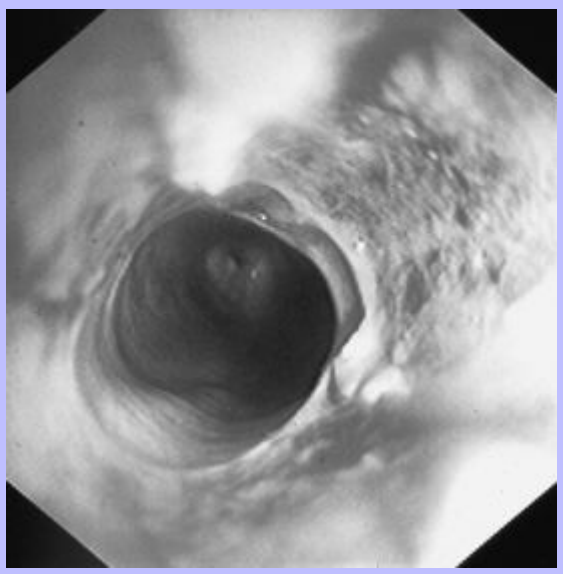
Figure 220-10 Balloon dilatation procedure using maximum balloon inflation pressure.

Figure 220-11 Iatrogenic esophagitis that occurs secondary to aggressive balloon dilatation. Reader should note the significant hemorrhage and fibrous tissue tears at the dilated stricture site.



Medical therapy of esophagitis is required after mechanical dilatation. The clinician should withhold feedings for 24 hours or place a gastrostomy tube for enteral feedings in animals with severe mucosal trauma. To prevent further injury to the esophageal mucosa from gastroesophageal reflux, H_2-blockers, drugs to enhance LES tone, or both should be administered. Animals with severe esophagitis are also treated with an oral sucralfate slurry (0.5 to 1.0 g dissolved into 5 ml water, orally, three times a day). The use of corticosteroids (prednisone 0.5 to 1.0 mg/lb orally, divided twice a day for 10 to 14 days) may prevent healing by fibrosis and stricture recurrence. Dietary management and medical therapy of gastroesophageal reflux should be continued for 10 to 14 days after balloon dilatation.

The prognosis for benign strictures is good with successful dilatation. Surgical resection of benign strictures is less desirable because success rates are less than with balloon dilatation procedures. Furthermore, restricture at the surgical site is a common sequellae. Malignant esophageal strictures carry a poor prognosis and are treated with a combination of surgical resection (if possible), balloon dilatation (if needed), and appropriate postsurgical irradiation, chemotherapy, or both.

220.7 MEGAESOPHAGUS AND ESOPHAGEAL HYPOMOTILITY

Megaesophagus is a disorder characterized by diffuse esophageal dilation and aperistalsis. This syndrome may occur as a congenital idiopathic disorder (uncommon), or it may manifest in adult animals as an idiopathic (common) or acquired lesion. A familial predisposition for congenital megaesophagus has been suggested for the Irish setter, Great Dane, German shepherd, Labrador retriever, Chinese Shar Pei, Newfoundland, miniature schnauzer, and fox terrier breeds.[1,3,6] Congenital megaesophagus in cats is rare, but Siamese cats may be predisposed. The pathogenesis of congenital idiopathic megaesophagus is poorly understood but may involve a defect in vagal afferent innervation of the esophagus.[15,16]

The underlying pathophysiologic mechanism for acquired idiopathic megaesophagus is unknown. Functional responses of the upper and LESs remain intact, and a defect in the afferent neural pathway responsive to esophageal distension is suspected.[17,18] Acquired secondary megaesophagus may result from many disorders, especially diseases causing diffuse neuromuscular dysfunction (Table 220-2). MG accounts for at least 25% of the acquired causes in dogs.[19,20] Dysautonomia is a generalized autonomic neuropathy in which megaesophagus and esophageal hypomotility are consistent findings.[21] This idiopathic disorder is more frequently recognized in cats and is attributed to degenerative lesions involving autonomic ganglia that affect esophageal function. Other causes of segmental or diffuse esophageal hypomotility include foreign bodies, stricture, vascular ring anomalies, and esophagitis. Esophageal dysfunction in Chinese Shar Peis may also result from segmental hypomotility and esophageal redundancy.[22]

220.7.1 Clinical Signs

Regurgitation is the salient clinical sign seen with megaesophagus. Considerable variability exists in the frequency and timing of regurgitation episodes after meal ingestion. Puppies with congenital megaesophagus often begin regurgitating when weaned to solid foods. Weight loss and emaciation occur secondary to malnutrition in animals having long-standing disease. Respiratory distress (moist cough, dyspnea) and fever indicate aspiration pneumonia, which is the most common complication of megaesophagus. Additional clinical signs including muscle pain and stiff gait with polymyositis, generalized weakness with neuromuscular disease, and GI signs with lead toxicity or Addison's disease may be detected in animals having mega-esophagus associated with an acquired disorder.

220.7.2 Diagnosis

The clinician should suspect megaesophagus in any adult animal, particularly dogs, with a history of regurgitation. Survey radiographs of the cervical neck and thorax usually reveal the presence of a dilated air-, fluid-, or ingesta-filled esophagus (Figure 220-12). The presence of pulmonary alveolar opacities are indicative of aspiration pneumonia. Barium contrast radiography (esophagram) confirms dilatation and provides evidence of other structural abnormalities (mechanical obstruction). Esophageal motility is best evaluated with fluoroscopy, which assesses the presence and intensity of esophageal peristalsis. Routine hematology, serum biochemistry, and urinalysis should be performed to screen for acquired causes of mega-esophagus. An acetylcholine receptor antibody titer should be performed to evaluate for acquired MG, even in the absence of generalized muscle weakness, because MG may mimic idiopathic megaesophagus. Additional laboratory tests are performed on the basis of clinical suspicion (see Table 220-2). Esophagoscopy is rarely required for diagnosis of megaesophagus, except when obstructive disease (neoplasia) or reflux esophagitis are suspected. A clinical diagnosis of dysautonomia is made in most cases based on the unique historical (depression, anorexia, constipation, regurgitation) and physical examination (dry mucous membranes, pupillary dilation, prolapsed nictitating membranes, diminished pupillary light response, bradycardia, and areflexic anus) findings.[21]

220.7.3 Treatment

Animals with acquired secondary megaesophagus are treated specifically for the disorder causing abnormal esophageal motor function (see Table 220-2). Treatment of idiopathic megaesophagus and those acquired forms that fail to respond to specific medical therapy is primarily supportive and symptomatic. The clinician should offer small, frequent meals from an elevated or upright position to assist passage of ingesta into the stomach. Food consistency should be varied (gruel versus bulk boluses) to determine which types of food are best tolerated. Animals that are severely malnourished or that have aspiration pneumonia should have a gastrostomy tube placed for enteral nutritional support. Broad-spectrum antibiotics should be given for treatment of aspiration pneumonia. Clients should be counseled that recurrent pneumonia is a common problem necessitating prompt detection and treatment for long-term success.

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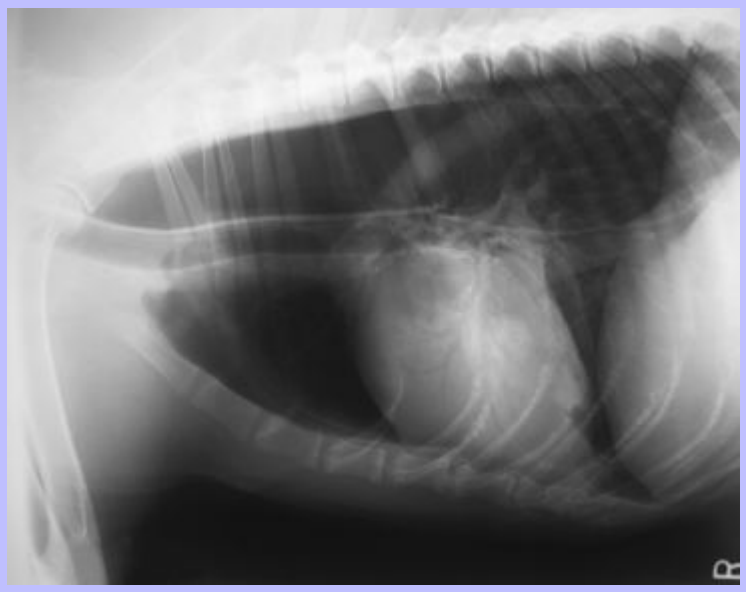
Table • 220-2 Diagnosis and Treatment of Megaesophagus

CAUSE	DIAGNOSTIC TEST	TREATMENT
Neuromuscular Disease		
Idiopathic	Diagnosis of exclusion	Small, frequent elevated feedings
Myasthenia gravis (MG)	Acetylcholine receptor antibody titer, tensilon test, +/−EMG	Pyridostigmine (0.5–1.5 mg/lb PO bid, +/−prednisone (0.5–1.0 mg/lb PO, SC bid)
Systemic lupus erythematosis (SLE)	ANA, skin biopsy	Prednisone (0.5–1.0 mg/lb PO, SC bid)
Polymyositis/polymyopathy	CK, muscle biopsy, EMG	Prednisone (0.5–1.0 mg/lb PO, SC bid)
Glycogen storage disease (type II)	Muscle/liver biopsy, urine metabolic screening	Supportive/symptomatic care
Dermatomyositis	Skin/muscle biopsy	Prednisone (0.5–1.0 mg/lb PO bid)
Dysautonomia	Clinical diagnosis	Supportive/symptomatic care
Distemper	CSF tap, distemper titer	Supportive care
Tetanus	EMG, serum toxin assay	Supportive care
Esophageal Obstruction		
Neoplasia	Contrast radiography, esophagoscopy and biopsy	Surgical resection, chemotherapy
Vascular ring anomaly	Survey/contrast radiography	Surgical correction
Stricture	Contrast radiography, esophagoscopy	Balloon dilatation
Foreign body	Survey/contrast radiography, esophagoscopy	Endoscopic retrieval
Toxicity		
Lead	Hematology, blood lead	Chelation therapy (calcium EDTA)
Organophosphate	Blood cholinesterase activity	Gastric lavage, atropine (0.1 mg/lb SC once) Pralidoxime chloride (5–7.5 mg/lb slow IV)
Miscellaneous		
Hypoad renocorticism	ACTH stimulation test	Prednisone (0.05 mg/lb PO bid), fludrocortisone (0.005 mg/lb PO bid)
Hiatal hernia	Contrast radiography, esophagoscopy	Surgical correction
Gastric dilatation-volvulus	Survey radiography	Surgical correction, supportive care
Esophagitis	Esophagoscopy	Sucralfate (0.5–1.0 g slurry PO tid), ranitidine (0.5–1.0 mg/lb PO ranitidine (0.5–1.0 mg/lb PO bid), metoclopramide (0.2 mg/lb PO tid)
Thymoma	Survey radiography, thymic aspirate	Surgical resection

Adapted from Washabau RJ: Diseases of the esophagus. *In* Ettinger SJ, Feldman ED (eds): *Textbook of Veterinary Internal Medicine,* 5th ed. Philadelphia, WB Saunders Co, 2000, p 1150.

Figure 220-12 Survey thoracic radiograph (lateral view) performed in a 10-year-old dog with idiopathic megaesophagus. A diffusely dilated, air-filled esophagus is readily visualized.



Promotility drugs are currently of unproven benefit in the management of idiopathic megaesophagus in dogs. Both metoclopramide and cisapride are smooth muscle prokinetic agents that have no effect on the striated muscle of the esophageal body.[23] Indeed, preliminary data indicate that cisapride actually decreases the esophageal transit rate of a food bolus in healthy dogs.[24] Cisapride may be a useful prokinetic agent in cats with distal esophageal motility disturbances because of the smooth muscle component in this segment of the feline esophagus.

Affected animals should be re-evaluated at 1-to 2-month intervals to monitor disease progression. Thoracic radiographs should be repeated to assess esophageal dilatation and aspiration pneumonia. Some animals with congenital idiopathic mega-esophagus may improve over time (months) with diligent supportive care. The prognosis with acquired idiopathic mega-esophagus is generally poor. These animals usually succumb to repeated episodes of aspiration pneumonia or are euthanized because of their irreversible disease. Animals with acquired secondary megaesophagus may respond to specific drug therapy. The prognosis in dogs with megaesophagus caused by acquired MG is favorable, with approximately 50% of dogs responding to supportive therapy.[19]

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220.8 VASCULAR RING ANOMALY

Vascular ring anomalies are congenital malformations of the major arteries of the heart that entrap the intrathoracic esophagus and cause esophageal obstruction. Persistent right aortic arch (PRAA) is the best-documented anomaly in both dogs and cats; it occurs when the embryonic right aortic arch (rather than the left fourth aortic arch) becomes the functional adult aorta. Circular entrapment of the esophagus occurs by the

aorta on the right, the ligamentum arteriosum dorsolaterally on the left, the pulmonary trunk on the left, and the heart base ventrally. This anomaly is considered to have a familial tendency because German shepherds and Irish setters appear to be predisposed.[6] Other less common vascular anomalies include persistent right or left subclavian arteries, double aortic arch, persistent right dorsal aorta, left aortic arch and right ligamentum arteriosum, and aberrant intercostal arteries.

220.8.1 Clinical Signs

Affected puppies and kittens usually present for regurgitation of solid foods at the time of weaning. Weight loss with failure to thrive despite a good appetite is commonly observed. The presence of a moist cough, dyspnea, and fever suggest aspiration pneumonia. Physical examination often reveals a thin, stunted animal that is otherwise normal.

220.8.2 Diagnosis

Vascular ring anomalies should be differentiated from other causes of regurgitation in young animals such as congenital idiopathic megaesophagus, esophageal foreign body, and cricopharyngeal dysphagia. The signalment and a compatible history of regurgitation since weaning are very suggestive of a vascular ring anomaly. Survey thoracic radiographs usually demonstrate esophageal body dilation cranial to the base of the heart. Radiographic abnormalities to the caudal esophagus are seldom seen. A barium esophagram should be performed to confirm the location of esophageal obstruction and severity of esophageal distension (Figure 220-13). Fluoroscopy is useful to evaluate for segmental or generalized esophageal motility disturbances. Angiography is occasionally performed for definitive confirmation of the type and location of the vascular anomaly prior to surgery. Esophagoscopy will differentiate intraluminal stricture from extraluminal compression. Strictures appear as distinct intraluminal fibrous rings that remain static when viewed endoscopically; whereas with vascular ring anomaly, rhythmic pulsations of the great arteries compressing the esophagus externally are observed (Figure 220-14).

Figure 220-13 Contrast esophagram (lateral view) performed in a 7-month-old dog with a persistent right aortic arch. Abrupt attenuation of the liquid barium contrast column is observed at the base of the heart along with segmental (cranial) esophageal dilatation.

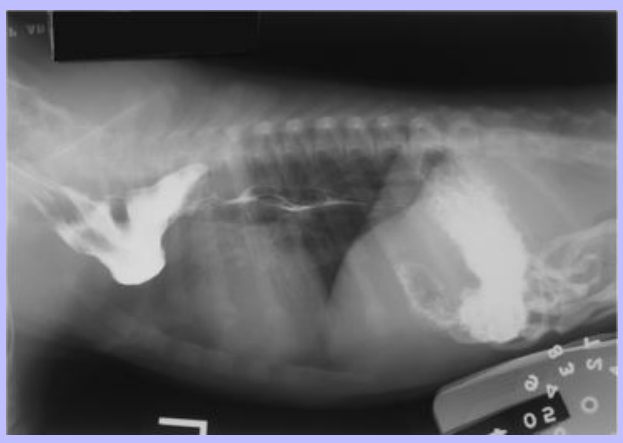
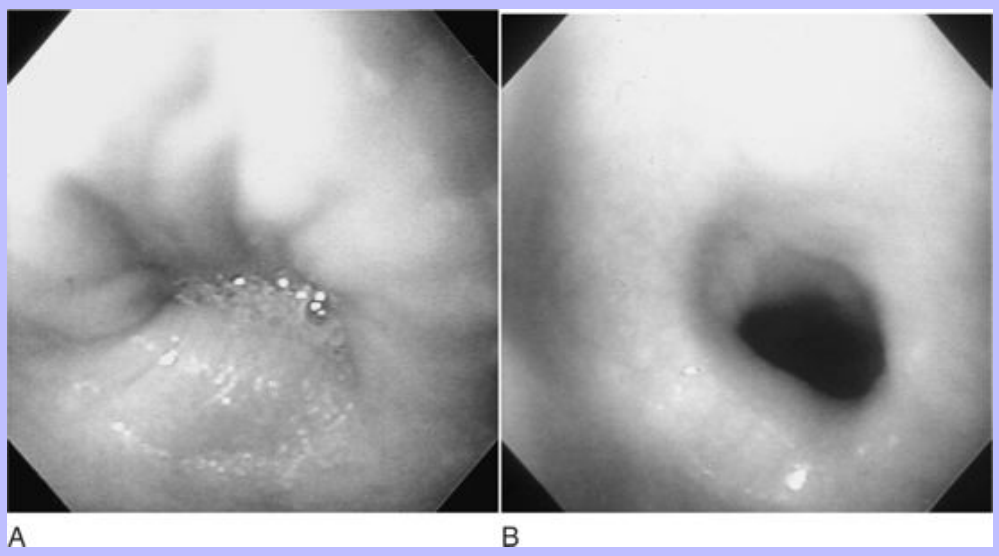


Figure 220-14 Dynamic endoscopic appearance of persistent right aortic arch in a 3-year-old dog (see Figure 220-13). Extraluminal pulsations of blood through the anomalous artery cause the stenosis to intermittently "close" **(A)** and "open" **(B)**.



220.8.3 Treatment

Definitive therapy for PRAA is surgical ligation and transection of the ligamentum arteriosum. Animals with severe debilitation from malnutrition will require enteral nutritional support via gastrostomy tube feedings. Aspiration pneumonia should be effectively treated with broad-spectrum antibiotics before surgery. Significant clinical improvement usually follows corrective surgery, although esophageal hypomotility and regurgitation may persist. In these instances, affected animals are managed with elevated feedings as described for idiopathic megaesophagus.

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The best prognosis for return of normal esophageal function is obtained with early diagnosis and prompt surgical intervention. Progressive esophageal dilatation that causes irreversible myenteric nerve degeneration and esophageal hypomotility may occur if a diagnosis is not made at an early age.

220.9 ESOPHAGEAL DIVERTICULA

Esophageal diverticula are rare pouchlike sacculations of the esophageal wall that may be congenital or acquired. Congenital diverticula are due to developmental abnormalities of the esophagus that permit herniation of the mucosa through the muscularis. Acquired diverticula are classified as either *pulsion* or *traction* forms. Pulsion diverticula result from conditions of increased intraluminal pressure secondary to obstruction (stricture or foreign body) or altered motility.[25,26] Traction diverticula result from periesophageal inflammation and fibrosis. With the traction form, contraction of fibrotic adhesions leads to eversion and out-pouching of the esophageal wall. The

accumulation of ingesta (impaction) within diverticula leads to esophagitis, mechanical obstruction (seen with large diverticula), and disturbed esophageal motility.

220.9.1 Clinical Signs

Large multilobulated diverticula are most likely to cause signs of regurgitation, odynophagia, and retching. Postprandial regurgitation results from mechanical obstruction and motility disturbances. Severe cases with mucosal ulceration may eventually perforate and cause signs of mediastinitis and respiratory distress. Clinical signs may not occur with small diverticula.

220.9.2 Diagnosis

Survey thoracic radiographs may reveal an air or soft-tissue opacity adjacent to the esophagus. Diverticula should not be confused with the normal esophageal redundancy seen in young brachycephalic breeds and Chinese Shar Peis. Performance of contrast radiography shows a focally dilated segment of the esophagus that fills partially or completely with contrast material. Esophagoscopy confirms a saclike out-pouching of the esophageal lumen containing impacted ingesta and having localized esophagitis.

220.9.3 Treatment

Diverticulectomy is the preferred therapy. Large diverticula will require greater excision and reconstruction of the esophageal wall. Small diverticula may be managed medically with smaller-sized, upright feedings of a liquid or semiliquid diet to minimize impaction of ingesta in the diverticulum. Traction diverticuli are often managed with broad-spectrum antibiotics, whereas pulsion diverticula are treated for their specific cause (see Esophagitis, Stricture, earlier in this chapter). Most cases warrant a guarded prognosis because complications, such as stricture formation and segmental hypomotility, may persist after surgery.

220.10 ESOPHAGEAL FISTULA

An esophageal fistula is an abnormal communicating tract between the esophagus and usually the respiratory system (esophagopulmonary, esophagotracheal, and esophago-bronchial fistula). Both congenital and acquired fistulas have been described. Acquired fistulas are usually associated with retained esophageal foreign bodies, especially bones. Other causes include trauma, neoplasia, or periesophageal inflammation. In most cases, the lodged foreign body causes mural necrosis, esophageal perforation, and leakage of esophageal contents into adjacent tissues. Healing leads to development of a communicating tract with resultant airway contamination from esophageal contents. Esophageal fistula is relatively uncommon in the dog and cat.

220.10.1 Clinical Signs

Clinical signs are primarily associated with respiratory tract and include coughing and dyspnea. Coughing after drinking is a common presenting sign. Dysphagia and regurgitation are less commonly observed in association with an esophageal foreign body. Anorexia, lethargy, weight loss, and fever are seen with mediastinitis or aspiration pneumonia. The physical examination findings of cough, fever, pulmonary crackles, and weight loss reflect chronic respiratory disease.

220.10.2 Diagnosis

Survey thoracic radiographs usually reveal a localized alveolar, bronchial, or interstitial lung pattern (or a combination of these patterns). The right caudal lung lobe in dogs and the left caudal and accessory lobes in cats are most commonly affected.[27] Radiopaque foreign bodies may be observed in the esophagus. A barium esophagram is required for definitive diagnosis of esophageal-airway communication. Clinicians should avoid using iodinated contrast agents in these procedures because they are hyperosmolar and potentially irritating to exposed tissues. Endoscopic examination (esophagoscopy, bronchoscopy) is of limited value in confirming small fistulas. A CBC may reflect associated inflammation (periesophagitis, pneumonia) and nonregenerative anemia.

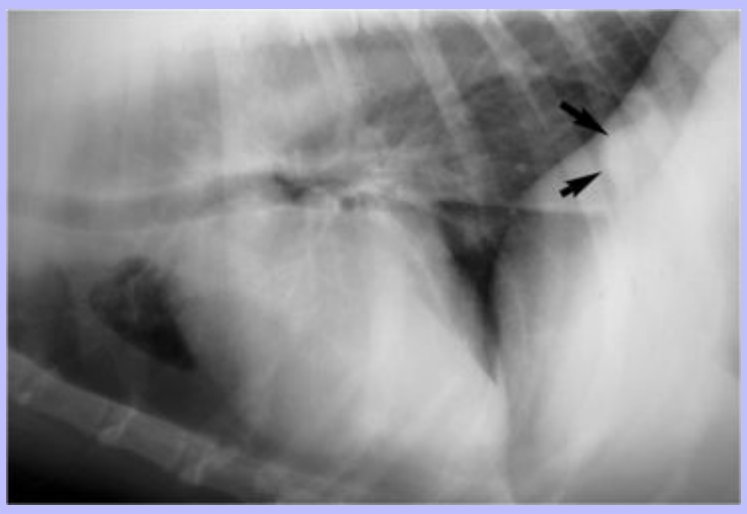
220.10.3 Treatment

Surgical correction of the fistulous tract is required. Esophagotomy for a retained esophageal foreign body should be performed. Lobectomy may be necessary as a result of pulmonary consolidation or foreign material contained within the airways. Postsurgical therapy includes esophageal rest and administration of appropriate antibiotics for infection (based on culture and susceptibility testing of involved tissues). A good prognosis is given to animals after successful surgery. The prognosis is guarded if severe complications, such as dehiscence, stricture, or pulmonary abscessation, are present.

220.11 ESOPHAGEAL NEOPLASIA

Tumors of the esophagus are rare, accounting for less than 0.5% of all cancers in the dog and cat.[28] Neoplasms may be of primary esophageal, periesophageal, or metastatic origin. Esophageal fibrosarcoma and osteosarcoma are the most common malignant tumors in dogs, developing from malignant transformation of esophageal granulomas associated with *Spiracerca lupi* infection.[29] Squamous cell carcinoma is the most commonly diagnosed primary esophageal tumor in cats. Other less commonly reported primary esophageal tumors in the dog and cat include leiomyo(sarco)ma and undifferentiated carcinoma. Periesophageal tumors arising from a variety of adjacent structures (lymph nodes, thyroid, thymus, and heart base) cause local esophageal invasion, direct mechanical obstruction, or both. Metastatic lesions (thyroid, pulmonary, and gastric carcinomas) commonly involve the esophagus but less frequently cause clinical signs of esophageal disease.

Figure 220-15 Survey thoracic radiograph (lateral view) showing generalized esophageal dilatation (megaesophagus) in a 9-year-old rottweiler. A distinct soft-tissue opacity (*arrows*) is visualized in the distal esophagus at the level of the lower esophageal sphincter (LES).

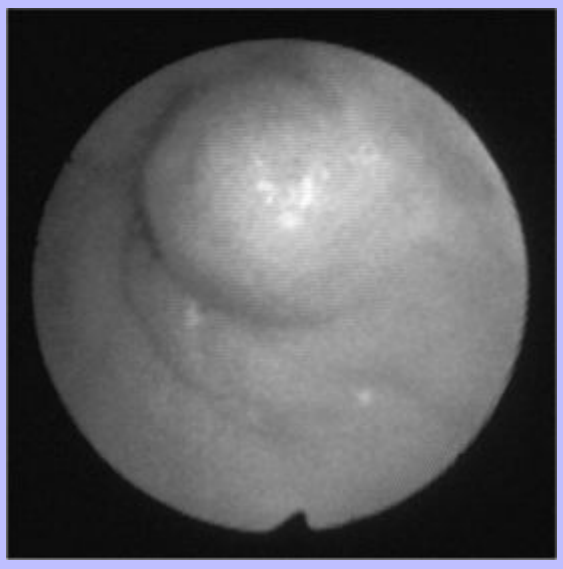


220.11.1 Clinical Signs

Animals with esophageal neoplasia have signs consistent with progressive esophageal obstruction, including chronic regurgitation, dysphagia, odynophagia, and ptyalism. Anorexia, weight loss, and depression are more typical of advanced disease (metastasis, systemic effects of cancer) and malnutrition resulting from the inability to retain food. The physical examination findings may reveal weight loss and emaciation, and large periesophageal masses involving the cervical esophagus might be palpable.

Figure 220-16 Contrast esophagram (ventrodorsal view) in a 10-year-old cat. Cervical esophageal dilation with narrowing of the barium contrast column caused by partial esophageal obstruction is observed. Reader should note the lateral displacement of the air-filled trachea suggestive of a periesophageal mass.

Figure 220-17 Endoscopic appearance of an esophageal mass located adjacent to the lower esophageal sphincter (LES) in a dog (see Figure 220-15). Histopathology proved the mass to be a leiomyosarcoma.



220.11.2 Diagnosis

Clinicians should consider a diagnosis of esophageal neoplasia in middle-aged and older animals having chronic progressive signs of obstructive esophageal disease. Survey thoracic radiographs may be normal or reveal variable esophageal dilatation, an intraluminal mass, or evidence of a periesophageal lesion displacing the esophagus (Figures 220-15 and 220-16). The lungs should be evaluated for aspiration pneumonia (alveolar opacities) and metastasis (nodular opacities). A barium esophagram typically confirms the presence of an intraluminal mass or obstructive lesion. Esophagoscopy with mucosal biopsy and exfoliative cytology is required for definitive diagnosis of esophageal neoplasia (Figures 220-17 and 220-18). Endoscopic biopsy of the esophagus is difficult because the mucosa is tough and it is technically demanding to position the biopsy instrument (forceps) perpendicular to the mucosa. Biopsies with small pinch forceps often provide nonrepresentative superficial epithelial specimens. Both mucosal biopsy and exfoliative cytology are most beneficial in the diagnosis of epithelial-based neoplasms, such as squamous cell carcinoma and lymphosarcoma.

Figure 220-18 Endoscopic appearance of an invasive periesophageal mass in a cat causing near complete esophageal obstruction (see Figure 220-16). Endoscopic exfoliative cytology confirmed a diagnosis of lymphoblastic lymphosarcoma (see Figure 220-20).

220.11.3 Treatment

Successful treatment of malignant esophageal neoplasia is uncommon because the disease is often well advanced at the time of diagnosis. This is especially true for animals having secondary complications such as severe malnutrition, esophageal hypomotility, and aspiration pneumonia. Chemotherapy, radiation therapy, and surgery are palliative techniques for treatment of malignant tumors. In contrast, benign esophageal neoplasms (leiomyoma) carry a good prognosis with complete surgical resection.[30] Lymphosarcoma (typically diagnosed as a periesophageal mass) is generally responsive to multiple drug chemotherapy regimens.

220.12 HIATAL HERNIA

Hiatal hernia may present at two distinct entities in the dog and cat: (1) sliding hiatal hernia, which is a cranial displacement of the distal esophagus and stomach into the mediastinum through the esophageal hiatus, and (2) periesophageal hiatal hernia, which involves cranial displacement of a portion of the stomach into the mediastinum through a defect adjacent to the esophageal hiatus.[31,32] Sliding hiatal hernia is the most common form and may occur as a congenital or acquired lesion in the dog and cat.

Most hiatal hernias are probably congenital and occur as developmental defects (enlargement) of the esophageal hiatus or phrenicoesophageal ligament. Males and Chinese Shar Pei dogs appear to have an increased incidence and develop clinical signs shortly after weaning.[6] Acquired hiatal hernias occasionally occur secondary to trauma (via damage to diaphragmatic nerves and muscles resulting in hiatal laxity) and respiratory distress (caused by

increased negative intrathoracic pressure seen with intermittent airway obstruction [laryngeal paralysis]). Regardless of the cause, hiatal herniation reduces LES pressure and leads to gastroesophageal reflux, esophagitis, and segmental or diffuse esophageal hypomotility.

220.12.1 Clinical Signs

Intermittent signs of reflux esophagitis (persistent regurgitation, vomiting, occasional hematemesis and hypersalivation) predominate. Weight loss may be observed in animals having chronic disease. Dyspnea is common due to aspiration pneumonia and compression of the lungs seen with large hernias. Affected animals may be thin on physical examination.

220.12.2 Diagnosis

Survey thoracic radiographs often reveal the presence of a caudodorsal, gas-filled, soft-tissue opacity. Varying degrees of esophageal dilatation and alveolar opacities (consistent with aspiration pneumonia) may also be observed. Performance of a positive contrast esophagram confirms hiatal herniation and the presence of esophageal dilatation. Fluoroscopy is useful in evaluation of the magnitude of esophageal hypomotility present. Esophagoscopy, generally not a first-choice diagnostic test, may confirm reflux esophagitis and cranial displacement of both the LES and rugal folds of the stomach into the esophageal lumen.

220.12.3 Treatment

Reconstructive surgery is indicated for treatment of large congenital hiatal hernias. Normal hiatal anatomy is restored by performance of diaphragmatic crural apposition, esophagopexy, and left fundic tube gastropexy techniques.[31,33] Animals having smaller, intermittent hiatal hernias should be medically managed for reflux esophagitis, using H_2 receptor antagonists (to reduce gastric acidity), sucralfate suspensions (as a mucosal cytoprotectant), and drugs (cisapride or metoclopramide) to enhance LES tone, which inhibits gastroesophageal reflux. Animals failing medical management will require surgical intervention.

A good prognosis is warranted in animals after successful surgery. A guarded prognosis is given to animals with concurrent esophageal motility disturbances.

220.13 MISCELLANEOUS ESOPHAGEAL DISORDERS

Major causes for *esophageal perforation* include esophageal foreign bodies (large or angular-shaped bones and those objects retained for a prolonged period causing pressure necrosis) and penetrating trauma to the cervical esophagus caused by bite wounds (Figure 220-19). Predominant signs of anorexia, depression, odynophagia, moist cough, fever, and a rigid stance are observed. A diagnosis is often suspected based on history and survey radiographic findings that show a pneumomediastinum, pneumothorax, and mediastinal or pleural effusion. A contrast esophagram using a water-soluble contrast agent (Omnipaque) should be performed to determine the location and extent of the esophageal tear. Esophagoscopy may detect large tears but is an insensitive tool for localizing small tears. Treatment is generally conservative, using broad-spectrum antibiotics, fluid therapy, and nutritional support by tube gastrostomy feedings. Clinicians should monitor therapeutic responses by repeating thoracic radiographs. Large perforations will require surgical correction.

Periesophageal obstruction is uncommonly associated with intrathoracic mass lesions (neoplasia, lymphadenopathy, large abscess) that cause partial extraluminal compression. Clinical signs usually indicate

slowly progressive esophageal dysphagia, often accompanied by extra-esophageal signs of dyspnea, cough, and exercise intolerance. Survey thoracic radiographs usually identify an intrathoracic mass with esophageal encroachment. A contrast esophagram may or may not determine whether intraluminal versus extraluminal compression is present. Esophagoscopy is more useful in characterizing whether or not the stenosis is extraluminal, and whether potential mucosal invasion has occurred. Definitive diagnosis depends on identification of the mass lesion with fine needle aspiration, endoscopic exfoliative cytology (Figure 220-20), or biopsy via thoracotomy.

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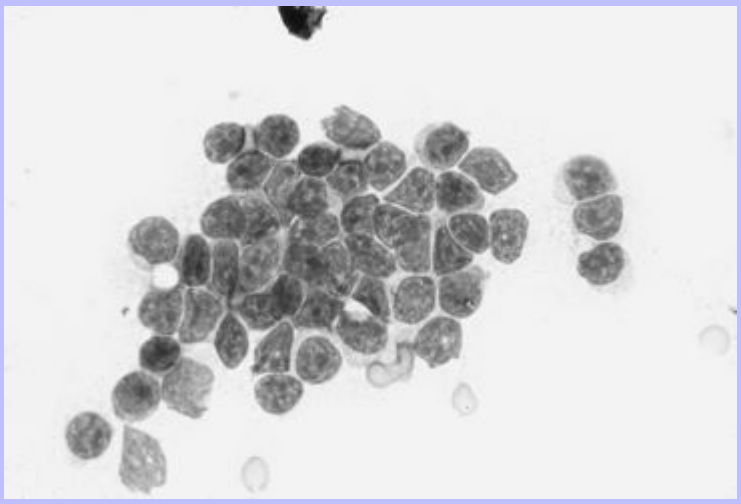
Figure 220-19 Endoscopic appearance of cervical esophageal perforation in a dog caused by penetrating bite wounds to the neck. The dog responded completely to conservative medical management.

GI intussusception is a rare disorder of young dogs caused by invagination of the stomach, and occasionally other structures such as the spleen, proximal duodenum, and pancreas, into the esophagus.[34] Prolapse of a large portion of the stomach causes abrupt clinical deterioration with mortality rates in excess of 95% reported.[35] The cause for GI intussusception is unknown; however, congenital megaesophagus possibly predisposes to this disorder due to decreased esophageal motility and reduced LES tone. Animals with GI intussusception usually have histories of acute vomiting, regurgitation, dyspnea, hematemesis, and abdominal discomfort. Survey abdominal radiographs confirm the presence of a soft tissue and gas opacity in the dorsocaudal mediastinum. A contrast esophagram usually shows gastric rugae within the esophageal lumen and the presence of esophageal obstruction. Esophagoscopy may also confirm a bulging mass (gastric rugal folds) contained within the lumen of the esophagus. Treatment of large intussusceptions necessitates manual reduction and gastropexy to prevent recurrence. Small lesions may be carefully reduced endoscopically and subsequently managed medically for reflux esophagitis.

Figure 220-20 Endoscopic exfoliative cytology obtained from a cat with an invasive periesophageal mass (see Figure 220-18). A uniform population of lymphoblasts, consistent with lymphosarcoma, is present. Multidrug chemotherapy resulted in complete clinical remission for 9 months.



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221 CHAPTER • 221 Diseases of the Stomach

Kenneth W. Simpson*

221.1 FUNCTIONAL ANATOMY

The stomach's main function is to act as a reservoir that controls the size and rate of passage of ingesta into the small intestine. The stomach also initiates the digestion of protein and fat and facilitates the absorption of vitamins and minerals.

Anatomically the stomach is composed of four regions, the cardia, fundus, body, and antrum (Figure 221-1). The fundus and body expand to accommodate ingesta. The antrum is thick and muscular and grinds food into small particles that are triturated into the duodenum. The lower esophageal sphincter prevents reflux of ingesta into the esophagus and the pyloric sphincter controls efflux into the duodenum.

The gastric wall has three layers: the mucosa, muscularis, and serosa. The mucosa has a superficial epithelium, gastric glands, and an innermost layer of smooth muscle, with fine structure and function varying depending on the gastric region (Figure 221-2). The mucosa in the cardia and pylorus is thinner and less glandular than in the fundus and body. The mucosa of the body contains mucous neck cells (pepsinogen A, gastric lipase), parietal cells (acid, pepsinogen A, intrinsic factor), and chief cells (pepsinogen A).[1–3] A variety of neuro-endocrine cells involved with the secretion of gastric acid are interspersed between the glands. The predominant cells are enterochromaffin-like and somatostatin-producing cells in the fundus, and gastrin and somatostatin-producing cells in the antrum. Localized small aggregates of lymphoid tissues are observed at the base of the gastric glands. Intertwined between gastric glands is a rich network of blood vessels and lymphatics and nerves. Beneath the submucosa are two layers of smooth muscle that run perpendicuar to each other. The serosa is the outermost layer.

221.1.1 Regulation of Acid Secretion

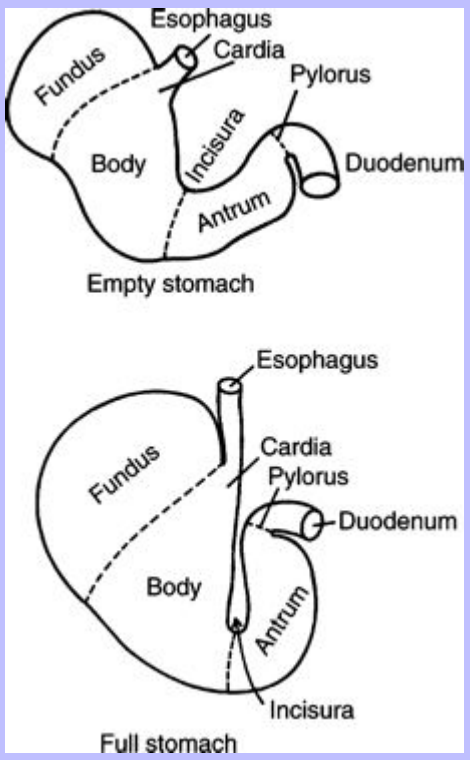
Acid secretion is regulated by a variety of neurochemical and neurohumeral stimuli.[4,5] Luminal peptides, digested protein, acetylcholine, and gastrin-releasing peptide (GRP) stimulate gastrin secretion from G cells and effect histamine release from enterochromaffin-like cells (ECL cells) (Figure 221-3).

Histamine release from mast cells and binding of acetylcholine and gastrin to parietal cells also contribute to secretion. Somatostatin released in response to gastric pH levels below 3 decreases gastrin, histamine, and acid secretion.

Unstimulated acid secretion in dogs and cats is minimal (dogs <0.04 mmol/kg.75/hr)[6] and H^+/K^+-ATPase, "the acid pump," is present in tubulovesicles within the cytoplasm of parietal cells.[7] In the stimulated state H^+/K^+-ATPase and KCl transporters are incorporated into the parietal cell canalicular membrane and hydrogen ions, derived from the ionization of water within the perietal cells, are transported into the gastric lumen in exchange for K^+ by H^+/K^+-ATPase. Potassium and chloride transporters in the canalicular membrane enable luminal transfer of potassium and chloride. OH^- combines with CO_2, catalyzed by carbonic anhydrase, to form HCO_3^-, which diffuses into the blood (the "alkaline tide"). Stimulation results in a rapid

increase in fluid and hydrogen ion secretion, with pH rapidly declining to around pH 1. The concentrations of K^+ (10 to 20 mmol/L) and Cl^- (approximately 120 to 160 mmol/L) in gastric juice are higher than in plasma.

Figure 221-1 Gastric anatomy of the empty and full stomach. (From Guilford, Strombeck, 1996, p 239, Saunders.)



The stomach is protected from gastric acid by a functional unit known as the *gastric mucosal barrier* (GMB).[8–10] The GMB comprises tightly opposed epithelial cells coated with a layer of bicarbonate rich mucus and an abundant mucosal blood supply that delivers bicarbonate, oxygen, and nutrients. Local production of prostaglandins (PGE_2) is important in modulating blood flow, bicarbonate secretion, and epithelial cell renewal. When damage occurs, epithelial cells rapidly migrate over superficial mucosal defects aided by the local production of growth factors such as EGF (epidermal growth factor).

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221.1.2 Gastric Motility

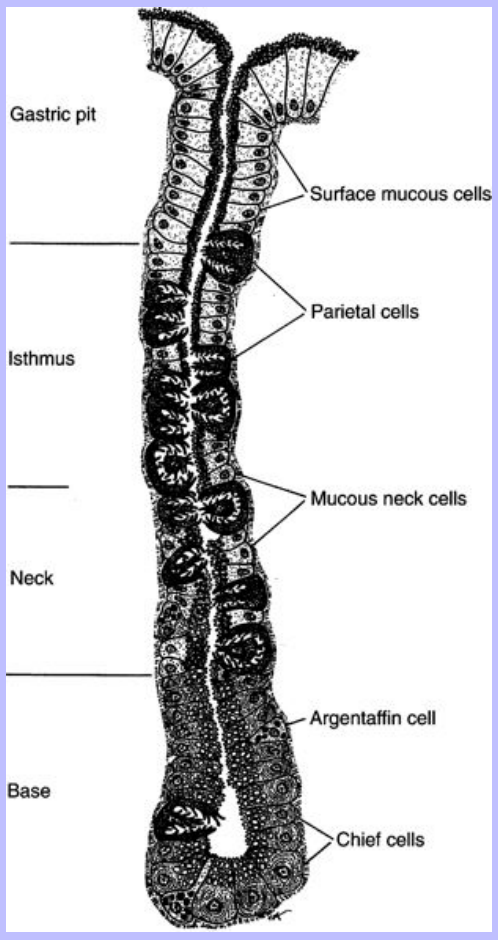
Normal gastric motility is the result of the organized interaction of smooth muscle with neural and hormonal stimuli. The rate of gastric emptying is determined by the difference in pressure between the stomach and the duodenum and the resistance to flow across the pylorus. Liquids are expelled more rapidly than solids and the rate of expulsion of liquids increases with volume. The rate of expulsion of solids depends on caloric density. In dogs, digestible solids smaller than 2 mm are emptied into the duodenum and gastric emptying is modulated via intestinal osmo-and chemoreceptors. Carbohydrates, amino acids, and especially fats retard gastric

emptying. The release of cholecystokinin (CCK) in response to fatty and amino acids, such as tryptophan, is one factor that slows gastric emptying. Large, undigestible solids are expelled from the stomach in the fasted state by phase III of the migrating motility complex (MMC) in response to the release of motilin.

221.1.3 Digestion and Assimilation of Nutrients

The stomach has a limited role in the digestion of proteins, fats, and micronutrients. Pepsin, which digests proteins, is secreted as pepsinogen in response to acetylcholine and histamine in tandem with gastric acid. Dog gastric lipase, which digests fat, is secreted in response to pentagastrin, histamine, prostaglandin E_2, and secretin and parallels the secretion of gastric mucus. Although pepsin is active only at acid pH, dog gastric lipase remains active in the small intestine and constitutes up to 30% of total lipase secreted over a 3-hour period.[11] Although gastric lipase and pepsin are not essential for the assimilation of dietary fat and protein, the entry of peptides and fatty acids into the small intestine likely helps to coordinate gastric emptying and pancreatic secretion.

Figure 221-2 Histologic appearance of the cardiac, fundic, pyloric gastric mucosa.



Intrinsic factor, which is necessary for cobalamin (vitamin B_{12}) absorption, is produced by parietal cells and cells at the base of antral glands in the dog but not the cat.[1,12] The importance of gastric intrinsic factor secretion in dogs is questionable as the pancreas is the major site of secretion in both dogs and cats. Gastric acidity may also have an effect on the availability of minerals such as iron and calcium.

221.1.4 Gastric Flora

The concept of the stomach as a sterile place was completely dispelled by the isolation of the gastric bacterium *Helicobacter pylori* from people in 1983.[13] The stomach of dogs and cats also harbors a diverse spectrum of large, spiral, acid-tolerant *Helicobacter* species and a variety of aerobes and anaerobes that may play a role in the development of gastritis or possibly cancer (see chronic gastritis). A mixed flora of aerobes and anaerobes (approximately 10^6 to 10^7cfu/mL is rapidly established soon after birth in dogs,[14] and colonization with *Helicobacter* spp., which are likely acquired from the dam, has been documented as early as 6 weeks of age. *Helicobacter* spp. are adapted to life in an acid environment and produce urease that catalyzes the formation of ammonia from urea to buffer gastric acidity. Other bacterial species, such as *Proteus*, *Streptococcus,* and *Lactobacillus,* cultured from the canine stomach, may transiently increase after a meal or coprophagia. Acid secretion and gastric emptying likely regulate much of this transient flora and bacteria may proliferate in the event of gastric acid hyposecretion due to glandular atrophy or pharmacologic inhibition. From a diagnostic standpoint it is important to realize that bacteria such as *E. coli* and *Proteus* spp. produce urease that can lead to a false-positive test result for *Helicobacter* spp.

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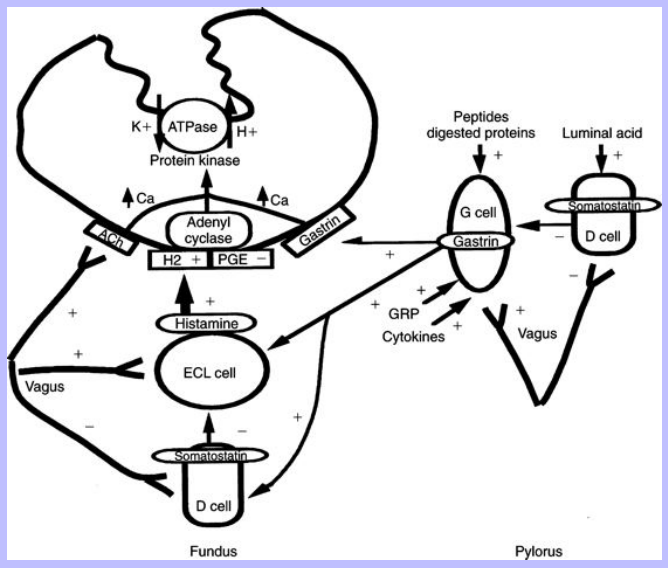
Figure 221-3 Regulation of acid secretion. *ECL,* Enterochromaffin like cell; *GRP*, gastrin releasing peptide; *H_2,* histamine H_2 receptor; *PGE,* prostaglandin E_2 receptor; *ACh,* acetylchline receptor. (From Simpson KW: In Dibartola, editor: *Fluid therapy in small animal practice*, ed 2, Philadelphia, Saunders, 1996.)



221.2 DISEASES OF THE STOMACH

Gastric disease is usually the result of inflammation, ulceration, neoplasia, or obstruction and manifests clinically as vomiting, hematemesis, melena, retching, burping, hypersalivation, abdominal distension, abdominal pain, or weight loss. The clinical approach is simplified by considering gastric diseases as a group of clinical syndromes based on the combination of etiology, pathology, and clinical presentation (Table 221-1).

Because a large and varied group of non-gastric disorders can cause similar clinical signs, a systematic approach is essential to determine if gastric disease is the cause. The diagnostic approach initially focuses on historical and physical findings, with clinicopathologic testing and diagnostic imaging employed in patients with systemic involvement or chronic signs.

221.2.1 Signalment, History, and Physical Examination

The age and breed of the patient are helpful in diagnosis of certain gastric disorders. Young dogs are more likely to ingest foreign bodies or to suffer from outflow obstruction caused by *Pythium insidiosum*, whereas gastric cancer is typically encountered in much older dogs and cats. Gastric dilatation and volvulus are typically encountered in giant breed or dogs with deep chests such as Great Danes and Irish Setters. There are also breed predispositions to hypertrophic gastropathy (Drentse patrijshond, basenji, and small breed brachycephalic dogs, such as shih tzu), atrophic gastritis (Lundehund) and gastric cancer (Belgian shepherd, rough Collie, Staffordshire bull terrier, beagle, Lundehund).

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Table • 221-1 Diseases of the Stomach

CLINICAL SYNDROME	PREDOMINANT FEATURES
Acute gastritis	Vomiting of sudden onset
Ulceration or erosion	Vomiting, hematemesis, melena, ± anemia
Gastric dilatation/volvulus	Non-productive retching, abdominal distention, tachycardia
Chronic gastritis	Chronic vomiting of food or bile
Delayed gastric emptying	Acute to chronic vomiting more than 8 to 10 hr after feeding
Neoplasia	Chronic vomiting, weight loss, ± anemia

Vomiting is the principal clinical sign of gastric disease (see Table 221-1), and a major objective of the history is to distinguish vomiting from regurgitation (active abdominal effort, presence of bile), and to obtain a clear picture of the vomiting episodes (duration, frequency, contents, color, progression, relation to eating). Where vomiting cannot be adequately distinguished from regurgitation it is important to observe “vomiting episodes” and the animal eating. Where regurgitation is still a possibility, thoracic radiographs help to detect esophageal dilatation or obstruction.

A thorough review of the environment (indoor, outdoor, single or multi-animal household), access to foreign bodies, toxins or medications, vaccination status, body systems (attitude, mentation, presence of polyuria, polydipsia, weight loss, diarrhea, coughing, sneezing, exercise tolerance), past medical history, and physical examination helps to discriminate many non-gastric from gastric causes of vomiting.

Physical examination is frequently normal in patients with primary gastric disease. Abdominal distension may be detected in those with GD/GDV or delayed gastric emptying. Abnormal perfusion, hydration status,

temperature, respiratory rate, mucosal pallor, and abdominal pain often accompany diseases such as GD/GDV, gastric outflow obstruction, ulceration, and perforation.

Historical and physical findings are integrated to determine if the patient is systemically well or unwell, and clinical signs are acute (lasting less than 10 days), chronic, mild, or severe (Figure 221-4). Non-productive vomiting, retching, and abdominal distension in deep-chested large breed dogs are frequently associated with gastric dilatation/gastric dilatation and volvulus (GDV), which requires rapid diagnosis and treatment.

The presence of fresh or digested blood ("coffee grounds"), in vomitus, with or without melena raises the possibility of gastric ulcers or erosions.

Vomiting of food greater than 8 to 10 hours after ingestion suggests delayed gastric emptying and requires investigation to distinguish gastric outflow obstruction from defective gastric propulsion.

Weight loss is infrequently associated with gastric disease but can accompany cancer, fungal infections, outflow obstruction, and gastropathies that are part of a more generalized disease process, such as basenji and Lundehund gastroenteropathy.

If vomiting is acute and the animal is systemically well, with no historical or physical "red flags," further diagnostic testing is often postponed in favor of symptomatic therapy. If the animal is systemically unwell or has significant historical or physical abnormalities the emphasis is on efficiently identifying conditions that require surgical intervention, such as gastric dilatation and septic peritonitis, and ruling out non-gastrointestinal causes of vomiting, before proceeding to more specialized or invasive diagnostic procedures aimed at detecting primary gastric and intestinal disorders (see Figure 221-4).

221.2.2 Clinicopathologic Testing

Clinicopathologic testing helps to differentiate primary gastro-intestinal disease form non-GI disease, and to ascertain the metabolic consequences of GI disease. Blood and urine samples should be obtained prior to treatment.

In sick patients, the rapid evaluation of microhematocrit (PCV), total solids (TS), blood glucose, blood urea nitrogen, urine specific gravity, glucose, ketones and protein, and plasma concentrations of sodium and potassium help to detect life threatening diseases such as renal failure (azotemia and unconcentrated urine) and hypoadrenocorticism (Na:K <27:1), and guide initial management pending more definitive testing.

Abnormalities in *complete blood count* are infrequent with primary gastric disease. Hemoconcentration as a consequence of dehydration or shock frequently accompanies GDV, gastric perforation, or gastric obstruction. The combination of a hematocrit level greater than 55% and normal or decreased protein concentrations is encountered in dogs with hemorrhagic gastroenteritis (see Chapter 222). Anemia, erythrocyte microcytosis, and thrombocytosis may be present in dogs with chronic gastric bleeding. Stomatocytosis has been described in Drentse patrijshond dogs with familial stomatocytosis-hypertrophic gastritis. Basophilic stippling of red cells suggests lead toxicity.

Biochemical abnormalities in primary gastric disease are usually restricted to alterations in electrolytes and acid-base, pre-renal increases in creatinine and BUN, and occasionally hypoproteinemia.

Vomiting of gastric and intestinal contents usually involves the loss of chloride, potassium, sodium and bicarbonate containing fluid and dehydration is variably accompanied by hypochloremia, hypokalemia, and

hyponatremia.[15,16] Determination of *acid-base status* by measurement of total CO_2 or venous blood gas analysis enables the presence of metabolic acidosis or alkalosis to be detected.

Metabolic acidosis is generally more common than metabolic alkalosis in dogs with GI disease.[15] Where the gastric outflow tract or proximal duodenum is obstructed, the loss of chloride may exceed that of bicarbonate, and hypochloremia, hypokalemia, and metabolic alkalosis occur.[15–17] The metabolic alkalosis is enhanced by elevated HCO_3^- conservation due to volume, and potassium and chloride depletion.[18] The net effect is a preferential conservation of volume at the expense of the extracellular pH. The renal reabsorption of almost all filtered bicarbonate and the exchange of sodium for hydrogen in the distal tubule promote an acid urine pH despite an extracellular alkalemia ("paradoxical aciduria").[18,19]

Metabolic alkalosis in patients with gastrointestinal signs is not invariably associated with outflow obstruction and has been encountered in dogs with parvovirus enteritis and acute pancreatitis.[20] Diseases characterized by acid hypersecretion, such as gastrinoma, may also be associated with metabolic alkalosis and aciduria. Basal gastric acid secretion in two dogs with gastrin-producing tumors (1.7 and 2.7 mmol/hr/kg.[75] HCl) was maximal in the unstimulated state.[21] In this situation hypochloremia, hypokalemia, metabolic alkalosis, and dehydration is likely due to the hypersecretion of gastric acid and its loss in vomitus.[21] Venous blood gases and *plasma osmolality* are often determined in animals suspected of ethylene glycol ingestion, with the findings of metabolic acidosis and a high osmolal gap (calculated by subtracting calculated from measured osmolality) supportive of ingestion.

Elevated BUN in the absence of elevated creatinine may indicate gastric bleeding. Low albumin may be detected in basenji or Lundehund dogs with protein-losing gastroenteropathy, dogs with *Pythiosis,* and dogs or cats with gastric neoplasia. Elevated globulin concentrations have been observed in basenji gastro-enteropathy, *Pythium* infection, and gastric plasmacytoma. Elevations in creatinine, urea, calcium, potassium, glucose, liver enzymes, bilirubin, cholesterol, triglycerides, and globulin and decreases in sodium, calcium, urea, or albumin frequently herald non-GI causes of vomiting.

Urine should be evaluated for specific gravity, pH, glucose, casts, crystals, and bacteria. Thorough urinalysis is important; for example, white cell casts in the urine may be the only evidence that pyelonephritis is the cause of vomiting and should not be overlooked.

Coagulation testing is indicated in patients with melena or hematemesis to detect underlying coagulopathies and in those with acute abdomen to detect DIC. Infectious diseases associated with vomiting and diarrhea require *fecal examination* (giardia, endoparasites, *Salmonella* spp., *Campylobacter* spp., and parvovirus [ELISA] or *serologic testing* [FelV, FIV]) for diagnosis.

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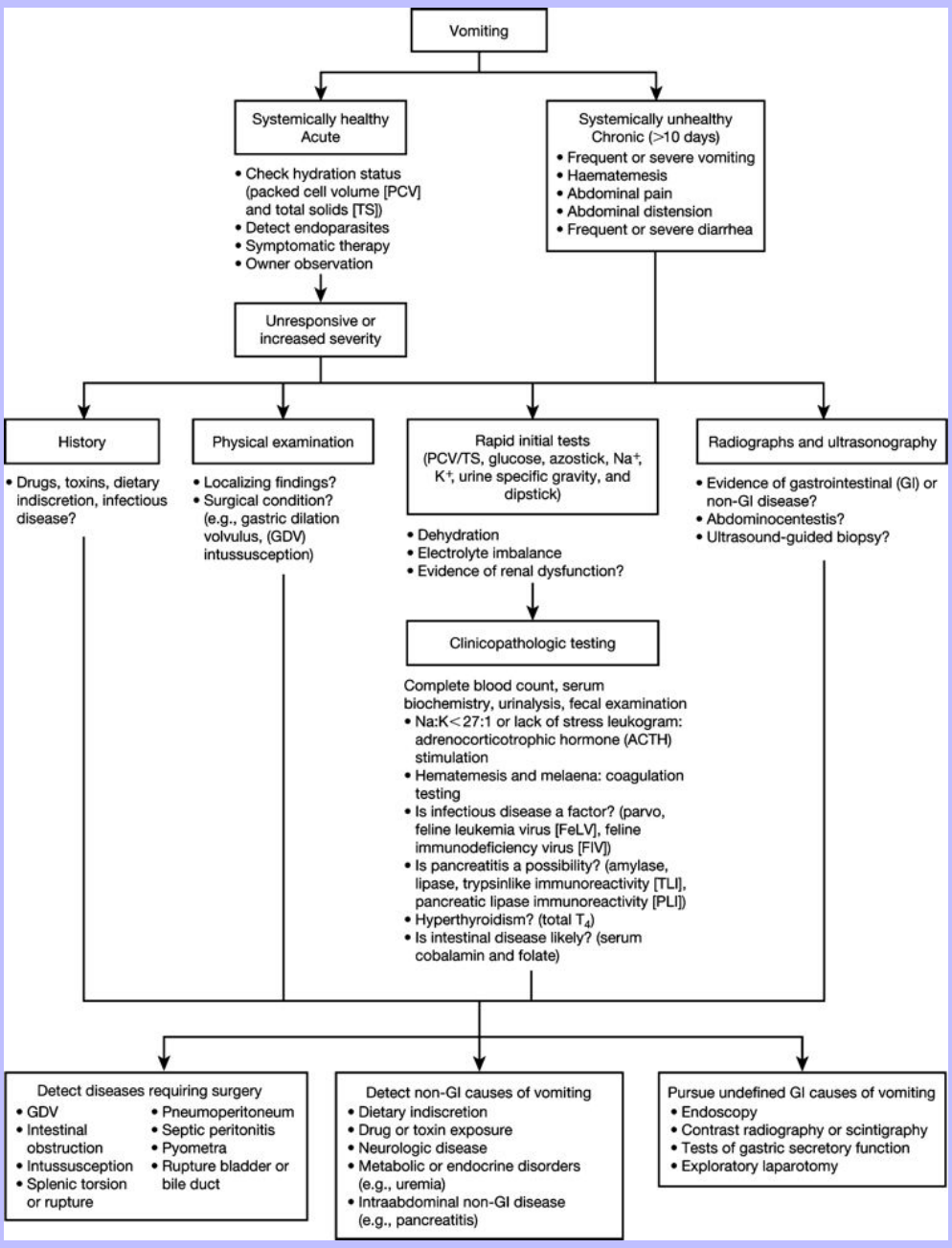
Figure 221-4 Diagnostic approach to the vomiting patient.



Additional clinicopathologic tests are required to detect hypoadrenocorticism (ACTH stimulation), liver dysfunction (pre-and post-prandial bile acids), hyperthyroidism in cats (T_4), pancreatitis (amylase, lipase

[pancreas-specific where possible], and trypsin-like immunoreactivity), and intestinal disease (serum cobalamin and folate).

221.3 IMAGING

Abdominal radiography is the test of choice for the initial evaluation of gastric disease, vomiting, and abdominal pain. Survey radiographs provide information on gastric position and contents that help to diagnose gastric distension/GDV, foreign bodies, and gastric outflow obstruction. They also enable the evaluation of the size and shape of the liver, kidneys, and spleen and detection of intussusception, peritonitis, pneumoperitoneum, and changes suggestive of pancreatitis.

Contrast radiographs may provide further information when survey radiographs are inconclusive. However, the combination of ultrasonography and endoscopy is generally more effective for detecting obstructive, inflammatory, and neoplastic GI disorders than contrast radiographic procedures, and contrast radiography is often restricted to the investigation of delayed gastric emptying associated with defective propulsion or "functional" intestinal disorders.[22] Ultrasonography can be employed to evaluate gastric wall thickness and gastric emptying, but its major value is usually the detection of non-gastric lesions in those with signs of GI disease.

When ultrasound and endoscopy are not available, distension of the stomach with air (negative contrast) may reveal gastric thickening, masses, or foreign bodies. Positive contrast with barium sulfate can provide further information and is also used to evaluate patency of the gastric outflow tract. The combination of fluoroscopy and positive contrast is helpful for evaluating pyloric patency and gastric emptying. In the absence of endoscopy and ultrasonography contrast radiographic procedures can be followed up with surgical biopsy to achieve a definitive diagnosis.

221.3.1 Endoscopy

Endoscopy enables direct visualization and biopsy of the stomach and duodenum and is the best way of diagnosing primary gastric inflammation, ulceration, or neoplasia; removing small foreign bodies; and evaluating patients prior to quantification of gastric emptying. It does not provide good information on submucosal lesions or functional diseases. With mural thickening or gastric masses, endoscopic biopsies are frequently too superficial and surgical biopsy is required for accurate diagnosis. Further information on equipment and techniques and photographs of a wide range of gastrointestinal lesions and can be found in endoscopic atlases.[23,24]

221.3.2 Evaluation of Gastric Emptying

Procedures used to evaluate delayed gastric emptying include barium contrast (liquid or mixed with food), barium-impregnated polyspheres (BIPs), nuclear scintigraphy, and the ^{13}C-octanoate breath test.[25,26] Tests of gastric emptying are often used to confirm a suspicion of delayed gastric emptying in patients with normal or equivocal survey radiographs. They are also used where gastric outflow obstruction and obvious causes of defective propulsion have been ruled out prior to and after prokinetic drugs. The limitations and benefits of these approaches are discussed under Delayed Gastric Emptying and Motility Disorders.

221.3.3 Gastric Secretory Testing

Gastric secretory testing is primarily performed in patients with esophagitis, gastrointestinal ulceration, mucosal hypertrophy, or copious amounts of gastric fluid that are suspected of having acid hypersecretion.

In its simplest form, fasting gastric pH and serum gastrin are measured to determine if acid hypersecretion is likely. Antisecretory therapy should be discontinued for 48 hours prior to testing, and renal and hepatic dysfunction detected, as these increase circulating gastrin. The broad range of fasting, unstimulated gastric pH in dogs and cats (pH 1 to 8) makes definitive statements regarding acid production difficult. However, the presence of a gastric pH of less than 3 in the face of a high serum gastrin rules out the possibility of achlorhydria, or mast cell tumor, and raises the possibility of gastrinoma.[21] Dogs with mast cell tumors and hyperhistaminemia induced acid hypersecretion have low serum gastrin concentrations[27], whereas dogs with achlorhydria likely have a high gastrin, but a gastric pH greater than 3.

Measurement of serum gastrin following the intravenous infusion of secretin or calcium is used to further investi-gate the possibility of exogenous gastrin production by pancreatic tumors, gastrinomas (Zollinger-Ellison syndrome) (see Chapter 244). Basenji dogs with gastroenteropathy and diarrhea have been reported to have elevated gastrin release in response to secretin stimulation, without evidence of gastrinoma.[28] Provocative testing of gastric acid secretion with penta-gastrin or bombesin stimulation may be performed to detect achlorhydria in patients with atrophic gastritis, or elevated serum gastrin and gastric pH levels higher than 3, and in those with idiopathic small intestinal bacterial overgrowth to determine if achlorhydia is a contributing factor. Pentagastrin stimulated acid secretion in dogs reaches a peak of 28 mL/kg$^{.75}$/hr, 4.1 mmol HCl/kg.^{75}/hr, 0.34 mmol K^+/kg$^{0.75}$/hr and 0.09 Na^+ mmol/kg$^{0.75}$/hr.[6] Sedation with oxymorphone and acepromazine is an alternative to anaesthesia for secretion studies in dogs.[28] In cats, acid output (mean±SD) in response to pentagastrin (8 μg/kg/hr) ranges from pH 0.9 to 1.1, with secretion rates (median values) of 1.2 mmol/15 min to 1.4 ± .5 mmol/15 min in conscious cats and 1.2 (0.6 to 2.7) mmol/kg$^{.75}$/hr in anesthetized cats.[29]

221.4 ACUTE GASTRITIS

Acute gastritis is the term applied to the syndrome of vomiting of sudden onset presumed to be due to a gastric mucosal insult or inflammation (Box 221-1). In most patients the cause is inferred from the history, such as dietary indiscretion, the diagnosis is rarely confirmed by biopsy, and treatment is symptomatic and supportive. 1315
Animals with acute gastritis associated with drug toxicity, foreign body ingestion, or meta-bolic disorders 1316
frequently present with hematemesis, melena, concurrent diarrhea, or other signs of systemic illness and require a more thorough diagnostic approach to determine the cause (as discussed above) and to provide optimal care. This author has found little evidence in the literature to support the role of viral infections such as parvovirus, distemper, or infectious canine hepatitis in acute gastritis.

221.4.1 Box • 221-1 Causes of Acute Gastritis

Dietary indiscretion or intolerance (non-allergic and allergic)

Foreign bodies, e.g., bones, toys, hairballs

Drugs and toxins, e.g., NSAIDs, corticosteroids, heavy metals, antibiotics, plants, cleaners, bleach

Systemic disease, e.g., uremia, liver disease, hypoadrenocorticism

Parasitic, e.g., *Ollulanus, Physalloptera* spp.

Bacterial, e.g., bacterial toxins,?*Helicobacter*

Possibly viral

221.4.2 Clinical Findings

Vomiting of sudden onset is the principal clinical sign. In some instances it is accompanied by hematemesis or melena and a variable degree of systemic abnormality. The history may reveal access or ingestion of spoiled food, garbage, toxins, medications, or foreign bodies. Signs of toxicity may be evident, such as jaundice and pallor with zinc ingestion, salivation or defecation with organophosphates toxicity or mushroom ingestion, or salivation and oral ulceration with chemical ingestion.

221.4.3 Diagnosis

A diagnosis of acute gastritis is usually based on clinical findings and the response to symptomatic treatment. A specific diagnosis may be sought if the patient has access to foreign objects or toxins, is systemically unwell, or has hematemesis, melena, or vomiting that fails to respond to symptomatic therapy, or other signs of more serious disease (see above). Laboratory testing in most animals with primary acute gastritis reflects mild dehydration, and is often not performed in the absence of a suspicion of more serious disease. Abdominal radiographs can be taken to detect foreign objects or gastrointestinal obstruction. Further diagnostics such as ultrasonography and endoscopy are rarely indicated as most animals with simple gastritis respond to symptomatic therapy.

221.4.4 Treatment

Therapy for uncomplicated acute gastritis is symptomatic and supportive and includes fluids, dietary restriction and modification, mucosal protectants or adsorbents, and possibly antacids.

221.4.4.1 Fluid Therapy

Small amounts of oral fluids, given little and often, can be given in the face of vomiting, with the volume increasing as vomiting subsides. Subcutaneous administration of an isotonic balanced electrolyte solution may be sufficient to correct mild fluid deficits (<5%) but is insufficient for patients with moderate to severe dehydration. Patients requiring intravenous fluids should undergo a more extensive diagnostic evaluation.

221.4.4.2 Dietary Restriction and Modification

Where vomiting is acute, oral intake is discontinued for at least 24 hours. Small amounts of a liquid diet can be offered in the face of vomiting to maintain GI barrier function and to determine if vomiting has resolved. A bland diet (non-spicy, fat restricted), either homemade (e.g., boiled chicken and rice, low-fat cottage cheese, and rice [1:3]) or commercial (usually fat restricted and rice based), is then introduced (fed little and often) with a gradual transition made back to a normal diet over a week or so.

221.4.4.3 Protectants/Adsorbents

Bismuth-subsalicylate, kaolin-pectin, activated charcoal and magnesium, aluminum-and barium-containing products are often administered in acute vomiting or diarrhea to bind bacteria and their toxins and to coat the gastrointestinal mucosa. These agents are probably safer and more efficacious than antibiotics or motility modifiers in acute gastroenteritis. Pepto bismol (1 mL/5 kg PO TID), bismuth subcitrate, kaolin-pectin (1 to 2 mL/kg PO TID) and sucralfate (0.25 to 1 g PO TID) are often employed. Acid-reducing drugs such as H_2-receptor antagonists can be administered but are usually reserved for patients with signs of gastric erosion or ulceration (melena/hematemesis) or persistent gastritis as described below.

Table • 221-2 Association of Gastric Ulceration and Erosion with Specific Diseases

GASTRIC PROBLEM	RELATED DISEASES
Metabolic/Endocrine	Hypoadrenocorticism, uremia, liver disease, mastocytosis, d.i.c. Hypergastrinemia and other APUDomas
Inflammatory	Gastritis
Neoplastic	Leiomyoma, adenocarcinoma, lymphosarcoma
Drug-induced	Nonsteroidal and steroidal anti-inflammatories
Hypotension	Shock, sepsis
Idiopathic	Stress, spinal surgery, exercise induced (sled dogs)

The author generally avoids anti-emetics in patients with acute gastritis to enable response to therapy to be ascertained. Patients who continue to vomit require further investigation.

221.4.5 Prognosis

The prognosis for uncomplicated acute gastritis is usually complete recovery.

221.5 GASTRIC EROSION AND ULCERATION

Gastric erosions and ulcers are associated with a number of primary gastric and non-gastric disorders (Table 221-2). Clinical signs range in duration and severity, from acute to chronic and mild to life threatening. The pathomechanisms underlying gastric damage can be broadly attributed to impairment of the gastric mucosal barrier (defined above) through direct injury, interference with gastroprotective prostaglandins (PGE_2), mucous or bicarbonate, decreased blood flow, and hypersecretion or gastric acid.

Perhaps the most predictable recipe for gastric erosion is the combination of a non-steroidal anti-inflammatory and a glucocorticoid, either alone, or in combination with intervertebral disk disease.[30]

Nonsteroidal anti-inflammatory drugs cause direct mucosal damage and interfere with prostaglandin synthesis.[9] Flunixin meglumine, aspirin, and ibuprofen have all been associated with erosions in healthy dogs. To circumvent toxicity caused by the inhibition of "friendly prostaglandins" (PGE_2), drugs that preferentially block "inducible" cyclooxygenase (COX-2) have been developed. These COX-2 selective agents, such as carprofen, meloxicam, derccoxib, and potentially etodolac, are less ulcerogenic in normal dogs.[31,32] However, even COX-2 selective drugs such as meloxicam are ulcerogenic in combination with dexamethasone,[33] and their safety in sick animals remains to be determined.

High doses of glucocorticoids alone, such as dexamethasone and methylprednisolone, have also been associated with gastric erosions[34] but the mechanisms by which they induce damage are not clear. Unlike NSAIDs, their effects are not ameliorated by PGE_2 analogs.[35]

Hypersecretion of gastric acid in response to histamine release from mast cell tumors, and gastrin from gastrinomas has also been clearly implicated as a cause of gastroduodenal ulceration and esophagitis in dogs and cats.

Renal failure, hepatic failure, hypoadrenocorticism, and hypotension are frequently proposed as risk factors for gastric erosion or ulceration, although few details have been published on the pathogenesis, frequency, or severity of gastric damage in these conditions. In a recent study of dogs with renal failure, ulceration was present in only 1 of 28 dogs. The predominant findings in these dogs were mucosal edema, vasculopathy, and mineralization that correlated to the degree of azotemia and calcium phosphorous product.[36]

Sled dogs in the Iditarod are prone to develop gastric erosions and/or ulcers.[37] This finding is similar to exercising humans and horses in whom the pathogensis is not understood but is responsive to acid suppression.

Erosions and ulcers are also a sequela of gastric cancer and gastritis and are discussed elsewhere in this chapter.

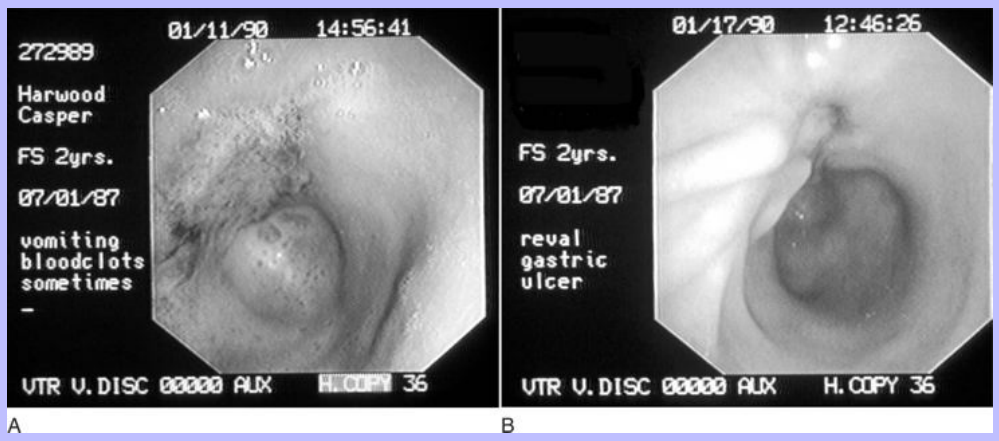
221.5.1 Clinical Findings

Vomiting, hematemesis, and melena may be present in patients with gastric erosions or ulcers. Pale mucous membranes, abdominal pain, weakness, inappetance, hypersalivation (potentially associated with esophagitis as a consequence of gastric acid hypersecretion), and evidence of circulatory compromise are more variably present. Access to toxins and drugs, particularly NSAIDs, should be determined.

Clinicopathologic testing is directed at identifying diseases associated with gastric erosions and ulcers (see Table 221-2) and the consequences of erosion/ulceration. The CBC may reveal anemia that is initially regenerative but can progress to become microcytic, hypochromic, and minimally regenerative. When accompanied by thrombocytosis and decreased iron saturation or low serum ferritin, these findings are characteristic of chronic bleeding and iron deficiency. Lack of a stress leukogram and eosiniphilia in dogs is supportive of hypoadrenocorticism. Eosinophilia could also be consistent with dietary allergy, eosinophilic gastroenteritis, mastocytosis, or a hyperseosinophilic syndrome. A neutrophilic leukocytosis and a left shift may indicate inflammation or possible gastric perforation. Examination of a buffy coat smear may help to detect mastocytosis.

Biochemistry and urinalysis may reveal findings consistent with dehydration (azotemia and hypersthenuria), renal failure (e.g., azotemia and isosthenuria), hepatic disease (e.g., increased liver enzymes or bilirubin; decreased cholesterol, albumin, BUN), or hypoadrenocorticism (i.e., Na^+:K^+ ratio <27:1). It will also identify electrolyte and acid base abnormalities associated with vomiting and GI ulceration. The presence of a metabolic alkalosis, hypochloremia, hypokalemia, and acid urine is consistent with upper GI obstruction (physical or functional) or a hypersecretory state. Testing should be performed to detect abnormalities in primary and secondary hemostasis that may be associated with GI bleeding. Serum gastrin and potentially histamine concentrations can be evaluated where acid hypersecretion is suspected as a cause of ulceration.

Figure 221-5 Gastric ulceration caused by ibuprofen ingestion before and after (1 week) treatment with cimetidine and sucralfate. (Images courtesy of The Ohio State University.)



221.5.2 Diagnosis

221.5.2.1 Diagnostic imaging

Plain radiographs are not usually helpful in diagnosing gastric erosions or ulcers but may help to rule out other causes of vomiting, such as foreign bodies, peritonitis, and gastric perforation. Contrast radiographs may reveal filling defects but do not allow detailed mucosal evaluation or sampling.

Ultrasonography can be performed to evaluate the gastric wall for thickening associated with ulcers and masses and also helps to rule out non-gastric causes of vomiting. The information provided by radiography and ultrasound is complementary to endoscopic evaluation, which is the diagnostic test of choice (Figure 221-6).

Endoscopy allows the direct evaluation of gastric damage and mucosal sampling. NSAID-associated ulcers tend to be found in the antrum and are not usually associated with marked mucosal thickening or irregular edges (Figure 221-5). This contrasts with ulcerated tumors that frequently have thickened edges and surrounding mucosa (Figure 221-17, *A*). Ulcers should be biopsied at the periphery to avoid perforation. Endoscopic biopsies are not ideal for diagnosing infiltrative gastric tumors and several biopsies from the

same site are usually taken to enable sampling of deeper tissue. Endoscopic guided fine-needle aspirates, with use of a needle and tubing in the biopsy channel, can also be used to sample deep lesions. Even with this approach the diagnosis may be missed, and surgical biopsy required for a definitive diagnosis.

The combination of mucosal erosion or ulceration, antral mucosal hypertrophy, copious gastric juice, and esophagi-tis is highly suggestive of a gastric hypersecretory state (Figure 221-7). It is prudent to measure gastric pH and serum gastrin in patients with gastric erosion/ulceration that is not associated with drugs or gastric tumors. Dogs with mast cell tumors and hyperhistaminemia-induced acid hyper-secretion have low serum gastrin concentrations. [38] Finding a combination of gastric pH less than 3 and a high serum gastrin concentration prompts further investigation of gastrinoma by secretin stimulation test, ultrasonography (liver and pancreas), and pentertreotide scintigraphy. [21]

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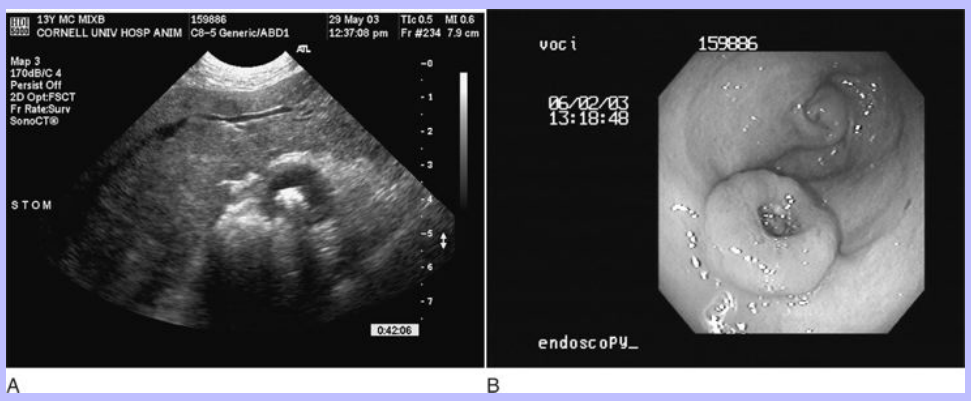
Figure 221-6 Ultrasonography and endoscopy provide complementary information. The ultrasonogram **(A)** shows a mass projecting into the lumen of the stomach of a dog presented for the investigation of vomiting and hyperglobulinemia (IgA). Endoscopy **(B)** confirmed the presence of a mass and enabled a biopsy diagnosis of gastric plasmacytoma. (Images courtesy of Cornell University, Ithaca, NY.)



221.5.3 Treatment

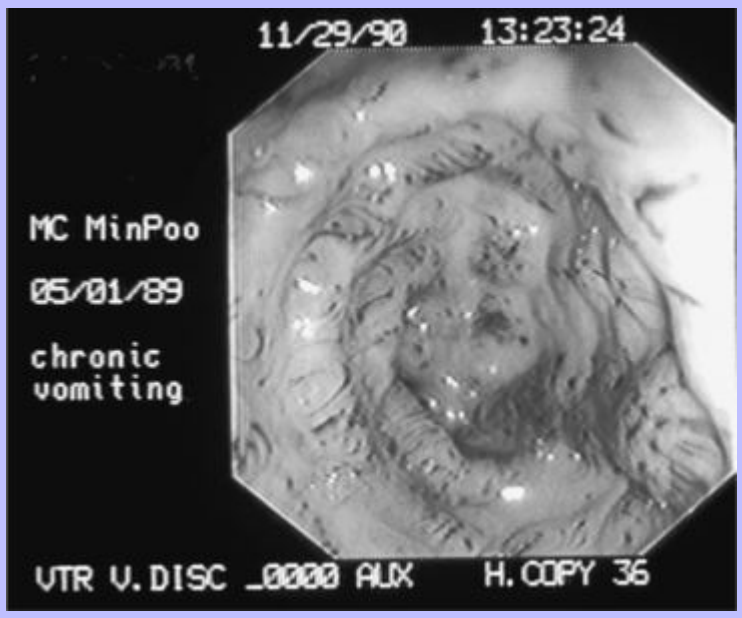
Treatment of gastric erosions and ulcers is directed at the underlying cause, which ensures adequate hydration and perfusion, including blood transfusion if needed, and restoring electrolyte and acid base disturbances. Additional support is directed at shoring up the gastric mucosal barrier by enhancing mucosal protection and cytoprotection, and decreasing gastric acid secretion. Where vomiting is persistent, antiemetics may help to reduce fluid loss, discomfort, and the risk of esophagitis.

221.5.4 Fluid Therapy

The rate of fluid administration depends on the presence or absence of shock, the degree of dehydration, and the presence of diseases (e.g., cardiac or renal), which predispose to volume overload. Patients with a history

of vomiting who are mildly dehydrated are usually responsive to crystalloids (e.g., LRS or 0.9% NaCl) at a rate that will provide maintenance and replace both deficits and ongoing losses over a 24-hour period. Potassium depletion is often a consequence of prolonged vomiting or anorexia, and most polyionic replacement fluids contain only small amounts of potassium. Therefore KCl is added to parenteral fluids on the basis of serum levels.

Figure 221-7 Gastric erosion and mucosal hypertophy in a dog with gastrinoma. (Courtesy of The Ohio State University.)



Patients with signs of shock require more aggressive support. The volume deficit can be replaced with crystalloids at an initial rate of 60 to 90 mL/kg/h, then tailored to maintain tissue perfusion and hydration. Colloid solutions can also be used to treat animals in shock to reduce the amount of crystalloid required (e.g., Hetastarch, hemaccel at 10 to 20 mL/kg IV over 4 to 6 hours). Plasma, colloids, packed cells, or whole blood is occasionally required to treat severe hypoproteinemia or anemia, which can develop in vomiting animals with severe ulceration or HGE.

Central venous pressure monitoring and evaluation of urine output are necessary in patients with severe GI disease, particularly those complicated by third space losses of fluid into the gut or petitoneum.

The effect of vomiting on acid-base balance is hard to predict and therapeutic intervention to correct acid-base imbalances should be based on blood gas determination. Where severe metabolic acidosis is present (pH <7.1, HCO^{3-} <10 mmol/L), sodium bicarbonate (1 mmol/kg) can be given under careful supervision for the development of worsening hypokalemia, and hypocalcemia, and CSF acidosis. Further bicarbonate supplementation is based on repeated blood gas analysis. Metabolic alkalosis usually responds to replacing volume deficit, chloride, and potassium with IV 0.9%NaCl+KCl. Diagnostic investigations should initially center on ruling out upper GI obstruction. The administration of anti-secretory drugs such as H_2 antagonists may help to limit Cl^--efflux into gastric juice.

221.5.4.1 Reducing Acid Secretion and Providing Mucosal Protection

Pharmacologic inhibition of acid secretion (see Figure 221-3) can be effected by blocking H_2 (cimetidine, ranitidine, famotidine), gastrin (proglumide), and acetylcholine (atropine, pirenzipine) receptors, and by inhibiting adenyl cyclase (PGE analogs) and H^+/K^+ ATPase (e.g., omeprazole).[39] Long-acting somatostatin analogs such as octreotide directly decrease the secretion of gastrin and gastric acid.

Decreasing gastric acid secretion with an H_2 receptor antagonist has been shown to promote mucosal healing in dogs with a variety of experimentally induced ulcers and erosions (see Figure 221-5). Famotidine is an attractive choice as it does not inhibit P450 enzymes and can be given once daily. The additional prokinetic activity of ranitidine or nizatidine (mediated by anticholinesterase activity) may make them good choices in the face of delayed gastric emptying associated with defective propulsion.[25] In patients with severe or persistent gastric ulceration that is refractory to H_2 antagonists, more complete inhibition of gastric acid secretion can be achieved with a H^+/K^+-ATPase inhibitor such as omeprazole (0.2 to 0.7 mg/kg SID PO—dogs). Omeprazole is the initial drug of choice in patients with acid hypersecretion secondary to mast cell tumors and gastrinoma (Zollinger-Ellison syndrome). Omeprazole has been shown to have few long-term side effects in dogs, but it should be used with caution in patients with liver disease and reviewed for interactions with drugs such as cisapride.

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In sled dogs with exercise-associated gastric hemorrhage treatment with omeprazole significantly reduced mean gastric severity score compared to placebo but also was associated with increased frequency of diarrhea (omeprazole 54%, placebo 21%).[37] The authors recommended further investigation of diarrhea associated with omeprazole treatment before omeprazole can be recommended for routine prophylactic treatment in these athletes.[37]

The combination of omeprazole and the long acting somatostatin analog Octreotide effectively reduced vomiting in a dog with gastrinoma (Octreotide 2 to 20 µg/kg SC TID).[40] Octreotide can also be employed to rapidly decrease gastric acid secretion in patients discovered to have large ulcers at endoscopy and may also be useful for controlling gastric bleeding (see human studies).

221.5.4.2 Mucosal Protectants

The PGE_2 analog, misoprostol, protects against NSAID-induced erosions in dogs at doses that do not inhibit acid secretion (3 to 5 µg/kg PO TID in dogs) and may be given to dogs receiving chronic NSAIDs for arthritis.[41,42] The main side effect of misoprostol is diarrhea and it should not be given to pregnant animals.

The mucosal protectant polyaluminum sucrose sulfate (sucralfate) binds to areas denuded of mucosal epithelium regardless of the underlying cause and is useful for treating gastric erosions and ulcers and esophagitis. Sucralfate can be given to patients receiving injectable antacids, but it may compromise absorption of other oral medications and is probably best separated from these by 2 hours or so.

In contrast to the efficacy of misoprostol and H_2 antagonists in preventing NSAID-induced erosions, the prophylactic administration of various combinations of misoprostol, cimetidine, and omeprazole has not been shown to prevent gastric erosions in dogs with or without intervertebral disk disease receiving

high-dose glucocorticoids.[34,43,44] However, these drugs may speed healing of gastric lesions in these patients. Sucralfate is probably the drug of choice for treating GI ulceration in patients receiving high doses of corticosteroids because it is not dependent on the premise that acid is causing or delaying healing.

Mast cell tumors are also worth considering separately as gastric ulceration is a frequent and severe complication. Mast cell tumors are thought to cause vomiting via the central effects of histamine on the CRTZ and the peripheral effects of histamine on gastric acid secretion (with resultant hyperacidity and ulceration). Treatment of mastocyosis with H_1 and H_2 histamine antagonists (e.g., diphenhydramine and famotidine) should reduce the central and peripheral effects of histamine. Corticosteroids are used to decrease tumor burden. Where acid hypersecretion is present, or is suspected, it is likely best managed with proton pump inhibitors (e.g., omeprazole 0.2 to 0.7 mg/kg SID). Somatostatin analogs may also be useful for controlling refractory gastric acid hypersecretion (Octreotide 2 to 20 μg/kg SC TID).[21]

221.5.4.3 Antiemetics

Antiemetics can be used where vomiting is severe or compromising fluid and electrolyte balance, or causing discomfort.[39] The initial agent used in dogs is usually metoclopramide, which antagonizes D_2-dopaminergic and $5HT_3$-serotonergic receptors and has cholinergic effects on smooth muscle (1 mg/kg/24h CRI IV). Phenothiazine derivatives such as chlorpromazine and prochlorperazine are antagons of α_1 and α_2-adrenergic, H_1-and H_2-histaminergic, and D_2-dopaminergic receptors in the vomiting center and CRTZ and are used if metoclopramide is ineffective and the patient is normotensive. Nonselective cholinergic receptor antagonists (other than the M_1 specific antagonist-pirenzipine) such as atropine, scopolamine, aminopentamide, and isopropamide are generally avoided as they may cause ileus, delayed gastric emptying, and dry mouth.

221.5.4.4 Antibiotics and Analgesia

Prophylactic antibiotic cover (e.g., cephalosporins, ampicillin) may be warranted in animals with shock and major GI barrier dysfunction. Leukopenia, neutrophilia, fever, and bloody stools are additional indications for prophylactic antibiotics in animals with vomiting or diarrhea. Initial choices in these situations include ampicillin or a cephalosporin (effective against gram-positive and some gram-negative and anaerobic bacteria), which can be combined with an aminoglycoside (effective against gram-negative aerobes) when sepsis is present and hydration status is adequate. Enrofloxacin is a suitable alternative to an aminoglycoside in skeletally mature patients at risk of nephrotoxicity from an aminoglycoside.

Analgesia can be provided using opioids like buprenorphine (0.0075 to 0.01 mg/kg IM).

Surgery may be required when the cause of ulceration is unclear or to resect large non-healing ulcers or those about to perforate.

221.6 GASTRIC DILATATION AND VOLVULUS

Gastric dilatation and gastric dilatation and volvulus are characterized by the dramatic distension of the stomach with air. With volvulus the stomach twists about its axis, moving dorsally and left of the fundus. Both dilatation and dilatation and volvulus cause caudal caval obstruction and impair venous return to the heart. This results in hypovolemic shock that can be exacerbated by devitailization of the gastric wall, splenic torsion or avulsion, congestion of the abdominal viscera, endotoxic shock, and DIC.

No single cause of gastric dilatation (GD) or dilatation and volvulus (GDV) has been identified. Large breed dogs with deep chests such as akita, bloodhound, collie, great Dane, Irish setter, Irish wolfhound, Newfoundland, Rottweiler, Saint Bernard, standard poodle, and Weimaraner are at greater risk. Cumulative incidence of GDV has been estimated at 6% for large breed and giant breed dogs. The lifetime risk is influenced by breed, ranging from of 3.9% for Rottweilers to 39% in great Danes.[45] In large breed and giant dogs, factors significantly associated with an increased risk of GDV include increasing age, having a first-degree relative with a history of GDV, having a faster speed of eating, once daily feeding, and having a raised feeding bowl and aerophagia.[46,47] The personality of the dogs may also have an impact, with happier dogs having a decreased incidence.[48]

Analysis of gastric gas supports aerophagia as the cause of distension, with dilatation explained by an inability to eructate or empty air into the intestines. Studies in dogs with GDV recovering from gastropexy suggest that abnormal electrical activity and gastric emptying may be related to the development of gastric dilatation.[49] The interrelationship of volvulus and gastric distension is unclear, although the length of the hepatogastric ligament may facilitate torsion.

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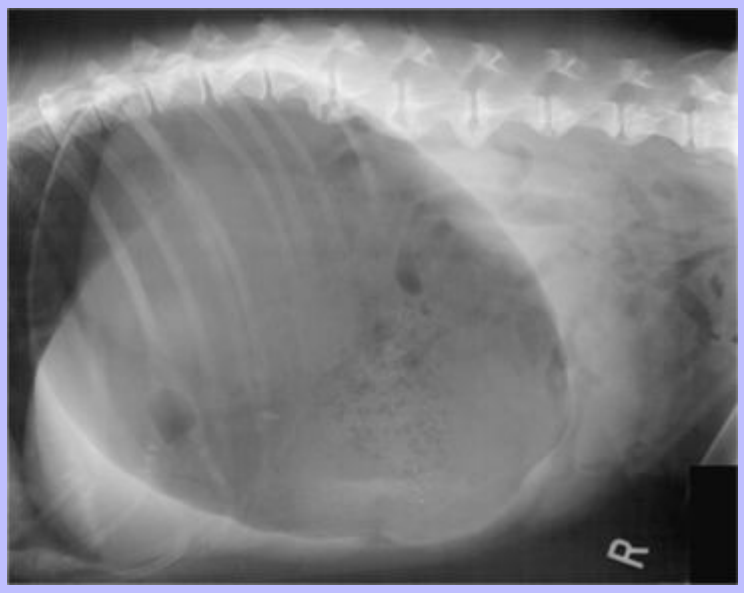
Figure 221-8 Survey radiograph of gastric dilatation (R lateral). The fundus is distended with air. (Courtesy of Cornell University, Ithaca, NY.)

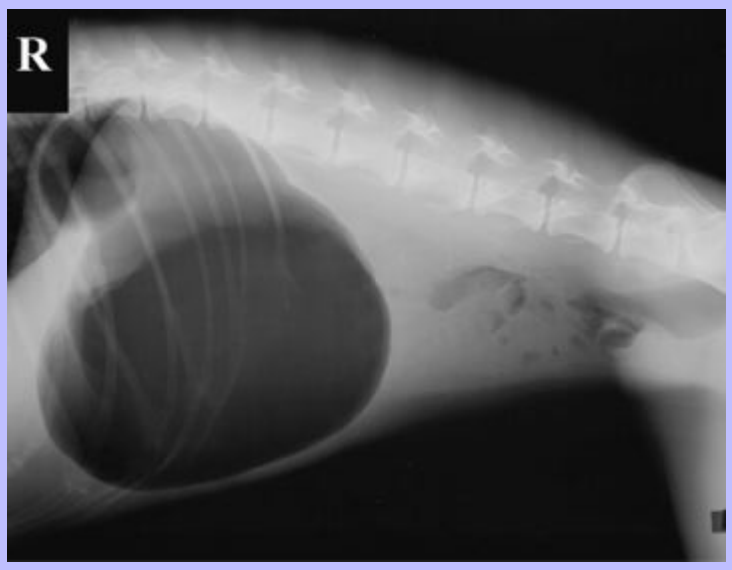


221.6.1 Diagnostic Features

A history of non-productive retching, salivation, abdominal distention, weakness, or collapse raises the possibility of gastric dilatation or volvulus, particularly in large breed and deep-chested dogs. Physical findings usually include abdominal distension and tympany, tachycardia, and mucosal pallor. Hypothermia, depression, and coma may be seen when shock is severe. Cardiac arrythmias such as ventricular premature beats or ventricular tachycardia may be detected on the initial examination or develop up to 72 hours after presentation.

Radiography is usually performed after fluid support and decompression and helps to distinguish simple dilatation from dilatation and volvulus. Right and left lateral recumbent views are usually acquired. Dilatation is associated with gas distension and on a right lateral position air is present in the fundus (Figure 221-8). With volvulus the pylorus moves dorally and left and the stomach is compartmentalized. On a right lateral radiograph the fundus is viewed as a large ventral compartment with the smaller, gas-filled pylorus located dorsally and separated from the fundus by a band of soft tissue, forming the “the Popeye's arm” sign (Figure 221-9). Loss of abdominal contrast may indicate gastric rupture or bleeding from avulsed splenic vessels, whereas increased contrast due to pneumo-peritoneum suggests gastric rupture.

Figure 221-9 Survey radiograph of gastric dilatation and volvulus (GDV). With gastric volvulus, the pylorus moves dorsally, cranially, and to the left. It is easiest to detect GDV in the right lateral view, where the pylorus is viewed as the smaller air-filled compartment dorsal to the larger air-filled fundus and seperated from the fundus by a soft tissue density. (Images courtesy of Cornell University, Ithaca, NY.)



221.6.2 Clinicopathologic Findings

Hematologic changes are often restricted to an increase in hematocrit. A variety of acid-base and electrolyte disturbances have been observed in dogs with GDV.[50,51] Metabolic acidosis and hypokalemia were the most common abnormalities in one study and occurred in 15 out of 57 and 16 out of 57 dogs, respectively.[50] Metabolic acidosis is likely due to tissue hypo-perfusion, anaerobic metabolism, and the accumulation of lactic acid.[50] Metabolic alkalosis may also occur and may be related to the sequestration of gastric acid or vomiting.[50]

Respiratory acidosis and alkalosis have been variably observed and reflect hypoventilation or hyperventilation, respectively. The variable nature of acid-base and electrolyte abnormalities in dogs with GDV indicates that fluid therapy should be individualized on the basis of blood gas and electrolyte measurements. Monitoring and correction of acid-base abnormalities are important because they may predispose to cardiac arrythmias and muscle weakness.

Coagulation abnormalities are usually consistent with disseminated intravascular coagulopathy (thrombocytopenia, increased D-dimer or FDPs, reduced ATIII, prolongation of the APTT).

221.6.2.1 Treatment

Fluid support and gastric decompression are the most important emergency treatments.

221.6.2.2 Fluid Support

Fluid therapy has traditionally consisted of shock doses of LRS (60 to 90 mL/kg/h) given via large-bore catheters into the cephalic or jugular veins. Experimental studies that have compared crystalloids (60 mL/kg, followed by 0.9% NaCl 20 mL/kg/h) with hypertonic saline (7% NaCl in 6% dextran, 5 mL/kg, followed by 0.9% NaCl 20 mL/kg/h) in dogs with GDV-induced shock, indicate that hypertonic saline maintains better myocardial performance, higher heart rate, and lower systemic vascular resistance than crystalloid.[52] The resuscitative dose of hypertonic saline was delivered in 5 to 10 minutes versus an hour for cystalloid. Fluid therapy should be aggressively monitored by frequent measurement of blood pressure, heart rate, PCV, and total solids and urine output. Potassium and bicarbonate are best administered on the basis of blood gas and electrolyte measurements. Hypokalemia is common after fluid therapy and 30 to 40 mEq KC l/L should be added to fluids after the initial shock dose.

221.6.2.3 Gastric Decompression

Decompression can be performed by oragastric intubation with a well-lubricated stomach tube, or a 16-g catheter can be used to trocarize the stomach. Oral decompression can also be performed after trocarization. Decompression should be maintained until surgery. Sedation with butorphanol (0.5 mg/kg IV) or oxymorphone (0.1 mg/kg IV) and diazepam (0.1 mg/kg slow IV) may be necessary to pass a stomach tube.

221.6.2.4 Adjunct Therapy for Endotoxic Shock and Reperfusion Injury

Adjunct therapy frequently includes prednisolone sodium succinate (10 mg/kg IV) or dexamethasone sodium phosphate (10 mg/kg IV) for shock, and broad-spectrum antibiotics such a cephalosporin in combination with a fluroquinolone to circumvent bacterial translocation and endotoxemia. Some clinicians advocate flunixin meglumine for endotoxic shock, but the author does not.

The administration of agents to decrease lipid peroxidation (U70046F) and chelate iron (desferoxamine) has decreased mortality attributed to reperfusion injury in dogs with experimental GDV.[53,54] These agents are best given before reper-fusion occurs, that is, prior to untwisting a torsion.

221.6.2.5 Cardiac Arrythmias

Cardiac arrhythmias such as ventricular premature complexes and ventricular tachycardia are relatively frequent (approximately 40% of patients) and may or may not contribute to mortality.[55,56] The arrhythmias can develop up to 72 hours after presentation and are considered a consequence of electrolyte, acid base, and hemostatic abnormalities, as well as due to reperfusion injury. Arrhythmias should be treated if they are associated with weakness or syncope, as well as if persistent ventricular tachycardia at rates greater than 150 beats per minute are demonstrated. The arrythmias are managed by correcting underlying acid-base electrolyte and hemostatic disturbances and administering lidocaine either as a bolus (1 to 2 mg/kg IV) or continuously (up to 50 to 75 µg/kg/min) and procainamide (10 mg/kg IM q6h and then orally if effective) where persistent. It is important that plasma concentration of K^+ and Mg^{2+} are normalized to enable effective antiarrythmic therapy (see Chapter 202).

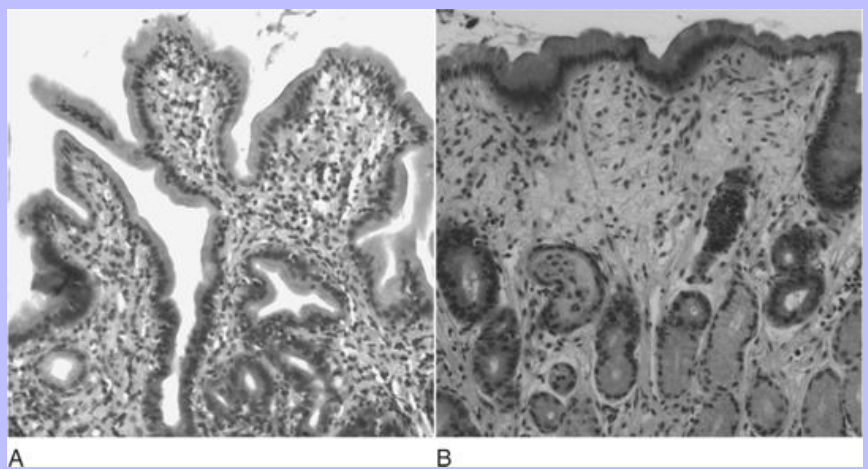
221.6.2.6 Surgery

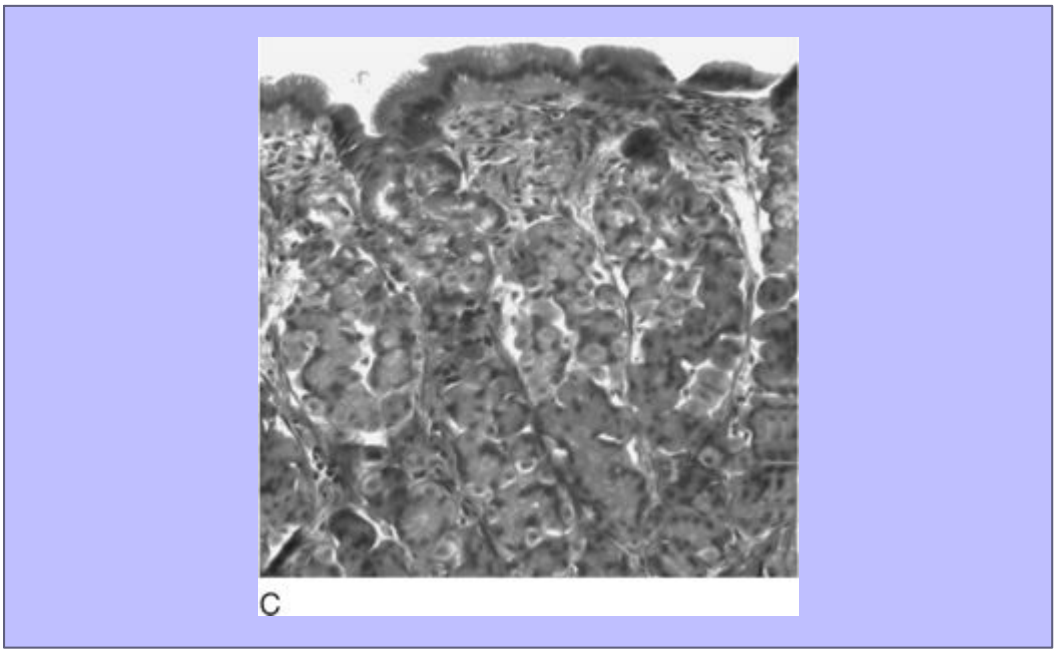
The aims of surgery are to reposition the stomach and spleen and to perform a gastropexy to enable short-term decompression and prevent recurrence. Surgery is complicated by the presence of gastric necrosis, which requires partial gastrectomy, and avulsion or torsion of the spleen, which may require resection or removal.

221.6.3 Prognosis

Mortality rate for dogs with gastric dilatation and volvulus is approximately 15%.[56] Dogs with gastric necrosis, gastric resection or splenectomy have a higher mortality rate (>30%).[55–57]

Figure 221-10 Grading schemes for gastritis. **A.** A visual analog cartoon system proposed by Happonen et al, 1998, and **B.** A standardized photograpic scale for atrophy, fibrosis and cellular infiltrate. (Courtesy Wiinberg, Simpson and MacDonough.)





The presence of gastric necrosis can be predicted by measuring plasma lactate concentration, with [lactate] greater than 6 mmol/L yielding a specificity of 88% and a sensitivity of 66% for necrosis.[57]

221.6.4 Prophylaxis

The recurrence rate of GD/GDV has been estimated at 11% over 3 years in one study, with median survival of 547 versus 188 days for dogs with a gastropexy versus those without.[58]

Prophylactic gastropexy in Great Danes, Irish Setters, Rottweilers, standard poodles, and Weimariners reduced mortality from as little as 2.2-fold in Rottweilers to as much as 29.6-fold in great Danes.[45]

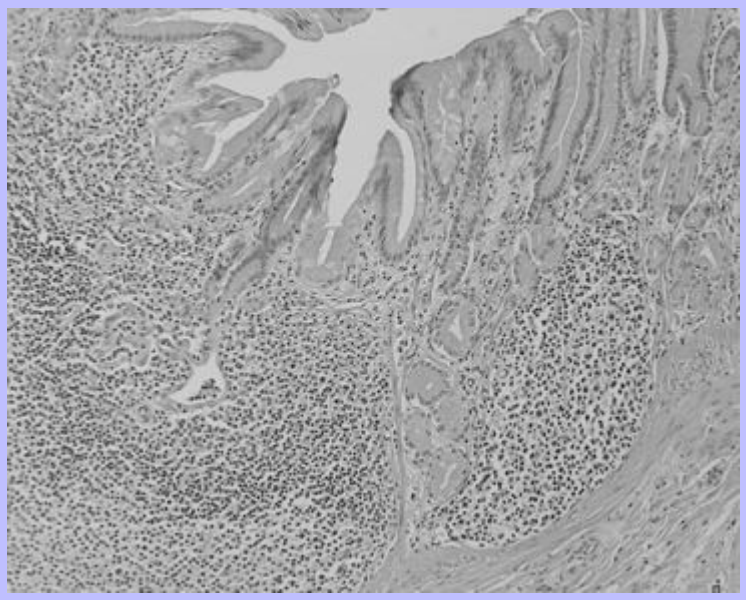
221.7 CHRONIC GASTRITIS

Gastritis is a common finding in dogs, with 35% of dogs investigated for chronic vomiting and 26% to 48% of asymptomatic dogs affected.[59,60] The prevalence in cats has not been determined. The diagnosis of chronic gastritis is based on the histologic examination of gastric biopsies and it is usually subclassified according to histopathological changes and etiology.

221.7.1 Histopathologic Features of Gastritis

Gastritis in dogs and cats is usually classified according to the nature of the predominant cellular infiltrate (eosinophilic, lymphocytic, plasmacytic, granulomatous, lymphoid follicular), the presence of architectural abnormalities (atrophy, hypertrophy, fibrosis, edema, ulceration, metaplasia), and their subjective severity (mild, moderate, severe). A standardized visual grading scheme has been proposed by Happonen et al[60] and has been adapted for pathologists[61] (Figure 221-10).

Figure 221-11 Lymphoid follicle hyperplasia and lymphoplasmacytic gastritis in a cat with *H. felis* infection.



The most common form of gastritis in dogs and cats is mild to moderate superficial lymphoplasmacytic gastritis with concomitant lymphoid follicle hyperplasia (Figure 221-11). Eosinophilic, granulomatous, atrophic, and hyperplastic gastritis are less common.

221.7.2 Etiology

Despite the high prevalence of gastritis an underlying cause is rarely identified, and in the absence of systemic disease, ulcerogenic or irritant drugs, gastric foreign objects, parasites (*Physalloptera* and *Ollulanus* spp.), and in rare instances fungal infections (*Pythium insidiosum, Histoplasma* spp.), it is usually attributed to dietary allergy or intolerance, occult parasitism, or a reaction to bacterial antigens, or unknown pathogens. Treatment is often empirical but can serve to define the cause of gastritis, such as diet responsive, antibiotic responsive, steroid responsive, or parasitic.

Although the basis of the immunologic response in canine and feline gastritis is unknown, recent studies in experimental animals have shed light on the immunologic environment in the gastrointestinal tract and reveal a complex interplay between the GI microflora, the epithelium, immune effector cells such as lymphocytes and macrophages, and soluble mediators such as chemokines and cytokines.[46,62] In health, this system avoids active inflammation by antigen exclusion and the induction of immune tolerance. The development of intestinal inflammation in mice lacking the cytokines IL-10, TGFβ, or IL-2 indicates the central importance of cytokines in damping down mucosal inflammation. In many of these murine models GI inflammation only develops in the presence of indigenous intestinal microflora, leading to the hypothesis that spontaneous mucosal inflammation may be the result of a loss of tolerance to the indigenous GI microflora. The role of these mechanisms in outbred species such as the dog and cat remains to be determined, but clearly loss of tolerance to bacterial of dietary antigens should be considered.

The epithelial cell is also emerging as a "general" in the inflammatory response, with gram-negative or pathogenic bacteria inducing proinflammatory cytokine (e.g., IL-8, IL1-β) secretion from epithelial cells, whereas commensal or bacteria such as *S. fecium* or *Lactobacillus* spp. induce the production of the immunomodulatory cytokines TGFB or IL-10.[62] The pro-inflammatory cytokines produced by epithelial cells are modulated by the production of IL-10 from macrophages and potentially by the epithelial cells themselves.[63] In this context, dogs with lymphoplasmacytic gastritis of undetermined etiology showed a correlation between the expression of the immunomodulatory cytokine IL-10 and proinflammatory cytokines (IFN-γ, IL-1β, IL-8).[61] Simultaneous expression of IL-10 and IFN-γ mRNA has also been observed in the intestines of beagle dogs (lamina propria cells and the intestinal epithelium) in the face of a luminal bacterial flora that was more numerous than that of control dogs.[64] Thus it is tempting to visualize a "homeostatic loop" consisting of proinflammatory stimuli and responses, countered by immunomodulation and repair, with an imbalance in either of these arms manifested as gastritis.

The importance of unknown pathogens in the development of mucosal inflammation is best demonstrated by the gastric bacterium *Helicobacter pylori*, a gram-negative bacterium, which chronically infects more than half of all people worldwide.[13] Chronic infection of human adults with *H. pylori* is characterized by the infiltration of polymorphonuclear and mononuclear cells and the up-regulation of pro-inflammatory cytokines and the chemokine IL-8. Mucosal T cells in infected individuals are polarized toward the production of gamma interferon (IFN-γ), rather than IL-4 or IL-5 indicating a strong bias toward a T_H-1 type response).[65,66] This sustained gastric inflammatory and immune response to infection appears to be pivotal for the development of peptic ulcers and gastric cancer in people.[67]

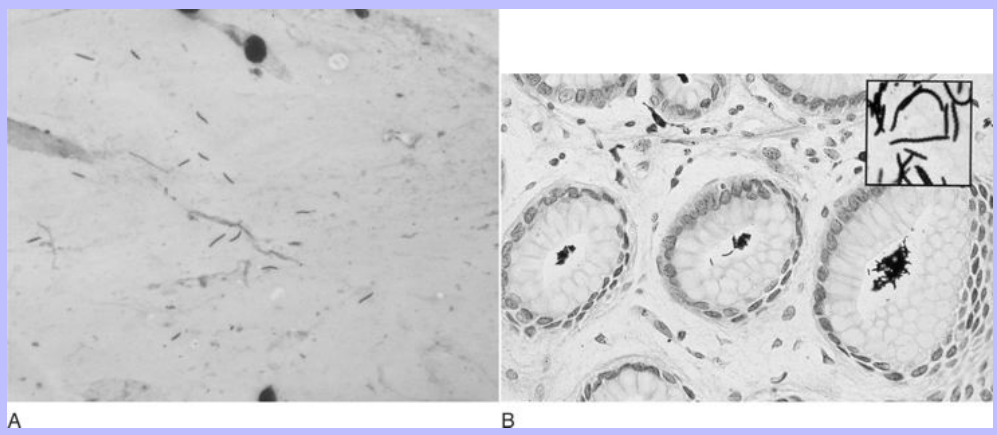
There is also a high prevalence of gastric *Helicobacter* spp. infection in dogs (67% to 100% of healthy pet dogs, 74% to 90% of vomiting dogs, 100% of laboratory beagles) and cats (40% to 100% of healthy and sick cats).[68–70] In contrast to people, in whom *Helicobacter pylori* infection predominates, dogs and cats are colonized by a variety of large spiral organisms (5 to 12 μ) (Figure 221-12). In cats from Switzerland, United States, and Germany, *Helicobacter heilmannii* is the predominant species, with *Helicobacter bizzozeronii* and *Helicobacter felis* much less frequent. In dogs from Finland, Switzerland, the United States, and Denmark *H. bizzozeronii* and *H. salomonis* are most common followed by *H. heilmanni* and *H. felis. H. bilis* and *Flexispira rappini* have also been described. Cats can also be colonized by *H. pylori* (2 to 5 μ) but infection has been limited to a closed colony of laboratory cats.

Ownership of dogs and cats has been correlated with an increased risk of infection of *H. heilmannii* in people.[71] Case reports have also suggested the transmission of *Helicobacter* spp. from pets to man. Recent studies clearly confirm that dogs and cats harbor *H. heilmannii*, but the subtypes of *H. heilmannii* present in dogs and cats (types 2 and 4) are of minor importance (approximately 15% of cases) to humans, who are predominantly colonized by *H. heilmannii* type 1 (the predominant *Helicobacter* sp. in pigs).[72]

The effect of eradicating *Helicobacter* spp. on gastritis and clinical signs, the main form of evidence supporting the pathogenic role of *H. pylori* in human gastritis, has not been thoroughly investigated to date in dogs and cats. An uncontrolled treatment trial of dogs and cats with gastritis and *Helicobacter* spp. infection showed that clinical signs in 90% of 63 dogs and cats responded to treatment with a combination of metronidazole, amoxicillin, and famotidine, and that 14 of the 19 animals re-endoscoped had resolution of gastritis and no evidence of *Helicobacter* spp. in gastric biopsies.[73]

Controlled clinical trials are required to confirm these observations but have been hampered by a much higher apparent recrudescence or re-infection rate than the 1% to 2% per year observed after treatment of *H. pylori*-infected people. With such limited information from eradication trials, most current knowledge about the pathogenicity of *Helicobacter* spp. for dogs and cats comes from the evaluation of animals with and without infections and clinical signs, and a small number of experimental infections. 1322 1323

Figure 221-12 *Helicobacter* spp. visualized on **(A)** an impression smear (Diff-Quick stain) and **(B)** endoscopic biopsy (Steiner stain).



The large *Helicobacter* species found in dogs an cats do not attach to the epithelium but colonize the superficial mucus and gastric glands, particularly of the fundus and cardia, and may also be observed intracellularly.[68,69] Degeneration of gastric glands, with vacuolation, pyknosis, and necrosis of parietal cells is more common in infected than uninfected animals. Inflammation is generally mononuclear in nature and ranges from mild to moderate in severity. Gastric lymphoid hyperplasia is common and can be extensive in dogs and cats infected with *Helicobacter* spp. (particularly when full thickness gastric biopsies are evaluated). In addition to this local gastric immune response, a systemic response characterized by increased circulating anti-*Helicobacter* IgG has been detected in sera from naturally infected dogs and cats. However, the gastritis observed in cats and dogs infected with large HLOs is generally less severe than that observed in *H. pylori* infected humans (where neutrophilic aggregates, and moderate to severe gastritis, are commonly encountered), and gastro-intestinal ulcers, gastric neoplasia, or changes in serum gastrin or acid secretion have not been associated with *Helicobacter* spp. infection in dogs and cats.

These differences between people, dogs, and cats may be attributed to differences in the virulence of the infecting *Helicobacter* spp., or the host response. Studies that address this issue indicate that *H. pylori* evokes a more severe pro-inflammatory cytokine and cellular response in dogs and cats than natural or experimental infection with large *Helicobacter* spp.[74,75] The limited mucosal inflammatory response and absence of clinical signs in the vast majority of dogs and cats infected with non-*H. pylori Helicobacter* spp., despite significant antigenic stimulation (evidenced by seroconversion and lymphoid follicle hyperplasia) suggest that large gastric *Helicobacter* spp. are more commensal than pathogenic. With this in mind, it is interesting to speculate that it is the loss of tolerance to gastric *Helicobacter* spp., rather than the innate pathogenicity of these bacteria, that explains the development of gastritis and clinical signs in some dogs and cats. However, much still remains to be learned about the role of *Helicobacter* spp. in canine and feline gastritis.

221.7.3 Clinical Findings

The major clinical sign of chronic gastritis is vomiting of food or bile. Decreased appetite, weight loss, melena, or hematemesis is variably encountered. The concurrent presence of dermatologic and gastrointestinal signs raises the likelihood of dietary sensitivity.[76] Access to toxins, medications, foreign bodies, and dietary practices should be thoroughly reviewed. The signalment should not be overlooked as it may increase the probability that chronic gastritis is the cause of vomiting. Hypertrophy of the fundic mucosa is frequently associated with a severe enteropathy in basenjis[77] and stomatocytosis, hemolytic anemia, icterus, and polyneuropathy in Drentse Patrijshond.[78] Hypertrophy of the pyloric mucosa is observed in small brachycephalic dogs such as Lhasa apso and is associated with gastric outflow obstruction (see Delayed Gastric Emptying and Motility Disorders). Atrophy of the gastric mucosa that may progress to adenocarcinoma has been reported in Lundehunds with protein-losing gastroenteropathy.[79]

Young, large breed, male dogs in the Gulf states of the United States may have granulomatous gastritis caused by *Pythium* spp. with infection more prevalent in fall, winter, and spring.[80] Physical examination is often unremarkable. Abdominal distension may be related to delayed gastric emptying caused by obstruction or defective propulsion. Abdominal masses, lymphadenopathy, or ocular changes may be encountered in dogs with gastric fungal infections.

221.7.4 Diagnosis

A biochemical profile, complete blood count, urinalysis, and T_4 (cats) should be performed as a basic screen for metabolic, endocrine, infectious, and other non-GI causes of vomiting, as well as the acid base and electrolyte changes associated with vomiting, outflow obstruction, or acid hypersecretion. Clinicopathologic tests are often normal in patients with chronic gastritis.

Eosinophilia may prompt the consideration of gastritis associated with dietary hypersensitivity, endoparasites, or mast cell tumors. Hyperglobulinemia and hypoalbuninemia may be present in basenjis with gastropathy/enteropathy, or dogs with gastric pythisosis. Panhypoproteinemia is a feature of gastro-enteropathy in Lundehunds, moderate to severe generalized inflammatory bowel disease, GI lymphoma, and GI histoplasmosis. More specific testing, such as an ACTH stimulation test, or serology for *Pythium insidiosum*, is performed based on the results of these initial tests. Determination of food specific IgE has not been shown to be useful in the diagnosis of dietary sensitivity in dogs or cats. The utility of noninvasive tests, such as serum pepsinogen and gastric permeability to sucrose, used to diagnose gastritis in people has not been determined in dogs and cats.

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Abdominal radiographs are frequently normal in dogs and cats with gastritis but may show gastric distention or delayed gastric emptying (food retained more than 12 hours after a meal). Contrast radiography may reveal ulcers or thickening of the gastric rugae or wall but has largely been supersceded by the combination of ultrasonography to detect mural abnormalities and endoscopy to observe and sample the gastric mucosa.[22]

Endoscopic examination enables the visualization of foreign bodies, erosions, ulceration, hemorrhage, rugal thickening, lymphoid follicle hyperplasia (evident as mucosal pock marks), increased mucus or fluid (clear or bile stained), and increased or decreased mucosal friability. Discrete focal or multifocal mucosal nodules may be observed with *Ollulanus* spp. infection.

Gastric phycomycosis can be associated with irregular masses in the pyloric outflow tract and may prompt serologic testing by ELISA, Western blotting, and culture of fresh gastric biopsies. Parasites such as *Physalloptera* spp. may be observed as 1-to 4-cm worms. Large amounts of bile stained fluid is suggestive of duodenogastric reflux-associated gastritis, whereas lots of clear fluid my indicate hypersecretion of gastric acid. Gastric fluid can be aspirated for cytology (*Helicobacter* spp., parasite ova or larvae) and pH measurement. Impression smears of gastric biopsies are an effective way of looking for *Helicobacter* spp. (5 to 12 μ spirals) and are more sensitive than the biopsy urease test (*Helicobacter* spp. produce urease). Serum gastrin should be measured in the face of unexplained gastric erosions, ulcers, fluid accumulation, or mucosal hypertrophy.

The endoscopic procedure of dribbling dietary antigens onto the gastric mucosa to ascertain the presence of food allergy has not been useful in dogs or cats: it is highly subjective, detects only immediate hypersensitivity, and does not correlate with the results of dietary elimination trials.[76] The stomach should be biopsied even when it looks grossly normal (usually three biopsies from each region-pylorus, fundus, and cardia). Thickened rugae may require multiple biopsies, and a full-thickness biopsy is often required to differentiate gastritis from neoplasia or fungal infection and to diagnose submucosal or muscular hypertrophy. The results of gastric ultrasonography can help to forewarn the clinician of these possibilities and are complement to the endoscopic findings.

Gastric sections should be stained with H&E for evaluation of cellularity and architecture, and modified Steiner stain for gastric spiral bacteria (Figure 221-12, *B*). Further special stains, such as Gomori's methenamine silver, are indicated if pyogranulomatous inflammation is present to detect fungi. Masson's trichrome can be used to highlight gastric fibrosis, whereas sirius red and alcian blue help to reveal eosinophils and mast cells, respectively. Immunocytochemistry can be employed to help distinguish lymphoma from severe lymphocytic gastritis. Mucin staining has been performed in Lundehunds with gastric atrophy and showed an abnormal presence of mucus neck cells and pseudo-pyloric metaplasia.[81]

The interpretation of gastric biopsies has important implications for patient care because biopsy findings are often used to guide treatment. For example, moderate lymphoplasmacytic gastritis without *Helicobacter* spp. infection is often treated with corticosteroids, whereas mild lymphoplasmacytic gastritis may be treated with a change in diet. As the histopathologic evaluation of gastric biopsies has not been standardized, the prudent clinician should carefully review histologic sections to get a feel for the pathologist's interpretation. Even with optimum evaluation similar histologic changes can be observed in patients with different underlying etiologies, so well-structured treatment trials often form the basis of an etiologic diagnosis.

221.7.5 Treatment

Treatment of gastritis initially centers on the detection and treatment of underlying metabolic disorders and the removal of drugs, toxins, foreign bodies, parasites, and fungal infections.

221.7.5.1 Parasitic Gastritis

Ollulanus tricuspis is a microscopic worm (0.7 to 1 mm long, 0.04 mm wide) that infects the feline stomach.[82] Its predominant cat-to-cat transmisison is through ingestion of vomitus. It can also undergo internal autoinfection with worm burdens reaching up to 11,000 per stomach. Mucosal abnormalities range from none, to rugal hyperplasia, and nodular (2 to 3 mm) gastritis.

Histologic findings include lymphoplasmacytic infiltrates, lymphoid follicular hyperplasia, fibrosis, and up to 100/hpf globular leukocytes. *Ollulanus* spp. are not detected by fecal examination and require evaluation of gastric juice, vomitus, or histologic sections for larvae or worms. Gastric lavage and xylazine-induced emesis have been described to aid diagnosis. Treatment with fenbendazole 10 mg/kg PO SID 2d may be effective.

Physalloptera spp. are about 2 to 6 cm long worms that are sporadically detected in the stomachs of dogs and cats. *Physalloptera rara* are most commonly described and appear to be primarily a parasite of coyotes. Diagnosis is difficult as worm burden is often low and the eggs are transparent and difficult to see in sugar floatation. Treatment with pyrantel pamoate (5 mg/kg PO: dogs single dose; cats two doses 14 days apart) may be effective. Control of infection may be difficult due to the ingestion of intermediate hosts, such as cockroaches and beetles, and paratenic hosts, such as lizards and hedgehogs.

Given the difficult diagnosis of *Ollulanus* and *Physalloptera* spp., empirical therapy with an anthelminthic such as fenbendazole may be warranted in dogs and cats with unexplained gastritis.

Gastric infection with *Gnathostoma* spp. (cats), *Spirocerca* spp. (dogs), and *Aonchotheca* spp. (cats) has been associated with gastric nodules that have been treated by surgical resection of affected gastric tissue.[83]

221.7.5.2 Gastric Pythiosis

The presence of transmural thickening of the gastric outflow tract (Figure 221-13, *D*) and histology that indicates pyogranulomatous inflammation raise the possibility of infection with fungi such as *Pythium insidiosum*.[80] Special staining (Gomoris methenamine silver), culture, serology, and PCR of infected tissues can be used to help confirm the diagnosis. Treatment consists of aggressive surgical resection combined with itraconazole (10 mg/kg PO SID) and terbinafine (5 to 10 mg/kg PO SID) for 2 to 3 months post-surgery. ELISA titers of pre-and post-treatment samples may show a marked drop during successful treatment and drugs can be stopped. Medical therapy is continued for another 2 to 3 months if titers remain elevated. The prognosis is poor and fewer than 25% of afflicted animals are cured with medical therapy alone.[80]

221.7.5.3 Helicobacter-Associated Gastritis

The general lack of knowledge of the pathogenicity of gastric *Helicobacter* spp. has meant that veterinarians are faced with the dilemma of either treating or ignoring spiral bacteria observed in biopsies from patients with chronic vomiting and gastritis. In light of their pathogenicity in man, ferrets, cheetahs, and mice, it would seem prudent that eradication of gastric *Helicobacter* spp. is attempted prior to initiating treatment with immunosuppressive agents to control gastritis. However, this must be decided on an individual basis. For example, in the patient with a lymphoplasmacytic infiltrate of the stomach and small intestine with a concomitant gastric *Helicobacter* spp. infection, should one treat for inflammatory bowel disease, *Helicobacter,* or both? 1324 1325

The author recommends treating only symptomatic patients that have biopsy-confirmed *Helicobacter* spp. infection and gastritis. Current treatment protocols are based on those found to be effective in humans infected with *H. pylori*. An uncontrolled treatment trial of dogs and cats with gastritis and *Helicobacter* spp. infection showed that clinical signs in 90% of 63 dogs and cats responded to treatment with a combination

of metronidazole, amoxicillin, and famotidine, and that 74% of 19 animals re-endoscoped had no evidence of *Helicobacter* spp. in gastric biopsies.[73]

Unfortunately these promising results regarding the eradication of *Helicobacter* spp. have not been borne out by more controlled studies in asymptomatic *Helicobacter*-infected dogs and cats. Treatment combinations that have been critically evaluated are (1) amoxicillin (20 mg/kg PO BID 14d), metronidazole (20 mg/kg PO BID 14d), and famotidine (0.5 mg/kg PO BID 14d) in dogs[84]; (2) clarithromycin (30 mg PO BID 4d), metronidazole (30 mg PO BID 4d), ranitidine (10 mg PO BID 4d), and bismuth (20 mg PO BID 4d) (CMRB) in *H. heilmannii* infected cats[85] and (3) azithromycin (30 mg PO SID 4d), tinidazole (100 mg PO SID 4d), ranitidine (20 mg PO SID 4d) and bismuth (40 mg PO SID 4d)(ATRB) in *H. heilmannii*-infected cats.[85] Re-evaluation of infection status at 3 days (dogs) or 10 days (cats) after treatment revealed six of eight dogs and 11 of 11 CMRB and four of six ATRB-treated cats to be *Helicobacter* spp. free on the basis of histology and urease testing (dogs) or ^{13}C-urea breath test (dogs and cats).[85,86] However, at 28 days (dogs) or 42 days (cats) after completing antimicrobial therapy, eight of eight dogs and four of eleven cats that received CMRB, five of six cats that received ATRB were found to be re-infected. A transient effect of combination therapy (amoxicillin 20 mg/kg PO TID 21d, metronidazole 20 mg/kg PO TID 21d, and omeprazole 0.7 mg PO SID 21d) on bacterial colonization has also been observed in six cats with *H. pylori* infection.

Further analysis of gastric biopsies from infected dogs and *H. pylori* infected cats using PCR and *Helicobacter*-specific primers revealed persistence of *Helicobacter* DNA in gastric biopsies that appeared negative on histology and urease testing. These studies suggest that antibiotic regimens that are effective against *H. pylori* in people may only cause transient suppression, rather than eradication, of gastric *Helicobacter* spp. in dogs and cats.

The author has recently employed the combination of amoxicillin (20 mg/kg PO BID), clarithromycin (7.5 mg/kg PO BID) and metronidazole (10 mg/kg PO BID) for 14 days to eradicate *Helicobacter pylori* infection in cats. Further controlled trials of antibiotic therapy in infected dogs and cats, particularly symptomatic patients with gastritis and *Helicobacter* spp. infection, are clearly required before guidelines regarding the treatment of gastric *Helicobacter* spp. in dogs and cats can be made.

221.7.5.4 Chronic Gastritis of Unknown Cause

Lymphocytic plasmacytic gastritis of unknown cause is common in dogs and cats. It may be associated with similar infiltrates in the intestines, particularly in cats (who should also be evaluated for the presence of pancreatic and biliary disease). The cellular infiltrate varies widely in severity and it may be accompanied by mucosal atrophy or fibrosis, and less commonly hyperplasia.

Patients with mild lymphoplasmacytic gastritis are initially treated with diet. The diet is usually restricted in antigens to which the patient has been previously exposed, such as a lamb-based diet if the patient has previously been fed chicken and beef, or contains hydrolyzed proteins (usually chicken or soy) that may be less allergenic than intact proteins. Many of these diets are also high in carbohydrate and restricted in fat, which facilitates gastric emptying, and may contain other substances such as menhaden fish oil or antioxidants that may alter inflammation.

The test diet is fed exclusively for a period of about 2 weeks while vomiting episodes are recorded.[76] If vomiting is improved a challenge with the original diet is required to confirm a diagnosis of food

intolerance. The introduction of a specific dietary component to the test diet, such as beef, is required to confirm dietary sensitivity. If vomiting is unresponsive the patient may be placed on a different diet for another 2 weeks, usually the limit of client tolerance, or started on prednisolone (1 to 2 mg/kg/day PO, tapered to every other day at the lowest dose that maintains remission over 8 to 12 weeks).

Patients with moderate to severe lymphoplasmacytic gastritis are usually started on a combination of a test diet and prednisolone. If the patient goes into remission they are maintained on the test diet while prednisolone is tapered and potentially discontinued. Antacids and mucosal protectants are added to the therapeutic regimen if ulcers or erosion are detected at endoscopy or if hematemesis or melena is noted.

If gastritis is unresponsive to diet, prednisolone, and antacids, additional immunosuppression may be indicated. Gastric biopsies should be carefully re-evaluated for evidence of lymphoma. In dogs immunosuppression is usually increased with azathioprine (PO2 mg/kg SID for 5d then EOD, on alternating days with prednisolone). Chlorambucil may be a safer alternative to azathioprine in cats (PO) and has been successfully employed in the management of inflammatory bowel disease and small cell lymphoma (see below). Prokinetic agents such as metoclopramide, cisapride, and erythromycin can be used as an adjunct where delayed gastric emptying is present. These are discussed below.

Diffuse eosinophillic gastritis of undefined etiology is usually approached in a similar fashion to lymphoplasmacytic gastritis. The presence of eosinphilia, dermatologic changes, and eosinophilic infiltrates may be even more suggestive of dietary sensitivity. In cats it should be determined if it is part of a hypereosinophilic syndrome. Treatment for occult parasites, dietary trials, and immunosuppression can be carried out as described above. Focal eosinophilic granulomas can be associated with parasites or fungal infection that should be excluded prior to immunosuppression with corticosteroids.

221.7.5.5 Atrophic Gastritis

Atrophic gastritis in dogs and cats is often associated with a marked cellular infiltrate (see Figure 221-10). In people atrophy is associated with *Helicobacter* spp. infection and inflammation, and immune-mediated destruction.[87] Gastric disease is often not discovered until the patient presents with pernicious anemia secondary to cobalamin deficiency caused by a lack of gastric intrinsic factor. In people, atrophic gastritis, intestinal metaplasia of the gastric mucosa, and hypochlorhydia are thought to precede the development of gastric cancer.[88] The host inflammatory response is also thought to contribute to the development of atrophy and pro-inflammatory IL-1β and IL-10 gene polymorphisms in people are associated with increased inflammation, gastric atrophy, hypochlorhydria, and gastric cancer.[89,90]

Atrophic gastritis has been infrequently described in dogs and cats but does share some similarities with people. Atrophy has been associated with gastric adenocarcinoma in Lundehunds[81] and in dogs with lymphoplasmacytic gastritis of undetermined cause atrophy correlates with the expression of mRNA for IL-1β and IL-10 and the presence of neutrophils. However, there is no clear evidence that lymphoplasmacytic gastritis progresses to atrophy and gastric cancer in dogs or cats,[91] and the role of *Helicobacter* spp. or antigastric antibodies in the development of atrophy in dogs and cats remains to be determined.

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In contrast to humans, dogs and cats with atrophic gastritis have not been reported to develop cobalamin deficiency. This is probably because the pancreas, rather than the stomach, is the main source of intrinsic factor in these species. Achlorhydria has been described in dogs and may enable the prolifera-tion of bacteria in the stomach and upper small intestine, although this has not been proven. The treatment of

atrophic gastritis has received limited attention, but *Helicobacter* spp. eradication and immunosuppression have been effective in people.

221.7.5.6 Hypertrophic Gastritis

Hypertrophy in the fundic mucosa is uncommon and is often part of the breed-specific gastropathies or gastroenteropathies mentioned above (Figure 221-13). Concurrent hypergastrinemia should prompt consideration of underlying hepatic or renal disease, achlorhydria, or gastrin-producing tumors, which should be pursued appropriately. Basenji gastoenteropathy is variably associated with fasting hypergastrinemia and exaggerated secretin stimulated gastrin, and anecdotal reports suggest that affected basenjis may respond to antimicrobial therapy. Antral hypertrophy of brachycephalic dogs causes outflow obstruction and is treated with surgery (see below).

221.8 DELAYED GASTRIC EMPTYING AND MOTILITY DISORDERS

Disorders of gastric motility can disrupt the storage and mixing of food and its expulsion into the duodenum.[25] Normal gastric motility is the result of the organized interaction of smooth muscle with neural and hormonal stimuli. Delayed gastric emptying is the most commonly recognized manifestation of gastric motility disorders. Rapid gastric emptying and motility disorders associated with retrograde transit of bile or ingesta are less well defined.

Delayed gastric emptying is caused by outflow obstruction or defective propulsion (Table 221-3) and is usually suspected by the vomiting of food at least 8 and often 10 to16 hours after a meal.

221.8.1 Diagnosis

Vomiting of food some time after ingestion (more than 8 hours) is the most common sign. Vomiting may be projectile with pyloric stenosis. Abdominal distension, weight loss, melena, abdominal discomfort, distention, bloating, and anorexia are more variably present.

The signalment and history may be helpful narrowing down the cause. Development of vomiting at weaning raises the possibility of pyloric stenosis. Access to foreign bodies, bones, and medications is of obvious relevance to outflow obstruction. Brachycephalic, middle-aged, small breed dogs, such as shih tzus, seem predisposed to the syndrome of hypertrophic pylorogastropathy, where vomiting is secondary to pyloric outflow obstruction caused by hypertrophy of the pyloric mucosa and/or muscularis.[92,93] Gastric neoplasia is usually detected in older animals, and weight loss, hematemesis, and pallor may be present. Gastric pythiosis is more prevalent in young large breed dogs in the Gulf states of the United States. Large breed, deep-chested dogs are more prone to GDV that may have an underlying problem with gastric emptying (see GD/GDV above).

A thorough physical examination is performed to detect causes of vomiting such as string foreign bodies, or intestinal masses or thickenings, non-gastrointestinal (GI) causes, including thyroid (nodules-cats), liver (jaundice, hepatomegaly) or kidney disease (renomegaly, lumpy or small), and the systemic effects of vomiting, such as dehydration and weakness.

Table • 221-3 Causes of Delayed Gastric Emptying

Outflow Obstruction
Congenital stenosis
Foreign bodies
Hypertrophy of pyloric mucosa
Granuloma
Polyps
Neoplasia
Extragastric masses
Defective Propulsion
Gastric disorders
Gastritis
Ulcers
Neoplasia
Gastroenteritis
Peritonitis
Pancreatitis
Metabolic (hypokalemia, hypocalcemia, hypoadrenocorticism)
Nervous inhibition (trauma, pain, stress?)
Dysautonomia
GDV
Surgery
Drugs (e.g., anticholinergics, narcotics)
Idiopathic

The diagnostic approach is to confirm delayed gastric emptying and to detect causes of gastric outflow obstruction that may require surgery, and non-gastric disorders associated with defective propulsion. Historical and physical findings are combined with clinicopathologic testing, plain radiographs, and ultrasonography.

Hematology, serum biochemistry, urinalysis, fecal analysis (e.g., parasites, parvo), and serology (e.g., FelV) are employed to detect non-GI causes of vomiting or delayed gastric emptying and to determine the consequences of vomiting. Laboratory findings vary depending on the severity of vomiting and completeness of pyloric obstruction and the presence of disorders associated with blood loss or inflammation. The CBC is often normal, but anemia may accompany gastric ulcers or neoplasia. Hyperglobulinemia may be present where outflow obstruction is secondary to fugal granuloma. The presence of hypochloremia, hypokalemia, and metabolic alkalosis, with or without aciduria, should increase suspicion of an upper GI obstruction or potential hypersecretion of gastric acid.

Radiographs are essential to confirm the retention of food or fluid in the stomach longer than 8 hours, and often 12 to 16 hours, after a meal, and to detect extra gastric disorders such as peritonitis. Ultrasound may detect mural thickening or irregularity of the stomach suggestive of neoplasia, granuloma, or hypertrophy. Ultrasound may also reveal radiolucent foreign objects and detect non-gastric causes of delayed emptying, such as pancreatitis. Contrast radiography can be used to detect mural abnormalities and to confirm a suspicion of gastric obstruction where plain radiographs are inconclusive (Figure 221-14). However, endoscopy is usually favored over radiographic procedures for confirming gastric outflow obstruction and gastric and duodenal causes of decreased propulsion (e.g., ulcers, gastritis) (see Figure 221-13). Measurement of gastric pH and serum gastrin can help to differentiate idiopathic hypertrophic pylorogastropathy from hypertrophy associated with hypergastrinemia. Pancreatic polypeptide-producing tumors may also be associated with mucosal hypertrophy. Endoscopy is hampered by the recent administration of barium so it is

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often performed first. Endoscopic biopsy is limited to the superficial mucosa and surgical biopsy is frequently required to achieve a definitive diagnosis of granulomatous, neoplastic, or hypertrophic conditions.

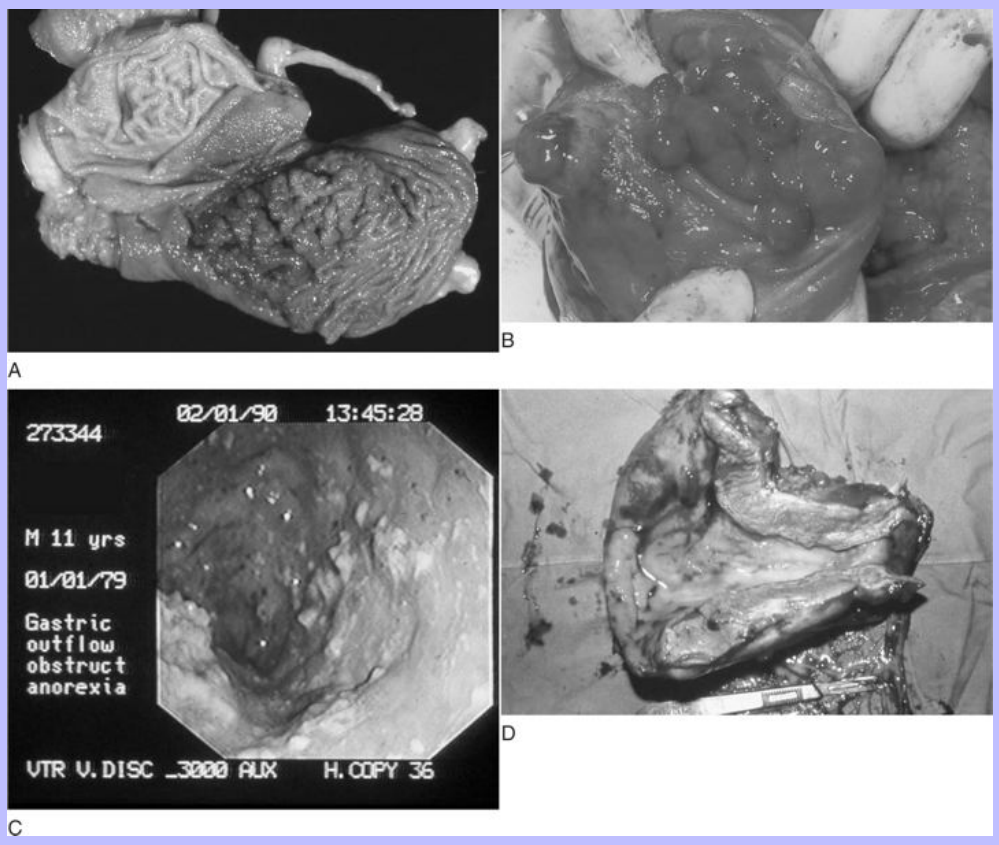
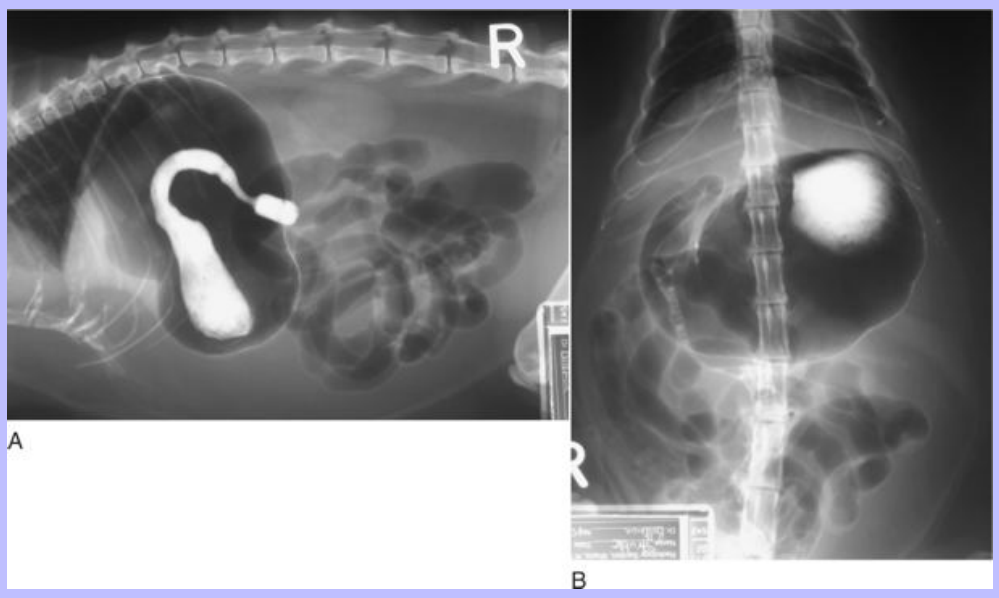


Figure 221-13 Gross appearance of hypertrophic gastropathies. **A,** Diffuse fundic hypertrophy; **B,** multifocal fundic hypertrophy; **C,** antral mucosal hypertrophy (idiopathic hyperplastic pylorogastropathy in a brachycephalic dog); **D,** thickening of the pyloric outflow tract due to *Pythium* spp. (*A, B,* and *D,* Courtesy of Cornell University; *C,* courtesy of The Ohio State University.)

Figure 221-14 Marked gastric dilation and retention of liquid barium in a 12-year-old domestic short hair cat. Full thickness gastric biopsies showed submucosal infiltration with neutrophils and lymphocytes. (Courtesy of Cornell University.)



More sophisticated procedures to directly evaluate gastric emptying and motility are usually employed to determine if vomiting is due to an undefined gastric motility disorder and to optimize prokinetic therapy (Table 221-4).[25,26] Radiographic contrast procedures are readily available but are hampered by the wide variability in emptying times for barium in liquid or meal form. The administration of barium impregnanted polyspheres (BIPS) is a simplified contrast procedure suited to routine clinical practice as it requires many fewer radiographs than traditional barium series and is standardized in terms of test performance and interpretation but its utility in clinical patients remains to be determined. Scintigraphic techniques are generally considered the most accurate way to evaluate emptying but are restricted to referral institutions. Ultrasound can be useful for detecting gastric wall abnormalities and measuring contractile activity. A test employing the labeled ^{13}C-octanoic acid has been evaluated in people and dogs and found to reflect gastric emptying (the values are longer than scintigraphy as ^{13}C-octanoate has to be absorbed and metabolized before $^{13}CO_2$ is liberated).

Table • 221-4 A Review of Methods for Assessment of the Rate of Gastric Emptying in the Dog and Cat[26]

METHOD	SPECIES	TEST MEAL	n	GASTRIC HALF EMPTYING TIME (t½)*
Radioscintigraphy	Dog	Eggs, starch +glucose	27	66 min (median), 45–227 min (95% CI)
		Beef baby food +kibble	6	4.9 ±1.96 hours (mean ±sd)
		Liver	4	About 2 hours
		Canned dog food +egg	6(18 tests)	172 ± 17 min (mean ±se)
		Canned dog food +egg	7(14 tests)	285 ± 34 min (mean ± sd); 294 ±39 min (mean ±sd)
		Canned dog food	6	77 min (mean)
	Cat	Dry cat food	10	2.47 ±0.71 hours (mean ±sd)
		Liver +cream	6(15 tests)	163 ± 11 min (mean ±se)
		Canned cat food	20	2.69 ±0.25 hours (mean ±sd)
		Dry cat food	20	3.86 ±0.24 hours (mean ±sd)
		Eggs	10	330 min (median), 210–769 min (range)
Radiography		Dry dog food +radio-opaque solids	10	3.5 hours (median), 1–6 hours (range)
		Canned dog food +egg +BIPS	6(18 tests)	Small BIPS 416 ± 81 min (mean ±se)
	Dog	Canned dog food +BIPS	20	Small BIPS 6.05 ± 2.99 hr (mean ±sd) Large BIPS 7.11 ± 3.60 hr (mean ±sd)
		Kibble +BIPS	8	Small BIPS =8.29 ± 1.62 hr (70% of dogs ± se) Large BIPS =29.21 ± 18.31 hr (70% of dogs ±se)
		Kibble +liquid barium	9(27 tests)	Total gastric emptying time =7–15 hr (range)
		Kibble +liquid barium	4	Total gastric emptying time =7.6 ± 1.98 hr (mean ±se)
	Cat	Canned cat food +BIPS	10	Small BIPS 6.43 ± 2.59 hr (mean ±sd) Large BIPS 7.49 ± 4.09 hr (mean ±sd)
		Canned cat food +BIPS	6	Small BIPS-7.7 hr (median), 3.5–10.9 hr (range) Large BIPS-8.1 hr (median), 5–19.6 hr (range)
		Canned cat food +BIPS	10	Small BIPS-5.36 hr (median) Large BIPS-6.31 hr (median)
		Cat food +liquid barium	8	Gastric emptying time =11.6 ± 0.9 hr (mean ±sd)
Gastric Emptying	Cat	Canned cat food	6	Peak ^{13}C-excretion =56.7 ± 9.8 min (mean ±sd)
Breath Test	Dog	Bread, egg +margarine	6(18 tests)	3.43 ± 0.50 hr (mean ±sd)

* Gastric emptying rate is expressed as gastric half emptying time, unless otherwise stated. (Reproduced with permission of Wyse et al, *JVIM* 2003,17:604–621.)

221.8.2 Treatment

Treatment of gastric emptying disorders is directed at the underlying cause. Gastric ulcers, erosions, and inflammation should be investigated and managed medically as described above. Foreign bodies are removed either endoscopically or surgically. Pyloric stenosis, polyps, and hypertrophic gastro-pathy that is not associated with hypergastrinemia are managed surgically. When hypertrophic gastropathy, ulcers or erosions,

or excessive gastric juice is encountered at endoscopy, intravenous H_2-antagonists can be given during the endoscopic procedure to try to prevent postoperative perforation or esophagitis. Neoplasia, polyps, and granulomas may require extensive gastric resection and Billroth procedures.

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Dietary modification to facilitate gastric emptying may be beneficial irrespective of cause.

Small amounts of semi-liquid, protein-and fat-restricted diets fed at frequent intervals may facilitate emptying, such as an “intestinal disease diet” blended with water and mixed with an equal volume of boiled rice.

In nonobstructive situations gastric emptying can be enhanced and duodenogastric reflux inhibited by prokinetic agents such as metoclopramide, cisapride, erythromycin, or ranitidine.[25,39,94] The choice of prokinetic depends if a central antiemetic effect is required (e.g., metoclopramide), if a combined antacid prokinetic is indicated (e.g., ranitidine), or if treatment with one agent has been ineffective or caused adverse effects (e.g., behavioral changes with metoclopramide). Metoclopramide (0.2 to 0.5 mg/kg PO SC TID) has central antiemetic properties in addition to its prokinetic activity in the stomach and upper GI tract and is frequently an initial choice in patients with underlying metabolic diseases associated with vomiting and delayed gastric emptying.

However, metoclopramide may only facilitate the emptying of liquids and is less effective in promoting organized gastroduodenal and intestinal motility than cisapride. Cisapride (0.1 to 0.5 mg/kg PO TID) has no central antiemetic effects but is generally more potent in promotion of the gastric emptying of solids than metoclopramide, but it does have more drug inter-actions and its availability is limited. Erythromycin (dog: 0.5 to 1.0 mg/kg PO TID, between meals) releases motilin and acts at motilin receptors and mimics phase III of the interdigestive migrating myoelectric complex (MMC) promoting the emptying of solids. Niaztidine and ranitidine (0.25 to 0.5 mg/lb PO TID) have prokinetic activity attributed to an organophosphate-like effect.

No controlled trials in dogs and cats have evaluated the efficacy of different prokinetics in different disease states, and treatment is usually based on a best guess/least harmful basis. Where true prokinetic activity is required, cisapride and erythromycin appear to be the most efficacious.[25] Treatment trials with prokinetics should probably be structured to last between 5 and 10 days to determine benefit. A diary of clinical signs and the objective assessment of gastric emptying using the tests described above, before and after therapy helps to optimize treatment. Combination therapy, such as erythromycin and cisapride, is not recommended due to the potential for adverse drug interactions. The prognosis for patients with delayed gastric emptying depends on the cause.

A suspected motility disorder characterized by duodenogastric reflux is thought to account for a syndrome known as the bilious vomiting syndrome. Affected dogs usually vomit early in the morning. Remission may be achieved by feeding the animal late at night. Prokinetic agents may also be employed.

221.9 GASTRIC NEOPLASIA

Gastric neoplasia represents less than 1.0% of all reported canine and feline neoplasms.[95] Malignant tumors are more common than benign tumors and most types of gastric neoplasms have been reported to occur more frequently in males, except adenomas, which occur more frequently in females.[95] Other gastric malignancies reported are leiomyosarcoma, lymphosarcoma, fibrosarcoma, rare anaplastic sarcomas, and gastric extramedullary plasmacytoma. Table 221-5 summarizes the prevalence, breed predisposition, and distribution of gastric tumors in dogs.

221.9.1 Benign Tumors

Benign tumors of the stomach include leiomyomas and less frequently, adenomatous polyps. Canine gastric leiomyoma is a tumor of old dogs, median age 16 years, and many are discovered incidentally at necropsy or when they are presented for GI bleeding and microcytic anemia (Figure 221-15).

Table • 221-5 Characteristics of Gastric Neoplasia in Dogs

TUMOR	MOST COMMON LOCATION	MEDIAN AGE (YEARS)	REPORTED BREED PREDISPOSITION
Adenocarcinoma	Pyloric antrum, lesser curvature	10	Belgian shepherd Rough Collie Staffordshire Bull terrier Lundehund
Leiomyoma	Cardia	16	Beagle
Leiomyosarcoma		7	none
Lymphosarcoma	Diffuse	10	none

Adenomatous polyps are rare in dogs but have been reported as either raised, sessile or pedunculated, single or multiple growths in the stomach. The most common site is the terminal pyloric antrum and although most are discovered incidentally, they may also cause signs of gastrointestinal upset with vomiting (Figure 221-16). In humans, adenomatous polyps are generally regarded as possible premalignant lesions and changes considered focally malignant have been found in dogs. Benign GI neoplasia in the cat occurs at a much lower frequency than in the dog, where up to 36% of all GI neoplasia is reported to be benign.

221.9.2 Malignant Tumors

221.9.2.1 Adenocarcinoma

Malignant adenocarcinoma is the most common gastric neoplasm in dogs and accounts for 47% to 72% of all canine gastric malignancies.[96–99] Gastric adenocarcinoma is extremely rare in cats. The peak age of dogs with gastric carcinomas has been reported to be from 11 to 12 years with a range of 3 to 13 years and an average age of 9.1 to 10 years. A breed predilection for gastric carcinoma in related Belgian shepherd dogs and rough collie and Staffordshire bull terrier has been suggested, although the majority of studies show no significant breed predilections. Lundehunds with atrophic gastritis seem overrepresented, and gastric atrophy and inflammation may precede tumorigenesis as it does in humans.[79,88]

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Figure 221-15 An ulcerated gastric leiomyoma in the cardia of a dog. (Courtesy of The Ohio State University.)

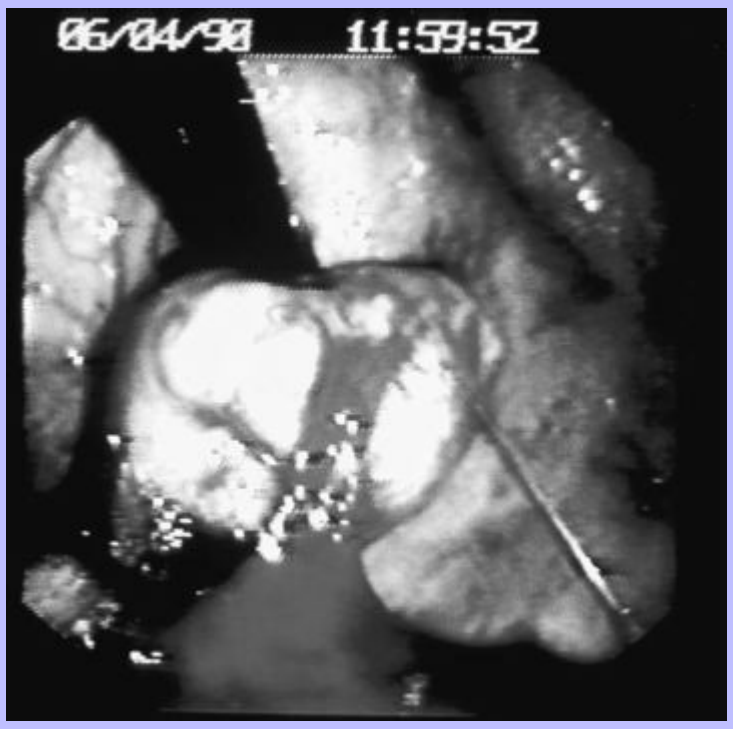
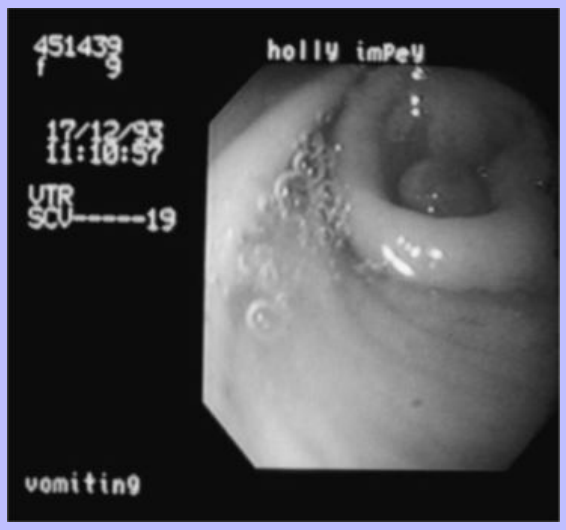
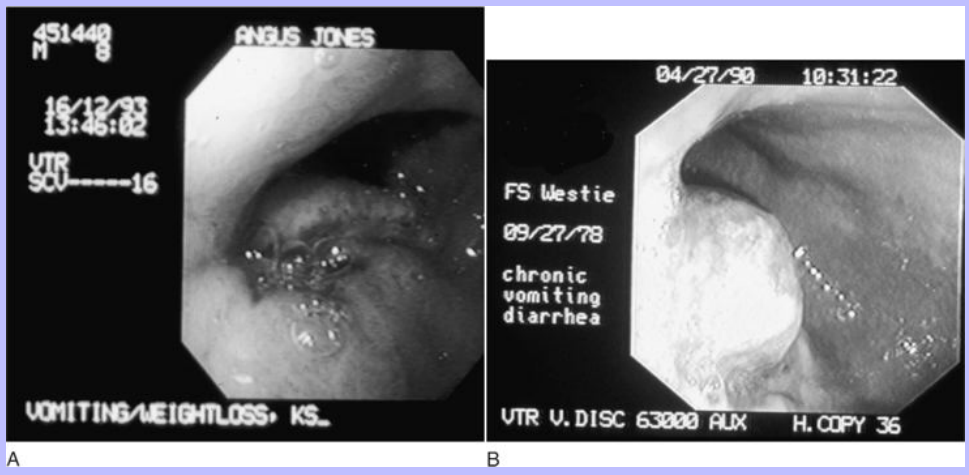


Figure 221-16 Adenomatous polyp in the pyloric outflow tract of a dog. (Courtesy of University of London.)



Gastric carcinomas of dogs occur most commonly in the lesser curvature and pyloric region as annular or stenosing lesions and metastasis is frequent with involvement of lymph nodes, lung, and liver (Figure 221-17). Carcinomas can be further divided into three morphologic patterns of distribution: (1) Diffusely infiltrating non-ulcerating lesions that involve most of the stomach and are consistent with the "leather bottle" appearance described in man, (2) Localized, raised thickened plaque usually containing a raised, excavating central ulcer, and (3) Raised, polypoid, sessile lesion projecting into the lumen of the stomach.

Figure 221-17 Endoscopic appearance of diffuse **(A)** and focal **(B)** gastric adenocarcinoma in a dog. (Courtesy of The Ohio State University.)



Two histologic types of gastric carcinoma exist in man: the diffuse and intestinal or tubular type. The diffuse type consists of widespread random infiltrates of neoplastic cells dispersed between stromal elements of the gastric wall. The intestinal type is characterized by a tubular, glandular structure. These same two classifications have been shown to exist in dogs with the diffuse type being more common.

221.9.2.2 Lymphosarcoma

The most common gastrointestinal neoplasm in both cats and dogs is lymphosarcoma, although it most often involves several segments of the intestinal tract. In canine lymphosarcoma (LSA) or lymphoma originating in the gastric submucosa the tumor type can be described as diffuse or nodular with the diffuse infiltrate being more common (Figure 221-18). Involvement of the liver, regional lymph nodes, small intestine, and bone marrow is common. Feline gastric lymphoma is not associated with FelV infection and has been recently categorized as large cell or small cell, with small cell lymphoma being more localized to the GI tract and carrying a much better prognosis than large cell lymphoma.[100]

In both dogs and cats, lymphocytic-plasmacytic inflammation has been found to precede or coexist with gastric LSA, and it has been suggested that lymphocytic-plasmacytic enteritis (LPE) is a prelymphomatous change in the GI tract. The development of gastric lymphoma in response to chronic antigenic stimulation

and inflammation is exemplified by gastric MALT lymphoma in people with *H. pylori*-associated gastritis. Whether a similar situation is present in dogs and cats remains to be determined.

221.9.2.3 Leiomyosarcoma

Leiomyosarcomas are slow growing tumors of smooth muscle origin. The median age for of affected dogs is greater than 10 years. Intestinal leiomyosarcoma has been found to be more common in female dogs and a predilection was reported in the German shepherd breed. However, neither breed nor sex predilection has been reported for gastric leiomyosarcoma.[101] In one study, dogs with leiomyosarcoma of the spleen, stomach, small intestine, and cecum were grouped together with 79% showing no evidence of metastases at surgery and 64% survived longer than 2 weeks.[101] Invasion of the gastric wall by leiomyosarcomas and lymphosarcomas is often diffuse. These tumors may cause ulceration, grossly resembling adenocarcinomas or appear as discrete masses. The median survival of these dogs was 10 months (range 1 month to 7 years). Of the stomach/small intestine group, 29% died of leiomyosarcoma eventually. Leiomyosarcoma and leiomyoma have been associated with paraneoplastic hypoglycemia and seizures presumed due to the production of insulin-like growth factors.[102]

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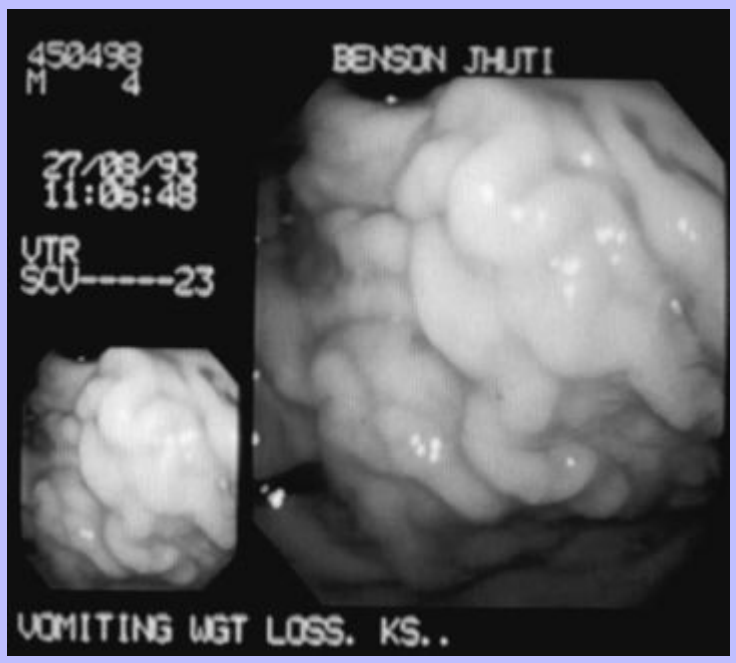
Figure 221-18 Gastric rugal thickening due to lymphoma. (Courtesy of University of London.)



221.9.3 Clinical Findings

The most common clinical signs associated with gastric neoplasia are chronic vomiting, weight loss, anorexia, diarrhea, and hematemesis, melena, or pallor if ulceration is present. Some dogs will also show abdominal

pain or a distended abdomen. With GI lymphoma, the onset of clinical signs is often insidious and gradually increases in severity, becoming refractory to symptomatic treatment.

221.9.4 Diagnosis

Survey radiographs may be completely normal or suggest focal gastric wall thickening, an abdominal mass, or evidence of peritonitis, rupture of a viscus, splenomegaly, hepatomegaly, or lymphadenopathy.

Ultrasonography may reveal mural thickening or irregularities that forewarn the endoscopist the lesion may be more submucosal or muscular than superficial. Lympadenopathy or regional metasasis may be evident.

Gastroscopy is able to efficiently detect most gastric tumors and has largely replaced contrast radiography. Lymphosarcoma is seen as a diffuse, smooth, or cobblestone-like thickening of the rugae with a mucosa that is pink or white and may have scattered petechial or ecchymotic hemorrhages. Gastric carcinomas tend to be focal dark pink to red masses that may appear slightly pedunculated. Discolored purple to black areas indicate hemorrhage, whereas yellow to brown foci often represent necrotic ulcers. In some cases, lesions may be submucosal and the endoscopist gets the impression that something is indenting the stomach or the wall seems less distensible or thick.

Several biopsy samples should be taken from suspicious areas and masses should be biopsied multiple times in the same place to get deeper into tissue as gastric tumors may have superficial necrosis, inflammation, and ulceration. These centers of ulcers and craters should be avoided, taking biopsies at the periphery to avoid perforation. Surgical biopsies should be taken where the gross endoscopic appearance does not match the histologic diagnosis, such as a large focal gastric mass with an endoscopic biopsy result of lymphoplasmacytic gastritis.

When endoscopy is not available contrast radiography may be useful with features of gastric neoplasia including thickening of the gastric wall, filling defects and derangement of normal rugal pattern, and delayed gastric emptying with retention and irregular pooling of barium. Surgery is then performed to sample the affected area.

221.9.5 Treatment

Except for lymphosarcoma, surgery is the most common form of treatment for gastric cancer. Resection may be curative if the affected area is localized or if the tumor is benign. If a widespread area is involved, a partial gastrectomy or antrectomy followed by gastroduodenostomy (Billroth I) may be attempted. However, many patients are presented at a late stage of disease and the lesions are often too extensive to resect. Gastric adeoncarcinoma often metastasizes and regional lymph nodes and liver should be inspected and biopsied. Even with surgery the prognosis for malignant gastric neoplasia is poor, with most patients dying within 6 months from recurrent or metastatic disease. Leiomyosarcoma is an exception and carries a good to excellent prognosis if the mass is surgically resectable. Even if gross metastasis is evident at surgery, a favorable outcome may be achieved because the tumor is slow growing. Survival in dogs with stomach, small intestinal, splenic, and cecal leiomyosarcoma ranges from 0 to 47 months after surgery and the median survival is 12.5 months.[101]

Gastrointestinal lymphosarcoma has a poor prognosis in dogs.[103] In cats the prognosis depends if the tumor is small or large cell. Small cell lymphomas achieve substantial remission when treated with chlorambucil and

prednisolone.[100] Large cell lymphoma is treated with combination cyclical chemotherapy and carries a much poorer prognosis.

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222 CHAPTER • 222 Diseases of the Small Intestine

Edward J. Hall

Alexander J. German

The small intestine (SI) must be capable of performing digestive and absorptive functions while simultaneously protecting the body from a multitude of environmental threats. Thus it is the largest and most complex immunologic organ in the body, and armed with an understanding of its immunologic role, the clinician will be better able to understand and treat many intestinal diseases.

Considering the complex, paradoxical roles of the small intestine, minor daily variations in stool quality must be considered normal. *Diarrhea,* a significant increase in the frequency, fluidity, or volume of feces, is the cardinal sign of SI malfunction. However, diarrhea may also be a manifestation of disease elsewhere in the gastrointestinal (GI) tract or even in other organ systems (Box 222-1). Furthermore, diarrhea is not present in all cases of SI disease, and many other signs of SI disorder are nonspecific and may be overlooked (Box 222-2). Nevertheless, an understanding of normal SI function, in particular the small intestine's role as an immunologic organ, allows a logical approach to diagnosis and treatment.

222.1 STRUCTURE AND FUNCTION OF THE SMALL INTESTINE

222.1.1 Normal Structure

222.1.1.1 Gross Structure

The small intestine runs from the pylorus of the stomach to the ileocolic valve (Figure 222-1, *A*). It is divided anatomically into three arbitrary segments: the proximal duodenum (Figure 222-2), the jejunum, and the distal ileum.[1]

222.1.1.2 Microstructure

The small intestine is in essence a tube connected to the external environment (Figure 222-1, *B*). Its basic cross-sectional structure of serosa, muscularis, submucosa, and mucosa is present throughout (Figure 222-1, *C*) but varies in proportions, reflecting the varying functions of each region.

The *mucosa* is the most clinically important layer of the intestine. It is responsible for secretion and absorption and serves as a barrier. It comprises the epithelium and the lamina propria and is modified by gross folds and fingerlike processes, the *villi* (see Figure 222-1, *C*). Mucosal capillaries are fenestrated; in conjunction with a central villus lymphatic (*lacteal*), they carry away protein-rich tissue fluid. Loss of epithelial integrity permits leakage of the protein-rich fluid and the development of a protein-losing enteropathy (PLE). The lamina propria contains aggregates of lymphoid tissue and nonaggregated immunocytes (see Gastrointestinal Immune System).

222.1.2 Functional Anatomy

222.1.2.1 Surface Area of the Small Intestine

The surface area of the small intestine is increased almost 600-fold, compared with that of a simple tube, by folds in the mucosal wall (~3 fold), cylindrical projections into the intestinal lumen called villi (~10 fold), and microscopic microvilli on the surface of each epithelial cell (~20 fold) (see Figure 222-1). Villus atrophy or even just microvillar damage is likely to produce profound malabsorption and diarrhea.

222.1.2.1.1 Box • 222-1 Causes of Diarrhea

222.1.2.1.1.1 Gastrointestinal Disease

Primary small intestinal disease

Primary large intestinal disease

Dietary-induced causes (food poisoning, gluttony, sudden change of diet)

Gastric disease

- Achlorhydria*
- Dumping syndromes*

Pancreatic disease

- Exocrine pancreatic insufficiency
- Pancreatitis
- Pancreatic neoplasia

Liver disease

- Hepatocellular failure
- Intrahepatic and extrahepatic cholestasis

222.1.2.1.1.2

Nongastrointestinal Disease

Polysystemic infection (e.g., distemper, leptospirosis, infectious canine hepatitis in dogs; FIP, FeLV, FIV in cats)

Endocrine disease

- Hypoadrenocorticism
- Hyperthyroidism†
- Hypothyroidism
- APUDomas (gastrinoma or Zollinger-Ellison syndrome)*

Renal disease

- Uremia
- Nephrotic syndrome

Miscellaneous

- Toxemias (pyometra, peritonitis)
- Congestive heart failure
- Autoimmune disease
- Metastatic neoplasia
- Various toxins and drugs

* Rare conditions.

† Rare in dogs only.

APUD, amine precursor uptake and decarboxylation tumor

FeLV, feline leukemia virus

FIP, feline infectious peritonitis

FIV, feline immunodeficiency virus

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222.1.2.1.2 Box • 222-2 Clinical Signs of Small Intestinal Disease

222.1.2.1.2.1 Primary Sign

Diarrhea (increase in frequency, volume, and consistency of bowel movements)

222.1.2.1.2.2 Secondary Signs

Vomiting

Weight loss and/or failure to thrive

Hematemesis

Melena

Altered appetite (inappetence/anorexia)

Polyphagia, coprophagia, pica

Abdominal discomfort, pain

Abdominal distension

Borborygmi and flatus

Halitosis

Dehydration

Polydipsia

Ascites and edema

Shock

222.1.2.2 Crypt-Villus Unit

A villus and its associated crypts comprise the functional unit of the small intestine (see Figure 222-1, *D*). Crypts continually produce undifferentiated epithelial cells, mainly enterocytes. After further division of daughter cells as they pass up the crypt, cells undergo a final division before differentiating into immature enterocytes.

222.1.2.3 Mucosal Epithelial Cells

The intestinal surface is covered by an epithelial cell monolayer. Enterocytes predominate, interspersed mainly with mucus-secreting goblet cells. The epithelial basement membrane is permeable to nutrients, and by expressing glycoproteins, called *laminins,* it promotes enterocyte adhesion, growth, polarization, and differentiation through interaction with integrins expressed by enterocytes.[2]

Crypt cells have a potent secretory capacity. However, as enterocytes migrate to the villus tip, maturation involves loss of secretory activity and the development of digestive and absorptive properties. The duration of migration from crypt to villus tip is 3 to 5 days in dogs and cats. The majority of enterocytes are exfoliated at the tips of the villi.

Goblet cell density in the mucosa varies, being highest in the ileum. The cells secrete protective mucus and novel trefoil peptides, which act as growth factors. Endocrine-and paracrine-secreting epithelial cells, as well as transforming growth factors α and β (TGFα) and epidermal growth factor (EGF), have important trophic activities. Receptors for EGF on the luminal and basolateral surfaces of enterocytes suggest they respond both to blood-borne EGF and to luminal EGF secreted from salivary and pancreatic tissue or delivered in milk.

222.1.2.4 Enterocytes

The *mucosal barrier* is formed by the intestinal epithelium; tight junctions encircle the lateral aspects of enterocytes, excluding antigens and bacteria. Effete enterocytes are shed from the villus tip (see Figure 222-1, D), but the integrity of the tight junctions is probably loosest in the crypts, where fluid secretion occurs.

Enterocyte function dictates normal digestion and nutrient absorption. Function depends on the polarity of the enterocyte, involving a specialized portion of the cell membrane on the luminal surface, the *microvillar membrane (MVM)*. The MVM, also called the *brush border* because of its microscopic appearance (see Fig. 222-1, *E* and *F*), consists of thousands of parallel cylindrical processes, the microvilli, bearing digestive enzymes and specific carrier proteins (see Figure 222-1, *F*). Maximum enzyme and transport activities are expressed in the midvillus region. As enterocytes migrate to the villus tip, enzymes are cleaved from the brush border by bacterial and pancreatic proteases and released into the lumen to form the succus entericus, which is thus not a true secretion.

Enterocyte metabolism is geared toward the production of brush border proteins and the transfer of nutrients from the lumen to the blood. Basolateral cell membranes export sodium from the cell via energy-dependent sodium-potassium adenosine triphosphatase (Na/K ATPase). Water can follow osmotically, or compensatory sodium influx at the luminal surface can drive carrier-mediated nutrient absorption. Natural inhibition of glycolysis in enterocytes facilitates the transfer of glucose from the lumen to the blood. Enterocytes can utilize ketone bodies, but their major energy source is glutamine. Both are derived from the lumen, which explains the decline in villus structure, epithelial integrity, and absorptive function in starvation and anorexia and therefore the clinical importance of attempting to maintain enteral nutrition.[3]

Brush border enzyme activities are variable, tending to be highest in the proximal SI and declining in an aborad gradient. Digestive enzymes, especially disaccharidases and transport proteins, may be inducible in response to the composition of the diet. This has been shown in dogs[4] but not in cats,[5] perhaps reflecting

the carnivorous nature of cats. A sudden change in diet in dogs may cause diarrhea through transient intolerance until either existing enterocytes upregulate expression of specific enzymes and carriers or new enterocytes expressing induced proteins differentiate, thus rendering the diarrhea self-limiting.

222.1.3 Digestion

Major dietary constituents must be hydrolyzed from their initial polymeric structure to monomers to be transported across the MVM. This is largely achieved in the SI by bile salts and luminal enzymes. The intestine provides the optimum environment in terms of solute, temperature, and pH. Most enzymes are secreted by the pancreas, and exocrine pancreatic insufficiency (EPI) is a major cause of malabsorption. Normally only terminal digestion is performed by MVM enzymes; the reserve capacity called into function after significant intestinal resection probably represents both increases in brush border protein expression and compensatory hypertrophy of the remaining tissue (see Short Bowel Syndrome).

Lactose is found almost exclusively in dairy products, and its hydrolysis by brush border lactase is most important in the nursing animal. At weaning, activities of lactase decline, especially in cats,[5] and animals may become lactose intolerant, although congenital lactase deficiency has not been demonstrated in dogs or cats.

222.1.4 Absorption

Digested nutrients are delivered to the body across the mucosal barrier and then via the lymphatics or bloodstream. Uptake can occur by passive diffusion or by active or facilitated carrier-mediated transport. Receptor-mediated endocytosis enables the uptake of small amounts of a specific intact nutrient, such as cobalamin. Endocytosis of small, antigenic peptides is of no nutritional significance but is crucial to the mucosal immune response.

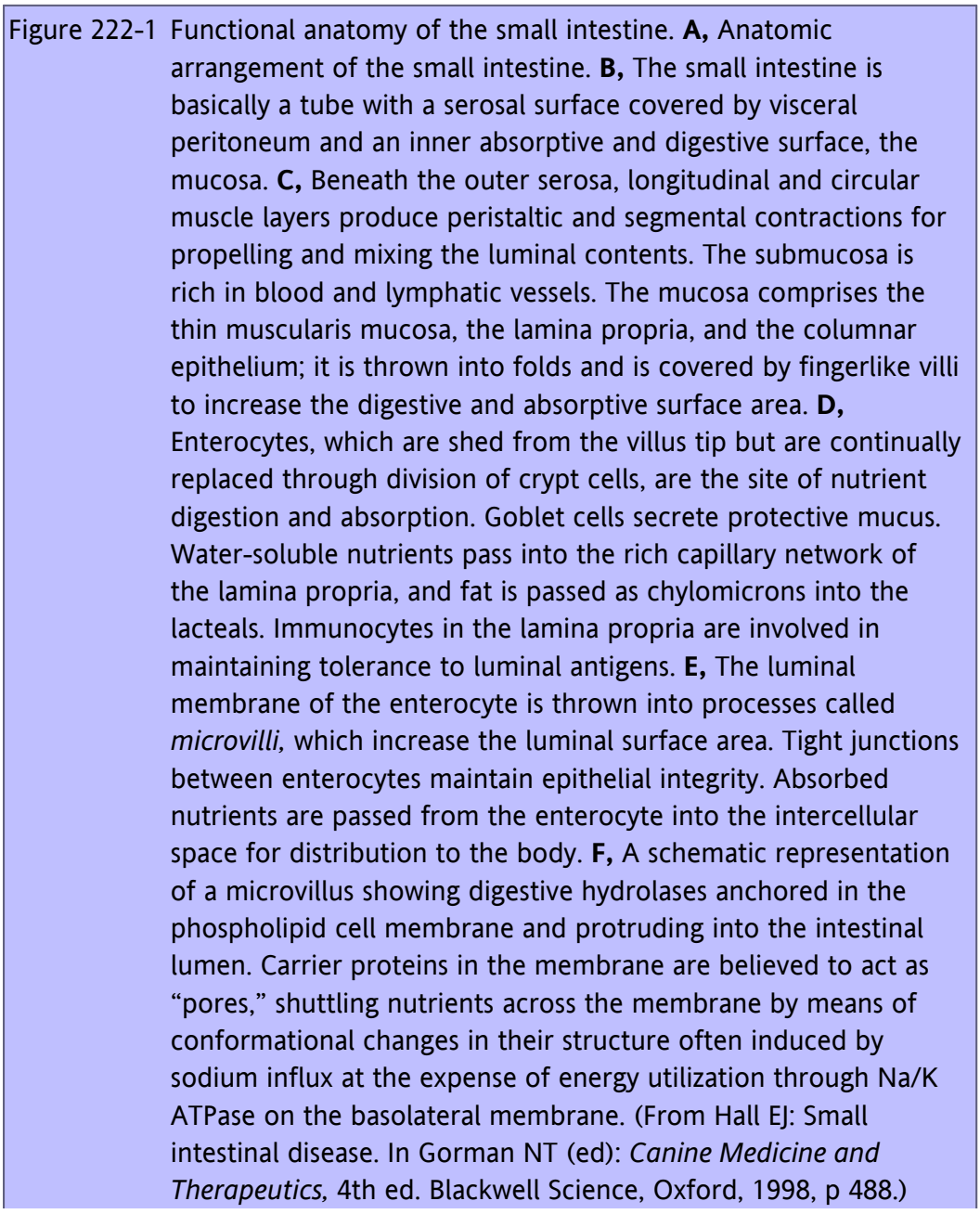

Figure 222-1 Functional anatomy of the small intestine. **A,** Anatomic arrangement of the small intestine. **B,** The small intestine is basically a tube with a serosal surface covered by visceral peritoneum and an inner absorptive and digestive surface, the mucosa. **C,** Beneath the outer serosa, longitudinal and circular muscle layers produce peristaltic and segmental contractions for propelling and mixing the luminal contents. The submucosa is rich in blood and lymphatic vessels. The mucosa comprises the thin muscularis mucosa, the lamina propria, and the columnar epithelium; it is thrown into folds and is covered by fingerlike villi to increase the digestive and absorptive surface area. **D,** Enterocytes, which are shed from the villus tip but are continually replaced through division of crypt cells, are the site of nutrient digestion and absorption. Goblet cells secrete protective mucus. Water-soluble nutrients pass into the rich capillary network of the lamina propria, and fat is passed as chylomicrons into the lacteals. Immunocytes in the lamina propria are involved in maintaining tolerance to luminal antigens. **E,** The luminal membrane of the enterocyte is thrown into processes called *microvilli,* which increase the luminal surface area. Tight junctions between enterocytes maintain epithelial integrity. Absorbed nutrients are passed from the enterocyte into the intercellular space for distribution to the body. **F,** A schematic representation of a microvillus showing digestive hydrolases anchored in the phospholipid cell membrane and protruding into the intestinal lumen. Carrier proteins in the membrane are believed to act as "pores," shuttling nutrients across the membrane by means of conformational changes in their structure often induced by sodium influx at the expense of energy utilization through Na/K ATPase on the basolateral membrane. (From Hall EJ: Small intestinal disease. In Gorman NT (ed): *Canine Medicine and Therapeutics,* 4th ed. Blackwell Science, Oxford, 1998, p 488.)

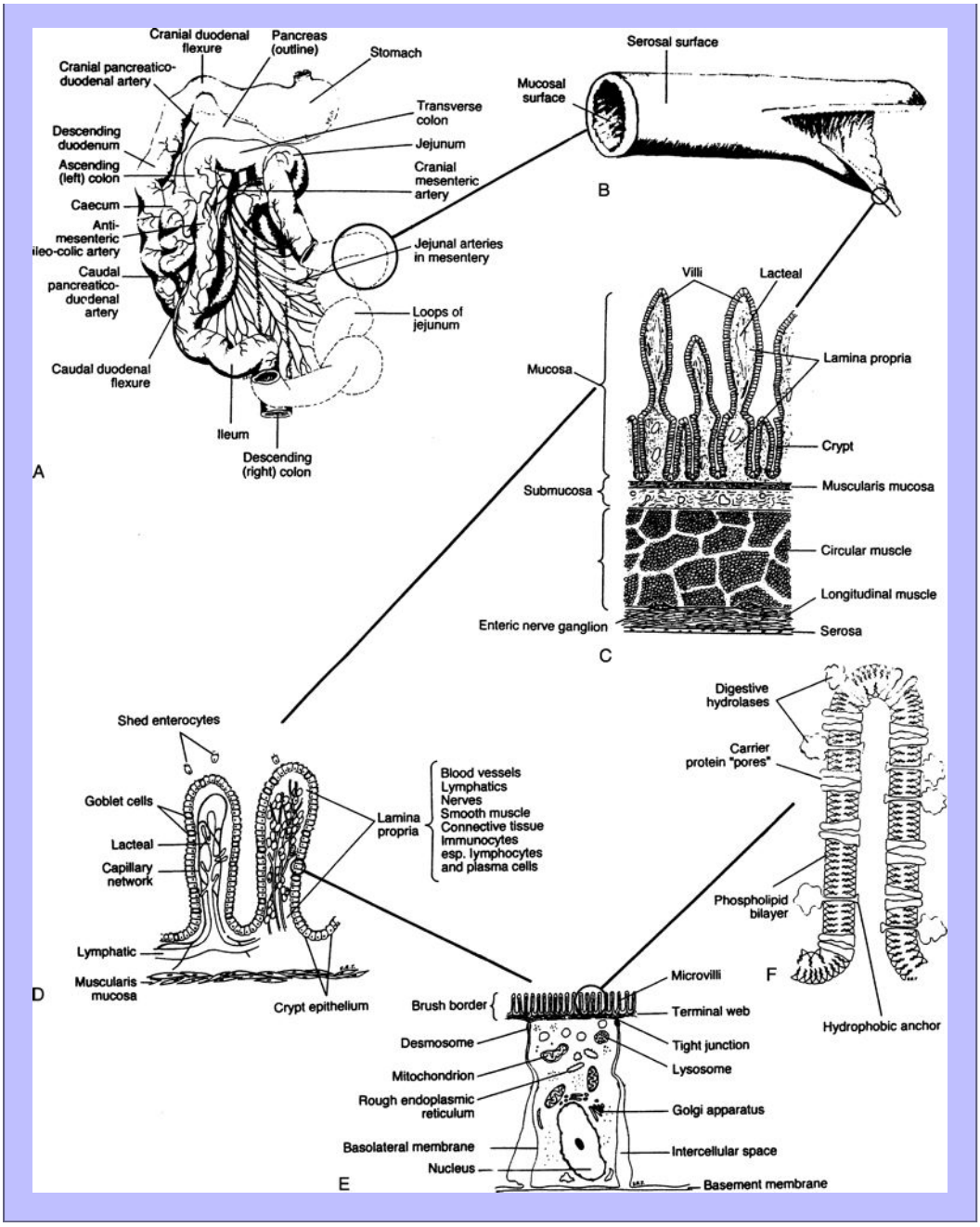
Cranial duodenal flexure
Pancreas (outline)
Stomach
Cranial pancreatico-duodenal artery
Transverse colon
Descending duodenum
Jejunum
Ascending (left) colon
Cranial mesenteric artery
Caecum
Anti-mesenteric ileo-colic artery
Jejunal arteries in mesentery
Caudal pancreatico-duodenal artery
Loops of jejunum
Caudal duodenal flexure
Ileum
Descending (right) colon
A
Serosal surface
Mucosal surface
B
Villi
Lacteal
Lamina propria
Mucosa
Crypt
Submucosa
Muscularis mucosa
Circular muscle
Longitudinal muscle
Enteric nerve ganglion
Serosa
C
Digestive hydrolases
Carrier protein "pores"
Shed enterocytes
Goblet cells
Blood vessels
Lymphatics
Nerves
Smooth muscle
Connective tissue
Immunocytes esp. lymphocytes and plasma cells
Lamina propria
Lacteal
Capillary network
Phospholipid bilayer
Lymphatic
Muscularis mucosa
Crypt epithelium
D
F
Microvilli
Brush border
Terminal web
Hydrophobic anchor
Desmosome
Tight junction
Lysosome
Mitochondrion
Rough endoplasmic reticulum
Golgi apparatus
Basolateral membrane
Intercellular space
Nucleus
Basement membrane
E

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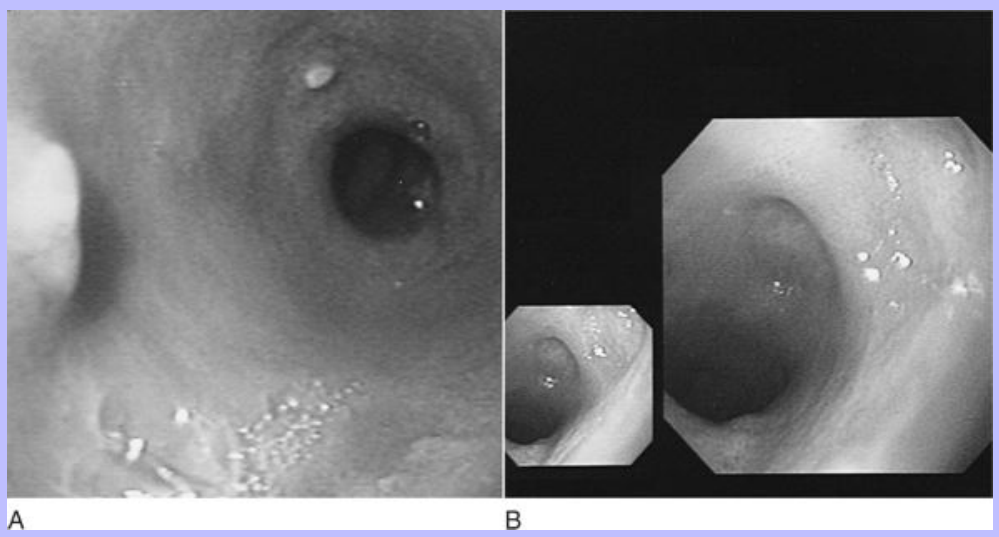
Figure 222-2 Video-endoscopic appearance of the upper small intestine. **A,** Major and minor duodenal papillae in a normal canine duodenum. **B,** Peyer's patches on the antimesenteric side of the duodenum, appearing as a line of mucosal depressions.



222.1.4.1 Carbohydrate Absorption

Glucose is transported across the MVM with energy expenditure by the basolateral Na/K ATPase on the sodium-glucose cotransporter protein SGLT 1. The glucose transporter GLUT 5 on the MVM allows facilitated diffusion of fructose and D-xylose. Fructose uptake in cats is low, which perhaps explains why the xylose absorption test is unhelpful in cats. GLUT 2 on the basolateral membrane of enterocytes shuttles glucose, galactose, and fructose out of the enterocyte by facilitated diffusion.

222.1.4.2 Protein Absorption

L-amino acids are absorbed on stereo-specific carriers by sodium-linked active transport.

222.1.4.3 Lipid Absorption

The products of fat digestion are absorbed by passive diffusion from mixed micelles. The limiting factor, assuming normal pancreatic function, is the intestinal surface area, and villus atrophy is likely to cause fat malabsorption.

222.1.4.4 Fat-Soluble Vitamins

Vitamins A, D, E, and K are solubilized in mixed micelles before passive diffusion across the brush border. Fat malabsorption associated with inadequate amounts of bile salts (i.e., biliary obstruction), lymphangiectasia, or severe villus atrophy may result in vitamin deficiency.

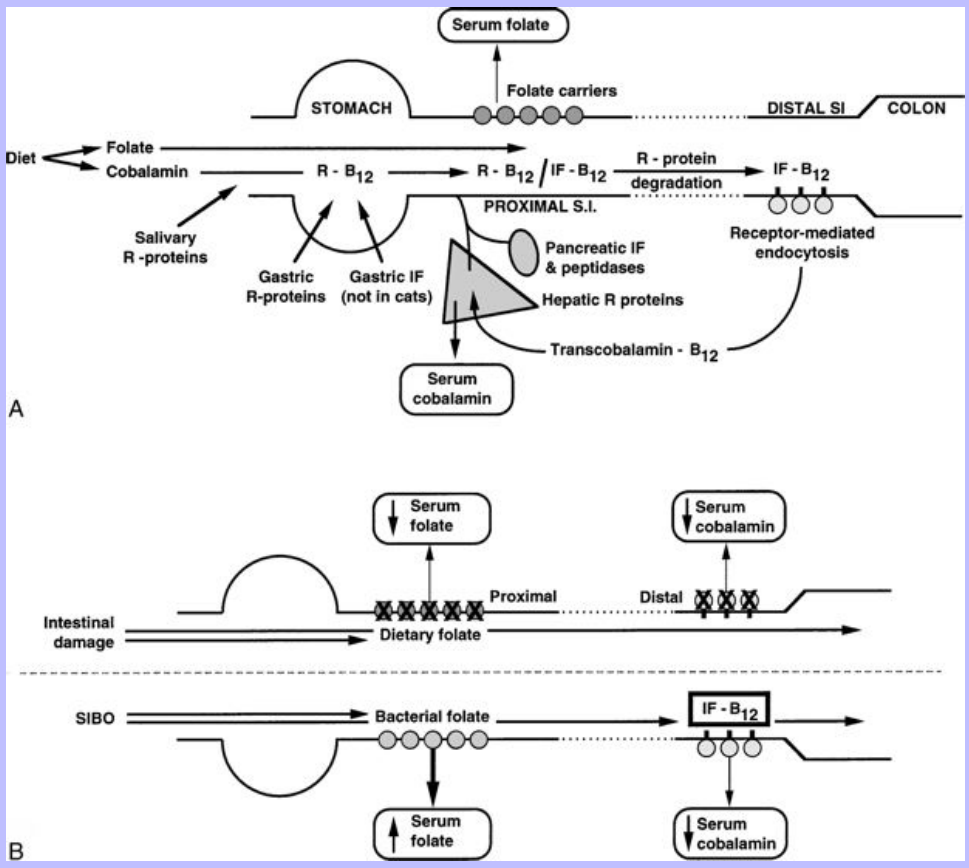
222.1.4.5 Water-Soluble Vitamins

Water-soluble B vitamins are absorbed by a variety of passive, facilitated, and active mechanisms. The absorptive mechanisms for folic acid and vitamin B_{12} are complex (Figure 222-3, *A*) and important clinically because they may be helpful in determining the site and nature of the intestinal disease (Figure 222-3, *B*).

Folic acid is absorbed in the proximal SI through a carrier-mediated process at low luminal concentrations. 1335

Cobalamin (vitamin B_{12}) is absorbed by means of receptor-mediated endocytosis in the ileum, in a complex process that permits intact cobalamin absorption and exclusion of potentially harmful analogs. Intrinsic factor (IF) promotes cobalamin absorption in the ileum; IF-bound cobalamin passes to the ileum, where the complex binds specific receptors and undergoes endocytosis. The source of IF is the stomach and pancreas in dogs and solely the pancreas in cats.[6,7] Cats and dogs have less capacity to store cobalamin than do humans, and severe cobalamin malabsorption can deplete the vitamin's stores in cats and dogs within a month. 1336

Figure 222-3 Diagrammatic representation of the absorption of folate and cobalamin. **A,** In normal intestine, folate is absorbed in the proximal SI by means of carrier-mediated diffusion, and cobalamin is absorbed in the ileum through receptor-mediated endocytosis. **B,** In diseased intestine, proximal and distal mucosal damage causes folate and cobalamin malabsorption, respectively; bacterial overgrowth may cause an increase in folate uptake because of bacterial folate synthesis and a decrease in cobalamin uptake because of bacterial binding.



222.1.5 Intestinal Motility

Slow wave motion and segmental and peristaltic contractions of the SI are generated by the co-ordinated contraction of smooth muscle in response to spontaneous electrical activity modulated by co-ordinated neurohumoral and neurochemical molecules.[8] Many of these neurohumoral and neurochemical molecules are also involved in the regulation of intestinal secretion and absorption and the mucosal immune response.[9]

Intestinal motility in the fasted state in dogs is characterized by three phases. A cycle comprising a quiescent phase (lasting about 1 hour), minor contractile activity (15 to 40 minutes), and migrating myoelectric complexes (MMCs) (4 to 8 minutes) is repeated approximately every 3 hours.[10] The short MMC phase is a period of intense contractile activity that sweeps undigested food, secretions, desquamated cells, and bacteria down the intestine. This process is known as the "intestinal housekeeper" wave and is induced by motilin secretion. The pattern of intestinal motility in cats is different, but a migrating spike complex correlates with the MMC.

In the fed state, the pattern of motility is most similar to phase two fasting motility. Its duration is determined by the nature of the diet, with fats and fiber prolonging it. Segmental contractions slow intestinal transit and ensure mixing and digestion of nutrients, and peristalsis propels ingesta. Reduced segmental motility may lead to rapid transit, and decreased peristalsis delays transit, conditions manifesting clinically as diarrhea and ileus, respectively.

222.1.6 Fluid Balance

The ability of the intestine to absorb fluid and electrolytes varies according to the site, with water absorption becoming increasingly efficient distally. The net amount of fluid and electrolytes in the GI tract reflects a balance between absorption and secretion, with net absorption in health.

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222.1.6.1 Intestinal Secretion

Intestinal secretion, a function of villus crypt cells, is believed to occur by electrogenic transport of chloride across the basolateral membrane into the enterocyte and by chloride efflux through chloride channels in the MVM. Passive flux of water follows chloride secretion into the intestinal lumen.

222.1.6.2 Absorption

In a 20-kg dog, approximately 2.7L of fluid (oral intake, stomach juice, saliva, pancreatic juice, bile, and SI secretion) is presented to the SI each day. The jejunum absorbs 50%, the ileum, 75%, and the colon, 90% of the fluid volume presented to it, leaving 0.05 L in feces.[11] This gradient in absorptive ability is a function of enterocyte pore size, membrane potential difference, and the type of transport processes associated with each intestinal segment.[12] The site of the enterocyte on the villus is also important; villus enterocytes absorb, whereas crypt cells secrete.

The absorption of water is passive and follows transport of solutes across the GI epithelium by one of three processes: passive absorption, active absorption, or solvent drag.

222.1.6.2.1 Jejunum

Because the jejunum is highly permeable, passive transport provides the major contribution to sodium (Na) and chloride (Cl) movement in this segment.

222.1.6.2.2 Ileum

In the ileum, sodium is absorbed predominantly through neutral NaCl absorption.

222.1.6.2.3 Colon

Colonic absorption is important in SI disease, because it compensates for fluid losses. Furthermore, patients with SI disease may present with signs of large intestinal (LI) dysfunction, because the colonic reserve capacity may be overwhelmed. In addition, products from the SI, such as hydroxylated fatty acids and deconjugated bile acids, stimulate colonic secretion.

222.1.6.3 Control of the Absorption and Secretion of Water and Electrolytes

Fluid balance is largely an autonomous process regulated by the neurocrine systems in the submucosal plexus.[12] Vasoactive intestinal polypeptide (VIP) and acetylcholine are major mediators of secretion; at the cellular level they increase intracellular calcium and cyclic adenosine monophosphate (cAMP), inhibit neutral sodium and chloride absorption, and facilitate transcellular chloride efflux. Many bacterial agents exert diarrheogenic effects by increasing intraenterocytic cAMP. The principal regulators of absorption—noradrenaline, somatostatin, and opioids—lower intracellular cAMP and calcium concentrations and stimulate neutral NaCl absorption and thereby can have therapeutic antidiarrheal effects.

222.1.7 Bacterial Flora

The normal SI bacterial flora is a diverse mixture of aerobic, anaerobic, and facultatively anaerobic bacteria. Common aerobes include *Staphylococcus* spp., *Streptococcus* spp., Enterobacteriaceae, *Escherichia coli, Bacillus* spp., *Proteus* spp., *Pasteurella* spp., *Corynebacterium* spp., *Lactobacillus* spp., and *Enterococcus* spp. Frequent anaerobes are *Clostridium* spp. and *Bacteroides* spp.

The flora increases in number from duodenum to colon. Factors maintaining this aboral gradient are luminal patency, motility, substrate availability, bacteriostatic and bacteriocidal secretions (e.g., gastric acid, bile, and pancreatic secretions), and an intact ileocolic valve. Abnormalities or dysfunction of any of these factors may lead to quantitative or qualitative abnormalities in the flora.

Quantitative bacteriology performed on samples of undiluted intestinal juice has revealed bacterial counts in healthy cats range from 10^2 to 10^8 colony-forming units (CFU) per milliliter of total bacteria in the proximal small intestine.[13,14] These numbers are considerably higher than the less than 10^5 CFU/mL reported in healthy humans and subsequently extrapolated to dogs. However, no consensus exists as to what constitutes a normal SI flora count in healthy dogs; some studies suggest that the proximal SI of healthy dogs can harbor up to 10^9 CFU/mL total bacteria.[15] Therefore the cutoff for normal flora in dogs and cats cannot be extrapolated from humans, and descriptions of small intestinal bacterial overgrowth (SIBO) in dogs using the cutoff value of 10^5 may be spurious.[15]

The resident bacterial flora is an integral part of the healthy SI and influences a wide variety of parameters, such as villus size, enterocyte turnover, brush border enzyme turnover, and intestinal motility. The digestion and assimilation of fats, carbohydrates, proteins, amino acids (e.g., taurine), and vitamins (e.g., cobalamin and folate) are also affected by bacteria.

The presence of a stable enteric flora is important for preventing colonization by pathogens; it also stimulates the development of the enteric immune system. The host response to a bacterium is likely to be as important as

the intrinsic pathogenicity of the organism. Loss of tolerance to the normal bacterial flora may precipitate intestinal inflammation, abnormal intestinal function, and perhaps even neoplasia. Inability to tolerate a normal bacterial flora may explain antibiotic-responsive enteropathy in German shepherd dogs (see Small Intestinal Bacterial Overgrowth).

The SI flora is relatively resistant to dietary changes. Studies using different diets or the addition of fructo-oligosaccharides to the diet have failed to demonstrate significant effects on the number or type of bacteria in the proximal SI of dogs,[16,17] but some effects have been seen on the colonic flora in cats.[18] Given the intimate inter-relationship of a healthy intestine with its flora, indiscriminate use of anti-biotics in dogs and cats with diarrhea or gastroenteritis is ill-advised and may enhance antibiotic resistance. Although the consequences of inappropriate antibiotic therapy are often mild and self-limiting, postantibiotic salmonellosis has had fatal consequences in cats.[19]

222.1.8 ## Gastrointestinal Immune System

The SI mucosa has a general barrier function (Box 222-3); however, it must also generate a protective immune response against pathogens while remaining "tolerant" of harmless environmental antigens such as commensal bacteria and food. Despite recent advances in our understanding of the structure of and interactions in the immune system, it is still unclear what prompts the SI to respond to or to become tolerant of a particular antigen.

222.1.8.1 ### Box • 222-3 Components of the Intestinal Mucosal Barrier

Protein denaturation by gastric acid

Protein degradation by proteolytic enzymes and bacteria

Clearance of waste by peristalsis

Unstirred water layer

Surface mucous layer

Secretory IgA

Enterocyte microvillus membrane

Epithelial tight junctions

Mucosal-associated lymphoid tissue

222.1.8.2 Structure of the Mucosal Immune System

The gut-associated lymphoid tissue (GALT) consists of inductive and effector sites.[20] Inductive sites comprise Peyer's patches (PPs), isolated lymphoid follicles, and the mesenteric lymph nodes (MLNs); effector sites comprise the intestinal lamina propria (LP) and epithelium. Such a distinction is not absolute, however, and the functions of these different sites overlap.

The PPs are the main sites of induction of the immune response and may also function as sites of B-lymphocyte development. The PP consists of an overlying follicle-associated epithelium (FAE), a subepithelial dome (SED), multiple B-cell follicles, and interfollicular regions. Within the FAE is a specialized population of antigen transport cells (microfold cells or M cells), which act as portals through which the underlying immune cells receive antigen. The MLNs receive afferent lymph from the intestine and are also important in the generation of immune responses.

The LP consists of a matrix of connective tissue with a prominent immune cell component. A large leukocyte population, composed principally of lymphocytes (intraepithelial lymphocytes [IELs]), also exists between enterocytes. Accumulating evidence indicates that *cross-talk* (two-way immunoregulatory signals mediated by cytokines and adhesion molecules) occurs between IELs and enterocytes.[21]

222.1.8.3 Cells and Molecules of the Mucosal Immune System

222.1.8.3.1 Lymphocytes

B lymphocytes are present in the Peyer's patches and the lamina propria. In the PPs they are found predominantly in follicular regions. In the LP, B cells are largely represented by plasma cells, mostly of the IgA isotype. Most plasma cells are present around the intestinal crypts, and the numbers vary along the length of the small intestine.[22]

In the SI, most *T lymphocytes* are of the conventional alpha/beta type.[23] An evolutionarily older (gamma/delta) T-cell population also exists and is considered a primitive first-line defense.[23] T lymphocytes can be further subdivided on the basis of expression of cell surface markers, in particular CD4 and CD8 molecules. CD4+ T cells (classical “helper” T cells) recognize antigenic peptide presented by major histocompatibility complex class II (MHC II) molecules, whereas CD8+ T cells (usually cytotoxic cells) are MHC class I restricted.

In the canine LP, T cells are most numerous in the upper villus regions and are mostly the alpha/beta, CD4+ phenotype.[22–24] However, in the feline LP, CD8+ T cells outnumber the CD4+ population.[25] Most LP lymphocytes are highly differentiated, which implies that they receive continuous antigenic and mitogenic stimulation, probably from the endogenous microbial flora.

The T cells in the intestinal epithelium (i.e., IELs) are a heterogeneous population; most are CD8+ cells, which may be of either the alpha/beta or the gamma/delta phenotype, depending on the species. Known functions of IELs include cytolytic activity and cytokine production, which suggests that these cells play roles in epithelial surveillance and the maintenance of mucosal immune homeostasis.

222.1.8.3.2

Dendritic cells

Dendritic cells (DCs) function predominantly as antigen-presenting cells and can be found in both inductive (PP) and effector (LP) tissues. In effector tissues their main function is antigen sampling, whereas in inductive sites they are responsible for generating acquired immune responses. Follicular dendritic cells (FDCs) are a unique population of cells[26] that take up and store antigen to provide continued stimulation to memory B cells. Immature DCs can efficiently acquire and process antigen but cannot present it or initiate immune responses.[27] Conversely, mature DCs cannot take up or process antigen but are efficient at antigen presentation and lymphocyte stimulation.[27]

222.1.8.3.3

Other immune cells

Macrophages are present in the PP and LP. Their functions include phagocytosis, antigen presentation, and immunoregulatory roles. They secrete cytokines, chemokines, and inflammatory mediators, including tumor necrosis factor-α (TNF-α), eicosanoids, and leukotrienes. Neutrophils are present in small numbers, although their numbers increase with mucosal inflammation. Both mast cells (MCs) and eosinophils can be found in the LP; they also actively produce chemical mediators (e.g., histamine, heparin, eicosanoids, and cytokines). Mast cells express the high-affinity IgE receptor (FceRI), which can bind IgE, causing MC degranulation and release of inflammatory mediators.[28] In dogs, eosinophils are a prominent population in the LP, especially in the crypts. Eosinophils[22] may have proinflammatory roles, especially in allergic processes, because they are a rich source of proinflammatory mediators, cytokines, and chemokines.[28] Triangular cross-talk may occur among eosinophils, MCs, and T cells.

222.1.8.3.4

Enterocytes

In addition to absorptive functions, enterocytes have important immune functions. First, they are an important component of the mucosal barrier, controlling uptake of antigens. Second, they may be capable of antigen presentation, through expression of MHC II and nonclassical antigen-presenting molecules. In dogs, MHC II is expressed by enterocytes, most abundantly in crypt epithelium.[29] In contrast, MHC II is largely absent from the intestinal epithelium of cats, except in regions adjacent to Peyer's patches.[25] Third, enterocytes can produce inflammatory mediators, chemokines, and cytokines and may regulate immune responses in both epithelial and LP compartments. Cross-talk between enterocytes and IELs may also occur through cell to cell interactions (e.g., between E-cadherin expressed on the enterocyte and the integrin $alpha_{\varepsilon}/beta_{7}$, expressed by IEL).[30]

222.1.8.3.5

Enteric neurons

The SI also contains a well-developed nervous system with extensive ramification in both inductive and effector sites.[31] These neurons can release immunoactive neuropeptides (including substance P and VIP), which can cause *neurogenic* inflammation. Bidirectional communication may also exist, in which release of mediators by immune cells (e.g., mast cells) can generate axon reflexes and thereby perhaps modulate intestinal motility, secretion, and absorption.

222.1.8.3.6

Cytokines

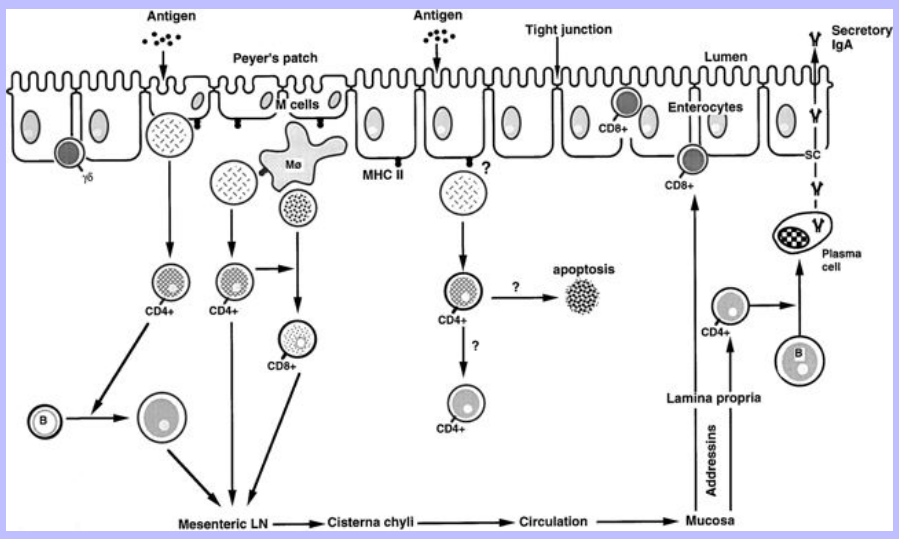
A large array of cytokines is present in the SI, and these cells can be grouped into proinflammatory, immunoregulatory, and chemokinetic types.[32] CD4+ T cells are a major cytokine-producing cell population. Different CD4+ T-cell populations have different patterns of cytokine secretion and can differentially regulate distinct arms of the immune system (e.g., humoral and cell mediated). *In vitro,* two principal populations of CD4+ T cells exist: a T helper 1 (Th1) population (which produces interleukin-2 [IL-2], interferon-γ [IFN-γ], and TNF-β), and a T helper 2 (Th2) population (which produces IL-4, IL-5, IL-6 and IL-10).[33] Other populations with downregulatory functions also have been identified, which predominantly secrete TGF-β or IL-10.[34] Many other cell types also may produce cytokines (see above) and, consequently, an overall cytokine "milieu," which determines the predominant type of immune response that develops, is created.

222.1.8.4

Homing of Lymphocytes in Gut-Associated Lymphoid Tissue

To mount an effective immune response, lymphocytes must traffic between the inductive and the effector sites. Such homing pathways are mediated by complex leukocyte-endothelial interactions. Those governing 1338
recirculation to mucosal tissues are distinct from systemic tissues,[35] because differential expression of 1339
homing receptors (addressins) determines the specificity of homing. Virtually all naïve mucosal lymphocytes can home to the PPs, MLNs, and other nodes in the body. In contrast, mucosal memory lymphocytes home preferentially to effector sites in the GALT.

Figure 222-4 Diagrammatic representation of the mucosal-associated lymphoid tissue, showing M cells in a Peyer's patch sampling luminal antigen, presentation of the antigen to the associated lymphoid tissue, priming of B and T cells, and their circulation to the lamina propria, with subsequent IgA secretion.



Tissue migration of cells from the blood vessel is a multistage process involving a number of molecular interactions. The most important interaction for mucosal lymphocytes occurs between $alpha_4$/$beta_7$ on the lymphocyte and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) on the endothelial cell.[23]

Inflammation causes increased activation of both lymphocytes and endothelial cells, which alters the expression of both homing receptors and vascular addressins. Enhanced expression of MAdCAM-1 leads to increased recruitment of specific mucosal lymphocytes, whereas expression of other vascular addressins (e.g., E-selectin, P-selectin and peripheral node addressin) can lead to recruitment of a broader range of lymphocyte specificities.[36]

A final factor important to the homing of lymphocytes is the chemokines and their receptors.[37] Because chemokine receptors can be selectively expressed on different CD4+ T cell subsets (Th1 versus Th2), the chemokine milieu of a particular tissue determines which T-helper cell types (and which other immune cell subsets) are recruited.

222.1.8.5 Acquired Immune Responses of Gut-Associated Lymphoid Tissue

Acquired immune responses develop after a series of steps involving antigen uptake, presentation to naïve lymphocytes, costimulation by helper cells, clonal expansion, homing to effector sites, and performance of effector functions. The specific mechanisms involved are described in detail elsewhere.[38]

222.1.8.5.1 Antigen uptake and presentation

Most antigen uptake occurs through the M cells of the Peyer's patches; the antigen then is transported to macrophages and dendritic cells in the subepithelial dome (Figure 222-4). Macrophages and DCs act as antigen-presenting cells (APCs), presenting antigen, in the context of MHC II molecules, to lymphocytes (Figure 222-5). Enterocytes may also be capable of taking up antigen and presenting it to T cells.

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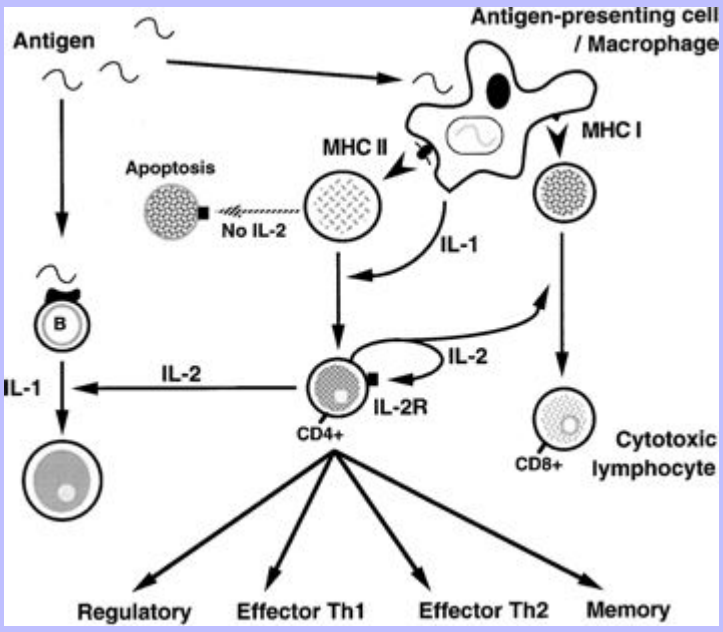
Figure 222-5 Activation of mucosal CD4+ T cells by antigen presentation in association with major histocompatibility complex (MHC) class II molecules; the result is either clonal expansion into memory and effector cells or apoptosis, depending on the synthesis of interleukin-2 receptor (IL-2R) and IL-2. CD8+ T cells are activated by antigen presentation in association with MHC class I molecules and, under the influence of CD4+ T cell–derived cytokines, develop into intraepithelial lymphocytes. γδT cells also form a part of the intraepithelial cell compartment.



222.1.8.5.2 B-cell responses

The primary function of the B lymphoid lineage is generation of humoral immune responses, and the synthesis of IgA predominates in the intestinal mucosa. In the PP follicles, antigen on the surface of DCs stimulates B cells through the B-cell receptors (secretory immunoglobulin M [sIgM] and immunoglobulin D [IgD]). Costimulation to B cells is provided by CD4+ T cells, which enables the B cells to undergo clonal expansion. During the process of B-cell development, a switch occurs such that the effector cells are capable of producing a single immunoglobulin class (e.g., IgG, IgE, and IgA). The switching process is assisted by CD4 T-helper cells, which produce cytokines such as TGF-β, IL-4, and IFN-γ (for IgA, IgE, and IgG switching, respectively).

After class switching, B cells undergo further expansion and then traffic to effector sites to differentiate terminally into plasma cells. After synthesis, IgA (and to a lesser extent IgM) is released and then

transported into the intestinal lumen by the polymeric immunoglobulin receptor (pIgR) on the enterocytes.[39] This complex passes through the enterocyte and is delivered across the microvillar membrane. On the luminal surface, the extracellular fragment of the pIgR is cleaved, forming *secretory component* (*SC*), which associates with pIgA and protects it from degradation in the intestinal lumen. The main function of sIgA is immune exclusion; that is, to bind its respective antigen and neutralize it. Immune exclusion limits the amount of antigen absorbed into the intestinal mucosa and thus the amount available to stimulate active immune responses. This helps maintain tolerance (see below) and protects the mucosa from antigen invasion.

Responses to parasites also occur through generation of antigen-specific plasma cells. These cells, found in the mesenteric lymph nodes, produce IgE that binds to the FcεRI on mucosal mast cells. When subsequently exposed to antigen, MC degranulation occurs and the associated parasite is expelled. Inappropriate IgE responses to food antigens also can be generated, providing a potential mechanism for food allergy.

222.1.8.5.3 Cytotoxic lymphocyte responses

Cytotoxic lymphocyte (CTL) responses are present in the SI mucosa, and their main function is to remove tumor cells or cells infected with intracellular bacteria, viruses, or parasites. CD8+ alpha/beta T cells, the main cytotoxic cells, are generated in a manner similar to B cells except that the former are found in interfollicular regions. Again, help is provided by CD4+ T cells, under the influence of cytokines such as IFN-γ. CD4+ cells themselves can participate in cytotoxicity, and γ/δ IELs may also be cytotoxic.

222.1.8.6 Mucosal Tolerance

The above descriptions relate to specific immune responses to pathogens, but such responses are the exception rather than the rule, and the default mucosal response to antigens is tolerance. This is not surprising, given that the majority of luminal antigens are derived from innocent dietary components or endogenous microflora. Generation of active immune responses to such ubiquitous molecules is both wasteful and potentially harmful, because it could lead to uncontrolled inflammation. Although the mechanisms by which mucosal tolerance actually occurs have been well characterized, the fundamental question of what prompts GALT tolerance or an immune response remains unresolved.

Mucosal tolerance can result either from anergy/deletion (apoptosis) of antigen-specific T cells or from active suppression by antigen-specific suppressor cells (secreting downregulatory cytokines, including IL-10 and TGF-β).[40]

The CD4+ α/β T-cell subsets that mediate active suppression either produce downregulatory cytokines (e.g., TGF-β or IL-10)[34,40] or achieve their effect through cell to cell interactions (e.g., through CD25+, IL-2 receptor). However, any cell capable of producing similar cytokine profiles could play a role and therefore tolerance could arise from the effects of CD8+ T cells, macrophages, stromal cells, and enterocytes. Furthermore, because TGF-β and IL-10 are also important in IgA production, generation of mucosal tolerance potentially could occur in parallel to specific IgA responses, which help to maintain tolerance through immune exclusion.

222.1.8.7 Mucosal Immune System Response or Tolerance

As mentioned previously, the mucosal immune system is prompted either to generate specific immune responses (e.g., toward a pathogen) or to remain tolerant (e.g., to commensal bacteria or food components). The best current hypothesis for the determination of which effect occurs is the "danger theory,"[41] which is based on the supposition that the type of response depends on the context in which the antigen is presented.

The normal intestinal mucosa has an intact mucosal barrier and an environment dominated by downregulatory cytokines (e.g., IL-10 and TGF-β). Therefore most immune responses that develop are tolerance responses. Furthermore, the same cytokine milieu encourages IgA responses, which limit mucosal antigen exposure through immune exclusion.

However, when the mucosa is invaded by a pathogen or toxin, cell damage leads to the release of "danger signals," such as inflammatory mediators (e.g., prostaglandins, leukotrienes), proinflammatory cytokines (e.g., IL-1, IL-6, and TNF-α), and chemokines (e.g., IL-8). In this altered environment, the nature of the immune response generated changes from tolerance to an active immune response. This active response can be either Th1 dominated (e.g., cytotoxicity and IgG responses) or Th2 dominated (i.e., IGE responses). The powerful responses that develop aim to eliminate the pathogen completely, but the potential for bystander damage to host cells is great.

If the antigenic challenge is contained, the danger signals diminish, the mucosa enters a repair phase, and the normal "tolerogenic" environment returns. However, if the danger persists, either because the mucosal barrier remains breached and the pathogenic insult continues unabated or because of an inherent abnormality in the GALT, a state of chronic inflammation ensues. This may also lead to a breakdown in tolerance to harmless environmental antigens (food components and commensal bacteria) and inflammation. Chronic inflammation ultimately leads to histopathologic changes, which are similar regardless of the inciting cause.

222.2 PATHOPHYSIOLOGIC MECHANISMS IN INTESTINAL DISEASE

222.2.1 Motility Disorders

Alterations of intestinal motility as a primary cause of diarrhea have not yet been well characterized.[42] Irritable bowel syndrome may be associated with altered intestinal motility (see below). Secondary alterations in motility often occur, such as with intestinal obstruction, pseudo-obstruction, adynamic ileus, or inflammatory or infectious enteropathies. In malabsorption conditions, unabsorbed solutes decrease transit time because osmotically retained fluid causes intestinal distension and hypermotility. Hyperthyroidism decreases transit time in cats and causes diarrhea. Rapid waves of contractions have been demonstrated in enterotoxigenic diarrhea.

However, in most instances diarrhea is actually associated with intestinal hypomotility. Abnormal dilatation of the intestine caused by hypomotility or obstruction is known as *ileus*. *Adynamic ileus* is a transient and reversible functional obstruction of the intestine with a number of causes (Box 222-4). In enteric viral infections, for example, ileus is common, promoting diarrhea by stasis, which allows bacterial fermentation. Hypomotility and constipation are expected with hypothyroidism, but occasionally antibiotic-responsive diarrhea is found.[43]

222.2.1.1 Box • 222-4 Causes of Ileus

222.2.1.1.1 Physical

Intestinal obstruction

Overdistention by aerophagia

222.2.1.1.2 Neuromuscular

Anticholinergic drugs

Dysautonomia

Spinal cord injury

Visceral myopathies

222.2.1.1.3 Metabolic

Hypokalemia

Uremia

Endotoxemia

222.2.1.1.4 Functional

Abdominal surgery

Ischemia

Inflammatory causes

Peritonitis

Pancreatitis

Parvovirus

222.2.2 Luminal Disturbances

Lack of pancreatic enzymes in EPI or increased destruction of enzymes by acid hypersecretion (e.g., Zollinger-Ellison syndrome) or SIBO results in failure of digestion. Bacteria may also compete for nutrients (e.g., binding of cobalamin in SIBO).

Interruption of enterohepatic circulation and lack of bile salt micelles result in fat malabsorption and can be caused by portosystemic shunting, intrahepatic or extrahepatic cholestasis, bacterial deconjugation of bile salts

in the gut lumen, or ileal disease. Surgical resection of the ileum (e.g., with ileocolic intussusception) and inflammatory bowel disease (IBD) affecting the distal SI cause both bile salt and cobalamin malabsorption.

222.2.3 Villus Atrophy

Villus atrophy causes loss of intestinal surface area and results in malabsorption of fat. Also, carrier-mediated uptake is rate limited, because there is a finite number of nutrient transporters. Villus atrophy results in a loss of carriers critical to carbohydrate and protein digestion.

Atrophy is caused either by a decrease in the production of enterocytes or an increase in the rate of enterocyte loss. Infectious agents that damage enterocytes may infect the villus tip (e.g., rotavirus) or midvillus (e.g., coronavirus), causing cell loss and a mild to moderate diarrhea. Destruction of crypt cells (e.g., parvovirus infection) causes loss of enterocyte production, complete villus collapse, and severe diarrhea.

A persistently increased rate of enterocyte loss through immune-mediated mechanisms results in a compensatory increase in the crypt cell proliferation rate, and if the cell loss is matched by the increased proliferation, villus height does not decrease. However, a significant effect still is exerted on the digestive and absorptive ability of the SI, because prematurely lost mature enterocytes are replaced by immature, suboptimally functioning enterocytes. If enterocyte loss outpaces increased proliferation, villus atrophy results. If the initiating cause can be removed, villus atrophy is completely reversible. Cytotoxic drugs (e.g., vincristine) and parvovirus infection (which cause crypt arrest and destruction, respectively) can be devastating, causing complete villus and crypt collapse. However, assuming some stem cells survive the insult, regeneration is possible, although it is likely to take several days.

222.2.4 Enteroctye Dysfunction

Even if enterocytes are only damaged, the loss of brush border proteins still is often clinically important. Interference with enterocyte function can occur without histologic damage through the action of various bacterial secretions. Malnutrition and ischemia also impair function and increase epithelial permeability.

222.2.5 Microvillar Membrane Damage

The MVM is clearly damaged when overt histologic villus damage can be seen, but even without light microscopic changes, massive impairment of mucosal function can occur if the microvilli are damaged. Such damage is seen with enteropathogenic *Escherichia coli* infection or lectins, which cause a loss of surface area and brush border enzymes and carriers. Bacterial overgrowth is associated with subtle but specific damage to the membrane. Obligate anaerobes are very effective at degrading membrane glycoproteins or releasing brush border enzymes.[44]

222.2.6 Brush Border Membrane Disease

Primary brush border membrane diseases are biochemical abnormalities that occur in the absence of histologic damage. They are well characterized in humans, but equivalent defects in dogs and cats have rarely been demonstrated. Relative lactase deficiency does occur in dogs and particularly in cats.[5] Defects in ileal cobalamin–intrinsic factor complex uptake have been documented in giant schnauzers, collies, and beagles, resulting in cobalamin deficiency with consequent methyl-malonic aciduria.[45] Clinical signs include inappetence, failure to thrive, neutropenia, and anemia.

222.2.7 Mucosal Barrier Disruption

The mucosal barrier is crucial in maintaining oral tolerance and excluding pathogens. In animal models, malnutrition results in villus atrophy with increased transepithelial macromolecular absorption, abnormal mucin, and reduced IgA secretion.[46]

In the N-cadherin dominant negative chimaeric mouse, intestinal inflammation is restricted to regions of the gut where the mutant gene is expressed and consequently where epithelial integrity is disrupted because of a lack of expression of E-cadherin.[47]

Natural causes of decreased barrier function include luminal aggressive factors and endogenous inflammatory mediators such as IFN-γ (Box 222-5). Barrier damage may lead to entry of antigens, subsequent allergic and/or inflammatory reactions, and even translocation of bacteria into the circulation. Leakage of protein-rich tissue fluid in the opposite direction is also of clinical significance, causing a protein-losing enteropathy (PLE).

222.2.8 Hypersensitivity

Sensitization of a patient to a dietary antigen may provoke an IgE-mediated allergic reaction when the animal is next exposed. The release of numerous mast cell mediators (e.g., histamine, serotonin, heparin, interleukins) may have remote effects (e.g., pruritus, urticaria) and even generalized systemic effects (anaphylaxis). Mast cell mediators also have local effects on the intestine, acting directly on epithelium, muscle, and endothelium and indirectly through fibroblast and nerve activity.[48] They induce rapid changes in absorption and secretion, mucus secretion, epithelial and endothelial permeability, and gut motility, causing vomiting and diarrhea.

1341 1342

222.2.8.1 Box • 222-5 Examples of Agents that Can Damage the Mucosal Barrier

222.2.8.1.1 Luminal Aggressive Factors

Enteric infections

Endotoxin

Drugs

Ethanol

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Cytotoxic drugs

Bile salts

222.2.8.1.2 Endogenous Factors

Malnutrition (starvation, malabsorption)

Ischemia

Reperfusion injury

Nitric oxide

Remote inflammatory disease and burns

Intestinal inflammation

Interferon-γ

Neutrophil migration

Mast cell mediators (e.g., histamine, bradykinin)

222.2.9 Mucosal Inflammation

Inflammation is a cellular and vascular response to a number of inciting causes, including infection, ischemia, trauma, toxins, neoplasia, and immune-mediated reactions. The normal mucosa is continually bombarded by a vast array of antigens derived from endogenous bacteria and food components and can be considered to be in a state of "controlled inflammation." Anything that overloads this system is likely to trigger uncontrolled inflammation.

Experimental models of gastrointestinal inflammation have allowed researchers to understand better the pathogenesis of mucosal inflammation and the mechanisms that trigger it (Table 222-1). These genetically engineered rodents have a variety of spontaneously arising or induced disruptions of the mucosal immune system that lead to chronic inflammation, the end results of which are histologically similar. The disruptions usually are induced in one of three ways: through disruption of the mucosal barrier (e.g., the N-cadherin dominant negative chimaeric mouse)[47]; through dysregulation of the mucosal immune system; or through disruption of the endogenous microflora. Disruption of the mucosal immune system, either through targeted deletion of cytokines (e.g., IL-2, IL-10, or TGF-β knockout mice) or through abnormalities in the CD4+ T-cell compartment, results in dysregulated immune responses and, consequently, uncontrolled mucosal inflammation.[49] Extracellular proteolysis by matrix metalloproteinases is critical in the pathogenesis of IBD in humans.[50]

Either mucosal barrier disruption or immune system dysregulation (or both) is required for the development of uncontrolled inflammation; however, the presence of an enteric flora is essential for expression of disease. In this regard, chronic intestinal inflammation generally does not develop when the rodent in these model systems is reared in a germ-free environment.[49] This demonstrates the importance of the endogenous flora in the pathogenesis of uncontrolled mucosal inflammation, as confirmed by studies showing that normal humans are tolerant to their own intestinal microflora but that this tolerance is broken in patients with IBD.[51]

Table • 222-1 Experimental Rodent Models of Chronic Intestinal Inflammation

TYPE OF INFLAMMATION	MODEL
Spontaneous	Ulcerative colitis in
	Cotton-top tamarin
	C3H/HeJBir mouse
Induced	Chemical
	Acetic acid enema
	Immune complex/formalin enema
	TNBS/ethanol enema
	Indomethacin
	Microbial products
	Dextran sulphate sodium
	Carrageenan
	Lymphogranuloma venereum
	Peptidoglycan-polysaccharide
Genetically manipulated	Cytokine perturbations
	IL-2 deficiency
	IL-2R deficiency
	IL-10 deficiency
	TGF-βdeficiency
	IL-7 transgenic
	T-cell or MHC perturbations
	TCR-αchain deficiency
	HLA-B27/β2m transgenic
	Cyclosporin A colitis
	Epithelial perturbations
	Gαi2 deficiency
	N-cadherin–dominant negative transgenic chimera
	Mdr-1 deficiency
Leukocyte transfer to immunodeficient mice	CD45RBhiCD4 T cell into SCID mouse
	CD45RBhiCD4 T cell into
	RAG-deficient rats
	T-cell transfer into SCID mouse
	Bone marrow transfer into Tgε26 mice
	Transfer of cells from mice infected with murine retrovirus

From German AJ et al: Chronic intestinal inflammation and intestinal disease in dogs. J Vet Intern Med 17:8, 2003.
CD, cluster of differentiation; IL, interleukin; HLA, human leukocyte antigen; MHC, major histocompatibility complex; SCID, severe combined immunodeficiency; TCR, T cell receptor; TGF, transforming growth factor.

222.2.10 Neoplasia

Solitary tumors can cause diarrhea, probably through the effects of partial obstruction, stasis of ingesta, and secondary bacterial overgrowth. More typically the tumor is associated with such signs as intestinal obstruction (i.e., vomiting, abdominal pain, absence of feces), bleeding, and cancer-associated anorexia. Mast cell tumors may cause duodenal perforation and peritonitis through histamine-mediated gastric acid hypersecretion. *1342*

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Diffuse tumors, such as lymphoma, that infiltrate the mucosa cause diarrhea. Malignant cells may simply obstruct blood and lymphatic flow, but enterocyte function is likely to be impaired or the mucosa may be ulcerated.

222.2.1.1 Nutrient Delivery Failure

After absorption nutrients are delivered to the body via blood and lymph; only lymphatic diseases are described in animals. Primary lymphatic obstruction (lymphangiectasia) that causes malabsorption may be idiopathic or may be associated with lymphangitis. Secondary lymphangiectasia is seen with lymphatic obstruction.

222.3 SMALL INTESTINAL DISEASE

222.3.1 Signs

222.3.1.1 Diarrhea

Diarrhea is an increase in fecal mass caused by an increase in fecal water and/or solid content. It is accompanied by an increase in frequency and/or fluidity and/or volume of feces. Yet it must be remembered that the absence of recognizable diarrhea does not preclude the possibility of significant SI disease.

Diarrhea can be classified in several ways (Box 222-6). These categories are not mutually exclusive, and they allow the problem to be viewed from different perspectives, facilitating diagnosis and the choice of appropriate treatment. A mechanistic approach is simple, and many SI diseases have a component of osmotic diarrhea, but even in a situation as simple as lactase deficiency, other mechanisms become involved (Figure 222-6). Osmotic diarrhea in lactose malabsorption causes intestinal distension, which induces peristalsis and rapid transit, and bacterial fermentation products in the colon cause secretion. Bacterial fermentation of unabsorbed solutes is often a complicating factor in malabsorption. The fecal pH is often low because of the production of volatile fatty acids, and some products of fermentation (e.g., hydroxylated fatty acids, unconjugated bile acids) can cause colonic inflammation and secretion, and therefore signs of LI diarrhea frequently accompany prolonged SI disease.

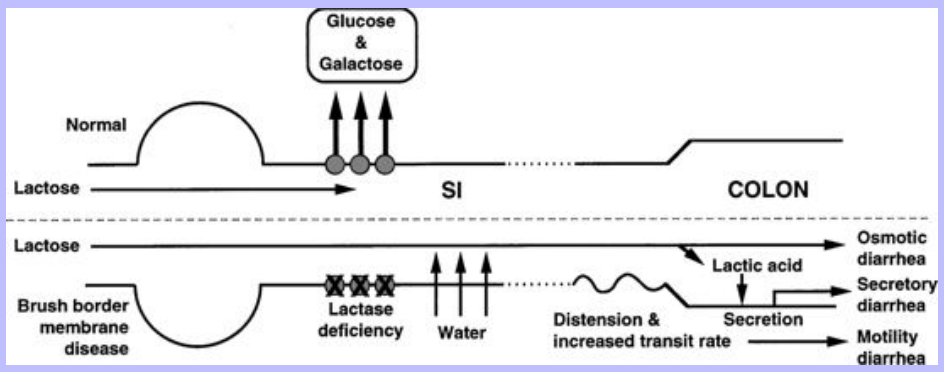
222.3.1.1.1 Osmotic diarrhea

Excess water-soluble molecules in the intestinal lumen retain water osmotically and overwhelm the absorptive capacity of the SI and colon (e.g., sudden diet change, overeating, and malabsorption). The diarrhea typically resolves when food or laxatives are withheld.

222.3.1.1.2 Secretory diarrhea

Stimulation of SI secretion such that the reserve absorptive capacity is overwhelmed results in diarrhea even though the absorptive ability of the SI and colon may not actually be impaired. Treatment with oral rehydration fluids containing glucose and amino acids (e.g., glycine) to increase water absorption is appropriate.

Figure 222-6 Diagrammatic representation of the mechanisms of diarrhea caused by lactase deficiency.



222.3.1.1.2.1 Box • 222-6 Classifications of Diarrhea

222.3.1.1.2.1.1 Mechanistic

Osmotic

Secretory

Permeability (exudative)

Dysmotility

Mixed

222.3.1.1.2.1.2 Temporal

Acute

Chronic

222.3.1.1.2.1.3 Anatomic

Extraintestinal

Small intestinal

Large intestinal

Diffuse

222.3.1.1.2.1.4 Pathophysiologic

Biochemical

Allergic

Inflammatory

Neoplastic

222.3.1.1.2.1.5 Etiologic

Diet; bacterial, viral, parasitic causes; other

222.3.1.1.2.1.6 Causal

Exocrine pancreatic insufficiency, salmonellosis, lymphoma, other

222.3.1.1.2.1.7 Clinical

Acute, nonfatal, self-limiting

Acute potentially fatal

Acute systemic disease

Chronic

Typically secretory diarrhea does not resolve with fasting but does not cause weight loss unless anorexia, vomiting, or additional SI damage is a factor. Morbidity and even mortality are associated with the dehydration that results from excessive fluid loss. Secretory diarrhea typically is caused by chemical toxins and toxins elaborated by enteric bacteria (Box 222-7). 1343 1344

222.3.1.1.2.2 Box • 222-7 Causes of Secretory Diarrhea

Bacterial enterotoxins and endotoxins (e.g., *Clostridium perfringens, Escherichia coli, Salmonella* spp., *Shigella* spp., *Yersinia enterocolitica*)

Unconjugated bile acids from bacterial fermentation

Hydroxylated fatty acids from bacterial fermentation

Giardia infection

Possibly hyperthyroidism

Laxatives (castor oil, dioctyl sodium sulfosuccinate, bisacodyl)

Cardiac glycosides

Amine precursor uptake and decarboxylation (APUD) neoplasms (excess vasoactive intestinal polypeptide, serotonin, prostaglandins, substance P)

Intestinal inflammation

222.3.1.1.3 Permeability (exudative) diarrhea

Intestinal inflammation can stimulate increased fluid and electrolyte secretion and impair absorption. Leakage of tissue fluid, serum proteins, blood, and mucus may occur from sites of inflammation, ulceration, or infiltration or if portal hypertension or lymphatic obstruction is present. Increased permeability severe enough to cause loss of plasma proteins in excess of their rate of synthesis results in a PLE.

222.3.1.2 Malabsorption

Failure of food assimilation is sometimes classified as primary failure to digest (maldigestion) or primary failure to absorb (malabsorption). However, such a classification is misleading, because failure of absorption is an inevitable consequence of failure to digest. The preferred use of the term *malabsorption* is to describe defective absorption of dietary constituent resulting from interference with the digestive and/or absorptive phases in the processing of that molecule.

Within this broad definition, the site of the primary abnormality may be found in the luminal, mucosal, or transport phase (Table 222-2). Also, the reserve capacity of the distal SI and colon may prevent overt diarrhea despite significant malabsorption and weight loss. The clinical manifestations of malabsorption, namely diarrhea, weight loss, and altered appetite (polyphagia, coprophagia, pica), are largely a result of the lack of nutrient uptake and the losses in feces. Animals are often systemically healthy and have an increased appetite unless an underlying neoplastic or a severe inflammatory condition is present. Only when the patient is quite malnourished or develops hypoproteinemia does it become ill.

222.3.1.3 Melena

The presence of dark, tarry, oxidized blood in feces, a condition called *melena,* reflects either swallowed blood or generalized or localized GI bleeding, which usually occurs proximal to the large intestine (Table 222-3). Medication with ferrous sulfate or bismuth subsalicylate (Pepto-Bismol) also can impart a black color to the feces. It has been estimated that the loss of 350 to 500 mg/kg of hemoglobin into the GI tract is required for melena to be visible.[52] The presence of microcytosis with or without thrombocytosis is suggestive of iron deficiency secondary to chronic blood loss. An increased blood urea nitrogen (BUN) to creatinine ratio (from bacterial digestion of blood) provides supporting evidence. Hypoproteinemia may indicate significant blood loss or the presence of a PLE.

Table • 222-2 Pathophysiologic Mechanisms of Malabsorption

MECHANISM	EXAMPLE
Luminal Phase	
Dysmotility	
Rapid intestinal transit	Hyperthyroidism
Defective substrate hydrolysis	
Enzyme inactivation	Gastric hypersecretion
Lack of pancreatic enzymes	Exocrine pancreatic insufficiency
Fat maldigestion	
Decreased bile salt delivery	Cholestatic liver disease, biliary obstruction
Increased bile salt loss	Ileal disease
Bile salt deconjugation	Bacterial overgrowth
Fatty acid hydroxylation	Bacterial overgrowth
Impaired release of CCK, secretin	Impairment of pancreatic secretion due to severe small intestine disease
Cobalamin malabsorption	
Intrinsic factor deficiency	Exocrine pancreatic insufficiency Giant schnauzer defect
Competition for cobalamin	Bacterial overgrowth
Mucosal Phase	
Brush border enzyme deficiency	
Congenital	Trehalase (cats)
Acquired	Relative lactose deficiency
Brush border transport protein deficiency	
Congenital	Intrinsic factor receptor
Acquired	Secondary to diffuse SI disease
Enterocyte defects	
Enterocyte processing defects	Abetalipoproteinemia
Reduction in surface area	Villus atrophy
Immature enterocytes	Increased enterocyte turnover
Mucosal inflammation	Inflammatory bowel disease
Transport Phase	
Lymphatic obstruction	
Primary	Lymphangiectasia
Secondary	Obstruction caused by neoplasia, infection, or inflammation
Vascular compromise	
Vasculitis	Infection, immune mediated
Portal hypertension	Hepatopathy, right heart failure, cardiac tamponade

The general approach to melena is to rule out bleeding diatheses, ingestion of blood, and underlying metabolic disorders before pursuing primary GI causes. Ultrasonography is particularly useful for detecting gastrointestinal masses and thickening. The next step for investigating upper GI blood loss is endoscopy. If the source of GI bleeding is still undetermined, tagged red cell scintigraphy, exploratory laparotomy, angiography, and enteroscopy may be used to localize the site.[53]

Table • 222-3 Causes of Melena

MECHANISM	SOURCE
Ingestion of blood	Oral, nasal, pharyngeal, or pulmonary bleeding
Coagulopathies	Thrombocytopenia, factor deficiencies, DIC
Gastrointestinal erosion/ulceration	
Metabolic	Uremia, liver disease
Inflammatory	Gastritis, enteritis, HGE
Neoplastic	Leiomyoma, adenocarcinoma, lymphosarcoma
Paraneoplastic	Mastocytosis, hypergastrinemia and other APUDomas
Vascular	A-V fistula, aneurysms, angiodysplasia
Ischemia	Hypovolemic shock, hypoadrenocorticism, thrombosis/infarction, reperfusion
Drug induced	Nonsteroidal and steroidal anti-inflammatory agents
Foreign objects	

APUD, amine precursor uptake and decarboxylation tumor; A-V, arteriovenous; DIC, disseminated intravascular coagulation

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222.3.1.4 Borborygmi and Flatulence

Borborygmus is a rumbling noise caused by the propulsion of gas through the intestines. Swallowed air and bacterial fermentation of ingesta are the main causes of borborygmi and flatulence. Feeding a diet that is highly digestible, with a low fiber content (e.g., cottage cheese and rice in a 1:2 ratio) leaves little material present in the intestine for bacterial fermentation and can effect a cure in some cases. If borborygmi or flatulence continues despite dietary modification, the animal may be excessively aerophagic or may have malabsorption, especially if diarrhea or weight loss are also present.

222.3.1.5 Weight Loss or Failure to Thrive

General causes of weight loss are reduced nutrient intake, increased nutrient loss, and increased catabolism or ineffective metabolism. The history should reveal whether the type and amount of diet fed is adequate and whether anorexia, dysphagia, or vomiting is a potential cause. Weight loss or failure to thrive accompanied by diarrhea often is a feature of malabsorption, and the diagnostic approach is the same as for chronic diarrhea. However, diarrhea does not invariably accompany malabsorption that causes weight loss.

222.3.1.6 Protein-Losing Enteropathy

When SI disease is severe enough for protein leakage into the gut lumen to exceed protein synthesis, hypoproteinemia develops.[54] Chronic diarrhea associated with hypoproteinemia usually requires intestinal biopsy to define the cause of the PLE (Table 222-4). Nonintestinal diseases, which may potentially be associated with intestinal protein loss (e.g., portal hypertension), usually present with ascites before diarrhea. Hypoproteinemia associated with GI disease is much less common in cats than in dogs and most often accompanies GI lymphoma.

222.3.1.6.1 Clinical presentation

Breeds that appear to be predisposed to PLE are the basenji, lundehund, soft-coated wheaten terrier, Yorkshire terrier, and Shar Pei (see below). Clinical signs associated with PLE include weight loss,

diarrhea, vomiting, edema, ascites, and pleural effusion. Weight loss frequently is the predominant feature, and diarrhea is not invariably present, particularly with lymphangiectasia and focal intestinal neoplasia. Physical findings may include edema, ascites, emaciation, thickened intestines, and melena. Thromboembolism is a feature of some cases of PLE.

Table • 222-4 Protein-Losing Enteropathies

CAUSES	EXAMPLES
Lymphangiectasia	Primary lymphatic disorder, venous hypertension (e.g., right heart failure, hepatic cirrhosis)
Infectious	Parvovirus, salmonellosis, histoplasmosis, phycomycosis
Structural	Intussusception
Neoplasia	Lymphosarcoma
Inflammation	Lymphocytic-plasmacytic, eosinophilic, granulomatous
Endoparasites	*Giardia, Ancylostoma* spp.
Gastrointestinal hemorrhage	HGE, neoplasia, ulceration

HGE, hemorrhagic gastroenteritis

222.3.1.6.2 Diagnosis

The serum concentrations of both albumin and globulin are reduced in most patients with PLE. Exceptions are raised hyperglobulinemia with hypoalbuminemia found in histoplasmosis and immunoproliferative SI disease in the basenji (see below). Renal and hepatic causes of hypoalbuminemia are eliminated by assay of serum bile acids and urinary protein loss respectively. Hypocholesterolemia and lymphopenia are common in PLE. Hypocalcemia and hypomagnesemia are also reported.[55] Measurement of fecal loss of alpha$_1$-protease inhibitor may be a sensitive test for PLE.[56]

Survey abdominal radiographs often are normal in patients with PLE, but ultrasound scans may reveal intestinal thickening, mesenteric lymphadenopathy, or abdominal effusion. Thoracic radiographs may show pleural effusion, metastatic neoplasia, or evidence of histoplasmosis. Although intestinal function tests may confirm the presence of malabsorption, they rarely provide a definitive diagnosis, and intestinal biopsy is more appropriate. Because many intestinal causes of PLE are diffuse, endoscopy is the safer way to obtain biopsies, but surgical biopsy may be required to obtain a definitive diagnosis for lymphoma and for diseases that cause secondary lymphangiectasia (Box 222-8).

222.3.1.6.3 Treatment

Plasma transfusion may be indicated during the perioperative period when collecting biopsy specimens, and diuretics may reduce ascites. Spironolactone (1 to 2 mg/kg given orally twice daily) may be more effective than furosemide for treating ascites. Thromboembolism is a feature of some cases of PLE. Specific treatments are discussed later.

222.3.2 Diagnosis of Small Intestinal Disease

Most cases of diarrhea are acute, nonfatal, and self-limiting and require only symptomatic support without a definitive diagnosis. However, some cases are life-threatening, may have an infective potential for other animals, or may present a potential zoonotic risk to humans. If significant hypovolemia or dehydration is present, fluid and electrolyte deficits must be addressed simultaneously with the diagnostic effort. The extent

of diagnostic investigations required for acute diarrhea varies; investigations are appropriate if diarrhea is hemorrhagic, accompanied by systemic signs, or unresponsive to symptomatic treatment. By definition, chronic diarrhea is not self-limiting, and an etiologic diagnosis usually is required to allow specific treatment. Diagnostic approaches to acute and chronic diarrhea are discussed in detail elsewhere.

222.3.2.1 Box • 222-8 Relative Advantages of Endoscopic and Surgical Intestinal Biopsy

222.3.2.1.1 Endoscopy

Advantages

Minimally invasive

Allows visualization and biopsy of focal lesions

Permits multiple biopsies

Minimal adverse reactions

Allows steroids to be started early

Disadvantages

Requires general anesthesia

Permits access only to duodenum (and distal ileum?)

Allows only small, superficial (and crushed) biopsies

Requires expensive equipment

Technically demanding

222.3.2.1.2 Laparotomy

Advantages

Allows biopsy of multiple sites

Permits large, full-thickness biopsies

Allows inspection of other organs

Offers potential for corrective surgery

Disadvantages

Requires general anesthesia

Poses a surgical risk

Requires convalescence

Requires delay before steroids can be started

The aim of the diagnostic approach is to eliminate extra-intestinal diseases and to differentiate SI from LI disease (Table 222-5). The history (Boxes 222-2 and 222-9 and Table 222-6) and physical examination (Table 222-7) are crucial steps toward reaching a diagnosis and in some cases may be all that is required. Preliminary investigations may also include collection of baseline data (i.e., hematology, serum biochemistry, urinalysis, and fecal examination). Diagnostic imaging may be indicated, especially if a disease requiring surgical intervention is likely. Further investigations include exclusion of EPI, indirect tests of intestinal function and damage and, ultimately, direct examination of the SI by endoscopy or surgery with histologic examination of biopsies.

222.3.2.2 Fecal Examination

Fecal examinations are an important part of the investigation of SI disease. Tests such as quantification of fecal fat excretion are unsuitable for practice, and bacteriologic culture is sometimes of questionable value, but identification of parasites is important.

222.3.2.2.1 Direct smear

Staining of smears for undigested starch granules (Lugol's iodine), fat globules (Sudan stain), and muscle fibers (Wright's or Diff Quik stain) may indicate malab-sorption but is unreliable. Fungal elements and sporulating clostridia may be seen, but rectal cytology is more useful. Unstained wet mounts may be used to identify protozoal trophozoites.

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Table • 222-5 Clinical Signs Associated with Small and Large Bowel Disease

SIGNS	SMALL INTESTINAL DISEASE	LARGE INTESTINAL DISEASE
Feces		
Stool volume	Large	Small
Mucus	Rare	Common
Blood (if present)	Melena	Fresh blood
Fat	Sometimes	Absent
Color	Variable	Normal
Defecation		
Tenesmus	Rare	Common
Undigested food	Occasionally	Absent
Frequency	Normal: Two to three times a day	Normal: More than three times a day
Urgency	Uncommon	Common
Other signs		
Vomiting	Sometimes	Uncommon
Gas	Sometimes	Absent
Weight loss	Common	Rare

222.3.2.2.1.1

Box • 222-9 Historical Information Useful in the Diagnosis of Small Intestinal Disease

222.3.2.2.1.1.1

Patient Information

Age

Gender

Breed (see Table 222-6)

222.3.2.2.1.1.2

Environmental History

Indoor versus outdoor

Free roaming

Scavenging

Exposure to parasites

Contact with infected animals

Recent change of environment

Endemic disease area

222.3.2.2.1.1.3

Past Medical History

Vaccination status

Worming status

Previous abdominal surgery

Previous excision of cutaneous mast cell tumor

Drug history

222.3.2.2.1.1.4

Progression of Clinical Signs

Severity

Duration

Frequency

Continuous or intermittent in nature

Length of sign-free intervals

Factors that improve or worsen signs (e.g., treatments, diets)

Order of appearance of signs

Table • 222-6 Some Suspected and Confirmed Breed Susceptibilities to Small Intestinal Disease in Dogs and Cats

BREED	CONDITION
Basenji	Lymphocytic-plasmacytic enteritis (also called immunoproliferative disease)
Beagle	Cobalamin deficiency
Border collie	Cobalamin deficiency
German shepherd	Idiopathic antibiotic-responsive; inflammatory bowel disease (lymphoplasmacytic, eosinophilic)
Giant schnauzer	Defective cobalamin absorption
Irish setter	Gluten-sensitive enteropathy
Lundehund	Lymphangiectasia
Retrievers	Dietary allergy
Rottweiler	Susceptibility to parvovirus
Soft-coated wheaten terrier	Protein-losing enteropathy/nephropathy
Shar Pei	Lymphocytic-plasmacytic enteritis, cobalamin deficiency
Toy breeds	Hemorrhagic gastroenteritis
Yorkshire terrier	Lymphangiectasia

Enterotoxin production by *Clostridium perfringens* is a potential cause of diarrhea. The presence of a large number of clostridial endospores (more than 5 per oil field) on Diff Quik–stained smears may be suggestive, but a positive fecal enterotoxin assay (enzyme-linked immunosorbent assay [ELISA] or reverse passive latex agglutination) is more significant.

222.3.2.2.2 Fecal concentration methods

For detection of most parasites, fecal concentration methods are more rewarding (Figure 222-7). Examination of three fecal samples by zinc sulfate flotation is recommended to detect *Giardia* oocysts. A direct smear, sedimentation, or the Baermann technique can identify larvae of *Strongyloides* spp.

222.3.2.2.3 Bacteriologic examination

Routine culture of all bacteria from a fecal sample is of little value, but targeted evaluation for potential pathogens may be helpful. Culture of feces is indicated in animals with hemorrhagic diarrhea or pyrexia or with an inflammatory leukogram or neutrophils on rectal cytology. Identification of *Salmonella* spp., *Campylobacter jejuni,* and *Clostridium difficile* may be helpful, although the significance of a positive isolate should be interpreted in the light of the clinical history, because these organisms can be present in clinically healthy animals. Furthermore, although fecal flora might be representative of colonic bacterial populations, they do not necessarily reflect the SI flora and cannot be used to diagnose SIBO. *E. coli* can be cultured from most fecal samples, but only certain strains are pathogenic, and molecular probes have recently been used to detect pathogenicity markers of *E. coli* in small animal medicine.[57] However, the significance of a positive result needs further assessment, because these organisms can be isolated from both healthy and ill dogs. Feces can be cultured for fungi, such as *Histoplasma capsulatum,* but isolation is difficult and slow.

222.3.2.2.4 Virologic examination

Viral diarrhea is usually acute and self-limiting and does not require a positive diagnosis. Electron microscopy can be used to identify the characteristic viral particles of rotavirus, coronavirus, and parvovirus. A fecal ELISA for parvovirus is also available (see below).

Table • 222-7 Significant Physical Findings in Animals with Signs of a Small Intestinal Disorder

FINDINGS	INTERPRETATION
General	Rule out other systemic disease
Oropharynx	
Mucous membranes	Hydration status, cardiovascular status, anemia, icterus
Tongue	Linear foreign body
Cervical Region	
Thyroid gland	Thyroid nodule (hyperthyroidism)
Abdominal Palpation and Auscultation	
Palpation	Effusions, masses, bunching of intestinal loops, foreign bodies, abnormal accumulations of ingesta, associated pain, feces, lymphadenopathy, other systemic disease
Auscultation	Ileus, borborygmi
Rectal Examination	
Digital examination	Masses, foreign bodies, hemostatic disorders, dehydration
Collection of stool sample	Laboratory analysis, melena
Rectal mucosal scrape	Cytology
Cutaneous Examination	
Poor coat condition, scale	Malnutrition
Pruritus	Food hypersensitivity
Pedal pruritus	*Uncinaria stenocephala* infection (larval migration)

222.3.2.2.5 Giardia antigen

A commercially available ELISA can be used to detect *Giardia* antigen in feces.

222.3.3 Occult blood

These tests are used to search for intestinal bleeding from ulcerated mucosa and benign or malignant tumors. Unfortunately, all versions nonspecifically test for hemoglobin and are very sensitive, reacting with any meat diet and not just patient blood. Therefore the patient must be fed a meat-free diet for at last 72 hours for a positive result to have any reliability.[52,58]

222.3.3.1 Alpha$_1$-protease inhibitor

This test assays the presence in feces of a naturally occurring endogenous serum protein that is resistant to bacterial degradation if it is lost into the intestinal lumen. To improve diagnostic accuracy, three fresh fecal samples should be sampled. The assay is valid only if used on fecal samples collected after voluntary evacuation, because abrasion of the colonic wall during manual evacuation is enough to elevate

alpha$_1$-protease inhibitor (alpha$_1$-PI) concentrations. It appears to be of value for the diagnosis of PLE[59] and may prove to be more a sensitive marker than measurement of serum albumin for the detection of early disease.[60]

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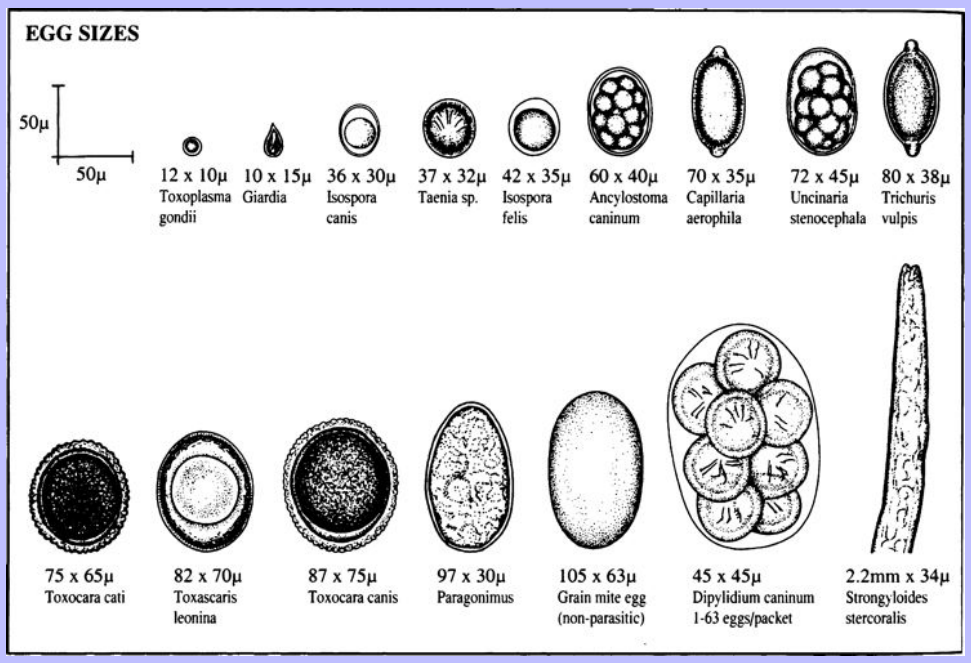
Figure 222-7 Identification of protozoan cysts and worm eggs that may be found in the feces of dogs and cats. (Hoechst-Roussel-Agri Vet Company, USA.)



222.3.3.2 Rectal cytology

At the end of the rectal examination, the rectal wall is mildly abraded, the gloved finger rolled on a microscope slide, and the smear stained. Although the result is often negative and, when positive, probably more representative of LI disease, an increased number of neutrophils may be suggestive of a bacterial problem, indicating the need for fecal culture. Clostridial endospore elements (*Histoplasma, Aspergillus, Pythium,* and *Candida* spp.) may be identified. The test is fast and simple but in all cases confirmatory tests are indicated.

222.3.4 Imaging

Until recently, imaging of the intestinal tract was limited to plain and contrast radiographs. This has been dramatically altered by the use of ultrasound and endoscopy. Scintigraphy, computed tomography (CT), and magnetic resonance imaging (MRI) scanning are rapidly being adopted, and “virtual endoscopy” by helical CT is becoming available.

222.3.4.1 Radiography

222.3.4.1.1 Survey radiographs

Plain radiographs are most useful in the investigation of primary vomiting, diarrhea associated with vomiting, abdominal pain, and palpable abnormalities. Diagnostic yield is improved if both lateral views are taken,[61] although a single lateral radiograph is all that is required if radiography is combined with ultrasonography. Generally the aim is the detection of (acute) surgical disease; these radiographs allow detection of foreign bodies, masses, obstructions, decreased serosal detail, free peritoneal gas, and ileus (Table 222-8).

Ileus is an abnormal dilatation of an immotile segment of intestine, and the differential diagnosis depends on whether it is localized or generalized and whether an accumulation of gas or fluid is present (Box 222-10). The usefulness of plain radiographs in malabsorption is minimal.

222.3.4.1.2 Contrast radiography

Since the introduction of abdominal ultrasonography and endoscopy, contrast radiographic studies have had limited value in the assessment of SI disease.

222.3.4.1.2.1 Barium follow-through examinations.

Studies using microfine barium suspensions can identify ulcers and irregular mucosal detail and may confirm the presence of radiolucent foreign bodies. Such studies are of limited use in identifying mural masses and partial obstructions, and they rarely provide more information than a good-quality survey film (Figure 222-8). Furthermore, although contrast studies allow assessment of the intestinal transit rate, they provide limited etiologic information, and dysmotility may occur secondary to other causes. Also, administration of barium may delay endoscopy for at least 24 hours.

222.3.4.1.2.2 Barium-impregnated polyethylene spheres (BIPS).

BIPS are solid-phase radiopaque markers that provide information on gastric emptying, intestinal transit, and obstructive disorders (Figure 222-8, *D*). Given that the transit time of BIPS is highly variable,[62] their use for transit studies is limited. However, they may be more helpful in the detection of obstructive disorders.

222.3.4.2 Ultrasonography

Transabdominal ultrasound examination of the SI is now a routine part of the investigation of intestinal disease. In the future, endoscopic ultrasound will allow the mucosal wall and adjacent viscera (e.g., pancreas) to be examined in more detail. A conventional ultrasound examination can detect layering of the wall, peristalsis, and luminal contents and can measure intestinal wall thickness.[63] It has excellent sensitivity for the detection of lesions such as intussusceptions,[64] masses,[65] radiolucent foreign bodies, intestinal wall thickening, and lymphadenopathy in chronic inflammatory and neoplastic enteropathies (Figure 222-9). Values for normal SI wall thickness have been reported for dogs and cats,[63] and thickness

decreases from proximal to distal. Ultrasound-guided fine needle aspiration for cytologic examination is possible. Disruption of the normal five-layered sonographic appearance (mucosal surface, mucosa, submucosa, muscularis, serosa) is typical of neoplasia, although loss of layering can also result from other infiltrative disorders and bowel wall edema. Intussusceptions are usually recognized in the transverse plane as multiple concentric rings[65] and longitudinally as a thick, multilayered segment.

Table • 222-8 Helpful Survey Abdominal Radiograph Findings in Patients with Intestinal Disease

FINDINGS	INTERPRETATION
Radiopaque foreign bodies	Visible on survey films
Ileus	Either adynamic/paralytic or obstructive (see Box 222-4)
Abnormal soft tissue shadow	Abdominal mass
Displacement of viscera	Abdominal mass, enlargement of intraperitoneal or retroperitoneal organ, rupture or hernia
Bunching of intestines	Excess intra-abdominal fat, large mass, adhesions, linear foreign body
Bowel wall thickness	Edema, infiltrative (inflammatory, neoplastic disease)
Bowel wall irregularity	Enteritis, neoplasia, ulcers
Loss of serosal detail	Emaciation and immaturity, peritoneal effusion (ascites in hypoproteinemiaand/or portal hypertension, peritonitis, carcinomatosis)

222.3.4.2.1

Box • 222-10 Differential Diagnosis of Ileus

222.3.4.2.1.1

Gas Ileus

Generalized

Aerophagia

Smooth muscle paralyzing drugs

Generalized peritonitis

Enteritis

Localized

Localized peritonitis (e.g., pancreatitis)

Early-stage bowel obstruction

Disruption of mesenteric arterial supply

222.3.4.2.1.2

Fluid Ileus

Generalized

Enteritis

Diffuse intestinal neoplasia

Localized

Foreign body

Tumor causing obstruction

Intussusception

222.3.5 Special Tests

In cases of malabsorption, intestinal biopsy is usually necessary to obtain a definitive diagnosis. However, EPI should be ruled out before biopsy, because signs of malabsorption are nonspecific. It is also well recognized that biopsies from up to 50% of patients are considered normal by light microscopy. Therefore, usually before biopsy, a number of indirect tests are performed to assess for intestinal damage, altered permeability, and dysfunction.

222.3.5.1 Diagnosis of Exocrine Pancreatic Insufficiency

Because the signs of EPI cannot be distinguished from primary causes of SI, serum trypsin-like immunoreactivity (TLI) measurement must be performed in all cases.

222.3.5.2 Serum Folate and Cobalamin Concentrations

The assay of serum folate and cobalamin concentrations can be performed on the same serum sample taken for the TLI test. This assay has limited value in the diagnosis of SI diseases, but subnormal folate and cobalamin concentrations secondary to GI disease may be detected. Cobalamin deficiency is more common, and the response to treatment of the underlying GI disease may be suboptimal if this vitamin deficiency is not corrected. In dogs, the severe cobalamin deficiency recognized in several breeds has been linked to an IF-cobalamin receptor deficiency.[45,66] Cobalamin deficiency is a common sequel to small intestinal disease in cats,[67] and systemic metabolic consequences have been recognized. Determination of the serum folate and cobalamin concentrations is not recommended for the diagnosis of canine SIBO (see below).

222.3.5.3 Indirect Assessment of Intestinal Absorption

Attempts to assess intestinal function by measuring the mediated absorption of numerous substrates (e.g., lactose, glucose, vitamin A, D-xylose, triglyceride, and starch tolerance tests) are no longer performed because of a similar lack of sensitivity and specificity.

222.3.5.3.1 Xylose/3-O-methyl-D-glucose test

The differential absorption of these two sugars eliminates the nonmucosal effects that blight the xylose test, and initial results suggest that the test may be of value in dogs and cats.[68]

222.3.5.4 Intestinal Permeability

Intestinal permeability is an index of mucosal integrity and is assessed by measuring unmediated uptake of nondigestible probe markers. Tests use a nonmetabolizable probe marker that is excreted in the urine. The permeability probe chromium-51-labeled ethylenediamine tetra-acetic acid (^{51}Cr-EDTA) was used in original studies,[69] but the need for a γ-emitter limited its safe use.

Errors related to nonmucosal factors (including the gastric emptying rate, intestinal transit time, and completeness of urine collection) can be eliminated by concurrently measuring the absorption of two probes with different pathways of absorption (Figure 222-10). Calculation of their excretion ratio eliminates errors from extramucosal factors because both probes should be affected equally. The ratio, which is altered by villus atrophy or epithelial damage or both, offers a simple, sensitive diagnostic test.

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Figure 222-8 Identification of an intestinal mass in a Siamese cat. **A,** Annular adenocarcinoma in the ileum demonstrated at laparotomy. **B,** Prior plain lateral radiograph showing a dilated loop of bowel associated with this caudal abdominal mass. **C,** Ventrodorsal radiograph after oral administration of barium suspension showing a dilated loop of SI in the midline, colonic filling, and narrowing of the intestinal lumen at the site of the mass. **D,** Ventrodorsal radiograph after oral administration of BIPS showing accumulation of the larger markers at the site of the partial obstruction caused by the mass. (Courtesy A.H. Sparkes.)

A 5-hour urine collection is performed after oral administration of two sugars. A number of candidates can be used for the probe molecules, and a mixture of one large simple sugar (e.g., lactulose, cellobiose, raffinose) and one small one (e.g., rhamnose, arabinose, mannitol) can be chosen. The cellobiose/mannitol excretion ratio and lactulose/mannitol ratio have been used in companion animals,[70] but with advances in the high-performance liquid chromatography (HPLC) assay of these sugars, the lactulose/rhamnose test has become the standard test of SI permeability.

222.3.5.5 Tests for Protein-Losing Enteropathy

Historically, intestinal protein loss has been detected by measuring the fecal loss of ^{51}Cr-labeled albumin.[71] The test is unpleasant to perform and potentially hazardous and has largely been discarded, although it remains the standard by which other tests, such as the assay of fecal alpha$_1$-PI (see above), are judged.

222.3.5.6 Breath Tests

Breath tests are used to assess bacterial metabolism in the GI tract. Bacteria synthesize a gas, which is absorbed and excreted in breath. Breath hydrogen tests have been used most extensively because mammalian cells cannot produce hydrogen, and therefore any that is measured must be bacterial in origin. Such tests can assess carbohydrate malabsorption, bacterial colonization of the SI, and oro-cecal transit time.

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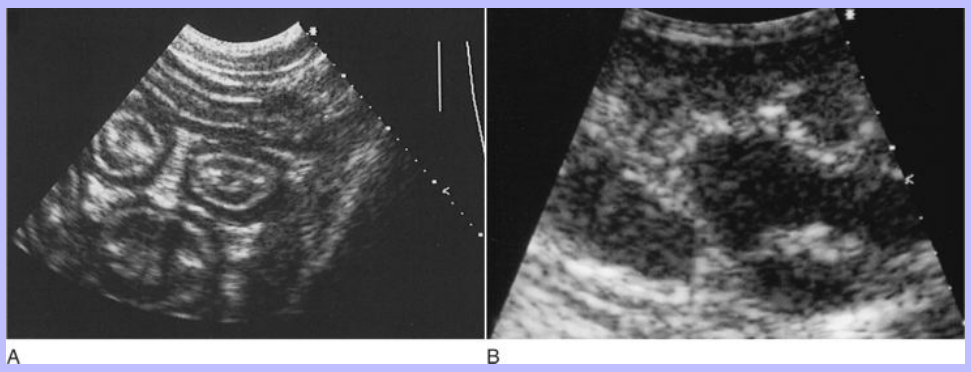
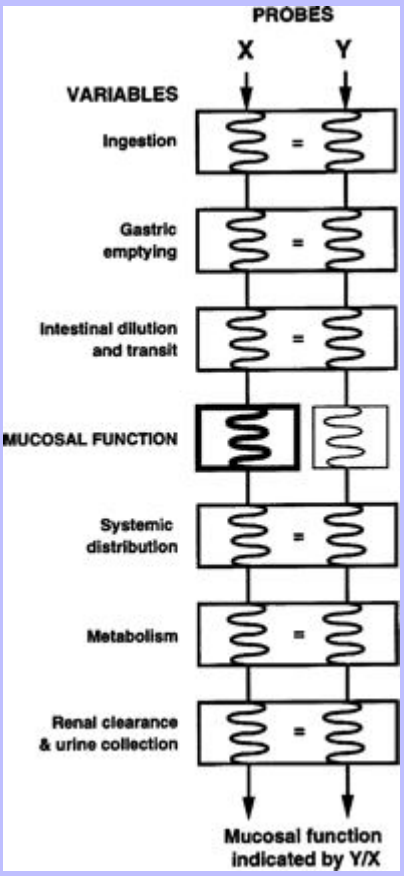
Figure 222-9 Ultrasound images of the abdomen showing **(A)** transverse image of three loops of bowel with normal layering of the small intestinal wall in a dog and **(B)** mesenteric lymphadenopathy in a cat with alimentary lymphoma. (**A,** Courtesy F.J. Barr. **B,** Courtesy H. Rudorf.)



A variety of protocols has been used, including xylose to assess malabsorption, lactulose to assess oro-cecal transit, and a test meal to assess SI bacterial fermentation. Also, a number of recent studies have attempted to standardize the techniques for companion animals.[72–75] However, these techniques are not widely used even in referral centers.

Figure 222-10 Principle of differential permeability testing. Simultaneous administration of two probes selected to respond identically to each variable except mucosal permeability. The Y/X ratio provides a specific index of mucosal permeability. (Hall EJ: Small intestinal disease: Is endoscopic biopsy the answer? J Small Anim Pract 35:408, 1994.)



222.3.5.7 Unconjugated Bile Salts

The principle of the serum conjugated bile acids test is that conjugated bile salts secreted into the intestine in bile are deconjugated by certain bacterial species and absorbed by the SI. Therefore, in theory, increases in SI bacterial numbers might result in an increase in serum unconjugated bile acids (SUBA). Preliminary work suggested that the test was sensitive and specific for canine SIBO,[76] although a recent study has questioned its utility.[77]

222.3.5.8 Miscellaneous Tests

A number of tests for intestinal bacterial metabolites have been devised to detect SIBO. These include the nitrosonaphthol test, urinary indican excretion, bacterial release of sulfapyridine from sulfasalazine, and bacterial release of p-amino benzoic acid (PABA) from a bile salt conjugate (PABA-UDCA). However, none of these tests are widely used in companion animals.

222.3.6 Endoscopy

Flexible endoscopy allows gross examination of the SI mucosa and collection of tissue samples without the need for invasive surgery. The proximal small intestine can be viewed during gastroduodenoscopy (see Figure 222-2), and the distal SI often can be visualized by passing the endoscope retrograde through the ileocolic valve. Therefore only the midjejunum cannot be satisfactorily examined by routine endoscopy. However, given that most cases of malabsorption involve diffuse disease, this limitation may not be significant. Enteroscopy, which was developed in humans and which uses a much narrower, thinner endoscope, may allow examination of most of the jejunum.

Abnormal findings on gross endoscopic examination include mucosal granularity and friability, erosions/ulcers, retained food, mass lesions, and hyperemia/erythema. However, none of these characteristics is pathognomonic for particular disease conditions, and gross findings frequently do not correlate with those of the histopathologic examination. A milky white appearance or a milky exudate is suggestive of lymphangiectasia, and the presence of intraluminal parasites may be diagnostic in some cases.

222.3.7 Intestinal Biopsy

In most cases of acute diarrhea, a tissue diagnosis is not needed, and intestinal biopsy is never performed. 1351
However, in chronic diarrhea a definitive diagnosis often depends ultimately on histologic examination of 1352
intestinal tissue, although this procedure has major limitations (see below). Biopsy specimens are collected, either endoscopically or surgically. The clear advantages of endoscopy to the patient and client are balanced by a number of drawbacks (see Box 222-8), and the client should always be warned that surgical biopsy might ultimately be required for definitive diagnosis. A surgical option is also preferred if there is any possibility of extraintestinal disease or focal intestinal pathology. Biopsies should always be taken, even in the absence of gross abnormalities, because microscopic changes may be present. Multiple endoscopic biopsies (eight or more) should be taken, because the size of the specimens, crush artifacts, and fragmentation can make interpretation difficult.[78]

The duodenum and proximal jejunum (if possible) are biopsied routinely by endoscopy, whereas ileal biopsies may be obtained via colonoscopy. Full-thickness, longitudinal, elliptical surgical biopsies usually are taken from at least three sites, the duodenum, the jejunum, and the ileum.

222.3.7.1 Examination of Biopsies

Although histopathologic assessment of intestinal biopsies remains the gold standard for diagnosis of intestinal disease, it has marked limitations. Biopsy specimens can be normal by light microscopy, which suggests that many diseases have a functional rather than a morphologic abnormality (Box 222-11) or that sampling problems have occurred.[78] Agreement between histopathologists often is poor. In a recent study,

some histopathologists made a diagnosis of lymphoma after assessing tissues from healthy dogs.[79] Histopathologic scoring schemes and standardized criteria have been suggested as a means of improving agreement (Box 222-12), but marked variability still exists. Therefore the primary clinician should always interpret results cautiously and in light of the clinical presentation, and results should be questioned if the tissue diagnosis does not fit the clinical picture or if the response to apparently appropriate therapy is poor. In some cases, repeat biopsy (e.g., by exploratory laparotomy) may be required. Cytologic examination of endoscopic biopsy squash preparations or mucosal brushings may be a useful adjunct to histopathologic examination.[80] Alternate examinations are largely research tools, but they can provide significant information. Examinations available include electron microscopy; biochemical assay of brush border enzymes; immunocytochemical characterization of B cells, T cells, and their subsets (e.g., CD4 and CD8 cells)[22–24] and MHC expression[24,29]; cytokine expression[81]; and assessment of T-cell clonality.[82]

222.3.7.1.1

Box • 222-11 Causes of Chronic Diarrhea for which Small Intestinal Biopsy May Be Normal*

SIBO, ARD

Dietary indiscretion

Food intolerance

Type I hypersensitivity to food (if dog is starved before biopsy)

Toxigenic/secretory diarrheas

Motility disorders/irritable bowel syndrome

Brush border membrane disease (e.g., hypolactasia)

Patchy mucosal disease not sampled

Intestinal sclerosis (if biopsies are not full thickness)

Undiagnosed EPI or colonic or systemic disease

* Detection of histologic abnormalities depends on the size and quality of the biopsy, the quality of processing, and the expertise of the pathologist.

ARD, antibiotic-responsive diarrhea; EPI, exocrine pancreatic insufficiency; SIBO, small intestinal bacterial overgrowth.

222.3.7.1.2 **Box • 222-12 Criteria for Histologic Assessment of Intestinal Biopsies**

222.3.7.1.2.1 **Crypt-Villus Unit**

- Villus height and width
- Villus clubbing/fusion
- Crypt depth
- Mitotic index
- Crypt abscessation
- Crypt to villus ratio

222.3.7.1.2.2 **Epithelium**

- Erosions
- Enterocyte height
- Intraepithelial lymphocyte density
- Goblet cell number/size

222.3.7.1.2.3 **Lamina Propria**

- Immune cell density
- Predominant cell type
- Lymphangiectasia

222.3.7.1.2.4 **Miscellaneous**

- Hyperemia or congestion
- Edema
- Fibrosis
- Infective agents
- Neoplasia

222.3.7.2 Duodenal Juice

Duodenal juice can be collected during duodenoscopy through a sterile polyethylene tube passed down the biopsy channel or by needle aspiration through the intestinal wall at laparotomy. However, collection of sufficient sample without blood and tissue contamination can be difficult. The sample can be examined for *Giardia* trophozoites, although this has not proved reliable in diagnosis.[83] Alternatively, quantitative and qualitative aerobic and anaerobic cultures can be performed. This is the gold standard for diagnosis of SIBO, although there are major problems in interpretation. First, problems may arise from differences in the methods of collection (e.g., endoscopic aspiration versus needle aspiration) and from insufflation with air during endoscopy or dilution with endoscopic wash fluid, gastric juice, bile, or blood. Second, laboratory protocols for bacteriology may vary among laboratories, especially for obligate anaerobes. Third, large intraindividual variation exists in duodenal juice culture results,[16] with one report documenting a 7 log-unit difference between bacterial counts obtained on two separate occasions from an individual animal.[84] 1352
Fourth, because bacterial overgrowth may occur in pockets, a single upper SI culture may not be entirely 1353
representative. Despite these problems, a strict cutoff for the upper limit of normal bacterial counts is often applied; this is inappropriate, because healthy dogs can have numbers in excess of this limit without showing clinical signs. Finally, a recent study has suggested that it does not aid in decision making for cases of GI disease.[77] Therefore, given all these limitations, routine diagnostic use of duodenal juice bacterial culture is not recommended.

222.3.8 Acute Small Intestinal Disease

Potential causes of acute diarrhea are listed in Table 222-9, but whether a complete diagnosis is pursued and when therapy is instituted are clinical judgments. The diagnostic approach to acute diarrhea is discussed elsewhere.

Patients that are bright, alert, and not dehydrated may require no further investigation, because signs are often self-limiting. Further investigation of acute diarrhea is indicated under the following circumstances:

- The patient is dull or depressed, febrile, dehydrated, tachycardic or bradycardic or is having abdominal discomfort, melena, bloody mucoid stools, or frequent vomiting.
- Obvious physical abnormalities (e.g., intestinal masses, thickening, or plication) localize the problem to the SI, and diagnostic imaging, noninvasive biopsy, or surgery can define the cause.
- Systemic abnormalities are present, as defined by a minimum database and other clinicopathologic tests.

It is important that the patient be regularly re-evaluated to monitor the response to therapy and to detect any new abnormalities that may arise.

222.3.8.1 Treatment of Acute Diarrhea

The initial management of acute diarrhea associated with systemic illness is symptomatic and supportive, and is commenced on the basis of clinical findings, in particular the presence of dehydration, while the results of the initial data base and further tests are pending.

222.3.8.1.1

Fluid therapy

Oral fluid and electrolyte replacement therapy may be sufficient if acute diarrhea is associated with only mild or insignificant dehydration, and if vomiting is infrequent or absent,[85] although its efficacy should still be monitored. However, when diarrhea is accompanied by significant vomiting or dehydration, parenteral fluids should be administered at a rate that replaces deficits, supplies maintenance needs and compensates for ongoing losses. Patients with marked hypovolemia require more aggressive support.

Table • 222-9 Causes of Acute Diarrhea

CAUSES	EXAMPLES
Dietary	Hypersensitivity (allergy), intolerance, sudden diet change, food poisoning (poor quality, spoiled foods/bacterial)
Toxic	Food or other sources
Infectious	Parvovirus, coronavirus, paramyxovirus, adenovirus, may or may not be FeLV/FIV related; also *Salmonella, Campylobacter, Clostridium* spp. (?) and *Escherichia coli* (?)
Parasites	Helminths; *Coccidia, Giardia* spp.
Acute pancreatitis	
Anatomic	Intussusception
Metabolic	Hypoadrenocorticism

FeLV, feline leukemia virus; FIV, feline immunodeficiency virus.

The type of fluid and requirement for potassium supplementation is best judged by performing a minimum data base and blood gas analysis. Parenteral fluids are usually best given intravenously. The intraosseous route can be used if venous access is unavailable, but subcutaneous administration of fluids is likely to be inadequate.

222.3.8.1.2

Diet

Studies examining the role of diet in the treatment of acute diarrhea in dogs and cats are scarce.[86] Current recommendations are based on common sense and anecdotal evidence. Best practice generally is considered to be withholding food for 24 to 48 hours and then feeding a bland diet, given little and often, for 3 to 5 days. Thereafter the original diet is gradually reintroduced. In animals with no other significant clinical findings, this may be the only therapy required. Common choices of a bland, fat-restricted diet for dogs are boiled chicken or white fish or low-fat cottage cheese with boiled rice. Cats seem to have a lower tolerance to dietary starch and may benefit from a diet with a higher fat content. Little attention is paid to the overall nutritional adequacy of home-prepared bland diets when fed in the short term.

This dogma of *intestinal rest* has been challenged by studies that demonstrate that feeding human infants during diarrhea promotes recovery. The success of such *feeding through diarrhea* varies depending on the cause, with most benefit seen in secretory diarrhea. However, in dogs and cats, secretory diarrhea is less common, the increased volumes of diarrhea may be cosmetically unacceptable, and the frequently contemporaneous vomiting may preclude this approach. The inclusion of glutamine, a nutrient utilized preferentially by enterocytes, may also promote recovery and decrease bacterial translocation,[87,88] although experimental proof of improved intestinal integrity in animals is lacking.[89]

Theoretically, any intestinal disease may predispose the animal to the development of a food sensitivity, therefore feeding of a novel protein source during these periods may preclude the development of sensitivity to the staple diet. However, this concept of feeding of a *sacrificial protein* is supported only by circumstantial evidence.

222.3.8.1.3 Protectants and adsorbents

Bismuth-subsalicylate, kaolin-pectin, montmorillonite, activated charcoal and magnesium, and aluminum and barium-containing products are often administered in acute diarrhea to bind bacteria and their toxins and to coat and protect the intestinal mucosa, but they may also have an antisecretory effect. Therapy for acute diarrhea with protectants, absorbents or motility modifying agents (see below) should not exceed 5 days.

222.3.8.1.4 Motility-and secretion-modifying agents

Anticholinergics and opiates or opioids (loperamide, diphenoxylate) are frequently used for the symptomatic management of acute diarrhea, but anticholinergic agents can potentiate ileus and are not recommended. Opiate analgesics were thought to exert their effects by stimulating segmental motility, but they actually act mainly by decreasing intestinal secretion and promoting absorption and can be used in the short-term symptomatic management of acute diarrhea in dogs. They are contraindicated in cases involving obstruction or an infectious etiology.

222.3.8.1.5 Antimicrobial therapy

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Antimicrobials are indicated only in animals with a confirmed bacterial or protozoal infection, those in which a breach of intestinal barrier integrity is suspected from evidence of GI bleeding, and hence in those at risk of sepsis. Leukopenia, neutrophilia, pyrexia, the presence of blood in the feces, and shock all are indications for prophylactic antibiotics in animals with diarrhea. Initial choices in these situations include ampicillin or a cephalosporin (effective against gram-positive and some gram-negative and anaerobic bacteria). If systemic translocation of enteric bacteria is suspected, antimicrobials effective against anaerobic organisms (e.g., metronidazole or clindamycin) and “difficult” gram-negative aerobes (e.g., an aminoglycoside or a fluoroquinolone) are indicated. Intravenous quinolones have been shown to reach therapeutic concentrations in the canine gut lumen and can be effective against enterococci, *E. coli,* and anaerobes.[90] Oxytetracycline, tylosin, and metronidazole are suitable for the treatment of SIBO.

A four-quadrant, intravenous antibacterial regimen may be required if septicemia is likely, and suitable combinations would be a cephalosporin (or amoxicillin) or a fluoroquinolone (or amikacin) with metronidazole or clindamycin. However, aminoglycosides should not be given until the patient is volume-expanded.

222.3.8.1.5.1 Probiotics

Traditionally, many practitioners have recommended feeding live yogurt as a way of repopulating the intestine with beneficial lactobacilli after an acute GI upset. There is evidence in other species that probiotics do exert a positive effect on intestinal permeability and mucosal immune responses, although the effects may be species specific and present only while the probiotic is continuously

administered.[91] Probiotics are now available for use in dogs and cats, and emerging data exist to support their use.[92]

222.3.8.2 Acute Diarrhea Induced by Diet, Drugs, or Toxins

Altered food intake, probably the most common cause of acute, self-limiting diarrhea in dogs, includes rapid diet change, dietary indiscretion, dietary intolerance, hypersensitivity, and food poisoning. Dietary hypersensitivity (food allergy) is probably rare. Ingestion of drugs (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs] or antibacterials) or toxins (e.g., insecticides) also may cause vomiting and diarrhea. The history may allow an educated, presumptive diagnosis to be made. However, the exact cause often is never determined because the patient is not systemically unwell and responds to symptomatic therapy. The prognosis usually is excellent, and only if the diarrhea does not respond or the patient deteriorates is further investigation necessary.

222.3.8.3 Hemorrhagic Gastroenteritis

There are numerous potential causes of bloody vomiting and diarrhea, but *hemorrhagic gastroenteritis* (*HGE*) is the name given to a syndrome characterized by acute hemorrhagic diarrhea accompanied by marked hemoconcentration. The cause of the syndrome is unknown. It may represent an intestinal type 1 hypersensitivity reaction or could be a consequence of *C. perfringens* enterotoxin production.[93]

222.3.8.3.1 Clinical findings

Dogs present with acute hemorrhagic diarrhea, with small breed dogs most frequently affected. Pyrexia is unusual, but vomiting, depression, and abdominal discomfort are common. The onset may be peracute and can be associated with marked fluid shifts into the SI, leading to severe hypovolemic shock even before signs of dehydration (e.g., decreased skin turgor) appear.

222.3.8.3.2 Diagnosis

A presumptive diagnosis of HGE can be made on the basis of appropriate clinical findings associated with a packed cell volume (PCV) of 55% to 60% or more. Total protein is often normal or not as high relative to the PCV, probably because of intestinal plasma loss. Radiographs may demonstrate ileus. The absence of leukopenia and the presence of marked hemoconcentration help distinguish HGE from parvovirus. Positive fecal tests may support a diagnosis of clostridiosis, but direct evidence of SI infection is rarely obtained.[93]

222.3.8.3.3 Treatment

Intravenous fluids are essential in treating patients with HGE. Some patients become hypoproteinemic, and plasma or colloid support may be required. Parenteral antibiotics are often administered because of potential clostridial infection and the high risk of sepsis. Clinical improvement is usually noted within a few hours, though the diarrhea may take several days to resolve. Close patient monitoring is essential; patients that have not responded within 24 hours should be re-evaluated for parvovirus, intussusception, or foreign objects. Once the patient is in the recovery phase, standard dietary therapy for acute diarrhea

can be instigated. The prognosis for most animals with HGE is good, but if HGE is complicated by severe hypoproteinemia or sepsis, the prognosis is more guarded.

222.3.8.4 Infectious and Parasitic Causes of Acute Diarrhea

Diarrhea caused by infectious and parasitic agents is considered common in animals that are young, immunologically naïve or immunocompromised, housed in large numbers, or housed in unsanitary conditions. Parvovirus, *Giardia, Salmonella,* and *Campylobacter* spp., and some helminths can be significant causes of diarrhea. The importance of coronavirus, *C. perfringens,* and *E. coli* as causes of diarrhea has yet to be defined. The zoonotic potential of many of these infections has not been clearly elucidated, but basic hygienic precautions should always be adopted. Specific SI infections are discussed below, but the reader is referred elsewhere for detailed information on other viruses such as paramyxoviruses, adenoviruses, feline leukemia, and immunodeficiency viruses, which also cause diarrhea but affect many other organ systems apart from the GI tract.

222.4 VIRAL ENTERITIDES

Most viral enteritides of dogs and cats, especially the parvovirus infections, cause an acute and usually self-limiting diarrhea, although severe cases in young or immunocompromised patients may be fatal. Canine parvovirus infection is described here as the index case for viral enteritides.

222.4.1 Canine Parvovirus

Canine parvovirus type 2 (CPV-2) is a highly contagious cause of acute enteritis.[94] It emerged as a pathogen in the late 1970s, perhaps from a mutation of a feline vaccine as it is related to feline panleukopenia and mink enteritis viruses. CPV-2b has emerged as the most prevalent antigenic variant. There have been reports of cats being infected with CPV-2, but the severity of signs is much reduced.

Infected dogs shed massive quantities of virus particles in feces during the acute illness and then for about 8 to 10 days afterward. Parvovirus is extremely stable and can remain infectious in the environment for many months. Infection is acquired via the fecal-oral route and is more common in the summer months. The virus has an affinity for rapidly dividing cells and localizes to the intestine (crypt cells), bone marrow, and lymphoid tissues. It causes apoptotic cell death, leading to intestinal crypt necrosis and severe diarrhea, leukopenia, and lymphoid depletion.[95]

222.4.1.1 Clinical Findings

Clinical signs of diarrhea typically occur 4 to 7 days after infection. Anorexia, depression, fever, vomiting, diarrhea (often profuse and hemorrhagic), and dehydration are common. Hypothermia and disseminated intravascular coagulation (DIC) are associated with terminal bacterial sepsis or endotoxemia. Dogs of any age can be affected, but the incidence of clinical disease is highest in puppies between weaning and 6 months. Puppies younger than 6 weeks usually are protected by maternal antibody. In dogs older than 6 months, males are more likely to become infected than females. Overcrowding, intestinal parasitism, concurrent infection with distemper virus, coronavirus, *Giardia, Salmonella,* or *Campylobacter* spp. can increase the severity of illness.

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Puppies infected *in utero* or shortly after birth may develop myocarditis and either die suddenly or develop cardiomyopathy if maternal antibody is absent. This situation rarely arises nowadays because widespread vaccination and infection have left few seronegative dams. Yet death still occurs, especially in young puppies, and particularly in susceptible breeds such as rottweilers, Dobermans, English springer spaniels, and American pit bull terriers.[96] Death is usually attributed to dehydration, electrolyte imbalances, hypercoagulability, endotoxic shock, or overwhelming bacterial sepsis related to mucosal barrier disruption and leukopenia. Infected dogs are immunosuppressed and susceptible to catheter infections.[97] Endotoxemia, TNF activity, coliform septicemia, and proliferation of enteric *C. perfringens* determine morbidity and mortality.[98]

222.4.1.2 Diagnosis

Parvovirus should be suspected in young dogs with sudden onset of vomiting and diarrhea, especially if they are also depressed, febrile, or leukopenic or if they have been in contact with infected dogs. Leukopenia (often 500 to 2000 white blood cells per microliter) may be detected in up to 85% of field cases and is very suggestive of parvovirus infection. It reflects neutropenia and lymphopenia. Neutropenia results from impaired bone marrow production with concurrent neutrophil loss through the damaged GI tract, and severe neutropenia crudely correlates with a poor prognosis.

In the absence of leukopenia, clinical signs are indistinguishable from those of other bacterial or viral enteritides, GI foreign bodies with peritonitis, or intussusception. Abdominal radiographs may reveal non-specific gas and fluid accumulation, and ileus. Biochemical abnormalities often include hypokalemia, hypoglycemia, prerenal azotemia, and increased bilirubin or liver enzymes.

Definitive diagnosis requires demonstration of CPV-2 virus (or viral antigens) in the feces. Fecal ELISA is regarded as an accurate and specific diagnostic test but is most sensitive in the first 7 to 10 days when virus excretion is greatest. Single anti-CPV antibody determination in serum (by hemagglutination inhibition) is not useful for diagnosis except in the presence of typical clinical signs in an unvaccinated animal. A rising IgG titer by paired serology provides only a retrospective diagnosis. Serum IgM analysis may provide evidence of recent infection.

222.4.1.3 Treatment

Treatment is supportive and is similar to regimens used in most animals with severe gastroenteritis. Intravenous fluid therapy usually is indicated and is continued until vomiting stops and oral intake resumes. A balanced electrolyte solution (e.g., lactated Ringer's solution) supplemented with potassium and 2.5% glucose is often used. Plasma or whole blood infusions are given to treat severe hypoproteinemia or anemia. Antibiotics are used to control potentially fatal sepsis (see above).

Traditionally, oral intake is withheld until vomiting has stopped for at least 24 hours; this may take 3 to 5 days in severe cases. Rather than avoid the oral route completely, it may be better to trickle feed small amounts of glutamine-containing solutions to reduce bacterial translocation.[87,88] Once vomiting has been controlled, small amounts of a bland diet are fed initially. Frequent or persistent vomiting can be managed with intermittent injections or constant-rate infusion of metoclopramide, once intestinal obstruction has been ruled out. Phenothiazines (e.g., chlorpromazine) can be used if metoclopramide is ineffective and the animal has been rehydrated.

Administration of corticosteroids is of unproven benefit and is probably best limited to dogs with severe endotoxic shock. Flunixin meglumine is best avoided because of its adverse effects on the GI tract and kidneys. Antiendotoxin therapy has been useful in some patients,[99] but the timing of antiendotoxins in relation to antibiotic therapy may be important. Because antibiotics may increase endotoxin liberation, it may be preferable to administer antiendotoxin serum before antibiotics. However, one study showed that the use of the antiendotoxin $rBPI_{21}$ had no beneficial effect on survival,[100] and in another study, use of antiendotoxin was correlated with decreased suvival.[101] Administration of recombinant human granulocyte colony-stimulating factor (G-CSF) to neutropenic parvoviral enteritis patients may raise neutrophil counts but is of no clinical benefit,[102] because the endogenous G-CSF concentration is already elevated.[103] In contrast, administration of feline interferon-omega was found to improve clinical signs and reduce mortality.[104]

222.4.1.4 Prognosis

Severe infection and leukopenia are associated with a high mortality rate, but most dogs with parvovirus recover if dehydration and sepsis are treated appropriately. Complications include hypoglycemia, hypoproteinemia, anemia, intussusception, and secondary bacterial or viral infections.

222.4.1.5 Prevention

Prevention is achieved by limiting exposure to the virus, adequate disinfection (1:32 dilution of sodium hypochlorite bleach), and vaccination.[94] Vaccination is an effective means of preventing and controlling CPV-2, but maternal antibody interference is a problem. Maternally derived antibodies (MDAs) can persist for up to 18 weeks and can interfere with vaccination, although most modern vaccines can overcome MDAs by 10 to 12 weeks of age. Modified live CPV-2 vaccines are most commonly used; killed vaccines provide less duration of immunity but may be recommended in pregnant dogs and puppies younger than 5 weeks. Vaccines may differ in efficacy; low-passage, high-titer vaccines are considered most effective, and only one injection at or after 12 weeks may be needed.[105] In susceptible breeds and dogs in high-risk areas, vaccination may begin at 6 to 8 weeks of age and be repeated every 3 to 4 weeks until 18 weeks of age. There is good correlation between the antibody titer and resistance to infection with canine parvovirus. Annual revaccination is currently recommended.

222.4.2 Feline Parvovirus (Feline Panleukopenia)

Feline panleukopenia is a highly contagious infection of cats that causes severe acute diarrhea and death, similar to canine parvovirus. Mortality in young kittens is high (50% to 90%), therefore the prognosis is guarded until the vomiting and diarrhea stop and the leukopenia resolves.

222.4.3 Canine Coronavirus

Canine coronavirus (CCV) can cause diarrhea of variable severity in dogs.[94] Transmission is by the fecal-oral route. The incubation period is 1 to 4 days, and infected dogs may shed virus intermittently for months after clinical recovery. However, the significance of coronavirus as a primary pathogen is unclear. Experimental inoculation is associated with only mild disease and CCV infection, and antibodies against CCV are present in

many healthy and diarrheic dogs. Infection is very prevalent, particularly in animal shelter and laboratory dogs. Most CCV infections are probably subclinical, although severe enteritis may occur in dense populations or with concurrent infections. In such situations, vaccination may be helpful. 1355 1356

222.4.4 Feline Enteric Coronavirus

Feline enteric coronavirus (FECV) is ubiquitous in the cat population. Mild to moderately severe diarrhea, which may be associated with weight loss, is seen in kittens infected with FECV. Inapparent infection is common in normal cats, many of which shed FECV in feces and are seropositive. FECV infection is important, because enteric coronaviruses may mutate to feline infectious peritonitis virus (FIPV).

222.4.5 Intestinal Feline Infectious Peritonitis

An unusual manifestation of feline infectious peritonitis (FIP) of isolated mural intestinal lesions has been reported.[106] Predominant clinical signs were diarrhea and vomiting, and all cats had a palpable mass in the colon or ileocecocolic junction. Affected intestine was markedly thickened and nodular, with multifocal pyogranulomas extending through the intestinal wall.

222.4.6 Feline Immunodeficiency Virus

Infection with feline immunodeficiency virus (FIV) is associated with a 10% to 20% incidence of chronic enteritis. Although secondary and opportunistic infections may be responsible for signs, sometimes no other etiologic agent can be identified.[107] Anorexia, chronic diarrhea, and emaciation are typical. Palpably thickened bowel loops reflect chronic enteritis with transmural granulomatous inflammation.

222.4.7 Feline Leukemia Virus

Among its many manifestations, feline leukemia virus (FeLV) infection can be associated with fatal peracute enterocolitis and lymphocytic ileitis.

222.4.8 Torovirus

A torovirus-like agent has been isolated from the feces of cats afflicted with a characteristic syndrome of chronic diarrhea and protruding nictitating membrane.[108] However, a clear association with clinical signs was not demonstrated.

222.5 BACTERIAL ENTERITIDES

Most GI infections by pathogenic bacteria are associated with acute diarrhea; however, because these bacteria sometimes can be isolated from healthy animals and from those with chronic diarrhea, confusion exists about the significance of these organisms. Enteroinvasive bacteria such as *Campylobacter* spp., *Salmonella* spp., *Shigella* spp., and *Yersinia enterocolitica* all can be pathogenic and yet may be isolated from healthy animals. The incidence of infection is greatest in young, kenneled animals and immunocompromised patients. Although these organisms may present a zoonotic risk, attempting to eradicate them with antibiotics may be unhelpful and unnecessary and may even induce a carrier state.

222.5.1 *Campylobacter* spp.

Campylobacter jejuni and *C. upsaliensis* have been associated with intestinal disease in dogs and cats, although experimental infection of dogs causes only transient signs.[109] Most infections are asymptomatic, with carriage rates in healthy dogs and cats of up to 50%; kenneled and young animals have the highest isolation rates. Clinically significant disease is usually restricted to young, parasitized, or immunocompromised animals. Clinical signs are watery, mucoid, or hemorrhagic diarrhea accompanied by vomiting, tenesmus, pyrexia, and anorexia. Concurrent infection with *Giardia* or *Salmonella* spp., parvovirus, or coronavirus causes more severe disease.

222.5.1.1 Diagnosis

Because the bacteria are fragile, the diagnosis is best made by isolating them from fresh feces. The presence of slender, seagull-shaped bacteria on a stained fecal smear yields a presumptive diagnosis.

222.5.1.2 Treatment

Animals with severe hemorrhagic mucoid diarrhea should be treated with erythromycin, or quinolone antibiotics such as enrofloxacin. Fluoroquinolones may be preferred, because erythromycin may cause vomiting, but the efficacy of the former has not been critically evaluated. Resistance to antibiotics has been reported, and post-treatment cultures should be performed to document eradication. It is important that the owner be instructed in hygienic precautions to prevent zoonotic infection.

222.5.1.3 Prognosis

The prognosis for recovery usually is good.

222.5.2 *Salmonella* spp

Salmonella organisms are gram-negative motile rods that can cause significant clinical signs in dogs and cats and that have a zoonotic potential. Asymptomatic carriage is common, and *Salmonella* bacteria have been isolated from the feces of up to 30% of healthy dogs and 18% of healthy cats. Clinically significant disease is unusual and occurs most frequently in young, parasitized, kenneled, or immunocompromised animals.

222.5.2.1 Clinical Findings

Three scenarios may follow infection: asymptomatic carriage, gastroenteritis, or bacteremia and endotoxemia. Significant infection causes acute diarrhea that ranges from mild to severe and bloody, as well as anorexia, pyrexia, abdominal pain, and vomiting. Bacterial translocation from the gut lumen may result in septicemia, endotoxemia, DIC, and death in susceptible animals.

Cats with *Salmonella* infection may show only vague signs (e.g., pyrexia, leukocytosis, and conjunctivitis) and no gastrointestinal signs. An acute febrile illness and diarrhea, known as songbird fever, has been reported in cats after ingestion of dead songbirds infected with *Salmonella typhimurium*.

222.5.2.2 Diagnosis

Diagnosis is based on the isolation of *Salmonella* organisms from feces or from blood in septicemic patients. Clinicopathologic features are nonspecific. Hyperkalemia and hyponatremia, suggestive of hypoadrenocorticism, may occur.

222.5.2.3 Treatment

Antibiotic treatment may promote bacterial resistance and a carrier state and is not recommended when *Salmonella* bacteria are isolated from healthy infected animals or stable animals with acute diarrhea. In animals with severe hemorrhagic diarrhea, marked depression, shock, persistent pyrexia, or sepsis, parenteral antibiotics should be given. The choice of antibiotic should be governed by sensitivity testing when possible, but fluoroquinolones appear to be effective against many *Salmonella* spp.[110] Therapy initially should be given for 10 days, but prolonged therapy may be required. The feces should be recultured on several occasions to ensure that the infection has been eliminated.

222.5.2.4 Prognosis

The prognosis for diarrhea associated with *Salmonella* infection in most cases is good. A guarded prognosis should be given in patients with septicemia. Negative prognostic indicators include peracute onset, marked pyrexia (temperature over 40°C), hypothermia, severe hemorrhagic diarrhea, degenerative left shift, and hypoglycemia. 1356 1357

222.5.3 *Clostridium* spp.

C. perfringens, C. difficile, and other clostridial species are part of the normal resident microflora of dogs and cats but may cause diarrhea as a consequence of enterotoxin production.[111,112]

C. difficile can produce two toxins (A and B) and is responsible for antibiotic-associated pseudomembranous colitis in humans. It has been incriminated as a cause of chronic diarrhea in dogs.

Enterotoxin-producing *C. perfringens* has been associated with diarrhea in hospital kennels and with acute and chronic GI signs. Examination of a Diff Quik-stained fecal smear for safety pin–shaped, *C. perfringens*–containing spores has been suggested as a simple screening test, because enterotoxin elaboration was believed to coincide with sporulation. However, this supposition has been disproved by the measurement of *C. perfringens* enterotoxin in feces in the absence of spore formation.[113] Furthermore, enterotoxin can be detected in the feces of healthy dogs, Although SI diarrhea may occur, most dogs show signs of LI diarrhea, and a causal relationship to diarrhea remains to be proven.

222.5.4 *Escherichia coli*

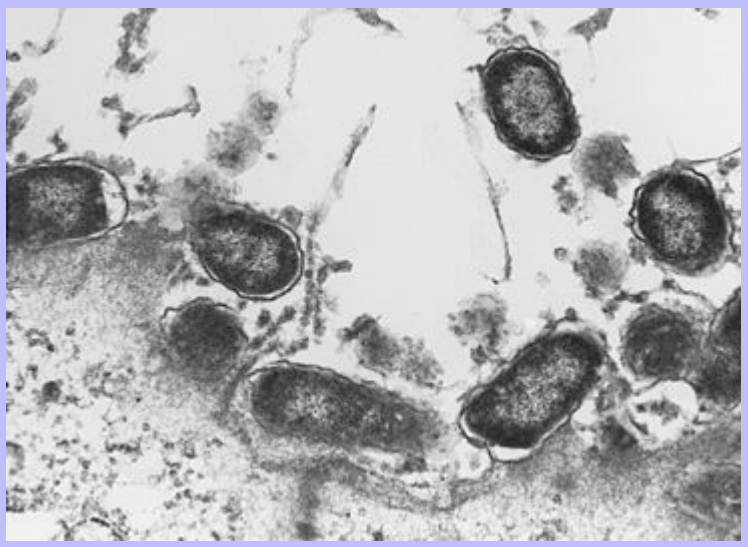
The role of enteropathogenic (EPEC) and enterotoxigenic (ETEC) *E. coli* as a cause of diarrhea in dogs and cats is unresolved. Although many strains are normal commensals, some are a significant cause of acute diarrhea, and other isolates may cause chronic diarrhea.[57] The attachment of ETEC organisms and subsequent release of heat-labile, heat-stable and Shiga-like toxins may cause acute diarrhea. EPEC bacteria attach to the

mucosa, cause effacement of microvilli, and produce profound malabsorption and diarrhea without causing marked changes on light microscopy (Figure 222-11).[114] Identification of pathogenic strains requires specialized assays, such as bioassays for toxins and genome probes for identification of pathogenicity markers, and isolation does not prove causation.[57]

222.5.5 Enteroadherent Organisms

Enteroadherent *E. coli* and other adherent organisms, including *Streptococcus* spp., have been reported to cause chronic diarrhea in dogs.

Figure 222-11 Electron micrograph showing attaching and effacing *Escherichia coli* organisms on the luminal surface of an enterocyte, causing widespread microvillus damage. (Courtesy R.J. Higgins and G.R. Pearson.)



222.5.6 *Yersinia pseudotuberculosis*

Yersinia pseudotuberculosis can be ingested when cats eat infected rodents or birds. The bacteria infect the GI tract, liver, and lymph nodes, causing marked weight loss, diarrhea, anorexia, lethargy, jaundice, and mesenteric lymphadenopathy. Treatment may be attempted with oxytetracycline or trimethoprim-sulfa, but the disease usually is progressive and fatal.

222.5.7 Tuberculosis

In dogs and cats, *Mycobacterium* spp. cause multisystemic, granulomatous infections that occasionally involve the GI tract. Cats may develop SI infection with *Mycobacterium bovis* from drinking infected cow's milk; the infection is associated with vomiting, diarrhea, weight loss, mesenteric lymphadenopathy, and peritonitis.

222.5.8 Miscellaneous Bacteria

Many GI bacteria may be opportunistic pathogens, and occasionally clinical signs are related directly to a specific organism. *Bacillus piliformis* is a rare disease that causes acute, fatal diarrhea in puppies and kittens (Tyzzer's disease). No effective treatment has been described. *Providencia alcalifaciens* was reported to cause primary bacterial enteritis in three dogs.[115]

222.6 RICKETTSIAL DIARRHEA (SALMON POISONING)

Neorickettsia helminthoeca and *Neorickettsia elokominica* are found in the metacercariae of the fluke *Nanophyetus salmonicola,* which is present in salmon in the western regions of the Cascade Mountains from northern California to central Washington. About a week after ingestion of infected salmon by dogs, the rickettsiae emerge from the mature fluke and cause a disease characterized by high fever, hemorrhagic gastroenteritis, vomiting, lethargy, anorexia, polydipsia, nasal-ocular discharge, and peripheral lymphadenopathy. Mortality is extremely high in untreated patients.

The diagnosis is based on a history of ingestion of raw fish in an endemic area, the detection of operculated fluke eggs in feces, and the presence of intracytoplasmic inclusion bodies in macrophages from lymph node aspirates. Oxytetracycline (7 mg/kg given intravenously three times a day) is the treatment of choice and should be continued for at least 5 days. The trematode vector is eradicated with praziquantel.

222.7 ALGAL INFECTIONS

Toxic algal blooms can lead to acute gastroenteritis and death in animals that drink contaminated water. Blue-green algae can synthesize an anticholinesterase that induces vomiting, diarrhea, ataxia, and rapid death in dogs. *Prototheca* spp. are achlorophyllous algae that cause protothecosis. Typically a cutaneous infection in cats, in dogs it can involve the intestine. LI disease is more common, but fatal disseminated disease affecting the SI has been reported.

222.8 FUNGAL INFECTIONS

Low numbers of fungi are found in the normal intestinal microflora and are generally not pathogenic. However, under the right circumstances, such as immunosuppression, they may invade the intestinal mucosa and even disseminate throughout the body. The incidence of these diseases varies worldwide; some are ubiquitous, some are localized to tropical and subtropical areas, and some are endemic in restricted areas. Intestinal infection with a variety of poorly septate molds and fungi is called *phycomycosis*. Of all cases, infection with *Pythium* spp. (pythiosis) is by far the most common. *Pythium insidiosum* may cause a primary intestinal infection.

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222.8.1 Pythiosis

Pythiosis occurs sporadically throughout the world in tropical and subtropical climates. In the United States, pythiosis is most common in the states bordering the Gulf of Mexico. Animals may develop intestinal infection by ingestion of zoospore-contaminated water. Intestinal disease is seen most commonly from fall to spring after infection in late summer, when environmental conditions of warm, swampy water favor fungal growth.

222.8.1.1 History and Clinical Signs

Infection is more common in dogs than cats and typically occurs in young, large breed dogs under 3 years of age. Hunting dogs working in swamplike environments are the most likely to be exposed to infection. The organism can infect any part of the GI tract, but SI infection causes chronic, intractable, and sometimes bloody diarrhea. Vomiting, anorexia, depression, and progressive weight loss are usually noted. Infection is characterized by regions of transmural pyogranulomatous inflammation and ulceration. The bowel wall becomes greatly thickened, which may eventually result in partial or complete obstruction.

222.8.1.2 Diagnosis

On physical examination the most consistent findings in dogs with intestinal pythiosis are emaciation, with either one or more palpable abdominal masses or a thickened, irregular segment of bowel. Mild to moderate nonregenerative anemia and a mild neutrophilia with or without a left shift are typical. Definitive diagnosis can be made only by demonstration of branching, poorly septate or nonseptate hyphae in the tissues, because grossly, the mass or masses can resemble neoplasia at laparotomy. The organisms stain poorly with hematoxylin and eosin or periodic acid–Schiff (PAS) but are evident with Gomori methenamine silver stain. Recently an ELISA and a polymerase chain reaction (PCR) test have been developed.[116,117]

222.8.1.3 Treatment and Prognosis

The prognosis for phycomycosis is grave. Conventional treatment involves surgical excision followed by antifungal treatment. However, lack of ergosterol in the cell membrane makes azole derivatives largely ineffective. Euthanasia is often necessary, either because surgical excision is impossible or because of recurrence and wound dehiscence.

222.8.2 Zygomycosis

Other organisms have been isolated sporadically from cases of phycomycosis and are opportunistic pathogens in immunosuppressed patients. They are from the Zygomycetes class (zygomycosis), and include members of the Entomophthoraceae (e.g., *Basidiobolus* spp., *Conidiobolus* spp.) and Mucoraceae (e.g., *Absidia* spp., *Rhizopus* spp., *Mucor* spp., *Mortierella* spp.).

222.8.3 Histoplasmosis

H. capsulatum sometimes disseminates throughout the body, including the GI tract.

222.9 HELMINTHS

Helminthic infestation is common in dogs and cats. Some species are pathogenic in large numbers, and others are nonpathogenic.

222.9.1 Roundworm Ascarids

Toxocara canis and *Toxascaris leonina* are found in dogs, and *Toxocara cati* and *Toxascaris leonina* are found in cats. *T. canis* can be transmitted across the placenta and *T. canis* and *T. cati* through the milk. Infection is also caused by ingestion of the ova or of other hosts, such as rodents. The adult nematodes live in the SI. Migrating juvenile *T. canis* can cause hepatic, pulmonary, and occasionally ocular damage. *T. canis* presents a public health problem (i.e., visceral and ocular *larva migrans*).

222.9.1.1 Clinical Findings

Roundworms most often cause disease in young animals, and common signs are diarrhea, weight loss, or failure to thrive. A poor haircoat and a potbelly may be evident in puppies or kittens. Intestinal obstruction and perforation have been described in severe cases.

222.9.1.2 Diagnosis

Almost all puppies can be presumed to have *T. canis* infection. The diagnosis is made by fecal flotation (see Figure 222-7).

222.9.1.3 Treatment

A wide range of anthelmintics is effective against roundworms (Table 222-10). Treatment should be repeated at 2-to 3-week intervals in affected animals. Young animals should be routinely wormed at 2, 4, 6, 8, 12, and 16 weeks of age and then at least at 6-month intervals. It is important to ensure proper hygiene to stop reinfection or spread. *T. canis* can be controlled by administering fenbendazole to pregnant bitches at an oral dosage of 50 mg/kg given daily from day 40 to 2 days after whelping.

222.9.2 Hookworms

Ancylostoma caninum is the most important hookworm of dogs and is associated with blood loss and hemorrhagic enteritis. *Ancylostoma tubeforme* is the most common hookworm in cats but is less pathogenic. *Ancylostoma braziliense* occurs in dogs in the southern United States.

Uncinaria stenocephala is the hookworm of dogs in western Europe, although it also occurs in the northern United States and in Canada. Infection is most commonly reported in kenneled dogs, particularly greyhounds, and can be acquired prenatally, during lactation, by ingesting larvae, by migration of larvae through the skin, and by ingestion of a paratenic host.

222.9.2.1 Clinical Findings

Diarrhea, weakness, pallor, vomiting, dehydration, poor growth, and anemia are common in puppies with *A. caninum* infection. The infection can cause a rapid and fatal anemia or a more chronic iron deficiency anemia. *U. stenocephala* does not suck large quantities of blood and cause anemia, although severe infestations may be associated with diarrhea. Larval migration of *U. stenocephala* causes pedal pruritus.

222.9.2.2 Diagnosis

The diagnosis is made by demonstrating ova in feces (see Figure 222-7).

222.9.2.3 Treatment

Appropriate anthelmintics are detailed in Table 222-10. For *Ancylostoma* infection in anemic puppies, pyrantel pamoate has been suggested as the treatment of choice because it acts very rapidly and is comparatively safe. Anemic puppies may require blood transfusion and supportive care. Monthly administration of milbemycin or ivermectin plus pyrantel pamoate has been approved for the prevention or control of hookworm in dogs.

222.9.3 Tapeworms

Dipylidium caninum is the most common tapeworm infecting dogs and cats in the United States and Europe. Fleas are the intermediate host. *Echinococcus granulosus* is a tapeworm that uses dogs as definitive hosts, but humans and sheep are intermediate hosts. *E. granulosus* infection is not associated with clinical signs in dogs but is an important zoonosis. Various other *Taenia* spp. are also common in dogs and cats.

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Table • 222-10 Common Anthelmintic Medications for Dogs

			SPECTRUM OF ACTIVITY	
DRUG	**DOSAGE**	**USUAL FORMULATION**	**NEMATODE**	**CESTODE**
Piperazine	83.2–300 mg/kg	Tablet	Yes	No
Pyrantel	5 mg/kg	Paste	Yes	No
Selamectin	6 mg/kg monthly	Topical Spot-on	Yes	No
Fenbendazole	20–100 mg/kg for 1–3 days	Granules, paste, suspension	Yes	*Taenia* sp.
Mebendazole	50 mg/kg for 2 days	Tablet	Yes	*Taenia, Echinococcus* spp.
Nitroscanate	50 mg/kg	Tablet	Yes (not *Trichuris* sp.)	*Taenia, Dipylidium caninum, (Echinococcus)* spp.
Pyrantel, febantel, praziquantel (combination)	1 tablet/10 kg	Tablet	Yes	*Taenia, Echinococcus* spp., *D. caninum*
Pyrantel, febantel (combination)	1 mL/kg	Suspension	Yes	*Taenia* sp., *D.caninum*
Dichlorophen	200 mg/kg	Tablet	No	*Taenia* sp., *D.caninum*
Praziquantel	5 mg/kg	Injection, tablet	No	*Taenia, Echinococcus* spp., *D. caninum*

222.9.3.1 Clinical Findings

Heavy infestations of *D. caninum* are only rarely associated with diarrhea, weight loss, and failure to thrive. There are usually no clinical signs except “rice grains” (proglottids) in the perineal area or feces.

222.9.3.2 Diagnosis

A diagnosis of *D. caninum* infection is made by demonstrating characteristic egg capsules, contained in proglottids, obtained from the perineal area or feces (see Figure 222-7).

222.9.3.3 Treatment

Treatment of *D. caninum* infection involves adequate flea control (the animal and the environment) and administration of an appropriate anthelmintic (see Table 222-10). *E. granulosus* and other *Taenia* spp. are best controlled by routine administration of praziquantel (see Table 222-10).

222.9.4 *Strongyloides* sp.

Strongyloides stercoralis is a small nematode that may cause hemorrhagic enteritis in young puppies. Infective larvae are ingested, transmitted transmammary or through penetration of the skin, and after migration through the lung develop in the SI.

222.9.4.1 Clinical Findings

Signs of hemorrhagic enteritis occur in young puppies.

222.9.4.2 Diagnosis

Fecal evaluation using the Baermann technique or demonstration of motile first-stage larvae in smears of fresh feces (see Figure 222-7) helps differentiate larvae from Filaroides and mature hookworms.

222.9.4.3 Treatment

Infection is treated with thiabendazole or possibly fenbendazole or ivermectin (see Table 222-10).

222.10 PROTOZOA

222.10.1 Coccidia

222.10.1.1 Isospora spp.

Isospora spp. are the most common coccidial parasites of dogs *(Isospora canis, Isospora ohioensis)* and cats *(Isospora felis, Isospora rivolta)*. Transmission occurs by ingestion of ova or paratenic hosts. Sporozoites are liberated in the SI and enter cells to begin development. The prepatent period ranges from 4 to 11 days, depending on the species. *Isospora* organisms are rarely associated with clinical signs. Puppies and kittens kept in unhygienic conditions or immunosuppressed animals may develop heavy infestations, which occasionally are associated with diarrhea that is often mucoid but sometimes bloody.

Isospora oocysts are found on direct examination of a fecal smear or by flotation. The infection is often self-limiting, but sulfadimethoxine (50 mg/kg given orally once daily for 10 days) or trimethoprim-sulfa (15

to 30 mg/kg given orally once daily for 5 days) can be used when clinical signs warrant treatment. The prognosis for recovery is good.

222.10.1.2 Cryptosporidium sp.

Cryptosporidium parvum, a significant pathogen in humans, is not a single species but is composed of genetically distinct genotypes. Transmission occurs by the fecal-oral route. Molecular studies have shown that dogs may transmit the cattle genotype to humans but that specific cat and dog genotypes also exist.[118] *C. parvum* has been associated with self-limiting diarrhea in dogs and cats and severe hemorrhagic diarrhea in immunocompromised animals.

Cryptosporidial oocysts are extremely small (approximately 1/10 the size of *Isospora* oocysts) and require identification by fecal flotation and oil immersion microscopy or by intestinal biopsy. 1359 1360

Paromomycin was reported to be effective against *Cryptosporidium* organisms in a cat. However, more recent studies have demonstrated that the drug's efficacy is poor and that it may cause acute renal failure. No other drugs are consistently efficacious, although nitazoxanide may prove to be effective. Fortunately, the disease is usually self-limiting in immunocompetent animals.

222.10.2 *Giardia* sp.

Giardia sp. can affect both dogs and cats. The prevalence of infection in canine studies ranges from less than 2% to 100% in kennels. Cats are less commonly infected than dogs. The parasite is usually transmitted via the fecal-oral route. Ingested oocysts excyst in the upper SI, and trophozoites attach to the intestinal mucosa from the duodenum to the ileum. After multiplication of trophozoites, oocysts are passed in the feces at 1 to 2 weeks after infection. Molecular epidemiologic studies indicate that giardiasis may be a zoonosis.[119]

222.10.2.1 Clinical Findings

Most infections are not associated with clinical signs. Clinical signs range from mild, self-limiting, acute diarrhea to severe or chronic small bowel diarrhea associated with intestinal protein loss and weight loss.

222.10.2.2 Diagnosis

Giardia infection can be diagnosed by demonstration of motile trophozoites in duodenal juice or on a fresh fecal smear or by demonstration of cysts by zinc sulfate fecal flotation. Shedding of cysts occurs intermittently, and three fecal analyses are 95% sensitive. *Giardia* antigen can also be detected by means of a fecal ELISA, and this is the preferred method of diagnosis compared to zinc sulfate flotation performed by inexperienced technicians.

222.10.2.3 Treatment

Metronidazole is the drug most commonly used to treat *Giardia* infection in small animals. The standard dosage recommended for dogs is 25 mg/kg given orally twice daily for 5 days; the standard dosage for cats is 10 to 25 mg/kg given orally twice daily for 5 days. The drug is effective at eliminating *Giardia* infection in two thirds of infected dogs but may cause side effects at these high doses.

Albendazole (25 mg/kg given orally twice daily for 2 days) and fenbendazole (50 mg/kg given orally twice daily for 3 days) also eliminate *Giardia* infection.[120] Fenbendazole is preferred, because albendazole has been associated with bone marrow toxicosis.[121] Febantel (in a combination product with praziquantel and pyrantel pamoate) is also effective in dogs.

Decontamination of the patient's coat by bathing and the patient's habitat by steam cleaning or cleaning with quaternary ammonium compounds is advised to prevent reinfection. A *Giardia* vaccine is available for use in high-risk areas, and it has been shown to be effective in clearing infection from dogs that failed to respond to standard drug therapy.[123]

222.10.2.4 Prognosis

The prognosis is usually good. Some patients may require several treatments to eliminate infection, because reinfection is a significant problem.

222.11 CHRONIC IDIOPATHIC ENTEROPATHIES

Chronic enteropathies have historically been defined by histologic description of the tissue, which provides little information as to the nature of the intestinal dysfunction or its etiology. Furthermore, tissue samples collected from many cases have no obvious morphologic changes. In the future, new methods of investigation may better characterize functional and immunologic abnormalities.

222.11.1 Management of Chronic Enteropathies

The management of idiopathic enteropathies is essentially symptomatic. If a specific diagnosis is made (e.g., lymphangiectasia, severe IBD, lymphoma), specific treatment modalities can be used (see below). However, in many circumstances the diagnosis is not obvious, often because of a lack of specific or marked histopathologic changes, and it usually is most appropriate to perform treatments sequentially. It is safest to commence with antiparasiticides, then a dietary trial, followed by an antibacterial trial, before finally attempting immunosuppression. Such an approach may identify occult parasitism, antibiotic-responsive diarrhea (ARD) and diet-responsive conditions. However, because different treatments also lack specific activities, caution should be exercised in using treatment trials for diagnosis without prior investigation.

222.11.1.1 Antiparasiticides

An appropriate trial of an antiparasiticide should eliminate the possibility of parasitic diseases, such as chronic giardiasis, that are difficult to diagnose. Fenbendazole (50 mg/kg given orally every 24 hours for 3 days) is the most appropriate drug for these circumstances, although alternatives exist (e.g., metronidazole or a febantel/pyrantel/praziquantel combination). Given the highly infectious nature of *Giardia* organisms, all in-contact animals may need to be treated concurrently or reinfection may occur, which might suggest apparent treatment failure.

222.11.1.2 Dietary management

Dietary management is a very important treatment modality in most chronic enteropathies and can be used in different ways. For diagnosis and treatment of adverse food reactions, an antigen-limited exclusion diet

is most appropriate (see below). Dietary management also can be important in the symptomatic management of many idiopathic enteropathies. The ideal diet is highly digestible, moderately fat restricted, lactose free, gluten free, not markedly hypertonic, nutritionally balanced, and palatable.

Inclusion of moderately fermentable fiber (e.g., psyllium, ispaghula) is known to promote colonic health, and soluble fiber also promotes small intestinal health.[124] However, because dietary fiber can delay intestinal transit, its inclusion may be contraindicated for some intestinal diseases. Feeding the daily requirement in divided meals (usually between two and four) reduces the load on a compromised intestine. Feeding more frequently is unnecessary, because the rate of gastric emptying imposes natural trickle feeding of the intestine.

Additional supplements include prebiotics such as fructo-oligosaccharides (FOS) and mannanoligosaccharides.[16,17,125,126] FOS has been shown to alter the constituents of the fecal flora, but the effect on the SI flora is limited.

222.11.1.3 Antibacterials

Antibacterials are indicated for specific conditions in which a bacterial pathogen has been documented (see above), in the treatment of ARD or secondary SIBO, and in other chronic enteropathies, such as IBD, in which modulation of the flora may be required. The drugs most commonly used in these circumstances are oxytetracycline, metronidazole, and tylosin. The beneficial effects of such drugs may go beyond their antibacterial activity, with potential effects on the mucosal immune system.

222.11.1.4 Immunosuppressive medication

Immunosuppressive or anti-inflammatory drugs are indicated when evidence of mucosal inflammation is present and no underlying cause is found. However, given that immunosuppression may lead to clinical deterioration in some cases, the diagnosis should be reviewed before institution of such therapy, especially if the diagnosis was made on the basis of endoscopic biopsy alone.

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222.12 ADVERSE REACTIONS TO FOOD

An adverse reaction to food is a repeatable, unpleasant response to a dietary component that is a manifestation of an immunologic reaction to a dietary antigen (i.e., a true food allergy) or a nonimmunologic reaction (i.e., an intolerance). Although different pathogenetic mechanisms are responsible for the two groups, the clinical signs are similar, and the approach to treatment is the same, usually involving exclusion of the offending food component.

Food intolerance may be associated with a single ingredient of a prepared food (e.g., lactose, preservative) that may be present in immunologically unrelated foods. Conversely, confirmed allergy to a specific food may impart allergy to related foods. In humans, food intolerance is diagnosed more frequently than hypersensitivity, but its true prevalence in small animals is unknown. A recent study in cats demonstrated that 29% of cats had adverse food reactions, and a further 20% responded completely to diet and did not relapse.[127] However, the number of these reactions that were immunologically mediated was not documented.

222.12.1 Food Allergy (Hypersensitivity)

The prevalence of true food allergy is unknown because no reliable diagnostic tests are available. Furthermore, food allergy with GI signs may be more difficult to prove than cases in which dermatologic signs prevail. This is partly because other GI diseases may also respond (for nonallergenic reasons) to dietary manipulation (Box 222-13). The management of food allergy is simple: feed any food that does not contain the allergen, and the animal will be healthy. The difficulty for the clinician lies in the recognition of food allergy and the identification of foods that must be excluded.

222.12.1.1 Mechanisms

Currrent hypotheses of food allergy propose one or a combination of mechanisms that lead to breakdown of oral tolerance: an inadequate mucosal barrier, abnormal presentation of dietary antigens to the mucosal immune system, or immune system dysregulation (see earlier discussion). Such hypotheses could explain both genetic susceptibility to the development of allergy and the development of allergies after a primary GI insult that damages the mucosal barrier. For example, viral or parasitic enteritis can both damage the mucosal barrier and provide danger signals in the intestinal mucosa. Active immune responses, rather than tolerance, can then occur to bystander antigens (i.e., sensitization to dietary antigen). Dietary hypersensitivity may involve a variety of mechanisms, including type I (IgE mediated, immediate), type II (immune complex mediated), and type IV (delayed hypersensitivity) reactions.

222.12.1.1.1 Box • 222-13 Conditions that May Improve Clinically in Response to Dietary Modification

Food allergy

Food intolerance

Small intestinal bacterial overgrowth

Inflammatory bowel disease

Lymphangiectasia

Exocrine pancreatic insufficiency

Pancreatitis

Chronic gastritis

Gastroesophageal reflux

Gastric emptying disorders

Portosystemic shunt

222.12.1.2 Clinical Signs

A contemporaneous association between ingestion of a particular food and the onset of signs is suggestive of an immediate (type I) IgE-mediated hypersensitivity, but mixed or delayed reactions are also possible. In such cases the inevitable delay between food ingestion and onset of signs obscures any causative link, particularly if repeated ingestion causes chronic disease.

Clinical signs of food allergy generally involve the skin and GI tract (Box 222-14). Most case studies have focused on dermatologic signs, with few reports of food-allergic GI disease.[128] Systemic signs (anorexia, lethargy) are rarely recorded, and urticaria-angioedema and even anaphylaxis seem rare. Concurrent skin and GI signs can occur but have been reported only rarely.[129] However, only 5% of human patients with gluten-sensitive skin lesions (dermatitis herpetiformis) have GI signs, yet intestinal histologic examination shows a subclinical enteropathy in 95% of these individuals.

222.12.1.2.1 Food-allergic skin disease

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The major sign of food-allergic skin disease is pruritus, which is nonseasonal and has no characteristic distribution, although pedal pruritus, facial pruritus, and otitis externa may be noted. Excoriation, crusting, scaling, and lichenification arise through self-trauma and may predispose to secondary pyoderma. In cats, food allergy may also result in miliary dermatitis, eosinophilic granuloma complex, or symmetric alopecia.

222.12.1.2.1.1 **Box • 222-14 Clinical Signs Recognized as Manifestations of Food Allergy**

222.12.1.2.1.1.1 **Systemic Signs**

Anorexia

Lethargy

Peripheral lymphadenopathy (cats)

Urticaria-angioedema

Anaphylaxis

222.12.1.2.1.1.2 **Cutaneous Signs**

Primary papules

Erythroderma

Pruritus and self-trauma

Secondary pyoderma

Scaling

Otitis externa

Miliary dermatitis (cats)

Eosinophilic granuloma complex (cats)

222.12.1.2.1.1.3 Gastrointestinal Signs

Vomiting

Hematemesis

Diarrhea

Small intestinal–like signs

Colitis-like signs

Abdominal pain, “colic”

Weight loss and/or stunting

Altered appetite

222.12.1.2.2 Food-allergic gastrointestinal disease

Signs of food-allergic gastrointestinal disease are not pathognomonic and include vomiting, diarrhea, abdominal pain, flatulence, borborygmi, and weight loss or failure to thrive.

222.12.1.3 Diagnosis

The cornerstone of the diagnosis of a food allergy is the response to dietary manipulation. Clinical signs should resolve on exclusion of the offending dietary component and return with rechallenge. Unfortunately, objective criteria by which to judge such a response are lacking, and other diseases also may respond to dietary manipulation (see Box 222-14). Furthermore, diagnosis requires confirmation with rechallenge studies, but many clients refuse to pursue this.

222.12.1.3.1 Indirect tests

Given the difficulties of diet trials, indirect tests for food allergy have been devised; unfortunately, none are reliable in veterinary medicine.

Antigen-specific serum antibodies to food components can be measured *in vitro* (by radioallergosorbent testing [RAST] or ELISA), and a number of laboratories now offer this commercially. In most situations IgG and/or IgE responses to different food components are assessed. Subjectively, clinicians who use such tests believe them to be of value, but critical appraisal suggests that they are unhelpful.[130] The use of such tests is flawed for many reasons. First, antibodies to food components can be found in normal individuals, therefore the presence of antibody in an affected individual may be incidental. Second, because vaccines may contain bovine serum albumin, individuals may develop antibodies to beef antigens. Third, some tests assess only IgG responses, therefore they may miss humoral responses of other antibody classes and cell-mediated responses. Fourth, because the affinity of antibodies formed to a particular antigen in different individuals may vary, not all may be detected in the immunoassay, and some may not react at all (if the *in vitro* antigen is not relevant). Fifth, the presence of antibodies does not necessarily prove primary food hypersensitivity, because the antibodies they may have arisen secondary to another underlying disease process (e.g., IBD).

It has been shown that dogs with chronic GI disease arising from a number of causes had greater levels of food-specific IgG than healthy or atopic dogs.[130] However, these findings did not correlate with the animals' response to exclusion diet trials. Thus any perceived benefit of dietary modification after food antigen testing may be coincidental. Given that most clinicians do not go on to prove a causal association by food provocation, such an coincidence is misinterpreted.

Skin testing has also proved unreliable in the diagnosis of food-allergic skin disease.

Gastroscopic food sensitivity testing (*GFST*), in which dietary antigens are instilled directly onto the gastric mucosa in an anesthetized patient, theoretically should give more specific results for cases presenting with GI signs. However, correlation between the results of GFST and the results of clinical challenge trials is poor. The method is tedious, technically demanding, and prone to artifacts and detects only immediate hypersensitivities. Using the colonic mucosa as the testing surface [colonoscopic allergen provocation (COLAP) testing] may be simpler but has not been widely adopted.[131,132]

222.12.1.3.2 Dietary trial (see below)

Dietary trial is the only reliable way to confirm the presence of dietary sensitivity, although such trials do not distinguish food intolerance from allergy.

222.12.2 Food Intolerance

Gluttony, scavenging, and food poisoning are common and may be considered examples of food intolerance. However, these tend to occur as isolated incidents causing acute GI signs. In contrast, true food intolerances are repeatable, but they may be either predictable or unpredictable. Predictable food intolerances occur in any animal after ingestion of a contaminated foodstuff or after consumption of a recognized toxin or excessive amounts of food. In contrast, unpredictable food intolerances (although repeatable in a susceptible individual) are the result of idiosyncratic reactions. Reasons for idiosyncrasies include differences (genetic or otherwise) in intestinal enzyme activities, intestinal permeability, postabsorption metabolism, and mast cell stability, as well as differences in the intestinal flora.

222.12.2.1 Mechanisms

Most of the suggested mechanisms of food intolerance are complex and often extrapolated from humans and consequently may not be valid for dogs and cats.

222.12.2.1.1 Food poisoning

Food poisoning incidents are most common in dogs that scavenge. Clinical signs are the result of toxicosis, usually caused by the presence of a toxin or by contamination with toxin-producing organisms. Furthermore, the term *food poisoning* also can be applied to infection by organisms that have multiplied in the food and subsequently cause acute GI signs.

222.12.2.1.2 Pharmacologic intolerances

These food intolerances result from the presence of pharmacologically active compounds (e.g., chocolate poisoning caused by excessive intake of methylxanthines). In humans, intolerances may result from naturally occurring compounds (e.g., vasoactive amines, cardiac glycosides, plant alkaloids, and fungal hallucinogens) or substances produced by intestinal bacterial metabolism. Similar reactions are likely to occur in animals, although reports are lacking.

222.12.2.1.3 Pseudoallergic mechanisms

These adverse reactions are histamine mediated, although they arise from nonimmunologic mechanisms. A high histamine concentration may be present naturally in some foods (e.g., tuna, mackerel, and some commercial dog foods) or because of histamine-producing bacteria (e.g., cheese or canned fish contaminated with *Proteus* or *Klebsiella* organisms). Some foods (e.g., shellfish, strawberries) and food additives (e.g., tartrazine) can cause histamine release from mast cells without IgE mediation. This mechanism is well documented in humans,[133] but its relevance to small animal food intolerances is unknown.

222.12.2.1.4 Metabolic reactions

Such reactions are poorly documented in small animals. Carbohydrate malabsorption and intolerance may be features of a number of intestinal diseases, whereas specific intolerance to lactose can be associated with lactase deficiency (see earlier). However, allergy to bovine milk proteins or previously subclinical intestinal disease may be the reason for clinical signs in animals that react adversely to milk ingestion.

222.12.2.2 Clinical Signs

The clinical signs of food intolerance, which are related to the GI tract, include vomiting, diarrhea, and abdominal discomfort. However, pruritus and even anaphylaxis are possible if histamine release is involved.

222.12.2.3 Diagnosis

The only reliable means of diagnosing food intolerance is by monitoring the responses to an exclusion diet and subsequent diet challenge. Again, such trials do not define the exact pathogenetic mechanism involved. The results of serologic food allergy testing are unhelpful and may even complicate the diagnosis.

222.12.2.4 Treatment

Treatment is simple once a diagnosis has been made: avoidance of the offending food prevents the occurrence of signs.

222.12.3 Dietary Trials for Adverse Food Reactions

Dietary trials are required to diagnose both food hypersensitivity and intolerance, but they do not distinguish between them. Objectivity in assessing the response to diet can be enhanced by measuring changes in intestinal permeability,[134] although not all adverse reactions may cause such changes. Although histopathologic changes could also be used to monitor response, the lack of pathognomonic findings for food sensitivity makes interpretation difficult.

222.12.3.1 Preliminary investigations

There are no pathognomonic signs for adverse food reactions, and other major differential diagnoses (which may also respond to dietary change) should be ruled out before an exclusion diet trial is begun (see Box 222-13). After a minimum database has been compiled, specific investigations of the skin and GI tract should be performed. Ectoparasites and secondary skin infections, as causes of pruritus, should be diagnosed and treated before a food trial is considered. Endoparasites should be excluded through examination of three fecal samples or by empirical fenbendazole treatment. Intestinal biopsy should be performed to look for morphologic diseases, although in many cases no histologic changes are apparent or there may be overlap with changes seen in idiopathic IBD (Box 222-15).

222.12.3.2 Exclusion

The principle of an exclusion (elimination) diet is to feed dietary components to which the animal has not previously (or recently) been exposed. This diet should be the sole source of nutrition for the duration of the trial. Complete owner compliance is essential, and it must be stressed that all treats and supplements must be withheld. Options for exclusion diets include home-prepared diets, single-source protein diets, and hydrolyzed protein diets. Home-cooked diets have been preferred to commercial diets because of reports of relapse when patients are switched to an equivalent commercial diet.[135,136] However, many clinicians recommend the use of a commercial diet initially, because it is easier for the owner and thus compliance is enhanced.

222.12.3.2.1

Box • 222-15 Histologic Gastrointestinal Biopsy Changes Sometimes Suspected to be Manifestations of Food Allergy but also Seen in Other Gastrointestinal Diseases

Intraepithelial lymphocyte infiltration

Villus atrophy (partial or subtotal)

Decreased enterocyte height

Lymphoplasmacytic gastritis

Lymphoplasmacytic enteritis

Eosinophilic gastroenteritis

A traditional *exclusion diet* is composed of single protein and carbohydrate sources. If a home-cooked diet is used, it is unlikely to be nutritionally balanced, but this is not important for the short duration of the trial. Lamb or chicken with rice have been the standard choices, but given the increased diversity of commercial pet foods, these components are not always appropriate. Thus more esoteric food sources have become a requirement. An alternative to home-prepared diets is use of a commercial exclusion diet, and a wide range is now available, containing different sources of protein (e.g., chicken, soy, fish, catfish, venison, or duck) and carbohydrate (e.g., rice, corn [maize], tapioca, or potato). It should be possible to find an appropriate diet in most cases, although manufacturers cannot always guarantee a constant supply of diets with more exotic components.

Recently, hydrolyzed protein diets, usually based on either chicken or soy protein, have become available. In principle, the hydrolysis process splits proteins into components of a molecular weight below that which would be expected to elicit an immune response.[137] To completely abolish all antigenicity, peptides probably need to be less than 1 kD, and at that size they have a bitter taste. At the size achieved in palatable hydrolyzed diets (7 to 10 kD), antigens should still be unable to cross-link IgE molecules on mast cells, and type I reactions would be abolished. However, the hydrolysis process itself might expose hidden antigenic epitopes. Hydrolyzed diets are also significantly more expensive to produce than standard exclusion diets, and both palatability and owner compliance may be problematic. Nevertheless, such diets are currently the easiest way to guarantee the feeding of novel antigens, and this approach may become the preferred method in the future. Preliminary studies have suggested a beneficial effect of such diets,[138,139] although it had not been proved that such diets have an advantage over traditional single-source protein exclusion diets.

222.12.3.3

Challenge

Once remission is achieved, the animal should be challenged with the original diet to demonstrate relapse and confirm the diagnosis. Some animals may not relapse,[127] perhaps because the mucosal barrier has been

restored and further reactions are prevented. However, some clients refuse challenge, particularly if relapse is likely to bring recurrence of diarrhea.

222.12.3.4 Rescue and provocation

After relapse on challenge, for clients who are willing, a series of provocation tests can be performed to identify the offending food or foods. Remission is regained by "rescue" with the exclusion diet, and single foodstuffs are then introduced sequentially as provocation tests. If there is no relapse, the food is identified as "safe," and the next food is tested; if there is a relapse, rescue is repeated and the food is identified as "unsafe."

222.12.3.5 Maintenance

When all the offending foods have been identified, or at least sufficient safe ones have been recognized to permit the choice of a regular diet, the animal is maintained on a safe commercial version. Studies in both cats and dogs have shown that, subsequent to the food trial, most animals can be maintained on one of the available antigen-limited diets.[135,136]

222.12.3.6 Protocol

A standardized protocol for food trials has not been established. The optimum duration for an exclusion diet trial is unknown, and 3 weeks has been chosen arbitrarily. However, cases of food-allergic skin disease may require up to 10 weeks to respond. Response is considered to be quicker in cases of food-allergic GI disease, such that it is rarely necessary to feed the exclusion diet for this length of time when it may become difficult to maintain owner compliance. Challenge trials and provocation tests are usually conducted for up to 14 days but are discontinued earlier if signs recur on 2 consecutive days.

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222.12.3.7 Treatment

A number of gluten-free proprietary diets based on lamb, fish, or chicken are available; these are often suitable as maintenance diets, and they are preferred over home-prepared meals because they are nutritionally balanced. Hydrolyzed diets are an alternative. Assuming a correct diagnosis, dietary management should be all that is required, and the diagnosis should be re-evaluated if treatment failure occurs.

222.12.4 Gluten-Sensitive Enteropathy

SI disease induced by the presence of dietary wheat gluten has been clearly documented in Irish setters.[140,141] The condition resembles gluten-sensitivity (celiac disease) in humans, although intestinal damage and clinical signs are less marked. Celiac disease shows a clear genetic predisposition with a strong association with the MHC II haplotype HLA-DQω2. In Irish setters, it is a familial condition with an autosomal recessive mode of inheritance.[142] However, unlike human celiac disease, there is no relationship with major histocompatibility genes DQA and DQB,[142,143] and the pathogenesis is different. The disease may affect other dog breeds, but it has not been reported in cats. Gluten sensitivity has been suggested in soft-coated wheaten terriers[144,145] with protein-losing enteropathy and/or nephropathy.

222.12.4.1 Pathogenesis

Despite the apparent similarities with celiac disease, the pathogenesis of gluten-sensitive enteropathy (GSE) is different.[146] Clinical signs are caused by ingestion of the wheat protein gluten (or one of its digestion products), which is either directly toxic to the intestinal mucosa or induces an adverse immune reaction. Remission of clinical signs and histologic and biochemical changes occurs on a wheat/gluten-free diet, and signs relapse when gluten-containing diets are reintroduced.

In some studies, abnormal mucosal permeability that precedes the development of disease has been documented in affected Irish setters.[147] This implies that a breakdown in the mucosal barrier may play an important role in the pathogenesis by permitting abnormal entry of gluten peptide.[147] In contrast with human celiac disease, immunoglobulin responses to gluten or endomysial antigens are not noted.[146] However, involvement of the immune system is suggested by the fact that increased lamina propria CD4+ T-cell populations and decreased CD8+ populations have been described in affected dogs.[148]

The age of the animal at which gluten is introduced and the dose may affect expression of the disease, with some dogs becoming asymptomatic later in life.[149] The pathogenesis of Irish setter GSE, therefore, remains incompletely characterized, and mechanisms distinct from those underpinning human celiac disease are likely.

222.12.4.2 Clinical Signs

Affected Irish setters typically present with poor weight gain and chronic intermittent diarrhea in the months after weaning. Histologic changes in jejunal biopsies show partial villus atrophy and intraepithelial lymphocyte infiltration, with a variable lamina propria infiltrate. These changes resolve when a gluten-free diet is fed and relapse on wheat and gluten challenge.[141]

222.12.4.3 Treatment

Successful treatment depends on the exclusion of gluten from the diet, and the use of a proprietary gluten-free food (i.e., lacking wheat, barley, or rye) is recommended.

222.13 SMALL INTESTINAL BACTERIAL OVERGROWTH

Normally the bacterial population of the SI is controlled by a number of mechanisms (see above). Bacterial overgrowth is the uncontrolled proliferation of these bacteria[150] and, in humans, occurs secondary to a number of underlying disorders that interfere with the control mechanisms. Although the existence of SIBO in humans is not disputed, the subject is a source of controversy in small animal gastroenterology. In dogs, SIBO is best considered a clinical sign or a pathogenetic mechanism rather than a diagnosis. Historically, the term *idiopathic SIBO* was used to describe an antibiotic-responsive condition of large breed (especially German shepherd) dogs[44] for which no underlying cause could be recognized. However, given concerns as to whether a true overgrowth exists in these cases, the alternative name of *antibiotic-responsive diarrhea* has been suggested.[77,151] Although cats might feasibly suffer from secondary SIBO, an idiopathic antibiotic-responsive condition similar to that seen in German shepherds has not been documented in this species.[152]

222.13.1 Definition

Genuine bacterial overgrowth is defined by an increase in the absolute number of bacteria in the upper SI during the fasted state (i.e., the number of colony-forming units cultured per milliliter of duodenal juice [CFU/mL]). The upper limit for normal bacterial numbers was defined in humans, and that number has been extrapolated to dogs. Controversy exists as to its validity, however, because the original work used a small number of dogs and questionable bacteriologic techniques.[15] Subsequent studies with different collection methods and improved anaerobic culture techniques have demonstrated that a count equal to or greater than 10^7 CFU/mL total bacteria is commonly found in asymptomatic dogs.[15] Therefore, although a genuine bacterial overgrowth may exist in conditions equivalent to those in humans, defining the presence of SIBO based on the original numeric limit is flawed. In this chapter, cases with a documented underlying cause are defined as *secondary SIBO,* and the term *idiopathic ARD* is used for idiopathic antibiotic-responsive conditions without an obvious underlying cause.

222.13.2 Etiology and Pathogenesis

222.13.2.1 Secondary SIBO

SIBO can occur secondary to (1) diseases that result in excess substrate in the intestinal lumen (e.g., EPI, motility disorder, blind loop), (2) diseases that affect the clearance of bacteria (e.g., partial obstruction, abnormal motility), or (3) morphologic or functional derangement of the mucosa (Box 222-16). Increased numbers of bacteria in the upper SI cause malabsorption and diarrhea through several mechanisms. First, bacteria compete for nutrients; for example, by binding cobalamin and reducing its availability for absorption. Second, bacterial metabolism of nutrients can create products that provoke diarrhea (e.g., hydroxylated fatty acids and deconjugated bile salts), leading to diarrhea from fat malabsorption and stimulation of colonocyte secretion. Finally, the bacterial flora may damage the mucosal brush border, and alterations in enzyme activity, which reverse on antibiotic treatment, can be detected.[44,153]

222.13.2.2 Idiopathic ARD

A number of hypotheses exist as to the cause of idiopathic ARD. Historically, hypotheses were based on the belief that a genuine increase in SI bacterial numbers was present and therefore pathogenesis was related to the mechanisms described above. An underlying defect allowing overgrowth was not obvious, and suggested mechanisms such as abnormal intestinal motility or achlorhydria were not proved.

Given that recent studies have questioned whether a genuine increase in bacterial numbers occurs, recent hypotheses now focus on host-bacterial interactions. As was suggested for mouse models of enteric inflammation (see Table 222-1), ARD may develop secondary to defects in the mucosal barrier, aberrant mucosal immune responses, qualitative changes in the enteric bacterial flora, or a combination of these mechanisms. Defects in the mucosal barrier are supported by studies documenting abnormal permeability and the presence of brush border enzyme defects.[44,153] A possible underlying selective IgA deficiency in the German shepherd breed has been postulated.[154] German shepherds with intestinal disease have defective small intestinal IgA production, although mucosal IgA+ plasma cell numbers in affected dogs are either normal or increased. The cause of this IgA deficiency is not clear, but a complex defect is likely,

involving abnormalities either in the production and release of IgA from the plasma cell or in the pathway of translocation of IgA across the epithelium during secretion.

222.13.2.2.1

Box • 222-16 Causes of Secondary Small Intestinal Bacterial Overgrowth

- Achlorhydria
  - Spontaneous (atrophic gastritis)
  - Acid blockers
- Exocrine pancreatic insufficiency
- Partial intestinal obstruction
  - Chronic intussusception
  - Stricture
  - Tumor
- Abnormal anatomy
  - Surgical resection of ileocolic valve
  - Blind loop
- Motility disorder
  - Primary
  - Hypothyroidism
- Mucosal disease
  - Latent primary pathogens (?)
  - Inflammatory bowel disease (cause or effect?)
  - Chronic giardiasis

Dietary sensitivity (?)

Studies demonstrate that dogs with ARD have increased lamina propria CD4+ T cells and increased expression of certain cytokines.[81,155] It therefore is tempting to speculate that this represents immune dysregulation and perhaps a loss of tolerance toward endogenous bacterial antigens. Such a hypothesis is supported by the fact that antibacterials lead to resolution of clinical signs and decreased cytokine expression but not to a decline in bacterial numbers.[81] The fact that the most effective antibacterials are those with immune-modulating properties (e.g., oxytetracycline, metronidazole, tylosin) may support this hypothesis.

An alternative hypothesis is that an unidentified pathogen is involved; candidates include intestinal *Helicobacter* spp. or enteropathogenic *E. coli*. The predisposition of German shepherds to this syndrome could therefore be explained by genetic susceptibility to infection as a result of MHC II antigen expression.

222.13.3 Clinical Presentation

222.13.3.1 Idiopathic antibiotic-responsive diarrhea

Idiopathic ARD is most commonly recognized in young German shepherds, although cases have been reported in other dog breeds (but not in cats). Affected dogs show signs of chronic intermittent diarrhea accompanied by weight loss and/or stunting. Intermittent, watery diarrhea, often associated with excessive gas production (manifested as borborygmi and flatus), is seen most frequently. However, vomiting and signs of colitis are sometimes reported, and occasionally dogs are stunted yet do not have diarrhea. Activity levels are normal, and appetite is variable; most affected dogs have polyphagia, pica, or coprophagia, but few are anorectic. A positive response to antibiotics is expected, and the clinical condition may deteriorate if corticosteroids are given. The major differential diagnoses are EPI and IBD, both of which are common in German shepherds.

222.13.3.2 Secondary SIBO

SIBO may occur secondary to numerous primary conditions (see Box 222-16), and clinical signs usually relate to the underlying condition. However, signs of secondary SIBO also can been seen and are indistinguishable from those of idiopathic ARD, with diarrhea predominating. When SIBO develops secondary to a partial obstruction or focal dysmotility, bacterial numbers can exceed 10^9 CFU/mL.[150] Clinical signs may be noted intermittently, because recurrent diarrhea can temporarily flush out the overgrowth.

Using the historical numeric cutoff of 10^5 CFU/mL total bacteria, secondary SIBO was considered common in chronic enteropathies.[156] In reality, true secondary SIBO is uncommon, with the exception of SIBO secondary to EPI. An increase in SI bacterial numbers has been documented in experimentally induced EPI, although bacterial numbers decrease upon treatment of EPI with enzyme replacement. Therefore in many cases the SIBO itself is of no significance. However, a proportion of naturally occurring EPI cases respond suboptimally to pancreatic enzyme supplementation alone and may require concurrent antibiotic therapy. Given that the majority of dogs affected with EPI are German shepherds, it is not clear whether this is the result of secondary SIBO or of a concurrent idiopathic ARD.

222.13.4 Diagnosis

The diagnosis of SIBO and ARD is controversial. In all cases it is critical that a thorough investigation be conducted to eliminate causes of secondary SIBO before the patient is treated with antibacterials. In this regard, diagnostic imaging, especially ultrasonography, is useful for ruling out partial intestinal obstructions. Systemic disorders should be ruled out with a minimum database, and EPI is eliminated by serum TLI assay. Fecal examination for parasitic and bacterial diseases is also mandatory.

222.13.4.1 Idiopathic ARD

Although both direct and indirect tests were previously advocated for idiopathic SIBO, recent studies have suggested that they are all of limited value.[77] One recent study demonstrated that neither indirect biochemical markers (folate, cobalamin, unconjugated bile acids) nor quantitative bacterial culture could reliably identify cases of ARD. Therefore the only available diagnostic test for ARD is response to an antibacterial trial. However, such a diagnostic modality is appropriate only after thorough diagnostic investigations have eliminated all other causes of an antibacterial responsiveness.

222.13.4.2 Secondary SIBO

Although numerous tests are available to document secondary overgrowth (see below), in practice it is more important to identify the underlying cause.

222.13.4.3 Duodenal juice culture

Quantitative aerobic and anaerobic culture of duodenal juice previously formed the gold standard for diagnosis. For dogs, increases in either total or anaerobic bacteria above the upper cutoff (10^5 CFU/mL total bacteria or 10^4 CFU/mL anaerobic bacteria) were considered diagnostic. However, the validity of these cutoffs has been questioned. A count of 10^7 CFU/mL total duodenal bacteria has been documented commonly in healthy dogs, and numbers as high as 10^9 CFU/mL have been found occasionally in cats and asymptomatic dogs.[13–15] Some of the discrepancies may reflect difficulties and differences in the methodology, because numbers vary widely when individual animals are repeatedly sampled.[84] Use of an inappropriately low cutoff value leads to overdiagnosis of SIBO, which probably explains why it has been reported in 50% of dogs with chronic intestinal disease.[156] Culture of endoscopic biopsies has not been shown to be of greater diagnostic utility.[84]

The flora present in idiopathic antibiotic-responsive diarrhea may be comprised predominantly of either aerobic or anaerobic bacteria, but it tends to be a mixed population, with staphylococci, streptococci, coliforms, enterococci, and corynebacteria and anaerobes such as bacteroids, fusobacteria, and clostridia. These bacteria generally are commensals found normally in the oropharynx, small intestine, and large intestine. However, culture of fecal bacteria cannot be correlated with SI bacterial numbers and cannot be used to diagnose this condition.

222.13.4.4 Indirect tests for SIBO/ARD

Indirect tests include serum biochemical markers and breath hydrogen analysis.

222.13.4.4.1 Serum folate and cobalamin concentrations

Bacteria synthesize folate and bind cobalamin, preventing its absorption. Therefore SIBO would be predicted to be associated with an increased serum folate concentration or a decreased cobalamin concentration, or both. Although such results would be expected in cases of genuine SIBO (e.g., secondary SIBO), no studies have specifically assessed the usefulness of these tests in those diseases. Alterations of serum folate and cobalamin noted in EPI may reflect pancreatic dysfunction rather than secondary SIBO.

Furthermore, recent studies have demonstrated that these tests are of limited value in the diagnosis of idiopathic ARD.[77] This poor performance may be related to dietary factors, the presence of concurrent disease, or the use of drugs that alter serum vitamin concentrations. The other possibility (for idiopathic ARD) is that disease pathogenesis is not related to genuine increases in bacterial numbers. Although these tests are often the only tests available to practitioners, they are generally unhelpful in the diagnosis of idiopathic ARD.

222.13.4.4.2 Serum unconjugated bile acids

Bile acids are synthesized and conjugated in the liver and excreted into the intestine via the biliary tract. Some SI bacterial species can deconjugate bile acids, which then are absorbed passively by the SI. Studies in humans have suggested that increased serum unconjugated bile acid (SUBA) concentrations are an indirect indicator of SIBO. A preliminary study in dogs suggested that SUBA concentrations increased in SIBO.[76] However, these results have been contradicted by another recent study, which demonstrated that SUBA concentrations were neither sensitive nor specific for diagnosis of idiopathic ARD.[77] Further work may be required to clarify the diagnostic value of SUBA concentrations in dogs.

222.13.4.4.3 Other biochemical tests

Measurement of increased amounts of a bacterial product made either naturally or after oral administration of a test substance could be used to diagnose SIBO, but none of these are reliable.

222.13.4.5 Breath hydrogen excretion

Bacterial fermentation in the intestinal tract releases hydrogen which, after systemic absorption, is exhaled and can be measured in breath samples. Theoretically, SIBO can result in a high resting breath hydrogen concentration or an early (or double) hydrogen peak after ingestion of a test meal. However, increased breath hydrogen can also be seen with carbohydrate malabsorption or decreased orocecal transit time. Given these problems with interpretation and the fact that protocols have not been standardized, breath hydrogen testing has not been widely adopted.

222.13.4.6 Intestinal permeability

Intestinal permeability, as measured by ^{51}Cr-EDTA and differential sugar absorption, can be abnormal in SIBO and can improve after antibiotic treatment. However, such findings are not pathognomonic for either secondary SIBO or idiopathic ARD.

222.13.4.7 Lack of histologic changes on intestinal biopsy

Histopathologic examination of intestinal biopsies is most often normal or demonstrates only subtle abnormalities. However, such findings are not pathognomonic, because other conditions yield similar results. Despite the lack of histologic evidence of inflammation, disturbances in immune cell populations have been noted, most notably increases in IgA+ plasma cells and CD4+ cells. However, such techniques have not been applied for routine diagnostic purposes.

222.13.4.8 Empiric response to antibiotics

Currently, the best diagnostic test for idiopathic ARD is, logically, the response to empirical therapy. However, a response to antibacterials is not specific and indeed may be beneficial in IBD, infectious diarrhea, and even a range of nonenteric diseases such a portovascular anomalies. Furthermore, response to antibiotic therapy does not discriminate idiopathic ARD from secondary SIBO. Therefore an empirical response to antibiotics is valid only after thorough diagnostic investigations have eliminated other possible causes.

The suggested criteria for a diagnosis of idiopathic ARD are (1) a positive response to the antibiotic trial based on resolution of relevant clinical signs; (2) relapse of signs upon withdrawal of treatment; (3) remission on reintroduction of antibiotics; and (4) elimination of other etiologic causes based on the results of other diagnostic tests and histopathologic assessment.

222.13.5 Treatment

222.13.5.1 Secondary SIBO

Although antibacterial therapy improves clinical signs, appropriate treatment for the underlying condition is preferable. For EPI, pancreatic enzyme supplementation can reduce bacterial numbers because exogenous proteases have antibacterial properties.

222.13.5.2 Idiopathic ARD

No cure is available for idiopathic ARD, but signs can be controlled with antibacterials. A broad-spectrum antibiotic is indicated; suitable choices include oxytetracycline (10 to 20 mg/kg given orally every 8 hours), metronidazole (10 to 20 mg/kg given orally every 8 hours), and tylosin (20 mg/kg given orally every 8 or every 12 hours). Oxytetracycline (OTC) is cheap, and because systemic absorption is not required, it can be given with food. It cannot be used before permanent tooth eruption because it causes staining of tooth enamel. Some authors have criticized the use of OTC because it is associated with rapid development of plasmid-mediated antibiotic resistance.[151] However, given that long-term efficacy is maintained in most

cases, OTC may not be acting through its antibacterial properties, because it does not significantly reduce SI bacterial numbers.[81] Rather, it may provide a selective pressure on the intestinal flora, encouraging the establishment of less harmful bacteria, or it may exert immunomodulatory effects, which this antibiotic group has. Immunomodulatory activity has also been suggested for other antibacterials commonly used to treat ARD, namely metronidazole and tylosin.

Whichever antibacterial is chosen, a 4-to 6-week course is appropriate initially, although the antibiotic should be changed after 2 weeks if the response has been suboptimal. In some cases, premature cessation of treatment can lead to relapse, and prolonged therapy often is necessary. In some animals a delayed relapse occurs several months after cessation of antibiotics, and such cases require either repeated courses or indefinite therapy. Efficacy is often maintained despite a reduction in dosage frequency from three times to even once daily. Dogs may also "outgrow" the problem with age, either as a result of a decrease in caloric intake or because of developing maturity of the mucosal immune system. It has also been suggested that idiopathic ARD in German shepherds may predispose some of these dogs to IBD later in life, but currently no direct evidence supports this supposition.

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222.13.5.3 Ancillary treatments

Dietary manipulation can be a useful adjunct to the treatment both of idiopathic ARD and of secondary SIBO. In general, a highly digestible, low-fat diet is desired to reduce the substrate available for bacterial use. Addition of FOS has been advocated to reduce SI bacterial numbers, although evidence of efficacy is conflicting. Administration of probiotics has not been thoroughly assessed in idiopathic ARD. Finally, if low cobalamin concentrations are documented, parenteral cobalamin therapy is warranted.

222.14 INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease is a collective term that describes a group of disorders characterized by persistent or recurrent GI signs and histologic evidence of intestinal inflammation on biopsy material. The disease bears little resemblance to IBD (Crohn's disease and ulcerative colitis) of humans, and indiscriminate use of the term "IBD" is no more useful than a dermatologist making a diagnosis of "chronic dermatitis." Although a number of recognized diseases are associated with chronic intestinal inflammation (Box 222-17), the cause of idiopathic IBD is, by definition, unknown. Variations in the histologic appearance of the inflammation suggest that idiopathic IBD is not a single disease entity (Figure 222-12), and the nomenclature reflects the predominant cell type present. Lymphocytic-plasmacytic enteritis (LPE) is the most common form reported; eosinophilic (gastro-) enteritis (EGE) is less common; and granulomatous enteritis is rare. Neutrophilic infiltration is a feature of human IBD but is infrequent in idiopathic IBD of dogs and cats.

222.14.1 Box • 222-17 Causes of Chronic Small Bowel Inflammation

Chronic infection

Giardia sp.

Histoplasma sp.

Toxoplasma sp.

Mycobacteria sp.

Protothecosis

Pythiosis

Pathogenic bacteria (*Campylobacter, Salmonella* spp., pathogenic *Escherichia coli*)

Food allergy

Small bowel inflammation associated with other primary gastrointestinal diseases

Lymphoma

Lymphangiectasia

Idiopathic causes

Lymphocytic-plasmacytic enteritis (LPE)

Eosinophilic gastroenterocolitis (EGE)

Granulomatous enteritis (same as regional enteritis?)

222.14.2 Clinical Presentation

Idiopathic IBD is a common cause of chronic vomiting and diarrhea in dogs and cats, but its true incidence is unknown. In reality it is often overdiagnosed because of difficulties in interpretation of histopathologic specimens and failure to eliminate adequately other causes of mucosal inflammation. No apparent gender predisposition occurs in dogs and cats, but in both species IBD is most common in middle-aged animals. GI signs, which may have been variably controlled by dietary manipulation, are sometimes seen from an earlier age. Although IBD can potentially occur in any dog or cat breed, certain predispositions are recognized, such as LPE in German shepherds and Siamese cats, lymphoproliferative enteropathy in basenjis, and protein-losing enteropathy/protein-losing nephropathy (PLE/PLN) in soft-coated wheaten terriers (see Table 222-6). Shar Peis often have a severe LPE with hypoproteinemia and extremely low serum cobalamin concentrations. In cats an association, called *triaditis,* has been reported for IBD, lymphocytic cholangitis, and chronic pancreatitis.[157]

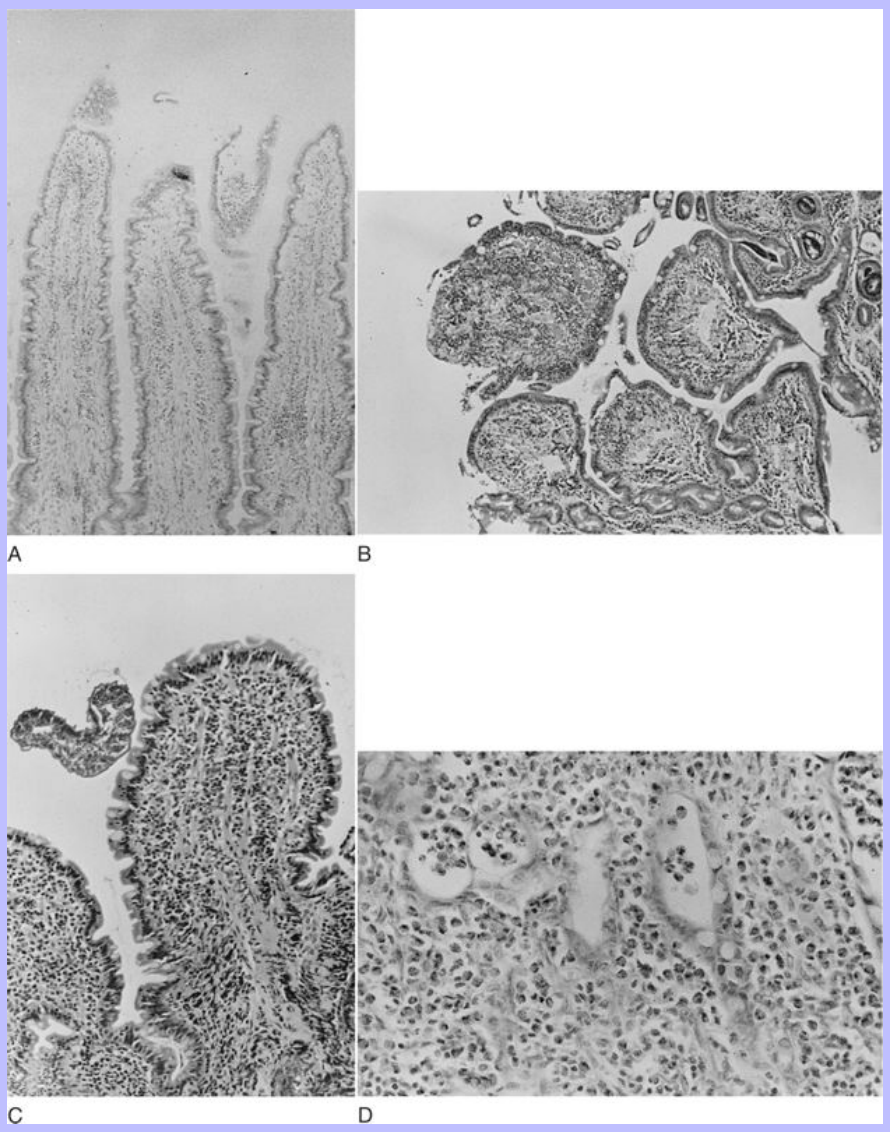
Vomiting and diarrhea are the most common clinical signs, but an individual case may show some or all of the signs in Box 222-18. Sometimes an obvious precipitating event (e.g., stress, dietary change) is present in the history, but clinical signs may wax and wane. The nature of signs crudely correlates with the region of the GI tract affected: gastric signs are more common if gastric or upper SI inflammation is present; in cats, vomiting is often the predominant sign of small intestinal IBD; and LI-type diarrhea may be the result of colonic inflammation or may result from prolonged SI diarrhea. The presence of blood in the vomit or diarrhea is associated with more severe disease, especially eosinophilic inflammatory infiltrates. Severe disease is associated with weight loss and PLE, with consequent hypoproteinemia and ascites. Appetite is variable; polyphagia may be present in the face of significant weight loss, whereas anorexia occurs with severe inflammation. Milder inflammation may not affect appetite, although postprandial pain can be significant even without other signs. Systemic consequences of IBD can occur, although reports are sparse.[158]

222.14.3 Etiology and Pathogenesis

The underlying etiology of small animal IBD is unknown, and comparisons have been made with similar human conditions. In this regard, the breakdown of immunologic tolerance to luminal antigens (bacteria and dietary components) is thought to be critical,[49] perhaps resulting from disruption of the mucosal barrier, dysregulation of the immune system, or disturbances in the intestinal microflora (see above). Therefore antigens derived from the endogenous microflora are likely to be important in disease pathogenesis, and a potential role for diet-related factors is suggested by the clinical benefit of dietary therapy in some cases of canine IBD.

Genetic factors are likely to contribute to the pathogenesis of IBD,[159,160] and in humans the strongest associations are with genes of the human MHC (human leukocyte antigen [HLA]). Furthermore, some human patients with Crohn's disease have a mutation in the NOD2 gene on chromo-some 16.[161,162] This gene's product detects bacterial lipopolysaccharide and can activate the proinflammatory transcription factor NF-κB. Such a link may explain the development of aberrant immune responses to bacteria in certain individuals. Genetic factors are also likely in dogs, given the recognized breed predispositions, although studies are lacking.

Figure 222-12 Histologic appearance of **(A)** normal jejunum, showing long, slender villi and minimal numbers of cells in the lamina propria; **(B)** idiopathic lymphoplasmacytic enteritis in a Dachshund, showing stunted villi and a lymphoplasmacytic infiltrate; **(C)** lymphoplasmacytic intestinal inflammation associated with *Strongyloides* infection (a worm is actually visible in the section on the mucosal surface); and **(D)** eosinophilic enteritis in a German shepherd, showing massive infiltration of the crypt area with eosinophils. (Courtesy G.R. Pearson.)



222.14.4 Diagnosis

Intestinal biopsy is necessary for a definitive diagnosis of IBD, although the clinical signs and physical findings may be suggestive (see Box 222-18). The term *idiopathic IBD* is limited to cases in which histologic evidence of inflammation is found without an obvious underlying cause. All other etiologies, including infectious, diet-responsive, and antibacterial-responsive conditions, should be excluded. Therefore before intestinal biopsy is undertaken, laboratory evaluation and diagnostic imaging are performed. Such tests cannot provide a definitive diagnosis of IBD, but they can help eliminate the possibility of anatomic intestinal disease (e.g., tumor, intussusception), extraintestinal disease (e.g., pancreatitis), and known causes of intestinal inflammation. Furthermore, by determining whether focal or diffuse intestinal disease is present, the clinician can choose the most appropriate method of intestinal biopsy.

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222.14.4.1 Box • 222-18 Clinical Signs Associated with Inflammatory Bowel Disease

- Vomiting of bile with or without hair in cats and grass in dogs
- Hematemesis
- Small intestinal–type diarrhea
  - Large volume
  - Watery
  - Melena
- Thickened bowel loops
- Large intestinal–type diarrhea
  - Hematochezia
  - Mucoid stool
  - Frequency and tenesmus
- Abdominal discomfort/pain
- Excessive borborygmi and flatus
- Weight loss
- Altered appetite

Polyphagia

Decreased appetite/anorexia

Eating grass

Hypoproteinemia/ascites

222.14.4.2 Hematology

Occasionally neutrophilia, with or without a left shift, is noted. Eosinophilia may suggest EGE, but it is neither pathognomonic nor invariably present. Anemia may reflect chronic inflammation or chronic blood loss.

222.14.4.3 Serum biochemistry

No pathognomonic changes are seen in IBD, but diseases of other organ systems should be recognized and excluded. Hypoalbuminemia and hypoglobulinemia are characteristic of PLE, whereas hypocholesterolemia may suggest malabsorption. Intestinal inflammation in dogs may cause a "reactive hepatopathy," with mild elevations in liver enzymes (alanine aminotransferase [ALT] and alkaline phosphatase [ALP]). In contrast, because of the shorter half-lives of liver enzymes in cats, increases are more likely to be the result of hepatocellular or cholestatic disease.

222.14.4.4 Fecal examination

Fecal examination is most important for eliminating other causes of mucosal inflammation, such as nematodes (e.g., *Trichuris, Uncinaria, Ancylostoma,* and *Strongyloides* spp.), *Giardia* infection, and bacterial infection (e.g., *Salmonella* or *Campylobacter* spp. or clostridia). Given that fecal parasitology may not always detect *Giardia* organisms, empirical treatment with fenbendazole is recommended in all cases.

Increased fecal $alpha_1$-PI concentrations would be expected in dogs with IBD, as well as significant intestinal protein loss even before hypoproteinemia develops (see above).

222.14.4.5 Folate and cobalamin

Serum concentrations of both these vitamins are affected by intestinal absorption, therefore proximal, distal, or diffuse inflammation can result in subnormal folate concentrations (proximal inflammation) or cobalamin concentrations (distal inflammation) or both (diffuse inflammation). Although such alterations are not pathognomonic for IBD, deficiencies may require therapeutic correction. Measurement of serum folate and cobalamin is now commercially available for cats, and cobalamin deficiency associated with IBD has been documented. Cobalamin deficiency has systemic metabolic consequences,[45] and anecdotal evidence suggests that deficient cats with IBD require parenteral supplementation to respond optimally to immunosuppression.

222.14.4.6 Diagnostic imaging

Imaging studies document whether focal or diffuse disease is present and whether other abdominal organs are affected. Such information, in conjunction with specific clinical signs, allows the clinician to choose the most appropriate method of biopsy. Plain radiographs may be useful for detecting anatomic intestinal disease; contrast studies rarely add further information. Ultrasonographic examination is superior to radiography for documenting focal anatomic intestinal disease and is particularly useful in cats with IBD.[163] Ultrasonography permits evaluation of intestinal wall thickness[63,163] and can document mesenteric lymphadenopathy. Ultrasound-guided fine needle aspiration (FNA) can provide samples for cytologic analysis, which may aid in diagnosis.

222.14.4.7 Intestinal biopsy

Intestinal biopsy is necessary to document intestinal inflammation. Endoscopy is the easiest method of biopsy, but it has limitations, because samples are superficial and in most cases can be collected only from the proximal SI (see Box 222-8). In some cases exploratory laparotomy and full-thickness biopsy are necessary, although the procedures are more invasive and can be problematic if severe hypoproteinemia is present. These techniques may be more suitable for cats, given the tendency in this species for multiorgan involvement.

Histopathologic assessment of biopsy material remains the gold standard for IBD diagnosis, and the pattern of histopathologic change depends on the type of IBD present (see below). However, the limitations of histopathologic interpretation of intestinal biopsies are recognized. The quality of specimens can vary,[78] agreement between pathologists is poor, and differentiation between normal specimens and those showing IBD and even lymphoma can be difficult.[79] Grading schemes for the histopathologic diagnosis of IBD have been suggested,[158] but these have not yet been widely adopted.

222.14.4.8 IBD activity index

In humans, activity indices are used to quantify the severity of IBD; this helps practitioners to assess the response to treatment and to make a prognosis by allowing comparisons between published studies in the literature. Recently an activity index was suggested for canine IBD,[164] and this may aid disease classification in the future.

222.14.4.9 Other diagnostic investigations

Given the limitations of histopathology, other modalities are required. One approach would be the use of immunohistochemistry or flow cytometry to analyze immune cell subsets. However, such techniques are labor intensive and poorly standardized and are unlikely to be generally available in the foreseeable future.

222.14.5 Treatment

Whatever the type of IBD, treatment usually involves a combination of dietary modification and antibacterial and immunosuppressive therapy. Unfortunately, objective information on efficacy is lacking, and most recommendations are based on individual experience. The authors usually recommend a staged approach to

therapy whenever possible; initial treatment involves antiparasiticides to eliminate the possibility of occult endoparasite infestation. Thereafter, sequential treatment trials with an exclusion diet and antibacterials are pursued; immunosuppressive medication is used only as a last resort. However, in some cases, clinical signs or mucosal inflammation is so severe that early intervention with immunosuppressive medication is essential. If clinical signs are intermittent, the owners should keep a diary to provide objective information as to whether treatments produce genuine improvement.

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222.14.5.1 Dietary modification

The diets recommended for patients with IBD are antigen limited, based on a highly digestible, single-source protein preparation. An exclusion diet trial should be undertaken to eliminate the possibility of an adverse food reaction, and most clients are happy to try this, given concerns over the side effects of immunosuppressive drugs. An easily digestible diet decreases the intestinal antigenic load and thus reduces mucosal inflammation. Such diets may also help resolve any secondary sensitivities to dietary components that may have arisen from disruption of the mucosal barrier. After the inflammation has resolved, the usual diet often can be reintroduced without fear of an acquired sensitivity.

Well-cooked rice is the preferred carbohydrate source because of its high digestibility, but potato, corn starch, and tapioca are also gluten free. Fat restriction reduces clinical signs associated with fat malabsorption. Modification of the n3 to n6 fatty acid ratio may also modulate the inflammatory response and may have some benefit both in treatment and in maintenance of remission, as in human IBD.[165,166] However, no direct studies have been done to prove a benefit in canine IBD. Supplementation with oral folate and parenteral cobalamin is indicated if serum concentrations are subnormal.

222.14.5.2 Antibacterial therapy

Treatment with antimicrobials can be justified in IBD, partly to treat secondary SIBO and partly because of the importance of bacterial antigens in the pathogenesis of IBD.[50] Ciprofloxacin and metronidazole are often used in human IBD,[167] and metronidazole is the preferred drug for small animals. The efficacy of metronidazole may not be related just to its antibacterial activity, because it may exert immunomodulatory effects on cell-mediated immunity. Furthermore, other antibacterials (e.g., tylosin) may also have immunomodulatory effects and have efficacy in canine IBD.

222.14.5.3 Immunosuppressive drugs

The most important treatment modality in idiopathic IBD is immunosuppression, although this should be used only as a last resort. In human IBD, glucocorticoids and thiopurines (e.g., azathioprine, 6-mercaptopurine) are used most widely.[168] In dogs, glucocorticoids are used most frequently, and prednisone and prednisolone are the drugs of choice. Dexamethasone should be avoided, because it may have deleterious effects on enterocytes. In severe IBD, prednisolone can be administered parenterally, because oral absorption may be poor. The initial dosage of 1 to 2 mg/kg given orally every 12 hours is given for 2 to 4 weeks and then tapered slowly over the subsequent weeks to months. In some cases therapy can be either completely withdrawn or at least reduced to a low maintenance dose given every 48 hours.

Signs of iatrogenic hyperadrenocorticism are common when the highest glucocorticoid dose is administered. However, signs are transient and resolve as the dosage is reduced. If clinical signs of IBD consistently recur when the dosage is reduced, other drugs can be added to provide a steroid-sparing effect

(see below). Budesonide, an enteric-coated, locally active steroid that is destroyed 90% first-pass through the liver, has been successful in maintaining remission in human IBD with minimal hypothalamic-pituitary-adrenal suppression. A preliminary study showed apparent efficacy in dogs and cats,[169] but limited information is available on the use of this drug.[170]

In dogs, azathioprine (2 mg/kg given orally every 24 hours) is commonly used in combination with prednisone/prednisolone when the initial response to therapy is poor or when glucocorticoid side effects are marked. However, azathioprine may have a delayed onset of activity (up to 3 weeks) and, given its myelosuppressive potential, regular monitoring of the hemogram is necessary. Azathioprine is not recommended for cats; chlorambucil (2 to 6 mg/m^2 given orally every 24 hours until remission, followed by drug tapering) is a suitable alternative. Other immunosuppressive drugs are methotrexate, cyclophosphamide, and cyclosporine. Methotrexate is effective in the treatment of human Crohn's disease,[171] but it is not widely used in companion animals; it often causes diarrhea in dogs. Cyclophosphamide has few advantages over azathioprine and is rarely used. However, cyclosporine may show promise for the future, given its T lymphocyte–specific effects and efficacy in canine anal furunculosis. Unfortunately, it is expensive, and studies in human IBD have shown variable efficacy and toxicity.[172,173]

222.14.5.4 Novel therapies for IBD

Novel therapies are increasingly used for human IBD in an attempt to target more accurately the underlying pathogenetic mechanisms. These therapies include new immunosuppressive drugs, monoclonal antibody therapy, cytokines and transcription factors, and dietary manipulation (Table 222-11).[174] In the future, such therapies may be adopted for small animal IBD.

Mycophenolate mofetil recently has been used to treat human IBD, although its efficacy is variable.[175] Drugs that target TNF-α (e.g., thalidomide and oxpentifylline) may be suitable for the treatment of canine IBD because of the importance of this cytokine in disease pathogenesis. Human open-label trials have demonstrated a beneficial effect for thalidomide in refractory Crohn's disease.[176] Oxpentifylline has shown efficacy in studies *in vitro*, but clinical results have been less rewarding.[177] Anti–TNF-α monoclonal antibody therapy, which has also undergone trials in human IBD, has the additional beneficial effect of inducing apoptosis in inflammatory cells.[178] Species-specific monoclonal antibodies will be needed for canine and feline IBD.

Finally, modulation of the enteric flora with probiotics or prebiotics may have benefits in targeting the pathogenesis of IBD. A *probiotic* is an orally administered living organism that exerts health benefits beyond those of basic nutrition. In addition to having direct antagonistic properties against pathogenic bacteria,[91] they modulate mucosal immune responses by stimulating either innate (e.g., phagocytic activity) or specific (e.g., secretory IgA) immune responses.[179] However, care should be taken to select the most appropriate organisms, which are likely to vary between host species.

Prebiotics are selective substrates used by a limited number of “beneficial” species, which therefore cause alterations in the luminal microflora. The most frequently used prebiotics are nondigestible carbohydrates, such as lactulose, inulin, and FOS. Both probiotics and prebiotics can reduce intestinal inflammation in mouse models of IBD.[180] Preliminary placebo-controlled trials with probiotics and prebiotics in human

IBD patients have shown promising results,[181] although similar trials in canine and feline IBD are still awaited.

222.14.6 Lymphocytic-Plasmacytic Enteritis

Lymphocytic-plasmacytic enteritis (LPE) is the most common form of idiopathic IBD. It is characterized by a mucosal infiltrate of lymphocytes and plasma cells (see Figure 222-12). However, there are numerous other causes of lymphocytic-plasmacytic infiltration of the SI (see Box 222-17 and Figure 222-12), including enteric pathogens, bacteria, and *Toxoplasma* organisms. All such underlying causes must be excluded before a diagnosis of idiopathic LPE is confirmed.

Table • 222-11 Novel Therapies for Human Inflammatory Bowel Disease

THERAPY	MECHANISM OF ACTION
Drug Therapy	
Tacrolimus	Immunosuppressant macrolide
Mycophenolate	Inhibits lymphocyte proliferation; reduces IFN-gamma production
Leukotriene antagonists (zileuton, verapamil)	Inhibit arachidonic acid cascade
Prostaglandin (PG) targeting agents	Mucosal protection from PG analogs; anti-inflammatory effects from PG antagonists
Thromboxane synthesis inhibitors	Anti-inflammatory effects
Ridogrel	
Picotamide	
Oxpentifylline	Inhibits TNF-alpha expression
Thalidomide	Inhibits TNF-alpha and IL-12 expression; reduces leukocyte migration; impairs angiogenesis
Bone Marrow and Stem Cell Transplantation	
Bone marrow grafts	Unknown; immunomodulation (?)
Dietary Manipulation	
Protein hydrolysate diets	"Hypoallergenic"
Fish oil therapy	Diverts eicosanoid metabolism to LTB_5 and PGE_3
Short chain fatty acid therapy	
Butyrate	Provides nutrition for enterocytes
Probiotics and prebiotics	Antagonize pathogenic bacteria; immunomodulatory effects
Cytokine Manipulation	
Systemic IL-10	Down-modulatory cytokine
Anti–IL-2 monoclonal antibody (MAb)	Counteracts proinflammatory effects
Anti–IL-2R (CD25) MAb	Inhibits IL-2 effects
Anti–IL-12 MAb	Counteracts proinflammatory effects
Anti–IL-11 MAb	Downregulates TNF-alpha and IL-1beta
Recombinant IFN-alpha	Anti-inflammatory; antiviral (?)
Anti–IFN-gamma MAb	Immunomodulatory effect on Th1 cells
Anti–TNF-alpha MAb	Counteracts proinflammatory effects; induces inflammatory cell apoptosis
Endothelial Cell Adhesion Molecules and Their Manipulation	
ICAM-1 (antisense oligonucleotide)	Reduces immune cell trafficking
Anti-$alpha_4$/$beta_7$ MAb	Reduces immune cell trafficking
Other Immune System Modulations	
Intravenous immunoglobulin	Saturates Fc receptors; other (?)
T-cell apheresis	Immunomodulation
Anti-CD4 antibodies	Immunomodulation
Transcription Factors	
NF-κB antisense oligonucleotide	Inhibits proinflammatory cytokine expression
ICAM-1 antisense oligonucleotide	Reduces immune cell trafficking

Modified from Forbes 2003, German and others 2003.

IFN, interferon; IL, interleukin; ICAM, intercellular adhesion molecule; LTB, leukotriene B; MAb, monoclonal antibody; PG, prostaglandin; PGE, prostaglandin E; Th1, T helper 1; TNF, tumor necrosis factor

222.14.6.1 Pathogenesis

Idiopathic LPE is believed to reflect immune dysregulation, and the spectrum of severity ranges from mild to severe infiltration. Alterations in immune cell populations in canine LPE have been documented,

including increases in lamina propria T cells (especially CD4+ cells), IgG+ plasma cells, macrophages, and granulocytes.[154]

Increased concentrations of acute-phase proteins (e.g., C-reactive protein), which normalize after treatment, have been documented in canine LPE.[164] Marked alterations in cytokine patterns also were recently documented in canine LPE, with increased expression of Th1 (IL-2, IL-12, and IFN-gamma), Th2 (IL-5), proinflammatory (TNF-alpha), and immunoregulatory (TGF-beta) cytokines.[81] These studies confirm that the mucosal immune response is upregulated in canine IBD.

1371 1372

222.14.6.2 Clinical Signs

Clinical signs of LPE include diarrhea and weight loss, but these are not pathognomonic. Chronic vomiting may be the predominant sign, especially in cats. LPE is prevalent in German shepherds, Shar Peis, and purebred cats, and in dogs it often causes a PLE. Severe LPE (immunoproliferative disease) is recognized in basenjis. Protein-losing enteropathy with or without concurrent protein-losing nephropathy has also been described in soft-coated wheaten terriers.[144] LPE typically affects older animals; it is uncommon (but not impossible) in individuals less than 2 years of age.

222.14.6.3 Diagnosis

The approach to diagnosis of LPE is the same as for any chronic enteropathy, although definitive diagnosis ultimately depends on documentation of characteristic histopathologic changes in the absence of an underlying cause. Such changes include the presence of increased numbers of lymphocytes and plasma cells in association with architectural disturbances. Complete or partial villus atrophy may be present, and villus fusion and crypt abscessation may be noted in severe cases. The distinction between severe LPE and alimentary lymphoma is sometimes difficult, and discrepancies may arise between endoscopic biopsies and postmortem examination of the same patient. It is hypothesized that such discrepancies arise because the two conditions may be present concurrently in the SI, because prolonged intestinal inflammation may ultimately result in transformation to lymphoma, or because low-grade lymphoma is initially misdiagnosed.

Another major concern is the criteria by which a diagnosis of LPE is made. In this regard, major discrepancies exist in interpretation of intestinal biopsies by different histopathologists.[79] Interpretation of the degree of inflammation is subjective; inflammation may be patchy, and the presence of edema (due to hypoproteinemia) may make cell density difficult to assess. Furthermore, discrepancies exist between gross endoscopic and histologic findings, and proximal endoscopic biopsies may not be representative. Attempts have been made to standardize interpretation by using grading schemes; those that assess morphologic abnormalities in conjunction with changes in cellularity are most appropriate.[158]

222.14.6.4 Treatment and Prognosis

The treatment of LPE is that outlined for idiopathic IBD above. First-line treatment usually involves dietary manipulation and metronidazole. The prognosis for severe LPE is guarded. Some patients respond dramatically and can ultimately be weaned off all medication; other cases, however, require persistent, low-dose maintenance immunosuppressive therapy.

222.14.7 Basenji Enteropathy

A severe, hereditary form of LPE has been well characterized in basenjis,[182] although the mode of inheritance is unclear.[183] It has been likened to immunoproliferative small intestinal disease (IPSID) in humans, because both conditions involve intense intestinal inflammation. However, IPSID is characterized by an associated gammopathy (alpha heavy chain disease) and a predisposition to lymphoma. Affected basenjis often have hyperglobulinemia but not alpha heavy chain disease and may be predisposed to lymphoma. The intestinal lesions in basenjis are characterized by increases in CD4+ and CD8+ T cells.[182]

222.14.7.1 Clinical Signs

Signs of chronic intractable diarrhea and emaciation are most common. Lymphocytic-plasmacytic gastritis, with hypergastrinemia and mucosal hyperplasia, may be seen in addition to the enteropathy. PLE often occurs, with consequent hypoalbuminemia, although edema and ascites are not common. Clinical signs are usually progressive, and spontaneous intestinal perforation may occur.

222.14.7.2 Diagnosis

The approach to diagnosis is the same as before, and ultimately depends on histopathological examination of biopsy specimens.

222.14.7.3 Treatment

Treatment generally is unsuccessful, with dogs dying within months of diagnosis. However, early, aggressive combination treatment with prednisolone, antibiotics, and dietary modification may achieve remission in some cases.

222.14.8 Familial Protein-Losing Enteropathy and Protein-Losing Nephropathy in Soft-Coated Wheaten Terriers

Recently a clinical syndrome unique to soft-coated wheaten terriers was characterized.[144,184] Affected dogs present with signs of PLE or PLN or both. A genetic basis is likely, and although the mode of inheritance is not yet clear, pedigree analysis of 188 dogs has demonstrated a common male ancestor.[185] The disease is probably immune mediated, given the presence of inflammatory cell infiltration. A potential role for food hypersensitivity has been suggested, because affected dogs have demonstrated adverse reactions during provocative food trials and alterations in antigen-specific fecal IgE concentrations.[145,184,186]

222.14.8.1 Clinical Signs

Signs of PLE tend to develop at a younger age than PLN. Clinical signs of the PLE include vomiting, diarrhea, weight loss, and pleural and peritoneal effusions. Occasionally, thromboembolic disease may occur.[187]

222.14.8.2 Diagnosis

Preliminary laboratory investigations, as in most dogs with PLE, demonstrate panhypoproteinemia and hypocholesterolemia. In contrast, hypoalbuminemia, hypercholesterolemia, proteinuria, and ultimately azotemia are seen with PLN.[185] Histopathologic examination of intestinal biopsy material reveals evidence of intestinal inflammation, villus blunting, and epithelial erosions, as well as dilated lymphatics and lipogranulomatous lymphangitis.

222.14.8.3 Treatment and Prognosis

The treatment for PLE is similar to that described for general IBD, but the prognosis is usually poor.

222.14.9 Eosinophilic Enteritis

Eosinophilic enteritis (EE) is reported to be the second most common form of IBD. It frequently also involves the stomach and/or colon in eosinophilic gastroenteritis (EGE) and/or colitis. Segmental EE has also been reported.[188] Histologically, variable mucosal architectural disturbances (e.g., villus atrophy) are present in conjunction with a mixed infiltrate of inflammatory cells in which eosinophils predominate (see Figure 222-12). However, as with LPE, diagnostic criteria vary among pathologists; some define EE based purely on subjective increases in mucosal eosinophil numbers, whereas others apply stricter criteria, requiring that eosinophils predominate in the lamina propria. Another criterion is the presence of eosinophils between epithelial cells of the villus and crypt, which suggests transepithelial migration. Nevertheless, the number of mucosal eosinophils can vary markedly in normal dogs,[22] and therefore this condition may be overdiagnosed. As with other forms of IBD, a diagnosis of EE should be made only after other causes of eosinophilic infiltration have been eliminated.

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222.14.9.1 Clinical Signs

EE may be seen in dogs and cats of any breed and age, although it is most common in younger adult animals. Boxers and Dobermans may be predisposed, and an increased incidence in German shepherds has been suggested. EGE may also be associated with systemic eosinophilic disorders in both cats and dogs. The clinical signs reported, which depend on the area of GI tract involved, include vomiting, SI diarrhea, and LI diarrhea. Mucosal erosion/ulceration may occur more frequently in EE than in other forms of IBD, therefore hematemesis, melena, or hematochezia may be seen. Severe EGE has been associated with PLE and hypoproteinemia and, rarely, spontaneous perforation of the GI tract.[189]

222.14.9.2 Pathogenesis

An eosinophilic mucosal infiltrate may be related to dietary sensitivity, endoparasitism, or idiopathic EGE. The eosinophil infiltration is likely to be the result of local and systemic production of cytokines and chemokines, such as IL-5, and members of the eotaxin family.[190] These mediators may be produced by the Th2 subset of CD4+ T cells.

222.14.9.3 Diagnosis

The diagnosis of EGE is made by histopathologic assessment of intestinal biopsies after exclusion of parasites and food allergy. Peripheral eosinophilia is neither invariably present nor pathognomonic for EGE, because it may also be seen in parasitism, hypoadrenocorticism, allergic cutaneous or respiratory disease, and mast cell neoplasia.

222.14.9.4 Treatment

Given that eosinophilic mucosal infiltrates may also be related to endoparasitic diseases, empirical treatment with fenbendazole is always advisable. Subsequent to this, an exclusion diet trial should be instigated to eliminate the possibility of dietary sensitivity before immunosuppressive therapy is considered. The prognosis in idiopathic EGE is guarded, even with a good initial response to treatment, because recurrence is common.

222.14.10 Other Forms of Inflammatory Bowel Disease

222.14.10.1 Granulomatous Enteritis

Granulomatous enteritis is a rare form of IBD characterized by mucosal infiltration with macrophages, resulting in the formation of granulomas. The distribution of inflammation can be patchy. This condition is probably the same as “regional enteritis,” in which ileal granulomas have been reported. Granulomatous enteritis has some histologic features in common with human Crohn's disease, but obstruction, abscessation, and fistula formation are not noted. Conventional therapy is not usually effective, and the prognosis is guarded, although a combination of surgical resection and anti-inflammatory treatment was reported to be successful in one case.[191] In cats, a pyogranulomatous transmural inflammation has been associated with FIPV infection.

222.14.10.2 Proliferative Enteritis

Proliferative enteritis is characterized by segmental mucosal hypertrophy of the intestine. Although many species can be affected, the condition is most common in pigs. A similar but rare condition has been reported in dogs.[192] There have been suggestions of an underlying infectious etiology, and *Lawsonia intracellularis* has been implicated, although this has not yet been proved. Other infectious agents with a proposed link are *Campylobacter* spp. and *Chlamydia* organisms.

222.15 LYMPHANGIECTASIA

222.15.1 Definition and Cause

Intestinal lymphangiectasia is characterized by marked dilatation and dysfunction of intestinal lymphatics. Abnormal lymphatics leak protein-rich lymph into the intestinal lumen, ultimately causing PLE and hypoproteinemia. Lymphangiectasia may be a primary disorder or can develop secondary to lymphatic obstruction.

Primary lymphangiectasia usually is limited to the intestine, although it may be part of a more widespread lymphatic abnormality involving, for example, chylothorax.[193] It is considered congenital, although clinical signs are not usually present from birth. The development of associated lipogranulomatous lymphangitis, superimposed on the congenital abnormalities, is one reason for a progressive disorder. The disease is most commonly seen in small terrier breeds (e.g., Yorkshire, Maltese) and the Norwegian lundehund (Figure 222-13), suggesting a genetic predisposition.

Secondary lymphangiectasia is caused by intestinal lymphatic obstruction. Underlying causes include (1) infiltration or obstruction of lymphatics by an inflammatory, fibrosing, or neoplastic process; (2) possibly obstruction of the thoracic duct; and (3) right heart failure due to congestive heart failure or cardiac tamponade. Lipogranulomatous lymphangitis is sometimes reported in association with lymphangiectasia, but it is not clear which is the primary event; lymphangitis could cause lymphatic obstruction, or leakage of lymph could cause granuloma formation.

222.15.2 History and Clinical Signs

The clinical manifestations of lymphangiectasia are largely attributable to the effects of the enteric loss of lymph. Other intestinal functions remain intact, and hypoproteinemia may be present without diarrhea.[194] Diarrhea, steatorrhea, profound weight loss, and polyphagia are more typical, and vomiting, lethargy, and anorexia are reported occasionally. Signs may have an insidious onset and an intermittent pattern. Ascites or subcutaneous edema may develop if hypoproteinemia is marked. The ascitic fluid usually is a pure transudate, but if right heart failure causes secondary lymphangiectasia, a modified transudate develops through portal hypertension. Lymphangiectasia has been associated with granulomatous hepatopathy[195] and in lundehunds with chronic gastritis and gastric carcinoma.[196]

Figure 222-13 Normal lundehund (*left*) and one affected with lymphangiectasia, showing abdominal distension caused by hypoproteinemic ascites. (Courtesy D.A. Williams.)

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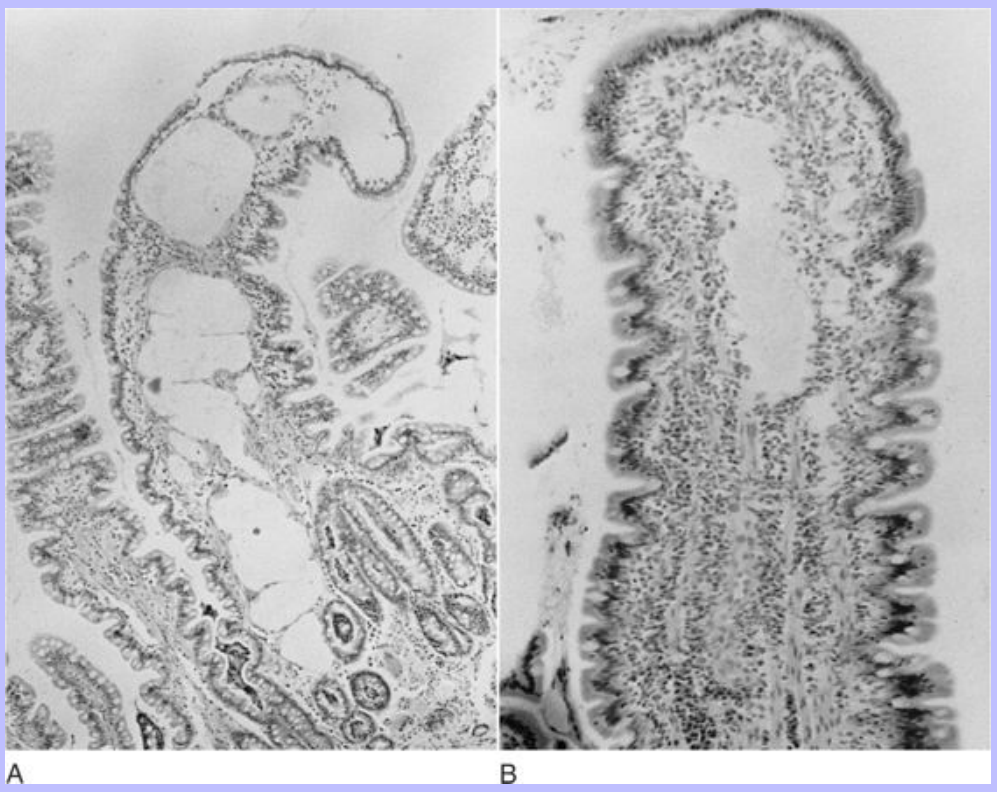
222.15.3 Diagnosis

Given that lymph is rich in lipoproteins and lymphocytes, laboratory analysis often shows panhypoproteinemia, hypo-cholesterolemia, and lymphopenia. Hypocalcemia and hypomagnesemia have been reported.[55,197] The hypocalcemia is the result not only of hypoalbuminemia, but also of the development of ionized hypocalcemia. Therefore other mechanisms, including vitamin D and calcium malabsorption, may be involved. PLE can be documented by measuring[51] Cr-albumin leakage or fecal concentrations of $alpha_1$-PI. In affected lundehunds, increased permeability has been documented by both methods, and the increases in the fecal $alpha_1$-PI concentration were seen before changes in serum proteins.[198]

Gross findings at endoscopy include the presence of white lipid droplets or prominent mucosal blebs, which are likely the result of villus tip distension with chyle. Endoscopic biopsies may be supportive of the diagnosis, but full-thickness biopsies may be required to make a definitive diagnosis. At exploratory laparotomy, most dogs show gross abnormalities, including thickened small intestine, dilated lymphatics (in the mesentery and intestinal serosa), and occasionally adhesions.[199] Mesenteric lymph nodes may also be enlarged, and yellow-white nodular masses (1 to 3 mm in diameter) are often observed in and around the mesenteric and serosal lymphatics. The nodules are lipogranulomas, consisting of accumulations of lipid-laden macrophages, and result from perilymphatic extravasation of chyle or are associated with a lymphangitis.

Characteristic histopathologic changes include “ballooning dilatation” of lymphatics, not only in the mucosa but also in the submucosa. This true lymphangiectasia must be distinguished both from normal postprandial dilatation of lacteals and from the secondary lacteal dilatation occasionally noted in other enteropathies (e.g., IBD) (Figure 222-14). Genuine cases are less common than currently believed, and failure to recognize an underlying inflammatory cause may explain the success of steroid treatment in some cases. Assessment of the degree of inflammatory cell infiltrate in the lamina propria is subjective, and if edema is present, the LP cell density may be underestimated.

Figure 222-14 Histologic appearance of a jejunal biopsy from **(A)** a Jack Russell terrier with a protein-losing enteropathy, in which markedly dilated lacteals consistent with a diagnosis of lymphangiectasia are present, and **(B)** a retriever with moderate lymphoplasmacytic enteritis and mild secondary ectasia of the lacteals.



222.15.4 Treatment

Secondary lymphangiectasia is managed by specific treatment of underlying disease, such as pericardiocentesis or pericardectomy for cardiac tamponade. The aim of treatment of primary lymphangiectasia is to decrease the enteric loss of plasma protein, resolve associated intestinal or lymphatic inflammation, and control any edema or effusions. Dietary manipulation and glucocorticoids are the most important treatment modalities.

The ideal diet for cases of lymphangiectasia is markedly fat restricted, calorie dense, and highly digestible. Weight reduction diets, although low in fat, are inappropriate, because patients require a high level of nutrition. Previously, administration of medium chain triglycerides (MCT) was recommended, because these lipids were thought to be absorbed directly into the portal blood. However, this theory was recently

contradicted.[200] Supplementation with fat-soluble vitamins is advised, and there are anecdotal reports of improvement with glutamine supplementation.

Glucocorticoid therapy (prednisolone, 1 to 2 mg/kg given orally divided daily and then tapered) may be beneficial in some cases, especially if associated lymphangitis, lipogranulomas, and a lymphocytic-plasmacytic infiltrate are present in the lamina propria. Unfortunately, not all cases respond to such therapy. The use of antimicrobials such as tylosin or metronidazole has not shown any obvious success. Diuretics are indicated in the management of effusions, and combinations of diuretics are preferred (e.g., furosemide and spironolactone); administration of plasma or colloid may also help if hypoproteinemia is marked. The response to treatment is unpredictable, but cessation of clinical signs may be achieved temporarily, with remissions of months to several years. However, the overall long-term prognosis is poor, and patients eventually succumb to severe malnutrition, incapacitating effusions, and intractable diarrhea.

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222.16 MISCELLANEOUS CAUSES OF PROTEIN-LOSING ENTEROPATHY

Common causes of PLE include lymphoma and IBD. However, there have also been recent reports of PLE associated with intestinal crypt lesions[201,202] without evidence of lymphangiectasia or inflammation in most cases. The underlying etiology of such lesions is not known. Response to therapy with antibacterials and immunosuppressive medication is variable; some dogs deteriorate suddenly and can die from thromboembolic disease.

222.17 INTESTINAL NEOPLASIA

Lymphomas, adenocarcinomas, and mast cell tumors are the most common GI tumors in cats, whereas adenocarcinomas and leiomyomas are more common in dogs. Intestinal fibrosarcomas, hemangiosarcomas, carcinoids, and plasma cell tumors are rare. Clinical signs usually include weight loss, although a spectrum of signs may be seen, including diarrhea, anorexia, melena, vomiting, abdominal discomfort, abdominal effusion, and anemia. Other consequences of intestinal neoplasia include intussusception, intestinal perforation, and a variety of paraneoplastic effects.

222.17.1 Intestinal Lymphoma

Lymphoma is characterized by mucosal, submucosal, and/or epithelial infiltration of neoplastic lymphocytes,[203,204] which can invade the intestine in either a diffuse or a focal manner (Figure 222-15). Focal forms may cause obstruction; diffuse infiltration is more common and usually results in malabsorption. Most affected cats test negative for the feline leukemia virus (FeLV) at the time of diagnosis. Progression from LPE to lymphoma has been reported.

222.17.1.1 Clinical findings

Middle-aged or older dogs and cats are most commonly affected. Weight loss, chronic diarrhea, and progressive inappetence are common features, although vomiting and melena may also be noted. Diffusely thickened intestines, intestinal mass lesions, mesenteric lymphadenopathy (see Figure 222-15), or abdominal pain may be noted on abdominal palpation. Concurrent hepatosplenomegaly and generalized lymphadenopathy are suggestive of multicentric lymphoma or an alimentary form involving the liver. Clinical signs of hypoproteinemia may develop if diffuse lymphoma results in severe PLE.

222.17.1.2 Diagnosis

Hematologic examination may demonstrate anemia, characterized as either normocytic-normochromic nonregenerative or microcytic and hypochromic. Neutrophilia may also be evident. Routine biochemistry tests may reveal panhypoproteinemia in dogs and cats with diffuse lymphoma, although B-cell neoplasms may present with hyperglobulinemia as a result of monoclonal gammopathy. Alterations in serum folate or cobalamin concentrations may be the result of malabsorption or of SIBO secondary to intestinal obstruction. Ultrasonography may demonstrate diffuse or focal intestinal wall thickening, loss of intestinal wall layering, and mesenteric lymphadenopathy; it also facilitates fine needle aspiration of focal lesions. Samples for cytologic evaluation can be collected at endoscopy by cytology brush or squash preparation, but in many cases intestinal biopsy is required. Full-thickness biopsy material is preferable to endoscopic pinch biopsies, which may miss the lesion or simply demonstrate adjacent LPE. However, exploratory laparotomy is a risky procedure, because many patients are severely debilitated and hypoproteinemic.

Although histopathologic assessment of biopsy material is the gold standard for diagnosis of alimentary lymphoma, differentiation from LPE can be difficult. Immunohistochemistry may aid in the diagnosis if all lymphocytes are of a single lineage. In the future, immunohistochemistry,[204] flow cytometry,[205] and assessment of T-cell clonality by PCR may prove to be more accurate methods of diagnosis.[82]

222.17.1.3 Treatment and prognosis

Dogs with diffuse alimentary lymphosarcoma (LSA) usually respond poorly to therapy, and there is a risk of intestinal perforation. In contrast, the prognosis in cats is more favorable; some attain prolonged remission.[206,207] Response to combination chemotherapy has been reported, either with standard multidrug protocols or with an “oral only” regimen (e.g., prednisolone and chlorambucil).[206] The latter treatment is well tolerated and may be particularly applicable to cases in which the differentiation between lymphoma and LPE is uncertain.

222.17.2 Intestinal Adenocarcinoma

Intestinal adenocarcinoma is most common in middle-aged to older dogs and cats, and Siamese cats may be over-represented. In dogs these tumors have a predilection for the duodenum, whereas the jejunum and ileum are more commonly affected in cats (see Figure 222-8).

222.17.2.1 Clinical findings and diagnosis

Adenocarcinomas are locally infiltrative, and clinical signs usually relate to partial obstruction or peritonitis when perforation has occurred. Abdominal palpation may reveal focal thickening of the intestine. Melena and signs of anemia may be present if significant ulceration has occurred. Hematologic examination may demonstrate anemia, which usually is strongly regenerative and either normocytic-normochromic or hypochromic and microcytic. Occasionally the anemia is Coombs' positive. Diagnostic imaging may delineate a mass lesion, although definitive diagnosis requires percutaneous aspiration or surgical biopsy.

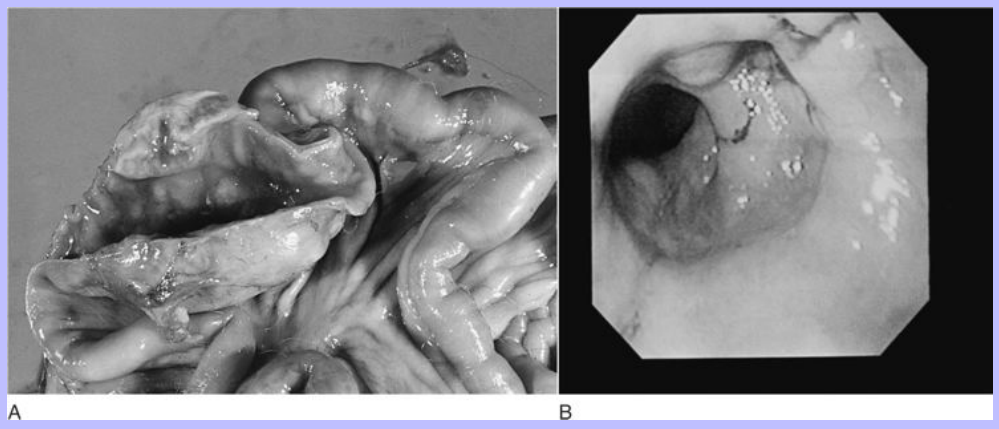
222.17.2.2 Treatment and prognosis

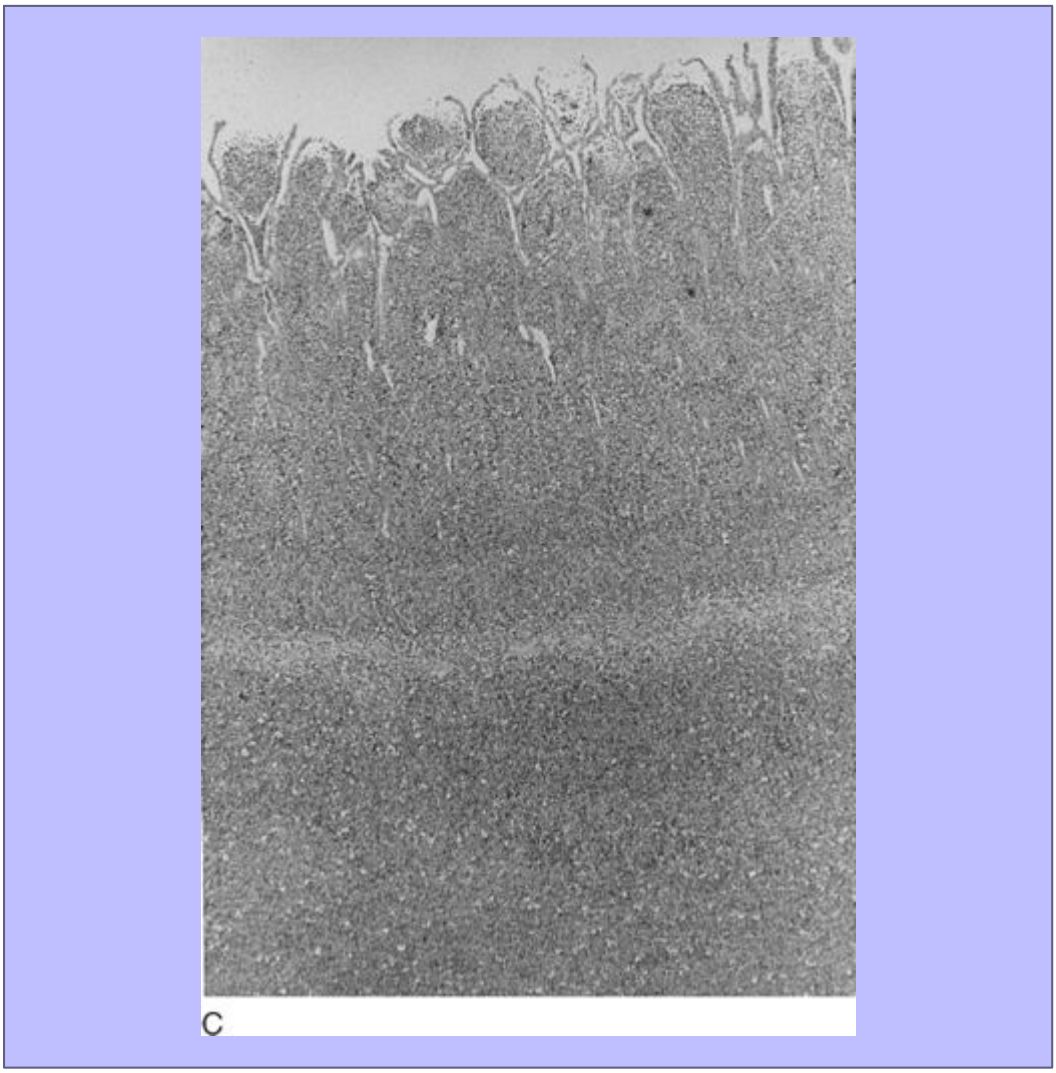
Surgical resection is the treatment of choice. However, the prognosis is usually grave, because tumors almost invariably have spread at the time of diagnosis. Metastatic spread commonly involves local lymph nodes and the liver, and metastasis to the testes was recently reported.[208] Remission times from surgery of up to 2 years have been reported, but survival time is usually less than 6 months. Chemotherapy has not been demonstrated to be effective.

222.17.3 Smooth Muscle Tumors of the Small Intestine

Smooth muscle tumors of the intestine (including leiomyoma and leiomyosarcoma) are uncommon in dogs and rare in cats.[209] Differentiation of smooth muscle tumors from other types of stromal neoplasia can be difficult and may require immunohistochemical procedures.[210] Presenting clinical signs can vary but may include vomiting, diarrhea, anorexia, polyuria, polydipsia, melena, acute collapse, and weight loss. Although some of these signs are the result of local tumor effects (i.e., obstruction, hemorrhage), paraneoplastic effects 1375
are reported, especially hypoglycemia,[211,212] which is thought 1376
to be the result of production of an insulin-like growth factor II-like peptide.[213] Other paraneoplastic syndromes associated with leiomyosarcomas include nephrogenic diabetes insipidus[214] and erythrocytosis.[215]

Figure 222-15 Intestinal lymphosarcoma. **A,** Nodular mass in the jejunum of a 10-year-old Pekinese cut open to demonstrate the mucosal wall thickening caused by focal lymphoma. **B,** Endoscopic image of the duodenum of a 6-year-old retriever, showing bulging of the mucosa caused by diffuse infiltration of lymphoma. **C,** Histologic appearance of lymphoma, showing loss of the normal epithelium and infiltration of all layers with malignant lymphocytes. (Courtesy G.R. Pearson.)





Laboratory findings may reflect the consequences of direct or paraneoplastic effects, but they also may be unremarkable. Diagnostic imaging may aid the identification of a mass lesion, and upper GI endoscopy may confirm the presence of a lesion if it is within reach and disrupting the mucosa. However, pinch biopsies are too superficial, and exploratory laparotomy is the technique of choice both for diagnosis and for treatment. Leiomyosarcomas are slow to grow and metastasize. If surgical resection is complete and if the dog survives the initial postoperative period, the prognosis is good, with median survival times of 21 months reported.[209] Even if metastasis is evident at the time of surgery, the prognosis is reasonable, with prolonged survival reported in some cases. The prognosis for leiomyomas is excellent after surgical excision.

222.17.4 Amine Precursor Uptake and Decarboxylation Tumors

Other functional amine precursor uptake and decarboxylation tumors (APUDomas), such as vasoactive intestinal peptide tumors (VIPomas), pancreatic polypeptide tumors (PPomas), and functional carcinoids, have yet to be adequately described in dogs and cats.

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222.17.5 Other Neoplasms

Fibrosarcomas, mast cell tumors, and nonfunctional carcinoid tumors tend to be focally invasive and usually present with clinical signs similar to those of intestinal adenocarcinomas. The diagnosis is based on histologic and occasion-ally immunohistochemical confirmation of the tumor type. Hemangiosarcoma rarely arises in the SI, and signs relate to hemorrhage. Adenomatous polyps affecting the SI have been reported in middle-aged cats,[216] with clinical signs that include vomiting, hematemesis, or diarrhea. However, in some cases chronic, low-grade blood loss may occur, and animals instead present with microcytic anemia.

222.18 ADYNAMIC ILEUS AND INTESTINAL PSEUDO-OBSTRUCTION

Adynamic ileus is a common sequel to parvoviral enteritis, abdominal surgery, pancreatitis, peritonitis, endotoxemia, hypokalemia, and dysautonomia (see Box 222-10).[217] The term *intestinal pseudo-obstruction* describes a condition in which patients show clinical evidence consistent with an obstruction, but no mechanical cause can be found.[218–220] The condition has been associated with both visceral neuropathies and myopathies in humans, and such causes may occur in small animals. Most canine cases are associated with idiopathic sclerosing enteropathy, with fibrosis and a mononuclear cell infiltrate of the tunica muscularis. A case of feline intestinal pseudo-obstruction occurred secondary to intestinal lymphoma.

After the possibility of a mechanical obstruction has been eliminated, management of both adynamic ileus and intestinal pseudo-obstruction is aimed at identifying any underlying cause and providing specific treatment. Symptomatic therapy to stimulate intestinal motility is also indicated.[221] Suitable prokinetic agents include the 5-HT_4 receptor agonist cisapride, the D_2 dopaminergic antagonist metoclopramide, and motilin-like drugs such as erythromycin. In dogs and cats cisapride appears to be the most effective agent, but it is no longer marketed in many countries. Antibacterials may also be appropriate, given the probability of secondary SIBO, and immunosuppressive medication may be appropriate if an underlying IBD is suspected. Feeding is beneficial in humans, and nutritional support can be continued indefinitely, although vomiting, constipation, and diarrhea usually continue. Unfortunately, most cases reported in the veterinary literature responded poorly to therapy, and the prognosis is grave.

222.19 INTESTINAL OBSTRUCTION

Intestinal obstruction can be classified as acute or chronic, partial or complete, and simple or strangulated. Obstruction can be the result of extraluminal, intramural, or intraluminal mass lesions.[222] The most common extraluminal cause of obstruction is intussusception. Younger animals are more likely to develop intussusception after a case of gastroenteritis or after having intestinal surgery, although an increased risk in postparturient queens has also been reported.[223] Intestinal neoplasia is the more frequent cause of intussusception in middle-aged and older animals. Intramural causes include intestinal neoplasia (most common), hematomas, granulomas (e.g., focal FIP), IBD, stricture, and phycomycosis. Most intraluminal obstructions are caused by

foreign objects, such as stones, fruit pits, and toys in dogs and linear foreign objects in cats.[224] *Intestinal volvulus* describes a condition in which the intestines rotate around the mesenteric axis, compromising the cranial mesenteric artery, and complete vascular obstruction may lead to strangulation. Reports are sporadic, but a predisposition in German shepherds has been reported.[225]

The prognosis depends on the cause of the obstruction and the severity of associated abnormalities. The outcome is likely to be favorable with simple foreign bodies, but it is grave for animals with volvulus or metastatic intestinal neoplasia. The patient may be at risk of developing short bowel syndrome if a significant length of intestine must be removed (see below).

222.20 SHORT BOWEL SYNDROME

Short bowel syndrome refers to a syndrome that occurs when large lengths of the SI (more than two thirds) are absent because of resection or, rarely, a congenital anomaly.[226,227] Clinical signs (e.g., diarrhea) result because the animal has an insufficient functional mass of SI for assimilation of nutrients and electrolytes. The degree of malabsorption depends on the length of intestine resected; in dogs, experimental studies suggest that removal of up to 85% of the intestine can be tolerated. The site of resection is also important; resection of the jejunum causes malabsorption of food, water, and electrolytes; resection of the ileum causes malabsorption of cobalamin and bile acids. Massive resection of the SI also precipitates changes in GI hormonal regulation, leading to hypergastrinemia and subsequently increased acid secretion. In some cases, the syndrome may occur only transiently after resection, because adaptive hyperplasia in the remaining intestine may lead to subsequent improvement.

222.20.1 Clinical Signs

The signs of intestinal malabsorption, i.e., intractable diarrhea and weight loss.

222.20.2 Diagnosis

The diagnosis usually is based on a history of intestinal resection with consequent diarrhea and weight loss. If a congenital lesion is suspected, contrast radiography can demonstrate the shortened SI length.

222.20.3 Treatment

After massive resection, aggressive parenteral fluid therapy and total parenteral nutrition should be instigated. Oral feeding is restricted but not withheld completely, because the presence of food, bile, and pancreatic secretions in the gut are important stimuli for intestinal adaptation. An isotonic, oligomeric, fat-restricted liquid diet can be fed initially, with a gradual transition first to a polymeric liquid diet and then to an easily assimilable, fat-and fiber-restricted diet. Malabsorption of fat-and water-soluble vitamins and of minerals (zinc, copper, and calcium) may also occur, and dietary or parenteral supplementation may be required. Parenteral cobalamin supplementation is essential if the ileum has been resected. Acid blockers (e.g., H_2-receptor antagonists) may be used in the postoperative period to counteract possible hypergastrinemia. Antimicrobial agents may be necessary if the ileocecocolic valve has been resected or if secondary SIBO is suspected. If the response to diet and antibiotics is poor, antisecretory agents (loperamide, diphenoxylate, or octreotide) may be required. Bile salt–binding resin (e.g., cholestyramine) may help reduce colonic secretion caused by bile salts malabsorbed after ileal resection.

Complications of short bowel syndrome in humans include gallstones, oxalate uroliths, and lactic acidosis. In refractory cases, experimental surgical modifications of the gut to try to slow intestinal transit and increase absorptive surface area have been described. Intestinal transplantation may be feasible in the future.

222.20.4 Prognosis

The prognosis depends on the amount of intestine left and the response to therapy. Some animals undergo remarkable adaptive hyperplasia and may return to a normal diet, whereas others never respond adequately. 1377 1378

222.21 IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is characterized by recurrent, usually acute, episodes of abdominal pain, borborygmi, and diarrhea. In the absence of morphologic changes, a functional disorder is considered the cause of this enigmatic problem. Disordered intestinal motility may be of primary importance, and a number of mechanisms have been proposed for IBS in humans (Box 222-19).[228] However, it is not known whether any are responsible in dogs and cats. A variety of treatments, including antispasmodics (anticholinergics and also smooth muscle relaxants, such as mebeverine), anxiolytics (e.g., diazepam, chlordiazepoxide) and dietary modification (low-fat diet, increased fiber) have been tried with no consistent results. IBS probably will remain a frustrating condition to diagnose and treat successfully until its etiology is better understood.

222.21.1 Box • 222-19 Causes of Irritable Bowel Syndrome

Primary motility disorders

Visceral hyperalgesia

Psychosomatic disorders

Food intolerance

Undiagnosed inflammatory disease

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223 CHAPTER • 223 Diseases of the Large Intestine

Robert J. Washabau

David E. Holt

The large intestine of the dog and cat has evolved to serve two major functions: (1) extraction of water and electrolytes from the fluid contents of the lumen and (2) control of defecation. The large intestine accomplishes these functions by regulating fluid transport, bacterial fermentation, motility, immune surveillance, and blood flow. Sodium and water absorption serve to dehydrate the feces prior to defecation; mucus glycoproteins serve to trap bacterial pathogens and prevent bacterial translocation; epithelial cells, lymphocytes, plasma cells, macrophages, and dendritic cells serve to regulate the bacterial flora and the immune response to microbes; and motility serves to facilitate storage or defecation of feces. Perturbations in any of these functions may result in the problems of diarrhea, constipation, or the systemic inflammatory response syndrome (SIRS).

223.1 STRUCTURE

223.1.1 Macroscopic Anatomy

The large intestine consists of the cecum, colon, rectum, and anal canal (Figure 223-1). In dogs and cats, the ileum communicates directly with the colon, and what is referred to as the *cecum* in the dog and cat is actually a diverticulum of the proximal colon. The colon is further compartmentalized into ascending, transverse, and descending portions, each segment having slightly different functions and properties. The right colic or hepatic flexure separates the ascending and transverse colon, and the left colic or splenic flexure separates the transverse and descending colon. In dogs and cats, the large intestine contributes 20% to 25% of the total (small and large) intestinal length.[1,2]

The cranial and caudal mesenteric arteries provide the arterial blood supply to the colon, and venous return from the colon is transmitted to the main portal vein via the cranial and caudal mesenteric veins. Lymph is circulated from the colon to the right, middle, and left colic lymph nodes, and eventually into the cisterna chyli and thoracic duct. Parasympathetic innervation arises from the vagus nerve in the proximal colon, and from the pelvic nerves in the distal colon. Sympathetic innervation arises from the paravertebral ganglia and follows the lumbar splanchnic nerves and mesenteric arteries to the colonic mucosa and muscularis. Parasympathetic preganglionic fibers and sympathetic postganglionic fibers synapse on cell bodies and neurons of the enteric nervous system, respectively.

223.1.2 Microscopic Anatomy

As with the small intestine, the cross-sectional structure of the large intestine consists of four distinct layers (i.e., mucosa, submucosa, muscularis, serosa) (Figure 223-2). The large intestine differs from the SI in the following important ways: villi are absent in the large intestine, the microvilli of the large intestine epithelial cells are much less abundant, goblet cells are more prominent in the large intestine, endocrine cells are less prominent in the large intestine, and crypt-to-epithelial migration is a much slower process in the large intestine.

The mucosa of the large intestine is a flat absorptive surface area differing from the small intestine in that villi are not present. However, numerous straight tubular glands (400 to 600 μm) are present in parallel cylinders,

and they extend from the muscularis mucosa to the mucosal surface.[3] The glands are lined by a continuous sheet of columnar epithelial cells, which are separated from the mesenchymal tissue of the lamina propria by a well-defined basement membrane. The epithelium in the lower half of the crypts is composed of proliferating undifferentiated columnar cells, mucus-secreting goblet cells, and at least three types of endocrine cells.[4]

Cellular proliferation is predominantly in the lower part of the crypts in both dogs and cats. The epithelium of the upper half of the crypts consists of differentiating columnar cells, goblet cells, and a few endocrine cells. The flat absorptive surface is lined by many columnar cells and a moderate number of goblet cells (10 to 25 goblet cells per 100 epithelial cells),[3,5] most of which are largely depleted of their mucous granules. Intraepithelial lymphocytes (IELs) are relatively sparsely distributed throughout the epithelium (one to seven lymphocytes per 100 epithelial cells),[3,5] and as in the small intestine, the predominant T cell subset is the cytotoxic-suppressor (CD8+) type.[6,7] The cellular elements of the lamina propria of the large intestine resemble closely those found in the small intestine and include lymphocytes, many plasma cells, mast cells, macrophages, eosinophils, enteric neurons, and fibroblasts.

Figure 223-1 **A,** Radiographic anatomy of the feline colon—lateral projection, barium enema. **B,** Radiographic anatomy of the feline colon—ventrodorsal projection, barium enema.

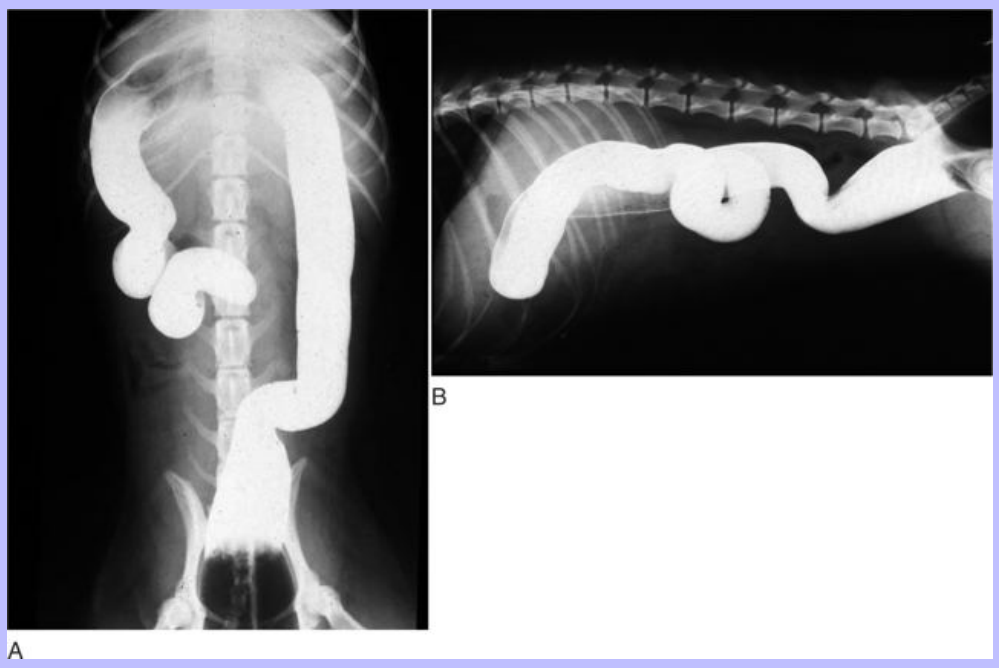

Figure 223-2 Microscopic anatomy of the canine colon.

The innermost layer of the mucosa is separated from the submucosa by the muscularis mucosae, a layer of smooth muscle cells roughly 8 to 10 cells (or 70 to 80 μm) thick. The submucosa of the colon resembles the submucosa of the other tubular digestive organs. It contains many blood and lymph vessels, dense connective tissue sparsely infiltrated by cells (fibroblasts, lymphocytes, plasma cells, mast cells, macrophages, and eosinophils), and the unmyelinated nerve fibers and ganglion cells that form the submucosal plexus.

The muscularis is composed of an inner circular muscular layer forming a tight spiral circumferentially along the course of the colon and an incomplete outer longitudinal muscle layer. The ganglion cells of the myenteric plexus of Auerbach are found between the circular and longitudinal muscle layers. Unmyelinated postganglionic fibers are also found in the circular muscle layer and communicate with the submucosal (Meissner's) plexus. The interstitial cells of Cajal, which are located on the submucosal surface of the circular smooth muscle, play a dual role as pacemaker cells and as mediators of neuromuscular transmission in the colon.[8–10]

The serosa is composed of mesothelial cells and covers only the portions of the large bowel found within the peritoneal cavity (cecum and colon). Several classification systems for colonic mucosal architecture and cellularity have been proposed. One such classification system[11] is outlined in Table 223-1. It should be emphasized that important *age*,[12] *site*,[1,3] *diet*,[13–16] and *procedure*-related[3] differences exist in the cellularity and architecture of the colonic mucosa, and these differences must be taken into account when interpreting colonic histology. For example, the protein and fiber content of the diet have significant effects on colonic mucosal morphology (e.g., crypt depth, cellularity).[14–16] The pathologist should always take these factors into account when interpreting colonic biopsy specimens. The method of biopsy also influences the architecture and cellularity of the mucosa. Compared with full-thickness biopsies, gland length is 25% to 30% shorter and goblet cell numbers are 70% to 75% less in endoscopic biopsies from the same animals. The shallow depth of the endoscopic biopsy apparently causes glandular collapse, and enema or cathartic preparative solutions are believed to cause discharge of mucous goblets.[3,11]

Table • 223-1 Guidelines for Histologic Interpretation of the Canine and Feline Colonic Mucosa

PARAMETER	NORMAL	FREQUENT ABNORMAL FINDINGS
Overall mucosal appearance	Crypts straight, dominated by goblet cells throughout, separated from muscularis mucosae by no more than four layers of leukocytes (or 15 to 20 µm)	Crypts irregularly distributed, tortuous, lifted from muscularis mucosae by more than four-cell thicknesses
	Lamina propria sparse so that crypts are closely applied to adjacent crypts	Crypts obviously separated from adjacent crypts by edema, fibrosis, or leukocytes
	Proprial cell population is sparse and leukocytes almost all lymphocytes and plasma cells; neutrophils absent and eosinophils sparse except at base of crypts	Increase in lymphocyte and/or plasma cell numbers; presence of eosinophils in superficial half of lamina propria. Neutrophils anywhere are abnormal
	Mitotic figures are found in basilar 50% to 60% of each crypt, averaging 2 to 3 per crypt	Basal third of crypts excessively basophilic, mitotic figures in superficial third of crypt
	Overall crypt length 10 or 20 cm proximal to the anus averages 384 to 406 µm	Overall mucosal thickness substantially<or >400 µm (only valid if section is well oriented and includes muscularis mucosae)
Epithelium	Columnar epithelium, basal oval nucleus; a few surface enterocytes may be cuboidal and more basophilic than the neighboring cells	Surface epithelium focally missing with pyknosis or flattening of adjacent enterocytes (versus artifactual loss in which adjacent cells are normal); surface or cryptal epithelium cuboidal or squamous, abnormally basophilic, with suprabasilar nucleus
	Intraepithelial lymphocytes are few (1 to 2 per 100 enterocytes)	Obvious increase in intraepithelial lymphocytes
	Goblet cells diffusely distributed, least numerous at crypt base and on luminal surface; mucin expulsion easily induced by pre-biopsy manipulations (so clinician should evaluate mucin loss into dilated crypt lumens with caution)	Loss of mucin from goblet cells, thus crypts seem depleted of goblet cells and may be dilated with intraluminal mucin
Lamina propria	Inconspicuous except in zone between base of crypt and muscularis mucosae that normally contains mixture of lymphocytes, plasma cells, and eosinophils	Increase in distance between crypts and between crypt base and muscularis mucosae; increases in lymphocytes, plasma cells, eosinophils, and collagen are frequent but not mutually exclusive
	Edema is a frequent biopsy artifact, impossible to distinguish from serious inflammation; similarly, physiologic congestion or hyperemia cannot be distinguished from inflammatory hyperemia	Edema must be regarded with skepticism unless accompanied by other evidence of inflammation or other changes in vascular permeability (e.g., hemorrhage, thrombosis)
Submucosa	Few lymphocytes or plasma cells; no neutrophils or eosinophils	Any type of leukocyte around dilated submucosal vessels (rarely observed except in eosinophilic colitis or invasive bacterial infection); if lymphocytes cross muscularis mucosae into submucosa, clinician should consider lymphoma
	Loosely interwoven collagen	Fibrosis

Adapted from Wilcock B: Endoscopic interpretation in canine or feline enterocolitis, *Semin Vet Med Surg (Small Anim)* 7:162, 1992. Used with permission.

223.2 FUNCTION

223.2.1 Electrolyte Transport

The large intestine regulates the electrolyte and water composition of the feces. Distinct differences exist in the mechanisms of electrolyte transport between the ascending and descending colon,[17,18] but in general the canine and feline colon absorbs water, sodium, and chloride while secreting potassium and bicarbonate.

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Table • 223-2 Anatomic and Physiologic Differences—Large versus Small Intestine

	LARGE INTESTINE	SMALL INTESTINE
Villous projections (villi)	Absent	Present
Brush border microvilli	Sparse	Prominent
Goblet cells	Abundant	Sparse
Endocrine cells	Three cell types	>20 cell types
Crypt-to-epithelial migration	Slow	Rapid
Amino acid +glucose absorption	Absent	Present
Lipid absorption	Absent	Present
Vitamin absorption	Absent	Present
Glucose-stimulated Na absorption	Absent	Present
Electrogenic Na absorption	Present	Absent
Mineralocorticoid-stimulated Na absorption	Significant	Negligible
SCFA production and absorption	Prominent	Minimal

The mechanisms of absorption and secretion in the large intestine are in many ways similar to those of the small intestine (Chapter 222), but several important differences exist (Table 223-2). Active nutrient (glucose, amino acid, monoglyceride) transport is prominent in the small intestine, but no evidence indicates active glucose or amino acid absorption in the colon except during the early neonatal period. Sodium transport also differs in the colon. Glucose-and amino acid–stimulated sodium transport is a well-established property of the small intestine, so much so that oral glucose-electrolyte solutions have been used to reduce the morbidity of cholera and other infectious diarrheal diseases of the small intestine. In contrast, glucose-coupled sodium transport does not take place in the colon and glucose-electrolyte solutions are of no benefit in diarrheal diseases of the large intestine. Sodium transport in the colon instead relies upon electrogenic transport.[18,19] The large intestine also differs in its response to mineralocorticoids. Aldosterone markedly increases sodium transport in the colon, but it has only a modest effect in the small intestine. Net sodium absorption ceases in the colon only when the luminal sodium concentration is reduced below 30 to 50 mEq/L, whereas net sodium absorption in the jejunum occurs only at luminal sodium concentrations above 130 mEq/L.[19]

Chloride absorption in the colon has both passive and active properties. Passive chloride absorption primarily represents a potential-dependent process secondary to the electrical potential generated by electrogenic sodium absorption.

Bicarbonate secretion is an important feature of colonic electrolyte function and helps to neutralize acids produced by bacterial fermentation. Chloride-bicarbonate ($Cl\text{-}HCO_3$) exchange is the primary cellular mechanism responsible for bicarbonate secretion.

The descending colon possesses both potassium absorptive and potassium secretory processes that are regulated by luminally and hormonally mediated mechanisms, and the overall net potassium movement represents the balance of these oppositely directed transport mechanisms.[18,19] Therefore the colon has the potential to serve as an important regulatory system for the maintenance of overall potassium balance. Although renal potassium transport is critical in the overall control of potassium balance, the colon also contributes to the maintenance of potassium balance by modifying both potassium secretion and absorption, especially when kidney function is impaired.

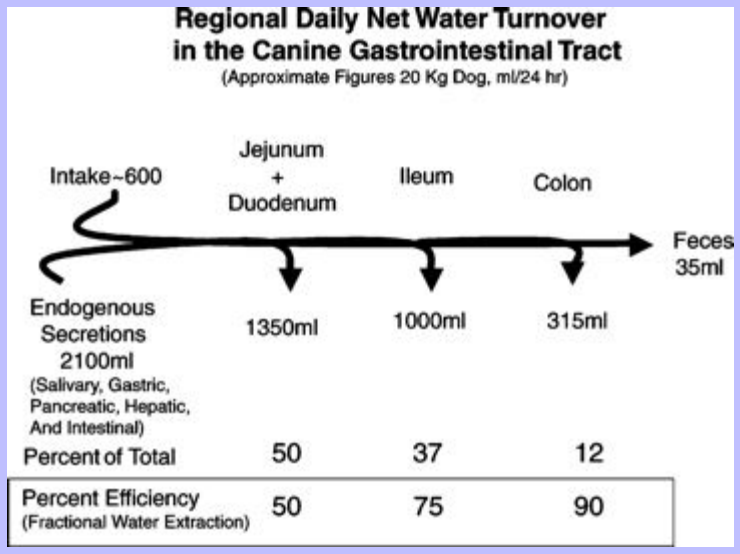
223.2.2 Water Absorption

In health, approximately 2.7 L of fluid (oral intake, saliva, gastric fluid, bile, pancreatic fluid, and intestinal secretions) is presented each day to the small intestine of a 20 kg dog. About 1.35 L is absorbed in the jejunum, 1.0 L in the ileum, and 315 mL in the colon, leaving 35 mL in feces.[20] Thus the jejunum absorbs 50%, the ileum 75%, and the colon 90% of fluid volume presented to it (Figure 223-3). This fluid absorptive capacity of the colon is largely determined by basal electrolyte (primarily sodium) transport and by the ability of several agonists (aldosterone and glucocorticoids) to augment electrogenic and electroneutral sodium absorption. As long as ileocecal flow is less than the colonic absorptive capacity, significant alterations in small intestinal fluid movement may be present, but colonic absorption will prevent the development of diarrhea. On the other hand, when small intestinal absorption and ileocecal flow are normal, a relatively small decrease in colonic absorption (inflammatory bowel disease [IBD]) will produce significant increases in fecal water output.

223.2.3 Mucus Secretion

A lubricant layer of mucus forms a crucial physiologic barrier between the colonic mucosa and the luminal environment. Mucus is a constantly changing mix of secretions and exfoliated epithelial cells, the chief determinants of which are high molecular weight glycoproteins or mucins.[21] Gastrointestinal (GI) mucins are secreted from goblet cells as they ascend from their origin in the crypts up to the colonic epithelium. Mucin secretion is dependent upon the close integration of the cystic fibrosis transmembrane regulator (CFTR), chloride secretion, and granule exocytosis. In addition to their physiologic role as a mucosal barrier, mucins may also have a pathologic role in the metastases of epithelial tumors and enhanced susceptibility to infection.[21]

Figure 223-3 Regional daily water turnover in the canine gastrointestinal (GI) tract. (Adapted from Burrows CF: Chronic diarrhea in the dog. Vet Clin North Am Small Anim Pract 13:521, 1983, with permission.)



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223.2.4 Bacterial Fermentation

The colon contains the largest concentration of bacteria in the GI tract, up to 10^{11} organisms per gram of feces. The colonic microflora play an important role in the nutrition of the animal primarily via the production of short chain fatty acids (SCFAs).[22] Major fiber fermentation substrates include cellulose, hemicellulose, and pectin, substrates that typically are not digested by pancreatic or intestinal amylases. Acetate, propionate, and butyrate account for more than 85% of formed SCFAs, and they accumulate in concentrations up to 150 mmol/L in the colon of dogs.[23] SCFAs are rapidly absorbed by the colonic mucosa, are readily metabolized by colonic epithelial cells, and have various physiologic effects. Among their physiologic effects, SCFAs promote differentiation and proliferation of colonocytes,[24] stimulate absorption of water and electrolytes,[25] provide 7% to 10% of an animal's overall energy requirements,[23] and influence or modify motility of the GI tract.[26]

The colonic flora is influenced by many factors, including host species, breed, developmental stage, dietary history, environmental conditions, geographic locale, colonic motility patterns, disease, and medication history.

In general, anaerobic bacteria (*Bacteroides* spp., *Bifidobacterium* spp., *Clostridium* spp., and *Lactobacillus* spp.) predominate in the canine colon, accounting for up to 90% of the colonic microflora. Most are facultative or aerotolerant anaerobes, not true obligate anaerobes.[27] Enterobacteria and streptococci are the predominant aerobic bacteria found in the canine colon. In the cat, approximately equal numbers of anaerobic and aerobic bacteria are found in the colonic lumen.[28]

The colonic flora changes significantly with developmental stages. The aging canine colon becomes more readily populated by *Clostridium perfringens* and other obligate anaerobes, and less populated by aerobes and aerotolerant anaerobes.[27,29] This change takes place in the ascending and descending colon, but it is most significant in the descending colon where anaerobic conditions tend to predominate. Senescent changes in bacterial populations of the colon conform to the principles of successional ecology.[30] Over time, changes in pH, redox potential, bacterial competition, and nutrient availability facilitate the proliferation of anaerobic bacteria permitting them to eventually displace the aerotolerant forms.

An animal's breeding and genetic background may also influence the colonic flora. For example, far fewer *Bifidobacterium* spp. are recovered from the feces of beagle dogs than are recovered from other dog breeds.[29,31] This represents a problem for studies of colonic bacteriology because many of the reference studies have been generated from beagle dogs.

Diet has a major impact on numbers and types of bacteria recovered from the colon. *Bacteroides* spp. appear to be particularly susceptible to changes in the diet.[31–33] The protein, carbohydrate, and fiber content of the diet all appear to influence the ability of bacteria to grow within the colon. Thus dietary history should always be considered when interpreting results of fecal or colonic bacterial cultures.

Geographic locale and environmental conditions can also influence colonic bacteriology in the dog. *Bifidobacterium* spp. are readily isolated from dogs from Japan, but they are inconsistently found in American dogs.[29,31] Housing conditions appear to be another confounding factor. Open housing environments[27] appear to facilitate colonization of a greater proportion of facultative anaerobic bacteria compared with closed facility conditions.[34]

Motility patterns of the colon influence the bacterial ecology of the colon. The antiperistaltic activity of the ascending and transverse colon particularly facilitates the mixing of fecal material with endogenous bacteria. Abnormalities in the motility patterns of this part of the colon lead to changes and proliferation of obligate anaerobes similar to that found in the descending colon.[35]

Disease and medical therapies, particularly antibiotics, alter the microbial characteristics of the colon. These changes are poorly understood in dogs and cats, but they very likely contribute to clinical symptomatology.

223.2.5 Immune Surveillance

The colon contains a diverse array of immune cells, including T and B lymphocytes, plasma cells, macrophages, dendritic cells, antigen-presenting cells, mast cells, eosinophils, and neutrophils.[3,5–7,36–39] Immune cells are found in the epithelium, lamina propria, and submucosa of the colon. As in the small intestine, appropriate interactions between these different cell types are essential in generating either immune responsiveness or tolerance to the large array of luminal antigens.[40,41] Much less is known about colonic immunity, but some generalizations may be made. In the colon, CD8+ T cells are found primarily in the epithelium; very few CD8+ T cells are found in the lamina propria or submucosa. Most IELs are CD3+ and CD8+, a phenotype consistent with suppressor-cytotoxic functions. Lamina propria T cells, on the other hand, are predominantly of the CD4+ helper phenotype. Immunoglobin A (IgA)-containing plasma cells are more prominent than IgG-or IgM-containing plasma cells in the lamina propria. Thus in the normal colonic mucosa, a balance would appear to be maintained between helper and suppressor T cell populations, which allows specific antigen responsiveness while avoiding hyper-reactivity.[5,6,42] A more detailed discussion of GI

immunity may be found in Chapter 222, Diseases of the Small Intestine. Many similarities exist in the immune systems at both sites, but important differences exist in the immune response of the small and large intestine (discussed in Inflammation).

223.2.6 Motility

The colon has evolved to serve two important functions: (1) extraction of water and electrolytes from the luminal contents in the ascending and transverse colon and (2) control of defecation in the descending colon. This specialization of function has been attributed to regional differences in colonic motility patterns.[35,43–46] Electrical slow wave frequency and rhythmic phasic contractions (RPCs) are slower in the proximal portion of the colon, thus facilitating extraction of water from the fecal mass by diffusion and active transport. Retrograde giant contractions (RGCs) and antiperistalsis further facilitate the mixing of contents in the proximal colon. In contrast to that of the proximal colon, motility of the distal colon is characterized primarily by migrating spike bursts and powerful giant migrating contractions (GMCs) that propagate the fecal mass toward the rectum.[46]

Colonic smooth muscle generates at least four different types of contractions to perform the complex motility functions of mixing and propulsion: (1) tone, (2) RPCs, (3) RGCs, and (4) GMCs. The time course, frequency, and force generated by each of these contractions are significantly different from each other.[43–46] The precise role of tone in circular muscle cells is not known, but the resulting decrease in the diameter of the colon may enhance the efficiency of the phasic contractions in mixing and propulsion. Tone is normally of small to moderate force and can last for prolonged periods of time (several minutes to hours). RPCs produce mixing and net slow distal propulsion of luminal contents in the postprandial and fasting state. Phasic contractions occur rhythmically at a few cycles per minute, last for about 3 to 5 seconds, and generate a moderate force (75 to 100 g). RGCs occur infrequently, last for about 20 seconds, generate a very strong force (> 150 g), and are propagated from their point of origin into the ascending colon. RGCs facilitate mixing in the ascending colon. The GMCs are of a similar magnitude and frequency to the RGCs, but they generate mass movements from their point of origin to the anorectal junction. It has been suggested that different signal transduction pathways are used by smooth muscle cells to trigger different contractions.[47,48] It is remarkable that the same smooth muscle cells can generate so many different types of contractions using a limited number of second messengers.

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223.3 DIAGNOSTIC EVALUATION

223.3.1 History and Physical Examination

Inflammation is the most important pathophysiologic condition of the colon. Colitis is responsible for the major clinical signs of hematochezia, mucus in the feces, dyschezia, abdominal discomfort, tenesmus, urgency, and increased frequency of defecation. The colon is an important target organ for IBD in the dog, whereas the upper GI tract (stomach and small intestine) is more frequently involved in feline IBD. Clinical signs are useful in localizing the anatomic site of the diarrhea to the small or large bowel (Table 223-3), although some animals will have diffuse involvement of the small and large intestines.

The history should include specific questions about diet, parasite control, environment, travel history, concurrent medical disease, and drug history. Dietary sensitivity reactions[49] and parasitism are major causes of colitis in many pet populations. Dietary history should include information regarding type of diet, incidence

of dietary indiscretion, supplements, snacks, and treats. Information concerning previous fecal examinations and anthelmintic use may provide useful clues to the cause of the diarrhea. Environmental history should identify other pets in the household, the composition of their diets, and any behavioral interactions or hierarchies that might influence the development of clinical signs. The travel history may yield important information about exposure to histoplasmosis, pythiosis, and heterobilharziasis, all of which have regional distributions. Concurrent medical disease (e.g., Addison's disease, IBD, pancreatitis) will also help place the current episode of colitis in context. The drug history should include information about the use of alternative and complementary medicines that could contribute to clinical symptomatology.

The physical examination may be normal in many cases of colitis. The most consistent physical examination findings are pain and irregularities of the colonic mucosa on digital rectal examination. The perineum should be examined carefully to exclude perineal diseases such as perineal hernia and perianal fistula. Physical examination may reveal other important findings, including *fever* (IBD, cecal or colonic perforation, fungal infection), *abdominal pain* (IBD, colonic neoplasia, cecal or colonic perforation), *abdominal mass* (colonic neoplasia, granulomatous colitis, intussusception), *small intestinal thickening* (concurrent SI IBD, SI lymphoma), *mesenteric lymphadenopathy* (SI IBD, SI lymphoma), *hepatosplenomegaly* (lymphoma, disseminated fungal infection), and *uveitis* (protothecosis, lymphoma). A scoring system has been developed to relate clinical signs with histologic findings in canine IBD.[50]

Table • 223-3 Clinical Signs Associated with Diarrhea—Large Bowel versus Small Bowel

SIGNS	SMALL BOWEL	LARGE BOWEL
Weight loss	May be present	Uncommon
Vomiting	May be present	Uncommon
Flatulence	Present with malassimilation	Unusual
Defecation frequency	Normal to mild increase	Marked increased frequency
Fecal volume	Increased	Normal to mild increase
Urgency	Absent	Usually present
Tenesmus	Absent	Usually present
Mucous in feces	Usually absent	Frequently present
Hematochezia	Absent	Often present
Melena	Sometimes present	Absent
Steatorrhea	Present with malassimilation	Absent

Constipation is the second most important pathophysiologic condition of the colon. Clinical signs include reduced, absent, or painful defecation for a period of time ranging from days to weeks or months. Physical examination findings will depend on the severity and pathogenesis of constipation. Dehydration, weight loss, abdominal pain, and mild to moderate mesenteric lymphadenopathy are common findings in cats with idiopathic constipation. Physical examination might also reveal *abdominal mass* (cecal or colonic neoplasia, granulomatous colitis), *abdominal pain* (foreign bodies, colonic perforation), *autonomic neuropathy* (dysautonomia), *hindlimb paresis* (lumbar spinal cord pathology), *pelvic fracture* (pelvic outflow obstruction), and *perineal hernia* (cause or complication of constipation).

223.3.2 Laboratory Data

For both inflammation and constipation, the scope of the medical investigation will be shaped by prior history, suspected cause, chronicity, and signs of systemic illness[51,52] (Figure 223-4).

Complete blood count (CBC), serum chemistry, and urinalysis should be considered in animals with signs of colonic disease, particularly those with signs of systemic disease. These tests may provide evidence of *anemia* (chronic disease, GI blood loss), *leukocytosis* (IBD, neoplasia, cecal or colonic perforation), *eosinophilia* (parasitism, Addison's disease, mast cell disease, hypereosinophilic syndrome), *thrombocytopenia* (concurrent immune thrombocytopenia), *hypoproteinemia* (protein-losing enteropathy [PLE]), *hyperglobulinemia* (FIP, IBD, infection, neoplasia), *hypercalcemia* (neoplasia, fungal disease), *hypoglycemia* (leiomyosarcoma), and *hyponatremia* and *hyperkalemia* (Addison's or pseudo-Addison's disease). This minimum data base is also useful to screen animals prior to anesthesia and colonoscopy. If fungal, *Oomycetes*, or algal infections are possible causes in the pet's geographic area, special serologic tests are available for the diagnosis of some of these diseases (Table 223-4). Feline leukemia virus (FeLV) and Feline immunodeficiency virus (FIV) testing are warranted in cats with unexplained, chronic diarrhea.

223.3.3 Fecal Parasitic Evaluation

Direct fecal smears and fecal flotation studies should be performed to evaluate for helminth, protozoa, and some bacterial infections (see Table 223-4). Direct fecal smears may be useful in detecting *Giardia*, *Tritrichomonas*, and *Campylobacter* organisms. Zinc sulfate flotation is the most accurate and practical fecal flotation test available, and it may be more sensitive for the detection of *Giardia* and *Tritrichomonas* infections. Some animals may have intermittent shedding of helminth ova, *Giardia* trophozoites and cysts, or both; therefore suspected infections should always be treated with anthelmintics or antiprotozoal agents before animals are subjected to colonoscopy.

223.3.4 Fecal Bacterial Culture

Fecal cultures should be considered in animals with suspected bacterial infections of the intestine and colon. Risk factors for bacterial colitis include young age, crowded or poor hygienic environmental conditions, co-infection with helminth or protozoal parasites, viral immunosuppression,[53] boarding or kenneling conditions, and multiple-pet households. Bacterial pathogens associated with colitis or enterocolitis lesions in dogs and cats have included *Brachyspira pilosicoli*, *Campylobacter* spp., *Clostridium perfringens* and *C. difficile*, certain *Escherichia coli* (enterotoxigenic, enteroinvasive, enteropathogenic, enterohemorrhagic, enteroadherent), *Salmonella* spp., and perhaps *Yersinia enterocolitica* (see Table 223-4). Culture results should always be interpreted in light of clinical signs, other findings such as coinfections, and substantiating laboratory data such as serologies or polymerase chain reaction (PCR) results. Fecal cultures should not be performed for the purpose of diagnosing small intestinal bacterial overgrowth (Chapter 222).

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Figure 223-4 **A,** Diagnostic approach to large intestinal diarrhea. **B,** Diagnostic approach to constipation. *PCR,* Polymerase chain reaction; *RT-PCR,* reverse transcriptase polymerase chain reaction.

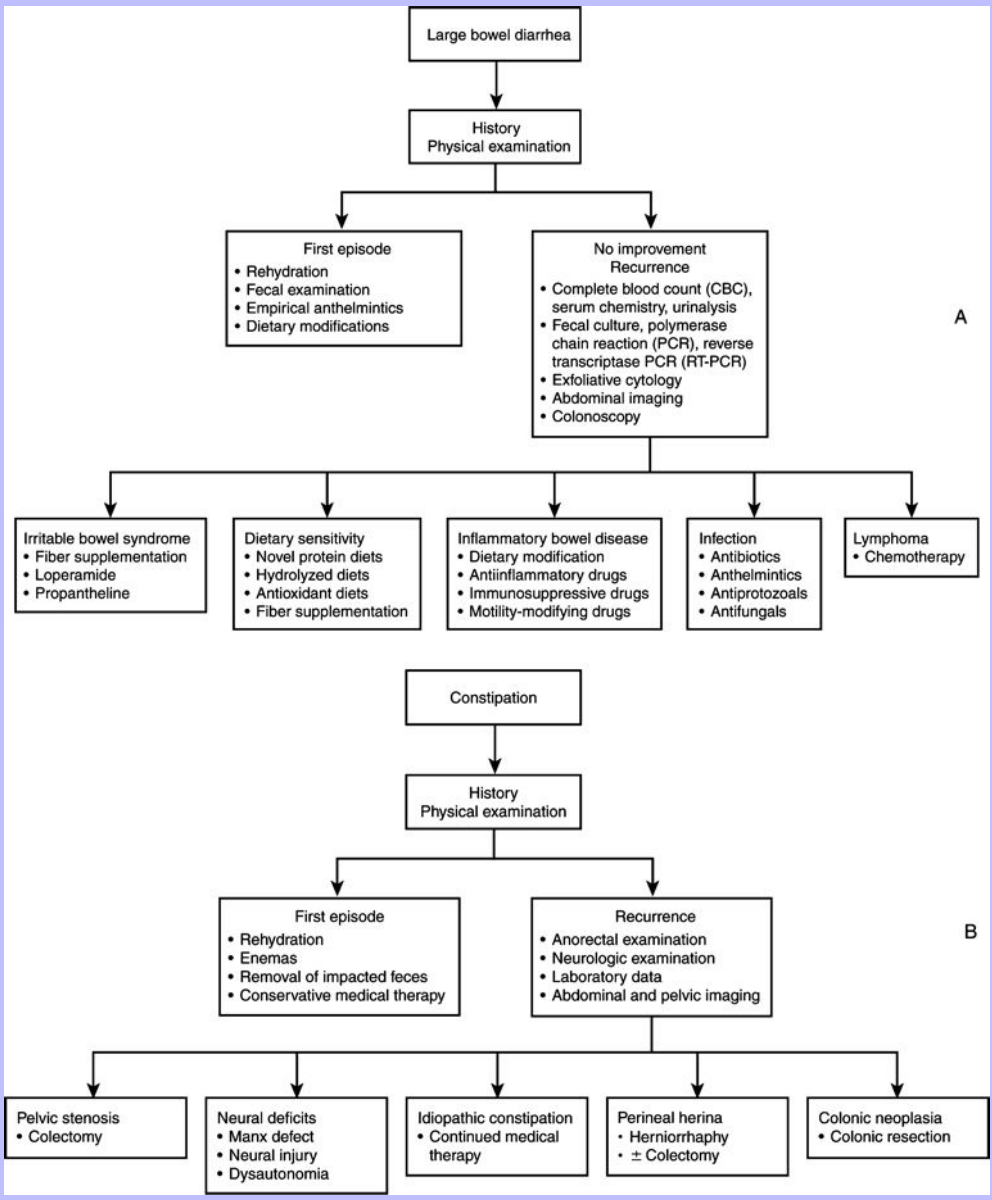

Table • 223-4 Definitive, Suspected, and Unproved Pathogens of the Large Intestine of Dogs and Cats

CLASSIFICATION/ORGANISM	TISSUE TROPHISM	EVIDENCE OF PATHOGENICITY	DIAGNOSIS	REFERENCES
Helminths				
Trichuris vulpis	Cecum, colon	Good evidence	Fecal flotation	63,64
Trichuris serrata, *T. campanula*	Cecum, colon	Moderate evidence	Fecal flotation	63,64
Ancylostoma caninum	Intestine, colon	Good evidence	Fecal flotation	63,71,116,117
Heterobilharzia americana	Colon	Good evidence	Fecal flotation, histology	66,67,68
Protozoa				
Balantidium coli	Colon	Poor evidence	Fecal flotation	69,70
Entamoeba histolytica	Colon	Weak evidence	Fecal flotation	71,72,73
Giardia spp.	Intestine, colon	Moderate to good evidence	Fecal flotation, ELISA, IFA, duodenal/colonic aspiration	74–87
Isospora ohioenesis—dogs	Intestine, cecum, colon	Weak evidence	Fecal flotation	88,89
Tritrichomonas foetus—cats	Ileum, cecum, colon	Moderate to good evidence	Fecal flotation, culture, PCR	90–95
Fungi				
Histoplasma capsulatum	Intestine, colon	Good evidence	Exfoliative cytology, histology	96–100
Oomycetes				
Pythium insidiosum	Stomach, intestine, colon	Good evidence	Histology, immunohistochemistry, ELISA, PCR	101–107
Algae				
Prototheca zopfii/wickerhamii	Eyes, skin, colon, CNS	Good evidence	Exfoliative cytology, histology	108,109
Bacteria				
Brachyspira pilosicoli	Ileum, colon	Moderate evidence	Culture, PCR, histology	110–114
Campylobacter coli, *C. jejuni*, *C. upsaliensis*, *C. helveticus*	Intestine, colon	Moderate to good evidence	Culture, PCR	115–124
Clostridium perfringens	Colon	Moderate to good evidence	Gram staining, culture, ELISA, PCR	126–133
Clostridium difficile	Colon	Weak to moderate evidence	Culture, Toxin A ELISA, genotyping	131–136
E. coli (ET, EI, EP, EH, EA)	Intestine, colon	Good evidence	Culture, serotyping, PCR	137–144
Salmonella spp.	Intestine, colon	Good evidence	Culture, serotyping, PCR	145–147
Yersinia enterocolitica	Colon	Poor evidence	Culture	148,149

ELISA, Enzyme-linked immunosorbent assay; IFA, indirect fluorescent antibody; PCR, polymerase chain reaction.

223.3.5 Molecular Diagnosis

A number of PCR and reverse transcriptase (RT)-PCR assays have been developed for gene amplification products and messenger RNAs of infectious organisms. Assays are now available for the molecular diagnosis of *Tritrichomonas foetus*, *Pythium insidiosum*, *Campylobacter jejuni*, *Clostridium perfringens*, *C. difficile*, *E. coli*, *Salmonella* spp., and *Brachyspira pilosicoli*, and many more are likely forthcoming. Molecular detection has become the standard for infectious disease diagnosis in many instances.[54]

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223.3.6 Exfoliative Cytology

Exfoliative rectal or endoscopic cytology may be useful in identifying causative agents (e.g., fungal elements, neoplastic cells) and inflammatory cells (e.g., lymphocytes, eosinophils). Rectal smears may be obtained with cotton-tipped applicator or conjunctival spatula during anorectal examination or with a cytology brush at the time of endoscopy. A good correlation (specificity: 97%; sensitivity: 93%) has been shown between exfoliative cytology and subsequent endoscopic or surgical biopsy in one study.[55] Additional studies will be needed to verify the diagnostic value of this test.

223.3.7 Imaging

Survey abdominal radiographs may occasionally document colonic foreign objects, mesenteric or sublumbar lymphadenopathy, intussusception, and extraluminal compression; however, survey radiographs are generally nonspecific in the diagnosis of colonic disease. Contrast studies (i.e., barium enema) are performed infrequently because of their poor sensitivity and requirement for general anesthesia. Ultrasonographic imaging has proved more useful in documenting mass lesions, lymphadenopathy, intussusceptions, and bowel thickening. Abdominal ultrasound may also be used to facilitate percutaneous aspiration of luminal masses, mucosal thickenings, and lymph nodes.[56,57] Computed tomography (CT) colonography, also known as *virtual colonoscopy*, has been successfully implemented in human medicine and has been studied experimentally in the dog.[58]

223.3.8 Colonoscopy

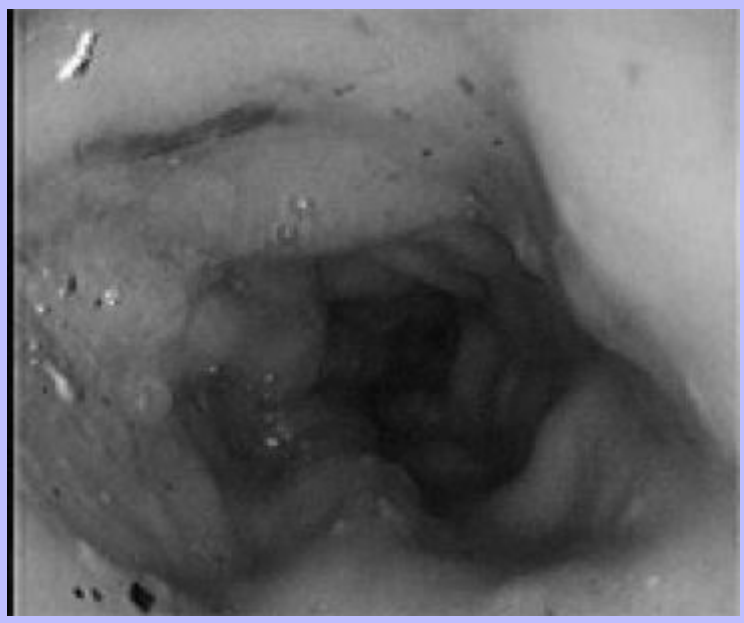
Colonoscopy is indicated for the diagnosis of colitis-type diarrhea unresponsive to dietary modification and medical therapy, suspected colorectal neoplasia, chronic constipation, unexplained stricture, and evaluation of prior surgical or medical treatment.[59] Colonoscopy is performed after other noninvasive diagnostic tests (e.g., fecal parasitologic examination, fecal bacteriologic examination, exfoliative cytology, abdominal ultrasonography, survey ± barium contrast radiography) have failed to diagnose the disease.

Rigid or flexible endoscopy may be performed, but flexible endoscopy provides better visualization and examination of the entire colon. The normal colonic mucosa is pink in color, smooth in texture, and glistening in appearance (Figure 223-5). Unlike the esophageal, gastric, and duodenal mucosa, submucosal blood vessels are readily apparent. The mucosa should not hemorrhage when abraded by the endoscope; active hemorrhage usually implies an underlying disorder such as inflammation or infection. The colonoscopic procedure should include examination of the more proximal structures (e.g., ascending colon, cecum, ileocecal sphincter, distal ileum) whenever possible. The proximal colon is an important site of inflammation, parasitism, ileocolic intussusception, cecal inversion, and neoplasia.

Fecal materials must be completely evacuated before the colonic mucosa can be properly examined. Incomplete bowel preparation is the major reason for an unsuccessful colonoscopic examination. Patient permitting, food should be withheld for 36 to 48 hours so that fecal material does not accumulate in the colon. The patient should also be given warm-water enemas, GI lavage solutions, or both. Lavage solutions are preferable to warm-water enemas,[60–62] but both may be given to facilitate successful colonoscopy. Polyethylene glycol solutions are isosmotic, administered orally, and induce a diarrhea that rapidly removes fecal material from the bowel. Large volumes may be administered without inducing significant changes in

water or electrolyte balance.[60] Electrolyte solutions should be given at a dose of 25 mL/kg at 24 and 12 hours prior to colonoscopy. Warm-water enemas should be performed gently, without irritating substances, at 24, 6, and 2 hours before colonoscopy. The combination of a 36 to 48 hour food-fast, GI lavage solution, and enemas will usually result in a colon that is free of fecal fluids and solids. Endoscopic examination of the colon is described in detail (see Chapter 101).[59]

Figure 223-5 Normal endoscopic appearance of the canine large intestine.



Diseased tissue, nondiseased tissue, and the transition zone between diseased and nondiseased tissue should be biopsied during colonoscopic procedures. This standard helps to verify the extent of the disease, ensures that disease in the submucosa has not been missed, and provides representative tissue samples to the pathologist to diagnose the disease. In some cases of severe IBD or colonic neoplasia, advanced tissue necrosis may prevent the diagnosis of the disease process in the central part of the lesion. In the absence of gross mucosal abnormalities, three to five biopsy specimens should be obtained from each of the midascending, midtransverse, and mid-descending colonic regions.

223.4 INFECTION

The colon may be colonized by several types of infectious organisms. The most important of these are the helminths (*Trichuris* spp., *Ancylostoma* spp., *Heterobilharzia* spp.), protozoa (*Giardia* spp., *Tritrichomonas* spp.), fungi (*Histoplasma* spp.), Oomycetes (*Pythium* spp.), algae (*Prototheca* spp.), and bacteria (*Brachyspira* spp., *Campylobacter* spp., *Clostridium* spp., enteropathogeneic and enterotoxigenic *E. coli*, and *Salmonella* spp.). The routine medical investigation of any dog or cat affected with chronic large bowel diarrhea should include direct and indirect fecal examinations for helminth and protozoa, bacterial culture of feces, and serologies (see Table 223-4). Some organisms appear to be of low pathogenicity, but it should be emphasized that even commensal organisms may become pathogens given the appropriate circumstance.

223.4.1 Helminths

223.4.1.1 Trichuris

223.4.1.1.1 Cause

Trichuris vulpis is perhaps one of the most common causes of chronic large bowel diarrhea in dogs.[63] 1386
Cats are occasionally infected with *T. serrata* and *T. campanula*. Clinical signs in *Trichuris*-infected 1387
dogs and cats may vary from asymptomatic infections to mild intermittent episodes of mucousy feces to acute-onset bloody diarrhea with tenesmus and dyschezia.

223.4.1.1.2 Pathophysiology

The fecal-oral route of transmission is the canonical route of infection. After ingestion of infective *Trichuris* ova, eggs hatch in the small intestine and larvae migrate to the cecum and colon where they attach to the mucosa. The pathogenicity of any infection is generally related to the magnitude of the host immune response. Factors contributing to the pathogenicity and clinical signs include the number of mature worms present, the location of the worms, the degree of inflammation, the severity of anemia or hypoproteinemia, nutritional status of the host, and the presence of other GI parasites and micro-organisms.[64]

223.4.1.1.3 Clinical examination

Affected animals generally have mild clinical signs of typhlitis and colitis, although some dogs develop a clinical scenario of signs and laboratory findings (e.g., hyponatremia, hypochloremia, hyperkalemia) consistent with hypoadrenocorticism. When tested, *Trichuris*-infected dogs are normoreactive to ACTH stimulation and are instead referred to as *pseudo-Addisonian*.[65] Eosinophilia, anemia, and hypoalbuminemia are possible, but these are more common laboratory findings with other GI helminth infections (e.g., hookworms).

223.4.1.1.4 Diagnosis

Trichuris ova can be identified on routine fecal flotation procedures; however, they may be missed because of intermittent shedding. Empiric treatment for occult *Trichuris* infection should always be performed before moving on to a more detailed, costly, and unnecessary medical investigation.

223.4.1.1.5 Treatment

Many safe and effective therapeutic agents are available for *Trichuris* spp. Fenbendazole, febantel with praziquantel, milbemycin, and ivermectin with pyrantel pamoate all have established efficacy against whipworms. Treatment should be repeated in 3 weeks and again in 3 months, and pet owners should be advised to decontaminate the environment.

223.4.1.1.6 Prognosis

The prognosis for recovery and cure is excellent.

223.4.1.2 Ancylostoma caninum.

Hookworms are primary pathogens of the small intestine (Chapter 222), but they occasionally infect the cecum and colon with overwhelming infestations. Diagnosis is achieved by demonstrating hookworm ova in the feces, and treatments are similar to those used for whipworm infections (Chapter 222).

223.4.1.3 Heterobilharzia americana

223.4.1.3.1 Cause

H. americana is considered the primary agent of schistosomiasis in dogs. It is an uncommon infection in dogs and is encountered almost exclusively in the southern Atlantic and Gulf Coast states in the United States. In addition to the dog, nutria, raccoons, rabbits, and mice serve as important reservoir hosts. Although uncommon, heterobilharziasis is an important consideration in the differential diagnosis of acute and chronic large bowel diarrhea in endemic areas.[66,67]

223.4.1.3.2 Pathophysiology

The life cycle of *H. americana* is complex and involves an intermediate (snail) and definitive (dog) host and various life stages. Dogs are infected when motile cercaria from snails penetrate their skin. The schistosomulae migrate from the skin to the liver of the definitive host, where they develop into mature male and female worms. Adult schistsomes lay eggs in the terminal mesenteric venules, and egg migration through the bowel wall elicits an intense granulomatous response. It is usually the host response that gives rise to the clinical symptomatology.

223.4.1.3.3 Clinical examination

Clinical signs vary from none to acute signs of vomiting, weight loss, bloody diarrhea, and progressive emaciation. Affected animals may have biochemical evidence of hypoalbuminemia, hyperglobulinemia, hypercalcemia, and liver enzyme elevation.[68]

223.4.1.3.4 Diagnosis

Diagnosis is confirmed by demonstration of ova on direct fecal examination or tissue biopsy. Serologic tests have not yet been successfully implemented in companion animals.

223.4.1.3.5 Treatment

Fenbendazole in combination with praziquantel appears to be effective in the treatment of *H. americana*.

223.4.1.3.6 Prognosis

The prognosis for acute infections is generally favorable, although severe liver involvement may portend chronic liver disease and cirrhosis.

223.4.2 Protozoa

223.4.2.1 Balantidium coli

B. coli is primarily a pathogen of sheep. Only one case report of natural infection in the dog has ever been published.[69] In another report, a total of 375 fecal samples of 56 mammalian species belonging to 17 families of 4 orders were examined for the detection of *Balantidium coli. B. coli* organisms were detected in several animal species, but not in dogs or cats.[70]

223.4.2.2 Entamoeba histolytica

Two isolated case reports of colitis in dogs[71] and one in cats[72] are associated with recovery of *E. histolytica* from the feces. *E. histolytica* can be recovered from the feces of healthy dogs and cats, but it appears to be of low pathogenicity in dogs and cats.[73]

223.4.2.3 Giardia

223.4.2.3.1 Cause

Giardia spp. are protozoal parasites that primarily infect the small intestine of dogs and cats. The cecum and colon are only occasionally colonized by *Giardia*. All mammalian isolates are currently classified as *Giardia lamblia*, although some nomenclature systems use the name *G. duodenalis* or *G. intestinalis*.[74] Recent DNA sequence technology suggests that one or two distinct *Giardia* genotypes can be isolated exclusively from dogs,[75,76] and a distinct genetic group can be isolated from cats.[77] It is not clear whether differences in pathogenicity exist between these genotypes. *Giardia* species have a worldwide distribution. Because *Giardia* is maintained in nature primarily by fecal-oral transmission, more cases are associated with crowded and unsanitary conditions. A recent study showed a prevalence in the dog of 7.2%.[78]

223.4.2.3.2 Pathophysiology

Giardia spp. are found on the surface of enterocytes, where the trophozoites attach to the brush border of the epithelium. Specific histologic changes have not been reported, but persistence of infection may promote apoptosis and inhibition of re-epithelialization.

223.4.2.3.3 Clinical examination

Although infected animals may remain asymptomatic, clinical signs such as acute or chronic diarrhea, weight loss, or even acute or chronic vomiting may develop. Although *Giardia* cysts and trophozoites have been found in the feces of dogs with both small bowel and large bowel diarrhea, *Giardia* infection is primarily a problem of the small intestine (Chapter 222).

223.4.2.3.4 Diagnosis

Giardia infections can be diagnosed by demonstrating motile trophozoites on fresh fecal smears or cysts by zinc sulfate sedimentation.[79,80] Commercial enzyme-linked immunosorbent assay (ELISA) kits have also been used to detect *Giardia* antigen in fresh fecal samples. ELISA assays may be slightly more sensitive and specific than a single zinc sulfate concentrating technique in diagnosing *Giardia* infections in dogs.[78,80] A direct immunofluorescent antibody test has been used in the diagnosis of *Giardia* infections in humans, but it has not yet been validated in the dog. Duodenal aspirates during GI endoscopy appear to be ineffective in diagnosing *Giardia* infection.[81]

223.4.2.3.5 Treatment

Metronidazole, ipronidazole, fenbendazole, albendazole, and a praziquantel, pyrantel pamoate, febantel combination have all been used in the treatment of *Giardia* infections with varying levels of success.[82–85] A *Giardia* vaccine has been shown to be effective in prevention and therapy in dogs,[86,87] but efficacy has not yet been established in cats.[74]

223.4.2.3.6 Prognosis

The prognosis for long-term health and recovery is generally very favorable.

223.4.2.4 Isospora canis, I. ohioensis, I. felis, I. neorivolta.

The *Isospora* species are the most common coccidial parasites of dogs (*I. canis* and *I. ohioensis*) and cats (*I. felis* and *I. neorivolta*). The coccidia are primarily parasites of the small intestine (Chapter 222), but *I. ohioensis* may induce cecal and colonic pathology in puppies and young dogs.[88,89] Sulfadimethoxine (50 mg/kg orally, once a day for 10 days) or sulfatrimethoprim (15 to 30 mg/kg orally, once a day for 5 days) may be used where clinical signs warrant treatment.

223.4.2.5 Tritrichomonas foetus

223.4.2.5.1 Cause

Tritrichomonas foetus is a flagellated protozoan parasite that is an important venereal pathogen in cattle. *T. foetus* has also been identified as an intestinal pathogen in domestic cats from which intraluminal infection of the colon leads to chronic large bowel diarrhea.[90] Infected cats are usually young and frequently reside in densely populated housing such as catteries or animal shelters. Cats often have a

history of infection with *Giardia* spp.; these infections are subsequently identified as *trichomoniasis* after failure to eradicate the organisms with standard antiprotozoal treatment (e.g., metronidazole or fenbendazole).

223.4.2.5.2 Pathophysiology

After experimental inoculation in cats, *T. foetus* organisms have been shown to colonize the ileum, cecum, and colon, reside in close contact with the epithelium, and are associated with transient diarrhea that is exacerbated by coexisting cryptosporidiosis.[91]

223.4.2.5.3 Clinical examination

Infected animals have clinical signs that are consistent with chronic colitis-type diarrhea.

223.4.2.5.4 Diagnosis

Diagnosis of trichomonosis in cats is made by direct observation of trichomonads in samples of freshly voided feces that are suspended in physiologic saline (0.9% NaCl) solution and examined microscopically at ×200 to ×400 magnification.[92] *T. foetus* can also be grown from feces via incubation at 37°C in Diamond's medium.[93] The sensitivity of direct examination of a fecal smear for diagnosis of *T. foetus* in naturally infected cats is unknown but is suspected to be poor. A commercially available culture system that is sensitive and specific for culture of *T. foetus* will improve the diagnostic outcome. These kits are most useful when inoculated with less than or equal to 0.1 g of fresh feces at 25° C. More recently, a single-nested tube PCR technique has been developed that is ideally suited for diagnostic testing of feline fecal samples that are found negative by direct microscopy and by definitive identification of microscopically observable or cultivated organisms.[94]

223.4.2.5.5 Treatment

At this time the origin of the infection in most cats is unknown, and no effective antimicrobial treatment exists for *T. foetus* infection. Metronidazole and fenbendazole may improve clinical signs but generally do not resolve infection. Nitazoxanide eliminates shedding of *T. foetus* and *Cryptosporidium* oocysts, but diarrhea and oocyst shedding recur with discontinuation of treatment. A series of cats that were treated with paromomycin for *T. foetus* infection subsequently developed kidney failure.[95] Consequently, paromomycin should probably not be used in cats.

223.4.2.5.6 Prognosis

The prognosis for eradication of the organism is not encouraging at this time.

223.4.3 Fungi

223.4.3.1 Histoplasma capsulatum

223.4.3.1.1 Cause

Histoplasmosis is a systemic fungal disease of dogs and cats caused by *H. capsulatum*. In the environment, *H. histoplasma* organisms are mycelial, saprophytic soil fungi. In infected tissue or when cultured at 30 to 37° C, the organism is a yeast. The fungus is endemic throughout most of the temperate and subtropic regions of the world. Most cases of histoplasmosis in the United States occur in the central states, with the geographic distribution following the Mississippi, Ohio, and Missouri Rivers.[96,97]

223.4.3.1.2 Pathophysiology

Infection is probably via inhalation or ingestion of infective conidia from the environment. The respiratory system is thought to be the primary route of infection in cats and dogs, although the GI tract may also be an important route in the dog. After inhalation or ingestion, conidia transform from the mycelial phase and are phagocytized by macrophages, where they grow as facultative intracellular organisms. Hematogenous and lymphatic dissemination results in multisystemic disease. Organisms can be disseminated to any organ system, but the lungs, GI tract, lymph nodes, liver, spleen, bone marrow, eyes, and adrenal glands are the most common organs of dissemination in the dogs; lungs, liver, lymph nodes, eyes, and bone marrow are most commonly affected in cats. Cell-mediated immunity induces a granulomatous inflammatory response in most infections.[98]

223.4.3.1.3 Clinical examination

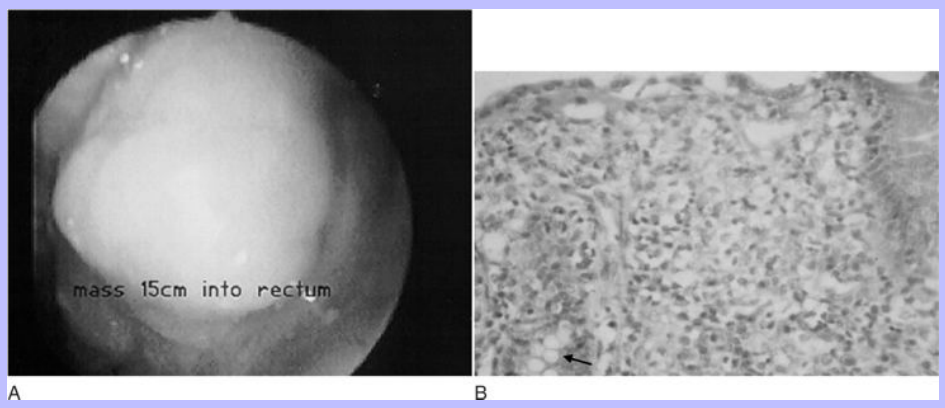
Dogs with GI histoplasmosis typically have mild fever, anorexia, lethargy, weight loss, vomiting, diarrhea, hematochezia, and tenesmus. Cachexia is a common physical examination finding. Other historical and physical examination findings (dyspnea, cough, ascites, lameness, oropharyngeal ulcerations, chorioretinitis, neuropathy) will depend upon organ and tissue involvement. The full clinical spectrum of histoplasmosis infection is outlined in Chapter 174.

223.4.3.1.4 Diagnosis

Endoscopic examination usually reveals severe granulomatous inflammation of the large intestine (Figure 223-6, *A*). Organism identification is required for definitive diagnosis. The most common means of organism identification is cytology. Cytology from affected tissue reveals pyogranulomatous inflammation, often with numerous small, round to oval intracellular yeast cells (2 to 4 μm in diameter) characterized by a basophilic center and a light halo (Figure 223-6, *B*). Exfoliative cytology during colonoscopy is particularly useful in diagnosing the disease.[55] Histopathology is helpful if cytology is nondiagnostic or inconclusive. Multiple endoscopic colonic biopsies are usually sufficient to diagnose the disease. The yeast form does not stain well with routine hematoxylin-eosin (H&E) stains, so special stains such as PAS and Gomori's methenamine silver stain are often used to demonstrate organisms.

Fungal culture from affected tissue can be used for diagnosis but is rarely needed in clinical cases. Currently available serologies have poor specificity and sensitivity.[98]

Figure 223-6 **A,** Endoscopic appearance of granulomatous colitis in a dog infected with *Histoplasma* spp. **B,** Histologic appearance of granulomatous colitis in a dog infected with *Histoplasma* spp. Arrow indicates numerous small, round to oval intracellular yeast cells (2 to 4 µm in diameter) (Hematoxylin-eosin [H&E] stain).



223.4.3.1.5 Treatment

Itraconazole (5 mg/kg orally, twice a day for 2 to 4 months) is considered the treatment of choice for feline histoplasmosis. In one study, itraconazole therapy cured histoplasmosis infections in all eight study cats.[99] Ketoconazole and amphotericin B have been described as the treatments of choice for canine histoplasmosis. With colonic involvement, additional GI therapy may be useful in affected dogs (e.g., dietary modification, treatment for small intestinal bacterial overgrowth, direct antidiarrheal therapy). Corticosteroids may have been used successfully in the treatment of airway obstruction secondary to hilar lymphadenopathy in chronically infected dogs.[100]

223.4.3.1.6 Prognosis

There may be important species differences in prognosis, although the paucity of reports, especially of prospective clinical trials, makes it difficult to generalize. It would seem that the prognosis is guarded in dogs but fair to good in cats.

223.4.4 Oomycetes

223.4.4.1 Pythium insidiosum

223.4.4.1.1 Cause

P. insidiosum is an aquatic oomycete that causes severe GI pathology in a range of hosts in the tropic and subtropic climates.[101] Based on ribosomal RNA gene sequence data, members of the Class Oomycetes are phylogenetically distinct from the Kingdom Fungi and are more closely related to algae than to fungi.[102] The Oomycetes differ from fungi in two important properties (i.e., cell wall and cell membrane composition). Chitin is an essential component of the fungal cell wall, but it is generally lacking in the oomycete cell wall. Oomycetes also differ from fungi in that ergosterol is not a principal sterol in the oomycete cell membrane. This difference may explain why ergosterol-targeting drugs like itraconazole are less effective in the medical treatment of pythiosis.[102]

223.4.4.1.2 Pathophysiology

The infective state of *P. insidiosum* is thought to be the motile zoospore, which is released into stagnant water in warm environments and likely causes infection either by encysting in the skin or by being ingested into the GI tract. Ingested zoospores encyst and adhere to the gastric, jejunal, and colonic epithelium with a polarity oriented toward the submucosa for rapid tissue penetration after germ tube eruption. *Pythium* induces a chronic pyogranulomatous response in the GI tract and mesenteric lymph nodes. The gastric outflow tract and ileocolonic junction are the most frequently affected portions of the GI tract, and it is not uncommon to find two or more segmental lesions in the same patient.[103] Inflammation in affected regions is typically centered on the submucosa, with variable mucosal ulceration and occasional extension of disease through serosal surfaces, resulting in adhesion formation and peritonitis.

223.4.4.1.3 Clinical examination

Weight loss, vomiting, diarrhea, and hematochezia are the most important clinical signs. Physical examination often reveals emaciated body condition and a palpable abdominal mass. Signs of systemic illness such as lethargy and depression are not typically present unless intestinal obstruction, infarction, or perforation occurs.

223.4.4.1.4 Diagnosis

Ileocolonic wall thickening, obliteration of the normal layered appearance, and regional lymphadenopathy are common ultrasonographic features of canine intestinal pythiosis.[104] Of course, these findings cannot be readily differentiated from those associated with intestinal malignancy. Definitive diagnosis requires histologic demonstration or immunohistochemical staining of the organism, positive ELISA or PCR assays, or a combination of these techniques. The histologic findings associated with pythiosis generally are characterized by eosinophilic granulomatous to pyogranulomatous inflammation with fibrosis. Affected tissue typically contains multiple foci of necrosis surrounded and

infiltrated by neutrophils, eosinophils, and macrophages. Discrete granulomas composed of epithelioid macrophages, plasma cells, multinucleate giant cells, and neutrophils and eosinophils may also be observed. *Pythium* zoospores may be cultured directly from affected tissue in antibiotic-containing (e.g., streptomycin, ampicillin) media. More recently, sensitive and specific ELISA and PCR assays have been developed for the accurate diagnosis of pythiosis in dogs.[105–107]

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223.4.4.1.5 Treatment

Aggressive surgical resection remains the treatment of choice for pythiosis in dogs. Because it provides the best opportunity for long-term cure, complete resection of infected tissue should be pursued whenever possible. Segmental lesions of the GI tract should be resected with 3 to 4 cm margins whenever possible. Medical therapy for the oomycetes has not been very promising. This may relate to the absence of ergosterol (cell membrane target of most currently available antifungal drugs) in the oomycete cell membrane. Clinical and serologic cures have been obtained in a small number of dogs after therapy with amphotericin B lipid complex (2 to 3 mg/kg every other day, administered to a cumulative dose of 24 to 27 mg/kg) or itraconazole (5 mg/kg every 12 hours for 6 to 9 months).

223.4.4.1.6 Prognosis

Unfortunately, most dogs with GI pythiosis are not presented to the veterinarian until late in the course of the disease, when complete excision is not possible. The anatomic site of the lesion (e.g., pylorus, ileocolic sphincter) may also prevent complete excision. Consequently, the prognosis is usually grave in most animals.[102]

223.4.5 Algae

223.4.5.1 Prototheca zopfii and P. wickerhamii

223.4.5.1.1 Cause

Three species have been recognized within the genus *Prototheca: P. stagnosa*, *P. wickerhamii*, and *P. zopfii*; a fourth species, *P. salmonis*, has been proposed. Of these three species, *P. wickerhamii* and *P. zopfii* have demonstrated pathogenicity. *Prototheca* spp. are ubiquitous in nature and are found in sewage systems, soil, lakes, rivers, ponds, and in feces. The organism has been documented to cause disease in dogs and cats and a variety of other species. *P. wickerhamii* is the causative organism in virtually all instances of cutaneous protothecosis, and *P. zopfii* is the causative organism in most instances of disseminated disease.[108]

223.4.5.1.2 Pathophysiology

Cutaneous infection with granuloma formation is the most common manifestation of protothecosis in most species, including cats and humans. Dissemination does not readily occur in cats or humans, but the infection readily disseminates to distant sites in dogs.

223.4.5.1.3 Clinical examination

Of the 26 canine cases reported in the veterinary literature, 20 either had ocular signs on presentation or developed them later.[108] Sixteen cases had GI signs, usually colitis-type diarrhea, vomiting, and weight loss. Six cases had neurologic signs in the form of paresis, head tilt, cervical pain, circling, and ataxia. *P. zopfii* accounts for most of the cases of canine disseminated protothecosis.

223.4.5.1.4 Diagnosis

Contrast radiography or abdominal ultrasonography may reveal diffuse colonic wall thickening or obstruction, but these are nonspecific findings. Fecal parasitologic examination is generally of little use in demonstrating the organism, but exfoliative cytology, histology, or both readily identifies the organism.[109] Aqueous or vitreous centesis can also be performed in dogs with ocular pathology and is generally useful in documenting organisms in the ocular fluid.

223.4.5.1.5 Treatment

The management of systemic protothecosis has been challenging in all animal species. Amphotericin B and itraconazole (5 mg/kg orally, twice a day for 1 month and then 5 mg/kg orally, once a day thereafter) have been used in several patients. Short-term improvement was reported in only two dogs.

223.4.5.1.6 Prognosis

Like pythiosis, the prognosis for protothecosis is grave. The course of the disease is so insidious that, by the time a definitive diagnosis has been reached, the organism has often disseminated throughout the body.

223.4.6 Bacteria

223.4.6.1 Brachyspira pilosicoli

223.4.6.1.1 Cause

Brachyspira spp., formerly *Serpulina* spp. or *Treponema* spp., are intestinal spirochetes of dogs, pigs, guinea pigs, rodents, nonhuman primates, and humans.[110] In pigs, they cause two important diarrheal syndromes: (1) *B. hyodysenteriae* causes swine dysentery and (2) *B. pilosicoli* causes porcine intestinal spirochetosis. The consequences of colonization by intestinal spirochetes in animals other than pigs and in humans is controversial. Some investigators believe the bacteria may be responsible for various GI disturbances, whereas others have questioned their clinical importance and claimed that shedding of large numbers of spirochetes in connection with diarrhea may be blamed on dislodgment from the crypts by diarrhea induced by other causative agents.

Intestinal spirochetes have been found in both healthy and diarrheal dogs. In a recent study it was suggested that canine intestinal spirochetes consist of *B. pilosicoli* and a group of nonpathogenic

spirochetes, provisionally designated *Brachyspira* (*Serpulina*) *canis*.[111] Infection with *B. pilosicoli* in the colon of dogs might be subclinical, but massive infection, which may occur in environments with poor hygiene or in dogs with a compromised intestinal function because of concurrent causative factors, may cause diarrhea.[111] *B. pilosicoli* may be associated with diarrhea in colony[112] and pet shop dogs.[113]

223.4.6.1.2 Pathophysiology

Severity of clinical signs appears to be associated with attachment of spirochetes to the epithelial surface of the colon, persistence of *B. pilosicoli* in the cecal and colonic crypt lumina, chronic inflammation caused by spriochetal invasion into the lamina propria, and translocation to extraintestinal sites.[114]

223.4.6.1.3 Clinical examination

Infected animals have clinical signs consistent with large bowel-type diarrhea.

223.4.6.1.4 Diagnosis

Brachyspira infections can be diagnosed by fecal culture, colonic histopathology, and PCR of fresh fecal samples. *Brachyspira* spp. are most effectively grown on either trypticase soy agar with 5% sheep blood or selective BJ agar at 42°C under anaerobic conditions. PCR amplification of the 16S rRNA gene has been used to further clarify natural infections.[111]

223.4.6.1.5 Treatment

The best treatments for *Brachyspira* spp. infection have not yet been identified.

223.4.6.1.6 Prognosis

The prognosis for health and recovery appears to be quite favorable.

223.4.6.2 Campylobacter

223.4.6.2.1 Cause

Campylobacter jejuni, *C. coli*, *C. upsaliensis*, and *C. helveticus* are commensal organisms found in the GI tract of healthy dogs and cats throughout the world.[115–117] The high prevalence of these organisms in healthy nondiarrheic dogs (*C. jejuni,* 49%; *C. coli,* 5%; *C. upsaliensis,* 19%) and cats (*C. jejuni,* 46%; *C. coli,* 1%; *C. upsaliensis,* 5%; *C. helveticus,* 22%) complicates diagnosis.[118–121] Under certain conditions, however, *Campylobacter* can induce significant GI tract pathology. Young age, immunoincompetence, concurrent GI infections, prior therapeutic interventions (e.g., antibiotics), and poor hygienic conditions appear to be the greatest risk factors for the development of infection.[122]

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223.4.6.2.2 Pathophysiology

At some point, *Campylobacter* organisms become enteroinvasive and induce the host inflammatory response. *C. jejuni* localizes in mucus-filled crypts of the intestine and colon where it induces a superficial erosive enterocolitis.[122,123] Colonic epithelial glands undergo hyperplasia and thickening with exfoliation of the brush border and goblet cells. The colonic epithelium becomes cuboidal, crypt height is reduced, and crypt abscess is present. Shallow crypts and blunt irregular villi are features of the ileum response to infection.

223.4.6.2.3 Clinical examination

Clinical signs are watery diarrhea, often containing mucous and blood pigments, tenesmus, anorexia, fever, and vomiting.[123,124] Concurrent infections with *Salmonella*, *Giardia*, or parvovirus cause more severe disease.

223.4.6.2.4 Diagnosis

Direct examination of a fresh fecal sample is the method of diagnosis in many instances. Large numbers of curved, highly motile bacteria along with increased numbers of leukocytes is presumptive evidence of *Campylobacter* infection. With Gram staining, large numbers of faintly staining gram-negative, slender, curved (gull wing shaped) rods are evident. Fecal cultures or PCR are the most conclusive ways to determine the presence of *Campylobacter*.[118,120] *C. jejuni* is best cultured microaerophilically at 42°C for 48 hours on special *Campylobacter* blood agar plates.

223.4.6.2.5 Treatment

Erythromycin is the treatment of choice, although tetracyclines, aminoglycosides, clindamycin, and quinolones are also effective. Post-treatment cultures should be performed to confirm eradication. Pet owners should be advised on the importance of proper hygiene.

223.4.6.2.6 Prognosis

The prognosis for recovery and cure are generally excellent unless an underlying immunosuppressive condition has increased the susceptibility to infection.

223.4.6.3 Clostridium perfringens

223.4.6.3.1 Cause

C. perfringens is a gram-positive, spore-forming, obligate anaerobic rod-shaped bacterium that contributes to the microbial ecology and nutrition of the colon in healthy dogs and cats.[27] Under certain conditions, proliferation and sporulation of *C. perfringens* permits enterotoxin A (or CPE) production which may then induce mucosal damage, fluid secretion and large bowel-type diarrhea. Evidence for and against a role for *C. perfringens* in the pathogenesis of large bowel diarrhea has been put forward.

Enterotoxigenic *C. perfringens* has been associated with canine nosocomial diarrhea,[125] hemorrhagic enteritis,[115] and acute and chronic large bowel diarrhea.[126,127] On the other hand, many dogs harbor *C. perfringens* and CPE in the GI tract without developing clinical signs.[116,117,122] Until more definitive evidence is obtained, including the fulfillment of Koch's postulates, *C. perfringens* should probably be considered as a suspected pathogen in large bowel diarrhea.

223.4.6.3.2 Pathophysiology

The presumed pathogenicity of *C. perfringens* requires an anaerobic environment, sporulation, and enterotoxin production. However, problems exist with this hypothesis: enterotoxin may be demonstrated in the feces without sporulation, and enterotoxin may be found in the feces of healthy dogs. *C. perfringens* isolates are classified as one of five toxigenic types (A to E) based on the production of one or more of four major (α, β, ε, ζ) and seven minor (δ, θ, κ, λ, μ, ν, and sialidase) toxins.[128] Although all five types of *C. perfringens* are capable of producing CPE, the majority is produced by type A strains. As with enterotoxigenic *E. coli* (ETEC) strains, CPE is believed to induce crypt epithelial cell secretion.

223.4.6.3.3 Clinical examination

Clostridium perfringens-associated colitis is believed to be a major cause of acute, nosocomial, chronic large bowel diarrhea. Acute nosocomial diarrhea often begins within 1 to 5 days of boarding or kenneling. Affected dogs develop diarrhea, often with blood pigments, mucous, and tenesmus. These diarrheas are usually self-limiting and may resolve with supportive care alone. Chronic large bowel diarrheas associated with *C. perfringens* are similar to other large bowel-type diarrheas (i.e., chronic, intermittent, and recurring signs of colitis).

223.4.6.3.4 Diagnosis

No gold standard exists for the diagnosis of *C. perfringens*–associated diarrhea. Ideally, the diagnosis would be made on the basis of positive test results with Gram staining, fecal culture, ELISA enterotoxin (CPE) assay, PCR enterotoxin (*cpe*) genotyping, and rule-out of other colonic diseases on colonoscopy and biopsy.[129–132] Compared with normal dogs (without diarrhea), diarrheic dogs are more often CPE ELISA and *cpe* PCR positive, but many normal dogs are positive on both assays.

223.4.6.3.5 Treatment

Recent *in vitro* antimicrobial susceptibility testing suggests that *C. perfringens* should be susceptible to ampicillin, erythromycin, metronidazole, and tylosin.[133] These antibiotics have also been used in vivo with good success. It should be emphasized that many of the same patients respond to supportive care, including intravenous fluids, intestinal protectants, and bland or fiber-supplemented diets.

223.4.6.3.6 Prognosis

Affected animals usually respond to appropriate therapy within a matter of days. The prognosis for recovery is excellent.

223.4.6.4 Clostridium difficile

Clostridium difficile is believed to share many ecological factors with *Clostridium perfringens*,[134,135] but the role of this organism as a pathogen in dogs and cats has not been firmly established. Compared with normal dogs (without diarrhea), diarrheic dogs are more often toxin A ELISA positive, even though they may be *toxin A* PCR negative.[132] As with *C. perfringens*, many healthy dogs and cats carry *C. difficile* without developing clinical signs. In one recent study, it was difficult to experimentally infect dogs with this organism, and those that were infected did not develop clinical signs.[136] Antibiotic-associated diarrheas develop in dogs and cats, but they may have a pathogenesis other than *C. difficile*.

223.4.6.5 Escherichia coli

223.4.6.5.1 Cause

Most strains of *E. coli* are true commensal organisms that are not associated with clinical signs. Strains of *E. coli* that cause diarrhea in animals can be grouped into five main categories: (1) enterotoxigenic (ETEC), (2) enteroinvasive (EIEC), (3) enteropathogenic (EPEC), (4) enterohemorrhagic (EHEC), and (5) enteroadherent (EAEC) organisms.[137] Identification of pathogenic strains requires modern molecular technology such as bioassays, DNA hybridization, and PCR amplification.

223.4.6.5.2 Pathophysiology

Infection may result in enteritis, colitis, or both.[138] Enterotoxigenic (ETEC) strains adhere to the surface of epithelial cells and produce toxins that are heat labile, heat stable, or both, and that induce crypt epithelial cell secretion. EIEC strains of *E. coli* invade, replicate in, and destroy epithelial cells. EPEC strains are neither enterotoxigenic nor enteroinvasive, but they do attach to and efface the brush border of the enterocytes. EHEC strains produce verocytotoxins that induce hemorrhagic ileitis and colitis. EAEC strains of *E. coli* also induce enterocyte pathology, but their mechanism of action is poorly understood. Enterotoxigenic, enteropathogenic, and enterohemorrhagic *E. coli* have all been isolated from dogs and cats with diarrhea. *E. coli* endotoxin colonic absorption of water and sodium and contributes to the diarrhea seen during and after episodes of sepsis.[139]

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223.4.6.5.3 Clinical examination

Affected animals typically have diarrhea and hematochezia with clinical signs relevant to the small intestine, colon, or both.

223.4.6.5.4 Diagnosis

E. coli can be grown from the feces of healthy dogs and cats, so a positive culture does not necessarily reveal the identity of an underlying pathogen. In addition to positive culture, diagnosis may require enterotoxin assays and DNA hybridization and PCR amplification.[140–144]

223.4.6.5.5 Treatment

Antibiotics should be used only in those cases in which firm evidence of bacterial infection exists. Fluoroquinolones appear to be a very effective classification for the treatment of enteric *E. coli* infections.

223.4.6.5.6 Prognosis

The prognosis is generally good for recovery and cure if infection is recognized early in the clinical course.

223.4.6.6 Salmonella

223.4.6.6.1 Cause

Salmonella spp. are predominantly motile, gram-negative facultative anaerobic rod-shaped bacteria found in the feces of normal and diarrheic animals.[116–117] As with many other commensal organisms of the GI tract, the high prevalence of these organisms complicates diagnosis. From 1% to 30% of the fecal samples or rectal swabs taken from healthy domestic pet dogs, 16.7% of dogs boarded in kennels, and 21.5% of hospitalized dogs were found to be positive on bacteriologic culture for *Salmonella*. From 1% to 18% of healthy cats and 10.6% of random source research colony cats are also culture-positive for *Salmonella* (summarized in reference 122). Despite these findings, several species of *Salmonella* have been impugned in the pathogenesis of acute enterocolitis in dogs and cats. *S. typhimurium* is the species most commonly isolated from diarrheic feces of dogs and cats, although other species have been identified.[145–147]

223.4.6.6.2 Pathophysiology

Those most at risk for *Salmonella* infection are young and immunoincompetent animals, those with concurrent GI infections (e.g., parvoviral or parasitic infections), and those animals who have had prior therapeutic interventions (e.g., antibiotics or glucocorticoids).[122] *Salmonella* is an enteroinvasive organism that induces an acute inflammatory response resulting in enterocolitis, mucosal sloughing, and secretory diarrhea. Most *Salmonella* infections are resolved via the local immune response, but bacterial translocation and septicemia may evolve into SIRS and multiple organ dysfunction syndromes (MODS) in some patients. Early recognition is important in preventing this sequela.

223.4.6.6.3 Clinical examination

The main clinical signs of *Salmonella* enterocolitis are anorexia, lethargy, fever, vomiting, diarrhea with mucous and blood pigments, dehydration, abdominal pain, and tenesmus. With bacterial translocation and septicemia, affected animals may have evidence of pale mucous membranes, weakness, tachycardia, tachypnea, and vascular collapse.

223.4.6.6.4 Diagnosis

Culture, serotyping, and PCR are the best methods of diagnosing *Salmonella* infections.[145]

223.4.6.6.5 Treatment

Treatment varies according to the severity of the clinical signs. Mild, self-limiting forms of enterocolitis may in fact resolve with little more than supportive therapy. Antibiotic therapy in such cases may prolong fecal shedding and encourage development of the carrier state. In animals with severe hemorrhagic diarrhea, history of immunosuppression, suspected or documented septicemia, evidence of SIRS, or a combination of these symptoms, parenteral antibiotics should definitely be used. If culture results are unavailable, therapy should include enrofloxacin, amoxicillin, or trimethoprim-sulfa, all of which are effective against *Salmonella*. Post-treatment cultures should be performed to confirm eradication, and pet owners should be advised of the public health importance of the disease.

223.4.6.6.6 Prognosis

The prognosis for recovery in nonsepticemic patients is generally good, although some animals may remain chronic carriers with recrudescence during periods of stress or unrelated disease. The prognosis for the septicemic patient is more guarded.

223.4.6.7 Yersinia enterocolitica

Y. enterocolitica is a commensal organism of the GI tract of some dogs and cats that may be a rare cause of acute colitis.[148] It is a motile, gram-negative facultative anaerobic coccobacillus bacterium that may be transmitted to animals via ingestion of raw pork[149] or contaminated water. If suspected, animals should be treated with cephalosporins or trimethoprim-sulfa. The prognosis is unknown because of the paucity of case reports.

223.5 INFLAMMATION

223.5.1 Inflammatory Bowel Disease

223.5.1.1 Cause

IBD may be defined using clinical, histologic, immunologic, pathophysiologic, and genetic criteria.

223.5.1.2 Clinical criteria

IBD has been defined clinically as a spectrum of GI disorders of an unknown cause that is associated with chronic inflammation of the stomach, intestine, or colon.[40] A clinical diagnosis of IBD is considered only if affected animals have: (1) persistent (> 3 weeks in duration) GI signs (anorexia, vomiting, weight loss, diarrhea, hematochezia, mucosy feces), (2) failure to respond to symptomatic therapies (parasiticides, antibiotics, GI protectants) alone, (3) failure to document other causes of gastroenterocolitis by thorough

diagnostic evaluation, and (4) histologic diagnosis of benign intestinal inflammation.[50] Small bowel and large bowel forms of IBD have been reported in both dogs and cats, although large bowel IBD appears to be more prevalent in the dog.

223.5.1.3 Histologic criteria

IBD has been defined histologically by the type of inflammatory infiltrate (neutrophilic, eosinophilic, lymphocytic, plasmacytic, granulomatous), associated mucosal pathology (villus atrophy, fusion, crypt collapse), distribution of the lesion (focal or generalized, superficial or deep), severity (mild, moderate, severe), mucosal thickness (mild, moderate, severe), and topography (gastric fundus, gastric antrum, duodenum, jejunum, ileum, cecum, ascending colon, descending colon).[11] Typical histologic changes associated with IBD are shown in Figure 223-7. As with small intestinal IBD, subjective interpretation of large intestinal IBD lesions has made it difficult to compare tissue findings between pathologists. Subjectivity in histologic assessments has led to the development of several IBD grading systems.*

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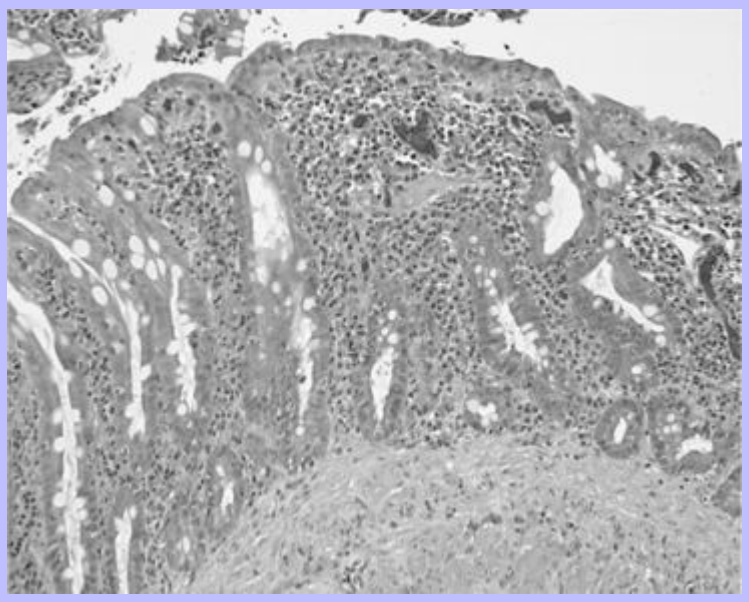
Figure 223-7 Histologic appearance of inflammatory bowel disease (IBD) of the canine colon. Crypts are separated from adjacent crypts by edema, fibrosis, and inflammatory cells. Increased numbers of lymphocytes are present in the lamina propria, and reduced goblet cells are present in the epithelium. (Photomicrograph courtesy of Dr. Mattie Hendrick, University of Pennsylvania.)



* References 3, 11, 13, 36, 37, 38, 150, 151.

223.5.1.4 Immunologic criteria

IBD has been defined immunologically by the innate and adaptive response of the mucosa to GI antigens. Although the precise immunologic events of canine and feline IBD remain to be determined, a prevailing hypothesis for the development of IBD is the loss of immunologic tolerance to the normal bacterial flora or food antigens, leading to abnormal T cell immune reactivity in the gut microenvironment.[152] Genetically engineered animal models (e.g., IL-2, IL-10, T cell receptor knockouts) that develop IBD involve alterations in T cell development, function, or both, suggesting that T cell populations are responsible for the homeostatic regulation of mucosal immune responses.[153] Immunohistochemical studies of canine IBD have demonstrated an increase in the T cell population of the lamina propria, including CD3+ cells and CD4+ cells, macrophages, neutrophils, and IgA-containing plasma cells. Many of the immunologic features of canine IBD can be explained as an indirect consequence of mucosal T cell activation. Enterocytes are also likely involved in the immunopathogenesis of IBD. Enterocytes are capable of behaving as antigen-presenting cells, and interleukins (e.g., IL-7, IL-15) produced by enterocytes during acute inflammation activate mucosal lymphocytes. Up-regulation of Toll-like receptor 4 (TLR4) and Toll-like receptor 2 (TLR2) expression contribute to the innate immune response of the colon.[154] Thus the pathogenesis and pathophysiology of IBD appears to involve the activation of a subset of CD4+ T cells within the intestinal epithelium that overproduce inflammatory cytokines with concomitant loss of a subset of CD4+ T cells and their associated cytokines, which normally regulate the inflammatory response and protect the gut from injury. Enterocytes, behaving as antigen-presenting cells, contribute to the pathogenesis of this disease.[155]

223.5.1.5 Pathophysiologic criteria

IBD may be defined pathophysiologically in terms of changes in transport, blood flow, and motility. The clinical signs of IBD, whether small or large bowel, have long been attributed to the pathophysiology of malabsorption and hypersecretion, but experimental models of canine IBD have instead related clinical signs to the emergence of abnormality motility patterns.

223.5.1.6 Genetic criteria

IBD may be defined by genetic criteria in several animal species. Crohn's disease and ulcerative colitis are more common in certain human genotypes, and a mutation in the NOD2 gene (nucleotide-binding oligomerization domain2) has been found in a subgroup of patients with Crohn's disease.[155] Genetic influences have not yet been identified in canine or feline IBD, but certain breeds (e.g., German shepherds, boxers) appear to be at increased risk for the disease.

223.5.1.7 Pathophysiology

The pathophysiology of large intestinal IBD is explained by at least two interdependent mechanisms: (1) the mucosal immune response and (2) accompanying changes in motility.

223.5.1.7.1

Immune responses

A generic inflammatory response involving cellular elements (B and T lymphocytes, plasma cells, macrophages, and dendritic cells), secretomotor neurons (e.g., vasoactive intestinal polypeptide, substance P, cholinergic neurons), cytokines and interleukins, and inflammatory mediators (e.g., leukotrienes, prostanoids, reactive oxygen metabolites, nitric oxide [NO], 5-HT, IFN-γ, TNF-α, platelet-activating factor) is typical of canine and feline IBD.[156,157] Many similarities exist between the inflammatory response of the small and large intestine, but recent immunologic studies suggest that IBD of the canine small intestine is a mixed Th1 and Th2 response,[40,158,159] whereas IBD of the canine colon may be more of a Th1 type response with elaboration of IL-2, IL-12, INF-γ, and TNF-α[160] (Figure 223-8). Other studies of canine colonic IBD have demonstrated increased numbers of mucosal IgA-and IgG-containing cells,[36,161–163] nitrate,[162] CD3+ T cells, NO,[164] and inducible nitric oxide synthase (iNOS)[164] in the inflamed colonic mucosa (Table 223-5). Increases in the $CD3^{+}$ positive T cell population of the inflamed colon are consistent with changes reported in the inflamed canine intestine. Thus important similarities exist, as do differences between small (Chapter 222) and large bowel IBD.

223.5.1.7.2

Motility changes

Experimental studies of canine large intestinal IBD have shown that many of the clinical signs (diarrhea, passage of mucus and blood, abdominal pain, tenesmus, and urgency of defecation) are related to motor abnormalities of the colon. Ethanol and acetic acid perfusion of the canine colon induces a large bowel form of IBD syndrome indistinguishable from the natural condition.[165,166] Inflammation in this model suppresses the normal phasic contractions of the colon, including the migrating motility complex, and triggers the emergence of GMCs. The appearance of these GMCs in association with inflammation is a major factor in producing diarrhea, abdominal cramping, and urgency of defecation. GMCs are powerful lumen-occluding contractions that rapidly propel pancreatic, biliary, and intestinal secretions in the fasting state (and undigested food in the fed state) to the colon to increase its osmotic load.[43,45,46] Malabsorption results from direct injury to the epithelial cells and from ultrarapid propulsion of intestinal contents by GMCs so that sufficient mucosal contact time is not allowed for digestion and absorption to take place.

Figure 223-8 Immunopathology of canine large bowel inflammatory bowel disease (IBD) and canine ulcerative colitis. IBD of the canine colon may be more of a Th1-type response, whereas ulcerative colitis is more a Th2-type response. *MHC,* Major histocompatibility complex; *APC,* antigen-presenting cell; *IL,* interleukin; *IFN,* interferon; *TNF,* tumor necrosis factor.

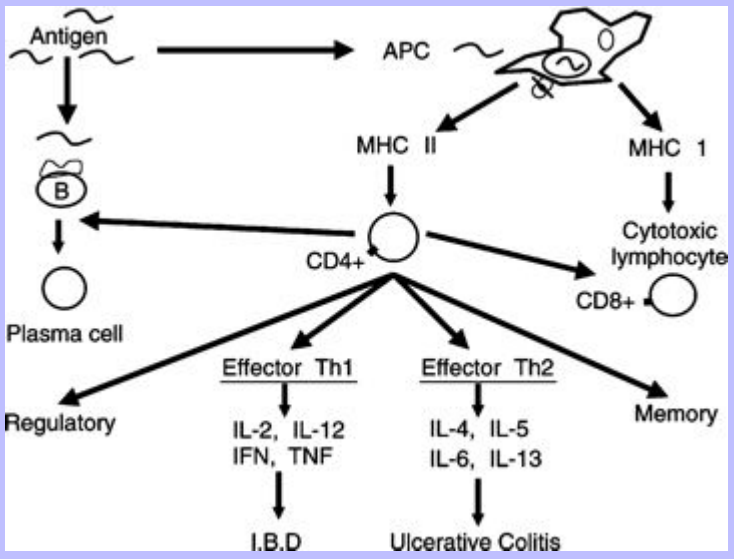


Table • 223-5 Immunologic and Motility Abnormalities in Canine Large Bowel Inflammatory Bowel Disease

HISTOLOGIC FINDINGS	IMMUNOLOGIC ABNORMALITIES	REFERENCE
Lymphocytic-plasmacytic colitis	Increased nitric oxide and IgG in colonic lavage fluid	162
Lymphocytic-plasmacytic colitis	Increased expression of inducible nitric oxide synthase mRNA	164
Lymphocytic-plasmacytic colitis	Increases in T cells and B cells in lamina propria	36
Lymphocytic-plasmacytic colitis	Increases in CD3+T cells and in IgA+and IgG+plasma cells	163
Lymphocytic-plasmacytic colitis	Increased IL-2 and TNF-αmRNA expression	160
TISSUE/CELL TYPE	**MOTILITY ABNORMALITIES**	**REFERENCE**
Colon	Loss of spontaneous phasic contractions	165,166
	Decreased frequency of migrating motor complexes (MMCs)	165,166
	Increased frequency of giant migrating contractions (GMCs)	165,166
Colonic circular smooth muscle cells	Decreased amplitude and duration of the slow wave plateau potential	167
	Shift from the M3 to M2 muscarinic receptor subtype	169
	Reduced calcium influx through L-type calcium channel	170
	Reduced L-type calcium channel expression	171
	Decreased open probability of KCa channels	172
	Down-regulation of PKC α, β, ϵ, expression and activation	174
	Reduced phospholipase A2 expression	173
	Increased NF-κB expression and activation	175
Colonic enteric neurons	Sensitization to substance P during colonic inflammation	168
Colonic interstitial cells of Cajal	Reduced density of interstitial cells	167
	Cytoplasmic vacuolation and damage to cellular processes	167

IgG, Immunoglobulin G; *IgA,* immunoglobulin A; *IL-2,* interleukin-2; *TNF-α,* tumor necrosis factor alpha; *PKC,* protein kinase C; *M,* muscarinic; *NF-κB,* nuclear factor-κB; *KCa,* calcium-activated potassium channel.

Inflammation impairs the regulation of the colonic motility patterns at several levels (i.e., enteric neurons, interstitial cells of Cajal, circular smooth muscle cells; summarized in Table 223-5). Inflammation-induced changes in the amplitude and duration of the smooth muscle slow wave plateau potentials contribute to the suppression of RPCs.[165] These alterations likely have their origin in structural and functional damage to the interstitial cells of Cajal.[167] At the same time that inflammation suppresses the RPCs, inflammation sensitizes the colon to the stimulation of GMCs by the neurotransmitter substance P.[168] These findings suggest that SP increases the frequency of GMCs during inflammation and that selective inhibition of GMCs during inflammation may minimize the symptoms of diarrhea, abdominal discomfort, and urgency of defecation associated with these contractions.[168]

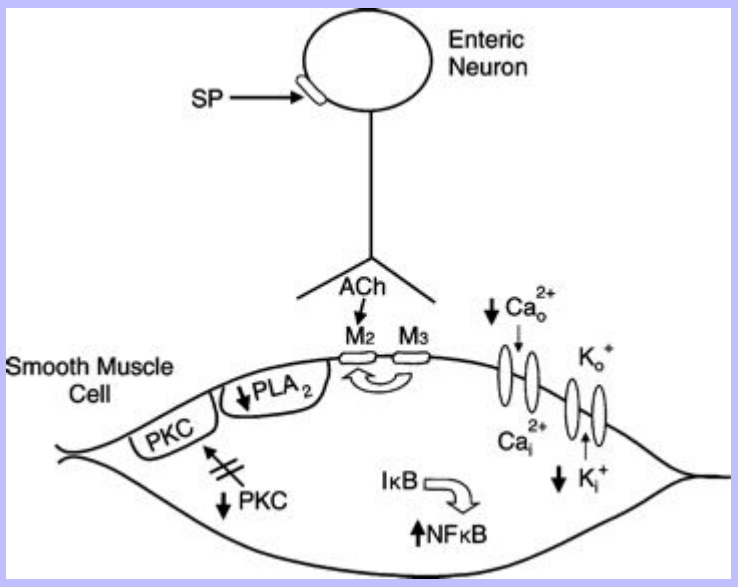
Inflammation suppresses the generation of tone and phasic contractions in the circular smooth muscle cells through multiple molecular mechanisms (see Table 223-5; Figure 223-9). Inflammation shifts muscarinic receptor expression in circular smooth muscles from the M_3 to the M_2 subtype.[169] This shift

has the effect of reducing the overall contractility of the smooth muscle cell. Inflammation also impairs calcium influx[170] and down-regulates the expression of the L-type calcium channel,[171] which may be important in suppressing phasic contractions and tone while concurrently stimulating GMCs in the inflamed colon. Changes in the open-state probability of the large conductance calcium-activated potassium channels (K_{Ca}) partially attenuate this effect.[172] Inflammation also modifies the signal transduction pathways of circular smooth muscle cells. Phospholipase A_2 and protein kinase C (PKC) expression and activation are significantly altered by colonic inflammation,[173,174] and this may partially account for the suppression of tone and phasic contractions. PKC α, β, and ε isoenzyme expression is down-regulated, PKC ι and λ isoenzyme expression is up-regulated, and the cytosol-to-membrane translocation of PKC is impaired.[174] The L-type calcium channel, already reduced in its expression, is one of the molecular targets of PKC. Inflammation also activates the transcription factor NF-κB that further suppresses cell contractility.[175]

223.5.1.8 Clinical Examination

The clinical signs of large intestinal IBD are those of a large bowel-type diarrhea (i.e., marked increased frequency, reduced fecal volume per defecation, blood pigments and mucous in feces, and tenesmus). Anorexia, weight loss, and vomiting are occasionally reported in animals with severe IBD of the colon or concurrent IBD of the stomach, small intestine, or both. Clinical signs usually wax and wane in their severity. A transient response to symptomatic therapy may occur during the initial stages of IBD. As the condition progresses, diarrhea gradually increases in its frequency and intensity and may become continuous. In some cases the first bowel movement of the day may be normal or nearly normal, whereas successive bowel movements are reduced in volume and progressively more urgent and painful. During severe episodes, mild fever, depression, and anorexia may occur.

Figure 223-9 Motility abnormalities in canine large bowel inflammatory bowel disease (IBD). Inflammation impairs motility by inducing changes in receptor, signal transduction, and ion channel activity in smooth muscle cells and enteric neurons. Changes include but not are limited to a shift in muscarinic receptor expression from M_3 to M_2 receptor subtype; impaired calcium mobilization; down-regulation of L-type calcium channel expression; changes in the open-state probability of the large conductance calcium-activated potassium channels (K_{Ca}), down-regulation of phospholipase A_2 and protein kinase C (PKC) α, β, and ϵ isoenzymes; and activation of the transcription factor NF-κB in smooth muscle cells. Inflammation also sensitizes the colon to the stimulation of GMCs by the neurotransmitter substance P. *PKC,* Protein kinase C; *PLA_2,* phospholipase A_2; *M,* muscarinic; *NF-κB,* nuclear factor-κB; *K_{Ca},* calcium-activated potassium channel; *SP,* substance P; *Ach,* acetylcholine.



There does not appear to be any sex predilection, but age may be a risk factor, with IBD appearing more frequently in middle-aged animals (mean age approximately 6 years with a range of 6 months to 20 years).[50,51] German shepherd and boxer dogs are at increased risk for IBD, and pure-breed cats appear to be

at greater risk. Cats more often have an upper GI form of IBD, whereas dogs are at risk for both small and large bowel IBD.

Physical examination is unremarkable in most cases. Thickened bowel loops may be detected during abdominal palpation if the small bowel is concurrently involved. Digital examination of the anorectum may evoke pain or reveal irregular mucosa, and blood pigments and mucous may be evident on the examination glove.

223.5.1.9 Diagnosis

CBCs, serum chemistries, and urinalyses are often normal in mild cases of large bowel IBD. Chronic cases may have one or more subtle abnormalities. One review of canine and feline IBD reported several hematologic abnormalities including mild anemia, leukocytosis, neutrophilia with and without a left shift, eosinophilia, eosinopenia, lymphocytopenia, monocytosis, and basophilia.[51] The same study reported several biochemical abnormalities including increased activities of serum alanine aminotransferase and alkaline phosphatase, hypoalbuminemia, hypoproteinemia, hyperamylasemia, hyperglobulinemia, hypokalemia, hypocholesterolemia, and hyperglycemia. No consistent abnormality in the CBC or serum chemistry has been identified.

A scoring index for disease activity in canine IBD was recently developed that relates severity of clinical signs to serum acute-phase protein (C-reactive protein [CRP], serum amyloid A) concentrations.[50] The canine IBD activity index (CIBDAI) assigns levels of severity to each of several gastroenterologic signs (e.g., anorexia, vomiting, weight loss, diarrhea), and it appears to be a reliable index of mucosal inflammation in canine IBD. Interestingly, both the activity index and serum concentrations of CRP improve with successful treatment, suggesting that serum CRP is suitable for the laboratory evaluation of therapy in canine IBD.[50] Other acute-phase proteins were less specific than CRP. One important caveat that should be emphasized is that altered CRP is not *prima facie* evidence of GI inflammation. Concurrent infections or other inflammatory conditions could cause an acute-phase response, including CRP, in affected patients.

223.5.1.10 Treatment

223.5.1.10.1 Dietary therapy

The precise immunologic mechanisms of canine and feline IBD have not yet been determined, but a prevailing hypothesis for the development of IBD is the loss of immunologic tolerance to the normal bacterial flora or food antigens. Accordingly, dietary modification may prove useful in the management of canine and feline IBD.[176,177] Several nutritional strategies have been proposed including novel proteins, hydrolyzed diets, antioxidant diets, medium chain triglyceride supplementation, low-fat diets, modifications in the omega-6 (ω-6) and omega-3 (ω-3) fatty acid ratio, and fiber supplementation. Of these strategies, some evidence-based medicine has emerged for the use of novel protein, hydrolyzed, and fiber-supplemented diets.

Food sensitivity reactions were suspected or documented in 49% of cats presented because of gastroenterologic problems (with or without concurrent dermatologic problems) in a prospective study of adverse food reactions in cats.[178] Beef, wheat, and corn gluten were the primary ingredients responsible for food sensitivity reactions in that study, and most of the cats responded to the feeding of a chicken-or

venison-based selected protein diet for a minimum of 4 weeks. The authors concluded that adverse reactions to dietary staples are common in cats with chronic GI problems and that they can be successfully managed by feeding selected protein diets. Further support for this concept comes from studies in which gastroenterologic[179–181] or dermatologic[182] clinical signs were significantly improved by the feeding of novel proteins.

Evidence is accruing that hydrolyzed diets may be useful in the nutritional management of canine IBD. The conceptual basis of the hydrolyzed diet is that oligopeptides are of insufficient size and structure to induce antigen recognition or presentation.[183,184] In one preliminary study, dogs with IBD showed significant improvement after the feeding of a hydrolyzed diet, although they had failed to respond to the feeding of a novel protein.[183] Clinical improvement could not be solely attributed to the hydrolyzed nature of the protein source because the test diet had other modified features (i.e., high digestibility, cornstarch rather than intact grains, medium-chain triglycerides, an altered ratio of ω-6 to ω-3 polyunsaturated fatty acids). Additional studies will be required to ascertain the efficacy of this nutritional strategy in the management of IBD.

Fiber-supplemented diets may be useful in the management of irritable bowel syndrome (IBS) in the dog. IBS is a poorly defined syndrome in the dog that may or may not bear resemblance to IBS in humans. Canine IBS has been defined as a chronic large bowel-type diarrhea without known cause and without evidence of colonic inflammation on colonoscopy or biopsy.[185] Dogs fulfilling these criteria were successfully managed with soluble fiber (psyllium hydrophilic mucilloid) supplementation of a highly digestible diet.[185]

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223.5.1.10.2 Exercise

Experimental IBD in the dog is accompanied by significant abnormalities in the normal colonic motility patterns. Physical exercise has been shown to disrupt the colonic MMCs and to increase the total duration of contractions that are organized as nonmigrating motor complexes during the fed state.[186] Exercise also induces GMCs, defecation, and mass movement in both the fasted and fed states. The increased motor activity of the colon and extra GMCs that result from physical exercise may aid in normal colonic motor function.[186]

223.5.1.10.3 Pharmacologic therapy

Animals with mild to moderate forms of large bowel IBD generally respond favorably to dietary modification alone, but pharmacologic therapy will be required with more severe forms of large bowel IBD. Medical therapy includes *anti-inflammatory* (sulfasalazine and other 5-aminosalicylates, metronidazole, prednisone, budesonide), *immunosuppressive* (azathioprine, cyclosporine, chlorambucil), and *motility-modifying* (loperamide) drugs (Table 223-6).

223.5.1.10.4 Sulfasalazine

Sulfasalazine is a highly effective prostaglandin synthetase inhibitor that has proven efficacy in the therapy of large bowel IBD in the dog. Sulfasalazine is a compound molecule of 5-aminosalicylate (meselamine) and sulfapyridine linked in an azochemical bond. After oral dosing, most of the sulfasalazine is transported to the distal GI tract where cecal and colonic bacteria metabolize the drug to

its component parts. Sulfapyridine is largely absorbed by the colonic mucosa but much of the 5-aminosalicylate remains in the colonic lumen where it inhibits mucosal cyclooxygenase and the inflammatory cascade. Sulfasalazine has been recommended for the treatment of canine large bowel IBD at doses of 10 to 25 mg/kg orally, three times a day for 4 to 6 weeks. With resolution of clinical signs, sulfasalazine doses are gradually decreased by 25% at 2-week intervals and eventually discontinued while maintaining dietary management.[187] Salicylates are readily absorbed[188] and induce toxicity in cats; therefore this drug classification should be used with great caution in cats. If used in cats, some authors have recommended using half of the recommended dog dose (i.e., 5 to 12.5 mg/kg orally, three times a day).[187] Sulfasalazine use has been associated with the development of keratoconjunctivitis sicca in the dog,[189,190] so tear production should be assessed subjectively (by the pet owner) and objectively (by the veterinarian) during use.

223.5.1.10.5 Other 5-aminosalicylates

This drug classification was developed to reduce the toxicity of the sulfapyridine portion of the parent molecule (sulfasalazine) and to enhance the efficacy of the 5-aminosalicylate portion. Meselamine (Dipentum, Asachol) and dimeselamine (olsalazine) are available for use in the treatment of canine large bowel IBD. Olsalazine has been used at a dose of 5 to 10 mg/kg orally, three times a day in the dog. Despite the formulation of sulfa-free 5-aminosalicylate preparations, instances of keratoconjunctivitis sicca have still been reported in the dog.[189,190]

223.5.1.10.6 Metronidazole

Metronidazole (10 to 20 mg/kg orally, twice a day to three times a day) has been used in the treatment of mild to moderate cases of large bowel IBD in both dogs and cats. Metronidazole has been used either as a single agent or in conjunction with 5-aminosalicylates or glucocorticoids. Metronidazole is believed to have several beneficial properties, including antibacterial, antiprotozoal, and immunomodulatory effects.[191] Side effects include anorexia, hypersalivation, and vomiting at recommended doses and neurotoxicity (ataxia, nystagmus, head title, and seizures) at higher doses.[192] Side effects usually resolve with discontinuation of therapy, but diazepam may accelerate recovery of individual patients.[193]

223.5.1.10.7 Glucocorticoids

Anti-inflammatory doses of prednisone or prednisolone (1 to 2 mg/kg orally, once a day) may be used to treat IBD in dogs that have failed to respond to dietary management, sulfasalazine, or metronidazole, and as adjunctive therapy to dietary modification in feline IBD. Prednisone or prednisolone are used most frequently, because both have short durations of action, are cost-effective, and are widely available. Equipotent doses of dexamethasone are equally effective but may have more deleterious effects on brush border enzyme activity. Prednisone should be used for 2 to 4 weeks depending upon the severity of the clinical signs. Higher doses of prednisone (e.g., 2 to 4 mg/kg orally, once a day) may be needed to control severe forms of eosinophilic colitis or hypereosinophilic syndrome in cats.

Combination therapy with sulfasalazine, metronidazole, or azathioprine may reduce the overall dose of prednisone needed to achieve remission of clinical signs. As with sulfasalazine, the dose of glucocorticoid may be reduced by 25% at 1-to 2-week intervals while (it is hoped) maintaining remission with dietary modification.

Because of steroid side effects and suppression of the hypothalamic-pituitary-adrenal axis, several alternative glucocorticoids have been developed that have excellent topical (i.e., mucosal) anti-inflammatory activity but are significantly metabolized during first pass hepatic metabolism. Budesonide has been used for many years as an inhaled medication for asthma, and an enteric-coated form of the drug is now available for treatment of IBD in humans (and animals). Little clinical evidence supports of the use of this medication in canine or feline IBD, but doses of 1 mg/cat or 1 mg/dog per day have been used with some success in anecdotal cases.

223.5.1.10.8 Azathioprine

Azathioprine is a purine analog that, after DNA incorporation, inhibits lymphocyte activation and proliferation. It is rarely effective as a single agent and should instead be used as adjunctive therapy with glucocorticoids. Azathioprine may have a significant steroid-sparing effect in IBD. Doses of 2 mg/kg orally, every 24 hours in dogs and 0.3 mg/kg orally every 48 hours in cats have been used with some success in IBD. It may take several weeks or months of therapy for azathioprine to become maximally effective. Cats particularly should be monitored for side effects, including myelosuppression, hepatic disease, and acute pancreatic necrosis.

223.5.1.10.9 Cyclosporine

Cyclosporine has been used in the renal transplantation patient for its inhibitory effect on T cell function. In more recent times, cyclosporine has been used in a number of immune-mediated disorders, including keratoconjunctivitis sicca, perianal fistula (anal furunculosis), and IMHA. Evidence-based medicine studies will be needed to establish efficacy, but anecdotal experience would suggest that cyclosporine (3 to 7 mg/kg orally, twice a day) may be useful in some of the more difficult or refractory cases of IBD.

223.5.1.10.10 Chlorambucil

Chlorambucil (2 mg/m^2 orally, every other day) has been used in place of azathioprine in some difficult or refractory cases of feline IBD.

223.5.1.10.11 Motility-modifying drugs

The mixed μ,δ-opioid agonist, loperamide, stimulates colonic fluid and electrolyte absorption while inhibiting colonic propulsive motility.[194–197] Loperamide (0.08 mg/kg orally, three times a day to four times a day) may be beneficial in the treatment of difficult or refractory cases of large bowel-type IBD.

223.5.1.10.12 Probiotic therapy

Probiotics (see Table 223-6) are living organisms with low or no pathogenicity that exert beneficial effects (e.g., stimulation of innate and acquired immunity) on the health of the host. The gram-positive commensal lactic acid bacteria (e.g., *Lactobacilli*) have many beneficial health effects, including enhanced lymphocyte proliferation, innate and acquired immunity, and anti-inflammatory cytokine production. *Lactobacillus rhamnosus* GG, a bacterium used in the production of yogurt, is effective in preventing and treating diarrhea, recurrent *Clostridia difficile* infection, primary rotavirus infection, and

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atopic dermatitis in humans.[198] *Lactobacillus rhamnosus* GG and *Lactobacillus acidophilus* (strain DSM13241) have been safely colonized in the canine GI tract, although probiotic effects in the canine intestine have not been firmly established.[199a,199b] The probiotic organism, *Enterococcus faecium* (SF68), has been safely colonized in the canine GI tract, and it has been shown to increase fecal IgA content and circulating mature B (CD21+/MHC class II+) cells in young puppies. It has been suggested that this probiotic may be useful in the prevention or treatment of canine GI disease.[200] This organism may, however, enhance *Campylobacter jejuni* adhesion and colonization of the dog intestine, perhaps conferring carrier status on colonized dogs.[201]

Table • 223-6 Drug Index—Large Bowel Diarrhea

DRUG CLASSIFICATION AND EXAMPLES	DOSE	INDICATION
Anthelmintic Drugs		
Albendazole	25 mg/kg PO SID × 2 days	*Giardia* infection
Febantel	10 mg/kg PO SID × 3 days—adult dogs	*Trichuris* infection
	15 mg/kg PO SID × 3 days—puppies	*Trichuris* infection
Fenbendazole	50 mg/kg PO SID × 3 days	*Trichuris, Ancylostoma, Giardia* infection
Ivermectin	200 µg/kg SQ once	Larvicidal for *T. canis*
Mebendazole	22 mg/kg PO SID × 3 days	*Trichuris* infection
Metronidazole	25 mg/kg PO BID × 5 days	*Giardia* infection
Milbemycin oxime	0.5 mg/kg PO once per month	*Trichuris* preventive
Praziquantel	44 mg/kg PO once	*Heterobilharzia*
Pyrantel pamoate	5 mg/kg PO dog, 20 mg/kg cat	*Ancylostoma, Toxocara*
Antibiotics		
Ampicillin	22 mg/kg PO IV TID	*Salmonella, E. coli, Clostridium perfringens*
Cefadroxil	22 mg/kg PO BID	*Salmonella, E. coli*
Chloramphenicol	44 mg/kg PO TID—dogs	*Campylobacter*
	11 mg/kg PO BID—cats	*Campylobacter*
Enrofloxacin	5 mg/kg PO IM SQ BID	*Salmonella, E. coli*
Erythromycin	15–20 mg/kg PO TID	*Campylobacter, C. perfringens*
Metronidazole	10–20 mg/kg PO BID-TID	*C. perfringens*
Orbifloxacin	2.5–7.5 mg/kg PO SID	*Salmonella, E. coli*
Trimethoprim sulfonamide	30 mg/kg PO IM SQ BID	*Salmonella*
Tylosin	40–80 mg/kg PO SID	IBD, *C. perfringens*
Antifungal Drugs		
Amphotericin B	2–3 mg/kg IV QOD administered to a cumulative dose of 24–27 mg/kg	Histoplasmosis, pythiosis, protothecosis
Itraconazole	5 mg/kg PO BID for several months	Histoplasmosis, pythiosis, protothecosis
Ketoconazole	10–15 mg/kg PO BID several months	Histoplasmosis, pythiosis, protothecosis
Anti-Inflammatory Drugs		
Budesonide	1 mg/cat or 1 mg/dog PO SID	IBD
Meselamine	10 mg/kg PO TID	IBD
Metronidazole	10–20 mg/kg PO BID-TID for 4–6 weeks	IBD
Olsalazine	5–10 mg/kg PO TID for 4–6 weeks	IBD
Prednisolone	4.0–6.0 mg/kg PO SID for 4–6 weeks	Feline eosinophilic colitis
Prednisone	1.0–2.0 mg/kg PO SID for 4–6 weeks	IBD
Sulfasalazine	10–25 mg/kg PO TID for 4–6 weeks—dogs	IBD, ulcerative colitis
	5–12.5 mg/kg PO TID for 2–4 weeks—cats	Refractory IBD
Immunosuppressive Drugs		
Azathioprine	2 mg/kg PO SID for 4–6 weeks—dogs	IBD
Chlorambucil	2 mg/m^2 PO every other day for 4–6 weeks	IBD
Cyclosporine	3–7 mg/kg PO BID for 4–6 weeks	IBD
Motility-Modifying Drugs		
Loperamide	0.08 mg/kg PO TID-QID	IBD, IBS
Propantheline	0.25 mg/kg PO BID-TID	IBS
Aminopentamide	0.01–0.03 mg/kg PO BID-TID	IBS
Probiotics		
Enterococcus faecium (SF68)	5 × 10^8 colony-forming units/day	IBD

Lactobacillus rhamnosus GG	1×10^9 to 5×10^{11} colony-forming units/day	IBD

PO, per os; SID, once per day; IV, intravenous; TID, three times per day; BID, twice per day; QOD, every other day.

Two recent studies have shown that many commercial veterinary probiotic preparations are not accurately represented by label claims. Quality control appears to be deficient for many of these formulations.[202,203] Until these products are more tightly regulated, veterinarians should probably view product claims with some skepticism.

223.5.1.10.13 Behavioral modification

IBD and IBS very likely have underlying behavioral components. Abnormal personality traits and potential environmental stress factors were identified in 38% of dogs in one study.[185] Multiple factors were present in affected households, including travel, relocation, house construction, separation anxiety, submissive urination, noise sensitivity, and aggression.[185] The role of behavior in the pathogenesis and therapy of canine and feline GI disorders remains largely unexplored.

223.5.1.11 Prognosis

Most reports indicate that the short-term prognosis for control of IBD is good to excellent. After completion of drug therapy, many animals are able to maintain remission of signs with dietary management alone. Treatment failures are uncommon and are usually due to (1) incorrect diagnosis (it is especially important to rule out alimentary lymphosarcoma), (2) presence of severe disease such as histiocytic ulcerative colitis and PLE or irreversible mucosa lesions such as fibrosis, (3) poor client compliance with appropriate drug and dietary recommendations, (4) use of inappropriate drugs or nutritional therapy, and (5) presence of concurrent disease such as small intestinal bacterial overgrowth or hepatobiliary disease.[187] The prognosis for cure of IBD is poor, and relapses should be anticipated.

223.5.2 Histiocytic Ulcerative Colitis

223.5.2.1 Cause

Histiocytic ulcerative colitis is a rare disorder of the dog that has been reported sporadically since 1965.[204–209] Most cases have been reported in the boxer breed, although recent reports have included the French bulldog, mastiff, Alaskan Malamute, and Doberman pinscher breeds. The disease typically affects the young boxer, with the majority (78%) developing clinical signs before 2 years of age. Males and females appear to be equally affected. The pathogenesis of this disorder is incompletely understood, but a bacterial pathogenesis has recently been proposed.[209a] As with Whipple's disease in humans and Johne's disease in cattle, the presence of periodic acid-Schiff (PAS)-positive macrophages and intralesional bacteria have suggested a number of infectious agents such as mycobacteria, rickettsiae, chlamydiae, and mycoplasmae.[208] Vascular abnormalities of the colonic mucosa and intrinsic abnormalities of the PAS^+ histiocytes have also been implicated in the pathogenesis of this syndrome.

223.5.2.2 Pathophysiology

Histiocytic ulcerative colitis lesions are characterized by increased numbers of IgG+, IgG3+, and IgG4+ plasma cells, CD3+ T cells, MHC class II+ cells, L1+ cells, and PAS+ cells in the lamina propria, and decreased goblet cell numbers in the epithelium (see Figure 223-8).[208] Canine histiocytic ulcerative colitis appears to be more typical of a Th2-type response (similar to human ulcerative colitis), whereas canine large intestinal IBD appears to be more of a Th1-type response.[160]

223.5.2.3 Clinical Examination

Affected animals have classic signs of large bowel disease (e.g., mucoid bloody diarrhea, frequent episodes of urgency and straining to defecate). As the disease progresses, continuing intestinal blood and protein loss causes some animals to lose significant amounts of body weight. The most remarkable findings on physical examination are pain during digital palpation of the anorectum and thickened rectal mucosa along with blood pigments. Moderate to severe cachexia may be a clinical feature of more chronically affected animals.

223.5.2.4 Diagnosis

Colonoscopy and biopsy are the diagnostic methods of choice.[206] Endoscopic findings are variable and include diffusely hyperemic and irregular colonic mucosa with multifocal, petechial hemorrhages; nodular and corrugated mucosa; edema and fibrosis; and, multifocal, scattered ulcers throughout the mucosa.[206,207] Histopathologically, a marked expansion of the lamina propria occurs with a diffuse infiltration of PAS-positive histiocytes. Histiocytic infiltration is often accompanied by multifocal, superficial mucosal ulcers with neutrophil, lymphocyte, and plasma cell infiltration.

223.5.2.5 Treatment.

Sulfasalazine has been the drug of choice for this disorder, and affected animals showed some initial clinical improvement only to experience relapses during the course of the disease. The disease was thought to be progressive and requiring lifelong therapy. More recently, therapeutic cures have been reported with enrofloxacin therapy, again implying an underlying bacterial pathogenesis.[209a]

223.5.2.6 Prognosis

If histiocytic ulcerative colitis is at an advanced stage at the time of diagnosis, treatment often does not improve clinical signs and a poor prognosis is warranted.

223.5.3 Typhlitis

223.5.3.1 Cause

Primary inflammation or infection of the cecum is a rare clinical problem in the dog and cat. Typhlitis more often develops secondarily as part of a typhlocolitis or ileotyphlocolitis syndrome.[210] Eosinophilic typhlitis, for example, has been reported in association with eosinophilic coloproctitis and ileitis in one dog,[210] and

neutrophilic typhlocolitis was observed in a group of gnotobiotic dogs experimentally infected with *Campylobacter* spp.[124] Typhlitis usually responds to the same medical therapies that are used to treat ileocolitis. In rare cases, surgical resection may be required due to obstruction and abscessation.[211]

223.5.3.2 Pathophysiology

The cecum responds pathophysiologically in much the same way that the colon responds to inflammation, except that size and orientation predispose the cecum to obstruction, abscessation, and rupture.

223.5.3.3 Clinical Examination

Dogs affected with typhlocolitis may have mild discomfort on abdominal palpation, or there may be severe abdominal pain with cecal obstruction and abscessation.

223.5.3.4 Diagnosis

Abdominal ultrasonography may be useful in documenting thickening of the cecal mucosa in some cases of typhlocolitis, but definitive diagnosis usually requires direct endoscopic examination. Ultrasonography is more useful in the diagnosis of obstructive lesions of the cecum (e.g., abscessation, neoplasia). Survey radiography is not that useful unless sequelae to infection are noted (e.g., abscessation, inversion, rupture). 1398

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223.5.3.5 Treatment

Infectious typhlitis is best treated with antimicrobial and other therapy as outlined for treatment of inflammatory and infectious colitis.

223.5.3.6 Prognosis

The prognosis for typhlocolitis lesions is generally favorable, particularly if they are diagnosed prior to the onset of smooth muscle hypertrophy and obstruction.

223.5.4 Colitis Associated with Perianal Fistula

Perianal fistula or anal furunculosis is a chronic and painful perianal disease of dogs, characterized by inflammation, ulceration, and sinus tracts involving the tissues surrounding the anus.[212,213] Clinical signs include tenesmus, hematochezia, and an ulcerated malodorous perianal region, resulting in pain, anorexia, and weight loss. Inflammation and sinus tracts may involve the rectum and descending colon in some animals, and it may be difficult, if not impossible, to attribute clinical signs to the colitis or the perianal fistula. Because of the high incidence of colitis in dogs affected with perianal fistula, it has been suggested that colonic biopsies should be obtained in all animals affected with perianal fistula.[213] It has also been suggested that affected animals should be managed with a novel protein diet as part of the overall medical therapy.[212] A more detailed discussion of perianal fistula may be found in Chapter 224.

223.6 OBSTRUCTION

223.6.1 Neoplasia

223.6.1.1 Cause

In dogs, tumors of the large intestine are more common than tumors of the stomach and small intestine. The mean age of dogs affected with colonic neoplasia is variably reported between 7 and 11 years of age.[214] Most colonic tumors of dogs are malignant and include the adenocarcinomas, lymphosarcomas, and GI stromal tumors (leiomyosarcoma, neurofibrosarcoma, fibrosarcoma, and ganglioneuroma).[215–224] Leiomyosarcomas are the most common (91%) of the GI stromal tumors.[217–220] Most colonic neoplasia develop in the descending colon and rectum, although leiomyosarcomas more frequently develop in the cecum.[217,219] Local tumor invasion apparently occurs at a slower rate with canine colonic neoplasia, and metastasis to distant sites is relatively uncommon. Benign colonic neoplasia (e.g., adenomas, adenomatous polyps, leiomyomas) also occur, although they are less common than malignant tumors. Malignant transformation of adenomatous polyps to carcinoma *in situ* and invasive adenocarcinoma has been demonstrated in the dog just as it has in humans.[214,225,226,226b] Extramedullary plasmacytomas are an uncommon tumor of the GI tract but occur in the large intestine and rectum.[227,228] All of the aforementioned tumors are associated with signs of inflammation and obstruction (i.e., hematochezia, tenesmus, dyschezia). Carcinoids (rare 5-hydroxytryptamine [5-HT]-secreting tumors) are occasionally associated with diarrhea because of the effects of 5-HT on secretion and motility.

In cats, adenocarcinoma (46%) is the most common tumor of the large intestine, followed by lymphosarcoma (41%) and mast cell tumors (9%).[229–231] The mean age of cats affected with colonic neoplasia is 12.5 years. The descending colon (39%) and the ileocolic sphincter (28%) are the most common sites of colonic neoplasia in the cat. Unlike colonic tumors in the dog, feline colonic tumors have a high rate (63%) of metastasis and, of course, metastasis is associated with decreased survival time. Metastatic sites include colonic lymph nodes, mesenteric lymph nodes, liver, spleen, bladder, urethra, omentum, mesocolon, lungs, duodenum, and peritoneum.

223.6.1.2 Pathophysiology

Mechanical obstruction is the most common pathophysiologic consequence of locally invasive colonic tumors. Other non-neoplastic processes such as intussusception, FIP granuloma, fibrosing stricture, linear and nonlinear foreign bodies, hematoma, and phycomycosis lesions also cause intraluminal obstruction. Prolonged obstruction induces smooth muscle hypertrophy proximal to the site of the obstruction.[232] Other pathophysiologic consequences of intestinal obstruction are pronounced fluid secretion and malabsorption of water and solutes; fluid, electrolyte, and acid-base disturbances; proliferation and translocation of luminal bacteria; and inflammation, devitalization, and perhaps even perforation of the colon. Secretory diarrheas have been reported with carcinoids of the rectum, colon, and intestine.

223.6.1.3 Clinical Examination

Most affected dogs have signs of hematochezia, mucoid feces, tenesmus, and dyschezia of varying severity. Importantly, the clinical signs observed with colorectal neoplasia are often indistinguishable from other causes of obstruction or chronic colitis. Hematochezia is infrequently reported with leiomyosarcomas or leiomyomas, presumably because these tumors do not typically involve the mucosa. Other clinical signs depend on the tumor type and location. Vomiting, malabsorption, and cachexia may be observed, for example, when multifocal or diffuse tumors (e.g., lymphosarcoma) involve the proximal portions of the GI tract. GI stromal tumors, particularly the leiomyomas, have been associated with hypoglycemia and the resulting clinical signs of muscular weakness and seizure activity.[233] Functional plasmacytomas secrete a single class of immunoglobulin and affected animals may go on to develop hyperviscosity syndrome (e.g., retinal bleeding, epistaxis). If colonic perforation has occurred, animals may be presented moribund with fever, lethargy, anorexia, vomiting, abdominal pain, and collapse.

Vomiting (65%), diarrhea (52%), and weight loss (46%) are common clinical signs in cats with colonic neoplasia.[229] Most cats with colonic (and alimentary) lymphosarcoma are FeLV-negative. These lymphomas are thought to be caused by FeLV, with integrated virus causing neoplastic transformation in the absence of viral replication. Although most lymphomas in cats appear to be comprised of malignant T lymphocytes, most colonic (and alimentary) lymphomas are of B cell origin. Alimentary and colonic lymphomas originate primarily from submucosal lymphocytes, mucosal lymphoid follicles, or both, although one recent study reported an epitheliotropic form of T cell intestinal lymphomas.[234] Epitheliotropic T cell lymphomas have not yet been reported in the feline colon.

223.6.1.4 Diagnosis

Canine rectal adenocarcinomas are palpable in 60% to 80% of clinical cases, but colonic and cecal lesions are not as readily apparent on physical examination.[214,226,232,235,236] More than 50% of cats with colonic masses have a palpable abdominal mass.[229]

Survey and contrast radiographic and ultrasonographic studies have been used with varying levels of success in the diagnosis of canine and feline colonic neoplasia. Annular stenotic lesions associated with adenocarcinoma of the colon may manifest as proximal colonic dilation on survey radiographs.

Radiographic contrast material more precisely outlines the narrowing of the lumen at the site of the tumor. Although still of some clinical utility, contrast studies have been largely superceded by ultrasonography and other imaging modalities. Ultrasonography is presently considered to be the most effective means of diagnosing colonic tumors in dogs and cats and appears to be useful in evaluating mural lesions and associated abdominal changes such as lymphadenopathy.[236] Ultrasonography was reported to be useful 84% of the time in localizing feline colonic neoplasia in one study.[229] Ultrasonographic features of colonic tumors include transmural wall thickening with complete loss of the normal wall layering, fluid accumulation proximal to the lesion, and reduced regional motility.[236] Transabdominal fine needle aspiration, peritoneal fluid cytology, and endoscopic exfoliative cytology may be useful in the diagnosis of lymphoma, but histopathology is generally required for a definitive diagnosis of other colonic neoplasia. CT and magnetic resonance imaging (MRI) scanning have not been sufficiently evaluated at this time for reasonable comparisons to be made with ultrasonography.

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Flexible colonoscopy with mucosal biopsy is the preferred method of diagnosis for colonic neoplasia. Endoscopic abnormalities may include mass effect, mucosal bleeding, increased mucosal friability, erosions and ulcers, and circumferential luminal narrowing with submucosal infiltrative lesions. Multiple biopsy specimens should always be taken from diseased tissue, adjacent healthy tissue, and the transition zone between healthy and diseased tissue. With tumor necrosis, the pathologist will have a much better chance of diagnosing and staging the disease by evaluating non-necrotic tissue.

223.6.1.5 Treatment

The treatment of colonic neoplasia will depend upon tumor type, anatomic location, and presence and extent of metastases. Complete surgical excision is the recommended therapy for focal adenocarcinomas, cecal leiomyosarcomas, and obstructive lymphomas. Multiagent chemotherapy (prednisone, vincristine, cyclophosphamide) has been used to treat colonic lymphoma, but it does not appear to alter survival time in affected cats.[229] Cyclo-oxygenase II (COX II) up-regulation may contribute to the growth characteristics of some canine colonic neoplasia.[237–239] Selective COX II inhibitors (e.g., piroxicam, meloxicam) may therefore be useful in the treatment of some canine colonic neoplasia. Plasmacytomas may be managed with adjuvant chemotherapy (e.g., prednisone, melphalan) after surgical excision. Radiation therapy has been used to palliate recurrent adenocarcinomas with varying results and complications; however, postradiation peritonitis and perforation have been reported in some cases.[240]

223.6.1.6 Prognosis

The prognosis for adenomatous polyps, leiomyomas, and fibromas is generally favorable. Adenocarcinomas, lymphosarcomas, and plasmacytomas tend to recur, metastasize, or both to distant sites. Dogs with annular colorectal adenocarcinomas have a particularly poor prognosis with a median survival time (MST) of only 1.6 months.[214,235] The prognosis for most malignant tumors is generally guarded. Surgical resection alone results in 22 month (dogs) and 15 month (cats) average survival times in dogs and cats.[214,229] It should be noted that cats undergoing subtotal colectomy for colonic adenocarcinoma had a longer survival time than those receiving mass resection only (MST of 138 days versus 68 days).[229] Not surprisingly, cats with metastatic lesions had much shorter survival times, 49 days versus 259 days.[229]

223.6.2 Intussusception

223.6.2.1 Cause

Intussusception is an invagination of one segment of the GI tract into the lumen of an adjoining segment. The *intussusceptum* is the invaginated segment of the alimentary tract, whereas the *intussuscipiens* is the enveloping segment. Invagination may occur in an antegrade (aborad) or retrograde (orad) direction, but is most commonly in the antegrade direction. Any portion of the alimentary tract may be involved, but enterocolic intussusceptions account for almost two thirds of the published cases in dogs and cats. Enterocolic intussusceptions can be further divided into three types: (1) cecocolic (or cecal inversion), with the inverted cecum forming the apex[241]; (2) ileocolic, with the ileum forming the apex; and (3) ileocecal, with the ileum forming the apex.[242] Of these three forms of enterocolic intussusception, the ileocolic intussusception is the one most frequently encountered in clinical practice. A number of conditions are

reported to predispose to intussusception, including intestinal parasitism, viral enteritis, foreign bodies, and masses, but in dogs and cats most intussusceptions are idiopathic.[243–245]

223.6.2.2 Pathophysiology

The initiating events in an intussusception are often difficult to identify retrospectively, but all intussusceptions appear to share three important features: (1) inhomogeneity in a bowel segment—a region in which the GI tract undergoes a sudden anatomic change in diameter (e.g., ileocolic junction) or a bowel segment that is either flaccid or indurated; (2) mechanical linkage of nonadjacent segments—which can be intraluminal (e.g., linear foreign bodies, parasites) or extramural (e.g., fibrous adhesions or bands); and (3) peristaltic activity of the gut.[242]

Invagination begins as a result of peristaltic contraction. Once the invagination has begun, its progress may be rapid, involving as much as several centimeters of intestinal tract within just a few hours. Invagination and intussusception result in luminal obstruction, which may be partial or complete. Obstruction usually results in distension of the bowel segment proximal to the intussusception. The degree of distension is dependent upon the completeness and duration of the obstruction, volume of fluid secretion, degree of vascular compromise, and volume of gas production from bacterial fermentation. Because the mesentery and blood supply are included in the invaginating segment, vascular compromise can occur, which initially leads to intramural hemorrhage and edema and eventually to ischemia and necrosis of the bowel. Full-thickness necrosis may ensue, but perforations are rare.

223.6.2.3 Clinical Examination

The most important clinical signs with ileocolic intussusceptions are intermittent vomiting, progressive loss of appetite, mucoid bloody diarrhea, and a palpable cylinder-shaped mass in the cranial abdomen. Abdominal pain is not a consistent finding in affected animals. Clinical signs may persist for several weeks, and affected animals eventually succumb to the effects of starvation rather than dehydration, electrolyte imbalances, or acid-base disturbances.

223.6.2.4 Diagnosis

With some ileocolic intussusceptions, the intussuscepted bowel may protrude through the anus and must be differentiated from a rectal prolapse. This is accomplished by passing a blunt probe between the protruding segment and the anal sphincter. If the probe can be passed cranial to the pubis without reaching a fornix, then the protruding bowel is the apex of an intussusception rather than rectal prolapse.

Survey abdominal radiographic findings may be suspicious for intussusception (Figure 223-10, *A*). Barium contrast studies (barium enema or upper GI series) are often diagnostic, but abdominal ultrasonography is the preferred method of diagnosis. The appearance of a targetlike mass (consisting of two or more hyperechoic and hypoechoic concentric rings in transverse section) or the appearance of multiple hyperechoic and hypoechoic parallel lines in longitudinal section is virtually diagnostic of an intussusception (Figure 223-10, *B*).[246] The ultrasound scan might also identify a mass associated with the intussusception. Endoscopy may be performed in suspected cases of suspected neoplasia, otherwise endoscopy does not confer any additional benefits over abdominal ultrasound or CT scanning.

223.6.2.5 Treatment

The surgical management of ileocolic intussusception involves either reduction or resection, and anastomosis, or both.[247,248] Secretory diarrhea may persist after relief of the obstruction, and affected animals may need continuous crystalloid and colloidal therapy. If possible, the ileocecal sphincter should be preserved to reduce reflux and contamination of the distal small bowel. Cecocolic intussusceptions or inversions should also be treated with surgical resection. Surgical resection of the cecocolic intussusceptions is generally curative. Enteroplication procedures have been recommended,[249] but they do not appear to reduce recurrence rates.[247,248]

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Figure 223-10 **A,** Survey lateral radiographic appearance of ileocolic intussusception in a 6-month-old puppy. **B,** Ultrasonographic appearance of ileocolic intussusception in a 10-year-old cat. (Digital image courtesy of Dr. Rafe Van Knox, University of Pennsylvania.)

223.6.2.6 Prognosis

The most common complications after treatment of intussusception are recurrence, dehiscence of the anastomosis, ileus, intestinal obstruction, peritonitis, and short bowel syndrome. The recurrence rate in dogs is reported to be between 11% and 20%. In dogs in which no surgical procedure was performed to prevent recurrence, intussusception recurred in 25% of dogs that underwent manual reduction alone and in 19% of dogs that underwent resection and anastomosis. Enteroplication does not appear to reduce recurrence rates any further.[247,248] Indeed, 19% of dogs undergoing enteroplication in one study experienced severe complications that required a second surgery. Intestinal obstruction was a complication of the enteroplication in those patients.[248]

223.7 HYPOMOTILITY AND DYSMOTILITY

223.7.1 Constipation

223.7.1.1 Cause

The etiopathogenesis of idiopathic megacolon is still incompletely understood. Several reviews have emphasized the importance of considering an extensive list of differential diagnoses (e.g., neuromuscular, mechanical, inflammatory, metabolic and endocrine, pharmacologic, environmental, and behavioral causes) for the obstipated cat (Box 223-1; reviewed in reference 250). A review of published cases suggests that 96% of cases of obstipation are accounted for by idiopathic megacolon (62%), pelvic canal stenosis (23%), nerve injury (6%), or Manx sacral spinal cord deformity (5%).[52] A smaller number of cases are accounted for by complications of colopexy (1%) and colonic neoplasia (1%); colonic hypo-or aganglionosis was suspected, but not proved, in another 2% of cases. Inflammatory, pharmacologic, and environmental and behavioral causes were not cited as predisposing factors in any of the original case reports. Endocrine factors (e.g., obesity, hypothyroidism) were cited in several cases, but were not necessarily impugned as part of the pathogenesis of megacolon. It is important to consider an extensive list of differential diagnoses in an individual animal, but it should be kept in mind that most cases are idiopathic, orthopedic, or neurologic in origin. Behavioral (e.g., stress) or environmental (e.g., competition for the litter box) factors, or both, may play an important role in the development of this lesion, but they have not been very well characterized in retrospective or prospective studies.

223.7.1.2 Pathophysiology

Megacolon develops through two pathologic mechanisms: (1) *dilation* and (2) *hypertrophy. Dilated megacolon* is the end stage of colonic dysfunction in idiopathic cases. Cats affected with idiopathic dilated megacolon have permanent loss of colonic structure and function. Medical therapy may be attempted in such cases, but most affected cats eventually require colectomy. *Hypertrophic megacolon*, on the other hand, develops as a consequence of obstructive lesions (e.g., malunion of pelvic fractures, tumors, foreign bodies).

Hypertrophic megacolon may be reversible with early pelvic osteotomy, or it may progress to irreversible dilated megacolon if appropriate therapy is not instituted.[251]

Constipation and *obstipation* are earlier manifestations of the same problem. Constipation is defined as infrequent or difficult evacuation of feces but does not necessarily imply a permanent loss of function. Many cats suffer from one or two episodes of constipation without further progression. Intractible constipation that has become refractory to cure or control is referred to as *obstipation*. The term *obstipation* implies a permanent loss of function. A cat is assumed to be obstipated only after several consecutive treatment failures. Recurring episodes of constipation or obstipation may culminate in the syndrome of *megacolon*.

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223.7.1.2.1 **Box • 223-1 Differential Diagnosis of Constipation in the Cat**

223.7.1.2.1.1 **Neuromuscular Dysfunction**

Colonic smooth muscle: idiopathic megacolon, aging

Spinal cord disease: lumbosacral disease, cauda equina syndrome, sacral spinal cord deformities (Manx cat)

Hypogastric or pelvic nerve disorders: traumatic injury, malignancy, dysautonomia

Submucosal or myenteric plexus neuropathy: dysautonomia, aging

223.7.1.2.1.2 **Mechanical Obstruction**

Intraluminal: foreign material (bones, plant material, hair), neoplasia, rectal diverticula, perineal hernia, anorectal strictures

Intramural: neoplasia

Extraluminal: pelvic fractures, neoplasia

223.7.1.2.1.3 **Inflammation**

Perianal fistula, proctitis, anal sac abscess, anorectal foreign bodies, perianal bite wounds

223.7.1.2.1.4 **Metabolic and Endocrine**

Metabolic: dehydration, hypokalemia, hypercalcemia

Endocrine: hypothyroidism, obesity, nutritional secondary hyperparathyroidism

223.7.1.2.1.5 **Pharmacological**

Opioid agonists, cholinergic antagonists, diuretics, barium sulfate, phenothiazines

223.7.1.2.1.6 **Environmental and Behavioral**

Soiled litter box, inactivity, hospitalization, change in environment

The pathogenesis of idiopathic dilated megacolon appears to involve functional disturbances in colonic smooth muscle. *In vitro* isometric stress measurements have been performed on colonic smooth muscle obtained from cats suffering from idiopathic dilated megacolon.[252,253] Megacolonic smooth muscle develops less isometric stress in response to neurotransmitter (acetylcholine, substance P, cholecystokinin), membrane depolarization (potassium chloride), or electrical field stimulation, when compared with healthy controls.[252,253] Differences have been observed in longitudinal and circular smooth muscle from the descending and ascending colon. No significant abnormalities of smooth muscle cells or of myenteric neurons were observed on histologic evaluation. These studies initially suggested that the disorder of feline idiopathic megacolon is a generalized dysfunction of colonic smooth muscle and that treatments aimed at stimulating colonic smooth muscle contraction might improve colonic motility. More recent studies suggest that the lesion may begin in the descending colon and progress to involve the ascending colon over time.[254]

223.7.1.3 Clinical Examination

223.7.1.3.1 History

Constipation, obstipation, and megacolon may be observed in cats of any age, sex, or breed; however, most cases are observed in middle-aged (mean: 5.8 years) male cats (70% male, 30% female) of domestic shorthair (DSH) (46%), domestic longhair (15%), or Siamese (12%) breeding.[52] Affected cats are usually presented for reduced, absent, or painful defecation for a period of time ranging from days to weeks or months. Some cats are observed making multiple, unproductive attempts to defecate in the litter box, whereas other cats may sit in the litter box for prolonged periods of time without assuming a defecation posture. Dry, hardened feces are observed inside and outside of the litter box. Occasionally, chronically constipated cats have intermittent episodes of hematochezia or diarrhea due to the mucosal irritant effect of fecal concretions. This may give the pet owner the erroneous impression that diarrhea is the primary problem. Prolonged inability to defecate may result in other systemic signs, including anorexia, lethargy, weight loss, and vomiting.

223.7.1.3.2 Physical examination

Colonic impaction is a consistent physical examination finding in affected cats. Other findings will depend upon the severity and pathogenesis of constipation. Dehydration, weight loss, debilitation, abdominal pain, and mild to moderate mesenteric lymphadenopathy may be observed in cats with severe idiopathic megacolon. Colonic impaction may be so severe in such cases as to render it difficult to differentiate impaction from colonic, mesenteric, or other abdominal neoplasia. Cats with constipation due to dysautonomia may have other signs of autonomic nervous system failure, such as urinary and fecal incontinence, regurgitation due to megaesophagus, mydriasis, decreased lacrimation, prolapse of the nictitating membrane, and bradycardia. Digital rectal examination should be carefully performed with sedation or anesthesia in all cats. Pelvic fracture malunion may be detected on rectal examination in cats with pelvic trauma. Rectal examination might also identify other unusual causes of constipation, such as foreign bodies, rectal diverticula, stricture, inflammation, or neoplasia. Chronic tenesmus may be associated with perineal herniation in some cases.[250] A complete neurologic examination, with special emphasis on caudal spinal cord function, should be performed to identify neurologic causes of constipation (e.g., spinal cord injury, pelvic nerve trauma, Manx sacral spinal cord deformity).

223.7.1.3.3

Diagnosis

Although most cases of obstipation and megacolon are unlikely to have significant changes in laboratory data (e.g., CBC, serum chemistry, urinalysis), these tests should nonetheless be performed in all cats presented for constipation. Metabolic causes of constipation, such as dehydration, hypokalemia, and hypercalcemia may be detected in some cases. Basal serum T_4 concentration and other thyroid function tests should also be considered in cats with recurrent constipation and other signs consistent with hypothyroidism. Although hypothyroidism was documented in only one case of obstipation and megacolon, obstipation is a frequent clinical sign in kittens affected with congenital or juvenile-onset hypothyroidism.[52] Constipation could also theoretically develop after successful treatment of feline hyperthyroidism.

Abdominal radiography should be performed in all constipated cats to characterize the severity of colonic impaction and to identify predisposing factors such as intraluminal radio-opaque foreign material (e.g., bone chips), intraluminal or extraluminal mass lesions, pelvic fractures, and spinal cord abnormalities (Figure 223-11). The radiographic findings of colonic impaction cannot be used to distinguish between constipation, obstipation, and megacolon in idiopathic cases. First or second episodes of constipation in some cats may be severe and generalized but may still resolve with appropriate treatment.

Ancillary studies may be indicated in some cases. Extraluminal mass lesions may be further evaluated by abdominal ultrasonography and guided biopsy, whereas intraluminal mass lesions are best evaluated by endoscopy. Colonoscopy may also be used to evaluate the colon and anorectum for suspected inflammatory lesions, strictures, sacculations, and diverticula. Barium enema contrast radiography may be used if colonoscopy is not possible. Both colonoscopy and barium enema contrast radiography will require general anesthesia and evacuation of impacted feces. Cerebrospinal fluid analysis, CT or MRI, and electrophysiologic studies should be considered in animals with evidence of neurologic impairment. Finally, colonic biopsy or anorectal manometry will be necessary to diagnose suspected cases of aganglionic megacolon.

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Figure 223-11 Barium enema in a 12-year-old cat with idiopathic constipation and megacolon.

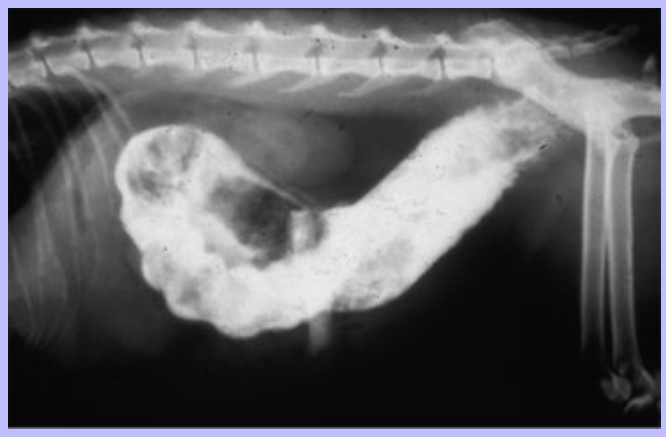
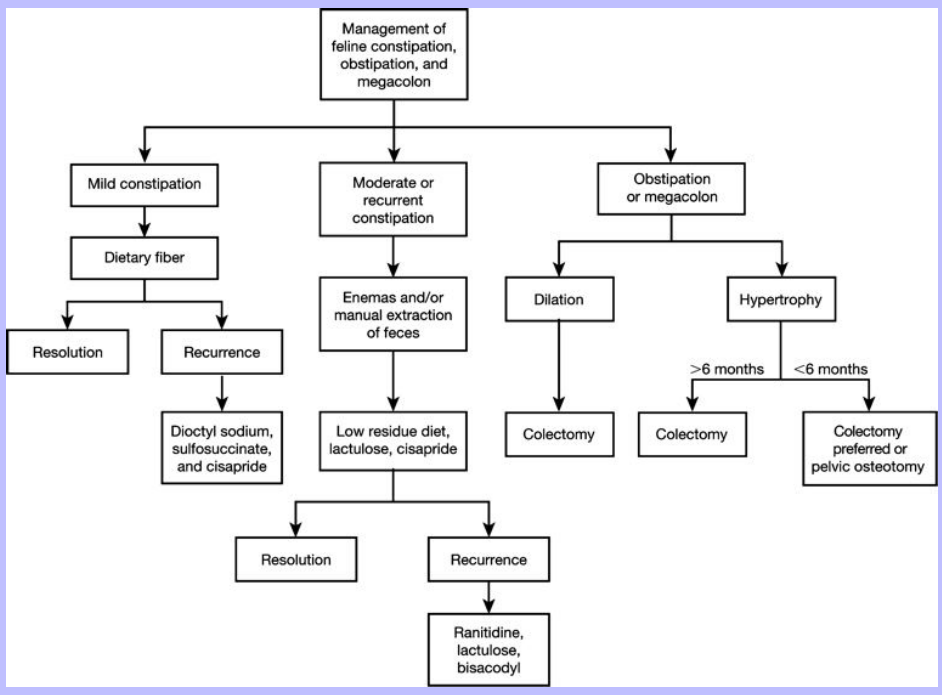


Figure 223-12 Therapeutic approach to feline constipation and megacolon.



223.7.1.3.4 Treatment

The specific therapeutic plan will depend upon the severity of constipation and the underlying cause (Figure 223-12; Table 223-7).[250] Medical therapy may not be necessary with first episodes of constipation. First episodes are often transient and resolve without therapy. Mild to moderate or recurrent episodes of constipation, on the other hand, usually require some medical intervention. These cases may be managed, often on an outpatient basis, with dietary modification, water enemas, oral or suppository laxatives, colonic prokinetic agents, or a combination of these therapies. Severe cases of constipation usually require brief periods of hospitalization to correct metabolic abnormalities and to evacuate impacted feces using water enemas, manual extraction of retained feces, or both. Follow-up therapy in such cases is directed at correcting predisposing factors and preventing recurrence. Subtotal colectomy will become necessary in cats suffering from obstipation or idiopathic dilated megacolon. These cats, by definition, are unresponsive to medical therapy. Although pelvic osteotomy is described for cats with pelvic canal stenosis,[225] subtotal colectomy is an effective treatment and is considered the standard of surgical care.[280] An algorithm for the therapeutic approach to the constipated, obstipated, and megacolonic cat is outlined in Figure 223-12.

223.7.1.4 Removal of Impacted Feces

Removal of impacted feces may be accomplished through the use of rectal suppositories, enemas, or manual extraction.

223.7.1.4.1

Rectal suppositories

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A number of pediatric rectal suppositories are available for the management of mild constipation. These include dioctyl sodium sulfosuccinate (emollient laxative), glycerin (lubricant laxative), and bisacodyl (stimulant laxative). The use of rectal suppositories requires a compliant pet and pet owner. Suppositories can be used alone or in conjunction with oral laxative therapy.

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Table • 223-7 Drug Index—Constipation

DRUG CLASSIFICATION AND EXAMPLE	DOSE
Rectal Suppositories	
Dioctyl sodium sulfosuccinate (Colace, Mead Johnson)	1–2 pediatric suppositories
Glycerin	1–2 pediatric suppositories
Bisacodyl (Dulcolax; Boehringer Ingelheim)	1–2 pediatric suppositories
Enemas	
Warm tap water	5–10 mL/kg
Warm isotonic saline	5–10 mL/kg
Dioctyl sodium sulfosuccinate (Colace, Mead Johnson)	5–10 mL/cat
Dioctyl sodium sulfosuccinate (Disposaject, PittmanMoore)	250 mg (12 ml) given pre rectum
Mineral oil	5–10 mL/cat
Lactulose (Cephulac, Merrell Dow; Duphalac, Reid Rowell)	5–10 mL/cat
Oral Laxatives	
Bulk laxatives	
Psyllium (Metamucil, Searle)	1–4 tsp mixed with food, every 24 or 12 hours
Canned pumpkin	1–4 tsp mixed with food, every 24 hours
Coarse wheat bran	1–4 tblsp mixed with food, every 24 hours
Emollient laxatives	
Dioctyl sodium sulfosuccinate (Colace, Mead Johnson)	50 mg orally, every 24 hours
Dioctyl calcium sulfosuccinate (Surfax, Hoechst)	50 mg orally, every 24 or 12 hours as needed
Lubricant laxatives	
Mineral oil	10–25 ml orally, every 24 hours
Petrolatum (Laxatone, Evsco)	1–5 ml orally, every 24 hours
Hyperosmotic laxatives	
Lactulose (Cephulac, Merrell Dow; Duphalac, Reid Rowell)	0.5 ml/kg orally, every 12 to 8 hours as needed
Stimulant laxatives	
Bisacodyl (Dulcolax, Boehringer Ingelheim)	5 mg orally, every 24 hours
Prokinetic Agents	
Cisapride (compounding pharmacies)	0.1–1.0 mg/kg orally every 12 to 8 hours
Tegaserod (Zelnorm, Novartis)[257]-dogs	0.05–0.10 mg/kg orally, twice a day
Ranitidine (Zantac, Glaxo SmithKline)	1.0–2.0 mg/kg orally, every 12 to 8 hours
Nizatidine (Axid, Eli Lilly)	2.5–5.0 mg/kg orally, every 24 hours

223.7.1.4.2

Enemas

Mild to moderate or recurrent episodes of constipation may require administration of enemas, manual extraction of impacted feces, or both. Several types of enema solutions may be administered, such as warm tap water (5 to 10 mL/kg), warm isotonic saline (5 to 10 mL/kg), dioctyl sodium sulfosuccinate (5 to 10 mL/cat), mineral oil (5 to 10 mL/cat), or lactulose (5 to 10 mL/cat). Enema solutions should be administered slowly with a well-lubricated 10 to 12F rubber catheter or feeding tube. Enemas containing

sodium phosphate are contraindicated in cats because of their propensity for inducing severe hypernatremia, hyperphosphatemia, and hypocalcemia in this species.[256]

223.7.1.4.3 Manual extraction

Cases unresponsive to enemas may require manual extraction of impacted feces. Cats should be adequately rehydrated and then anesthetized with an endotracheal tube in place to prevent aspiration should colonic manipulation induce vomiting. Water or saline is infused into the colon while the fecal mass is manually reduced by abdominal palpation. Sponge forceps may also be introduced rectally (with caution) to break down the fecal mass. It may be advisable to evacuate the fecal mass over a period of several days to reduce the risks of prolonged anesthesia and perforation of a devitalized colon. If this approach fails, colotomy may be necessary to remove the fecal mass. Laxative or prokinetic therapy (or both) may then be instituted once the fecal mass has been removed.

223.7.1.5 Laxative Therapy

Laxatives promote evacuation of the bowel through stimulation of fluid and electrolyte transport or increases in propulsive motility. They are classified as bulk-forming, emollient, lubricant, hyperosmotic, or stimulant laxatives according to their mechanism of action. Hundreds of products are available for the treatment of constipation. Table 223-7 summarizes those products that have been used with some success in cats.

223.7.1.5.1 Bulk-forming laxatives

Most of the available bulk-forming laxatives are dietary fiber supplements of poorly digestible polysaccharides and celluloses derived principally from cereal grains, wheat bran, and psyllium. Some constipated cats will respond to supplementation of the diet with one of these products, but many require adjunctive therapy (e.g., other types of laxatives or colonic prokinetic agents). Dietary fiber is preferable because it is well tolerated, more effective, and more physiologic than other laxatives. Fiber is classified as a bulk-forming laxative, although it has many other properties. The beneficial effects of fiber in constipation include increased fecal water content, decreased intestinal transit time, and increased frequency of defecation.[26,257] Fiber supplemented diets are available commercially, or the pet owner may wish to add psyllium (1 to 4 teaspoon per meal), wheat bran (1 to 2 tablespoon per meal), or pumpkin (1 to 4 tablespoon per meal) to canned cat food. Cats should be well hydrated before commencing fiber supplementation to maximize the therapeutic effect. Fiber supplementation is most beneficial in mildly constipated cats, prior to the development of obstipation and megacolon. In obstipated and megacolon cats, fiber may in fact be detrimental. Low-residue diets may be more beneficial in obstipated and megacolonic cats.

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223.7.1.5.2 Emollient laxatives

Emollient laxatives are anionic detergents that increase the miscibility of water and lipid in digesta, thereby enhancing lipid absorption and impairing water absorption. Dioctyl sodium sulfosuccinate and dioctyl calcium sulfosuccinate are examples of emollient laxatives available in oral and enema form. Anecdotal experience suggests that dioctyl sodium sulfosuccinate therapy may be most useful in animals with acute but not chronic constipation. As with bulk-forming laxatives, animals should be well hydrated before emollient laxatives are administered. It should be noted that clincial efficacy has not been

definitively established for the emollient laxatives. Dioctyl sodium sulfosuccinate, for example, inhibits water absorption in isolated colonic segments *in vitro*, but it may be impossible to achieve tissue concentrations great enough to inhibit colonic water absorption *in vivo*. Dioctyl sodium sulfosuccinate at a dose of 30 mg/kg/day had no effect on fecal consistency in beagle dogs.[258] Further studies are required to determine the clinical efficacy and therapeutic role of dioctyl sodium sulfosuccinate in the management of the constipated cat.

223.7.1.5.3 Lubricant laxatives

Mineral oil and white petrolatum are the two major lubricant laxatives available for the treatment of constipation. The lubricating properties of these agents impede colonic water absorption and permit greater ease of fecal passage. These effects are usually moderate, however, and, in general, lubricants are beneficial only in mild cases of constipation. Mineral oil use should probably be limited to rectal administration because of the risk of aspiration pneumonia with oral administration, especially in depressed or debilitated cats.

223.7.1.5.4 Hyperosmotic laxatives

This group of laxatives consists of the poorly absorbed polysaccharides (e.g., lactose, lactulose), the magnesium salts (e.g., magnesium citrate, magnesium hydroxide, magnesium sulfate), and the polyethylene glycols. Lactose is not effective as a laxative agent in all cats.[259] Lactulose is the most effective agent in this group. The organic acids produced from lactulose fermentation stimulate colonic fluid secretion and propulsive motility. Lactulose administered at a dose of 0.5 mL/kg body weight every 8 to 12 hours fairly consistently produces soft feces in the cat. Many cats with recurrent or chronic constipation have been well managed with this regimen of lactulose. The dose may have to be tapered in individual cases if flatulence and diarrhea become excessive. Magnesium salts are not currently recommended in the treatment of feline constipation and idiopathic megacolon. Some veterinarians have reported anecdotal successes with the polyethylene glycols.

223.7.1.5.5 Stimulant laxatives

The stimulant laxatives (bisacodyl, phenolphthalein, castor oil, cascara, senna) are a diverse group of agents that have been classified according to their ability to stimulate propulsive motility. Bisacodyl, for example, stimulates NO-mediated epithelial cell secretion and myenteric neuronal depolarization.[260] Diarrhea results from the combined effect of increased mucosal secretion and colonic propulsion. Bisacodyl (at a dose of 5 mg orally, every 24 hours) is the most effective stimulant laxative in the cat. It may be given individually or in combination with fiber supplementation for long-term management of constipation. Daily administration of bisacodyl should probably be avoided, however, because of injury to myenteric neurons with chronic use.[250]

223.7.1.6 Colonic Prokinetic Agents

Previous studies of feline colonic smooth muscle function have suggested that stimulation of colonic smooth muscle contraction might improve colonic motility in cats affected with idiopathic dilated megacolon.[252,253,261] Unfortunately, many of the currently available GI prokinetic agents have not proved useful in the therapy of feline constipation, either because of significant side effects (e.g., bethanechol) or

because the prokinetic effect is limited to the proximal GI tract (e.g., metoclopramide, domperidone, erythromycin). The 5-HT_4 serotonergic agonists (e.g., cisapride, prucalopride, tegaserod, mosapride) appear to have the advantage of stimulating motility from the gastroesophageal sphincter to the descending colon with relatively few side effects. Cisapride, for example, increases gastroesophageal sphincter pressure, promotes gastric emptying, and enhances small intestinal and colonic propulsive motility.[262] Cisapride enhances colonic propulsive motility through activation of colonic neuronal or smooth muscle 5-HT receptors in a number of animal species.[263,264] *In vitro* studies have shown that cisapride stimulates feline colonic smooth muscle contraction,[253,264] although it has not yet been conclusively shown that cisapride stimulates feline colonic propulsive motility *in vivo*. A large body of anecdotal experience suggests that cisapride is effective in stimulating colonic propulsive motility in cats affected with mild to moderate idiopathic constipation; cats with long-standing obstipation and megacolon are not likely to show much improvement with cisapride therapy. Cisapride was widely used in the management of canine and feline gastric emptying, intestinal transit, and colonic motility disorders throughout most of the 1990s.[262,265,266] Cisapride was withdrawn from the American, Canadian, and certain Western European countries in July 2000 after reports of untoward cardiac side effects in human patients. Cisapride causes QT interval prolongation and slowing of cardiac repolarization via blockade of the rapid component of the delayed rectifier potassium channel (I_{Kr}).[267] This effect may result in a fatal ventricular arrhythmia referred to as *torsades de pointes*. Similar effects have been characterized in canine cardiac Purkinje fibers,[267] but *in vivo* effects have not yet been reported in dogs or cats. The withdrawal of cisapride has created a clear need for new GI prokinetic agents, although cisapride continues to be available from compounding pharmacies throughout the United States. Two new prokinetic agents, tegaserod and prucalopride, are in differing stages of drug development and may prove useful in the therapy of GI motility disorders of several animal species.[261]

Tegaserod is a potent partial nonbenzamide agonist at 5-HT_4 receptors and a weak agonist at 5-HT_{1D} receptors.[269,270] Tegaserod has definite prokinetic effects in the canine colon, but it has not yet been studied in the feline colon. Intravenous doses of tegaserod (0.03 to 0.3 mg/kg) accelerate colonic transit in dogs during the first hour after intravenous administration.[269] Tegaserod at doses of 3 to 6 mg/kg orally has also been shown to normalize intestinal transit in opioid-induced bowel dysfunction in dogs,[271] and it may prove useful in other disorders of intestinal ileus or pseudo-obstruction. Gastric effects of tegaserod have not been reported in the dog, so this drug may not prove as useful as cisapride in the treatment of delayed gastric emptying disorders. *In vitro* studies suggest that tegaserod does not prolong the QT interval or delay cardiac repolarization as has been occasionally reported with cisapride. Tegaserod was marketed under the trade name of Zelnorm in the United States in September 2002 for the treatment of constipation-predominant IBS in women. As with many other drugs in companion animal medicine, tegaserod has not been licensed for the treatment of canine or feline GI motility disorders.

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Prucalopride is a potent 5-HT_4 receptor agonist that stimulates GMCs and defecation in the dog and cat.[272,273] Prucalopride also appears to stimulate gastric emptying in the dog.[274] In lidamidine-induced delayed gastric emptying in dogs, prucalopride (0.01 to 0.16 mg/kg) dose-dependently accelerates gastric emptying of dextrose solutions. Prucalopride has not yet been marketed in the United States or elsewhere.

Misoprostol is a prostaglandin E_1 analogue that reduces the incidence of nonsteroidal anti-inflammatory drug (NSAID)-induced gastric injury. The main side effects of misoprostol therapy are abdominal discomfort, cramping, and diarrhea. Studies in dogs suggest that prostaglandins may initiate a giant

migrating complex pattern and increase colonic propulsive activity.[275] *In vitro* studies of misoprostol show that it stimulates feline and canine colonic smooth muscle contraction.[276] Given its limited toxicity, misoprostol may be useful in cats (and dogs) with severe refractory constipation.

Ranitidine and nizatidine, classic histamine H_2 receptor antagonists, may also stimulate canine and feline colonic motility. These drugs stimulate contraction apparently through inhibition of tissue acetylcholinesterase and accumulation of acetylcholine at the motor endplate. It is not yet clear how effective these drugs are *in vivo*, although both drugs stimulate feline colonic smooth muscle contraction *in vitro*.[277] Cimetidine and famotidine, members of the same classification of drug, are without this effect.

223.7.1.7 Surgery

Colectomy should be considered in cats that are refractory to medical therapy (Figure 223-13; see Surgery). Cats have a generally favorable prognosis for recovery after colectomy, although mild to moderate diarrhea may persist for weeks to months postoperatively in some cases.[278,279] Although pathologic hypertrophy may be reversible with early pelvic osteotomy in some cases,[255] subtotal colectomy is an effective treatment for this condition regardless of duration, and pelvic osteotomy is not required.[280]

Figure 223-13 Surgical appearance of feline idiopathic megacolon.

223.7.1.8 Prognosis

Many cats have one or two episodes of constipation without further recurrence, although others may progress to complete colonic failure. Cats with mild to moderate constipation generally respond to conservative medical management (e.g., dietary modification, emollient or hyperosmotic laxatives, colonic prokinetic agents). Early use of colonic prokinetic agents (in addition to one or more laxative agents) is likely to prevent the progression of constipation to obstipation and dilated megacolon in these cats. Some

cats may become refractory to these therapies, however, as they progress through moderate or recurrent constipation to obstipation and dilated megacolon. These cats eventually require colectomy. Cats have a generally favorable prognosis for recovery after colectomy, although mild to moderate diarrhea may persist for 4 to 6 weeks postoperatively in some cases.

223.7.2 Irritable Bowel Syndrome

A fiber-responsive large bowel diarrheal syndrome similar to IBS in humans has been characterized in dogs.[185] Affected animals have a chronic idiopathic large bowel-type diarrhea characterized by excessive fecal mucous, hematochezia, and tenesmus. Pet owners occasionally report abdominal pain and weight loss. Multiple diet changes and empiric medications fail to relieve clinical signs. Medical investigation is negative for bacterial and other pathogens, colitis, and colonic neoplasia, and the term *chronic idiopathic large bowel diarrhea* is applied to the patient's disorder. Dogs affected with this syndrome may respond to the feeding of a highly digestible diet that is supplemented with soluble fiber.[185] Dogs that have failed to respond to fiber supplementation may respond to medical treatment with loperamide or anticholinergic agents.[187]

223.8 ULCER

223.8.1 Cause

Colonic ulcers may develop after glucocorticoid therapy and neurosurgery in dogs with spinal cord injury.[281,282] Gastric ulcers are of greater prevalence in this circumstance, but colonic ulcers may be equally devastating. Several factors are likely to contribute to colonic ulcerogenesis, including glucocorticoid-induced inhibition of immune function, epithelial renewal, prostaglandin production, mucus secretion, and collagen production; neurosurgery-induced increases in sympathetic tone; and the inhibitory effects of spinal injury on colonic motility and blood flow. The risk of colonic ulcer formation is greatly increased by concurrent NSAID administration. Why this lesion develops in some dogs but not others is not readily explained.

223.8.2 Pathophysiology

The left colic flexure or proximal portion of the descending colon appears to be at greatest risk for colonic ulceration and perforation; two thirds of the published cases were reported at this site.[282] Nonambulatory neurosurgical patients treated with dexamethasone are at greatest risk for development of colonic perforation. Colonic perforation is often preceded by variable nonspecific signs, most frequently depression, anorexia, and emesis. Perforation appears to be associated with 100% mortality, emphasizing the importance of prevention and early clinical recognition.

223.8.3 Clinical Examination

Middle-aged, male dogs are most often affected, usually within 5 to 7 days of surgery. Depression, anorexia, emesis, abdominal pain, constipation, melena, and fever are the most important clinical signs. Many of these signs are subtle and easily missed by some pet owners. The immunosuppressive properties of glucocorticoids may mask the initial signs of peritonitis associated with colonic perforation.

223.8.4 Diagnosis

If suspected, patients at risk should be carefully evaluated for perforation and peritonitis. Imaging studies (radiography and ultrasonography), abdominocentesis, peritoneal lavage, and exploratory surgery, if indicated, should be considered in patients at risk.

223.8.5 Treatment

Patients with colonic ulcer, perforation, and peritonitis should be explored immediately. Therapy should be aimed at excision of the ulcer, anastomosis of healthy bowel segments, lavage of the peritoneal cavity, open peritoneal drainage (if indicated), and postoperative antibiotics.

223.8.6 Prognosis

Colonic ulcer and perforation is generally associated with a poor prognosis. A preventive approach to this complication appears to be warranted in high-risk patients: (1) use of less-potent glucocorticoids (e.g., prednisone, prednisolone) instead of dexamethasone, (2) limited or no use of glucocorticoids.

223.9 SURGERY

223.9.1 Indications

In dogs the most frequent indication for colonic and rectal surgery is either neoplastic disease or rectal prolapse. Other conditions, including cecal neoplasia, cecocolic volvulus, colonic entrapment, congenital anomalies, traumatic perforation, and perforation associated with intervertebral disc disease and corticosteroid treatment are less common indications for large intestinal surgery.[283] The most frequent indications for colonic surgery in cats is intractable megacolon.

223.9.2 Preoperative Considerations

In dogs with rectal or colonic tumors, appropriate staging is vital to determine the extent of local and systemic disease. In many cases, a careful digital rectal examination can delineate the extent of local disease in the rectum and provide subjective information on the enlargement of regional lymph nodes. Thoracic radiographs are made to rule out pulmonary metastatic disease. Abdominal ultrasonography is used to rule out abdominal metastatic disease and to guide aspiration and biopsy of enlarged iliac lymph nodes. Proctoscopy and colonoscopy show the local extent of neoplastic disease. It is vital that the entire colon be assessed with colonoscopy even after a rectal tumor has been identified, because additional neoplasms are reported in the colon in a percentage of these cases.[235,284] Preparation for evaluation and biopsy of the rectum and colon is performed using an orally administered GI lavage solution.[60,61]

Animals with anal or rectal prolapse are carefully examined to determine the underlying cause of tenesmus. In younger animals, parasitism is the most frequent predisposing cause identified. In older animals, tumors, colitis, urolithiasis, dystocia, and perineal herniation have all been associated with rectal prolapse.[284,285]

Mechanical cleansing is recommended before surgery of the large intestine in humans.[286] However, in cats undergoing surgery for megacolon, preoperative enemas are probably unwarranted because they create a liquid slurry that oozes through noncrushing clamps and contaminates the surgical field. Instead, the dry, hard feces associated with chronic constipation can easily be manipulated into the segment of colon to be resected and then removed. Preoperative enemas are contraindicated in cases of suspected large intestinal perforation.

Perioperative antibiotics are administered to minimize the chance of surgical infection. Randomized, controlled clinical trials of antimicrobial prophylaxis in canine and feline colonic surgery have not been conducted. However, based on human trials,[287] antibiotics effective against aerobes and especially the anaerobes that predominate in the large intestine are administered intravenously once at the beginning of surgery. Antibiotics are not administered again unless either contamination occurs at surgery or the procedure takes longer than 2 hours. In the latter case a second intravenous dose of antibiotics is administered. Antibiotics are continued postoperatively in cases with preoperative or surgical contamination based on the results of operative culture and sensitivity testing.

223.9.3 Surgical Considerations

In animals requiring surgery for cecal or colonic disease, a ventral midline laparotomy is performed. After conducting a thorough abdominal exploration for concurrent or metastatic disease, the affected area of the large intestine is packed off with moistened laparotomy sponges. Resection of the cecum can be performed with or without preservation of the ileocolic junction, depending on the extent of the local disease. In most cases of cecal neoplasia a complete resection and jejuno-or ileocolonic anastomosis is performed to ensure adequate tumor removal.

Subtotal colectomy is an effective treatment for feline idopathic megacolon or megacolon secondary to the mechanical obstruction created by old, healed pelvic fractures. Recommendations for removal of the ileocolic valve and ileum vary in cats with megacolon. The ileocolic blood vessels tether the distal ileum and proximal ascending colon, preventing anastomosis to the distal colon; therefore if a complete colectomy is performed, these vessels must be sacrificed. This necessitates removing the ileum, which has important normal functions in water, vitamin B_{12}, and bile salt resorption, and performing a jejunocolonic anastomosis. In spite of this concern, postoperative intestinal function was normal in four cats evaluated after subtotal colectomy and jejunocolonic anastomosis.[279] The ileocolic valve also minimizes colonic bacterial access to the small intestine,[288] so preservation of the valve would be ideal to minimize small intestinal bacterial overgrowth and deconjugation of bile salts. However, preservation of the ileocolic junction necessitates leaving several centimeters of the ascending colon to ensure a tension-free anastomosis, possibly predisposing these cats to recurrent constipation. To evaluate these concerns, cats with megacolon treated with colectomy were studied retrospectively. Cats with excision of the ileocolic junction had significantly looser stool on long-term follow-up.[289] However, there was no difference in the incidence of constipation between cats with preservation versus excision of the ileocolic junction.[289] This is perhaps explained by *in vitro* experiments with ascending and descending colonic smooth muscle from cats with clinical megacolon showing that smooth muscle dysfunction is less severe in the ascending colon.[254]

When the ileocolic junction is preserved, the ascending colon is transected approximately 3 cm distal to the ileocolic junction to ensure a tension-free anastomosis. An end-to-end colocolostomy is performed using single interrupted sutures of 4/0 polydioxanone.[283] The omentum is wrapped around the anastomotic site and

the abdomen is thoroughly lavaged with a warm, balanced electrolyte solution. All lavage fluid is aspirated from the peritoneal cavity before the incision is closed.

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Prior to surgery, rectal prolapse must be differentiated from a prolapsed intussusception of intestine or colon. A well-lubricated, blunt instrument is passed between the anus and the prolapsed tissue. In animals with a prolapsed intussusception, the probe passes easily. Conversely, in animals with a simple rectal prolapse, the probe cannot pass because the prolapsed tissue joins the mucocutaneous junction of the anus.[284] The viability of the prolapsed tissue is assessed based on gross appearance, color, and bleeding. In cases of simple prolapse where the tissue is healthy, the prolapse is digitally reduced and a purse string suture is inserted in the mucocutaneous junction of the anus, avoiding the anal sacs and the anal sac ducts. The suture is tightened sufficiently to prevent prolapse while leaving a small orifice for the passage of soft feces. The suture is removed after several days and the animals carefully observed for recurrence of the prolapse. In cases of recurrent or substantial prolapse where the rectal tissue is still healthy, a colopexy is performed. Rectal resection is performed in animals with traumatized, necrotic, or irreducible rectal prolapse. The reader is referred elsewhere for the details of these procedures.[284]

Various techniques and surgical approaches have been described for removal of rectal tumors.[284] The approach and technique vary with the extent and location of the mass or masses. Tumors in the proximal rectum may be accessed by a ventral midline laparotomy combined with a pelvic osteotomy. Healing of the distal colon, the proximal rectum, or both is complicated by the poor blood supply to this area of the large intestine.[290] A dorsal approach has been described for tumors involving the middle third of the rectum,[284,291] however, many tumors in this area are also amenable to resection via a rectal pull-through.[284,292] The plexus of pelvic nerves at the peritoneal reflection is vital to postoperative fecal continence. In an experimental study on healthy dogs, transection alone or resection of 4 cm of rectum via a dorsal approach resulted in fecally continent dogs. Resection of 6 cm of the rectum, including the peritoneal reflection, caused fecal incontinence.[291] This limitation on resection is problematic in animals with larger rectal tumors, as a 2 cm gross margin is recommended on both sides of the tumor.[284]

223.9.4 Postoperative Considerations

Postoperative treatment depends largely on the underlying reason for cecal, colonic, or rectal surgery. Pre-or postoperative epidural anesthesia using a combination of local anesthetic and narcotic provides effective pain relief. Animals receiving epidural anesthesia may not be able to urinate normally for 12 to 24 hours; hence bladder size must be evaluated frequently and the bladder gently expressed or catheterized if needed. Narcotics, mixed narcotic agonists and antagonists, partial mu opioid agonists, and COX-II inhibitory class NSAIDS are alternatives for pain management in dogs. Mixed narcotic agonists and antagonists are effective in cats.

Cats recovering from colectomy are maintained on intravenous fluids until they commence eating and drinking. Electrolytes are supplemented if necessary. Bowel movements may be soft or loose and more frequent than normal. A highly digestible, low residue diet is fed. In cats with profuse postoperative diarrhea in which small intestinal bacterial overgrowth is suspected, a short course of antibiotics is administered.

Adequate nutrition is vital for dogs and cats recovering from large intestinal surgery. Early feeding increases anastomosis strength and promotes enteric epithelial proliferation and function.[293,294] Ideally, the diet should provide a source of soluble fiber which, when hydrolyzed to SCFAs, stimulates colonic mucosal

proliferation.[293] In animals with fecal continence difficulties after extensive rectal resection, a low-residue diet is fed twice daily. The animal is then walked for 20 to 30 minutes after eating. In many cases the gastrocolic reflex will result in defecation and near complete emptying of the colon during this time, minimizing subsequent fecal soiling in the house.

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224 CHAPTER • 224 Rectoanal Disease

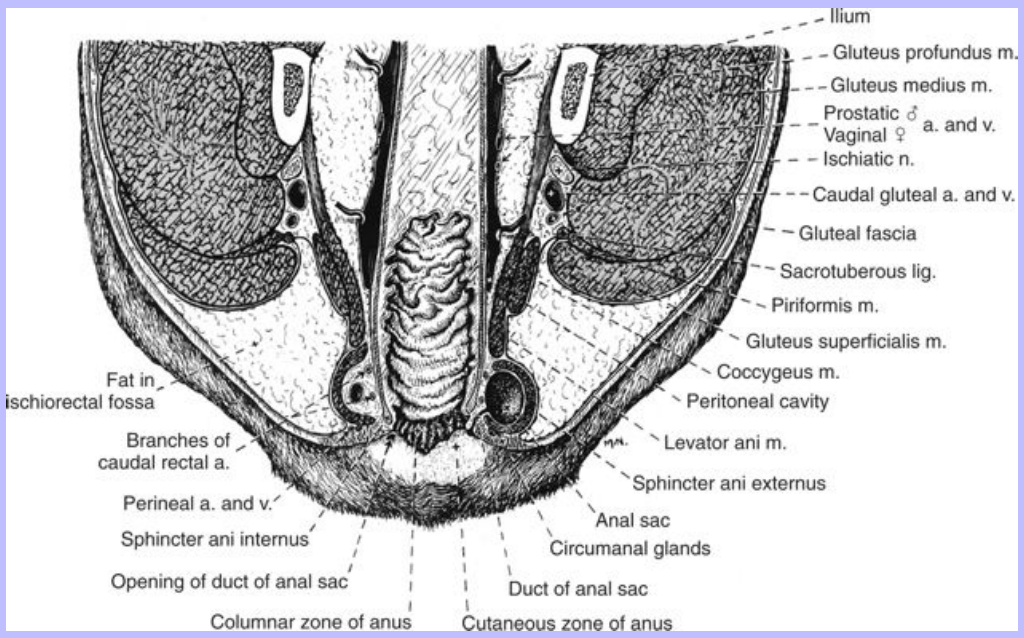
Debra L. Zoran

The storage and voluntary evacuation of feces are under the control of the muscles and nerves serving the pelvic canal, rectum, and anus. These elimination functions are controlled by complex interactions involving smooth muscles, striated muscles, and the intrinsic and extrinsic neurons that innervate them. The ability to retain fecal content, to perceive that the rectum is full, and to determine appropriate defecation is called *fecal continence*. Abnormal function of these muscles or nerves results in loss of fecal continence or constipation but rarely leads to hematochezia or mucoid diarrhea. Alternatively, inflammatory disorders of the rectal mucosa result in tenesmus, increased fecal mucus, hematochezia, or frequent defecation. In dogs with severe rectal inflammatory disease, fecal incontinence may occur secondary to reservoir function failure. Even though many of these conditions are not as serious as other diseases of the gastrointestinal (GI) tract, their social impact makes them a significant influence on the human-animal bond and on the owners' willingness to manage their pet's condition.

224.1 ANATOMY

The rectum, anal canal, internal and external anal sphincters, muscles of the pelvic canal, and the skin and subcutaneous structures of the perianal region make up the anorectum (Figure 224-1).[1] The rectum originates at the pelvic inlet, a continuation of the distal colon, and ends at the anal canal.[1] The rectal muscularis layer includes the longitudinal muscles, which are continuous with the muscularis layers of the colon, and the inner circular muscle layer. The two layers, which provide tone and structural support for the rectal mucosa and submucosa, are controlled and supported by the myenteric plexus neurons and the caudal rectal arteries, respectively.[2] The rectal mucosa contains columnar epithelium rich in goblet cells and numerous solitary lymph follicles. The secretion of mucus from goblet cells is regulated by a submucosal neuronal plexus in the rectal mucosa.[2] Inflammation of the mucosa causes stimulation of this neuronal plexus, resulting in the clinical signs of anorectal disease (e.g., mucoid feces, hematochezia, tenesmus, and dyschezia). As with Peyer's patches in the small intestine, these lymph follicles can be visualized endoscopically as either raised or punctuate depressions in the rectal mucosa. At the junction of the rectum and anus, the mucosal epithelium transitions to squamous epithelium. This transition point defines the junction of the rectum and the internal and external anal sphincters.

Figure 224-1 Cross section through the anorectum of a dog. (From Evans HE: Miller's Anatomy of the Dog, 3rd ed. Philadelphia, WB Saunders, 1993.)



The short anal canal extends from the rectum to the anal opening and forms the terminal opening of the alimentary canal. The involuntary smooth muscle of the internal anal sphincter and striated skeletal muscle of the voluntary external anal sphincter surround the anal canal and determine its function. The mucosa of the anal canal is divided into three zones, the columnar, intermediate, and cutaneous zones.[2] The columnar zone connects the rectum to the anus and is composed of longitudinal ridges of columnar mucosa. The intermediate zone is the transition area between the columnar mucosa and the stratified squamous epithelium that makes up the cutaneous zone. The cutaneous zone is the most caudal portion of the anus and is subdivided into two regions. The innermost region contains the paired anal sacs, which lie ventrolateral to the anus, and the termination of the anal sac ducts.[2] The outermost region is keratinized and hairless and peripheral to the anus itself. The anal opening is formed by the plane that separates the two cutaneous zones. The anal sacs contain coiled, apocrine, sudoriparous glands and a few sebaceous glands.[2,3] The secretions from these glands, which are serous to pasty in composition, accumulate in the anal sacs, along with desquamated epithelium and bacteria. Anal sacs are of clinical importance because they may become impacted with secretions, which often causes discomfort and sometimes leads to infection or abscessation.

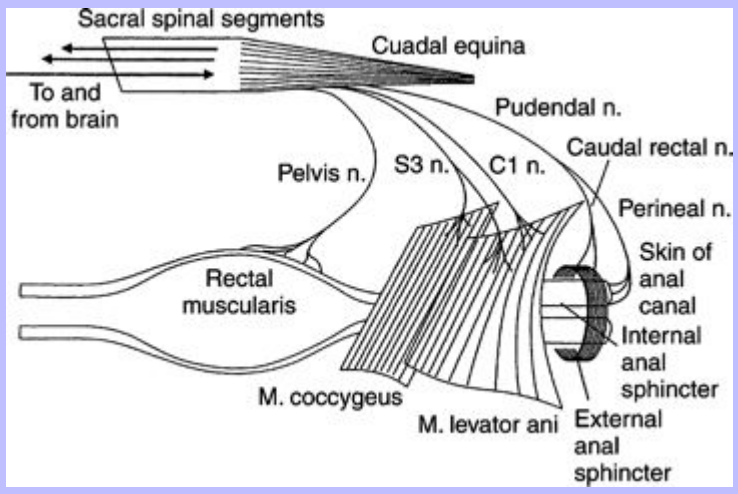
Two other types of glands present in the anal area. *Circumanal (hepatoid) glands* are nonsecretory, subcutaneous sebaceous glands in the anal subcutaneous zone.[2,3] These glands may become clinically important in intact male dogs, because they grow throughout life and form adenomas late in life as a result of constant androgen exposure. The *anal glands* are tubuloalveolar sweat glands located craniolateral to the circumanal glands.[2,3] The anal

glands produce a fatty secretion, the function of which is unknown. The ducts from these glands open in the intermediate zone of the anus.

The innervation of the anorectum is similar to that of the colon in that it comprises a well-defined enteric nervous system consisting of a myenteric and a submucosal plexus.[2] This segment of the autonomic nervous system controls the many sensory, integrative, and motor neurons that characterize the functions of the rectum and anus (Figure 224-2).[1] In particular, these neurons control the secretions of goblet cells and integrate movements of the colon and rectum to ensure appropriate storage and transport of feces. The innervation of the anus is more complex. The pelvic plexus, specifically the sacral nerve branches of the pelvic nerve, provides parasympathetic fibers that are excitatory to the rectum and inhibitory to the internal anal sphincter.[2,4] Conversely, the sympathetic fibers that arise from the hypogastric nerves of the caudal mesenteric ganglion are inhibitory to the rectum (i.e., cause relaxation) and excitatory to the internal anal sphincter (i.e., cause contraction), thus allowing appropriate storage of feces.[2,4]

Relaxation of the internal and external anal sphincters in conjunction with rectal contraction permits defecation. The external anal sphincter is a striated muscle with several muscle bundles that surround the internal sphincter. 1409
These muscles are reflexively able to increase anal sphincter pressure, mediated via somatic nerve fibers in the 1410
anal branch of the pudendal nerve, while still allowing accommodation of feces in the rectum.[2,4] A properly functioning external anal sphincter allows maximal distention (e.g., storage of feces in the rectum) while maintaining anal control. When the pudendal nerve is damaged, the external anal sphincter is incompetent, and clinically apparent fecal incontinence develops.

Figure 224-2 Neural control of defecation. (From Strombeck DR, Guilford WG: Small Animal Gastroenterology, 2nd ed. Davis, California, Stonegate Publishing, 1990.)



The pelvic diaphragm constitutes the final aspect of anatomic control of anorectal function. These muscles support the rectal and anal canal and participate in the maintenance of fecal continence and appropriate defecation by providing structural support and additional muscular control. The muscles that participate in this activity include the right and left ventral sacrococcygeal muscles and the levator ani.[2] The sacrococcygeal

muscles originate on either side of the rectum and attach dorsally to the base of the tail (see Figure 224-1).[1] These smooth muscles, which are innervated by the pelvic plexus, shorten the rectum during defecation, assisting in the evacuation of feces. The levator ani muscles are striated muscles (innervated by the sacral and caudal nerves) that surround the rectum and assist in compression of the rectum during defecation.[2]

224.2 PHYSIOLOGY OF DEFECATION

Normal anorectal function and the act of defecation are primarily pressure-based functions that rely heavily on complex interactions between peripheral pressure receptors, myenteric neurons, somatic and autonomic afferent nerve fibers, spinal cord, brain stem, somatic and autonomic efferent nerve fibers, and smooth and striated muscle of the rectum and anal sphincters[1,5–7] (see Figure 224-2). When the rectum is empty, intraluminal rectal pressure is low. Increased intraluminal pressure is the primary component of maintenance of fecal continence; it is generated by contraction of the internal anal sphincter, either in response to a sudden increase in intra-abdominal pressure (e.g., coughing or sneezing) or by an increase in rectal filling.[1,5] The main stimulus for defecation is increased pressure in the rectum caused by distention. The rectoanal inhibition reflex allows relaxation of the internal anal sphincter, along with contractions of the external anal sphincter, to allow slow but continuous filling of the rectum.[1,5,8] As the fecal volume increases in the rectum, conscious awareness of rectal filling is perceived by means of sensory signaling of information transmitted via sacral afferent fibers to the cerebral cortex.[4,6,9] The rectoanal inhibition reflex allows continued filling of the rectum until defecation is appropriate. If the volume of feces remains small (and stretch is minimal) or if defecation is not appropriate, the internal anal sphincter returns to a state of contraction, resulting in propulsion of feces back into the colon. This activity is also stimulated by descending inputs from motoneurons in the sacral spinal cord and pudendal nerve that mediate voluntary contraction of the external anal sphincter and levator ani.[4,6,9,10] This back-and-forth process is repeated until the volume of feces is sufficient both to initiate rectal distention and to come into contact with the anal mucosa, resulting in a stronger urge to defecate.

When defecation is initiated, distention of the rectum activates parasympathetic efferents that control contraction of colonic smooth muscle (resulting in mass movement of the distal colon) and inhibition of the external anal sphincter and pelvic muscles (resulting in relaxation of the sphincters).[11–13] The rectum itself produces only small contractions that are not propulsive, therefore the main propulsive force for expelling feces from the body is the contraction of colonic smooth muscles. Thus the rectum serves primarily as a conduit during the process of defecation and as a storage depot in the periods between. Defecation is facilitated by proper posture and generation of increased abdominal pressure (closure of the glottis, fixation of the diaphragm, and contraction of the abdominal wall muscles).[2,5,12,13] Conscious suppression of defecation is facilitated by descending impulses to sacral nerves and the pudendal nerve, which mediate contraction of the levator ani and external anal sphincter, resulting in maintenance of fecal continence.[9,12,13]

224.3 HISTORY AND PHYSICAL EXAMINATION

The close association of the anorectum and colon results in similar clinical signs of disease for these two components and creates difficulty in localizing signs to a specific region of the lower GI tract. A careful history and complete physical examination are required to determine whether tenesmus and dyschezia are the result of colonic disease or of anorectal disease alone. In general, diseases of the anorectum are either inflammatory (with signs of hematochezia, tenesmus, mucoid feces, or dyschezia predominating) or they result in altered motility (e.g., constipation or fecal incontinence). It is unusual for systemic signs, such as anorexia, weight loss, vomiting,

or diarrhea, to occur in animals with rectoanal disease; their occurrence suggests concurrent systemic disease or disorders in other segments of the GI tract.

The physical examination of the perineum should always include careful visual inspection for evidence of inflammation, swelling, tumor masses, herniation, rectoanal prolapse, or fistulas. After the visual inspection a digital examination should be performed, including palpation of the anal sphincter tone, the pelvic diaphragmatic musculature, and the size and expressibility of the anal sacs; determination of the diameter of the rectal lumen; and tactile examination of the texture, regularity, and surface of the mucosa. Other structures that should be palpated are the prostate in males, the vaginal vault in females, and the pelvic urethra. In pets with severe inflammation of the anorectum, digital palpation may be impossible without sedation or complete anesthesia. In general, cats should be sedated prior to rectoanal palpation to prevent patient or operator injury.

Hematochezia, blood dripping from the anus, or excess mucus with normally formed feces is often a good indicator of rectoanal disease, especially inflammatory diseases such as proctitis, perianal fistulas, anal sacculitis, polyps, or neoplasia. Tenesmus is a hallmark of both anorectal and colonic disease and must be differentiated from *dyschezia* (painful defecation), which is much more typical of diseases of the anorectum. Both conditions are typically associated with inflammatory diseases of the colon or anorectum; they result in increased frequency and urgency of defecation and straining during defecation (Box 224-1).[14] Because many owners may confuse the signs of dyschezia and tenesmus, it is often necessary to observe the animal during the act of defecation. Furthermore, owners often are unable to determine whether straining is associated with defecation or urination, therefore urogenital disease must be considered until the clinical signs can be localized.

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224.3.1 Box • 224-1 Causes of Tenesmus and Dyschezia

224.3.1.1 Colorectal Disease

Constipation

Colitis-proctitis

Inflammatory bowel disease

Histoplasma capsulatum (histoplasmosis)

Clostridium perfringens (enterotoxicosis)

Prototheca zopfii (protothecosis)

Rectal stricture

Neoplasia–polyps

Foreign material

Irritable bowel syndrome

224.3.1.2 Perineal-Perianal Disease

Anal sacculitis, impaction, or abscess

Anal sac neoplasia

Perianal fistula

Perineal hernia

224.3.1.3 Urogenital Disease

Cystitis-urethritis-vaginitis

Cystitis–urethral calculi

Prostatitis–prostatic abscess

Parturition

Neoplasia of the urethra, bladder, prostate, or vagina

224.3.1.4 Miscellaneous Causes

Caudal abdominal cavity mass

Pelvic fracture–neoplasia

In most cases of anorectal disease, routine hematology and biochemical tests are seldom helpful for identifying a specific diagnosis. However, they are important in the identification of concurrent or complicating conditions that may influence further diagnostic tests or therapy, especially in older animals. In any animal with an abnormal fecal stream, multiple fecal flotations, cytologic examination of feces, and specific tests for infectious causes of GI disease (e.g., enzyme-linked immunosorbent assay [ELISA] for clostridial toxin, *Giardia* spp., cryptosporidia, and viruses) are strongly recommended. The most common parasitic cause of tenesmus and hematochezia in dogs is *Trichuris vulpis* (whipworm) infection, and because of the pattern of intermittent shedding, empirical anthelmintic therapy is recommended even in the absence of identification of ova in feces.

In dogs and cats with acute onset of hematochezia and tenesmus, dietary therapy using high-fiber diets is a reasonable initial therapeutic approach. If further diagnostic evaluation is deemed necessary, specific imaging techniques directed toward assessment of the anorectum are indicated. Imaging of the anorectum by conventional means (e.g., abdominal radiography and ultrasonography) is generally unrewarding for most cases of anorectal disease. However, these modalities can be helpful for identifying some causes of colonic disease (e.g., neoplasia, infiltrative disease, constipation, or foreign bodies) that may have a similar clinical presentation. Intrarectal ultrasonography can help the examiner to determine the extent of intraluminal or intramural tumor involvement and to evaluate pararectal structures. However, ultrasound units with these probes are not universally available. Contrast radiography is rarely helpful in the diagnosis of anorectal disease, because most rectal strictures, polyps, or hernias can be either palpated or observed during proctoscopic examination. However, in dogs with severe rectal strictures or tumors that obstruct passage of a colonoscope or proctoscope, this technique may provide the examiner with additional information.

In general, rigid proctoscopy, with or without colonoscopy, is the diagnostic tool of choice for examination, biopsy and, in some cases, treatment of rectoanal disease. Proctoscopy is technically less difficult, and the instrumentation is less expensive, than that required for flexible colonoscopy. With either a proctoscope or colonoscope, the rectal mucosa can be visualized for color, texture, friability, masses, and bleeding, and biopsies of the colonic or rectal mucosa can be readily obtained. Furthermore, any lesions of the terminal rectum (e.g., polyps) that are identified can often be directly visualized by gently prolapsing the rectum and anus using tissue forceps. This technique also allows surgical removal of small polyps or masses.

224.4 DISEASES OF THE RECTUM

224.4.1 Perineal Hernia

Perineal hernias have been clinically recognized in the dog for more than 100 years and are most common in older, intact male dogs.[15,16] They are rarely seen in cats or female dogs.[17] Four types of perineal hernias have been described, but the most common type is the caudoventral perineal hernia, which occurs between the levator ani, external anal sphincter, and internal obturator muscles.[18,19] Sciatic hernias occur between the sacrotuberous ligament and the coccygeus muscle, dorsal hernias occur between the levator ani and coccygeus muscles, and ventral hernias occur between the levator ani and ischiourethralis or ischiocavernosus muscles.[19] Most perineal hernias are unilateral, although bilateral herniation can occur, with the right side being predisposed.[15,16] Herniation may involve only rectal tissues, but eventually prolapse of pelvic organs, such as the urinary bladder, prostate, or other abdominal tissues (e.g., fat, intestine), into the weakened area can occur. In dogs, neurogenic atrophy of the levator ani muscles, gender-based variations in pelvic muscle anatomy, and gonadal hormonal influence are all thought to be factors in the development of perineal hernias.[19] The degree of stretching and deviation of the rectal wall and the presence or absence of abdominal organs in the hernia are all factors that determine clinical signs.

224.4.1.1 History and Physical Examination

In more than 90% of affected dogs, perineal swelling and tenesmus are the most common clinical signs[15,18,19]; however, constipation, dyschezia, and hematochezia are also reported. Dysuria and stranguria accompany the signs of rectoanal disease if the bladder is retroflexed and trapped in the ischiorectal fossa. With longstanding bladder entrapment, azotemia and signs of renal failure (e.g., anorexia, vomiting) also occur. Less commonly, persistent dribbling of urine or other signs of urinary incontinence may be present instead of signs of urinary obstruction. In cats with perineal herniation, concurrent severe obstipation or megacolon is the most common predisposing factor.[17] The physical examination often reveals a visible perineal swelling or a reducible perineal swelling (Figure 224-3). External palpation of a defect in the musculature just lateral to the external anal sphincter is often sufficient for confirmation of the hernia. However, in some pets the hernia is palpated rectally only as a defect in the pelvic diaphragm. A digital examination can also be performed to detect any other rectal wall abnormalities (e.g., deviation, sacculation, or diverticulum). In general, the combination of historical and physical examination findings is sufficient to confirm the diagnosis of perineal hernia. Further evaluation, either with ultrasonography or contrast studies, may be necessary to determine the extent of hernia contents (e.g., the presence of intestine, bladder, or prostate) prior to repair. The major differential diagnoses are rectal diverticulum, neoplasia, prostatic or paraprostatic cyst, and seroma/hematoma.

Figure 224-3 Perineal swelling in an 8-year-old dog with a perineal hernia.

224.4.1.2 Pathogenesis

The pathogenesis of perineal hernias is not completely understood. Because most patients are older male dogs, gonadal hormonal influences have been strongly suggested. The evidence supporting this idea derives from the fact that castrated dogs are rarely affected with perineal hernia; however, no difference in the levels of testosterone and estrogen 17-beta have been found between normal dogs and dogs with perineal hernia.[20] Some have suggested that, rather than hormone concentrations, the number or affinity of hormone receptors may be the important factor in the development of perianal muscle weakness.[21] Another potential factor is that in male dogs, the levator ani muscles are weaker and thinner and have a weaker attachment to the external anal sphincter.[18,22,23] The fact that brachycephalic breeds (e.g., Boston terrier, boxer, Welsh corgi, and Pekinese) appear to be predisposed to the development of perineal hernias suggests that an anatomic or breed-specific defect is important.[19] Evidence against a strictly hormonal cause for hernia development is the fact that in cats, the benefits of castration have not been demonstrated, a finding illustrated by a retrospective study in which 19 of 20 cats with perineal hernias had been either castrated or spayed.[17]

Aside from anatomic and hormonal theories, another factor considered important in disease development is damage to the pudendal nerve or to the first, second, or third sacral nerves, which results in neurogenic atrophy of the levator ani muscles.[23] However, it is not known whether damage precedes development or occurs as a result of the hernia.

In addition to primary predisposing factors, perineal hernias in dogs may occur secondary to persistent tenesmus and constipation, which results in muscular weakness in the pelvic floor[15,16] or may occur as a result of severe prostatic disease or paraprostatic cysts.[24] In cats, perineal hernias most commonly occur secondary to constipation resulting from megacolon.[17] Other factors associated with perineal hernias in cats are perianal masses, chronic fibrosing colitis, and previous perineal urethrostomy.[17]

224.4.1.3 Therapy

Definitive surgical repair (perineal herniorrhaphy) is the treatment of choice in most instances. The primary aim of the surgical repair is to replace muscular support of the pelvic diaphragm. Preoperative preparations may include preanesthetic blood work, electrocardiography, abdominal ultrasound, and chest radiographs if indicated to rule out complicating factors for anesthesia or secondary causes of hernia formation. Stool softeners (e.g., lactulose) and a highly digestible diet (i.e., to reduce fecal volume) should be initiated several days before surgery.[19] If the bladder is retroflexed and trapped within the hernia, catheterization should be attempted immediately. If this is unsuccessful, the bladder should be emptied by cystocentesis; then, with the bladder decompressed, the hernia is reduced and the bladder is pushed back into the abdominal cavity if possible.

Regardless of whether the bladder is properly repositioned, a transurethral Foley urinary catheter should be placed and a closed collection system should be attached until surgery can be performed. Urine cultures should be obtained and appropriate antibiotics administered for all animals with perineal hernia involving bladder entrapment. Preoperative antibiotics (e.g., cefoxitin used as a single agent) are recommended for protection against contamination by enteric coliforms.

Several techniques for perineal hernia repair have been reported, including standard herniorrhaphy, transposition of the superficial gluteal muscle, an internal obturator transposition technique, a combination of the gluteal and obturator muscle transpositions, and a special technique in which small intestinal submucosa is used to repair the defect.[19,25–28] The reader is referred to a surgical text for a detailed description of the specific surgical techniques used in herniorrhaphy. Traditional hernia repair involves closure of the triangular area formed by the external anal sphincter, levator ani, coccygeus, and obturator muscles. However, with this method of repair, the rate of hernia recurrence is high (10% to 45%), and postoperative complications are common.[27]

The current standard for repair is the obturator transposition technique because of its much lower rate of recurrence and lower complication rate. The use of porcine small intestinal submucosa as a biomaterial for perineal herniorrhaphy is relatively new and has shown promise both as a primary means of repair and as an augmentation technique when the internal obturator muscle is weak or when a salvage procedure is required.[19,28] Other surgical procedures that may be required in the repair of this disorder include repair of diverticuli or rectal deviations, removal of prostatic cysts and, in cats with megacolon, a subtotal colectomy. Castration is recommended but is not an essential aspect of treatment, especially if the length of the procedure increases the risk for an older dog.

After surgery, a highly digestible (low residue) diet and stool softeners should be provided indefinitely to prevent straining and recurrence. Local perineal swelling is common and resolves with application of hot compresses. In dogs for which surgical repair is not possible, the treatment approach is to reduce fecal volume, impaction, and straining by feeding a low-residue diet and administering stool softeners, laxatives (e.g., lactulose), and enemas as needed. In most cases, dietary and conservative management of hernias is not rewarding in the long term.

224.4.1.4 Prognosis

In general, the prognosis for long-term repair of perineal hernias is guarded. The rates of recurrence are related to the type of surgical repair done and the skill of the surgeon. Most surgeons agree that the obturator transposition technique, combined with one of the other approaches, is the best surgical option currently available.[19,26,28] However, the more severe the preoperative clinical signs, the longer the signs have been present, and the existence of bilateral involvement all increase the likelihood of a higher recurrence rate, regardless of the technique used. Other postoperative complications include infection, seroma or hematoma formation, fecal incontinence, rectal prolapse (especially if a bilateral repair is required), sciatic nerve paralysis or sciatic pain, and urinary complications, including incontinence or obstruction (caused by sutures in or scarring of the urethra).[18,19]

224.4.2 Rectal Tumors

Tumors of the intestine, which are uncommon in dogs and cats, represent fewer than 1% of all malignancies reported.[29] In dogs, rectal or colonic adenocarcinoma is the most common malignant intestinal tumor, whereas adenomatous polyps of the rectum are the most common benign tumor.[29] Lymphoma is the most common intestinal tumor of cats, and although it occurs more frequently in the small intestine, colorectal lymphoma is the most common large bowel tumor of cats.[29] Lymphosarcoma of the rectum is less common in dogs than in cats, but it is more prevalent than colonic lymphosarcoma. Siamese cats are reported to have a higher incidence of intestinal (including colonic) adenocarcinoma, but in one study, domestic shorthair cats had a higher frequency of rectal adenocarcinoma than Siamese cats.[29,30] Other rectal tumor types that have been reported include leiomyoma, leiomyosarcoma, plasmacytoma, and fibrosarcoma.[29–33] Polyps that occur in the rectum are generally focal, pedunculated, or sessile and rarely metastasize, although they can in some instances invade locally into the lamina propria and submucosa.[1,29,34] In dogs, locally invasive polyps, although histologically benign, are referred to as *carcinoma in situ*.[29]

224.4.2.1 History and Physical Examination

The signalment of dogs and cats affected with rectal tumors is typical in that older dogs (mean, 9 years of age) and cats (mean, 10 years of age) are more likely to be affected.[29] In dogs the incidence is higher in males, whereas in cats the opposite is true.[29,35] Breeds predisposed to the development of intestinal cancers include boxers, collies, and German shepherds, and this appears to be true for rectal tumors as well.[29] The clinical signs seen in animals with rectal tumors include hematochezia, mucoid feces, tenesmus, and dyschezia of varying severity. Other clinical signs may be observed (e.g., weight loss, inappetence), depending on the tumor type, location, and behavior.

A digital rectal examination may reveal a prominent mucosal mass, narrowing of the rectal lumen, pain during the examination, or blood on the gloved finger. Rectal adenocarcinomas may have either a prominent mass or a stenotic annular ring lesion that encircles the rectum. If significant obstruction is present, colonic distention may be detected on abdominal palpation due to persistent constipation or incomplete evacuation of the bowel. Conversely, in animals with persistent straining, rectal prolapse may occur.

224.4.2.2 Diagnosis

Palpation of a rectal mass or annular ring stricture in a dog or cat with a typical signalment and clinical signs is often suggestive; however, biopsy of the affected tissue, either using proctoscopy or by direct visualization, is necessary to make the definitive diagnosis. In most cases a mucosal tissue biopsy is adequate for analysis; however, in some submucosal tumors (e.g., lymphosarcoma, leiomyosarcoma), an excisional biopsy or collection of deeper tissues is required. Radiography and ultrasound examination of the region and drainage of lymph nodes are very helpful for defining the depth of the lesion and staging the extent of metastasis.

224.4.2.3 Therapy

For all tumors of the rectum except lymphosarcoma, surgical excision of the cancer is the recommended initial course of action, because this provides patient relief and debulks the tumor mass.[29,35] For dogs with rectal lymphosarcoma, treatment with standard chemotherapy protocols is initiated unless a mass is obstructing the rectum and debulking is necessary.[29]

Radiation therapy, cryosurgery, and laser therapy have all been used to treat colorectal tumors after surgical excision, with variable success.[36–39] Electrosurgery or cryosurgery is recommended for dogs with nonannular masses or polyps that can be easily prolapsed. Full-thickness resection of annular rectal cancers can be attempted, but wound dehiscence, infection, rectal stricture, and fecal incontinence are common complications.

More recently, local excision combined with cryosurgery has been used to extend the life of affected dogs significantly; however, the complication rate (e.g., for strictures, prolapse, and perineal hernia) is still high (82%).[36] As an alternative, high-dose radiotherapy has been reported to be an effective form of treatment for distal rectal adenocarcinomas that can be completely prolapsed through the anal opening. Polyps and carcinoma in situ are generally easily excised or treated with cryosurgery or electrocautery, with good to excellent postsurgical results and few recurrences.[29,34] Preliminary work suggests that treatment of dogs with rectal tubulopapillary polyps using piroxicam is also effective.[40]

224.4.2.4 Prognosis

The prognosis for rectal polyps, carcinoma in situ, leiomyoma, and fibroma is generally good; postoperative complications are few, and the recurrence rate is low. Adenocarcinoma, lymphosarcoma, and plasmacytomas all tend to recur, and because of their aggressive nature, treatment with surgery or other means may lead to secondary complications.[29] Annular colorectal adenocarcinoma is a particularly aggressive tumor and is often associated with a very poor prognosis (e.g., mean survival of 1 to 2 months)

because of the complications of treatment, secondary effects (e.g., constipation), and recurrence (e.g., due to difficulty in removing all of the tumor).[29,39]

224.4.3 Rectal Prolapse

Rectal prolapse is defined as eversion or prolapse of the rectum through the anal opening. A prolapse can be partial or complete; a *partial prolapse* involves a protrusion of the rectal mucosa, whereas a *complete prolapse* involves the entire rectum and may include part of the anus as well.

224.4.3.1 History and Physical Examination

Rectal prolapse shows no breed, age, or gender predisposition in dogs or cats. However, it is more prevalent in young animals with typhilitis or proctitis secondary to endoparasites.[1] Manx cats with neurologic dysfunction of the anorectum also appear to have a higher predilection for the condition.[19] Other factors that increase tenesmus and are associated with an increased risk of rectal prolapse include rectal polyps or neoplasia, rectal deviation, dystocia, urolithiasis, prostatic disease, and colonic or rectal foreign bodies.[1,19,41] Rectal prolapse has also been reported as a sequela of perineal urethrostomy in the cat.[42] The diagnosis is made by finding the everted, edematous, and hyperemic prolapsed rectal tissue. In longstanding cases of rectal prolapse, the tissues may be ulcerated and necrotic. A complete rectal prolapse typically appears as a cylindrical mass with a depression at the end, which represents the bowel lumen. The mass usually is sensitive or painful to the touch (Figure 224-4).

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224.4.3.2 Diagnosis

Although a diagnosis of rectal prolapse is made by finding the everted rectal tissue on physical examination, the condition must be distinguished from a small or large intestinal intussusception, which can cause similar presenting signs and can have a similar physical appearance. The easiest way to differentiate the two is to pass a well-lubricated, blunt probe between the rectal wall and the prolapsed tissue. With a rectal prolapse, the probe cannot pass between the tissues because the everted rectal tissue converges with the mucocutaneous junction of the anus.[1,14] Intussusception is also typically associated with signs of intestinal obstruction (e.g., vomiting, anorexia), whereas a rectal prolapse is not associated with systemic signs. Anal prolapse must also be distinguished from rectal prolapse; however, in most cases anal prolapse is not associated with a large amount of protruding mucosa and may appear to worsen after defecation. Most cases of anal prolapse are self-limiting and temporary, and the condition frequently occurs secondary to repair of a perianal hernia.

Figure 224-4 Complete rectal prolapse in a cat with colorectal adenocarcinoma and severe tenesmus.

224.4.3.3 Pathogenesis

Dyschezia and tenesmus are common signs of rectoanal disease, yet concurrent development of rectal prolapse is uncommon. This suggests that an individual predisposition probably contributes to the development of a prolapse; such predispositions may include weakness of the perirectal and perianal connective tissues or musculature or uncoordinated peristaltic contractions of the rectum in association with rectal or anal inflammation.[1,43] However, no carefully conducted studies have been done that further evaluate these possible connections.

224.4.3.4 Therapy

The first goal of treatment is to identify and eliminate, if possible, any underlying causes of the prolapse. If the prolapsed tissue is healthy and the amount of exposed mucosa is minimal, a conservative treatment approach can be used. This technique involves rehydrating the tissue with a warm isotonic saline solution, followed by application of a watersoluble gel lubricant, gentle massage and manipulation to reduce edema, and gentle but immediate attempts to reduce the prolapsed tissue. If this regimen is successful, a loose purse-string perianal suture (enough to allow passage of soft feces) is placed to prevent recurrence. Postoperative straining can be prevented by administration of a narcotic epidural or topical anesthetic drops. Adjunctive therapy includes feeding a highly digestible diet and administration of a stool softener or laxative for 2 to 3 weeks. The purse-string suture can be removed in 2 to 3 weeks, once the underlying problem has been corrected.

If conservative therapy fails, a colopexy procedure, to fix the rectum and colon in place, is indicated.[43,44] This procedure places a slight amount of cranial traction on the descending colon, because four to six nonabsorbable mattress sutures are placed in the descending colon, which is attached to the left abdominal wall. If the rectal or colonic tissue is devitalized, lacerated, or irreducible, it must be amputated in conjunction with a full-thickness anastomosis of the remaining rectal segments.[43,44] Postoperative management of these animals is the same as the conservative management of rectal prolapse: a purse-string suture is placed to reduce the possibility of recurrence, a low-residue diet is fed to reduce stool volume, and stool softeners are given for 2 to 3 weeks to keep feces soft and able to pass through the purse-string opening.

224.4.3.5 Prognosis

The prognosis for the first rectal prolapse episode or for animals with a partial prolapse is generally good. Animals with a complete prolapse or recurrence after conservative therapy often require a colopexy and have a guarded to good long-term prognosis. The prognosis for patients that require amputation of the prolapsed tissue is more guarded because of the technical demands of the surgery, the great potential for leakage and infection during the postoperative period, and the increased risk of development of a rectal stricture.[14,43]

224.4.4 Rectal or Anal Stricture

Rectal or anal strictures cause narrowing of the lumen due to scar tissue that forms as a result of rectal inflammation, rectal trauma (from injury or surgery), or proliferative neoplastic disease in the rectum. The clinical picture (e.g., constipation, dyschezia, and, ultimately, vomiting or anorexia) is indistinguishable from that presented by extraluminal narrowing of the colon due to neoplasia, prostatic disease, or pelvic fracture.

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224.4.4.1 History and Physical Examination

The typical history is an older dog that has chronic constipation or progressively more difficulty defecating. Affected dogs have persistent tenesmus, prolonged posturing to defecate, and frequent attempts to defecate, with only a narrow ribbon of feces or no feces produced.[14] If concurrent colorectal inflammatory or neoplastic disease is present, hematochezia, mucoid feces, or diarrhea may be observed. As the duration

and severity of the obstruction worsen, other systemic signs may be observed (e.g., lethargy, anorexia, vomiting, weight loss). Several conditions can predispose dogs to the development of a rectal stricture, including recent rectal or anal surgery, chronic rectal or anal inflammation, rectal neoplasia, and ingestion of foreign material that causes rectal trauma as it is passed.

Digital rectal examination is sufficient to identify a narrow and often very tight rectal or anal opening (Figure 224-5). Benign strictures are firm, thick, annular fibrotic bands that must be differentiated from neoplastic strictures, which tend to be asymmetric, masslike formations. However, annular rectal adenocarcinoma cannot be distinguished from a benign fibrotic stricture by palpation alone. The only other physical abnormality found in dogs with rectal stricture is an enlarged colon with hard or impacted feces.

224.4.4.2 Diagnosis

In most dogs, the history and physical examination are sufficient to identify a stricture. The key aspect of diagnosis is determining whether the stricture is malignant or benign. Radiographs and ultrasound scans of the abdomen and pelvis are important, because they rule out other causes of constipation/obstipation, such as pelvic fractures, prostatomegaly, and abdominal masses that affect the colon or sublumbar lymphadenopathy. Contrast radiography is not usually necessary to make a diagnosis of stricture, but it may be helpful for determining the extent of the stricture if the opening is too narrow for physical analysis. Rectal probe ultrasonography can be used to determine the extent of rectal involvement or to detect other lesions. Ultimately, however, biopsy is necessary to determine whether the lesion is benign or malignant. Biopsy of tissue can be obtained through rigid proctoscopy, flexible endoscopy, or direct visualization by prolapse of the affected rectal tissues. A major limitation on the use of either a rigid or a flexible scope to obtain biopsy specimens is that passage of the scope and distention of the rectum (for visualization) often is impossible. In such cases, direct prolapse or surgical biopsies must be obtained.

Figure 224-5 Severe rectal stricture identified on digital rectal examination.

224.4.4.3 Therapy

Previously, rectal strictures were managed by surgical techniques, such as rectal pull-through or rectal myotomy procedures.[14] More recently, bougienage and balloon dilatation techniques have gained favor, because when performed properly, they are often successful in dilating the stricture site without incurring the severe complications that frequently accompany surgical correction (e.g., fecal incontinence, infection, dehiscence, or restricture).[14] To facilitate appropriate visualization and comfort for these procedures, the dog or cat should be anesthetized, and if possible the procedure should be done with endoscopic or fluoroscopic assistance.

For bougienage of rectal strictures, a metal bougie of increasing size (over several separate but successive procedures) is passed into the stricture site and advanced slowly, stretching the fibrous tissue without causing significant tearing, which tends to increase inflammation and the likelihood of restricture.

Like esophageal strictures, rectal strictures also can be successfully dilated using balloon dilatation techniques, and this approach is frequently preferred over bougienage. The diameter of the balloon and the number of dilatations required to achieve a sustained opening in the rectal lumen are quite variable, but chronic strictures in larger animals may require several procedures to achieve functional success. In general, for small dogs (less than 7 kg) and cats, balloons with a diameter of 10 to 15 mm are used; for medium-sized dogs, the balloon diameter is 20 to 30 mm; and for large dogs (greater than 16 kg), it is 30 to 40 mm.[14] These numbers are guidelines, because animals with severe rectal strictures may require much smaller balloons for the initial procedure to prevent excessive tissue tearing. In dogs with recent strictures or those without excessive fibrosis, one or two dilatation procedures 4 to 5 days apart may be all that is required to dilate the affected tissue successfully. However, when rectal wall thickening is present or the reduction in the lumen is greater than 75%, four to six dilatation procedures may be required to achieve functional success.[14] The purpose of performing multiple procedures several days apart (but no more than 7 days) is to increase the diameter of the stricture waist gradually, without excessive tearing or inflammation; this gradual approach reduces the likelihood of restricture (which tends to occur in 7 to 10 days).[14] Careful visualization of the procedure ensures that tearing and hemorrhage are kept to a minimum and reduces the risk of deep tears or significant hemorrhage, which increase the likelihood of restricture or rectal perforation. Adjunct therapy should include administration of broad-spectrum antibiotics, a highly digestible (low-residue) diet, and use of lactulose or stool softeners to maintain a soft fecal consistency. The use of corticosteroids to reduce the occurrence of restricture has not been studied, and such therapy should be undertaken cautiously if rectal tears or bacterial contamination is suspected.

224.4.4.4 Prognosis

For most benign rectal strictures, the prognosis is guarded to fair, because balloon procedures may allow return to near normal functionality; however, unless the predisposing cause of the stricture is corrected, it is likely to recur. The risk of severe complications after balloon procedures is lower than for surgical repair techniques, primarily because the risk of inducing fecal incontinence is greatly diminished. The prognosis for all neoplastic strictures is poor, owing both to the difficulty in managing the primary problem and to the poor response to balloon or other management techniques.

224.5 DISEASES OF THE ANUS

224.5.1 Atresia Ani

Atresia ani, a congenital condition that affects the anal opening and rectum, may occur in both puppies and kittens. The several anatomic variations of atresia ani have been classified as types I through IV, but all generally result in an abnormal anal outlet and/or rerouting of feces from the rectum to another outlet.[14,45] Pets with type I, or imperforate anus, have a membrane over the anal opening, but the rectum ends as a blind pouch just cranial to the anal opening. Type II is similar to type I, but the rectal pouch ends much more cranial to the anal opening. In type III, or rectal atresia, the rectum ends in a blind pouch in the abdomen (cranial to the pelvis), and the remaining rectum and anus are normal. Type IV, which occurs only in females and may occur with or without imperforate anus, is characterized by a persistent communication between the rectum and vagina (rectovaginal fistula) or urethra (rectourethral fistula).[45]

224.5.1.1 History and Physical Examination

The clinical signs are often noticed at weaning (4 to 6 weeks) or earlier in affected puppies and kittens. In general, types I, II, and III create similar problems: straining to defecate, bulging of the perineum, absence of feces, no visible anal opening, abdominal distention with palpable fecal material, and abdominal or perineal discomfort.[14] Initially, the puppy or kitten eats and appears to grow, but with increasing fecal distention of the colon, lethargy or restlessness, loss of appetite, and vomiting are noted. Type IV often is associated with tenesmus but is characterized by the passage of small amounts of watery feces via the vagina or urethra, with associated perivulvar erythema and infection.

224.5.1.2 Diagnosis

The diagnosis is based on finding the typical physical abnormalities in a puppy or kitten of appropriate age that has a concurrent history of tenesmus or lack of ability to defecate normally. For type I or II atresia ani, absence of an anal opening is diagnostic. In type III, radiography or ultrasonography may be helpful for defining the end of the rectal pouch. In type IV, the presence of fecal material exiting through the vaginal opening is suggestive.

Another congenital anomaly that may occur in dogs and cats and that can be confused with atresia ani is anogenital cleft. This condition occurs in females and is characterized by continuity of the mucosa of the anus, rectum, and vagina along the perineal midline.[45] A similar anomaly can occur in male cats resulting from a rectourethral cleft, which is a communication that allows a common opening for the rectum and urethra.

224.5.1.3 Therapy

The only treatment available is surgical correction, which may require staged procedures, depending on the type of anomaly present. Type I atresia ani is the simplest to correct, because opening of the anus and ballooning of the stricture may be all that is required in some animals. In animals for which this procedure is unsuccessful, the stenotic segment often must be surgically removed. Types II and III require significant and technically demanding surgical procedures to return functionality. In all three circumstances, fecal

incontinence is a major and often life-threatening complication. Type IV lesions require technically demanding surgery to close the rectal, vaginal, and urethral defects.

224.5.1.4 Prognosis

Regardless of the anomaly, young and weak puppies or kittens often do not survive the procedure. In addition, the prognosis is guarded to poor for complete return of normal anal or rectal function for any type of atresia ani. This is primarily because of the likelihood of injury to the external anal sphincter or its innervation during surgical repair. Another common surgical complication of this procedure is the development of rectal or anal strictures. Also, many affected puppies and kittens have concurrent megacolon, which develops as a result of persistent fecal impaction and which may be irreversible, requiring indefinite aggressive medical management or a subtotal colectomy.

224.5.2 Perianal Fistula

Perianal fistula is a chronic, often debilitating disease of the perianal tissues in dogs characterized by one or, more often, multiple draining tracts surrounding the anus. Anal furunculosis, an alternate descriptor, is typically a progressive disease characterized by ulcerative, painful, malodorous lesions resulting from the associated tissue destruction and infection. In severe cases, the entire anus is surrounded with ulcerative, draining tracts that often lead to fecal incontinence or rectal stricture formation (Figure 224-6). The fistulas usually do not involve the anorectal canal directly; however, typical signs include self-mutilation, dyschezia, and rectal stenosis, resulting in fecal incontinence or constipation.

224.5.2.1 History and Physical Examination

Perianal fistulas occur primarily in older, large breed dogs with a broad-based tail and lower tail carriage, which may create an environment that predisposes these breeds to perianal problems. The two breeds with the highest incidence of perianal fistula are German shepherds and Irish setters, but sheepdogs, retrievers, and spaniels also may develop the disorder.[46–49] No distinct gender or age predilection appears to exist, but the condition is more prevalent in male dogs over 5 years of age.[46,49] Because of the animal's low tail carriage, the disease may not be noticed by the owners until obvious lesions are present or the discharge or odor becomes overpowering. The only abnormality reported by some owners, especially early in the course of the disease, is persistent licking of the anus. Other clinical signs that may be reported include hematochezia, dyschezia, perianal discharge, constipation, and tenesmus. In severely affected dogs, anorexia, weight loss, and behavioral changes may occur as a result of the discomfort.

Physical examination may be difficult, if not impossible, without sedation because the simple act of having the tail lifted is painful to the animal. The examiner may also need to clip the hair and cleanse the area to fully assess the extent of the perianal involvement. Visual inspection reveals multiple, ulcerated, draining tracts that extend into the tissues surrounding the anus. The lesions are often extremely malodorous and, in outdoor dogs, may contain fly maggots. Rectal strictures, abnormal anal tone, or granulomatous rectal mucosa may be found during a digital rectal examination. In addition, in some dogs with perianal fistulas, the anal sacs are involved in the fistulation, which may result in anal sac obstruction or abscessation.

Figure 224-6 Severe fistulating and ulcerative perianal fistula in a German shepherd.

224.5.2.2 Diagnosis

A diagnosis of perianal fistula is usually made based on the combination of typical signalment and history and physical examination findings. Important differentials for this condition include chronic anal sac abscessation with secondary fistulas, aggressive perianal tumors (e.g., adenocarcinoma), caustic injury, and untreated dog bite wounds.[14] A digital rectal examination and probing of the extent of the lesions while the dog is under general anesthesia confirms the diagnosis. Because German shepherds are predisposed to this condition and often have other concurrent colonic or rectal abnormalities, a proctoscopic or colonoscopic examination is also recommended.[48]

224.5.2.3 Pathogenesis

The factor long considered to be the most important contributor to formation of perianal fistulas is anatomic predisposition,[47] including (1) a broad-based tail (e.g., German shepherds), (2) low tail carriage (e.g., Irish setters), and (3) increased density of apocrine sweat glands in the zona cutanea.[47,49] More recently, an immune-mediated basis for the disease has been suggested by clinical trials, which have demonstrated a positive response to prednisone therapy in affected German shepherds.[48] This proposed etiology is further supported by the positive response to treatment seen in clinical trials using azathioprine, cyclosporine, and tacrolimus.[50–54] In humans, food allergy is believed to be a component of the development of perianal fistulas; although this has not been proved in dogs, it may also be a contributing factor in this species. The development and pathogenesis of perianal fistulas likely constitute a multistage process, in which an inflammatory condition sets the stage (e.g., immune-mediated, allergic, or anatomic causes) and is followed

by the development of a secondary bacterial infection that results in severe epidermal ulceration and necrosis.

224.5.2.4 Therapy

The two basic approaches that have been used in the management of perianal fistulas are medical management and surgical excision. In many cases, medical management alone is sufficient for control; however, in severe cases, a combination of medical and surgical treatment often is necessary. Recently, laser surgical excision has met with some success in a limited number of cases; however, as with surgical approaches, fecal incontinence is a potential complication.[19,37,55]

Medical management of perianal fistulas has four components: (1) removal of perineal hair and tissue cleansing, (2) immunosuppressive therapy, (3) antibacterial therapy, and (4) dietary therapy.[19] In one study, a combination of high-dose prednisone (2.2 mg/kg PO2) and dietary therapy using novel antigen diets resulted in complete resolution of signs in one third of the dogs, improvement in another third, and no change in the remaining one third.[48] More recently, immunosuppressive therapy with azathioprine (50 mg/kg every 24 hours PO) or cyclosporine (1 mg/kg every 12 hours PO) has proved effective in controlling (90% had complete resolution within 2 weeks, 50% had no recurrence in 12 months) or reducing disease, whether used alone or in combination with surgical therapy.[50,51,53,54] In another study, the addition of ketoconazole to cyclosporine therapy proved helpful by allowing a dramatic reduction in the cyclosporine dose (by 80% to 90% in all dogs).[50,54] In most dogs, antibacterial therapy with a first-generation cephalosporin is used to control bacteria typically associated with infections of the skin (e.g., staphylococci). The use of novel antigen diets in the management of perianal fistulas in dogs has not been evaluated in a controlled setting, therefore the effectiveness of this aspect of therapy is unknown; however, in one study the use of these diets was helpful.[48]

For dogs with severe perianal fistulas or those who do not respond to medical management alone, surgical or laser surgical excision of the affected tissue is recommended. A variety of surgical procedures may be necessary, including deroofing (removing the skin covering the fistulous tract) followed by electrofulguration (or electrocoagulation), anal sacculectomy, excision or debridement of diseased tissue, rectal pull-through procedures when rectal strictures are involved and, in some cases, tail amputation.[46,49,55] Carbon dioxide (CO_2) laser therapy may be a very effective means of debridement for dogs requiring surgical therapy, because the laser reduces bleeding, pain and postsurgical swelling.[37]

224.5.2.5 Prognosis

The overall prognosis is guarded in dogs with a perianal fistula, even though most methods, whether medical or surgical, have met with some degree of success. The most common complications of surgical approaches are fecal incontinence, rectal stricture, and recurrence. Therefore medical therapy with prednisone and cyclosporine should be used as the first-line approach in the majority of dogs, with surgical palliation kept a last resort.

224.6 DISEASES OF THE ANAL SACS

224.6.1 Impaction, Anal Sacculitis, and Abscessation

Several common infectious or inflammatory diseases affect the anal sacs, including anal sac impaction, anal sacculitis, and abscessation of the anal sacs. These diseases are more common in dogs than cats, affecting up to 12% of the canine population.[56]

224.6.1.1 History and Physical Examination

The most common clinical signs of anal sac disease are anal pruritus or pain, which elicits licking or biting at the tail or anal region, "tail chasing" behavior, scooting or rubbing of the anus on the ground, and reluctance to sit or discomfort when sitting.[14,57] In more severely affected dogs, pain may cause dyschezia, tenesmus, or reluctance to defecate. Dogs with longstanding anal sac disease may develop large swellings in the area over the anal sac, and if the abscessed sac ruptures, a draining fistula will extend from the affected anal sac.

External or internal digital palpation of the anal sacs may be required in some cases to detect diseased or impacted anal sacs. Normal anal sac secretions are liquid, brown, and foul smelling but easily expressed from the sac through the ducts to their openings on the anus.[57,58] In dogs with anal sac impaction, the material often becomes pasty or even dried and may be difficult to express without causing the animal pain. The material present in infected or abscessed anal sacs is often thicker, may be purulent or bloody, and frequently is very malodorous.

224.6.1.2 Diagnosis

In most pets the history of anal pruritus, along with visual inspection of a perianal swelling at either the 4 to 5 o'clock or the 7 to 8 o'clock position lateral to the anus, is highly suggestive. In the absence of significant visible external swelling, a digital rectal examination is sufficient to confirm anal sac involvement. Some dogs and all cats require sedation for safe performance of a rectal examination because of the accompanying discomfort. Impaction of the anal sacs is confirmed by removal of thick, pasty anal sac material or by inability to empty the sacs easily with appropriate technique. If the anal sacs are painful when gently palpated or if the material expressed is purulent or a color other than light tan to brown, anal sacculitis should be suspected. If doubt exists, a sample of the material can be cytologically examined for large numbers of neutrophils, bacteria, or yeast (e.g., *Malassezia* sp.).[58] If the anal sac is infected or abscessed, fever may also be present. The major differentials in dogs and cats with these clinical signs are perianal fistulas, perianal or anal tumors, and bite wounds (cats) or other trauma.

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224.6.1.3 Pathogenesis

The most common cause of inflammation or infection of the anal sac is obstruction of the ducts, which prevents normal (frequent) expulsion of the material and allows bacteria normally present (e.g., *Escherichia coli, Streptococcus faecalis,* and *Clostridium* spp.) to set up a secondary infection.[58] Anatomic conformation also may play an important role in the tendency to develop anal sacculitis or abscessation; for example, smaller than normal ducts or aberrant duct placement on the anus decreases effective emptying.

Other contributing factors may be dogs that produce thicker secretions, the development of abnormal anal tone, the production of soft feces, and recent estrus in females.[57,59]

224.6.1.4 Therapy

Treatment of simple anal sac impaction is straightforward, requiring that the anal sacs be emptied by gentle digital manipulation. If the sacs cannot be easily or completely emptied, they should be gently flushed with warm saline or mineral oil to loosen the concretions and pasty material. Once the sacs are empty, an antibiotic and steroid ointment or solution can be instilled to reduce local infection and inflammation. The sacs should be kept empty for several weeks to prevent recurrence or possible abscessation. In dogs with chronic impaction, the owners can be taught to express the anal sacs at home or, as an alternative, the anal sacs can be surgically removed.

Dogs with anal sacculitis or abscessed anal sacs must also have the sacs emptied, but because of the associated discomfort, sedation or anesthesia is usually required. In dogs with anal sacculitis alone, the sacs should be gently flushed with an antiseptic solution (e.g., dilute [0.5%] chlorhexidine) and antibiotic solution instilled into the sacs. Broad-spectrum oral antibiotic therapy is recommended for 10 to 14 days, along with application of hot compresses to reduce swelling and pain and frequent anal sac expression. In most cases managed this way, the infection resolves completely, and further therapy is not necessary. However, for dogs that have frequent recurrence of anal sacculitis, anal sac removal should be considered.[60–62]

Abscessation of the anal sacs is managed as is other abscessed tissue: the abscess must be surgically opened, flushed, and debrided. This procedure should be repeated daily for 2 to 4 days to help keep the area open and draining and to help remove any additional material that forms in the sacs. A broad-spectrum antibiotic should be administered for 10 to 14 days. Application of hot compresses several times daily for 3 to 5 days also helps reduce the swelling and pain. Surgical removal of the abscessed anal sac is not recommended unless there is recurrence after appropriate treatment. In addition, the surgery should not be performed until antibiotic therapy has been administered long enough to ensure tissue healing. Anal sac removal is recommended when all other options fail, primarily because of the risk of complications, especially fecal incontinence. A recent retrospective report revealed that closed anal sacculectomy procedures were 13 times less likely to have postoperative complications compared with open techniques,[60] which makes the closed approach considerably more viable.

224.6.1.5 Prognosis

The prognosis for anal sac impactions and anal sacculitis is generally good, because these cases typically respond completely to conservative medical management. Most dogs and cats with anal sac abscesses also respond well to aggressive medical management of the infection; however, because these conditions may be more difficult to treat or may recur, surgical anal sac removal may be required. The prognosis for animals requiring anal sacculectomy is guarded to good, depending on the technique used and the surgeon's skill. The primary risk postoperatively is the development of fecal incontinence, especially in older dogs that have reduced anal sphincter tone or function.

224.6.2 Anal Sac, Anal, and Perianal Tumors

Tumors of the anus and perianal integument are relatively uncommon in dogs, and their clinical importance can vary widely. These tumors can range from the benign perianal gland adenoma of older intact male dogs to the malignant perianal gland adenocarcinoma that is most common in older intact or spayed female dogs.[63,64] Anal sac adenocarcinomas and perianal gland tumors are reported primarily in dogs, although a Siamese cat with an anal sac adenocarcinoma recently was reported.[65] Other anal and perianal tumors can occur in cats and dogs but are extremely uncommon. These tumors include perianal adenocarcinoma, squamous cell carcinoma, and melanoma.[64] Large breed dogs, especially German shepherds and Alaskan huskies, appear to be predisposed to the development of perianal adenocarcinomas.[64]

224.6.2.1 History and Physical Examination

The typical history of a dog with an anal sac adenocarcinoma is an older (greater than 10 years) female dog with dyschezia or perineal swelling. However, male dogs are occasionally affected, and the tumor can occur in younger dogs without an identifiable external swelling. This aspect of the disease illustrates the importance of a digital rectal examination as part of a complete physical examination, even in female dogs without clinical signs of tenesmus, dyschezia, or hematochezia. In dogs with paraneoplastic hypercalcemia of malignancy, a common complication of this tumor, the owner may also note polyuria, polydipsia, muscle weakness, or vomiting. Tumors of the anal sac are detected by careful palpation of the anal sac and its associated structures. Most of these tumors are unilateral, and they may be quite small (0.2 to 1 cm), which is why the examination must be performed carefully.[64] With few exceptions, these tumors, regardless of their size, have metastasized to the external iliac (sublumbar) lymph nodes by the time of the examination.[66] Other sites of metastasis include the liver, spleen, abdominal lymph nodes, and lungs. Most hypercalcemic animals become systemically ill, which suggests the need for a complete hematologic and biochemical evaluation; however, all hypercalcemic animals should have a thorough digital rectal examination initially to rule out anal sac adenocarcinoma.

The benign perianal gland tumors (circumanal gland, or hepatoid, adenomas) affect all breeds of dogs, but cocker spaniels, bulldogs, beagles, and Samoyeds appear to be over-represented.[64] Because these tumors develop and grow under the influence of plasma androgens, more than 85% of them are found in older intact male dogs. In most dogs, the tumor is visible in the perianal integument, but it can be found in a variety of sites, including the prepuce, inguinal region, or ventral tail skin.[64] The tumors are usually firm, single, nodular masses of variable size. They can ulcerate, bleed, necrose, or cause intense pruritus of the anal region that may lead to difficulty in defecation, scooting, and other signs of anal disease.

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224.6.2.2 Diagnosis and Pathophysiology

Diagnosis of benign perianal tumors is based on the finding of a mass in an intact male dog with the typical signalment and history and physical examination findings. The diagnosis is confirmed by fine needle aspiration cytology or excisional biopsy. The main differences between malignant perianal tumors and their benign counterparts are that the malignant tumors are not influenced by androgens, they behave more like anal sac adenocarcinomas (e.g., have metastasized by the time of diagnosis), and they are difficult to excise completely because of their location, rapid spread, and local infiltration.[64]

A presumptive diagnosis of an anal sac adenocarcinoma, based on the history and physical examination findings and with or without concurrent hypercalcemia, should be followed by histopathologic confirmation. In addition to diagnosis of the tumor, the evaluation should include a thorough systemic examination, including a complete blood count, serum biochemistry profile, urinalysis, and survey radiographs of the chest and abdomen to assess for tumor metastasis and paraneoplastic effects. Abdominal ultrasonography is also frequently used to assess the size and involvement of abdominal lymph nodes or the liver, because metastasis has occurred in greater than 50% of affected dogs by the time of diagnosis.[66] Humoral hypercalcemia of malignancy is present in 50% to 90% of dogs with anal sac adenocarcinoma. The molecular basis for the development of these anomalies is not completely understood, but the tumor results in expression of a gene for parathyroid hormone–related peptide (PTH–rP), which has functions similar to that of naturally occurring parathyroid hormone.[63,64] In some cases, the hypercalcemia may be severe enough to lead to multiple organ dysfunction. After complete removal of the tumor, hypercalcemia may resolve; however, hypercalcemia persists in dogs with metastatic disease or incomplete removal of the anal sac tumor.

224.6.2.3 Therapy and Prognosis

Castration and removal of the primary tumor by surgical excision or cryotherapy constitute the treatment of choice for perianal gland adenomas.[64] It is a more difficult procedure for large tumors and in those cases is more frequently associated with postoperative side effects (e.g., wound dehiscence, fecal incontinence, and hernia). In general, benign perianal gland tumors are slow growing; consequently, they are effectively treated with surgical excision, cryosurgery, electrocautery, and laser surgery, and they rarely recur (rate is less than 10%). The long-term prognosis is excellent except in cases of large tumors that cannot be completely excised.

Malignant perianal tumors are rapid growing, do not regress after castration, and because of their rapid metastasis are often not completely removed by surgical excision. For both perianal and anal sac adenocarcinomas, aggressive surgical removal with adequate margins, along with excision of regional lymph nodes, is recommended.[64] Despite aggressive surgical approaches, a local recurrence rate of 50% is reported for female dogs with adenocarcinoma.[64] Some oncologists suggest combination therapy, comprising surgical removal followed by platinum or doxorubicin chemotherapy to further control metastasis and local recurrence. Intraoperative irradiation of regional lymph nodes has proved successful at stopping metastasis in a limited number of cases.[64]

Nevertheless, the average survival of dogs with anal sac adenocarcinoma is reported to be 8 months (range, 2 to 39 weeks).[60,64] If the tumor is discovered early, before metastasis, and is completely excised, the prognosis is good. The prognosis for smaller tumors is slightly better (e.g., fair) than for those greater than 5 cm, because the surgery is more effective and is associated with fewer complications. With large tumors, tumors with obvious metastasis, or concurrent hypercalcemia, the long-term prognosis is poor (survival rate of less than 40% at 1 year).

224.6.3 Fecal Incontinence

Fecal incontinence is defined as the inability to control defecation and retain feces until voluntary, conscious defecation is initiated.[14] Animals with fecal incontinence pass feces involuntarily and are often euthanized

because of the difficult social issues that result. Fecal incontinence can be caused by neurologic disorders that affect function of the anal sphincter, primary disorders of the external anal sphincter (e.g., non-neurogenic sphincter disorders), or diseases that affect the normal reservoir function of the colon or rectum (e.g., reservoir incontinence) (Box 224-2).[14] In general, animals with sphincter incontinence have more severe signs (e.g., lack of conscious posture to defecate, uncontrolled passage of feces) and are likely to be irreversibly affected. Animals with severe inflammatory disease may also have loss of voluntary control of defecation as a result of urgency to defecate, tenesmus, or hematochezia, but the problem may resolve with appropriate treatment of the disease.

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224.6.3.1

Box • 224-2 Causes of Fecal Incontinence

224.6.3.1.1

Neurologic Disease

Sacral spinal cord

Congenital vertebral malformation

Meningomyelocele

Sacrococcygeal hypoplasia of Manx cats

Sacral fracture

Sacrococcygeal subluxation

Lumbosacral instability

Viral meningomyelitis

Discospondylitis

Degenerative myelopathy

Neoplasia

Peripheral neuropathy

Trauma

Repair of perineal hernia

Perianal urethrostomy

Penetrating wounds

Dysautonomia

Hypothyroidism

Diabetes mellitus

224.6.3.1.2 Non-Neurologic Disease

Colorectal causes

Inflammatory bowel disease

Neoplasia

Constipation

Anorectal causes

Trauma

Surgery (anal sac, perineal hernia, rectal resection)

Perianal fistula

Neoplasia

Miscellaneous causes

Severe diarrhea

Irritable bowel syndrome

Decreased mentation

Old age

224.6.3.2 History and Physical Examination

Determination of the cause of fecal incontinence requires a careful, complete history. In particular, it is important to distinguish fecal incontinence from urgency to defecate. Furthermore, the mere presence of fecal material accumulating around the anus must be distinguished from lack of ability to control the anal sphincter and fecal dribbling. Examples of diseases or circumstances that may damage nerves or muscles and lead to fecal incontinence include previous spinal cord disease, pelvic trauma, dystocia, chronic constipation, and anorectal surgery.[14] Animals with frequent, conscious defecation associated with normal posturing usually have normal anal sphincter and nerve function but may have incontinence as a result of loss of reservoir function. The most common causes of reservoir dysfunction are inflammatory, infectious, and neoplastic diseases of the colon, rectum, or anus that cause decreased compliance and abnormal motility. Severe large bowel diarrhea secondary to colonic inflammation can cause fecal incontinence for the same reason. In most animals with neurogenic or non-neurogenic sphincter incontinence, the fecal stream is normal. Furthermore, in animals with neurogenic sphincter incontinence, abnormal micturition often occurs concurrently because of the common neural pathways.[4] The urinary abnormalities may include dribbling urine, incomplete voiding, or inability to void, and when these occur in conjunction with fecal incontinence, neurologic dysfunction should be strongly considered.

The physical examination should include careful inspection of the perineum for evidence of abscesses, fistulas, hernias, masses, or other abnormalities. After the visual inspection, a digital rectal examination is performed to assess for normal anal sphincter tone, fecal impaction, strictures, or masses. Abdominal palpation is necessary to determine the presence of colonic impaction, as well as bladder size and expressibility. A distended, flaccid bladder from which urine is easily expressed is consistent with a lesion of the sacral spinal cord, the sacral nerves, or the pudendal nerve.[4] A complete neurologic examination, including observation of gait and posture, evaluation of myotactic and postural responses, and assessment of lumbosacral pain, is required in any animal suspected of having fecal incontinence. The neurologic deficits that may be present in dogs with neurogenic sphincter incontinence are abnormal posture, hindlimb gait abnormalities, decreased myotactic reflexes, or an abnormal pudendal (anal) reflex.[67] The anal reflex, which is a measure of perianal sensation and sacral spinal cord function (via the pudendal nerve), is tested by pinching the perianal skin, which results in an immediate contraction of the anal sphincter. This reflex should be present on both the right and left sides of the anus. The pudendal-anal reflex (bulbocavernosus reflex) is tested by squeezing the penis or vulva while observing for normal anal contraction. Lesions of the perineal afferent nerves, the sacral spinal cord, or the pudendal efferent nerves can decrease or abolish these reflexes and cause a dilated anus, loss of perineal sensation, and a loss of micturition control.[67]

224.6.3.3 Diagnosis

When loss of colorectal reservoir function is suspected, the diagnostic plan should include an examination of the fecal stream (e.g., fecal floatation, cytology) and proctoscopy or colonoscopy with biopsy to identify the primary disease. If signs of systemic disease are also detected, further evaluation (e.g., hematology, serum chemistries, radiographs, ultrasonography) is warranted as indicated. Sphincter incontinence (either neurogenic or non-neurogenic) is usually apparent from the history and physical examination. Neurogenic and non-neurogenic dysfunction are differentiated by neurologic examination. If further confirmation is necessary, anal sphincter electromyography or monometry is used to prove sphincter incompetence; however, this is rarely necessary and not universally available. When lesions of the lumbar spinal cord or the cauda equina are suspected, vertebral radiographs, myelography, computed tomography, magnetic resonance imaging, or cerebral spinal fluid analysis may be indicated.[67] The causes of fecal incontinence are listed in Box 224-2.

224.6.3.4 Pathophysiology

Control of fecal continence is maintained by the muscles of internal and external anal sphincters, the rectum, and the coccygeus and levator ani muscles of the pelvis, which are innervated by the pelvic, hypogastric, pudendal, and sacral nerves.[4,67] Both motor and sensory impulses are integrated into the sacral spinal cord to coordinate normal fecal continence. The non-neurogenic causes of sphincter incontinence are usually due to reservoir incontinence (e.g., colitis, neoplasia) or to trauma to the anorectal muscles (e.g., surgery, hernia, fistula, neoplasia) (see Box 224-2).[14]

224.6.3.5 Therapy and Prognosis

The treatment of fecal incontinence depends entirely on the primary cause; for example, loss of reservoir function due to colitis often resolves completely with appropriate treatment, whereas loss of neurologic function is permanent and rarely treatable. Some forms of non-neurogenic incontinence are transient (e.g.,

postoperative complication, trauma), and some forms of neurogenic incontinence may improve after specific treatment (e.g., spinal surgery to reduce compression or subluxation). However, in these cases no specific drugs or diets are particularly effective. Highly digestible diets may be beneficial, because they reduce the volume of fecal material. Enemas and exercise may stimulate defecation at desired times and can be used to help control the social unacceptability of the problem.[68] A surgical technique using an implanted Silastic sling, and placement of an autogenous muscle graft to augment the muscles of continence, have been described, but the success rates for these procedures are not satisfactory.[69] Recently, a technique to create a new sphincter using muscle transplants has shown promise for providing a functional stomal sphincter in dogs with chronic fecal incontinence.[70] Nevertheless, in many pets euthanasia is chosen because in most cases the prognosis is poor for return to normal or acceptable sphincter function.

224.7 REFERENCES

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225 CHAPTER • 225 History, Clinical Signs, and Physical Findings in Hepatobiliary Disease

Cynthia R.L. Webster

The liver plays a central role in a diverse array of processes including carbohydrate, lipid, and protein metabolism; detoxification of metabolites and xenobiotics; storage of vitamins, trace metals, fat and glycogen; fat digestion; and immunoregulation. The clinical signs, physical findings, and clinicopathologic abnormalities that accompany hepatic disease reflect deficiencies in these varied functions. The liver, however, has a tremendous reserve capacity to perform these functions. Thus the appearance of relatively specific signs of hepatobiliary disease such as icterus, hypoglycemia, bleeding tendencies, hepatic encephalopathy (HE), or ascites, which reflect exhaustion of the liver's functional reserves, occur only late in disease progression. Early clinical signs of hepatic disease, such as intermittent anorexia, polyuria/polydipsia (PU/PD), vomiting, and lethargy, mimic those seen with disease in other organ systems. In most cases, early detection of hepatobiliary disease relies on clinicopathologic evaluation and histopathologic examination of hepatic tissue.[1]

Although most early signs of liver disease are nonspecific, several clues should raise one's awareness as to the presence of hepatobiliary disease; these include strong breed predispositions and the occurrence of several clinical recognizable syndromes that accompany hepatobiliary disease, including gastrointestinal (GI) ulceration, HE, tissue jaundice, coagulopathies, and ascites.

Several breed predispositions occur in hepatobiliary disease. Congenital portosystemic vascular anomalies (PSVASs) are most frequent in purebred dogs particularly Irish wolfhounds, Australian cattle dogs, Maltese terriers, Cairn terriers, miniature schnauzers, Yorkshire terriers, dachshunds, Labrador retrievers, and golden retrievers. Feline PSVASs occur most often in mixed breed cats, but Persians and Himalayans are over-represented. Bedlington terriers have a congenital abnormality in hepatic copper metabolism that results in hepatic copper overload and subsequent development of chronic inflammatory hepatobiliary disease. Less well-defined copper-associated hepatopathies occur in West Highland white terriers, dalmatians, Skye terriers, and Siamese cats. Several breeds have a predisposition to develop idiopathic chronic inflammatory hepatobiliary disease, including Doberman pinschers, American and English cocker spaniels, standard poodles, and Labrador retrievers. Hepatic amyloidosis occurs in Chinese Shar Pei dogs and in Abyssinian, Oriental, and Siamese cats.

Historical findings that suggest the presence of hepatobiliary disease include recent ingestion of a known hepatotoxic substance or treatment with a potentially hepatotoxic drug.[2] Stunted growth or anesthesia or drug intolerance (or a combination of these factors) in a young animal, particularly in a predisposed breed, suggests the presence of PSVASs. A recently stressed obese cat that becomes anorexic is a classic historical example of a cat with idiopathic hepatic lipidosis.

The clinical signs associated with hepatobiliary disease are typically referable to the GI, renal, neurologic, or hematopoietic systems (Table 225-1). In addition, a rare dermatologic syndrome called *superficial necrolytic dermatitis* marked by ulcerative crusting dermatitis of the face and distal extremities, accompanies a unique form of chronic liver disease in the dog (hepatocutaneous syndrome).

Intermittent GI signs such as diarrhea, anorexia, and vomiting, are common signs of hepatobiliary disease. Chronic hepatic disease predisposes dogs to gastroduodenal ulceration, so a myriad of clinical signs referable to ulcer disease, such as hematemesis, abdominal pain, and melena, should prompt consideration of an underlying hepatopathy.

HE is neurologic condition associated with failure of the liver to detoxify inhibitory neurotoxins generated in the intestinal tract. The clinical signs are those of diffuse cerebral disease. HE is most often seen with PSVASs or with hepatopathies associated with acquired portosystemic shunts, but may also accompany acute fulminant hepatic failure. In acute failure the neurologic signs of HE can be confused with those associated with hypoglycemia. Either or both problems commonly accompany severe acute hepatic failure. Cerebral edema, an ominous consequence of fulminant hepatic failure, can also cause neurologic signs mimicking HE. These signs include disorientation, stupor, and coma.

An important differential for the presence of abdominal fluid accumulation is hepatobiliary disease. Chronic liver disease, particularly in the dog, can be associated with the development of ascites secondary to the presence of portal hypertension. Portal hypertension develops either due to capillarization of the hepatic sinusoidal endothelium from fibrosis, increased hepatic blood flow such as occurs with arteriovenous fistula, or is secondary to disease or obstruction of the portal vein or its tributaries. Ascites may accompany primary or metastatic hepatobiliary disease or can signal the presence of bile peritonitis from rupture of the biliary tract.

A highly variable, but often predominant, early clinical sign in many dogs and cats with chronic hepatobiliary disease or PSVASs is the presence of polyuria, polydipsia, or both. The mechanism for the polyuria and polydipsia is unknown, but the following six have been hypothesized[3]: (1) psychogenic polydipsia, (2) alterations in portal vein osmoreceptors, (3) decreased hepatic urea production resulting in disruption of the renal medullary concentration gradient, (4) potassium depletion, (5) stimulation of thirst centers due to HE, and (6) increased endogenous cortisol levels associated with increased adrenal production or decreased hepatic degradation.

Animals with hepatobiliary disease may also have signs referable to ammonium biurate urolithiasis such as stranguria, pollakiuria, or hematuria. Ammonia biurate stones form secondary due to chronic hyperammonemia and decreased hepatic processing of uric acid.

The most significant physical finding that should prompt a consideration of hepatobiliary disease is icterus, a yellow discoloration of the mucous membrane associated with accumulation of bilirubin. Pale mucous membranes, abdominal enlargement due to ascites or hepatomegaly, and poor body condition score might be other findings on physical examination of dogs or cats with hepatobiliary disease.

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Table • 225-1 Pathophysiology of Common Clinical Signs and Physical Examination Findings in Hepatobiliary Disease

CLINICAL SIGNS	PATHOPHYSIOLOGY	PHYSICAL FINDINGS	PATHOPHYSIOLOGY
Gastrointestinal (GI)		Icterus	Decreased uptake, conjugation or export of bilirubin into bile
Vomiting	Direct stimulation of CRTZ	Hepatomegaly	Hepatic infiltration with inflammatory cells, neoplasia, amyloid, fat, glycogen
	Gastroduodenal ulceration		
	Concurrent intestinal inflammatory disease		
Diarrhea	Concurrent intestinal inflammatory disease	Abdominal fluid	Ascites:
	Steatorrhea		Portal hypertension Avid renal sodium and water retention
	Portal hypertensive enteropathy		Hypoalbuminemia
			Bile: rupture gallbladder/biliary tract
			Neoplastic effusion
Acholic feces	Extrahepatic bile duct obstruction	Poor body condition score	Poor appetite
			Increased metabolic rate
			GI malabsorption
Melena	Gastroduodenal ulceration	Abdominal pain	Cholecystitis
	Coagulopathy		GI ulceration
			Bile peritonitis
			Pancreatitis
Neurologic		Fever	Leptospirosis
			Rickettsial disease
Personality change	Hepatic encephalopathy (HE)		Protozoal disease: *Toxoplasma*,*Neospora*
Weakness	Hypoglycemia		
Anorexia, lethargy	Cerebral edema		Feline Infectious Peritonitis (FIP)
Ptyalism (cats)	Vitamin B1 deficiency		*Salmonella*
Head pressing			Bacterial cholecystitis
Disorientation →stupor → coma			Supporative hepatitis
Irritability/aggression			
Seizures			
Renal			
Polyuria/polydipsia (PU/PD)	Primary polydipsia		
	Decreased hepatic urea production with subsequent disruption renal medullary interstitial gradient		
	Increased circulating cortisol		
	Manifestation of HE		
Pollakiuria, stranguria, dysuria	Ammonium biurate urolithiasis		
Bilirubinuria	Hyperbilirubinemia		
Hematologic	Anemia		

Pale mucous membranes	Blood loss from coagulopathy or GI bleeding Anemia chronic disease

225.1 LABORATORY EVALUATION OF HEPATOBILIARY DISEASE

225.1.1 Clinical Enzymology

Evaluation of serum values of hepatobiliary enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and γ-glutamyl transpeptidase (GGT), are commonly used to screen for the presence of hepatobiliary disease, because consistent increases in the serum concentration of these enzyme activities occur after hepatobiliary injury.[4] Although these serum enzymes have a high sensitivity for the detection of hepatobiliary disease, interpretation of abnormalities is hampered by their lack of specificity for hepatobiliary disease. The central role of the liver in metabolism and its high blood flow make it uniquely sensitive to secondary injury. Thus several clinical conditions exist in which liver enzymes may be elevated but in which clinically significant hepatobiliary disease may not be present (Table 225-2). Although the magnitude of serum enzyme elevation is usually proportional to the severity of active hepatobiliary damage, the degree of elevation is not predictive of hepatobiliary functional capacity. Marked increases in serum enzymes may indicate substantial hepatobiliary injury but, due to tremendous hepatic regenerative capacity, are not necessarily indicative of a poor prognosis. Alternatively, in severe end-stage chronic liver disease, serum enzymes may be normal or only mildly increased, because replacement of hepatocytes by fibrosis, prolonged enzyme leakage, or both has resulted in depletion of total liver enzyme content. A single serum enzyme determination should never be used to establish a prognosis. The prognostic value of serum enzymology is improved by following sequential serum enzyme determinations, especially in conjunction with a hepatic function test or hepatic biopsy.

Alanine aminotransferase (ALT) is a liver-specific cytosolic enzyme. The largest increases in serum ALT, a leakage enzyme, are seen with acute hepatocellular necrosis and inflammation. The magnitude of ALT elevation is roughly proportional to the number of injured hepatocytes. The serum $t_{1/2}$ in dogs is around 2.5 days. No published values exist for feline serum ALT $t_{1/2}$. In acute liver disease in the dog, the finding of a 50% decrease in sequential serum ALT determinations over 2 to 3 days is considered a good prognostic sign. In dogs, serum ALT may also increase with severe muscle necrosis.

In dogs, phenobarbital and corticosteroids increase serum ALT.[4–7] In most dogs, drug induction results in mild increases in ALT (two-to fourfold), but in some individuals increases approach those seen with acute hepatocellular injury. Whether these larger elevations in serum ALT activity represent enzyme induction or are reflective of possible corticosteroid or phenobarbital hepatotoxicity is still unclear. Serum ALT may increase with primary or metastatic hepatic neoplasia.[8] Mild to moderate increases are seen in 70% to 80% of dogs with hepatocellular or bile duct carcinoma. Occasionally hepatic nodular hyperplasia results in increased serum ALT.

Serum AST is more sensitive than serum ALT in the detection of hepatobiliary disease, although considerably less specific because significant amounts of AST are also contained in muscle. The $t_{1/2}$ of serum AST is 5 to 12 hours in the dog and 77 minutes in the cat. In general, increases in serum AST parallel increases in serum ALT and, like ALT, are associated with leakage after altered membrane permeability. In instances where serum AST is much higher than serum ALT, a muscle source for the elevations should be explored. Alternatively, because AST is present within the mitochondria and the cytosol, an elevated AST to ALT ratio

may be indicative of acute severe irreversible injury. In dogs, serum AST is mildly increased by corticosteroids and phenobarbital. Increases in serum AST may be more sensitive than ALP or ALT in the detection of hepatic metastasis.[8]

Table • 225-2 Conditions in which Increases in Serum Hepatobiliary Enzyme Concentrations May Occur in the Absence of Primary Liver Disease

Drug Induction:
Corticosteroids (dogs): (↑↑↑ALP, ↑↑GGT, ↑ALT, ↑AST)
Anticonvulsants: (phenobarbital, phenytoin, primidone) (↑ALT, ↑ALP, ↑AST, ↑GGT)
Endocrinopathies:
Hyperthyroidism (cats): (↑ALP, ↑ALT)
Hypothyroidism (dogs): (↑ALP)
Diabetes mellitus: (↑ALP)
Hyperadrenocorticism (dogs): (↑↑↑ALP, ↑ALT, ↑GGT, ↑AST)
Neoplasia:
Adenocarcinomas: pancreatic, intestinal, adrenocortical, mammary
Sarcomas: hemangiosarcoma, leiomyosarcoma
Hepatic metastasis: (↑AST, ↑ALT, ↑ALP)
Unique enzyme induction: (↑↑ALP, ↑↑GGT)
Miscellaneous:
Systemic infections Pregnancy (cats): (↑placental ALP)
Colostrum fed neonates (dogs):(↑GGT)
Hypoxia/Hypotension: (↑↑ALT, ↑ALP, ↑GGT, ↑AST)
Congestive heart failure (CHF)
Septic shock
Hypoadrenocorticism
Circulatory shock
Severe acute blood loss
Status epilepticus
Hypotensive crisis
Surgery
Muscle Injury: (↑ALT, ↑↑AST)
Acute muscle necrosis/trauma
Malignant hyperthermia
Myopathies
Bone Disorders: (↑ALP)
Young animals (up to 7 months)
Osteosarcoma
Osteomyelitis

Although serum ALP elevation is a sensitive indicator of hepatobiliary disease, its low specificity for liver disease confuses interpretation. ALP's low specificity is associated with the presence of several isoenzymes and a unique sensitivity to drug induction. Isoenzymes of ALP are present in the liver, kidney, intestine, bone, and placenta. The intestinal, kidney, and placental isoenzymes do not contribute to serum ALP due to their short $t_{1/2}$. An exception is in late-term feline pregnancy, where the placental ALP isoenzyme represents a significant source of the serum enzyme. The bone isoenzyme, B-ALP, contributes about one third of total serum ALP.[9] Increased osteoblastic activity associated with growing bones in young animals or with pathologic conditions such as osteomyelitis or osteosarcoma can increase serum B-ALP. These conditions typically cause mild increases in the total serum ALP.

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Two liver isoenzymes contribute to the serum ALP in dogs; a liver (L-ALP) and corticosteroid-induced isoenzyme (C-ALP). Cats have only one liver isoenzyme. In the dog and cat, L-ALP is a membrane-bound enzyme found on the hepatocyte canalicular membrane and the luminal surface of biliary epithelial cells.[10] Canine C-ALP is a hyperglycosylated form of the isoenzyme produced by hepatocytes and is also located on the hepatocyte canalicular membrane. The serum $t_{1/2}$ of both L-ALP and C-ALP in the dog is about 70 hours. The $t_{1/2}$ of the cat liver isoenzyme is only 6 hours. Increases in serum ALP in the dog and cat are the result of increased de novo synthesis, elution of the enzyme from cellular membranes, or both.

In a series of 270 dogs with histologically confirmed hepatic disease, the highest serum ALP activities were seen with cholestasis (median: tenfold increase) followed by chronic hepatitis, corticosteroid-induced hepatopathy, and hepatic necrosis (approximately sixfold).[4] Although the specificity of serum ALP determination for hepatobiliary disease was only 51%, the sensitivity was quite high (approximately 80%). Canine bile duct carcinoma and hepatocellular carcinoma can be accompanied by moderate to marked increases in serum ALP (see Table 225-2). Hepatic nodular regeneration, a common hepatic lesion in old dogs is frequently accompanied by mild to moderate increases in ALP.

Exposure of dogs to excess endogenous or exogenous corticosteroids increases serum ALP.[5,6,11] In experimental studies, dogs given immune-modulating doses of prednisone had increases in serum ALP by the third day that continued to rise throughout the period of corticosteroid administration. Serum ALP elevation in corticosteroid-treated dogs is accompanied by changes in hepatic morphology. Morphologic changes include ballooning enlargement of hepatocytes and development of intracytoplasmic hepatic vacuolation due to glycogen accumulation.[6] In some studies, focal areas of hepatocyte necrosis have been described. In dogs treated with prednisone, these morphologic changes begin by the second day and gradually progress in severity as corticosteroid treatment continues.

One of the challenges in the interpretation of canine serum ALP elevations is distinguishing between increases associated with cholestatic hepatic disease and those secondary to exposure to corticosteroids. In theory, serum ALP isoenzyme analysis should separate these two groups, because hepatobiliary disease should increase L-ALP and corticosteroid exposure should increase C-ALP. In reality, considerable overlap exists between isoenzyme distributions in these two conditions. The most widely used technique for serum ALP isoenzyme analysis is levamisole inhibition.[9] This technique is based on the fact that levamisole inhibits L-ALP and B-ALP but not C-ALP. In dogs with normal total serum ALP, C-ALP represents from 5% to 20% of total serum ALP. In experimental dogs treated with corticosteroids, the initial rise in serum ALP is associated with induction of L-ALP, and only after several days of treatment does C-ALP become the prominent isoenzyme. Chronic corticosteroid exposure due to hyperadrenocorticism or iatrogenic hypercortisolism from parenteral, oral, or topical corticosteroid administration, is consistently associated with increases in C-ALP. Serum C-ALP also increases in chronically ill animals, apparently from long-term endogenous cortisol excess. Although highly sensitive for the detection of exposure to corticosteroids, the specificity of isoenzyme analysis is low. Further, many dogs with hepatobiliary disease also have increases in serum C-ALP.[12]

Phenobarbital induces mild (two-to sixfold) increases in serum ALP.[2,7] Phenobarbital may induce either L-ALP, C-ALP, or both.[10] Interpretation of increased serum ALP activity in phenobarbital-treated dogs is complicated by the fact that this drug is a hepatotoxin. Because ALT, AST, and GGT are also mildly induced by anticonvulsants, they may be of no value in differentiating serum ALP increases due to microsomal induction from those associated with morphologic injury. If the serum abnormalities in these enzymes are

greater than two to three times the upper limit of normal, the possibility of phenobarbital-induced hepatotoxicity should be explored. Dogs on chronic anticonvulsant therapy with enzyme induction should have determination of serum albumin, bilirubin, and bile acids to monitor hepatobiliary function.

Because feline ALP is not susceptible to drug induction, elevations in serum ALP are more specific for feline hepatobiliary disease. The magnitude of serum ALP elevations in feline hepatobiliary disease, however, are not as great as those in the dog due to the short $t_{1/2}$ of feline ALP and the fact that hepatic stores of feline ALP are less than in the dog. Thus feline serum ALP is a less sensitive indicator of hepatic disease than in the dog. Clinically, the largest increases in feline ALP are seen in hepatobiliary conditions associated with intrahepatic or extrahepatic cholestasis.

GGT is present in many tissues, although serum GGT concentrations are primarily derived from the liver. Hepatic GGT is located on the hepatocyte canalicular membrane. Serum elevations in GGT are most common with cholestatic disorders and are associated with increased de novo synthesis and membrane elution.

In dogs, moderate to marked increases in GGT are seen with intrahepatic and extrahepatic cholestasis, whereas mild elevations are seen with acute hepatocellular injury. In a series of dogs with histologically confirmed hepatic disease, serum GGT was more specific (87%) than serum ALP (51%) in the detection of hepatobiliary disease, but it was less sensitive (50%) than SAP (80%).[4]

When serum GGT and ALP were used in series, their specificity for the detection of hepatobiliary disease increased to 94%. In a series of 36 dogs with primary or metastatic hepatic neoplasia, 39% had high serum GGT values. Phenobarbital and corticosteroids cause mild (two to threefold) increases in serum GGT in the dog.

In a series of 69 cats with hepatobiliary disease, the largest increases in serum GGT were associated with extrahepatic bile duct obstruction (EHBDO) and cholangiohepatitis. Serum GGT had a higher sensitivity than serum ALP (86% versus 50%, respectively), but lower specificity (67% versus 93%, respectively) for the detection of hepatobiliary disease.[4] In some cats with cirrhosis, EHBDO, or cholangitis, serum GGT may be considerably greater than serum ALP values. In idiopathic hepatic lipidosis, however, serum GGT values may be normal or mildly increased (two-to sixfold), whereas serum ALP values are markedly increased (tenfold).

225.2 PLASMA PROTEINS IN HEPATIC DISEASE

The liver synthesizes many plasma proteins and detoxifies ammonia, the major breakdown product of protein metabolism. The clinical consequences of disruptions in hepatic protein metabolism are decreases in plasma oncotic pressure due to hypoalbuminemia, bleeding tendencies associated with coagulation protein deficiencies, and the development of HE due to ammonia retention.

225.2.1 Albumin

The liver is the exclusive site of albumin synthesis. Because synthesis occurs at 33% of maximum capacity and the serum $t_{1/2}$ of albumin is 8 to 9 days, serum hypoalbuminemia is most often seen in chronic hepatic disorders such as cirrhosis and PSVASs. In cirrhotic dogs, serum hypoalbuminemia, portal hypertension, and avid sodium and water retention lead to the development of ascites. In ascitic animals, serum hypoalbuminemia may reflect both third-party sequestration of albumin in the abdominal fluid and hepatic synthetic failure. Hypoalbuminemia is not specific for hepatic disease and may occur with protein-losing enteropathies, protein-losing nephropathies, exudative cutaneous lesions, vasculitis, or acute blood loss.

Inadequate nutrition can curtail hepatic albumin synthesis. Because albumin is a negative acute phase reactant, systemic inflammatory disease may shut down hepatic albumin synthesis.

225.2.2 Globulins

The serum globulin fraction is composed of immunoglobulins and nonimmunoglobulins. Because the liver synthesizes many of the nonimmunoglobulins including α-globulins and β-globulins, hepatic synthetic failure can be accompanied by serum hypoglobulinemia. However, because many nonimmunogloblins are acute-phase reactants whose production that is increased in response to systemic inflammatory disease, early chronic inflammatory liver disease may be accompanied by hyperglobulinemia.[4,13,14]

Immunoglobulins are not synthesized in the liver but may be increased in chronic inflammatory hepatic disease. A polyclonal increase in γ-globulins has been documented in chronic canine hepatic disease and is seen in 50% of feline cases of chronic cholangiohepatitis. Hypergammaglobulinemia in chronic liver disease may be associated with enhanced systemic immunoreactivity due to abnormal Kupffer cell processing of portal antigens or secondary to autoantibody production. Low titers of antinuclear antibodies have been detected in 50% of dogs with chronic inflammatory hepatic disease.[15] In a series of dogs with chronic inflammatory hepatic disease, 48% had antibodies that reacted with canine liver membrane preparations.[16] Although dogs with positive titers tended to have higher serum ALT and bilirubin values and more severe histopathologic lesions than dogs without antibody responses, it remains to be determined whether these autoantibodies have any role in disease progression.

225.2.3 Coagulation Proteins

The liver plays an important role in hemostasis. Hepatocytes synthesize all of the coagulation factors, except factor VIII, as well as critical inhibitors of coagulation and fibrinolysis (antithrombin III, antiplasmin) and fibrinolytic proteins (plasminogen). In addition, the liver is responsible for clearance and catabolism of activated coagulation factors, plasminogen activators, and breakdown products of fibrinolysis such as fibrin degradation products (FDP). The liver is also the site of vitamin K–dependent activation of factors II, VII, IX, and X and protein C.

Assessment of coagulation status is important in animals with liver disease because altered hemostasis can contribute to clinical manifestations of hepatic disease and complicate invasive diagnostic procedures. The complexity and overlap of the liver's synthetic and clearance functions, however, makes the interpretation of hemostatic testing difficult. The commonly used tests to assess coagulation include determination of prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, and FDPs. Abnormalities in these coagulation tests in hepatobiliary disease may be indicative of hepatic synthetic failure, vitamin K deficiency, or the presence of a consumption coagulopathy such as disseminated intravascular coagulation (DIC).

Coagulation abnormalities are quite common in dogs and cats with hepatobiliary disease.[4] In dogs with naturally occurring hepatic disease, 50% and 75% had an abnormal PT and APTT, respectively. Specific factor analysis revealed that greater than 90% of the dogs had at least one abnormality. Because factor depletion must be greater than 70% to show prolongation of coagulation times, it is not surprising that many more dogs had abnormalities in the concentration of coagulation factors than had prolongation of PT or APTT. In cats with naturally occurring hepatobiliary disease, 82% had at least one coagulation abnormality.[17] The most common abnormalities were an increase in PT (16 of 22) and low factor VII activity (15 of 22).

Despite the presence of abnormalities in coagulation tests, spontaneous hemorrhage in animals with hepatic disease is rare. Hemorrhage is more likely to occur after a challenge to hemostasis such as venipuncture, hepatic biopsy, or gastric ulceration. Because coagulation tests are relatively poor predictors of an individual's tendency to bleed, one should assume that animals with hepatobiliary disease have a higher than normal risk of bleeding after provocative procedures regardless of the results of coagulation testing.

Assessment of coagulation has prognostic significance in hepatic disease. In dogs with chronic inflammatory liver disease, prolongation of PT and PTT to 1.3 to 1.4 times normal was associated with survival less than 1 week.[18] Although prognostic and useful in managing and predicting the complications of hepatic disease, PT and APPT are not sensitive or specific indicators of hepatic disease and should not be used as screening or diagnostic tests.

Vitamin K deficiency may develop during hepatobiliary disease for several reasons. Prolonged bile duct obstruction interrupts the enterohepatic circulation of bile acids resulting in intestinal bile acid deficiency and resultant fat-soluble vitamin K malabsorption. Oral antibiotics may alter the normal intestinal bacterial flora, resulting in the destruction of vitamin K–generating bacteria. Inadequate dietary consumption of vitamin K, although rarely a primary cause of vitamin K deficiency, may be contributory. This is especially true in disorders such as feline idiopathic hepatic lipidosis, which is marked by prolonged anorexia. Vitamin K is a cofactor in the carboxylation and resultant activation of factor II, VII, XI, and X and protein C. Prolongation of PT is the first coagulation abnormality seen with vitamin K deficiency, because factor VII has the shortest plasma $t_{1/2}$. In vitamin K deficiency, vitamin K–dependent factors circulate in an inactive form. The concentration of these inactive factors can be measured and is referred to as *proteins induced by vitamin K absence or antagonists* (PIVKAs). The presence of increased PIVKAs is more sensitive than changes in PT to detect vitamin K deficiency.[19] When either PIVKAs or prolongation of PT were used to detect vitamin K deficiency, 50% to 75% of cats with naturally occurring hepatobiliary disease had vitamin K deficiency.[19,17] Failure to activate vitamin K–dependent factors also may occur as the result of hepatic synthetic failure. Parenteral administration of vitamin K readily (within 24 to 48 hours) corrects coagulation abnormalities due to vitamin K deficiency, but has little to no effect on coagulation abnormalities due to hepatic synthetic failure.

Due to the liver's central role in coagulation and fibrinolysis, it can be quite challenging to differentiate whether coagulation abnormalities are associated with DIC or are due to severe liver disease. Typically DIC is recognized by prolongation of PT, APTT, decreased fibrinogen, thrombocytopenia, and increased FDPs, all of which may accompany hepatic failure. Increases in PT and APTT may accompany hepatic synthetic failure or vitamin K deficiency. In early liver disease, fibrinogen concentrations may be normal to increased (fibrinogen is an acute-phase reactant), but as hepatic function deteriorates, fibrinogen concentrations typically decrease due to reduced hepatic synthesis. Increases in FDPs have been detected in 14% of dogs with chronic hepatic disease and in 30% of cats with idiopathic hepatic lipidosis.[4,11] These increases may represent impaired hepatic clearance of FDPs.

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Both quantitative and qualitative platelet defects accompany hepatobiliary disease. Although quantitative platelet abnormalities have been poorly documented in small animals with hepatic disease, many dogs with chronic hepatic disease have mild thrombocytopenia (120,000 to 180,000). The reason for this thrombocytopenia is unknown. Thrombocytopenia is rare in cats with hepatobiliary disease unless DIC is present. Studies in dogs with hepatobiliary disease have demonstrated the presence of qualitative defects in platelet aggregation.

225.3 BLOOD AMMONIA

The liver is responsible for the majority of ammonia detoxification. Ammonia is generated primarily in the GI tract by bacterial degradation of amines, amino acids, and purines; by the action of bacterial urease on urea; and by intestinal catabolism of glutamine. Ammonia readily diffuses through the intestinal mucosa and into the portal circulation where it travels to the liver. After uptake by hepatocytes, ammonia is detoxified either by enzymatic conversion to urea in the mitochondrial urea cycle or by consumption in the synthesis of glutamine. Urea then undergoes renal excretion. Ammonia, which escapes hepatic metabolism, enters the systemic circulation where other tissues, including the kidney, muscle, brain, and intestines, detoxify it by the formation of glutamine.

Failure of the liver to detoxify ammonia or shunting of portal blood away from the liver results in hyperammonemia. Because the urea cycle operates at only 60% capacity, hepatic failure must be fairly advanced for blood ammonia concentrations to rise. Because intrahepatic or extrahepatic shunting of portal blood directly deposits ammonia in the systemic circulation, blood ammonia concentrations are more sensitive in the detection of hepatobiliary disorders associated with shunting.[4,20] Hyperammonemia also occurs in animals with urea cycle enzyme deficiencies and with pathologic conditions that result in decreased availability of urea cycle substrates. Hyperammonemia has been described in dogs with a deficiency of the urea cycle enzyme, argininosuccinate synthetase, and in cats fed a diet deficient in arginine, an essential substrate in the urea cycle.[21,22]

The biggest obstacle in the clinical use of blood ammonia determinations is the difficulty in sample handling. Samples must be drawn directly into cold heparinized tubes, immediately transferred to the laboratory on ice for refrigerated centrifugation, and preferably assayed within 1 hour. Feline, but not canine, plasma samples may be frozen at −20°C for 48 hours without sacrificing accuracy. Because erythrocytes contain two to three times the amount of ammonia as does plasma, if they are not separated from the plasma immediately or if hemolysis is found in the sample, spurious increases in blood ammonia will result.

Technical limitations aside, blood ammonia determination is important for evaluating dogs and cats suspected of having hepatobiliary disease. Hyperammonemia is an important, although not exclusive, cause of HE and is the only toxin implicated in this condition that can be measured clinically. The presence of hyperammonemia can therefore be used to verify the presence of HE. Not all animals with HE, however, will have abnormal blood ammonia levels. Hyperammonemia also reliably occurs in pathologic conditions associated with significant shunting of portal blood away from the liver. Thus 80% of dogs and 90% of cats with PSVASs demonstrate fasting hyperammonemia. Fasting hyperammonemia occurs less often with chronic parenchymal disease, being abnormal in approximately 50% of dogs with chronic hepatitis.[13] Elevations in blood ammonia are unusual with acute hepatic disease, unless it is fulminant.

The diagnostic value of blood ammonia can be improved by performing an ammonia tolerance test (ATT).[4] In an ATT, a baseline blood ammonia value is determined after a 12-hour fast. The animal is then given an exogenous load of ammonium orally or per rectum and blood ammonia determined postchallenge. In the classic oral ATT, NH_4Cl_2 is given at a dose of 100 mg/kg in a dilute solution (not to exceed a concentration of 20 mg/mL and a total dose of 3 g) and blood ammonia determined 30 minutes later. In the rectal ATT, a warm-water enema is given 12 hours prior to the administration of 2 mL/kg of 5% NH_4Cl_2 via a catheter inserted into the rectum. Samples for blood ammonia are taken at 20 and 40 minutes postchallenge. In normal animals after oral or rectal challenge, blood ammonia should not increase any more than twofold. In animals with hepatic insufficiency or PSVASs, ammonia values generally increase three to tenfold. Virtually all dogs and cats with PSVASs and 90% of dogs with chronic hepatitis have abnormal ATT.[9,11] Rarely an ATT will precipitate HE.

A recent study evaluated a modified oral ATT in which dogs were fed a small test meal supplying 33 kcal/kg (25% of daily metabolizable energy requirement) with a protein concentration of 30.3% dry matter.[20] When blood ammonia concentrations were determined at zero time and 6 hours later, a sensitivity of 81% and 91% was found for the detection of PSVASs. The test had poor sensitivity in detecting dogs with parenchymal hepatocellular disease. Unlike classic ammonia tolerance tests, this provocative test was not associated with adverse side effects such as the induction of vomiting or HE.

225.4 SERUM UREA NITROGEN

Approximately 65% of dogs and cats with PSVASs have a decreased serum urea nitrogen (SUN).[3] Decreases in SUN are thought to arise secondary to decreased urea production in the atrophied liver. Decreased SUN is not specific for liver disease because it can be influenced by hydration status and dietary protein content, GI hemorrhage, glomerular filtration rate, and fluid or solute diuresis.

225.5 BILIRUBIN

Bilirubin is a yellow pigment formed in the reticuloendothelial cell system (RES) by the enzymatic processing of heme. Bilirubin released from RES cells is not water soluble and is transported in plasma reversibly bound to albumin. This unconjugated bilirubin is extracted by the liver and conjugated by esterification with glucuronic acid. Water-soluble conjugated bilirubin is actively secreted against a concentration gradient into the bile. The bilirubin in bile enters the intestinal tract via the bile duct, where it is either excreted unchanged in the feces or is converted to urobilinogen by the action of enteric bacteria. Most of the urobilinogen is further degraded into the brown-pigmented stercobilins. The absence of stercobilins in the feces results in pale-colored acholic stools. Small amounts of urobilinogen enter the portal venous system and undergo enterohepatic circulation. The majority is re-excreted into the bile, but a small amount undergoes urinary excretion.

Icterus is the clinical manifestation of bilirubin retention within tissues (see Figure 225-1). Although less sensitive than serum liver enzymes for the detection of hepatobiliary disease, serum hyperbilirubinemia is more specific. Hyperbilirubinemia occurs when an abnormality in the processing of bilirubin exists and can be divided into three categories: (1) prehepatic, (2) hepatic, and (3) posthepatic. Prehepatic hyperbilirubinemia is associated with increased production of bilirubin due to the need to process large amounts of heme such as occurs during severe hemolytic anemia. It is readily differentiated from hepatic and posthepatic causes by determining hematocrit. Hepatic hyperbilirubinemia is associated with impaired hepatic uptake, conjugation, or excretion of bilirubin. It is seen in hepatic disorders in which severe intrahepatic cholestasis develops. Hepatic hyperbilirubinemia may also accompany severe extrahepatic infections.[23,24] In this condition, referred to as the *cholestasis of sepsis*, circulating cytokines directly inhibit hepatocyte bilirubin transport. In a series of 29 septic cats, 63% had hyperbilirubinemia.[23] Posthepatic hyperbilirubinemia is associated with interruption of flow within the extrahepatic bile ducts.

The differentiation of hepatic and posthepatic icterus can be quite challenging clinically and yet is extremely important because these conditions demand different interventional strategies. Posthepatic hyperbilirubinemia usually requires surgical decompression of the biliary tract, whereas hepatic hyperbilirubinemia is typically treated medically. The clinical differentiation between hepatic and posthepatic hyperbilirubinemia is best made by ultrasound evaluation of the biliary system combined with careful consideration of clinical history, physical examination, and ancillary laboratory testing.

During prolonged cholestasis, excess conjugated bilirubin may become irreversibly bound to albumin. These so-called biliproteins are clinically significant in that they are measured as direct reacting bilirubin, but their $t^1/_2$ approximates that of albumin.[4] Their presence can result in persistently elevated serum bilirubin weeks after the resolution of the underlying cholestatic liver disorder.

225.6 BILE ACIDS

Bile acids are synthesized exclusively in the liver from cholesterol. After conjugation to either taurine or glycine, bile acids are excreted into bile and collected, stored, and concentrated in the gallbladder. After ingestion of a meal, cholecystokinin release stimulates gallbladder contraction and the transport of bile acids into the intestine. In the intestinal lumen, bile acids aid in the solubilization and absorption of fats. When the bile acids reach the ileum, they are efficiently transported back into the portal circulation from which they are re-extracted by the hepatocyte sinusoidal bile acid transporter. This enterohepatic circulation of bile acids operates at 98% efficacy.

Disruption of the enterohepatic circulation of bile acids results in increases in the concentration of total serum bile acids (TSBAs). In normal animals, TSBA concentrations are determined by the spillover of bile acids that escape from the enterohepatic circulation. During fasting, when the enterohepatic circulation of bile acids is low, TSBAs are low. After a meal, bile acids are released into the intestines and subsequently absorbed into the portal circulation. Increased portal vein bile acid concentrations are reflected in a transient elevation in TSBAs. This endogenous challenge to the enterohepatic circulation of bile acids is used clinically. In a typical bile acid test, TSBAs are determined after a 12-hour fast, a test meal is fed and then postprandial TSBAs determined 2 hours later.

The most commonly used method for the determination of TSBAs is an enzymatic method that relies on the reaction of 3-α-hydroxy bile acids with bacterial 3-α-hydroxysteroid dehydrogenase. Normal values for fasting TSBA concentrations using this method are 1.7 ± 0.3 μM and 2.3 ± 0.4 μM in cats and dogs, respectively. Two-hour postprandial values are 8.3 ± 2.2 μM in the dog and 8.3 ± 0.3 μM in the cat.[4] Sample collection for this assay is easy because serum bile acids are stable even at room temperature. Hemolysis and lipemia should be avoided because they interfere with the assays spectrophotometric endpoint.

Numerous studies have demonstrated the efficacy of fasting and postprandial TSBAs in the diagnosis of feline and canine hepatobiliary disease and PSVASs.[3,4] In a series of 108 cats with hepatobiliary disease, when cutoff values of greater than 15 μM were used as abnormal, fasting TSBAs were more specific (96%) than increases in serum ALP, ALT or GGT in predicting the presence of hepatobiliary disease. The sensitivity at this cutoff value (54%) was about the same as for serum enzyme determination. The determination of postprandial TSBAs using a cutoff of greater than 20 μM as abnormal improved both the sensitivity (100%) and the specificity (80%) of bile acid testing in the detection of feline hepatobiliary disease. Postprandial TSBAs had a greater sensitivity than fasting TSBAs for the detection of all categories of feline hepatobiliary disease except hepatic necrosis.

In a series of 107 dogs with histologically confirmed hepatic disease, the specificity of fasting TSBAs using a cutoff of greater than 5 μM as abnormal was 83%.[4] Using a cutoff of greater than 15 μM as abnormal, postprandial TSBAs had a specificity of 89% and a sensitivity of 82%. When cutoff values for abnormal fasting and postprandial TSBAs were increased to greater than 20 μM and greater than 25 μM respectively, the specificity of both tests was 100%. Sensitivity at these cutoff values was 59% and 74% for fasting and postprandial samples, respectively. At the higher cutoff values, neither fasting nor postprandial TSBAs

outperformed the other. A notable exception was improved performance of postprandial TSBAs in the detection of inactive cirrhosis or PSVASs.

Maltese dogs may have increased postprandial TSBAs in the absence of hepatobiliary disease.[25] In a screening of 200 Maltese dogs, 79% had postprandial TSBAs above the reference range using the enzymatic method. Nine dogs with abnormal postprandial TSBAs had normal rectal ATT and no evidence of hepatobiliary disease on hepatic biopsy. Two dogs with abnormal postprandial TSBAs had abnormal ATT and PSVASs. The cause of increased postprandial TSBA values in Maltese dogs with normal liver biopsies remains undetermined.

A number of factors that influence the enterohepatic circulation of bile acids in normal animals can affect TSBA values.[4] These include the completeness of gallbladder emptying, the rate of gastric emptying, intestinal transit rate, the efficiency of ileal bile acid reabsorption, and the frequency of enterohepatic cycling. Inadequate fat or amino acid content in the test meal or consumption of an insufficient amount of food can result in failure of cholecystokinin release and gallbladder contraction. In general it is recommended that the animal eat a meal of regular dog or cat food, although 2 teaspoons of food for pets less than 10 lbs and 2 tablespoons for larger animals has been reported to be adequate. Visual confirmation of meal consumption is mandatory. The presence of concurrent disease that delays gastric emptying may result in failure to stimulate gallbladder contraction. Alterations in intestinal transit time so that the movement of conjugated bile acids to the ileum is delayed can result in less than optimum timing for determination of the postprandial values. Severe ileal disease can result in decreased bile acid reabsorption and inadequate challenge to the enterohepatic circulation. The presence of small bowel overgrowth leads to bacterial deconjugation of bile acids and decreased ileal absorption of bile acids.

Occasionally, fasting TSBA concentrations are higher than postprandial values. This happens when interdigestive gallbladder contraction occurs during the course of the fast preceding the test. It may also be associated with individual variations in gastric emptying, response to cholecystokinin release, and intestinal transit time.

The interpretation of abnormal TSBA is subject to a number of limitations. First, TSBAs are not capable of discriminating one hepatobiliary disease from another. A second limitation of TSBA determination is that little, if any, correlation exists between the severity of histologic changes or the degree of portosystemic shunting and the extent of TSBA elevation. A TSBA value is either normal or abnormal. When evaluating serial determinations of TSBAs to monitor disease progression or response to therapy, only a return to normal can be used as a reliable indicator of clinical remission.

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225.7 CARBOHYDRATE METABOLISM

The major function of the liver in carbohydrate metabolism is to maintain normoglycemia during the fasting state. The liver has a large reserve for maintaining glucose homeostasis so that greater than 70% of hepatic function must be lost before hypoglycemia occurs. Hypoglycemia occurs most often in acute fulminant hepatic failure and in small breed dogs with PSVAs.[3] In acute hepatocellular injury, hypoglycemia may be a relatively early indicator of severe hepatic failure. Up to 35% of dogs with congenital PSVAs are periodically hypoglycemic. In these dogs, hypoglycemia may be due to impaired hepatic glucose production, decreased hepatic glycogen stores, reduced responsiveness to glucagons, or a combination of these factors. Inadequate glycogen stores may reflect immaturity of the carbohydrate metabolizing enzyme systems or be a consequence of chronic stimulation of glycogenolysis. Hypoglycemia is a rare complication of end-stage chronic inflammatory liver disease and is a negative predictor of survival.[18]

Hypoglycemia may occur as a paraneoplastic syndrome in dogs with hepatic neoplasia.[8] Proposed mechanisms for the hypoglycemia include increased glucose use by the tumor or secretion of an insulin-like substance that inhibits gluconeogenesis and promotes glycogenolysis. Insulin levels, when measured, have been normal.

Glycogen storage diseases may cause hypoglycemia.[11] In dogs, a congenital deficiency in amylo-1,6-glucosidase has been associated with fasting hypoglycemia and the development of hepatomegaly due to glycogen accumulation.

225.8 CHOLESTEROL AND LIPID METABOLISM

The liver has several functions in lipid metabolism. Plasma fatty acids released from adipose tissue are extracted by the hepatocytes, after which they are either converted to triglycerides or undergo mitochondrial β-oxidation. Triglycerides are either stored or packaged as very low–density lipoproteins and released into the vasculature. The liver also extracts chylomicron remnants and low-density lipoproteins from plasma. This is the major route by which cholesterol enters into the liver, although the liver is also capable of cholesterol synthesis. Hepatic cholesterol can be esterified and then packaged and secreted in lipoproteins or stored in the liver. The majority of unesterified (free) cholesterol in the liver undergoes biliary excretion.

Hypercholesterolemia is associated with increased hepatic synthesis, decreased biliary excretion of cholesterol, or both. In the dog and cat, EHBDO is accompanied by increases in serum cholesterol. Hypocholesterolemia occurs in approximately 62% of dogs and 67% of cats with PSVAs and may be due to decreased cholesterol synthesis or increased incorporation of cholesterol into bile acids.[3] Hypocholesterolemia also occurs with late-stage chronic liver disease in dogs.[13]

225.9 URINALYSIS

Between 40% to 74% of dogs and 15% of cats with PSVAs have ammonia biurate crystalluria.[3] Repeated examination of fresh urine specimens may be necessary to document the presence of these crystals. Uric acid, a by-product of purine nucleotide catabolism, is normally converted to allantoin by hepatic urate oxidase. In hepatic disease, a deficiency of this enzyme may lead to hyperuricemia. In the presence of concurrent hyperammonemia, increased concentrations of both ions appear in the urine, resulting in the precipitation of ammonia biurate crystals.

Bilirubinuria is the presence of conjugated bilirubin in the urine. Bilirubinuria in the dog is not abnormal, because dogs have a low renal threshold for bilirubin and their renal tubular epithelium is capable of bilirubin production. Because cats have a high renal threshold for bilirubin and feline kidneys do not make bilirubin, feline bilirubinuria is always abnormal and suggests the presence of a hepatobiliary or hemolytic disorder.

225.10 HEMATOLOGIC ABNORMALITIES

Anemia may be present in dogs or cats with hepatobiliary disease. Regenerative anemia is most often associated with blood loss. Although spontaneous bleeding associated with coagulopathies is rare in animals with hepatic disease, blood loss may occur after provocative procedures or secondary to GI ulceration. Nonregenerative anemia, a more common finding in hepatic disease, is usually normocytic and normochromic and often associated with inefficient use of systemic iron stores (anemia of chronic disease). A microcytic, hypochromic, nonregenerative anemia should prompt consideration of chronic GI blood loss. Erythrocyte microcytosis occurs

in dogs and cats with congenital PSVAs,[3] in dogs with acquired shunting secondary to cirrhosis and in some cats with idiopathic hepatic lipidosis. Studies investigating the cause of this microcytosis in dogs with PSVAs have documented a relative iron deficiency that may be associated with impaired iron transport.[26] Target cells and poikilocytes may be seen in dogs and cats with hepatic disease. These morphologic changes may be associated with alterations in the erythrocyte plasma membrane lipoprotein content resulting in altered cell deformability.

225.11 HEPATIC BIOPSY ACQUISITION AND INTERPRETATION

Because patterns of clinicopathologic abnormalities do not reliably differentiate one form of hepatic disease from another, it is often necessary to obtain hepatic tissue for histopathologic or cytologic evaluation. The indications for examination of hepatic tissue include persistent increases in serum liver enzymes, increased serum bile acids or bilirubin, unexplained abdominal effusion or ascites, unexplained hepatomegaly, to assess response to therapy or disease progression, and to evaluate for breed-specific hepatopathies. Because the most common complication encountered in the procurement of hepatic tissue is hemorrhage, before undergoing hepatic tissue acquisition, all dogs and cats should have a PT, APTT, and platelet count assessed. Determination of PIVKAs and buccal mucosal bleeding time may improve the sensitivity of detecting bleeding tendencies. Due to the high frequency of vitamin K deficiency in hepatic disease and the ease with which it is treated, many clinicians routinely pretreat all patients with parenteral vitamin K_1 24 hours prior to hepatic biopsy. Acquisition of hepatic tissue is contraindicated in the presence of a severe coagulopathy, although some animals may be biopsied safely after the administration of fresh frozen plasma to supply deficient coagulation factors.

In general, hepatic biopsy is preferred over fine needle aspirate (FNA) to characterize liver disorders. However, in animals with bleeding disorders or those with large cavitary lesions or suspected abscesses, ultrasound guided fine needle aspiration (22 gauge needle) can safely be performed with minimal danger of hemorrhage or spread of infection. In studies done comparing FNA to hepatic biopsy, complete agreement is typically seen in around 30% of cases. While FNAs may be helpful in identifying vacuolar or neoplastic disease such as lymphoma, they frequently miss the presence of necroinflammatory or vascular disease.

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Hepatic biopsy can be obtained by ultrasound-guided needle biopsy, laparoscopic biopsy, or wedge biopsy by laparotomy. The advantages of the latter two methods are the ability to grossly evaluate the liver at the time of biopsy, the acquisition of relatively large tissue samples, and the identification and control of postbiopsy hemorrhage. An obvious disadvantage of these techniques is their invasive nature and, in the case of laparoscopy, the need for special equipment and technical expertise. Ultrasound-guided needle biopsy using automated spring-triggered biopsy needles has proven to be a safe, effective, minimally invasive means of obtaining biopsy material in most animals. Ultrasound guidance allows accurate sampling of focal lesions and permits visualization of the needle tract to minimize complications. When obtaining ultrasound-guided needle biopsy, particular care should be taken to obtain adequate samples (two to three specimens that fill at least three fourths of the 18-(in cats) or 16-(in dogs) gauge biopsy needle chamber should be obtained). Complications of ultrasound-guided needle biopsy (other than hemorrhage) are rare but include perforation of biliary structures, pneumothorax, and bacterial peritonitis. When an intrahepatic abscess is suspected or a highly vascular lesion is present, hepatic needle biopsy is contraindicated due to the high probability of infection and bleeding, respectively. Postbiopsy, animals should be monitored with ultrasound for the presence of postbiopsy bleeding and have PCV checks for up to 6 hours after the procedure.

Because the tissue obtained by wedge or needle biopsy represents only a tiny fraction (maybe 1/10,000) of the entire liver, one of the major limitations of hepatic biopsy is sampling error. Sampling error arises due to uneven distribution of lesions in what appears by diagnostic imaging to be diffuse disease. A recent study demonstrated significant discordant between the morphologic diagnoses obtained when needle and wedge biopsies from the

same animal were evaluated by the same pathologist.[28] This discordance most likely reflects sampling error. This same study also demonstrated that individual pathologists disagree on the morphologic diagnosis 44% and 65% of the time when the same wedge or needle biopsies, respectively, were evaluated. This emphasizes the need for a constant stream of communication between clinician and hepatic histopathologists. Clinicians should always be the final judges as to whether the histopathologic morphologic diagnosis fits with the clinical picture. Opinions from more than one pathologist on hepatic biopsy material may be necessary to arrive at an accurate morphologic diagnosis. In addition, internist and pathologist should both be willing to accept the limitations of hepatic biopsy and be prepared to rebiopsy, if warranted.

To fully appreciate the value of histopathologic evaluation of the liver, one must understand what information to reasonably expect from tissue samples.[29] One should expect the sample to determine the category of disease (necroinflammatory, neoplastic, vacuolar, or vascular), to define the extent of disease (mild, moderate, or severe) and to access the chronicity of the lesion (presence of fibrosis, type of cellular infiltrate). One should not expect every hepatic biopsy to provide a etiologic diagnosis. The biopsy, however, may provide clues as to cause. Special stains can help to identify infectious agents or determine if copper overload exists. Samples for anaerobic and aerobic culture may confirm suspicion of primary or secondary bacterial infection. Certain infectious diseases or toxins may cause lesions with characteristic anatomic distributions (e.g., passive congestion and acetaminophen toxicity cause centrilobular lesions), whereas infections such as salmonellosis or toxoplasmosis cause focal or multifocal lesions. Vacuolar change indicates cytoplasmic accumulation of lipid, water (hydropic degeneration), or glycogen (steroid hepatopathy). The liver can have a similar histologic reaction pattern to different insults. Macroscopic or microscopic PSVAs, primary hypophasia of the portal vein and arteriovenous fistula cause a characteristic histologic pattern (hepatic cord atrophy, portal vein attenuation, and portal arteriolar proliferation). Chronic inflammatory lesions provide the biggest challenge in interpretation, because the liver responds to many chronic insults (whether caused by toxins, infection, or immune stimulation) with the same reaction pattern. The important points to remember in evaluating inflammatory biopsies is to pay attention to the type of inflammatory cell present (neutrophilic: acute, active, or both; eosinophilic: allergic or parasitic; lymphoplasmacytic: subacute to chronic), whether inflammation breaks through the limiting plate (the disease is more severe if it does), and to note the extent of fibrosis (confined to portal regions, bridging portal tracts). Bridging fibrosis is consistent with severe disease and is a negative prognostic factor.[18]

225.12 DIAGNOSTIC IMAGING

225.12.1 Radiography

Radiography can be used to assess changes in the size and opacity of the liver.[30] Diffuse hepatomegaly is indicated by rounding of the liver edges, extension of the hepatic shadow beyond the costal arch, and caudal displacement of the stomach axis. Hepatomegaly may occur due to congestion, infiltrative disease (neoplasia, lipidosis, glycogen accumulation, amyloidosis), inflammatory disease, RES cell hyperplasia, or extramedullary hematopoiesis. Focal hepatomegaly can be discerned by observing displacement of the structures bordering the liver, and it may occur with cysts, granulomas, neoplasia, regenerative nodules, hematomas, or abscesses. Microhepatica is visualized radiographically by a decreased size of the hepatic shadow and a shift of the gastric axis to a more upright orientation with cranial displacement. Microhepatica is observed with hepatic atrophy and fibrosis.

Normally the liver is visualized as a homogenous soft tissue opacity. Cholelithiasis or choledocholithiasis may be visualized as mineralization in the liver. The former is recognized as a discrete round opacity in the cranial right ventral liver shadow, and the latter is seen as diffuse mineralization. Focal mineralization may also be

seen with chronic gallbladder infection or neoplasia, granulomatous lesions, abscesses, resolving hematomas, and within regenerative nodules.

Gas opacities in the liver may be associated with hepatic abscesses, emphysematous cholecystitis, or after long-term bile duct obstruction. The finding of gas within the portal vessel indicates the entry of GI gas or infection with gas-producing organisms and is a grave sign seen with gastric torsions and severe necrotizing gastroenteritis.

Radiographic contrast imaging of the portal venous system is used to localize PSVAs. It can be accomplished via three methods. The first, cranial mesenteric arteriography, involves cannulation of the cranial mesenteric artery via the femoral artery and injection of iodinated contrast followed by rapid fluoroscopic imaging. These studies are fraught with technical difficulties and are seldom performed. The second method, splenoportography, involves injection of contrast agent directly into the spleen, either percutaneously or at the time of laparotomy. Complications include splenic infarction and hemorrhage. The best method to demonstrate PSVAs is operative mesenteric portography. This involves intraoperative jejunal vein catherization and injection of iodinated contrast.

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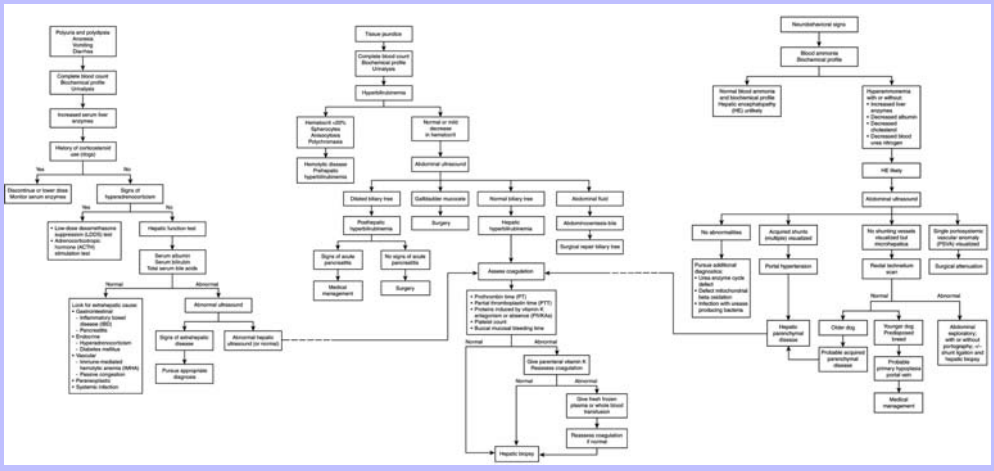
Figure 225-1 Laboratory diagnosis of hepatobiliary disease.



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Colorectal scintigraphy is used in small animals for the detection of PSVAs.[31] In these studies, a small amount of ^{99m}technetium pertechnetate is administered rectally and absorbed across the colon into the portal venous system. In the normal dog, radioactivity is visualized in the liver within 10 to 22 seconds and subsequently moves to the heart and lungs. In animals with PSVAs, radioactivity reaches the heart and lungs first or at the same time as the liver. Rectal technetium scans are abnormal in dogs with macroscopic PSVAs or acquired shunts from chronic parenchymal disease and normal in dogs with microvascular dysplasia or parenchymal disease without acquired shunts.

225.12.2 Ultrasonography

Ultrasonography enables differentiation between focal and diffuse disease, evaluation of alterations in hepatic parenchyma in diffuse disease, evaluation of the biliary system and portal vasculature, and procurement of tissue for hepatic histopathology.[32,30]

The normal liver has a homogenous echogenicity that is isoechoic to slightly hyperechoic to the renal cortex. It has sharp, smooth edges and contains numerous variably sized circular and tubular anechoic structures that represent hepatic and portal veins. Hepatic arteries and intrahepatic bile ducts are not routinely visualized. The gallbladder is seen as an anechoic structure with thin walls varying from oval to pear shaped. It may be bilobed in the cat. The common bile duct can be visualized as a tubular anechoic structure just ventral to the portal vein. During hepatobiliary disease, changes in hepatic size, vascularity, and echogenicity may occur. It must be emphasized that few hepatic lesions have diagnostic sonographic features and that a normal hepatic ultrasound does not rule out the possibility of diffuse hepatic disease.

The determination of liver size by sonography is, at best, subjective. A large liver may be easily imaged and has rounded edges. There will be a relatively large distance between the diaphragm and stomach. A small liver may be difficult to image, with a narrow distance identified between the diaphragm and stomach.

In diffuse hepatic disease the liver may appear hyperechoic or hypoechoic. The hyperechoic liver is brighter than the renal cortices. Portal vein margins become indistinct in the hyperechoic liver. Increased echogenicity may accompany fibrotic liver disease, lipidosis, corticosteroid hepatopathy, or hepatic neoplasia (lymphoma, bile duct adenocarcinoma). The fibrotic liver can be distinguished from the other causes of increased echogenicity by its small size, the presence of regenerative nodules, and its association with ascites. In a series of cats with various hepatobiliary disorders, the finding of a hyperechoic liver that was isoechoic to falciform fat was highly suggestive of the presence of hepatic lipidosis. A hypoechoic liver is less echogenic than the renal cortices and has enhanced visualization of portal vasculature. It may accompany moderate to severe suppurative hepatic disease, passive congestion, or hepatic lymphoma.

The sonographic appearance of hepatic lymphoma can be quite variable. The liver may be diffusely hyper-or hypoechoic. There may be focal or multifocal poorly circumscribed hypoechoic masses or well-circumscribed hyperechoic nodules surrounded by areas of hypoechogenicity (so called target lesions).

A variety of focal hepatic lesions can be recognized with ultrasonography. Hepatic cysts appear as round, smooth-walled, anechoic structures with acoustic enhancement. Biliary cysts appear as thin-walled, circular, anechoic structures. Hematomas have a variable appearance, depending on their state of resolution. Early hematomas are hyperechoic and progress to hypoechoic; once they mature, they are anechoic. They may have areas of mineralization. Regenerative nodules also have a variable appearance. They may be hypoechoic, isoechoic, hyperechoic, or have mixed echogenicity. Variably sized multiple hypoechoic areas often exist; some areas may appear anechoic if necrosis occurs within them. Abscesses or granulomas have a variable appearance, depending on their cellular composition and duration. Early abscesses are hyperechoic with poorly defined margins. As they mature they become more hypo-to anechoic and may have mixed echogenicity. The presence of gravity-dependent hyperechoic cellular material may be demonstrated. Occasionally they may contain gas or mineralization. Some posterior acoustic enhancement may occur.

Primary hepatic neoplasia may have a variable appearance.[8] It usually is a large, solitary, moderately circumscribed mass that bulges beyond the normal liver margins with an echo texture similar to normal liver.

Metastatic neoplasia appears as one or more spherical lesions that may be hypoechoic, hyperechoic or isoechoic. It may also appear as a target lesion.

Ultrasonography is important in determining the presence of EHBDO.[32] The first indication of EHBDO is distention of the gallbladder with loss of tapering of the neck into the cystic duct. This occurs 24 hours after experimental bile duct ligation in the dog. The common bile duct distends by 48 hours postligation. Extrahepatic bile ducts dilate by 72 hours and are visible as many tortuous anechoic structures at the portal hepatis between the gallbladder and the pancreas. Intrahepatic bile ducts distend by 1 week and are seen as tortuous, irregularly branching anechoic structures with echogenic walls throughout the liver. In cats, distention of the common bile duct to greater than 5 mm is consistent with EHBDO.[33] Ultrasound also enables visualization of the cause of the obstruction that may be associated with intraluminal (neoplasia, strictures, choleliths) or extraluminal (pancreatitis, neoplasia) disorders.

Abdominal ultrasonography has an accuracy rate of about 90% for the diagnosis of PSVAs.[31] Animals with PSVAs have small livers with a decrease in portal vascular structures and may have bilateral renomegaly and uroliths. The abnormal connection between the portal vein and the systemic vasculature may be visualized. In general, intrahepatic shunts are easier to visualize than extrahepatic shunts. Portoazgous shunts are the most difficult extrahepatic shunts to identify. Doppler capabilities can enhance the ability to detect extrahepatic shunts. Dogs with extrahepatic shunts have high-velocity turbulent flow in the portal vein, and preliminary studies show a decreased portal vein size as assessed by comparison of the portal vein with the aorta or caudal vena cava. Acquired portosystemic shunts are more difficult to visualize by ultrasound but can be seen in the retroperitoneum near the kidneys or medial to the spleen. Other signs of portal hypertension such as ascites, decreased or reversed portal blood flow, and microhepatica are seen when acquired shunts are present.

Hepatic arteriovenous fistulas can be seen with as tortuous, tubular, anechoic structures within or adjacent to the liver. Doppler-assisted ultrasonography demonstrates areas of turbulent blood flow. The hepatic artery and portal vein branches may be dilated and tortuous. Celiac arteriography is used to identify arteriovenous fistulas and to define the limits of surgical resection.

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226 CHAPTER • 226 General Principles in the Treatment of Liver Disease

Jan Rothuizen

226.1 INTRODUCTION

Many generally accepted and clinically used medications for liver disease lack critical evaluation of their effectiveness. A scientific basis for proof of effect of a medication may be obtained in different ways.

First, there may be a well understood and direct connection with the pathophysiologic basis of the disease. An example is the use of thyroid hormone to treat hypothyroidism caused by decreased production in the thyroid glands. A firm and direct relationship should be present between cause of disease and medication to accept such as a basis. A proven pathophysiology-based therapy in human medicine supports the use for comparable lesions in veterinary medicine. An example is ursodeoxycholic acid (UDCA) therapy in nonobstructive cholestatic diseases. Proof in humans, however, is not proof for dogs or cats and does not eliminate the need for veterinary studies.

The second way a therapy can be accepted as scientifically based is when an effect has been proven in clinical trials. The best method is a randomized, double-blind, placebo-controlled study. No reports exist in the literature of any randomized, placebo-controlled, double-blind studies on the effect of a treatment of liver disease of dogs or cats. Because few, if any, clinics have a sufficient case load to perform a number of such studies within a reasonable time, the only way to test therapies for liver diseases is to perform multicenter studies. Bearing in mind that sound studies on the effectiveness of a drug can only be performed by evaluating one (additional) drug per trial, it is clear that a lot of work must be done. Accepting the need for multicenter studies identifies the need for standardization of the nomenclature and diagnostic criteria for diseases. The diagnosis of the majority of canine and feline liver diseases depends largely on the histologic evaluation of liver tissue, obtained by one of several possible biopsy techniques. It is well known that evaluation of one liver specimen by different histopathologic produces different interpretations, often even a range of different diagnoses. Moreover, in different countries or continents, the same disease may be known under different names without clinicians realizing that it is one disease. The need for standardization of diagnostic criteria of diseases and stages of disease, as well as the unification of nomenclature, has recently been recognized by the World Small Animal Veterinary Association (WSAVA), in cooperation with the American and European Colleges of Veterinary Internal Medicine, ACVIM and ECVIM. This group has agreed on the standardization of nomenclature and histopathologic interpretation of liver tissues of known liver diseases of dogs and cats. The results are being published in a book (see www.wsava.org), providing descriptions and color slides of histologic features. These standards will be updated every 3 years. The availability of standardized criteria and nomenclature will aid multicenter studies on liver diseases.

226.2 DRUGS USED FOR TREATMENT OF LIVER DISEASES

226.2.1 Glucocorticoids (Prednisone and Prednisolone)

The use of corticosteroids has been common practice in human medicine for 30 to 40 years. Mononuclear inflammatory cells, lymphocytes, and plasma cells in chronic hepatitis leads to the assumption that (auto-) immune reactions were the main cause of ongoing, chronic hepatitis leading to the development of cirrhosis. The recognition of hepatitis viruses A and B limited this category to nonA-nonB hepatitis and later

nonA-nonB-nonC hepatitis after discovery of hepatitis C virus. These terms have been abandoned in human medicine. Many different viruses cause many different forms of hepatitis. Only a small and well-defined group remains classified as autoimmune hepatitis that is treated with corticosteroids. The different forms of viral hepatitis require specific antiviral treatment or only supportive treatment. Recognition of new canine viral and metabolic causes may lead to development of specific treatments for different forms of hepatitis that are now taken together as idiopathic hepatitis. Presently, steroid therapy is the best-documented and most generally used therapy for chronic hepatitis. Many anecdotal reports exist. Only one publication[1] reports the evaluation of the effect of glucocorticoids on the survival in a large series of dogs with chronic hepatitis in which there was a highly significant increased survival found in treated compared with untreated dogs. Complete remission was described, and no relapse occurred when recovery from hepatitis was reached. This report was a retrospective, uncontrolled study. The general experience of veterinary hepatologists is that glucocorticoids are often effective in treating chronic hepatitis in dogs. Prednisone needs to be metabolized into prednisolone by the liver. It is logical to use prednisolone in case of liver disease. Prednisolone can be regarded as a treatment of first choice for idiopathic chronic hepatitis. For cases in which a defect in copper metabolism is known, leading to copper storage and oxidative damage of the liver, specific chelating therapy instead of steroids is indicated. Corticosteroids have anti-inflammatory effects but also antifibrotic and choleretic effects. Their principle indication remains immunomodulation. For stimulation of choleresis, UDCA is much more effective, and the weak effect on formation of fibrosis does not justify the use of corticosteroids for treatment of fibrosis without mononuclear inflammation.

Glucocorticoids are contraindicated for infectious diseases of the liver and biliary system. They should be reserved for chronic hepatitis with mononuclear inflammation of which no infectious cause is known. Toxins, viruses, and so on may cause acute hepatitis, but the specific cause remains unknown in most cases. Most acute hepatitis cases recover spontaneously without treatment or with only symptomatic support (antiemetics, fluid therapy). Given the similarities between hepatitis in dogs and other species in which hepatitis is nearly always caused by viral infections, at least some dogs with acute hepatitis may have an active viral infection. This may be overcome by the immune response so that the dog recovers or in some cases develops a chronic inadequate (auto-) immune response. In the chronic stage of disease, immunosuppression may help to reduce the inflammatory effects without treating the underlying cause. In acute cases such medication is contraindicated. The author has seen a number of dogs with acute hepatitis develop a sudden fatal deterioration when corticosteroids were given. Side effects of glucocorticoids are detailed in Chapter 242.

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226.2.2 Azathioprine

If immunosuppression is the desired action of therapy and glucocorticoids yield unacceptable adverse effects, azathioprine is an alternative drug. By combining azathioprine and glucocorticoids, the steroid dose can be reduced so that side effects can be avoided or made acceptable. A disadvantage of azathioprine is bone marrow suppression. It is more expensive than glucocorticoids and is also potentially toxic to humans. The owner should use gloves during administration, and tablets should be chosen so that they do not need to be broken, thereby exposing the owner to inhalation of small particles. No studies have reported the effects of azathioprine in liver diseases. Azathioprine is not a preferred drug to treat liver diseases other than in rare cases that do not tolerate glucocorticoids. Azathioprine should be avoided in cats because severe side effects are common.[2]

226.2.3 Ursodeoxycholic Acid

UDCA is one of the natural bile acids in the enterohepatic circulation.[3] It is synthesized and manufactured as tablets or capsules (e.g., Actigall, Ursochol) that are used in both human and veterinary medicine. Bile acids are produced and conjugated in the liver, and they are kept very efficiently in the enterohepatic cycle. The primary bile acids (those primarily formed in the liver) are transformed by intestinal bacteria into secondary and tertiary bile acids so that a mixture of bile acids circulates. Some bile acids are highly toxic, especially in the liver where they are concentrated. The less hydrophilic the more toxic the specific bile acid tends to be[4]; the most toxic bile acid is lithocholic acid. The hydrophilic UDCA is nontoxic in concentrations encountered in normal or diseased liver. Toxic bile acids have a number of negative effects. They induce apoptosis[5] of hepatocytes by activation of the Fas receptor, which activates intracellular signaling of the apoptosis pathway. Liver cell necrosis is also induced by altered permeability of the mitochondrial membrane due to high concentrations of bile acids. Disruption of the mitochondrial electron transport chain leads to formation of free radicals and oxidative damage to the cells.

The proposed positive actions of the nontoxic bile acid UDCA are fourfold. UDCA has been shown to prevent cells from entering the apoptosis pathway and to prevent mitochondrial damage. The exact mode by which these actions occur is not known. One explanation is that toxic bile acids, such as lithocholic acid, circulate in the enterohepatic circulation and accumulate in the liver cholestasis. They are displaced from the bile acid pool by constant enrichment of the pool with UDCA. Another explanation is induction of an increased bile flow by UDCA. Active bile acid excretion into the bile canaliculi by hepatocytes is one of the main mechanisms in which bile is formed because excretion of bile acids against a huge concentration gradient is followed by water, building the flow of bile.[6] Addition of external bile acids to the pool induces the need for hepatocytes to excrete more bile acids, thereby enhancing the bile flow and efflux of toxic bile acids. The enhanced bile flow explains also why UDCA is contraindicated in cases of extrahepatic bile duct obstruction. The third action of UCDA is modulating the immune system, resulting in reduction of the immune response, which may be favorable in cases where autoimmunity is part of the trigger for ongoing disease.

Finally, UDCA has recently been shown to increase the production of glutathione (GSH)[4] and metallothionein in hepatocytes, which could help to prevent oxidative damage.

Both dogs and cats are given 15 mg/kg/day, divided over two doses. UDCA has virtually no side effects in therapeutic doses. It is therefore a safe drug that at least does no harm to the patient. However, no published studies are available on the clinical effect of UDCA in dogs or cats. Although in theory UDCA may be used in a wide spectrum of diseases, it has only been proven effective in human chronic cholestatic disease such as primary biliary cirrhosis.[7–9] At present, the main indication in analogy to use in human medicine seems to be chronic severe cholestatic diseases such as destructive cholangiolitis in dogs and lymphocytic cholangitis in cats.

226.2.4 Antioxidants

Oxidative stress and damage of cells by free oxygen radicals is a mechanism extensively studied in recent years. Factors such as reduced blood perfusion, inflammatory reactions, and accumulation of copper or iron in the liver may be incriminated in the development of hepatocyte necrosis and hepatitis. Copper toxicosis results in chronic hepatitis or hemolysis, specifically by oxidative damage caused by free copper in the cell. Oxidation is also the principle mechanism by which phalloidin,[9–11] produced by the mushroom *Amanita*

phalloides and acetaminophen[12–14] may cause severe, sometimes fulminant liver failure. Oxidative stress is also a key step in the pathogenesis of ethanol-associated liver injury in man. The main sources of free radicals are hepatocyte mitochondria, cytochrome P450 enzymes, and endotoxin-activated macrophages (Kupffer cells).[15] Free radicals take up electrons from neighboring molecules, causing oxidative damage to lipids, proteins, and DNA. The normal cellular defense mechanisms against oxidative stress are superoxide dismutase (SOD), catalase, and GSH peroxidase. Depletion of GSH may cause exhaustion of part of the cellular defense and oxidative damage. Nutritional vitamins C and E act also as free-radical scavengers.

It is logical to separate the liver diseases in which oxidation is the principle event leading to tissue damage and inflammation (such as amanita and acetaminophen intoxication and copper storage diseases) and liver diseases (such as viral or idiopathic hepatitis) where oxidative stress may be one factor in a series of events but not the key factor. The beneficial effect of antioxidant therapies has been well-proven in amanita-and acetaminophen-induced damage, both in experimental animal models[9,11–13] and in human[10] and veterinary medicine.[14] For copper storage diseases in which free intracellular copper is the trigger for free-radical formation, the best therapy remains direct elimination of free copper by copper-chelating drugs such as penicillamine. No reports exist on the effect of antioxidant therapy in copper storage diseases of dogs; therefore clinicians have no reason to consider such therapies in addition to chelating drugs. The only event in copper storage diseases in which use of antioxidants is logical is hemolytic crisis that has at least been described in Bedlington terriers, similar to humans with Wilson's disease. Such an acute and severe oxidative stress requires all possible medications available to save the animal, and chelating therapy together with antioxidants may be life saving. The use of antioxidant therapy in other liver diseases is much more speculative, because oxidative damage is only one factor in a complex pathogenesis. Several antioxidants may be used as therapy; however, no scientific reports exist on efficacy and use is speculative. The main antioxidants are vitamin C, vitamin E, silymarin, and S-adenosyl-L-methionine (SAMe). In addition, zinc and UDCA have antioxidant function.

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226.2.5 Vitamins C and E

These vitamins are normally synthesized by dogs and cats, whereas humans cannot make vitamin C (ascorbate). Vitamin C is one of the physiologically soluble intracellular antioxidants. It is not known whether deficiency can occur in disease, and no reports exist regarding the clinical effect of supplementation. In LEG rats with hepatic copper storage due to Wilson's disease, addition of vitamin C to the diet prolonged their lives and retarded hepatitis and jaundice.[16] Vitamin E (alpha tocopherol) is also a nutritional antioxidant that protects against different routes of membrane peroxidation. It is not known if vitamin E is deficient in liver diseases, and no systematic evaluations of the effect of supplementation in such diseases exist. It is a lipid-soluble vitamin so, theoretically, it is expected to be helpful in cholestatic diseases. Excess of vitamin E has no side effects.

226.2.6 S-Adenosyl-L-methionine

SAMe is a natural metabolite in the hepatocytes. It is a precursor for cysteine, which is one of the amino acids of GSH. GSH forms one of the main defense mechanisms of the cell against intoxications, and depletion causes oxidative stress. Depletion might occur by exhaustion due to exposure to toxic substances. SAMe is important in the defense against free oxygen radicals.[12–14] The precursor of SAMe is methionine, which is activated by SAMe-synthetase. Theoretically, deficient capacity of this liver enzyme as a consequence of liver disease could cause inadequate production of SAMe and GSH. SAMe is nontoxic, and administration of

exogenous SAMe could restore deficient GSH in the hepatocytes. One report[17] exists of GSH levels in the liver of naturally occurring liver diseases of dogs and cats. This report showed greater variation (both decreased and increased) of GSH levels in disease than in health, which makes it difficult to conclude that low levels are a critical factor in the pathogenesis of such liver diseases. No evidence-based reports are available of clinical trials on the effect of SAMe treatment.

226.2.7 Silymarin

Silymarin or silibilin is the active component extracted from the fruit of *Silybum marianum,* milk thistle. Silymarin has been used for centuries in human medicine as treatment for liver diseases. It appears to be a strong free-radical scavenger by increasing cellular SOD. Many reports exist concerning its protective and even life-saving actions on the liver after intoxications with the mushroom toxin phalloidine[9–18] or acetaminophen, both of which exert their toxic effects by oxidation. Both experimentally and in human clinical medicine it appears very effective against these toxins. The typical oxidative changes of the mitochondria can be prevented in experimental intoxications with mushroom toxins, and this leaves no doubt about the therapeutic potential of silymarin. Treated dogs had lower liver enzymes, reduced prolongation of prothrombin times, and survived in one trial, whereas one third of the placebo-treated dogs died.[9] It is not known how long after intoxication silymarin has beneficial effects; reports vary from 10 minutes[9] to 5 hours.[18] This may also depend on the amount of toxin and the effective dose of the milk thistle extract. No studies have compared the protective effect of silymarin with other antioxidants such as vitamin E, SAMe, or N-acetyl-cysteine.[10]

No evidence proves that antioxidants have a beneficial effect in liver diseases not primarily caused by oxidative damage. For intoxications with phalloidine or acetaminophen, both silymarin and SAMe proved to be protective in experimental rodent studies and dogs; however, no comparison exists that is most effective. For liver diseases caused by congenital copper storage diseases, antioxidant therapy may be additional to chelating drugs. A beneficial effect has only been proven in LEG rats with Wilson's disease,[16] and no studies have shown that combining chelating drugs with vitamin yields better results than chelation alone.

226.2.8 Antifibrotic Drugs

Fibrosis is the unavoidable sequel of chronic liver disease, and untreated or untreatable chronic liver diseases end in fibrosis, cirrhosis, and incapacity of the liver to regenerate. Increased lipid peroxidation in hepatocytes activates the mesenchymal hepatic stellate cells (HSCs). Transforming growth factor beta-1 (TGF-β) is the principle and most potent fibrogenic cytokine and is produced by Kupffer cells and HSCs.[19,20] HSCs are also the primary target cells that produce extracellular collagen matrix.[21] Specific drugs to inhibit TGF-β[20] are not clinically available. Hepatocyte growth factor (HGF) is the principle hepatotrophic factor for liver regeneration, and it suppresses hepatic fibrogenesis in animal experiments. Inhibitors of HSC also exist.[19,20] These three most promising routes (inhibition of TGF-β, inhibition of HSC, and stimulation of HGF) to actively reduce liver fibrosis and stimulate liver regeneration are not beyond the experimental stage. Presently the reduction of lipid peroxidation (which reduces HSC activation) is the only clinically available method. Silymarin, SAMe, and vitamin E are most promising in this respect, but no clinical studies exist. One certain way to stop fibrogenesis of the liver to prevent cirrhosis is to treat the underlying disease and thereby stop progression of fibrosis. This is certainly an explanation of why drugs such as prednisolone, azathioprine, penicillamine, zinc, and vitamin E have been mentioned as having antifibrotic effects.

Colchicine is the only drug used specifically to stop and reduce fibrosis. It is thought to act via stimulation of collagenase activity. The disadvantage is that side effects have been reported, such as vomiting, diarrhea, and neurologic signs but side effects are rare. Neither in human medicine nor in veterinary medicine has the clinical effect been proven. In large clinical studies in humans, no effect was shown[22,23]; in veterinary medicine only several anecdotal reports exist in which colchicine was always part of multidrug therapy. No reports exist concerning the use of colchicine to treat liver diseases in cats. The use of colchicine in veterinary medicine should be postponed until it has been firmly proven effective.

226.2.9 Anticopper Medications

One cause for chronic hepatitis which is rare in humans but may be much more important in dogs is storage of copper in the liver, which can induce oxidative damage due to free intracellular copper. Copper toxicosis in Bedlington terriers has been the historical example of this form of chronic hepatitis that is caused by a deletion in the Murrl gene.[24] A number of forms of chronic hepatitis exist in different breeds that have been attributed to copper storage as the causative factor. These breeds are Bedlington terriers,[24] Skye terriers,[25] Dalmatians,[26] West Highland white terriers,[27] and Turkish shepherds.[28] Copper may also accumulate as a result of impaired biliary excretion secondary to cholestatic diseases. Thus hepatitis in Dobermans and Labrador retrievers may be a primary copper metabolic disease or secondary copper accumulation due to intrahepatic cholestasis in the course of hepatitis.[29] The increasing list of diseases in which hepatic copper accumulation may be the primary cause, indicates that specific therapies aimed at reducing free copper in the liver may become more important. Excessive copper is generally stored and encapsulated in the hepatocyte lysosomes, and cannot be reached by chelating drugs. Because it is the free cytoplasmatic (and not the lysosomal copper) that causes oxidative damage, quantitative copper measurement does not necessarily reflect the success of chelating or other therapy. Only diseases in which copper accumulation is the primary defect need specific anticopper medication. If copper accumulates as the consequence of a cholestatic disease, specific treatment of the underlying disease will reduce the amount of free cellular copper. The rationale for additional chelating medication has never been proven for such diseases. Chelating drugs should be used with some care because dogs treated for long periods with chelators can develop copper deficiency.

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Three forms of anticopper medications are available for treatment of primary copper storage diseases. First, chelating drugs can actively bind free extracellular copper, upon which the complex is excreted into the urine by the kidneys. Extracellular copper exchanges with free intracellular copper so that by constant exhaustion of the extracellular copper pool, the toxic intracellular excess is also removed. At present two copper chelators are available. D-penicillamine has been the first drug successfully used to treat humans with Wilson's disease, and it has also been widely used to treat Bedlington terriers with copper toxicosis.[30,31] The author's experience in about 100 Bedlington terriers diagnosed at 1 year of age is that medication with penicillamine from young age on prevents the development of hepatitis and clinical signs. This was, however, not tested in a double-blind, placebo-controlled, and randomized study. The alternative copper chelating drugs are 2,2,2-and 2-3-2-tetramine tetrahydrochloride.[32] The 2-3-2-tetramine form gives higher cupriuresis in healthy dogs, and it has been used in one clinical study. However, only the 2,2,2-tetramine form (Trientene) is commercially available. Trientene may be more efficient in copper chelation than penicillamine, because copper deficiency as a result of chronic use has only been reported for Trientene.[31] The advised dose for both chelators is identical: 10 to 15 mg/kg twice daily. The effect of Trientene in copper storage diseases has only been mentioned anecdotally. It is therefore difficult to advise that it is the most appropriate copper chelating drug for dogs. Based on the facts that much more experience exists with D-penicillamine in dogs, and that it

remains the preferred drug for humans with Wilson's disease, the author's preference is to use D-penicillamine. Penicillamine may have infrequent side effects, mainly nausea and vomiting. It is therefore preferred to give it twice daily together with meals. This is also the best time of administration because the blood levels will be highest at the time alimentary copper is absorbed. A second anticopper medication is zinc[33] gluconate or acetate in capsules for oral use (10 mg elemental zinc/kg twice a day). In the intestinal tract, zinc induces metallothionein in the enterocytes. This protein binds copper, and the complex is sequestered with the senescent enterocyte into the intestinal lumen. Unlike chelating drugs, zinc salts should be given 1 hour before each meal, so induction of metallothionein has taken place when alimentary copper is absorbed. Combinations of chelators and zinc salts should be avoided, because when the chelator binds zinc the removal of copper becomes less effective. The positive effect of zinc therapy has been evaluated critically in humans and has been reported anecdotally in dogs with copper storage disease. The indications for zinc therapy and chelating drugs are different. Chelators bind free copper actively and thus are an effective way to quickly remove the free intracellular copper that causes the hepatic damage. Copper chelators should be used as a routine for about 3 months to achieve complete inactivity of the hepatitis. Zinc should be used as a preventive drug to avoid accumulation of free copper in the liver. It is therefore especially effective when given to young dogs in which copper storage has been diagnosed but in which no hepatitis is present yet. This was usually done by copper measurement in liver biopsies of Bedlington terriers when they were 1 year old. At that age copper accumulation is sufficient to be diagnostic but not yet enough to produce hepatitis. The author's clinic has treated about 70 young Bedlington terriers with subclinical copper toxicosis life-long with zinc gluconate (clinical disease has been prevented in all cases). Presently, DNA tests can be performed at young age so that liver biopsies can be avoided. It is also possible to treat dogs with clinical disease due to copper excess for several months with D-penicillamine; when liver biopsies prove recovery from hepatitis, renewed accumulation can be prevented with life-long zinc medication. Zinc gluconate has side effects other than transient inappetence in rare cases. Very long treatment can induce copper deficiency.[32] It is cheap and therefore the preferred form of treatment to prevent copper-associated hepatitis. When higher than the recommended doses are given very long, zinc intoxication can cause hemolytic anemia. The third potential form of medication for copper storage diseases is through antioxidants. It is more logical to treat the cause by removing copper by chelation rather than to fight the effects. However, in rare cases in which excessive copper causes hemolytic crisis,[34] it may be advisable to combine chelating drugs and antioxidants such as SAMe, silymarin, or vitamin E.

226.2.10 Treatment of Ascites in Chronic Liver Disease

Ascites typically is a late sign of decompensation in the course of chronic liver diseases, such as chronic hepatitis, cirrhosis, and portal vein hypoplasia in dogs. Cats very rarely have ascites due to chronic liver disease. The portal blood pressure is only high enough to cause ascites without hypoalbuminemia in cases of acute complete obstruction of the portal vein by thrombosis and congenital arteriovenous fistulas. Whatever the cause, in all liver diseases associated with ascites the high portal pressure may also lead to formation of portosystemic collateral vessels and various grades of hepatic encephalopathy (HE). The potential risk for HE brings the need to use diuretics with caution.[35] The main complicating factors by which HE may induce coma that may be lethal are alkalosis and hypokalemia. Only the nonionized NH_3 form of ammonia penetrates cellular (neuronal) membranes. In any form of alkalosis the reaction equilibrium: $NH_3+H^+ \times NH_4^+$ shifts to the left. Therefore ammonia is much more toxic in alkalosis. In case of hypokalemia the plasma potassium is replenished by shift of potassium from the cells, in exchange with sodium and hydrogen ions. The resulting hydrogen shift causes alkalosis in the extracellular fluid and acidosis in the cells so that ammonia can easily penetrate cells. Intracellularly it becomes ionized in which form it cannot leave the cell. Blood ammonia,

which is the best parameter to monitor HE, may then be surprisingly low in relation to the severity HE because most of it is trapped inside the cells. This cellular ammonia trap is easily activated with the use of most diuretics. It is therefore better to use potassium-sparing aldosterone receptor antagonizing diuretics, such as spironolactone (2 to 4 mg/kg twice a day). Only if the dog eats well enough to have adequate supply of alimentary potassium to substitute the renal loss can loop diuretics be used. Combinations of furosemide and spironolactone may be very effective to treat ascites. It is important to monitor blood pH and potassium and to correct potassium deficiency.

In a relatively short period of several days or weeks, the abdominal accumulation of free fluid can account for more fluid than the entire circulating volume. In this period the renin-angiotensin-aldosterone system is highly activated, resulting in sodium and water retention and potassium loss. Intravenous fluid therapy and potassium compensation is necessary when the dog does not eat or drink sufficiently. Complete paracentesis of ascetic fluid may complicate HE and should be avoided in liver patients.

Chronic hepatitis and even cirrhosis with active inflammation may improve so much upon treatment with corticosteroids that the disappearance of the inflammatory infiltrates provides enough reduction of portal pressures to induce remission of ascites. A low-sodium diet may help to keep the ascites controlled. 1438 1439

226.2.11 Treatment of Hepatic Encephalopathy

The source of the known toxins causing brain neurotransmitter changes known as *HE* is protein digestion in the intestinal tract. Ammonia and aromatic amino acids are the two main factors.[35] Both require portosystemic collateral circulation, either congenital or acquired due to chronic portal hypertension, to reach the systemic circulation and the blood-brain barrier. The reserve capacity of the liver in dogs is enough to prevent HE in liver disease without collateral circulation. Cats do not make the essential amino acid arginine, and HE may occur without shunting as a result of fasting. Arginine is an essential intermediate of the hepatic urea cycle, and deficiency causes inadequate detoxification of ammonia. These cats often develop hepatic lipidosis simultaneously. Lipidosis and HE are a manifestation of their inability to synthesize several essential amino acids. Large variations in susceptibility to these effects exist between cats.

Management of HE is different for dogs and cats with congenital or acquired portosystemic shunting and cats with HE due to fasting hyperammonemia resulting from arginine deficiency. Portosystemic encephalopathy, which is by far the most common form, should be treated with an appropriate diet of reduced protein content with specific reduction of sources of aromatic amino acids. Very strict reduction of proteins may be counterproductive; dog studies have shown that prevention of catabolism (i.e., negative energy balance) is more important than strict maintenance of low-protein intake. Another important factor is that lactulose and soluble fiber in the diet helps to reduce ammonia uptake from the large intestines. Lactulose and soluble fibers have many effects on ammonia metabolism; the most important effect is that it is metabolized by the colonic bacterial flora to produce acids that reduce the pH of colonic content. Ammonia is then present in the ionic form that is not absorbed and thus lost with the feces. Well-balanced commercial liver-support diets are available that meet these requirements of adequate energy content, sufficient reduction of protein with special emphasis on aromatic amino acids, and presence of soluble fiber. These diets are also low in copper and sodium. Sodium reduction may be important if portal hypertension is present, because in these cases not only HE but also ascites may form with interrelated metabolic complications as described previously. Low copper is not necessary in relation with HE or ascites, but is important in the management of those forms of canine hepatitis that are thought to be caused by copper metabolic diseases.

If diet alone is not sufficient to manage cases with portosystemic encephalopathy, clinicians can improve the HE status by giving oral lactulose. Lactulose was developed to treat constipation, because the disaccharide molecule is metabolized in the colon into multiple smaller molecules that increase the osmotic content of the colon and attracts water into the feces. The best guideline for use of lactulose for management of HE is to give just enough (twice daily) to reach slightly softer stool. The combination of diet and lactulose is often sufficient to manage chronic HE for many years in cases in which the underlying cause cannot be treated (inoperable portosystemic shunts, arteriovenous fistula, portal vein hypoplasia, inactive cirrhosis).

Deterioration of HE may occur due to several instances (see Ascites), the most important being catabolism, dehydration, alkalosis, hypokalemia, and formation of ascites. Sudden high intestinal ammonia production in the face of portosystemic collateral circulation may also cause sudden aggravation of HE. This may be caused by intestinal bleeding from gastroduodenal ulcers, which may be associated with chronic liver diseases. Blood is the most ammoniagenic protein, and in sudden deterioration it may be important to examine and treat possible gastrointestinal (GI) bleeding. Furthermore, key rules to control HE are measurement of blood pH, potassium, and ammonia, correction of hypokalemia, correction of hypovolemia, and intravenous feeding to correct catabolism. It should be understood (see Ascites) that the blood level of ammonia and potassium are reflections but not exact representations of what is going on in the neurons.

One factor in the pathogenesis of HE is an increased activity of the neuronal GABA/benzodiazepine receptor system, which suppresses neuronal activity. For this reason, one should be extremely careful in using any sedation or anesthesia exploiting this receptor system. If necessary, inhalation anesthesia is safest, because it exploits different receptors and does not depend on liver function.

Finally, additional measures exist with beneficial effects that have never been proven in veterinary cases. One of them is the use of antibiotics such as neomycin to eradicate or change the intestinal flora. In humans, lactulose and neomycin can have synergistic effects. Neomycin may be an option to use as an enema in combination with lactulose in rare cases of HE crisis.

226.2.12 Hepatic Encephalopathy and Liver Lipidosis in Cats

Cats can have portosystemic encephalopathy just like dogs and humans. However, the cats, which are susceptible to develop liver lipidosis when fasting, are also prone to develop HE due to deranged metabolism. Having a shared metabolic basis, feline hepatic lipidosis and nonportosystemic HE require essentially the same therapy. With this understanding, the general rules concerning the influence of hypokalemia and alkalosis also apply to HE in cats.

Hepatic lipidosis in cats is essentially a consequence of catabolism from anorexia due to any cause. Lipidosis can develop within a few days but may also take 2 weeks to occur. Some cats can withstand prolonged fasting without developing clinically significant lipidosis at all. The precise pathogenesis of lipidosis is not known in detail, but catabolism leads to decreased insulin-to-glucagon ratio in the circulation, which stimulates hormone-sensitive lipase to release fatty acids. The liver is the main place for their metabolism. One of the principle routes by which the liver can make fat stores suitable for use in other tissues is by the formation of very low–density lipoproteins (VLDL). One of the essences of this complex metabolic disorder is the unavailability of essential amino acids. These are necessary for different liver functions, such as formation of apoproteins for composition of VLDL in which form accumulating triglycerides can be exported from the liver cells, and the urea cycle in which arginine is essential. For treatment of both HE and lipidosis it is therefore essential to restore the energy balance especially by giving proteins. High-energy diets containing predominantly fats or sugars do not help these cats. Feeding liquefied baby food or commercial high-energy

and high-protein veterinary formulations are equally good. The goal is to restore the energy balance and supplement amino acid deficiencies, especially arginine and taurine. L-carnitine may be an important factor because it may help the hepatocytes to exploit fatty acids in beta oxidation.[36] This is the only form of HE requiring high-instead of low-protein feeding. A daily caloric intake around 75 kcal/kg is adequate. The supplementation of vitamins by multivitamins may be beneficial in cats with long-term anorexia. When the cat is not yet too ill, a dedicated owner can often force-feed with a syringe. Otherwise a gastrotomy tube is most appropriate for long-term force-feeding without stress for the cat.[37] Force-feeding is often required for several weeks until the cat starts eating spontaneously. It is dangerous to stimulate appetite by diazepam administration. The risk for HE is a contraindication for drugs activating the GABA/benzodiazepine receptor system, over stimulation of which is part of the pathogenesis of HE. Cats with hepatic lipidosis can easily develop insulin resistance with hyperglycemia, which may gradually increase to glucose levels as seen in diabetes mellitus. The insulin resistance implies that very large doses of insulin would be needed, with the inherent risk for sudden hypoglycemia. A benefit of treatment with insulin has never been demonstrated, and it is advised to restrict therapy to forced feeding.

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Glucocorticoids are contraindicated because they stimulate lipolysis and fatty acid accumulation in the liver, induce catabolism, and increase the risk for hyperglycemia. Some authors advocate the use of antibiotics for cats with hepatic lipidosis, but a positive effect has never been proven. In the author's clinic, antibiotics are not given as a routine.

It is essential to try to identify the primary cause of anorexia. Not eating is very nonspecific and occurs for multiple reasons. It is often impossible to find an underlying disease. The reader should note that this may also be a primary liver disease[38] that may remain undiscovered when the diagnosis of lipidosis is based on thin needle aspirates of the liver. Neutrophilic or lymphocytic cholangitis and hepatic lymphosarcoma are the most frequent hepatobiliary diseases causing lipidosis. Finally, it is important to realize that some cats are metabolically predisposed to develop lipidosis and nonportosystemic HE, whereas other cats can withstand negative energy balance reasonably well. The predisposed cats will easily develop the same syndrome later in their lives, and it is important that owners understand this risk. Successful management is primarily dependent on early recognition of these metabolic disorders.

226.2.13 Dietary Therapies for Liver Disease

The most important requirements for dietary management of liver diseases have already been mentioned under ascites, HE, and feline hepatic lipidosis. Only the copper content of dog food requires an additional remark. Several copper-associated forms of chronic hepatitis exist in dogs. With careful evaluation of the causes of hepatitis in different breeds, clinicians may discover more forms of hepatitis in which abnormal copper metabolism is the primary problem. The goal is not only to treat these cases successfully with chelating and other drugs but also to prevent disease. This may at least in part be achieved by feeding a low-copper diet. It is very difficult to formulate a home-cooked diet containing very low copper. A realistic alternative is to use one of the commercial liver diets that contain much lower copper than regular diets.

226.3 PARENCHYMAL LIVER DISEASES

Parenchymal liver diseases may be divided into metabolic diseases affecting the liver (such as steroid hepatopathy, lipidosis of the liver in case of diabetes, or induced by catabolism in fasting cats), systemic diseases secondarily involving the liver (hypoxic necrosis of the liver, nonspecific reactive hepatitis due to endotoxemia), primary hepatitis (chronic or acute) of toxic, viral or unknown cause, copper storage diseases with secondary

hepatitis, and the end-stage of each form of chronic hepatitis: cirrhosis. Many of the metabolic diseases and the diseases in which the liver is secondarily involved do not require specific treatment. The regenerative capacity of the liver will result in spontaneous recovery upon successful treatment of the underlying disease. Parenchymal liver diseases that need specific treatment are acute and chronic hepatitis (including lobular dissecting hepatitis) and copper-associated hepatitis in dogs, cirrhosis in dogs, hepatic abscesses in dogs, and hepatic lipidosis in cats.

226.4 HEPATITIS IN DOGS

226.4.1 Acute Idiopathic Hepatitis

The cause of hepatitis is not known in most cases. Viruses may be the cause of acute idiopathic hepatitis in dogs in analogy to many other species. This implies that treatments with immunosuppressive drugs (prednisolone, azathioprine) that are being used for chronic hepatitis are contraindicated for acute hepatitis in which there may be florid viral infection. Most cases of acute hepatitis recover spontaneously and need only supportive care with antiemetics and fluid therapy. Oxidative intracellular damage may in theory be part of the pathogenesis of many liver diseases, including acute and chronic hepatitis. However, a positive effect of antioxidants has never been shown in acute idiopathic hepatitis. Acute hepatitis in dogs is almost never caused by bacterial infection. Therefore treating with antibiotics is not needed. In acute hepatitis the liver reserve capacity is almost never exhausted, so prevention of sepsis resulting from insufficient liver function by antibiotic medication is also not necessary. As a routine, idiopathic acute hepatitis, which is a histopathologic diagnosis, does not need specific treatment. Supportive care may be indicated: antiemetics in case of severe vomiting and fluid therapy in case of dehydration. The most important point in making the diagnosis of acute idiopathic hepatitis is that the disease may progress into chronic hepatitis. Usually recovery takes place in about 3 weeks. In a small number of cases, the author has seen acute hepatitis become chronic. This usually begins as a subclinical chronic hepatitis without clinical signs and is often unnoticeable with blood examination. It is therefore recommended to take a control biopsy 4 to 5 weeks after the diagnosis of acute idiopathic hepatitis so that the onset of chronic hepatitis can be discovered in an early phase. Beginning forms of chronic hepatitis can be treated very successfully with prednisolone (5 to 6 weeks 1 mg/kg/day, divided over two doses), preventing advanced fibrosis or cirrhosis. Untreated cases will become clinical in the very chronic stage, which is about 4 to 8 months later. In that stage it is usually not possible to achieve complete recovery of fibrotic damage.

226.4.2 Hepatitis and Necrosis Due to Phalloidine or Acetaminophen Intoxication

It is important to ask the owner if acetaminophen or mushroom toxins (phalloidine) may have been ingested recently. These toxic forms of hepatitis are caused by oxidative damage and require specific treatment. Phalloidine intoxication should be treated with silymarin (50 mg/kg/day) for 3 to 5 days. The success depends on early recognition and immediate therapy. Silymarin has been reported to lose its effect when given a few hours after intoxication. Any other antioxidant therapy such as SAMe should also be useful, but reports have focused on silymarin.[9] Supportive care, induction of vomiting in very acute intoxication, and measures to prevent or reduce HE are also indicated. Many dogs die within 1 week due to liver and kidney failure. Acetaminophen intoxication should be treated similar to phalloidine intoxication. Several reports exist concerning the favorable effect of SAMe treatment[12–14] for acetaminophen intoxication (800 mg/kg/day), but the classical treatment is with the combination of N-acetylcysteine[10] (140 mg/kg orally, every 6 hours during 3 days), vitamin C (25 to 35 mg/kg orally, every 6 hours for 2 days), and cimetidine 5 mg/kg twice a day for 4 days. Historically, acetaminophen and phalloidine intoxication have different treatments, but it is logical to

expect good effect of both silymarin and SAMe, in conjunction with symptomatic therapy. Dogs with acetaminophen intoxication may have hemolysis and blood transfusion may be required.

226.4.3 Leptospirosis

Leptospirosis is an acute disease, primarily of the kidneys, but it also causes a nonspecific reactive hepatitis with intrahepatic cholestasis. Icterus is therefore common, although the symptoms arise mainly from acute nephritis.[39–40] Each dog with acute disease displaying icterus and acute renal failure should be treated immediately with ampicillin or amoxicillin and clavulanate.[40,41] Early institution of antibiotic therapy may be life saving. If the diagnosis is confirmed by high immunoglobulin M (IgM) titers, antibiotics are continued until kidney function is restored. Then latent bacteria in tubular epithelial cells that may cause leptospiruria should be eradicated with streptomycin given for 2 consecutive days. The acute renal failure should also be treated with fluid therapy.

226.4.4 Liver Abscess

Liver abscesses are rare in dogs and cats. Treatment is by surgical removal after pretreatment with antibiotics. The choice for specific antibiotics should be based on culture of an ultrasound-guided thin needle aspirate. *Staphylococcus* and *Clostridium* are most common. Antibiotics should be administered long-term, (6 to 8 weeks). Hepatic abscesses occur predominantly in older dogs, and in the author's experience many cases have a liver cell carcinoma with central necrosis that became secondarily infected. This can easily be missed; therefore clinicians should also take histologic biopsies from the margins of the abscess.

226.4.5 Chronic Idiopathic Hepatitis

Chronic hepatitis is one of the most frequent liver diseases in dogs. In most cases it is not possible to indicate a cause (idiopathic hepatitis). The inflammatory cells are lymphocytes and plasma cells, indicating that at least part of the pathogenesis may be immune-mediated. The only well-documented therapy is with glucocorticoids. Prednisolone should be given until the inflammation (liver cell necrosis and infiltration with inflammatory cells) has recovered completely.[1] This cannot be concluded based on clinical signs or blood examination because both will be influenced by the glucocorticoid treatment. Therefore the only reliable way to evaluate the result is with repeated liver biopsies. It is usually possible to predict approximately how long the medication should be continued. High activity (necrosis of hepatocytes and presence of inflammatory cells) of the inflammation and high degree of fibrosis indicate the need for longer treatment than in cases of low active inflammation with little fibrosis. As a rule, chronic hepatitis should be treated for at least 6 weeks; severe cases require longer treatment up to 10 to 12 weeks. Dose regimens vary. Our routine is to use a continuous dose of 1 mg/kg/day, divided over two daily doses. In the author's experience, lower doses (0.5 mg/kg/day), medication on alternating days, or both is often less effective to achieve complete remission of the disease. If unacceptable side effects indicate the need to decrease the prednisolone, combination therapy with azathioprine can be given (both drugs 0.5 mg/kg/day).

Complete remission of the disease occurs in most of the cases. Fibrotic changes are usually permanent. When inflammation disappears the dogs are usually symptomless. Severe fibrosis or cirrhosis may require life-long support by dietary measures and lactulose.

226.4.6 Copper-Associated Hepatitis

Copper-associated forms of hepatitis occur in Bedlington terriers, West Highland white terriers, Skye terriers, Dalmatian dogs, and Turkish shepherds. If active hepatitis is found, treatment should be with copper chelating drugs such as penicillamine. Prevention of clinical disease in cases diagnosed early or maintenance therapy with chelation when the inflammation has stopped can be achieved with zinc salts. Details are given in the general section of this chapter. Dobermans, especially 5 to 7 years old females, may display a specific form of hepatitis, called *Doberman hepatitis*. The prognosis of this disease has generally been reported to be bad, and in the author's clinic almost all Dobermans with this disease die on the usual medications. In the author's clinic, Doberman hepatitis has been treated with penicillamine alone, and this has resulted in complete remission of the disease. This may be regarded as support for the hypothesis that copper storage plays a causative role in this disease. Double blind, placebo-controlled, randomized studies are needed.

226.4.7 Lobular Dissecting Hepatitis

This is a very severe form of hepatitis that develops rapidly and is usually lethal within 2 to 4 weeks. Extremely pronounced fibrosis occurs, which is the reason that despite the acute course, this disease is classified under the chronic forms of hepatitis. The disease occurs more in younger dogs and affects all breeds and both sexes. Medication with immunosuppressive drugs is usually without success. No reports exist on successful medical treatment for this disease. Treatment with colchicine[22,23] is appropriate for this disease.

226.5 DISEASES OF THE BILIARY SYSTEM

226.5.1 Destructive Cholangiolitis in Dogs

This is strictly not a form of hepatitis but an idiosyncratic reaction in dogs, nearly always to drugs containing sulfonamides. Necrosis of the smaller intrahepatic bile ductules is the result, and these dogs display extremely severe intrahepatic cholestasis. The first action is immediate withdrawal of the sulfonamide medication. The necrosis of the intrahepatic bile ductules is irreversible, and the only hope is that it is possible to save and exploit the remaining biliary system. In the author's experience, it is essential to start treatment with UDCA immediately. As a rule, life-long medication is needed to exploit the remaining biliary system optimally. When the dog shows enough response to justify hope for a long-term survival, the clinician should evaluate the long-term reaction in the liver. Chronic cholestasis may induce a chronic damage to the liver with continuous loss of functional hepatocytes and activation of the deposition of fibrous tissue. This may finally produce portoportal bridging fibrosis in the liver (biliary fibrosis) that, although the architecture of the liver lobules remains in tact, can give rise to portal hypertension. Ascites and formation of acquired portosystemic shunting may result. Long-term progress can often be predicted by evaluating liver biopsies 2 to 3 months after the start of treatment. If enough capacity of the intrahepatic biliary system remains, some dogs may be maintained with continuous ursodeoxycholic acid medication. In decompensating cases, supportive treatment or prevention of HE or ascites is indicated.

226.5.2 Neutrophilic Cholangitis in Cats

This disease is characterized by a neutrophilic inflammation of the biliary tract. The synonym is suppurative or acute cholangitis. This is essentially a septic disease, and it is therefore required to sample bile from the gall bladder by ultrasound-guided puncture with a thin needle for cytologic evaluation and both aerobic and

anaerobic culture with sensitivity testing. In the vast majority of cases *E. coli* is cultured, but *Staphylococci* or other bacteria may also be identified. It may in some cases be an infection superimposed on pre-existing bile duct obstruction associated with cholelithiasis, pancreatic, or intestinal disease.[42] Bile duct obstruction 1441
requires surgical decompression and antibiotic medication guided by culture of bile. The true uncomplicated 1442
neutrophilic cholangitis is an acute disease characterized only by bacterial infection of the bile ducts, as evaluated with the combination of bile culture, liver histology, and ultrasonography. Uncomplicated neutrophilic cholangitis responds quickly to antibiotic therapy. Amoxicillin-clavulanate, amoxicillin, or ampicillin may be the first choice treatment until the results of culture become available. Treatment for at least 4 weeks is necessary. If pre-existing bile duct disease is present, the treatment should be adjusted accordingly. The additional use of UDCA is often advised, but in the author's experience single antibiotic therapy is adequate in nearly all uncomplicated cases.

226.5.3 Lymphocytic Cholangitis in Cats

This is a very chronic disease of the bile ducts (both intra-and extrahepatic). Secondary inflammation with fibrosis may also affect the portal tracts. Both in the bile system and in the portal tracts, lymphocytes are the predominant inflammatory cell type. Because the principle site of the disease is the bile system and not the liver, the standardized name is *lymphocytic cholangitis* (synonyms cholangiohepatitis, chronic or lymphoplasmacytic or nonsuppurative cholangitis, sclerosing cholangitis). The cause is unknown, but a similar form of chronic cholangitis may be due to liver fluke infestation, which occurs on all continents. The very chronic bile duct inflammation of lymphocytic cholangitis causes irregularly distended, fibrotic bile ducts that are prone to secondary bacterial infection. The wide, irregular, but still more or less patent bile ducts that are visible on ultrasonography, should be distinguished from distension due to extrahepatic bile duct obstruction. In case of obstruction, treatment with UDCA is contraindicated,[4] whereas it is one of the most useful medications for lymphocytic cholangitis. In most cases the difference can only be made with histologic examination of a liver biopsy. The two diseases have different histological characteristics. Liver fluke eggs may also be visible histologically in the bile ducts, but they should also be evaluated with fecal examination.

Agreement on treatment of lymphocytic cholangitis is not yet settled. Similarities exist (with human primary sclerosing cholangitis and primary biliary cirrhosis) for which the pathogenesis is equally unknown but has been proposed to be autoimmune. This has prompted treatment of these cats with glucocorticoids (2 to 4 mg/kg/day). However, this has been found to be ineffective in most cases.[42] As confirmed by the author's experience, any response to even very long-term high-dose glucocorticoid medication is rare. Alternatively, methotrexate in addition to glucocorticoids has been proposed,[42] because this is used for human autoimmune disorders. However, this treatment is not without risk, and a positive effect has not yet been reported. Similarly, metronidazole may have an effect on cell-mediated immunity, and it has been advocated in combination with glucocorticoids. However, no reports are available on the evaluation of this combination.

UDCA may be the only generally advised drug for which at least a theoretic basis exists. It has beneficial effects on cholestatic diseases in different ways. Positive effects on nonobstructive cholestatic disease have been proven in human cholestatic diseases. UDCA (15 mg/kg/day, divided over two doses) is advised as the main therapy for this disease. Treatment should be given until the disease has resolved, which in many cats implies life-long medication. No adverse effects of this therapy have been reported in dogs or cats. It is imperative to exclude extrahepatic bile duct obstruction before starting UDCA medication.

Antibiotics may have a place in the treatment of cats with lymphocytic cholangitis, but no reports exist concerning the effect of chronic antibiotic medication. It is not logical to treat all cats with antibiotics. The bile culture (aerobic and anaerobic) is positive in some cats, presumably due to secondary infection of the

abnormal biliary system. It is advised to perform gall bladder puncture to obtain bile for culture and cytologic examination in all cats with cholangitis. Cats with a positive culture require antibiotics, based on the sensitivity tests. Long-term treatment is needed (6 to 8 weeks). At present, one should accept that the cause and pathogenesis of lymphocytic cholangitis is unknown, and that therapy is in most cases does not induce remission. Clinical improvement and slackening of the progression may occur.

If liver fluke infestation is present or suspected based on liver histology, the preferred treatment is with praziquantel (Droncit). Medication for 3 days (20 mg/kg/day) is most commonly given, but reinfections may occur. It is important to evaluate feces for fluke eggs after medication.

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227 CHAPTER • 227 Inflammatory Canine Hepatic Disease

Michael D. Willard

227.1 CHRONIC HEPATITIS

Chronic hepatitis (CH) refers to a syndrome that has previously been identified by several names (e.g., chronic active hepatitis, chronic persistent hepatitis, chronic lobar hepatitis). In this chapter, *CH* will refer to chronic (i.e., ε6 months) canine hepatic disease in which a hepatocellular necrosis exists that is associated with a predominately lymphoplasmacytic inflammation that typically progresses to fibrosis and cirrhosis. The cause, if known, should be included as an adjective (e.g., drug-induced CH, copper-associated CH); otherwise the CH is termed *idiopathic*. Additional descriptors (i.e., mild, moderate, severe) of the severity of the inflammation and of the chronicity as indicated by fibrosis are desirable.[1–3]

CH may have various causes (e.g., copper, drugs, infectious agents), and familial tendencies exist. Breeds that have been reported to have an increased frequency of CH include Doberman pinschers, Bedlington terriers, West Highland white terriers, Cocker spaniels, dalmatians, Skye terriers, standard poodles, Labrador retrievers, German shepherd dogs, Scottish terriers, and beagles.[1,2,4,5] Dogs 4 to 7 years old seem more commonly affected. Some papers suggest that females are more commonly affected, whereas others suggest that both sexes are at risk. However, particular breeds have definite sex predilections (e.g., female Doberman pinschers, male cocker spaniels).[1–3]

Most dogs with CH have idiopathic disease, and immune mechanisms may play an important role in some animals.[2,3] In one recent study, CD3+ lymphocytes were the most common lymphoid cells in the liver of 16 dogs with CH. The number of CD3+ cells was positively correlated with necrosis, and these lymphoid cells occasionally surrounded degenerating hepatocytes. Inflammation was worse in the earlier stages but then decreased as the livers became cirrhotic.[6] Whether this immune response was the cause of or an effect of the hepatitis remains to be elucidated. This is in keeping with another report that found that 54% of the hepatic lymphocytes in normal dogs were CD3+ cells.[7] Antinuclear antibodies and antibodies to liver membrane proteins have also been found in some dogs with CH, but again, cause and effect has not been clarified.[1,2]

Copper accumulation has been associated with CH in several breeds (Box 227-1). In Bedlington terriers, hepatic copper accumulation is the cause of the hepatitis; however, copper may accumulate secondary to cholestasis. In most other breeds the relationship between copper and CH is either uncertain or the copper accumulation is thought to be an epiphenomenon. Excessive hepatic copper accumulation secondary to hepatitis may be clinically insignificant, but hypothetically it might be able to further aggravate hepatic injury. Normal dogs generally have less than or equal to 400 µg copper/gm hepatic tissue, dry weight (i.e., parts per million [ppm]).[8] Dogs with greater than 2000 ppm usually have hepatic disease caused by copper, although one author stated that dogs may have 3500 ppm before hepatic disease occurs.[9] In dogs with hepatic disease, hepatic copper levels less than 1000 ppm are probably secondary to hepatic disease, concentrations greater than 2000 ppm are probably primary causes of hepatic disease, and concentrations greater than 1000 ppm are possibly primary causes.[8,10]

227.1.1 **Box • 227-1 Breeds That Have Been Associated with Increased Hepatic Copper Concentrations**

Bedlington terrier

Airedale terrier

Bull terrier

Bulldog

Cocker spaniel

Collie

Dachshund

Dalmatian

Doberman pinscher

German shepherd dog

Golden retriever

Keeshond

Kerry blue terrier

Labrador retriever

Norwich terrier

Old English sheepdog

Pekingese

Poodle

Samoyed

Schnauzer

Skye terrier

West Highland white terrier

Wire fox terrier

From Rolfe DS, Twedt DC: Copper-associated hepatopathies in dogs. Vet Clin North Am Small Anim Pract 25:399, 1995.

Iron also accumulates in the livers of dogs with hepatic disease. In one study, 54 of 95 dogs (56 of which had histologic evidence of hepatic disease) had excessive hepatic iron,[11] whereas in another study, 32 of 34 dogs with CH had increased hepatic iron.[12] Normal hepatic iron is 400 to 1200 ppm, but some dogs had up to 7680 ppm with a mean of 1354 ppm.[11] The presence of iron was correlated with the presence of hepatic injury, but there was not a linear relationship between the amount of iron and the degree of hepatic pathology. The iron accumulated in Kupffer cells and macrophages but not hepatocytes; therefore it was not hemochromatosis as reported in people. Rather, iron accumulation seems secondary to inflammation, necrosis, or copper accumulation (or a combination of these conditions). Some have hypothesized that such secondary iron accumulation in the hepatic parenchyma may aggravate existing hepatic damage.[11]

Alpha-1 antitrypsin (α1-AT), also known as alpha-1 protease inhibitor, has been hypothesized to be a cause of canine CH.[1] Accumulation of a genetically defective α1-AT in hepatocytes in people causes hepatocyte death and low circulating concentrations of α1-AT. As hepatocytes accumulate α1-AT, they die and attract mononuclear cells with cytokines that cause production of more α1-AT. In a study of 57 dogs with hepatic disease, 37 had α1-AT in their livers.[13] The authors noted that α1-AT accumulation was more frequently seen in dogs with chronic progressive hepatitis or cirrhosis. However, it was uncertain whether the α1-AT was the cause or effect of hepatic disease.

Clinical signs of dogs with CH vary with the stage at which they are diagnosed. Because CH is a slow, insidious disease, clinical signs are seldom apparent until the disease is relatively advanced. A patient with a sudden onset of clinical signs may have advanced disease. Dogs presenting in severe hepatic failure (e.g., with cirrhosis) typically are lethargic, depressed, anorexic, vomiting, weak, and have weight loss, polyuria/polydipsia (PU/PD), and/or ascites (or a combination of these problems).[1,2] Diarrhea is relatively common, but is typically not as prominent as is seen in patients with intestinal disease. Icterus is relatively uncommon, and seizures (e.g., hepatic encephalopathy), bleeding, and fever tend to be relatively rare. Dogs that have somewhat advanced disease but are not in severe failure often show lethargy, poor appetite, weight loss, and vomiting as prominent findings. Some animals are fortuitously diagnosed when routine health screening or blood testing for other diseases reveals

occult hepatic disease. These patients may be clinically normal and yet have reasonably advanced disease (even hepatic fibrosis) for which the patient is still compensating. This has major ramifications when considering anesthetic procedures. Hepatocutaneous syndrome is not typically associated with CH, although West Highland white terriers and Cocker spaniels seem to be at increased risk for both.[14]

Clinical laboratory findings in dogs with CH are primarily characterized by increased alanine aminotransferase (ALT),[1–3,12] and approximately 90% have ALTs five to 18 times the upper limit of normal.[2] Serum alkaline phosphatase (SAP) is often increased, but the pattern is often not that of the common steroid hepatopathies in which the SAP is typically many times higher than the ALT. However, if CH progresses to cirrhosis, hepatic enzymes may decrease to the reference range. Hypoalbuminemia, hypocholesterolemia, or both are often present when hepatic insufficiency occurs, and finding these two changes simultaneously strongly suggests either hepatic insufficiency (e.g., cirrhosis) or protein-losing enteropathy. Hyperglobulinemia occurs less commonly (25%) than hypoalbuminemia (40%).[2] Decreased blood urea nitrogen (BUN) may be due to hepatic insufficiency, decreased protein intake, or excessive loss due to polyuria; all of which may occur in patients with CH. Serum bile acids and ammonia tolerance testing are usually abnormal in dogs with CH.

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Hypoalbuminemia was reported to be prognostic in one study[2] but not in another.[15] Approximately 75% of cirrhotic patients are hypoalbuminemic[2]; however, not all dogs with hypoalbuminemia have progressed to cirrhosis. Hypoalbuminemia coupled with normal or increased alpha-1 antitrypsin and haptoglobin has been reported in patients with severe hepatic disease that have the potential to recover.[16] Hypoglycemia is rare and has been suggested to have ominous prognostic implications.[2]

Expected hematologic abnormalities include minor anemia (e.g., anemia of chronic disease), sometimes with microcytosis, leukocytosis, and thrombocytopenia (if consumption of platelets occurs). Approximately 10% to 60% of cases have prolonged prothrombin time (PT) and partial thromboplastin time (PTT),[2,3] and a prolonged PT may be prognostic.[2] If ascites is present, it is usually either a modified transudate or a low-protein transudate associated with fibrosis or cirrhosis.

Physical examination is often relatively unremarkable unless ascites is present. Icterus is uncommon, but poor body condition is reasonably typical. Abdominal radiographs are usually unrevealing unless ascites or microhepatia is present. Ultrasonographic changes are typically nonspecific unless obvious microhepatia, ascites, or nodularity of the liver is found. Sometimes multiple acquired portosystemic shunting is detected. Rarely, ultrasound will reveal target lesions.

Definitive diagnosis of CH requires histology. Tru-Cut® needle biopsies can be diagnostic, but they can also miss important histologic changes that surgical or laparoscopic samples are more likely to find. Laparoscopy and surgery allow biopsy of multiple hepatic lobes and can detect gross changes not revealed with ultrasound, thus allowing one to direct biopsy to specific areas of the liver.

Diagnosing CH requires finding inflammation and piecemeal necrosis (i.e., necrosis of the hepatocytes adjacent to the portal tract—the “limiting plate”).[1,3] The inflammation consists primarily of lymphocytes and plasma cells. Small numbers of neutrophils and macrophages may be present; however, granulomatous reactions are not expected in CH. Necrosis first involves destruction of hepatocytes adjacent to the limiting plate, but with time the necrosis extends from the portal area to the central veins (i.e., bridging necrosis). Copper is often present and can be detected by special stains (e.g., rubeanic acid and rhodanine) when it exceeds 400 ppm or by quantitative analysis.[1] Atomic absorption analysis requires approximately 1 g of tissue. The tissue sample should be shipped

frozen or refrigerated to the lab in a copper-free serum blood tube. Formalin may contain copper and can confuse the analysis.[8] Increased Kupffer cell iron stores have been reported in some affected dogs.

Hydropic change (i.e., vacuolar change typical of steroid hepatopathy) is common and may reflect excessive endogenous steroid release due to disease. Nodular regeneration is also commonly seen.[2] Fibrosis is expected in dogs with advanced CH, and cirrhotic change (i.e., regenerative nodules plus severe bridging fibrosis) may be seen. Rarely, portal vein thrombosis occurs, although this is more commonly seen in other inflammatory disorders.

Therapy for CH involves reducing inflammation, alleviating the cause when possible (e.g., reducing hepatic copper levels when they pose a risk to the patient), antioxidant therapy, reducing or preventing fibrosis, treating hepatic encephalopathy, and supportive therapy. (See elsewhere in this text for a detailed discussion of therapeutic principals.)

Reducing inflammation typically involves glucocorticoid therapy.[1,2] Steroids are thought to benefit the patient by their anti-inflammatory effects and by their ability to inhibit fibrosis and stimulate appetite. Glucocorticoids purportedly also decrease intestinal copper absorption. Glucocorticoids typically make the patient feel better and seem to prolong life in patients diagnosed before end-stage hepatic disease occurs.[5] However, if the patient shows signs of advanced hepatic failure, steroids seldom help much. Dexamethasone tends to cause more side effects (e.g., hemorrhagic gastroenteritis) than prednisolone. Iatrogenic hyperadrenocorticism should be avoided. Prednisolone (2.2 mg/kg orally, once a day) is administered, and the dose is tapered as soon as clinical signs and hepatic enzymes evidence substantial improvement. Repeated pulses of high-dose therapy may be needed. Steroids typically cause a further rise in the SAP, although the ALT should decrease if the CH is being controlled. If steroid therapy is ineffective or if excessive side effects occur, azathioprine (Imuran) given at 2.2 mg/kg orally, every other day may be beneficial. Concurrent use of allopurinol increases the likelihood of toxicity from azathioprine.[2]

Oxidation is a significant mechanism of hepatic damage, as seen when excessive copper is accumulated[2]; therefore antioxidants are typically administered. Although no critical studies are available that demonstrate efficacy in dogs with CH, water-soluble Vitamin E is typically administered (400 to 600 IU orally, once a day) because of its safety, minimal cost, and potential benefit. S-adenosyl-L-methionine (SAMe), a precursor of glutathione and a methyl donor for methylation reactions, has benefited animals and people exposed to excessive alcohol.[17] Milk thistle, a herbal compound used for hepatic disease in people, has silymarin as the active complex. Silymarin increases superoxide dismutase in cells and serum concentrations of glutathione and glutathione peroxidase.[18] A meta-analysis showed that milk thistle was safe and well tolerated in people with chronic hepatic disease. It did not have a demonstrable effect on outcome in most cases, but one study showed that people with alcoholic cirrhosis were benefited.[18]

Ursodeoxycholic acid has a hepatoprotective effect, probably due to displacing hydrophobic bile acids (e.g., lithocholic acid) from hepatocyte membranes, and has also been touted as having immunomodulatory properties.[2] Its use at 15 mg/kg orally, once a day in a dog with CH was associated with improvement of hepatic enzymes.[1] It rarely causes diarrhea, but does have a hypercholeretic effect and should not be administered to dogs with biliary tract obstruction.

Patients with excessive hepatic copper accumulation (2000 ppm) should be treated with copper chelation therapy, oral zinc therapy, or both to prevent absorption of copper. Copper chelation typically involves administering penicillamine (10 to 15 mg/kg orally, twice a day). Affected Belingtons treated with penicillamine can lose 900

ppm copper per year,[8] whereas other breeds (e.g., Doberman pinschers) may respond faster.[1] Some patients experience clinical improvement despite persistence of hepatic copper concentrations. Penicillamine seems to have anti-inflammatory effects and inhibits fibrosis. Penicillamine therapy causes vomiting in approximately 30% of treated animals, and administering it with food may decrease such side effects. Trientine (10 to 15 mg/kg orally, twice a day) may be substituted if penicillamine cannot be tolerated. Trientine causes fewer side effects, may affect a different body pool of copper than penicillamine, and is effective in patients with hemolytic anemia due to copper release from necrotic hepatocytes.[8] One dog developed clinical copper deficiency (i.e., microcytic anemia and hepatic dysfunction) due to trientine chelation therapy coupled with a controlled copper diet.[19] 2,3′, 2-tetramine is more effective at chelating copper than trientine, but it is not commercially available.[8]

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Chelation therapy can be combined with oral administration of zinc to decrease intestinal copper absorption. It has been suggested that zinc therapy only prevents further accumulation of copper; however, in one study of three Bedlingtons and three West Highland white terriers administration of zinc significantly decreased hepatic copper concentrations after 2 years of therapy.[8] Administering zinc salts (e.g., zinc acetate or zinc gluconate initially given at 5 to 10 mg elemental zinc/kg twice a day) 1 hour before meals induces metallothionein (a copper-binding protein) in enterocytes. Dietary copper binds to this protein, is not absorbed, and is eventually evacuated from the body when the enterocyte is sloughed. Excessive zinc can cause hemolytic anemia, and blood zinc concentrations need to be checked periodically. Diets lower in copper can augment other therapy, but such diets are inadequate by themselves if the patient is already symptomatic for excessive hepatic copper concentrations.[8]

H-2 receptor antagonists, Carafate, or both are sometimes administered because hepatic disease has been suggested to cause gastroduodenal ulceration.

227.2 FIBROSIS AND CIRRHOSIS

Fibrosis and cirrhosis may result from any severe or chronic hepatic insult. Inflammatory cells cause hepatocellular necrosis, which creates space (i.e., hepatocyte dropout) that is filled by more inflammatory cells. The liver's response to necrosis is to produce hepatocytes and bile duct epithelium. However, lysosomal proteases and radicals released by inflammatory cells disrupt normal hepatic extracellular matrix (ECM) and cellular membranes causing release of substances (e.g., transforming growth factor-beta [TGF-β]) that attract collagen-producing cells. Fibrosis causes ECM modification, and hepatocytes growing on it may have functional alterations.[2,20]

Dogs with acute massive necrosis or CH often develop hepatic fibrosis. Because fibrosis follows the course of inflammation and necrosis, a disease that produces inflammation in the portal areas that reaches out to lobules and other portal areas causes bridging fibrosis (i.e., there is a “bridge” of fibrous connective tissue from one portal area to another). In some cases, fibrosis extends from the portal triad to the hepatic veins. When bridging fibrosis causes permanent distortion of the liver associated with regenerative nodules, it is termed *cirrhosis*. Fibrosis that cuts across acinar zones causes micronodular cirrhosis. Fibrosis that divides the liver into groups of acini with more than one portal tract within each nodule causes macronodular cirrhosis. Fibrosis that only surrounds bile ducts causes biliary cirrhosis. If fibrosis is severe, collagen limits the ability of vessels and sinusoids to distend, thereby increasing resistance to blood flow. Collagen around hepatocytes impairs sinusoidal blood flow and the sinusoidal endothelium's selective permeability, decreasing hepatocyte function. As cirrhosis persists, the type of collagen laid down may be less susceptible to collagenase activity, making it harder to remove.[2] Cirrhotic patients are at increased risk for anesthetic-related complications.

Preventing fibrosis is an important long-term goal in patients with any chronic inflammatory disease. Prednisolone, azathioprine, penicillamine, zinc, and vitamin E appear to have antifibrotic effects.[1,20] Once severe fibrosis has occurred, colchicine therapy may be considered. Colchicine is a microtubule assembly inhibitor that increases collagenase activity. Colchicine (0.03 mg/kg orally, once a day) was associated with improved histology (i.e., decreased fibrosis) in one dog. It has been used in other dogs, but it is difficult to confidently ascribe beneficial results to colchicine because of limited experience.[2] Although frequently prescribed, no controlled drug trials have proven its value.

227.2.1 Chronic Hepatitis in the Doberman Pinscher

Middle-aged, female Doberman pinschers are at increased risk for severe CH with subsequent cirrhosis.[1,2,21] Clinical presentation and clinical pathology findings are as described under CH, but PU/PD, splenomegaly, neutrophilic leukocytosis, normal to increased PCV,[2] and bleeding may be more common than in affected patients of other breeds. Because these dogs are particularly prone to severe CH and cirrhosis, they are noticeably fragile; even minimal anesthesia can cause severe, acute decompensation. Many patients with clinical illness die within weeks of first signs of disease. Some affected Dobermans are referred for suspected diabetes insipidus due to severe PU/PD. If CH is diagnosed fortuitously in an asymptomatic dog, the life expectancy after diagnosis is presumably longer; however, early therapy in asymp-tomatic patients has not been proven to substantially increase life span.

Approximately 8% of Dobermans in Finland had an increased ALT; however, not all Dobermans with an increased ALT had CH.[1] Some Dobermans with increased ALT values lived for months and in some cases years without clinical signs of CH.[22] In a more recent study, 18 Dobermans with subclinical CH were biopsied, and all had excessive hepatic copper concentrations. Initially there was parenchymal and portal inflammation, but the parenchymal inflammation diminished and the portal inflammation increased as the disease progressed. There was expansion of portal areas with necrosis, fibrosis, and bile duct proliferation.[21] Five dogs lived for 3 years; as a group they were asymptomatic for an average of 19 months.

Even though female Doberman pinschers are clearly at risk for severe CH, not all Doberman pinschers with hepatic disease have CH. Doberman pinschers also appear to be at risk for drug-induced hepatic disease (e.g., diethylcarbamazine, oxibendazole, amiodarone). Therefore hepatic biopsy is recommended for Dobermans with an increased ALT if the patient is not an undue anesthetic and biopsy risk. Periportal copper accumulation, hepatonecrosis, and inflammation are expected in early cases,[1,2] although one report suggested that the earliest inflammatory and fibrotic lesions are around hepatic veins.[23] Eventually a substantial hepatic necrosis occurs, with neutrophilic and macrophage infiltrates. Excessive hepatic copper levels are common, and Doberman pinschers as a breed have been suggested to have higher hepatic copper levels than some other breeds. However, five of 35 Dobermans with CH had normal hepatic copper levels,[23] and even Dobermans with substantial copper accumulation generally do not attain the concentrations often seen in severely affected Bedlington terriers.[2] Therefore although it is not clear if the copper accumulation is innocuous or pathogenic, it is not an initiating cause of CH as in Bedlington terriers. Hepatic iron concentrations tend to be increased. Because of their increased risk for CH, it is reasonable to routinely screen Doberman pinschers for biochemical evidence of hepatic disease. Therapy depends upon the stage of the disease, but usually consists of antioxidants and glucocorticoids ± azathioprine. Copper chelation and antifibrotic therapy are used as indicated by histopathology.

227.2.2 Chronic Hepatitis Associated with Copper Accumulation in the Bedlington Terrier

Bedlington terriers in the United States have historically had a high incidence of an autosomal-recessive metabolic defect in biliary copper excretion (approximately 60% of tested dogs).[8] The gene responsible for this defect is different from that causing Wilson's disease in people. Bedlingtons homozygous for the trait progressively accumulate copper in their livers, which typically causes oxidative mitochondrial damage after reaching approximately 2000 ppm. Bedlingtons may begin accumulating copper *in utero*.[24] Their hepatic copper content continually increases throughout their lives (see following) and may reach 12,000 ppm.[2] Once sufficient copper has accumulated in the liver, otherwise insignificant stress may trigger acute hepatic necrosis, possibly with acute hemolysis and renal failure due to release of large amounts of copper from dying hepatocytes.[1,2]

An increased ALT is usually the first clinicopathologic evidence of disease; however, this increase does not occur until excessive hepatic copper accumulation is associated with hepatocyte damage and inflammation. Younger dogs with excessive hepatic copper but no inflammation often have normal ALTs.[2] As hepatic damage occurs, increased ALTs may be found in clinically normal animals. Clinical signs may be those of acute hepatic disease (e.g., vomiting, anorexia, lethargy) from which they may recover; chronic hepatic failure (e.g., anorexia, vomiting, depression, loss of body condition) that ultimately progresses to obvious hepatic failure with jaundice, ascites, and hepatic encephalopathy; or acute hepatic failure coupled with hemolytic anemia and jaundice.[2]

Measuring serum or plasma copper or ceruloplasmin concentrations is not helpful; definitive diagnosis requires hepatic histopathology. Accumulation of copper in lysosomal granules is the first histologic abnormality. As hepatic copper levels increase, random areas of focal inflammation occur. Inflammatory infiltrates extend out from the portal triads as the disease progresses, with occasional bridging necrosis and some fibrosis. Finally cirrhosis occurs.[8] Hepatic copper levels increase until about 6 years of age, and then they begin to decrease, probably because copper-laden hepatocytes are replaced with scar tissue or regenerative nodules.[1,2] Hepatic iron concentrations are also increased.

Identifying and removing affected dogs from the breeding pool is the desired approach. Selective breeding in the Netherlands has decreased the prevalence from 46% (1976 to 1986) to 11% (1990 to 1997).[25] When screening asymptomatic animals, one may biopsy at 6 and 15 months of age. Unaffected dogs will have normal amounts of hepatic copper both times, heterozygotes will initially have a high copper concentration that lessens by the second biopsy, and homozygotes will initially have excessive copper that is increased at the second biopsy.[8] The Orthopedic Foundation for Animals (www.offa.org/index.html) has a registry for unaffected Bedlington terriers that uses a DNA marker tightly linked to the expression of copper toxicity.[26] However, a study of 154 hepatic biopsies from Bedlingtons found that the DNA marker did not reliably identify copper intoxication in individual dogs.[27] This discrepancy may have been due to studying different subpopulations of Bedlingtons. Fecal excretion of ^{64}copper discriminates between affected and nonaffected West Highland white terriers and Bedlingtons.[28] However, the test requires special facilities and is not as specific as desired.

Feeding a relatively low copper diet and administering oral zinc is usually beneficial in affected, asymptomatic dogs. Chelator therapy may also be used, and penicillamine therapy has apparently prevented

disease progression in some dogs that continue to have excessive copper. Affected animals may live a normal life if therapy starts when they are young.[8]

227.2.3 West Highland White Terriers

West Highland white terriers have a genetic tendency toward higher hepatic copper concentrations than most other breeds, and CH is more common in West Highland white terriers. However, not all West Highland white terriers with CH have inflammation that is clearly associated with excessive hepatic copper accumulation.[1,2] Furthermore, many West Highland white terriers with modest copper accumulation do not develop CH. In distinction to what occurs in Bedlington terriers, West Highland white terriers that accumulate copper in their livers do not do so for their entire lives, and the values tend to decrease over time.[9] Finally, West Highland white terriers usually do not achieve hepatic copper levels greater than 3500 ppm, in distinction to Bedlington terriers, which often achieve levels greater than or equal to 5000 ppm.

Histopathology of West Highland white terriers livers may show normal liver with excessive copper; multifocal hepatitis with excessive copper, and cirrhosis with excessive copper.[2] Dogs with CH are treated as previously described.

227.2.4 Dalmatians

Dalmatians have recently been recognized to develop necroinflammatory hepatitis associated with increased hepatic copper concentrations.[4] Too few animals have been diagnosed to delineate whether or not an age or sex predilection exists. Affected animals have typical signs of hepatic disease (e.g., anorexia, vomiting, lethargy). Increased ALT was the predominant clinicopathologic finding, whereas lesser increases in SAP were common. Hypoalbuminemia and hyperbilirubinemia were seen in some dogs. Ultrasound findings were typically normal. Piecemeal necrosis and bridging fibrosis were the most common histologic findings, and inflammatory infiltrates were either lymphocytic or neutrophilic. Hepatic copper concentrations ranged from 754 to 8390 ppm, with an average of 3197 ppm. Average life span after diagnosis was 80 days, with some animals living to 240 days postdiagnosis.

227.2.5 Skye Terriers

At least some bloodlines of Skye terriers seem to have a tendency to have CH. Although not well characterized, it appears that the CH occurs first and that hepatic copper accumulation is an inconsistent secondary effect of the inflammatory lesion. Hepatic copper concentrations up to 2257 ppm have been reported. The first histologic lesion is intracanalicular cholestasis.[1,2]

227.2.6 Cocker Spaniels

Young male cocker spaniels are at increased risk for early onset CH that quickly becomes cirrhotic. The mean age at presentation of 16 affected dogs was 5.6 years, and males were preferentially affected.[29] Most had ascites (11 of 16) of less than 2 weeks' duration. A mature neutrophilic leukocytosis and ascites (either a transudate or a modified transudate) were typical. ALT was usually increased, but hyperbilirubinemia was a mild, inconsistent finding. Biopsy typically reveals a periportal hepatitis consisting primarily of plasma cells and lymphocytes with limiting plate destruction. Severe bile duct duplication was common. Copper accumulation was inconsistent. One study looking at α1-AT and its relationship to CH in cocker spaniels

concluded that the two were not related.[13] Because the disease is typically advanced at the time of diagnosis, prognosis is grim. Most clinically affected dogs die within a month of diagnosis, although occasional patients may live for up to a year with supportive therapy.[2]

227.2.7 Infectious Canine Hepatitis and its Possible Association with Chronic Hepatitis

Canine adenovirus was found in the liver of five out of 53 dogs with CH; however, another study failed to find it in any of 45 dogs with hepatic disease.[1,2] Whether a cause-and-effect relationship exists is unknown. Some people have hypothesized that the viral infection initiates a self-perpetuating inflammatory hepatic disease. Experimental exposure of partially immunized dogs has produced CH.[2]

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227.3 CHOLANGIOHEPATITIS

Cholangiohepatitis is diagnosed by finding mixed inflammatory infiltrates in the periportal (i.e., zone I) area, usually with inflammation extending through and into the bile ducts.[12,15] Icterus is common, and ALTs, SAPs, and serum bile acids tend to be higher than is seen with CH. However, one cannot discriminate between dogs with CH and those with cholangiohepatitis based upon laboratory values. In one study, median survival time (MST) was 25 months.[2,15]

227.4 DRUG-ASSOCIATED HEPATITIS

Although almost any drug will eventually be associated with hepatotoxiciy in some individual, some drugs are frequently associated with hepatic damage. Most hepatotoxic drugs cause hepatocellular degeneration, necrosis, or fibrosis with minimal inflammation. Inflammatory infiltrates have been associated with trimethoprim-sulfadiazine, phenobarbital, diethylcarbamazine and oxibendazole, and amiodarone, although they are usually relatively mild and do not closely resemble CH. However, the degree of inflammation associated with apparent drug toxicity is variable, and some animals have substantial inflammation. Whether the inflammation is due to the drug or some other, concurrent problem is unknown.[1,30,31]

227.5 ACIDOPHIL CELL HEPATITIS

This is a transmissible disease (apparently viral) that has been reported affecting dogs in the United Kingdom. In the acute phases, it is associated with relatively little hepatic inflammation. However, it is believed that CH and cirrhosis may result. Increased hepatic enzymes are expected, and diagnosis requires hepatic biopsy. The characteristic lesion is finding acidophil cells throughout the parenchyma with an angular shape and acidophilic cytoplasm.[1,2]

227.6 LEPTOSPIROSIS

The most common clinical presentation of dogs with leptospirosis is acute renal failure. Depending upon the serovar involved, dogs may or may not have concurrent hepatic disease (i.e., increased SAP and hyperbilirubinemia). In one recent study, 20 of 36 dogs with leptospirosis had hepatic involvement[32]; however, the lesion characteristic of acutely affected dogs is edema and sinusoidal congestion, with perhaps a mild neutrophilic and eosinophilic infiltrate. Serovar grippotyphosa has been suggested to be able to cause CH. In one kennel, five American foxhounds were diagnosed with CH. Four had leptospires in their canaliculi. In another

report, beagles vaccinated against leptospirosis developed CH, and leptospires were found in their bile canaliculi.[1,2]

227.7 LOBULAR DISSECTING HEPATITIS

This is characterized by finding inflammatory cells diffusely throughout the hepatic lobule as opposed to primarily in the periportal regions, and collagen and reticulin fibers dissecting around small groups of hepatocytes and sometimes single hepatocytes.[1,2] Copper may be found in the liver, but it appears to be a secondary event. This syndrome appears most commonly in neonatal and juvenile dogs (e.g., mean of 11 months old in one series). Hepatic enzymes are typically increased, and ascites associated with portal hypertension is probably the most common presenting clinical sign. Standard poodles may be at increased risk for hepatitis, but it is not certain that it is lobular dissecting hepatitis. One paper reported three standard poodles with a disease that resembled lobular dissecting hepatitis but which did not cause ascites.[33] Regardless of whether or not these dogs had lobular dissecting hepatitis, a breed predisposition seemed likely.

227.8 GRANULOMATOUS HEPATITIS

Granulomatous hepatitis is an uncommon hepatopathy differing from CH in that macrophages are a predominate finding. The lesion tends to be multifocal and can be caused by numerous bacteria (e.g., *Nocardia*, *Mycobacterium*, *Rhodococcus*, *Borrelia*, *Bartonella*), fungi (e.g., histoplasmosis, coccidioidomycosis), and parasites (e.g., *Hepatozoonosis*, *Heterobilharzia*). In people, occult lymphoma has been implicated. However, many cases of canine granulomatous hepatitis are idiopathic.[2] One report of nine dogs with granulomatous hepatitis found intestinal lymphangiectasia in two, lymphosarcoma in one, and histiocytosis in one.[34] In three cases, the cause was uncertain. Clinical signs vary widely, and no breed or age predisposition is recognized for idiopathic disease. Special stains for bacteria and fungi are warranted, as is serology for selected agents. Culture for bacteria including atypical mycobacteria (which can be hard to find, even with special stains) is desirable. If one cannot find a cause, it is usually prudent to first treat for a possible undiscovered agent (e.g., atypical mycobacteria, *Bartonella* spp.) and only resort to immunosuppressive therapy after diagnostic efforts and therapeutic trials have failed.

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228 CHAPTER • 228 Feline Inflammatory Liver Disease

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Timothy J. Gruffydd-Jones

The most important and common hepatic disorders of cats in which inflammation is the predominant pathologic change are the different forms of the cholangitis and cholangiohepatitis complex. Inflammatory lesions are a feature of some other feline disorders that affect the liver, but other pathologic features dominate. These include infectious diseases such as feline infectious peritonitis (FIP), protozoal infections (most notably toxoplasmosis), bartonellosis, and hepatotoxicities particularly associated with drugs including diazepam and tetracyclines.

228.1 CHOLANGITIS AND CHOLANGIOHEPATITIS COMPLEX

The cholangitis and cholangiohepatitis complex is regarded as the second most common hepatic disorder in cats in the USA after idiopathic hepatic lipidosis.[1] In countries in which hepatic lipidosis is less common, such as the United Kingdom, the cholangitis and cholangiohepatitis complex may constitute the most common primary hepatic disorder of cats.

Considerable confusion exists over the classification and terminology used to describe different forms of the cholangitis and cholangiohepatitis complex, and this is the most contentious issue relating to feline inflammatory liver disease.

228.1.1 Pathology and Classification

Different variants of the complex have been described based on histopathologic features of the lesions including the predominant nature of the inflammatory cellular infiltrate (i.e., neutrophilic, lymphocytic) and bile duct proliferation and presence of fibrosis.[2]

It is currently difficult to devise a classification of feline inflammatory liver diseases incorporating cholangitis and cholangiohepatitis that will reconcile all the previously reported cases and forms of the classification used. The most striking feature of the lesions is generally whether they are suppurative with a prominent neutrophilic infiltration or whether the inflammatory infiltrate is predominantly lymphocytic in nature. This is the basis for the classification of cholangitis and cholangiohepatitis. It correlates with distinctly different clinical presentations and has practical relevance to the management of affected cats.

228.1.2 Suppurative Cholangitis and Cholangiohepatitis

The dominant feature in suppurative cholangitis and cholangiohepatitis is evidence of a suppurative process within the bile ducts. The infiltrate is primarily of neutrophils, although there may be a range of inflammatory cells including lymphocytes and plasma cells. Disruption of the limiting plate occurs with infiltrate extending into the portal areas.[2] Periportal necrosis is common. The bile ducts themselves show necrosis and degeneration with pyknosis, variation in nuclear appearance, and cytoplasmic vacuolation. The extent of fibrosis is variable and probably reflects the duration or stage of the disease process (Figure 228-1B).

Other specific disease entities frequently accompany suppurative cholangitis. The most commonly reported of these is pancreatitis, characterized histologically by periductal infiltration, acinar degeneration, fibrosis, and nodular hyperplasia. The extent of the pancreatitis is generally mild. Coexisting pancreatitis has been described in the majority of reported cases of cholangiohepatitis and was identified in 50% of 18 cases of cholangiohepatitis in a retrospective pathologic study.[3]

Inflammatory bowel disease (IBD) has been recognized more recently as a coexisting feature in cholangiohepatitis. It was diagnosed in 83% of cats with cholangiohepatitis in a retrospective pathologic study.[3] Although the intestinal inflammatory infiltrate was predominantly lymphocytic and plasmacytic in nature, in some cases a neutrophilic element was present.

The term *triaditis* has been used to describe a syndrome of concurrent cholangiohepatitis, pancreatitis, and IBD. The association of these entities may indicate a common underlying disease process in some cases. Suppurative cholangitis is believed to result from ascending infection of the biliary tract. Bacteria can generally be cultured from the bile of affected cats, and a mixed growth of bacteria is often recovered (comprised of common inhabitants of the intestinal gut flora). Ascending infection from the intestine is also believed to be an important factor in the development of pancreatitis.[4] The pancreatic and bile ducts are joined before entering the duodenum and this may predispose to concurrent development of pancreatitis and suppurative cholangitis. It is possible that the presence of IBD may predispose to ascending infection. In triaditis the predominant clinical features are most often associated with the cholangitis, with the pancreatitis and IBD being identified as complications.

228.1.3 Lymphocytic Cholangitis

In some cases of feline inflammatory liver disease the inflammatory infiltrate is predominantly lymphocytic.[5,6] (Figure 228-2B) In a proportion of these cases the inflammatory infiltrate consists purely of lymphocytes and is restricted to the portal areas. It has been suggested that this is a specific form of feline inflammatory liver disease that has been termed *lymphocytic portal hepatitis*.[7] It is reported to occur in older cats.[7] Assessment of the significance of this pathologic change is complicated by the recognition that lymphocytic portal infiltrates are common in older cats not showing any clinical evidence of liver disease. Over 90% (29 of 30) of cats more than 15 years of age were described as having portal lymphocyte infiltrates in one survey.[8]

In other cases, although lymphocytes predominate, the inflammatory infiltrate is mixed with variable numbers of other inflammatory cells, particularly neutrophils. The infiltrate may be more extensive, appearing as marked aggregates of lymphocytes in the form of lymphoid follicles sometimes surrounding bile ducts or as a more diffuse infiltrate within portal areas. Changes are evident in the biliary tree, with bile duct proliferation and sometimes inflammatory changes within the walls of the bile ducts. However, usually no epithelial degeneration or inflammatory infiltrate exists within the lumen of the bile ducts. Fibrosis is present to a variable extent, and this may be severe in chronic cases. This initially has a distinctive septal or monolobular pattern, with bridging fibrosis between the portal areas. The fibrosis is not associated with venules and does not lead to pseudolobule formation but frequently results in prominent nodular hyperplasia. There may be disruption of the vasculature with increased prominence of small blood vessels on the surface of the liver.

Table • 228-1 Comparison of Suppurative and Lymphocytic Cholangitis

	LYMPHOCYTIC CHOLANGITIS	SUPPURATIVE CHOLANGITIS
Predispositions	Younger cats Persians	Middle aged/older cats
Clinical Features	Often bright	Usually depressed, ill
Appetite	May show polyphagia	Usually anorexic
Jaundice	±	+
Ascites	±	–
Lymphadenopathy	±	–
Hepatomegaly	±	–
Laboratory Changes		
Neutrophilia	±	+
Lymphopenia	±	–
↑ALT	+	+
↑ALP	+	+
±Bilirubin +	+	+
+Bile acids	±	+
↑Globulins	+	–
Ultrasound	±Hyperechoic liver	±Hyperechoic liver biliary stasis
Pathology		
Cellular infiltrate	Primarily lymphocytes	Primarily neutrophils
Distribution of lesions	Mainly portal	Mainly bile ducts
Fibrosis	Variable/can be extensive	–
Association with other disorder	? Pancreatitis	Pancreatitis/IBD
Treatment	Immunosuppressive corticosteroids	Antibiotics Choleretics

Parallels have been drawn between lymphocytic cholangitis and some forms of inflammatory liver disease in man that are characterized by lymphocytic infiltration such as sclerosing cholangitis, biliary cirrhosis, and pericholangitis; however, important differences in the histopathologic features exist. In occasional cats the fibrosis may be prominent around the bile ducts as a concentric distribution, and this has been termed *sclerosing cholangitis*.[9] However, differences exist compared with sclerosing cholangitis in man, and it may simply represent a variant form in the distribution of fibrosis of lymphocytic cholangitis.

It is not clear whether what has been termed as *lymphocytic portal hepatitis* is a distinct separate entity or a variant of lymphocytic cholangitis. The similarities in terms of the lymphocytic predominance, biliary involvement, and pattern of fibrosis, are more striking than the differences; therefore the latter appears more likely. IBD and pancreatitis have been reported to be common in cases described as lymphocytic portal hepatitis.[3] Pancreatitis has been recognized in combination with lymphocytic cholangitis but previous reports do not reveal any evidence of a striking association.[5]

There has been some preliminary characterization of the immune-cell infiltration in lymphocytic cholangitis.[10] The infiltrative lymphocytes are predominantly CD3-positive T cells with smaller numbers of associated B cells. Occasional IgA-positive plasma cells are present, and increased MHC II expression by a variety of immune cells occurs. The nature of this infiltrate suggests, not unexpectedly, that an immune-mediated mechanism may play a role in the pathogenesis of the liver pathology. In the liver diseases of man that bear some similarity, sclerosing cholangitis and biliary cirrhosis, autoantibodies against liver cell components are identified. However in the limited studies that have been reported, no evidence of such antibodies have been found in affected cats.[5]

There may be some initiating factor that triggers the development of lymphocytic cholangitis leading to immune-mediated mechanisms that perpetuate liver pathology. Clinical signs may not arise until this stage has been reached.

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It has been postulated that lymphocytic cholangitis and suppurative cholangitis may be essentially part of the same disease syndrome, with lymphocytic cholangitis representing a chronic stage of an earlier suppurative process.[1] A mixed inflammatory cell infiltrate in some cats is identified that probably represents progression of suppurative cholangitis to a more chronic form (see following), but the authors believe that this is distinct from lymphocytic cholangitis. Key features suggest lymphocytic cholangitis is a separate, distinct disease syndrome:

- No evidence suggests that cats diagnosed with lymphocytic cholangitis have had earlier episodes of liver disease or that cats with suppurative cholangitis are at greater risk of developing lymphocytic cholangitis.
- Lymphocytic cholangitis occurs most frequently in younger cats, but suppurative cholangitis tends to occur in middle-aged to older cats.
- An inflammatory infiltrate is found in the bile ducts of cats with suppurative cholangitis but not in lymphocytic cholangitis.
- Concurrent pancreatitis is common in cats with suppurative cholangitis but is unusual in lymphocytic cholangitis.

These two latter findings implicate ascending infection in the pathogenesis of suppurative cholangitis, but no evidence suggests it plays a role in the development of lymphocytic cholangitis.

228.1.4 Mixed Inflammatory Infiltrates

A small proportion of cats with inflammatory liver disease show a mixed cell infiltrate consisting of both neutrophils and lymphocytes. They show bile duct proliferation with epithelial degeneration and necrosis but also have inflammatory infiltrates within the lumen of the bile ducts that differentiate them from the cases of lymphocytic cholangitis with a mixed cell infiltration. It is plausible that these cases represent a chronic stage of earlier episodes of suppurative cholangitis.

228.2 SUPPURATIVE CHOLANGITIS AND CHOLANGIOHEPATITIS

228.2.1 Clinical Features

Suppurative cholangitis occurs more frequently in middle-aged and older cats. In one series of reported cases, all affected cats were over 10 years of age.[7] No apparent sex or breed predisposition exists. Most cats in which a diagnosis of suppurative cholangitis is made are presented as sick cats with acute illness.[1] They are usually anorexic and may be pyrexic. Jaundice is the most consistent specific clinical sign and is caused by intrahepatic cholestasis, sometimes with extrahepatic biliary obstruction. There may be evidence of abdominal pain and resentment on abdominal palpation. Some cats with suppurative cholangitis may have milder or more chronic disease that may be overlooked.

228.2.2 Diagnosis

The most consistent changes on routine laboratory evaluation are increases in ALT and bilirubin. Cholestatic enzymes, ALP, and γGT are usually increased, and usually raised fasting or postprandial (or both) serum bile acid concentrations are found. It is reported that some cats with cholangitis have normal liver enzymes, although in the authors' experience this is rare. The most common finding on hematology is a leukocytosis with neutrophilia and left shift. There may be suppression of hepatic production of clotting factors in the form of prolonged clotting times and increased PIVKA levels,[11] although spontaneous clinical complications of impaired hemostatic function are rare.

The principal abnormalities on imaging are related to the extrahepatic biliary tract. Evidence of gallbladder distension usually exists, and the bile duct may appear prominent.

Cholelithiasis is occasionally seen in cases of suppurative cholangitis, and the majority of reported cases of cholelithiasis have been associated with suppurative cholangitis. It is not clear whether cholelithiasis is the primary problem leading to suppurative cholangitis as a complication, or, as seems more plausible, suppurative cholangitis predisposes to cholelithiasis. Gallstones can be radiolucent, although calcification is a common feature (Figure 228-1A). On ultrasonography, choleliths cause acoustic shadowing. This can aid diagnosis of translucent stones, although inspissated bile, inflammatory, and neoplastic masses may have a similar appearance. Other ultrasonographic features that may be seen with suppurative disease include thickening of the gallbladder (wall thickness >1 mm), distension of the bile duct (>5 mm), and the presence of sludging or inspissation of bile.[12] There may be general patchy echogenicity of the liver.[13]

Histopathology is necessary for confirmation of diagnosis of suppurative cholangitis. A number of techniques can be used to obtain suitable biopsies for histopathologic examination. Fine needle aspirates offer the most noninvasive method of collecting samples. These may confirm the presence of a suppurative process but do not allow assessment of liver architecture and can be misleading.[14,15] Fine needle aspirates can be submitted for bacteriologic isolation and should be maintained in an anaerobic environment until culture is performed. Wedge biopsy at exploratory laparotomy enables direct visualization of the liver and biliary tree and provides the ideal specimen for pathologic assessment. The patency of the bile duct can be established by applying gentle pressure to the gallbladder. Bile should be aspirated for gross assessment and to provide a sample for culture. Immediate cytologic evaluation of a smear of bile will confirm neutrophilic infiltration in suppurative cases. The bile frequently becomes extremely inspissated in suppurative cholangitis, and aspiration may necessitate use of a wide bore needle. Exploratory laparotomy provides the opportunity to examine the pancreas for evidence of pancreatitis and to obtain biopsies where appropriate. It also enables collection of full-thickness intestinal biopsies to investigate the possibility of concurrent IBD. Biopsies suitable for assessment of hepatic architecture can be obtained percutaneously using a suitable liver biopsy needle such as a Tru-Cut° biopsy needle. Ultrasound guidance allows more accurate placement of the biopsy needle. If the required equipment and expertise is available, laparoscopy offers the best compromise between minimizing invasiveness while allowing visualization and biopsy. Hepatic biopsies should be submitted for bacteriologic culture in addition to histopathology.

228.2.3 Treatment

Antibiotic treatment is the priority for suppurative cholangitis. The choice of antibiotic should ideally be based on the results of culture of bile and sensitivity tests. However initial selection of antibiotic must be made before results of bacteriologic culture are available. *E. coli* is the most frequently isolated organism but a

mixed growth (including anaerobes such as *Bacteroides* spp. and other organisms that constitute the normal small intestinal bacterial flora), is frequently found, reflecting ascending infection from the gut. The ideal feature of an antibiotic selected for empiric use is that it should be broad spectrum, bactericidal, achieve therapeutic levels in bile, and not require hepatic metabolism for activation or excretion. The authors' initial choice is therefore generally a potentiated synthetic penicillin (e.g., amoxicillin-clavulanate), cephalosporin (e.g., cephalexin), or fluoroquinolone combined with metronidazole for additional activity against anaerobes. Chloramphenicol has sometimes been recommended[1]; however, high levels can accumulate in the presence of biliary stasis, and toxic effects may result. Antibiotic treatment is maintained for at least 4 to 6 weeks to minimize the risk of recurrence.

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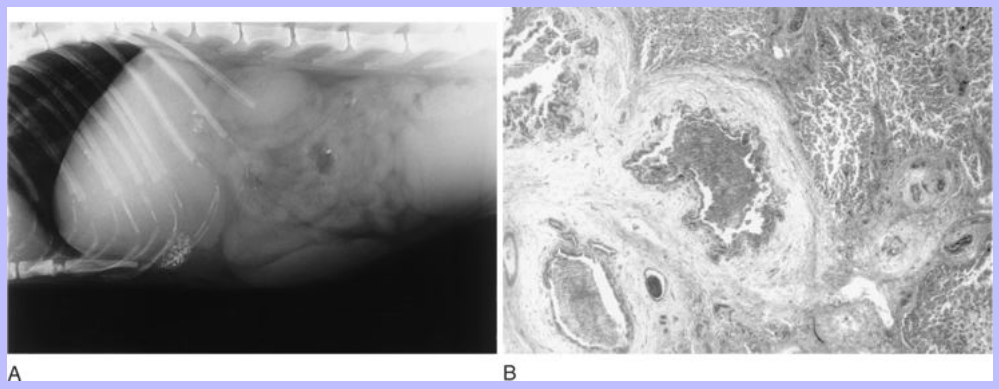
Figure 228-1 **A** and **B,** Lateral radiograph of a cat with suppurative cholangitis showing a calcified choleliths. Hepatic histology from the same case.



The benefits of corticosteroid therapy are widely accepted for lymphocytic cholangitis (see following) and probably also for chronic nonsuppurative cholangitis associated with mixed inflammatory infiltrates. The use of corticosteroids for acute suppurative cholangitis may have benefits in some cases when used judiciously at anti-inflammatory doses for short periods (e.g., prednisolone at 1 mg/kg daily) based on facilitating bile flow through reducing biliary tract inflammation.

Cholecystectomy may be necessary in some cases to remove inspissated bile. This should be followed by lavage and flushing to ensure patency. This may require cannulation of the duodenal papilla. If complete obstruction of biliary flow is identified at laparotomy, cholecystoduodenostomy is indicated to re-establish biliary flow. The peri-and postoperative mortality rate for cats requiring surgical intervention is high.[16]

Supportive measures aid in the management of suppurative cholangitis. Fluid therapy is likely to be required initially, and in most cases nutritional support is also needed. In the longer term modified diets formulated for liver support are indicated, but in the early stages maintenance of calorific intake is the priority. Suitable diets should be easily digested with reduced protein and supplemented with arginine and carnitine.

Choleretics are of value in promoting bile flow, and this is indicated if extraheptic biliary obstruction is not present. The beneficial effects of ursodeoxycholic acid include changing the composition of the bile acid pool by reducing the proportion of hydrophobic bile acids that have toxic effects on hepatocellular membranes. A dose of 10 to 15 mg orally, once a day is used. No controlled clinical trials have been reported to demonstrate

a beneficial effect of UDCA, but it is widely used and appears to be safe.[17] Vitamin K supplementation is indicated if defects in clotting function are identified, particularly prior to any biopsy or surgical procedure. A dose of 5 mg of Vitamin K is given orally or subcutaneously. The response to treatment can be assessed by monitoring PIVKA concentrations and clotting function, which are usually restored to normal in a few days.[11]

More recently S-adenosyl-L-methionine (SAMe) has been used as a nutraceutical agent in the support of cats with liver disease. One beneficial effect is believed to be the restoration of glutathione levels that are reduced in liver disease, leading to increased oxidative damage and exacerbation of liver disease. Other beneficial effects may be to increase levels of cysteine and taurine, which are required for bile acid conjugation and a cytoprotective effect. Although theoretic potential benefits to SAMe exist, no trials have been reported that confirm this.

228.2.4 Prognosis

Information on the prognosis for suppurative cholangitis is limited. In one study just over half (8 of 15) of cats survived for more than 1 year after the diagnosis was made with a median survival time (MST) of 29 months.[18] This concurs with the authors' limited experience that suppurative cholangitis has a reasonable prognosis. Some cases do appear to recur shortly after initial treatment and this risk may be reduced by ensuring prolonged antibiotic treatment, preferably selected on the basis of culture and sensitivity testing. Suggestions that suppurative cholangitis may progress to lymphocytic cholangitis is not supported by evidence, and the authors have not observed any cases of such progression. The prognosis for cats that require surgical intervention to restore bile flow is much more guarded.[16] Concurrent presence of pancreatitis and IBD complicates the prognosis for suppurative cholangitis and the choice of treatment. Management of pancreatitis in cats is challenging. It is not known whether the high doses of corticosteroids usually used for cats with IBD have any deleterious effects on cholangitis and pancreatitis in cats with triaditis. The authors' clinical impression, based on limited experience, is that while this may produce short-term clinical improvements, the longer-term benefits are more questionable.

228.3 LYMPHOCYTIC CHOLANGITIS

228.3.1 Clinical Features

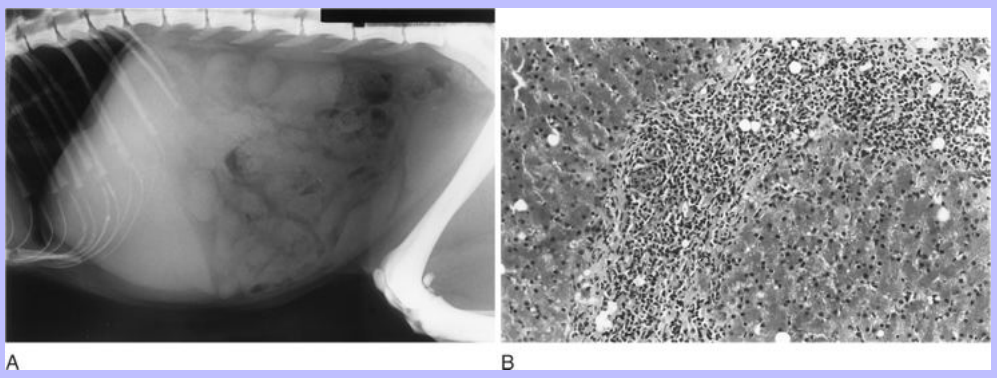
In contrast to suppurative cholangitis, lymphocytic cholangitis occurs more often in young cats, with more than 50% of cases in cats under 4 years of age.[5] A predisposition exists in Persian cats, but no sex bias is seen.[5] This form of inflammatory liver disease is seen much more frequently than suppurative cholangitis in the authors' clinic.

The etiology of this disease is unknown, although an immune-mediated mechanism is believed to contribute to the pathogenesis.

The two main presenting signs in lymphocytic cholangitis are (1) jaundice and (2) progressive ascites. 1451
Occasionally both clinical signs are present. In contrast to suppurative cholangitis, 1452 cats with lymphocytic cholangitis often do not appear ill. Appetite is often maintained and some cases show a noticeable polyphagia. There may be severe weight loss, but other cases retain reasonable bodily condition. It is unusual for pyrexia to be present. Hepatomegaly may be detectable on abdominal palpation, and in some cases this can be striking. Mild generalized lymph node enlargement is a common finding. This is most apparent on palpation of the

superficial lymph nodes but may also involve the mesenteric lymph nodes. In the later stages of the disease with extensive cirrhosis and portal hypertension, hepatic encephalopathy may develop.

Figure 228-2 **A** and **B,** Lateral radiograph of a cat with lymphocytic cholangitis showing severe hepatomegaly. Hepatic histology from the same case.



228.3.2 Diagnosis

An increase in liver enzymes (ALT, ALP, and GGT) and bile acids is usually seen that can be severe. Bilirubin levels may be increased, frequently corresponding with jaundice. Serum globulin levels are often raised, and this may reflect an increase in γ globulins detectable on serum protein electrophoresis. The most consistent change on hematology is lymphopenia. There may be some neutrophilia and mild anemia. If ascitic fluid is present, abdominal paracentesis will show this to be clear to yellow tinged. It is generally thick with a high protein content, the majority of which is globulin. The cellular content is generally low, with a nonspecific mixture of inflammatory cells.

Radiography may be complicated by the presence of ascites but may reveal hepatomegaly (Figure 228-2*A*). The liver may have a heterogeneous appearance on ultrasonography with irregular margins. If extensive cirrhosis occurs, the liver may have a hyperechoic appearance.

Histopathology is required to make a definitive diagnosis. Fine needle liver aspirates may reveal a lymphocytic infiltrate but will not show the characteristic changes in liver architecture, the location of the infiltration, or the pattern of fibrosis. Percutaneous core biopsy techniques generally provide diagnostic samples. However, the prominent presence of blood vessels on the surface of the liver, together with possible compromise of liver-dependent clotting factors, leads to a significant risk of postbiopsy hemorrhage; therefore biopsy at laparotomy provides the advantage of enabling better hemostatic control. Laparotomy also enables larger biopsies to be obtained, as well as selection of biopsy sites, including assessment and biopsy (if appropriate) of other abdominal organs.

The most important differential diagnoses for lymphocytic cholangitis are other causes of jaundice and ascites but particularly FIP and other liver diseases. The lymphadenopathy and preponderance of lymphocytes infiltrating the liver can potentially lead to confusion with lymphosarcoma, especially if needle aspirates are used, but can be differentiated on histopathology. Many similarities exist in the clinical and laboratory features of FIP and lymphocytic cholangitis—jaundice, ascites, raised liver enzymes, hyperglobulinemia, neutrophilia,

lymphopenia, and ascitic fluid with high globulin content. There may be pointers in the clinical presentation that may help to differentiate these two diseases, but this is complicated by the very variable clinical presentation of cats with FIP. Other features suggestive of FIP may be identified such as uveitis, neurologic signs, and pleural effusion. Reliable differentiation may depend on histopathologic investigations.

228.3.3 Treatment

Corticosteroids are the mainstay of treatment used based on countering immune-mediated damage to the liver. Considerable clinical experience supports their beneficial effect. Prednisolone is frequently used at an initial immunosuppressive oral dose of 1 to 2 mg/kg twice a day, which is gradually reduced over an extended period of 6 to 12 weeks according to the progress of the case. Other immunosuppressive agents are occasionally used (e.g., cyclosporine, chlorambucil, methotrexate, cyclophosphamide), but experience of their use and value is limited. Colchicine may be used at a dose of 0.03 mg/kg once a day in an attempt to combat fibrosis, although there have been no controlled trials to confirm any beneficial effect. Choleretics, SAMe, and nutritional support (see Suppurative Cholangitis) may be helpful. If ascites is severe, particularly if this is causing dyspnea due to pressure on the diaphragm, drainage by abdominal paracentesis may be indicated. Loop diuretics such as furosemide (1 to 2 mg/kg twice a day) combined with restriction of dietary salt may be helpful in mild ascites. Potassium-sparing diuretics (e.g., spironolactone) and angiotensin-converting enzymes (e.g., enalapril) are alternative agents for treating ascites.

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Figure 228-3 Ultrasound of abdomen of a cat with suppurative cholangitis showing a dilated, tortuous bile duct.

228.3.4 Prognosis

Limited information is available about the prognosis for cats with lymphocytic cholangitis, but the majority of cats respond well to treatment. The mean survival in 25 cats in which portal hepatitis was described was 37 months, with 16 cats surviving for more than 1 year.[18] The authors' experience is that the prognosis is better in cats with jaundice compared to those with ascites. Lymphocytic cholangitis has been seen to resolve

spontaneously in occasional cases. Some cats will need repeated courses of prednisolone or may need to be maintained on long-term lower doses. Response to treatment is based initially on resolution of clinical signs. Monitoring of liver biopsies can be used to assess response to treatment but is usually declined by owners, and subsequent progress has to be based on monitoring laboratory features (particularly liver enzymes and bile acids).

228.4 MIXED INFLAMMATORY CHOLANGITIS

This form of cholangitis is seen less frequently and is less well characterized. It usually appears as a chronic disease with gradual loss of condition, although in some cases an initial episode of acute illness occurs with depression that may reflect acute suppurative cholangitis, leading to subsequent chronic liver disease. Jaundice is frequently present. The laboratory changes are similar to those seen in the other forms of cholangitis but are less consistent and frequently milder. The major dilemma in treatment of cats with cholangitis-involved mixed inflammatory infiltrates is whether antibiotics or corticosteroids are most appropriate for treatment. Limited experience suggests that the best response is achieved with prolonged corticosteroid treatment, but antibiotics are frequently administered in combination initially.

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229 CHAPTER • 229 Vascular Liver Diseases

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229.1 EMBRYOLOGY AND ANATOMY

The portal vein is formed within the mesentery dorsal to the right limb of the pancreas by the confluence of the cranial and caudal mesenteric portal branches. It receives blood from the gastrointestinal (GI) tract and spleen via numerous mesenteric veins, the gastroduodenal, splenic, and gastric veins.[1] As the portal vein approaches the liver, it sweeps from right to left and divides into right and left branches, which further divide into branches supplying the individual liver lobes. The main right branch supplies the right lateral and caudate process of the caudate lobe, whereas the main left branch supplies all other lobes.[2] Within the hepatic parenchyma, the portal blood exits the portal triads, traverses the sinusoids, and ultimately enters the systemic circulation via the hepatic veins. The left hepatic vein is the only hepatic vein not hidden by hepatic parenchyma as it enters the caudal vena cava just caudal to the diaphragm.

Congenital extrahepatic portosystemic shunts (PSSs) are usually single vessels that connect the portal venous system to the systemic circulation, and as such may arise from any portal vessel. Most empty into the abdominal vena cava, but many will traverse the diaphragm prior to emptying into the thoracic vena cava or azygos vein. Intraoperatively, clinicians can easily locate most shunts by retracting the descending duodenum and examining the vena cava cranial to the left renal vein. If the shunt vessel is not located in this area, the surgeon retracts the liver to the right so that the esophageal hiatus may be examined for evidence of a portoazygous shunt. Occasionally, the omental bursa must be opened to gain access to shunt vessels dorsal to the stomach. This is done by tearing the ventral leaf of the greater omentum followed by cranioventral retraction of the stomach. Intraoperative imaging may be required in some cases to locate the shunt or to help make or exclude a diagnosis of microvascular dysplasia (MVD).

Many intrahepatic venous PSSs result from failure of the ductus venosus to close in infancy. Oxygenated blood from the placenta is carried from the left umbilical vein and umbilical sinus to the systemic circulation via the ductus venosus. It is not known why the ductus fails to close in some individuals. Pathology of the ductus wall or portal hypertension due to inadequate development of the portal venous tree has been speculated.[2] The cause of right-sided congenital intrahepatic and extrahepatic PSSs is unknown. Congenital extrahepatic PSSs are abnormal communications between the cardinal and vitelline venous systems.[3] Intrahepatic PSSs connect portal vein branches after their divergence from the portal vein proper to the hepatic veins or abdominal vena cava, thereby bypassing the hepatic sinusoids. They are usually hidden from view by the hepatic parenchyma. Left-sided shunts (patent ductus venosus [PVD]) arise from the left portal vein branch, pass through the left liver lobes or papillary process of the caudate lobe, and then empty into a venous ampulla cranial to the liver at its confluence with the left hepatic vein.[4,5] Central shunts pass through the right medial or quadrate lobes, and right-sided shunts pass through the caudate process of the caudate lobe or the right lateral liver lobe before emptying into the vena cava.[5,6]

Arterioportal fistulae (APF) are congenital vascular malformations that allow communication between the hepatic arterial blood supply and the portal venous system. The location of APF can vary; one or more lobes may be involved.[7–11]

229.1.1 Diagnostic Evaluation

229.1.1.1 History and Clinical Findings

For vascular anomalies that connect the portal venous system to the systemic venous system as the primary defect (i.e., single PSS, congenital mild diffuse or multifocal intrahepatic portovascular dysplasia), the signs, physical examination abnormalities, clinicopathologic changes, and certain histopathologic findings in liver biopsy specimens are directly related to diversion of portal blood flow around the liver. Intrahepatic portal pressure is normally higher than caudal vena cava pressure; therefore in the presence of a single patent anomalous conduit, portal blood flows preferentially around the liver. Exposure of the central nervous system (CNS) to shunted gut-derived toxins (e.g., ammonia and other encephalotoxins, absorbed bacteria, endotoxins) that would otherwise be removed by the liver results in signs of hepatic encephalopathy (HE), whereas lack of trophic factor-rich portal blood and oxygen (50% of that delivered) leads to poor hepatocyte growth and function.

In conditions that are characterized by high portal pressure (i.e., severe chronic hepatitis such as idiopathic noncirrhotic portal hypertension [NCPH] or single or multiple APF), previously rudimentary multiple extrahepatic shunt vessels connecting the portal vein with the caudal vena cava open to modulate portal pressure. These vessels are commonly found clustered around the left kidney, and occasionally in the submucosa of the esophagus, primarily in dogs and rarely in cats. Additional pathophysiologic consequences and signs of this acquired shunting are directly related to the underlying cause (e.g., high alanine transaminase activity in dogs with chronic hepatitis) and the existence of high portal pressure (e.g., ascites, GI bleeding).

229.1.1.1.1 Portosystemic shunt

Most cats and dogs with PSSs are examined because of signs of illness at less than 2 years of age,[12–28] but some animals have been 10 years of age or older at presentation.[14,15,27] Diagnosis may be missed in some individuals because the signs are subtle, or because owners believe that certain long-standing behaviors are “normal.” A gender bias has not been convincingly identified, although one study from Britain describing 45 dogs with intrahepatic PSSs reported that twice as many affected dogs were male as were female.[23] Male cats often outnumber females in the literature. A familial predisposition for single extrahepatic PSS is suspected in several small purebred dogs.[*] The inheritance pattern of PSS in Yorkshire terriers has been investigated through pedigree analysis and trial breeding, but it remains unclear.[25] A recent study that evaluated breed association in over 2000 dogs with vein-to-vein PSS in North America identified six breeds as having odds ratios near 20 or greater for having PSS: Havanese, Yorkshire terrier, Maltese, Dandie Dinmont terrier, Pug, and miniature schnauzer.[15]

Large purebred dogs, such as retrievers, Australian cattle dogs, Old English sheepdogs, and Irish wolfhounds, are more likely to have intrahepatic PSS.[*] PSSs are much less common in cats than in dogs.[20] As with small breed dogs, the majority of feline PSSs are congenital, single, and extrahepatic. Most cats with PSS are domestic shorthairs, but among purebred cats, the Himalayan and Persian are predisposed.[20,22,26] The history most commonly includes failure to thrive, neurologic signs that could include bizarre behavior such as yelping, staring, aggression, head pressing, and wall hugging, seizures, and intermittent blindness. These signs are usually present in cats by 6 months of age. Intermittent

ptyalism, which is a consistent finding in approximately 75% of cats, may be a subtle manifestation of GI disturbance or HE.[18,20,26,28] GI signs, including intermittent anorexia, vomiting, or diarrhea, are observed in about 30% of affected dogs[13] but less frequently in cats.[20,22,26] Anesthetic or sedative intolerance has also been recorded infrequently. Dogs that are older at the time of diagnosis can be presented because of polyuria-polydipsia (PU/PD), which has been reported to be associated with increased ACTH secretion and hypercortisolism,[29,30] or urate stone formation.[15,31]

Owners of affected dogs may remark that their pets have a dietary preference for fruits and vegetables. Onset of signs correlates with meal ingestion approximately 30% to 50% of the time. Some cats have a history of improved behavioral arid neurologic signs after antibiotic therapy.[12]

High portal pressure is not a feature of vein-to-vein vascular anomalies, so abdominal effusion does not form in animals with PSS unless they have profound hypoalbuminemia. Many cats are of small stature, poor body condition, and have an unkempt haircoat[12,14,20,22]; neurologic signs (e.g., amaurosis, dementia) and ptyalism may also be evident on examination. There may be evidence of other congenital defects; cryptorchidism was noted in about 30% of male cats in one study[20] and 50% of the male dogs in another study. Coexistent heart murmur has also been reported.[16,20,26] Bilateral renomegaly is seen in both species, and copper-colored irises inappropriate for the breed in cats may also be noted in dogs (Yorkshire terrier, Maltese, Dandie Dinmont terrier, pug, and miniature schnauzer).[15]

* References 13, 16, 18, 19, 21, 25, 27.
* References 13, 16, 18, 19, 21, 23.

229.1.1.1.2 Mild diffuse or multifocal intrahepatic portovascular dysplasia

A disorder first described in 82 dogs and 23 in cats in which the signalment and signs resemble those of animals with PSS but a macroscopic vascular anomaly cannot be identified[32] has been termed microvascular dysplasia (MVD).[32,39] This condition can occur as the sole anomaly or jointly with PSS. Based on histopathologic changes in liver specimens and detailed portography, the anatomic site of vascular abnormality is believed to be the terminal portal veins. In Cairn terriers, MVD is believed to be an autosomal inherited trait; the specific mode of inheritance has not been established.[35]

The same dog breeds that are predisposed to PSS are those that have been described with MVD,[33,34,38,39] and cats are typically domestic shorthairs.[32] Common presenting signs include vomiting, diarrhea, and signs of HE, especially in dogs with both defects. Dogs with only MVD are somewhat older,[34,36] and many have mild to no signs of illness.

229.1.1.1.3 Idiopathic noncirrhotic portal hypertension

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A category of hepatopathies in human patients characterized by intra-abdominal portal hypertension, a patent portal vein, and relatively unremarkable liver biopsy findings has been described and termed noncirrhotic portal hypertension (NCPH).[40–44] Two unusual previously reported diseases of primarily young dogs (≤2.5 years) might be able to be grouped under this same name: *hepatoportal fibrosis* in 3 dogs[45,46] and *primary hypoplasia of the portal vein* in 42 dogs).[47] Two more recent reports describe a syndrome resembling idiopathic NCPH in four Doberman pinscher dogs,[48] three of which were related,

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and a similar condition in 33 dogs of various breeds.[49] NCPH has also been reported as an incidental finding in a colony of dogs with mucopolysaccharidosis Type I.[50] This condition is seen most often in purebred dogs 4 years of age or younger, of either gender, weighing over 10 kg. Individual cases had been described earlier but were buried in reports of PSS. Presenting signs include abdominal enlargement associated with effusion, GI abnormalities, polydipsia, weight loss, and less consistently, signs of HE. The cause for this group of conditions has not been identified, but the unifying thread amongst the theories is severe, diffuse intrahepatic vascular malformation. Dogs with NCPH have similar signs, clinicopathologic test results, and diagnostic imaging findings as dogs with cirrhosis, but they differ substantially in histopathologic changes in liver biopsy specimens and prognosis. This condition may represent severe diffuse or multifocal intrahepatic portovascular dysplasia.

229.1.1.1.4 Arterioportal fistulae

Clinical signs associated with APF are usually acute in onset during the first year of life and are primarily associated with the portal hypertension that results from conference of high-pressure arterial blood to the normally low-pressure portal venous system. Young medium to large breed dogs are most commonly reported, although small breeds may also be affected.[10] This appears to be a rare condition in cats.[51] Nearly all animals with APF have ascites[9,11,51,52] (Figure 229-1). Vomiting, diarrhea, lethargy, and weight-loss are also commonly reported.[8] Signs consistent with HE have been reported less frequently. In some animals with APF, the sound of turbulent blood flow through macroscopic fistula or fistulae, resembling the heart murmur in animals with patent ductus arteriosus, can be ausculted across the body wall over the affected lobe or lobes.

229.1.1.2 Clinicopathologic Test Results

Clinicopathologic findings in over 50% of affected dogs, regardless of the type of vascular anomaly, are typical of global hepatic dysfunction: hypoalbuminemia, euglycemia, hypoglycemia, hypocreatinemia, hypocholesterolemia, normal to low blood urea nitrogen (BUN) concentration, postchallenge hyperammonemia, and normal or high fasting with high postprandial serum bile acid (SBA) concentrations.[13,16,18,28] Clinicopathologic evidence of hepatic dysfunction eliminates the possibility of certain inborn errors of metabolism that cause hyperammonemia in young animals (e.g., urea cycle enzyme deficiency,[53] methylmalonic academia[54]) or hyperammonemia associated with urethral obstruction.[55] Target cells can be seen in some dogs, but microcytosis is the most common hematologic change in dogs; iron sequestration or ineffective iron transport have been proposed as causes for iron-deficient erythropoiesis.[56,57] Two to threefold increases in serum alkaline phosphatase (AP) and alanine aminotransferase (ALT) activities are commonly recorded; the origin of high serum AP activity is unknown. The AP isoenzyme of bone origin could be part of the high serum total AP activity in growing dogs, but subcellular hepatic organelle injury and increased release or decreased elimination of canalicular AP has also been proposed.[58] A study comparing dogs with intrahepatic PSS versus dogs with extrahepatic PSS made no particularly surprising discoveries; dogs with intrahepatic PSS weighed more and had higher blood glucose concentration and serum AP values than did dogs with extrahepatic PSS.[19]

Figure 229-1 Preoperative photograph of a typical puppy with an hepatic arterioportal fistula. Ascites has resulted in a pot-bellied appearance. Numerous catheters and monitors have been placed, including a cephalic venous catheter for fluid and plasma administration, arterial catheter to monitor blood pressure, and a jugular catheter to monitor central venous pressure (CVP). The patient is placed on a warm-air blanket to help prevent hypothermia. (Courtesy of Dr. Chick Weisse.)

Dogs with MVD may have similar but less dramatic changes as dogs with other vascular anomalies, but never have microcytic red blood cells (RBCs).[35–37,39] In fact, high SBA concentrations may be the only clinicopathologic finding in young purebred dogs with MVD that have been screened for PSS before sale or that are ill for nonhepatic reasons. The authors of one study attempted to distinguish dogs with MVD from dogs with MVD and PSS by use of a regression equation developed from four variables that were the most discriminating values in multiple regression analyses:

$$\begin{aligned}\text{diagnosis} = {} & 2.851 - (0.00135 \times \text{cholesterol concentration}) \\ & - (0.234 \times \text{albumin concentration}) \\ & (0.0209 \times \text{MCV}) + (0.000517 \\ & \times \text{postprandial SBA concentration}).\end{aligned}$$

Values approaching one were most consistent with a diagnosis of MVD and PSS, where values closer to 0 were likely associated with MVD alone.[36] Essentially, the lower the values for serum cholesterol and albumin concentrations, and MCV, and the higher the SBA concentration, the more likely the diagnosis of PSS.

In cats, poikilocytosis is common, and about 30% have erythrocytic microcytosis. Serum albumin, urea, and cholesterol concentrations can be strikingly normal or in the low-normal range. Serum glucose concentration is usually normal as are liver enzyme activities. The most consistent clinicopathologic abnormality in cats with PSS is high SBA, hyperammonemia, or both.[*]

As many as 50% or more of affected animals of both species may have dilute or hyposthenuric urine, but fewer numbers inconsistently have ammonium biurate crystalluria in a freshly voided and analyzed urine specimen. Persistent hyperammonemia and decreased ability to convert uric acid to allantoin favor

formation of ammonium urate uroliths independent of urinary pH,[63,64] which, in some cats and dogs with PSS, may be the only presenting complaint.[20,31] Rarely, bilirubinuria can be seen in the absence of other chemical or sediment abnormalities. Other than concentrating defects and urinary sediment findings typical of animals with hepatic vascular anomalies, little information is available concerning characteristic renal consequences. Arising from preliminary observations that a small group of dogs with PSS had glomerular sclerosis, renal tissue from 12 dogs with PSS that had died or were euthanatized was examined retrospectively.[66] In six of nine dogs in which urinalysis was done, trace to 1± protein by dipstick analysis was found. All 12 dogs however, had light microscopic evidence of glomerulopathy, with severity scores assigned as moderate to severe in nine of 10 dogs in which paraffin-embedded tissue was available. The renal changes were believed to be associated with shunted antigens from the GI tract; direct immunoperoxidase staining failed to consistently identify immunoglobulin deposition. Renal volume and glomerular filtration rate were compared with reference values in 21 dogs with confirmed PSS, with renal volume compared pre-and postsurgical correction in five dogs. Values for both decreased after surgery, perhaps explaining in part why many dogs with PSS are polydipsic before surgery and that this directly relates to the presence of shunting.[67] Primary polydipsia was also documented in three dogs with PSS and theorized to be another reason for increased water consumption.[68] In animals with abdominal effusion associated with NCPH or APF, fluid analysis is consistent with a pure transudate.

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* References 12, 14, 20, 24, 25, 59-62.

229.1.1.3 Hepatic Histopathologic Findings

Microscopic findings in liver specimens from dogs and cats with naturally occurring PSS mimic those of dogs with surgically created PSS, which was first described by Nicholas Eck in 1877.[69] Mild to moderate lobular hepatocellular atrophy with close approximation of portal venules, inconspicuous portal vein tributaries of small caliber, arteriolar duplication, lipidosis and vacuolar change, smooth muscle hypertrophy and increased lymphatics around central veins, and Ito cell hypertrophy are the findings in both species. Some animals have mild fibrosis around central veins. Minimal, if any, evidence of necrosis or inflammation is seen.[12,18,23,70–72] Random intralobular thin-walled blood vessels can also be seen and may represent a compensatory response to decreased portal blood flow. The histopathologic changes in the liver are considered identical in dogs with PSS, MVD, and NCPH,[32,35,37,39,47–50] and can be over-or misinterpreted among boarded pathologists (Table 229-1).

Histologic changes in liver tissue at some distance from the vascular malformation or malformations in animals with APF are similar to those of other vascular anomalies, presumably associated with portal blood deprivation.[9,11,52] Findings in liver tissue in close proximity to the fistula include dilated portal venules, marked arteriolar hyperplasia, and sinusoidal capillarization. Some portal veins in resected lobes manifest evidence of previous thrombus formation and recanalization.[9]

229.1.1.4 Diagnostic Imaging

Microhepatia is found on survey radiographs in about 50% of cats,[12,14,20] and 60% to 100% of dogs[15,17,18,36] with PSS. Bilateral renomegaly may also be documented. In dogs with MVD, the liver and kidneys are usually of normal size radiographically,[35,37] but the liver can be small in some cases.[36] Ammonium biurate uroliths are discovered in the bladder most commonly, but they can develop in the

kidney, urethra, or both. They can be radiolucent, but usually contain enough calcium salts and magnesium ammonium phosphate to make them moderately radiopaque.

Confirmation of vascular communication or communications between the portal system and the systemic circulation may be achieved by using a variety of imaging modalities including ultrasonography, nuclear scintigraphy, portography, computed tomography (CT), and magnetic resonance imaging (MRI).

Ultrasonographic evaluation of potential PSS is both sensitive (80% sensitivity for canine extrahepatic shunts, 95% overall for canine shunts) and specific (67% specificity for extrahepatic shunts, 98% overall).[6,73] It is less invasive than portography, doesn't require the licensure and handling precautions needed for administration of radioisotopes, and unlike CT does not require general anesthesia. Abdominal ultrasonography should therefore be strongly considered for all patients with possible PSS. Sensitivity improves with intrahepatic PSS (100%) as the shunt vessel is surrounded by hepatic parenchyma (Figure 229-2), whereas extrahepatic PSSs are generally smaller and may be obscured by sound wave attenuation "shadowing" secondary to the presence of gastric or intestinal gas.[6,73] The authors' experience with ultrasonographic evaluation of canine extrahepatic PSS suggests that results are highly operator dependent. The experience level of the operator must be taken into account when evaluating results. Origin and termination of the shunt vessel or vessels may be identified in many cases, but an understanding of the geometry and location of complex, tortuous shunts may be difficult to appreciate using two-dimensional ultrasonography. In patients with complex intrahepatic shunts, intraoperative ultrasonography may improve the surgeon's ability to locate and define the morphology of the shunt, although this has not been well described. Color flow and pulse wave Doppler ultrasonography offers the added advantage of visualization of blood flow direction, turbulence, and measurement of portal blood flow velocity. Portal flow velocity was decreased in dogs with experimentally induced cirrhosis with secondary portal hypertension and multiple extrahepatic shunts[74]; therefore it may also be decreased in dogs that develop multiple shunts secondary to naturally occurring liver disease or after surgical attenuation of shunt vessels. The normal portal flow velocity for dogs is around 15 cm/sec, and flow velocity and direction is relatively uniform. Portal flow velocity was increased or variable in 9/17 (53%) dogs with a congenital extrahepatic shunt, and in 12 of 13 (92%) dogs with an intrahepatic shunt. Increased flow velocity may be due to decreased resistance to cranial flow because of the presence of the shunt.

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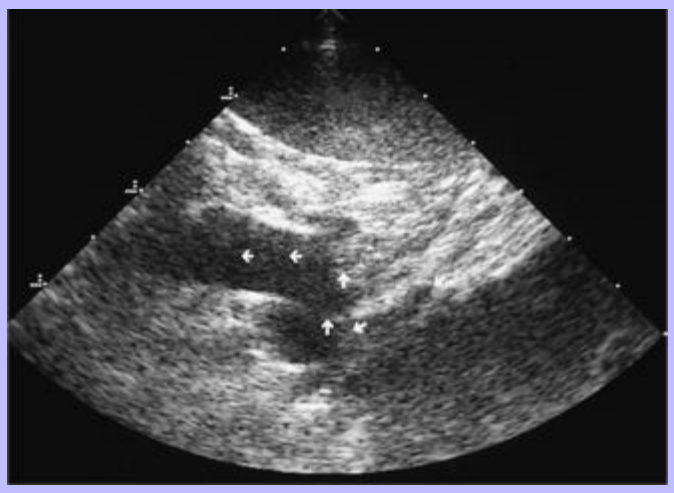
Table • 229-1 Histopathologic Diagnoses of Two Pathologists Compared with the Medical Record Diagnosis in 33 dogs with Hepatic Vascular Anomalies and in Two Normal Dogs

CASE NUMBER	MEDICAL RECORD DIAGNOSIS	PATHOLOGIST 1 (BLIND EVALUATION)	PATHOLOGIST 2 (BLIND EVALUATION)
1	CPS	MVD	CPS
2	CPS	NCPH	CPS
3	CPS	CPS	N/CPS
4	CPS	MVD	N
5	CPS	CPS	CPS
6	CPS	MVD	CPS
7	NCPH	MVD	CPS/NCPH/MVD
8	NCPH	CPS	CPS/NCPH/MVD
9	CPS	CPS	CPS
10	NCPH	NCPH	NCPH
11	NCPH	MVD	CPS
12	NCPH	CPS	N
13	MVD	MVD	CPS/NCPH/MVD
14	NCPH	NCPH	NCPH
15	CPS	NCPH	CPS
16	CPS	CPS	CPS
17	MVD	N	N
18	CPS	MVD	CPS
19	NCPH	NCPH	NCPH
20	NCPH	MVD	N
21	NCPH	NCPH	CPS
22	MVD	MVD	N
23	MVD	CPS	N
24	NCPH	MVD	CPS/NCPH/MVD
25	NCPH	NCPH	Unclear
26	CPS	MVD	CPS/NCPH/MVD
27	CPS	CPS	CPS
28	NCPH	CPS	CPS/NCPH/MVD
29	CPS	MVD	Lobular dissecting hepatitis
30	N	N	N
31	N	N	N
32	MVD	N	N
33	MVD	CPS	N
34	MVD	N	N
35	MVD	NCPH	N

CPS, Portosystemic venous shunt; *MVD*, microvascular dysplasia; *NCPH*, noncirrhotic portal hypertension; *N*, normal.

Figure 229-2 Sonogram of an intrahepatic portosystemic shunt surrounded by hepatic parenchyma. The arrows indicate direction of blood flow determined by color flow Doppler ultrasonography. (Courtesy of Dr. Kathy Spaulding.)



A variety of rectally administered radiopharmaceuticals have been used to identify the presence of PSSs.[76–79] ^{99m}Technetium pertechnetate is most commonly used because it is rapidly absorbed, relatively inexpensive, and has a short half-life.[76,79,80] After absorption by the colonic mucosa, ^{99m}technetium enters the colonic venous (portal) circulation and is transported cranially to the liver. The patient is placed in right lateral recumbency on the surface of a gamma camera, which detects the location of the isotope. This information is displayed on a computer monitor. In dogs with normal portal circulation, the liver is visualized as a bright area on the monitor as the isotope is initially delivered to the hepatic microcirculation (Figure 229-3). With time, the isotope enters the hepatic veins, caudal vena cava, and cardiopulmonary vasculature at which time the heart can be visualized on the monitor.

Although special handling of the isotope and patient are required, the study may be performed in less than 5 minutes and requires only light sedation. Morphology, number, and location of PSSs, if present, often cannot be ascertained using scintigraphy. By drawing regions of interest (ROI) around the liver and thorax using computer software, an estimate of shunt fraction is calculated based on the counts per pixel within each ROI (Figure 229-4). Normal dogs have a shunt fraction less than l5% (i.e., the image of the liver is significantly more intense than that of the thorax at the time of image acquisition).[81] In contrast, in animals with PSS the image of the heart is initially more apparent as the isotope bypasses the liver via the shunt (see Figure 229-3). Shunt fractions in dogs with macrovascular intra-and extrahepatic shunts often exceed 80%, whereas the reported mean shunt index for five cats was only 52% in one study.[82] The range of shunt fractions for dogs with MVD is thought to be lower than those with macrovascular shunts, although this has not been reported. Shunt fraction estimation is inexact and prone to inter-and intraoperator variability.[83] As such, changes in shunt fraction over time should be cautiously interpreted. Despite its limitations, per rectal scintigraphy is quite useful in determining if significant shunting is present. If ultrasonography has failed to

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identify the presence of a shunt, yet clinical signs or laboratory test results are consistent with shunting, then scintigraphy should be considered.

Figure 229-3 Lateral per rectal technetium scintigrams. The head is to the right. Colonic technetium deposition site (*C*), liver (*L*), and thoracic (*T*) regions of interest. Technetium reaches the liver prior to the thorax in a normal dog (*top*). The situation is reversed in a dog with a portosystemic shunt (*bottom*).

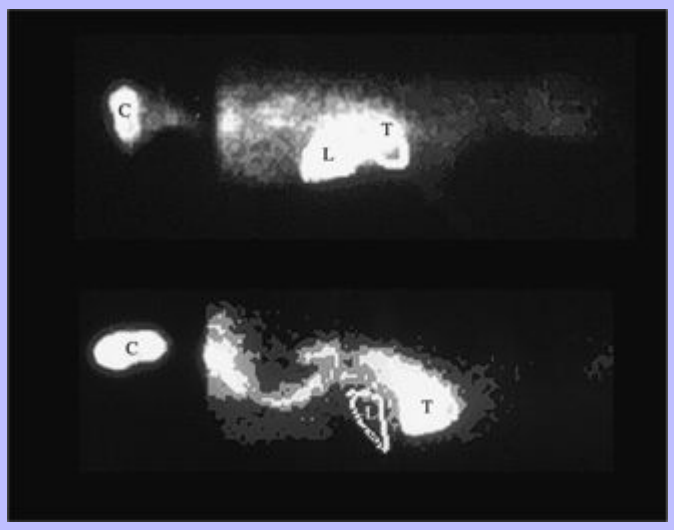
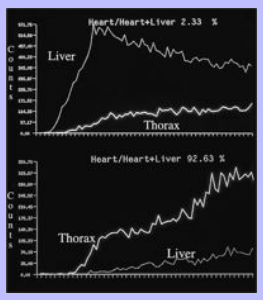


Figure 229-4



Time (seconds)/radioactivity (counts) curves of the normal (*top*) and shunt dog (*bottom*) depicted in Figure 229-3. Radioactivity in the liver is greater than that in the thorax in the normal dog (*top*). The situation is reversed in the dog with a portosystemic shunt (*bottom*). Shunt fraction is calculated by using data collected over 12 seconds starting at the separation of the curves using the formula:

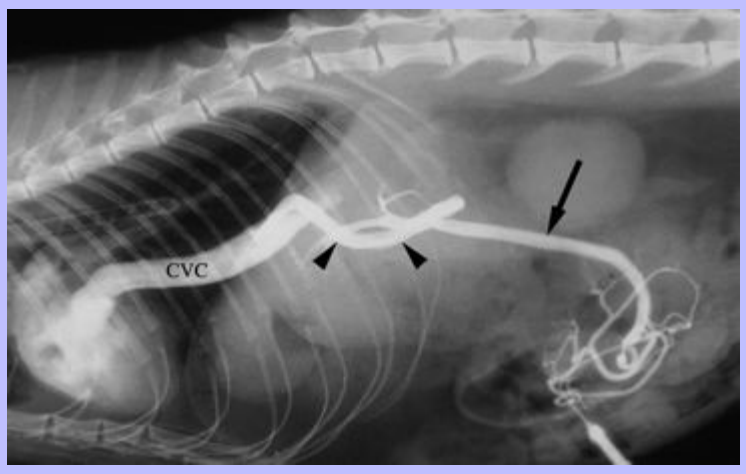
[Σ total heart counts over time]/[Σ(total heart counts) + (total liver counts) over time].

Shunt fraction was 2.3% in the normal dog and 92% in the dog with a shunt.

Portography, although less commonly performed because it is more invasive than ultrasonography and scintigraphy, has the advantage of offering a “global snapshot” of the patient's portal circulation. By injecting contrast medium into the portal circulation, the relative location and number of PSSs may be identified with fluoroscopy, plain radiography, or CT (Figure 229-5).[84] Percutaneous splenoportography may be performed preoperatively by injecting contrast into the splenic parenchyma with or without ultrasound guidance. Caudally located shunts may be missed with this technique. Injection of contrast medium into the mesenteric artery via a femoral artery catheter is now rarely performed because of less invasive options and because it results in a poorer quality study due to dilution as the contrast medium passes from the intestinal arterial to the portal circulation. Alternatively, a fluoroscopically guided catheter may be inserted in the right jugular vein and advanced into the caudal vena cava, shunt, and portal system in dogs with large intrahepatic shunts prior to insertion of thrombotic coils (see discussion of treatment of intrahepatic shunts), or it may be used in the minority of dogs in which the results of ultrasonography and scintigraphy are inconclusive or discordant.[85,86] Portographic imaging may be used intraoperatively by catheterization of a mesenteric or splenic vein to evaluate the morphology of the portal vasculature, to confirm the location of hard to find macrovascular shunts, or to rule out their presence in dogs suspected of suffering from MVD.[34,35,38,87,88] The same catheter is used to measure portal pressures during shunt manipulation. Intraoperative portography can be cumbersome, because it requires either a portable radiographic unit or temporary closure of the abdominal incision and transport of the patient. Sensitivity of intraoperative portography has been reported to be between 85% and 100% and is dependent on patient positioning.[89]

Computed tomography (CT) is primarily performed in dogs with complex intrahepatic shunts. Contrast medium injected into a peripheral vein highlights both the systemic and portal venous circulation. Alternatively in large dogs, the contrast medium may be injected into a splenic vein using ultrasound guidance.[90] Because the radiopacity of the vasculature changes rapidly, helical CT is preferred because it allows rapid acquisition of data over a large anatomic area.[91,92] Transverse images of the liver and its vasculature are then reconstructed after data acquisition. Three-dimensional images of the shunt created with specialized computer software are especially useful to surgical planning. Disadvantages to CT are the need for general anesthesia and the cost. A second anesthetic event may be eliminated if the CT scan is performed immediately prior to surgery; however, this allows the surgeon little time for evaluation of the images, especially if three-dimensional reconstruction is contemplated.

Figure 229-5 Lateral intraoperative mesenteric portogram of a cat. A large extrahepatic shunt vessel (*arrowheads*) originates from a branch of the portal vein (*arrow*) and terminates at the caudal vena cava (*cvc*). (Courtesy of Dr. Daniel Brockman.)



Two- and three-dimensional magnetic resonance angiography (MRA) have been reported as reliable techniques for evaluating shunt vessels in human patients.[93] Two-dimensional MRA, without contrast enhancement, has been evaluated in dogs with shunts and found to have the following sensitivities and specificities: multiple extrahepatic shunts (63% to 97%)[94] and single congenital shunts (79% to 97%). The use of gadolinium-enhanced and three-dimensional MRA as preoperative planning tools for animals with complex shunt anatomy has not been reported to date.

APF are seen as numerous tortuous vascular communications with ultrasound or celiac arteriography (Figure 229-6).[11] Microscopic hepatic arteriovenous fistulae were suspected in one young dog.[52] Ultrasonographic evidence of reversed portal blood flow (hepatofugal flow) and diminished forward (hepatopetal) flow are present in all cases. The portal venous system is often markedly distended. Multiple acquired PSSs may develop as a compensatory mechanism to diminish portal blood pressure and protect against splanchnic congestion (Figure 229-7).[9,11] Multiple shunts are most easily imaged in the region of the left kidney.

229.1.1.4.1 Differential diagnoses

If an animal suspected of having PSS is older than average at presentation, or if a young dog has signs of portal hypertension, other primary hepatopathies must be considered, such as chronic hepatitis; liver biopsy is needed. If a PSS cannot be identified by ultrasonography, transcolonic scintigraphy, surgery, or portography in a dog (or less commonly, a cat) suspected of having PSS, MVD is likely. Liver biopsy in such cases would provide evidence to exclude a more serious hepatopathy.

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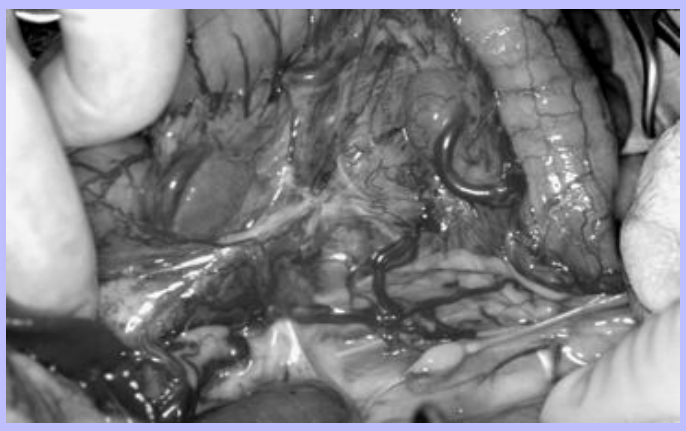
Figure 229-6 Sonogram of a left-sided arterioportal fistula. The patient's head is to the left, and ventral is toward the top of the image. Diaphragm (*arrows*), ascites (*a*), atrophied hepatic parenchyma (*). The APF (*arrowheads*) is seen as numerous thin-walled tortuous vessels. (Courtesy of Dr. Kathy Spaulding.)

Figure 229-7 Intraoperative photograph of multiple acquired extrahepatic shunt vessels, which resulted from portal hypertension in a dog with an APF. (Courtesy of Dr. Chick Weisse.)



If APF are not found in a young dog with ascites, a normalized to small liver and clinicopathologic evidence of hepatic dysfunction, lobular dissecting hepatitis (or other form of chronic hepatitis), and NCPH are possibilities. Histopathologic examination of liver tissue will distinguish these disorders. An algorithm to facilitate diagnosis of vascular disorders in dogs and cats is provided in Figure 229-8.

229.1.2 Surgical Management

229.1.2.1 Preoperative and Operative Considerations

Clinicians have good reason to believe that signs of HE should be controlled before surgical correction is attempted. In one study, asymptomatic dogs had a better prognosis for complete recovery after surgery. To start, a diet moderately restricted in protein (minimum 20% on a dry matter basis [2 g protein/kg/day] for dogs; 30% on a dry matter basis [3 g crude protein/kg/day] with adequate amounts of taurine and arginine for cats) is recommended.[95–98] If signs are not controlled with dietary modification alone, an oral disaccharide (e.g., lactulose, lactitol), antibiotics, and soluble fiber may be added. For animals with ascites secondary to portal hypertension, a diet that is moderately restricted in sodium (0.20% to 0.25% on a dry-matter basis) is beneficial.

After a diagnosis of PSS has been made, many clinicians prefer to preload patients with PSS on anticonvulsant medications to diminish the risk of postoperative seizure activity. Potassium bromide (dogs: 100 mg/kg, orally every 24 hours; cats: 30 mg/kg, orally every 24 hours) may be started 2 weeks prior to surgery, and the dose adjusted (30 to 100 mg/kg, orally every 24 hours) to obtain a serum concentration of 100 to 200 mg/dL.[99] The lower end of the dose should be used in cats, because many develop coughing as an adverse effect.[100] Similarly, phenobarbital may be started (2.2 mg/kg, orally every 12 hours) and the serum concentration evaluated prior to surgery. Oral lactulose, antibiotics, and a low-protein diet are generally started at the same time.

Given that most animals undergoing surgical correction of a PSS are hypoalbuminemic, and because current methods used to detect diminished hepatic production of clotting factors are insensitive (e.g., prolonged PTT), fresh frozen plasma is commonly administered pre-and intraoperatively (6 to 10 ml/kg, intravenously).[101] Dextrose-containing fluids should also be considered in the perioperative period. Anemia combined with intraoperative fluid loading and blood loss may result in the need for cross-matching and blood transfusions.

Intraoperative portography may be needed if the macrovascular shunt is difficult to locate, or if MVD is suspected and macrovascular shunting needs to be ruled out.

Placement of a jugular catheter preoperatively is recommended so that central venous pressure (CVP) can be monitored during shunt attenuation and postoperatively.[102] An arterial catheter is also helpful in many cases for monitoring blood pressure.

Without intraoperative warming, PSS shunt patients are at risk for developing profound hypothermia. Fluid-line warmers, warm-air devices, heating blankets, or a combination of these devices should be used in all cases.

Patients undergoing surgical correction of an intrahepatic shunt may require additional surgical exposure cranial to the liver. A partial median sternotomy and diaphragmatic incision may need to be performed. In these cases, placement of a chest tube will be required prior to surgical closure.

229.1.3 Correction of Extrahepatic Portosystemic Shunts

Many extrahepatic PSSs (48% to 68%) cannot be completely occluded with a single surgery without causing life-threatening portal hypertension.[102–104] Once the shunt has been surgically identified, surrounding tissues are dissected away as close to the vena cava or diaphragm as possible (Figure 229-9). A suture is passed around the shunt so that temporary occlusion may be performed while measuring portal pressures. A variety of parameters are then evaluated during temporary occlusion to determine if complete ligation of the vessel is prudent. Significant increases in portal pressure as measured by a manometer attached to a catheter placed within a jejunal vein, increased intestinal peristalsis, intestinal and pancreatic venous congestion, and decreases in CVP are all indications that complete occlusion should not be attempted.[102,105] Perioperative mortality rates after partial or complete ligation are generally between 10% to 20%.[13,28,103,105] Most dogs with a partially ligated shunt vessel improve clinically and often can be taken off of symptomatic treatment for some time. However, up to 41% to 50% of animals with partially ligated extrahepatic shunts redevelop clinical signs months to years postoperatively (mean: 3 years).[28,103,106] Because of this, repeat laparotomy to attempt complete ligation, before clinical signs recur, has been recommended. Parameters to determine appropriate timing for reoperation have not been documented. Of 24 dogs that underwent partial occlusion of their extrahepatic shunt, complete shunt occlusion occurred spontaneously in 15 (63%) 1 to 6 months postoperatively.[107] This would argue against repeat surgery within this time period.

Staged or gradual occlusion of the shunt vessel can result in complete resolution of shunting in many animals. By placing materials around the shunt that result in its gradual closure, acute portal hypertension associated with complete ligation may be avoided and perioperative mortality diminished. In addition, multiple surgeries are not required. Two implantable materials (ameroid rings and cellophane bands) have been evaluated for this purpose. Ameroid rings are composed of hydrophilic casein that swells over time (Figure 229-10). They are surrounded by a stainless steel collar, which limits outward expansion. They were originally designed as a cardiovascular research tool to create gradual occlusion of coronary and other vessels and have been adopted as a treatment tool by veterinary surgeons. Placement around a shunt vessel results in occlusion in 30 days in most animals, although delayed closure of up to 90 days has been reported.[72] Shunt occlusion has been thought to be due partly to ring swelling, and partly due to an inflammatory reaction with fibrosis around the ring. The mechanisms by which the portal circulation accommodates increased flow have not been reported, but it is clear that acute increases result in life-threatening portal hypertension, whereas gradual increases in portal flow lead to increased liver size. Portal hypertension associated with sudden complete shunt occlusion is generally not a problem after ameroid ring placement unless the weight of the ring kinks the vessel postoperatively, or excessive manipulation of the shunt vessel during ameroid placement results in thrombotic shunt occlusion.[72] A recent study investigating ameroid ring placement on external iliac veins in six dogs showed that the luminal area of the ring only decreased by 23%. All dogs had evidence of venous thrombosis at the site, with complete occlusion occurring by the sixth day in half of the dogs.[108] This rate of PSS occlusion after ameroid placement may be too rapid, and could theoretically result in subclinical portal hypertension and subsequent development of multiple extrahepatic PSSs. Multiple acquired shunts have been reported in approximately 10% to 20% of dogs, and are even more common in cats, after ameroid placement (see Feline Portosystemic Shunts: Unique Considerations).[72,109] In these patients, symptomatic treatment may

need to be continued indefinitely. It is interesting to note that four of 24 dogs (17%) < in one study that had an extrahepatic PSS partially ligated) also went on to develop multiple acquired shunts despite continued flow through the original shunt.[107]

Figure 229-8 Suggested diagnostic path for animals suspected of having a portovascular anomaly.

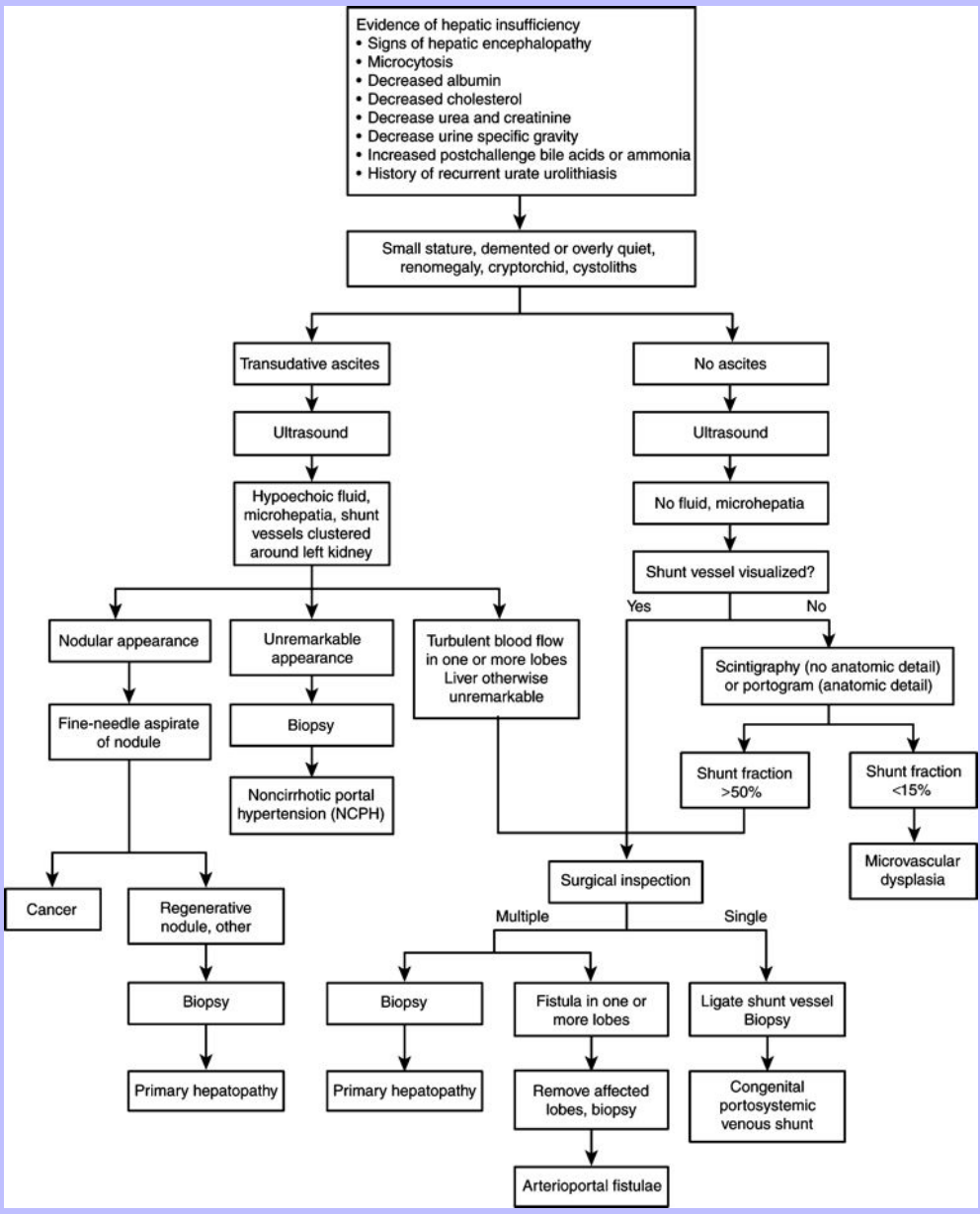
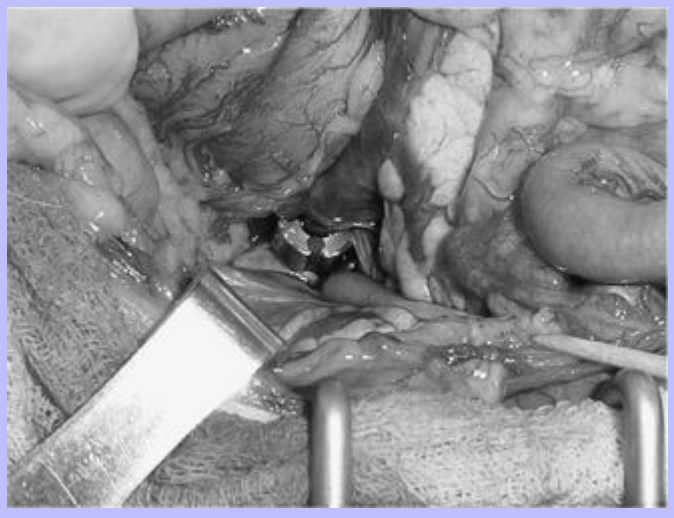


Figure 229-9 Intraoperative photograph of a large splenic vein to abdominal vena cava portosystemic shunt vessel (*arrow*). (Courtesy of Dr. Chick Weisse.)

Figure 229-10 Intraoperative photograph of the same PSS seen in Figure 229-5 after placement of an ameroid ring around the vessel. (Courtesy of Dr. Chick Weisse.)



An alternative to the ameroid ring is cellophane tape or film, which is derived from plant cellulose. Cellophane incites an inflammatory reaction that results in gradual attenuation of the shunt vessel. Progressive occlusion is slower and potentially less complete than with ameroid constrictors; however, potentially diminished risks are associated with placement, including less risk of tearing the shunt, less shunt manipulation required, and less risk of kinking the shunt postoperatively. Additionally, because occlusion is slower, there may be a diminished risk of developing multiple acquired shunts. When placed around the femoral vein in six dogs occlusion was progressive over a 6-week period in four of six dogs, and was incomplete in all.[110] Of eleven dogs with extrahepatic PSSs treated with cellophane banding, 10 had resolution of shunting. In eight dogs, shunt occlusion occurred by 8 weeks, whereas occlusion did not occur until 7 and 11 months in the remaining two dogs.[111]

229.1.3.1 Correction of Intrahepatic Portosystemic Shunts

Intrahepatic shunt vessels are hidden from the surgeon by hepatic parenchyma in most cases. Because of their large diameter, complete ligation is rarely accomplished with one surgery. The location of the shunt may be confirmed intraoperatively by a variety of means. Palpation of the liver will often reveal a soft spot with accompanying fremitus in the affected liver lobe. Intraoperative mesenteric portography or ultrasonography may also be performed.[112] The portal vein branch that feeds the shunt vessel, as well as the exit point of the shunt, can be identified by passing a catheter through a purse-string suture and small incision in the portal vein. The catheter is passed cranially through the shunt and into a prehepatic venous ampulla or thoracic caudal vena cava. A left-sided shunt (PDV or patent ductus venosus) empties into a venous ampulla, which also receives the LHV prior to emptying into the vena cava at the level of the diaphragm.[113] The shunt vessel, LHV-ampulla, or both are bluntly dissected free from the surrounding tissues between the liver and the diaphragm. The shunt vessel, LHV-ampulla, or both are then either partially ligated while monitoring portal venous pressures, or a large ameroid constrictor or strip of cellophane is placed.[114] Experimental occlusion of the LHV in normal dogs resulted in transient congestion of the left and central hepatic lobes, but it had no clinical effect.[115] New information indicates that dissection and partial ligation of the LHV or ampulla is not needed because left-sided shunts may be dissected prior to their entry into the ampulla in most cases.[5] If the shunt vessel empties directly into the vena cava (most right-sided and central shunts), a determination is made as to whether the portal vein branch that feeds the shunt can be dissected free from the surrounding tissues.[116,117] If possible, partial ligation, ameroid ring or cellophane band placement on this vessel is performed.[118] Shunt vessels that empty directly into the vena cava, and for which the feeding portal branch cannot be isolated, are either partially ligated after inflow vascular occlusion of the liver, or an extrahepatic shunt may be created by placing a jugular vein graft or grafts between the portal vein and abdominal vena cava. After graft placement, complete resection of the shunt and its surrounding liver lobe has been reported. Inflow vascular occlusion of the liver requires that the patient or liver be hypothermic at the time of surgery to limit ischemic damage to the liver. Whole body hypothermia has been reported in dogs with good results, despite complications that include severe hypotension, arrhythmias, acidemia, and cardiac arrest secondary to increased myocardial irritability.[119] Topical cooling of the liver with cold saline may protect it from ischemia and reperfusion injury without the systemic side effects seen with whole-body hypothermia; however, this has not been evaluated in dogs with PSS.[120] To perform inflow occlusion, the aorta (or celiac and cranial mesenteric arteries), portal vein, and abdominal and thoracic vena cava are temporarily occluded. This allows the surgeon to make an incision into the thoracic vena cava or the portal vein,

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identify the shunt, and place a circumferential suture around it.[116,121] Once the venotomy has been closed and blood flow to the liver has been reestablished, the circumferential ligature is slowly tightened while monitoring portal pressures as for extrahepatic shunts. The significant blood flow through large intrahepatic shunts cannot be suddenly obstructed by the surgeon without the development of life-threatening portal hypertension. Intraoperative shock (hemorrhagic and septic), cardiac arrest, and portal hyper-and hypotension have been listed as causes of intraoperative death. Postoperative survival rates vary from 75% to 89%, with peritonitis, portal vein thrombosis, and portal hypertension listed as the most common causes of death in the postoperative period.[17,19,23,28,116] Predictors for the development of postoperative complications were low body weight (<10 kg) and hypoproteinemia or hypoalbuminemia in one study.[122] Shunt location had no effect on short or long-term outcome. One-and 2-year survival rates were 60% and 55%, respectively, for partially attenuated shunts. After 4 months, euthanasia because of failure to show clinical improvement, was the most common cause of death. Another study followed 37 dogs that survived initial intrahepatic PSS attenuation. Twenty-eight (76%) became clinically normal and required no medical management (mean follow-up: 16 months).[23] Nine dogs had persistent or recurrent encephalopathy of which three were euthanized without surgery. Six dogs were reoperated, three successfully ligated, and three euthanatized at surgery.

Complete occlusion requires multiple-staged procedures, unless a vein graft is placed between the portal vein and the vena cava. By placing the graft, portal hypertension may not develop after complete occlusion of the intrahepatic shunt. Splenectomy followed by anastomosis of the splenic vein to the abdominal vena cava has been used to alleviate portal hypertension in one dog as an emergency procedure.[123] Intraoperative hemorrhage from an intrahepatic PSS in this dog necessitated resection of the involved liver lobe and created life-threatening portal hypertension. As a planned procedure, a jugular vein may be harvested and used to create a bridge between the portal vein and the abdominal vena cava. With this technique, the surgeon essentially moves the shunt to an extrahepatic location, which allows for ligation or resection of the intrahepatic shunt. This new extrahepatic shunt can then be treated by placing an ameroid constrictor around the graft in an attempt to achieve complete resolution of all portosystemic shunting. This technique has been reported in a limited number of cases.[124,125] Eight of 10 dogs could have their intrahepatic PSS completely ligated using this technique in one study.[124] Nine of these dogs had an excellent clinical outcome, despite the development of multiple PSS in four of eight dogs reevaluated 8 to 10 weeks postoperatively.

Given the invasiveness and complexity of surgical correction, interventional radiologic techniques may become more routinely performed in the future. Transjugular coil embolization of canine intrahepatic PSS has been reported, and the short-term results are promising.[86,126] A fluoroscopically guided catheter is advanced from the right jugular vein to the caudal vena cava and shunt vessel. Contrast studies and measurement of portal pressures before and after coil placement are performed. A cylindric wire mesh stent is placed in the caudal vena cava at the level of the shunt to prevent coil migration. Catheter-delivered thrombogenic coils are then placed in the shunt (Figure 229-11). Complete or near complete occlusion of the shunt requires multiple-staged coiling sessions to prevent the development of acute portal hypertension.

229.1.3.2 Feline Portosystemic Shunts: Unique Considerations

Complete ligation of feline PSS is only possible in one of three cases. Most importantly, the prognosis after partial surgical ligation is less favorable than that reported for dogs. Although clinical improvement is usually seen after surgery, only 57% of 22 cats had a good to excellent long-term outcome.[60] Persistence or

recurrence of clinical signs has been reported in the majority of partially ligated cases.[12,20,59–61] For this reason, staged attempts to completely ligate the shunt vessel are advocated,[20,24] with resolution of clinical signs possible if complete ligation is eventually achieved.

Given the poorer prognosis associated with partial ligation when compared with dogs, gradual occlusion of feline PSSs with ameroid constrictors has also been investigated.[25,62] After ameroid placement, many cats (33% to 77%) experience postoperative complications, including central blindness (zero to 45%), hyperthermia (zero to 27%), seizures (8% to 14%), and frenzied behavioral changes (zero to 23%). Most of these complications are temporary. It should be noted that postoperative hypothermia and hypoglycemia are commonly reported in studies evaluating feline response to PSS ligation. Despite the high frequency of complications, the postoperative mortality rate is low (zero to 4%) and compares favorably to surgical attenuation (complete or partial ligation) of feline PSS (11%).[20] However, at recheck evaluation 8 to 10 weeks postoperatively, persistent shunting is common (57%). This is most likely due to the development of subclinical portal hypertension resulting in multiple acquired extrahepatic shunts, although this has been documented in only a few cases. As with dogs, too rapid closure of the shunt vessel or an underdeveloped portal system (or both) may contribute to portal hypertension. Long-term results vary between studies with 33% to 75% of cats reported as having a good to excellent clinical outcome[25,62] and 18% to 66% having a poor outcome. Owners contemplating surgical treatment for their cats' extrahepatic PSSs should be made aware of the discordant results reported in the current literature.

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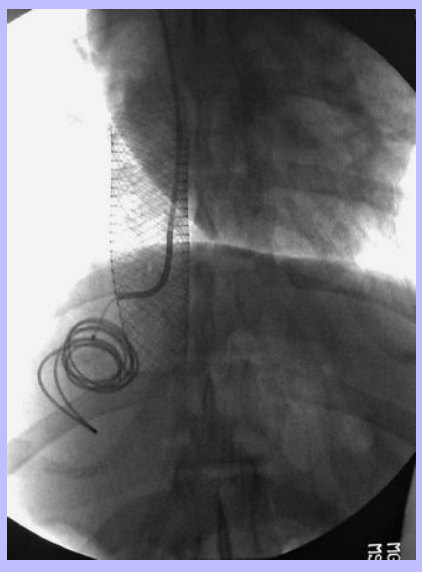
Figure 229-11 Ventrodorsal fluoroscopic image of a catheter-delivered thrombogenic coil being placed into a large right-sided intrahepatic portosystemic shunt (PSS). The dog's head is toward the top of the image. A cylindric braided wire stent has been placed in the caudal vena cava at the level of the diaphragm to prevent cranial migration of the coil. (Courtesy of Dr. Chick Weisse.)



Fewer than 10% of feline shunts are intrahepatic, and acquired shunts are rarely reported, therefore less can be said regarding their long-term prognosis.[20,127] A left-sided intrahepatic shunt consistent with a PDV is most common, although shunts involving the right and central liver lobes have been reported. As in dogs, feline PDVs empty into a venous dilatation or ampulla that receives contributions from the PDV, left hepatic veins, and phrenic veins prior to emptying into the caudal vena cava at the level of the diaphragm.[128,129] Partial ligation of the intrahepatic shunt cranial to the hepatic parenchyma has been reported in 10 cats.[129] Most cats survived these procedures.[70,128,129] Complete occlusion of the shunt by ligation of the portal vein branch feeding the shunt and transjugular coil embolization has been reported in one cat each.[70,130] Both cats survived and were clinically normal at long-term follow-up. This is in contrast to canine intrahepatic shunts, which can rarely be completely occluded with a single procedure.

229.1.3.3 Correction of Arterioportal Fistulae

Surgical treatment by resection of the affected liver lobe is successful in the majority of cases that have not gone on to develop multiple shunts. Partial hepatectomy has been successfully performed with and without temporary occlusion of the hepatic vasculature.[7,8,10] Portal hypertension resolves immediately after liver lobectomy, although this resolution is incomplete in many cases.[7,8,10] After surgery, animals that have formed multiple shunts may need to be treated medically with low-protein diets and medications as previously discussed for other forms of portosystemic communications. Upon review of 11 dogs with APF from four reports, eight of the dogs had developed multiple shunts by the time of surgery.[7,10,131,132] Two dogs died or were euthanized at surgery; one died 15 hours postoperatively (hypovolemic shock); one dog each was euthanized at 1 month (esophageal stricture), 14 months (recurrent hepatoencephalopathy), 26 months (hemorrhagic diarrhea), and 31 months (recurrent vomiting). Four of the 11 dogs (36%) were still alive at 5, 24, 26, and 36 months postoperatively. One dog still suffered from episodic HE 24 months postoperatively; the others were reportedly normal and off all medications and dietary management.

229.1.3.4 Multiple Acquired Portosystemic Shunts

Multiple acquired shunts form in response to increase portal blood pressure. Cirrhosis, APF, and NCPH are some conditions that may result in formation of multiple shunts (see Figure 229-11). Treatment is aimed at controlling the underlying problem if possible, and the prognosis is guarded unless the underlying problem can be ameliorated (see discussion of symptomatic treatment of PSS). Surgical treatment has been performed in the past by partially occluding the abdominal vena cava in an attempt to raise caval pressures above portal pressures and thus eliminate portosystemic shunting. Long-term survival and quality of life were no different between medically managed and surgically managed groups after hospital discharge in one study.[133] There appears to be no place for vena cava banding in animals with conditions causing portal hypertension.

229.1.3.5 Postoperative Complications

Despite preloading with anticonvulsants, postoperative seizure activity can still occur in PSS in some patients regardless of the shunt type or the surgical procedure performed.[134–138] Other residual neurologic deficits, such as transient blindness in cats, have also been reported.[62] In some cases, life-threatening status epilepticus may develop up to 3 days postoperatively. Some reports suggest that older animals are more

prone to developing this complication,[135,137] but this complication may occur regardless of age.[139] A few of the causes that have been suggested include alterations in brain amino acid and neurotransmitter profiles, and withdrawal of gut-derived benzodiazepine agonists.[140–142] Postoperative seizures in these patients appear to be most responsive to intravenous barbitutate[134] or a continuous rate infusion (CRI) of propofol (0.01 to 0.25 mg/kg/mm),[136] and management may require ventilatory and parenteral nutritional therapy.

Life-threatening portal hypertension is uncommon, but it may develop in the early postoperative period.[36,72,102,103] Clinical signs may include abdominal pain, hypotension, ascites, and vomiting. Reoperation to remove the suture or ameroid ring that is obstructing blood flow through the shunt vessel must be performed immediately. Successful outcome after reestablishment of shunt patency is uncommon.

Portal vein thrombosis may occur after shunt manipulation regardless of the surgical procedure.[105,143,144] Potential contributing factors to this condition include portal venous stasis or turbulent flow, endothelial damage, and hypercoagulability.[144] The authors have seen this occur in both dogs and cats with both intra-and extrahepatic shunts. Increases in portal venous pressures may result in the development of multiple shunts and continuation of clinical signs, or they may be severe enough to result in life-threatening GI venous stasis. The optimal method and duration of treatment is not clear. Treatment with anticoagulants, thrombolytic compounds such as tissue-plasminogen activator,[145] or both should be considered.

229.1.4 Treatment for Animals with Nonsurgical Conditions

For dogs with partially occluded PSS, inoperable PSS, NCPH, or for animals with owners who decline definitive treatment, symptomatic management is recommended for life. Quality of life is improved temporarily, but fluctuating neurologic signs and occurrence of urate urolithiasis can be expected. The current ability to manage clinical signs in dogs with congenital PSS primarily with diet is limited unless a purified diet is used, but it is no substitute for surgical correction. In a study of the long-term effects of surgically created end-to-side portocaval shunts in adult dogs, the diet used was a purified, carbohydrate-based diet formulated with a specific ratio of branched chain amino acid to aromatic amino acid composition. Both dogs with created portocaval shunt and sham-operated dogs lived comfortably for nearly 1 year, free of signs of HE and weight loss. These diets are not made commercially, so they are inaccessible to owners. Another study evaluated 23 dogs with congenital PSS that did not have corrective surgery but had symptomatic treatment for at least 3 years.[147] About half of the dogs had been euthanatized within 1 year of diagnosis, mostly because of uncontrollable HE, but nine dogs lived a reasonable quality of life for 3 to 8 years. Similar studies have not been performed in cats. Despite these encouraging findings in dogs, hepatic deterioration associated with poor portal blood flow progresses as long as the abnormal vascular pattern persists. The same regimen is used for cats with inoperable PSS or for cats whose owners decline surgery.

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No surgical remedy for MVD exists, so symptomatic management for HE (if present) is the only treatment recommended. Affected dogs seem to live comfortably in good to excellent condition for at least 5 years without serious consequences.[25]

For dogs with NCPH, one study concluded that affected dogs might live as long as 9 years after diagnosis with minimal symptomatic treatment for ascites, and for some, HE. Four dogs were euthanatized because of problems related to persistent portal hypertension (e.g., duodenal ulceration, urate urolithiasis).[49]

For treatment of animals that have acquired portosystemic shunting associated with primary hepatobiliary disease, see elsewhere in this text.

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230 CHAPTER • 230 Toxic, Metabolic, Infectious, and Neoplastic Liver Diseases

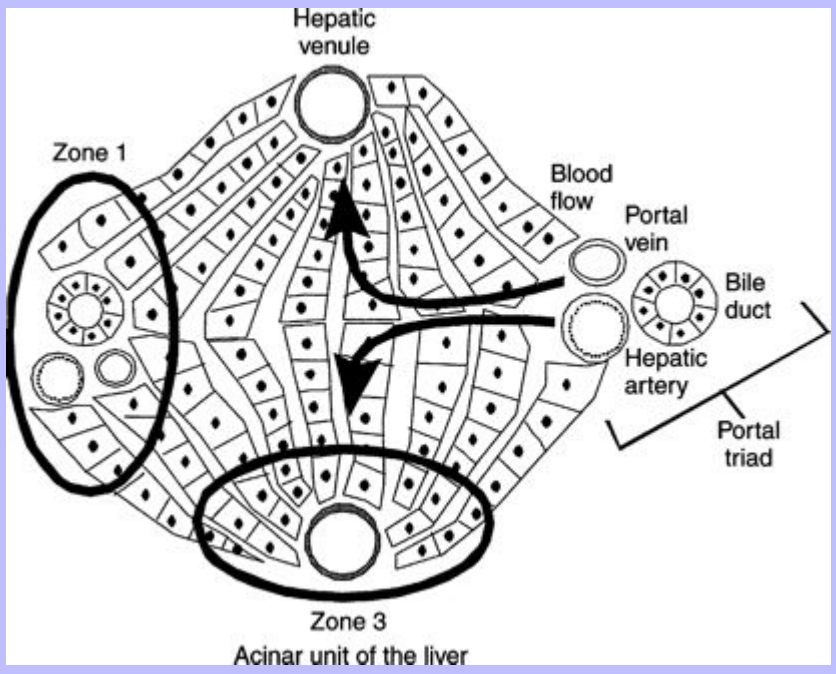
Margie A. Scherk

Sharon A. Center

230.1 INTRINSIC AND IDIOSYNCRATIC XENOBIOTIC HEPATOTOXICITY

Deriving 75% of its circulation directly from splanchnic venous drainage, the liver receives direct and concentrated delivery of xenobiotics (drugs and environmental chemicals) absorbed from the gut. Consequently, because of this central position in drug metabolism and disposition, the liver is a preferential target for adverse xenobiotic reactions. Many xenobiotics are capable of causing some degree of liver injury; these are broadly classified as intrinsic or idiosyncratic, although a combination of reactions also may occur.[1] Intrinsic hepatotoxicity is a result of the direct action of a xenobiotic or its metabolite on vital cell targets; a prototype of this form of injury is acetaminophen. Biochemical and morphologic features of intrinsic hepatotoxins reflect either extrinsic mechanisms or intracellular events and many damage zone 3 (Figure 230-1). The most common hepatic reaction with intrinsic drug toxicity is necrosis without an inflammatory infiltrate. Although drug-metabolizing enzymes detoxify many xenobiotics and toxins, they also enhance the toxicity of some.

Figure 230-1 Microscopic liver architecture: acinar unit of the liver.



Unlike intrinsic toxicity, idiosyncratic injury is thought to commonly involve immune-mediated mechanisms that either invoke specific cell surface death receptors, signaling apoptosis or necrosis, or involve hapten and

neoepitope expression on the hepatocyte surface. Idiosyncratic hepatotoxicity can exhibit either a regional or mixed zonal pattern.

Because the liver has an enormous regenerative capacity, replacement of lost hepatocytes may mask detection of drug-induced injury. The outcome of intrinsic and idiosyncratic xenobiotic hepatotoxicity varies widely, ranging from cell survival to apoptosis or complete cytolytic necrosis. Nutritional status affects xenobiotic toxicity, with obesity favoring the accumulation of lipid-soluble toxic metabolites and anorexia or protein: calorie restriction resulting in reduced hepatic glutathione (GSH) concentrations that can increase the hepatotoxicity of certain agents. 1465

230.1.1 Xenobiotic Hepatotoxicity: Morphologic Lesions

Drug-induced liver injury can mimic all forms of spontaneous liver disease. Lesions that may be linked with xenobiotic hepatotoxicity, include hepatocellular necrosis, toxic hepatitis, steatosis, and cholestasis (canalicular stasis with periportal inflammation). A summary of xenobiotics-related hepatotoxic reactions is provided in Table 230-1. The most common effects are described below.

Hepatocellular necrosis associated with xenobiotic toxicity may be zonal (often zone 3) or panlobular. Clinically, illnesses may range from an asymptomatic increase in transaminase activity to jaundice and overt hepatic failure. Intrinsic hepatotoxins can produce vague gastrointestinal (GI) signs, abdominal discomfort within a few hours to days of exposure (e.g., diazepam (cats) and carprofen (dogs)). In some cases, clinical signs resolve within days of xenobiotic withdrawal, however, in others, overt liver failure develops within 1 week and is associated with sequentially increasing liver enzymes, jaundice, coagulopathies, evidence of proximal renal tubular injury (i.e., granular casts, renal glucosuria), acute renal failure, and neurobehavioral changes indicative of hepatic encephalopathy.

Toxic hepatitis is characterized by diffuse or multifocal hepatic necrosis and degeneration with or without canalicular cholestasis. Hepatic acinar structure is maintained, but areas of necrosis and degeneration are surrounded by viable hepatocytes (+/− degenerative features) and an inflammatory infiltrate (mononuclear, macrophages, or eosinophils). Illness can range in spectrum from asymptomatic increases in transaminases to signs of overt liver failure and jaundice.

Steatosis (cytosolic fatty vacuolation) reflects the abnormal accumulation of triglycerides in hepatocytes in either a macrovesicular or microvesicular pattern. With the exception of hepatic lipidosis in cats, mild to moderate fatty vacuolation of hepatocytes may accompany “toxic” hepatitis. Microvesicular steatosis is thought to reflect severe metabolic disruptions associated with abnormal mitochondrial function. When diffuse, this lesion often accompanies inflammation and hepatocellular necrosis.

Cholestasis induced by xenobiotic toxicity results from the disruption of bile production or flow and may present as a periportal inflammatory lesion causing hepatocanalicular cholestasis or a less obtrusive, canalicular dysfunction without inflammation or necrosis. The major evidence for this form of injury involves sequential increase in alkaline phosphatase (ALP) and GGT activity, and the development of hyperbilirubinemia. 1465 1466

Table • 230-1 Histologic Patterns of Xenobiotic Associated Hepatic Injury

PATTERN OF INJURY	MECHANISMS	PROTOTYPE XENOBIOTICS
Zonal necrosis	Xenobiotic adducts, free radicals, neoantigens	Acetaminophen, halothane
Toxic hepatitis	Hapten formation →neoantigen	Phenytoin, sulfonamide, isoniazid
Microvesicular steatosis	Impaired hepatic B-oxidation of fatty acids	Tetracycline, valporic acid, tamoxifen
Macrovesicular steatosis	Increased triglyceride synthesis, reduced egress	Anabolic steroids in inappetent cats
Phospholipidosis	Formation of lysosomal inclusions	Amiodarone
Canalicular Cholestasis	Decreased membrane fluidity, Na/K ATPase	Anabolic hormones, estrogens, androgens
Hepatic cholestasis	Inflammation, Damage to bile canaliculi	Chlorpromazine
Veno-occlusive disease	Occlusion of terminal hepatic venules	Azathioprine, 6-thioguanine
Peliosis hepatica	Damage to sinusoidal membranes	Anabolic androgenic hormones
Hepatic xeoplasia	Unclarified	Sex hormones
Mixed inflammatory patterns	Immune-mediated to product/adduct	Many drugs

230.1.1.1

Box • 230-1 Known Hepatotoxins

Azathioprine

Carprofen (dogs)

Clonazepam (cats)

Diazepam (cats)

Danazol (dogs)

Acetaminophen (dogs and cats)

Diethylcarbamazine (*Dirofilaria immitis* microfilaria-positive dogs)

Diethylcarbamazine

Galactosamine

Glucocorticoids (dogs)

Halothane (dogs)

Ketoconazole

Mebendazole (dogs)

Methimazole (cats)

Methoxyflurane (dogs)

Mitotane (dogs)

Oxibendazole (dogs)

Phenytoin (dogs)

Primidone (dogs)

Phenobarbital (dogs)

Stanozolol (cats)

Thiacetarsemide (dogs)

230.1.1.1.1 Commonly Reported Toxins

Amanita mushrooms

Aflatoxins/mycotoxins

Blue-green algae: cyanobacteria

Cycad (Sago palm nuts)

Chlorinated compounds

Dimethylnitrosamine

Dinitrophenol

Heavy metals (Pb, Zn, Mn, Ar, Fe, Cu)

Phenols (especially cats)

230.1.1.1.2 Endotoxins and Enterotoxins

Enteric organisms: *Clostridium perfringens*, *C. difficile*

Food poisoning: Staphylococcal, *Escherichia coli*, *Salmonella*, *Bacillus cereus*

230.1.2 Specific Hepatic Xenobiotic Toxicities

A list of known hepatoxins follows.

230.1.2.1 Antimicrobial Hepatotoxicity

Antimicrobial hepatotoxicity, Table 230-2, has been widely recognized in humans and less commonly reported in veterinary patients. Trimethoprim-sulfa reactions are the best recognized example in dogs. Tetracycline therapy can result in fulminant hepatic failure in both dogs and cats as well as hepatic lipidosis.

230.1.2.2 Anticonvulsants: Phenobarbital, Phenytoin, and Primidone

Phenobarbital hepatotoxicity is the best-characterized "idiosyncratic" reaction in the dog, and has been well studied in this species as an enzyme inducer. It is clinically recognized as a hepatotoxin in some epileptic dogs. Clinical signs may include sedation and ataxia due to impaired drug metabolism. Anorexia, ascites, jaundice, and coagulopathy develop when liver damage is severe. A direct dose-related hepatotoxicity is not consistent. Clinical signs can develop within several months or years of phenobarbital initiation. Most dogs have been treated for over 1 year before showing clinical signs. Despite substantial hepatic injury, dogs may appear to be physically healthy despite abnormal serum chemistry values. Remission of clinicopathologic features and improvement in hepatic injury may occur after drug discontinuation. Dose reduction may produce improvement, but this is not well documented. Necropsies in dogs succumbing to hepatic insufficiency usually confirm chronic liver injury or cirrhosis. Lesions are identical to those described in dogs with primidone hepatotoxicity as 25% of primidone is metabolized to phenobarbital, and cannot be differentiated from dogs with other forms of chronic parenchymal liver injury.[2] Combination therapy of phenobarbitol and primidone increase the risk of hepatotoxicity.

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Table • 230-2 Antimicrobial Hepatotoxicity

ANTIBIOTICS	TYPE OF LIVER INJURY
Penicillins	
Amoxicillin	Hepatocellular
Ampicillin	Hepatocellular
Amoxicillin/clavulanic acid	Cholestatic*, mixed vanishing bile duct lesions, granulomatous
Carbenicillin	Mixed
Nafcillin	Cholestatic
Oxacillin	Cholestatic, granulomatous
Penicillin G, V	Hepatocellular
Timentin	Cholestatic
Cephalosporins	Mixed, cholestatic
Ceftriaxone	Biliary sludge/stones
Cephalexin	Granulomatous
Tetracyclines	Hepatic lipidosis*,* fulminant hepatic failure* (dogs, cats)
Macrolides	
Erythromycin	Cholestatic*, vanishing bile duct lesions
Azithromycin	Cholestatic
Clarithromycin	Cholestatic
Clindamycin	Acute hepatocellular injury
Sulfonamides	Cholestatic*, hepatocellular*, mixed, granulomatous, fulminant liver failure*
Trimethoprim-Sulfa	Cholestatic, hepatocellular, mixed, granulomatous, fulminant liver failure* (dogs)
Antifungal	
Ketoconazole	Hepatocellular*, mixed, fulminant liver failure
Fluconazole	Hepatocellular*, cholestatic
Itraconazole	Hepatocellular
Flucytosine	Hepatocellular
Griseofulvin	Hepatocellular, cholestasis (cats)*
Antiparasitic Agents	
Albendazole	Hepatocellular, mixed
Mebendazole	Hepatocellular*, mixed, fulminant hepatic failure*
Thiabendazole	Mixed*, vanishing bile duct syndrome with diethylcarbamazine, necrosis (dogs)
Oxibendazole	

From Brown SJ, Desmond PV, Hepatotoxicity of antimicrobial agents. *Seminar Liver Dis* 2002; 22:157-67

* Antimicrobial drug hepatotoxicity reported in humans but pertinent to veterinary patients.

Phenytoin, a potent enzyme inducer can cause hepatitis, jaundice, and death in dogs when used as an anticonvulsant, especially when administered in combination with either phenobarbital or primidone. A dose-independent chronic hepatitis may progress to cirrhosis and appears to be reversible if the drug is discontinued promptly after initial signs of illness. Rarely, acute hepatotoxicosis has been observed.

230.1.2.3 Diazepam

Diazepam-associated hepatotoxicity in cats appears to be an idiosyncratic reaction. It causes severe panlobular hepatocellular necrosis sparing the biliary epithelium. Affected cats received these agents for behavior modification (e.g. inappropriate urination). Hepatotoxicity is recognized within the first week (several days) of oral drug administration. Initial clinical signs include inappetence, vomiting, and severe lethargy associated with transaminases progressively rising levels. After several days, ALP GGT and

bilirubin levels progressively increase activities progressively and cats become overtly jaundiced. Clinicopathologic abnormalities may progress to reflect fulminant hepatic failure, including hypoglycemia, profound coagulopathies, high creatinine kinase activity (muscle and myocardial necrosis), granular casts, and acute renal failure. Cats who have survived fulminant hepatic failure have received blood transfusions, plasma, vitamin K_1, water-soluble vitamins, parenteral feeding, and aggressive fluid and electrolyte support. Administration of N-acetylcysteine (NAC) is recommended. Surviving animals have persistently high ALP and GGT activity for several weeks to months after recovery due to regeneration, and hyperplastic biliary epithelium. Similar toxicity has been observed in cats receiving oral clonazepam.

230.1.2.4 Oxibendazole and Mebendazole

Administration of a combination heartworm-hookworm preventative containing diethylcarbamazine and oxibendazole has been associated with lethal hepatotoxicity in dogs. Clinical signs developed 2 to 4 weeks after the initiation of treatment and included lethargy, anorexia, vomiting, diarrhea, polydipsia, polyuria, and weight loss. Biochemical profiles reflected hepatocellular injury and cholestasis.

230.1.2.5 Methimazole

Methimazole used to treat hyperthyroid cats may be associated with cholestatic hepatotoxicity. This usually occurs within the first month of therapy and is indicated by increased liver enzyme activity (transaminases, ALP) and jaundice. Liver injury appears to be reversible with early drug discontinuation. Because metabolism of toxic intermediates involves GSH, it is postulated that patients with subnormal hepatic GSH concentrations may beat an increased risk for hepatotoxicity.[3] Although not yet studied in the cat, hyperthyroidism in other species reduces hepatic GSH concentrations, possibly from to increased oxidative stress associated with the enhanced metabolic rate. Because catabolism and protein deficiency states can enhance hepatic GSH depletion, certain symptomatic hyperthyroid cats may be at increased risk for methimazole toxicity. Cats with pre-existent liver disease associated with GSH depletion (e.g., cholangitis, cholangiohepatitis) may also be at increased risk.[4] This coincides with the observation that cats with cholangitis/cholangiohepatitis may become increasingly symptomatic when hyperthyroid.

230.1.2.6 Nonsteroidal Anti-inflammatory Drugs

Because NSAIDs are being used more often in the treatment of inflammatory and painful conditions, it is important to be observant for not only gastric and renal effects of prostaglandin inhibition but also for potential hepatotoxic effects. The mechanism by which hepatic toxicity occurs with most NSAIDs is not known, but it is not related to prostaglandin inhibition. NSAID-associated hepatopathy is believed to be idiosyncratic. Thus it is reasonable to obtain baseline biochemistry values (alanine aminotransferase [ALT], alkaline phosphatase [ALP], blood urea nitrogen [BUN], creatinine, total protein, packed cell volume [PCV]) because these agents can be associated not only with idiosyncratic hepatotoxicity but also with dose-dependent GI bleeding and exacerbation of renal insufficiency.

Nearly all nonsteroidal anti-inflammatory drugs (NSAIDs) can cause an asymptomatic increase in transaminase activity in humans. Usually enzyme activity normalizes rapidly upon treatment of cessation. Virtually all NSAIDs can cause some form of liver injury. There is no clear correlation between chemical class of NSAID and risk of hepatotoxicity. The histologic type of injury varies within and between classes. Although hepatocellular injury is most common, cholestatic injury, mixed injury, steatosis, and granulomatous reactions also are described in humans. Since many toxic metabolites are normally

detoxified by GSH, some metabolites may become more injurious when hepatic GSH stores are depleted (e.g. in patients with chronic necroinflammatory and cholestatic liver disease).[5]

Two NSAIDs are directly hepatotoxic: aspirin and phenylbutazone. In humans, the effects of aspirin are predominantly dose-dependent, anicteric, rarely fatal, and are reversible when treatment is discontinued. Carprofen (see below), a propionic acid derivative is recognized to cause severe and sometimes lethal idiopathic hepatotoxicity in dogs. Reye's syndrome, an unusual adverse response to aspirin, occurs in children with viral infections and results from mitochondrial toxicity.

230.1.2.6.1 Acetaminophen

Acetaminophen is widely recognized to provoke hepatotoxicity through induction of the p450 enzyme and impairment of hepatic GSH concentrations. Treatment with thiol donors to restore circulating and liver GSH status, or that directly conjugate toxic adducts can attenuate acetaminophen hepatotoxicity. Both NAC and S-adenosyl-L-methionine (SAMe) have been proven to do this. Dogs have an apparent predisposition to acetaminophen-induced liver damage due to their intrinsically low hepatic GSH concentrations relative to that of other species.[5] Cats have higher hepatic GSH concentrations and do not succumb to hepatotoxicity. Rather, they develop oxidative damage to their rbcs (red blood cells) (Heinz body anemia, methenoglobinemia) because of labile sulfhydry bonds in their hemoglobin, and endothelial toxicity.

230.1.2.6.2 Carprofen

Carprofen is a lipophilic, propionic acid class NSAID useful for the amelioration of pain associated with osteoarthritis. It can provoke idiosyncratic cytotoxic hepatotoxicity in some dogs.[6] Severity of cytotoxic injury varies among dogs and appears unrelated to dose or duration of treatment. Most dogs have received treatment for at least 2 weeks before showing vague signs of toxicity: anorexia, vomiting, lethargy, and polyuria/polydipsia (PU/PD). Some dogs with occult hepatic injury lack clinical illness. Common clinicopathologic abnormalities include modest to markedly increased transaminases (exceeding increases in ALP). Renal toxicity (granular casts, glucosuria in the absence of hyperglycemia, and proteinuria) may also occur. Some dogs succumb to fulminant hepatic failure, although most recover after drug withdrawal and 1–2 weeks of hospitalized supportive care. It is unclear whether chronic inflammatory liver disease precedes or follows acute toxicity.

230.1.2.7 Natural or Herbal Remedies

Awareness of the potential hepatotoxicity of herbal preparations and other botanicals Many herbal remedies are believed to be harmless and are commonly used without adequate medical supervision. The true frequency with which botanicals cause hepatic damage is unclear but it is important to remain alert for a causal relationship when liver injury is identified. A list of hepatotoxic associations with different herbal remedies is provided in Table 230-3.[5] 1467 1468

Table • 230-3 Herbal Remedies Associated with Hepatotoxicity

AGENT/PRODUCT NAME	TOXIC INGREDIENT	EVIDENCE/TYPE HEPATOBILIARY INJURY
African remedy	*Atractylis gummifera*	Diffuse hepatic necrosis; acute onset within hours
(Mediterranean/African regions)	*Callilepsis laureola*	Mitochondrial toxins
Bajiaolian	Podophyllotoxin	Abnormal liver tests
Chaparral leaf	*Larrea tridentata*, nordihydroguaiaretic acid	Fulminant hepatic necrosis, zone 3 necrosis, chronic hepatitis, cholestasis, cirrhosis
Chinese Herbal Medicine	Glycyrrhizin	Vanishing bile duct syndrome
Chinese Herbal Tea	*T u san-chi' I* (*Compositae*)	Veno-occlusive disease
Comfrey (*Symphytum officinale*) (gordolobo yerba, tea, maté)	Pyrrolizidine alkaloid	Veno-occlusive disease
Dai-saiko-to (differs from Sho-saiko-to in proportion of components)		Acute and chronic hepatitis
European remedy	*Chelidonium majus*, other *Neoclerodane diterpenes*,	Hepatitis, fibrosis, eosinophilic inflammation Zone 3 hepatitis, necrosis,
Germander	*Teucrium chamaedrys*	fibrosis, cirrhosistoxicity enhanced by p450 cytochrome induction and glutathione (GSH) depletion
Herbal teas comfrey, *Heliotroprium*, *Senecio*, *Crotalaria*, *Symphytum*, *T'u-san-*[*Compositae*]	Pyrrolizidine alkaloid	Veno-occlusive disease
Jin Bu Huan	*Lycopodium serratum*	Acute/chronic hepatitis, fibrosis, steatosis
Kombucha "mushroom"	Yeast-bacterial aggregate	Abnormal liver tests
Ma-huang	Ephedrine many other ingredients	Acute hepatitis
Margosa oil	*Azadirachta indica*	Hepatic lipidosis associated with diffuse mitochondrial failure
Mediterranean traditional remedy	*Teucrium polium*	Zone 3 necrosis, fibrosis, acute liver failure
Mixed preparations: mistletoe, valerian, skullcap	Unknown	Hepatic injury, laboratory abnormalities
Natural laxatives	Senna, podophyllin, aloin	Abnormal liver tests
Oil of cloves	Eugenol	Direct-dose hepatotoxin
Pennyroyal oil (home-made tea)	Labitae (mint)	Zone 3 necrosis, liver test abnormalities, pulegone depletes glutathione
	Mentha pulegium; pulegone → menthofuran pulegone	
Prostata	Saw palmetto *Serenoa serrulata, Pygeum africanum, other ingredients*	Hepatitis, fibrosis, cholestasis
Sassafras	*Sassafras albidum*	Hepatic carcinogen (animals)
Sho-saiko-to (TJ-9)	*Scutellaria*, others	Zonal, bridging necrosis, fibrosis, microvesicular steatosis, cholestasis
Chinese name: Xiano-Chai-Hu-Tang	Many components	Acute hepatitis, focal steatosis
	Venencapsan (horse chestnut leaf, sweet clover, celandine, milk thistle, dandelion root, milfoil)	
Zulu remedy	*Callilepsis laureola*	Hepatic necrosis

230.1.3 General Treatment Recommendations

If acute ingestion of a hepatotoxin within the preceding 8 hours, prompt is suspected emesis, gastric lavage, high enema cleansing, and administration of activated charcoal (orally and by enema) is recommended. Animals with reduced consciousness or active enteric bleeding should not be made to vomit or have vigorous enema manipulations performed for fear of causing aspiration pneumonia or exacerbating hemorrhage. Activated charcoal may importantly reduce enterohepatic circulation of certain toxins and should be administered. Antioxidant supplementation is warranted. Although not clearly a direct antidote for every form of xenobiotic hepatotoxicity, administration of NAC is safe, and may guard against hepatocellular thiol depletion. It is important that NAC be injected as a slow bolus rather than as a constant rate infusion. Using a nonpyrogenic 0.2 μm filter, give 140 mg/kg; subsequently give 70 mg/kg up to 4–6 times daily slow IV. Once oral medications can safely be administered, initiate same 20 mg/kg PO. Same is best administered on an empty stomach to ensure availability of this pivotal metabolic substrate. Supplementation with alpha-tocophetol (vitamin E, 101 u/kg orally per day) is also suggested. In fulminant hepatic failure, provision of clotting factors by administration of fresh frozen plasma is advised (2 to 5 mL/kg intravenously), along with vitamin K_1 (0.5 to 1.5 mg/kg subcutaneously, every at 12-hour intervals for three doses). For certain xenobiotics, particularly early after acetaminophen ingestion, cimetidine is administered with the intent of impairing cytochrome p450 activity responsible for generation of toxic adducts. Fluid therapy is provided to ensure adequate hydration, not only for normal circulatory support, but also for maximal biliary and renal excretion of toxic adducts. Fluids should be supplemented with B complex vitamins (1 to 2 mL/liter of fluid), along with KCl (judiciously using conventional sliding scale doses), phosphate, and magnesium according to needs. Glucose supplementation is important for patients in fulminant hepatic failure or demonstrating proximal renal tubule injury with glucosuria when hypoglycemia is recognized. For toxins that are highly protein bound and difficult to eliminate, administration of medications with competitive protein binding may exacerbate toxicity. For animals with declining oncotic pressure, administration of synthetic colloids (hetastarch, Dextran-70) is advised. Because colloids may result in platelet-associated bleeding tendencies, fresh frozen plasma is preferred in animals in fulminant hepatic failure prior to colloid administration.

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Clinical use of Milk Thistle (silibinin) remains controversial, except for intervention of amanitin-associated mushroom toxicity.[5] The active constituents, flavonolignans including silibinin, isosilibinin, silidianin, and silicristin, are collectively known as *silymarin*; silibinin is the principle active ingredient. This herbal product is thought to be a hepatoprotective, antioxidive, antiinflammatory, antifibrotic, and to promote hepatic regeneration. No evidence indicates that silymarin poses a toxic effect, although standardization of products and purity is unregulated. Doses of 20 to 50 mg/kg of 60% to 80% potency silymarin extract may be appropriate for dogs; studies of *Amanita phalloides* hepatotoxicosis used 50 to 150 mg/kg successfully.[5]

Nutritional support is critical for animals recovering from acute xenobiotic toxicity. Protein restriction should not be imposed unless signs of hepatic encephalopathy are recognized; undue restriction may impair a positive nitrogen balance needed for tissue regeneration.

Sequential evaluation of liver enzymes (transaminases in particular), total bilirubin (where elevated), and serum bile acids (SBA) (in those with normal bilirubin) can be used to monitor resolution of hepatocellular toxicity and improving liver functions. For lesions associated with reactive biliary epithelial hyperplasia, the serum ALP and GGT activities may increase for days after clinical improvement is firmly established.

Discontinuation of the suspected hepatotoxin is the most important interventional treatment for chronic xenobiotic hepatotoxicity. Intervention with glucocorticoids or other immunomodulating medications should

only be based on liver biopsy findings. Common involvement of *oxidative stress* argues for intervention with antioxidants, especially thiol donors (SAMe), and vitamin E until clinicopathologic findings indicate recovery. Ursodeoxychol acid is specifically indicated when high bile acid concentrations are a part of the disease process, but it has limited value in acute xenobiotic toxicity. If cholestasis is a component of chronic disease, accumulation of membranocytolytic hydrophobic bile acids justifies its use.[3]

230.2 METALS AND LIVER DISEASE

Because the liver is the first organ perfused by portal blood containing absorbed minerals, it can serve as a "sink" or "reservoir" for excessive quantities of absorbed materials or toxic metals. Copper and iron play a critical role in formation of reactive oxygen species (ROS); selenium and zinc contribute to ROS detoxification. Excess copper is primarily eliminated through the biliary system, thereafter undergoing an enterohepatic circulation. The transition metals copper and iron have been proven to accumulate in the liver tissue of dogs and cats with necroinflammatory liver disorders where they may enhance hepatic vulnerability to oxidant injury.[8]

230.2.1 Copper

Because copper is a transition metal, it has both pro-and antioxidant effects. Pathologic hepatocellular copper overload has been well described in Bedlington terriers as a genetic defect and has been observed randomly in other pure and mixed breed dogs and in a few cats. Serum ALT activity has been shown to correlate with mitochondrial copper concentrations, hepatocellular oxidant damage, and cytolysis in patients with inherited copper storage hepatopathy. The familial tendency for hepatic copper accumulation described in the West Highland white terrier does not consistently lead to liver injury. Copper retention is more commonly observed as a complicating feature of chronic cholestatic liver disease.

230.2.2 Iron

In approximately 80% of dogs with chronic necroinflammatory liver disease, tissue iron concentrations exceed the normal range.[9] Recent work suggests that although this iron appears morphologically isolated in hepatic Kupffer cells, other macrophages or lipogranulomatous inflammatory foci in liver tissue, it remains biologically active and may contribute to ROS formation and hepatic fibrosis.[7,9]

It is clear that iron is a profibrogenic factor based on extensive study of humans with hemochromatosis, a genetic defect resulting in hepatocyte iron loading. A central role in liver fibrogenesis associated with iron overload is the Kupffer cell, which in turn, activates nearby stellate cells, directly mediating collagen gene activation.

Therapeutic intervention in iron-related liver injury has been studied. High hepatic iron concentrations are associated with subnormal concentrations of vitamin E and a reduced GSH/GSSG balance in liver tissue. Hepatocytes depleted of GSH are more susceptible to iron-induced lipid peroxidation. In hemochromatosis, phlebotomy is the treatment of choice along with administration of antioxidant and hepatoprotective agents. Both vitamin E and silibinin attenuate iron-associated oxidative liver injury in this disorder.[10,11] One of the authors has rarely diagnosed apparent hemochromatosis-like hepatic disease in dogs and cats. These have been managed with phlebotomy (i.e., biweekly removal of no greater than 15% of blood volume), repeated based on circulating ferritin concentrations and serum iron indices (as well as chronic supplementation with antioxidants).

230.3 METABOLIC DISORDERS

230.3.1 Amyloidosis

Amyloidosis involving the liver is uncommon but may occur as a component of systemic amyloidosis, a syndrome resulting from multiorgan extracellular amyloid deposition. Amyloid is made up of a number of different amyloidogenic proteins reflecting a diversity of disease processes. All amyloid proteins share a pleated structure, resulting in a characteristic green birefringence when stained with Congo red and viewed with polarized light. In systemic amyloidosis of dogs and cats, the precursor protein is typically amyloid A (AA), an amino terminal fragment of the acute-phase protein, serum amyloid A (SAA). This protein may occur secondary to sustained acute-phase reactions associated with chronic inflammatory, infectious, or neoplastic diseases or as a familial trait as it does in man.

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In systemic amyloidosis, the clinical signs vary corresponding to the pattern and extent of tissue involvement. In familial AA amyloidosis in Chinese Shar Pei dogs and in Abyssinian cats, the most common presentation involves renal involvement. Systemic familial amyloidosis involving the liver has been described in a small number of dogs, and in Siamese, Oriental shorthair, Devon Rex, Burmese, and DSH cats.[12–15] Investigation of amyloid protein in Siamese and Abyssinian cats suggests a unique isotype in the Siamese. Diffuse hepatic involvement predisposes to spontaneous hepatic rupture, owing to increased organ fragility and the presence of a coexistent coagulopathy (inhibition or deficiency of factors, binding of ionized calcium, or deficiency of vitamin K). Cats present suddenly dead or hypothermic with acute signs of hemorrhage from ruptured liver lobes (anemia, hemorrhagic abdominal effusion). A regenerative anemia, presence of Howell Jolly bodies due to splenic dysfunction from amyloid deposition, a “stress” leukocytosis, and poikilocytes are observed. Thrombocytopenia and abnormally prolonged clotting times are common in cats with hepatic rupture; some cats respond to vitamin K_1. Increased ALT is common, but some cases lack biochemical features indicating hepatic involvement. A familial cluster of cases is common. Hepatic ultrasonography initially may reveal a diffusely hypoechoic liver.

Definitive diagnosis requires tissue biopsy and histopathologic demonstration of amyloid. Cytologic evaluation of an hepatic aspirate may suggest (but not definitively confirm) the presence of amyloid, based on the identification of pink amorphous material adjacent to hepatocytes (with a modified Wright's-Giemsa stain). Caution is warranted before collecting liver samples because either aspiration or biopsy may initiate uncontrollable hemorrhage. On gross inspection, affected liver or spleen appear pale and enlarged, with rounded edges. The intestines may be dilated reflecting dysmotility secondary to amyloid deposition.

Colchicine is used in the treatment of familial Mediterranean Fever in man (similar to the periodic fever syndrome in Shar Pei dogs). It attenuates inflammation by interfering with release of inflammatory mediators, neutrophil participation, and deposition of amyloid fibrils. Clinical signs (several dogs) and histologic severity of hepatic amyloid deposition (as reported in one dog) have been blunted in Shar Pei dogs treated with colchicine (0.03 mg/kg orally per day). No experience exists with colchicine in cats with systemic amyloidosis and liver involvement. Colchicine has been used in a few cats with hepatic fibrosis (0.03 mg/kg orally, once a day to every other day). Acute treatment of liver hemorrhage requires generous provision of fresh whole blood and plasma transfusions. A grave prognosis is warranted for cats with hepatic amyloid; survivors eventually succumb to renal failure or acute hypovolemic shock from liver lobe fracture.

230.3.2 Feline Lipoprotein Lipase Deficiency

Lipoprotein lipase (LPL) regulates the dispersal of fatty acids to muscle and adipose. Deficiency disturbs fat metabolism leading to hypertriglyceridemia, hyperchylomicronemia, and systemic sequela of these aberrations. Several kindreds of cats with familial LPL deficiency have been studied; this defect is an autosomal recessive trait.[16,17] Compared with normal cats, affected cats have more than tenfold increase in circulating triglycerides yet normal total cholesterol. Kittens do not exhibit clinical signs other than fasting lipemia; they grow normally and show clinical signs at 8 to 9 months of age, including fasting hyperlipemia, lipemia retinalis, cutaneous xanthogranulomas (lipogranulomas), and peripheral neuropathies due to the compression of lipogranulomas in areas of minor trauma. Treatment involves feeding a diet restricted in fats and triglycerides. Peripheral neuropathies may resolve or improve after several months on a fat-restricted diet.

230.3.3 Canine Hyperlipidemia

Abnormalities in canine lipid metabolism have received limited attention. Affected breeds include Miniature Schnauzers, Shetland Sheepdogs, Briards, Beagles, certain terrier breeds (especially Scottish terriers, West Highland white terriers, Cairn terriers), and some mixed breed dogs. Hyperlipidemia in the dog predisposes to development of a diffuse vacuolar hepatopathy or biliary mucocele. Vacuolar hepatopathy may be associated with excess hepatocyte glycogen and/or lipid inclusions. Biliary mucocele formation may reflect the influence of hypercholesterolemia on biliary cholesterol concentrations and appears to be augmented by age-related cystic hyperplasia and possible dysmotility of the gallbladder wall.

In the developmental stage, biliary mucoceles are asymptomatic and are serendipitously discovered during abdominal ultrasound performed for unrelated reasons. Dogs with large biliary mucoceles may present for associated necrotizing cholecystitis or they may be found ultrasound investigation for high liver enzyme activity (especially ALP). Many cases have a coexistent diffuse vacuolar hepatopathy causing a diffuse or multifocal hepatic parenchymal hyperechogenicity, hypoechoic nodules, nongravitational gallbladder “sludge,” and a thickened, bi-or trilaminar appearance of the gallbladder wall. The appearance of a “kiwi” fruit echoimage within the gallbladder lumen is diagnostic for a firm, well-established mucocele. These must be surgically removed, the urgency depending on clinical evidence of necrotizing cholecystitis (hyperbilirubinemia, high liver enzymes, cranial abdominal pain, leukocytosis). Dogs with severe hypothyroidism can also develop pathologically significant hypercholesterolemia, hepatic vacuolation, high liver enzyme activity associated with abnormally increased SBA concentrations, hyperbilirubinemia, and biliary mucoceles. Initiating thyroxin therapy for 1 to 2 weeks before elective surgical removal of a biliary mucocele is advised in these dogs if clinical signs of the mucocele are minimal. Although liver lesions resolve with institution of thyroxine, mucoceles usually require surgical removal. At surgery, the gallbladder should be excised because mucoceles have been observed to reform. Chronic life-long treatment with a fat-restricted diet (in hyperlipidemic patients) and chronic administration of ursodeoxycholic acid (15 mg/kg orally per day) is recommended for dogs with biliary mucoceles, even after their removal.

230.3.4 Canine “Steroid or Glycogen” Vacuolar Hepatopathy

The hepatic response to glucocorticoids varies remarkably among species. In the dog, rapid change in hepatic morphology and induction of liver enzymes is well recognized. High dose glucocorticoid administration usually causes significantly increased ALP and ALT activity within 2 to 3 days if given by injection and within 1 to 2 weeks if given orally.[18] Individual variation in response, different potencies of glucocorticoid

agents, and route of exposure (endogenous, parenteral, oral, cutaneous, ocular) influence changes in hepatic morphology, clinicopathologic features, and clinical signs. Typically, increased ALP and GGT activity develop in parallel as these enzymes undergo induction and subsequent release from sinusoidal and canalicular membranes. Initially, (during the first week of glucocorticoid exposure) a liver-ALP isoenzyme predominates. This is rapidly replaced (within 1 week) with a glucocorticoid-ALP isoenzyme.[19] Because most canine patients with increased ALP activity produce the glucocorticoid-ALP isoenzyme, clinical utility of isoenzyme fractionation is low.

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In the seminal study of glucocorticoid hepatopathy in the dog (injectable prednisone daily for 14 days), hepatocellular glycogen gradually increased, achieving maximal values on the fifteenth day. Glycogen accumulated first in zone 1 but thereafter predominated in zone 3 resulting in typical *ballooning degeneration*. After discontinuation of glucocorticoids exposure, hepatocellular glycogen slowly diminished over a period of weeks. Ultrasonographic features of vacuolar hepatopathy include diffuse or multifocal parenchymal hyperechogenicity with variable appearance of hypoechoic nodules. Distinction from other chronic necroinflammatory or fibrosing liver disorders is impossible without tissue sampling.

A similar clinical scenario as that described for exogenous glucocorticoids occurs in dogs with adrenal hyperplasia syndromes, where high steroid sex hormone production or high cortisol production occurs. A confusing aspect of the vacuolar hepatopathy syndrome in dogs is its association with a variety of chronic health problems. These may reflect an aspect of patient stress response correlating with acute phase responses, resulting in enhanced production of endogenous corticosteroid or nonglucocorticoid steroid hormones (Box 230-2). If clinical scrutiny fails to disclose an underlying health problem or cortisol values consistent with classic hyperadrenocorticism in a dog with a prominent vacuolar hepatopathy associated with high ALP activity (often with modestly increased SBA concentrations), a sex hormone profile conducted before and after ACTH administration should be pursued. Samples may be sent to the University of Tennessee Endocrinology laboratory (UTCVM Clinical Endocrinology Laboratory Tests, Department of Comparative Medicine, Room A105, 2407 River Drive, Knoxville, TN 37996-4500; (865) 974-5638). Because severe vacuolar hepatopathy has been observed to progress to the severe lesions associated with the hepatocutaneous syndrome, one of the authors (SAC) has recently taken a more aggressive approach. Treatment is undertaken in patients with abnormally high sex steroids (single or multiple abnormalities involving androgen, progesterone, or estrogen hormones, without cortisol abnormalities) in the following circumstances: marked vacuolar remodeling with formation of reticulin-bound nodules, or clinical signs such as PU/PD, polyphagia, or evidence of compromised liver function (e.g., high bilirubin, high bile acids). Treatment with mitotane (op' DDD) has been successful; experience with trilostane is limited at present. L-deprenyl and melatonin treatment has been discouraging, and no experience exists with estrogen aromatase inhibitors in this syndrome.

230.3.5 Hepatic Lipidosis Syndrome in the Cat

Cats have a propensity for accumulating triglycerides (TG) in their hepatocytes. Systemically ill cats usually develop some degree of hepatocellular fatty vacuolation. The development of lipid vacuoles within hepatocytes is not directly noxious but rather reflects an underlying metabolic disorder. Hepatic TG accumulation is not problematic until the degree of vacuolation is morphologically severe. In a normal feline liver, the fat content comprises less than 5% of total organ weight. The liver of a cat with the HL syndrome may double or triple in weight from accumulated fat.

TGs accumulate when the rate of hepatic synthesis exceeds their dispersal. Hepatic TGs are produced from fatty acids derived from the systemic circulation (dietary lipids, adipose stores) and from *de novo* hepatic synthesis. Overnutrition, especially with carbohydrates, augments hepatic fat accumulation as a result of a

positive energy balance and an inhibitory metabolic influence on mitochondrial fat oxidation. Many cats developing HL are obese; unrestricted release of fatty acids from excessive adipose stores promotes HL, because up to one third of mobilized fat resides in the liver at any time. HL reflects the liver's inability to match fat dispersal with delivery from systemic sources. The balance of TG lipolysis and accumulation is modulated by blood glucose concentration, hormonal, neural, and pharmacologic mechanisms. The activity of hormone sensitive lipase (HSL, promoting lipolysis) and LPL (promoting fat uptake) directly regulate adipocyte fat metabolism. Norepinephrine, epinephrine, growth hormone, glucagon, corticosteroids, and thyroxin increase HSL activity, whereas insulin inhibits HSL. Because cats release catecholamines readily, 1471
stress may exacerbate HSL activity. This effect is augmented in the absence of insulin resulting in occult or 1472
overt HL in unregulated diabetic cats. The LPL activity promotes fat uptake into adipocytes in the well-fed individual. In starvation however, although LPL activity declines, HSL increases, this balance favoring hepatocellular fat accumulation. An obese individual undergoing self-imposed starvation (anorexia) consequently has increased risk for peripheral fat mobilization and hepatocellular uptake.

230.3.5.1 Box • 230-2 Differential Diagnoses for Canine Vacuolar Hepatopathy

230.3.5.1.1 Hyperadrenocorticism

Spontaneous disease

Pituitary or adrenal origin

Iatrogenic: glucocorticoids therapy:

PO, IM, SQ, topical: skin, eye, ear

230.3.5.1.2 Adrenal Hyperplasia Syndrome

Abnormal sex hormone production

230.3.5.1.3 Hepatocutaneous Syndrome

230.3.5.1.4 Chronic Stress

Illness > 4 weeks

230.3.5.1.5 Severe Dental Disease:

Infection

230.3.5.1.6 Chronic Infections or Inflammation

(e.g., Pyelonephritis, chronic dermatitis)

230.3.5.1.7 Inflammatory Bowel Disease (IBD)

Chronic

Lymphoplasmacytic

Eosinophilic

230.3.5.1.8 Neoplasia

Lymphoma, other

230.3.5.1.9 Disorders Influencing Lipid Metabolism

Diabetes mellitus

Idiopathic hyperlipidemia

(e.g., schnauzer, sheltie, other)

230.3.5.1.10 Pancreatitis

Chronic

230.3.5.1.11 Hypothyroidism: Severe

230.3.5.1.12 Congestive Heart Failure (CHF)

The fate of fatty acids is diverse, including their consumption by beta-oxidation, conversion to phospholipids, use in formation of TG, cholesterol esters, to be packaged with apoproteins for dispersal as lipoproteins. An important mechanism of hepatic TG egress or dispersal is through formation of very low–density lipoproteins (VLDL). A variety of subcellular activities regulate VLDL dispersal from the hepatocyte, including lipid transport through subcellular compartments, combination with apoprotein, formation of secretory particle and vesicle, and expulsion into the perisinusoidal space. Impairment at any step or imbalance between essential lipoprotein components may compromise hepatic fat mobilization. The essential interaction of fatty acids and L-carnitine at the mitochondrial membrane for intraorganelle delivery and formation of activated fatty acid necessary for beta-oxidation may also play a role in development of the HL syndrome. The recently demonstrated deficiency of GSH in hepatocytes of these cats could represent dysfunction of the transsulfuration pathway. This, collectively considered with the common finding of B_{12} deficiency in the HL cat (especially those with substantial intestinal disease), supports defective availability or use of SAMe necessary for methylation reactions and de novo synthesis of L-carnitine. Studies of the influence of L-carnitine on fatty acid oxidation in the cat, and in modeled HL, support this association.[20,21]

Ultrastructural study of hepatocytes in HL cats documents reduced number of peroxisomes—organelles needed for oxidation of long chain fatty acids prior to mitochondrial delivery. This may further interfere with normal fat oxidation. Given the complexity of lipid metabolism, a multitude of factors likely predisposes any given cat to HL. Possible scenarios include an increased presentation of fat to the liver as a result of obesity, catabolism, chronic over-nutrition, enhanced *de novo* hepatic fatty acid synthesis, or impaired fatty acid oxidation or VLDL dispersal.

Cats of any age may be affected by HL; most commonly cats are between 4 to 15 years of age. Domestic shorthair cats are more commonly affected, which may reflect breed popularity. Initial clinical features

include inappetence and anorexia, weight loss, vomiting, lethargy, and weakness.[22] Physical findings include dehydration, variable icterus, an unkempt appearance, and palpable liver margins. Although fat may become depleted on the limbs and dorsal trunk, abdominal fat stores are spared.

Hematologic tests may disclose a nonregenerative anemia and a stress leukogram reflecting the disease causing anorexia. Poikilocytosis is common and may reflect altered red blood cell (RBC) membrane lipids, metabolism and oxidative stress altering cell membrane flexibility.

Biochemical changes reflect cholestasis, and to a lesser degree, altered hepatocellular membrane permeability and viability. Because the feline HL syndrome lacks necroinflammatory lesions, release of transaminase and ALP usually coexist. Rarely, a cat with HL will have high transaminases with only modest ALP activity. In HL without pancreatitis or inflammatory disease involving biliary structures, the GGT activity usually remains quiet. Hyperbilirubinemia and high SBA concentrations are common. Hypokalemia reflects inappetence and is significantly associated with failure to survive if uncorrected.[22] Hypochloremia may reflect vomiting. Hypophosphatemia reflects a multitude of effects on the intercompartmental homeostasis of phosphate, but most importantly it may occur as a consequence of a refeeding syndrome. A urinalysis reveals urobilinogen, bilirubin crystals, and bilirubin pigmenturia.

Ultrasound evaluation characteristically shows a hyperechoic hepatic parenchyma. Liver aspirates demonstrate hepatocellular lipid vacuolation. Aspiration cytology is good for identifying HL, hepatic lymphoma, and overt hepatic sepsis, but it is unreliable for detection of necroinflammatory disorders, especially cholangitis and cholangiohepatitis. Ultrasound examination is also important for inspection of disorders involving the pancreas, stomach, intestines, and biliary structures, which may have initiated the inappetence resulting in HL. Surgical or laparoscopic biopsy of the liver reveals a yellow-tan hepatic color and friable tissue. Histopathology of hepatic biopsies reveals profound vacuolation of hepatocytes. Presence of lipid within vacuoles is verified using Oil Red-O stain on frozen sections not paraffin embedded. It is important to look for other findings in the liver biopsy and in other sampled tissues for an underlying primary disease process.

Appropriate treatment requires client education regarding the likelihood of an underlying primary disease, the importance of critical supportive care, without which the condition has a poor prognosis and the infrequency of recurrence of lipidosis in survivors. Treatment may require weeks to months of assisted alimentation and metabolic support. Concurrent medical conditions must be managed. A recovery rate exceeding 85% can be achieved if a primary disease is identified and ameliorated or cured and the patient survives the initial 72 hours of critical supportive care.

The most important treatment is provision of a balanced feline diet delivering adequate energy intake (60 kcal/kg/day). Feeding is usually achieved using a feeding tube (esophagostomy tube being least invasive and easiest to manage with fewest complications). The number of feedings per day is determined based on the volume of food tolerated per meal. The diet is balanced to prevent protein-to-calorie malnutrition. Fat supplementation is contraindicated. Carbohydrate supplementation is ill advised (e.g., dextrose infusion) because of its inhibitory influence on fatty acid oxidation. Dietary protein restriction is reserved only for patients with irrefutable signs of hepatic encephalopathy. Placement of a large bore feeding tube is recommended after the patient is stable enough to tolerate anesthesia and bleeding tendencies have been circumvented by administration of vitamin K_1. Nasoesophagostomy tubes are used only short term to start patient nutritional support. Gastrostomy tubes may be placed at the time of surgery; esophagostomy tubes may be placed under a shorter anesthetic or at the time of surgery. The inappetent cat has increased risk for food aversion when confronted with forced oral alimentation. Tube placement is discussed in Chapter 92.

Vomiting must be controlled. Although this can be achieved medically (see Chapter 38), it may also be alleviated by reducing the feeding volume, increasing the number of meals per day, or by use of a *trickle feeding approach* with a syringe or fluid pump. Trickle feeding is accomplished by placing liquefied food into an empty fluid bag and administering it gravitationally or by pump assistance via an intravenous line attached to the large bore feeding tube or by use of a large syringe filled with food and syringe pump. Care must be taken to renew food and delivery tubing and syringe at 6-to 8-hour intervals to avoid bacterial contamination.

Fluid support is best provided intravenously with a nonlactate and nonglucose containing fluid. Lactate intolerance is suspected in the severe HL cat, and steady glucose infusion is thought to potentiate hepatic TG accumulation. Hydration is critical in any animal with severe hepatic insufficiency as is thought to exist in the HL cat. Dehydration impairs hepatic circulation, which can compromise normal detoxification processes. 1472
Azotemia increases diffusion of urea into the gut and subsequently, enteric ammonia production. Constipation 1473
may be augmented by dehydration and prolongs contact with and absorption of endotoxic enteric material. Cats demonstrating signs consistent with hepatic encephalopathy may benefit from lactulose administration. Aggressive attention to correction of hypokalemia is essential; this is accomplished using the customary sliding scale for fluid potassium supplementation.

Hypophosphatemia may precede initiation of nutritional support but more commonly reflects a refeeding phenomenon. Treatment of hypophosphatemia accomplished using potassium phosphate (delivered at 0.01 to 0.03 nmol/kg/hr) monitoring serum phosphate every 6 hours. Phosphate supplementation is discontinued when serum phosphorus greater than 2 mg/dL. Iatrogenic hyperkalemia is possible if the clinician fails to appropriately reduce KCl infusion rate given concurrently. Parenteral phosphate requirements resolve once alimentation is established.

Water-soluble vitamins should be added to intravenous fluids (1 to 2 mL vitamin B complex per liter). Cobalamin (vitamin B_{12}) deficiency should be suspected in HL cats with thickened intestines on palpation; treat by giving 1 mg B_{12} subcutaneously. Administration of B_{12} in a deficient cat with HL is critical because this imposes a significant metabolic deficit, limiting methylation reactions and endogenous SAMe production. Thiamine (vitamin B_1) deficiency also has been observed in cats presented for HL based on dramatic response to vitamin supplementation. Affected cats usually show severe neck ventroflexion; this also may occur with substantial hypo-phosphatemia, hypokalemia, hepatic encephalopathy, and a variety of disorders influencing neuromuscular or cervical vertebral function. Anaphylaxis may occur as a result of injected thiamine; oral rather than parenteral thiamine administration (50 to 100 mg per cat per day for 1 week in those demonstrating consistent clinical signs) may be preferable.

Cats with HL are often deficient in vitamin K as proven by the PIVKA (proteins induced in vitamin K absence or antagonism) or prothrombin time (PT) tests. Lack of dietary intake, altered intestinal bacterial flora as a consequence of antimicrobial treatment, impaired vitamin K epoxidase cycle associated with hepatic dysfunction are considered underlying causes. Subcutaneous treatment with vitamin K is recommended for three doses (0.5 to 1.5 mg/kg at 12-hour intervals). Further treatment may induce RBC oxidation and hemolysis. Correction of PIVKA clotting abnormalities typically occurs within this time. Vitamin K treatment must precede insertion of feeding appliances, jugular venipuncture, cystocentesis, hepatic aspiration, or hepatic biopsy.

Supplementation with 250 to 500 mg L-carnitine per day is warranted based on experimental data and on observed clinical response. L-carnitine is an essential cofactor of fatty acid oxidation. Although it may be derived from the diet, it also is normally synthesized endogenously from lysine and methionine. Methionine metabolism may be compromised in the HL cat, limiting transformation of methionine to SAMe. Because

SAMe generates GSH through the transsulfuration pathway and L-carnitine via methylation reactions, both depletion of GSH and L-carnitine may result. L-carnitine prevents accumulation of free fatty acids in the hepatocyte cytoplasm, as well as acetyl groups in the mitochondria where they inhibit beta-oxidation. It is surmised that the HL cat maintains a "relative" local hepatocellular carnitine deficiency regardless of adequate plasma or muscle carnitine concentrations. Taurine may also be supplemented (250 to 500 mg/day); this essential amino acid in the cat is necessary for normal bile acid conjugation. Owing to the compromised hepatic GSH shown in a small number of HL cats tested, antioxidant supplementation using vitamin E (10 IU/kg per day in food) and the thiol donor NAC intravenously during initial crisis (Heinz body hemolysis, recumbency) followed by SAMe there, (20 to 40 mg/kg through feeding tube is suggested. A higher dose SAMe than is normally used may be necessary because removal of the enteric coating for administration through the feeding appliance theoretically limits SAMe availability. Alternately administer 90 mg/day in an uncrushed tablet orally. Treatment of HL is summarized in Box 230-3.

230.3.5.2

Box • 230-3 Treatment of Hepatic Lipidosis in Cats

1. Supply 60 kcal/kg/day of balanced diet: protein restriction is contraindicated unless encephalopathy is present.
2. Correct dehydration and maintain hydration using non-lactate, non-glucose—containing fluids.
3. Supplement with vitamin k1 (0.5–1.0 mg/kg/day SC for 3 treatments at 12-hr intervals).
4. Place a large bore-feeding tube as soon as possible.
5. Correct hypokalemia.
6. Correct hypophosphatemia.
7. Supplement with 250–500 mg L-carnitine/day.
8. Supplement with water-soluble vitamins.
9. Supplement with 250–500 mg tawire/day.
10. Supplement with vitamin E (10 IU/kg/d PO), NAC for crisis intervention, SAMe (20–40 mg/kg/d via feeding tube).

230.4

STORAGE DISORDERS INVOLVING THE LIVER

230.4.1

Lysosomal Storage Disorders

Lysosomal storage disorders comprise a group of inherited juvenile or adult-onset disorders that show different clinical features depending on the particular metabolic aberration. Most of these are autosomal recessive traits and express as a consequence of line breeding.[24,25] Normal lysosomes degrade cellular and extracellular macromolecules, providing amino acids, fatty acids, nucleic acids, and carbohydrate residues for reuse. Primary lysosomes, derived from the Golgi apparatus, may fuse with other membrane-bound vesicles forming secondary lysosomes. Secondary lysosomes contain material derived from outside the cell through endocytosis or from within the cell by autophagy. Storage diseases are defined by the nature of the lysosomal hydrolase deficiency and resultant accumulating metabolic substrates or products. Disorders are suspected

based on clinical signs, including progressive neurologic dysfunction, ocular abnormalities, visceromegaly (including hepatomegaly), and skeletal abnormalities; signs may overlap clinically with nonlysosomal storage disorders.[24]

The different disorders that may be associated with hepatocellular or Kupffer cell storage product accumulation are described in Table 230-4. The mucopolysaccharidoses (MPSs) and disorders associated with interrupted catabolism of oligosaccharides can be crudely determined by specific urine tests (e.g., toluidine blue for detection of glycosaminoglycans reflecting MPS). Evaluation of peripheral leukocytes (looking for unusual lysosomal granules in granulocytes, lymphocytes, and monocytes) and staining blood smears with acid phosphatase (to confirm lysosomal vacuolation) can be helpful. Juvenile forms of certain storage diseases may be suspected from the appearance of vacuolated lymphocytes or monocytes in peripheral blood (e.g., mannosidosis, GM1-GM2-gangliosides, mucolipidoses). Ultrastructural examination of skin also can demonstrate lysosomal storage disorders, however it is not specific. Genetic testing for many disorders is available. Where this isn't possible, plasma, leukocyte, and tissue sampling with verification of storage products and enzyme deficiencies is necessary. For reliable assessments, samples from an age-and sex-matched peer group should be evaluated concurrently.

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Treatment is limited for these disorders. Bone marrow transplantation and enzyme replacement studies have been conduced on canine MPS type I and VII, feline MPS type VI, canine fucosidosis, and feline α-mannosidosis. Although variable improvements have been documented, this is not a practical recommendation and without neutering permits perpetuation of the genetic defect. Bone marrow transplant failed to improve advanced ceroid-lipofuscinosis in English setters.

230.5 HEPATOBILIARY INFECTIONS

The central position of the liver between the enteric and systemic circulation makes it an important interventional mechanism guarding against infectious agents. Normally, enteric flora entering the portal venous circulation by enteric transmural migration are killed or extracted by the hepatic macrophages (Kupffer cells), migrating macrophages, with neutrophils, and some being eliminated in bile. Locally produced immunoglobulins, primarily IgA, cooperate in providing innate immune defense. A number of conditions are known to predispose to hepatobiliary infections (Box 230-4).[23] Ischemic and hypovolemic injury decrease hepatic perfusion and impair macrophage function. The interruption of normal choleresis as occurs in cholestasis of any cause may result in infections derived from normal enteric organisms as rapid elimination of bacteria becomes compromised.

Table • 230-4 Storage Disorders Involving the Liver

CLASS	STORED PRODUCT/DEFICIENT ENZYME	TISSUES IMPACTED	REPORTED IN
Sphingolipidoses	Sphingolipids	Nervous tissues, liver, macrophages, granulocytes	Dogs and cats
Glycoproteinosis	Sugars	Hepatocytes, renal and neural cells	Cats: Persians, DSH
Mannosidosis			Springer spaniels, other dogs
Fucosidosis			
Mucopolysaccharidoses (MPSs)	Glycosaminoglycans (GAGs) (sulfates of dermatan, heparan, keratan, & chondroitin)	Wide tissue involvement, growth deformities, may observe storage produce in: Hepatocytes, Kupffer cells, neural cells, MPS VI skeletal tissues	Dogs and cats
MPS I			Dogs
MPS II			Dogs
MPS IIIA			Cats (Siamese, DSH)
MPS VI			Dogs
MPS VII			
Mucolipidoses	Features of sphingolipidosis & MPS, deficiency of acetylglucosamine-1-phosphotransferases	Growth deformities; involves many tissues including: cartilage, skin, connective tissue, Kupffer cells, no hepatomegaly	Cats
Ceroid-lipofucinoses	Lipopigments (lipofuscin, ceroid) protein products	Neural cells, Kupffer cells	Dogs and cats
Niemann-Pick types A & C (Sphingomyelinosis)	Cholesterol (defective esterification)	Hepatocytes, fibroblasts	Dogs and cats
Glycogen storage diseases	Storage: glycogen	Liver, heart, skeletal muscle, kidney, CNS, RBCs: varies with defect	Dogs and cats, depending on form
GSD IA	Deficiency: Glucose-6-phosphate dehydrogenase	Fail to thrive, obtunded, hepatomegaly causing abdominal distention	Maltese dog, toy breed puppies
GSD II	α-glucosidase	Muscle, megaesophagus, neurons	Swedish Lapland dog
GSD III	Amylo-1,6-glucosidase	Like GSD IA, but mild hypoglycemia	German shepherd dog, Akita
GSD IV	α-1,4-D-glucan (glycogen branching enzyme)	Lethal perinatally, cardiac signs, skeletal muscle atrophy	Norwegian Forest cat
GSD VII	Phosphofructose kinase deficiency	RBC hemolysis (with alkalosis), skeletal muscle weakness, lacks hepatic involvement	English springer spaniel American cocker spaniels, cross breed dogs

Infection, sepsis, and endotoxemia may each cause hepatic injury and cholestasis. Clinical signs variably include hepatosplenomegaly, fever, lethargy, and jaundice. Hematologic abnormalities may include a nonregenerative anemia (chronic inflammation), leukopenia, or leukocytosis with a left shift, and toxic changes in neutrophils. Biochemical abnormalities include increased transaminase and ALP activities and variable hyperbilirubinemia. 1474 Sepsis-related hypoglycemia might be recognized. Successful therapy requires judicious provision 1475 of fluid and electrolyte support, supplemental glucose for sepsis-related hypoglycemia, and appropriate antimicrobial

coverage. Importantly, the underlying causal factor must be identified and either eliminated or controlled. Nutrition should focus on avoiding a negative nitrogen balance. Antioxidant support with thiol donors (NAC in crisis that can be used as an intravenous treatment; SAMe for more chronic oral administration) and vitamin E may be helpful.[23]

230.5.1 Box • 230-4 Conditions Predisposing to Hepatobiliary Infections Disorders in Dogs and Cats with Culture Positive Hepatobiliary Infections

230.5.1.1 Obstructed Bile Flow

Extrahepatic bile duct occlusion

Disease of the gall bladder:

- Dysmotility
- Cholelithiasis
- Cystic duct occlusion
- Cholecystic neoplasia

Parenchymal cholestasis

- Destruction of intrahepatic bile ducts: ductopenia (e.g., certain cats with chronic cholangitis/cholangiohepatitis)
- Microcholelithiasis (intrahepatic bile ducts)

Pancreatitis

230.5.1.2 Impaired Hepatic Perfusion ± Oxidant Injury:

Chronic necroinflammatory liver disease: chronic hepatitis, chronic cholangiohepatitis

Cirrhosis

Copper storage hepatopathy

Acquired portosystemic shunting

Congenital portosystemic shunting

Liver lobe torsion

Hepatic neoplasia

Primary: development of a necrotic center

Hepatocellular carcinoma, Hepatoma

Metastatic:

Lymphosarcoma, adenocarcinoma, malignant histiocytosis

Portal venous thrombosis

Pancreatitis

Trauma: automobile accident, bite wounds, penetrating wounds

230.5.1.3 Compromised Immunocompetence

Hyperadrenocorticism

Diabetes mellitus

Severe hypothyroidism

FIV/FeLV

Treatment with immunomodulatory drugs: glucocorticoids, azathioprine, methotrexate, chemotherapy

Amyloidosis

230.5.1.4 Increased Translocation of Enteric Organisms

Inflammatory bowel disease

Enteric neoplasia: lymphosarcoma, adenocarcinoma

Chronic liver disease

Extrahepatic bile duct occlusion

Reduced bowel motility

Pancreatitis

230.5.1.5 Neonatal

Omphalitis

230.5.1.6 Visceral larval migrans

Toxocara

230.5.1.7 Iatrogenic

Extension from a feeding device

Surgical infection

From Center SA[23]; in press.

In general, hepatobiliary infections, and especially focal abscesses, are uncommon. Focal abscesses may result from trauma, ascending biliary tree infection, or ischemic lesions within the liver (e.g., necrotic liver tumor, thromboembolic lesions).[23,26,29] Immunocompromised patients are at greatest risk especially for hepatic abscessation.[23] Multifocal abscess formation and microabscessation may involve a variety of organisms derived from systemic infections by hematogenous or lymphatic distribution, or by infection ascending the biliary tree.[23,27,28] Early signs of hepatic abscessation are often vague (lethargy, fever, dehydration, trembling, anorexia, vomiting, diarrhea, and weight loss). Localization of disease to the abdomen may be indicated by abdominal tenderness and hepatomegaly. Hematologic features usually include a leukocytosis with or without a left shift and toxic neutrophils, as well as monocytosis; if chronic, a nonregenerative anemia may develop. Biochemical features include increased transaminase and ALP activities, hyperglobulinemia, and sometimes, sepsis-induced hypoglycemia. Should an abscess rupture, septic peritonitis and abdominal effusion develop. Diagnosis is greatly facilitated by abdominal ultrasound, which may disclose discrete focal lesions in the hepatic parenchyma and abdominal effusion. Cytologic evaluations of abdominal effusion or aspiration from discrete parenchymal lesions usually disclose neutrophils in various conditions (necrotic, degenerative, toxic) and bacterial organisms. Culture of blood or urine may identify occult infectious agents. Submission of both aerobic and anaerobic microbial cultures from sampled lesions or effusion is critical for optimized therapy. Polymicrobial infections nearly always involve an anaerobic organism; approximately 50% of solitary hepatic abscesses in dogs appear to be polymicrobial.[23] Because anaerobes are difficult to culture, they should be suspected and treated when cytologic evaluation discloses a polymicrobial population. Further, therapy should continue even if no organisms are cultured or only a few aerobic organisms are grown. Anaerobes may potentiate infection with other organisms and alter the course of disease.[28,30,31] When causal factors remain illusive, hepatic biopsy may be indicated looking for underlying neoplasia or other primary hepatic processes predisposing to infection.

Good initial therapy for hepatic abscessation is achieved with combination of penicillin and a fluoroquinolone or an aminoglycoside. Metronidazole or clindamycin can be substituted for penicillin to provide an anaerobic spectrum.[23] Dose reduction of metronidazole by 50% is indicated in patients with jaundice or reduced hepatic function (adjusted dose for dogs and cats is 7.5 mg/kg orally, twice a day to three times a day).[23] Fluoroquinolones provide broader gram-positive coverage compared with aminoglycosides and are thought to have better penetration across an abscess wall. First-generation cephalosporins, potentiated sulfonamides, and aminoglycosides, are uniformly ineffective against anaerobes. Animals with cholestasis also should receive

ursodeoxycholic acid (10 to 15 mg/kg per day) to facilitate brisk choleresis. Hydration must be maintained to achieve this objective.

Ultrasound-guided abscess aspiration as a primary mode of abscess treatment has been successfully applied to veterinary patients.[23] This approach is recommended for several reasons: (1) as a method of confirming the diagnosis, (2) to provide time for patient stabilization before surgical exploration for liver lobe resection, and (3) because it is successful as a solitary means of therapy in a subset of patients. Major factors arguing against this technique are unsafe access, contamination or lesion depth exceeding aspiration needle length. It is always essential to anticipate a need for immediate surgical intervention when aspirating a suspected hepatic abscess in the event of abscess rupture into the peritoneal cavity.

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Successful management of multifocal microabscessation can be accomplished with intravenous antibiotics if the involved organisms are identified and sensitivity defined. Treatment requires extensive supportive care and long-term administration (months) of a tailored antibiotic regimen targeting involved pathogens along with identification and management of the underlying predisposing cause. Disseminated sepsis should initiate a search for an underlying condition compromising immune defense.[23]

230.5.2 Hepatic Involvement in Systemic Infectious Disease

A number of systemic infectious diseases can involve the liver (see Box 230-4).[23,32] Agents with tropism for endothelium, parenchymal hepatic cells or macrophages are particularly prone to secondarily involve the liver. Infectious canine hepatitis caused by adenovirus type 1 is a unique pathogen because it is the only recognized virus with primary tropism for the liver. Along with severe hepatic necrosis and initiation of chronic hepatitis, glomerulonephritis, corneal edema, and uveitis may develop. This is currently a rare condition in North America due to high efficacy of vaccination programs.[33,34]

230.5.2.1 Granulomatous Hepatic Inflammation

Granulomatous hepatic inflammation is an uncommon diagnosis characterized by multiple discrete, sharply defined nodular infiltrates consisting of macrophage aggregates (and with or without epithelioid cells), surrounded by or intermixed with lymphocytes and plasma cells. Lesions may be focal, multifocal, or diffuse. Underlying causes include many infectious agents. Differential diagnoses that should be considered include metazoal (e.g., schistosomiasis, dirofilariasis), fungal (e.g., histoplasmosis, paecilomycosis), protozoal (e.g., visceral leishmaniasis, toxoplasmosis), bacterial (e.g., mycobacteria, *Nocardia*, *Bartonella*, *Brucella*, *Borrelia*, *Propionibacterium acnes*), and viral (e.g., feline coronavirus infectious peritonitis [FIP]) infections, and visceral larval migrans (*Toxocara* migration). Noninfectious disorders may be caused (drug reactions, lymphangiectasia, histiocytosis or histiocytic neoplasia, lymphosarcoma, and immune-mediated inflammation. The last may be associated with a positive antinuclear antibody test.[1] Until recently, causative factors have remained elusive in at least 50% of cases. However, with increased molecular surveillance for infectious causes, more definitive diagnoses are anticipated.

Table • 230-5 Hepatic Neoplasia

DOGS	CATS
*Primary Hepatic Tumors (26%)	*Primary Hepatic Tumors (20%)
Hepatocellular carcinoma	Biliary carcinoma
Hepatocellular adenoma	Hepatocellular carcinoma
Hepatic hemangiosarcoma	Hepatic hemangiosarcoma
Biliary carcinoma	
Other	**Other**
Leiomyosarcoma	Biliary cystadenoma
Liposarcoma	Myelolipoma
Myxosarcoma	Hepatic carcinoid
Fibrosarcoma	
Biliary adenoma	
Hepatic carcinoid	
Hemolymphatic Neoplasia (28%)	**Hemolymphatic Neoplasia (60%)**
Lymphosarcoma	Lymphosarcoma
Mast cell tumor (MCT)	MCT
Plasma cell tumor	Plasma cell tumor
Metastatic Neoplasia (46%)	**Metastatic Neoplasia (20%)**

* Primary tumors: in order of prevalence.

230.6 HEPATOBILIARY NEOPLASIA

The most common primary and secondary types of hepatic neoplasia in the dog and cat are shown in Table 230-5. Retrospective studies show an incidence of primary hepatobiliary neoplasia in less than 1.5% of all canine and less than 2.9% of all feline neoplasms.[35–41] Hemolymphatic neoplasia in the liver is more common. The peak incidence of hepatobiliary cancer occurs at 10 to 12 years of age in both species. In cats, malignant tumors develop at a younger age than benign tumors do.[38–41,48] It remains unclear whether previously eliminated feline leukemia virus (FeLV) may induce oncogenic transformation resulting in feline hemolymphatic neoplasia in the liver. In dogs, hepatic carcinoids occur at a mean age of 8 years.[37,43] No significant breed predilections exist for primary liver cancer; however, female dogs may be predisposed to biliary carcinoma (BC), while male dogs and cats to hepatocellular carcinoma (HCC).[37,43–46] Although no evidence indicates that chronic inflammatory liver disease predisposes to HCC in dogs, cats with chronic cholangitis may have an increased predisposition to BC.

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Primary liver tumors may be classified as hepatocellular, biliary, neuroendocrine or as sarcomas. Secondary metastasis of neoplasia to the liver is common in both species, and represents the largest proportion of hepatic cancers in dogs.[47–49] Lymphoreticular neoplasia involving the liver occurs in both species and represents the largest proportion of cancer in feline liver.[50]

Hepatic nodular hyperplasia is common in geriatric dogs, but unlike in humans, does not appear to represent a preneoplastic change. Biliary cystadenomas are considered benign tumors in older cats, and may be focal or multifocal.[51–53] Some of these may have a malignant behavior due to location in the porta hepatis. In younger cats, multiple hepatic cysts may express as a manifestation of polycystic disease, with or without renal lesions. Confusion in histologic diagnosis of these lesions with biliary cystadenomas may occur in some patients.

Clinical signs of hepatic neoplasia are often vague and nonspecific including chronic lethargy, inappetence, dehydration, PU/PD, and fever. Less commonly, vomiting, diarrhea, jaundice, and ascites may develop. PU/PD is

more commonly linked to primary liver tumors (up to 50% of dogs). Rarely, neurologic signs may occur in dogs and these reflect hypoglycemia or hepatic encephalopathy.[37,54,55] Weakness due to myasthenia gravis associated with carcinoma was described in a dog.[56] Many animals (25% dogs, 50% cats) will be asymptomatic. Finding a cranial abdominal mass or hepatomegaly is the most common physical abnormality.

Clinicopathologic features are usually vague and nonspecific. Hematologic tests may reveal a nonregenerative anemia and a neutrophilic leukocytosis reflecting neoplasia-associated inflammation. Hepatic hemangiosarcoma may produce a regenerative anemia, acanthocytosis, and schistocytosis. Mast cell tumors (MCTs) may produce eosinophilia and signs associated with release of biogenic amines.[54,55] Lymphoma may be accompanied by circulating lymphoblasts, eosinophilia, thrombocytopenia, thrombocytosis, and hematologic effects attributable to bone marrow involvement.

Biochemical changes reflect hepatocellular or biliary epithelial damage or biliary stasis (increased transaminase and ALP activities, hyperbilirubinemia, high SBA concentrations). Hepatic enzyme activity does not reflect the degree of hepatic neoplastic involvement. High SBA concentrations develop in 50% to 75% of dogs and in 33% of cats with hepatic cancer. Despite the more common prevalence of biliary neoplasia in the cat, only 33% have hyperbilirubinemic. In dogs, hypercalcemia (implying lymphoma), hyperglobulinemia, and hypoglycemia are more common. Hypoglycemia may be a dominant marker of large tumor mass (metabolic consumption) or reflect paraneoplastic phenomena due to production of an insulin-like protein.[54,55] Hypoalbuminemia, more common in dogs, may reflect a negative acute phase response, catabolism and poor nutritional intake, or hepatic insufficiency. Increased serum pancreatic lipase (PL) activity was reported in dogs (n = 6) with either pancreatic or hepatic neoplasia.[57] It was proposed that some hepatic tumors produce PL. Alpha-fetoprotein (AFP), a glycoprotein produced by fetal, neoplastic, and regenerating hepatocytes, may increase in dogs with hepatocellu-lar carcinoma, chronic hepatitis, or rapidly regenerating liver tissue.[50,58,59]

If ascites is present, fluid should be evaluated for protein, cell typers, #'s, and morphology. Imaging remains the most valuable, noninvasive method for localizing hepatic mass lesions and for detecting of overt metastasis. Abdominal radiography may show caudal and lateral displacement of the stomach. Occasionally, dystrophic mineralization of mass lesions or involved biliary tissues may be recognized. Pulmonary metastases occur late in the disease process.

Abdominal ultrasound is a better imaging modality for the detection of mass lesions, with a sensitivity (true positive, all patients with neoplastic lesions) ranging between 20% to 84% depending on operator, equipment and tumor type.[60,61] Although echogenicity and distribution can suggest a tumor type, broad overlap of patterns occur and findings do not closely correlate with histologic type.[62] Lesions may be localized or diffuse, hypo-, hyper-, or of mixed echogenicity; target lesions (hypoechoic margin surrounding a hyperechoic core) may be observed with carcinomas and other tumor types. Most variable in appearance are lymphomas as these may assume nearly any echogenic appearance or remain indiscernible despite diffuse hepatic involvement. Ultrasound may fail to detect neoplasia, and mass lesions from other causes may be erroneously assumed to be neoplasia.[63] Hematomas acquired from needle aspiration or Tru-Cut® biopsy sampling may subsequently be observed as mass lesions. Doppler (color flow) assessment of the mass may show vascularization more consistent with a tumor versus a benign process.[50,64] Computed tomography (CT) or magnetic resonance imaging (MRI) can provide information valuable in tumor staging and planning for attempted surgical resection.

Collection of cells by fine needle aspiration or tissue (via Tru-Cut® needle, laparoscopic, or surgical biopsy) for histopathology is required for definitive diagnosis.[65,66] Cytologic diagnoses of lymphoma, MCT, and carcinomas

may be accomplished in some cases. Bleeding tendencies must be considered before invasive tissue sampling. Usually, fine needle aspiration poses little threat.

Treatment and prognosis of different forms of hepatic neoplasia depends on its distribution, localization, and tumor type. Removal of focal mass lesions or liver lobe resections are recommended for neoplasia restricted to the liver. Tumors involving the porta hepatis cannot be resected. The considerable regenerative capability of the liver can permit successful resection of up to 80% of the liver if the remaining tissue is normal functionally and critical supportive care provides fluid, electrolyte, glucose, water-soluble vitamin, and coagulation factor support.[67] Caution is warranted in diagnosing apparent metastatic disease on the basis of gross appearance of the liver at the time of surgery, because hyperplastic nodules may be mistaken for cancer. Mass resection may offer palliation in the circumstance of a bleeding mass, despite irrefutable evidence of metastasis. Biliary tree diversion (biliary enteric anastomoses) should be considered for obstructive lesions involving the extrahepatic biliary structures because long-term palliation is possible. Chronic biliary tree occlusion results in cirrhosis within 6 to 8 weeks.

A fair to good prognosis may follow excision of focal canine HCC and benign feline tumors. However, dogs with BC and cats with malignant tumors have a poorer prognosis. HCC can be confusing because it may present as diffuse, multifocal, or solitary lesions. Histopathologic subtype and anaplastic characteristics also influence whether a HCC will metastasize. Metastasis is highest (100%) with diffuse HCC and lowest (37%) with solitary mass HCC. After surgical resection of HCC, a median survival time (MST) of 377 days was reported (n = 18).[42] Adjunctive, postoperative chemotherapy (5-fluorouracil, cisplatin, actinomycin D) has not been shown to provide significant benefit in dogs. However, one of four dogs treated with mitoxantrone had a complete response.[68] No comparable information is available for cats.

Biliary carcinoma shows a high metastatic rate in both dogs and cats (56% to 88% and 67% to 78%, respectively).[48,69] Surgical resection is more difficult than for HCC due to multifocal or diffuse extension and involvement of the porta hepatis. Little information exists regarding adjunctive chemotherapy. In cats, surgical resection of biliary adenomas or myelolipomas may provide several years of tumor-free survival or cure. Despite the benign character of these tumors, removal is recommended because malignant transformation has been suggested.[49]

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Postoperative adjunctive chemotherapy has been beneficial in inducing remission and prolonging survival in dogs with hepatic hemangiosarcoma. Surgery is indicated for removal of bleeding or large resectable masses. Chemotherapeutic protocols include a combination of vincristine, doxorubicin, and cyclophosphamide.[50]

Hepatic carcinoids and lymphosarcomas in dogs have a high metastatic rate (86% to 93%). Carcinoids are a rare and aggressive neuroendocrine tumor.[35,37,43]

Hepatic tumors metastasize first to regional lymph nodes then lung, and peritoneum in the dog and peritoneum in the cat. Biliary tumors in the cat may extend into the pancreas. Metastatic extension to brain, spinal cord, bone, kidney, adrenal gland, and spleen is less common in each species.

Canine MCT involving the liver can be controlled with cyclophosphamide, vinblastine, and prednisone.[50,70] Many protocols are recommended for control of lymphoma in dogs and cats; most include vincristine, cyclophosphamide, and prednisone, with variable combinations of L-asparaginase, methotrexate, and doxorubicin.

Radiation therapy is not a feasible option for hepatic cancers, owing to the exquisite sensitivity of this organ to even low amounts of radiation.[71] Although liver transplantation, directed delivery of chemotherapeutic agents (intra-arterial chemotherapy), transarterial chemoembolization, and immunotherapeutic regimes using a-FP as a tumor-specific antigen have been used in humans with HCC, these have not been explored in animals.[72,73]

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231 CHAPTER • 231 Diseases of the Gallbladder and Extrahepatic Biliary System

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231.1 ANATOMY

Bile is formed by hepatocytes and discharged into the canaliculi lying between the hepatocytes. Canaliculi unite to form interlobular ducts, which ultimately merge to form lobar or bile ducts. The gallbladder plus the hepatic, cystic, and common bile ducts constitute the extrahepatic biliary system. Bile drains from the bile ducts into the cystic and common bile ducts and is stored and concentrated in the gallbladder (Figure 231-1). The gallbladder lies between the quadrate lobe of the liver medially and the right medial lobe laterally.[1] It is a pear-shaped organ that, in a medium-sized dog, normally holds approximately 15 mL of bile. The rounded end of the gallbladder is the fundus. Between the neck of the gallbladder (i.e., the tapering end leading into the cystic duct) and the fundus is the body.

The cystic duct extends from the neck of the gallbladder to the junction with the first tributary from the liver.[1] From this point to the opening of the biliary system into the duodenum, the duct is termed the *common bile duct*. The common bile duct runs through the lesser omentum for approximately 5 cm and enters the mesenteric wall of the duodenum. The canine common bile duct terminates in the duodenum near the opening of the minor pancreatic duct. This combined opening of the minor pancreatic duct and common bile duct is the major duodenal papilla. The feline common bile duct usually joins the major pancreatic duct before entering the duodenum.[1]

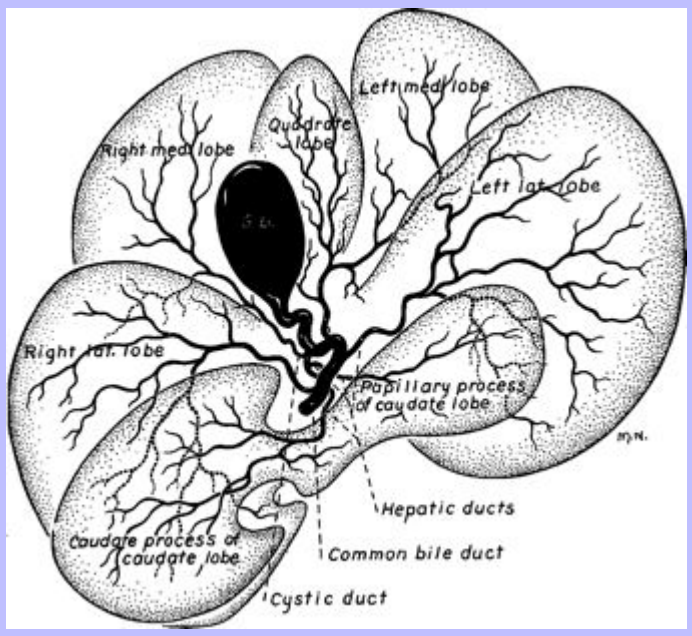
231.2 PHYSIOLOGY

Bile primarily contains water, conjugated bile acids, bile pigments, cholesterol, and inorganic salts. Over 90% of bile salts are reabsorbed from the intestinal tract, transported back to the liver via the portal vein, and re-excreted (i.e., enterohepatic circulation). Bilirubin and biliverdin produce the typical yellow color of bile. Bile is continually secreted into the gallbladder, where it is stored and modified. Gallbladder emptying is normally induced by neural (vagal parasympathetics) and humoral (cholecystokinin) stimuli. Parasympathomimetic drugs and magnesium sulfate[2] cause gallbladder contraction, whereas anticholinergic drugs and somatostatin inhibit contraction.[1]

231.3 DIAGNOSTIC TOOLS FOR EVALUATING THE GALLBLADDER AND BILE DUCTS

Icterus, vomiting, abdominal pain, and ascites are all consistent with biliary tract dysfunction. Complete blood count (CBC), serum biochemistry profile, and urinalysis are indicated if biliary tract dysfunction is suspected. The CBC inconsistently reflects cholecystic inflammation. Increased alanine aminotransferase (ALT) is common if inflammation ascends into the hepatic parenchyma. Increased serum alkaline phosphatase (SAP), with or without hyperbilirubinemia, is typical in extrahepatic biliary tract obstruction (EHBO)[3] and inflammatory disease ascending from the biliary tract. Cats tend to have lesser elevations of SAP than dogs.

Figure 231-1 Anatomy of the canine gallbladder. (From Evans HE, Christensen GC: Miller's Anatomy of the Dog, 3rd ed. Philadelphia, WB Saunders Co, 1993, p 750.)



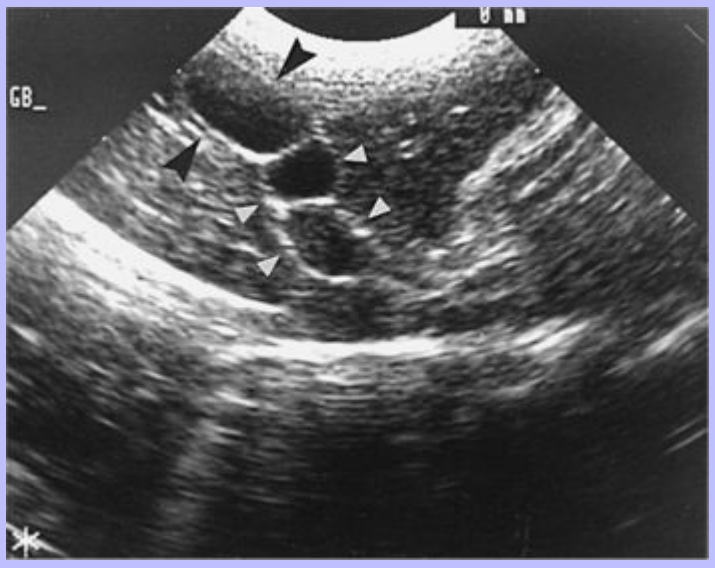
Hypercholesterolemia may occur secondary to EHBO. Bilirubinuria occurs before hyperbilirubinemia. Imaging, surgery, or both are usually required to differentiate icterus due to hepatic disease versus biliary tract disease.

Abdominal radiographs may reveal radiodense objects (e.g., gallstones) or air in the gallbladder. Animals with EHBO due to pancreatitis may have a soft tissue mass or poor serosal detail in the region of the pancreas. Contrast radiographs of the biliary tree are rarely useful, and endoscopic retrograde pancreatography is rarely performed in icteric animals.

Ultrasonography is the most useful nonsurgical technique to distinguish hepatic parenchymal from biliary tract disease. It can identify abnormalities within the lumen of the gallbladder (e.g., stones, tumors, flocculent material) and most biliary tract obstructions (Figure 231-2).[3] Finding "sludge" is not informative because many normal dogs have this finding.[4] Anorexic animals often have marked cholecystic enlargement, which can be misdiagnosed as obstruction. Dilatation of the gallbladder plus loss of the tapering of the gallbladder neck typically occur within 24 hours of ligation of the bile duct. This is followed by dilatation of the common duct at 48 hours and of the extrahepatic ducts at 72 hours. Similar changes occur in the intrahepatic bile ducts within 1 week.[5] The common bile duct is typically less than 3 mm in diameter in medium-sized dogs[6] and less than 2.5 mm in cats.[3] One study found that 28 cats without EHBO had a common bile duct 4 mm or less in diameter, whereas a common bile duct greater than 5 mm in diameter meant EHBO in six of seven cats.[7] Distension of the gallbladder plus the common bile duct was the most common finding in 22 cats.[8] If the clinician is unsure whether EHBO is present after performing ultrasonography, repeating the examination in 2 to 4 days or after

inducing gallbladder contraction (e.g., feeding a high-fat meal) is often definitive. However, loss of elasticity of the bile ducts may occur as a result of aging, inflammation, or chronic obstruction (especially in cats), and some ducts never return to their original diameter after obstruction.[5,6] Rarely, EHBO will not be diagnosed until laparoscopy or laparotomy.

Figure 231-2 Distention and convolution of the gallbladder body *(black arrowheads)* and neck *(white arrowheads)* in a cat with common bile duct obstruction. (Courtesy of Dr. L. Homco, Texas A&M University.)



Gallstones are typically identified ultrasonographically as hyperechoic foci or by the observation of acoustic shadowing originating from the gallbladder.[5] Sediment (sometimes referred to as *sludge*) is occasionally noted in the gallbladder, but its significance is uncertain. Supposedly, bile becomes progressively thicker as water is absorbed during biliary stasis.

Soft tissue changes of the gallbladder (e.g., tumors, granulation tissue, congenital defects) may be seen ultrasonographically. Cholecystitis may cause gallbladder wall thickening, edema, or both, which can produce a layered or "double-wall" ultrasonographic appearance[5]; however, one cannot reliably diagnose cholecystitis ultrasonographically. Finding a stellate or striated pattern within the gallbladder with immobile contents is suggestive of mucocele.[9]

Bile (for culture or cytologic examination) can be aspirated from the gallbladder by ultrasound-guided fine-needle aspiration using a 22-to 25-gauge needle.[10] As much bile as possible is withdrawn to lessen the likelihood of subsequent bile leakage into the abdomen. This procedure appears to be relatively safe, although vagal-induced severe bradycardia and other problems have occurred in people.[1] Aerobic and anaerobic cultures of bile (and hepatic parenchyma) are recommended if bacterial cholecystitis is suspected.

Laparoscopy or exploratory laparotomy should be performed in animals with suspected leakage of bile into the abdomen, as well as those with EHBO, neoplasia, parasites, stones, infiltrates, and other mass lesions of or within the biliary tract. Laparoscopy can be particularly valuable in helping the clinician decide if exploratory surgery is warranted. During exploration, patency of the common bile duct must be ensured by compressing the gallbladder or catheterizing the duct. Readers are referred to surgery texts for detailed information regarding extrahepatic biliary tract surgery.[11] Nuclear scintigraphy is rarely used to define canine or feline biliary disease, owing to the need for specialized equipment and facilities.

231.4 SPECIFIC PROBLEMS SEEN WITH GALLBLADDER AND BILIARY TRACT DISEASE

Vomiting, icterus, and anorexia are common in animals with inflammatory or obstructive biliary tract disease.[12,13] Fever and abdominal discomfort also occur, but not as consistently. Icterus is often helpful for localizing the problem to the biliary tract. After hemolytic disease is eliminated, ultrasonography helps distinguish hepatic parenchymal from biliary tract disease. Ascites may occur owing to leakage of bile into the peritoneal cavity. Bilious effusions are obvious because the fluid looks like bile. If one is unsure whether abdominal fluid is bilious or bile stained, bilirubin concentrations in serum and in effusion should be compared. Bilious effusions have fluid bilirubin concentrations greater than serum concentrations.

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Acute abdomen (i.e., shock, sepsis, pain due to abdominal disease) may be caused by leakage of bile into the peritoneal cavity, particularly if the bile is septic. Hematemesis is uncommon in animals with cholecystic disease, but intracystic bleeding may allow blood to exit into the duodenum, where it is refluxed into the stomach and vomited.

231.5 SPECIFIC DISEASES OF THE GALLBLADDER

231.5.1 Obstructive Disease

Pancreatic disease is the most common cause of canine EHBO,[3] whereas tumors and inflammatory disease of the biliary tract, pancreas, or both are the most common causes in cats.[8] Stones can cause EHBO, but they do so uncommonly.[14] Therefore the prognosis for dogs with EHBO is generally much better than it is for cats.

Pancreatitis may cause scar formation in or around the duct or compress the duct by inflamed tissue, abscesses, or cysts. Treatment of EHBO secondary to benign pancreatitis initially consists of medical management of the pancreatitis. If this is unsuccessful or if ascending bacterial infection is suspected, cholecystoduodenostomy or cholecystojejunostomy may be considered but should generally be avoided unless absolutely necessary. In extremely ill animals with EHBO that cannot undergo surgical exploration, temporary decompression of the gallbladder with a Foley catheter or a self-retaining accordion catheter may be warranted.

Neoplasia (especially biliary tract or pancreatic adenocarcinomas) may cause EHBO. Surgery for pancreatic neoplasia is generally unrewarding, because most such tumors are malignant. Cholecystojejunostomy may be palliative if the intestinal lumen is patent. Pancreatic-duodenal resection (i.e., Billroth II) is possible; surgical cures are unlikely, whereas morbidity may be substantial. Biliary, intestinal, hepatic, or lymph node malignancy may also obstruct the bile ducts; biopsy is imperative to obtain a diagnosis. The prognosis is typically poor; however, chemotherapy benefits some animals with lymphosarcoma.

Choleliths (see Nonobstructive Disease) that obstruct the common bile duct should be removed. Cholecystectomy is the treatment of choice when clinical signs are secondary to cholelithiasis.[13] If stones are present in the common bile duct, the duct can be catheterized via the duodenum and the stones flushed into the gallbladder. Alternatively, enlarged bile ducts can be incised (choledochotomy) and the stones removed; however, care is needed when closing the common bile duct to avoid iatrogenic stricture formation. Much greater mortality occurs in people with cholelithiasis when a choledochotomy is performed versus cholecystectomy.

A gallbladder mucocele is an abnormal accumulation of inspissated mucus that distends the gallbladder and often causes some degree of EHBO.[9] Affected dogs will usually be icteric and have abdominal pain plus increased ALT, SAP, or bilirubin. Mucoceles typically cause a striated or stellate appearance on ultrasound with immobile bile. Cocker spaniels might be over-represented. Infection sometimes occurs. Left untreated, necrosis of the gallbladder with subsequent rupture may occur. Cholecystectomy seems the preferred therapy. Miscellaneous causes of EHBO include diaphragmatic hernia[15] and biliary pseudocysts.[16]

231.5.2 Nonobstructive Disease

Cholecystitis (i.e., inflammation of the gallbladder) usually involves the associated bile ducts. It is typically due to a bacterial infection caused by bacteria ascending from the intestine via the common bile duct or by hematogenous seeding, and it can often be cured with antibiotics. However, if cholecystitis recurs repeatedly despite appropriate use of antibiotics, cholecystectomy is usually curative. Cholecystitis may take one of several courses.

Bacterial cholangitis and cholangiohepatitis occur if the infection ascends the biliary tree into the liver. This appears to be more common in cats than in dogs, but Shetland sheepdogs may have a higher than expected incidence. Any bacteria may be responsible; *Escherichia coli* seems especially common. These animals often present to veterinarians because of icterus, anorexia, vomiting, or a combination of these symptoms. Fever is uncommon. Increased serum ALT, SAP, and bilirubin are typical, but neutrophilia is inconsistent. Imaging is seldom diagnostic but helps eliminate other diseases. Cats with a gallbladder wall greater than 1.0 mm thick typically have histologic abnormalities of the gallbladder, but cats with a less thick gallbladder wall may also have disease.[17] Fine needle aspirate of the gallbladder with subsequent cytology of bile may reveal bacteria (Figure 231-3). Hepatic biopsy with aerobic and anaerobic culture of bile and hepatic parenchyma is indicated. The prognosis is variable, but good results are expected when the correct antibiotics are promptly administered. Enrofloxacin plus amoxicillin is reasonable until culture results are available. Vitamin K_1 should be administered if coagulopathy is suspected.

Necrotizing cholecystitis occurs when a bacterial infection severely damages the gallbladder wall, sometimes rupturing it (Figure 231-4) and spilling bile into the abdomen.[18] This usually causes generalized septic peritonitis. If the bile is inspissated, rupture causes spillage of a relatively thick, gelatinous mass into the cranial abdomen, producing a localized peritonitis. These animals tend not to become as sick as quickly as those with diffuse peritonitis. Sometimes pain can be localized to the anterior abdomen. If diagnosed before the gallbladder ruptures, signs are similar to those of localized peritonitis. Adhesions or fistulous tracts around the gallbladder occasionally occur. Diagnosis is usually made by ultrasonography or exploratory laparotomy. Surgical exploration should be performed once the animal is stable. Treatment consists of cholecystectomy, antibiotics, and appropriate therapy for peritonitis. Salvaging the gallbladder by closing the defect is inappropriate because the wall is typically necrotic and will dehisce. The common bile duct must not be

ligated when the gallbladder is removed. The mortality rate was 39% in a study of 19 dogs with necrotizing cholecystitis; delayed diagnosis probably contributed to this high mortality.[18]

Figure 231-3 Photomicrograph of bile obtained by cholecystocentesis showing bacteria.

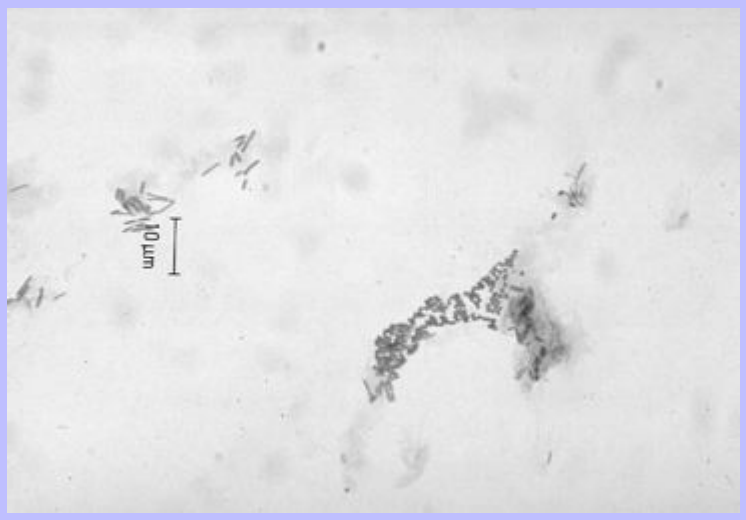


Figure 231-4 Photograph of a ruptured gallbladder that has been resected from a dog. Rupture was spontaneous and was due to necrotizing cholecystitis. Forceps are in the cystic duct.

Emphysematous cholecystitis occurs when gas-forming bacteria infect the gallbladder and gas fills the lumen or invades the wall (tympanic and emphysematous cholecystitis, respectively).[19] Once considered pathognomonic of diabetes mellitus, emphysematous cholecystitis can develop in any animal. Signs may be similar to those described for bacterial and necrotizing cholecystitis. Plain radiographs are diagnostic (Figure 231-5), and treatment consists of antibiotics. Knowing that gas-forming bacteria (e.g., *E. coli, Clostridium perfringens*) must be responsible helps guide antibiotic selection (e.g., enrofloxacin plus amoxicillin).

Choleliths are often fortuitous findings at necropsy or during imaging.[1] They often cause no problems (Figure 231-6); however, they may be associated with cholecystitis or rupture.[13] If found in an animal with biliary tract disease, they should be removed. Although people commonly develop dietary-induced cholesterol gallstones, canine gallstones usually contain bilirubin, calcium, and mucin.

Parasites of the gallbladder, bile ducts, or both are seldom diagnosed. *Platynosomum fastosum* (previously *P. concinnum*) is a fluke principally found in animals from Florida, Hawaii, and the Caribbean. It typically infects cats that eat lizards or toads (i.e., a second intermediate host). The fluke may ultimately be found in the gallbladder, bile ducts, or both, where it may be asymptomatic or cause fibrosis, obstruction, or both. Signs of infection can be similar to those of cholecystitis. Diagnosis is by ultrasonography or by finding ova by fecal sedimentation examination (not fecal flotation), assuming that complete biliary tract obstruction does not occur. Therapy may be attempted with praziquantel (20 mg/kg subcutaneously, once a day for 3 days). Prognosis is uncertain, but severe hepatic disease warrants a guarded prognosis.[1] *Amphimerus pseudofelineus* has also been associated with cholangitis, cholangiohepatitis, and distention of the feline common bile duct.[20] High-dose (40 mg/kg) praziquantel therapy administered orally once a day for 3 days reportedly eradicated the infection. *Metorchis conjunctus* and *Eurytrema procyonis* may also be found in the feline biliary tract.

Figure 231-5 Lateral radiograph of a dog showing a pear-shaped, air-filled structure (*arrows*). This is the gallbladder of a dog with emphysematous, tympanic cholecystitis. (Courtesy of Dr. Robert Toal, College of Veterinary Medicine, University of Tennessee.)

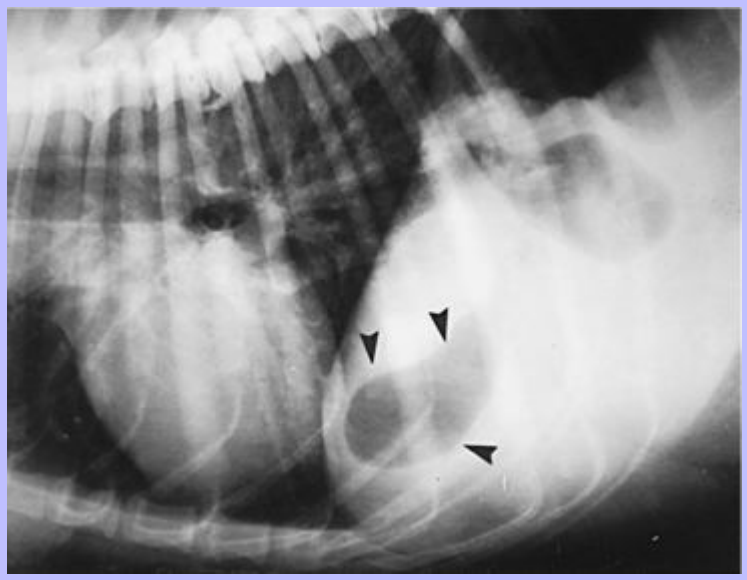
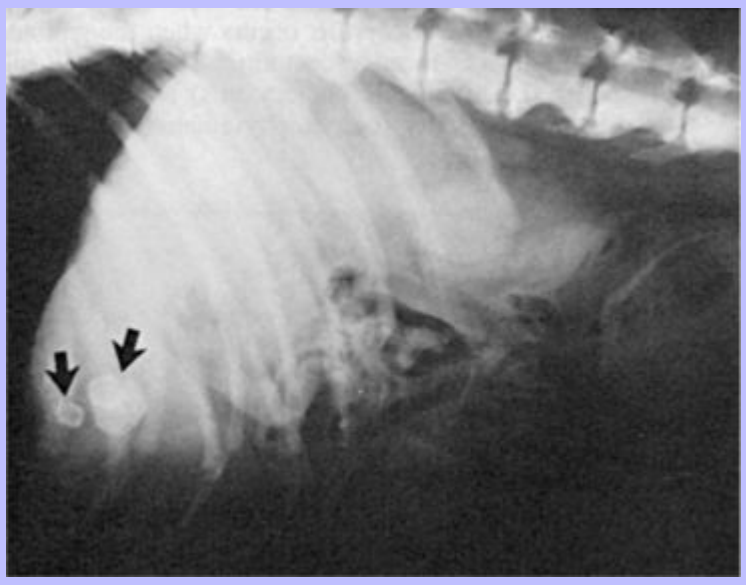


Figure 231-6 Lateral radiograph of a dog showing mineral densities in the region of the gallbladder *(arrows)*. These were gallstones that were not causing clinical disease in this dog.



Neoplasia of the gallbladder or extrahepatic biliary tract is rare. Bile duct carcinomas have been reported in cats and dogs.[19] Metastasis of bile duct carcinomas commonly occurs before clinical signs manifest; therefore surgery is rarely curative. Surgical therapy of cholecystic tumors may be curative if no metastasis exists.

Congenital dilatation of intrahepatic and extrahepatic bile ducts may occur without obstruction in dogs with Caroli's disease. Affected animals are generally less than 3.5 years old and usually experience vomiting, polyuria, anorexia, ascites, and increased hepatic enzymes. The gallbladder and common bile duct are generally normal in size. Renal fibrosis and cystic changes are common in affected animals.[21]

231.5.3 Rupture of the Gallbladder or Extrahepatic Biliary Ducts

Extrahepatic biliary duct or gallbladder rupture may be iatrogenic or associated with blunt abdominal trauma, cholecystitis, or obstruction secondary to stones, neoplasia, or parasites. Trauma usually causes rupture of the bile duct rather than the gallbladder. Ductal rupture probably occurs when a force is applied adjacent to the gallbladder sufficient to cause a shearing force on the duct. The most common site of ductal rupture appears to be the common bile duct just distal to the entrance of the last hepatic duct; however, rupture may occur in the distal common bile duct, cystic duct (rare), or hepatic ducts. Gallbladder rupture is more commonly associated with necrotizing cholecystitis or cholelithiasis, with or without obstruction of the common bile duct.[18]

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Early diagnosis of biliary tract rupture is imperative. Leakage of infected bile causes clinical signs of bile peritonitis to develop quickly. In a study of 24 dogs and two cats with biliary tract rupture, there was 54% mortality, which was limited to animals with infected bile. *E. coli* was the bacterium most commonly cultured

from infected animals.[12] Ascites and icterus may be the only signs in dogs with sterile bile in the peritoneal cavity due to traumatic rupture; however, necrosis and changes in mucosal permeability secondary to the bile can allow secondary bacterial infection.[19] Delayed diagnosis of a ruptured biliary tract results in necrotic tissues and adhesions, which complicate surgical repair. Diagnostic peritoneal lavage may assist in the early diagnosis of sterile bile peritonitis.

Surgical treatment for a ruptured common bile duct involves repair of the duct or biliary diversion. Repair is often possible if the rupture is diagnosed early, but it becomes difficult once adhesions develop. In such cases, cholecystojejunostomy is generally easier and safer. Ruptured hepatic ducts are usually ligated. Gallbladder rupture should be treated by cholecystectomy.

231.5.4 Miscellaneous Findings

Cystic mucinous hypertrophy is occasionally found in older animals, either at necropsy or during ultrasonography. It is not clearly associated with disease, although progestational drugs may produce it.[1] Unless evidence of significant gallbladder dysfunction exists, this lesion does not warrant further evaluation. Congenital defects of the gallbladder are occasionally observed. Bifid gallbladders have been reported in cats, although their significance is unknown. Nonbiliary tract disorders may also produce cholecystic lesions. Gallbladder edema is reportedly common in infectious canine hepatitis. In other diseases, however, gallbladder lesions are seldom significant. Even in canine salmonellosis, the gallbladder is rarely important as a reservoir of infection.

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232 CHAPTER • 232 Canine Exocrine Pancreatic Disease

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Jörg M. Steiner

Exocrine pancreatic disease occurs commonly in dogs. Pancreatitis is by far the most common disorder, followed by pancreatic adenocarcinoma, exocrine pancreatic insufficiency (see Chapter 234), and other less commonly observed conditions.

232.1 PANCREATITIS

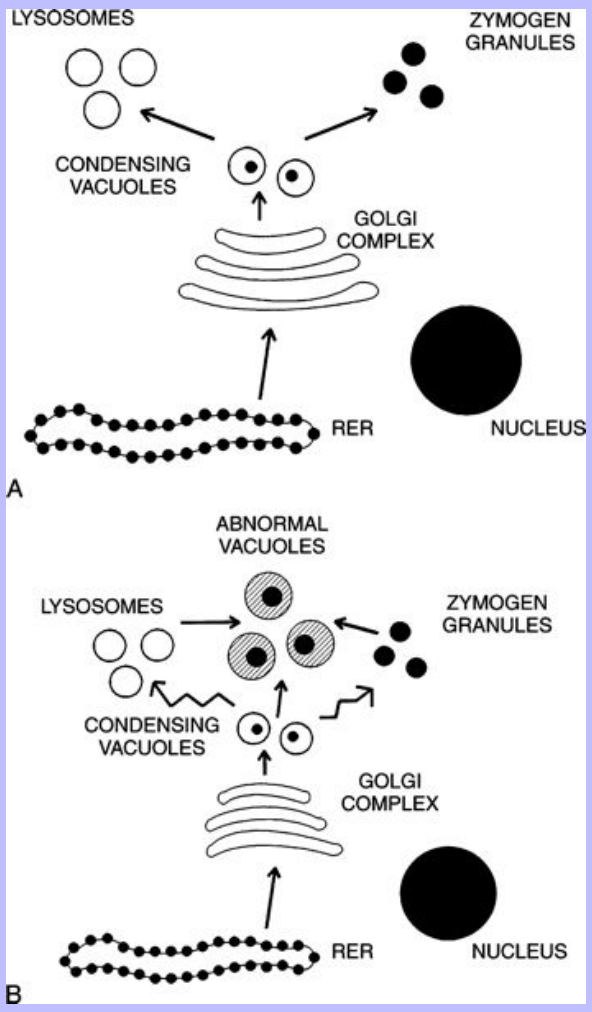
Classification of inflammatory disease of the pancreas in human beings has been standardized and simplified during the last two decades; however, the same is not true in veterinary medicine, and different authors classify pancreatitis differently. The following classification is based on the system currently used in humans.[1] *Acute pancreatitis* refers to pancreatic inflammation that, after removal of the inciting cause, is completely reversible.[1] Chronic pancreatitis, on the other hand, is a long-standing inflammation of pancreatic tissue associated with irreversible histopathologic changes, most importantly fibrosis and atrophy.[1] Acute and chronic pancreatitis cannot be differentiated clinically and can be mild or severe; however, chronic cases are more commonly mild and acute cases more commonly severe. Although mild pancreatitis is associated with few systemic effects, minimal pancreatic necrosis, and a low mortality, severe pancreatitis is characterized by extensive pancreatic necrosis, multiple organ involvement, and a poor prognosis.[1] Another classification parameter is the presence or absence of pancreatic complications, such as acute fluid accumulations around the inflamed pancreas (previously also known as *pancreatic phlegmon*), infected necrosis, pancreatic pseudocyst, and pancreatic abscess.[1] Classification based on cause is desirable but unfortunately cannot be achieved in most cases.

Numerous experimental procedures including hyperstimulation by administration of caerulein, carbamylcholine, or scorpion venom; obstruction of the pancreatic duct; intraductal injection of bile, fatty acids, or enzymes; pancreatic ischemia; and certain dietary manipulations all induce pancreatitis in dogs.[2] Some of these factors may also play a role in the development of spontaneous pancreatitis.[2,3] Ultimately, pancreatitis develops as a consequence of autodigestion of the pancreas resulting from premature zymogen activation within acinar cells. An early event in many experimental models of pancreatitis is abnormal fusion of lysosomes and zymogen granules (Figure 232-1). Lysosomal proteases, such as cathepsin B, are capable of activating trypsinogen, and the low pH in the fusion vacuoles also favors trypsinogen activation.

Several mechanisms are in place that prevent autodigestion of the pancreas by the enzymes it secretes. First, proteolytic and phospholipolytic enzymes are synthesized, stored, and secreted in the form of catalytically inactive zymogens. These zymogens are activated by enzymatic cleavage of a small peptide—the activation peptide—from the amino-terminal of the polypeptide chain.[2] Enzymes from several sources, including some lysosomal proteases, are capable of activating pancreatic zymogens, but ordinarily activation of zymogens does not occur until they are secreted into the small intestine. The enzyme enteropeptidase, which is synthesized by duodenal enterocytes, is particularly effective at cleaving the activation peptide from trypsinogen and plays a crucial role in the activation of digestive enzymes.[2] Active trypsin subsequently cleaves the activation peptide from other digestive zymogens. During synthesis, processing, storage, and secretion, digestive enzymes are strictly segregated from other, potentially damaging, cellular enzymes, such as lysosomal enzymes.[2] Should

spontaneous intrapancreatic activation of trypsinogen occur, at least two mechanisms help to limit activation of other zymogens. Trypsin is quite effective at hydrolysing itself, so that activation of small amounts of trypsin tends not to be catastrophic. However, should significant activation occur, acinar cells contain a specific trypsin inhibitor—pancreatic secretory trypsin inhibitor (PSTI)—that is synthesized, segregated, stored, and secreted along with the digestive enzymes (Table 232-1).[2] PSTI is believed to inhibit trypsin activity should there be significant activation of trypsinogen within the acinar cell or duct system.[2] However, this mechanism fails at the low pH in the fusion vacuoles.

Figure 232-1 Normal **(A)** and abnormal **(B)** intracellular routing of digestive and lysosomal enzymes by the pancreatic acinar cell. The abnormal intracellular routing of digestive enzymes during pancreatitis results in mixing of zymogens and lysosomal proteases in intracellular vacuoles. Subsequent activation of zymogens by lysosomal proteases is considered to initiate the development of pancreatitis.



Once intracellular and intraductal activation of trypsinogen to trypsin takes place, further activation of all zymogens (particularly proelastase and prophospholipase) will amplify pancreatic damage. Activation of progressively larger amounts of protease and phospholipase within the gland is associated with progression of mild edematous pancreatitis to hemorrhagic or necrotic pancreatitis with multisystem involvement and consumption of plasma protease inhibitors.[2,4]

Plasma protease inhibitors (see Table 232-1), particularly α-macroglobulins, are vital in protecting against the otherwise fatal effects of proteolytic enzymes in the vascular space.[2,4] Dogs die rapidly from acute disseminated intravascular coagulation (DIC) and shock once α-macroglobulin is depleted, because free proteases concurrently activate the kinin, coagulation, fibrinolytic, and complement systems.[2,4] Binding of proteases by α-macroglobulin results in a conformational change that allows the complex to be rapidly cleared from the plasma by the reticuloendothelial system (RES). This removal of α-macroglobulin–bound proteases by the RES is important because proteases bound to α-macroglobulin retain catalytic activity, particularly against low molecular weight substrates.

The primary function of α_1-proteinase inhibitor (α_1-PI) is to inhibit neutrophil elastase during inflammation (see Table 232-1). Although pancreatic proteases do bind to α_1-PI and are effectively inhibited, the binding is reversible and the availability of α_1-PI during pancreatitis is not life saving.[2] Alpha$_1$-PI probably serves as a transient inhibitor and intermediary in the transport of proteases to α-macroglobulin, particularly in the extravascular space, into which the large α-macroglobulin molecules cannot permeate.

Once enzyme activation is initiated, numerous inflammatory mediators and free radicals are important in the progression of pancreatitis.[4,5] These mediators are mostly released from neutrophils and macrophages and include tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-2, IL-6, IL-8, IL-10, interferon-α (INF-α), INF-γ, nitric oxide (NO), and platelet activating factor (PAF).[5]

232.1.1 Cause

The inciting cause of pancreatitis in the dog is usually unknown, but the following potential causes and risk factors should be considered.[2] It has been suggested that pancreatitis is more prevalent in obese animals,[2] and it has been shown that the disease is less severe when induced in lean dogs.[2] Evidence also shows that a low-protein high-fat diet induces pancreatitis, and that pancreatitis is more severe when induced in dogs being fed a high-fat diet.[2]

Hyperlipidemia, often grossly apparent, is common in dogs with acute pancreatitis, and may develop as a result of abdominal fat necrosis or may be a cause of the disease in some cases. Some familial hyperlipidemias in human beings are associated with frequent episodes of pancreatitis that respond to control of serum triglyceride concentrations. It is widely believed that the high prevalence of pancreatitis observed in Miniature Schnauzers may be related to idiopathic hyperlipidemia.[2]

Hereditary pancreatitis is well-documented in human beings. Several mutations of the cationic trypsinogen gene (and some other genes) have been identified, the most prevalent being replacement of the arginine in position 117 with a histidine (R117H) or replacement of the asparagine in position 21 with isoleucine (N21I).[6] The two mutations mentioned lead to conformational changes that protect trypsin from autodigestion. As a consequence, prematurely activated trypsin persists and can trigger activation of other zymogens.[6] The high

prevalence of pancreatitis in the Miniature Schnauzer suggests a possible hereditary component; however a recent study failed to identify any mutations in the cationic trypsinogen gene in this breed.

Table • 232-1 Major Protease Inhibitors in Canine Pancreas and Plasma

INHIBITOR	PANCREATIC SECRETORY TRYPSIN INHIBITOR (PSTI)	α_1-PROTEINASE INHIBITOR (α_1-ANTITRYPSIN) (α_1-PI)	MACROGLOBULINS (α-M_1 AND α-M_2)
Principal locations	Pancreas, pancreatic juice	Plasma, intercellular space	Plasma
Approximate molecular weight	6000	55,000	750,000
Specificity	Trypsin only	Broad spectrum (serine proteases)	Broad spectrum (serine and other proteases)
Inhibition	Temporary (slowly degraded by trypsin)	Transient (transfers enzyme to α-M)	Irreversible (permanent trap for captured enzyme)
Function	Inhibits intrapancreatic autoactivation of trypsin	Readily diffusible inhibitor present in the intercellular space	Traps proteases prior to removal by reticuloendothelial system (RES)

From Brown SJ, Desmond PV, Hepatotoxicity of antimicrobial agents. *Seminar Liver Dis* 2002;22:157–67

More than 50 drugs and drug classes have been implicated as a cause of pancreatitis in human beings, although absolute proof of a causal relationship is often lacking.[7] Suspect drugs that are also commonly used in veterinary medicine include L-asparaginase, azathioprine, estrogen, furosemide, potassium bromide, salicylates, sulfonamides, tetracyclines, thiazide diuretics, and vinca alkaloids.[2,8] Corticosteroids have recently been removed from the list of drugs that may induce pancreatitis in human beings. There is little credible evidence that glucocorticoid administration causes pancreatitis in dogs with the possible exception of the use of high doses in association with spinal trauma (e.g., surgical intervention for intervertebral disc disease). Nonetheless, it is probably wise to discontinue the use of any drug in patients with pancreatitis of undetermined cause unless a specific indication for continued use exists and no alternatives are available.

Administration of cholinesterase inhibitor insecticides and cholinergic agonists has been associated with the development of pancreatitis, probably by causing hyperstimulation.[2] Scorpion stings cause pancreatitis in human beings in Trinidad, and experimental administration of scorpion venom to dogs also elicits pancreatitis. Zinc toxicosis has also been reported to cause pancreatitis in the dog. Also, both spontaneous or iatrogenic hypercalcemia may cause pancreatitis in dogs.[2]

Experimental obstruction of the pancreatic ducts produces atrophy and fibrosis, although inflammation and edema may also develop when pancreatic secretion is stimulated.[9] Clinical conditions that may lead to partial or complete obstruction of the pancreatic ducts include biliary calculi, sphincter spasm, edema of the duct or duodenal wall, neoplastic conditions, parasites, trauma, and surgical interference. Biliary calculi are a major cause of pancreatitis in man, but this has not been reported in dogs, presumably because of the low prevalence of biliary stones in this species and because dogs have an accessory pancreatic duct that does not communicate with the common bile duct and serves as the main pancreatic duct.[10] Congenital anomalies of the pancreatic duct system may predispose to pancreatitis in man, and similar mechanisms may occur in the dog but have not been documented.

Reflux of duodenal juice into the pancreatic ducts secondary to surgical creation of a closed duodenal loop causes severe acute pancreatitis. Under normal circumstances such reflux is unlikely to occur because the duct opening is surrounded by a specialized compact smooth mucosa over the duodenal papilla and is equipped

with an independent sphincter muscle; however, this antireflux mechanism may sometimes fail owing to an abnormally high duodenal pressure, such as may occur during vomiting or after blunt trauma to the abdominal cavity.

Surgical manipulation and blunt abdominal trauma are also potential causes of pancreatitis, but reports of pancreatitis after such insults are rare.[2] Pancreatitis after pancreatic biopsy is extremely rare, and is also uncommon after resection of pancreatic neoplasms.[2]

Experimental and clinical reports have indicated that ischemia is important in the pathogenesis of acute pancreatitis, either as a primary cause or as an exacerbating influence. Pancreatic ischemia may develop during shock, secondary to hypotension during general anesthesia, or during temporary occlusion of venous outflow during surgical manipulation in the anterior abdomen. In some cases this may explain some instances of postoperative pancreatitis when areas remote from the pancreas have undergone surgery.

Viral, mycoplasmal, and parasitic infections may be associated with pancreatitis, although this is usually recognized as part of a more generalized disease process.[2] Recently, pancreatitis has been recognized as a potential complication of babesiosis.[11] It is unknown whether bacterial infection plays a role in the development of pancreatitis in some cases, but concomitant bacterial infection does increase the severity of experimental pancreatitis.[2] Pancreatitis may occur in association with end-stage renal failure, but this is rare. It is likely that renal failure secondary to acute pancreatitis is encountered more frequently.[2] Finally, autoimmune mechanisms have been incriminated in a small subset of human patients with pancreatic inflammation that responds to glucocorticoid therapy.[12]

232.2 DIAGNOSIS

232.2.1 History and Clinical Signs

Although dogs of any age and body condition may develop pancreatitis, affected animals are usually middle aged or older and are often overweight. Dogs with acute pancreatitis are usually presented because of vomiting, weakness, abdominal pain, depression, or diarrhea.[13] Severe acute disease may be associated with shock and collapse. Some dogs demonstrate abdominal pain by assuming a “prayer” position, with the forelimbs stretched out, the sternum on the ground, and the hindlimbs raised. Signs of pain may also be elicited by abdominal palpation, although some animals do not react even though they have severe acute pancreatitis. Abdominal pain is the most consistent clinical sign in human patients, being reported in more than 90% of cases. By comparison a study in dogs reported abdominal pain in only 59% of cases.[13] This probably reflects failure to detect abdominal pain rather than its absence. An anterior abdominal mass is palpable in some cases, and occasionally mild ascites occur. Dogs with severe disease are often dehydrated and may be febrile. Uncommon systemic complications of pancreatitis that may be apparent on physical examination include jaundice, respiratory distress, bleeding disorders, and cardiac arrhythmias.[2] In some patients the onset of signs may have followed ingestion of a large amount of fatty food.[13]

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The clinical signs of mild, acute, and chronic pancreatitis in dogs are poorly documented but are probably extremely variable and nonspecific. The disease may not be clinically apparent at all. As a consequence, mild disease remains undiagnosed in the vast majority of cases.

232.2.2 Diagnostic Imaging

Radiographic findings in dogs with pancreatitis include an increased density, diminished contrast (*ground glass* appearance), and granularity in the right cranial abdomen, displacement of the stomach to the left, widening of the angle between the pyloric antrum and the proximal duodenum, displacement of the descending duodenum to the right, presence of a mass medial to the descending duodenum, static gas pattern in or thickened walls of the descending duodenum, static gas pattern in or caudal displacement of the transverse colon, gastric distension suggestive of gastric outlet obstruction, and delayed passage of barium through the stomach and duodenum with corrugation of the duodenal wall. Unfortunately these findings are subjective, and definitive radiographic evidence of pancreatitis is usually not present. However, abdominal radiographs may provide evidence to rule in or rule out alternative diagnoses.

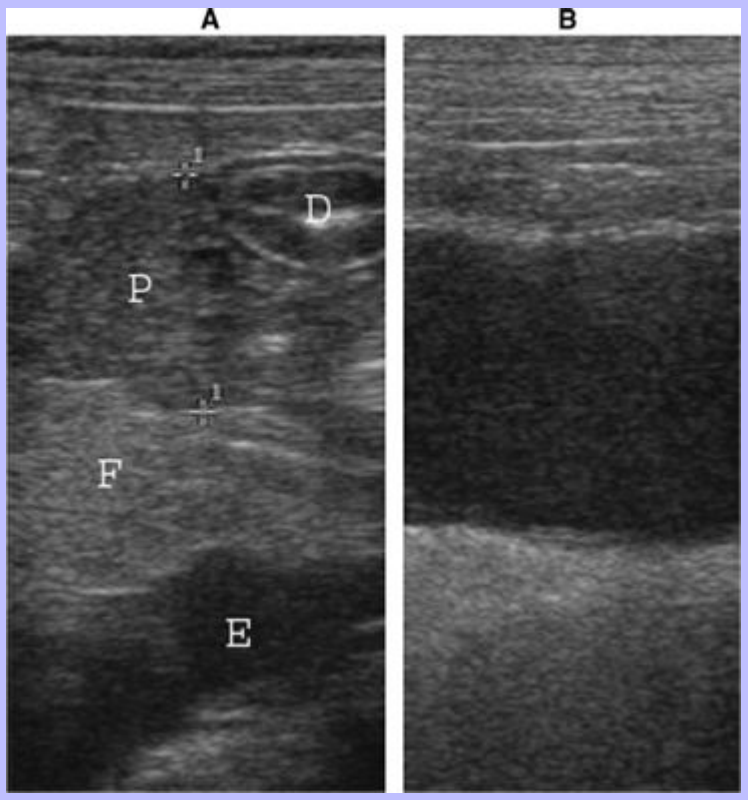
Abdominal ultrasonography is highly specific for pancreatitis when stringent criteria are applied, with a sensitivity of up to approximately 70% in dogs and 30% in cats.[13] Enlargement of the gland, localized peritoneal effusion, or both are not sufficient for a diagnosis. Changes in echogenicity are quite useful. A decrease in echogenicity indicates pancreatic necrosis, which is often associated with hyperechogenicity in the peripancreatic region (Figure 232-2). Hyperechogenicity of the pancreatic parenchyma itself indicates pancreatic fibrosis and can be seen in cases of chronic pancreatitis. Pancreatic duct dilation also has been reported in cats.[2,3] Serial examinations are particularly useful for identification and management of pancreatic complications such as pancreatic pseudocyst or abscess.

Computed tomography (CT) is the most useful modality for visualizing the pancreas and for identifying pancreatic necrosis in human patients, but financial considerations and the much smaller size of the pancreas will likely limit its usefulness in the dog.

232.2.3 Clinical Pathology

Leukocytosis, often associated with a left shift, is a common hematologic finding in acute pancreatitis. The packed cell volume (PCV) may be increased as a result of dehydration, but anemia is also frequently observed.[2,3,13] Azotemia is often present, usually reflecting dehydration, but it may also reflect secondary acute renal failure.[14] Activities of hepatic enzymes are often increased, reflecting either hepatic ischemia or exposure of the liver to high concentrations of toxic products from the pancreas.[2,15] Hyperbilirubinemia and clinically apparent icterus may occur, possibly indicating severe hepatocellular damage, intrahepatic and extrahepatic obstruction of bile flow, or both. Hyperglycemia is common as a result of hyperglucagonemia, stress-related increases in the concentrations of catecholamines and cortisol, or destruction of islet cells by pancreatic inflammation. Some dogs remain diabetic after recovery from acute episodes of pancreatitis.[2] Hypocalcemia has often been reported, usually secondary to hypoalbuminemia but is usually mild to moderate and rarely associated with clinical signs of tetany.[2,3] Hypocalcemia can also be due to deposition of calcium as soaps after excessive generation of fatty acids by the breakdown of fat. Hypercholesterolemia and hypertriglyceridemia are common, and hyperlipemia is often grossly apparent even though food has not been ingested recently. Hyperlipidemia may prevent accurate determination of some serum biochemical values.[2]

Figure 232-2 Ultrasonographic scans of the cranial abdomen in two dogs. The dog in panel **A** had severe pancreatitis. The duodenum can be seen in the upper right hand corner (*D*). The pancreas can be seen as an irregular mixed echoic structure (*P*). The dark areas within the pancreas represent areas of pancreatic necrosis. The hyperechoic area right below the mixed echoic structure represents peripancreatic fat necrosis (*F*). The hypoechoic area below the peripancreatic fat suggests peritoneal effusion (*E*). The changes seen here are highly specific for acute pancreatitis. The dog shown in panel **B** had a pancreatic abscess. A large uniformly hypoechoic structure exists that suggests a fluid-filled mass. Such a fluid-filled mass could represent a pancreatic pseudocyst or a pancreatic abscess and was diagnosed as a pancreatic abscess in this patient. (Images courtesy of Dr. Sharon Shull.)



Assays for several pancreatic enzymes and zymogens in serum have been evaluated for the diagnosis of canine pancreatitis, including amylase and lipase activities, serum trypsin-like immunoreactivity (cTLI), pancreatic

lipase immunoreactivity (cPLI), trypsin-α_1-proteinase inhibitor complexes, and serum and urinary trypsinogen activation peptide (TAP).[2,3,16]

Serum amylase and lipase activities have been used to diagnose canine pancreatitis for several decades, but both have been repeatedly shown to lack sensitivity and specificity.[10] In general, approximately 50% of patients with an elevated serum amylase activity, lipase activity, or both do not have pancreatitis. Trypsin complexed with plasma α_1-proteinase inhibitor and TAP in plasma or urine should act as specific markers for pancreatitis.[16] However, a recent study found urinary TAP concentration to be very insensitive even though it was highly specific.[16] Plasma TAP concentration was slightly more sensitive but also had a lower specificity of 77%.[16] Taking into consideration the cost of the assay, the limited availability of laboratories providing the assay, and the lack of stability of TAP, this assay is of little clinical usefulness for the diagnosis of canine pancreatitis. A recently developed assay for serum trypsin-α_1-proteinase inhibitor complex concentrations did not prove to be useful for the diagnosis of spontaneous pancreatitis in the dog. Serum cTLI concentration is specific for exocrine pancreatic function and is the test of choice for EPI, but its short half life renders it fairly insensitive for the diagnosis of canine pancreatitis.

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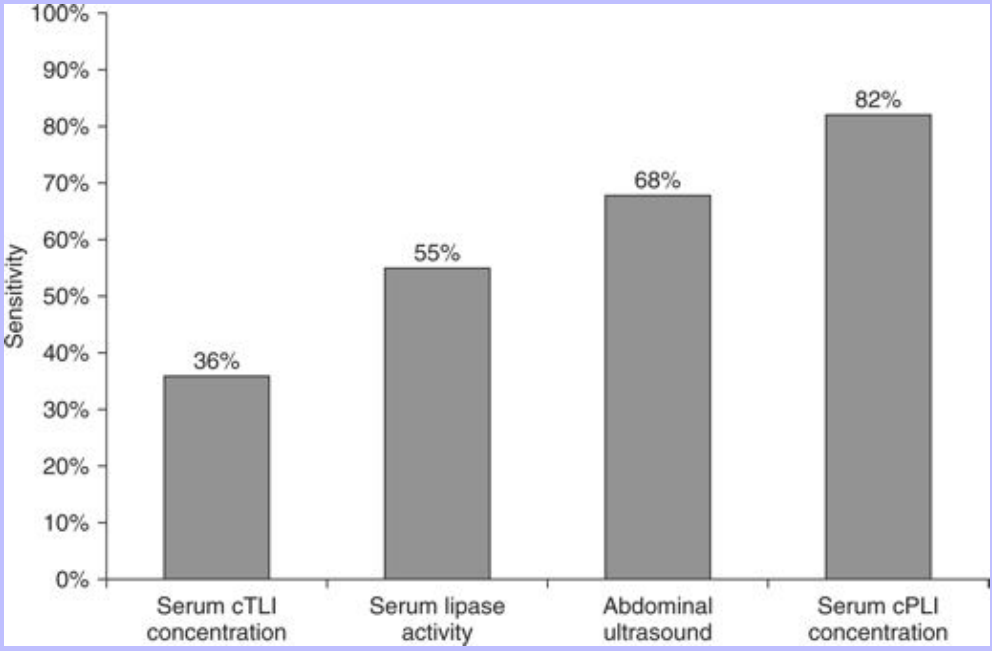
Serum cPLI concentration is highly specific for exocrine pancreatic function and appears to be a useful marker for pancreatic inflammation. In a recent study of 11 dogs with biopsy-confirmed pancreatitis, all 11 dogs had serum cPLI concentrations above the upper limit of the reference range, and nine of 11 dogs (82%) had concentrations above a cutoff value of 200 µg/L.[18] Serum cPLI is not elevated in dogs with gastritis and experimentally induced chronic renal failure; it is also not affected by administration of prednisone. Thus serum cPLI is the most sensitive (Figure 232-3) and specific diagnostic test for canine pancreatitis currently available.

Pancreatic biopsy obtained by exploratory laparotomy or laparoscopy is often considered the gold standard for diagnosing canine pancreatitis, but it has limitations. In a recent study, less than 10% of dogs with pancreatitis showed gross anatomic evidence of pancreatitis. In addition, histologic examination often reveals the distribution of pancreatitis to be patchy and highly localized. Thus although the presence of pancreatic inflammation, necrosis, or both can be considered definitive evidence for pancreatitis, a lack of such findings (even if multiple biopsies are evaluated) does not definitively exclude pancreatitis. Moreover, the risk of anesthesia may be elevated in patients with pancreatitis, making the collection of a biopsy potentially detrimental in such cases.

Figure 232-3 This figure shows a comparison of the sensitivity for different diagnostic modalities for a diagnosis of canine pancreatitis. The reader should note that serum cTLI concentration, abdominal ultrasound, and serum cPLI concentration have a high specificity for canine pancreatitis, whereas only approximately 50% of dogs with an elevated serum lipase activity have pancreatitis.[13,18]



232.3 TREATMENT

The classic therapy for acute pancreatitis is maintenance of fluid and electrolyte balance while the pancreas is "rested" by withholding food.[2] Recent reports have challenged the logic and wisdom of withholding food, however, and both parenteral and enteral nutrition have been well tolerated by patients with pancreatitis.[19] Evidence also indicates that enteral nutrition may be superior to parenteral nutrition. Oral intake should probably be restricted only in those patients with incessant vomiting, and then for as short a period as possible.

If drug-induced pancreatitis is suspected, any incriminated agents should be withdrawn and replaced by an unrelated alternative drug, if necessary. Other potential causative factors (see previous discussion) should similarly be investigated and, if possible, eliminated. Balanced electrolyte solution should be given intravenously to replace fluid deficits and provide maintenance requirements. Mild cases of pancreatitis are probably self-limiting and may improve without therapy. Other patients require aggressive fluid therapy over several days to treat severe dehydration and ongoing fluid and electrolyte loss due to vomiting. Many animals become hypokalemic during such therapy, and serum potassium should be monitored and supplemented parenterally if required. Serum creatinine and blood urea nitrogen (BUN) should also be monitored to document resolution of

azotemia, thereby ruling out associated renal failure. Although metabolic acidosis is probably common in acute pancreatitis, this may not always be the case, and vomiting patients may be alkalotic. Therefore blind correction of suspected acid-base abnormalities should not be attempted.[2] It is common practice to administer antibiotics to dogs with pancreatitis, particularly when toxic changes are evident on the hemogram or when the patient is febrile. Antibiotic therapy appears to be beneficial in human patients and in some experimental models of pancreatitis; in contrast to humans, dogs with pancreatitis rarely have infectious complications, and antibiotic therapy would appear to be of minimal benefit. However, for cases where good evidence for pancreatic infection exists, it should be noted that trimethoprim sulfa and enrofloxacin penetrate well into the exocrine pancreas in dogs.

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Analgesic therapy (subcutaneous meperidine hydrochloride, transdermal fentanyl, morphine by constant rate intravenous infusion, or intraperitoneal lidocaine) should be given to provide relief of pain, even if obvious signs of pain are not apparent.[20] Hyperglycemia is often mild and transient, but in some cases diabetes mellitus may develop, requiring treatment with insulin. Respiratory distress, neurologic problems, cardiovascular abnormalities, bleeding disorders, and acute renal failure are all poor prognostic indicators. Attempts should be made to manage these complications by appropriate supportive measures.

Some affected animals do not improve or continue to deteriorate in spite of intensive supportive care. Evidence indicates that, in severe pancreatitis, marked consumption of plasma protease inhibitors occurs and that saturation of available α-macroglobulins is rapidly followed by acute DIC, shock, and death.[21] Transfusion of plasma or whole blood to replace α-macroglobulins may be life saving in these circumstances, and it has the additional benefit of maintaining plasma albumin concentrations.[22] Low-molecular-weight dextrans have also been used to expand plasma volume, but they may aggravate bleeding tendencies, contain no protease inhibitor, and provide no major advantages over plasma administration. The use of corticosteroids in pancreatitis has been recommended by some because they stabilize lysosomal membranes, reduce inflammation, and alleviate shock, but they have not been shown to be of value in experimental studies.[2] Unless autoimmune pancreatitis is suspected, they should be given only on a short-term basis to animals in shock. Attempts to rest the pancreas by use of direct inhibitors of secretion such as atropine, acetazolamide, glucagon, calcitonin, and somatostatin or its analogues have not proved effective. Recent data have suggested that somatostatin may even have detrimental effects in experimental pancreatitis, and its use cannot be recommended. Administration of a variety of naturally occurring and synthetic enzyme inhibitors with selective actions against individual pancreatic digestive enzymes has shown promise in experimental studies, but these agents have not been shown to be beneficial in human patients with pancreatitis. Inhibition of gastric secretion by use of antacids or cimetidine and suctioning off gastric secretions have been used in an attempt to inhibit pancreatic secretion, however, none of these methods has been consistently shown to be effective. In one study the use of sodium selenite as an antioxidant was reported to lead to a significant decrease in mortality in dogs with pancreatitis. This study was not controlled, and controlled studies in human patients with pancreatitis failed to show any clinical benefit. The use of peritoneal dialysis to remove toxic material accumulated in the peritoneal cavity is believed by some to be useful in human patients with pancreatitis, but it has not been shown reproductivity to be useful and is rather impractical in canine patients with pancreatitis. In some cases pancreatitis may be localized to one lobe of the gland, and surgical resection of the affected area may be followed by complete recovery. Future clinical and experimental trials will probably be directed at the use of agents to modify events currently believed to be important in the pathogenesis of pancreatitis, including inhibitors of inflammatory mediators, free-radical scavengers, enzyme synthesis and transport inhibitors, and factors that may stabilize lysosomal and other cell compartment membranes.[5]

After vomiting has subsided, small amounts of water should be offered; if no exacerbation of clinical signs occurs, food may be gradually reintroduced. The diet should preferably have a high carbohydrate content (rice,

pasta, potatoes) because protein and fat are more potent stimulants of pancreatic secretion and are perhaps more likely to promote a relapse. If improvement continues, gradual introduction of a low-fat maintenance diet should be attempted.[19]

In many patients with a single episode of pancreatitis, the only long-term therapy recommended is to avoid feeding high-fat meals. In patients with repeated bouts of pancreatitis occur, and it may be beneficial to feed a fat-restricted diet permanently. In some patients, hypertriglyceridemia may need to be controlled pharmacologically. Despite all efforts, some animals experience recurrent disease.[23]

Some reports have indicated that oral pancreatic enzyme supplements decrease abdominal pain and discomfort that accompanies chronic pancreatitis in humans. It is unknown whether they are of similar value in dogs, but a trial period of enzyme therapy may be warranted in dogs with chronic signs of abdominal pain or anorexia.

232.4 PROGNOSIS

Pancreatitis is an unpredictable disease of widely varying severity, and it is difficult to give a prognosis. Life-threatening signs accompanying acute fulminating pancreatitis are usually followed by death in spite of supportive measures, but some dogs recover fully after an isolated severe episode. In other cases relatively mild or moderate chronic or recurrent pancreatitis persists despite all therapy, and the patient either dies during an acute severe exacerbation of the disease or undergoes euthanasia because of failure to recover and the expense of long-term supportive care. Most patients with uncomplicated pancreatitis probably recover spontaneously and do well as long as high-fat diets are avoided.

232.5 PANCREATIC PSEUDOCYST

A pancreatic pseudocyst is a collection of sterile pancreatic juice, enclosed by a wall of fibrous or granulation tissue and occurs as a complication of pancreatitis.[1] Recently, several cases of pancreatic pseudocysts in dogs have been described.[24] Clinical signs are usually nonspecific and mimic those of pancreatitis. On abdominal ultrasound a cystic structure in close proximity to the pancreas can be identified. Aspiration of the pseudocyst is relatively safe and should be attempted for diagnostic and therapeutic purposes.[24] In contrast to fluid from a pancreatic abscess, the drained fluid from a pancreatic pseudocyst should be of low cellularity and should not contain any evidence of inflammation. Pancreatic pseudocysts can be treated medically or surgically. Surgical correction can involve extirpation of the pseudocyst, external drainage, or internal drainage, but internal drainage is the preferred treatment in human patients. Medical management of pancreatic pseudocysts involves ultrasound-guided percutaneous aspiration and close monitoring of the size of the pseudocyst. This approach was successful in several cases described in the human medical literature.[24] However, surgical intervention should be considered in cases in which clinical signs persist or when the size of the pseudocyst does not decrease significantly over time.

232.6 PANCREATIC ABSCESS

A pancreatic abscess is another possible complication of pancreatitis.[1] A pancreatic abscess is a circumscribed collection of pus, usually in proximity to the pancreas, containing little or no pancreatic necrosis.[1] In dogs, bacterial infection is only rarely present.[25,26] Clinical signs are nonspecific, but may include vomiting, depression, abdominal pain, anorexia, fever, diarrhea, and dehydration. In some patients a mass in the cranial

abdomen can be identified upon abdominal palpation.[25] Common clinicopathologic findings are neutrophilia with a left shift, elevation of serum amylase and lipase activities, elevations of hepatic enzyme activities, and hyperbilirubinemia.[25,26] Surgical drainage and aggressive antimicrobial therapy are the treatment of choice in human patients with pancreatic abscess. Dogs may also respond favorably to surgical drainage.[25] However, in one report only five of nine patients survived the immediate postsurgical period.[26] Thus given the mixed results, risks, difficulties, and expenses associated with anesthesia, surgery, and postoperative care, one may want to avoid surgical intervention unless clear evidence exists of an enlarging mass, sepsis, or both in a patient that is not responding well to medical therapy. Antimicrobial therapy in dogs is of questionable value unless an organism is identified upon bacterial culture.

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232.7 EXOCRINE PANCREATIC NEOPLASIA

Pancreatic adenomas are benign tumors that are usually singular and can be differentiated from pancreatic nodular hyperplasia by the presence of a capsule. Pancreatic adenocarcinoma is the most common neoplastic condition of the exocrine pancreas in the dog; however, in contrast to humans, where pancreatic adenocarcinoma is the fifth most com-mon malignancy, it occurs rather infrequently in dogs. Adenocarcinomas usually originate from the duct system but can also originate from acinar tissue. A few cases of pancreatic sarcomas (i.e., spindle cell sarcoma, lymphosarcoma) have been reported. Whether these tumors are primary neoplastic lesions of the exocrine pancreas, metastatic lesions of tumors of other organs, or a localized lesion of a multicentric neoplasia is open to question.

232.7.1 Cause and Pathogenesis

The cause of neoplastic conditions of the exocrine pancreas is unknown. Benign neoplastic lesions can lead to transposition of cranial abdominal organs. However, these changes are subclinical in most cases, and the diagnosis is often made as an incidental finding at necropsy examination. In very few cases a benign growth can obstruct the pancreatic duct and cause secondary atrophy of the remaining exocrine pancreas leading to EPI. Adenocarcinomas can also cause transposition of cranial abdominal organs and obstruction of the pancreatic duct. In addition, adenocarcinomas can be associated with tumor necrosis and resulting pancreatic inflammation when the tumor outgrows its vascular supply. Pancreatic adenocarcinomas can also spread to neighboring or distant organs.

232.7.2 Clinical Signs and Diagnosis

The presentation of canine patients with exocrine pancreatic neoplasia is nonspecific, and clinical signs observed are often those of chronic pancreatitis such as vomiting, anorexia, diarrhea, or chronic weight loss. Multifocal necrotizing steatitis has been described in a few dogs that were ultimately diagnosed with pancreatic adenocarcinoma. Clinical signs related to metastatic lesions, such as lameness, bone pain, or dyspnea, have also been reported in some cases of pancreatic adenocarcinoma.

Neutrophilia, anemia, hypokalemia, bilirubinemia, azotemia, hyperglycemia, and elevations of hepatic enzymes have all been reported in affected patients, but results of routine blood tests may be unremarkable. Elevations of hepatic enzymes and serum bilirubin concentration are identified most commonly.[27] Hyperglycemia, when present, is related to concurrent destruction of pancreatic beta cells. Some dogs with pancreatic adenocarcinoma have extremely high serum lipase activities that reach values that are as high as 25

times the upper limit of the reference range. A single dog with a pancreatic adenocarcinoma and pseudohyperparathyroidism, leading to hypercalcemia, has been described in the literature.

Radiographic findings are also nonspecific in most cases. Abnormal findings include decreased contrast in the cranial abdomen, suggesting peritoneal effusion into this area, transposition of the spleen caudally, and shadowing in the pyloric region. In some cases abdominal radiographs can suggest the presence of a mass in the cranial abdomen.[27] In most cases a soft tissue mass can be identified by abdominal ultrasonography in the region of the pancreas.[27,28] However, in many if not most cases, the pancreatic origin of the mass cannot be conclusively established.[27] Similarly, neoplastic lesions of neighboring organs may be falsely presumed to be of pancreatic origin. In addition, patients with severe pancreatitis may show an ultrasonographic mass effect in the area of the pancreas that must not be confused with a pancreatic adenocarcinoma. If peritoneal effusion is identified on abdominal ultrasound, a sample should be aspirated and evaluated cytologically, but in most cases carcinoma cells do not readily exfoliate into the peritoneal effusion, and neoplastic cells are not routinely identified on cytology. Fine needle aspiration or transcutaneous biopsy under ultrasound guidance can be attempted when suspicious masses are identified and has been reported to be successful in approximately 25% of all cases.[27] The low success rate of fine needle aspiration is probably due to the lack of exfoliation of pancreatic adenocarcinoma cells. In other cases carcinoma cells can be identified, but the origin of the cells cannot be determined conclusively.[27] Ultrasound-guided biopsy with histopathologic evaluation of biopsies has been reported infrequently; however, in one study ultrasound-guided biopsy of a pancreatic mass resulted in a diagnosis of pancreatic adenocarcinoma in two of two cases.[27] In two of three more cases, biopsy of the liver revealed metastatic carcinoma.[27] In many cases the diagnosis is made at exploratory laparotomy or even on necropsy examination.

232.7.3 Therapy and Prognosis

Pancreatic adenomas are benign and theoretically do not need to be treated unless they cause clinical signs. However, because the definitive diagnosis of pancreatic adenocarcinoma is often made by histopathology, a partial pancreatectomy should be performed even in cases of suspected pancreatic adenoma. The prognosis in these cases is excellent. Pancreatic adenocarcinomas often present at a late stage of the disease. In human patients with pancreatic adenocarcinoma, metastatic disease is usually present at the time of diagnosis; this is also common in dogs with this disease. The most common sites of metastatic disease are the liver, abdominal and thoracic lymph nodes, mesentery, intestines, and the lungs, but various other metastatic sites have also been reported.[27] In those few cases when gross metastatic lesions are not identified at the time of diagnosis, surgical resection of the tumor may be attempted, but owners should be forewarned that clean surgical margins are only rarely achieved. Total pancreatectomy and pancreaticoduodenectomy, though theoretically possible, have not been described in dogs with spontaneous disease. Extrapolation from human patients suggest high morbidity and mortality for these procedures.[29] To this point, chemotherapy or radiation therapy have shown little success in human or veterinary patients with pancreatic adenocarcinomas. Overall, the prognosis for dogs and cats with pancreatic adenocarcinoma is grave.

232.8 NODULAR HYPERPLASIA

Nodular pancreatic hyperplasia occurs quite frequently in older dogs.[10] Disseminated small nodules can be found throughout the pancreas and can be differentiated from pancreatic adenomas by the absence of a capsule.[10]

Nodular hyperplasia does not lead to functional changes or clinical signs and is thus most frequently diagnosed incidentally during necropsy of older dogs.

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233 CHAPTER • 233 Feline Exocrine Pancreatic Disease

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Diseases of the exocrine pancreas, once believed to be rare in cats, are now known to occur frequently in this species. Pancreatitis is the most common disorder, followed by exocrine pancreatic neoplasia, exocrine pancreatic insufficiency (see Chapter 234), and other miscellaneous conditions.

233.1 PANCREATITIS

The overall prevalence of feline pancreatitis is unknown but as the diagnostic accuracy for this disease is improving, this disease is being diagnosed with increasing frequency. The classification of feline pancreatitis is analogous to the dog (see Chapter 232), but in contrast to dogs, cats are more likely to have chronic disease.

Pancreatitis is ultimately due to autodigestion of the exocrine pancreas by prematurely activated digestive enzymes, most importantly proteases and phospholipases. Pathogenetic mechanisms that initiate clinical disease are the same as in the dog, as are the protective mechanisms that normally protect the pancreas from autodigestion (see Chapter 232).

233.1.1 Etiology

The majority of feline pancreatitis cases are idiopathic; however, a number of causes and risk factors have been identified. A cause-and-effect relationship has been established for *Toxoplasma gondii* and the hepatic fluke *Amphimerus pseudofelineus* (see below), but other infectious organisms, such as panleukopenia and feline infectious peritonitis, have also been implicated. Blunt trauma to the abdominal cavity such as seen in cats that have been hit by car or fallen from great heights (“high-rise syndrome”) can cause pancreatitis, as can surgical manipulation and ischemia secondary to hypotension during anesthesia.

Drugs are an important cause of pancreatitis in human patients and a variety of drugs have been implicated in causing pancreatitis in human beings. However, a cause-and-effect relationship, although likely, has yet to be confirmed in cats. Pancreatitis due to organophosphate intoxication has been documented in cats.[1] The role of inflammatory diseases of the liver and the intestines in the pathogenesis of feline pancreatitis is unknown, but many cats with chronic pancreatitis also have inflammatory infiltrates of these organs. Indeed, diagnosis of chronic pancreatitis in cats should prompt diagnostic evaluation for potential concurrent inflammatory bowel disease (IBD), and vice versa.

233.1.2 Diagnosis

233.1.2.1 History and Clinical Signs

The history of cats with pancreatitis is extremely variable. Most cats with severe disease present with a history of lethargy and anorexia.[1] Key clinical signs of acute pancreatitis in dogs and human beings, vomiting and abdominal pain, have been reported in only 35% and 25%, respectively, of cats with severe

pancreatitis.[1] Hypothermia, dyspnea, diarrhea, and ataxia have also been reported.[1] Mild chronic pancreatitis may be subclinical or may cause anorexia and weight loss.

233.1.2.2 Diagnostic Imaging

Abdominal radiographs are only of limited usefulness for the diagnosis of pancreatitis. Possible findings are the same as in dogs and are also nonspecific in cats (see previous chapter). Thoracic radiographs may show pleural effusion in severe cases. Abdominal ultrasound is highly specific for feline pancreatitis if stringent criteria are applied. Again, findings are the same as in the dog (see Figure 232-2), but additionally pancreatic duct dilation has been reported during abdominal ultrasound examination.[2,3] Although highly specific for feline pancreatitis the sensitivity of abdominal ultrasound for pancreatitis has been reported to be only 10% to 35% when performed by a board-certified ultrasonographer.[4] A recent report assessing the clinical usefulness of contrast-enhanced computed tomography in cats with pancreatitis found this diagnostic modality to be even less sensitive than abdominal ultrasonography.[4]

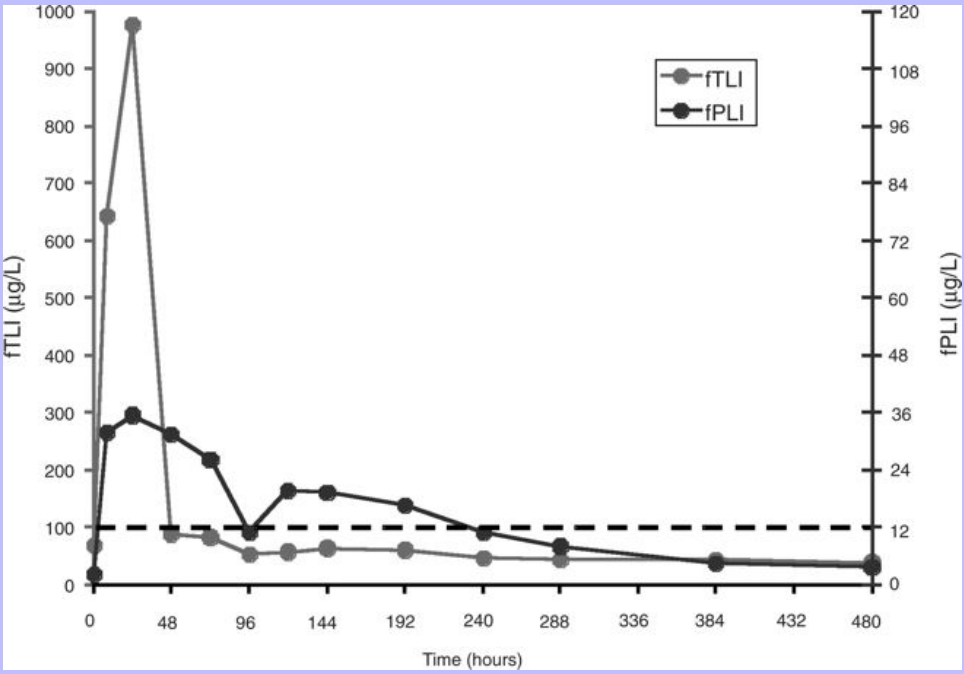
233.1.2.3 Clinical Pathology

Changes in the complete blood count and serum chemistry profile are often mild and nonspecific.[1] Elevations of liver enzymes are common in severe cases and indicate secondary hepatic lipidosis or concurrent cholangitis or cholangiohepatitis.[5,6]

Serum lipase activity increases and serum amylase activity decreases in feline experimental pancreatitis.[7] However, the only study that evaluates the clinical utility of these serum enzyme activities in cats with spontaneous disease found no difference in the mean or the ranges of serum lipase or amylase activities between 12 cats with severe pancreatitis, 43 normal cats, and 31 cats with other diseases. These results suggest that these tests are of no value in the diagnosis of feline pancreatitis.[8] Serum feline trypsin-like immunoreactivity (fTLI) concentration is specific for exocrine pancreatic function in the absence of azotemia, but depending on the study the sensitivity of this diagnostic test for feline pancreatitis ranges between 30% and 60%.

An assay for serum feline pancreatic lipase immunoreactivity (fPLI) has recently been developed and initial clinical studies have been promising. In a group of cats with experimentally induced pancreatitis, both serum fTLI and fPLI concentrations increased initially, but serum fPLI concentration stayed elevated much longer than did serum fTLI concentration (Figure 233-1).[9] Another study of cats with spontaneous pancreatitis showed serum fPLI concentration to be both more sensitive and more specific for diagnosing pancreatitis than serum fTLI concentration or abdominal ultrasonography.[10] At the time of writing both the fTLI and the fPLI assay are performed only at the authors' laboratory.[*]

Figure 233-1 Mean serum fTLI and fPLI concentrations over time in six cats with experimentally induced pancreatitis. The gray line shows the mean serum fTLI concentrations over time and the black line shows the mean serum fPLI concentrations. The broken line displays the currently recommended cut-off value for the diagnosis of pancreatitis for serum fTLI concentration of 100 µg/L and that for serum fPLI concentration of 12 µg/L. The elevation of mean serum fPLI concentration is of far greater duration than that of mean serum fTLI concentration. These data indicate that serum fPLI concentration is more sensitive than serum fTLI concentration for the diagnosis of feline pancreatitis.[9]



Traditionally, histopathology of a pancreatic biopsy has been considered the gold standard for diagnosis of feline pancreatitis. However, gross anatomic lesions are not consistently seen and pancreatic inflammation is often localized to a small area of the gland in both acute and chronic pancreatitis. Furthermore, although pancreatic biopsy per se is safe, it is expensive and may be contraindicated in patients at risk for anesthetic complications.

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233.1.3 Treatment

233.1.3.1 Treatment of Severe Pancreatitis

For the most part treatment of severe pancreatitis mirrors that of dogs (see previous chapter). However, special consideration must be given to nutritional support as most cats with pancreatitis present with a history of anorexia and hepatic lipidosis is common in these patients.[6] Cats that do not vomit should be offered a low-fat diet orally. If the cat is anorectic, as most cats will be, a nasogastric, esophageal, or gastrostomy tube is the most practical route of alimentation. If these routes are contraindicated a jejunostomy tube should be placed. Partial or total parenteral nutrition are other alternatives but a jejunostomy tube is preferable.

Abdominal pain is infrequently recognized in cats with pancreatitis but probably occurs in most patients. In many patients previous abdominal pain becomes apparent after analgesia has been instituted and thus analgesic therapy is indicated in all patients.

233.1.3.2 Mild Pancreatitis

As stated earlier, cats with mild pancreatitis often have evidence of concurrent inflammatory bowel disease and or cholangiohepatitis. Although corticosteroids are believed to be of no benefit in most patients with acute pancreatitis, the authors' experience indicates that corticosteroids can be safely used in cats with concurrent chronic pancreatitis and inflammatory bowel disease. Indeed, successful treatment of IBD with prednisolone appears to lessen the severity of pancreatitis in some of these cats. Cats with concurrent IBD often have subnormal serum cobalamin concentrations, and cobalamin supplementation is essential for optimal therapeutic response in these cases. Cats with mild pancreatitis also may benefit from a low fat diet, although the potential benefit of such diets is not as clear as in dogs. The use of exogenous pancreatic enzymes is commonly recommended in human beings with abdominal pain due to chronic pancreatitis. Exogenous pancreatic enzymes inhibit pancreatic enzyme secretion by a negative feedback mechanism in both dogs and human beings, and this may ameliorate pain in chronic pancreatitis. Although no data are available for cats, trial therapy with pancreatic enzymes should be considered in cats that show either abdominal pain or anorexia attributable to abdominal pain.

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The true prevalence of the hepatic fluke *Amphimerus pseudofelineus* in cats is unknown and infestation is usually missed during routine fecal examination. Thus, empiric treatment with praziquantel (see below) may be warranted in cats with chronic pancreatitis.

233.1.4 Prognosis

The prognosis for cats with pancreatitis is directly related to the severity of the disease, the extent of pancreatic necrosis, the occurrence of systemic and pancreatic complications, the duration of the condition, and to the presence of concurrent disease. In a recent report a plasma ionized calcium concentration below 1.00 mmol/L in cats with pancreatitis was a poor prognostic indicator associated with 77% mortality.[11]

As previously mentioned, common concurrent conditions in cats with pancreatitis include hepatic lipidosis, cholangiohepatitis, enteritis, diabetes mellitus, and interstitial nephritis, all of which may negatively influence

the overall prognosis of the patient.[12] However, most cats with IBD and concurrent pancreatitis respond well to treatment of IBD.

233.2 PANCREATIC PSEUDOCYST

A pancreatic pseudocyst is a common complication of pancreatitis in human beings but has been reported in only one cat to date.[13,14] The clinical signs observed in the cat described were nonspecific and similar to those seen in some cats with pancreatitis. A mass was palpated in the cranial abdomen and a cystic structure in close proximity to the left lobe of the pancreas was identified on abdominal ultrasonography.[13] Surgical correction is the treatment of choice for pancreatic pseudocysts in human beings in cases when they enlarge or do not regress. Surgical correction was also successfully employed in the management of the cat reported.[13]

233.3 PANCREATIC ABSCESS

A pancreatic abscess is another common complication of pancreatitis in human beings.[14] A pancreatic abscess is a circumscribed collection of pus, usually in proximity to the pancreas, and contains little or no pancreatic necrosis.[14] To date a pancreatic abscess in a cat has not been described.

233.4 EXOCRINE PANCREATIC NEOPLASIA

Pancreatic adenocarcinomas, adenomas, or other primary or metastatic neoplastic lesions have been reported in cats.[15,16] Adenocarcinomas are the most common neoplasia of the exocrine pancreas in cats. They are malignant and usually originate from the duct system but can also originate from acinar tissue.[15]

233.4.1 Etiology and Pathogenesis

Benign neoplastic lesions can lead to transposition of organs of the cranial abdomen, but these changes are subclinical in most cases and the diagnosis is often made as an incidental finding on necropsy examination. In some cases the pancreatic mass can obstruct the pancreatic duct and lead to pancreatic atrophy and clinical signs of exocrine pancreatic insufficiency or to pancreatic inflammation. Malignant neoplastic lesions can cause the same changes but can also be associated with tumor necrosis and pancreatitis. Malignant tumors can also spread to neighboring or distant organs.

233.4.2 Clinical Signs and Diagnosis

Cats with exocrine pancreatic neoplasia present with nonspecific clinical signs. In a report of 58 cases, clinical signs most commonly reported were anorexia (46%), weight loss (37%), lethargy (28%), vomiting (23%), icterus (14%), constipation (9%), and diarrhea (3%).[15] Clinical signs reported in other cases were polyuria, fever, dehydration, a distended cranial abdomen, and voluminous, pale, and soft stools.[16] Obstructive jaundice has also been described in a cat with pancreatic adenocarcinoma. Clinical signs due to metastatic lesions may also be observed and may include lameness, bone pain, or dyspnea. Recently several cases of paraneoplastic alopecia have been reported in cats with pancreatic adenocarcinoma.[17,18] The reported alopecia consisted of generalized alopecia of the ventrum, limbs, and face in most cases, and diffuse zones of alopecia in the remaining cats.[17,18]

Neutrophilia, anemia, hypokalemia, bilirubinemia, azotemia, hyperglycemia, and elevations of hepatic enzymes have all been reported in affected patients, but results of routine blood tests may be unremarkable.[15,16] Serum lipase and amylase activities may be elevated in isolated cases.

Radiographic and ultrasonographic findings in cats with exocrine pancreatic neoplasia are similar to those in dogs with this disease (see previous chapter). As in the dog cytologic evaluation of peritoneal effusion or of fine-needle aspirates are only useful in a small number of cases, but the low invasiveness and cost of these procedures warrant their use. In many cases pancreatic neoplasia is diagnosed at exploratory laparotomy or during necropsy examination.

233.4.3 Therapy and Prognosis

The considerations for treatment of exocrine pancreatic neoplasia in cats mirror those in dogs (see Chapter 232). Overall, the prognosis for cats with pancreatic adenocarcinoma is grave.

233.5 PANCREATIC PARASITES

Eurytrema procyonis, the pancreatic fluke of the cat, can be found in the pancreatic ductular system of foxes, raccoons, and cats. Little is known about the life cycle of this parasite. *Eurytrema procyonis* can lead to thickening of the pancreatic duct system and fibrosis. Even though a significant decrease of exocrine pancreatic secretion has been shown to occur in affected animals, cats presenting with clinical signs of EPI secondary to infestation with this parasite are extremely rare.[19] The diagnosis can be made by detection of characteristic dicrocoeliid eggs (average size 34 µm × 50 µm) with a single operculum in fresh feces during routine fecal floatation. Fenbendazole at a dose of 30 mg/kg per os once a day for 6 consecutive days has been recommended for therapy.[20]

The hepatic fluke of the cat, *Amphimerus pseudofelineus,* can also infest the pancreas and can lead to pancreatitis.[21] Infection with this parasite has been reported in cats from Illinois, Iowa, Louisiana, Maryland, Nebraska, Ohio, Texas, and Virginia.[21,22] The life cycle of this parasite is unknown, but it is presumed that similarly to other Opisthorchiidae, mollusces serve as first and freshwater fish as second intermediate host.[22] Diagnosis can be made on fecal examination by formalin-ethyl acetate sedimentation by identification of yellow-brown eggs of approximately 16 µm × 31 µm with a single operculum.[22] Eggs are destroyed during routine fecal floatation and infestation will be missed in those cases. In one report treatment with praziquantel at 40 mg/kg once daily for 3 consecutive days was successful in the management of *Amphimerus pseudofelineus* infestation.[22] Concurrent symptomatic therapy for pancreatitis, as outlined above, also needs to be instituted in these cases. The dose of praziquantel recommended is high when compared with the standard dose recommended for treatment of enteric parasites, but the therapeutic range for praziquantel is wide and the dose recommended is similar to that recommended for treatment of hepatic flukes in human beings.[22]

233.6 PANCREATIC BLADDER

A pancreatic bladder is an abnormal extension of the pancreatic duct. Pancreatic bladders can be congenital or acquired. Only a few cats with pancreatic bladders have been described in the literature. These patients were presented with clinical signs compatible with biliary duct obstruction. Appropriate management has not been studied, but surgical reconstruction may be of most benefit in cases presenting with clinical signs.

233.7 NODULAR HYPERPLASIA

As in older dogs, nodular pancreatic hyperplasia occurs quite frequently in older cats. Disseminated small nodules can be found throughout the exocrine portion of the pancreas. Pancreatic nodular hyperplasia can be differentiated from pancreatic adenomas by the absence of a capsule. Nodular hyperplasia does not lead to functional changes, does not cause any clinical signs, and is usually diagnosed incidentally during necropsy examination of older cats.

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234 CHAPTER • 234 Exocrine Pancreatic Insufficiency in Dogs and Cats

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234.1 CANINE EXOCRINE PANCREATIC INSUFFICIENCY

Chronic diseases of the exocrine pancreas may affect pancreatic function and lead to inadequate production of digestive enzymes, which causes maldigestion and then signs typical of exocrine pancreatic insufficiency (EPI). EPI is a functional diagnosis based on measurement of decreased pancreatic secretion capacity by pancreatic function tests. The exocrine pancreas has a large reserve secretory capacity and clinical signs of maldigestion do not occur until 90% of secretory capacity is lost. In dogs, underlying pathologic processes that may result in clinical signs of EPI are pancreatic acinar atrophy (PAA), chronic pancreatitis, pancreatic hypoplasia, and pancreatic neoplasia. Pancreatic acinar atrophy is reported to be by far the most common cause of severe EPI in dogs.[1,2]

234.1.1 Etiology

234.1.1.1 Pancreatic Acinar Atrophy

Pancreatic Acinar Atrophy (PAA) results from selective destruction of the digestive enzyme producing acinar cells, which may lead to almost complete loss of secretory capacity. The endocrine function of the pancreas usually is unaffected. PAA has been suggested to be a hypoplastic disease because of the young age of the affected dogs. However, general opinion has been that PAA is a progressive disease and it has been shown that the one dog that developed PAA later in life was born with grossly and histologically normal pancreas.[3]

Only a limited number of studies have been assessed the role of different environmental factors, nonmicrobial or microbial, in the development of PAA. In one study stress was suggested to be a possible triggering factor preceding the clinical disease.[4]

PAA has been reported in many breeds, but it is most common in German shepherd dogs and rough coated Collies. In both breeds, PAA has been suggested to be inherited.[5–7]

Recent studies in German shepherd dogs and rough-coated Collies have shown that PAA has features typical of autoimmune disease. With these two breeds it has been possible to diagnose the disease in a subclinical phase, before development of total acinar atrophy and the manifestation of clinical maldigestion signs.[8,9,10] Genetic susceptibility of the disease and the marked T-lymphocyte infiltration during the progression of acinar atrophy have been taken as primary evidence of autoimmune nature of the disease. The progression of acinar atrophy was divided into a subclinical phase, characterized by partial acinar atrophy and lymphocytic infiltration. The clinical phase is characterized by severe endstage atrophy. As

lymphocytic pancreatitis with active destruction of the acinar structures was shown to precede the end-stage atrophy, the term *autoimmune-mediated atrophic lymphocytic pancreatitis* is preferred to describe pathologic findings. Cellular immune mechanisms were shown to have a major role in the tissue destruction.[8–10]

234.1.1.2 Other Causes of EPI

Chronic pancreatitis is a common cause of EPI in cats and humans. It has been suggested as an underlying cause of EPI in older dogs, but its prevalence is still unclear. In chronic pancreatitis the clinical signs are usually those of nonspecific gastrointestinal disease. In this situation, the endocrine pancreas may also be affected. In chronic pancreatitis there can be a progressive destruction of both exocrine and endocrine pancreas, with fibrosis. Congenital exocrine or exocrine and endocrine pancreatic hypoplasia in young puppies is sometimes found. In conjunction with pancreatic neoplasia EPI is a rarely reported clinical sign.[1]

234.1.2 Diagnosis

Diagnosis of exocrine pancreatic dysfunction is based on typical findings in clinical histories and clinical signs. It is confirmed with pancreatic function tests. When it is needed to verify the underlying pathological process causing the clinical signs, morphologic examination of the pancreas is performed.

234.1.2.1 Clinical History and Clinical Signs

Typical clinical signs of EPI include yellowish or gray feces, increased fecal volume and defecation frequency, weight loss, and flatulence. Other signs include abnormally increased appetite; poorly digested, loose, and pulpy feces; and occasional coprophagia. Nervousness or aggressiveness have also been reported, and these are suspected to result from abdominal discomfort due to increased bowel movements and gas formation. Severe watery diarrhea is usually only temporary. Poor hair coat has also been reported in dogs with EPI.[4] Although these clinical signs are typical for EPI, they are not pathognomonic for the disease, as small intestinal disease may cause similar maldigestion signs.

234.1.2.2 Clinical Pathologic Evaluation

Results of standard laboratory analysis are usually not helpful in diagnosing of EPI. Some dogs have hypocholesterolemia and increases in serum alanine aminotransferase activities. This may reflect hepatocyte damage secondary to increased uptake of hepatotoxic substances through small intestinal mucosa. Serum amylase and lipase concentrations are of no value in diagnosing EPI.[1]

234.1.2.3 Pancreatic Function Tests

Various pancreatic function tests have been shown to be valuable in confirmation of the diagnosis of clinical EPI. The value of these tests lies of their ability to distinguish whether the clinical signs are due to exocrine pancreatic dysfunction or to small intestinal disease.[1]

234.1.2.4 Serum Trypsin-like Immunoreactivity

The measurement of serum canine trypsin-like immunoreactivity (cTLI) by radioimmunoassay has become one of the most commonly used pancreatic function tests to diagnose canine EPI. Serum cTLI measurement is species-and pancreas-specific. It measures only pancreatic trypsin and trypsinogen that has entered the bloodstream directly from the pancreas. The reference range for cTLI in healthy dogs is more than 5.0 to 35 μg/L.

Abnormally low serum cTLI concentrations (<2.5 μg/L), in association with the typical clinical signs of maldigestion, are considered highly diagnostic for severe EPI. Because trypsinogen is not absorbed from the intestinal lumen, intestinal disease does not affect cTLI measurement. Serum cTLI measurement is a practical test since usually only a single sample is needed to confirm the clinical diagnosis of EPI. Fasting samples (8 to 12 hours) are recommended as a postprandial increase of serum trypsinogen levels, even though slight and transient, may occur. Because trypsinogen is eliminated by glomerular filtration, renal dysfunction associated with pancreatic disease can cause a rise in serum cTLI.[11]

234.1.2.5 Fecal Proteolytic Activity

Low fecal proteolytic activity has been reported in dogs with severe EPI. The reliability of different fecal proteolytic activity tests varies. The X-ray film test is a simple method but not reliable. More valuable, semiquanititative methods for measuring fecal proteolytic activity are the azocasein method and radial enzyme diffusion into agar containing a casein substrate. Fecal proteolytic activity should be measured in repeated samples because of considerable daily variations in results and because healthy dogs may occasionally pass feces with low proteolytic activity. To prevent incorrect abnormal results, fecal proteolytic activity has been measured after giving dogs raw soybean in their food and determining activities by a radial enzyme diffusion method in fecal samples for 3 days (soybean stimulation test).[12]

234.1.2.6 Fecal Elastase Activity

A new fecal test for diagnosing exocrine pancreatic dysfunction is the measurement of fecal elastase using the ELISA method. Canine fecal elastase is a species-and pancreas-specific test. A single fecal sample is adequate for diagnosing severe EPI and an elastase concentration of less than 10 μg/g in association with clinical signs of EPI is suggestive of severe dysfunction. A drawback of this test is that abnormal results can occasionally be found in normal dogs.[13]

234.1.2.7 Diagnosis of Subclinical EPI and Partial PAA

Serum cTLI values within the subnormal range of 2.5 to 5.0μg/L have been shown to reflect decreased pancreatic function and can be used for the early diagnosis of EPI. In breeds predisposed to PAA, cTLI measurement can be used for diagnosis of the subclinical disease. Repeatedly subnormal serum cTLI values in dogs showing no typical signs of EPI indicate subclinical EPI and suggest partial PAA.

Despite low fasting serum cTLI values, the reserve secretory capacity of the pancreas may prevent the appearance of clinical signs. Some of the dogs with a subclinical disease may have cTLI values of less than 2.5μg/L. To diagnose subclinical disease, repeated cTLI measurements are needed to increase the accurance of the diagnosis. One single subnormal value is not diagnostic for pancreatic dysfunction. In addition

overlapping of cTLI results between subclinical and normal dogs is possible. A normal cTLI (>5.0 µg/L) does not exclude mild to moderate pancreatic dysfunction.[8]

234.1.2.8 Verification of Underlying Pathologic Process

Pancreatic morphologic examination is performed when it is necessary to identify the underlying pathologic process causing pancreatic dysfunction. In dogs with either partial or end-stage PAA, the clinical histories, clinical signs, and results of function tests are usually highly suggestive of the underlying pathologic process. With breeds predisposed to PAA, morphologic examination is rarely needed. Morphologic examination can be useful in atypical cases. The disadvantage of laparotomy and laparoscopy is that they are invasive methods. Further, the morphologic changes in the pancreas are usually unevenly distributed, thus the severity of findings is greatly dependent on the site of biopsy. Pancreatic biopsies can be taken by laparotomy to dissect a small pancreatic sample or by laparoscopy using crushing forceps.[3]

234.1.3 Treatment

234.1.3.1 Treatment and Prognosis of Subclinical EPI

Asymptomatic dogs with partial PAA and subclinical EPI do not need any treatment. The speed of the progression of atrophy from subclinical to clinical phase is variable, and the factors affecting the speed of progression are not yet identified. Early immunosuppressive treatment to halt the progression of the autoimmune mediated tissue destruction has been considered to prevent the clinical disease.

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Long-term follow-up of the dogs with partial PAA and subclinical EPI showed that the value of immunosuppressive treatment in slowing acinar atrophy is questionable. Dogs may stay in the subclinical phase for years or sometimes for life with or without medication. No diagnostic markers predicting which dogs will develop clinical disease have been found, thus immunosuppressive treatment is not recommended.[14] Some dogs with partial PAA may show chronic or intermittent gastrointestinal signs not typical for EPI. The gastrointestinal signs may be due to subnormal pancreatic function or an underlying small intestinal disease or a combination of both. The diagnostic workup and treatment for possible concurrent small intestinal disease is recommended. If no underlying small intestinal disorder is identified, a trial treatment with pancreatic enzymes should be initiated.[14]

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234.1.3.2 Treatment and Prognosis of Clinical EPI

234.1.3.2.1 Enzyme replacement therapy

When clinical signs of EPI appear, enzyme replacement therapy is indicated. Basic treatment for EPI is supplementation of each meal with enzyme extracts. Various pancreatic enzyme extracts are available. In dogs, the highest enzyme activity in the duodenum has been obtained with nonenteric-coated supplements; like raw chopped pancreas or powdered enzymes. In clinical trials, these two supplements have proved to be equally effective in controlling clinical signs. The choice between the preparations is therefore based on practical properties, availability, and costs. In many countries the use of raw pancreas is not allowed because of possibilities of zoonotic diseases. The maintenance dosage for the powdered enzyme preparation is usually 1 tsp/meal, and for raw, chopped pancreas 50 to 100 g/meal for dogs that

weigh 20 to 35 kg. The value of enteric-coated supplements has been demonstrated to be limited in dogs because of the delayed gastric emptying of the preparations.[1,15]

234.1.3.2.2 Supportive treatments

When the treatment response to nonenteric-coated enzyme supplements and ordinary dog food is not satisfactory, the supportive therapies should be considered.

Orally administered enzymes are largely destroyed by gastric acid and despite accurate enzyme therapy the digestive capacity does not return to normal. In some dogs the increase of enzyme dosage or change to another nonenteric-coated enzyme supplement may be beneficial. Inhibition of gastric acid secretion by H_2-antagonist has shown some positive effects. The routine use of H_2-antagonists is not recommended but is indicated when response to enzyme treatment is poor. Preincubation enzymes in food before feeding and supplementing with bile salts or antacids have been recommended to increase the efficiency of enzyme supplementation, but with no proven efficiency.[1]

234.1.3.2.3 Dietary modification

Clinical feeding studies have shown controversial results on the actual benefits of using special diets. In general, no dietary modification is needed and the dogs may continue to be fed with their ordinary food. However, special attention should be paid to individual needs and radical dietary changes should be avoided.[1,15]

In those dogs that do not show the satisfactory treatment response, dietary modification may be useful. A highly digestible, low-fiber and moderate-fat diet has shown to be able to alleviate such clinical signs as flatulence, borborygmi, increased fecal volume, and defecation frequency. Highly digestible diets may be of particular value in the initial treatment until nutritional status has improved. A low-fat diet has been considered to be valuable because enzyme supplements alone are unable to restore normal fat absorption. Lipase is most easily destroyed by gastric acid. Fat absorption may be affected also by the bacterial deconjugation of bile salts in a small intestinal disease, producing metabolites, which in turn may result in diarrhea. Dietary sensitivities may be a consequence of EPI. Therefore hypoallergenic diets may benefit some dogs with EPI, especially in the early treatment. No obvious clinical benefits have been demonstrated with adding medium-chain triglycerides to food.

234.1.3.2.4 Antibiotics

Antibiotics are the most commonly used adjunctive medications in treatment of EPI. Small intestinal bacterial overgrowth is common in dogs with EPI before and during enzyme replacement treatment. An increased amount of substrate for bacteria in the small intestinal lumen, a lack of bacteriostatic factors present in normal pancreatic juice, and changes in intestinal motility and immune functions are possible reasons for an abnormal accumulation of bacteria in the small intestine of dogs with EPI. Antibiotics have particularly been used during initial treatment in cases of poor treatment response to enzymes alone and when clinical signs, such as diarrhea, borborygmus, and flatulence have recurred during long-term treatment. Antibiotics reported to be effective are tylosin, oxytetracyclin, and metronidazole. Usually treatment with antibiotics for 1 to 3 weeks is effective.[1,15]

234.1.3.2.5 Cobalamin

Cobalamin deficiency is common in dogs with EPI. This deficiency is partly due to an increased uptake of cobalamin by intestinal bacteria and partly because of the lack of pancreatic intrinsic factor, demonstrated to have a major role in the absorption of cobalamin. Enzyme supplementation alone has not been found to be helpful for increasing serum cobalamin levels. Parenteral cobalamin treatment is needed when low serum cobalamin values are detected. The clinical signs of cobalamin deficiency are still poorly documented in canine EPI. The doses for cobalamin recommended are 250 to 500 μg parenterally. The vitamin treatment should be repeated based on the serum levels.[1,15]

234.1.3.2.6 Other supportive treatments

Malabsorption of fat soluble vitamins may be suspected in dogs with EPI. The clinical importance of vitamin A, D, E, K deficiency in dogs has not been reported. When treatment responses to enzymes and supportive therapies are insufficient, concomitant small intestinal disease and lymphoplasmacytic enteritis should be suspected. To date, no comprehensive studies on EPI and associated small intestinal diseases have been published. Glucocorticoids treatment is not recommended.[1]

234.1.4 Prognosis

Usually a lifelong enzyme treatment is needed. Response to enzyme treatment is usually seen during the first weeks of treatment, with weight gain, decrease in polyphagia and fecal volume, and cessation of diarrhea. The level of treatment response achieved during the initial treatment period seems to remain rather stable. Although some dogs show short relapses of clinical signs, usually no permanent deterioration of clinical condition is seen during the long-term enzyme treatment.[1,15]

During long-term treatment with nonenteric-coated supplements, 50% of dogs are almost totally controlled. However, despite similar treatment regimes, the treatment response has been shown to be variable, and about 20% of EPI dogs have a poor response. Although it is not always possible to eliminate all the signs, good resolution is found especially for more serious signs such as continuous diarrhea and malnutrition. Why some clinical signs are incompletely controlled and others so variable is not completely understood.

About 20% of the dogs diagnosed for EPI are euthanized during the first year after diagnosis. The most common reason for euthanasia is poor response to treatment. Another reason is owner reluctance for expensive and lifelong treatment.[15,16] A rare, but severe complication of EPI is mesenteric torsion. The etiology of mesenteric torsion remains unclear. Today mesenteric torsion is rare, probably because of the improvement of treatment regimes for EPI.

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234.2 FELINE EXOCRINE PANCREATIC INSUFFICIENCY

Exocrine pancreatic insufficiency (EPI), although uncommon, does occur in cats and therefore should be considered in the differential diagnosis for weight loss and diarrhea in this species. Although the pathophysiology, etiology, diagnosis, and treatment are similar to those of EPI in dogs, there are some important differences.[17] Chronic pancreatitis is the most common cause of EPI in the cat. Rare cases of EPI without pancreatitis have been reported due to duct obstruction associated with *Eurytrema procyonis* infestation.

Adenocarcinomas of the exocrine pancreas can lead to obstruction of the pancreatic duct, followed by atrophy of acinar tissue. Finally, the authors are aware of several reports of pancreatic acinar atrophy (PAA) that is histologically indistinguishable from that so commonly observed in dogs; whether the pathophysiology in such cases is the same as in dogs is not known.[17]

Classical clinical signs include loose, malodorous, and voluminous stools, with poor body condition. Weight loss, even in untreated cases, is rarely as extreme as in untreated dogs. As in dogs, polyphagia is not an invariable sign. It should be emphasized that most cats with polyphagia, weight loss, and diarrhea are ultimately diagnosed as having small intestinal disease associated with severe cobalamin deficiency. These cases are clinically indistinguishable from those with EPI. Indeed, the frequent occurrence of severely subnormal serum cobalamin concentrations, and somewhat less commonly serum folate concentrations, in cats with EPI (abnormalities seen far less often in dogs), indicate that many have severe concurrent small intestinal disease leading to vitamin malabsorption. Cats with EPI may exhibit a greasy, wet-looking and generally unkempt hair coat, especially in the perineal region, which may in part reflect severe cobalamin deficiency.

The differential diagnosis for cats with weight loss, diarrhea, and changes in appetite include chronic small intestinal disease (most commonly inflammatory bowel disease), hyperthyroidism, and diabetes mellitus. In older cats these conditions may be concurrent. Owing to the underlying pathophysiology of EPI in cats, diabetes mellitus is a far more frequent complication of EPI than it is in dogs. It has been reported that more than 50% of cats with diabetes mellitus have pancreatitis. Although it is unknown if this is a cause-and-effect or coincidental relationship, some of these patients do develop EPI.

Results of hematologic and serum biochemical testing, and abdominal radiography or ultrasonography are generally unremarkable, although lymphopenia, lymphocytosis, neutrophilia, eosinophilia, and elevations of hepatic enzymes have been reported sporadically. Many specific tests to evaluate exocrine pancreatic function in cats are either impractical or unreliable, including the bentiromide absorption test, plasma turbidity, microscopic examination of feces for undigested fat, starch, or muscle fibers. Fecal proteolytic activity (FPA) can be determined by either azocasein-or azoalbumin-based methods, or by a radial enzyme diffusion method, and most cats with EPI have undetectable FPA. Unfortunately, this finding is not specific for EPI; FPA is somewhat labile, and few diagnostic laboratories determine FPA using reliable assay methods. Furthermore, the requirement to collect and assay several fecal samples makes this approach expensive and inconvenient. Fortunately, a highly reliable and economical species specific radioimmunoassay for feline trypsin-like immunoreactivity (fTLI) has been developed and validated, and shown to be accurate in the diagnosis of feline EPI.[18,19] Similar to the situation in dogs, severely decreased serum fTLI concentration is diagnostic for EPI in the cats. The fTLI is presently only run at the laboratory directed by two of the authors, but serum fTLI is very stable and samples can readily be shipped worldwide directly to this laboratory. Numerous commercial laboratories will also forward samples to this laboratory on request.

234.2.1 Treatment

Cats with EPI will at least require dietary supplementation with pancreatic enzymes for resolution of clinical signs. It is important to recognize that in most cats, treatments in addition to enzyme supplementation will be required to achieve an optimal response. Dried powdered extracts (give 0.5 teaspoonfuls per meal) of porcine pancreas are available (e.g., Viokase, Pancrezyme, PancreVed). Tablets, capsules, and enteric-coated formulations are usually less effective. Raw pancreas (1 to 2 oz per meal) can also be offered and can be stored frozen for several months prior to feeding. Preincubation of the food with pancreatic enzymes, supplementation with bile salts, or concurrent antacid therapy are unnecessary.[17]

Since cats with EPI almost always have extreme depletion of total body cobalamin stores and undetectable serum cobalamin, it is not surprising that parenteral cobalamin (100 to 250 μg subcutaneously once weekly) is often beneficial. Uncorrected cobalamin deficiency may lead to villous atrophy, intestinal inflammation, and malasborption, with resultant failure to respond to pancreatic enzymes alone. Serum folate concentration is also subnormal in many affected cats, and in some cases serum concentrations can be very low. Oral folate supplementation (400 μg daily orally) will rectify any deficiency. Serum cobalamin and folate concentrations should be routinely evaluated in cats with suspected EPI and periodically assessed following initiation of therapy since deficiencies often recur. Some affected cats also have hypovitaminosis K, and if untreated this can lead to bleeding disorders, which can be fatal if they go unrecognized.

Some cats will not respond appropriately to enzyme supplementation and cobalamin and/or folate supplementation. These cats usually have concurrent small intestinal disease, perhaps associated with abnormal proliferation of bacteria in the upper intestine. In these cases treatment with oral prednisolone (initial dose 5 mg twice daily for 1 to 2 weeks) and/or oral metronidazole (100 mg twice daily for 2 to 4 weeks) is often beneficial. Long-term treatment with either antibiotics nor glucocorticoid is usually not required.

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235 CHAPTER • 235 Acromegaly and Pituitary Dwarfism

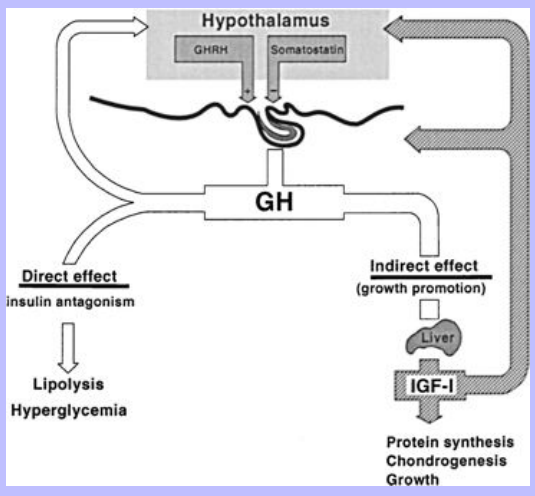
Hans S. Kooistra

235.1 GROWTH HORMONE

Growth hormone (GH) is a rather large single-chain polypeptide with a molecular weight of approximately 22 kDalton. The amino acid sequence of GH varies considerably between different species. The amino acid sequence of canine GH is, however, identical to that of porcine GH.[1]

Like the other hormones of the pituitary anterior lobe, GH is secreted in a pulsatile fashion. Pituitary GH secretion is regulated mainly by the opposing actions of the stimulatory hypothalamic peptide GH-releasing hormone (GHRH) and the inhibitory hypothalamic peptide somatostatin (Figure 235-1). The GH pulses predominantly reflect the pulsatile delivery of GHRH, whereas GH levels between pulses are primarily under somatostatin control. The release of GHRH and somatostatin is controlled by complex neural regulatory mechanisms. GH release can also be elicited by synthetic GH secretagogues. These GH secretagogues exert their effect on GH release by acting through receptors different from those for GHRH. In 1999 Kojima et al characterized the endogenous ligand for these receptors and called it *ghrelin*.[2] The main source of circulating ghrelin, which also is stimulatory for canine GH[3], appears to be the stomach.

Figure 235-1 The pituitary secretion of GH is under inhibitory (somatostatin) and stimulatory (GHRH) hypothalamic control and is also modulated by negative feedback control of IGF-I and GH itself. The direct catabolic (diabetogenic) actions of GH are shown on the left side of the figure, and the indirect anabolic actions are shown on the right. (Redrawn from Rijnberk A, editor: *Clinical endocrinology of dogs and cats*, Dordrecht, The Netherlands, 1996, Kluwer Academic Publishers.)



In the dog, circulating GH not only originates from the pituitary but also may be of mammary origin. In the 1970s and 1980s it was shown that administration of progestins to dogs could lead to elevated plasma GH levels. These progestin-stimulated plasma GH levels do not have a pulsatile secre-tion pattern, are not sensitive to stimulation with GHRH or the α-adrenergic agonist clonidine, and are not inhibited by somatostatin, which points to autonomous secretion. Furthermore it was shown that the progestin-induced elevated plasma GH levels do not decrease after hypophysectomy, which indicates that this GH originates from an extrapituitary site. In 1994 Selman et al published that the progestin-induced GH production in the dog originates from foci of hyperplastic ductular epithelium of the mammary gland.[4] It was also demonstrated that mammary GH is biochemically identical to pituitary GH and that the gene encoding GH in the mammary gland is identical to the gene in the pituitary gland.

The pulsatile secretion pattern of GH changes during progression of the luteal phase of the estrous cycle of healthy bitches, with higher basal GH secretion and less GH secreted in pulses during stages with a high plasma progesterone concentration.[5] It is likely that this is caused by a partial suppression of pituitary GH release by progesterone-induced GH production in the mammary gland. This indicates that progestin-induced mammary GH production is not just an aberration but a normal physiologic event during the luteal phase of the estrous cycle in healthy cyclic bitches. The GH-receptor is also present in the mammary gland, which supports the concept that the progesterone-induced mammary GH production may promote the physiologic proliferation of mammary gland tissue and the preparation for lactation during the luteal phase by local autocrine and paracrine effects. High concentrations of GH have also been found in mammary secretions, particularly in colostrum.[6] The high GH levels in colostrum, often 100 to 1000 times higher than plasma GH levels, may be of importance for the gastrointestinal development of neonates. The progestin-induced mammary GH production may also play a role in mammary gland tumor development or tumor progression.[7]

The effects of circulating GH can be divided into two main categories: rapid catabolic actions and slow (long-lasting) hypertrophic actions. The acute catabolic actions are mainly due to insulin antagonism and result in enhanced lipolysis, gluconeogenesis, and restricted glucose transport across the cell membrane. The net effect of these catabolic actions is promotion of hyperglycemia. The slow anabolic effects are mainly mediated via insulin-like growth factors (IGFs). IGFs are produced in many different tissues, and in most of these tissues they have a local (paracrine or autocrine) growth-promoting effect. The main source of circulating IGF-I is the liver. The chemical structure of IGFs has about 50% sequence similarity with insulin. In contrast to insulin, IGFs are bound to binding proteins (IGFBPs). As a result of this binding to carrier proteins they have a prolonged half-life, which is consistent with long-term growth-promoting effects. IGFs are important determinants in the regulation of body size, by stimulating protein synthesis, chondrogenesis, and growth. There is increasing evidence that GH exerts its growth-promoting effect not only via IGFs but also by a direct effect on the cells.

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IGF-I exerts an inhibitory effect on GH release, by stimulating the release of somatostatin and by a direct inhibitory influence at the pituitary level. In addition, GH itself has a negative feedback effect at the hypothalamic level (see Figure 235-1).

235.2 ACROMEGALY

235.2.1 Pathogenesis

Acromegaly is a syndrome of bony and soft tissue overgrowth and insulin resistance due to excessive GH secretion. The pathogenesis of acromegaly is completely different in dogs and cats. In middle-aged and elderly

female dogs, either endogenous progesterone (luteal phase of the estrous cycle) or exogenous progestins (used for estrus prevention) may give rise to GH hypersecretion of mammary origin. In the cat, acromegaly is caused by an acidophilic pituitary adenoma that secretes excessive amounts of GH. The condition is encountered most often in middle-aged and elderly, predominantly male, cats. Progestins may also induce GH expression in mammary tissue in the cat, but the hormone does not seem to reach the systemic circulation.

235.2.2 Clinical Manifestations

Signs and symptoms of GH hypersecretion tend to develop slowly and are characterized initially (particularly in the dog) by soft tissue swelling of the face and the abdomen. In some acromegalic dogs severe hypertrophy of soft tissues of the mouth, tongue (Figure 235-2), and pharynx causes snoring and even dyspnea. Affected dogs may also have polyuria (and sometimes polyphagia). The polyuria is usually without glucosuria, but manifest diabetes mellitus can develop due to insulin resistance. Physical examination may reveal thick skin folds, (especially in the neck), prognathism, and wide interdental spaces. Prolonged GH excess also leads to generalized visceromegaly, which results in abdominal enlargement. Laboratory investigations in dogs with acromegaly may demonstrate hyperglycemia and/or an abnormal glucose tolerance test. Plasma alkaline phosphatase activities may also be increased. This may, in part, be due to the intrinsic glucocorticoid activity of progestins.

Figure 235-2 The mouth of a 4-year-old beagle dog with progestin-induced GH excess. Note the hyperplasia of the gingiva, the widening of the interdental spaces and the relatively large tongue.

The physical changes in cats tend to be less pronounced than in dogs. The head may also become somewhat massive and may have rather pronounced features. The most common problem in acromegalic cats is (severe) insulin-resistant diabetes mellitus. There may also be proliferative changes that lead to a progressive degenerative arthropathy with lameness. Affected cats may have dyspnea due to hypertrophic cardiomyopathy and subsequent heart failure. Finally, when the pituitary adenoma causing acromegaly becomes large, it may cause neurological signs. For many acromegalic cats the only routine laboratory changes are the hyperglycemia and glucosuria due to the secondary diabetes mellitus.

235.2.3 Diagnosis

Acromegaly is an uncommon condition in diabetic cats. Conversely, insulin resistance or "apparent insulin resistance" is quite common in cats with diabetes mellitus. Thus the diagnosis of acromegaly should be considered only after all other causes for blood glucose concentrations that are persistently increased are eliminated from the differential diagnosis. A complete discussion of feline diabetes mellitus and its management strategy is provided in Chapter 241.

The diagnosis of GH excess can generally be established by measuring basal plasma GH levels. The basal plasma GH level in acromegalic animals often exceeds the upper limit of the reference range (6 μg/L). However, if the disease is mild or just beginning, the basal plasma GH concentration may be only slightly increased. Conversely, a high value may be the result of a secretory pulse in a normal animal. Nonresponsiveness of normal or increased plasma GH concentrations to stimulation may further support the diagnosis.[8] Because of the variation in amino acid sequence of GH in different species, GH should be determined in a homologous radioimmunoassay. Fortunately, feline GH can be measured reliably in a radioimmunoassay developed for the dog.

Measurement of plasma IGF-I concentration may also contribute to the diagnosis. As reviewed, the circulating IGF-I concentration is GH-dependent. Being bound to proteins, the IGF-I concentration is less subject to fluctuation than is GH. However, there is some overlap in plasma IGF-I concentrations between healthy animals and those with acromegaly. In addition, it has been reported that there may be increases in plasma IGF-I levels in diabetic cats unrelated to acromegaly. The amino acid sequence of IGF-I is less species specific than that of GH and therefore IGF-I can be determined in a heterologous (human) assay.

Excessive GH secretion in cats is due to a pituitary adenoma. Consequently, when acromegaly has been demonstrated in a cat, the pituitary should be visualized by computed tomography (CT) or magnetic resonance imaging (MRI) (Figure 235-3).

235.2.4 Treatment

Acromegaly in dogs can be treated easily and effectively by discontinuation of exogenous progestins and/or ovario(hyster)-ectomy. The animal may then change dramatically due to the reversal of the soft tissue changes. The bony changes appear to be irreversible but do not seem to cause problems. For dogs in which the GH excess did not lead to complete exhaustion of the pancreatic β-cells, the elimination of the progesterone source by ovario(hyster)ectomy may prevent persistent diabetes mellitus. In case of recent administration of exogenous progestins, synthetic progesterone receptor blockers may be useful, but experience with long-term administration of this class of drugs is lacking. In the end one may even decide for total mammectomy.

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In cats treatment should be directed at the pituitary tumor. In principle, there are three options: hypophysectomy, irradiation, and medication. There is little experience with any of the three. Medical treatment with drugs such as dopamine agonists does not seem to be effective. Long-acting somatostatin analogues have been shown to lower circulating GH levels in a single cat.[9] In others the drug was not effective. Therefore due to expense and lack of efficacy, it is questionable whether this drug will be used in clinical practice. The development of GH-receptor antagonists such as pegvisomant used in humans may hold promise for dogs and cats with acromegaly. Cobalt irradiation may result in temporary improvement and in (transient) discontinuation of insulin therapy.[10] Transspheniodal hypophysectomy has been performed

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successfully in cats with hyperadrenocorticism due to a pituitary corticotroph adenoma[11] and may also become an effective treatment option for cats with acromegaly.

Figure 235-3 Contrast-enhanced CT scanning of the pituitary fossa, in a 10-year-old castrated male cat with diabetes mellitus and acromegaly, showing a large pituitary tumor. (From Rijnberk A, editor: *Clinical endocrinology of dogs and cats,* Dordrecht, The Netherlands, 1996, Kluwer Academic Publishers.)

235.3 PITUITARY DWARFISM

235.3.1 Pathogenesis

Any defect in the organogenesis of the pituitary gland may result in a form of isolated or combined pituitary hormone deficiency. Congenital GH deficiency or pituitary dwarfism is the most striking example of pituitary hormone deficiency. Congenital GH deficiency has been mentioned to occur in cats and different dog breeds.[12] However, the condition is encountered most often as a simple, autosomal recessive inherited abnormality in the German shepherd dog. Inherited pituitary dwarfism in German shepherd dogs is due to combined pituitary hormone deficiency. German shepherd dwarfs have a combined deficiency of GH, TSH, and prolactin together with impaired release of gonadotropins. In contrast, ACTH secretion in German shepherd dwarfs is preserved (Figure 235-4).[13]

Originally, pituitary dwarfism in the German shepherd dog breed has been ascribed to pressure atrophy of the pituitary anterior lobe by cyst formation in Rathke's pouch. Indeed, in most German shepherd dwarfs pituitary

cysts are present. However, at a young age German shepherd dwarfs sometimes have no or only a very small pituitary cyst, unlikely to be responsible for pressure atrophy. Also the finding that the ACTH secretion is preserved in German shepherd dwarfs argues against cyst formation in Rathke's pouch as the primary cause of pituitary dwarfism in this breed. It is therefore more likely that the disorder is caused by a primary failure of differentiation of the craniopharyngeal ectoderm into normal tropic-hormone-secreting pituitary cells. In this view in German shepherd dwarfs the cyst formation in Rathke's pouch is rather a consequence of an underlying genetic defect than the cause of dwarfism.

235.3.2 Clinical Manifestations

By 2 to 5 months of age, pituitary dwarfs usually have proportionate growth retardation and an abnormally soft and woolly hair coat (Figure 235-5). The latter is due to retention of lanugo or secondary hairs and lack of primary or guard hairs. The lanugo hairs are easily epilated and there is gradual development of truncal alopecia, beginning at the points of wear. The alopecia typically spares the head and extremities. The skin becomes progressively hyperpigmented and scaly. Secondary bacterial infections of the skin are quite common. In male dwarfs unilateral or bilateral cryptorchidism is common, whereas in female dwarfs persistent anestrus is common. These abnormalities may be ascribed to the impaired release of gonadotropins.

Initially, pituitary dwarfs are usually lively and alert. With time the animals develop inappetence and become less active. This situation is usually reached at the age of two or three years and has been ascribed to secondary hypothyroidism and impaired renal function.[9]

235.3.3 Diagnosis

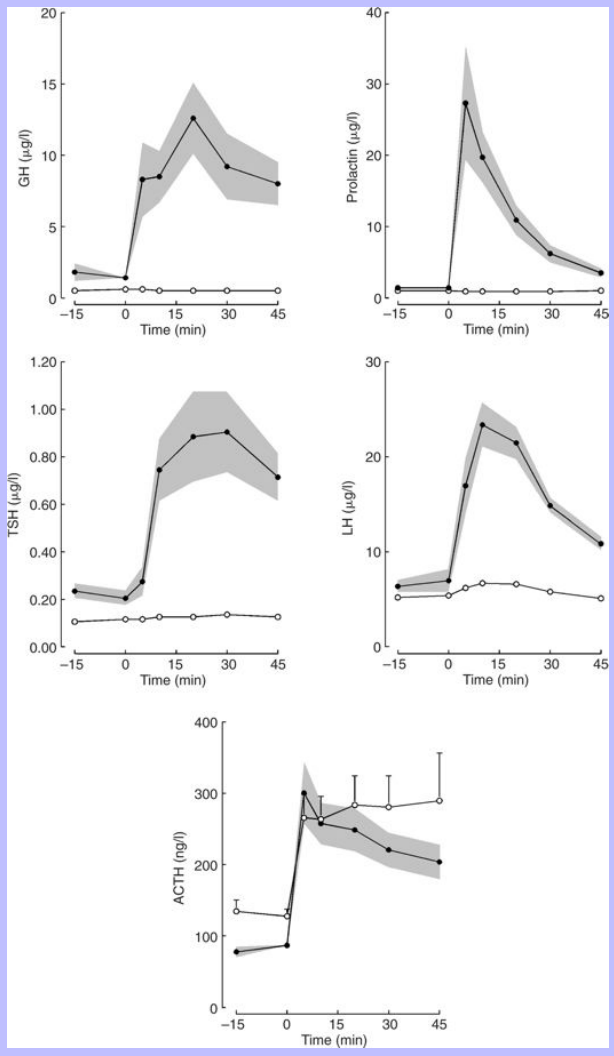
Although the physical characteristics of pituitary dwarfism may be obvious, other endocrine and nonendocrine causes of growth retardation and alopecia have to be excluded.

Routine laboratory examination usually does not reveal abnormalities, except for an elevated plasma creatinine concentration. GH deficiency is associated with maldevelopment of the glomeruli. In addition, renal function may be impaired due to a functionally decreased glomerular filtration rate as a result of the deficiencies of GH and thyroid hormones. As indicated above (see also Figure 235-4) the combined pituitary hormone deficiency includes secondary hypothyroidism. Consequently, a low plasma TSH concentration in combination with a plasma thyroxine level below the reference range is a common finding in pituitary dwarfs. Plasma IGF-I concentrations are also decreased in pituitary dwarfs, even when age and body size are taken into account. Nevertheless, a definitive diagnosis should rely on measurements of circulating GH concentration.

Since basal plasma GH values may also be low in healthy animals, the definitive diagnosis GH deficiency is based upon the results of a stimulation test. For this purpose GHRH (1 μg/kg body weight) or α-adrenergic drugs, such as clonidine (10 μg/kg body weight) or xylazine (100 μg/kg body weight), can be used. The plasma GH concentration should be determined immediately before and 20 to 30 minutes after intravenous administration of the stimulant. In healthy dogs, plasma GH concentrations should increase at least two-to fourfold after administration of the stimulant. In dogs with pituitary dwarfism there is no significant rise in circulating GH concentrations. Supra-pituitary stimulation with corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), and gonadotropin-releasing hormone (GnRH) may reveal the presence of other pituitary hormone deficiencies.

Diagnostic imaging of the pituitary area (CT or MRI) often reveals the presence of pituitary cysts in dogs with congenital GH deficiency. In the majority of young dogs with pituitary dwarfism the pituitary is quite small, in spite of the presence of cysts.[13] This is compatible with pituitary hypoplasia, that is, a lack of endocrine cells in the pituitary anterior lobe. As pituitary dwarfs age the pituitary cysts become larger.[14] It is important to understand that healthy dogs, especially brachycephalic dogs, may have pituitary cysts. Consequently, a definitive diagnosis of pituitary dwarfism cannot be based solely upon the presence of a cyst.

Figure 235-4 Results of a combined pituitary anterior lobe function test (mean and SEM) in eight German shepherd dogs with dwarfism (○) and in eight healthy beagle dogs (•). (From Kooistra HS et al: Combined pituitary hormone deficiency in German shepherd dogs with dwarfism, *Domest Animal Endocrinol* 19:177, 2000.)



235.3.4 Course

The long-term prognosis of German shepherd dwarfs is usually poor without treatment. By the age of 3 to 5 years the animal has usually become a bald, thin, and dull dog. These changes may be due to (1) progressive loss of pituitary functions, (2) continuing expansion of pituitary cysts, and (3) progressive renal failure. At this stage owners usually request euthanasia for their dog, if they have not done so long before this.[9] 1501 1502

Figure 235-5 A 6-month-old female German shepherd dog with growth retardation, retention of secondary hairs (puppy coat), and lack of primary hairs due to pituitary dwarfism.

235.3.5 Treatment

The long-term prognosis for German shepherd dwarfs is poor primarily because of the lack of an adequate therapy. Canine GH is not available for therapeutic use and hence there have been attempts to treat dogs that have congenital GH deficiency with porcine or human GH. However, antibody formation precludes the use of biosynthetic human GH.[15] As indicated above the amino acid sequence of porcine GH is identical to that of canine GH[1], and therefore porcine GH is an option.

The recommended subcutaneous starting dose for heterologous GH is 0.1 to 0.3 IU per kg body weight three times per week for 4 to 6 weeks. This treatment may result in GH excess and consequently side effects such as diabetes mellitus may develop. Weekly monitoring of the plasma concentrations of IGF-I and glucose is therefore of utmost importance. Long-term dose rates after the induction period should also depend on measurements of the plasma concentration of IGF-I. Treatment often does not result in a significant increase in body size, because the growth plates in most dwarfs have already closed or are about to close at the time

GH treatment is initiated. The hairs that grow back are primary lanugo hairs; growth of guard hairs is variable.[12]

The demonstration of the ability of progestins to induce the expression of the GH gene in the canine mammary gland and the subsequent release of this GH into the systemic circulation has raised the possibility of treating dogs with congenital GH deficiency with progestins. Treatment of young German shepherd dwarfs with subcutaneous injections of medroxyprogesterone acetate in doses of 2.5 to 5.0 mg per kg body weight, initially at 3-week intervals and subsequently at 6-week intervals, has resulted in some increase in body size and the development of a complete adult hair coat. Parallel with the physical improvements, plasma IGF-I concentrations rose sharply, whereas plasma GH concentrations did rise but never exceeded the upper limit of the reference range.[14] Also treatment of pituitary dwarfs with proligestone has been reported to result in the development of an adult hair coat, increased body weight, and elevated plasma IGF-I concentration.[16]

Treatment of dogs with congenital GH deficiency with progestins may give rise to side effects, such as recurrent periods of pruritic pyoderma and, infrequently, development of mammary tumors. As with the treatment using heterologous GH, monitoring of the plasma concentrations of IGF-I and glucose is important to prevent diabetes mellitus and acromegaly. Bitches should be ovariohysterectomized before the start of the progestin treatment, to prevent development of cystic endometrial hyperplasia. Finally, thyroid hormone replacement should be part of the treatment schedule.

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236 CHAPTER • 236 Diabetes Insipidus

Ad Rijnberk

Diabetes insipidus refers to the passage of large quantities of dilute urine and is actually synonymous with polyuria. In central diabetes insipidus the polyuria results from a lack of sufficient vasopressin to concentrate urine. The disease is characterized by three primary findings: (1) dilute urine despite strong osmotic stimuli for vasopressin secretion, (2) absence of renal disease, (3) a rise in urine osmolality following the administration of vasopressin.

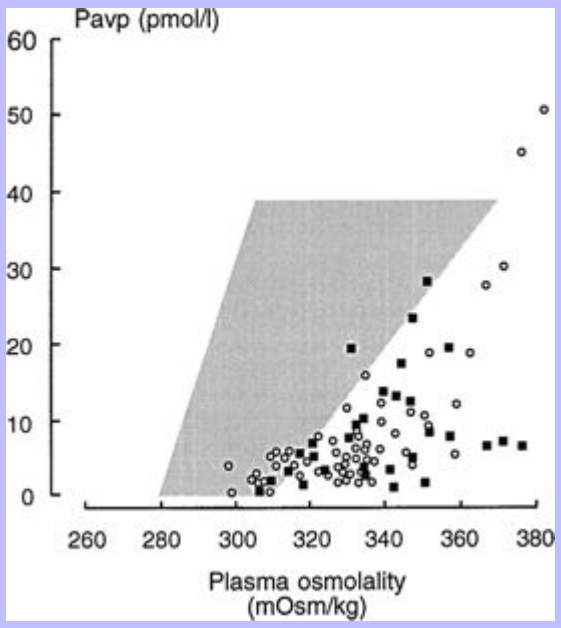
236.1 VASOPRESSIN

Vasopressin is released by the posterior lobe or neurohypophysis, which is an extension of the ventral hypothalamus. Together with the other neurohypophyseal hormone oxytocin, vasopressin is synthesized in both the supraoptic and paraventricular nuclei of the hypothalamus, from which axons extend through the pituitary stalk to the posterior pituitary. The hormones vasopressin and oxytocin are formed by separate neurons and migrate down the axons as part of precursor proteins. They are stored in secretory granules within the nerve terminals in the neurohypophysis and are released by exocytosis into the bloodstream in response to appropriate stimuli. As in most mammals, in dogs and cats arginine-vasopressin (AVP) or antidiuretic hormone (ADH) (in pigs: lysine-vasopressin) plays a vital role in water conservation. Oxytocin stimulates uterine contractions and milk ejection.

The nonapeptide AVP is synthesized as part of a large precursor molecule that is composed of a signal peptide, the hormone, a carrier protein termed neurophysin and a glycopeptide. The major determinant of the release of vasopressin is plasma osmolality. In addition, significant changes in circulating blood volume may influence the setting of the osmoregulation. Specialized neurons called *osmoreceptors* are concentrated in the anterolateral hypothalamus, which is near but separate from the supraoptic nuclei. This area is supplied with blood by small perforating branches of the anterior cerebral arteries. The major role of vasopressin is to regulate body fluid homeostasis by affecting water reabsorption. The antidiuretic effect is achieved by promoting the reabsorption of solute-free water in the distal and collecting tubules of the kidney. The cellular mechanism of AVP activity in the renal tubule involves binding to specific contraluminal V_2-receptor sites, an adenylate cyclase response, and phosphorylation of membrane proteins that lead to transient insertion of water channels in the luminal membrane of the cell. In the presence of these channels water molecules can move passively along an osmotic gradient, that is, from the distal and collecting tubules to the hypertonic renal medulla.

Cations, drugs, and hormones can influence the action of AVP and thereby cause polyuria. Calcium inhibits the adenylate cyclase response to vasopressin. Glucocorticoids also interfere with the action of AVP, although in dogs loss of reactivity of the osmoreceptor system also seems to contribute to corticosteroid-induced polyuria (Figure 236-1).[1] Even physiologic increases in cortisol inhibit basal vasopressin release in dogs.[2] Although much less pronounced than in the dog, also in humans with hyperadrenocorticism, there is decreased ability to concentrate urine. Interferences of glucocorticoids with vasopressin action, similar to those in dogs, have been reported in man.[3]

Figure 236-1 Relation of plasma vasopressin *(Pavp)* to plasma osmolality in nine dogs with pituitary-dependent hyperadrenocorticism (○) and six dogs with hyperadrenocorticism due to an adrencortical tumor (▪) during hypertonic saline infusion. The gray area represents the range in healthy dogs.[1] (Redrawn from Rijnberk A, editor: *Clinical endocrinology of dogs and cats,* Dordrecht/Boston, 1996, Kluwer Academic Publishers.)



236.2 PATHOGENESIS

Insufficient AVP release may be caused by defects at several functional sites in the chain of events that regulates discharge of the hormone into the blood. As a result, different forms of central diabetes insipidus can be distinguished. In dogs and cats only two forms have been recognized: complete and partial central diabetes insipidus. In the first type there is very little rise in urine osmolality with increasing plasma osmolality. These animals are essentially devoid of releasable AVP (Figure 236-2). In the second type AVP is released with increasing plasma osmolality but is subnormal in amount (Figure 236-3). In some cases this moderate AVP release only starts at rather high plasma osmolality values and therefore it may be said that not only is the secretory capacity limited but that there is also a high setting of the osmoreceptor.

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Figure 236-2 The effect of water deprivation on body weight, plasma osmolality *(Posm)* and urine osmolality *(Uosm)* in a 4-year-old castrated male cat with a history of head trauma. The arrow represents an injection of aquous vasopressin (lysine-vasopressin, LVP). In this case the dehydration-induced rise in Posm did not lead to an increase in Uosm. This in combination with the sharp rise in Uosm following vasopressin administration justified the diagnosis of complete central diabetes insipidus. (Redrawn from Rijnberk A, editor: *Clinical endocrinology of dogs and cats,* Dordrecht/Boston, 1996, Kluwer Academic Publishers.)

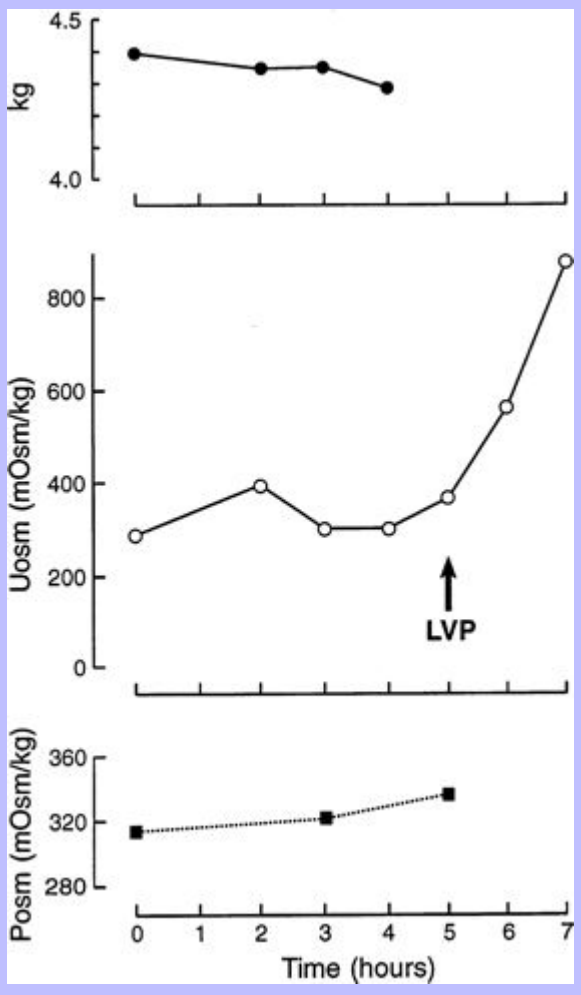
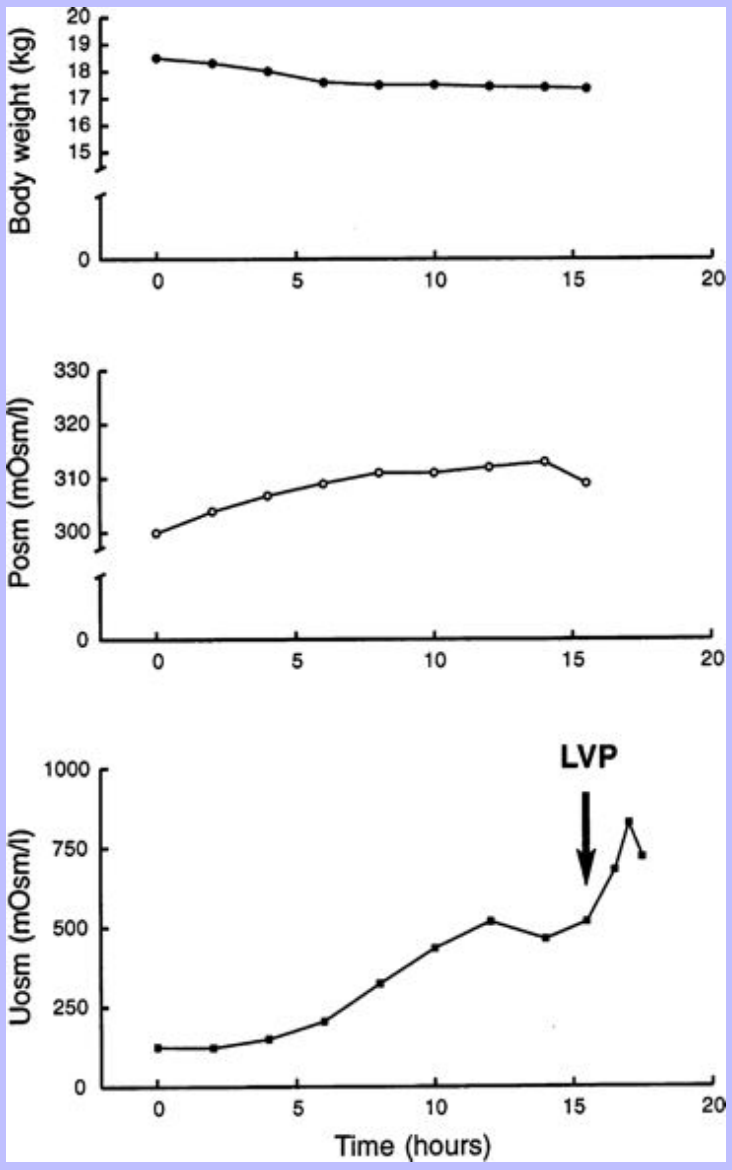


Figure 236-3 In a 5-month-old mongrel dog presented for polyuria, water deprivation led to a slow, subnormal rise in urine osmolality *(Uosm)*. At maximal Uosm, that is, when a "plateau" was reached, vasopressin (lysine-vasopressin, LVP) administration caused a 60% increase in urine osmolality. These observations are compatible with partial central diabetes insipidus. (Redrawn from Rijnberk A, editor: *Clinical endocrinology of dogs and cats,* Dordrecht/Boston, 1996, Kluwer Academic Publishers.)



Among the lesions leading to impaired vasopressin release, an intracranial tumor is a likely cause in middle-aged and old animals. This is most often a primary pituitary neoplasm, but a craniopharyngioma or a meningioma may also be the causative lesion.[4–7] Metastatic lesions and inflammatory and parasitic lesions may also cause central diabetes insipidus.[8] Severe head injury, usually associated with fractures of the skull, is a rare cause in dogs and cats (see Figure 236-2); spontaneous remission may occur, probably because of regeneration of disrupted axons in the pituitary stalk.[9] There is also a report on a dog with evidence for the combination of anterior pituitary hormone deficiency and diabetes insipidus; in this case the pathogenetic significance of the head trauma at early age was unclear.[10]

An increasingly common cause of central diabetes insipidus is pituitary surgery.[11,12] The diabetes insipidus develops immediately after surgery and in the large majority of cases disappears spontaneously after periods of days to months. When the pituitary stalk is sectioned high enough to induce retrograde degeneration of the hypothalamic neurons, the central diabetes insipidus may be permanent. Finally, there is the possibility of the so-called idiopathic form. This term is used in cases of central diabetes insipidus in which no lesion in the hypothalamic and/or pituitary region can be demonstrated. This diagnosis is most common in young animals, although the course of the disease and/or the autopsy may eventually reveal a lesion that could not be identified initially.[13]

236.3 CLINICAL MANIFESTATIONS

The major manifestations are polyuria, polydipsia, and a near-continuous demand for water. These clinical signs may be sudden in onset and the maximum urine flow reached in 1 or 2 days. In severe cases water intake and urine volume may be immense and require micturition almost every hour throughout day and night. However, in the incomplete forms the urine volume may be only moderately increased. In the severe cases the enormous water intake may interfere with food intake and result in weight loss. Animals in which a large neoplasm is the underlying cause may have additional neurologic signs.

The urine concentration will be below that of plasma (specific gravity [SG] <1.010 and urine osmolality [Uosm] <290 mosmol/kg), but in the mild cases higher osmolalities (up to 600 mosmol/kg) may be found. Blood examination usually does not reveal abnormalities except for a slight hypernatremia due to commonly inadequate replenishment of the excreted water. When water is withheld from animals with the complete form of the disease, they develop within a few hours a life-threatening hypertonic encephalopathy (plasma sodium [PNa^+] > 170 mmol/l; Posm >375 mosmol/kg), initially characterized by ataxia and stupor. This situation may also be encountered when the causative lesion extends to the thirst center and adipsia develops.[14]

236.4 DIFFERENTIAL DIAGNOSIS

Apart from central diabetes insipidus there are in principal only two basic disorders that can account for the polyuria. These disorders are (1) primary polydipsia and (2) nephrogenic diabetes insipidus. Primary polydipsia is said to occur in hyperactive young dogs that are left alone during the day for many hours or have gone through significant changes in their environment. It has been observed that placing of the animal in a completely different environment may stop the problem. In these dogs during serial measurements urine osmolality spontaneously may reach values greater than 1000 mosm/kg. This finding can be regarded as diagnostic and precludes the need for a water deprivation test.[15]

Dogs fulfilling the commonly accepted criteria of primary polydipsia may exhibit abnormalities of vasopressin release. It is not clear whether these changes in vasopressin secretion are the result of the polydipsia and polyuria or may play a causative role.[15]

There are a few individual case reports of congenital nephrogenic diabetes insipidus, the condition in which the kidney tubules are insensitive to the action of antidiuretic hormone. Familial occurrence has been documented in huskies, in which the defect could be ascribed to a mutation affecting the affinity of the V_2 receptor for ligand.[16]

However, in addition to these two basic and infrequently encountered differential diagnoses, a wide variety of conditions cause polyuria. In the young animal this may be congenital kidney disease, whereas at all ages 1504
acquired kidney disease may lead to polyuria. Especially in the middle-aged and elderly animals endocrine 1505
conditions such as diabetes mellitus, hyperadrenocorticism, hyperaldosteronism[17], hyperthyroidism, pyometra, progestin-induced (luteal phase) growth-hormone excess[18], hyperparathyroidism, hypercalcemia of malignancy, tumor-associated polyuria[19], and the syndrome of inappropriate vasopressin secretion[20] have to be considered. In several of these conditions impaired release of vasopressin and/or interference with its action may play a role in the polyuria (see earlier and Figure 236-1). This has been documented for conditions such as hyperadrenocorticism, hepatoencephalopathy, and polycythemia.[1,21,22] In polycythemia it is likely that increased blood volume causes the impairment of vasopressin release. This range of possibilities may make it a difficult task to come to a diagnosis in an animal with polyuria. The algorithm presented in Figure 236-4 may be helpful.

236.5 DIAGNOSIS

Urine osmolality (161–2830 mOsm/kg) and urine specific gravity (1.006–>1.050) vary widely among healthy pet dogs.[23] In some dogs urine osmolality fluctuates considerably during the day and values close to plasma osmolality may be reached (Figure 236-5). There is experimental evidence that water consumption increases with food intake and exercise.[24] For example, with dry food, dogs consumed 40% of the total daily water intake during 2 hours after food intake. After treadmill running for 30 minutes water intake was higher than the water losses during the excercise.[24] However, it is unlikely that the sometimes strong fluctuations in urine osmolality of pet dogs during the day can be explained solely as an effect of feeding. There may be individual differences in early satiation of thirst, as mediated through oropharyngeal receptors.[23]

Apparently, in most pet dogs, low urine osmolalities are associated with sufficiently high urine osmolalities at other times of the day so that the owners do not perceive their dog to be polydipsic or polyuric. However, in other dogs the situation may be more pronounced and the animals are brought to the veterinarian because of polyuria and polydipsia.[23] Some of these animals may be recognized as having primary polydipsia (see above, section differential diagnosis). Therefore it is advisable to start the evaluation of dogs with polyuria by repeated measurements of urine osmolality and/or urine specific gravity during the day. As in humans, this approach may limit further clinical studies.[25]

The water deprivation test combined with vasopressin administration[26], as exemplified in Figures 236-2 and 236-3, is most commonly used for differentiation of the causes of polyuria. The test is difficult to perform correctly, unpleasant for the animal, relies heavily on the emptying of the bladder, and is indirect because changes in urinary concentration are used as an index of vasopressin release. Furthermore, the stimulus to

vasopressin release is a combination of hypertonicity and hypovolemia, especially towards the end of the period of dehydration.

Briefly the procedure is as follows: After 12 hours of fasting, water is withheld and plasma and urine are collected every hour or every 2 hours, depending on the severity of the polyuria. Osmolality is measured in both samples. At each collection, the animal is weighed. When the weight loss approaches 5% of initial body weight, the test should be stopped. When, in the presence of an adequate osmotic stimulus (Posm >305 mOsm/kg), urine concentration is maximal (less than 5% increase in Uosm between consecutive collections), (lysine) vasopressin or a vasopressin analogue such as DDAVP (see below) is administered.

In both nephrogenic diabetes insipidus and central diabetes insipidus Uosm will remain low during water deprivation. In complete diabetes insipidus Uosm will rise by 50% or more following the administration of vasopressin, whereas in the partial forms of central diabetes insipidus the rise will be greater or equal to 15%, and in nephrogenic diabetes insipidus there will be very little or no rise in Uosm (see Figures 236-2 and 236-3). Probably in part due to the indirect character of the test, the results may not always be conclusive.[27]

A more direct way to differentiate between the three basic causes of polyuria rests on the measurement of plasma vasopressin during osmotic stimulation by hypertonic saline infusion (Figures 236-1 and 236-6).[28] The euhydrated animal is infused for 2 hours through the jugular vein with 20% NaCl solution at a rate of 0.03 mL/kg body weight per minute. Samples for plasma (arginine) vasopressin (AVP) and plasma osmolality are obtained at 20-minute intervals. In the severely polyuric animal there is the risk of inducing critical hypertonicity. The test requires close observation of the animal and monitoring of plasma osmolality. This, and the fact that vasopressin is sensitive to proteolytic breakdown, make it advisable that the test is performed in institutions that have developed experience with the test.[29]

As in humans this approach can improve the diagnostic accuracy. The advantage is not in the severe forms of central diabetes insipidus, as in these conditions the standard indirect test will give a correct diagnosis. In all other categories of polyuria (i.e., in animals that concentrate their urine to various degrees during dehydration), the indirect test may be less reliable. Dogs in which the polyuria had initially been attributed to renal disease or to primary polydipsia proved to have partial central diabetes insipidus in the direct test. However, with regard to primary polydipsia some reservation in the interpretation is needed, as it has been demonstrated for humans that this chronic overhydration downregulates the release of AVP in response to hypertonicity.[28] As indicated above, also in dogs with so-called *primary polydipsia* there are indications for abnormalities in vasopressin release.[15]

The use of this direct approach has been limited so far, but it is worth considering in the few unresolved cases that remain after exclusion of the many other causes of polyuria (see Figure 236-4). It is often a question of whether the animal must endure for many years a life hampered by thirst, a large bladder, and unwanted behavior.

236.6 TREATMENT

As for almost all peptides, orally administered vasopressin is ineffective. Aquous (lysine) vasopressin may be administered subcutaneously in doses of 2 to 5 U. It will act for only about 3 hours. Nevertheless a good response has been reported in one dog, which received 5 U each 48 hours.[6]

The vasopressin analogue desmopressin, (DDAVP, 1-deamino, 9-D-arginine vasopressin)[*], provides antidiuretic activity for about 8 hours. One drop (1.5 to 4 µg) placed twice daily in the conjunctival sac sufficiently controls the polyuria in most dogs with central diabetes insipidus. With the administration of three drops a day the urine

production usually returns to normal, but some owners (in part for financial reasons) prefer to apply the drug only twice daily. In one report on a cat with partial diabetes insipidus the effect of conjunctivally administered desmopressin was described as poor, which might have been due to incorrect placement because of the cat's struggling.[30] With the injectable preparation (4 µg once a day or every 12 hours) of desmopressin the water consumption could be adequately controlled. The analogue can also be effective when administered as tablet: one-half tablet of 0.1 or 0.2 mg, two or three times per day, depending on the size of the animal and the effect.

Figure 236-4 In the first part of this algorithm the approach of the problem polyuria/polydipsia (pu/pd) is based upon the information from history. As a second step urinalysis has been introduced as it may happen that an animal presented with a seemingly convincing history of pu/pd has only pd because the owner has changed the food to dry food. As indicated in the text, it may be advisable at this stage to ask the owner for urine collections at 2-hour intervals. When the routine clinical chemistry has not revealed a specific suspicion, tests such as water deprivation and hypertonic saline infusion with AVP measurements may be needed. (Redrawn from Rijnberk A, editor: *Clinical endocrinology of dogs and cats,* Dordrecht/Boston, 1996, Kluwer Academic Publishers.)

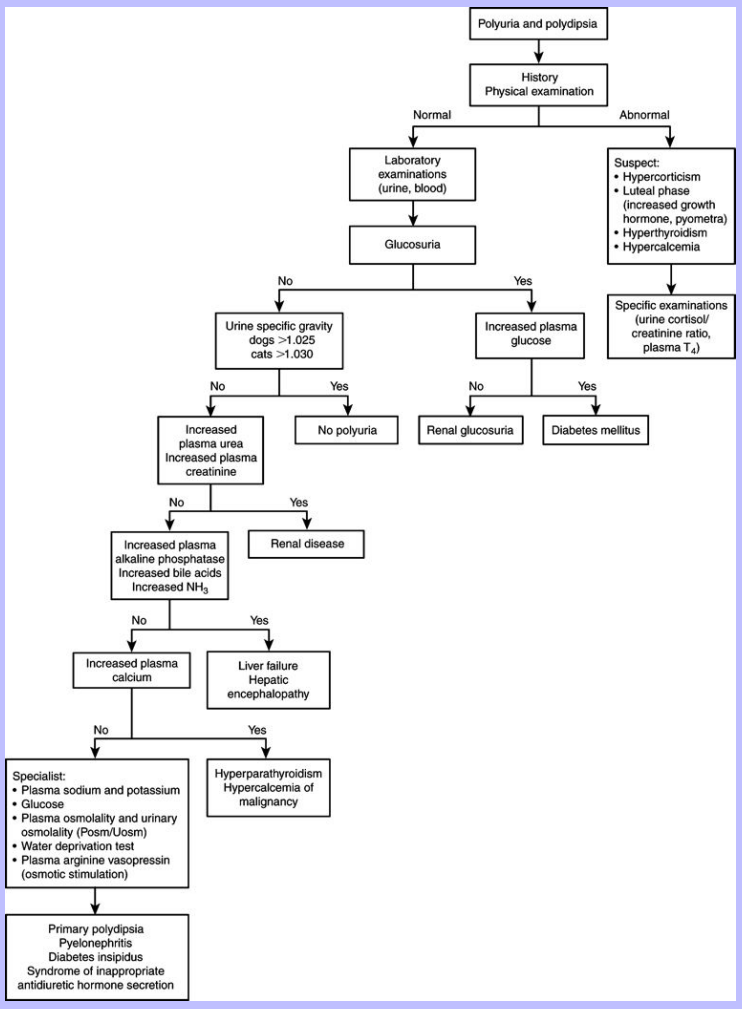
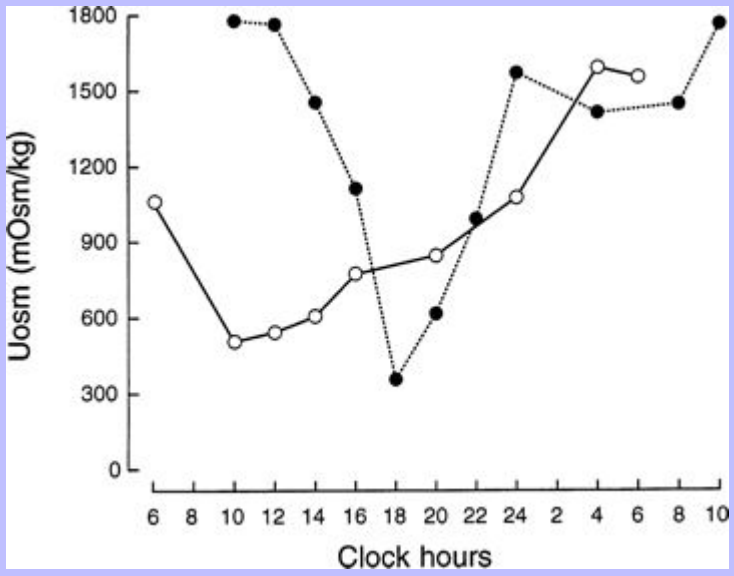


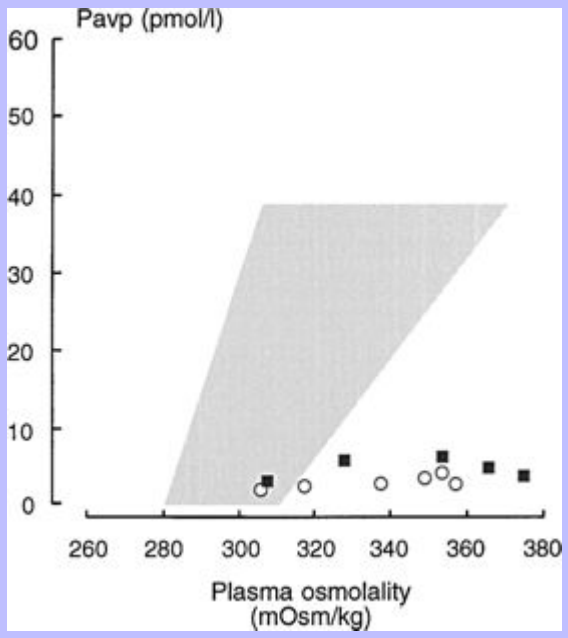
Figure 236-5 Fluctuation of Uosm during the day in a 9½-year-old castrated male Schnauzer (interrupted line) and a female 7½-year-old Belgian Shepherd (uninterrupted line). (Redrawn from Van Vonderen IK et al: Intra-and interindividual variation in urine osmolality and urine specific gravity in healthy pet dogs of various ages, J Vet Intern Med 11:30, 1997.)



In dogs and cats undergoing hypophysectomy the administration of desmopressin is begun immediately after surgery. In healthy dogs this prevents hypernatremia.[31] In dogs hypophysectomized for pituitary-dependent hyperadrenocorticism mild hypernatremia may occur in the first 24 hours after surgery, despite prophylactic administration of desmopressin. This is probably related to the fact that in these dogs the hypercortisolism-induced vasopressin resistance is insufficiently compensated in the postoperative period by infusions and water intake.[11]

In cases of polyuria, in which all of the above mentioned differential diagnoses have been excluded, including central diabetes insipidus, the suspicion of nephrogenic diabetes insipidus may arise; a rare congenital disorder. Such cases have been treated with thiazide diuretics and a low-sodium diet. Oral administration of hydrochlorothiazide (2 to 4 mg/kg twice daily) and a low-sodium diet may decrease urine volume, albeit probably without significant change in urine osmolality. It is thought that the thiazide diuretic and the low sodium diet reduce plasma sodium concentration. This would decrease the stimulation of the thirst center and consequently the water intake. This may lead to extracellular volume contraction, a decreased glomerular filtration rate, increased proximal tubular sodium and water reabsorption, and decreased delivery of water to the distal tubule. The net effect is a reduction in urine volume.[32]

Figure 236-6 Relation of plasma vasopressin with plasma osmolality (Pavp) during hypertonic saline infusion in two dogs with central diabetes insipidus caused by pituitary tumor.[4] See also legend to Figure 236-1. (Redrawn from Rijnberk A, editor: *Clinical endocrinology of dogs and cats,* Dordrecht/Boston, 1996, Kluwer Academic Publishers.)



* Minrin, Ferring AB, Malmö, Sweden (0.1 mg DDAVP/mL).

236.7 PROGNOSIS

In the absence of a neoplastic lesion the long-term prospects for cases with central diabetes insipidus are good. With appropriate treatment the animals become asymptomatic. Untreated animals with the complete form are always at risk of developing life-threatening dehydration when left without water for longer than a few hours. Animals with diabetes insipidus due to a pituitary tumor may lead acceptable lives for many months until the lesion has reached such size that neurologic signs develop.

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237 CHAPTER • 237 Disorders of the Parathyroid Glands

Edward C. Feldman

The parathyroid glands and their production of parathyroid hormone (PTH) control serum calcium concentrations. Dogs and cats normally have four glands (two pairs). Two glands are anatomically closely associated with each thyroid lobe. Primary parathyroid gland disorders involve excess secretion of PTH (primary hyperparathyroidism [PHPTH]) or deficiencies of PTH secretion (primary hypoparathyroidism). Both conditions are relatively uncommon, but PHPTH is diagnosed at a much greater frequency than its counterpart. Further, hypercalcemia is diagnosed relatively frequently in dogs, and the first challenge for the veterinarian is appreciating the differential diagnosis for hypercalcemia and then diagnosing the specific condition causing this biochemical abnormality in an individual dog or cat (Box 237-1).

237.1 PRIMARY HYPERPARATHYROIDISM AND HYPERCALCEMIA IN DOGS

237.1.1 Cause

The essential disorder in PHPTH is the excessive synthesis and secretion of PTH by abnormal, autonomously functioning parathyroid "chief" cells.[1,2] The cause of this hormonal excess is usually a solitary parathyroid adenoma, but an adenoma of more than one gland, adenomatous hyperplasia of one or more parathyroid glands, and parathyroid carcinomas have been identified in both dogs and cats. By contrast, other forms of hyperparathyroidism (e.g., renal or nutritional secondary hyperparathyroidism) are usually the result of nonendocrine alterations in calcium and phosphorus homeostasis. Such disturbances indirectly affect the parathyroid glands, causing diffuse hyperplasia. However, in these conditions the secretion of PTH is not autonomous. The "hyperplasia" occasionally diagnosed in the primary condition (PHPTH) is a condition associated with autonomous secretion of PTH. Therefore histologic descriptions may not indicate primary autonomous from secondary secretory patterns. Depending on cause, serum calcium concentrations in secondary disorders may range from low to normal to increased. PHPTH is virtually always associated with hypercalcemia.

237.1.1.1 Box • 237-1 Differential Diagnosis of Hypercalcemia

237.1.1.1.1 Common

Lymphosarcoma

Hypoadrenocorticism

Primary Hyperparathyroidism

Chronic renal failure

237.1.1.1.2 Uncommon

Apocrine gland carcinoma of the anal sac

Multiple myeloma

Vitamin D toxicosis

237.1.1.1.3 Uncommon to Rare

Spurious

Hemoconcentration

Carcinomas:

lung, mammary, nasal, pancreas, testicle, thymus, thyroid, vagina

Acute renal failure

Nutritional secondary hyperparathyroidism

Granulomatous disease blastomycosis, histoplasmosis, schistosomiasis

237.1.2 Pathophysiology

237.1.2.1 Calcium-Parathyroid Hormone Feedback System

Serum calcium is the major factor in regulation of PTH secretion. In normal animals, an inverse linear relationship exists between serum calcium and PTH concentrations.[3] In other words, as calcium concentrations in the serum decrease, PTH secretion is stimulated to maintain serum calcium concentrations at some specific level. The system functions as if there were a "calciostat" that operates at a serum calcium concentration set point of about 10.5 to 11.5 mg/dL. When serum calcium concentrations decrease below these levels, the rate of PTH secretion increases; when the serum calcium concentration exceeds the set point (as might occur after intake of a high-calcium meal), PTH secretion is suppressed. In PHPTH, normal negative-feedback homeostatic control is lost, and PTH secretion becomes chronically increased. This appearance of "autonomous" secretion may be a change in the "set point." The autonomous secretion of PTH is not suppressible by the increased concentration of calcium perfusing the parathyroid glands. Conversely, in secondary hyperparathyroidism, secretion by the parathyroid glands is normally suppressible by increased concentrations of calcium.

237.1.2.2 Severe Hypercalcemia

Hypercalcemia develops when the entry of calcium into the extracellular fluid (regardless of the source) overwhelms mechanisms that maintain normocalcemia. One such mechanism is suppressed secretion of PTH, a process obviously negated when the cause of hypercalcemia is autonomous secretion of PTH or a molecule with similar biologic activity. In cancer-associated hypercalcemia, the secretion of PTH is suppressed, but the humoral factor that activates osteoclasts is the autonomous secretion of a parathyroid hormone–related protein (PTHrP). PTHrP is a protein with a structure and biologic activity quite similar to that of PTH.[4,5]

In the setting of accelerated bone resorption, the kidney is the principal defense against hypercalcemia.[6] When renal and endocrine function is normal, any tendency for a rise in serum calcium is attenuated by increased urinary excretion of calcium. This process is inhibited by PTH in PHPTH or by PTHrP in hypercalcemia of malignancy. These hormones induce osteoclast-mediated bone resorption, intestinal absorption of calcium, and renal tubular reabsorption of calcium.[7] This impairs the ability of the kidneys to excrete the increased filtered load of calcium. Thus animals with an excess of PTH lack the first lines of defense against hypercalcemia. The hypercalcemic state also interferes with renal mechanisms for reabsorption of sodium and water, leading to polyuria. This is due to an acquired inability to respond to antidiuretic hormone (ADH)—in essence, a reversible form of nephrogenic diabetes insipidus. In PHPTH, hypercalcemia is enhanced by the increased production of vitamin D and by a decrease in the amount of serum phosphate available to form complexes with serum ionized calcium. The result is a decreased tubular reabsorption of phosphate, hyperphosphaturia, and hypophosphatemia. These actions are responsible for the development of the biochemical triad classic for PHPTH: hypercalcemia, hypophosphatemia, and hyperphosphaturia.

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237.1.3 Signalment

237.1.3.1 Age and Gender

PHPTH is typically diagnosed in older dogs and appears to be much less common, or at least less frequently diagnosed, in cats. The mean age of the 187 dogs with PHPTH seen at our hospital is 11.2 years, with a range of 4 to 17 years (Figure 237-1). More than 95% of the dogs are 7 years of age or older. No apparent sex predilection exists.

237.1.3.2 Breed

Reliable information regarding breed predisposition for any disorder requires sophisticated epidemiologic evaluation. To the author's knowledge, such an investigation has not been undertaken with respect to canine PHPTH. Regardless, it is reasonable to point out that the Keeshond is far from being the most popular breed of dog, as opposed to poodles, German shepherds, retrievers, and the like. In spite of this relative lack of popularity, 48 of the 187 dogs (26%) in our series have been Keeshonden. The other breeds represented three or more times in series include Labrador retrievers, German shepherd dogs, Cocker spaniels, golden retrievers, springer spaniels, Shih Tzu, poodles, Australian shepherds, Rhodesian ridgebacks, Doberman pinschers, and mixed breed dogs (Table 237-1). Several of these breeds, however, are simply popular. Whether or not breed predispositions exist awaits epidemiologic evaluation. However, two points should be made. First, the Keeshond is over-represented; second, dogs of any breed or mixed breeding and any age from 4 years of age and older can be afflicted by this condition.

Figure 237-1 Age distribution of 78 dogs with primary hyperparathyroidism. The mean age at the time of diagnosis was 10.5 years. (From Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, 3rd ed. Philadelphia, WB Saunders Co, 2004.)

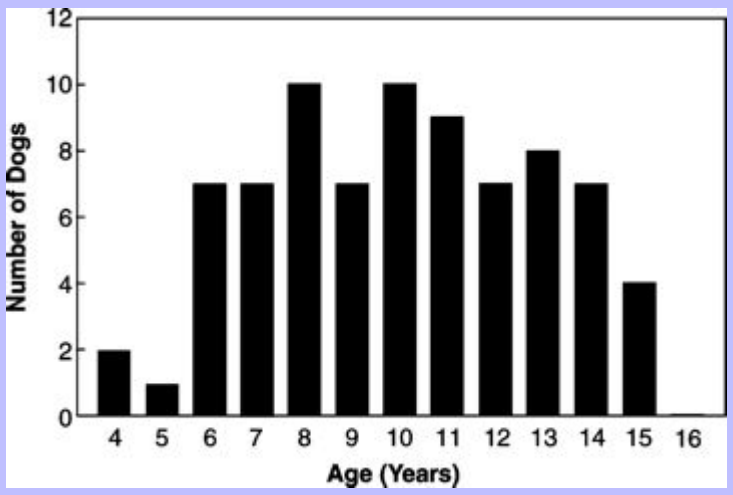

Table • 237-1 Breed Distribution of 187 Dogs with Primary Hyperparathyroidism

BREED	NUMBER OF DOGS	PERCENT OF DOGS
Keeshond	48	26%
Labrador retriever	18	10%
Cocker spaniel	14	7%
German shepherd dog	14	7%
Golden retriever	12	6%
Springer spaniel	9	5%
Standard poodle	8	4%
Shih Tzu	8	4%
Australian shepherd	7	4%
Rhodesian ridgeback	6	3%
Doberman pinscher	6	3%

237.1.3.3 Hereditary Disease

Hereditary neonatal PHPTH was reported in two German shepherd dogs.[8] The incidence of this syndrome in puppies and young dogs must be quite rare because no other report of neonatal disease has appeared in the literature. Our series of dogs with PHPTH does not include any less than 4 years of age.

237.1.4 Anamnesis: Clinical Signs

237.1.4.1 General

Clinical signs due solely to hypercalcemia, when observed by an owner, are mild in most dogs.[9] The only condition that has hypercalcemia as the sole problem is PHPTH. The most common signs associated with PHPTH include polyuria, polydipsia, decreases in appetite, decreases in body weight, decreased activity (muscle weakness?), and signs related to stones or infection within the urinary tract. Other signs reported secondary to hypercalcemia include the gastrointestinal (GI) signs of anorexia, vomiting, constipation, and, rarely, pancreatitis. Signs associated with the central nervous system (CNS) include mental dullness, obtundation, and even coma. One dog with PHPTH had ataxia and circling that resolved after resolution of the PHPTH. Again, clinical signs in dogs with PHPTH are almost always mild or not noticed. When a dog with hypercalcemia has worrisome signs, it almost always has a disease other than PHPTH. These worrisome signs therefore are almost always associated with the underlying cause for the hypercalcemia (e.g., cancer, renal failure, hypoadrenocorticism, toxin).

The mildest form of PHPTH may not be associated with any signs, and the hypercalcemia is identified serendipitously only after a standard biochemical panel has been obtained and reviewed. This is certainly true in humans, in whom *occult* primary hyperparathyroidism is more prevalent than the symptomatic form of the disorder.[10–13] When clinical signs in dogs do develop, they initially tend to be mild, insidious, and nonspecific. Most owners are unaware of specific clinical signs. It is not until their pet has been treated for PHPTH that owners, retrospectively, realize that their dog had signs. It is this concept that resulted in an editorial suggesting that all people with PHPTH be treated, because they may appreciate their illness that 1509
they have been ill until their disease has been resolved.[14] In our series of dogs with PHPTH, 35% had 1510
clinical signs related to PHPTH for more than 6 months and *all*, either retrospectively or prospectively, had signs for at least 1 month (Table 237-2). The clinical signs attributable to PHPTH and hypercalcemia usually involve one, two, or all three of these organ systems: renal, GI, or neuromuscular (Table 237-3).

Table • 237-2 Duration of Clinical Signs in 168 Dogs with Naturally Occurring Primary Hyperparathyroidism

DURATION (MONTHS)	PERCENT OF DOGS
<1	19%
1–3	20%
3–6	19%
6–12	24%
>12	18%

237.1.4.2 Renal: Kidneys, Bladder, and Urethra

237.1.4.2.1 Polydipsia, polyuria, or both

The most common clinical signs in dogs with PHPTH (152 of 187 dogs; 81%) are polyuria, polydipsia, and urinary incontinence (see Table 237-3). These signs are a result of impaired renal tubular response to ADH and impaired renal tubular resorption of sodium and chloride. Together, these alterations account for a significant increase in urine volume and are a direct result of hypercalcemia. This acquired and

reversible form of nephrogenic diabetes insipidus causes the production of relatively dilute, solute-free urine. Compensatory polydipsia develops to maintain normovolemia. Surprisingly, the polydipsia and polyuria either are not observed or are thought to be mild by most owners but are obvious on review of randomly obtained urine specific gravities (USGs). These specific gravities were much more dilute than would have been expected from owner comments. Of 187 dogs with PHPTH, 46 (24%) had USGs of 1.001 to 1.007; 69 dogs (38%) had USGs that were in the isosthenuric range of 1.008 to 1.012; 60 dogs (32%) had USGs of 1.013 to 1.020; only eight had values of 1.021 to 1.030 and 4 greater than 1.030. Thus 94% of dogs with PHPTH had USGs less than or equal to 1.020 (Table 237-4).

Table • 237-3 Frequency of Clinical Signs Reported in 168 Dogs with Naturally Occurring Primary Hyperparathyroidism

SIGN	PERCENT OF DOGS
Polyuria/polydipsia (PU/PD)	81%
Listlessness	53%
Incontinence	47%
Weakness, exercise intolerance	47%
Inappetence	37%
Urinary tract signs (straining, blood, frequency)	29%
Muscle wasting	17%
Vomiting	12%
Shivering	10%
Constipation	6%
Stiff gait	5%

Table • 237-4 Serum BUN, Creatinine, and Phosphate Concentrations and Urine Specific Gravities at the Time of Primary Hyperparathyroidism (PHPTH) Diagnosis in 187 Dogs*

	BUN (mg/dL)			SERUM CREATININE (mg/dL)			SERUM PHOSPHATE (mg/dL)			URINE SPECIFIC GRAVITY (USG)		
Reference range	18–28			0.5–1.6			3.0–6.2			—		
Mean (PHPTH dogs)	17.1			1.0			2.8			1.011		
Range (PHPTH dogs)	4–92			0.3–4.1			1.1–6.9			1.002–1.039		
Breakdown of individual results	Values	# Dogs	% Dogs	Values	# Dogs	% Dogs	Values	# Dogs	% Dogs	Values	# Dogs	% Dogs
	≤10	9	5	≤.5	2	1	<2	20	11	≤1.007	46	24
	11–17	112	60	0.6–0.9	84	45	2.0–2.9	99	53	1.008–1.012	69	37
	18–22	39	21	1.0–1.6	96	51	3.0–3.9	50	27	1.013–1.020	60	32
	23–28	18	10	1.7–2.0	3	2	4.0–4.9	12	6	1.021–1.030	8	4
	29–47	8	4	2.0–3.0	1	0.5	5.0–6.2	5	3	1.031–1.039	4	2
	>47	1	—	>3.0	1	0.5	>6.2	1	—			

* Reference range and mean values from the PHPTH dogs and arbitrary data listed.

237.1.4.2.2 Urinary tract calculi or infection

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Another of the more common causes for owner concern in dogs with PHPTH was observation of clinical signs consistent with urinary tract infection, calculi, or both. These signs included frequency, urgency, incontinence, hematuria, stranguria, or apparent urinary obstruction. At some time in the year preceding diagnosis, 123 of 168 owners (73%) had seen at least one of these clinical signs in their dogs. Sixty-one of 187 (33%) PHPTH dogs had uroliths, and 46 dogs (24%) had a urinary tract infection at the time of diagnosis.

237.1.4.3 Listlessness, Depression, and Decreased Activity

Listlessness or decreases in activity were observed in 99 (53%) of 187 dogs with PHPTH. Increased serum calcium concentrations depress the excitability of central and peripheral nervous tissue, which may be responsible for this clinical manifestation. Alternatively, these clinical signs may be a reflection of muscle weakness. Humans with this disorder may exhibit nonspecific neurologic abnormalities that include impaired mentation, mental depression, hypoactive deep tendon reflexes, and loss of pain perception.[13]

237.1.4.4 Weakness and Muscle Wasting

Weakness or exercise intolerance was observed in 88 (47%) of 187 dogs with PHPTH. Increased serum calcium concentrations decrease cell membrane permeability in nervous and muscular tissue. In addition, skeletal muscle weakness, primarily of the proximal muscle groups, may result from a primary neuropathy that ultimately causes muscle atrophy. Muscle wasting and weight loss were observed in 32 (17%) of the 187 dogs.

237.1.4.5 Inappetence

Owners observed some degree of reduced appetite in 69 (37%) of 187 dogs with PHPTH. This problem probably developed as a result of hypercalcemia-induced decreased excitability of GI smooth muscle or from direct effects on the CNS. Gastric ulcers, noted in some hypercalcemic people, has not been observed in dogs with PHPTH. Only one dog had concurrent pancreatitis. One common assumption is that hypercalcemia would induce secondary renal failure and tertiary loss of appetite. However, this is quite uncommon.

237.1.4.6 Shivering, Twitching, and Seizures

Shivering and muscle twitching have been observed in hypercalcemic dogs, and seizure activity has been reported in a dog with PHPTH.[15] These signs might result from cerebral microthrombi, vasospasm, or other conditions.

237.1.5 Physical Examination

A thorough physical examination is imperative in any animal with documented hypercalcemia. Physical examinations are usually unremarkable in dogs with PHPTH. When abnormalities exist, they are typically related to the presence of uroliths. Other abnormalities (weakness, muscle atrophy) are usually subtle or

nonspecific. Although parathyroid gland tumors are not palpable dogs with PHPTH, tumors have been palpable in four of ten cats with this condition. The most common cause of hypercalcemia in dogs is hypercalcemia of malignancy (Box 237-1). Lymphosarcoma, apocrine gland carcinoma of the anal sac, mammary gland adenocarcinoma, vaginal sarcoma, and multiple myeloma are among cancers capable of causing hypercalcemia that may be identified on examination. The diagnostic approach to a dog with confirmed hypercalcemia is to rule out the presence of malignancy before pursuing the diagnosis of PHPTH (see Figure 237-2). Non-neoplastic causes of hypercalcemia may be suspected after a thorough physical examination. For example, in renal failure, the kidneys may be palpably abnormal. Dogs with Addison's disease may have bradycardia, weak femoral pulses, melena, or a bloody rectal discharge.

237.1.6 Clinical Pathology: Hemogram, Serum Biochemical Profile, and Urinalysis

No typical hemogram abnormalities have been identified in dogs with PHPTH.

237.1.6.1 Serum Total Calcium Concentration

237.1.6.1.1 Results in dogs and humans

Hypercalcemia is the hallmark abnormality of PHPTH (Figure 237-3). The mean serum calcium concentration in 187 dogs with PHPTH was 15.3 mg/dL, with a range of 12.1 to 23.0 mg/dL (Table 237-5). This mean value could be arbitrarily inflated because evaluation of hypercalcemia is limited to those animals with serum calcium concentrations greater than 12.0 mg/dL (the upper reference range limit is 11.7 mg/dL). In most dogs, hypercalcemia was initially identified by a referring veterinarian on at least two occasions and then rechecked several times after referral. Of PHPTH dogs, 102 of 187 (55%) had an initial total serum calcium concentration of 12 to 14 mg/dL; 58 (31%) had an initial concentration of 14 to 16 mg/dL; 18 (9%) had an initial concentration of 16 to 18 mg/dL; and nine (5%) had an initial concentration of greater than 18 mg/dL (range of 18 to 23 mg/dL). Of these latter nine dogs with severe hypercalcemia, it is of interest to mention that their mean blood urea nitrogen (BUN) concentration was 22 mg/dL, with only one dog having a BUN above the reference range limit of 28 mg/dL.

Although it is assumed that untreated PHPTH will result in progressively increasing serum calcium concentrations, this has not been the experience in people. A group of 60 “asymptomatic” PHPTH people was not treated for 10 years. Their mean total serum calcium concentration, at the time of diagnosis, was 10.5 mg/dL (reference range 8.4 to 10.2 mg/dL), 5 years later it was 10.6, and a total of 10 years after diagnosis it was 10.3 mg/dL.[13] However, eight developed uroliths during the decade, leaving 52 who remained asymptomatic. Our experience with dogs suggest that hypercalcemia associated with PHPTH remains static or slowly increases with time.

237.1.6.1.2 Factors affecting serum calcium concentration

Marked lipemia can falsely increase total calcium values determined by some automated analyzers. Hemoconcentration (dehydration) can cause mild hypercalcemia (typically < 13 mg/dL). Hemolysis can also falsely increase the total serum calcium concentration measured with an automated analyzer. Young animals may have mild increases in serum calcium concentration, and postprandial samples may yield false increases. Excess use of oral phosphate binders may cause the serum calcium concentration to increase. Ethylenediamine tetra-acetic acid (EDTA) increases calcium values determined by atomic absorption spectrophotometry and decreases results obtained with other methods. Collecting and storing

samples in glassware or plastic containers that have been washed with detergents or exposed to chalk may increase calcium results and also cause spurious values for other electrolytes. Acidosis may decrease plasma protein-binding affinity for calcium and increase ionic calcium concentrations, creating mild physiologic hypercalcemia.

237.1.6.1.3 Plasma protein concentrations

Calcium in plasma or serum exists in three forms or fractions: ionized (free calcium), complexed or chelated (bound to phosphate, bicarbonate, sulfate, citrate, and lactate), and protein bound. In clinically normal dogs, protein-bound, complexed, and ionized calcium account for approximately 34%, 10%, and 56% of the total serum calcium, respectively.[16,17] Laboratories generally measure these components together and report them as a *total* calcium value. Ionized calcium is the biologically active component, and the protein-bound calcium serves as a "reservoir" or storage pool for the ionized fraction. However, changes in serum concentration of albumin and globulins may alter the measured *total* serum calcium concentration without altering ionized calcium levels. Despite an alteration in the total amount of plasma calcium resulting from hyperproteinemia or hypoproteinemia, the biologically active *ionized* calcium concentration usually remains within reference limits.

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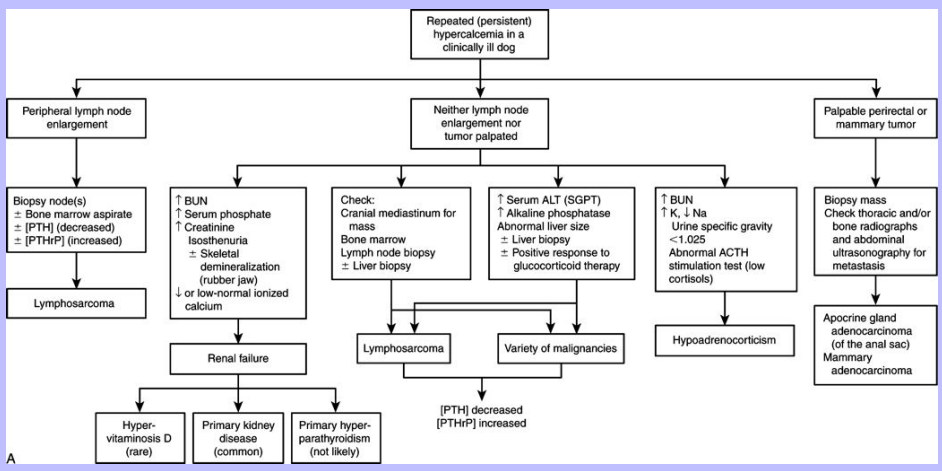
Figure 237-2 **A,** Algorithm for evaluating an ill hypercalcemic dog. **B,** Algorithm for evaluating a dog with hypercalcemia but without serious or worrisome clinical signs. (From Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, 3rd ed. Philadelphia, WB Saunders Co, 2004.)



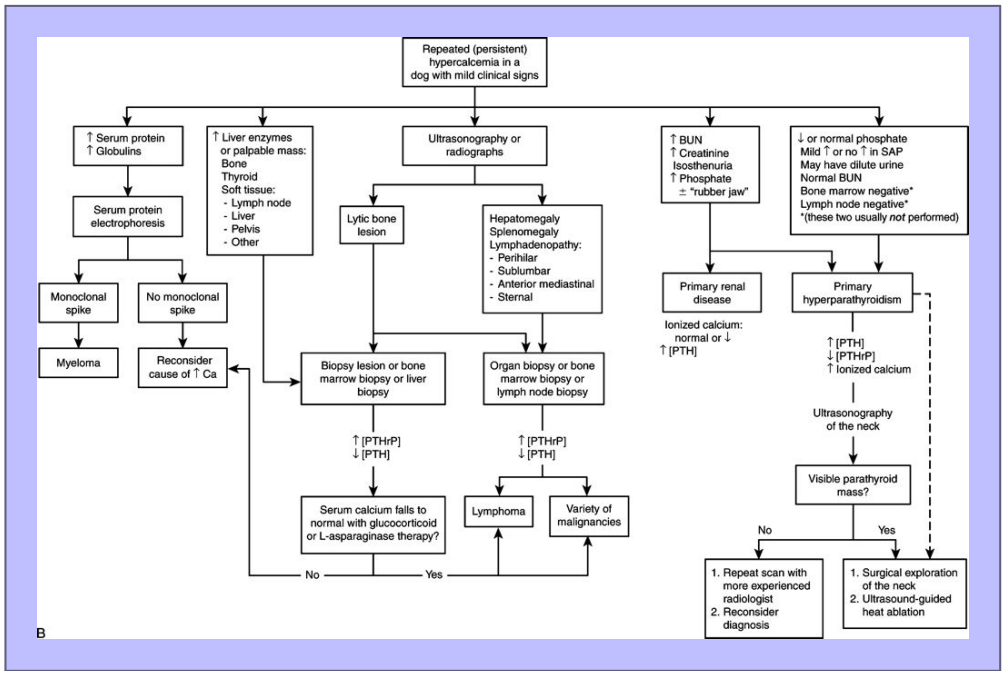
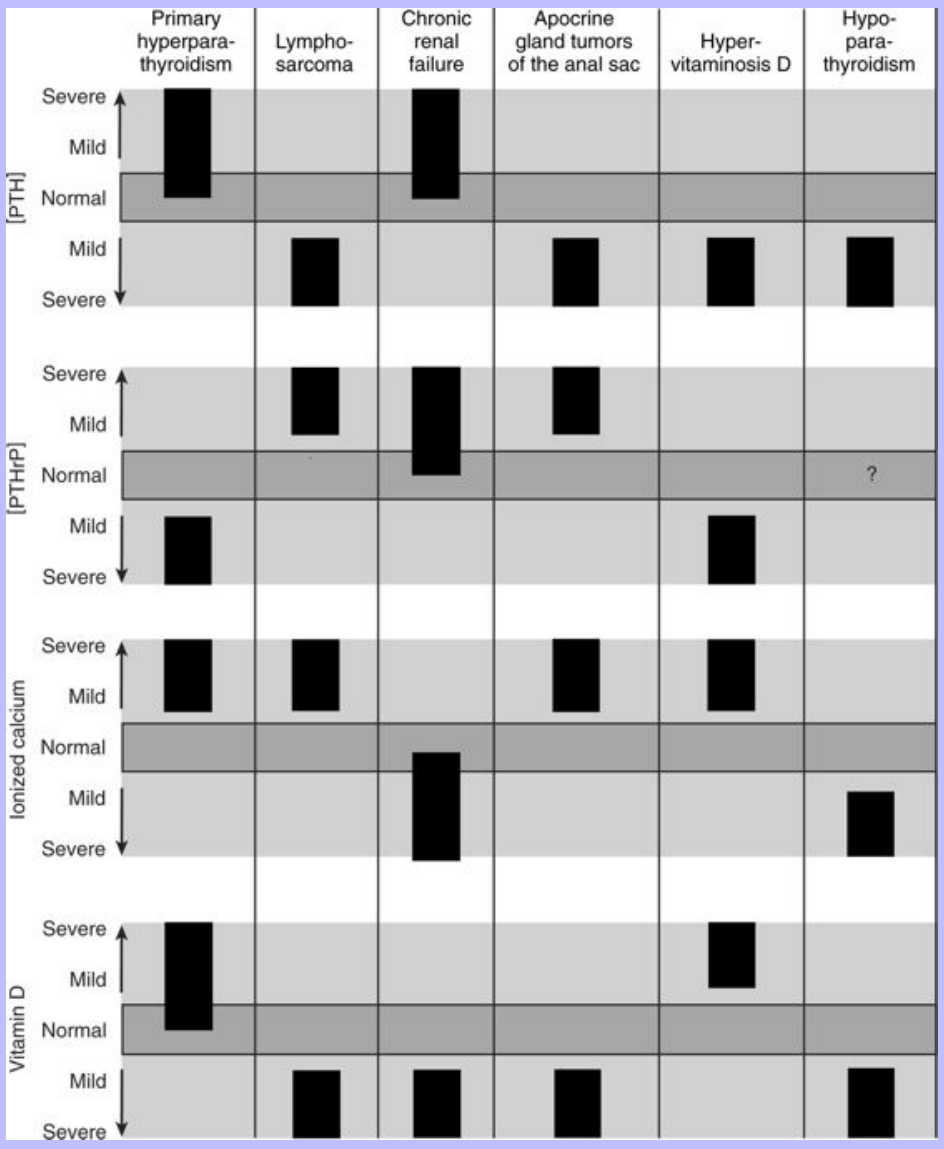

Repeated (persistent) hypercalcemia in a dog with mild clinical signs
↑ Serum protein
↑ Globulins
Serum protein electrophoresis
Monoclonal spike
No monoclonal spike
Myeloma
Reconsider cause of ↑ Ca
↑ Liver enzymes or palpable mass:
Bone
Thyroid
Soft tissue:
- Lymph node
- Liver
- Pelvis
- Other
Ultrasonography or radiographs
Lytic bone lesion
Hepatomegaly
Splenomegaly
Lymphadenopathy:
- Perihilar
- Sublumbar
- Anterior mediastinal
- Sternal
Biopsy lesion or bone marrow biopsy or liver biopsy
Organ biopsy or bone marrow biopsy or lymph node biopsy
↑ [PTHrP]
↓ [PTH]
↑ [PTHrP]
↓ [PTH]
Serum calcium falls to normal with glucocorticoid or L-asparaginase therapy?
Lymphoma
Variety of malignancies
No
Yes
↑ BUN
↑ Creatinine
Isosthenuria
↑ Phosphate
± "rubber jaw"
↓ or normal phosphate
Mild ↑ or no ↑ in SAP
May have dilute urine
Normal BUN
Bone marrow negative*
Lymph node negative*
*(these two usually not performed)
Primary renal disease
Ionized calcium: normal or ↓
↑ [PTH]
Primary hyperparathyroidism
↑ [PTH]
↓ [PTHrP]
↑ Ionized calcium
Ultrasonography of the neck
Visible parathyroid mass?
No
Yes
1. Repeat scan with more experienced radiologist
2. Reconsider diagnosis
1. Surgical exploration of the neck
2. Ultrasound-guided heat ablation
B

Figure 237-3 Graph showing the serum parathyroid hormone (PTH), parathyroid hormone-related peptide (PTHrP), ionized calcium, and vitamin D concentrations in the most common causes for hypercalcemia of dogs. (From Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, 3rd ed. Philadelphia, WB Saunders Co, 2004.)



Two formulas were developed for use in dogs to account for changes in the reported serum calcium value attributed to changes in serum protein values.[18] The formulas were of significant value prior to routine availability of ionized calcium assays. These formulas are:

$$\text{Corrected Total Ca (mg/dL)} = \text{Measured Total Ca (mg/dL)} - \text{albumin (g/dL)} + 3.5$$

or

$$\text{Corrected total Ca (mg/dL)} = \text{Measured total Ca (mg/dL)} - [0.4 \times \text{total protein (g/dL)}] + 3.3$$

Hypoalbuminemia is a common explanation for apparent hypocalcemia. However, this "hypocalcemia" usually causes no clinical signs and is associated with only mild changes from reference ranges. Although correction to normal limits implies that the ionized fraction is normal, the ionized fraction may yet be low. These formulas, developed more than 2 decades ago, were derived from serum albumin concentration results obtained with analytical methods no longer used by modern automated analyzers. At the time, a positive correlation was noted, but only 33% of the variability in serum total calcium concentration could be attributed to serum albumin concentration, and only 17% of the variability could be attributed to serum total protein. There was no association in cats between serum total protein and serum calcium concentrations, and only 18% of the variability in total calcium concentration could be attributed to albumin concentration.[19] In another study, only 17% and 29% of the variability in total serum calcium concentration in dogs and cats, respectively, could be attributed to serum albumin concentration.[20] For these reasons, use of these correction formulas are not recommended.[21]

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Table • 237-5 Serum Total (187 Dogs) and Ionized (136 Dogs) Calcium Concentrations, Serum Parathyroid Hormone (PTH) Concentrations (162 Dogs), and Ultrasonographically Identified Parathyroid Masses (98 Dogs, 11 of 98 had Two Masses Each) in Dogs With Primary Hyperparathyroidism

	TOTAL CALCIUM (mg/dL)			IONIZED CALCIUM (mmol/L)			PTH (pmol/L)			ULTRASOUND MASS SIZE (mm)		
Reference range	9.6–11.7			1.12–1.42			2–13			<4		
Mean (PHPTH dogs)	14.3			1.86			11.9			7		
Range (PHPTH dogs)	12.1–23.0			1.22–2.29			3.7–12.1			3–23		
Breakdown of individual results	Values	# Dogs	% Dogs	Values	# Dogs	% Dogs	Values	# Dogs	% Dogs	Size	# Masses	% Masses
	12–14	102	55	1.22–1.42	9	7	3.7–7.9	63	39	3–6	65	60
	14.1–16	5S	31	1.43–1.65	37	27	8.0–13.0	44	27	7–10	29	27
	16.1–18	18	9	1.66–190	64	47	13.1–20.0	25	15	11–l5	9	8
	≥18.1	9	5	≥1.91	26	19	≥20.1	30	19	>15	6	5

237.1.6.2 Serum Ionized Calcium Concentration

The ionized fraction of total circulating calcium concentration is the biologically active form. This information (together with the increasing availability of valid assays for ionized calcium and realization that dogs with chronic renal failure tend to have normal to low ionized concentrations versus the increased concentrations in other hypercalcemic conditions) has created a growing interest in results of this parameter in hyper- and hypocalcemic dogs. The mean ionized calcium concentration on initial blood samples in 136 dogs with PHPTH was 1.86 mmol/L, with a range of 1.22 to 2.29 mmol/L (reference range 1.12 to 1.42 mmol/L; see Table 237-5). Nine of the 136 dogs (7%) had a serum ionized calcium concentration within the referee range; 37 (27%) had results of 1.43 to 1.65 mmol/L; 64 (47%) had concentrations of 1.66 to 1.9 mmol/L, and 26 (19%) had concentrations greater than 1.9 mmol/L. In general, there was good correlation between serum total and ionized calcium results. However, no dog with PHPTH had a total calcium concentration within the reference range, whereas 7% had ionized calciums within the reference range. It is suspected that these ionized calcium concentrations within the reference range are the result of external (in vitro) factors (aerobic collection, pH).

237.1.6.3 Serum Phosphorus Concentration

Low or low-normal serum phosphorus concentrations (< 4.0 mg/dL) are typical of PHPTH (see Figure 237-3). Hypophosphatemia is the result of PTH-induced inhibition of renal tubular phosphorus resorption, resulting in excessive urinary loss. In 187 dogs with PHPTH, the mean serum phosphorus concentration was 2.8 mg/dL (< the lower limit of the reference range; 3.0 to 6.2 mg/dL), with a range of 1.5 to 6.8 mg/dL (see Table 237-4). Twenty of 187 dogs (11%) had serum phosphate concentrations less than 2.0 mg/dL; 99 (53%) had results of 2.0 to 2.9 mg/dL; 50 (27%) had results in the low normal range of 3.0 to 3.9 mg/dL; 12 (6%) had values in the mid-normal range of 4.0 to 4.9; 4 (3%) had values 5.0 mg/dL and only one of those four dogs had a serum phosphate concentration above reference limits (6.8 mg/dL). As a point of interest, nine of the 187 dogs had BUN values above the reference limit of 28 mg/dL. Of those nine dogs, eight had serum phosphate concentrations within the reference range.

The serum phosphorus concentration should always be evaluated relative to the serum calcium concentration and renal function. Hypophosphatemia, when dietary phosphate is adequate and when oral phosphate-binding agents are not being given, is consistent with either PHPTH or hypercalcemia of malignancy (see Figure 237-3). Other causes for hypophosphatemia are less common (Box 237-2). Hyperphosphatemia in the absence of azotemia suggests a nonparathyroid cause for hypercalcemia. When both hyperphosphatemia and azotemia are present, the clinician must rely on the history, physical examination, and other diagnostic tests to determine if the primary problem is hypercalcemia with secondary renal failure (rare) or renal failure with secondary hypercalcemia (common). Determination of the serum ionized calcium concentration can be of value. Dogs with renal failure and increases in total serum calcium concentration usually have ionized calcium concentrations that are normal or mildly decreased, dogs with PHPTH have increases in both fractions.

237.1.6.4 Blood Urea Nitrogen and Serum Creatinine Concentration

BUN (mean: 17 mg/dL) and serum creatinine concentrations (mean: 1.0 mg/dL) are usually within reference limits in dogs with PHPTH (see Table 237-4). Nine dogs (5%) had BUN concentrations less than 10 mg/dL; 112 (60%) had values of 10 to 17 mg/dL; 39 (21%) were 18 to 22 mg/dL; 18 (10%) were 23 to 28 mg/dL; 8 (4%) were 29 to 47 mg/dL, and one dog had a value of 92 mg/dL. Four of the nine dogs with

an abnormal BUN had a serum creatinine concentration within the reference range. The two highest serum creatinine concentrations were 2.3 and 4.1, respectively. This is most impressive when considering the mean age of these dogs (11.2 years). The literature strongly suggests that hypercalcemia, especially when chronic, may damage kidneys. However, it would appear that dogs with PHPTH are protected from renal damage, whether this protective effect is due to the low calcium × phosphate product or some other factor.

237.1.6.5 ## Urinalysis

The mean USG in 187 dogs with PHPTH was 1.011. Forty-six dogs (24%) had a USG on initial evaluation less than 1.008; 69 (38%) had specific gravities of 1.008 to 1.012; 60 (32%) had values of 1.013 to 1.020; eight (4%) had results of 1.021 to 1.030; and four had concentrations greater than 1.030 (see Table 237-4). Hypercalcemia interferes with ADH action and thereby causes a reversible form of nephrogenic diabetes insipidus. Isosthenuria (or hyposthenuria) may develop from *any* cause of hypercalcemia. Thus the combination of hypercalcemia and dilute urine is considered a "cause-and-effect" phenomenon but is not specific.

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237.1.6.5.1 ### Box • 237-2 Potential Causes for Hypophosphatemia

237.1.6.5.1.1 #### Decreased Intestinal Absorption

Decreased dietary intake

Malabsorption/steatorrhea

Vomiting/diarrhea

Phosphate-binding antacids

Vitamin D deficiency

237.1.6.5.1.2 #### Increased Urinary Excretion

Primary hyperparathyroidism

Diabetes mellitus ± ketoacidosis

Hyperadrenocorticism (naturally occurring/iatrogenic)

Fanconi's syndrome (renal tubular defects)

Diuretic or bicarbonate administration

Hypothermia recovery

Hyperaldosteronism

Aggressive parenteral fluid administration

Hypercalcemia of malignancy (early stages)

237.1.6.5.1.3 Transcellular Shifts

Insulin administration

Parenteral glucose administration

Hyperalimentation

Respiratory alkalosis

237.1.6.6 Urine Sediment

Hematuria, pyuria, bacteriuria, and crystalluria are identified frequently on urine sediment examination from dogs with PHPTH. Fifty-nine of 187 PHPTH dogs (31%) either had a history of uroliths removed by referring veterinarians within the 12 months preceding examination or were identified as having uroliths with radiographs or ultrasonography at the time of initial evaluation at our hospital. Urinary tract infection had been present or was present on initial examination at the author's hospital in 46 of 187 dogs with PHPTH (24%).

237.1.7 Electrocardiography

Experimentally induced hypercalcemia may increase myocardial contractility, shorten mechanical ventricular systole, and decrease myocardial automaticity. Potential electrocardiographic changes caused by hypercalcemia include a prolongation of the P-R interval and a shortening of the Q-T interval due to a shortened S-T segment. Theoretically, decreases in myocardial conduction velocity and shortened refractory periods could predispose the heart to arrhythmias. However, dogs with PHPTH rarely have abnormalities on electrocardiogram.

237.1.8 Radiology

237.1.8.1 Thoracic Radiographs

The major purpose of evaluating radiographs in the hypercalcemic dog or cat is to identify abnormalities that would help establish a cause. The anterior mediastinum, perihilar, and sternal lymph nodes should be evaluated for a mass or lymphadenopathy. Dogs with hypercalcemia secondary to lymphosarcoma may have a mediastinal mass. The ribs, vertebrae, and any long bones included in the film can be evaluated for osteolytic areas due to myeloma or other metastatic tumors. Lung fields should be assessed for possible masses that might represent primary or metastatic lesions.

237.1.8.2 Abdomen and Skeleton

The sublumbar area and mesenteric lymph nodes can be evaluated for enlargements that would support metastatic apocrine gland carcinomas of the anal sac or lymphoma. The liver and spleen can be evaluated for enlargement or irregularities associated with lymphoma. Other than calculi within the urinary system, radiographic abnormalities are not associated with PHPTH.

237.1.9 Ultrasonography

237.1.9.1 Neck

With continuing improvement in equipment and experience, normal parathyroid glands are now routinely visualized with ultrasonography in dogs.[22] Parathyroid nodules from dogs with PHPTH have been measured to be as small as 2 mm in diameter and as large as 23 mm in diameter. Most adenomas are 4 to 9 mm in diameter and are easily visualized.[23,24] One recent study demonstrated a statistically significant difference in lesion size, comparing hyperplastic parathyroid glands (2 to 6 mm, mean 2.9 mm) to parathyroid adenomas and adenocarcinomas (4 to 20 mm, mean 7.5 mm).[25]

Radiologists have evaluated the cervical area of 98 dogs in our series with confirmed PHPTH. Virtually all these dogs had one or more parathyroid gland (masses) visualized. Eleven of the 98 dogs had two parathyroid nodules each. Thus 109 nodules were identified in the 98 dogs. Sixty-five of 109 parathyroid masses (60%) were 3 to 6 mm in diameter; 29 (27%) were 7 to 10 mm in diameter; nine (8%) were 11 to 15 mm in diameter; and six (5%) were 16 to 23 mm in diameter (see Table 237-5; Figure 237-4). No dog had more than two parathyroid masses identified. Parathyroid masses are usually round or oval, well marginated, and hypoechoic to anechoic compared with surrounding thyroid gland parenchyma (Figure 237-4). However, not every parathyroid nodule is obvious. It is occasionally difficult to distinguish large parathyroid masses from thyroid. Another important issue that must be stressed, is the subjective nature of this tool. In one of our studies, experienced radiologists correctly identified a solitary parathyroid mass in 11 of 11 dogs and two parathyroid masses in another. However, less experienced radiologists identified a parathyroid mass in only four of seven dogs.[26]

The accuracy of cervical ultrasonography in dogs with PHPTH has been similar to that reported in humans: 90% to 95% of parathyroid adenomas and a smaller percentage of hyperplastic parathyroid glands can be visualized.[27] Experienced radiologists identify parathyroid masses with ultrasonography more consistently than surgeons during surgery because of the occasional parathyroid mass located within a thyroid lobe that is neither visible nor palpable to the surgeon. Therefore cervical ultrasonography is potentially an extremely valuable diagnostic aid.

237.1.9.2 Abdomen

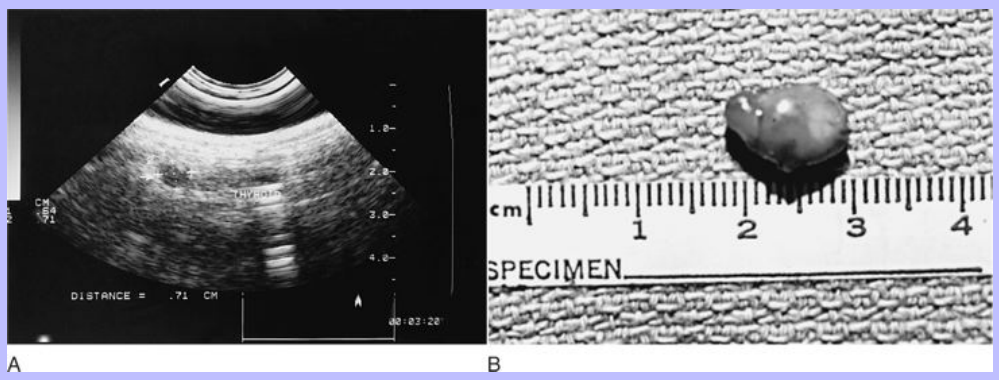
Ultrasonic scanning of the abdomen should also be a routine component of the diagnostic evaluation of hypercalcemic dogs and cats. If the liver, spleen, mesenteric lymph nodes, or other abdominal structures appear abnormal, percutaneous biopsy of that structure should be strongly considered. Ultrasonography has been an excellent tool for identifying uroliths as well. Most are seen within the bladder, but renal, ureter, and urethral stones have also been visualized.

237.1.10 Assays: PTH, PTHrP, Vitamin D (Calcitriol)

Dogs with PHPTH usually have serum PTH concentrations that range from within the reference range to being exceedingly increased (see Table 237-5 and Figure 237-3; Figure 237-5). In addition, serum PTHrP concentrations are usually undetectable, whereas calcitriol concentrations (not usually tested) would be normal to increased.[28] Serum PTH concentrations must always be evaluated in the context of the serum calcium

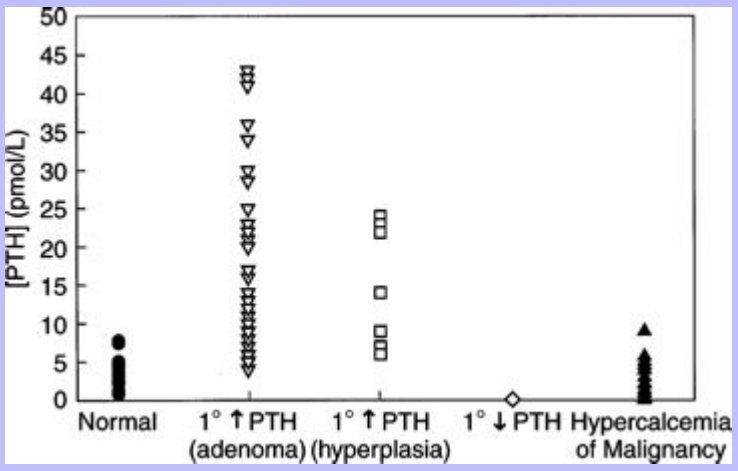
concentration. In healthy animals, as the serum calcium concentration increases, the serum PTH concentration decreases. Relative to their hypercalcemia (using total or, preferably, ionized calcium), virtually all dogs and cats with PHPTH have excessive PTH secretion. In other words, serum PTH concentrations within the reference range should be considered "excessive" in a dog or cat with hypercalcemia. Such results are consistent with autonomous secretion of hormone.

Figure 237-4 **A,** Cervical ultrasonogram from a dog with a functional parathyroid adenoma. The reader should note the right thyroid lobe, in which a well-marginated, hypoechoic mass *(arrows)* is visible at the cranial pole of the thyroid. **B,** Solitary parathyroid adenoma removed from a dog with primary hyperparathyroidism. (Ultrasound courtesy of Dr. Tom Nyland and Dr. Eric Wisner, Davis, Calif.)



The "sandwich" (two-site immunoradiometric [IRMA] assay system) for measuring PTH is considered the most reliable assay system currently available for dogs. At least one serum PTH concentration was obtained from each of 162 dogs with PHPTH (see Table 237-5). Most laboratories have similar PTH reference ranges (2 to 13 pmol/L). The mean serum PTH concentration in these untreated dogs (11.9 pmol/L) was within the reference range, and 107 of the 162 results (66%) were within that reference range. Sixty-three dogs (39%) had serum PTH concentrations of 3.7 to 7.9 pmol/L; 44 dogs (27%) had values of 8 to 13 pmol/L; 25 dogs (15%) had results of 13.1 to 20 pmol/L; and 30 dogs (19%) had results greater than 20 pmol/L. The availability of both PTH and PTHrP assay results has improved clinicians' ability to identify the specific problem causing hypercalcemia in many dogs. These assays are accessible for practitioners.

Figure 237-5 Serum PTH concentrations for normal dogs and those with various disorders of calcium homeostasis. The reader should note that some overlap exists in test results. (From Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, 3rd ed. Philadelphia, WB Saunders Co, 2004.)



237.1.11 Radionuclide Scans

Radionuclide procedures have been used as an aid for detecting and localizing parathyroid adenomas in humans.[29] The most commonly used radionuclide imaging technique uses technetium-99m-sestamibi.[30,31] Two reports suggested that this procedure might be helpful in localizing parathyroid adenomas in dogs with PHPTH.[32,33] In a subsequent study, double-phase parathyroid scintigraphy was evaluated in a group of hypercalcemic dogs, and only one of 10 dogs with PHPTH had a scan that correlated with surgery. The poor sensitivity and specificity achieved with scintigraphy led the authors to conclude that use of this tool could not be recommended.[34]

237.1.12 Selective Venous Sampling

An attempt was made to localize autonomously functioning parathyroid masses using serum PTH assay results from each jugular vein. The hypothesis was that the vein draining the side of the autonomously functioning mass would have greater amounts of PTH. Blood samples were obtained from each jugular vein prior to surgery from dogs with PHPTH caused by a solitary functioning adenoma. Unfortunately, a gradient between samples was only identified in one of 11 dogs, and the conclusion was that selective venous sampling was not reliable.[26]

237.1.13 Diagnostic Approach to the Hypercalcemic Dog or Cat

237.1.13.1 General

The list of differential diagnoses for hypercalcemia is relatively short (see Table 237-1; Box 237-3), allowing a logical approach to identifying its cause. The most common cause in the dog and cat is *malignancy-associated hypercalcemia*. In an attempt to be practical, logical, and cost-effective, the diagnostic approach should first identify or rule out an underlying malignancy.[35] Only after testing has failed to identify a malignancy should PHPTH be considered.

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237.1.13.1.1 Box • 237-3 Differential Diagnosis for Humoral Hypercalcemia of Malignancy

237.1.13.1.1.1 Hematologic Cancers

Lymphosarcoma

Lymphocytic leukemia

Myeloproliferative disease

Myeloma

237.1.13.1.1.2 Solid Tumors with Bone Metastasis

Mammary adenocarcinoma

Nasal adenocarcinoma

Epithelial-derived tumors

Pancreatic adenocarcinoma

Lung carcinoma

237.1.13.1.1.3 Solid Tumors without Bone Metastasis

Apocrine gland adenocarcinoma of the anal sac

Interstitial cell tumor

Squamous cell carcinoma

Thyroid adenocarcinoma

Lung carcinoma

Pancreatic adenocarcinoma

Fibrosarcoma

237.1.13.2 Review the History and Physical Examination

237.1.13.2.1 First steps

The diagnostic approach to the hypercalcemic dog or cat should be relatively straightforward (see Figure 237-2, *A* and *B*). The first step should be to confirm the presence of hypercalcemia by resubmitting a *second* blood sample for calcium and phosphorus determination, although the second sample virtually always has the same result as the first. Whenever possible, veterinary practitioners would be well served to submit appropriate samples for serum ionized calcium concentration. Such results, if increased, confirm hypercalcemia. If the ionized calcium concentration in a dog with confirmed increases in serum total calcium, is within or below the reference range, chronic renal failure or laboratory error should be considered. Review of the signalment, thorough history, and physical examination often allows the clinician to identify the cause for hypercalcemia or at least develop a likely list of high-priority possibilities. Both the history and physical examination should be repeated after the serendipitous finding of hypercalcemia.

237.1.13.2.2 Signalment

Signalment (age, gender, breed) is emphasized, in part, because of the remarkable incidence of PHPTH in the Keeshond and in dogs that are 8 years of age or older. Renal failure can occur at any age, but certain breeds are predisposed to familial renal problems (Shih Tzu, Lhasa Apso, Doberman pinscher). Young dogs are more likely to suffer from renal failure, malignancy (lymphosarcoma), or hypoadrenocorticism (especially in the female), whereas apocrine gland carcinoma of the anal sac, and other malignancies occur in older dogs.

237.1.13.2.3 History

The owner should be questioned about the pet's diet, vitamin-mineral supplementation, and exposure to rat and mouse poisons or houseplants that contain vitamin D analogues. One can attempt to determine if the pet is in pain (lytic bone lesions). Answers to questions regarding the presence of polydipsia, polyuria, appetite, and activity may be important. Generally, the more ill the pet appears the less likely that it has PHPTH (and the more likely it has a malignancy, renal failure, vitamin D toxicosis, granulomatous disease, or hypoadrenocorticism).

237.1.13.2.4 Physical examination

After assessing hydration status and severity of illness, the physical examination should include careful palpation of peripheral lymph nodes (lymphoma) and the mammary glands (mammary cancer). A thorough rectal and perirectal examination is imperative in the identification of an apocrine gland carcinoma of the anal sac. A digital vaginal examination should also be performed (vaginal tumor). The clinician should gently palpate as much of the skeleton as possible, searching for an area of focal bone pain that could then be pursued with radiographs (multiple myeloma). The kidneys should be palpated in an attempt to identify irregularities.

237.1.13.3 Initial Data Base

237.1.13.3.1 Blood and urine

The initial data base should include a hemogram (complete blood count [CBC]), a serum biochemical profile, serum ionized calcium concentration, urinalysis, and thoracic radiographs. The abdomen should be evaluated with ultrasonography, radiography, or both. If the serum phosphorus concentration is normal or low, renal failure, vitamin D toxicosis, and hypoadrenocorticism are less likely (see Figure 237-2, *A* and *B*). The serum creatinine, sodium, potassium, and BUN concentrations are extremely valuable in this assessment as well. A sodium-to-potassium ratio less than 27:1 is consistent with, but not diagnostic of, adrenal insufficiency. An ACTH stimulation test should be performed if this disease is possible. Low, low-normal, or normal serum phosphate concentrations are consistent with PHPTH and malignancy-associated hypercalcemia. Striking increases in total protein concentrations, specifically due to a monoclonal spike, are classic for multiple myeloma.

237.1.13.3.2 Parathyroid versus primary renal disease

A diagnostic dilemma exists when hyperphosphatemia and hypercalcemia coexist with azotemia. The clinician must determine whether the hypercalcemia is the cause or the consequence of renal disease. Other abnormalities in the initial data base may support renal failure as the primary problem. These abnormalities include marked increases in serum phosphorus concentration, low-normal or low serum ionized calcium concentrations, nonregenerative anemia, proteinuria, and palpably or radiographically small and irregular kidneys. The serum ionized calcium in dogs with PHPTH is increased. If the hypercalcemia dissipates with aggressive fluid therapy and diuresis, PHPTH is less likely than primary renal failure or hypoadrenocorticism.

237.1.13.3.3 Radiography and ultrasonography

Radiography of the thorax and ultrasonography of the abdomen should be evaluated for soft tissue masses, soft tissue calcification, evidence of fungal disease, organomegaly, osteolysis, or osteoporosis. The goal is to identify an abnormal area that could be biopsied to provide a definitive explanation for hypercalcemia. An anterior mediastinal mass is demonstrable radiographically in as many as 40% of hypercalcemic dogs with lymphosarcoma.[36] If hepatomegaly or splenomegaly is identified, histology of a biopsy (obtained percutaneously) taken from either of these organs should be evaluated to help establish a diagnosis. Adenocarcinomas derived from the apocrine glands of the anal sac may appear radiographically as a mass in the pelvic canal. Sublumbar lymphadenopathy due to tumor metastasis is also common. Soft tissue calcification is most frequently observed with hypervitaminosis D or chronic renal failure, although mineralization can be seen with any hypercalcemic disorder in association with hyperphosphatemia and a calcium × phosphorus product greater than 60 to 80.

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Discrete lytic lesions in the vertebrae or long bones are suggestive of either myeloma or malignancy-associated hypercalcemia with bone metastasis. Radionuclide bone scans can be performed at specialty centers to identify bone lesions not detected with radiographs. Concurrent hyperproteinemia is supportive of myeloma. Solid tumors with metastasis to bone are more likely if lytic bone lesions and normoproteinemia (especially normal serum globulin concentrations) are present. A core biopsy of a lytic lesion may be necessary to establish a definitive diagnosis.

Ultrasonography of the cervical region has been reviewed. This tool is noninvasive and easily used. Identification of a solitary mass within or near one thyroid lobe supports the diagnosis of PHPTH, if the dog is not in renal failure.[22] This tool requires the 10-MHz transducer and, most importantly, the results are subjective.

237.1.13.4 Lymph Node and Bone Marrow Evaluations

If the initial data base has not established a diagnosis, the next diagnostic steps should include evaluation of lymph nodes, bone marrow, or both. Because lymphosarcoma is the most common neoplasm associated with hypercalcemia in the dog and cat, peripheral nodes should be palpated. Ideally, the largest lymph node (*not* the submandibular node) should be assessed for histologic evaluation. Needle aspirates for cytology are occasionally acceptable, but pathologists may be hesitant to make a definitive diagnosis based on cytology alone. If any abnormalities are found on cytologic evaluation of an aspirate, histologic evaluation of a large biopsy sample or lymph node excision should be obtained to establish or rule out the diagnosis. This step should be omitted in dogs that are relatively healthy, based on an index of suspicion against the diagnosis of lymphosarcoma.

A bone marrow aspirate should also be considered in the hypercalcemic pet because the lymphosarcoma may be associated only with invasion of the marrow by neoplastic cells.[37] As with the peripheral lymph node evaluation, presence of a normal bone marrow aspirate does not definitively rule out lymphosarcoma. We usually omit a bone marrow aspirate when a dog is clinically well and when its CBC is unremarkable.

237.1.13.5 Serum PTH and PTHrP Concentrations

Assay for these hormone concentrations can be quite helpful. Because the evaluation of hypercalcemic dogs tends to be logical, each step has the potential for ruling out causes. The diagnosis of PHPTH can be reached by simple exclusion. In other words, as all other differential diagnoses are eliminated, PHPTH may remain as the only reasonable diagnosis. Treatment of most of the dogs in our series for PHPTH was completed before the results of serum PTH concentrations were available.

237.1.14 Acute Medical Therapy for the Hypercalcemic Dog

237.1.14.1 Primary Hyperparathyroidism versus (PHPTH) Other Disorders

237.1.14.1.1 PHPTH

The primary mode of therapy for severe hypercalcemia should be aimed at resolving its underlying cause. Surgical excision of abnormal parathyroid tissue is the most common therapy for dogs and cats with PHPTH. In these animals, however, hypercalcemia is neither an acute problem nor is the calcium × phosphate product greater than 60 to 80. Therefore conditions developing secondary to hypercalcemia (other than uroliths) are not usually a concern in dogs with PHPTH.

237.1.14.1.2 Renal failure or vitamin D toxicosis

Severity of clinical signs and degree of damage to nephrons appears dependent, in part, on serum phosphorus concentrations via the calcium × phosphate product. Renal damage (nephrotoxicity) induced by metastatic mineralization is thought to correlate with serum Ca × PO_4 product greater than 60 to 80.

Thus hypercalcemia associated with PHPTH is less worrisome and dangerous than the hypercalcemia associated with renal failure or hypervitaminosis D. The latter two disorders are almost always accompanied by hyperphosphatemia, a problem that amplifies the potential of soft tissue calcification (see Table 237-6).

237.1.14.2 Indications

237.1.14.2.1 Source of illness versus need for treatment

Clinically, both to owners and veterinarians dogs with PHPTH appear relatively healthy. Further, despite having dramatic increases in serum calcium concentration (mean serum calcium concentrations > 14 mg/dL; see Table 237-5), dogs and cats with PHPTH are usually not in need of acute therapy because, in part, their calcium × phosphate products are not worrisome (see Table 237-6). In contrast, dogs with concurrent lymphosarcoma and hypercalcemia often exhibit extremely worrisome clinical signs that are caused by their malignancy rather than the hypercalcemia. Treatment for cancer often indirectly decreases serum calcium concentrations. Dogs that have mild hypercalcemia and renal failure or vitamin D toxicosis also usually have worrisome clinical signs and moderate to severe hyperphosphatemia. They are at risk for tissue mineralization and they benefit from treatment directed specifically at decreasing the calcium × phosphorus product. Dogs with apocrine gland carcinoma of the anal sac or those with “other” malignancies (e.g., multiple myeloma) also tend to be much more ill than dogs with PHPTH.

237.1.14.2.2 Indications for symptomatic treatment

Because of the deleterious effects of hypercalcemia on renal, cardiovascular, or neurologic function, it may become necessary to treat a dog or cat symptomatically in an attempt to lower the blood calcium concentration while completing tests to establish a diagnosis. The decision to implement symptomatic therapy should be based on the severity of the pet's clinical signs, the rapidity of progression of these signs, and the status of renal, cardiac, and neurologic function. *No specific serum calcium concentration exists above which therapy must be initiated.*

Table • 237-6 Typical Serum Calcium and Phosphate Concentrations for Various Conditions

	TYPICAL SERUM CALCIUM (MG/DL)	TYPICAL SERUM PHOSPHATE (MG/DL)	TYPICAL CALCIUM × PHOSPHATE PRODUCT*
Normal dog	10	4.5	45
Primary hyperparathyroidism	14.3	2.8	40
Lymphosarcoma	15	3.0	45
Apocrine cell carcinoma of the anal sac	15	3.0	45
Chronic renal failure	11.5	10	115
Vitamin D toxicosis	11.5	10	115

* Aggressive therapy is recommended when the product of these two electrolytes exceeds 60 to 80. For most conditions causing hypercalcemia, emergency therapy is not necessary to reduce the serum calcium concentration.

Therapy for hypercalcemia is indicated when dehydration, azotemia, cardiac arrhythmia, severe neurologic dysfunction, or weakness exists.[6,38] Death or encephalopathy directly attributable to hypercalcemia (except after ingestion of large amounts of rat poison containing vitamin D) is extremely uncommon. Therapy (intravenous fluids ± furosemide) may be indicated in a relatively stable dog or cat in which progressive metastatic calcification of soft tissues is suspected. Tissue mineralization can be assumed when the calcium × phosphorus product exceeds 60 to 80. With a product below 60, no urgent need exists to lower the serum calcium concentration, because the risk for soft tissue mineralization is not great.[39] Several methods have been suggested to control acute or severe hypercalcemia (Box 237-4 and Table 237-7). In dogs and cats, saline diuresis, diuretic therapy with furosemide or ethacrynic acid, and corticosteroids are the most commonly used modes of therapy. As a general rule, diuretic therapy and saline diuresis can be initiated without interfering with the diagnostic evaluation. Because the incidence of hypercalcemia associated with lymphosarcoma is great, glucocorticoids should not be administered unless a specific diagnosis has been confirmed.

237.1.14.3 Fluid Therapy

237.1.14.3.1 Correction of fluid deficits

The primary indication for fluid therapy is dehydration. Decreases in fluid intake due to nausea and vomiting, plus an inability to concentrate urine, are common causes for dehydration in hypercalcemic dogs and cats. Dehydration, in turn, impairs calcium excretion by reducing GFR and increasing renal tubular absorption of calcium.[40] Dehydration also causes hemoconcentration, hyperproteinemia, and further increases in total and ionized serum calcium concentrations. Correction of fluid deficits should reduce the severity of hypercalcemia, although it usually does not return serum calcium concentrations to normal except in dogs with hypoadrenocorticism or those that are not, in fact, hypercalcemic. In humans, a rapid fall of 2 to 3 mg/dL in total serum calcium concentration is typical after rehydration.[3]

237.1.14.3.1.1

Box • 237-4 General Treatment of Hypercalcemia

237.1.14.3.1.1.1

Definitive

Remove underlying cause

237.1.14.3.1.1.2

Supportive

Initial considerations

- Fluids (0.9% sodium chloride)
- Furosemide
- Sodium bicarbonate
- Glucocorticosteroids

Secondary considerations

- Bisphosphonates
- Calcitonin

Tertiary considerations

- Mithramycin
- Ethylenediamine tetra-acetic acid (EDTA)
- Peritoneal dialysis, homodialysis

Future considerations

- Calcium channel blockers
- Somatostatin congeners
- Calcium receptor agonists

Nonhypercalcemic calcitriol analogues

237.1.14.3.2 Saline diuresis

Once fluid deficits have been corrected, saline diuresis should promote continuing renal loss of calcium; an effective short-term therapy for any cause of hypercalcemia. Physiologic saline promotes calciuresis because the large amount of filtered sodium competes with calcium for renal tubular resorption.[40] Increased sodium excretion leads to increased calcium excretion. Normal saline given at two to three times the maintenance rate (120 to 180 mL/kg/day) is usually effective. Potassium supplementation is often necessary to prevent hypokalemia. The pet should also be monitored carefully to detect adverse effects (e.g., pulmonary edema) resulting from administration of large fluid volumes. Monitoring body weight, urine output, blood pressure, central venous pressure (CVP), and auscultation of the thorax are recommended.

237.1.14.4 Diuretic Therapy

The use of potent diuretics, in conjunction with saline diuresis, ensures maximal urinary sodium excretion and, in turn, calciuresis. Volume expansion must precede administration of furosemide. Furosemide enhances the calciuric effects of volume expansion by inhibiting calcium reabsorption in the thick ascending limb of the loop of Henle. Furosemide should also prevent severe volume overload.[6] Recommended protocols typically suggest a 5 mg/kg intravenous bolus followed by 2 to 4 mg/kg given twice a day or three times a day.[41] Thiazide diuretics should not be used because they decrease renal calcium excretion and may exacerbate hypercalcemia by enhancing distal tubular reabsorption.[6]

237.1.14.5 Glucocorticoids

The beneficial effects of glucocorticoids in the symptomatic management of hypercalcemia include reducing bone resorption of calcium, decreasing intestinal calcium absorption, and increasing renal calcium excretion. Glucocorticoids are cytotoxic to neoplastic lymphocytes and inhibit growth of neoplastic tissue, accounting for their beneficial effects in lymphoma and multiple myeloma. They counteract effects of vitamin D toxicosis or granulomatous diseases. In general, nonhematologic cancers do not respond to glucocorticoids nor do animals with PHPTH.[42] Administration of glucocorticoids should be delayed until a definitive diagnosis has been established. Lymphosarcoma is the most common cause of hypercalcemia in the dog, but the administration of glucocorticoids may interfere with subsequent ability to confirm this diagnosis. Prednisone or prednisolone (1 to 2 mg/kg twice a day) or dexamethasone (0.1 to 0.2 mg/kg twice a day) can be used in the management of hypercalcemia. These drugs can be given orally, subcutaneously, or intravenously.

237.1.14.6 Bisphosphonates

The bisphosphonates are compounds structurally related to pyrophosphate, a normal metabolic by-product. The chief property of these compounds is their inhibitory effect on osteoclast function and viability.[43] GI absorption is poor (< 10%), but intravenous administration has been effective in treating hypercalcemic humans.[6] Considering the early occurrence of bone resorption and bone loss in humans with multiple

myeloma, for example, the benefit of bisphosphonates are impressive, even in humans who have no osteolytic lesions at the start of therapy. These drugs have beneficial skeletal effects and also slow tumor growth by inhibiting the production by osteoblasts of interleukin-6 (IL-6), a growth factor essential to myeloma cells.[44] Three bisphosphonates (etidronate, clodronate, and pamidronate) are approved in western countries for treatment of hypercalcemia in humans. Availability of other potent bisphosphonates (aminohexane bisphosphonate, risedronate, and alendronate) and other inhibitors of bone resorption (gallium nitrate, paclitaxel) open new avenues for more efficient treatment of hypercalcemia and bone disease. Clodronate was used successfully for treatment of lymphoma-induced hypercalcemia in one dog and vitamin D toxicosis in one dog.[45] Pamidronate has been used successfully to reverse vitamin D–induced toxicosis in dogs.[46,47]

Table • 237-7 Specific Treatment of Hypercalcemia (Not Needed in Primary Hyperparathyroidism)

TREATMENT	DOSE	INDICATIONS	COMMENTS
Volume Expansion			
SQ saline (0.9%)*	75–100 mL/kg/day	Mild hypercalcemia	Contraindicated if peripheral edema is present.
IV saline (0.9%)*	100–125 mL/kg/day	Moderate to severe hypercalcemia	Contraindicated in congestive heart failure and hypertension.
Diuretics			
Furosemide	2–4 mg/kg bid to tid IV, SQ, P0	Moderate to severe hypercalcemia	Volume expansion is necessary before use of this drug.
Alkalinizing Agent			
Sodium bicarbonate	1 mEq/kg IV slow bolus; may continue at 0.3 × base deficit × wt in kg/day	Severe hypercalcemia	Requires close monitoring.
Glucocorticoids			
Prednisone	1–2.2 mg/kg bid P0, SQ, IV	Moderate to severe hypercalcemia	Use of these drugs before identification of cause may make definitive diagnosis difficult!
Dexamethasone	0.1–0.22 mg/kg bid, IV, SQ		
Bone Resorption Inhibitors			
Calcitonin	4–6 IU/kg SQ bid to tid	Hypervitaminosis D	Response may be short-lived. Vomiting may occur.
Bisphosphonates			
EHDP-Didronel	15 mg/kg q24h to bid	Moderate to severe hypercalcemia	All are expensive, and use in dogs is limited.
Clodronate	20–25 mg/kg in a 4-hr IV infusion		Clodronate is approved for use in humans in Europe; availability in United States may be limited.
Pamidronate	1.3 mg/kg in 150 mL 0.9% saline in a 2-hr IV infusion, can repeat in 1 week		
Mithramycin	25 µg/kg IV in 5% dextrose over 2–4 hr q2-4 wk	Severe hypercalcemia, refractory HHM	Limited use in dogs and cats. Nephrotoxicity, hepatoxicity, thrombocytopenia.
Miscellaneous			
Sodium EDTA	25–75 mg/kg/hr	Severe hypercalcemia	Nephrotoxicity.
Peritoneal dialysis	Low calcium dialysate	Severe hypercalcemia	Short duration of response. Use in hypercalcemia not reported.

HHM, Humoral hypercalcemia of malignancy.

* Potassium supplementation is necessary. Clinician should add 5 to 40 mEq KCl/L depending on serum potassium concentration.

237.1.14.7 Calcitonin

Calcitonin reduces osteoclast activity and the formation of new osteoclasts. It may be effective, at least temporarily, in decreasing serum calcium concentrations in those cases of hypercalcemia associated with

excessive osteoclastic activity.[40] In humans, calcitonin has not been uniformly effective in lowering serum calcium concentration, either because the mechanisms of hypercalcemia induced by the disease are nonresponsive to calcitonin or because patients become refractory to its effects. The drug has been described as "weak," short-acting, and having few side effects.[6,48,49]

Salmon calcitonin (Calcimar solution, USV Laboratories, Tarrytown, New York) is the most potent congener available. Reports in the veterinary literature support use of this drug for the treatment of cholecalciferol rodenticide intoxication. Several doses have been reported, but the number of dogs and cats in which the drug has been used is too small for recommendations regarding their effectiveness. Some reported doses in dogs include 4.5 U/kg subcutaneously every 8 hours; 8 U/kg subcutaneously every 24 hours; and 5 U/kg subcutaneously every 12 hours.[50,51] In cats, 4 U/kg intramuscularly every 12 hours was used successfully.[52]

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237.1.14.8 Plicamycin (Mithramycin)

Plicamycin (previously termed *mithramycin*) is a cytotoxic compound initially evaluated as a cancer chemotherapeutic agent. This agent is a potent inhibitor of RNA synthesis in osteoclasts and an effective treatment for hypercalcemia. Significant toxicity, including thrombocytopenia, hepatic necrosis, renal damage, and hypocalcemia has been caused by the drug. Clinically significant toxicity was not observed in normal dogs after two IV treatments. Shivering was noted during the infusion, and osteoclastic activity was reduced.[53,54] Two doses have been reported: 25 g/kg and 50 g/kg once or twice weekly, to control hypercalcemia.[55] Effects of this drug on serum total and ionized calcium concentrations were studied in nine dogs with hypercalcemia of malignancy, one dog with PHPTH, and one dog with vitamin D toxicosis. High-dose mithramycin (100 g/kg) caused fatal acute hepatocellular necrosis in two dogs. Low doses (25 g/kg) were effective in normalizing total and ionized calcium concentrations within 24 to 48 hours in six of nine dogs, including a dog with vitamin D toxicosis. The effects were short lived (1 to 3 days) in three dogs and lasted longer (about 7 days) in three dogs. Side effects were mild in dogs treated with the low dose and included mild GI signs in three dogs and reduction in platelet counts in three dogs. The low dose did not cause evidence of hepatic disease, reduce tumor size, or reduce PTHrP concentrations.[54]

237.1.14.9 EDTA

The intravenous injection of sodium EDTA has been used to reduce ionized calcium concentrations immediately in humans with life-threatening hypercalcemia. Infused EDTA forms complexes with ionized calcium that are rapidly excreted by the kidney.[40] A dose of 25 to 75 mg/kg/hr has been suggested as a starting point for the treatment of hypercalcemia in the dog.[21] Unfortunately, EDTA is nephrotoxic, and acute renal failure may be a consequence of its infusion.

237.1.14.10 Bicarbonate

The ionized fraction of serum calcium is determined partly by an animal's acid-base status. Correcting acidosis or creating a slight alkalosis with bicarbonate therapy shifts ionized calcium to the protein-bound fraction, rendering it less harmful.[39] A dose of 1 to 4 mEq/kg has been recommended.[56] A single intravenous dose may last as long as 3 hours in normal cats.[57] The effect of the drug is mild, and it may be helpful when administered with other treatments.

237.1.14.1 Dialysis

Hemodialysis and peritoneal dialysis with calcium-free dialysate solutions have been used effectively in humans to lower serum calcium concentrations when other methods have failed.[3,40] These techniques are particularly effective in patients with severe renal failure because fluid and diuretic therapy depends on enhanced renal excretion of calcium. Significant quantities of phosphate may also be dialyzed from the blood. Because phosphate depletion may aggravate hypercalcemia, serum phosphorous concentrations should be monitored and supplements given as required.

237.1.14.2 Calcium Receptor Agonist Therapy

Medical therapy for PHPTH has been limited, although new approaches have followed discovery of a calcium-sensing receptor on parathyroid cells that down-regulate synthesis and secretion of PTH. Molecules that mimic the effect of extracellular calcium could also activate this receptor and inhibit parathyroid cell function. The Phenylalkylamine (R)-N-(3-methoxy-alpha-phenylethyl)-3-(2-chlorophenyl) -1-propylamine, or R-5658, is one such calcimemetic compound. The drug did reduce serum PTH and ionized calcium concentrations in postmenopausal women with primary hyperparathyroidism.[58]

237.1.15 Surgical Therapy for Primary Hyperparathyroidism

237.1.15.1 Assessing the Parathyroid Glands During Surgery

237.1.15.1.1 How many glands are involved?

Surgical techniques for removing parathyroid tumors are described in various textbooks. It is important to attempt identification and evaluation of all four parathyroid glands before deciding on which gland or glands to remove. However, most dogs with PHPTH only have one obvious gland because the others are atrophied. About 90% of dogs with PHPTH have a solitary, autonomously functioning, parathyroid mass. Virtually all of the remaining dogs have two abnormal glands. Once an ultrasonographer demonstrates competence at identifying parathyroid glands and parathyroid tumors, the clinician should be reluctant to send any dog suspected of having PHPTH to surgery if an abnormal parathyroid mass or masses are not seen via cervical ultrasonography. Visualizing a mass supports the diagnosis and informs the surgeon where abnormal tissue is located. The process of evaluating parathyroid tissue at surgery without prior ultrasound evaluation can be extremely easy or quite difficult. The surgeon may easily visualize enlargement of one (common), two (less common), or more than two glands (rare). However, abnormal parathyroid tissue may not be readily identified. Any enlarged or abnormal tissue should be removed and submitted for histologic evaluation, assuming that three or fewer parathyroids appear enlarged, discolored, or both. The remaining intact gland or glands should prevent permanent hypoparathyroidism, although transient hypocalcemia may develop after surgery due to atrophy of normal glands after chronic suppression by the autonomously functioning abnormal gland or glands. An attempt must be made to ensure that at least one parathyroid gland remains intact to maintain calcium homeostasis and prevent permanent hypocalcemia. If none of the parathyroid glands appear enlarged or if all appear small, the diagnosis of primary PHPTH must be questioned. Uniform enlargement of all four glands should make one suspicious of a secondary condition.

Intravenous methylene blue infusion (3 mg/kg) has been described as a tool for improving a surgeon's ability to recognize abnormal glands. Three dogs with PHPTH were evaluated, and each had a tumor identified after new methylene blue infusion. Two of the three dogs developed anemia, Heinz bodies, and red blood cell (RBC) "blistering" after the procedure.[59] This procedure is not recommended.

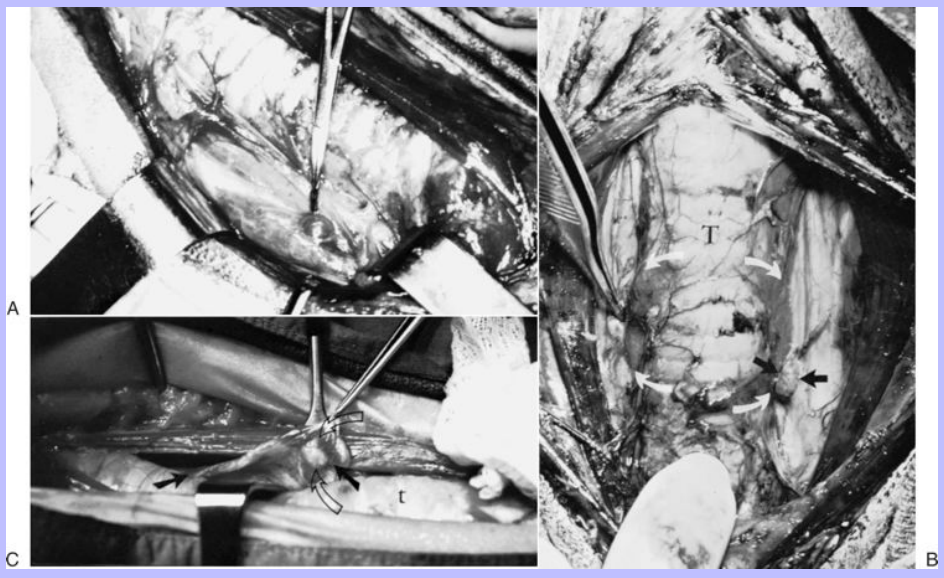
237.1.15.1.2 The solitary adenoma, hyperplastic nodule, or carcinoma

Almost all dogs with PHPTH have a solitary, easily identified, parathyroid adenoma. Fourteen of the 187 dogs with PHPTH in our series had parathyroid masses that at surgery appeared to be typical adenomas but histologically were diagnosed as carcinoma. Another 12 dogs had parathyroid masses that were classified as hyperplasia.[60] Approximately one half of tumors have been identified on the ventral surface of the thyroid glands. If not seen on the ventral surface, careful inspection of the dorsal surface of each thyroid lobe usually reveals the mass as a discrete structure on, or within, the adjacent thyroid tissue (Figure 237-6). "External" parathyroid adenomas have been easily removed without damage to surrounding tissue. Surgeons may choose to remove the entire thyroid-parathyroid structure in dogs with an "internal" parathyroid adenoma. In about 5% of dogs, the surgeon was not able to identify abnormal tissue and removed the thyroid lobe suggested by cervical ultrasonography as containing the parathyroid mass. In each case, that decision was correct.

237.1.15.1.3 Enlargement of multiple parathyroid glands

When more than one enlarged gland is identified, the concern is primary versus secondary (renal or nutritional) hyperparathyroidism. The presurgical evaluation, as reviewed, should identify or eliminate secondary disease. If the clinician is convinced that primary disease is present, a decision to remove two glands is straightforward. However, if four glands are involved (an extremely rare situation), the decision should be based on clinical status, renal function, and ability of the owner to treat permanent hypoparathyroidism.

Figure 237-6 **A,** Surgical site during removal of a solitary parathyroid adenoma *(tip of forceps)*. **B,** Surgical site during removal of a solitary parathyroid adenoma. White arrows delineate the cranial and caudal poles of the thyroid glands; black arrows point out the parathyroid adenoma. **C,** Surgical site during removal of an "internal" parathyroid adenoma. Solid arrows delineate the cranial and caudal poles of the thyroid, which is being retracted from the trachea to reveal the parathyroid adenoma *(open arrows)* on the dorsal surface of the thyroid. *T,* trachea. (From Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, 3rd ed. Philadelphia, WB Saunders Co, 2004.)



Only 14 of 187 dogs with PHPTH (7%) had enlargement of more than one gland each. Of these 14 dogs, each of 13 dogs had two enlarged glands and one had four enlarged glands. Each of three dogs had two "hyperplastic" parathyroids, each of three dogs had two parathyroid adenomas, each of three dogs had one adenoma and one hyperplastic gland, each of two dogs had one hyperplastic gland and one carcinoma, and one of the dogs with two masses had one adenoma and one carcinoma (histologic classification is discussed in a following section). One of the 187 PHPTH dogs had enlargement of all four glands.[60] Each of these four glands were classified histologically as being hyperplastic. Enlargement of all four glands suggests either multiple adenomas or, more likely, parathyroid hyperplasia.

237.1.15.1.4 Recurrence of PHPTH

Sixteen of 187 dogs with PHPTH in our series had a solitary parathyroid mass removed surgically with resolution and then recurrence of their disease. In each case, resolution of the PHPTH persisted for at least 6 months, and in 13 of the 16 dogs, PHPTH had resolved for 12 to 30 months, whereas in three it lasted 6 to 12 months. Each dog then had recurrence of hypercalcemia caused by a second solitary, autonomously functioning, surgically removed parathyroid mass. The initial diagnosis in 11 dogs was parathyroid adenoma, three had a parathyroid carcinoma, and two had parathyroid hyperplasia. The histology report after the second surgery was the same in 12 dogs. However, two of the three dogs that initially had a parathyroid carcinoma had an adenoma at recurrence and one dog with an adenoma initially had a carcinoma removed at the second surgery. One dog with hyperplasia initially had an adenoma removed at the second surgery. Thus it is possible for the disorder to recur, suggesting that periodic rechecks of the serum calcium concentration after stabilization would be warranted. Seven of the 16 dogs were Keeshonden, and this breed may warrant more routine evaluations after initial treatment.

237.1.15.1.5 No parathyroid mass at surgery

If an enlarged parathyroid gland is not identified after thorough inspection of both thyroid areas by an experienced surgeon, careful exploration of the ventral neck should be completed and any abnormal tissue excised. The most likely explanation for not finding a parathyroid mass includes hypercalcemia due to occult neoplasia, PTH production by a parathyroid tumor located outside of the typical cervical region (in the cranial mediastinum), or the presence of a nonparathyroid tumor producing PTH (i.e., ectopic hyperparathyroidism). Presurgical cervical ultrasonography should identify a parathyroid mass. Failure to visualize a parathyroid mass would best be managed by obtaining another ultrasound opinion or delaying surgery for 1 to 3 months and then rechecking the cervical ultrasonography.

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We have no experience with surgical exploration of the cranial mediastinum for a parathyroid mass. Such surgeries have inherent technical difficulties. The likelihood of finding ectopic abnormal parathyroid tissue is small. The greater likelihood of malignancy-associated hypercalcemia suggests that the decision to continue surgical exploration be carefully considered. Further diagnostic tests should be undertaken to identify occult neoplasia.

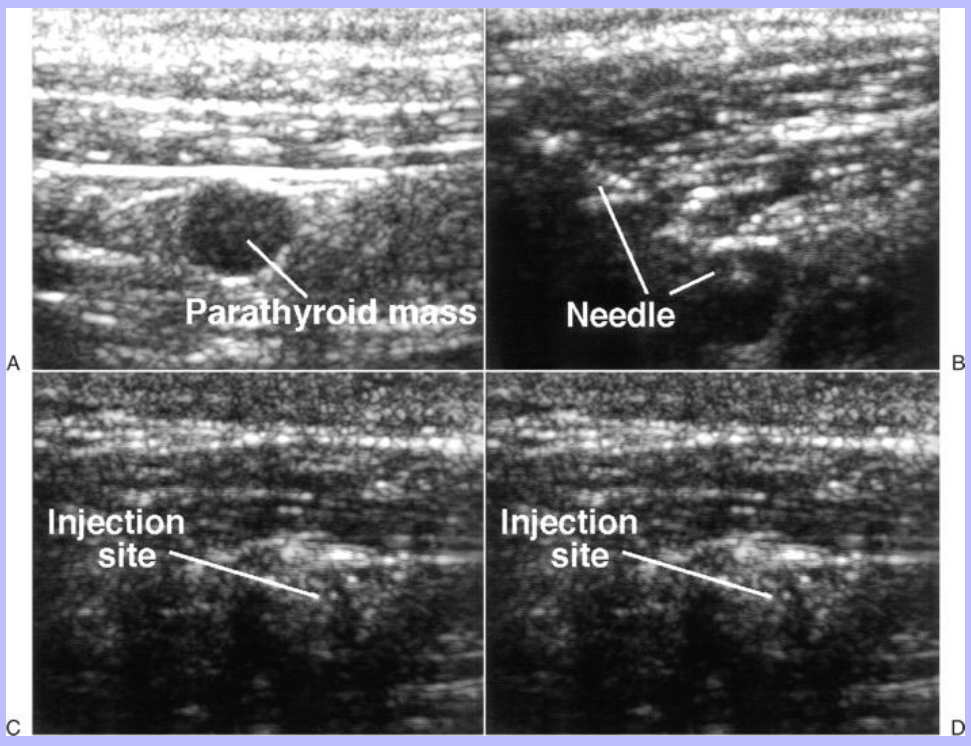
237.1.16 Novel Therapies for Primary Hyperparathyroidism in Dogs

237.1.16.1 Percutaneous Ultrasound-Guided Ethanol Ablation

Ultrasonography is an excellent method of identifying parathyroid masses in dogs with hypercalcemia secondary to PHPTH. Based on our experience with this tool as a diagnostic aid and studies performed on people with PHPTH,[61] we elected to assess the efficacy of ethanol ablation as a treatment for this disorder.[62] Ethanol causes coagulation necrosis and vascular thrombosis in the parenchyma of exposed tissue. PHPTH was diagnosed in 12 dogs. Their clinical and biochemical evaluation was typical for the disease. Each dog had a solitary hypoechoic round to oval mass near the thyroid gland on cervical ultrasonography. Parathyroid masses were identified on the right side of the neck in eight dogs and on the left in the other four. All the masses were 4 to 10 mm in length, located at the cranial aspect of one thyroid lobe in six dogs, within the caudal pole of a thyroid lobe in three dogs, and in the midbody of the thyroid

gland in three dogs. Calculated volume of the parathyroid masses ranged from 0.06 to 0.16 cm^3. It was assumed that each dog had a mass autonomously secreting PTH.

Figure 237-7 Ultrasonographic appearance of chemical ablation of a parathyroid mass in a dog. **A,** Sagittal view of the parathyroid mass prior to treatment. **B,** A 27-gauge needle is inserted into the mass. **C,** A test injection of 96% ethanol is used to confirm placement of the needle inside the mass. The reader should note that the ethanol is hyperechoic in relation to the parenchyma of the mass. **D,** After injection of the target dose of ethanol, the entire mass has an echogenic appearance. (From Long CD et al: Percutaneous ultrasound-guided chemical parathyroid ablation for treatment of primary hyperparathyroidism in dogs. J Am Vet Med Assoc 215:217, 1999, with permission.)



Each dog was placed under general anesthesia, and the ventral cervical region was clipped and aseptically prepared. The parathyroid mass was identified with ultrasound, and the tip of a 27-gauge needle, with tubing and syringe attached, was guided into the parathyroid using ultrasound (Figure 237-7). The approximate volume of the mass was matched with an equal volume of ethanol placed in the syringe. Ethanol was slowly injected into the mass with continuous ultrasound monitoring. The goal of therapy was

to inject enough ethanol to allow complete diffusion throughout the mass. The injection procedure requires a high-resolution transducer (10 MHz frequency) to allow assessment of the superficial tissues of the neck. Because parathyroid masses are small and sometimes in close proximity to nerves and vessels, considerable experience with ultrasound-guided needle placement is necessary.

Ethanol was easily seen with ultrasound during injection because it is hyperechoic (see Figure 237-7). Each parathyroid mass was injected with 50% to 150% of the calculated parathyroid volume. No dog was under anesthesia for more than 1 hour, and the mean duration of anesthesia was 38 minutes. A single injection was administered to 11 of the 12 dogs. One dog was injected a second time 48 hours after the first dose failed to decrease the serum calcium concentration into the reference range. All 12 dogs had decreases in serum total calcium concentration into the reference range. In 11 dogs this decrease was documented within 48 hours of injection (10 after the first injection and one after the second injection). One dog did not have resolution of its hypercalcemia until the fifth day post-treatment. One dog had a recurrence of hypercalcemia 30 days after injection and was treated surgically. Each of the other 11 dogs remained normal for more than 18 months. The only adverse side effect was a transient change in the "bark" in two dogs, potentially as a result of transient, unilateral, laryngeal paralysis injection of bilateral masses is not recommended. 1524 1525

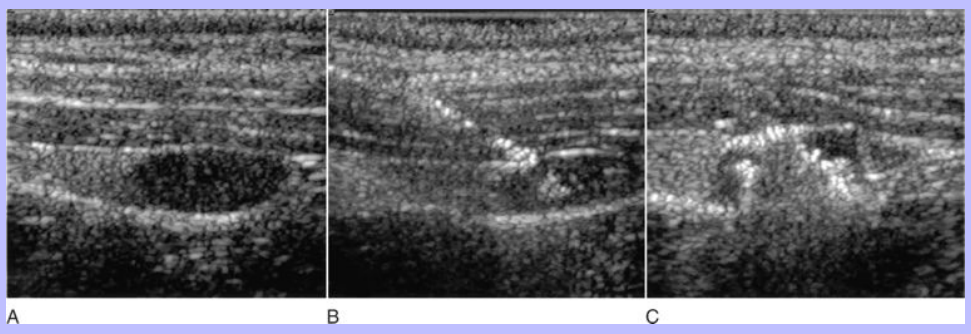
The conclusion of this study was that ultrasound-guided ethanol ablation was an efficacious mode of therapy for PHPTH in dogs. The cost of the procedure was considerably less than for surgery. Chemical ablation of parathyroid masses may be more effective in dogs than in humans because canine parathyroid masses are considerably smaller, thus requiring a smaller dose of ethanol for complete ablation.

237.1.16.2 Percutaneous Ultrasound-Guided Radiofrequency Heat Ablation

Heat destroys tissue by causing thermal necrosis. This form of therapy has several advantages as compared with ethanol ablation. First, radiofrequency damages a discrete quantity of tissue surrounding the noninsulated portion of the needle (no potential for "leakage" exists as with ethanol). Radiofrequency offers the additional advantage of not causing damage to regional vasculature. Vascular blood flow disperses heat from vessel walls. In humans, this treatment modality has a higher success rate than ethanol for ablation of masses, and fewer treatments are required to achieve remission. Radiofrequency heat ablation has been used in the treatment of multifocal hepatic masses and breast and nasal masses.[63,64] The disadvantage of radiofrequency is equipment cost.

Candidates for this procedure must have a parathyroid mass visible with ultrasonography; that mass must be large enough to have a needle inserted into it with ultrasound guidance (usually greater than 3 mm in diameter); the mass can not be subjectively considered too close to the carotid artery; and the dog should not have cystic calculi to be surgically removed because cervical surgery is a straight-forward addition to abdominal surgery. Since starting to use this treatment, 19 dogs did not meet the criteria for inclusion. An attempt was made to treat two dogs early in the study period, but the capsule could not be penetrated with the needle, and treatment was not attempted. Since then, a different more penetrating needle has been used. In one dog the parathyroid mass was too small for needle placement, and in four dogs the parathyroid mass was considered too close to the carotid artery for safe needle placement. Twelve dogs had cystic calculi that required surgical removal. In each of these dogs, parathyroid surgery and abdominal surgery were performed at the same time.

Figure 237-8 Left lateral sonographic images of an oval hypoechoic parathyroid nodule in a dog prior to heat ablation **(A)**, with the insulated needle passing through the superficial soft tissues into the cranial aspect of the mass **(B)**, and after heat ablation **(C)**. The reader should note the hyperechoic foci in the parenchyma of the gland in **C**. (From Pollard RE et al: Percutaneous ultrasonographically guided radiofrequency heat ablation for treatment of primary hyperparathyroidism in dogs. J Am Vet Med Assoc 218:1106, 2001, used with permission.)



Between September of 1999 and January of 2003, 33 dogs with PHPTH were treated with percutaneous heat ablation. Each dog had clinical and biochemical features that were typical for PHPTH. A solitary parathyroid nodule was identified by use of cervical ultrasonography in 26 dogs, seven dogs had two nodules each (a total of 40 masses in the 33 dogs). Five of these seven dogs had both nodules on the left side of the neck and two dogs had one nodule associated with each thyroid lobe. The ultrasonic appearance of the 40 masses was similar. All masses were spherical or ovoid and hypoechoic to the surrounding thyroid parenchyma. Length varied from 3 to 20 mm. Each dog with a solitary parathyroid mass was treated once. Each dog with two parathyroid nodules on the same side of the neck had both masses treated during the initial anesthesia. Each nodule was treated separately, 30 days apart, in the two dogs with one nodule on each side of the neck.

Each dog was placed under general anesthesia and the ventral cervical region was clipped and aseptically prepared. The parathyroid mass was identified with ultrasound, and the tip of a 20-gauge, over-the-needle (insulated) catheter, was directed into the mass using ultrasound guidance. An insulated wire connected the needle with the radiofrequency unit (Radiotherapeutics, Inc., Redwood City, California). Initially, 10 watts of energy was applied to the tissue for 10 to 20 seconds. If echogenic bubbles were not sonographically viewed at the needle tip during this time, the wattage was increased. Two-watt incremental increases were continued every 5 to 10 seconds until echogenic foci became apparent (Figure 237-8). Further, if an audible popping sound could be heard, the maximum heat application was arbitrarily determined to have been reached and additional wattage increases were not made. The needle was arbitrarily redirected multiple times, if necessary, in an attempt to completely ablate each mass. Mean anesthesia time was about 40 minutes, but this progressively decreased as experience with this procedure increased.[65]

The procedure was uniformly successful in these 33 dogs as demonstrated by the dramatic reduction in serum PTH and normalization of both total and ionized calcium concentrations that occurred within days of heat ablation. Serum calcium concentrations have remained within the reference range for more than 1 year. One dog improved for only 1 month and was treated surgically after hypercalcemia recurred. One dog with a unilateral parathyroid mass developed a transient voice change immediately after heat ablation, which resolved within 5 days. It is uncertain whether this voice change was secondary to intubation or the ablation procedure. Signs of pain, swelling, or respiratory distress were not detected in any of the dogs. Fifteen of the dogs required vitamin D therapy for postablation hypocalcemia (see following section). This is currently our preferred mode of treatment for dogs with PHPTH that do not have cystic calculi.

237.1.17 Post-Treatment Management of Potential Hypocalcemia

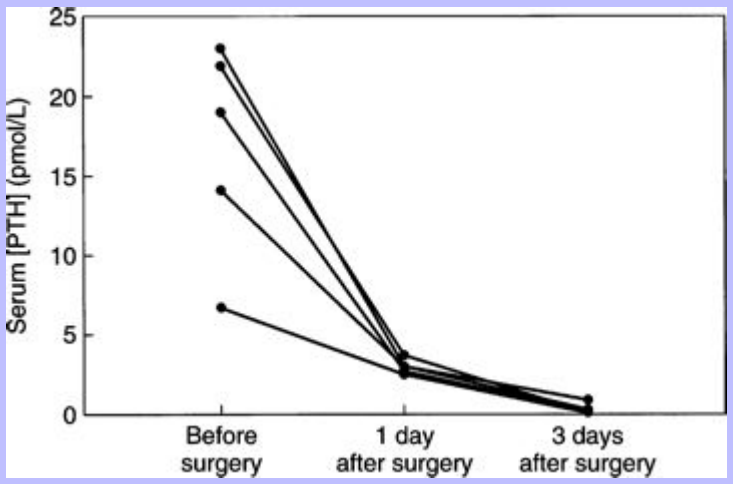
237.1.17.1 Background

Normal parathyroid glands atrophy if their function has been suppressed for a prolonged time due to autonomous secretion of PTH by a parathyroid adenoma, carcinoma, or primary hyperplasia. Surgical removal or ablation of this source for PTH results in a rapid decline in circulating PTH concentration (Figure 237-9) and a corresponding decline in serum calcium concentrations. This process typically takes place over a period of 1 to 7 days. Risk of post-treatment hypocalcemia correlates with the duration and severity of hypercalcemia prior to surgery (i.e., the higher the pretreatment calcium and the longer a dog has been hypercalcemic, the greater the risk of hypocalcemia after resolution of the PHPTH). Beginning vitamin D therapy immediately prior to or after surgery does not prevent decreases in serum calcium concentrations to or below the reference range but usually helps to avoid worrisome hypocalcemia or tetany.

237.1.17.2 Presurgical Serum Calcium Concentration Less than 14 mg/dL

If the serum calcium concentration prior to surgery is less than 14 mg/dL, the risk of postsurgical hypocalcemia is relatively small. Results between 14 and 15 mg/dL are inconsistent. The recommendation is to hospitalize such dogs for at least 5 days after surgery to monitor total serum calcium concentrations once or twice daily. Hospitalization also reduces a dog's activity by maintaining it in a cage or run. Active hypocalcemic dogs are at greater risk for clinical tetany than those kept quiet. If the total serum calcium concentration remains above 8.5 mg/dL (assuming a lower reference limit of 9 to 10 mg/dL), treatment for hypocalcemia is not recommended. If the serum ionized calcium concentration remains above 0.8 mmol/L (assuming a lower reference limit of about 1.1 mmol/L), treatment is not recommended. The reader should note, however, that these are general recommendations. It would never be incorrect to begin vitamin D therapy if one is concerned about rate of decrease in calcium or simply one wishes to be proactive. If the serum calcium concentrations decline below the limits suggested, or if clinical signs of hypocalcemia are observed (Box 237-5), treatment with vitamin D (± calcium) is suggested.

Figure 237-9 Serum PTH concentrations before and after surgery in eight dogs in which a solitary functional parathyroid adenoma was removed. (From Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, 3rd ed. Philadelphia, WB Saunders Co, 2004.)



237.1.17.3 Presurgical Serum Calcium Concentration Greater than 15 mg/dL

The higher the presurgical serum calcium concentration, the more chronic the hypercalcemic condition, or both, the more likely it is that a dog will become clinically hypocalcemic after resolution of PHPTH. Knowing the duration of hypercalcemia would be valuable but is often not possible in dogs or cats. It can be assumed that dogs with serum calcium concentrations persistently greater than 15 mg/dL due to PHPTH have been hypercalcemic for sometime. It is recommended to prophylactically attempt to avoid hypocalcemia after surgery in this population of dogs by beginning vitamin D (Hytakerol or Calcitriol) ± calcium therapy the evening before or the morning of surgery or immediately after recovery from anesthesia. In some cases we have begun vitamin D therapy 24 to 36 hours *before* surgery because of the known delay in onset of vitamin D action. This becomes important in dogs severely hypercalcemic prior to surgery (>18 mg/dL). Initiation of these treatments has not prevented decreases in serum calcium concentration to or below reference ranges after surgery. Each dog should be kept quiet in the hospital for at least 5 days after treatment. Postsurgical hypocalcemia has been documented as quickly as 12 hours after surgery to as long as 20 days later. Most become hypocalcemic between 2 and 6 days after surgery. Tetany, when it has occurred, is most commonly seen 4 to 7 days after treatment. The serum calcium concentration should be monitored once or twice daily.

The goal of calcium and vitamin D therapy is to maintain the serum calcium concentration slightly low to low-normal (i.e., 8 to 9.5 mg/dL). These serum calcium levels prevent clinical signs of hypocalcemia and minimize risk of hypercalcemia while simultaneously being low enough to stimulate recovery of function in atrophied parathyroid glands. In addition, one should avoid mid-to high-normal or increased serum calcium

concentrations. Such levels of calcium are typically associated with increases in serum phosphate concentrations and predispose the dog to tissue mineralization.

237.1.17.3.1

Box • 237-5 Clinical Signs Associated with the Acute Onset of Hypocalcemia

Panting

Nervousness

Muscle trembling, twitching

Leg cramping, pain

Ataxia, stiff gait

Facial rubbing

Focal or generalized seizures

Biting of the feet

As the parathyroid glands regain control of calcium homeostasis, calcium and vitamin D supplements can be gradually withdrawn. This process of returning parathyroid function in remaining glands is predictable, allowing the gradual withdrawal (tapering) of calcium and vitamin D supplements. Once the serum calcium concentration is stabilized and the dog has been returned to the owner, withdrawal of the supplements may be initiated. Vitamin D is usually withdrawn first by gradually extending the time between administration (e.g., twice daily to once daily for 2 weeks; to once every other day for 2 weeks; then once every third day for 2 weeks; then once every fourth day for 2 weeks; and finally once weekly for 2 to 4 weeks). The serum calcium concentration should be checked prior to each downward adjustment in dosing interval to prevent development of occult hypocalcemia. If the serum calcium concentration drops below 8 mg/dL, decreases in vitamin D supplementation should be delayed or the dose increased. The serum calcium concentration should remain above 8 mg/dL to minimize the risk of tetany. Once the vitamin D supplementation has been reduced to once weekly for a period of 2 to 4 weeks, it may be discontinued. If the serum calcium concentration remains within the normal range, the calcium supplements can then be gradually withdrawn. The entire withdrawal process for vitamin D and calcium usually takes 3 to 4 months. The clinician should remember that considerable individual variation occurs in response to therapy; therefore it is impossible to check the serum calcium concentration too frequently.

237.1.17.4

Vitamin D Resistance

Occasionally, dogs (but more often cats) seem resistant to vitamin D in tablet form. This problem is usually resolved by using the liquid form of dihydrotachysterol or by using oral or parenteral calcitriol. It is not

common for dihydrotachysterol to begin to have an effect within the first 24 hours of therapy. Rather, vitamin D gradually takes effect during the first several days of therapy and almost always within 4 to 7 days of the first dose.

237.1.18 Pathology

Abnormal, autonomously functioning parathyroid glands from humans, dogs, and cats have been characterized histologically as adenoma, carcinoma, and hyperplasia. Controlled studies of histologic interpretations by pathologists have shown that it is difficult to consistently distinguish adenoma from hyperplasia and that nonmalignant parathyroid tissue may, in some cases, have many of the histologic features of malignancy.[3] Thus histologic classification of parathyroid disease depends, to some degree, on gross features observed during surgery. The surgeon determines the number, size, and appearance of normal versus abnormal glands. The pathologist then determines whether removed tissue is parathyroid. Single-gland involvement (adenoma, carcinoma, or hyperplasia) occurs in about 80% of hyperparathyroid humans and multiple-gland involvement ("hyperplasia") in about 20%.[48,66] It appears that single-gland involvement occurs in about 90% of dogs with PHPTH and multiple glands (almost always two but not more than two) occurs in about 10%. The diagnosis of carcinoma is based on a combination of gross appearance, histology, and, ultimately, biologic behavior of the lesion. Less than 2% of autonomously secreting parathyroid glands in humans are malignant.[67] In dogs, about 5% to 10% of dogs have been assigned the diagnosis of carcinoma. Regardless of the histologic diagnosis, no dog with distant metastasis has been recognized in our of 187 cases, and recurrence rate (10%) is similar, regardless of the histologic diagnosis.

237.1.19 Prognosis

The prognosis in dogs with PHPTH is excellent. With proper monitoring and appropriate supplementation, hypocalcemia may occur after therapy but should be treatable, transient, and should not alter the prognosis. About 33% of the dogs developed clinically significant hypocalcemia after treatment. The routine use of vitamin D (dihydrotachysterol or calcitriol) and calcium supplementation has dramatically decreased the incidence of tetany. Clinicians should avoid overdosing vitamin D, because renal damage is much more likely in this situation than in dogs with PHPTH.

237.2 PRIMARY HYPERPARATHYROIDISM IN CATS

237.2.1 Differential Diagnosis for Feline Hypercalcemia

It is fair to state that, in general, the same differential diagnoses for hypercalcemia in dogs applies to cats. In a study of 71 hypercalcemic cats, their mean age at the time of diagnosis was about 9 years and their mean serum total calcium concentration was 12.2 (lower than hypercalcemic dogs). Anorexia and lethargy were the most common clinical signs (70%). Vomiting, diarrhea, or constipation were observed in 27% of the cats; polyuria, polydipsia, or both were observed in 24%; and urinary signs were observed in 23%. Neurologic signs were observed in 14%.[68]

Neoplasia was diagnosed in 30% of the cats. The most common cancers diagnosed included lymphoma and squamous cell carcinoma. Less common neoplasms included leukemia, osteosarcoma, fibrosarcoma, undifferentiated sarcoma, and bronchogenic carcinoma.[68,69] Renal failure was diagnosed in 25% of the cats, and half of those cats had urolithiasis. In a separate study, chronic renal failure in cats was usually associated

with total serum calcium concentrations within the reference range, whereas serum ionized calcium concentrations were low-normal to low.[70] Of cats with hypercalcemia, several had urolithiasis without renal failure. Six percent of the cats (four cats) had PHPTH and one had hypoadrenocorticism. Several cats had hyperthyroidism or diabetes mellitus, but it would not seem likely that either of these endocrine problems would contribute to hypercalcemia. Four cats (6%) had infectious or granulomatous disease (feline infectious peritonitis [FIP], toxoplasmosis, actinomyces, and cryptococcosis). Thus the differential diagnosis for hypercalcemia in cats is not dramatically different from that in dogs (see Box 237-1).[68,71] Other differential diagnoses (e.g., vitamin D toxicosis, other neoplastic conditions, various granulomatous diseases) should also be considered.

237.2.2 Idiopathic Hypercalcemia of Cats

Hypercalcemia is less common in cats than in dogs, but an increased frequency of hypercalcemia in cats has been observed in several geographically distinct veterinary centers since about 1990.[21,72,73] It is striking that this hypercalcemia has not been, thus far, explained. Veterinarians are identifying young, middle-aged, and old cats with mild to moderate hypercalcemia and no identifiable cause. Serum total calcium concentrations in some of these cats have been increased for years, often without clinical signs, but some have poor appetites, weight loss, and appear weak. Serum ionized calcium concentrations are also increased, sometimes out of proportion to the increase in total calcium concentration.[21]

Nephrocalcinosis or uroliths may be observed on radiographs or on abdominal ultrasonography in some hypercalcemic cats. It has been estimated that as many as 33% of cats with calcium oxalate urolithiasis have had hypercalcemia. Renal function (based on BUN and serum creatinine concentrations) is initially within reference ranges, but renal failure may develop in some cats. By definition, these cats have had no evidence of a neoplastic condition (including necropsy), and they are feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) negative. Serum PTH concentrations have been normal or low, PTHrP has not been detectable, and vitamin D concentrations have been within reference ranges. Venous blood gas analyses have not demonstrated significant abnormalities.[21] Exploratory surgery of the cervical region has not identified any abnormalities, and subtotal parathyroidectomy has failed to resolve the hypercalcemia. A change to high-fiber or to nonacidifying diets may be associated with transient improvement but also failed to permanently resolve the condition. Treatment with prednisone (usually 5 to 10 mg/cat/day) has resulted in long-term decreases in serum calcium concentrations in some but not all afflicted cats. Prednisone, regardless of the effect on serum calcium concentrations, has resulted in improved appetite and weight gain in some but not all cats.

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237.2.3 Primary Hyperparathyroidism in Cats

In addition to 10 cats with PHPTH in our series, an additional nine cats with PHPTH have been reported. Thus, only 19 cats with this condition, as compared with a much larger number of similarly afflicted dogs. Seven cats in the author's group of 10 with hypercalcemia due to PHPTH were described in one report, reported four cats were described in one report, two in each of two reports and one in another separate report.[21,74–77] The mean age of these 19 cats was approximately 13 years (range: 8 to 20 years), and various breeds were represented. The most common clinical signs described by owners were anorexia, lethargy, and vomiting. Less common signs were constipation, polyuria, polydipsia, and weight loss. A parathyroid mass was palpable in at least 11 of the 19 cats. The presence of a palpable mass and the owner observations contrast

with those of dogs, in which none had a palpable cervical mass and polyuria, polydipsia, and muscle weakness are common.

Table • 237-8 Clinical, Laboratory, and Histologic Findings in 10 Cats with Primary Naturally Occurring Hyperparathyroidism in the University of California, Davis Series

SIGNALMENT	CLINICAL SIGNS	SERUM Ca (mg/dL)	SERUM PO_4 (mg/dL)	BUN (mg/dL)	SERUM CREATININE (mg/dL)	URINE SPECIFIC GRAVITY (USG)	PARATHYROID HISTOLOGY
15 y.o. M/N/, DLH	Anorexia, vomiting	14.6	3.4	35	1.8	1.011	Solitary adenoma
14 y.o. F/S, Siamese	Anorexia, vomiting, muscle fasciculation	22.8	6.6	70	3.2	1.013	Solitary adenoma
1.5 y.o. M/N, Siamese	None	13.5	3.3	21	2.2	1.031	Solitary adenoma
15 y.o. F/S, Siamese	Polydipsia, polyuria	13.3	2.2	31	2.7	1.010	Solitary adenoma
8 y.o. F/S, DSH	Anorexia, weight loss	13.8	1.8	15	1.0	1.015	Solitary adenoma
14 y.o. F/S, DSH	Polydipsia, polyuria, lethargy	15.4	2.5	30	1.2	1.010	Solitary adenoma
9 y.o. F/S, Siamese	Anorexia	17.1	6.2	63	2.6	1.026	Bilateral cystadenoma
9 y.o. M/N, DSH	Anorexia, vomiting, lethargy, dysuria	15.2	2.6	59	3.6	1.015	Solitary carcinoma
14 y.o. M/NDSH	Constipation	13.4	3.7	41	2.2	1.022	Solitary adenoma
12 y.o. M/NDSH	Weight loss, lethargy, constipation	14.1	3.2	27	1.4	1.018	Bilateral carcinomas
Reference values		8.8–11.4	2.4–6.1	10–30	0.8–2.0		

y.o., Years old; *M,* male; *N,* neutered; *F,* female; *S,* spay/ovariohysterectomy; *DLH,* domestic longhaired; *DSH,* domestic shorthaired.

The only consistent abnormality on CBC and serum biochemical profiles was hypercalcemia (Table 237-8). All afflicted cats had persistent increases in both serum total and ionized calcium concentrations. Several cats had cystic calculi, and a large percentage had abnormalities in BUN and serum creatinine concentrations, findings not typical of their canine counterparts. Cervical ultrasonography was described as “normal” in several cats, but others had visible masses that would be considered huge in a dog. Cervical ultrasonography on two cats revealed parathyroid masses measuring 4.5 × 2 × 1 cm in one cat and 1.7 × 1.1 × 1 cm in the other.[77] Serum PTH concentrations, when measured, ranged from within the reference range (0 to 4 pmol/L) to increased. In one cat, seven separate serum PTH samples were assayed with five results being within the reference range and two being increased.

Most of the 19 cats had surgery and had resolution of the PHPTH after extirpation of the abnormal tissue. It seems that tetany has not been described in any cat treated with surgery, although several became hypocalcemic and were treated with vitamin D and calcium. Of the nine cats we followed after surgery, all lived well beyond 1 year from surgery, although at 1.5 years, one had recurrence of hypercalcemia and at necropsy was demonstrated to have both a parathyroid adenoma and a parathyroid carcinoma. Histologic evaluation of tissue from 13 cats had demonstrated parathyroid adenomas, three had carcinomas, two had hyperplasia (involving all four glands), and one had bilateral cystadenomas.

237.3 HYPOPARATHYROIDISM AND HYPOCALCEMIA

237.3.1 Background

Several historic landmarks in the understanding of parathyroid physiology, maintenance of homeostasis, and calcium regulation are significant with respect to hypocalcemia. Rickets (hypovitaminosis D) was first described in 1645. More than 200 years later (1884), an association was made between thyroidectomy in dogs and cats and the development of clinical hypocalcemia (tetany). In 1891, Gley proved that the parathyroids must be removed with the thyroids to produce tetany. Shortly thereafter, administration of calcium salts after parathyroidectomy was demonstrated to prevent tetany.

237.3.2 Pathophysiology

237.3.2.1 Initial Physiologic Alterations

Cessation of parathyroid function leads to a decrease in serum calcium concentration and an increase in plasma phosphate concentration. Urinary calcium and phosphate excretion diminishes. These changes are due to loss of PTH effects on mobilization of calcium and phosphate from bone, renal retention of calcium, enhanced renal excretion of phosphate, and increased absorption of calcium and phosphate from intestine.

237.3.2.2 Neuromuscular Activity

Ionized calcium is involved in the release of acetylcholine during neuromuscular transmission. Calcium is essential for muscle contraction, and it stabilizes nerve cell membranes by decreasing their permeability to sodium. Calcium's role as a membrane stabilizer is most obvious during severe hypocalcemia. When the extracellular concentration of calcium ion declines to subnormal levels, the nervous system becomes progressively more excitable owing to increased neuronal membrane permeability. Nerve fibers begin to discharge spontaneously, initiating impulses to peripheral skeletal muscles, where they elicit contractions. Consequently, hypocalcemia causes tetany. Dogs with untreated hypoparathyroidism have serum calcium concentrations consistently below 6.5 mg/dL. The onset of clinical tetany, however, is not entirely predictable.

In hypocalcemic dogs, “latent” tetany probably occurs. Owners mention that sudden excitement, activity, or petting unpredictably causes sporadic muscle cramping, lameness, facial rubbing, pain, irritability, or aggressive behavior. The nontetanic, severely hypocalcemic pet is often described by the owner as having a change in personality. Such signs are vague, but after hypocalcemia is diagnosed, the clinical signs are consistent with those of an animal in latent tetany. The various disturbances are completely and quickly reversible with therapy.

237.3.3 Clinical Features of Naturally Occurring Hypoparathyroidism—Dogs

237.3.3.1 Signalment

In reviewing the records of dogs in our series with naturally occurring primary hypoparathyroidism, the youngest dog was diagnosed at 6 weeks of age, the oldest was 13 years (average was 4.8 years), and 65%

were female.[78] The breeds most frequently identified as having primary hypoparathyroidism were poodles, miniature schnauzers, retrievers, German shepherds, and terriers.

237.3.3.2 Anamnesis

237.3.3.2.1 Duration of illness

The clinical course usually begins with an abrupt onset of intermittent neurologic or neuromuscular disturbances. Signs may be initiated or worsened by excitement or exercise. Signs associated with hypocalcemia had been observed for only 1 day in some dogs and for as long as 2 years in others. Many had been diagnosed and treated for nonspecific seizure disorders without the benefit of pretreatment laboratory testing. Most owners reported that their pets were "always" tense or nervous. Intense facial rubbing with the paws or on the ground was commonly observed but not usually mentioned by owners until specifically questioned. Additional signs included cramping and tonic spasm of leg muscles. Focal muscle twitching, generalized tremors, fasciculations, or trembling was frequently observed, as was a stiff, stilted, hunched, or rigid gait.

237.3.3.2.2 Seizures

Grand mal convulsions have been observed in 80% of dogs with primary hypoparathyroidism. Some of this seizure activity was atypical because there was no loss of consciousness and the dogs were not incontinent during the episode.[79] More than 80% of these dogs were observed, by a veterinarian, to have seizures or to be "in tetany." This represents a much higher incidence of veterinarian-witnessed neuromuscular signs than expected with most seizure disorders. The neuromuscular problems became so severe that several dogs, although not having seizures, were not able to stand or walk. Seizure episodes were as brief as 20 to 90 seconds and rarely lasted more than 30 minutes. Most, but not all, generalized seizures spontaneously abated.

237.3.3.2.3 Facial rubbing

More than 60% of the dogs in our series were observed to paw or rub violently at their muzzles, eyes, and ears, as well as rubbing their muzzles on the ground. These signs are thought to result from the pain associated with masseter and temporal muscle cramping caused by the hypocalcemia or from a "tingling" sensation around the mouth. Classic signs of hypocalcemia in humans include paresthesias—numbness and tingling that often occur around the mouth, in the tips of fingers, and sometimes in the feet.

237.3.3.3 Physical Examination

Other than signs related to hypocalcemia, dogs with primary hypoparathyroidism have no classic abnormalities on physical examination. A few dogs were thin, and several growled when examined. Retrospectively, the growling dogs were in pain or were anticipating that handling would result in pain because, after resolution of hypocalcemia, each became friendly. Cardiac abnormalities were apparent in about 40% of dogs on initial examination. These abnormalities consisted of paroxysmal tachyarrhythmias and muffled heart sounds with weak pulses. About half of the dogs appeared to be extremely tense, with splinted abdomens and stiff gaits. A smaller number had generalized muscle fasciculations, fever, or both.

Almost 50% had generalized seizures during their initial examination, and more than 80% had at least one convulsion during the initial 48 to 96 hours of hospitalization.

237.3.4 Clinical Features of Naturally Occurring Hypoparathyroidism—Cats

The clinical features of eight cats reported in the literature to have naturally occurring hypoparathyroidism are much like those reported in dogs. The clinical course for each cat was characterized by an abrupt or gradual onset of intermittent neurologic or neuromuscular disturbances that included focal or generalized muscle tremors, seizures, ataxia, stilted gait, disorientation, and weakness. Other commonly observed abnormalities included lethargy, anorexia, panting, and raised nictitating membranes.[80]

237.3.5 Diagnostic Evaluation—Dogs and Cats

237.3.5.1 Serum Calcium and Phosphate Concentrations

Severe hypocalcemia was a serendipitous finding in each of the dogs and cats with primary natural hypoparathyroidism (Table 237-9). Because therapy for hypocalcemia was quickly instituted, each animal had its serum calcium concentration monitored three to five times during the first 72 hours of hospitalization. In no dog or cat was the serum calcium concentration greater than 6.5 mg/dL until the therapy began to have an effect. Each dog and cat also had a serum phosphorus concentration higher than 1529
its calcium concentration, and all had normal BUN concentrations. 1530
The absence of an *absolute* hyperphosphatemia in some of dogs can be explained in part by the broad reference range provided by veterinary laboratories. No other abnormal laboratory findings were common.

Table • 237-9 Pertinent Findings in Dogs with Primary Hypoparathyroidism

DOG	AGE (Years)	GENDER	DURATION OF SIGNS (Days)	SERUM CALCIUM (mg/dL)	SERUM PHOSPHORUS (mg/dL)	SERUM MAGNESIUM (mg/dL)	BLOOD UREA NITROGEN (mg/dL)	SERUM ALBUMIN (mg/dL)	PARATHYROID HORMONE (pmol/L)	PARATHYROID HISTOLOGY
1	5	F/S	3	5.7	7.3	—	14	4.1	—	—
2	5	F/S	30	4.1	5.4	1.9	31	3.1	—	—
3	5	M	30	4.7	6.0	—	8	2.9	—	—
4	4	F	7	4.5	5.9	1.2	17	3.5	—	—
5	10	F/S	1	5.2	7.0	2.1	15	2.9	—	Lymphocytic parathyroiditis
6	11	F/S	3	5.6	8.9	—	4	3.7	—	—
7	1	F	14	4.2	9.8	—	20	3. 6	—	—
8	5	M	180	5.7	10.2	—	12	3.1	—	—
9	10	F	3	5.5	7.2	1.9	9	3.5	—	—
10	1	M	1	5.2	7.8	—	19	3.2	—	—
11	10	M	11	4.9	5.9	1.8	10	3.1	1.0	Lymphocytic parathyroiditis
12	10	M	1	6.0	6.3	—	13	4.5	0.1	Lymphocytic parathyroiditis
13	4	F/S	14	3.9	4.9	1.9	16	3.5	1.0	—
14	7	F/S	10	6.0	8.3	2.3	12	3.1	1.0	Lymphocytic parathyroiditis
15	9	M	4	3.6	5.8	—	9	3.3	0.05	—
16	0.5	F/S	2	3.9	8.4	1.9	11	2.6	0.1	—
17	13	M	6	4.2	7.1	—	15	3.6	0.1	Lymphocytic parathyroiditis
18	1	F/S	7	5.1	8.7	1.2	14	2.9	0.1	Lymphocytic parathyroiditis
19	0.5	F/S	7	4.8	10.2	2.0	22	2.5	—	Lymphocytic parathyroiditis
20	2	M	45	4.4	7.4	2.1	16	3.4	0.1	—
21	3	F/S	9	5.1	6.8		25	4.1	0.5	—
22	6	M	360	5.1	8.8	2.2	23	3.8	0.1	Lymphocytic parathyroiditis
23	8	M	3	3.9	8.3	1.9	19	3.7	0.5	—
24	12	F/S	2	4.6	8.5	2.3	18	3.7	0.1	—
25	6	M	3	5.5	8.5	2.2	19	4.1	0.7	—
Mean	6	—	30	4.8	7.6	1.9	15.6	3.4	0.3	—
Reference range	—	—	—	8.9–11.4	3.0–4.7	1.8–2.4	12–28	2.3–4.3	2–13	—

M, male; *F*, female; *S*, spay/ovariohysterectomy.

237.3.5.2 Electrocardiogram

Hypocalcemia prolongs the duration of the action potential in cardiac cells. The findings most consistent with hypocalcemia included deep, wide T waves; prolonged Q-T intervals; and bradycardia. No obvious ECG findings could explain the arrhythmias, weak pulses, or muffled heart sounds that were noted on several physical examinations.

237.3.5.3 Serum Parathyroid Hormone Concentration

Undetectable serum PTH concentrations in animals that are severely hypocalcemic confirm the diagnosis of primary hypoparathyroidism, assuming that the assay used is reliable and validated. Serum PTH concentrations may be detectable as “low-normal” in some animals with hypoparathyroidism if the assay used is quite sensitive. However, a low-normal or low value would not be “normal” in a hypocalcemic animal that has healthy parathyroid glands.

237.3.6 Differential Diagnosis for Hypocalcemia

The differential diagnoses for hypocalcemia are presented in Box 237-6 and Figure 237-10.

237.3.6.1 Parathyroid-Related Hypocalcemia

Naturally occurring hypoparathyroidism is a rare condition in dogs and cats. Iatrogenic primary hypoparathyroidism has been recognized in dogs and cats after thyroid, parathyroid, or other surgeries of the neck. Magnesium deficiency can cause hypocalcemia. Severe hypomagnesemia in humans can result in a condition characterized by being refractory to PTH or it inhibits synthesis or secretion of PTH.

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237.3.6.1.1 Box • 237-6 Differential Diagnosis of Hypocalcemia

- Parathyroid-related hypocalcemia
  - Primary hypoparathyroidism
    - Destruction of glands
      - Immune-mediated process
      - Iatrogenic: surgical complication
      - Any disease in neck causing damage
    - Idiopathic atrophy (autoimmune process?)
  - Pseudohypoparathyroidism
- Chronic renal failure
- Hypoalbuminemia
- Acute pancreatitis
- Puerperal tetany (eclampsia)
- Intestinal malabsorption syndromes

- Nutritional secondary hyperparathyroidism (rare)
- Anticovulsant therapy
- Acute renal failure
- Ethylene glycol toxicity
- Phosphate-containing enemas
- Miscellaneous diagnoses
  - Laboratory error
  - Use of EDTA-anticoagulated blood
  - Vitamin D deficiency
  - Transfusion using citrated blood
  - Soft tissue trauma
  - Medullary carcinoma of the thyroid
  - Primary and metastic bone tumors
  - Cancer chemotherapy

237.3.6.2 Acute Renal Failure and Ethylene Glycol Toxicity

Acute renal failure, such as occurs with urethral obstruction, ureter obstruction, or ethylene glycol poisoning, can result in abrupt and severe increases in serum phosphate concentration. An acute increase in serum phosphate concentration causes a reduction in serum calcium concentration. This hypocalcemia may be exaggerated in acute renal failure, because the rapid progression of these disturbances blunts compensatory mechanisms. Cats with ureteral or urethral obstruction and hyperphosphatemia often have associated hypocalcemia, hyperkalemia, azotemia, and sometimes seizures.[39] Ethylene glycol intoxication

can cause severe renal failure, acidosis, and death. The metabolites of this toxin can chelate serum calcium ions and cause tetany.

237.3.6.3 Chronic Renal Failure, Hypoalbuminemia, and Pancreatitis

Chronic renal failure is an extremely common disorder in dogs and cats. This condition is most commonly associated with increases in serum phosphate concentrations with concurrent normal serum calcium concentrations. However, either hypocalcemia or hypercalcemia may occur in animals with chronic renal failure. Serum ionized calcium concentrations from animals with renal failure are often low-normal to low.[81]

Reductions in total serum protein, serum albumin concentrations, or both are encountered in a variety of disorders. Decreased circulating albumin causes a decrease in the protein-bound fraction of circulating calcium. However, ionized calcium concentrations are typically normal. Hypocalcemia, when it occurs in dogs with acute pancreatitis, is usually mild and subclinical. Coexisting pancreatitis and acidosis, which is commonly present, increases the amount of serum calcium that is ionized and further reduces any chance of tetany.

237.3.6.4 Puerperal Tetany (Eclampsia)

Eclampsia is an acute life-threatening condition caused by extreme hypocalcemia in lactating bitches and queens. In most studies, dogs with eclampsia are severely hypocalcemic (< 6.5 mg/dL). Eclampsia is most common in small dogs, being less common in cats and large dogs.

237.3.6.5 Nutritional Secondary Hyperparathyroidism

Dogs and cats fed diets containing low calcium-to-phosphorus ratios, such as beef heart or liver, can develop severe mineral deficiencies. Dietary calcium deficiency results in transient decreases in serum calcium concentration, inducing increased PTH secretion, reduction in bone mass as calcium is removed from bone to replace that lacking in the diet, and diffuse skeletal disorders. Skeletal problems include bone pain and pathologic fractures and are the result of the normal physiologic processes that maintain serum mineral homeostasis. Usually these animals have normal serum concentrations of both calcium and phosphorus. Occasionally, such an animal is hypocalcemic. These dogs and cats should be treated by providing balanced diets and restricting activity until skeletal remodeling is complete. Diagnosis is based on recognizing skeletal disorders in a dog or cat given an improper diet.

237.3.6.6 Miscellaneous Causes of Hypocalcemia

Commercial phosphate-containing enemas may result in acute, marked hyperphosphatemia and, subsequent hypocalcemia after colonic adsorption of the enema solution, especially when administered to dehydrated cats with colonic atony and mucosal disruption. These rare problems include laboratory error, vitamin D deficiency, use of citrated blood, trauma, medullary carcinoma of the thyroid, primary and metastatic bone tumors, and some forms of chemotherapy.

237.3.7 Therapy for Hypoparathyroidism and Hypocalcemia

237.3.7.1 Emergency Therapy for Tetany

When treating a seizing animal without a specific diagnosis, diazepam is the initial drug usually chosen to control the signs. However, if this treatment fails or if a diagnosis is still not obvious, blood should be drawn for glucose, calcium, and any other parameter that may lead to a definite diagnosis. Hypocalcemic tetany improves after replacement of calcium, although these animals usually respond to diazepam. Calcium should be administered intravenously, slowly to effect. The dose is 1 to 1.5 mL/kg or 5 to 15 mg/kg, administered slowly over a 10-to 30-minute period. Calcium gluconate, as a 10% solution (Table 237-10), is recommended because, unlike calcium chloride, calcium gluconate extravasating outside a vein is not caustic. Calcium chloride can cause not only tremendous tissue sloughing but also calcinosis cutis.[82] Electrocardiographic monitoring is advisable. If bradycardia, premature ventricular complexes, or shortening of the Q-T interval is observed, the IV infusion should be briefly discontinued.[40] This rapid emergency therapy is invariably successful, with a response noted within minutes of initiating the infusion. However, the final dose needed to control tetany is somewhat unpredictable. The recommendation is to use the suggested dose (in mg/kg) as a guideline and patient response as the definitive factor in determining the volume administered. Infusion of calcium-rich fluids should proceed with caution in a dog or cat with hyperphosphatemia. The additional calcium could result in mineralization of soft tissue causing further damage to the kidneys in animals with coexisting renal insufficiency or failure.[39]

237.3.7.2 Fever

Fever frequently accompanies tetany. It is not unusual to have a dog or cat in tetany with a rectal temperature above 105° F. There is often temptation to treat both the hypocalcemia and the fever (with ice or alcohol baths; parenteral drugs). It is recommended, however, that with institution of calcium therapy, one should monitor but not treat fever. Fever usually dissipates rapidly with control of tetany. Additional measures to lower body temperature may result in hypothermia and the development of shock.

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Figure 237-10 Algorithm for diagnosing the various causes of hypocalcemia. (From Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, 3rd ed. Philadelphia, WB Saunders Co, 2004.)

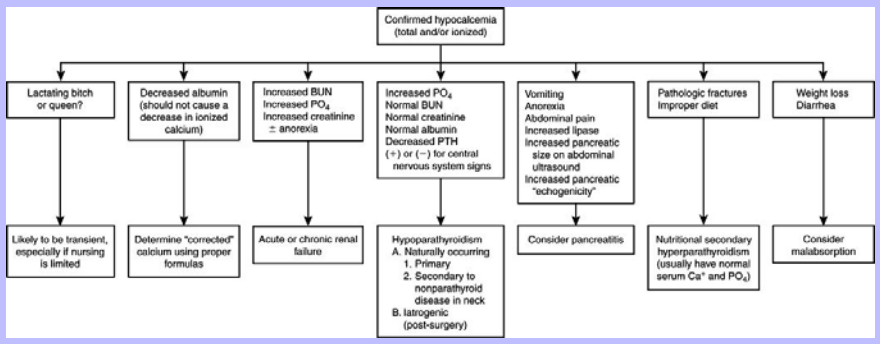

Table • 237-10 Some Available Calcium Preparations

PREPARATIONS AVAILABLE		APPROXIMATE CALCIUM CONTENT	DOSE
Oral			
Calcium carbonate/gluconate	Chewable tablet: 700 mg	250 mg Ca/tablet	Cats: 0.5–1 g/day
Calcium gluconate	Tablets: 325 mg	30 mg Ca/tablet	Dogs: 1–4 g/day
	500 mg	45 mg Ca/tablet	
	650 mg	60 mg Ca/tablet	
	1000 mg	90 mg Ca/tablet	
Calcium lactate	Tablets: 325 mg	42 mg Ca/tablet	
	650 mg	85 mg Ca/tablet	
Calcium carbonate	Capsules: 500 mg	145 mg Ca +155 mg P/capsule	
	650 mg	190 mg Ca +148 mg P/capsule	
	Tablets: 650 mg	190 mg Ca +148 mg P/tablet	
	1000 mg	295 mg Ca +228 mg P/tablet	
Calcium glubionate	Syrup: 360 mg/mL	20 mg Ca/mL	
Injectable			
Calcium gluconate (IV, SQ)	10% solution, 10-mL ampule	9.3 mg Ca/mL	1–1.5 mL/kg: 5–15 mg/kg: slowly
Calcium chloride (IV)	10% solution, 10-mL ampule	27.2 mg Ca/mL	Not recommended
Calcium gluceptate (calcium glucoheptonate) (IV, IM)	22% solution, 5 mL ampule	18 mg Ca/mL	—

Ca, Calcium; *P,* phosphate; *IV,* intravenous; *SQ,* subcutaneous; *IM,* intramuscular.

237.3.8 Post-Tetany Short-Term Maintenance Therapy

237.3.8.1 Subcutaneous Calcium

Once tetany has been controlled with intravenous bolus calcium gluconate, administration of subcutaneous calcium is effective, simple, and inexpensive. A dose of calcium gluconate equal to that needed for the initial control of tetany can be given subcutaneously every 6 to 8 hours. The calcium gluconate should be diluted in an equal volume of saline. This protocol has effectively supported serum calcium concentrations while waiting for oral vitamin D to take effect. It is a procedure that can be easily taught to owners, further decreasing their expense.

After serum calcium concentrations have been maintained for 48 hours, the frequency of subcutaneous injections should be decreased from every 6 to every 8 hours. If serum calcium concentrations remain stable for the ensuing 48 to 72 hours, the calcium can be tapered to twice daily. This protocol is continued until parenteral calcium has been completely discontinued. Obviously, the tapering process in each animal may not be this smooth, because response to oral Vitamin D therapy is variable. Ideally, the serum calcium concentration should be maintained above 8 mg/dL. Serum calcium concentrations below 8 mg/dL indicate the need to increase the dose of parenteral calcium, serum calcium concentrations of 8 to 9 mg/dL suggest that the current dose should be maintained, and values greater than 9 mg/dL suggest the need to reduce the parenteral calcium dose.

237.3.8.2 Repeating Intravenous Bolus

One alternative to the management of hypocalcemia in the immediate post-tetany period would be intravenous calcium by bolus, as needed. This procedure is not recommended except as required in an emergency.

237.3.8.3 Calcium Supplementation in a Continuous Intravenous Solution

Calcium can be administered slowly, intravenously, via an infusion solution. Calcium gluconate is administered in the infusion to attain a dose of 60 to 90 mg/kg per day (approximately 2.5 mL/kg of 10% calcium gluconate added to the infusion solution and administered every 6 to 8 hours). This calcium should not be added to a bicarbonate-containing solution because of potential precipitation problems. Serum calcium concentrations should be monitored once or twice daily, with the rate of infusion adjusted as needed.

237.3.9 Maintenance Therapy

237.3.9.1 Vitamin D

The need for vitamin D therapy is usually permanent in dogs and cats with primary naturally occurring parathyroid gland failure. Calcium supplementation, however, can often be tapered and then stopped, because dietary calcium is sufficient to meet the needs of the animal. Supplemental calcium in conservative doses, however, ensures that vitamin D, which raises serum calcium by promoting its intestinal absorption, has a substrate upon which to function. Iatrogenic hypoparathyroidism in cats that have had neck surgery is often transient, and lifelong therapy is not always needed. In contrast to treating tetany, when the immediate goal is to avoid recurrence of neuromuscular signs, the aim of long-term therapy is maintaining the serum calcium concentration at mildly low to low-normal concentrations (8 to 9.5 mg/dL). These calcium concentrations are above the level of risk for clinical hypocalcemia and below that which might be associated with hypercalciuria (risk of calculi formation) or severe hypercalcemia and hyperphosphatemia (risk of nephrocalcinosis and renal failure).

237.3.9.2 Vitamin D_2 (Ergocalciferol)

It is recommended that dihydrotachysterol or calcitriol be used for long-term treatment. For some owners, *1533*
however, these drugs are too expensive. Vitamin D_2 can be given as a less-than-ideal but less-expensive *1534*
alternative. It is a widely available drug (Table 237-11). Initially, large doses are required to induce normocalcemia. Dogs and cats can be given 4000 to 6000 U/kg once daily. These doses are needed to offset the decreased biologic potency of this product in hypoparathyroid animals. Additionally, large doses are required to saturate fat depots, because vitamin D is a fat-soluble vitamin. Effect of the medication is usually obvious 5 to 14 days after beginning therapy. Parenteral calcium can usually be discontinued 1 to 5 days after starting oral treatment.

Table • 237-11 Vitamin D Preparations

PREPARATION	DOSE FORM	COMMERCIAL NAME (MANUFACTURER)	DAILY DOSE	TIME REQUIRED FOR MAXIMAL EFFECT	TIME REQUIRED FOR TOXICITY RELIEF
Vitamin D_2 (ergocalciferol)	Capsules 25,000 U 50,000 U	Calciferol (Rorer)	Initial: 4000–6000 U/kg/day	5–21 days	1–18 weeks
		Drisdol (Winthrop-Breon)			
		Deltalin Lilly			
	Oral syrup 8000 U/mL	Drisdol (Winthrop-Breon)	Maintenance: 1000–2000 U/kg once daily-once weekly		
	IM injectable 50,000 U/mL	Calciferol (Rorer)			
		Vitadee (Gotham)			
Dihydrotachysterol	Tablets 0.125 mg 0.2 mg 0.4 mg	Dihydrotachysterol (Phillips-Roxane)	Initial: 0.02–0.03 mg/kg/day	1–7 days	1–3 weeks
	Capsules 0.125 mg	Hytakerol (Winthrop-Breon)	Maintenance: 0.01–0.02 mg/kg q24-48h		
	Oral solution 0.25 mg/mL	Hytakerol (Winthrop-Breon)			
Vitamin D_1 (calcitriol)	Capsules 0.25 µg 0.5 µg	Rocaltrol (Roche) (also generic)	Approximate: 0.03–0.06 µg/kg/day	1–4 days	24 hours-2 weeks
	Vitamin D3 injectable 1.0 µg/ml	Calcijex (Abbott Laboratories)	Approximate: 0.02 µg/kg/day		1 to 7 days/week

Dogs and cats receiving vitamin D_2 should be hospitalized, ideally, until the serum calcium concentration remains between 8 and 10 mg/dL without parenteral support. At this time, the pet can be returned to the owner and vitamin D given every other day. Serum calcium concentrations should be monitored weekly, with the vitamin D dose adjusted to maintain a serum calcium concentration of 8 to 9.5 mg/dL. The aim of therapy is to avoid hypocalcemic tetany, but the most common problem with therapy is induction of hypercalcemia. Once the pet appears stable, monthly rechecks are strongly advised for 6 months and then every 2 to 3 months, thereafter.

237.3.9.3 Dihydrotachysterol

The advantages of dihydrotachysterol versus vitamin D_2 are that it raises the serum calcium concentration faster (1 to 7 days) and its effects dissipate faster when administration is discontinued. Therefore the veterinarian has more control over the therapy. Dihydrotachysterol is readily available and is more expensive than vitamin D_2 (see Table 237-11). This product is more potent than vitamin D_2, 1 mg of dihydrotachysterol being equivalent to 120,000 U of vitamin D_2. Dihydrotachysterol is initially given at a dose of 0.03 mg/kg per day for several days or until effect is demonstrated, then 0.02 mg/kg per day for 2 days, and finally 0.01 mg/kg per day. As suggested with the less potent vitamin D, the pet should remain hospitalized until the serum calcium concentration remains stable between 8 and 9.5 mg/dL for several days. we have seen cats and dogs that appeared to be resistant to the tablet and capsule forms of this drug (0.125, 0.25, 0.4 mg) but responded readily to the liquid (0.25 mg/mL). Rechecks of the serum calcium

concentration on a weekly basis allow dose adjustment while avoiding prolonged hyper-or hypocalcemia. As with vitamin D_2, long-term rechecks at two to three month intervals are strongly encouraged.

Hypercalcemia (> 12 mg/dL) should be treated by discontinuing vitamin D therapy and, depending on the severity of the clinical signs and biochemistry abnormalities, possibly initiating intravenous fluids, furosemide, corticosteroids, or a combination of these treatments. The period from stopping dihydrotachysterol to noting a fall in the serum calcium concentration is between 4 and 14 days, a much briefer period than that seen with vitamin D_2.

237.3.9.4 1,25-Dihydroxyvitamin D (Calcitriol)

This drug offers the advantages of rapid onset of action (1 to 4 days) and short half-life (less than 1 day). If hypercalcemia results from overdose, it can be rapidly corrected by discontinuing the drug. Because 1,25-dihydroxyvitamin D does not require activation by the kidney, physiologic doses should readily maintain normocalcemia in a pet with hypoparathyroidism, a state in which renal 1-alpha-hydroxylase activity is low. In contrast, relatively larger pharmacologic doses of vitamin D_2 or dihydrotachysterol must be used to overcome this block in renal 1-hydroxylation. We have not used this drug for chronic maintenance therapy of dogs or cats with primary hypoparathyroidism.

237.3.10 Calcium

237.3.10.1 Initial Approach to Oral Calcium

Dietary calcium must be adequate when treating hypoparathyroidism, because the primary mode of therapy is the administration of vitamin D, which acts to increase absorption of calcium present in the intestinal lumen. Usually sufficient calcium is found in commercial pet foods. However, to avoid the catastrophic problems of hypocalcemia, especially early in the course of therapy, oral calcium supplementation is strongly recommended. Oral calcium and vitamin D therapy should be started while tetany is being controlled with parenteral calcium. After 24 to 96 hours, the parenteral calcium administration can often be discontinued while oral therapy is maintained. In this manner, smooth, continuous control is achieved.

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237.3.10.2 Calcium Supplements

Supplements can be provided by administering calcium as the gluconate, lactate, chloride, or carbonate salt. Each have disadvantages. Calcium gluconate and lactate tablets contain relatively small quantities of elemental calcium, so relatively large numbers of tablets must be given. Calcium chloride tablets contain large quantities of calcium but tend to produce gastric irritation. Calcium carbonate tablets also contain large quantities of calcium but tend to produce alkalosis, which may aggravate hypocalcemia. Calcium carbonate is 40% calcium. One gram yields 20 mEq of calcium, and gastric acid converts the calcium carbonate to calcium chloride. Calcium lactate is 13% calcium, and 1 g yields 6.5 mEq. Calcium gluconate contains 9% calcium, and 1 g yields 4.5 mEq. Obviously, numerous calcium preparations are available (Table 237-11). Calcium carbonate is the preparation of choice in treating hypoparathyroid humans because of its high percentage of calcium, ready availability in drugstores in the form of antacids, low cost, and lack of gastric irritation.[2] No specific research is available to support recommendations for use of this drug in dogs and cats, although the author's success with calcium carbonate has been excellent.

237.3.11 Treatment Protocol

In cats the dose of calcium is approximately 0.5 to 1 g per day, in divided doses. In dogs, the dose is usually 1 to 4 g per day, in divided doses. These recommendations are approximate, and the primary therapy that determines stability of the serum calcium concentration is the use of vitamin D. As the vitamin D dose reaches a steady level, the dose of calcium can be gradually tapered over 2 to 4 months. This method of treatment avoids unnecessary therapy, considering that dietary calcium should be sufficient to supply the needs of the pet and should decrease the demands of treatment placed on the owner. It must be emphasized that the ideal serum calcium concentration in these animals is 8 to 9.5 mg/dL. Concentrations above 10 are too high, are unnecessary in avoiding tetany, and increase the likelihood of unwanted hypercalcemia.

237.3.12 Parathyroid Histology in Primary Hypoparathyroidism

Animals have been classified as having idiopathic hypoparathyroidism when the clinician finds no evidence of trauma, malignant or surgical destruction, or other obvious damage to the neck or parathyroid glands. The glands are difficult to locate visually and are microscopically atrophied. Approximately 60% to 80% of the glands are replaced by mature lymphocytes, occasional plasma cells, extensive degeneration of chief cells, and fibrous connective tissue. Chief cells are randomly isolated in multiple small areas or bands at the periphery. In the early stages, infiltration of the gland with lymphocytes and plasma cells occurs, with nodular regenerative hyperplasia of remaining chief cells. Later, the parathyroid gland is completely replaced by lymphocytes, fibroblasts, and neocapillaries, with only an occasional viable chief cell. The final interpretation is one of lymphocytic parathyroiditis.[83,84]

237.3.13 Prognosis

The prognosis with primary hypoparathyroidism is dependent, for the most part, on the dedication of the owner and, to a lesser extent, on the experience of the veterinarian. With proper therapy, the prognosis is excellent. Twenty-one of 25 dogs that we observed, lived more than 5 years. However, proper management requires close monitoring of the serum calcium concentration, ideally once every one to three months once the pet is stabilized. The more frequent the rechecks, the better chance the pet has of avoiding extremes in serum calcium concentrations. The chance for a normal life expectancy is excellent with proper care.

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238 CHAPTER • 238 Hypothyroidism

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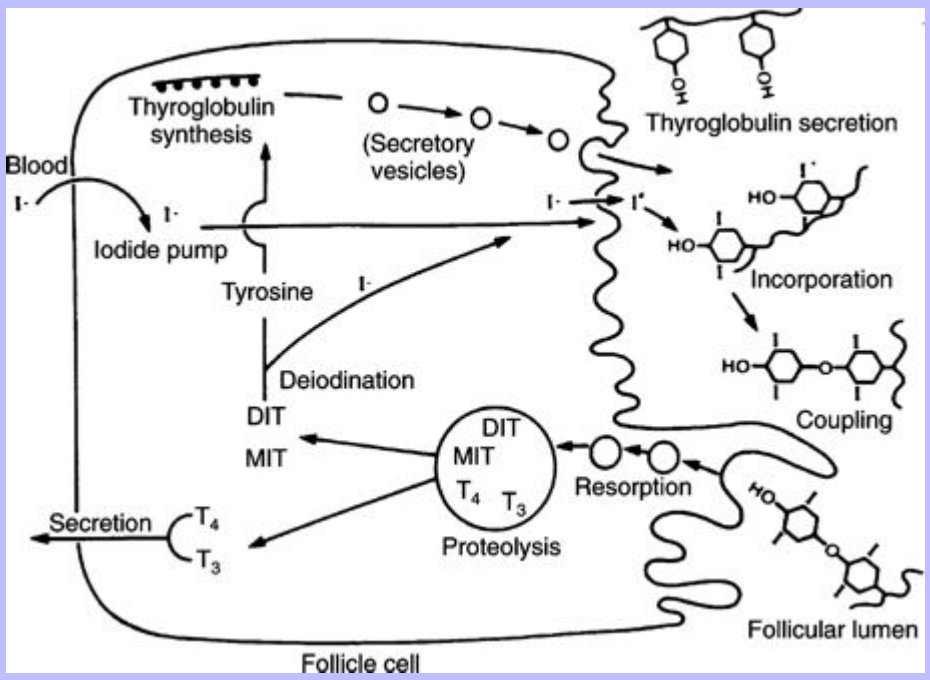
Hypothyroidism is the result of decreased production of thyroxine (T_4) and triiodothyronine (T_3) by the thyroid gland. Naturally occurring hypothyroidism is common in dogs but extremely rare in cats.

238.1 PHYSIOLOGY AND METABOLISM

Thyroid hormones are iodine-containing amino acids synthesized in the thyroid gland (Figure 238-1). All circulating T_4, but only 20% of T_3, is derived from the thyroid gland. The majority of T_3 is derived from extrathyroidal enzymatic 5′-deiodination of T_4. In the blood, more than 99% of T_4 and T_3 are bound to plasma proteins, with T_4 more highly bound than T_3. In the dog, the thyroid binding proteins are thyroid hormone-binding globulin (TBG), transthyretin, albumin, and apolipo-proteins, with most T_4 bound to TBG. Dogs have lower avidity of thyroid hormone binding to serum proteins than do humans, which results in lower total serum concentrations of T_4 and T_3, higher free hormone concentrations, and more rapid clearance rates.

Figure 238-1 Synthesis of thyroid hormones. The follicular cells of the thyroid gland concentrate iodide, which diffuses down a gradient into the colloid. Thyroglobulin is synthesized within thyroid follicular cells and secreted into the colloid. Iodide is oxidized and bound to tyrosine residues on the thyroglobulin molecule by thyroid peroxidase. Iodinated tyrosine residues (monoiodotyrosine [MIT] and diiodotyrosine [DIT]) within the thyroglobulin molecule then undergo oxidative condensation to form the iodothyronines (T_3 and T_4), which remain bound to thyroglobulin until secreted. Thyroglobulin is ingested by endocytosis from the colloid; the peptide bonds between the iodinated residues and the thyroglobulin are hydrolyzed; and MIT, DIT, T_4, and T_3, are released into the cytoplasm. MIT and DIT are deiodinated and the iodine is recycled, while T_4 and T_3 are released into the bloodstream. (From Mountcastle VB: *Medical physiology*, ed 14, vol 2. St Louis, 1980, Mosby.)



Only free hormone enters cells to produce a biologic effect or a negative feedback effect on the pituitary and hypothalamus. T_3 enters cells more rapidly, has a more rapid onset of action, and is three to five times more

potent than T_4. Thyroid hormones bind to receptors in the nuclei; the hormone receptor complex binds to DNA and influences the expression of a variety of genes coding for regulatory enzymes.

Thyroid hormone synthesis and secretion are regulated primarily by changes in the circulating concentration of pituitary thyrotropin (TSH) (Figure 238-2). Thyroid hormones are metabolized by progressive deiodination. Outer-ring deiodination of T_4 produces T_3, whereas inner-ring deiodination results in formation of biologically inactive reverse T_3 (rT_3). Deiodination is regulated by the relative activity of different deiodinase enzymes and is an important regulatory step in thyroid hormone metabolism. Thyroxine and T_3 are both concentrated in the liver and secreted in the bile.

Thyroid hormones have a wide variety of physiologic effects. Thyroid hormones increase the metabolic rate and oxygen consumption of most tissues, with the exception of the adult brain, testes, uterus, lymph nodes, spleen, and anterior pituitary. Thyroid hormones have positive inotropic and chronotropic effects on the heart. They increase the number and affinity of beta-adrenergic receptors, enhance the response to catecholamines, and increase the proportion of alpha-myosin heavy chains. Thyroid hormones have catabolic effects on muscle and adipose tissue, stimulate erythropoiesis, and regulate both cholesterol synthesis and degradation. Thyroid hormones are also essential for the normal growth and development of the neurologic and skeletal systems.

238.2 CANINE HYPOTHYROIDISM

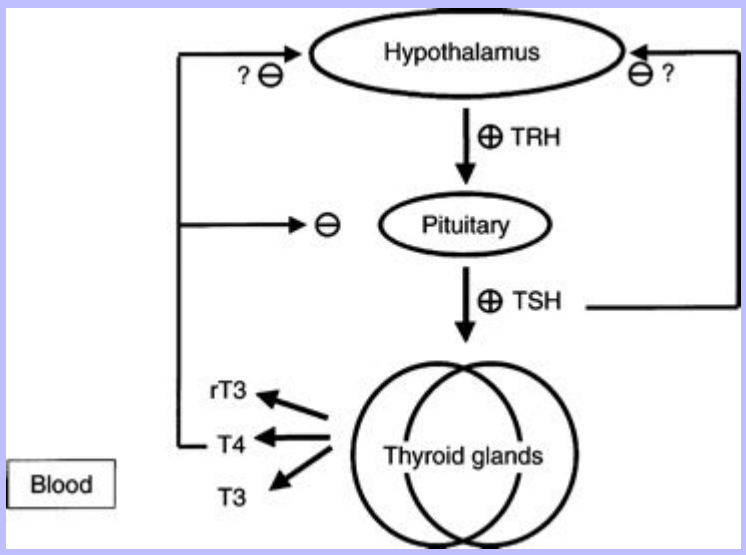
238.2.1 Pathogenesis

Hypothyroidism may result from dysfunction of any part of the hypothalamic-pituitary-thyroid axis (see Figure 238-2). Most acquired canine hypothyroidism is the result of lymphocytic thyroiditis or idiopathic thyroid atrophy.

Approximately 50% of canine primary hypothyroidism is due to lymphocytic thyroiditis.[1] Grossly, the thyroid gland may appear normal or atrophic. There is multifocal or diffuse infiltration of the thyroid gland by lymphocytes, plasma cells, and macrophages.[1] Remaining follicles are small, and lymphocytes, macrophages, and degenerate follicular cells may be found within vacuolated colloid. As thyroiditis progresses, parenchyma is destroyed and replaced by fibrous connective tissue.

Canine thyroiditis is believed to be immune-mediated[2], but the immunologic and molecular pathogenesis has not been well characterized. Antithyroglobulin antibodies are present in 36% to 50% of hypothyroid dogs[3–4], but whether these antibodies occur secondary to follicular cell damage from infiltrating T-cells, or are directly involved in the pathogenesis of thyroiditis is unclear. Thyroiditis is heritable in the beagle and the Borzoi.[5–7] The prevalence of antithyroglobulin antibodies varies significantly from breed to breed.[8]

Figure 238-2 Regulation of thyroid hormone concentrations. Thyroid hormone concentrations are controlled by the hypothalamic-pituitary-thyroid axis, which operates as a negative feedback loop. Thyrotropin (TSH) causes synthesis and release of T_4 and lesser amounts of T_3 from the thyroid gland. Intracellular T_3, derived from deiodination of T_4 within the pituitary gland, causes decreased TSH synthesis and secretion and is the main determinant of TSH concentration. Thyrotropin-releasing hormone (TRH), secreted by the hypothalamus, modulates TSH release from the pituitary gland. Increased thyroid hormone concentrations are also believed to decrease TRH synthesis and secretion. Hormones that inhibit TSH secretion include dopamine, somatostatin, serotonin, and glucocorticoids. TRH, prostaglandins, and alpha-adrenergic agonists increase TSH secretion.



In idiopathic follicular atrophy, there is loss of thyroid parenchyma and replacement by adipose connective tissue.[1] Degeneration of individual follicular cells occurs, with exfoliation of cells into the colloid. Because of the absence of fibrosis or inflammation it is unclear whether follicular atrophy is a distinct syndrome or the final result of thyroiditis.

Less commonly, hypothyroidism is caused by bilateral thyroid neoplasia or invasion of the thyroid by metastatic neoplasia.[9] Dogs with thyroid neoplasia remain euthyroid until at least 75% of the thyroid parenchyma has been destroyed. Lymphocytic thyroiditis has been identified as a risk factor for thyroid neoplasia.[5]

Secondary hypothyroidism (deficiency of TSH) is rarely described in dogs. Causes of acquired secondary hypothyroidism include pituitary malformations and pituitary neoplasia. Histologic changes observed in secondary hypothyroidism include flattening of follicular epithelial cells and distention of thyroid follicles with colloid.[10] Tertiary hypothyroidism (deficiency of thyrotropin releasing hormone [TRH]) has yet to be documented in the dog.

Congenital hypothyroidism (cretinism) is rarely diagnosed in dogs. Reported causes of congenital primary hypothyroidism include iodine deficiency, thyroid dysgenesis, and dyshormonogenesis.[11] Congenital hypothyroidism with goiter due to thyroid peroxidase deficiency was reported as an autosomal recessive trait in toy fox terriers.[12] A genetic test is available to detect carriers of the affected gene. Secondary congenital hypothyroidism due to apparent isolated TSH or TRH deficiency was reported in a family of young giant schnauzers and in a young boxer.[10,13] In both reports, central hypothyroidism was suspected because of increased T_4 secretion and increased uptake of ^{99m}Tc-pertechnetate after repeated administration of TSH. Congenital secondary hypothyroidism is also a feature of panhypopituitarism.

Iatrogenic causes of hypothyroidism include ^{131}iodine treatment, administration of antithyroid drugs, and surgical thyroidectomy. Because of the presence of accessory thyroid tissue, permanent hypothyroidism is rare after thyroidectomy.

238.2.2 Epidemiology

The reported prevalence of canine hypothyroidism is from 0.2% to 0.8%.[14–15] Mean age at diagnosis is 7 years, with a range of 0.5 to 15 years. Golden retrievers and Doberman pinschers are among the breeds reported to be at higher risk for hypothyroidism. Neutered males and females were reported in one study to be at increased risk for developing hypothyroidism compared with sexually intact animals[14]; however, in the most recent study of hypothyroid dogs in the United Kingdom there was no association with breed, gender, or neuter status.[15]

238.2.3 Clinical Signs

Because thyroid hormones influence the function of many organs, hypothyroidism is considered in the differential diagnosis of a wide range of problems. Clinical signs of hypothyroidism may be nonspecific and insidious in onset, and hypothyroidism is commonly misdiagnosed. Common clinical signs attributable to decreased metabolic rate include lethargy, mental dullness, weight gain, unwillingness to exercise, and cold intolerance.[14–15] Obesity occurs in approximately 40% of hypothyroid dogs, but most obese dogs suffer from overnutrition rather than hypothyroidism.

Dermatologic changes occur in 60% to 80% of hypothyroid dogs.[14–15] Common findings include dry scaly skin, changes in haircoat quality or color, alopecia, seborrhea (sicca or oleosa), and superficial pyoderma. Hyperkeratosis, hyperpigmentation, comedone formation, hypertrichosis, ceruminous otitis, poor wound healing, increased bruising, and myxedema may also occur. Alopecia is usually bilaterally symmetric and is first evident in areas of wear, such as the lateral trunk, ventral thorax, and tail. The head and extremities tend to be spared. The hair is often brittle and easily epilated, and loss of undercoat or primary guard hairs may result in a coarse appearance or a puppy-like haircoat. Fading of coat color may also occur, and failure of hair

regrowth after clipping is common. Signs of decreased metabolic rate in conjunction with dermatologic abnormalities should increase suspicion of hypothyroidism.

Hypothyroid dogs are predisposed to recurrent bacterial infections of the skin such as folliculitis, pyoderma, and furunculosis. *Malassezia* spp. infections and demodicosis are associated with hypothyroidism. Pruritus may occur with concurrent infection.

Myxedema (cutaneous mucinosis) is a rare dermatologic manifestation of hypothyroidism characterized by nonpitting thickening of the skin, especially of the eyelids, cheeks, and forehead. It is caused by deposition of hyaluronic acid in the dermis.[16] A rare complication of myxedema is cutaneous mucinous vesiculation.[17]

Female reproductive abnormalities attributed to hypothyroidism include prolonged interestrous interval, silent estrus, failure to cycle, spontaneous abortion, small numbers or low–birth-weight litters, uterine inertia, and weak or stillborn puppies; however, the evidence for this association is weak. Inappropriate galactorrhea apparently due to hyperprolactinemia has been reported in sexually intact hypothyroid bitches.[18] Male reproductive problems attributed to hypothyroidism include low libido, testicular atrophy, hypospermia, and azoospermia. However, a prospective study of six male beagles with ^{131}iodine-induced hypothyroidism showed no decrease in libido or sperm quality over a 2-year period.[19] Decreased testicular size, subfertility, or sterility were reported in association with thyroiditis and orchitis in a colony of beagles.[20]

Both the peripheral and central nervous systems may be affected by hypothyroidism. Peripheral neuropathy is the best documented neurologic manifestation.[21–22] Affected dogs have exercise intolerance, weakness, ataxia, quadriparesis or paralysis, deficits of conscious proprioception, and decreased spinal reflexes. Clinical signs resolve with *l*-thyroxine (T_4) supplementation. A subclinical myopathy also occurs in hypothyroid dogs.[23] Unilateral lameness reported in hypothyroid dogs may be a manifestation of generalized neuromyopathy.[24]

Dysfunction of multiple cranial nerves (facial, trigeminal, vestibulocochlear) and abnormal gait and postural reactions are also reported.[22,25] Hypothyroid dogs with vestibular deficits have abnormal brain stem auditory-evoked responses and some dogs also have electromyographic abnormalities of appendicular muscles. Clinical signs resolve with T_4 supplementation. Because dogs with vestibular disease may have resolution of clinical signs owing to compensation, a causal relationship is less clear.[22] Although laryngeal paralysis and megaesophagus have been reported in association with hypothyroidism, treatment of hypothyroidism does not consistently result in resolution of clinical signs, and a causal relationship has not been confirmed. Myasthenia gravis has been reported in association with hypothyroidism.[26] Concurrent hypothyroidism may exacerbate clinical signs of myasthenia gravis such as muscle weakness and megaesophagus.

Rarely, cerebral dysfunction occurs in hypothyroidism due to myxedema coma, atherosclerosis, or the presence of a pituitary tumor causing secondary hypothyroidism. Seizures, disorientation, and circling may occur due to severe hyperlipidemia or cerebral atherosclerosis.[27–28] In myxedema coma, profound mental dullness or stupor is accompanied by nonpitting edema, hypothermia with a lack of shivering, bradycardia, weakness, and inappetence.[29]

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Abnormalities of the cardiovascular system such as sinus bradycardia, weak apex beat, low QRS voltages, and inverted T waves occur in hypothyroid dogs.[14] Reduced left ventricular pump function has also been

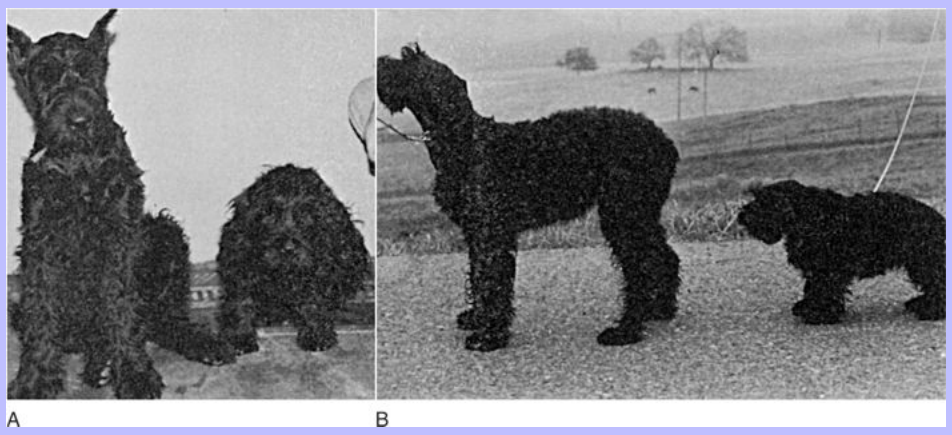
documented, and hypothyroidism may exacerbate clinical signs in dogs with underlying cardiac disease.[30] Although hypothyroidism rarely causes clinically significant myocardial failure in dogs, dilated cardiomyopathy and hypothyroidism may occur concurrently. A recent case report documented dramatic long-term improvement in cardiac function after treatment with T_4 in two Great Danes with concurrent dilated cardiomyopathy and hypothyroidism.[31]

Ocular abnormalities reported in canine hypothyroidism include corneal lipidosis, corneal ulceration, uveitis, lipid effusion into the aqueous humor, secondary glaucoma, lipemia retinalis, retinal detachment, and keratoconjunctivitis sicca, however a definite causal relationship has not been proven. Dogs with experimentally induced hypothyroidism did not develop ocular changes over a 6-month time period.[32]

Clinical signs of secondary hypothyroidism are similar to those of primary hypothyroidism, but clinical signs related to a deficiency of other pituitary functions may predominate, particularly if a pituitary neoplasm is present.

Congenital hypothyroidism results in mental retardation and stunted disproportionate growth due to epiphyseal dysgenesis and delayed skeletal maturation (Figure 238-3).[33] Affected dogs are mentally dull and have large, broad heads, short thick necks, short limbs, macroglossia, hypothermia, delayed dental eruption, ataxia, and abdominal distention.[10–13] Dermatologic findings are similar to those seen in the adult hypothyroid dog. Other clinical signs may include gait abnormalities, stenotic ear canals, sealed eyelids, and constipation. Affected puppies are often the largest in the litter at birth but start to lag behind their littermates within three to eight weeks. It is likely that many severely affected puppies die without a diagnosis in the first few weeks of life. Vertebral physeal fracture causing tetraparesis was reported in a dog with congenital hypothyroidism.[33]

Figure 238-3 Eight-month-old female giant schnauzer littermates. The dog on the left is normal, whereas the smaller dog on the right has congenital hypothyroidism (cretinism). Note the small stature; disproportionate body size; large, broad head; wide, square trunk; and short limbs in the cretin. (From Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction,* ed 2, Philadelphia, 1996, WB Saunders, p 83.)



238.2.4 Clinicopathologic Changes

Results of a hemogram, biochemical panel, and urinalysis often support a diagnosis of hypothyroidism and rule out other disorders. A mild nonregenerative anemia occurs in 30% of hypothyroid dogs.[14] Fasting hypercholesterolemia occurs in 75% of hypothyroid dogs, whereas hypertriglyceridemia occurs in up to 88%.[15] In rare cases hyperlipidemia may lead to atherosclerosis. Less common abnormalities include mild increases in alkaline phosphatase, alanine aminotransferase, and creatine kinase. Mild hypercalcemia has been reported in congenital hypothyroidism.

238.2.5 Hemostasis

Decreased plasma von Willebrand factor antigen (vWf:Ag) concentration was reported in hypothyroid dogs; however, studies have failed to demonstrate a relationship between vWf:Ag or factor VIII activity and thyroid hormone status.[34–36] Canine hypothyroidism is rarely associated with clinical bleeding, and platelet function and bleeding times are normal. Concentrations of vWf:Ag do not consistently increase during treatment of hypothyroid dogs with T_4.[35]

238.2.6 Polyendocrinopathies

Canine hypothyroidism may occur in association with other immune-mediated endocrine disorders such as hypoadrenocorticism and diabetes mellitus.[37–39] Hypothyroidism causes insulin resistance and may mask the classic electrolyte changes of hypoadrenocorticism.

238.2.7 Diagnosis of Hypothyroidism

238.2.7.1 Patient Selection

Appropriate patient selection is important in evaluation of thyroid function. The positive predictive value of diagnostic tests is highest when the prevalence of the disease is high. A complete history, physical examination and minimum database aid in identification of other diseases and determination of whether thyroid dysfunction is likely. Testing of healthy dogs prior to breeding or of obese dogs with no other clinical signs of thyroid disease increases the chance of false-positive test results.

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238.2.7.2 Basal Thyroid Hormone Concentrations

Thyroid hormones commonly measured include total T_4 (TT_4), total T_3 (TT_3), and free T_4 (fT_4). Assays for free T_3 (fT_3) and reverse T_3 (rT_3) are less commonly used. Assays must be validated for the dog. Serum antibodies directed against T_3 and T_4 may interfere with thyroid hormone assays because they compete for hormone with antibodies used in the assay. These antibodies may cause spuriously high or low results, depending on the assay used. Thyroid hormones are stable at 37° C for 5 days, provided the samples are stored in plastic rather than glass.[40] They are also stable when frozen, even with repeated freezing and thawing. Samples should be stored and shipped in plastic tubes.

238.2.7.2.1

Total T_4 concentration

Total T_4 concentration is an excellent screening test for canine thyroid dysfunction (Figure 238-4). A dog with a TT_4 concentration well within the reference range is euthyroid, unless anti-T_4 antibodies are causing a spurious increase in the TT_4 value. This is uncommon, because anti-T_4 antibodies are detected in less than 2% of samples from dogs with suspected hypothyroidism,[41] and antibody interference most commonly results in TT_4 measurements outside the reference range. Unfortunately, decreased TT_4 concentration is not specific for a diagnosis of hypothyroidism. Decreased TT_4 may be normal for an individual, a result of nonthyroidal illness, or secondary to drug administration. The reference range for TT_4 concentration depends on the laboratory but is usually 1.5 to 3.5 μg/dL. Time of day, age, breed, season, and ambient temperature may influence serum TT_4 concentration. In healthy euthyroid dogs, TT_4 concentration may decrease below the reference range as much as 20% of the time, but there is no predictable diurnal pattern.[42] Serum TT_4 concentrations in neonates are similar to those of young adult dogs; they then increase to more than two to five times the adult concentration by 3 weeks of age. Total T_4 concentrations return to that of the adult dog by 12 weeks of age, then gradually decline with age.[43]

Total T_4 concentrations do not differ significantly between males and females but are higher in small dogs than in medium and large breed dogs.[43] Greyhounds and Scottish deerhounds have lower TT_4 concentrations than other breeds.[44] During diestrus and pregnancy, TT_4 concentration increases owing to changes in thyroid hormone protein binding. Mild increases in TT_4 concentration may also occur in obese dogs.

238.2.7.2.2

Free T_4 concentration

Protein-bound hormone acts as a reservoir to maintain concentrations of free hormone in plasma despite fluctuations in release or metabolism of T_3 and T_4, or in plasma protein concentrations. Thus free hormone concentrations are less affected by changes in protein concentration and binding than are total hormone measurements. Because only free hormone can enter cells and bind to receptors, measurement of fT_4 should give a more accurate representation of thyroid function. In humans, fT_4 concentration often remains normal during nonthyroidal illness, but this does not always occur in dogs. The standard method for measuring fT_4 is equilibrium dialysis. Because this is expensive and time consuming, single-stage solid phase (analog) radioimmunoassays for human fT_4 are sometimes used for measurement of canine fT_4. These assays depend on the dominance of thyroid hormone binding by TBG, concentrations of which are lower in dogs than in humans. Canine fT_4 concentrations measured by analog methods are lower than those measured by equilibrium dialysis and have no diagnostic advantage over measurement of TT_4. A commercial fT_4 assay that uses an equilibrium dialysis step is more accurate than analog methods and is more sensitive and specific for canine hypothyroidism than is measurement of TT_4.[45,46] This assay is also unaffected by anti-T_4 antibodies and is the most accurate single hormone measurement for diagnosis of hypothyroidism.

238.2.7.2.3 Total T_3 concentration

Measurement of TT_3 concentration is less accurate than TT_4 measurement for distinguishing euthyroid from hypothyroid dogs, because TT_3 concentrations fluctuate out of the normal range even more than TT_4 concentrations in euthyroid dogs.[42] Spurious results may occur because of anti-T_3 antibodies.

238.2.7.2.4 Reverse T_3 and free T_3 concentrations

In humans, one mechanism for the euthyroid sick syndrome is decreased 5′-deiodinase activity. This results in a reciprocal relationship between T_3 and rT_3 concentrations. Although this change was documented experimentally in dogs[47], it does not occur predictably in all dogs with nonthyroidal illness. The clinical utility of measurement of rT_3 or fT_3 in dogs has not been demonstrated.

238.2.7.3 Effect of Drugs on Thyroid Hormone Concentrations

Drug administration can change thyroid hormone concentrations in dogs.[48] Glucocorticoids influence peripheral metabolism of thyroid hormones and inhibit TSH secretion. The effect of glucocorticoids is dependent on the dose and specific preparation. In most studies oral administration of glucocorticoids at immunosuppressive doses (1 to 2 mg/kg q12h) resulted in rapid decreases in TT_4, fT_4, and T_3, but little change in serum TSH.[48] Thyroid hormones return to normal within 1 week after stopping treatment if dosing is for 3 weeks or less. Longer treatment may prolong duration of suppression.

Sulfonamides block iodination of thyroglobulin and can cause clinical hypothyroidism in a dose and duration dependent manner. Trimethoprim-sulfadiazine (15 mg/kg q12h) had no effect on thyroid function but caused clinical hypothyroidism at a dose of 24 mg/kg every 12 hours for 40 days.[48] Trimethoprim-sulfamethoxazole at a dose of 30 mg/kg orally every 12 hours decreased TT_4 and TT_3 concentrations, increased TSH, and decreased response to TSH administration within 4 weeks. Effects are reversible within 2 to 4 weeks of discontinuation of therapy. Phenobarbital administration causes decreased TT_4 and fT4 concentrations and mild increases in TSH concentration. Whether dogs treated with phenobarbital have mild clinical signs of hypothyroidism is difficult to assess. Clomipramine results in decreased TT_4 and fT4 concentrations but no change in TSH concentration. Other drugs that may affect thyroid hormone concentrations in dogs include androgens, furosemide, heparin, nonsteroidal anti-inflammatory drugs, propranolol, amiodarone, radiocontrast agents, and iodide.[48]

238.2.7.4 Effect of Systemic Illness on Thyroid Hormone Concentrations

In nonthyroidal illness, thyroid hormone concentrations are often decreased. Changes in hormone binding to serum carrier proteins (e.g., decreased protein concentration, reduced binding affinity, circulating inhibitors of binding), or peripheral hormone distribution and metabolism (e.g., reduced 5′-deiodinase activity), inhibition of TSH secretion, and inhibition of thyroid hormone synthesis may occur. Cytokines such as interleukin-1, interleukin-2, interferon gamma, and tumor necrosis factor alpha decrease TT_4 concentrations.[49] In dogs, TT_4 concentration is more frequently decreased than is TT_3 concentration. The

magnitude of decrease depends on disease severity and is a predictor of mortality.[50] Thyroid hormone supplementation does not improve survival in euthyroid humans with decreased thyroid hormone concentrations. Conditions reported to decrease TT_4 concentrations in dogs include hyperadrenocorticism, diabetic ketoacidosis, hypoadrenocorticism, renal failure, hepatic disease, peripheral neuropathy, generalized megaesophagus, heart failure, critical illness or infection, and surgery or anesthesia.[50–54] In 59 euthyroid dogs with concurrent illness, 20% had low TT_4 concentrations and 17% had low fT_4 concentrations.[51] In 67 critically ill euthyroid animals, 61% had low T_4 concentrations and 56% had low T_3 concentrations.[50] In 42 dogs with hyperadrenocorticism, 38% had low TT_4, 24% had low fT_4, and 39% had low TT_3 concentrations.[52] Dogs with chronic weight loss had decreased TT_4 and TT_3 concentrations regardless of the cause of weight loss.[54]

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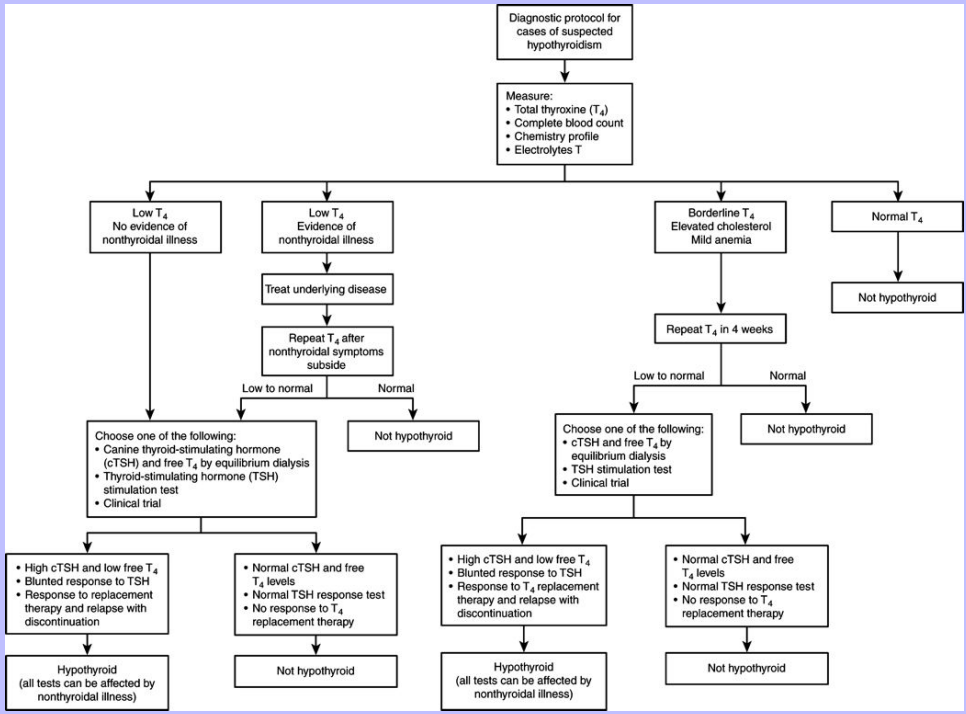
Figure 238-4 Algorithm for diagnosis of hypothyroidism.



238.2.7.5 Basal Thyrotropin (TSH) Concentration

Because of the negative feedback effect of TT_4 on the pituitary gland, measurement of canine TSH concentration should be an accurate indicator of thyroid dysfunction. However, current assays for canine TSH have poor sensitivity for diagnosis of hypothyroidism. From 13% to 38% of hypothyroid dogs have a TSH concentration within the reference range.[45,46,55,56] Possible reasons for a normal TSH concentration in hypothyroid dogs include secondary or tertiary hypothyroidism, fluctuation in TSH concentration, and effect of drugs or concurrent illness. In addition, the TSH assay may not detect all isoforms of circulating

TSH. Although some hypothyroid dogs with normal or low TSH concentrations have secondary or tertiary hypothyroidism, it is unlikely that this accounts for most hypothyroid dogs with normal TSH concentrations. Serum TSH concentrations in hypothyroid dogs fluctuate into the normal range, but there is no predictable pattern.[57] In hypothyroid humans, concurrent illness and drugs can decrease TSH concentration toward or into the high-normal range.

Specificity of TSH alone for diagnosis of hypothyroidism is lower than measurement of fT_4 or TT_4 because TSH concentrations are increased in 7% to 18% of euthyroid dogs. Reasons for increased TSH with a normal TT_4 include early hypothyroidism, effects of drugs and recovery from nonthyroidal illness. TSH concentrations remain within the reference range in most euthyroid dogs with concurrent illness.[58] Specificity of TSH for diagnosis of hypothyroidism in dogs with concurrently low TT_4 or fT_4 approaches 100% (Table 238-1).[45,55]

238.2.7.5.1

TSH response test

The TSH response test is a test of thyroid gland reserve and is the criterion standard for diagnosis of canine hypothyroidism. Clinical use of this test is limited by the availability and expense of medical grade bovine TSH. Life-threatening reactions may occur in some dogs following use of chemical grade TSH. The most widely accepted protocol for the TSH stimulation test is measurement of TT4 followed by intravenous administration of bovine TSH at 0.1 units/kg (maximum 5 units). A second sample for measurement of TT_4 is collected 6 hours later. Other protocols use a fixed dose of 1 to 5 units per dog; however, lower TSH doses result in smaller and less prolonged increases in TT_4 concentration and more borderline responses in pets. Recombinant human TSH may also be used at a dose of 25 to 100 µg IV but is expensive.[59] Reconstituted TSH may be refrigerated for up to 3 weeks or frozen at −20°C for up to 6 months.[60,61]

Table • 238-1 Performance of Various Diagnostic Tests for Hypothyroidism in Dogs*

	SENSITIVITY	SPECIFICITY	ACCURACY
Total T_4	89% to 100%	75% to 82%	85%
Free T_4	80% to 98%	93% to 94%	95%
TSH	63% to 87%	82% to 93%	80% to 84%
TSH/T4†	63% to 67%	98% to 100%	82% to 88%
TSH/free T_4†	74%	98%	86%

* The data are compiled from three published studies of a total of 100 hypothyroid dogs and 164 euthyroid dogs.45,46,56 Not all studies evaluated all diagnostic tests listed.

† A dog was considered to have hypothyroidism only if the T4 or free T4 was low and the TSH was high.

A diagnosis of hypothyroidism is likely if both pre-and post-TSH serum T_4 concentrations are below the reference range (<1.5 µg/dL). A post-TSH T_4 concentration greater than 3 µg/dL indicates euthyroidism.[60–63] Interpretation of intermediate results is more difficult and should take into consideration the clinical signs and severity of concurrent systemic disease. Change in TT_3 before and

after TSH administration is of little diagnostic utility. The TSH response test cannot be used to evaluate thyroid function in dogs receiving T_4, because treatment causes thyroid atrophy. Supplementation must be discontinued 6 to 8 weeks before testing.

238.2.7.5.2

TRH response test

The TRH response test is used in humans to differentiate primary from secondary hypothyroidism. In people with primary hypothyroidism response of TSH to TRH administration is exaggerated, whereas in secondary hypothyroidism there is no response. In contrast, most hypothyroid dogs have a decreased TSH response to TRH compared with euthyroid dogs.[64] The TRH response test is therefore not useful for differentiation of primary and secondary hypothyroidism in dogs.

In dogs, the TRH response test is most commonly used in place of the TSH response test, and change in TT_4 is usually measured. Doses ranging from 0.01 to 0.1 mg/kg of TRH have been evaluated.[63–66] Lower doses cause similar increases in TT4 as do higher doses and are less likely to result in side effects such as salivation, vomiting, urination, defecation, miosis, tachycardia, or tachypnea. A common protocol is administration of 200 μg TRH per dog intravenously with blood collected before and 4 hours after TRH administration.[64] Freshly reconstituted TRH may be frozen at −20°C for at least a week without a loss in potency. Euthyroidism is likely if the post-TRH TT_4 concentration is greater than 2 μg/dL. Euthyroidism is also more likely if there is a relative increase in TSH of greater than 100% at 30 minutes after TRH administration.[64] A diagnosis of hypothyroidism is possible if the post-TRH TT_4 concentration is below the reference range (< 1.5 μg/dL); however, some euthyroid dogs fail to respond to TRH. The TRH response test is therefore less reliable than the TSH response test for diagnosis of canine hypothyroidism.[66]

238.2.7.5.3

Scintigraphy

Few studies evaluate the use of scintigraphy for diagnosis of thyroid dysfunction in the dog. Dogs with normal thyroid function have a median thyroid: salivary (T:S) ratio of approximately 1 at 20 and 60 minutes after injection of ^{99m}Tc-pertechnetate.[67] Decreased thyroid uptake of pertechnetate is reported in hypothyroid dogs, but increased uptake of pertechnetate was documented in a hypothyroid dog with thyroiditis. Further evaluation of scintigraphic findings in canine hypothyroidism is necessary. Scintigraphy can identify the underlying cause in puppies with congenital hypothyroidism. In puppies with thyroid agenesis, minimal uptake of pertechnetate in the area of the thyroid gland is detected, whereas in those with iodination defects, thyroid lobes are large, with normal or increased T:S ratios. Scintigraphy may also help identify central hypothyroidism. Administration of TSH for 3 days does not alter the thyroid image in dogs with primary hypothyroidism but does result in increased thyroid uptake in dogs with central hypothyroidism.[10] Radioactive iodine uptake and perchlorate discharge tests may also be useful in characterization of dogs with congenital hypothyroidism.[12]

238.2.8 Diagnosis of Thyroiditis

238.2.8.1 Antithyroglobulin Antibody

Antithyroglobulin antibodies (ATA) are found in 36% to 50% of hypothyroid dogs.[3–4] A commercially available enzyme linked immunosorbent assay (ELISA) for ATA is a sensitive and specific indicator of thyroiditis, with false-positive results occurring in less than 5% of dogs with other endocrine disorders.[3] Importantly, a positive ATA titer is not diagnostic of abnormal thyroid function because subclinical thyroiditis may be present for long periods of time before progression to hypothyroidism. In addition, vaccination can result in transient increases in ATA titer.[68] It is unknown whether all dogs with ATA ultimately develop hypothyroidism. In 171 euthyroid dogs with ATA followed for 12 months, 4% progressed to overt hypothyroidism, 13% developed some evidence of thyroid dysfunction, and 15% became antibody negative.[8] It is likely that the natural history of thyroiditis varies from breed to breed. Breeds with increased prevalence of antithyroglobulin antibodies include the golden retriever, great Dane, English and Irish setters, Doberman pinscher, Old English sheepdog, dalmatian, basenji, Rhodesian ridgeback, boxer, Maltese, Chesapeake Bay retriever, Cocker spaniel, Shetland sheepdog, Siberian husky, border collie, and Akita.[8] Measurement of ATA has been advocated for screening breeding stock, with the aim of ultimately eliminating heritable forms of thyroiditis. Whether this is an effective approach has yet to be demonstrated.

238.2.8.2 Anti-T_3 and-T_4 Antibodies

Antibodies directed against T_3 and T_4 (THAA) also occur in canine thyroiditis, although they are less prevalent than ATA. Because T_3 and T_4 alone are small molecules, these antibodies probably develop against T_3-and T_4-containing epitopes of thyroglobulin. Anti-T_3 antibodies are found in only 5.7% of samples from dogs with clinical signs consistent with hypothyroidism but in 34% of confirmed hypothyroid dogs. Anti-T_4 antibodies are found in 1.7% of samples from dogs with clinical signs consistent with hypothyroidism but are found in 15% of confirmed hypothyroid dogs.[8,41] Because dogs with thyroiditis may still have adequate thyroid reserve, THAA are not diagnostic of hypothyroidism. Prevalence of THAA is highest in younger dogs (2 to 4 years), large-breed dogs, and females. Dog breeds with a high prevalence of THAA include pointers, English and Irish setters, Skye terriers, Old English sheepdogs, boxers, and Maltese terriers.[41]

238.2.8.3 Thyroid Biopsy

Lymphocytic thyroiditis is readily identified by histopathology, but it is more difficult to determine thyroid function. Thyroid biopsy is rarely indicated for clinical diagnosis of thyroid dysfunction.

238.2.9 Treatment and Therapeutic Monitoring

238.2.9.1 Hypothyroidism

The initial treatment of choice regardless of the underlying cause of the disease, is synthetic sodium *l*-thyroxine (T_4). Treatment with T_4 preserves normal regulation of T_4 to T_3 conversion, which allows normal physiologic regulation of tissue T_3 concentrations and therefore should decrease the likelihood of iatrogenic hyperthyroidism. Treatment with synthetic T_3 is not recommended because of an increased risk of iatrogenic hyperthyroidism. In addition, T_3 has a shorter half-life and requires administration three times daily. Treatment with T_3 may be indicated if there is inadequate gastrointestinal absorption of T_4. Gastrointestinal absorption of ingested T_3 approaches 100%, whereas oral bioavailability of T_4 is lower, at 10% to 50%. Treatment with T_3 was previously advocated in suspected hypothyroid dogs with a normal T_4 but a low T_3; however, this is no longer recommended. This scenario was thought to be due to a T_4 to T_3 conversion defect, but such a defect has not been documented in dogs. Rather, this hormone profile likely represents sick euthyroid syndrome, presence of anti-T_3 antibodies, or normal daily fluctuations in plasma T_3 concentration.

The use of desiccated thyroid extract, thyroglobulin, or “natural” thyroid preparations is not recommended because the bioavailability and T_4:T_3 ratio of these compounds is variable, making consistent dosing difficult. In humans, substitution of T_3 for some of the T_4 dose is associated with an improved psychologic state in some studies, possibly because tissues vary in their ability to convert T_4 to T_3.[69] Commercially available combination T_4/T_3 products contain a T_4:T_3 ratio of 4:1, and may predispose to iatrogenic hyperthyroidism because the normal ratio of T_4:T_3 secreted by the thyroid gland is approximately 20:1.

Optimum dose and frequency of supplementation varies among dogs because of variability in T_4 absorption and serum half-life.[70] A dose of 0.02 mg/kg q24h normalizes TSH concentration in most dogs; higher doses (0.04 mg/kg q12h) are required to consistently normalize T_3 concentration,[71–72] but there is little evidence that normalization of T_3 is necessary for a good clinical response. Treatment should be initiated at a dose of 0.02 mg/kg PO q12h and the dose adjusted based on the measured serum T_4 concentration (Figure 238-5). Twice daily treatment with T_4 is initially recommended to improve the likelihood of response to treatment. If clinical signs resolve and T_4 concentrations are within the therapeutic range, the frequency of T_4 administration may be decreased to once daily. It is advisable to use a brand-name product for initial treatment because studies in people have shown large variability in the bioavailability of generic products. Name brand canine and human products appear to have similar bioavailability.[72,73]

Adequacy of therapy should be confirmed by therapeutic monitoring 4 to 8 weeks after beginning supplementation. Serum T_4 concentration should be within the reference range immediately prior to administration of a dose, and at the high end or slightly above the reference range 4 to 6 hours after administration of a dose. This is a clinically effective approach but it may result in over-supplementation in some dogs. Current assays for TSH are not sensitive enough to distinguish a normal from a low TSH concentration and thus cannot distinguish between those dogs that are adequately supplemented and those that are over-supplemented. Dogs are believed to be relatively resistant to development of iatrogenic

hyperthyroidism because of the short half-life of T_4 in this species, however the risk of long-term over-supplementation of thyroid hormone in dogs has not been investigated. Serum T_4 concentrations should be measured at 6-to 8-week intervals during the first 6 to 8 months of treatment, because metabolism of T_4 changes as the metabolic rate normalizes. Frequency of serum T_4 measurement may then be decreased to once or twice a year. If the brand of supplement is changed, serum T_4 concentration should be measured 4 to 8 weeks after the change.

The majority of hypothyroid dogs demonstrate good control of their disease at a dose of 0.02 mg/kg T_4 administered orally once daily.[74] However, therapy should be individualized based on clinical response, therapeutic monitoring, and presence or absence of concurrent illness. Improvement in activity should occur within the first 1 to 2 weeks of treatment; weight loss should be evident within 8 weeks.[14] Achievement of a normal hair coat may take several months and the coat may initially appear worse as telogen hairs are shed.[75] Improvement in myocardial function is usually evident within 8 weeks, but may be delayed for as long as 12 months. Neurologic deficits improve rapidly after treatment but complete resolution may take 8 to 12 weeks.[22]

Inadequate supplementation with thyroid hormone results in an incomplete clinical response. It may be difficult to establish what is normal for some dogs, because subtle clinical signs of hypothyroidism may have been present for so long that the owners do not know what activity level is normal for their dog. This is one reason therapeutic monitoring is important. Some hypothyroid humans do not have complete resolution of clinical signs unless treated with a small amount of T_3 in addition to T_4. Whether this is also the case in some dogs is unknown.

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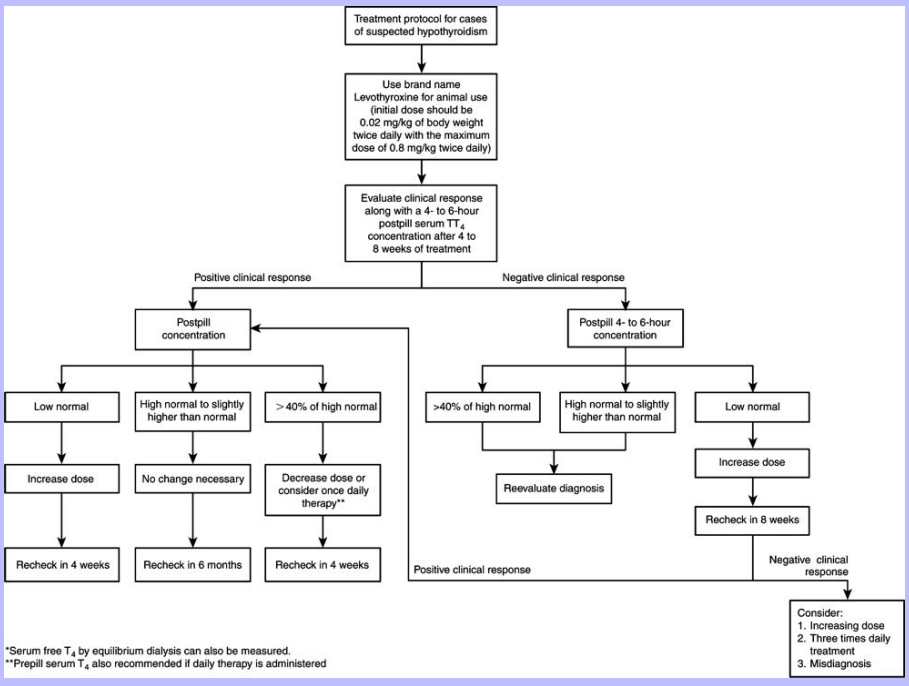
Figure 238-5 Algorithm for treatment of hypothyroidism.



In myxedema coma, T_4 should be administered initially intravenously (5 μg/kg) because of poor gastrointestinal absorption due to hypomotility. Other supportive care including appropriate fluid therapy, passive rewarming, and ventilatory support may also be necessary.

238.2.9.2 Concurrent Nonthyroidal Illness

238.2.9.2.1 Cardiomyopathy

In hypothyroid dogs with cardiac disorders, thyroid hormone supplementation increases myocardial oxygen demand and may cause cardiac decompensation. Initial doses of thyroid hormone replacement should be 25% to 50% of the usual starting dose. The dose may then be increased incrementally based on the results of therapeutic monitoring and reevaluation of cardiac function. Because euthyroid dogs with cardiac disease may have decreased thyroid hormone concentrations, it is important to adequately document hypothyroidism to avoid inappropriate treatment.

238.2.9.2.2 Hypoadrenocorticism

Replacement of mineralocorticoid and glucocorticoid deficiency should be initiated before treatment with T_4, because the increased basal metabolic rate may exacerbate electrolyte disturbances.

238.2.10 Treatment Failure

An incorrect diagnosis of hypothyroidism is the most common reason for treatment failure. Diseases such as hyperadrenocorticism, atopy, and flea hypersensitivity may have clinical signs similar to those of hypothyroidism and often are associated with decreased thyroid hormone concentrations (sick euthyroid syndrome). Other causes include insufficient absorption from the gastrointestinal tract or poor owner compliance. If poor gastrointestinal absorption is suspected, T_3 may be substituted for T_4 (4 to 6 μg/kg q8h).

238.2.11 Prognosis

Prognosis for return to normal function following treatment is excellent in most adult hypothyroid dogs. Prognosis in myxedema coma is dependent on early recognition. Resolution of clinical signs in puppies with congenital hypothyroidism is dependent on the age at which treatment is initiated.

238.3 FELINE HYPOTHYROIDISM

Naturally occurring hypothyroidism is rare in cats. The most common cause of low serum TT_4 in cats is nonthyroidal illness. Iatrogenic hypothyroidism occasionally occurs following treatment for hyperthyroidism. Clinical signs of hypothyroidism in cats are similar to those reported for dogs. Causes of spontaneous feline hypothyroidism include congenital hypothyroidism in domestic shorthair cats and Abyssinian cats[76–78] and lymphocytic thyroiditis reported in a 5-year-old cat and in young kittens.[79,80]

Diagnosis of feline hypothyroidism is confirmed by physical examination, history, measurement of serum TT_4 concentration, and results of TSH or TRH stimulation tests. For a TSH stimulation test, TSH is administered at 1

IU/cat intravenously or 2.5 to 5 IU/cat intramuscularly.[81] Blood samples are collected before injection and 4 to 7 hours after intravenous injection or 8 to 12 hours after intramuscular injection. Serum TT_4 concentration should double after TSH administration. The dose of TRH is 0.1 mg/kg given intravenously, with blood collected before and 4 to 6 hours after injection. Serum TT_4 concentration should increase by greater than 50% after TRH administration. Immediate transient side effects following TRH administration include salivation, vomiting, tachypnea, and defecation. A commercial assay for canine TSH has been validated for feline use. A high TSH measured using this assay in conjunction with a low T_4 in the presence of appropriate clinical signs supports a diagnosis of hypothyroidism.

Hypothyroid cats may be treated with T_4 at a dosage of 0.05 to 0.1 mg/cat given orally once daily. Therapeutic monitoring and dosage adjustments should be performed as recommended for dogs.

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239 CHAPTER • 239 Hyperthyroidism

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239.1 FELINE HYPERTHYROIDISM

Hyperthyroidism (thyrotoxicosis) is a multisystemic disorder arising from the excess production of the active thyroid hormones (triiodothyronine [T_3] and/or thyroxine [T_4]) from an abnormally functioning thyroid gland.[1] In cats, this condition was first definitively diagnosed in the late 1970s. Its prevalence has increased significantly such that it is now recognized not only as the most common endocrine disease of the cat but also as one of the more frequently diagnosed disorders in small animal practice.

239.1.1 Etiopathogenesis

Functional adenomatous hyperplasia (or less frequently adenoma) of one (approximately 30% of cases) or, more commonly, both (70% of cases) thyroid lobes is the most common abnormality associated with hyperthyroidism in cats.[1–6] On histologic examination, the normal thyroid follicular architecture is replaced by one or more, well-discernible foci of hyperplastic tissue that can form nodules ranging in size from less than 1 mm to greater than 3 mm, with wide variation in follicular size and architecture both within and between individual nodules.[4] Normal but compressed thyroid tissue is often found surrounding abnormal follicles, but occasionally zones of smooth transition between normal and hyperplastic tissue are present. Thyroid carcinoma, by contrast, is rare, accounting for less than 2% of hyperthyroid cases.[1,7]

Prior to 1979, when hyperthyroidism was first definitively diagnosed, there were a few anecdotal reports of thyroid abnormalities in cats but rarely with clinical signs.[7] However, the frequency with which hyperthyroidism is diagnosed has since increased dramatically.[8] Retrospective necropsy studies reveal few cats with thyroid abnormalities prior to 1979,[7] whereas clinical studies demonstrate a significant increase in cases since that time. In the Animal Medical Center, New York, approximately three hyperthyroid cases per month were seen in 1983; this increased to 22 cases per month in 1993, despite a similar feline caseload.[9] Increased awareness and easier availability of thyroid hormone assays alone is unlikely to account for the dramatic increased frequency of diagnosing this disease, and it has been suggested that it is truly a new disease of cats. However, it remains unclear whether this disorder is simply diagnosed more frequently because of both a general growth in the pet cat population and an overall increase in the longevity of the cat.[9]

Although the disorder and its pathologic lesions have by now been well described, the cause remains obscure. Histologically the disease most closely resembles human toxic nodular goiter, although the fact that bilateral involvement is more common (despite no clear anatomic link between the two thyroid lobes) is reminiscent of human Graves' disease. Graves' disease is an autoimmune disorder in which circulating antibodies (thyroid-stimulating immunoglobulins [TSIs]) bind to thyrotropin (thyroid-stimulating hormone [TSH]) receptors and mimic TSH. Initial studies in hyperthyroid cats suggested that autoantibodies (thyroid microsomal and antinuclear) were common and could be involved in the pathogenesis of the condition.[10] However, four separate studies, using three different techniques, including transfected cells expressing the TSH receptor gene, have failed to identify TSIs in hyperthyroid cats.[11–14] Increased titers of

growth-stimulating immunoglobulins have been demonstrated in hyperthyroid cats but their role in the pathogenesis of the condition is unclear.[13]

As in human toxic nodular goiter, adenomatous thyroid tissue from hyperthyroid cats retains its histologic appearance and continues to grow and function when transplanted onto nude mice.[4] Thyroid cells from affected cats, cultured in TSH-free media, also continue to grow and hyperfunction.[15] Somatic mutations of the TSH receptor gene are an important cause of toxic adenoma in humans. However, one research group investigating the possibility of such a cause in cats did not find any corresponding mutations between codons 480 and 640 of the feline TSH receptor gene—the area corresponding to the majority of human disease.[16] Extending such a study to include codons 66 to 530, allowing inclusion of the transmembrane and most of the extracellular part of the TSH receptor, also found no mutations, suggesting that the pathogenesis of hyperthyroidism in cats is unlikely to involve mutations in this gene.[17] After TSH binds to its receptor, signal transduction is cyclic adenosine monophosphate (cAMP)-dependent via a G protein–mediated pathway. Decreased expression of a G protein (specifically G_{i2}) that is normally involved in inhibition of a wide range of G protein–dependent intracellular signaling processes (amongst them the signal to secrete thyroid hormones) has been demonstrated in hyperthyroid cats.[18,19] A more recent study has suggested that mutations in the $G_{s\alpha}$ gene found in some hyperthyroid cats may play a role in the development of adenomatous hyperplasia.[17]

Thyroid tissue from hyperthyroid cats has also been examined immunohistochemically to identify expression of the oncogenes c-ras, bc12, and the tumor suppressor gene p53. Overexpression of the product of c-ras has been demonstrated but without detectable staining for either bc12 or p53. Gain-of-function mutations in this oncogene may therefore play a role in the etiopathogenesis of the feline disease.[20]

Several epidemiologic studies have attempted to uncover risk factors that may be implicated in the pathogenesis of the disease. Two separate studies have reported that two genetically related breeds, the Siamese and Himalayan, are at decreased risk of developing hyperthyroidism.[8,21] Cats fed almost entirely canned food and those using cat litter have an increased risk of developing hyperthyroidism.[8,21] In addition, cats that prefer to eat certain flavors of canned cat food (fish or liver and giblet flavor) have a significantly increased risk of developing hyperthyroidism.[22] Because of this dietary association, iodine has been implicated in the cause or progression of the disease. The iodine content of cat food is extremely variable and often up to 10 times the recommended level.[23,24] It has been postulated that wide swings in daily iodine intake may somehow contribute to the development of thyroid disease. Although serum free T_4 concentrations may be acutely affected by varying iodine intake, more prolonged ingestion has no apparent statistical effect.[25,26] Selenium status could also potentially modify thyroid function. One study found no difference in selenium status in cats from different geographic regions with high and low prevalence of hyperthyroidism but did find that cats had higher circulating selenium concentrations than other species (possibly as a result of increased intake) that may play a role in the pathogenesis of the condition.[27] Many other goitrogenic compounds exist (e.g., phthalates) that can contribute to the development of adenomatous lesions in exposed cats. These may be of particular importance because most are metabolized by glucuronidation, a metabolic pathway particularly slow in the cat. A recent study has shown that the potentially goitrogenic soy isoflavones, genistein, and daidzein, are common constituents of commercially available cat foods and may be present in concentrations sufficient to result in some biologic effect.[28]

239.1.2 Clinical Features

Hyperthyroidism is a disease of middle-aged to older cats, with an average age of onset of 12 to 13 years.[2,6,9,29] Although the reported age range is 4 to over 20 years, less than 5% of cats are younger than 10 years of age at the time of diagnosis.[1] There has been a recent report of hyperthyroidism in an 8-month-old kitten, but thyroid histologic changes were unlike those found in adult cats and are likely to represent a separate disease entity.[30] No sex predisposition exists, and despite the decreased risk of developing hyperthyroidism associated with certain breeds, most large case studies have failed to identify a breed predilection.[2,6,9,29]

Thyroid hormones are responsible for a wide variety of actions including the regulation of heat production and carbohydrate, protein, and lipid metabolism. They also interact with the nervous system, increasing overall sympathetic drive. Consequently, almost any organ can be involved, and a variety of clinical signs are possible in hyperthyroid animals. Table 239-1 lists the most common clinical signs recorded in cats from previous and more recent studies. Both the number and severity of the clinical signs vary in individual cats, depending on the duration of the condition, the ability of the cat to cope with the demands of thyroid hormone excess, and 1545 1546 the presence or absence of concomitant abnormalities in other organ systems.[6] The disease is insidiously progressive, and owners may consider the signs, when mild, as part of the generalized aging process. Therefore months may elapse before veterinary attention is sought. Cats are less symptomatic today compared with 10 or 15 years ago, presumably because of increased awareness and earlier diagnosis. It is now not unusual for hyperthyroidism to be confirmed before owners fully realize their cats are ill.[9,31] Although the combination of certain clinical signs (weight loss despite a normal or increased appetite, hyperactivity, intermittent gastrointestinal (GI) signs, palpable goiter, tachycardia, and cardiac murmur) is highly suggestive of hyperthyroidism, the presence or absence of any one sign cannot confirm or exclude the disorder. Clinical signs suggestive of dysfunction of only one organ system may predominate in some cats; as a consequence, hyperthyroidism is considered an important differential for many presenting features in older cats.

239.1.2.1 General Features

Weight loss is the most common feature of hyperthyroidism occurring in over 80% of cats, resulting in overt cachexia in severe cases.[2,6,9,29] This reflects the overall increase in metabolic rate that may be accompanied by a mild elevation in body temperature or heat intolerance.

Hyperthyroidism is associated with hyperactivity in many affected cats. This may be more noticeable during a physical examination than to the owners, because the cats are often restless, difficult to examine, and may become aggressive, when restrained. Hyperthyroid cats are often described as having an anxious or frantic facial expression and have an impaired tolerance to stress.[2,29,32] In severe cases, stressful events, such as blood sampling, can result in collapse, cardiac arrhythmias, and dyspnea; care should be taken to handle hyperthyroid cats appropriately. Some hyperthyroid cats wander aimlessly, pace, and circle (presumably reflecting a state of confusion, anxiety, and nervousness).[32] Sleep may be abbreviated, and cats may be awakened easily.[32] Focal or generalized seizures characteristic of epilepsy have developed in a few rare cases, with lessening or resolution of the seizures after treatment of the hyperthyroidism.[32]

Table • 239-1 Clinical Findings in 131 Cats (1983 Survey) Compared with 202 Cats (1993 Survey)

FEATURE	NUMBER (%) OF CATS 1983 SURVEY	NUMBER (%) OF CATS 1993 SURVEY
Weight loss	128 (98%)	177 (87%)
Polyphagia*	106 (81%)	99 (49%)
Hyperactivity*	99 (76%)	63 (31%)
Tachycardia*	87 (66%)	85 (42%)
Polyuria/polydipsia*	78 (60%)	73 (36%)
Vomiting	72 (55%)	89 (44%)
Cardiac murmur	70 (53%)	109 (54%)
Diarrhea*	43 (33%)	30 (15%)
Increased fecal volume*	41 (31%)	17 (8%)
Anorexia*	34 (26%)	14 (7%)
Panting*	33 (25%)	19 (9%)
Muscle weakness*	33 (25%)	24 (12%)
Congestive heart failure (CHF)*	16 (12%)	4 (2%)
Increased nail growth	15 (12%)	13 (6%)
Dyspnea	14 (11%)	20 (10%)
Alopecia	9 (7%)	6 (3%)
Ventroflexion of neck	4 (3%)	2 (1%)
Palpable goiter	118 (90%)	167 (83%)

Data from Peterson ME et al: Feline hyperthyroidism: pretreatment clinical and laboratory evaluation of 131 cases. J Am Vet Med Assoc 183:103, 1983; Broussard JD et al: Changes in clinical and laboratory findings in cats with hyperthyroidism from 1983 to 1993. J Am Vet Med Assoc 206:302, 1995.

* There was a significant decrease in the prevalence of the finding between the surveys.

Muscle weakness and muscle atrophy with fatigability are occasionally described. Owners may describe a decreased ability to jump or fatigue after short bursts of physical activity.[1,2,32] The pathophysiology of muscle weakness is unclear but presumably is related to the thyrotoxicosis-associated weight loss. Severe muscle weakness (exhibited by ventroflexion of the neck) is rarely described and may result from hypokalemia recently reported in hyperthyroid cats.[6,33]

In previous case series, hair and coat changes were common. Shorthaired cats frequently had an unkempt and even matted coat, presumably due to undergrooming, whereas some longhaired cats had alopecia, presumably due to excess grooming.[6,29] Excessive nail growth with increased fragility has also been described.[6,29] These signs are less commonly noted today.

Polyuria and polydipsia reportedly occur in less than 50% of hyperthyroid cats but can be marked in individual cats.[9] Various mechanisms may be responsible, including concurrent primary renal disease (not unexpected in a group of aged cats), increased renal blood flow decreasing medullary solute concentration gradient, electrolyte abnormalities, and primary polydipsia because of a hypothalamic disturbance induced by thyroid hormone excess.[1] Hyperthyroidism could contribute to the development of renal disease in cats. The systemic hypertension accompanying hyperthyroidism could be transmitted to glomeruli, and in the absence of autoregulation, intraglomerular hypertension and glomerular hyperfiltration potentially results.[34] These factors contribute to glomerular sclerosis and progression of renal failure in cats. On the other hand,

hyperthyroidism may prove beneficial in maintaining sustainable renal function in cats with pre-existing renal disease. Overt signs of renal dysfunction may be unmasked upon reversal of the hyperthyroid state, and it is this effect that appears to be of greatest concern when considering treatment of affected cats (see Effect of Treatment on Renal Function).

239.1.2.2 Gastrointestinal Features

While some hyperthyroid cats have no discernible change in appetite, approximately 50% are described as polyphagic.[9] Despite the increased appetite, caloric intake is rarely adequate to compensate for increased energy expenditure, and weight loss generally ensues. Up to 20% of hyperthyroid cats exhibit short periods of anorexia that alternate with longer periods of normal or increased appetite, although the reasons for this are unclear.[6] Cats with apathetic hyperthyroidism usually exhibit partial to complete anorexia (see Apathetic Hyperthyroidism).

Intermittent GI signs of vomiting and, less commonly, diarrhea (increased frequency or volume or steatorrhea) are frequently observed in hyperthyroid cats.[1,2,6,9,29] Rapid overeating may contribute to vomiting, particularly in multicat households; however, direct stimulation of the chemoreceptor trigger zone is also possible.[1,2] Intestinal hypermotility, excess fat intake, and a reversible reduction in pancreatic exocrine function all contribute to the diarrhea associated with hyperthyroidism in humans.[6] Many of these mechanisms have not yet been fully evaluated in cats. However, two separate studies evaluating 10 and 13 hyperthyroid cats each have reported an accelerated orocecal transit time compared with healthy cats and compared with hyperthyroid cats after successful treatment, respectively.[35,36]

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239.1.2.3 Cardiovascular Features

Cardiovascular signs are common in hyperthyroidism and are frequently the most significant findings on physical examination (alerting the clinician to the possibility of hyperthyroidism). They include tachycardia, systolic murmurs, a prominent apex beat, and less commonly arrhythmias.[6,29] Systolic murmurs appear to be more commonly recognized than tachycardia in more recent reports.[9] Congestive heart failure (CHF) appears to be uncommon; when it arises it may be associated with a gallop rhythm, coughing, dyspnea, muffled heart sounds, and ascites.[6,9] Hyperthyroidism is usually associated with a form of hypertrophic cardiomyopathy that can result in cardiac failure in the absence of any underlying myocardial abnormalities.[37] Less commonly, a dilated form of cardiomyopathy with severe signs of CHF has been described.[38] Cats with CHF require treatment for both their hyperthyroidism and cardiac failure, using those drugs recommended for the specific form of cardiomyopathy present. While often reversible, cardiomyopathy persists or worsens after treatment in some cats, suggesting a pre-existing cardiac defect or thyroid hormone–induced irreversible structural damage.[39] The exact mechanism for the cardiac abnormalities is unclear but appears to involve a combination of direct action of excess thyroid hormones on the heart, interactions between thyroid hormones and the sympathetic nervous system, and cardiac changes that compensate for altered peripheral tissue function.[2,37]

An early study suggested that mild to moderate hypertension that is reversible after successful induction of euthyroidism is relatively common in hyperthyroid cats.[40] Hypertension in cats has been associated with a variety of ocular abnormalities including retinal detachment, hemorrhage, edema, and degeneration with

resultant blindness.[41] However, in most studies of hyperthyroid cats, obvious ocular signs such as blindness are not reported.[42,29] In addition, fundoscopic examination in hyperthyroid cats rarely reveals retinal lesions even in the presence of hypertension.[41–43] A more recent study has suggested that hyperthyroidism, although causing mild increases in systolic blood pressure, is not often a cause of severe hypertension unless accompanied by renal failure.[44]

239.1.2.4 Respiratory Features

Respiratory abnormalities, chiefly tachypnea, panting, and dyspnea have been reported in hyperthyroid cats, although their prevalence, like other clinical signs, have decreased in recent years.[2,6,9,29] Obviously, these signs occur in cats with CHF. However, they may also be seen in cats without overt cardiac disease and in such cases are often precipitated by stressful events such as veterinary intervention. Proposed explanations include varying combinations of respiratory muscle weakness, increased ventilatory drive to breathing, increased airway resistance, diminished lung compliance and even, albeit rarely, tracheal compression due to an enlarged thyroid gland.[29]

239.1.2.5 Apathetic Hyperthyroidism

Apathetic (occasionally called *masked*) hyperthyroidism is an unusual form of thyrotoxicosis that is seen in approximately 10% of cats.[6,29] In such cases, hyperactivity is replaced by depression and polyphagia by anorexia; weight loss continues unabated. Affected animals can be extremely ill. In human medicine, the term *apathetic hyperthyroidism* is usually restricted to those patients with signs (particularly atrial fibrillation and CHF) induced by excess thyroid hormones and does not include those with concurrent disease.[29] In cats this distinction is not always made. Therefore although many cats are ill as a result of CHF, a significant proportion have concurrent illnesses such as renal failure or neoplasia that account for the majority of their clinical signs. In cats with apathetic signs, a thorough investigation for CHF and other illnesses is indicated because results may alter the therapeutic protocol and eventual prognosis.

239.1.2.6 Palpable Goiter

In healthy cats the thyroid gland is divided into two separate lobes positioned just below the cricoid cartilage. Each lobe extends ventrally over the first five or six tracheal rings and are not normally palpable. Enlargement of one or more thyroid lobes is detectable by palpation in over 80% of cases.[9] With progression of the disease and greater clinician experience, goiter may be detectable in over 95% of cases.[29] Thyroid lobes are loosely anchored to surrounding tissues and as they enlarge tend to migrate ventrally toward the thoracic inlet, occasionally entering the anterior mediastinum. Ectopic thyroid tissue, located anywhere from the base of the tongue to the base of the heart, can also be involved.[45]

Occasionally goiter is visible, but in most cases palpation is required. To palpate for goiter the cat should be restrained by holding its front legs in a sitting position. With the neck gently extended, the thumb and forefingers are placed on either side of the trachea and swept carefully downwards from the larynx to the manubrium. The fingertips should remain within the jugular furrows, but it is important to be gentle and to avoid hyperextension of the neck or the thyroid lobes can become embedded into muscle or deviated retrotracheally. Goiter is usually felt as a mobile subcutaneous nodule or “blip” that slides or slips under the fingertips.[1] When palpation is difficult, clipping the ventrocervical area and moistening the skin with

alcohol may help in the visualization of small mobile nodules. More recently a semiquantitative thyroid palpation technique has been described with the clinician positioned behind the cat and the head raised and turned alternatively to the right or left, depending on which side is being assessed.[46] The degree of enlargement is assigned a score between 1 and 6, linked to the severity of hyperthyroidism. Although considered sensitive, such a technique is highly subjective.

The presence of a cervical mass is not always synonymous with hyperthyroidism. Masses can be associated with lymph node enlargement or parathyroid hyperplasia and neoplasia. In addition, goiter may develop in cats without overt hyperthyroidism, although undoubtedly T_4 secretion increases in many of these individuals with time, necessitating careful and regular re-examinations.[47]

239.1.3 Diagnostic Procedures

A variety of procedures have been recommended for evaluating cats suspected of having hyperthyroidism. The results of screening laboratory tests, diagnostic imaging, and electrocardiography may provide supportive evidence of hyperthyroidism or detail extent of cardiac involvement. Screening laboratory tests are also useful in eliminating other diseases with similar clinical signs or in depicting concurrent disorders potentially masked by hyperthyroidism that may be important in treatment decisions and ultimate prognosis. Specific thyroid function tests are necessary for confirmation of the disorder.

239.1.3.1 Echocardiography and Radiology

Evidence exists of mild to severe cardiac enlargement on thoracic radiography in over 50% of hyperthyroid cats.[31] This is accompanied by evidence of pleural effusion and pulmonary edema in cats with CHF.[6,31] The most common echocardiographic abnormalities include hypertrophy of the left ventricular caudal wall (approximately 70% of cats), left atrial and ventricular dilation (70% and 45% of cats, respectively), and hypertrophy of the interventricular septum (40% of cases).[39] Myocardial hypercontractility, as evidenced by increased shortening fraction and velocity of circumferential fiber shortening, is often found.[39] These abnormalities usually resolve or improve once hyperthyroidism has been effectively treated.[39] Occasionally, hyperthyroidism is associated with a dilated form of cardiomyopathy with echocardiographic evidence of reduced myocardial contractility and marked ventricular dilatation.[38] Thoracic radiographs are necessary in cats suspected of having cardiac failure.

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239.1.3.2 Electrocardiography

Sinus tachycardia (approximately 60% of cases) and increased R-wave amplitude in lead II (approximately 30% to 50% of cats) were originally the most frequent abnormalities recorded on electrocardiographic examination of hyperthyroid cats.[2,6,48] Other recorded abnormalities included atrial and ventricular arrhythmias, prolonged QRS duration, shortened Q-T interval, intraventricular conduction disturbances, and ventricular pre-excitation.[2,6,48] A more recent study reported a reduced prevalence of tachyarrhythmias, increased R-wave amplitude in lead II, atrial and ventricular arrhythmias, and conduction disturbances, but an increased prevalence of right bundle branch block.[31] The reason for the latter is unclear.

239.1.3.3 Screening Laboratory Tests

In early reports of hyperthyroidism, mild to moderate erythrocytosis and macrocytosis were common.[2,9] In one study of 131 hyperthyroid cats, an increased packed cell volume (PCV), mean corpuscular volume (MCV), red blood cell (RBC) count, and hemoglobin concentration were reported in 47%, 44%, 21%, and 17% of cats, respectively; the prevalence of such changes remained as high in a study undertaken 10 years later.[6,9] Such changes are thought to reflect increased erythropoietin production resulting from increased oxygen consumption or direct thyroid hormone–mediated beta-adrenergic stimulation of erythroid marrow. Erythropoietin excess is also a potential factor in promoting the release of macrocytes into the circulation. However, in a similar study of hyperthyroid cats from the United Kingdom, there were minimal changes in red cell parameters and macrocytes were rare.[29] Although it is difficult to explain the differences between the studies, it is worth stressing that none of the previously mentioned abnormalities, if observed, is clinically important. Anemia appears to be rare.[6,29] When it occurs it is usually associated with severe hyperthyroidism and may result from bone marrow exhaustion, iron, or other micronutrient deficiency.[29] Despite the lack of overt anemia, a significantly higher prevalence of Heinz body formation has been reported in cats with hyperthyroidism compared with healthy cats, although with fewer and smaller Heinz bodies compared with other diseases.[49] Hyperthyroid cats also appear to have higher mean platelet size than healthy cats, but the significance of this remains unclear.[50]

Changes in white blood cell (WBC) parameters are not unusual in hyperthyroidism but are relatively nonspecific. The most frequent changes include leukocytosis, mature neutrophilia, lymphopenia, and eosinopenia, presumably reflecting a stress response.[2,6,9,29] However, eosinophilia and lymphocytosis have also been described and potentially result from a relative decrease in available cortisol because of excess circulating thyroid hormone concentrations.[29]

The most striking biochemical abnormalities observed in hyperthyroid cats are increases in liver enzyme activities. These include alanine aminotransferase (ALT), alkaline phosphatase (ALKP), lactate dehydrogenase (LDH), and aspartate aminotransferase (AST). In more recent and previous reports, at least one of these enzymes is abnormally increased in over 90% of hyperthyroid cats.[2,6,9,29] The elevations in these enzymes can be dramatic. However, at least in one study serum ALKP and total T_4 concentrations were significantly correlated, and concentrations of ALT and ALKP declined to within reference range with successful induction of euthyroidism.[51,52] As a consequence, the degree of elevation is subtle, if present at all, in early or mild cases of hyperthyroidism. If marked elevation in liver enzyme activities are seen with only mildly abnormal serum thyroid hormone concentrations, concurrent hepatic disease should be suspected and investigated.

Despite the marked increases in hepatic enzyme activities in some hyperthyroid cats, histological examination of hyperthyroid cat livers has revealed only modest and nonspecific change. These include increased pigment within hepatocytes, aggregates of mixed inflammatory cells in the portal regions, and focal areas of fatty degeneration.[2] In more severe cases, centrilobular fatty infiltration may occur together with patchy portal fibrosis, lymphocytic infiltration, and proliferation of bile ducts.[2,6] Suggested explanations for such abnormalities have included malnutrition, CHF, infections, hepatic anoxia, and direct toxic effects of thyroid hormones on the liver. However, several recent reports have examined the possibility of other sources of these enzymes and have shown that both liver and bone contribute to

increased ALKP activity in hyperthyroid cats.[51,53,54] The bone isoenzyme contributes approximately 20% to 30% of total ALKP activity; although frequently increased in hyperthyroid cats, a poor correlation is seen with total T_4 concentrations.[51,54]

Hyperphosphatemia, in the absence of azotemia, was originally reported in approximately 20% of cases, and this has more recently been reported in a higher percentage (36% to 43%) of hyperthyroid cats particularly when compared with an age-matched control group.[54,55] This, together with the increase in the bone isoenzyme of ALKP, is suggestive of altered bone metabolism. Circulating osteocalcin concentration, used as a measure of osteoblastic activity and bone remodeling, although variable, has been shown to be increased in hyperthyroid cats.[54] In human thyrotoxic patients, an increased risk of osteoporosis exists because of a direct effect of thyroid hormone on bone. The net bone loss leads to the release of calcium and a tendency toward hypercalcemia, hyperphosphatemia, hypoparathyroidism, and reduced concentrations of activated vitamin D.[6,55] Early reports suggested that despite hyperphosphatemia, circulating calcium concentration was largely unaffected by hyperthyroidism in cats.[6] However, only total calcium was measured. In two separate studies it has been shown that up to half of hyperthyroid cats have serum ionized calcium concentrations below the reference range.[54,55] In addition, hyperparathyroidism appears to be common and has been demonstrated in over 70% of hyperthyroid cats with maximum parathormone (PTH) values approaching 19 times the upper limit of the reference range.[55] Preliminary results suggest that circulating 1,25 Vitamin D concentrations are not suppressed in cats as in humans.[55] The cause of hyperparathyroidism, hyperphosphatemia, and ionized hypocalcaemia remain unclear and warrant further study. In addition, its clinical consequences are unknown, although the increased secretion of PTH necessary to maintain ionized calcium at the low end or below the reference range might contribute to the tendency of some cats to develop hypocalcemia after surgical thyroidectomy.

In early reports of hyperthyroidism, mild to moderate azotemia appeared to be common, occurring in 25% to 70% of cats.[2,6,29] Current figures suggest that just over 20% of hyperthyroid cats are azotemic.[9] Although such prevalence is not unexpected in a group of aged cats, the increase could be exacerbated by the increased protein catabolism, hypertension, and the possible prerenal uremia of thyrotoxicosis.[2,34] In hyperthyroid cats without azotemia, serum creatinine concentration is significantly lower compared with age-matched healthy animals.[55] This may be related to a loss of muscle mass and a reduction in the rate of formation of creatinine rather than any effect of thyrotoxicosis on tubular secretion of creatinine, because this is not considered to occur in cats. Whatever the cause of decreased creatinine concentrations, it is likely that this effect will tend to mask evidence of renal failure in cats. This has implications when assessing renal function in hyperthyroid cats prior to deciding on the best option for treatment (see Effect of Treatment on Renal Function).

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A number of other clinicopathologic abnormalities have been described in hyperthyroid cats. Clinically significant hypokalemia has been reported in four hyperthyroid cats, but the cause remains unclear.[33] Blood glucose concentrations may be increased in small number of hyperthyroid cats, presumably reflecting a stress response.[6,9] Hyperthyroidism is also associated with glucose intolerance characterized by delayed clearance of administered glucose from the plasma despite increased secretion of insulin.[56] This is not reversible after treatment, which may be related to weight gain as euthyroidism is achieved. Two separate studies have examined the effect of hyperthyroidism on circulating fructosamine concentration.[57,58] In both studies, serum fructosamine concentration was significantly lower in hyperthyroid compared with healthy cats, presumably as a result of increased protein turnover. Importantly, as many as 50% of cats had values

below the respective reference range. Caution is therefore advised in interpreting serum fructosamine concentration in hyperthyroid cats, particularly if concurrently diabetic. Other biochemical parameters such as cholesterol, sodium, chloride, bilirubin, albumin, and globulin are usually within their respective reference ranges in hyperthyroid cats unless affected by a concurrent nonthyroidal illness. Urinalysis is generally unremarkable. The urine specific gravity (USG) is extremely variable, ranging from 1.009 to 1.050, but is generally lower than in an age-matched population, presumably reflecting the effect of hyperthyroidism on renal concentrating mechanisms.[6,9,55]

239.1.3.4 Thyroid Function Tests

The diagnosis of hyperthyroidism is confirmed by the demonstration of increased production of the thyroid hormones or thyroidal radioisotope uptake.

239.1.3.4.1 Pathophysiology

In cats, T_4 rather than T_3 is the main secretory product of the thyroid gland. However, T_3 is three to five times more potent than T_4. Most circulating T_3 is produced from extrathyroidal 5′-deiodination of T_4 and, as a result, T_4 is often considered as a prohormone, and activation to T_3 a step that is autoregulated by peripheral tissues. Over 99% of circulating T_4 is protein bound, the remainder is free and metabolically active. Overall control of thyroid function is mediated via the negative-feedback effect of circulating T_4 and T_3 on thyrotropin-releasing hormone (TRH) from the hypothalamus and TSH from the anterior pituitary.

239.1.3.4.2 Basal circulating thyroid hormone concentrations

Increased basal circulating concentrations of total T_4 and T_3 concentrations are the biochemical hallmarks of hyperthyroidism and are extremely specific for its diagnosis. However, since the first reports of the disease, it has been recognized that although circulating total T_4 and T_3 concentrations are highly correlated, measurement of circulating total T_4 is preferable.[6,29] In early studies, a small percentage (< 10%) of cats with elevated circulating total T_4 concentrations had concurrent reference range total T_3 values. This has increased to approximately one third of cats tested in more recent reports (Figure 239-1).[9,59] Severe concurrent nonthyroidal illness may play a role in suppressing T_3 concentration by inhibiting peripheral conversion of T_4 to T_3, as it does in humans, although this appears to be a less common phenomenon in cats.[29] The majority of hyperthyroid cats with total T_3 concentration within reference range are classified as mildly affected, with only mild abnormalities in circulating T_4 concentration. It is likely that the total T_3 concentration would increase into the reference range if the disorder were allowed to progress untreated.[6]

Early reports suggested that all hyperthyroid cats had elevated total T_4 concentrations with values up to 19 times the upper limit of the reference range.[6,29] However, it has recently been recognized that up to 10% of hyperthyroid cats have reference range circulating total T_4 concentrations (Figure 239-2).[9,59] Such values are usually, but not exclusively, within the mid-to high end of the reference range.

Hyperthyroidism, therefore, should not be excluded based on finding a single reference range total T_4 value.

Nonspecific fluctuation of thyroid hormones has been reported in hyperthyroid cats and may account for the reference range total T_4 values found. In cats with markedly elevated serum thyroid hormone concentrations, the degree of fluctuation is of little diagnostic significance.[60,61] However, in mildly affected cats with marginally elevated total T_4 values, the degree of fluctuation can result in reference range values.[61] Increased thyroidal production could result in increased circulating concentration, but because the serum half-life of thyroid hormones is measured in hours, acute decreases presumably reflect fluctuations in binding proteins or other unclear hemodynamic changes. If mild hyperthyroidism is suspected in a cat with mid-to high reference range circulating total T_4 concentration, a repeat measurement is indicated. Because the degree of fluctuation is greater over a period of days than hours, further sampling should be deferred for 1 or 2 weeks.[1,61]

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Figure 239-1 Box plots of serum total triiodothyronine (T_3) concentrations in 172 clinically normal cats, 917 cats with untreated hyperthyroidism, and 221 cats with nonthyroidal disease (other illness). The box represents the interquartile range (i.e., 25% to 75% range or the middle half of the data). The horizontal bar in the box represents the median value. For each box plot, the T-bars represent the main body of the data, which in most instances is equal to the range. Open circles represent outlying data points. The shaded area indicates the reference range for serum T_3 concentration. To convert serum T_3 concentrations from nmol/L to ng/dL, one should divide the given values by 0.0154. (From Peterson ME et al: Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal illness. J Am Vet Med Assoc 218:529, 2001.)

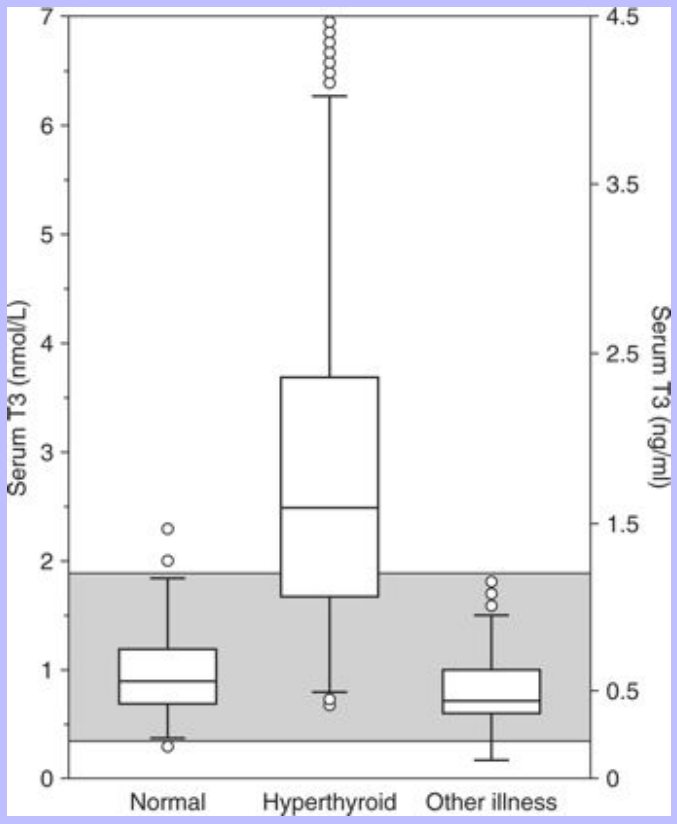
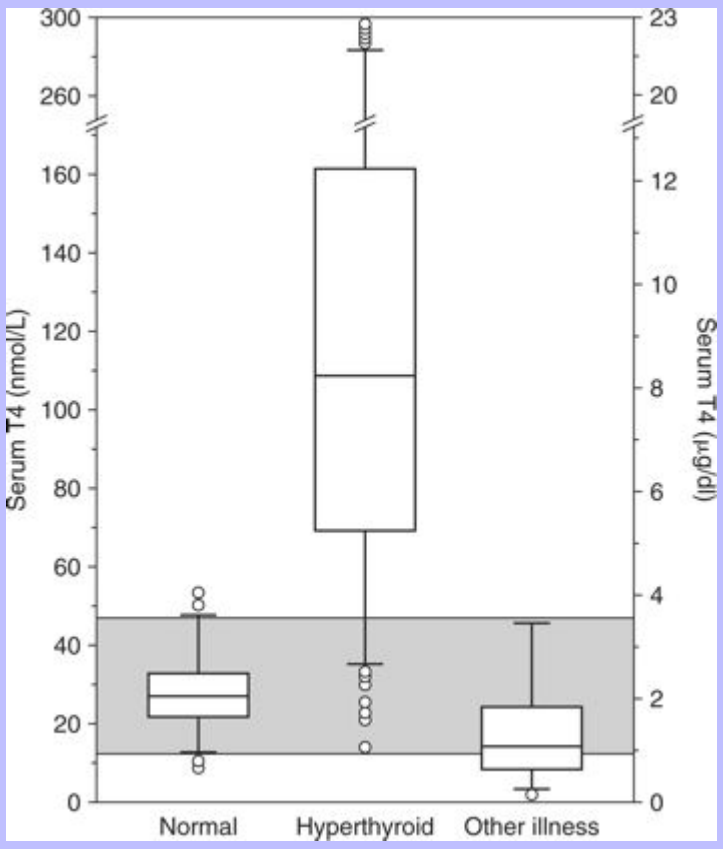


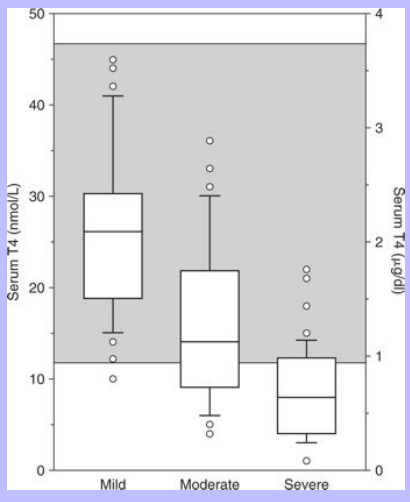
Figure 239-2 Box plots of serum total thyroxine (T_4) concentrations in 172 clinically normal cats, 917 cats with untreated hyperthyroidism, and 221 cats with nonthyroidal disease (other illness). Data are plotted (i.e., box plots) as described in the legend of Figure 239-1. The shaded area indicates the reference range for serum T_4 concentration. To convert serum T_4 concentrations from nmol/L to ng/dL, divide the given values by 12.87. (From Peterson ME et al: Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal illness. J Am Vet Med Assoc 218:529, 2001.)



Nonthyroidal illness is capable of suppressing circulating total T_4 concentration in cats as in dogs. The degree of suppression is correlated to the severity rather than the type of illness; because it is inversely correlated to mortality, it can be used as a prognostic indicator (Figure 239-3).[59,62,63] The mechanisms

remain unclear but are more likely to involve changes in protein binding or metabolism rather than any effect on the hypothalamic-pituitary-thyroid axis.[62,63] Similar suppression occurs in hyperthyroid cats with concurrent nonthyroidal illness. The degree of suppression has little diagnostic significance in hyperthyroid cats with markedly elevated serum total T_4 concentration.[29,62,64] However, in cats with mild or early hyperthyroidism, reference range circulating total T_4 concentrations may occur. In the largest study of 917 hyperthyroid cats, a concurrent illness was identified in 17 of 80 (22%) cats with mild hyperthyroidism and reference range serum total T_4 concentration.[59] In the majority of affected cats, serum total T_4 concentration is within the mid-to high end of the reference range. Occasionally, values are within the mid-to low end of the reference range, but such cats usually exhibit the most severe concurrent illnesses. Other signs, particularly detection of a palpable thyroid nodule, may indicate the need to further investigate hyperthyroidism in such cats.[59] Serum total T_4 values will increase into the thyrotoxic range upon stabilization of or recovery from the nonthyroidal illness.[1,62]

Figure 239-3 Box plots of serum total thyroxine (T_4) concentrations in 221 cats with nonthyroidal disease (other illness), grouped according to severity of illness. Of the 221 cats, 65 had mild disease, 83 had moderate disease, and 73 had severe disease. Data are plotted (i.e., box plots) as described in the legend of Figure 239-1. The shaded area indicates the reference range for serum T_4 concentration. To convert serum T_4 concentrations from nmol/L to ng/dL, one should divide the given values by 12.87. (From Peterson ME et al: Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal illness. J Am Vet Med Assoc 218:529, 2001.)



Measurement of circulating free T_4 concentration may provide an alternative means of diagnosing hyperthyroidism, particularly in cats with reference range total T_4 values. In humans, free T_4 measurement is considered a superior diagnostic test for hyperthyroidism because it is less affected by nonthyroidal factors than is total T_4 and provides a more accurate reflection of thyroid status.[65] Notably, when serum total T_4 concentration is increased, the concentration of free T_4 is disproportionately increased. This may be related in part to relative saturation of binding proteins by T_4 and subnormal concentration of the principle binding proteins.[65] In addition, serum free T_4 concentration remains increased in hyperthyroid patients with nonthyroidal illnesses when total T_4 concentration is suppressed into the reference range.[65] Measurement of free T_4 concentration has recently been evaluated in a large number of hyperthyroid cats and as in humans, appears to be an extremely sensitive diagnostic test (Figure 239-4).[59] In this study, serum free T_4 concentration was elevated in 903 (98.5%) of 917 hyperthyroid cats, whereas corresponding serum total T_4 values were elevated in only 837 (91.3%) cases. However, in all cats with an elevated serum total T_4 concentration, free T_4 concentration is concurrently high.[59] Thus measurement of free T_4 concentration offers no further diagnostic information. However, in 205 hyperthyroid cats categorized as mildly affected with or without a concurrent illness, serum total T_4 concentration was only elevated in 125 (61%) cases, whereas corresponding free T_4 concentrations were high in 191 (93.2%) cats (Figure 239-5). Free T_4 analysis is not without disadvantage. It is only reliably measured by methods involving dialysis that increase expense and are not always readily available.[1] In addition, it lacks diagnostic specificity compared with total T_4 measurement. In two separate studies, 6% to 12% of sick euthyroid cats had elevated circulating free T_4 concentrations.[29,59] These cats generally had corresponding total T_4 values in the lower half of or below the reference range. Serum free T_4 concentration should therefore be interpreted with caution if used as the sole diagnostic criterion for confirmation of hyperthyroidism. It is more reliable if interpreted together with a serum total T_4 concentration. A mid-to high reference range total T_4 and elevated free T_4 concentration is consistent with hyperthyroidism.[59] By contrast, low total T_4 and elevated free T_4 values are usually associated with nonthyroidal illness.[29,59]

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Identification of concurrent nonthyroidal illness, repeat total T_4 analysis or simultaneous free T_4 measurement usually provides enough evidence to confidently diagnose hyperthyroidism. However, dynamic thyroid function tests have been recommended as helpful in achieving a diagnosis. The methods for performing these tests are outlined in Table 239-2. Realistically they should be reserved for cats with clinical signs suggestive hyperthyroidism when repeated total T_4 concentration remains equivocal and serum free T_4 measurement is unavailable or unhelpful.[65]

239.1.3.4.3

Thyroid-stimulating hormone response test

In an early study it was suggested that the TSH response test was useful in confirming a diagnosis of hyperthyroidism because there was little difference in serum concentrations of T_4 before and after exogenous TSH administration.[6] In a larger study of 40 hyperthyroid cats, including those with

equivocal total T_4 values, the overall limited T_4 response to TSH stimulation was confirmed.[66] However, it was shown that hyperthyroid cats with equivocal basal total T_4 concentrations exhibit a response 1551
indistinguishable from that in healthy cats, suggesting that the abnormal thyroid glands do retain the 1552
ability to respond to TSH but are producing T_4 at maximal rates. Presumably hyperthyroid cats with the lowest basal total T_4 concentration have the greatest potential to respond to TSH, although it has been suggested that this response may be related to stimulation of normal thyroid tissue often found within hyperplastic glands.[66] Bovine TSH has traditionally been used for the TSH response test but is no longer commercially available as a pharmaceutical preparation. Recombinant human TSH has been evaluated in euthyroid cats and appears to be a safe and effective replacement for bovine TSH.[67] However, TSH is expensive and because of the difficulties in interpreting the test results, the TSH response test has significant limitations in the evaluation of hyperthyroidism in cats.

Figure 239-4 Box plots of serum free thyroxine (T_4) concentrations in 172 clinically normal cats, 917 cats with untreated hyperthyroidism, and 221 cats with nonthyroidal disease (other illness). Data are plotted (i.e., box plots) as described in the legend of Figure 239-1. The shaded area indicates the reference range for serum free T_4 concentration. To convert serum free T_4 concentrations from nmol/L to ng/dL, one should divide the given values by 12.87. (From Peterson ME et al: Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal illness. J Am Vet Med Assoc 218:529, 2001.)

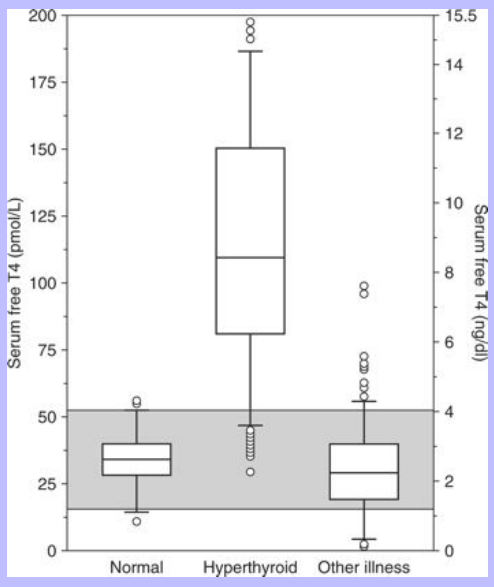

Figure 239-5 Box plots of serum total thyroxine (T_4), total triiodothyronine (T_3), and free T_4 concentrations in 205 cats with mild hyperthyroidism (defined as total T_4 concentration < 66 nmol/L). Data are plotted (i.e., box plots) as described in the legend of Figure 239-1. The shaded area indicates the reference range for each hormone. (From Peterson ME et al: Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal illness. J Am Vet Med Assoc 218:529, 2001.)

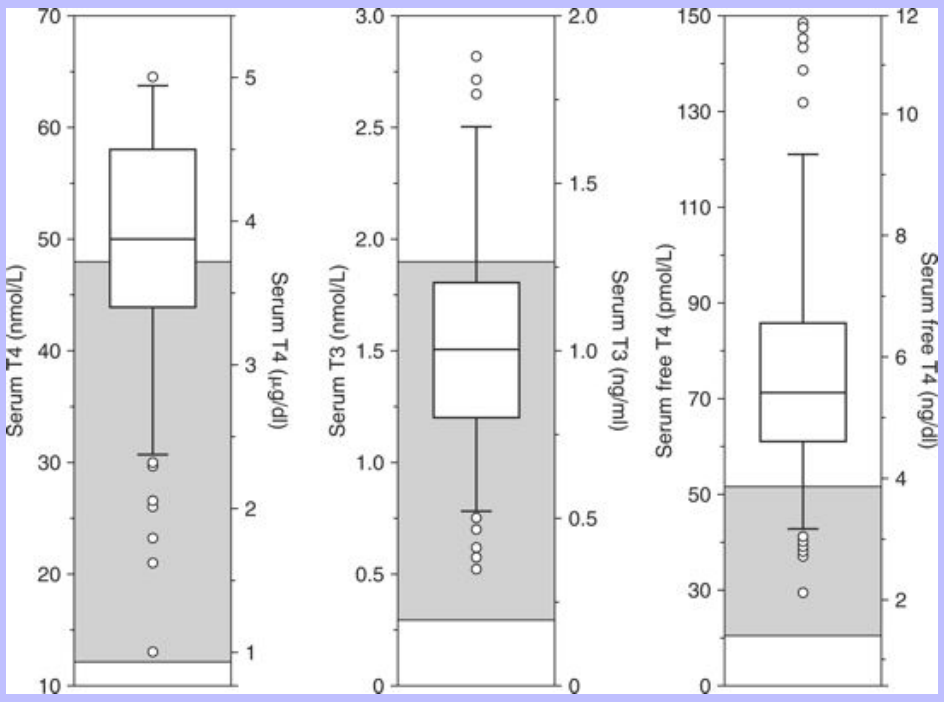

Table • 239-2 Protocols for Dynamic Thyroid Function Tests Used for Diagnosing Hyperthyroidism in Cats

TEST	TSH RESPONSE		TRH RESPONSE	T_3 SUPPRESSION
Drug	Bovine TSH	Recombinant human TSH*	TRH†	Liothyronine‡
Dose	0.5 IU/kg	0.025–0.20 mg/cat	0.1 mg/kg	15–25 g every 8 hours for 7 doses
Route	Intravenous	Intravenous	Intravenous	Oral
Sampling times	Zero and 6 hours	Zero and 6–8 hours	Zero and 4 hours	Zero and 2–4 hours after last dose
Assay	Total T_4	Total T_4	Total T_4	Total T_4 and total T_3

Data compiled from references 66–71.

* Thyrogen, Genzyme Corporation

† Relefact TRH, Hoechst-Roussel Pharmaceuticals; Thypinone, Abbott Diagnostics

‡ Cytomel, Jones Medical Industries

239.1.3.4.4 Thyrotropin-releasing hormone response test

In healthy cats, administration of TRH causes an increase in TSH and, in turn, thyroid hormone secretion. In hyperthyroidism, this pathway is less functional because of chronic TSH suppression from autonomous thyroid hormone production. A significant increase occurs in mean serum total T_4 concentration after TRH administration in healthy and hyperthyroid cats and those with nonthyroidal illness.[68] However, the percentage increase in total T_4 is considerably less in the hyperthyroid cats compared with healthy cats and those with other diseases. It has been suggested that a relative increase in total T_4 of less than 50% is consistent with mild hyperthyroidism, a value greater than 60% is suggestive of euthyroidism, and values between 50% and 60% remain equivocal.[68] Similar to the TSH response test, measurement of total T_3 concentration is unhelpful because of the greater variability in response both within and between healthy and sick cats.[66,68] Adverse reactions to TRH administration appear to be common, occurring within minutes of administration. Adverse reactions include vomiting, excessive salivation, tachypnea, and defecation. TRH possibly evokes these effects indirectly, via activation of central cholinergic and catecholaminergic mechanisms and directly, via central TRH-binding sites.[1] However, although these reactions are transient and usually resolve within hours, the diagnostic accuracy of the TRH response test has recently been questioned. Results of the TRH response test are largely indistinguishable between sick euthyroid and hyperthyroid cats with concurrent nonthyroidal illness and total T_4 concentrations within or below the reference range, thereby limiting its diagnostic usefulness.[69]

239.1.3.4.5 Triiodothyronine-suppression test

The T_3 suppression test relies on the ability of administered liothyronine, through negative feedback, to decrease T_4 production by the thyroid gland. In hyperthyroidism, because excess circulating thyroid hormone concentrations have already suppressed TSH production and secretion, additional T_3 has minimal effect on T_4 production. Therefore serum total T_4 concentration remains significantly higher

after liothyronine administration in hyperthyroid compared with euthyroid (both healthy and sick) cats, and the percentage decrease is consequently significantly lower.[70,71] Although individual laboratories vary, as a general guideline, postliothyronine serum total T_4 concentration tends to be greater than 20 nmol/L in hyperthyroid cats and less than 20 nmol/L in euthyroid cats (Figure 239-6). A greater overlap of results is seen in hyperthyroid and euthyroid cats when percentage change in total T_4 is calculated. However, suppression of 50% or more is consistent with euthyroidism, whereas hyperthyroid cats rarely have values exceeding 35%. Although the T_3 suppression test is a potential aid for confirming the diagnosis of hyperthyroidism, it has been suggested to be most useful in confirming euthyroidism and ruling out hyperthyroidism.[70] Unlike the TRH response test, it is not associated with any adverse reactions. However, it is a relatively prolonged test and highly dependent on good owner compliance in reliably administering liothyronine tablets and adequate GI absorption (necessitating confirmation by pre-and postserum total T_3 measurement).[7,70] If a dynamic thyroid function test is deemed necessary to investigate hyperthyroidism in a cat, the T_3 suppression test is preferred (given the problems of both the TSH and TRH response tests).

239.1.3.4.6

Thyroid radionuclide uptake and imaging

Hyperthyroid cats usually exhibit increased uptake of radioactive iodine (as ^{131}I or ^{123}I) or technetium-99m as pertechnetate ($^{99m}TcO_4^-$).[6,72–75] Percentage uptake of $^{99m}TcO_4^-$ or increased thyroid: salivary ratio at 20 minutes are strongly correlated with circulating thyroid hormone concentrations.[73,75] Preliminary studies suggest that $^{99m}TcO_4^-$ scans are a more sensitive means of diagnosing hyperthyroidism than basal thyroid hormone analyses or TRH response test results, but further studies are required in this area.[76,77] Care should be taken in interpreting uptake results in cats recently treated with antithyroid drugs. Radioisotope uptake is increased in healthy cats treated with methimazole with significant enhancement after drug withdrawal, and presumably the latter situation may exist in hyperthyroid cats.[78]

Determining percent uptake of radioisotopes is expensive and requires access to sophisticated equipment. However, qualitative scintigraphic imaging remains a useful procedure to determine unilateral or bilateral lobe involvement, alterations in the position of the thyroid lobes, the site of hyperfunctioning ectopic or accessory tissue, or distant metastases from a functioning thyroid carcinoma.[5] For such imaging $^{99m}TcO_4^-$ is preferred. It has a more rapid uptake and half-life; scanning can commence within minutes rather than hours, allowing for more rapid completion. In addition, higher doses can be used without delivering a high radiation dose, and the quality of the scans is consistently equal or superior to that when radioactive iodine is used.[5]

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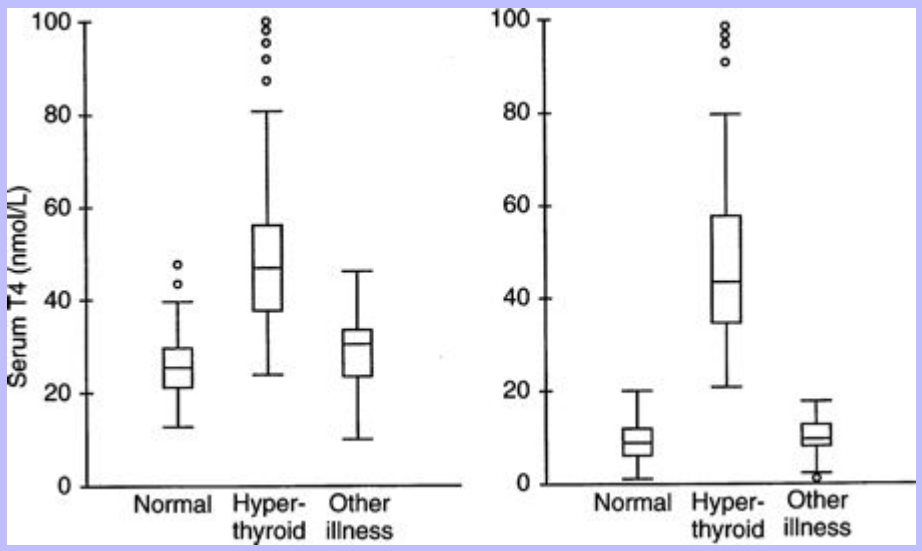
Figure 239-6 Box plots of the serum total thyroxine (T_4) concentrations before **(A)** and after **(B)** administration of liothyronine to 44 clinically normal cats, 77 cats with hyperthyroidism, and 22 cats with nonthyroidal disease. Data are plotted (i.e., box plots) as described in the legend of Figure 239-1. To convert serum T_4 concentrations from nmol/L to ng/dL, one should divide the given values by 12.87. (From Peterson ME et al: Triiodothyronine suppression test. An aid in the diagnosis of mild hyperthyroidism in cats. J Vet Intern Med 4:233, 1990.)



239.1.4 Treatment

Spontaneous remission of hyperthyroidism does not occur, and prevention is not possible because the cause is unknown. Failure to institute therapy will result in insidious progression to emaciation, severe metabolic and cardiac dysfunction, and ultimately death. However, because of the benign nature of the thyroid lesions, the disease carries a favorable prognosis with effective therapy. Treatment of hyperthyroidism is aimed at removing or destroying abnormally functioning thyroid tissue, pharmacologic inhibition of thyroid hormone synthesis, and release or amelioration of the influence of excess thyroid hormones on peripheral tissue. Surgical thyroidectomy or thyroid ablation using radioactive iodine are the only reasonable curative methods available. Medical management is noncurative; because of this, it is not recommended alone in the rare cases of functioning thyroid carcinoma.

Each treatment method has its own advantages and disadvantages. No one therapy can be recommended above another for all cats. The selection must be individualized for each cat, taking into account several factors including age, severity of thyrotoxicosis, presence of concurrent illnesses, facilities available, potential complications, cost, and the owner's willingness to accept the form of treatment advised.

239.1.4.1 Antithyroid Drugs and Other Medical Treatments

Numerous pharmacologic agents may be used in the medical management of feline hyperthyroidism. Indications, dose regimens, potential adverse reactions, and contraindications are summarized in Table 239-3. Chronic medical management is a practical treatment option for hyperthyroidism that requires no special facilities, is readily available, easy to implement, and reasonably inexpensive. Almost all cats are potential candidates, because unless it is suspected of thyroid carcinoma, few specific contraindications exist. When thyroid hormone production or secretion is inhibited, generally a rapid return to euthyroidism occurs. Anesthesia is avoided, as are the peri-and postoperative complications associated with surgical thyroidectomy. Unlike radioactive iodine therapy, hospitalization is unnecessary. On the other hand, few drugs are available for long-term control, daily medication is necessary, and a real risk of poor compliance exists (by the owner, the cat, or both) in regularly administering and accepting the medication. This impinges on efficacy and cost because it necessitates more frequent monitoring. In addition the development of adverse reactions may necessitate drug withdrawal; therefore not all cats initially managed medically can be maintained long-term with this form of therapy. A further consideration is that relapse of hyperthyroidism invariably occurs within 24 to 72 hours after drug withdrawal.[52,79] Although often considered a disadvantage, it may prove beneficial in cats that develop overt renal failure upon induction of euthyroidism (see Effect of Treatment on Renal Function).

Pharmacologic intervention is also necessary prior to surgical thyroidectomy to decrease the metabolic and cardiac complications associated with thyroid hormone excess. In addition, it may be desirable to provide some control, at least clinically, while awaiting radioactive iodine administration.

239.1.4.1.1 Thioureylene antithyroid drugs

The thioureylene antithyroid drugs include propylthiouracil, methimazole, and carbimazole. These drugs are actively concentrated by the thyroid gland and act as general inhibitors of thyroid peroxidase-catalyzed reactions including oxidation of iodide and iodination of tyrosyl residues in thyroglobulin. They also interfere with the coupling of iodotyrosines to iodothyronines via inhibition of thyroid peroxidase or by binding to and altering the structure of thyroglobulin, a reaction more sensitive to inhibition than the formation of iodotyrosines. The trapping of inorganic iodide by, or the release of preformed hormones from, the thyroid gland is not affected by these drugs.[1,52,78,79]

The thioureylene antithyroid drugs are the therapeutic mainstay in the medical management of both human and feline hyperthyroidism because of their consistent effect in lowering serum thyroid hormone concentrations. They are widely recommended to stabilize hyperthyroid cats prior to surgery and are the only drugs that can be used chronically for management of hyperthyroidism. Propylthiouracil is the least potent but is widely available and has an additional advantage of inhibiting peripheral T_3 production. However, it is associated with an unacceptably high incidence of serious hematologic complications in both healthy and hyperthyroid cats; therefore it is no longer recommended for use in this species.[65]

Methimazole is available in the United States (Tapazole, Jones Medical Industries) and is specifically licensed for use in hyperthyroid cats in the United Kingdom (Felimazole, Arnolds Veterinary Products Limited). Elsewhere, methimazole or carbimazole is variably available. Carbimazole is a carbethoxy derivative of methimazole and was originally developed in the hope of obtaining a drug with a longer duration of activity than methimazole for human use. Although possessing inherent antithyroid activity,

it exerts its antithyroid effect through immediate conversion to methimazole when administered orally.[80] Serum concentrations of methimazole achieved after carbimazole administration are less than after administration of an equal weight of methimazole, reflecting the molar ratio of the two drugs. This conversion results in a 5 mg dose of carbimazole being approximately equivalent to 3 mg of methimazole and may account for the slight differences in dose regimes recommended for the two drugs.[52,79] However, given the reduction in severity of thyrotoxicosis in cats seen currently, such differences have become less noticeable.

Table • 239-3 Indications, Doses, Adverse Reactions, and Contraindications for the Drugs Commonly Used to Manage Hyperthyroidism

DRUG	INDICATIONS	DAILY DOSE	ADVERSE REACTIONS	CONTRAINDICATIONS
Methimazole andcarbimazo le	Prior to surgery (2–3 weeks)	5–15 mg divided two or three times daily	Vomiting, anorexia, depression; facial excoriations; hematologic complications; hepatopathy	If adverse reactions occur; at the time of radiotherapy
	Chronic management	5–10 mg once or divided twice daily		
Propranolol	Symptomatic control	7.5–15 mg divided three times daily	Bradycardia, myocardial depression; bronchospasm; diarrhea	Asthma, uncontrolled heart failure; chronic management
Atenolol		6.25–12.5 mg once or twice daily		Chronic management
Propranolol with potassium iodate	Prior to surgery (3 weeks)	7.5–15 mg divided three times daily, days 1–21	Anorexia, depression, vomiting	Chronic management; immediately prior to ^{131}I therapy
		63.75 mg divided three times daily, days 11–20		
Calcium ipodate	Prior to surgery (up to 14 weeks)	100 mg divided twice daily	None	Chronic management

Pharmacological studies in healthy cats have shown that methimazole has good oral bioavailability with a serum half-life of between 4 and 6 hours.[81,82] After multiple-dose administration of methimazole, some evidence of drug-induced accelerated metabolism is seen; however, this has not been borne out by clinical studies.[82] Most pharmacokinetic parameters of methimazole in cats are not significantly altered by hyperthyroidism; although a trend toward faster elimination exists, this is not considered to be clinically important.[81]

Initially, methimazole should be administered orally at a dose of 10 to 15 mg/day, in divided doses every eight to 12 hours, depending on the severity of the thyrotoxicosis.[79] Carbimazole has been recommended at an initial oral dose of 15 mg, divided three times daily.[52] Attainment of biochemical euthyroidism is relatively rapid, occurring in a mean of approximately 6 days at least for carbimazole.[52] Not surprisingly the length of therapy is correlated with the basal serum total T_4 concentration. As cats are diagnosed with hyperthyroidism earlier, the trend toward using only twice-daily administration of low doses (2.5 to 5

mg) of carbimazole or methimazole increases.[83] Once-daily dosing, however, appears less effective in inducing euthyroidism.[83] For practical purposes, the initial dose is prescribed for a period of 2 to 3 weeks, which allows time for more obvious clinical improvement and ensures the attainment of euthyroidism in over 90% of cats.[52,79] At that time, a circulating total T_4 concentration is measured and, if within or below the reference range, surgery can be performed (administering the last dose on the morning of surgery). For severely affected cats, although biochemical euthyroidism is rapidly achieved, a longer course of preoperative therapy may be beneficial before the patient is considered a reasonable surgical candidate. In such cases, the dose is adjusted as in cats in which medical management has been selected as the sole therapy. If euthyroidism is not achieved within this initial period, the duration of therapy is increased or the dose altered in 2.5 to 5 mg increments. Rarely doses as high as 25 to 30 mg of methimazole are required to restore euthyroidism.[1,7,79] Lack of owner or cat compliance should be excluded as a possible reason for failure of therapy. Documenting a decline in the activities of the liver enzymes provides an inexpensive but nonspecific alternative to monitoring serum total T_4 concentration when assessing therapeutic efficacy.[52]

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For long-term therapy, once euthyroidism has been achieved, the daily dose is adjusted in 2.5 to 5 mg decrements, aiming for the lowest possible dose that effectively maintains euthyroidism. 1555 Further dose adjustments are based on circulating total T_4 concentrations assessed every 2 to 3 weeks until stable and every 3 to 6 months thereafter or as indicated clinically. Most cats require 10 mg methimazole per day, whereas a few require doses as high as 15 to 20 mg/day or as low as 2.5 to 5 mg/day.[79] Although divided doses are most successful in treating hyperthyroid cats (and despite the relatively short serum half-life), the intrathyroidal residence time may be approximately 20 hours as it is in humans. When owner compliance is problematic, once-daily dosing may prove effective chronically, although this has not been fully evaluated. Further increasing the time between dosing results in recurrent hyperthyroidism.[52,79] Carbimazole appears to be most effective if chronically administered at a dose of 5 mg twice daily.[52]

In many cats, such antithyroid therapy results in serum total T_4 concentrations below the reference range. However, clinical signs of hypothyroidism do not develop, and surgical risks are not increased. Corresponding serum total T_3 concentrations tend to remain within the reference range, and euthyroidism is maintained because T_3 is more metabolically active than T_4.[52] This may result from increased extrathyroidal T_4 to T_3 conversion or increased thyroidal secretion of T_3 because of intrathyroidal iodine deficiency or increased TSH production. In addition, serum free T_4 concentration, representing the active portion of T_4, appears to remain relatively higher than total T_4 concentration during methimazole therapy.[65] As a result, the aim is to suppress total T_4 into the lower half of the reference range; however, if severely depressed, the dose should be adjusted and the cat retested because at least some adverse reactions appear to be dose related.[79]

Methimazole and carbimazole have no effect on the underlying pathologic lesion in hyperthyroid cats. Thus over months to years of treatment, the thyroid nodule or nodules can continue to grow and enlarge. As a result it is common for the daily dose of antithyroid drugs to progressively increase. Some cats may no longer adequately respond to methimazole or carbimazole, and an alternative form of therapy is necessary.[1]

Although antithyroid dugs are routinely administered orally, compliance can be problematic in fractious or inappetant cats; absorption is potentially adversely affected by concurrent intestinal disease, and obvious difficulties exist in cats that vomit. Preliminary studies have shown that methimazole in a pluronic lecithin organogel (PLO) is effective in hyperthyroid cats when applied transdermally. However, subsequent studies of healthy cats have demonstrated poor bioavailability by this route, and further studies are required before widespread recommendation.[84]

Most clinical adverse reactions associated with methimazole or carbimazole occur within the first 3 months of therapy. They include vomiting, with or without anorexia and depression, usually within the first 4 weeks of therapy (occurring in 10% to 15% of cases).[52,79] These effects are more common with methimazole and may be related to its unpleasant bitter taste (compared with carbimazole, which is tasteless). However, these signs are usually transient and rarely require withdrawal of the drug. Self-induced excoriations of the head and neck have been seen in a small number of cats treated with methimazole or carbimazole within the first 3 months of therapy.[65,79] Drug withdrawal is usually required together with glucocorticoid therapy, and an alternative treatment for the hyperthyroidism is necessitated.

Early in the course of therapy, mild hematologic complications of eosinophilia, lymphocytosis, and leukopenia (with a normal differential count but without apparent clinical effect) occur in up to 16% of cases treated with methimazole and only 5% of cases treated with carbimazole.[52,79] More serious hematologic complications occur in less than 5% of cats treated with methimazole and include agranulocytosis and thrombocytopenia, either alone or concurrently, or more rarely, immune-mediated hemolytic anemia (usually occurring within the first 3 months of therapy).[7,79] These are apparently not dose related. While rarely reported for carbimazole, these worrisome problems can and do occur anecdotally. To predict such reactions, complete blood count (CBC) and platelet count is recommended every 2 weeks at least initially.[1,79] However, this is not cost-effective because of their low frequency and unpredictable occurrence. Therefore testing, if and when clinical signs develop, is more appropriate. There may however, be some merit in checking cats prior to surgery, particularly because thrombocytopenia is a potential risk.[1] Hepatic toxicity, exemplified by marked increases in the liver enzymes and bilirubin concentration, has also been described in less than 2% of cats treated with methimazole.[79] Cessation of therapy is required if either serious hematologic or hepatic reactions develop.

Serum antinuclear antibodies develop in approximately 50% of cats treated with methimazole for longer than 6 months, usually in cats on high-dose therapy (> 15 mg/day).[79] Although clinical signs of a lupuslike syndrome have not been reported, decreasing the daily dose is usually recommended. Such studies have not yet been carried out for carbimazole. A bleeding tendency without associated thrombocytopenia has been suggested to occur in cats treated with methimazole.[65] However, methimazole therapy had no effect on prothrombin time (PT) or activated partial thromboplastin time (APTT) after over 12 weeks of therapy, and it had no effect on thrombin clotting time or buccal mucosal bleeding time after 3 to 4 weeks of therapy in hyperthyroid cats.[85,86] However, a prolonged proteins induced by Vitamin K antagonism or absence (PIVKA) clotting time, together with melena, was reported in one cat, and this test is considered a more sensitive indicator of potential or actual bleeding tendencies than either PT or APTT.[86] Acquired myasthenia gravis (MG) and a cold agglutinin-like disease have been described in a few cats treated with methimazole.[1]

Editor's Note: There are numerous protocols for medical management of hyperthyroidism in cats. Our current recommendation is to administer 2.5 mg of methimazole orally once daily (or 2.0 mg of topical methimazole once daily) for 2 weeks. After this 2 week period, if the owners note any improvement or deterioration in their cats' condition, a serum total T_4 (with or without a CBC, serum biochemistry profile and urinalysis) should be obtained 4 to 6 hours after methimazole administration. If the value is within reference limits, that dose should be continued indefinitely. If neither improvement nor deterioration is appreciated or if the serum total T_4 concentration remains abnormally increased, the medication should be given BID for an additional 2 weeks. The cat should then be rechecked and the dose increased in 2 mg (topically) or 2.5 (orally) increments every 2 weeks, as needed. If administered topically, owners should be instructed to thoroughly rub the medication into the skin and then remove all excess vehicle within 30 minutes of each dose. If any abnormalities are detected that could be the result of methimazole, its' use should be discontinued until it can be demonstrated that continued use of the drug is warranted. It is further recommended that topical methimazole be compounded so that each dose is 0.05–0.10 cc this limits the problem of excess vehicle building upon the ears.

239.1.4.1.2

Other medical treatments

The thioureylene antithyroid drugs are preferred for the treatment of hyperthyroidism, but there may be occasions when alternatives are required either because of the development of adverse reactions or other specific contraindications. However, chronic management is only achieved with methimazole or carbimazole. Beta-adrenergic blockers, stable iodine, and calcium ipodate only provide short-term control, and a more permanent treatment option is subsequently required.

Propranolol (Inderal, Wyeth-Ayerst) and atenolol (Tenormin, ICI Pharma) are the most frequently used beta-blockers in hyperthyroid cats. They are usually used to symptomatically control the tachycardia, polypnea, hypertension, and hyperexcitability associated with hyperthyroidism and to prevent the arrhythmias that may occur when anesthetizing affected cats.[1] Traditionally these drugs were considered to have no direct effect on the thyroid gland or thyroid hormones; however, propranolol, at least, may inhibit peripheral conversion of T_4 to T_3 in cats as in humans.[87] They are usually used in combination with antithyroid drugs when rapid control of the clinical effects is required or with stable iodine to ensure a more effective response.[1,87] Because they do not affect uptake of radioactive iodine, they may be useful while awaiting such therapy or in cats that have a delayed return to euthyroidism after treatment.[1]

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Propranolol is a nonselective beta-adrenergic receptor–blocking agent and is therefore contraindicated in cats with asthma or pre-existing uncontrolled overt CHF. Atenolol, as a selective beta1 adrenoceptor–blocking agent is more useful in some of these situations and has the added advantage of a potential once-daily dosing regime. Propranolol is administered initially at a dose of 2.5 to 5 mg every 8 to 12 hours and subsequently titrated based on clinical effects and reduction in heart rate. Hyperthyroidism affects the pharmacokinetic profile of propranolol, and as such, low doses are recommended initially.[88] Atenolol is administered at a dose of 6.25 mg/cat either once or twice daily.

Large doses of stable iodine acutely decrease the rate of thyroid hormone synthesis (Wolff-Chaikoff effect) and thyroid hormone release. The mechanisms are unclear but are presumed to be protective. Its effects on reducing the vascularity and friability of thyroid tissue are controversial. Use of stable iodine has never gained widespread popularity because of its inconsistent, short-lived, and erratic effect in

inducing euthyroidism and the potential for escape from inhibition and exacerbation of thyrotoxicosis. In addition, it is contraindicated prior to radioactive iodine administration and is associated with a high incidence of adverse reactions (salivation and partial to complete anorexia), purportedly because of its unpleasant brassy taste.[1,7] However, a recent report has suggested using potassium iodate tablets together with propranolol in a staged regime for 20 days before surgery.[87] Propranolol is administered at a dose of 2.5 mg three times daily for 20 days before surgery, titrated to effect, and potassium iodate is administered at a dose of 21.25 mg three times daily from the tenth to the twentieth day. Using such a regime, serum total T_3 concentration decreases in most cats, and serum total T_4 concentration falls to within reference range in approximately one third of cats. Adverse reactions of potassium iodate are minimized by placing the tablets in a gelatin capsule prior to administration and using a relatively low dose for as short a period as possible. However, despite this, adverse reactions may still occur, albeit less frequently, suggesting a systemic rather than a local effect.[87]

Calcium ipodate, an oral cholecystographic contrast agent, is the only other drug that has been assessed in hyperthyroid cats. Its major effect is to acutely inhibit peripheral T_4 to T_3 conversion. In one study of 12 hyperthyroid cats treated with calcium ipodate at a dose of 100 mg divided twice daily, eight exhibited a good response as indicated by a reduction in serum total T_3 concentration to within the reference range within 2 weeks and an obvious improvement in clinical signs.[89] However, although associated with no adverse reactions, serum total T_4 concentration was unaffected, and cats were not evaluated for longer than 14 weeks. This drug is now of limited availability and further studies are unlikely.

239.1.4.2 Surgical Thyroidectomy

Surgical thyroidectomy is a relatively simple, quick, and curative procedure and is therefore often considered the preferred treatment option in practice. However, to decrease the cardiac and metabolic complications associated with anesthetizing hyperthyroid cats, prior medical management and control of the thyrotoxicosis is required. Once euthyroidism has been achieved, the main surgical considerations are whether to perform a unilateral or bilateral thyroidectomy, the type of technique to use, and the potential postoperative complications.

It is estimated that both thyroid lobes are affected in over 70% of hyperthyroid cats, thereby necessitating a bilateral thyroidectomy. In many of these cats, both thyroid lobes are palpably enlarged, grossly abnormal (or both) on visual examination. However, as many as 15% of cats with bilateral disease have one thyroid lobe that appears grossly normal and if left *in situ* results in recurrent hyperthyroidism usually within 12 months.[90] Thyroid imaging is obviously useful in depicting thyroid lobe involvement, but access to nuclear imaging facilities is required.[5] High resolution ultrasonography, capable of assessing thyroid lobe size and parenchymal appearance, is useful in characterizing thyroid tissue when scintigraphy is not available.[91] In the absence of imaging techniques and as surgical experience increases, many practitioners routinely perform bilateral thyroidectomies regardless of the gross appearance of thyroid lobes.[65] If not routinely attempted, both thyroid lobes must be carefully examined at the time of surgery.

Thyroidectomy can be performed by extracapsular or intracapsular techniques. With extracapsular thyroidectomy, the intact thyroid lobe and capsule is removed after ligation of the cranial thyroid artery while attempting to maintain blood supply to the cranial parathyroid gland. This technique is associated with an unacceptably high prevalence of postoperative hypoparathyroidism and is no longer

recommended.[92] With intracapsular thyroidectomy, the thyroid capsule is incised, the thyroid lobe removed, and the capsule left *in situ*, preserving the blood supply to the cranial parathyroid glands. However, this technique is associated with an unacceptably high risk of recurrence.[90,93] Both techniques have by now been modified to minimize the risk of postoperative hypoparathyroidism and recurrent hyperthyroidism.[92–94] The modified extracapsular technique uses bipolar cautery rather than ligatures, minimizing blunt dissection around the cranial parathyroid gland, whereas the modified intracapsular technique involves removal of the majority of the capsule after dissection. No significant difference is seen in the rate of postoperative hypocalcaemia or recurrence between these two methods, and both are considered equally appropriate for bilateral thyroidectomy in cats.[93] In unilateral cases, the choice of technique is not as important providing recurrence is avoided, because only one parathyroid gland is necessary to maintain eucalcemia.

Hypoparathyroidism resulting in hypocalcemia is the most significant potential postoperative complication. It has been suggested that the osteopenic effects of hyperthyroidism, rapidly reversed after surgical thyroidectomy, may exacerbate hypoparathyroidism in cats as in humans. However, the hyperparathyroidism and tendency toward ionized hypocalcemia reported in hyperthyroid cats suggests that such a phenomenon does not occur in this species.[55] While this in itself may play some role in postoperative hypocalcemia, hypoparathyroidism generally arises only if the parathyroid glands are injured, devascularized, or inadvertently removed during the course of a bilateral thyroidectomy. Revascularization of parathyroid tissue can occur even after removal and subsequent implantation to a nearby muscle belly.[95] Staged thyroidectomies (3 to 4 weeks apart) exploit this premise.[90] A more radical staged simplified complete thyroparathyroidectomy with parathyroid autotransplantation has been described in 10 cats with no postoperative hypocalcemia, which may be of particular benefit as a learning tool or if surgical experience is limited by a small throughput of cases.[65,96] However, a risk of simultaneous transplantation of diseased thyroid tissue exists, and increased costs and risk are associated with two general anesthetic procedures.[90,95]

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Mild hypocalcaemia develops in most cats after bilateral thyroidectomy, but treatment is not necessary until clinical signs develop.

Hypoparathyroidism is rarely permanent, and recovery of parathyroid function may occur days to months after surgery. In such cases the parathyroid damage is presumed reversible. Alternatively, accessory parathyroid tissue is activated or more likely, calcium homeostasis is maintained through a PTH-independent mechanism.[97] Other potential postoperative complications include Horner's syndrome, laryngeal paralysis, and voice change, but these are rare.[90]

Circulating thyroid hormone concentrations usually fall below the reference range for weeks to months after thyroidectomy. T_4 supplementation is often recommended, particularly after bilateral thyroidectomy.[1] However, it is not strictly necessary because clinical hypothyroidism is a rare sequelae. Presumably, eventual normalization of thyroid hormone production occurs, either because of activation of the contralateral lobe in unilateral cases or accessory thyroid tissue in bilateral cases. Recurrence of hyperthyroidism is always a possibility after thyroidectomy, and cats should be monitored every 6 to 12 months thereafter. If a unilateral thyroidectomy was originally performed, development of lesions in the contralateral gland should pose no additional surgical risk providing parathyroid function is maintained. However, in cases of recurrent hyperthyroidism after bilateral thyroidectomy, postoperative morbidity and

mortality is significantly increased and an alternative form of treatment for the hyperthyroidism is indicated.[93]

239.1.4.3 Radioactive Iodine

Administration of radioactive iodine as ^{131}I is considered to be the safest, simplest, and most effective therapy for feline hyperthyroidism. ^{131}I, like stable iodine, is actively concentrated by the thyroid gland, has a half-life of 8 days, and emits both β-particles and γ-radiation. The β-particles, cause over 80% of damage, but are locally destructive, traveling a maximum of 2 mm with an average path length of 400 μm. Therefore no significant damage occurs to adjacent parathyroid tissue, atrophic thyroid tissue, or other cervical structures. The aim of therapy is to restore euthyroidism with the smallest possible single dose of radiation, while avoiding the development of hypothyroidism or the persistence of hyperthyroidism.

Since its first use, controversy has surrounded the best method to calculate the optimum dose for individual cats. Tracer kinetic studies have been used that allow calculation of percentage iodine uptake, effective half-life, and estimation of thyroid gland weight—all factors known to influence the therapeutic dose.[98,99] The predictive value of tracer studies in estimating a therapeutic dose has been shown to be significantly closer to the therapeutic goal than the hypothetical administration of a fixed low dose (111 MBq).[100] However, this method requires access to sophisticated computerized nuclear medicine equipment, is time-consuming, expensive and can involve repeated sedation of the patient. It is therefore rarely used.

Another method is to use a relatively high fixed dose of between 148 and 250 MBq in all cats regardless of the size of the goiter or severity of the thyrotoxicosis.[101–105] Although this method is successful and simple, it potentially results in the under-or overtreatment of a significant proportion of cats. Extremely high fixed doses (> 1000 MBq) are retained for cats after surgical removal of a thyroid carcinoma.[106]

In most studies examining radioactive iodine therapy, it is recognized that markedly elevated pretreatment serum thyroid hormone concentration, the size of goiter, and the severity of the clinical thyrotoxicosis all potentially adversely affect the eventual response. The dose administered can be determined based on a scoring system that takes these factors into consideration.[107–109] When such a scoring system is used, doses range from 39 to 222 MBq, allowing titration to each individual cat and avoiding unnecessary under-or overtreatment. It is an extremely simple method that does not require access to sophisticated nuclear medicine equipment. Success is comparable to dose estimation by tracer kinetic studies.

Traditionally, ^{131}I is administered intravenously.[98,102–105,107–109] Oral administration has been attempted, but higher doses are generally required, the risks of radiation spillage are greater, and vomiting may occur.[101,104,110] Subcutaneous administration is equally effective, is simpler to administer, is safer to personnel, is less stressful to cats, and is currently preferred.[108,109,111] Whatever method of dose calculation or route of administration, attainment of euthyroidism is expected in over 90% of cats with a single dose (Figure 239-7). A small percentage of cats remain persistently hyperthyroid, but euthyroidism is eventually attained in some of these animals weeks to months later without further treatment.[108,109] Both hypothyroidism and recurrent hyperthyroidism can develop but appear to be rare, and other side effects are minimal.[112]

Several studies have estimated survival time in cats after treatment with hyperthyroidism. In one study of 66 cats followed for a mean of 13 months, 44 (67%) cats were alive and euthyroid 1 to 33 months after

treatment. The remaining cats had died of unrelated causes, including renal failure.[103] In a larger study of 524 cats, median survival time (MST) was 24 months (range 2 weeks to 7 years).[109] The percentage of cats alive at 1, 2, 3, and 4 years after treatment was 89%, 72%, 52%, and 34%, respectively. The most common causes of death in treated hyperthyroid cats are malignancy and renal disease.[109,113]

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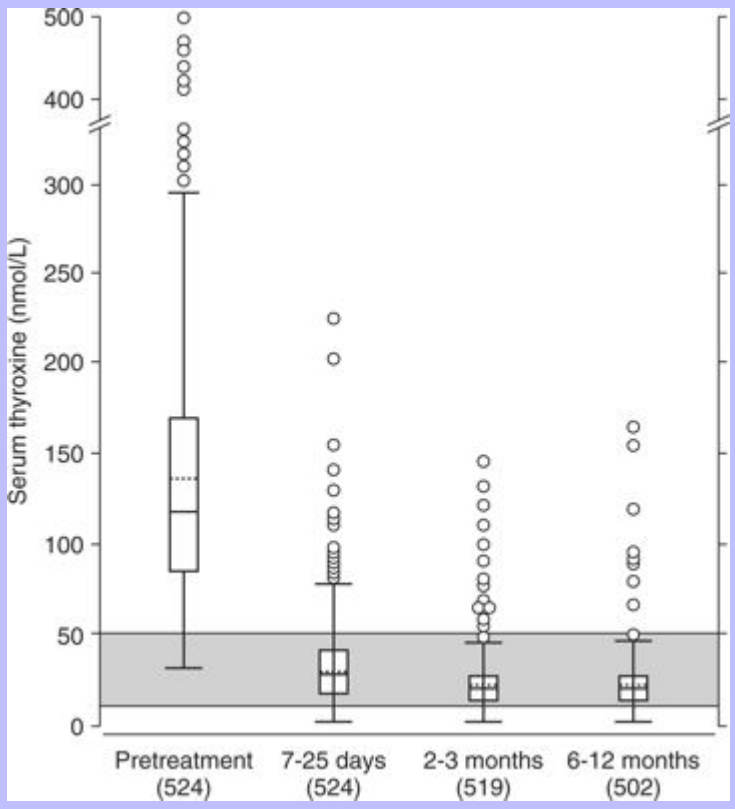
Figure 239-7 Box plots of serum total thyroxine (T_4) concentrations in 524 cats before and at various times after administration of radioiodine for treatment of hyperthyroidism. Data are plotted (i.e., box plots) as described in the legend of Figure 239-1. The shaded area indicates the reference range for serum T_4 concentration. To convert serum T_4 concentrations from nmol/L to ng/dL, divide the given values by 12.87. (From Peterson ME et al: Radioioidine treatment of 524 cats with hyperthyroidism. J Am Vet Med Assoc 207:1422, 1995.)



The effect of prior medical management on eventual outcome of radioactive iodine therapy is controversial. Obviously prior administration of stable iodine is contraindicated because of its inhibitory effect on the thyroid gland. Beta-blockers are often recommended because they have no effect on the thyroid gland *per*

se. However, prior methimazole (and therefore carbimazole) therapy has been suggested to enhance, worsen, or have no effect on radioiodine treatment outcome.[98,109,110,112] Methimazole does not inhibit thyroidal iodine uptake, but current administration adversely affects effective half-life of radioactive iodine and is not recommended.[100] However, iodine uptake is enhanced in healthy cats after recent methimazole withdrawal and this short-term rebound effect is potentially beneficial when treating with radioactive iodine.[78] A more recent study has shown that discontinuing methimazole for less than or greater than 5 days prior to radioactive iodine therapy has no effect on treatment outcome.[105]

The main drawback to widespread use of radioactive iodine is the requirement for special licensing and the isolation of the cat for variable periods after treatment. This can range from several days to several weeks, depending on the dose used and state or local radiation regulations.[1] Cats appear to tolerate these periods of hospitalization well.

239.1.4.4 Other Therapies

Intrathyroidal infusion of ethanol causes tissue necrosis and eventual induction of euthyroidism. Single injections in unilateral cases, preferably using ultrasound guidance, are efficacious in inducing euthyroidism in hyperthyroid cats.[114] Staged injections in bilateral cases are less successful in treating hyperthyroidism.[115] However, percutaneous ethanol injection is associated with a high incidence of adverse reactions such as transient dysphonia, Horner's syndrome, gagging, and laryngeal paralysis and cannot therefore be recommended for treatment of hyperthyroid cats.

Gene therapy could potentially be used to deliver cytotoxicity specifically to abnormally functioning thyroid cells. The feline thyroglobulin promoter has been characterized and its cell type specific activity demonstrated, paving the way for transcriptional targeting of gene therapy. However, a great deal of work is required before any such technology reaches veterinary practice.[116]

239.1.4.5 Effect of Treatment on Renal Function

Despite the potential adverse effect of hyperthyroidism on renal function, its presence can increase glomerular filtration rate (GFR), decrease serum creatinine concentration, and mask underlying renal disease.[34,55,117] Decreased GFR, increased serum urea and creatinine concentration, and development of overt clinical signs of renal disease have all been reported after successful treatment of hyperthyroidism, regardless of therapeutic modality utilized (methimazole, surgical thyroidectomy or radioiodine).[34,118–120] Assessment of GFR before treatment can act as a predictor of post-treatment renal failure with a low GFR in hyperthyroidism, indicating an increased risk for adverse clinical outcome.[119] However, techniques for assessment of GFR are impractical because they typically involve use of radioisotopes. Estimation of GFR is also possible using a plasma iohexol clearance test that requires no special licensing but is technically demanding.[120] In the absence of such estimations, accurate prediction of impending renal failure is difficult. However, serum urea and creatinine concentrations and USG should be carefully evaluated prior to treatment of hyperthyroidism. If both serum parameters are normal and the urine is concentrated, the risk of developing renal failure after therapy is minimized. Serum creatinine should be evaluated in light of the animal's muscle mass with lower values expected in emaciated cats.[34] If the serum creatinine and urea concentrations are higher than expected and the urine isosthenuric, a risk of developing renal failure exists. In such cases, trial therapy using either methimazole or carbimazole should be attempted and renal function

reassessed once euthyroidism is achieved. Initially low and then increasing doses of methimazole have been suggested in suspect cases, but limited scientific evidence exists to support this.[34] If no deterioration occurs after treatment of the hyperthyroidism, then a more permanent therapeutic option may be selected. If renal function declines, therapy should be instituted for renal failure and the dose of antithyroid medication adjusted to maximize renal function while attempting to control clinical signs. Maintenance of a mildly hyperthyroid state may be beneficial in some individuals. Avoidance of hypothyroidism is important because it may have its own detrimental effects on GFR.[34]

239.2 THYROID NEOPLASIA AND HYPERTHYROIDISM IN DOGS

Thyroid tumors account for 1.2% to 3.75% of all tumors and approximately 10% to 15% of all head and neck neoplasms in the dog. In pathologic studies, benign adenomas account for approximately 30% to 50% of all thyroid tumors, but these are usually small focal lesions uncommonly detected during life.[121,122] On the other hand, carcinomas, responsible for only 50 to 70% of all thyroid tumors diagnosed postmortem, account for up to 90% of those tumors detected antemortem. All thyroid masses detected during life should, therefore, be presumed malignant until proven otherwise. Carcinomas are usually larger than adenomas, coarsely multinodular, nonmobile, and often have necrotic or hemorrhagic centers or, occasionally, focal areas of mineralization or bone formation. Unilateral involvement is more than twice as common as bilateral involvement; when the latter occurs, the neoplastic process is usually extensive. It is therefore difficult to determine if the tumor arose in both thyroid lobes or if metastases occurred from one lobe to the other. Occasionally, ectopic thyroid tissue (arising from thyroglossal duct remnants) located anywhere from the base of the tongue to the base of the heart becomes neoplastic, and thyroid tumors must therefore be included in a range of differential diagnoses for oral, cervical, and thoracic masses.

Thyroid carcinomas are poorly encapsulated and commonly extend into or around the trachea, cervical muscles, esophagus, larynx, nerves, and blood vessels, although invasion into the esophageal or tracheal lumen is unusual. Metastatic spread to the retropharyngeal and cervical lymph nodes is common. However, early invasion into the cranial and caudal thyroid veins with the formation of tumor cell thrombi leads to multiple pulmonary metastases, often before involvement of regional lymph nodes. Other reported, but rare, sites of metastatic lesions include kidney, adrenal gland, liver, spleen, spinal cord, and bone.

Histopathologically, thyroid carcinomas are usually well differentiated and classified as follicular, compact (solid), mixed, or papillary. The majority of tumors in the dog are mixed, follicular, or less commonly, compact. The correlation between this histopathologic classification and ultimate prognosis is unclear. Undifferentiated (anaplastic) thyroid tumors appear to be highly malignant but are rare. Medullary (parafollicular, C-cell) carcinoma may have a more favorable prognosis, because distant metastatic spread is uncommon and they appear to be well encapsulated and easily resectable at the time of surgical thyroidectomy. However, specific immunocytochemical stains are required for diagnosis.[123] The probability of metastases clearly increases in proportion to the size of the tumor. Dogs with small thyroid tumors (< 20 cm^3) have a less than 20% incidence of metastatic disease, whereas nearly all dogs with large tumors (> 100 cm^3) have metastases.

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239.2.1 Clinical Features

Thyroid tumors occur in middle-aged and older dogs, with an average age at onset of 10 years. Almost all dogs are greater than 4 years old at the time of diagnosis. No sex predilection exists, unlike the situation in humans in which females are more than twice as likely to develop thyroid cancer as males at most ages.

Beagles and golden retrievers appear predisposed to the development of thyroid carcinomas and boxers to the development of both adenomas and carcinomas.

Thyroid tumors are occasionally coincidentally found as freely mobile masses when grooming, petting, or during a general health check. However, most dogs have a visible mass in the neck or have its associated consequences (coughing, gagging, dysphonia, dysphagia, retching, regurgitation, and vomiting). The duration of these signs varies from weeks to months. The mass is usually felt in the region of the thyroid gland, below the larynx, but occasionally, larger tumors may descend toward the thoracic inlet. Clinical signs referable to regional (enlarged lymph nodes or cording of local lymphatic and blood vessels) or distant (dyspnea from pulmonary metastases) metastatic spread may be apparent. A few dogs may have the additional clinical signs of hypothyroidism or hyperthyroidism. Dogs with hyperthyroidism exhibit similar clinical signs to those in cats (weight loss, polyphagia, polyuria/polydipsia [PU/PD], restlessness, tachycardia) but tend to be less symptomatic.

In general, canine thyroid tumors are nonfunctional, and euthyroidism is maintained throughout the course of the disease. It has been suggested that up to 30% of dogs with detectable thyroid tumors are hypothyroid.[124] Hypothyroidism may arise because of destruction of all normal thyroid tissue by aggressive bilateral carcinomas. Alternatively, large tumors could potentially produce excessive inactive thyroid hormones capable of pituitary TSH suppression and eventual atrophy of normal thyroid tissue, although this has not yet been substantiated. A diagnosis of hypothyroidism must be approached with caution because of the suppressive effect of nonspecific illness on circulating thyroid hormone concentrations. Hyperthyroidism occurs in approximately 10% to 20% of thyroid carcinomas but is unusual in the rare cases of detectable adenomas.

In humans, thyroid tumors form part of the multiple endocrine neoplasia (MEN) syndromes in which neoplasia or hyperplasia develops in several different endocrine organs simultaneously. MEN syndromes are classified as type 1 or type 2, the latter further divided into type 2A and 2B. The MEN syndromes tend to involve one or more specific polypeptide-and biogenic amine-producing cell types, exhibit a histologic progression from hyperplasia to adenoma and (in some cases) to carcinoma, and each has an autosomal dominant pattern of inheritance. MEN type 1 syndrome involves parathyroid, pancreatic islet, and pituitary hyperplasia or neoplasia. MEN type 2A is associated with the development of bilateral pheochromocytomas, medullary thyroid carcinomas and, less commonly, parathyroid hyperplasia or adenoma. The association of medullary thyroid carcinoma and pheochromocytoma with multiple mucosal neuromas is termed *MEN type 2B*. Some patients do experience unusual manifestations of these syndromes, but these are less well characterized. Although rare, it has been suggested that MEN syndromes exist in dogs,[124] and a careful clinical evaluation should be carried out in all dogs with thyroid carcinoma.

239.2.2 Diagnosis

The differential diagnoses for large cervical swellings include abscess, granuloma, thyroid tumor, other tumors, and salivary mucocele. Fine needle (21 to 23 gauge) aspiration is helpful in distinguishing many of these. Unfortunately, because of the vascular nature of thyroid tissue, samples are frequently heavily contaminated with blood and exfoliation of neoplastic cells can be poor.[125] Evaluation of wide bore needle biopsies, although of greater diagnostic yield, significantly increases the risk of hemorrhage and should only be carried out under ultrasound guidance. Even with such biopsies there may still be difficulty in distinguishing benign from malignant tumors, and the latter is often only confirmed by demonstration of vascular or capsular invasion in biopsies taken at the time of surgical thyroidectomy.

Results of postmortem studies show that up to 80% of dogs have evidence of distant metastatic spread, although this decreases to just over 60% in clinical cases.[126] Thus it is imperative that once a mass is identified as thyroid, a systematic search for metastatic spread should follow. Routine screening laboratory tests may be helpful in identifying secondary organ involvement or concurrent problems that may ultimately affect the prognosis. Local lymph nodes should be carefully examined and biopsied as necessary. Radiography of the cervical area may help to assess the size of the mass and the extent of local invasion. Thoracic radiography should always be evaluated for evidence of pulmonary spread even in the absence of clinical signs. Abdominal radiography and ultrasonography may be useful in cases where hepatic metastasis is suspected.

As in cats, thyroid scintigraphy using radioactive iodine or technetium may be useful because most thyroid tumors and their metastases retain the ability to trap iodine. Such scans do not provide any information with regard to thyroid function but are helpful in depicting location of the tumor and regional metastases.[127] Some thyroid tumors fail to adequately concentrate radioisotopes, and it has been suggested that these are less likely to respond to radioactive iodine administration.[124] Compared with thoracic radiography, thoracic scintigraphy to depict pulmonary metastases is not considered useful.

Measurement of serum total T_4 concentration is necessary in dogs with appropriate clinical signs of thyrotoxicosis. Elevations are generally moderate, compared with the marked elevations often seen in hyperthyroid cats. Measurement of circulating endogenous TSH concentration is not useful due to the poor sensitivity of currently available assays and their inability to detect suppressed values. However, free T_4 in combination with cTSH measurements will provide the most useful information to support hypothyroidism if clinical signs are suggestive.

239.2.3 Treatment

Currently, several possible treatment options exist for thyroid carcinoma. Clinicians find that the selection of any one option is complicated by poorly defined prognostic indicators, inconsistencies in case selection and reporting criteria amongst the different studies, and the variety and number of treatments attempted in individual patients. However, it is clear that the prognosis is excellent for mobile, nonfixed tumors; that local control may halt metastatic spread; and that metastatic spread may not ultimately affect outcome with certain treatment options. In addition, functional state appears irrelevant and clinical signs of hyperthyroidism can easily be controlled using carbimazole or methimazole at 5 mg orally three times daily initially and subsequently adjusted for effect.

Surgical thyroidectomy is approached as for cats. However, in dogs most tumors are unilateral and therefore it is not necessary to preserve parathyroid glands on the affected side. In dogs with no evidence of metastatic spread and operable thyroid tumors, resection alone results in long-term control without subsequent development of metastases.[128] However, in many cases extensive local tumor invasion precludes complete removal, and aggressive surgical attempts significantly increase the risk of extensive hemorrhage and damage to the recurrent laryngeal nerves and parathyroid glands. In such cases, surgery alone is only associated with a 25% survival rate at 1 year.[123] Surgical debulking followed by chemotherapy with cisplatin or doxorubicin has been recommended for such cases.[129,130] Administration of radioactive iodine may be helpful if iodine uptake is maintained but generally high, and multiple doses must be used, limiting its value clinically.[124,131] Two recent studies suggest that definitive or palliative radiotherapy may be associated with the best survival.[132,133]

In these studies, prior existence of metastatic spread did not appear to alter survival, and there was a decreased risk of metastatic spread with local control of tumor progression.

Standard dose T_4 supplementation is necessary after bilateral thyroidectomy. In addition, T_4 therapy is usually recommended after unilateral thyroidectomy. Receptor affinity and concentration and functional response to TSH are similar in healthy and carcinomatous thyroids.[134] Although it is unclear if TSH has any growth-stimulating properties in thyroid neoplasia *in vivo*, T_4 therapy seems a wise precaution.

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240 CHAPTER • 240 Insulin-Secreting Islet Cell Neoplasia

Rebecka S. Hess

Insulinoma is uncommon in the dog and rare in the cat. This chapter, therefore, focuses on canine insulinoma unless otherwise noted. The first case series documenting successful surgical therapy of insulinoma in human beings was reported by Whipple in 1935. *Whipple's triad* was defined as the presence of neurologic clinical signs associated with a low plasma glucose concentration and relieved by feeding or administration of glucose. Canine insulinoma was first described in 1935.[1]

240.1 PATHOLOGY

Insulin-secreting beta cell neoplasia is the most common islet cell neoplasia in the dog. This may be due to the fact that beta cells comprise approximately 70% of cells in the islets of Langerhans. Most canine insulinomas are malignant. In one immunocytochemical report, 17 of 18 insulinomas were carcinomas and only one was an adenoma.[2] About 80% of pancreatic tumors are solitary, and most are located in one of the two limbs of the pancreas rather than in the body.[3–5] Occasionally, no discrete nodule or nodules are apparent during gross examination of the pancreas, and histopathologic evaluation is needed to identify the tumor.

The rate of detected metastatic lesions in 179 dogs from different studies ranged from 45% to 64% and was higher in studies based on necropsy than in those based on surgical biopsies.[3,6,7] Clinical staging of pancreatic tumors according to the World Health Organization's tumor-node-metastasis (TNM) system defines stage I as $T_1N_0M_0$ (presence of a primary tumor and absence of regional lymph node or distant metastases), stage II as $T_1N_1M_0$, and stage III as $T_1N_1M_1$ or $T_1N_0M_1$. Most dogs with insulinoma have stage II or stage III disease.[8] The most common sites of metastases are regional lymph nodes and the liver. Other reported metastatic sites are the duodenum, mesentery, omentum, spleen, heart, and spinal cord.

Although the etiology of insulinoma is unknown, growth hormone production, which is not associated with increased plasma growth hormone concentrations, has been documented in primary and metastatic canine insulinoma lesions. Local growth hormone may affect insulinoma cell proliferation through paracrine or autocrine mechanisms.[9]

240.1.1 Pathophysiology

Proliferation of beta pancreatic cells results in excess secretion of insulin and therefore hypoglycemia. The most important compensatory mechanisms for hypoglycemia are inhibition of insulin secretion and stimulated secretion of counter-regulatory hormones.

Glucose is the primary regulator of insulin secretion. When glucose enters beta pancreatic cells, it is metabolized to adenosine triphosphate (ATP) and closes ATP-sensitive potassium (K^+) channels. Closure of the K^+ channels reduces K^+ efflux and results in depolarization of the beta cell and opening of voltage-sensitive calcium (Ca^{2+}) channels. An increase in the cytoplasmic Ca^{2+} concentration results in insulin exocytosis. In a normal animal, insulin secretion is completely inhibited when the blood glucose concentration is less than 65 to 80 mg/dL. However, insulin secretion from neoplastic beta cells occurs independent of the blood glucose concentration and persists despite a low blood glucose concentration.

Therefore the hallmark of an insulin-secreting tumor (insulinoma) is an increased blood insulin concentration despite a low blood glucose concentration.

The four counter-regulatory hormones secreted in response to hypoglycemia are glucagon, catecholamines, growth hormone, and glucocorticoids. Of these hormones, glucagon and catecholamines are most important in increasing the blood glucose concentration.

240.2 HISTORY AND CLINICAL SIGNS

The mean age of dogs with insulinoma is 9 years (range, 3 to 15 years). Although any breed can develop an insulinoma, the tumor has been reported mainly in medium to large breed dogs. Controlled studies of breed risk for insulinoma have not been published, and there is no apparent sex predilection for the disease.

Most clinical signs arise from the effect of hypoglycemia on the central nervous system (neuroglycopenia) or from hypoglycemia-induced release of catecholamines. Glucose is the single most important source of energy in the brain, and carbohydrate storage in neural tissue is limited. Brain function, therefore, depends on a continuous supply of glucose. Clinical signs attributable to neuroglycopenia include seizures, collapse, weakness, ataxia, disorientation, mental dullness, and visual disturbances. Clinical signs related to excess catecholamine release and stimulation of the sympathetic nervous system include tremors, hunger, and nervousness.

The severity of clinical signs increases as blood glucose drops, and severe hypoglycemia ultimately can result in coma and death. Clinical signs may also be related to the duration of the hypoglycemia and the rate at which it develops, because a gradual decrease in the blood glucose concentration may be less likely to stimulate catecholamine secretion. Occasionally clinical signs are episodic, because secretion of counter-regulatory hormones elevates the blood glucose concentration and temporarily resolves neuroglycopenic clinical signs. Feeding can result in either alleviation or exacerbation of clinical signs. If feeding restores the blood glucose concentration to normal, the clinical signs resolve. However, feeding may also stimulate insulin secretion and exacerbate the clinical signs. Fasting, exercise, or excitement can worsen clinical signs either by decreasing the blood glucose concentration or by increasing sympathetic stimulation.

Clinical signs reported in 198 dogs from several studies are listed in Table 240-1.[3–5,7,8,10] Although most dogs have more than one of these clinical signs, some dogs have none. The reported duration of clinical signs prior to diagnosis varies from 1 day to 3 years.

240.2.1 Physical Examination

The physical examination is unremarkable in most dogs with insulinoma.[4,6] Dogs may be overweight as a result of the anabolic effects of insulin, and postictal findings may be apparent if the dog has had a recent seizure. A peripheral polyneuropathy, characterized by tetraparesis and decreased or absent appendicular reflexes, has been described in association with insulinoma in 13 dogs.[8,11,12] The etiology of insulinoma-associated peripheral neuropathy is not known. It has been suggested that this polyneuropathy develops as a paraneoplastic immune-mediated disorder that is unrelated to the metabolic changes associated with insulinoma.[12]

240.3 DIFFERENTIAL DIAGNOSES

Differential diagnoses for hypoglycemia may be categorized as (1) those associated with excess secretion of insulin or insulin-like factors, (2) those associated with decreased glucose production, (3) those associated with excess glucose consumption, (4) drug-associated causes, and (5) spurious causes. Disorders in which the most important mechanism for hypoglycemia is excess secretion of insulin or insulin-like factors include insulinoma, extrapancreatic tumor, and islet cell hyperplasia. Conditions associated with decreased glucose production include hypoadrenocorticism, hypopituitarism, growth hormone deficiency, liver diseases, glycogen storage diseases, neonates, and toy breeds. Fasting, malnutrition, and pregnancy may also result in hypoglycemia. Excess glucose consumption may develop in sepsis or extreme exercise. Some of the many drugs reported to induce hypoglycemia in human beings include insulin, oral hypoglycemics (e.g., sulfonylurea), salicylates (e.g., aspirin), acetaminophen, beta blockers (e.g., propranolol), $beta_2$-agonists, ethanol, monoamine oxidase inhibitors, tricyclic antidepressants (e.g., amitriptyline), angiotensin-converting enzyme inhibitors (e.g., captopril), antibiotics (e.g., tetracycline), lidocaine overdose, and lithium. Factitious hypoglycemia may occur when blood cells are not promptly separated from serum or in cases of severe polycythemia or leukocytosis if serum separation is delayed longer than 1 hour.

Table • 240-1 Clinical Signs Reported in 198 Dogs from Several Studies[3–5,7,8,10]

CLINICAL SIGN	NUMBER OF DOGS
Seizure	95
Collapse	79
Generalized weakness	74
Shaking/trembling/muscle twitching	40
Ataxia	40
Exercise intolerance	30
Hindlimb weakness	28
Disorientation/bizarre behavior/hysteria	19
Polyphagia	16
Polyuria and polydipsia	16
Stupor/lethargy	12
Focal facial seizures	6
Obesity or weight gain	6
Blindness	5
Anorexia	5
Diarrhea	4
Head tilt	2
Nervousness	2

240.3.1 Diagnostic Evaluation

A clinical suspicion of insulinoma is established with documentation of appropriate clinical signs, hypoglycemia (blood glucose concentration less than 60 mg/dL), and concurrent hyperinsulinoma (serum insulin concentration greater than 20 μU/mL).[13] Identification of a pancreatic mass with imaging studies may strengthen this suspicion. The diagnosis of insulinoma is confirmed with histologic examination and immunohistochemical staining of the pancreatic mass.

The results of a complete blood count, chemistry screen, and urinalysis are usually unremarkable, aside from the low blood glucose concentration.[4,7] Although hypoglycemia is observed in most dogs with insulinoma, especially if the measurement is repeated twice,[7] it is important to remember that some dogs with insulinoma may have euglycemia on repeated measurements.[14] Mild hypokalemia and increased serum alkaline phosphatase or alanine aminotransferase activities have also been documented.[5,7]

If a dog suspected of having an insulinoma has euglycemia, it should be fasted and the blood glucose concentration should be measured every 1 to 2 hours. In most dogs with insulinoma, hypoglycemia develops within 12 hours of fasting. Blood for measurement of the insulin concentration should be collected when the animal is hypoglycemic, and it should then be fed. However, a small percentage of dogs do not exhibit hypoglycemia, even with repeated measurements and after a prolonged fast (48 to 72 hours).[7] A low fructosamine concentration has been used to strengthen the clinical suspicion of insulinoma in several dogs with euglycemia.[14] The glycosylated hemoglobin A1c concentration has been significantly low in some but not all dogs with insulinoma.[15] Repetition of serum insulin measurements may also aid in the diagnosis. One study of canine insulinoma found that 76% of dogs had an increased serum insulin concentration when it was measured once, and 91% of dogs had an increased serum insulin concentration when it was measured twice.[7]

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Other tests have been described as aids in the diagnosis of insulinoma in euglycemic dogs with a normal serum insulin concentration. However, insulin to glucose and glucose to insulin ratios are not recommended because of their low sensitivity, and the amended insulin to glucose ratio is not recommended because of its low specificity. Additional tolerance and stimulation tests have been described but are not advocated because of questionable usefulness and potentially fatal side effects, such as hypoglycemia and seizures.[16]

Most dogs with insulinoma have normal abdominal and thoracic radiographs.[4,6,8,17] According to the combined results of several studies in which abdominal ultrasound scans were performed in dogs with insulinoma, a pancreatic mass was identified in 49 of 87 (56%) dogs, and abdominal metastasis was noted in 17 of 87 (20%).[3,5,8,17] Although abdominal ultrasonography may be helpful in increasing the clinical suspicion of a pancreatic mass and metastases, both false-positive and false-negative results have been described.

Computed tomography (CT) is the most common imaging technique used for identification of pancreatic tumors in human beings; it detects about 50% of tumors greater than 2 cm in diameter and almost none of the smaller tumors.[18] CT has been reported in a small number of dogs with insulinoma, but its sensitivity in dogs has yet to be determined.[8] Intravenous administration of radioactively labeled synthetic somatostatin, followed by whole body scintigraphy, has been shown to be a sensitive and specific tool for pancreatic tumor imaging in humans[18] and has been reported in one dog with insulinoma.[19] Intravenous intraoperative administration of methylene blue was used to characterize pancreatic tumors in five dogs.[20]

240.4 TREATMENT

Therapy for insulinoma can be divided into treatment of the acute hypoglycemic crisis and long-term management. During an acute hypoglycemic crisis, dextrose can be given as a slow bolus (0.5 g/kg given intravenously, diluted in 0.9% sodium chloride at a 1:3 ratio). The bolus is followed by an intravenous continuous-rate infusion of dextrose (2.5% to 5% in water). Dextrose must be administered with caution because

it can stimulate insulin secretion and cause hypoglycemia. Fluid resuscitation is performed as necessary. In most dogs, neuroglycopenia resolves with administration of dextrose. However, if the animal fails to respond to dextrose administration alone, dexamethasone (0.5 mg/kg given intravenously over 6 hours, every 12 to 24 hours) and a somatostatin analog (20 to 40 μg given subcutaneously every 8 to 12 hours) may be administered. In severe cases the animal may have to be sedated with pentobarbital for several hours while the above treatment is continued and until seizures resolve.[21]

A continuous-rate infusion of glucagon (5 to 13 ng/kg/min with or without a concurrent 10% dextrose infusion) has been reported in one dog with insulinoma-associated hypoglycemia. Clinical signs attributed to the hypoglycemia resolved within 20 minutes, and the hypoglycemia resolved within 1 hour. Glucagon increases the blood glucose concentration by promoting glycogenolysis and gluconeogenesis. However, glucagon also increases insulin secretion, and animals should be monitored carefully for worsening hypoglycemia.[22]

The long-term treatment of choice for insulinoma is surgical resection of the tumor and gross metastases.[5] Surgical exploration and biopsy of the pancreatic mass also can confirm the diagnosis and may aid estimation of the survival time.[10] When postoperative hyperglycemia develops, it usually is transient and resolves once normal beta cells, which have been suppressed by excess insulin secretion from neoplastic cells, regain their function. However, about 10% of dogs develop diabetes mellitus and require treatment with exogenous insulin for 1 to 37 months.[6,7,10] Other postoperative complications include acute pancreatitis, diabetic ketoacidosis, delayed wound healing, ventricular arrhythmias and cardiac arrest, hemorrhage, sepsis, and leukopenia.[3,5,7]

The discussion of medical therapy is limited to clinically important agents reported as having been used in dogs with spontaneous insulinoma. The use of additional medications is discussed elsewhere.[21] Medical treatment is indicated prior to surgery, postoperatively if needed, and in cases in which surgery is not performed. Medical therapy can be divided into cytotoxic treatment directed at destroying insulin-secreting beta cells and treatment aimed at relieving the hypoglycemia.

Streptozocin is a nitrosourea antibiotic derived from the bacterium *Streptomyces achromogenes*. Streptozocin selectively destroys beta cells in the pancreas or metastatic sites. The drug is nephrotoxic and has been reported to cause acute renal failure and renal tubular atrophy in the dog. Diuresis with saline decreases the drug's contact time with renal tubular epithelial cells and may reduce the risk of nephrotoxicity. Successful use of streptozocin in veterinary medicine is limited to a study of 17 dogs, most of which had surgery with incomplete resection of gross lesions.[8] Dogs were treated with 0.9% sodium chloride (18 mL/kg/hr given intravenously) for 3 hours prior to streptozocin administration, during 2 more hours of streptozocin treatment, and for 2 additional hours after treatment. Streptozocin (500 mg/m^2) was given every 3 weeks. Butorphanol (0.4 mg/kg given intramuscularly) was administered immediately after streptozocin therapy as an antiemetic, but vomiting still occurred in about 30% of treatments. Other side effects included diabetes mellitus, transient hypoglycemia and seizures, transient hyperglycemia, transient increases in alanine aminotransferase activity, azotemia, mild thrombocytopenia, and mild neutropenia. The median duration of normoglycemia in dogs treated with streptozocin was 163 days, which was not significantly different from the median duration in control dogs treated surgically or medically. Further studies are needed to determine whether the benefits of streptozocin treatment outweigh its risks.

The main methods of relieving hypoglycemia include dietary modification and treatment with prednisone, diazoxide, or synthetic somatostatin. Small, frequent meals (every 4 to 6 hours) of a diet high in protein, fat, and complex carbohydrates are recommended, and simple sugars (present in soft, moist dog foods) should be avoided.

Prednisone increases the blood glucose concentration by increasing gluconeogenesis and glucose 6-phosphatase activity, decreasing blood glucose uptake into tissue, and stimulating glucagon secretion. Glucocorticoids can be administered intravenously in the form of dexamethasone during an acute hypoglycemic crisis or can be given orally once the dog is stable. Prednisone, the least expensive and most commonly used drug for the treatment of canine insulinoma, should be administered at a dosage of 0.5 to 4 mg/kg/day given orally, beginning with the lower end of the dosage and gradually increasing if necessary.[10,21]

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Diazoxide is a benzothiadiazine derivative, the main action of which is to inhibit closure of ATP-dependent K^+ channels in beta pancreatic cells. This prevents depolarization of beta cells and inhibits opening of voltage-dependent Ca^{2+} channels. Decreased Ca^{2+} influx results in decreased exocytosis of insulin-containing secretory vesicles. Diazoxide also increases the blood glucose concentration in pancreatized dogs by increasing glycogenolysis and gluconeogenesis and by inhibiting tissue uptake of glucose.[23] Diazoxide is administered at a dosage of 10 to 40 mg/kg/day given orally, divided every 8 to 12 hours, beginning at the lower end of the dosage and gradually increasing if needed. Approximately 70% of dogs with insulinoma respond to treatment with diazoxide.[7] Side effects in dogs, which are uncommon, include ptyalism, vomiting, and anorexia. However, in human beings, myocardial ischemia, salt retention, water retention, hyperglycemia, hypotension, and cerebral ischemia have also been reported.

Octreotide is a long-acting synthetic somatostatin analog, and its main mode of action is inhibition of insulin secretion. In human beings, octreotide's action depends on its binding affinity to any of five somatostatin receptor subtypes present in tumors. Dogs have only one somatostatin receptor subtype, and their response to octreotide is variable.[24] The lack of a dependable response to octreotide in dogs may be due to the drug's inhibition of glucagon and growth hormone secretion. If suppression of glucagon and growth hormone secretion is of greater magnitude and duration compared with suppression of insulin secretion, octreotide may actually worsen the hypoglycemia. Also, some canine insulinomas may not have somatostatin receptors. For these reasons, further studies are needed to determine octreotide's efficacy and safety in dogs. Octreotide has been administered to dogs with insulinoma at dosages of 2 to 4 µg/kg given subcutaneously every 8 to 12 hours.[25] Side effects have not been reported in dogs; in humans they are mild and include pain at the site of injection (which can be reduced if octreotide is warmed to room temperature before administration), nausea, vomiting, abdominal pain, constipation, and steatorrhea.

240.5 PROGNOSIS

The median survival time of 142 dogs that underwent partial pancreactomy, as reported in several studies, was 12 to 14 months, with a range of zero days to 5 years.[3–5,7,10] Several prognostic factors have been identified. Dogs with clinical stage I disease have a significantly longer disease-free interval, and about 50% are expected to be normoglycemic 14 months after surgery compared with only 20% of dogs with clinical stage II or stage III disease.[6] Young dogs have a worse prognosis.[6] Dogs with postoperative hyperglycemia or normoglycemia have a significantly better prognosis than those with hypoglycemia.[3]

A decreased mitotic rate is strongly associated with survival of human beings with insulinoma. Although a correlation between the number of mitotic figures per high-power field and local invasiveness of the tumor has been documented in dogs, a significantly worse prognosis in dogs with a high mitotic count has yet to be established.[10]

Age, sex, body weight, clinical signs and their duration, ultrasonographic detection of a pancreatic mass, tumor location, gross presence of metastatic disease, and the blood glucose or insulin concentration are not significantly associated with the prognosis.

240.6 INSULIN-SECRETING ISLET CELL NEOPLASIA IN THE CAT

Feline insulinoma is rare; it has been reported in five cats that were 12 to 17 years of age. Three of the cats were Siamese, and four were neutered males. The history and clinical signs are similar to those reported for dogs with insulinoma. The diagnosis is based on documentation of an increased serum insulin concentration at the time of hypoglycemia. Care must be taken to use an insulin radioimmunoassay validated for cats. Therapy consists of surgical resection of the pancreatic mass and metastases, followed by prednisone treatment and small frequent meals.[21,26]

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241 CHAPTER • 241 Diabetes Mellitus

Richard W. Nelson

The endocrine pancreas is composed of the islets of Langerhans, which are dispersed as “small islands” in a “sea” of exocrine-secreting acinar cells. Four distinct cell types have been identified in these islets on the basis of staining properties and morphology: *alpha cells,* which secrete glucagon; *beta cells,* which secrete insulin; *delta cells,* which secrete somatostatin; and *F cells,* which secrete pancreatic polypeptide. Dysfunction involving any of these cell lines ultimately results in either an excess or a deficiency of the respective hormone in the circulation. In the dog and cat, the most common disorder of the endocrine pancreas is diabetes mellitus, which results from an absolute or relative insulin deficiency due to deficient insulin secretion by the beta cells. The incidence of diabetes mellitus is similar for the dog and cat, with the reported frequency varying from 1 in 100 to 1 in 500.[1]

241.1 CLASSIFICATION AND ETIOLOGY

241.1.1 Overview of Classification

In humans, diabetes mellitus is classified as type 1 or type 2 based on the pathophysiologic mechanisms and the pathogenic alterations affecting the beta cells. Type 1 diabetes is characterized by a combination of genetic susceptibility and immunologic destruction of beta cells, with progressive and eventually complete insulin insufficiency. The presence of circulating autoantibodies against insulin, the beta cell, and/or glutamic acid decarboxylase (GAD) usually precedes the development of hyperglycemia or clinical signs. Type 2 diabetes mellitus is characterized by insulin resistance and “dysfunctional” beta cells; defects believed to be genetic in origin are evident for a decade or longer before hyperglycemia and clinical signs of diabetes develop, and the deleterious effects can be accentuated by environmental factors such as obesity.[2,3] Humans with type 1 diabetes are dependent on insulin for control of the disease (i.e., insulin-dependent diabetes mellitus [IDDM]), whereas control of the diabetic state in humans with type 2 diabetes is usually possible through diet, exercise, and oral hypoglycemic drugs. Insulin treatment may be necessary in some type 2 diabetics if insulin resistance and beta cell dysfunction are severe. As such, humans with type 2 diabetes can have IDDM or non-insulin-dependent diabetes mellitus (NIDDM).

It is more clinically relevant and perhaps more accurate to classify diabetes in dogs and cats as IDDM or NIDDM rather than as type 1 or type 2. The familial history is rarely available in diabetic dogs and cats, and the clinical presentation is usually not helpful in differentiating type 1 and type 2 diabetes, especially in cats. Insulin secretagogue tests are not routinely performed, and their results may be misleading. Autoantibody tests for type 1 diabetes are not readily available.[4,5] Therefore, as clinicians, veterinarians usually classify diabetic dogs and cats as either IDDM or NIDDM based on their need for insulin treatment. This can be confusing, because some diabetics, especially cats, initially can appear to have NIDDM progressing to IDDM, or they flip back and forth between IDDM and NIDDM as the severity of insulin resistance and the impairment of beta cell function waxes and wanes. Apparent changes in the diabetic state (i.e., IDDM and NIDDM) are understandable when one realizes that islet pathology may be mild to severe and progressive or static; that the ability of the pancreas to secrete insulin depends on the severity of islet pathology and can decrease with time; that the responsiveness of tissues to insulin varies, often in conjunction with the presence or absence of concurrent inflammatory, infectious, neoplastic, or hormonal disorders; and that all these variables affect the animal's need for insulin, the insulin dosage, and the ease of diabetic regulation.

241.1.2

Insulin-Dependent Diabetes Mellitus

The most common clinically recognized form of diabetes mellitus in the dog and cat is IDDM. In our hospital, virtually all dogs and 50% to 70% of cats have IDDM at the time diabetes mellitus is diagnosed. Insulin-dependent diabetes mellitus is characterized by permanent hypoinsulinemia and an absolute necessity for exogenous insulin to maintain glycemic control. The etiology of IDDM has been poorly characterized in dogs and cats but is undoubtedly multifactorial (Box 241-1).

In the dog, genetic predispositions have been suggested by familial associations (Table 241-1).[6,7] Common histologic abnormalities in dogs include a reduction in the number and size of pancreatic islets, a decrease in the number of beta cells within islets, and beta cell vacuolation and degeneration (Figure 241-1). In some dogs an extreme form of the disease may occur, represented by a congenital absolute deficiency of beta cells and pancreatic islet hypoplasia or aplasia. Less severe changes of pancreatic islets and beta cells may predispose the adult dog to diabetes mellitus after it has been exposed to environmental factors, such as insulin-antagonistic diseases and drugs, obesity, and pancreatitis. Environmental factors may induce beta cell degeneration secondary to chronic insulin resistance or may cause release of beta cell proteins that induce immune-mediated destruction of the islets.[8] The results of studies evaluating for anti–beta cell autoantibodies in diabetic dogs have been conflicting; the autoantibodies were identified in newly diagnosed diabetic dogs with IDDM in one study[9] but not in another.[10] Immune-mediated insulitis has also been described in diabetic dogs.[11] Seemingly, autoimmune mechanisms, in conjunction with genetic and environmental factors, may play a role in the initiation and progression of diabetes in dogs.

Common histologic abnormalities in cats with IDDM include islet-specific amyloidosis (see Noninsulin-Dependent Diabetes Mellitus), beta cell vacuolation and degeneration, and chronic pancreatitis (see Figure 241-1).[12] The cause of beta cell degeneration is not known. Still other diabetic cats have a reduction in the number of pancreatic islets and/or insulin-containing beta cells on immunohistochemical evaluation, a finding that suggests that additional mechanisms may be involved in the physiopathology of diabetes mellitus in cats. Although lymphocytic infiltration of islets, in conjunction with islet amyloidosis and vacuolation, has been described in two diabetic cats,[13] this histologic finding is uncommon, and beta cell and insulin autoantibodies have not been identified in newly diagnosed diabetic cats.[14] The role of genetics remains to be determined.

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241.1.2.1

Box • 241-1 Potential Factors in the Etiopathogenesis of Diabetes Mellitus in Dogs and Cats

241.1.2.1.1

Dog

Genetics

Immune-mediated insulitis

Pancreatitis

Obesity

Concurrent hormonal disease

Hyperadrenocorticism

Diestrus-induced excess of growth hormone

Hypothyroidism

Drugs

Glucocorticoids

Infection

Concurrent illness

Renal insufficiency

Cardiac disease

Hyperlipidemia

Islet amyloidosis (?)

241.1.2.1.2 Cat

Islet amyloidosis

Obesity

Pancreatitis

Concurrent hormonal disease

Hyperadrenocorticism

Acromegaly

Hyperthyroidism

Drugs

Megestrol acetate

Glucocorticoids

Infection

Concurrent illness

Renal insufficiency

Cardiac disease

Hyperlipidemia (?)

Genetics (?)

Immune-mediated insulitis (?)

Table • 241-1 Breed Risk for the Development of Diabetes Mellitus*

BREED	CASES	CONTROL	ODDS RATIO
Australian terrier	33	3	9.39
Standard schnauzer	96	14	5.85
Miniature schnauzer	526	88	5.10
Bichon frise	39	11	3.03
Spitz	34	10	2.90
Fox terrier	88	28	2.68
Miniature poodle	712	224	2.49
Samoyed	159	56	2.42
Cairn terrier	61	23	2.26
Keeshond	47	18	2.23
Maltese	42	20	1.79
Toy poodle	186	90	1.76
Lhasa apso	85	47	1.54
Yorkshire terrier	96	57	1.44
Mixed breed	1755	1498	1.00 (reference group)
English springer spaniel	62	77	0.69
Irish setter	66	84	0.67
Beagle	70	94	0.64
English setter	29	41	0.60
Basset hound	28	43	0.56
Rottweiler	37	62	0.51
Boston terrier	27	45	0.56
Doberman pinscher	103	180	0.49
Labrador retriever	199	375	0.45
Australian shepherd	32	62	0.44
Cocker spaniel	77	186	0.35
Golden retriever	91	274	0.28
Shetland sheepdog	27	109	0.21
Collie	25	104	0.21
German shepherd	68	317	0.18

From Guptill L et al: Is canine diabetes on the increase? *In* Recent Advances in Clinical Management of Diabetes Mellitus, Iams, Dayton, Ohio, 1999, p 24.

* Derived from analysis of the Veterinary Medical Database (VMDB) from 1970 to 1993. The VMDB comprises medical records of 24 veterinary schools in the United States and Canada. VMDB case records analyzed included those from first hospital visits of 6078 dogs with a diagnosis of diabetes mellitus and 5922 randomly selected dogs with first hospital visits for any diagnosis other than diabetes mellitus seen at the same veterinary schools in the same year. Only breeds with more than 25 cases of diabetes mellitus are included.

241.1.3 Noninsulin-Dependent Diabetes Mellitus

Clinical recognition of NIDDM occurs more often in the cat than in the dog, accounting for approximately 30% of diabetic cats seen at our hospital. Clinical recognition of NIDDM is uncommon in the dog and is usually associated with a concurrent insulin-antagonistic disease or drug. In humans, obesity, genetics, and islet amyloidosis are important factors in the development of NIDDM. Amyloid is a common pathologic finding in the pancreatic islets of diabetic cats. Islet amyloid polypeptide (IAPP), or amylin, is the principal constituent of amyloid isolated from the pancreatic tissue of humans with NIDDM and of adult cats with diabetes.[15] The amino acid sequence of human and feline IAPP is similar[16]; immunoelectron microscope

studies have identified IAPP in beta cell secretory granules in both cats and humans,[17,18] and amylin is cosecreted with insulin by the beta cell.[19] Stimulants of insulin secretion also stimulate the secretion of amylin. Amylin acts as a neuroendocrine hormone, having several glucoregulatory effects that collectively complement the actions of insulin in postprandial glucose control. These effects include a slowing of the rate at which nutrients are delivered from the stomach to the small intestine for absorption, suppression of nutrient-stimulated secretion of glucagon, and stimulation of satiety.[20,21] Chronic increased secretion of insulin and amylin, as occurs with obesity and other insulin-resistant states, results in aggregation and deposition of amylin in the islets as amyloid (see Figure 241-1). IAPP-derived amyloid fibrils are cytotoxic and are associated with apoptotic cell death of islet cells and a resultant defect in insulin secretion.[22–24] If deposition of amyloid is progressive, islet cell destruction progresses and eventually leads to diabetes mellitus (Figure 241-2). The severity of islet amyloidosis would determine in part whether the diabetic cat has IDDM or NIDDM (Figure 241-3). Total destruction of the islets results in IDDM and the need for insulin treatment for the rest of the cat's life. Partial destruction of the islets may or may not result in clinically evident diabetes, insulin treatment may or may not be required to control glycemia, and transient diabetes may or may not develop once treatment is initiated. If amyloid deposition is progressive, the cat progresses from a subclinical diabetic state to NIDDM and ultimately to IDDM.

The presence and severity of insulin resistance is an important variable that influences the clinical picture in cats with partial destruction of pancreatic islets. Insulin resistance increases the demand for insulin secretion, a demand that may not be met in some cats with partial destruction of islets. The more severe the insulin resistance and the loss of islets, the greater the likelihood that hyperglycemia will develop. Persistent hyperglycemia can in turn suppress function of remaining beta cells, causing hypoinsulinemia and worsening hyperglycemia (see Transient Diabetes Mellitus). A sustained demand for insulin secretion in response to insulin resistance can also lead to worsening islet pathology and a further reduction in the population of beta cells. Any chronic insulin-resistant disorder can have a deleterious impact on the population and function of beta cells and can play a role in the development of NIDDM or IDDM. Examples in the cat include obesity, chronic pancreatitis, acromegaly, hyperadrenocorticism, and chronic administration of glucocorticoids or megestrol acetate. Obesity-induced carbohydrate intolerance is the classic insulin-resistant disorder affiliated with the development of NIDDM in humans and has been identified as a potential causative factor in the development of diabetes in cats as well.[1,25] Obesity causes a reversible insulin resistance that is a result of downregulation of insulin receptors, impaired receptor binding affinity for insulin, and postreceptor defects in insulin action. Impaired glucose tolerance and an abnormal insulin secretory response have been documented in obese cats,[26,27] abnormalities that are reversible with correction of obesity.[28,29]

Our current understanding of the etiopathogenesis of diabetes in the cat suggests that the difference between IDDM and NIDDM is primarily a difference in the severity of loss of beta cells and the severity and reversibility of concurrent insulin resistance. Most cats with IDDM or NIDDM have islet amyloidosis, vacuolar degeneration of beta cells, or islet hypoplasia.[12,30] The more severe the islet pathology, the more likely the cat is to have IDDM, regardless of concurrent insulin resistance (see Figure 241-3). The less severe the islet pathology, the greater the role of concurrent insulin resistance in determining whether the cat has IDDM or NIDDM. The more severe and the less reversible the cause of the insulin resistance, the more likely the cat with mild islet pathology is to be insulin dependent, and vice versa. Fluctuations in the severity of insulin resistance, as occur with chronic pancreatitis, can cause a cat with mild islet pathology to oscillate between IDDM and NIDDM as the severity of pancreatic inflammation waxes and wanes. Persistent insulin resistance can also worsen islet pathology and cause the diabetic cat to progress from NIDDM to IDDM as the progressive loss of beta cells leads to worsening insulin deficiency.[30,31]

Figure 241-1 Pancreatic islet cell histology. **A,** Severe islet amyloidosis from a cat with insulin-dependent diabetes mellitus (IDDM) (hematoxylin and eosin stain [H&E], ×100). **B,** Severe islet cell degeneration and vacuolation from a cat with IDDM (H&E, ×200). (From Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, 2nd ed. Philadelphia, WB Saunders, 1996, p 341.)

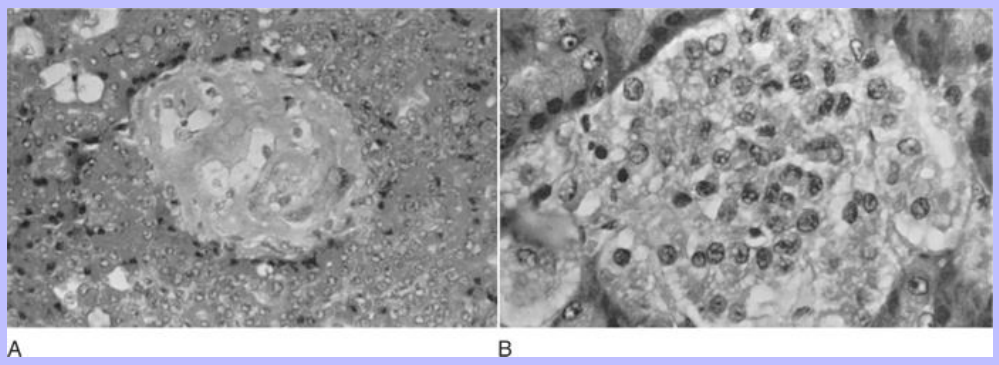
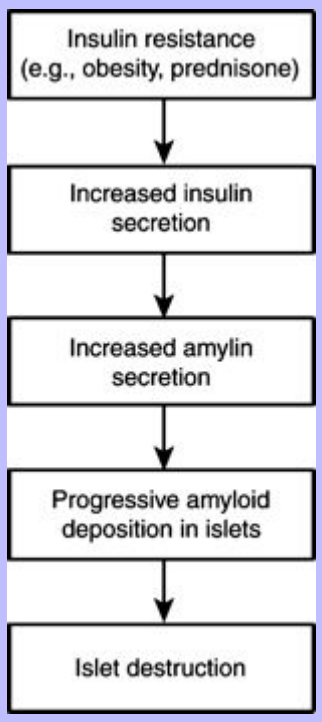


Figure 241-2 Schematic of the interplay between insulin resistance, amylin secretion, and amyloid deposition in the pancreatic islets. Insulin secretion increases to compensate for insulin resistance induced by environmental factors, insulin-antagonistic drugs, and concurrent illness. Because amylin and insulin are cosecreted, amylin secretion also increases in insulin-resistant states. If sustained, increased amylin secretion can lead to amylin aggregation and the formation of amyloid in the islets. (From Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, 3rd ed. Philadelphia, WB Saunders, 2004.)



241.1.4 Transient Diabetes Mellitus

Approximately 20% of diabetic cats become “transiently diabetic,” usually within 4 to 6 weeks of establishment of the diagnosis of diabetes and initiation of treatment. In these cats, hyperglycemia, glycosuria, and clinical signs of diabetes resolve, and insulin treatment can be discontinued. Some diabetic cats may never require insulin treatment once the initial bout of clinical diabetes mellitus has dissipated, whereas others become permanently insulin dependent weeks to months after resolution of a prior diabetic state. Based on findings from a recent evaluation of a group of cats with transient diabetes mellitus, the author theorizes that cats with transient diabetes are in a subclinical diabetic state that becomes clinical when the pancreas is stressed by exposure to a concurrent insulin-antagonistic drug or disease, most notably glucocorticoids,

megestrol acetate, or chronic pancreatitis (Figure 241-4).[30] Unlike healthy cats, those with transient diabetes mellitus have some abnormality of the islets (e.g., amyloidosis, vacuolar degeneration) and a significant reduction in the population of beta cells. Islet abnormalities impair the ability to compensate for concurrent insulin resistance, resulting in carbohydrate intolerance. Insulin secretion by beta cells becomes reversibly suppressed, most likely as a result of worsening carbohydrate intolerance. Chronic hyperglycemia impairs insulin secretion by beta cells and induces peripheral insulin resistance by promoting the downregulation of glucose transport systems and causing a defect in post-transport insulin action; this phenomenon is referred to as *glucose toxicity*.[32] Beta cells have an impaired response to stimulation by insulin secretagogues, thereby mimicking IDDM. The effects of glucose toxicity are potentially reversible upon correction of the hyperglycemic state. The clinician makes a correct diagnosis of diabetes and initiates appropriate treatment for diabetes and identifiable insulin-antagonistic disorders. Treatment improves hyperglycemia and insulin resistance, the suppressive effects of hyperglycemia decrease, beta cell function improves, insulin secretion returns, and an apparent IDDM state resolves. The future requirement for insulin treatment depends on the underlying abnormality in the islets. If the islet pathology is progressive (e.g., amyloidosis), eventually enough beta cells are destroyed to cause permanent IDDM.

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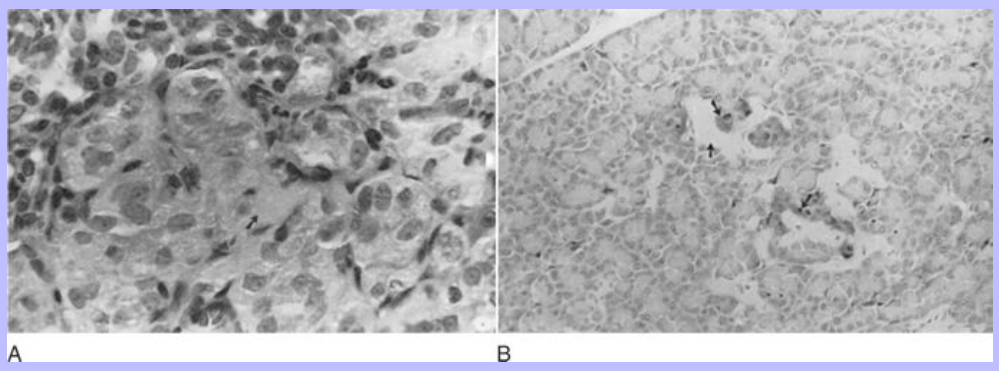
Figure 241-3 Pancreatic amyloidosis. **A,** Mild islet amyloidosis *(arrow)* and vacuolar degeneration in a cat with non-insulin-dependent diabetes mellitus (NIDDM) treated with diet and glipizide (H&E, ×200). **B,** Severe islet amyloidosis *(straight arrow)* in a cat with initial NIDDM that progressed to IDDM. Pancreatic biopsy was obtained during IDDM state. Residual beta cells containing insulin *(curved arrows)* are also present. (Immunoperoxidase stain, ×100). (From Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, 3rd ed. Philadelphia, WB Saunders, 2004, p 542.)



Transient or reversible diabetes is extremely uncommon in dogs and usually occurs in dogs with subclinical diabetes treated with insulin-antagonistic drugs (e.g., glucocorticoids) or in the early stages of an insulin-antagonistic disorder (e.g., diestrus in the bitch, hyperadrenocorticism). Such dogs have a reduced but adequate mass of functional beta cells to maintain carbohydrate tolerance when insulin resistance is not present but are unable to secrete an adequate amount of insulin to maintain euglycemia in the presence of insulin antagonism. Early recognition and correction of the insulin antagonism may re-establish euglycemia

without the long-term need for insulin therapy. Failure to correct the insulin antagonism quickly results in progressive loss of beta cells and the eventual development of IDDM.

241.1.5 Diagnosis of Insulin-Dependent versus Noninsulin-Dependent Diabetes Mellitus

Dogs and cats are not usually brought to a veterinarian until clinical signs of diabetes become obvious and worrisome to an owner. As such, at the time of diagnosis, all diabetic dogs and cats have fasting hyperglycemia and glycosuria, regardless of the type of diabetes mellitus that may be present. Once the diagnosis of diabetes has been established, the clinician must consider the possibility of NIDDM and the need for insulin treatment. Dogs should uniformly be considered to have IDDM and treatment with insulin should be initiated unless there is a strong suspicion of diabetes mellitus secondary to a concurrent insulin-antagonistic disorder (e.g., intact bitch in diestrus).

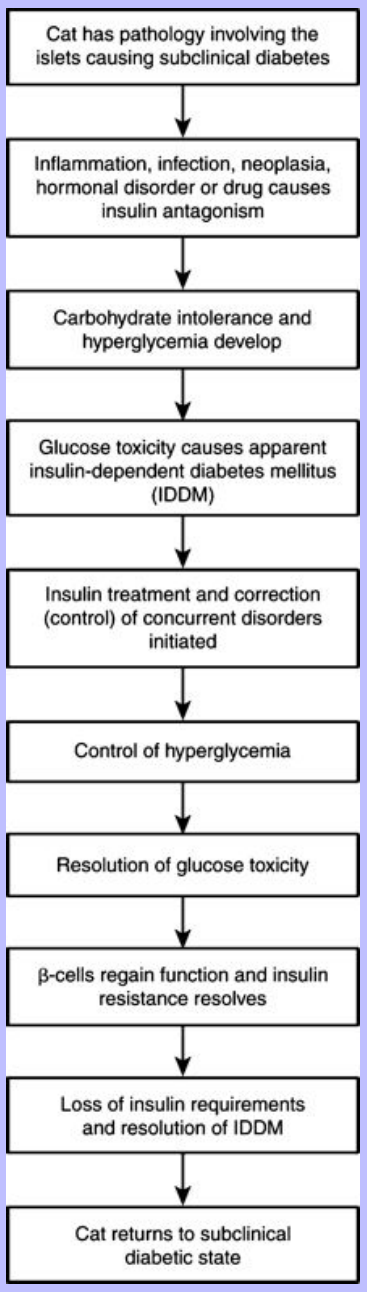
Because of the significant incidence of NIDDM and transient diabetes in cats and the successful treatment of some diabetic cats with diet and oral hypoglycemic drugs, it would be advantageous to be able to prospectively differentiate IDDM from NIDDM in cats. Unfortunately, measurements of the serum insulin concentration at baseline and after administration of an insulin secretagogue have not been consistent aids in the differentiation of IDDM from NIDDM in the cat.[4,5] A fasting serum insulin concentration greater than the normal mean concentration (greater than 12 μU/mL in our laboratory) or any postsecretagogue insulin concentration greater than one standard deviation (SD) above the reference mean (greater than 18 μU/mL in our laboratory) suggests the existence of functional beta cells and the possibility for NIDDM. Unfortunately, cats subsequently identified has having IDDM and many of those with NIDDM have a low baseline serum insulin concentration and do not respond to a glucose or glucagon challenge.[4,5,30] This apparent insulin deficiency in cats subsequently identified with NIDDM is presumably the result of concurrent glucose toxicity (see Transient Diabetes Mellitus). The ultimate differentiation of IDDM from NIDDM is often made retrospectively, after the clinician has had several weeks to assess the cat's response to therapy and to determine the animal's need for insulin. The initial decision between insulin treatment and oral hypoglycemic drugs is based on the severity of the clinical signs, the presence or absence of ketoacidosis, the cat's general health, and the owner's wishes.

241.2 PATHOPHYSIOLOGY

241.2.1 Nonketotic Diabetes Mellitus

Diabetes mellitus results from a relative or absolute deficiency of insulin secretion by the beta cells. Insulin deficiency in turn causes decreased tissue utilization of glucose, amino acids, and fatty acids; accelerated hepatic glycogenolysis and gluconeogenesis; and accumulation of glucose in the circulation, resulting in hyperglycemia. Glucose obtained from the diet also accumulates in the circulation. As the blood glucose concentration increases, the ability of the renal tubular cells to resorb glucose from the glomerular ultrafiltrate is exceeded, resulting in glycosuria. In dogs this typically occurs whenever the blood glucose concentration exceeds 180 to 220 mg/dL. The threshold for glucose resorption appears more variable in cats, ranging from 200 to 280 mg/dL. Glycosuria creates an osmotic diuresis, causing polyuria. Compensatory polydipsia prevents dehydration. The diminished peripheral tissue utilization of ingested glucose results in weight loss as the body attempts to compensate for perceived “starvation.”

Figure 241-4 Sequence of events in the development and resolution of an insulin-requiring diabetic episode in cats with transient diabetes. (From Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, 3rd ed. Philadelphia, WB Saunders, 2004, p 546.)



The interaction of the "satiety center" in the ventromedial region of the hypothalamus with the "feeding center" in the lateral region of the hypothalamus is responsible for controlling the amount of food ingested.[33] The feeding center, responsible for evoking eating behavior, is chronically functioning but can be transiently inhibited by the satiety center after food ingestion. The amount of glucose entering the cells in the satiety center directly affects the feeling of hunger; the more glucose that enters these cells, the less the feeling of hunger and vice versa. The ability of glucose to enter the cells in the satiety center is mediated by insulin. In diabetics with a relative or absolute lack of insulin, glucose does not enter satiety center cells, resulting in failure to inhibit the feeding center. Thus these individuals become polyphagic despite hyperglycemia.

The four classic signs of diabetes mellitus are polyuria, polydipsia, polyphagia, and weight loss. The severity of these signs is directly related to the severity of hyperglycemia. As these signs become obvious to the owner, the pet is brought to the veterinarian for care.

241.2.2 Ketoacidosis

Unfortunately, some cats and dogs are not identified by their owners as having signs of disease, and these untreated diabetics may ultimately develop diabetic ketoacidosis (DKA). Ketone bodies (i.e., acetoacetate, beta hydroxybutyrate, and acetone) are derived from oxidation of nonesterified or free fatty acids (FFAs) by the liver and are used as an energy source by many tissues during periods of glucose deficiency. The most important regulators of ketone body production are FFA availability and the ketogenic capacity of the liver.[34] For synthesis of ketone bodies to be enhanced, two major alterations in intermediary metabolism must occur: (1) mobilization of FFAs from triglycerides stored in adipose tissue must be enhanced, and (2) a shift in hepatic metabolism must occur from fat synthesis to fat oxidation and ketogenesis.[35,36] Insulin is a powerful inhibitor of lipolysis and FFA oxidation. A relative or absolute deficiency of insulin "allows" lipolysis to increase, thus increasing the availability of FFAs to the liver and in turn promoting ketogenesis.

Virtually all dogs and cats with DKA have a relative or absolute deficiency of insulin. In most dogs and cats with newly diagnosed DKA, circulating insulin concentrations are low or undetectable. Some dogs and cats have serum insulin concentrations similar to those observed in normal, fasted nondiabetics (i.e., 5 to 20 μU/mL). However, such insulin concentrations are inappropriately low ("relative" insulin deficiency) for the severity of hyperglycemia encountered. Some diabetic dogs and cats develop ketoacidosis despite receiving daily injections of insulin, and circulating insulin concentrations may even be increased. In this group, a "relative" insulin deficiency is also present, presumably because of concurrent insulin resistance caused by an increase in circulating glucose counter-regulatory hormones (i.e., epinephrine, glucagon, cortisol, growth hormone), increased plasma FFA and amino acid concentrations, and metabolic acidosis. With the development of insulin resistance, the need for insulin may exceed the daily injected insulin dose, leading to a predisposition to the development of DKA.

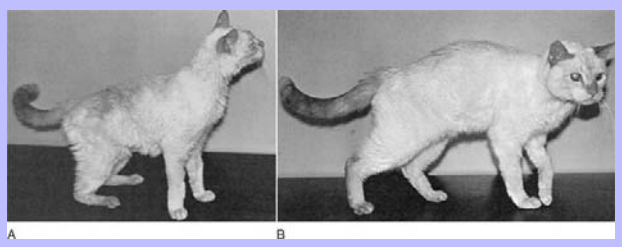
Circulating levels of the glucose counter-regulatory hormones typically are markedly increased in humans with DKA and presumably are in dogs and cats as well.[37] The body increases its production of the glucose counter-regulatory hormones in response to a wide variety of diseases and stress situations, such as pancreatitis, infection, renal insufficiency, and concurrent hormonal disorder. The net effects of these hormonal disturbances are accentuation of insulin deficiency through the development of insulin resistance; stimulation of lipolysis, leading to ketogenesis; and stimulation of gluconeogenesis, which worsens hyperglycemia. Recognition and treatment of disorders that coexist with diabetic ketoacidosis are critically important to the successful management of DKA.

The physiologic derangements that accompany DKA are a direct result of relative or absolute insulin deficiency, hyperketonemia, and hyperglycemia. Increasing plasma ketone concentrations eventually surpass the renal tubular threshold for complete resorption and spill into the urine, contributing to the osmotic diuresis caused by glycosuria and enhancing the excretion of solutes (e.g., sodium, potassium, and magnesium). 1568 1569 Insulin deficiency per se also contributes to the excessive renal losses of water and electrolytes. The result is an excessive loss of electrolytes and water, leading to volume contraction, underperfusion of tissues, and prerenal azotemia. As ketones continue to accumulate in the blood, the body's buffering system becomes overwhelmed, and progressively worsening metabolic acidosis results. Further loss of water and electrolytes occurs as a result of repeated bouts of vomiting or diarrhea combined with a lack of fluid intake, problems that often develop as the metabolic acidosis worsens. Excessive loss of electrolytes and water leads to further volume contraction, underperfusion of tissues, and worsening prerenal azotemia and dehydration. Renal excretion of glucose and to a lesser degree hydrogen ions becomes impaired, allowing glucose and ketones to accumulate in the vascular space more quickly. The result is increasing hyperglycemia and ketonemia and worsening metabolic acidosis. The rise in the blood glucose concentration raises the plasma osmolality, and the resulting osmotic diuresis further aggravates the rise in plasma osmolality by causing water losses in excess of the salt loss. The increase in plasma osmolality causes water to be shifted out of cells, leading to cellular dehydration and the eventual development of obtundation and coma. The severe metabolic consequences of DKA, which include severe acidosis, hyperosmolality, obligatory osmotic diuresis, dehydration, and electrolyte derangements, ultimately become life-threatening.

241.3 SIGNALMENT

Diabetes mellitus typically occurs in older dogs and cats, with a peak prevalence at 7 to 9 years of age in dogs and 9 to 11 years in cats.[1,12] Juvenile-onset diabetes occurs in dogs and cats less than 1 year of age and is uncommon. In dogs, females are affected about twice as often as males, whereas in cats, diabetes occurs predominately in neutered males.[1,12] Genetic predispositions for or against the development of diabetes have been suggested by familial associations in dogs and by pedigree analysis of keeshonden (see Table 241-1).[6,7] No apparent breed predisposition is seen in cats, although Burmese cats may be over-represented in Australia.[38]

Figure 241-5 **A,** Plantigrade posture in a cat with diabetes mellitus and exocrine pancreatic insufficiency. **B,** Resolution of hindlimb weakness and plantigrade posture after glycemic control was improved by adjustment of insulin therapy and initiation of pancreatic enzyme replacement therapy. (From Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, 3rd ed. Philadelphia, WB Saunders, 2004, p 548.)



241.4 ANAMNESIS

The history in virtually all diabetic animals includes the classic polydipsia, polyuria, polyphagia, and weight loss. Owners often bring a dog to the veterinarian because the pet can no longer make it through the night without having to be let outside to urinate or because it begins urinating in the home. A common complaint of cat owners is the constant need to change the litter and an increase in the size of the kitty litter clumps; problems that reflect the polyuria associated with diabetes mellitus. Additional clinical signs in cats include lethargy; decreased interaction with family members; lack of grooming behavior and the development of a dry, lusterless, unkempt, or matted haircoat; and decreased jumping ability, rear limb weakness, or the development of a plantigrade posture (Figure 241-5). Occasionally a dog owner may be concerned about sudden blindness caused by cataract formation. The classic signs of diabetes mellitus may have gone unnoticed or may have been considered irrelevant by the owner. If the clinical signs associated with uncomplicated diabetes are not observed by the owner, a diabetic dog or cat is at risk for developing systemic signs of illness (i.e., lethargy, anorexia, vomiting, weakness) as progressive ketonemia and metabolic acidosis develop. The time sequence from onset of initial clinical signs to development of DKA is unpredictable, ranging from a few days to several months.

241.5 PHYSICAL EXAMINATION

A thorough physical examination is imperative in any dog or cat suspected of having diabetes mellitus, in part because of the high prevalence of concurrent disorders that can affect the response to treatment. Physical examination findings in a dog or cat with newly diagnosed diabetes depend on whether DKA is present and if so, its severity; on the duration of diabetes prior to diagnosis; and on the nature of any other concurrent disorders. The nonketotic diabetic dog or cat has no classic physical examination findings. Many diabetic dogs and cats are obese but are otherwise in good physical condition. Dogs and cats with prolonged untreated diabetes may have lost weight but are rarely emaciated unless concurrent disease (e.g., pancreatic exocrine insufficiency, hyperthyroidism) is present. Lethargy may be evident. The haircoat of newly diagnosed or poorly controlled diabetic dogs may be sparse, with dry, brittle, lusterless hairs, as well as scales from hyperkeratosis; diabetic cats often stop grooming and develop a dry, lusterless haircoat. Diabetes-induced hepatic lipidosis may cause hepatomegaly. Lenticular changes consistent with cataract formation are another common clinical finding in diabetic dogs. Impaired ability to jump, weakness in the rear limbs, ataxia, or a plantigrade posture (i.e., the hocks touch the ground when the cat walks) may be evident in cats that develop diabetic neuropathy (see Figure 241-5). The distal muscles of the rear limbs may feel hard on digital palpation, and cats may object to palpation or manipulation of the rear limbs, presumably because of pain associated with the neuropathy.

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In the ketoacidotic diabetic dog or cat, physical examination findings include dehydration, depression, weakness, tachypnea, and sometimes a strong odor of acetone on the breath. With severe metabolic acidosis, slow, deep breathing (i.e., Kussmaul respiration) may be observed. Gastrointestinal signs of vomiting, abdominal pain, and distention may be present, and dogs and cats that develop severe hyperosmolarity are often extremely lethargic and may be comatose.

241.6 ESTABLISHING THE DIAGNOSIS OF DIABETES MELLITUS

A diagnosis of diabetes mellitus requires the presence of appropriate clinical signs (i.e., polyuria, polydipsia, polyphagia, weight loss) and documentation of persistent fasting hyperglycemia and glycosuria. Measurement of the blood glucose concentration using a portable blood glucose monitoring device and testing for the presence of glycosuria using urine reagent test strips (e.g., KetoDiastix; Ames Division, Miles Laboratories, Elkhart, Indiana)

allow rapid confirmation of a diagnosis of diabetes mellitus. Concurrent documentation of ketonuria establishes a diagnosis of diabetic ketosis or ketoacidosis.

It is important to document both persistent hyperglycemia and glycosuria to establish a diagnosis of diabetes mellitus, because hyperglycemia differentiates diabetes mellitus from primary renal glycosuria, whereas glycosuria differentiates diabetes mellitus from other causes of hyperglycemia (Box 241-2). Transient, stress-induced hyperglycemia is a common problem in cats and can cause the blood glucose concentration to increase above 300 mg/dL. Unfortunately, stress is a subjective state that cannot be accurately measured, it is not always easily recognized, and it may evoke inconsistent responses among individual cats. Glycosuria usually does not develop in cats with stress hyperglycemia because the transient increase in the blood glucose concentration prevents glucose from accumulating in urine to a detectable concentration. However, hyperglycemia and glycosuria can occur secondary to stress in cats. For this reason, the clinician should always document persistent hyperglycemia and glycosuria when establishing a diagnosis of diabetes mellitus in cats. If doubt exists, the "stressed" cat can be sent home with instructions for the owner to monitor the urine glucose concentration with the cat in the nonstressed home environment. Alternatively, a serum fructosamine concentration can be measured. Documentation of an increase in the serum fructosamine concentration supports the presence of sustained hyperglycemia; however, a serum fructosamine concentration in the upper range of normal can occur in symptomatic diabetic cats if the diabetes developed shortly before the cat was brought to the veterinarian.[39]

Mild hyperglycemia (i.e., 130 to 180 mg/dL) is clinically silent and is usually an unexpected and unsuspected finding. If the dog or cat with mild hyperglycemia is examined for polyuria and polydipsia, a disorder other than clinical diabetes mellitus should be sought. Mild hyperglycemia can occur up to 2 hours postprandial in some dogs and cats, in "stressed" dogs and cats, in early diabetes mellitus, and with disorders causing insulin resistance. A diagnostic evaluation for disorders causing insulin resistance is indicated if mild hyperglycemia persists in the fasted, unstressed dog or cat. Insulin therapy is not indicated in these animals because clinical diabetes mellitus is not present.

241.6.1 Box • 241-2 Causes of Hyperglycemia in Dogs and Cats

Diabetes mellitus*

"Stress" (cat)*

Postprandial effect (diets containing monosaccharides, disaccharides, and propylene glycol)

Hyperadrenocorticism*

Acromegaly (cat)

Diestrus (bitch)

Pheochromocytoma (dog)

- Pancreatitis
- Exocrine pancreatic neoplasia
- Renal insufficiency
- Drug therapy*
  - Glucocorticoids
  - Progestagens
  - Megestrol acetate
  - Thiazide diuretics
- Dextrose-containing fluids*
- Parenteral nutrition*
- Head trauma

* Common cause.

241.7 PATIENT EVALUATION

241.7.1 Nonketotic Diabetic Animal

A thorough clinicopathologic evaluation is recommended once the diagnosis of diabetes mellitus has been established. The clinician must be aware of any disease that might be causing or contributing to carbohydrate intolerance (e.g., hyperadrenocorticism), that may result from carbohydrate intolerance (e.g., bacterial cystitis), or that may force modification of therapy (e.g., pancreatitis). The minimum laboratory evaluation in any "healthy" nonketotic diabetic dog or cat should include a complete blood count (CBC), serum biochemical panel, serum thyroxine concentration (cat), and urinalysis with bacterial culture. The serum progesterone concentration should be determined if diabetes mellitus is diagnosed in an intact bitch, regardless of her cycling history. If available, abdominal ultrasonography is indicated to assess for pancreatitis, adrenomegaly, pyometritis in an intact bitch or queen, and abnormalities affecting the liver and urinary tract. Because of the relatively high prevalence of pancreatitis in diabetic dogs and cats, measurement of serum lipase or serum trypsin-like immunoreactivity (TLI) or serum pancreatic lipase immunoreactivity (PLI) should be considered

if abdominal ultrasonography is not available. Measurement of the baseline serum insulin concentration or an insulin response test is not routinely done, although it may be considered in cats prior to treatment with oral hypoglycemic drugs (see Diagnosis of Insulin-Dependent versus Noninsulin-Dependent Diabetes Mellitus). 1570
Additional tests may be warranted after the history has been obtained, the physical examination has been performed, or ketonuria has been identified. Potential clinicopathologic abnormalities are listed in Box 241-3. 1571

241.7.2 Ketoacidotic Diabetic Animal

The laboratory evaluation of apparently healthy dogs and cats with both glucose and ketones present in the urinalysis is similar to that for the nonketotic diabetic patient. The healthy ketotic diabetic can usually be managed conservatively, without fluid therapy or intensive care. In contrast, sick ketoacidotic diabetic dogs and cats are critical metabolic emergencies that require a much more aggressive therapeutic plan. To aid in the formulation of an appropriate treatment protocol, a group of critically important studies must be performed, including urinalysis, hematocrit, total plasma protein concentration, blood glucose, venous total carbon dioxide (CO_2) or arterial acid-base evaluation, blood urea nitrogen or serum creatinine, and serum electrolytes (sodium [Na], potassium [K], calcium [Ca], and phosphate [PO_4]). The results of these tests guide the proper choice of fluid therapy, as well as corrections that must be made with respect to electrolyte alterations, acidosis, and renal function. Additional data, such as radiographs, abdominal ultrasound scans, or further clinical pathologic studies, may be needed, depending on the results of the history and physical examination and the nature of concurrent disorders.

241.7.2.1 Box • 241-3 Clinicopathologic Abnormalities Commonly Found in Dogs and Cats with Uncomplicated Diabetes Mellitus

241.7.2.1.1 Complete Blood Count

Typically normal

Neutrophilic leukocytosis, toxic neutrophils (with pancreatitis or infection)

241.7.2.1.2 Biochemistry Panel

Hyperglycemia

Hypercholesterolemia

Hypertriglyceridemia (lipemia)

Increased alanine aminotransferase activity (typically <500 IU/L)

Increased alkaline phosphatase activity (typically <500 IU/L)

241.7.2.1.3 Urinalysis

Urine specific gravity typically >1.025

Glycosuria

Variable ketonuria

Proteinuria

Bacteriuria

241.7.2.1.4 Ancillary Tests

Hyperlipasemia (with pancreatitis)

Hyperamylasemia (with pancreatitis)

Serum trypsin-like immunoreactivity

- Usually normal
- Low with pancreatic exocrine insufficiency
- High with acute pancreatitis
- Normal to high with chronic pancreatitis

Serum pancreatic lipase immunoreactivity

- Usually normal
- Low with pancreatic exocrine insufficiency
- High with pancreatitis

Variable serum baseline insulin concentration

- Insulin-dependent diabetes mellitus: Low, normal
- Non-insulin-dependent diabetes mellitus: Low, normal, increased
- Insulin resistance induced: Low, normal, increased

241.8 THERAPY FOR THE ILL DIABETIC KETOACIDOTIC PATIENT

An aggressive therapeutic plan (Box 241-4) is indicated if the dog or cat has systemic signs of illness (i.e., lethargy, anorexia, vomiting); if the physical examination reveals dehydration, depression, weakness, and/or Kussmaul respiration; if the blood glucose concentration is greater than 500 mg/dL; or if severe metabolic

acidosis is present, as diagnosed by a total venous CO_2 or arterial bicarbonate concentration less than 12 mEq/L.

The goals of treatment for a severely ill, ketoacidotic, diabetic pet are (1) to provide adequate amounts of insulin to normalize intermediary metabolism, (2) to restore water and electrolyte losses, (3) to correct the acidosis, (4) to identify precipitating factors for the current illness, and (5) to provide a carbohydrate substrate when required by the insulin treatment. Proper therapy does not imply forcing as rapid a return to normal as possible. Because osmotic and biochemical problems can be created by overly aggressive therapy, as well as by the disease process itself, rapid changes in various vital parameters can be as harmful as or more harmful than no change. If all abnormal parameters can be slowly moved toward normal (i.e., over 36 to 48 hours), the likelihood of successful therapy is greater.

241.8.1 ## Fluid Therapy

Initiation of appropriate fluid therapy should be the first step in the treatment of DKA. Replacement of fluid deficiencies and maintenance of normal fluid balance are important for ensuring adequate cardiac output, blood pressure, and blood flow to all tissues. Improvement of renal blood flow is especially critical. In addition to the general beneficial aspects of fluid therapy in any dehydrated animal, fluid therapy can correct the deficiencies in total body sodium and potassium, dampening the potassium-lowering effect of insulin treatment. Fluid therapy can reduce blood glucose concentrations in diabetics even without insulin administration. Unfortunately, fluid therapy alone does not decrease the concentrations of acetoacetate and beta hydroxybutyrate or improve the severity of metabolic acidosis. For these reasons, insulin is always required.

The type of parenteral fluid initially used depends on the electrolyte status, blood glucose concentration, and osmolality. Most dogs and cats with DKA have severe deficits in total body sodium, regardless of the measured serum concentration. Unless serum electrolyte concentrations dictate otherwise, the initial intravenous fluid of choice is 0.9% sodium chloride with appropriate potassium supplementation. Most dogs and cats with severe DKA usually are sodium depleted and therefore are not suffering from dramatic hyperosmolality despite potentially remarkable increases in the blood glucose concentration. Other replacement crystalloid solutions that can be used if physiologic (0.9%) saline is not available are Ringer's solution, Ringer's lactated solution, Plasma-Lyte 148 (Baxter Healthcare, Deerfield, Illinois), and Normosol-R (Abbott Laboratories, Chicago, Illinois). Hypotonic fluids (e.g., 0.45% saline) are rarely indicated in dogs and cats with DKA even with severe hyperosmolality. Hypotonic fluids do not provide adequate amounts of sodium to correct the sodium deficiency. Rapid administration of hypotonic fluids can also cause a rapid decrease in plasma osmolality, which may result in cerebral edema, deterioration in mentation, and eventually coma. Hyperosmolality is best treated with isotonic fluids and judicious administration of insulin.

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241.8.1.1 ### Box • 241-4 Initial Management of the Dog or Cat with Severe Diabetic Ketoacidosis

241.8.1.1.1 #### Fluid Therapy

Type: 0.9% saline solution initially.

Rate: 60 to 100 mL/kg/24 hr initially; adjust based on hydration status, urine output, and persistence of fluid losses.

Potassium supplementation: Based on serum potassium (K^+) concentration; if concentration is unknown, initially add 40 mEq KCl to each liter of fluids.

Phosphate supplementation: Administer if serum phosphorus concentration is less than 1.5 mg/dL or if hemolytic anemia develops; initial IV infusion rate is 0.01 to 0.03 mmol/kg/hr in calcium-free fluids (e.g., 0.9% saline).

Dextrose supplementation: Not indicated until blood glucose concentration approaches 250 mg/dL; then begin 5% dextrose infusion.

241.8.1.1.2 Bicarbonate Therapy

Indication: Administer if plasma bicarbonate concentration is less than 12 mEq/L or total venous carbon dioxide (CO_2) concentration is less than 12 mmol/L; if concentration is unknown, do not administer unless animal is severely ill, and then give only once.

Amount: HCO_3^- (mEq) = Body weight (kg) × 0.4 × (12–Patient's HCO_3^-) × 0.5; if patient's HCO_3^- or total CO_2 concentration is unknown, use 10 in place of (12–Patient's HCO_3^-).

Administration: Add to IV fluids and give over 6 hours; do not give as bolus infusion.

Retreatment: Only if plasma bicarbonate concentration remains less than 12 mEq/L after 6 hours of therapy.

241.8.1.1.3 Insulin Therapy

Type: Regular crystalline insulin.

Administration

- Intermittent intramuscular (IM) technique: Initial dose, 0.2 U/kg IM; then 0.1 U/kg IM hourly until blood glucose concentration approaches 250 mg/dL; then switch to subcutaneous (SC) regular insulin q6-8h.
- Low-dose intravenous (IV) infusion technique: Initial rate, 0.05 to 0.1 U/kg/hr diluted in 0.9% sodium chloride and administered via infusion or syringe pump in a line separate from that used for fluid therapy; adjust infusion rate based on hourly blood glucose measurements; switch to SC regular insulin q6-8h once blood glucose concentration approaches 250 mg/dL. Decrease the hourly IM insulin dose or the IV insulin infusion rate for the initial 2 to 3 hours of treatment if the dog or cat is hypokalemic at the time of diagnosis.

Goal: Gradual decline in the blood glucose concentration (preferably at a rate of about 75 mg/dL/hr) until the concentration is less than 250 mg/dL.

241.8.1.1.4 Ancillary Therapy

Concurrent pancreatitis is common in diabetic ketoacidosis (DKA); nothing per os and aggressive fluid therapy usually are indicated.

Concurrent infections are common in DKA; broad-spectrum parenteral antibiotics usually are indicated.

Additional therapy may be needed, depending on the nature of concurrent disorders.

241.8.1.1.5 Patient Monitoring

Blood glucose measurement every 1 to 2 hours initially; adjust insulin therapy and begin dextrose infusion when the concentration approaches 250 mg/dL.

Hydration status, respiration, and pulse every 2 to 4 hours; adjust fluids accordingly.

Serum electrolyte and total venous CO_2 concentrations every 6 to12 hours; adjust fluid and bicarbonate therapy accordingly.

Urine output, glycosuria, and ketonuria every 2 to 4 hours; adjust fluid therapy accordingly.

Body weight, packed cell volume, temperature, and blood pressure daily.

Additional monitoring, depending on concurrent diseases.

Fluid administration should be directed toward gradual replacement of hydration deficits over 24 hours while maintenance fluid needs are supplied and ongoing losses are matched. Rapid replacement of fluids is rarely indicated unless the dog or cat is in shock. Once the animal is out of this critical phase, fluid replacement should be decreased in an effort to correct the fluid imbalance in a slow but steady manner. As a general rule, a fluid rate of one and one half to two times maintenance (i.e., 60 to 100 mL/kg/24 hr) is chosen initially, and subsequent adjustments are based on frequent assessment of hydration status, urine output, severity of azotemia, and persistence of vomiting and diarrhea.

241.8.2 Potassium Supplementation

Most dogs and cats with DKA initially have either normal or decreased serum potassium concentrations. During therapy for DKA, the serum potassium concentration may decrease because of rehydration (dilution), insulin-mediated cellular uptake of potassium (with glucose), continued urinary losses, and correction of acidemia (translocation of potassium into the intracellular fluid [ICF] compartment). Dogs and cats with hypokalemia require aggressive potassium replacement therapy to replace deficits and to prevent worsening, life-threatening hypokalemia after initiation of insulin therapy. The exception to potassium supplementation of fluids is hyperkalemia associated with oliguric renal failure. Potassium supplementation should initially be withheld in these dogs and cats until glomerular filtration has been restored, urine production increases, and hyperkalemia is resolving.

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Ideally the amount of potassium required is based on actual measurement of the serum potassium concentration. If an accurate measurement of serum potassium is not available, 40 mEq of potassium should be added initially to each liter of intravenous fluids (36 mEq should be added to Ringer's solution). Subsequent adjustments in potassium supplementation should be based on measurement of the serum potassium concentration, preferably every 6 to 8 hours until the dog or cat is stable and serum electrolyte values are in the normal range.

241.8.3 Phosphate Supplementation

Most dogs and cats with DKA have either normal or decreased serum phosphorus concentrations on pretreatment testing. Within 24 hours of initiation of treatment for DKA, the serum phosphorus concentration can decrease to worrisome levels (i.e., less than 1 mg/dL) as a result of the dilutional effects of fluid therapy,

the intracellular shift of phosphorus after initiation of insulin therapy, and continuing renal and gastrointestinal loss.[40] Hypophosphatemia affects primarily the hematologic and neuromuscular systems in dogs and cats. Hemolytic anemia is the most common problem and can be life-threatening if not recognized and treated. Weakness, ataxia, and seizures may also be observed. Severe hypophosphatemia may be clinically silent in many animals.

Phosphate therapy is indicated if clinical signs or hemolysis are identified or if the serum phosphorus concentration decreases to less than 1.5 mg/dL. Phosphate is supplemented by means of intravenous infusion. Potassium and sodium phosphate solutions contain 3 mmol of phosphate and either 4.4 mEq of potassium or 4 mEq of sodium per milliliter. The recommended dosage for phosphate supplementation is 0.01 to 0.03 mmol of phosphate per kilogram of body weight per hour, preferably administered in calcium-free intravenous fluids (e.g., 0.9% sodium chloride).[40] In dogs and cats with severe hypophosphatemia, the dosage may need to be increased to 0.03 to 0.12 mmol/kg/hr.[41] Because the dose of phosphate needed to replete an animal and the animal's response to therapy cannot be predicted, it is important initially to monitor the serum phosphorus concentration every 8 to 12 hours and to adjust the phosphate infusion accordingly. Adverse effects from overzealous phosphate administration include iatrogenic hypocalcemia and its associated neuromuscular signs, hypernatremia, hypotension, and metastatic calcification. The serum total (or preferably ionized) calcium concentration should be measured at the same time as the serum phosphorus concentration, and the rate of phosphate infusion should be decreased if hypocalcemia is identified. Phosphorus supplementation is not indicated in dogs and cats with hypercalcemia, hyperphosphatemia, oliguria, or suspected tissue necrosis. If renal function is in question, phosphorus should not be supplemented until the status of renal function and the serum phosphorus concentration are known.

241.8.4 Magnesium Supplementation

Hypomagnesemia is common in dogs and cats with DKA; it often worsens during the initial treatment of DKA but resolves without treatment as the DKA resolves.[42] Clinical signs of hypomagnesemia do not usually occur until the serum total and ionized magnesium concentration is less than 1 and 0.5 mg/dL, respectively, and even at these low levels, many dogs and cats remain asymptomatic. We do not routinely treat hypomagnesemia in dogs or cats with DKA unless problems with persistent lethargy, anorexia, weakness, or refractory hypokalemia or hypocalcemia are encountered after 24 to 48 hours of fluid and insulin therapy or some other cause of the problem cannot be identified.

241.8.5 Bicarbonate Therapy

The physical examination results, in conjunction with the plasma bicarbonate or total venous CO_2 concentration, should be used to determine the need for bicarbonate therapy. Bicarbonate supplementation is not recommended when the plasma bicarbonate (or total venous CO_2) concentration is 12 mEq/L or greater, especially if the animal is alert. An alert dog or cat probably has a normal or near-normal pH in the cerebrospinal fluid (CSF). The acidosis in these animals is corrected through insulin administration and fluid therapy. Improvement in renal perfusion enhances urinary loss of ketoacids, and insulin therapy markedly diminishes the production of ketoacids. Acetoacetate and beta hydroxybutyrate are also metabolically usable anions, and 1 mEq of bicarbonate is generated from each 1 mEq of ketoacid metabolized.

When the plasma bicarbonate concentration is 11 mEq/L or less (total venous CO_2 is below 12 mEq/L), bicarbonate therapy should be initiated. Many of these animals have severe depression that may be a result of concurrent severe central nervous system (CNS) acidosis. Metabolic acidosis should be corrected slowly to

avoid major alterations in the pH of the CSF. Only a portion of the bicarbonate deficit is given initially, over a 6-hour interval. The bicarbonate deficit (i.e., the milliequivalents of bicarbonate initially needed to correct acidosis to the critical level of 12 mEq/L over a period of 6 hours) is calculated as:

$$\text{Bicarbonate (mEq)} = \text{Body weight (kg)} \times 0.4 \times (12 - \text{Patient's bicarbonate measurement}) \times 0.5$$

or, if the serum bicarbonate is not known:

$$\text{Bicarbonate (mEq)} = \text{Body weight (kg)} \times 2$$

The difference between the animal's serum bicarbonate concentration and the critical value of 12 mEq/L represents the treatable base deficit in DKA. If the animal's serum bicarbonate concentration is not known, 10 should be used for the treatable base deficit. The factor 0.4 corrects for the extracellular fluid space in which bicarbonate is distributed (40% of body weight). The factor 0.5 provides one half of the required dose of bicarbonate in the intravenous (IV) infusion. In this manner, a conservative dose is given over a 6-hour period. Bicarbonate should *never* be given by bolus infusion. After 6 hours of therapy, the acid-base status should be re-evaluated and a new dose calculated. Once the plasma bicarbonate concentration is greater than 12 mEq/L, further bicarbonate supplementation is usually not needed.

241.8.6 Insulin Therapy

Insulin therapy is critical for the resolution of ketoacidosis. However, overzealous insulin treatment can cause severe hypokalemia, hypophosphatemia, and hypoglycemia during the first 24 hours of treatment. These are problems that can be minimized by appropriate fluid therapy, frequent monitoring of serum electrolytes and blood glucose concentrations, and modification of the initial insulin treatment protocol as indicated. The decision on when to start insulin therapy varies with the experiences of the veterinarian queried. Initiation of appropriate fluid therapy should always be the first step in the treatment of DKA. Delaying insulin therapy allows the benefits of fluid therapy to begin to be realized before the glucose-, potassium-, and phosphorus-lowering effects of insulin therapy commence. The question is how long to delay insulin therapy. The author typically delays insulin therapy for a minimum of 1 to 2 hours. Additional delays and decisions on the initial dosage of insulin are based on the serum electrolyte results. If the serum potassium concentration is within the normal range after 2 hours of fluid therapy, the author begins insulin treatment as described below. If hypokalemia persists, insulin therapy can be delayed an additional 1 to 2 hours to allow fluid therapy to replenish potassium, or the initial insulin dose can be reduced to dampen the intracellular shift of potassium and phosphorus. The more severe the hypokalemia, the more inclined the author is to delay insulin therapy and to reduce the initial insulin dose. However, insulin therapy should always be started within 4 hours of initiation of fluid therapy.

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Insulin protocols for the treatment of DKA include the hourly intramuscular (IM) technique, the continuous low-dose IV infusion technique, and the intermittent IM then subcutaneous (SC) technique. All three routes of insulin administration (IV, IM, SC) are effective in decreasing the plasma glucose and ketone concentrations. Successful management of DKA does *not* depend on the route of insulin administration; rather, it depends on proper treatment of each disorder associated with DKA.

241.8.6.1 Hourly intramuscular insulin technique

Dogs and cats with severe DKA should receive an initial regular crystalline insulin loading dose of 0.2 U/kg, followed by 0.1 U/kg every hour thereafter. The insulin dose can be reduced by 25% to 50% for the

first two or three injections if hypokalemia is a concern. The insulin should be administered into the muscles of the rear legs to ensure that the injections are intramuscular and not going into fat or subcutaneous tissue. Dilution of regular insulin 1:10 with sterile saline and the use of 0.3 mL U100 insulin syringes are helpful when small doses of insulin are required. The blood glucose concentration should be measured every hour with a point-of-care chemistry analyzer or portable blood glucose monitoring device, and the insulin dosage should be adjusted accordingly. The goal of initial insulin therapy is to lower the blood glucose concentration *slowly* to the range of 200 to 250 mg/dL, preferably over a 6-to 10-hour period; an hourly decline of 50 mg/dL is ideal.[43] This provides a steady, moderate decline and avoids large shifts in osmolality. A declining blood glucose concentration also ensures that lipolysis and the supply of FFAs for ketone production have been effectively turned off. Glucose concentrations, however, decrease much more rapidly than do ketone levels. In general, hyperglycemia is corrected within 12 hours, but ketosis often takes 48 to 72 hours to resolve.

Once the initial hourly insulin therapy brings the blood glucose concentration near 250 mg/dL, hourly administration of regular insulin should be discontinued, and regular insulin should be given intramuscularly every 4 to 6 hours or, if the hydration status is good, subcutaneously every 6 to 8 hours. The initial dosage is usually 0.1 to 0.3 U/kg, with subsequent adjustments based on blood glucose concentrations. In addition, at this point the intravenous infusion solution should have enough 50% dextrose added to create a 5% dextrose solution (100 ml of 50% dextrose added to each liter of fluids). The blood glucose concentration should be maintained between 150 and 300 mg/dL until the animal is stable and eating. Usually a 5% dextrose solution is adequate for maintaining the desired blood glucose concentration. If the blood glucose concentration dips below 150 mg/dL or rises above 300 mg/dL, the insulin dosage can be lowered or raised accordingly. Dextrose helps minimize problems with hypoglycemia and allows insulin to be administered on schedule. Delaying administration of insulin delays correction of the ketoacidotic state.

241.8.6.2 Constant low-dose insulin infusion technique

Constant intravenous infusion of regular crystalline insulin is also effective at decreasing blood glucose concentrations. The infusion is prepared by adding regular crystalline insulin (2.2 U/kg for dogs; 1.1 U/kg for cats) to 250 mL of 0.9% saline; it initially is administered at a rate of 10 mL/hr in a line separate from that used for fluid therapy.[44] This provides an insulin infusion rate of 0.05 U/kg/hr in cats and 0.1 U/kg/hr in dogs, a rate that has been shown to produce plasma insulin concentra-tions between 100 and 200 μU/mL in dogs. Because insulin adheres to glass and plastic surfaces, approximately 50 mL of the insulin-containing fluid should be run through the drip set before it is administered to the animal. The rate of insulin infusion can be reduced for the initial 2 to 3 hours if hypokalemia is a concern. Two separate catheters are recommended for treatment: a peripheral catheter for insulin administration and a central catheter for fluid administration and blood sampling. An infusion or syringe pump should be used to ensure a constant rate of insulin infusion.

Adjustments in the infusion rate are based on hourly measurements of the blood glucose concentration; an hourly decline of 50 mg/dL in the blood glucose concentration is ideal.[43] Once the blood glucose concentration approaches 250 mg/dL, the insulin infusion can be discontinued, and regular insulin can be given intramuscularly every 4 to 6 hours or, if the hydration status is good, subcutaneously every 6 to 8 hours, as discussed for the hourly IM protocol. Alternatively, the insulin infusion can be continued (at a decreased rate to prevent hypoglycemia) until the insulin preparation is exchanged for a longer acting product. Dextrose should be added to the IV fluids once the blood glucose concentration approaches 250 mg/dL, as discussed in the section on the hourly IM insulin technique.

241.8.6.3 Intermittent intramuscular/subcutaneous technique

The intermittent IM then SC insulin technique is less labor intensive than the other insulin administration techniques, but the decrease in blood glucose can be rapid and the risk of hypoglycemia is greater. The initial regular crystalline insulin dose is 0.25 U/kg given intramuscularly every 4 hours. Usually, insulin is administered intramuscularly only once or twice. Once the animal is rehydrated, subcutaneous administration is substituted for intramuscular administration, and insulin is given every 6 to 8 hours. Subcutaneous administration is not recommended initially because of problems with insulin absorption from subcutaneous sites of deposition in a dehydrated dog or cat. The dosage of IM or SC insulin is adjusted according to the blood glucose concentrations, which initially should be measured hourly beginning with the first IM injection. An hourly decline of 50 mg/dL in the blood glucose concentration is ideal.[43] Subsequent insulin dosages should be decreased by 25% to 50% if this goal is exceeded. Dextrose should be added to the IV fluids once the blood glucose concentration approaches 250 mg/dL, as discussed in the section on the hourly IM insulin technique.

241.8.6.4 Initiation of longer acting insulin

Longer acting insulin (e.g., NPH, Lente, protamine zinc insulin [PZI]) should not be administered until the dog or cat is stable, eating, maintaining fluid balance without any intravenous infusions, and no longer acidotic, azotemic, or electrolyte deficient. The initial dose of these longer acting insulins is similar to the regular insulin dose used just before the switch is made to longer acting insulin. Subsequent adjustments in the longer acting insulin dose should be based on the clinical response and measurement of blood glucose concentrations.

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241.8.7 Concurrent Illness

Therapy for DKA frequently involves the management of concurrent, often serious illness. Common concurrent illnesses in dogs and cats with DKA are acute and chronic pancreatitis, bacterial infection, cholangiohepatitis, renal insufficiency, cardiac disease, and insulin antagonism induced by hormonal disorders, most notably iatrogenic or naturally developing hyperadrenocorticism and diestrus.[45] Modifications in therapy for DKA (e.g., fluid therapy with concurrent heart failure) and/or additional therapy (e.g., antibiotics) may be required, depending on the concurrent illness. Insulin therapy, however, should never be delayed or discontinued; resolu-tion of ketoacidosis can be obtained only through insulin therapy. If nothing is to be given by mouth, insulin therapy should be continued and the blood glucose concentration maintained with intravenous dextrose infusions. If concurrent insulin-antagonistic disease is present, correction of the disease while the animal is still ill may be necessary to improve insulin effectiveness and resolve the ketoacidosis.

241.8.8 Complications of Therapy for Diabetic Ketoacidosis

Complications induced by therapy for DKA are common and usually result from overly aggressive treatment, inadequate patient monitoring, and failure to re-evaluate biochemical parameters in a timely manner. DKA is a complex disorder with a high mortality rate if it is improperly managed. To minimize the occurrence of therapeutic complications and to improve the chance of a successful response to therapy, all abnormal parameters must be *slowly* moved toward normal (i.e., over 36 to 48 hours); the animal's physical and mental status must be evaluated frequently (at least three to four times daily); and biochemical parameters (e.g., blood

glucose, serum electrolytes, blood gases) must be evaluated in a timely fashion. During the initial 24 hours, the blood glucose concentration should be measured every 1 to 2 hours and the serum electrolytes and blood gases every 6 to 8 hours. Fluid, insulin, and bicarbonate therapies typically require modification three or four times during the initial 24 hours of therapy. Failure to recognize changes in the status of DKA and to respond accordingly can lead to potentially serious complications. The more common complications are hypoglycemia, CNS signs secondary to cerebral edema, severe hypernatremia and hyperchloremia, severe hypokalemia, and hemolytic anemia from hypophosphatemia.

241.9 THERAPY FOR THE HEALTHY DIABETIC KETOACIDOTIC PATIENT

Diabetic dogs and cats that have ketonuria but not metabolic acidosis (i.e., diabetic ketosis) are often relatively healthy aside from the typical clinical signs of uncontrolled diabetes mellitus. Diabetic ketosis may be identified in newly diagnosed diabetic dogs and cats or in diabetic dogs and cats being treated with insulin. Identification of ketonuria in insulin-treated diabetic dogs and cats indicates that insulin treatment has become ineffective, usually because of a problem with the insulin treatment regimen or because a concurrent disorder has developed that causes insulin resistance, or both. The author typically treats dogs and cats with diabetic ketosis and no systemic signs of illness with short-acting regular crystalline insulin administered subcutaneously every 8 hours until ketonuria resolves. Because regular crystalline insulin is a potent insulin, the initial dose (0.1 to 0.2 U/kg per injection) is lower than that recommended for longer acting insulin preparations. To minimize hypoglycemia, the dog or cat should be fed one third of its daily caloric intake at the time of each insulin injection. Subsequent adjustments in the insulin dose are based on the clinical response and blood glucose values. Urine ketone concentrations should also be monitored. If the blood glucose concentration is well controlled, blood and urine ketone concentrations fall. Although the time until resolution of ketonuria is quite variable, most dogs and cats are negative for urine ketones within 3 to 5 days of initiation of three times a day regular crystalline insulin therapy. However, some dogs and cats require several weeks of regular crystalline insulin treatment before excessive hepatic production of ketones resolves. Prolonged ketonuria or recurring bouts of ketonuria are suggestive of a concurrent illness that is causing insulin resistance or of hyperglucagonemia, or both. Once the ketonuria has resolved, the dog or cat is stable, and control of glycemia is acceptable, a switch to a longer acting insulin preparation administered twice a day can be tried.

241.10 THERAPY FOR THE NONKETOTIC DIABETIC PATIENT

241.10.1 Goals of Therapy

The primary goal of therapy is elimination of the owner-observed signs that occur secondary to hyperglycemia and glycosuria. Persistence of clinical signs and the development of chronic complications (Box 241-5) directly correlate with the severity and duration of hyperglycemia. Limiting blood glucose concentration fluctuations and maintaining near-normal glycemia helps both to minimize the severity of clinical signs and to prevent the complications of poorly controlled diabetes. In the diabetic dog and cat, this can be accomplished through proper insulin therapy, diet, exercise, oral hypoglycemic medications, and the prevention or control of concurrent inflammatory, infectious, neoplastic, and hormonal disorders.

Although it is worthwhile to attempt to normalize the blood glucose concentration, the veterinarian must also guard against the development of hypoglycemia, a serious and potentially fatal complication of therapy. Hypoglycemia is most apt to occur as the result of overzealous insulin therapy. The veterinarian must balance the benefits of tight glucose control obtainable with aggressive insulin therapy against the risk of hypoglycemia.

241.10.1.1 Box • 241-5 Complications of Diabetes Mellitus in Dogs and Cats

241.10.1.1.1 Common

Iatrogenic hypoglycemia

Persistent polyuria, polydipsia, and weight loss

Cataracts (dog)

Bacterial infections, especially in the urinary tract

Pancreatitis

Ketoacidosis

Hepatic lipidosis

Peripheral neuropathy (cat)

241.10.1.1.2 Uncommon

Peripheral neuropathy (dog)

Glomerulonephropathy, glomerulosclerosis

Retinopathy

Exocrine pancreatic insufficiency

Gastric paresis

Diabetic diarrhea

Diabetic dermatopathy (dog)

241.10.2 Initial Insulin Therapy in Dogs

Once the diagnosis of diabetes has been established, dogs should be considered to have IDDM and treatment with insulin should be initiated. Intermediate-acting insulin (i.e., NPH, Lente) is the initial insulin of choice for establishing control of glycemia in diabetic dogs (Table 241-2). Recombinant human source insulin should be used to minimize the development of anti-insulin antibodies, which may interfere with control of glycemia. Insulin therapy is begun with recombinant human NPH or Lente insulin at an approximate dosage of 0.25 U/kg given twice a day. Dietary therapy is initiated concurrently (see below). Because the overwhelming majority of diabetic dogs require NPH or Lente insulin twice a day, we prefer to start with twice daily insulin therapy.[46] Establishing control of glycemia is easier and problems with hypoglycemia and the Somogyi effect (see Insulin Overdosing and Glucose Counter-Regulation [Somogyi Phenomenon]) are less likely when twice daily therapy is initiated while the insulin dosage is low (i.e., at the time insulin treatment is initiated).

241.10.3 Initial Insulin Therapy in Cats

Diabetic cats are notoriously unpredictable in their response to exogenous insulin. No single type of insulin is routinely effective in maintaining control of glycemia, even with twice a day administration. Ultralente insulin is the longest acting but least potent of the commonly used commercial insulins. Although considered a long-acting insulin, Ultralente insulin must be administered twice a day in most diabetic cats, and its absorption is inadequate for controlling glycemia in approximately 25% of cats. PZI is a longer acting insulin that is more consistently absorbed than Ultralente insulin and that has a more acceptable duration of effect than NPH insulin. However, the timing of the glucose nadir is quite variable and occurs within 9 hours of PZI administration in greater than 80% of treated diabetic cats.[47] The author routinely administers PZI twice a day. Lente and NPH insulin are more potent insulin preparations that are more consistently and rapidly absorbed after subcutaneous administration than is Ultralente insulin. Unfortunately, the duration of effect for Lente and especially NPH insulin can be considerably shorter than 12 hours in some diabetic cats, resulting in inadequate control of glycemia despite twice daily administration.

It is not possible to predict which type of insulin will work best in individual diabetic cats. The initial insulin of choice ultimately is based on the veterinarian's personal preference and experience. Currently, the author recommends either Lente insulin of recombinant human origin or PZI of beef/pork origin at a dosage of 1 to 2 U per cat administered twice daily. Dietary therapy is initiated concurrently (see below). Although the amino acid sequences of human and feline insulin differ, prevalence of insulin antibodies causing problems with control of glycemia is uncommon in cats treated with recombinant human insulin. Because greater than 80% to 90% of diabetic cats require recombinant human Lente insulin or beef/pork PZI twice a day, the author prefers to start with twice a day insulin therapy. Establishing control of glycemia is easier and problems with hypoglycemia and the Somogyi effect are less likely when twice daily insulin therapy is initiated while the insulin dosage is low (i.e., at the time insulin treatment is initiated).

Table • 241-2 Properties of Recombinant Human Insulin Preparations Used in Diabetic Dogs and Cats* and of Beef/Pork Protamine Zinc Insulin (PZI) Used in Diabetic Cats

			TIME OF MAXIMUM EFFECT POST INSULIN-ADMINISTRATION (hr)		DURATION OF EFFECT (hr)	
INSULIN TYPE	ROUTE OF ADMINISTRATION	ONSET OF EFFECT	DOG	CAT	DOG	CAT
Regular crystalline	Intravenous	Immediate	½-2	½-2	1–4	1–4
	Intramuscular	10–30 min	1–4	1–4	3–8	3–8
	Subcutaneous	10–30 min	1–5	1–5	4–10	4–10
NPH†	Subcutaneous	½-2 hr	2–10	2–8	6–18	4–12
Lente†‡	Subcutaneous	½-2 hr	2–10	2–10	8–20	6–18
Ultralente	Subcutaneous	½-8 hr	4–16	4–16	8–24	6–24
PZI‡	Subcutaneous	½-4 hr	—	4–14	—	6–20

* Purified pork insulin has similar properties; beef/pork insulin mixtures are less potent and may have a longer duration of action than recombinant human insulins.

† Initial insulin of choice for the diabetic dog.

‡ Initial insulin of choice for the diabetic cat.

Insulin glargine (Lantus; Aventis Pharmaceuticals, Bridgewater, New Jersey) is a long-acting insulin analog that forms microprecipitates at the site of injection, from which small amounts of insulin glargine are slowly released. Insulin glargine is currently recommended as a basal insulin (i.e., sustained long-acting insulin to inhibit hepatic glucose production) administered once a day at bedtime in human diabetics.[48,49] In a preliminary study involving healthy cats, most of the pharmacokinetic and pharmacodynamic properties were similar for insulin glargine and PZI.[50] Similar studies in diabetic cats have yet to be reported. In the author's experience, insulin glargine has a duration of effect ranging from 10 to 16 hours in most diabetic cats. The author has not yet encountered problems with inadequate absorption of insulin glargine, as described with Ultralente insulin, although it seems likely that this problem will be encountered as experience with this insulin analog accumulates. Currently, the author considers using insulin glargine when other insulin types are ineffective at controlling glycemia.

241.10.4 Storage and Dilution of Insulin

Freezing and heat inactivate insulin in the bottle. Although “room temperature” does not inactivate insulin, the author instructs owners to store insulin in the door of the refrigerator to maintain a consistent environment for the insulin preparation. Some veterinarians advocate replacing the insulin with a new bottle every month to avoid problems with loss of activity or sterility. The author has not appreciated a clinically significant loss of insulin action with time when insulin preparations are maintained in a constant environment (i.e., refrigerator) and handled appropriately. The author does not routinely recommend purchasing a new bottle of insulin every month, especially if the diabetic dog or cat is doing well. Loss of insulin activity in the bottle should always be considered whenever clinical signs recur, regardless of the amount of insulin in the bottle.

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Dilution of insulin is a common practice, especially in cats and small dogs. Although studies evaluating the shelf-life of diluted insulin have not been published, the author recommends replacing diluted insulin preparations every 4 to 8 weeks. Even using these guidelines, insufficient amounts of insulin are administered when diluted insulin is used in some dogs and cats, despite appropriate dilution and insulin administration techniques; these inadequacies are corrected when full-strength insulin is used.

241.10.5 Initial Adjustments in Insulin Therapy

Diabetic dogs and cats require several days to equilibrate to changes in the insulin dosage or preparation. Therefore newly diagnosed diabetic dogs and cats are typically hospitalized for no more than 24 to 48 hours so that the diagnostic evaluation can be finished and insulin therapy begun. During hospitalization, blood glucose concentrations typically are determined at the time insulin is administered and at 11 AM, 2 PM, and 5 PM. The intent is to identify hypoglycemia (blood glucose concentration less than 80 mg/dL) in those dogs and cats that are unusually sensitive to the actions of insulin. If hypoglycemia occurs, the insulin dosage is decreased before the dog or cat is sent home. The insulin dosage is not adjusted in dogs and cats that remain hyperglycemic during these first few days of insulin therapy. The objective during this first visit is *not* to establish perfect glycemic control before sending the dog or cat home; rather, the objectives are to begin to reverse the metabolic derangements induced by the disease, to allow the dog or cat to equilibrate to the insulin and change in diet, to teach the owner how to administer insulin, and to give the owner a few days to become accustomed to treating the diabetic dog or cat at home. Adjustments in insulin therapy are made on subsequent evaluations, which typically occur once a week until an effective insulin treatment protocol has been identified.

241.10.6 Dietary Recommendations for Diabetic Dogs

Adjustments in diet and feeding practices should be directed at correcting or preventing obesity, maintaining consistency in the timing and caloric content of meals, and furnishing a diet that helps minimize the postprandial increase in the blood glucose concentration. Correcting obesity and increasing the fiber content of the diet are perhaps the two most beneficial steps that can be taken to improve control of glycemia. Obesity can cause impaired glucose tolerance in dogs and may be an important factor in the variation in response to insulin therapy. Weight reduction improves glucose tolerance in obese dogs, presumably by correcting obesity-induced insulin resistance. Successful weight reduction usually requires a combination approach involving restriction of caloric intake, the feeding of low-calorie dense diets, and an increase in caloric expenditure through exercise.

Diets containing an increased fiber content are beneficial for improving control of glycemia in diabetics.[51,52] The ability of the food fiber to form a viscous gel and thus impair convective transfer of glucose and water to the absorptive surface of the intestine appears to be of greatest importance in slowing intestinal glucose absorption. The more viscous soluble fibers (e.g., gums, pectin) slow glucose diffusion to a greater degree than do the less viscous insoluble fibers (e.g., lignin, cellulose) and as such are believed to be of greater benefit in improving control of glycemia. Most commercial high-fiber diets predominantly contain insoluble fiber, although diets containing mixtures of soluble and insoluble fiber are becoming available. The amount of fiber varies considerably among products, ranging from 3% to 25% of dry matter (normal diets contain less than 2% fiber on a dry matter basis). In general, diets containing 12% or more insoluble fiber or 8% or more of a mixture of soluble and insoluble fiber are most likely to be effective in improving glycemic control in diabetic dogs.

Common complications of feeding high-fiber diets include excessive frequency of defecation (insoluble fiber); constipation and obstipation (insoluble fiber); soft to watery stools (soluble fiber); excessive flatulence (soluble fiber); hypoglycemia 1 to 2 weeks after the increase in the fiber content of the diet; and refusal to eat the diet. If firm stools or constipation becomes a problem with diets high in insoluble fiber, a mixture of insoluble and soluble fiber diets can be fed, or soluble fiber (e.g., psyllium, canned pumpkin) can be added to the diet to soften the stool. Alternatively, if soft or watery diarrhea or flatulence becomes a problem with diets containing soluble fiber, an insoluble fiber diet can be added and the quantity of the soluble fiber diet decreased. Problems with palatability are usually the result of too rapid a switch from the dog's usual diet to the high-fiber diet or of boredom after the fiber diet has been consumed for several months. Periodic changes in the types of high-fiber diets and mixtures of diets help alleviate the problem with boredom. High-fiber diets should not be fed to thin or emaciated diabetic dogs until control of glycemia has been established and a normal body weight attained using a higher calorie dense, lower fiber diet designed for maintenance.

241.10.7 Dietary Recommendations for Diabetic Cats

The general principles for dietary therapy are similar for dogs and cats. Correction of obesity and minimization of the diet's impact on the postprandial blood glucose concentration are especially important. Obesity is common in diabetic cats and results from excessive caloric intake, typically caused by free-choice feeding of dry cat food. Obesity causes reversible insulin resistance, which resolves as weight is lost.[26,28] Control of glycemia often improves and some diabetic cats may revert to a subclinical diabetic state after weight reduction. Unfortunately, correction of obesity is difficult in cats because it requires restriction of daily caloric intake with a minimal corresponding increase in caloric expenditure (i.e., exercise). Although several

diets are available that have been specifically formulated for weight reduction in cats, diets containing increased amounts of fiber or protein should be used in the diabetic cat for reasons discussed below.

During the past decade, high-fiber, moderately fat restricted diets (e.g., Prescription Diet w/d, Hill's Pet Products, Topeka, KS) have been recommended for diabetic cats based on studies that documented a significant improvement in glycemic control when diabetic cats consumed a canned insoluble fiber (cellulose) diet.[53] Recently, dietary recommendations for diabetic cats have come under scrutiny, in part because of the seemingly increasing prevalence of obesity, chronic pancreatitis, and inflammatory bowel disease in cats during the past decade. Cats are carnivores and as such have higher dietary protein requirements than omnivores such as humans and dogs.[54] The activity of hepatic enzymes responsible for the phosphorylation of glucose for subsequent storage or oxidation (glucokinase, hexokinase) and the conversion of glucose to glycogen for storage in the liver (glycogen synthetase) are lower in cats compared with that for carnivores with omnivorous dietary habits.[55] The low activity of these hepatic enzymes suggests that cats primarily use gluconeogenic amino acids and fat, rather than starch, in their diet for energy; it also suggests that diabetic cats may be predisposed to developing higher postprandial blood glucose concentrations after consumption of diets with a high carbohydrate load and vice versa. Two carbohydrate-restricted diets that have been recommended for diabetic cats are Purina DM (Ralston Purina, St. Louis, Missouri) and Science Diet Feline Growth (Hill's Pet Products, Topeka, KS).[56,57] Purina DM is a high-protein, low-carbohydrate, low-fiber diet, and Science Diet Growth is a high-fat, low-carbohydrate, low-fiber diet.

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The central theme in dietary studies in diabetic cats has been restriction of carbohydrate absorption by the gastrointestinal tract, by inhibiting starch digestion (acarbose), inhibiting intestinal glucose absorption (fiber), or decreasing carbohydrate ingestion (low-carbohydrate diets). Intuitively, the most effective means of minimizing gastrointestinal absorption of carbohydrates in the diabetic cat is to feed diets that contain minimal amounts of carbohydrate. The beneficial role in the control of glycemia, if any, of the high protein or high fat content of current carbohydrate-restricted diets is not yet known. It is also not known what effect, if any, a high protein intake may have on the development of ketosis or diabetic nephropathy, the induction of satiety, or maintenance of a stable body weight. Similarly, it is not known what effect, if any, a high fat intake may have on the development of obesity, hepatic lipidosis, and chronic pancreatitis or the induction of insulin resistance and increased hepatic glucose production secondary to the generation of nonesterified fatty acids, beta hydroxybutyric acid, and hypertriglyceridemia, especially in older cats that may have decreased lipoprotein and hepatic lipase activity.[58–60] For now, all three diets are considered viable choices for the management of diabetes in cats. Which diet will be most beneficial at improving control of glycemia in any given diabetic cat is unpredictable. As such, the initial diet of choice is based on the veterinarian's personal preferences and experience. If palatability or adverse effects become an issue or if poor control of glycemia persists despite adjustments in insulin therapy, a switch to one of the other diets should be considered.

241.10.8 Exercise

Exercise plays an important role in the maintenance of glycemic control by helping to promote weight loss and by eliminating the insulin resistance induced by obesity. Exercise also exerts a glucose-lowering effect by increasing the absorption of insulin from its injection site, increasing blood flow (and therefore insulin delivery) to exercising muscles, stimulating translocation of glucose transporters in muscle cells, and increasing glucose effectiveness (i.e., the ability of hyperglycemia to promote glucose disposal at basal insulin concentrations).[61,62] The daily routine for diabetic dogs should include exercise, preferably at the same time each day. Strenuous and sporadic exercise can cause severe hypoglycemia and should be avoided. The insulin dose should be decreased in dogs subjected to sporadic, strenuous exercise on days of anticipated increased

exercise. The reduction in the insulin dose required to prevent hypoglycemia is variable and is determined by trial and error. The author recommends reducing the insulin dose by 50% initially and making further adjustments based on the occurrence of symptomatic hypoglycemia and the severity of polyuria and polydipsia that develop during the ensuing 24 to 48 hours. In addition, owners must be aware of the signs of hypoglycemia and must have a source of glucose readily available to give their dog should any of these signs develop.

241.10.9 Identification and Control of Concurrent Problems

Concurrent diseases and administration of insulin-antagonistic drugs are both commonly identified in the dog and cat with newly diagnosed diabetes mellitus.[63,64] Concurrent disease and insulin-antagonistic drugs can interfere with tissue responsiveness to insulin as a result of a decreased number of insulin receptors at the surface of the cell membrane, alterations in insulin receptor binding affinity, or impairment in one of several postreceptor steps responsible for the activation of glucose transport systems. Loss of tissue responsiveness results in insulin resistance, which may be mild and easily overcome by increasing the dosage of insulin, or may be severe, causing sustained and marked hyperglycemia regardless of the type and dosage of insulin administered. Some causes of insulin resistance are readily apparent at the time diabetes is diagnosed, such as obesity and the administration of insulin-antagonistic drugs (e.g., glucocorticoids). Other causes of insulin resistance may not be readily apparent, and identification of these causes may require an extensive diagnostic evaluation. In general, any concurrent inflammatory, infectious, hormonal, or neoplastic disorder can cause insulin resistance and can interfere with the effectiveness of insulin therapy. Identification and treatment of concurrent disease plays an integral role in the successful management of the diabetic dog and cat. A thorough history and physical examination and a complete diagnostic evaluation are imperative in the newly diagnosed diabetic dog or cat.

241.10.10 Oral Hypoglycemic Drugs

In the United States, five classes of oral hypoglycemic drugs have been approved for the treatment of NIDDM in human beings: sulfonylureas, meglitinides, biguanides, thiazolidinediones, and alpha-glucosidase inhibitors. These drugs work by stimulating pancreatic insulin secretion (sulfonylureas, meglitinides), by enhancing tissue sensitivity to insulin (biguanides, thiazolidinediones), or by slowing postprandial intestinal glucose absorption (alpha-glucosidase inhibitors).[65] Although controversial, chromium and vanadium are trace minerals that may also function as insulin sensitizers. Studies have documented the efficacy of sulfonylureas for treating diabetes in cats[4,66] and of alpha-glucosidase inhibitors for improving glycemic control in diabetic dogs (see below).[67,68] The pharmacokinetic properties of the insulin-sensitizing drugs metformin (a biguanide) and troglitazone (a thiazolidinedione) have been evaluated in healthy cats.[69,70] Unfortunately, in one study metformin was ineffective as a sole therapeutic agent in a small number of newly diagnosed diabetic cats and was discontinued in most because of progressively worsening clinical signs or the development of ketoacidosis.[71] The only cat that responded to metformin had a fasting serum insulin concentration greater than 20 μU/mL, a finding consistent with the concept that metformin as an insulin-sensitizing drug is effective only in the presence of adequate blood concentrations of insulin. Similarly, oral chromium picolinate was ineffective in improving control of glycemia in a group of insulin-treated diabetic dogs.[72] Studies evaluating the efficacy of thiazolidinediones for the treatment of diabetes in dogs or cats have yet to be reported.

241.10.10.1 Sulfonylureas

Glipizide and glyburide are the sulfonylureas most commonly used to treat NIDDM. The primary effect of these drugs is direct stimulation of insulin secretion from the pancreas.[73] Some pancreatic insulin secretory capability must exist for sulfonylureas to be effective in improving glycemic control. Sulfonylurea treatment is ineffective as the sole form of treatment for IDDM and has not been effective in diabetic dogs, presumably because of the high incidence of IDDM in this species. The clinical response to glipizide and glyburide treatment in diabetic cats is variable, ranging from excellent (i.e., blood glucose concentrations decreasing to less than 200 mg/dL) to a partial response (i.e., clinical improvement but failure to resolve hyperglycemia), to no response.[4,66] Presumably, the population of functioning beta cells dictates the clinical response; that is, variation from an absence of functioning beta cells (severe IDDM) to a near-normal population of beta cells (mild NIDDM) results in a response range of none to excellent. Cats with a partial response to glipizide have some functioning beta cells but not enough to reduce the blood glucose concentration to less than 200 mg/dL. These cats may have severe NIDDM or the early stages of IDDM.

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No consistent parameters have been identified that allow the clinician to prospectively determine which cats will respond to glipizide or glyburide therapy. Identification of a high preprandial serum insulin concentration or an increase in the serum insulin concentration during an insulin secretagogue test supports a diagnosis of NIDDM, but failure to identify these changes does not rule out the potential for a beneficial response to glipizide or glyburide. Selection of diabetic cats for treatment with glipizide must rely heavily on the veterinarian's assessment of the cat's health, the severity of clinical signs, the presence or absence of ketoacidosis, other diabetic complications (e.g., peripheral neuropathy), and the owner's desires.

Currently, the author administers glipizide (Glucotrol; Pfizer, New York, NY) at a dosage of 2.5 mg per os twice a day in conjunction with a meal, to diabetic cats that are nonketotic and relatively healthy on physical examination (Figure 241-6). The history and complete physical examination findings; body weight and urine glucose/ketone measurements; and several blood glucose concentrations are evaluated 2 weeks after initiation of glipizide therapy. If adverse reactions (Table 241-3) have not occurred after 2 weeks of treatment, the glipizide dosage is increased to 5 mg twice a day and the cat is re-evaluated 2 weeks later. Therapy is continued as long as the cat is stable. If euglycemia or hypoglycemia develop, the glipizide dosage may be tapered or discontinued and blood glucose concentrations re-evaluated 1 week later to assess the need for the drug. If hyperglycemia recurs, the dosage is increased or glipizide is reinitiated at a reduced dosage in cats that previously developed hypoglycemia. Glipizide is discontinued and insulin therapy is initiated if clinical signs continue to worsen; if the cat becomes ill or develops ketoacidosis; if the blood glucose concentration remains greater than 300 mg/dL after 1 to 2 months of therapy; or if the owners become dissatisfied with the treatment. It is important to remember that stress-induced hyperglycemia can artificially elevate the results of blood glucose tests. Therefore, if an owner believes that the drug is effective but the blood glucose concentration remains greater than 300 mg/dL, assessment of the fructosamine or glycosylated hemoglobin level will distinguish the stressed cat from one that truly is not responding to the drug. In some cats, glipizide becomes ineffective weeks to months later, and exogenous insulin is ultimately required to control the diabetic state. Presumably, the transition from glipizide to insulin treatment is due to progression of the underlying pathophysiologic mechanisms (e.g., islet-specific amyloid deposition) responsible for the development of diabetes in the cat. The more rapid the rate of progression, the shorter the beneficial response to glipizide.

One theoretical adverse reaction of chronic glipizide therapy is accelerated loss of pancreatic beta cell function caused by glipizide-induced stimulation of amylin secretion and worsening islet amyloidosis. In a recent study using an induced model of diabetes in cats, mild to moderate islet amyloid deposition and moderate to severe islet vacuolar change were identified in three and one of four cats, respectively, that were treated with glipizide for 18 months and in one and three of four cats, respectively, that were treated with recombinant human NPH insulin for 18 months.[74] The results suggested that glipizide treatment could cause progressive amyloid deposition as a result of glipizide-induced insulin and amylin secretion. Does this mean that glipizide should not be used for the treatment of diabetes in cats? To answer this question, one has to look at the underlying reason for using this drug. Glipizide has no advantage over insulin therapy with regard to cost of treatment, time required to treat, efficacy of treatment, or frequency of re-evaluations by the veterinarian. However, glipizide gives many owners an initially more palatable option (i.e., pills versus injections) for the treatment of their newly diagnosed diabetic cat. Most owners who are unwilling to give insulin injections would euthanize their cat. Many of these people are willing to try oral medication. During the ensuing weeks, many of these owners become willing to try insulin injections if glipizide therapy fails. In the author's opinion, the real advantage of glipizide is that it keeps more diabetic cats alive by giving the owner treatment options in lieu of insulin injections and by not forcing a quick life-and-death decision at the time diabetes is diagnosed.

241.10.11 Alpha-Glucosidase Inhibitors

Acarbose and miglitol are complex oligosaccharides of microbial origin that competitively inhibit alpha-glucosidases (glucoamylase, sucrase, maltase, and isomaltase) in the brush border of the small intestinal mucosa. Inhibition of these enzymes delays digestion of complex carbohydrates and disaccharides to monosaccharides. This inhibition delays absorption of glucose from the intestinal tract and decreases postprandial blood glucose concentrations. Placebo-controlled clinical studies in healthy dogs documented a decrease in postprandial glucose absorption and insulin secretion when the dogs were treated with acarbose, compared with placebo. A decrease in the daily insulin dose and the blood glucose and glycated protein concentrations were documented in diabetic dogs treated with acarbose, compared with placebo.[67,68] Unfortunately, diarrhea and weight loss as a result of carbohydrate malassimilation were common adverse effects, occurring in approximately 35% of dogs. Diarrhea was more prevalent at higher doses of acarbose (i.e., 100 and 200 mg/dog) and typically resolved within 2 to 3 days of discontinuation of the medication. Because of the cost and prevalence of adverse effects, acarbose should be reserved for treatment of poorly controlled diabetic dogs in which the cause of the poor control of glycemia cannot be identified and insulin treatment by itself is ineffective at preventing clinical signs of diabetes. The initial acarbose dosage is 12.5 to 25 mg per dog at each meal. The benefit of this drug depends on its interaction with the meal; it should be given only at the time of feeding. A stepwise increase to 50 mg/dog and, in large dogs (greater than 25 kg), a further increase to 100 mg/dog can be considered in dogs that fail to show improvement in control of glycemia after 2 weeks on the 12.5 to 25 mg/meal regimen. Adverse reactions (especially diarrhea) are more likely to occur at these higher doses.

241.11 TECHNIQUES FOR MONITORING DIABETIC CONTROL

The basic objective of therapy is to eliminate the clinical signs of diabetes mellitus while avoiding the common complications associated with the disease. Common complications in dogs and cats include blindness caused by cataract formation (dogs); weakness, ataxia, and a plantigrade stance caused by peripheral neuropathy (cats); poor haircoat from lack of grooming (cats); weight loss; hypoglycemia; recurring ketosis; and poor control of

glycemia secondary to concurrent infection, inflammation, neoplasia, or hormonal disorders (see Box 241-5). The devastating chronic complications of human diabetes (e.g., nephropathy, vasculopathy, coronary artery disease) require several decades to develop and are uncommon in diabetic dogs and cats; as such, it is not necessary to establish near-normal blood glucose concentrations in these animals. Most owners are happy and most dogs and cats are healthy and relatively asymptomatic if most blood glucose concentrations are kept between 100 and 250 mg/dL.

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Figure 241-6 Algorithm for treatment of diabetic cats with the oral sulfonylurea drug glipizide. (From Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, 3rd ed. Philadelphia, WB Saunders, 2004, p 558.)

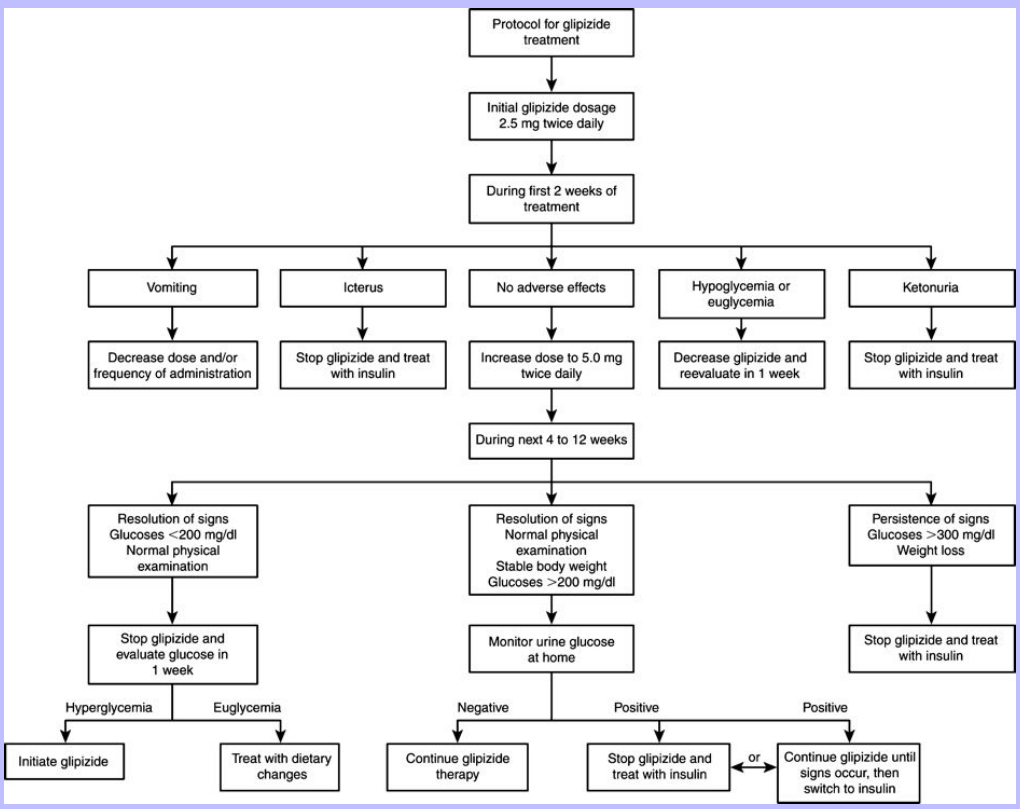

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Table • 241-3 Adverse Reactions to Glipizide Treatment in Diabetic Cats

ADVERSE REACTION	RECOMMENDATION
Vomiting within 1 hour of administration	Vomiting usually subsides after 2 to 5 days of glipizide therapy; decrease dose or frequency of administration if vomiting is severe; discontinue if vomiting persists longer than 1 week.
Increased serum hepatic enzyme activities	Continue treatment and monitor enzymes every 1 to 2 weeks initially; discontinue glipizide if cat becomes ill(lethargy, inappetence, vomiting) or if alanine transaminase activity exceeds 500 IU/L.
Icterus	Discontinue glipizide treatment; reinstitute glipizide treatment at lower dose and frequency of administration once icterus resolves (usually within 2 weeks); discontinue treatment permanently if icterus recurs.
Hypoglycemia	Discontinue glipizide treatment; recheck blood glucose concentration in 1 week; reinstitute glipizide therapy lower dose or frequency of administration if hyperglycemia recurs.

An important factor that affects the monitoring of diabetic cats more commonly than that of diabetic dogs is the propensity to develop stress-induced hyperglycemia as a result of frequent visits to the veterinary hospital for blood sampling. Once stress-induced hyperglycemia develops, it seems to be a perpetual problem, and blood glucose measurements can no longer be considered accurate. Veterinarians must remain wary of stress hyperglycemia in diabetic cats and should take steps to prevent its development. Micromanagement of diabetic cats should be avoided, and serial blood glucose curves should be done only when there is a perceived need to change insulin therapy. The determination of good versus poor control of glycemia should be based on the owner's subjective opinion regarding the presence and severity of clinical signs and the pet's overall health; the cat's ability to jump and its grooming behavior; the findings on physical examination, and the stability of body weight. Generation of a serial blood glucose curve should be reserved for newly diagnosed and poorly controlled diabetic cats unless stress-induced hyperglycemia is suspected. If this phenomenon is suspected, a switch should be made from reliance on serial blood glucose curves generated in the veterinary hospital to reliance on blood glucose results generated by the owner in the less-stressful home environment or on evaluation of sequential serum fructosamine concentrations, in addition to the history and physical examination findings.

241.11.1 History and Physical Examination

The most important initial parameters that should be assessed in the evaluation of control of glycemia are the owner's subjective opinion of the severity of clinical signs and the pet's overall health, the physical examination findings, and the stability of body weight. If the owner is happy with the results of treatment, if the physical examination is supportive of good glycemic control, and if the body weight is stable, the diabetic dog or cat is usually adequately controlled. Measurement of the serum fructosamine concentration can add further objective evidence of the status of glycemic control (see below). Poor control of glycemia should be suspected and additional diagnostics (i.e., serial blood glucose curve, serum fructosamine concentration, tests for concurrent disorders) or a change in insulin therapy should be considered if the owner reports clinical signs suggestive of hyperglycemia or hypoglycemia (i.e., polyuria, polydipsia, lethargy, weakness, ataxia) or peripheral neuropathy (changes in jumping ability, weakness, ataxia, plantigrade stance); if the physical examination identifies problems consistent with poor control of glycemia (e.g., thin or emaciated appearance, poor haircoat); or if the dog or cat is losing weight.[75]

Documentation of an increased blood glucose concentration does not *by itself* confirm poor control of glycemia. Stress or excitement can cause marked hyperglycemia that does not reflect the cat's or dog's responsiveness to insulin and can lead to the erroneous belief that the diabetic dog or cat is poorly controlled. If a discrepancy exists among the history, physical examination findings, and blood glucose concentration or if the cat or dog is fractious, aggressive, excited, or scared and the blood glucose concentration is known to be unreliable, the serum fructosamine concentration should be measured to further evaluate the status of glycemic control.

241.11.2 Serum Fructosamine Concentration

Fructosamines are glycated proteins synthesized after an irreversible, nonenzymatic, insulin-independent binding of glucose to serum proteins. Serum fructosamine concentrations are a marker of the mean blood glucose concentration during the circulating life span of the protein, which varies from 1 to 3 weeks, depending on the particular protein. The extent of glycosylation of serum proteins is directly related to the blood glucose concentration; the higher the average blood glucose concentration during the preceding 2 to 3 weeks, the higher the serum fructosamine concentration and vice versa. Serum fructosamine concentrations increase when glycemic control of the diabetic dog or cat worsens and decrease when glycemic control improves. The erum fructosamine concentration is not affected by acute increases in the blood glucose concentration, as occurs with stress or excitement-induced hyperglycemia, but it can be affected by hypoalbuminemia (less than 2.5 g/dL) and hyperlipidemia (triglycerides greater than 150 mg/dL).[39,76,77]

Fructosamine is measured in serum, which should be frozen and shipped on cold packs overnight to the diagnostic laboratory. In the author's laboratory, the normal reference ranges for serum fructosamine are 225 to 365 µmol/L in dogs and 190 to 365 µmol/L in cats.[39,78] Interpretation of the serum fructosamine level in a diabetic dog or cat must take into consideration the fact that hyperglycemia is common, even in well-controlled diabetic dogs and cats (Table 241-4). Most owners are happy with their pet's response to insulin treatment if the serum fructosamine concentration can be kept between 350 and 450 µmol/L. Values greater than 500 µmol/L suggest inadequate control of the diabetic state, and values greater than 600 µmol/L indicate serious lack of glycemic control. Serum fructosamine concentrations in the lower half of the normal reference range (i.e., less than 300 µmol/L) or below the normal reference range should raise concern that significant periods of hypoglycemia have occurred. Increased serum fructosamine concentrations (i.e., greater than 500 µmol/L) suggest poor control of glycemia and a need for insulin adjustment but do not identify the underlying problem.

Table • 241-4 Sample Handling, Methodology, and Normal Values for Serum Fructosamine Concentrations Measured in Our Laboratory in Dogs and Cats

Blood sample	1 to 2 mL serum
Sample handling	Freeze until assayed
Methodology	Automated colorimetric assay using nitroblue tetrazolium chloride
Factors affecting results	Hypoproteinemia and hypoalbuminemia (decreased), hyperlipidemia (decreased [dog]), azotemia (decreased [dog]), storage at room temperature (decreased)
Normal range	Dog: 225 to 365 µmol/L Cat: 190 to 365 µmol/L
Interpretation in diabetic dogs and cats	
Excellent control	350 to 400 µmol/L
Good control	400 to 450 µmol/L
Fair control	450 to 500 µmol/L
Poor control	>500 µmol/L
Prolonged hypoglycemia	<300 µmol/L

241.11.3 Urine Glucose Monitoring

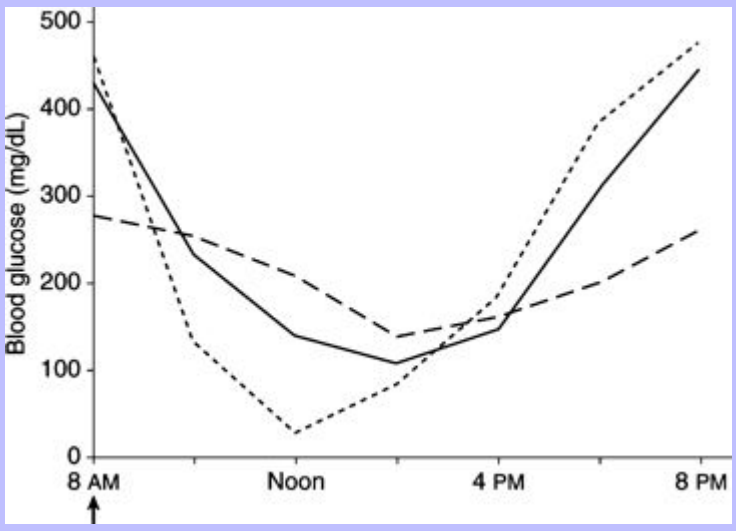
In diabetic dogs and cats that have problems with recurring ketosis or hypoglycemia, occasional monitoring of urine for glycosuria and ketonuria in the home environment is helpful for (1) determining whether ketonuria or persistent negative glycosuria, respectively, is present; (2) in cats that have reverted to a non-insulin-requiring diabetic state, for determining whether glycosuria has recurred; (3) in cats treated with oral hypoglycemic drugs, for determining whether glycosuria has improved or worsened; and (4) in cats with suspected stress-induced hyperglycemia, for differentiating transient from persistent hyperglycemia. For cats, a small amount of urine can be obtained by decreasing the amount of litter in the pan; by temporarily replacing the litter with nonabsorbable material, such as aquarium gravel; or by assessing the change in the color of urine glucose test squares (Glucotest Feline Urinary Glucose Detection System; Ralston Purina) that have been mixed into the kitty litter. We do not have the owner adjust daily insulin dosages based on morning urine glucose measurements in dogs except to decrease the insulin dose in dogs with recurring hypoglycemia and persistent negative glycosuria. In the author's experience, the vast majority of diabetic dogs develop complications as a result of owners being misled by morning urine glucose concentrations. For both dogs and cats, persistent glycosuria throughout the day and night suggests inadequate control of the diabetic state and the need for a more complete evaluation of diabetic control using techniques discussed in this section.

241.11.4 Serial Blood Glucose Curve

If an adjustment in insulin therapy is deemed necessary after a review of the history, physical examination findings, changes in body weight, and serum fructosamine concentration, a serial blood glucose curve should be generated to provide guidance for the adjustment, unless the blood glucose measurements are unreliable because of stress, aggression, or excitement. The serial blood glucose curve provides guidelines for rational adjustments in insulin therapy. Evaluation of a serial blood glucose curve is mandatory during the initial regulation of the diabetic dog or cat and is necessary in the dog or cat in which clinical manifestations of hyperglycemia or hypoglycemia have developed. Reliance on the history, physical examination findings, body weight, and serum fructosamine concentration to determine when a blood glucose curve is needed helps reduce the number of blood glucose curves generated and the number of venipunctures and also shortens the

time the dog or cat spends in the hospital. This may minimize the animal's aversion to evaluations and may improve the chance of obtaining meaningful results when a blood glucose curve is needed.

Figure 241-7 Blood glucose concentration curves in a dachshund receiving 0.8 U of recombinant human Lente insulin per kilogram of body weight twice a day *(solid line);* a miniature poodle receiving 0.6 U of recombinant human Lente insulin per kilogram of body weight twice a day *(broken line);* and a terrier-mix receiving 1.1 U of recombinant human Lente insulin per kilogram of body weight twice a day *(dotted line)*. Insulin and food were given at 8 AM. Interpretation of the blood glucose curves suggests a short duration of insulin effect in the dachshund, insulin underdosage in the miniature poodle, and the Somogyi effect in the terrier-mix. Note that the blood glucose concentrations were similar in the three dogs at 2 PM and 4 PM and that the glucose results at these times do not establish the diagnosis in any of the dogs. (From Nelson RW, Couto CG: Small Animal Internal Medicine, 3rd ed. St Louis, Mosby, 2003, p 741.)

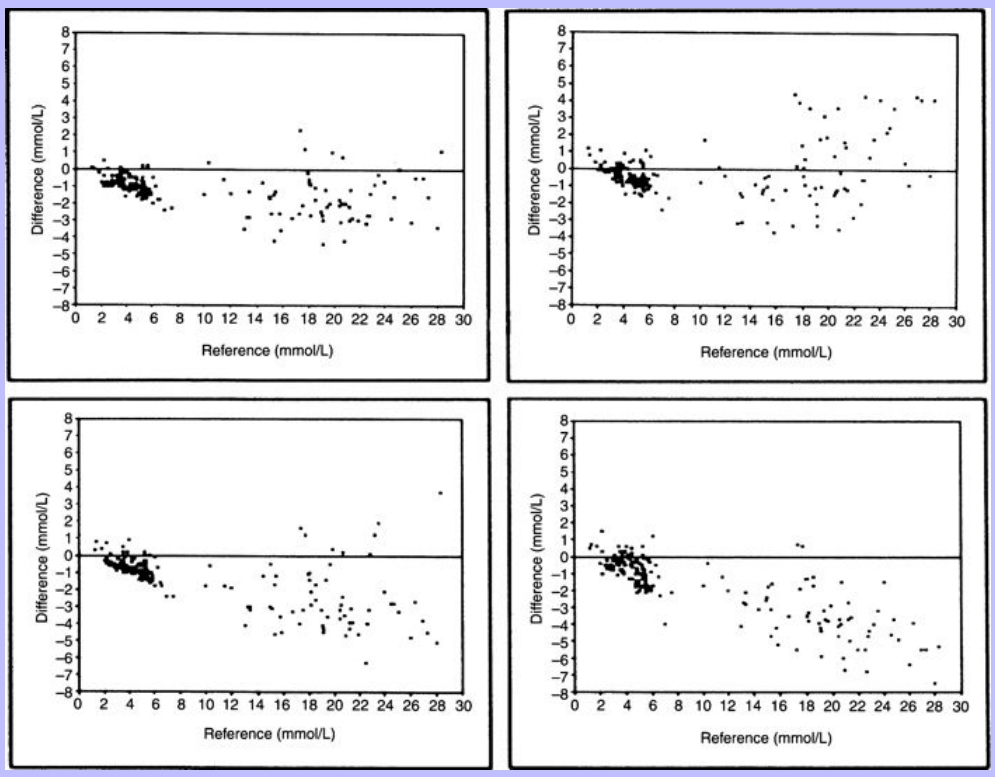


Blood glucose concentrations are typically determined with either a point-of-care glucose analyzer or a hand-held portable blood glucose monitoring device. Commercially available portable blood glucose monitoring devices provide blood glucose concentrations reasonably close to those obtained with reference methods, although the results often consistently overestimate or underestimate actual glucose values (Figure 241-8).[78,79] The blood glucose values determined by most portable blood glucose monitoring devices typically are lower than the actual glucose values determined by reference methods. This may result in an incorrect diagnosis of hypoglycemia or the misperception that glycemic control is better than it actually is. Failure to

consider this “error” could result in insulin underdosage and the potential for persistence of clinical signs despite apparently “acceptable” blood glucose results.

The author prefers to adjust insulin therapy based on interpretation of a single serial blood glucose curve, with the ideal goal of maintaining the blood glucose concentration between 100 and 250 mg/dL. We typically relies on owner perceptions of clinical response and the change in the serum fructosamine concentration to initially assess the impact of the insulin adjustment on control of glycemia. If problems persist, we consider repeating the blood glucose curve. We rarely perform blood glucose curves on multiple consecutive days because it promotes stress-induced hyperglycemia. In addition, information gained from a prior serial blood glucose curve should never be assumed to be reproducible on subsequent curves. Variables such as the actual amount of insulin drawn into the syringe and subsequently absorbed from the subcutaneous site of deposition and the interaction among insulin, diet, exercise, stress, excitement, any concurrent disorders, and secretion of the counter-regulatory hormones (i.e., glucagon, epinephrine, cortisol, growth hormone) change with time and affect the reproducibility of serial blood glucose curves. Lack of consistency in the results of serial blood glucose curves creates frustration for many veterinarians. It is important to remember that this lack of consistency is a direct reflection of all the variables that affect the blood glucose concentration in diabetics. Daily self-monitoring of blood glucose concentrations and daily adjustments in the insulin dose are recommended in human diabetics to minimize the effect of these variables on control of glycemia. A similar approach for diabetic dogs and cats undoubtedly will become more common in the future, as home glucose monitoring techniques are refined. For now, initial assessment of the control of glycemia is based on the owners' perception of their diabetic pet's health combined with periodic examinations by the veterinarian. Serial blood glucose measurements are indicated if poor control of glycemia is suspected. The purpose of serial blood glucose measurements is to obtain a glimpse at the actions of insulin in that diabetic animal and hopefully to identify a reason that could explain why the diabetic dog or cat is poorly controlled.

Figure 241-8 Scatterplots of the difference between blood glucose concentrations obtained with four portable blood glucose meters and concentrations obtained with a reference method versus concentration obtained with the reference method for blood samples from 170 dogs. (From Wess G, Reusch C: Evaluation of five portable blood glucose meters for use in dogs. J Am Vet Med Assoc 216:203, 2000.)



241.11.5 Generation of the Serial Blood Glucose Curve at Home

An alternative to hospital-generated blood glucose curves for cats is to have the owner generate the blood glucose curve at home using the marginal ear vein prick technique and a portable home blood glucose monitoring device that allows the owner to touch the drop of blood on the ear with the end of the glucose test strip (e.g., Glucometer Elite XL portable blood glucose meter; Bayer Diagnostics, Tarrytown, New York) (Figure 241-9). The marginal ear vein prick technique decreases the need for physical restraint during sample collection, thereby minimizing the cat's discomfort and stress. The accuracy of blood glucose results are similar when blood for glucose determination is obtained by ear prick and venipuncture.[79,80] However, blood glucose results obtained by portable blood glucose monitoring devices may overestimate or, more commonly, underestimate the actual blood glucose values obtained with reference methods, as discussed in the previous

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section.[81] This inherent error must be considered in the interpretation of blood glucose results obtained by a portable home blood glucose monitoring device. Several web sites on the Internet (e.g., www.sugarcats.net/sites/harry/) explain in detail the marginal ear vein prick technique in lay terms and provide information on owner experiences with the technique and with different portable home blood glucose meters. At the time diabetes is diagnosed, the author provides this web site URL to clients and asks them to read the information to decide if they would be interested in monitoring blood glucose concentrations at home. We spend time teaching the technique to individuals willing to give it a try, advise them on how often to perform a blood glucose curve (ideally no more frequently than one day every 2 to 4 weeks), and how often to measure the blood glucose concentration on the day of the curve (typically at the time of insulin administration and 3, 6, 9, and 12 hours later). We have had excellent results using the marginal ear vein prick technique in cats. Stress has been significantly reduced, and the reliability of the blood glucose results has improved immensely. The biggest problem has been overzealous owners who monitor blood glucose concentrations too frequently. A similar approach can be used in diabetic dogs, using either the ear or lip prick technique. However, the author does not push home glucose monitoring for dogs as much as for cats, primarily because stress-induced hyperglycemia is not as significant a problem in diabetic dogs.

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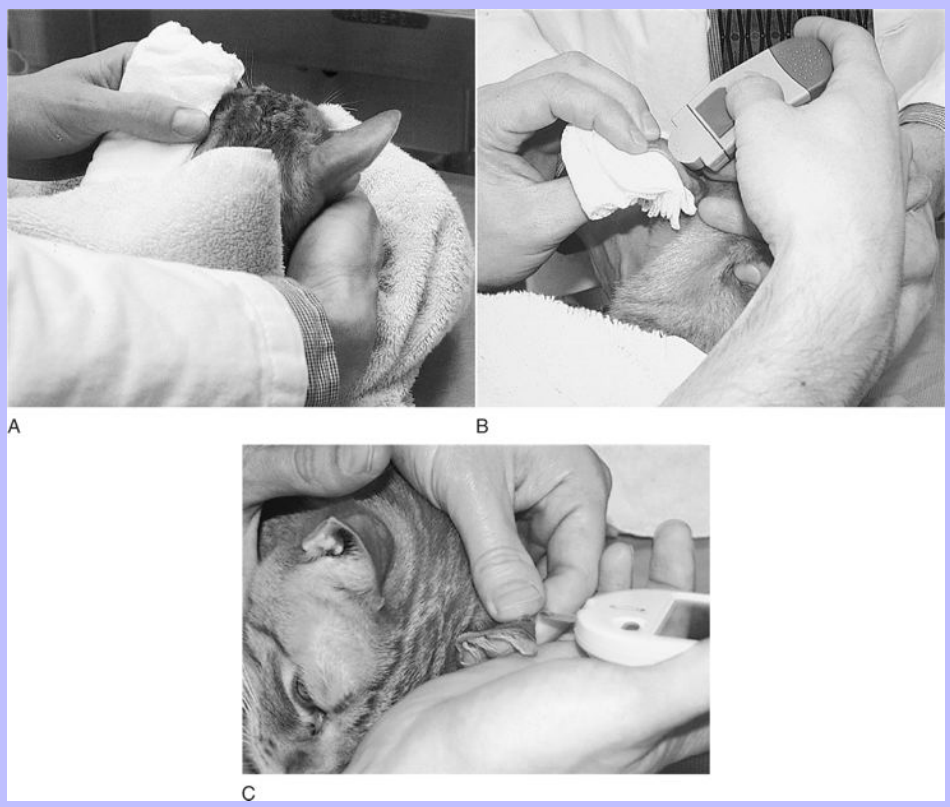
Figure 241-9 Marginal ear vein prick technique for measuring the blood glucose concentration. **A,** A hot washcloth is applied to the pinna for 2 to 3 minutes to increase circulation to the ear **B,** The marginal ear vein is identified on the periphery of the outer side of the pinna, and a thin coating of petrolatum jelly is applied to a small spot over the vein; the spot is then pricked with the lancet device supplied with the portable blood glucose meter. Gauze should be placed between the pinna and the digit holding the pinna to prevent pricking of the finger if the lancet's blade accidentally passes through the pinna. Petrolatum jelly is applied to help the blood form a ball on the pinna as it seeps from the lanced site. **C,** Digital pressure is applied in the area of the lanced skin to promote bleeding. The glucose test strip is touched to the drop of capillary blood that forms and is removed once enough blood has been drawn into the test strip to activate the meter. (From Nelson RW, Couto CG: Small Animal Internal Medicine, 3rd ed. St Louis, Mosby, 2003, p 759.)



For the marginal ear vein prick technique, the cat is allowed to remain in sternal recumbency with restraint only as needed to keep the animal stationary. The marginal ear vein is identified, and a damp cloth or gauze sponge previously warmed in water is applied to the vein for 15 to 30 seconds to increase perfusion. A thin film of petrolatum is placed over the sampling site to allow a drop of blood to form without dissipating into the fur, the pinna is immobilized with a digit, an automatic lancing device (e.g., Microlet automatic lancing device; Bayer Diagnostics) is placed over the vein, the ejected needle is used to nick the ear vein and, if necessary, the pinna in the region of the nick site is gently squeezed to promote formation of a drop of blood. A glucose test strip previously inserted into the blood glucose meter is applied to the drop of blood to measure the blood glucose concentration (see Figure 241-9). Digital pressure is then applied at the marginal ear vein prick site until bleeding stops. The skin puncture is rarely painful, and the puncture sites are barely visible even after numerous blood collections. Application of a thin film of petrolatum is critical for formation of the drop of blood. A small amount of padding, such as a cotton ball or gauze sponge, between the pinna and the digit used to stabilize the pinna helps prevent inadvertent pricking of the finger if the lancet goes through the pinna. Dehydration can interfere with the ability to obtain a drop of blood; a problem that occurs in some poorly controlled cats with marked hyperglycemia and severe polyuria and polydipsia. Administration of subcutaneous fluids may improve circulation to the ear. Only portable home blood glucose monitoring devices that allow the end of the glucose test strip to touch the drop of blood formed on the pinna while the strip is in the glucose monitoring device are used.

241.11.6 Evaluation of Aggressive, Excitable, or Stressed Diabetic Cats or Dogs

Hyperglycemia induced by stress, aggression, or excitement is the single biggest problem that affects the accuracy of the serial blood glucose curve. Stress can over-ride the glucose-lowering effect of the insulin injection, causing high blood glucose concentrations despite the presence of adequate amounts of insulin in the circulation, leading to a spiraling path of insulin overdosage, hypoglycemia, Somogyi phenomenon, and poor control of glycemia. The primary factors that induce stress hyperglycemia are hospitalization and multiple venipunctures. An alternative to hospital-generated blood glucose curves is to have the owner generate the blood glucose curve at home, as discussed above. Alternatively, serum fructosamine concentrations can be used to assess control of glycemia and the effectiveness of adjustments in insulin therapy in aggressive, excitable, or stressed diabetic cats or dogs. If a change in insulin therapy is deemed necessary, the clinician must make an educated guess as to where the problem lies (e.g., low insulin dose, short duration of insulin effect), adjust the insulin dose, and rely on the change in subsequent serum fructosamine measurements to assess the benefit of the change. The author measures serum fructosamine concentrations prior to and 2 to 3 weeks after changing insulin therapy. If the change has improved control of glycemia, the serum fructosamine concentration should decrease. If the serum fructosamine concentration is the same or has increased, the change was ineffective at improving glycemic control, another change in therapy can be tried, and the serum fructosamine measured again 2 to 3 weeks later.

241.12 COMPLICATIONS OF INSULIN THERAPY

241.12.1 Hypoglycemia

Hypoglycemia is a common complication of insulin therapy and is most apt to occur after sudden large increases in the insulin dose; with excessive overlap of insulin action in dogs and cats receiving insulin twice a day; during unusually strenuous exercise (dogs); after prolonged inappetence; after sudden decreases in insulin resistance; and in insulin-treated cats that have reverted to a non-insulin-dependent state. In these situations severe hypoglycemia may occur before glucose counter-regulation (i.e., secretion of glucagon, epinephrine,

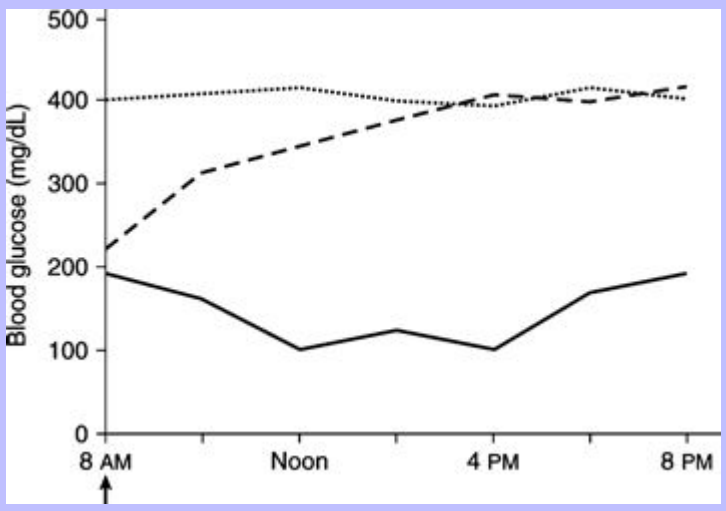
cortisol, and growth hormone) is able to compensate for and reverse the hypoglycemia. Signs of hypoglycemia include lethargy, weakness, head tilting, ataxia, seizures, and coma. The occurrence and severity of clinical signs depends on the rate of blood glucose decline and the severity of hypoglycemia. Symptomatic hypoglycemia is treated with glucose administered as food, sugar water, or intravenous dextrose. Whenever signs of hypoglycemia occur, the owner should be instructed to stop insulin therapy until glycosuria recurs. The adjustment in the subsequent insulin dosage is somewhat arbitrary; as a general rule, the insulin dosage initially should be reduced 25% to 50%, and subsequent adjustments in the dosage should be based on clinical response and blood glucose measurements. Failure of glycosuria to recur after a hypoglycemic episode suggests reversion to a non-insulin-dependent diabetic state or impaired glucose counter-regulation.

241.12.2 Stress Hyperglycemia

Transient hyperglycemia is a well-recognized problem in fractious or frightened cats. Hyperglycemia develops as a result of an increase in catecholamines and, in struggling cats, lactate concentrations and presumably increased hepatic glucose production.[82,83] Blood glucose concentrations typically exceed 200 mg/dL in these cats, and values in excess of 300 mg/dL are common. Diabetes mellitus may be inadvertently diagnosed in such cats if the diagnosis is based solely on the blood glucose concentration. Stress hyperglycemia can also significantly increase blood glucose concentrations in diabetic cats despite administration of insulin, an effect that seriously interferes with the clinician's ability to judge the effectiveness of exogenous insulin accurately. Induction of stress hyperglycemia is variable but usually starts during a venipuncture procedure and begins earlier and earlier on subsequent visits to the veterinarian, until eventually stress hyperglycemia is induced by hospitalization and ultimately by the car ride to the veterinary hospital. Blood glucose concentrations can remain greater than 400 mg/dL throughout the day, despite administration of insulin (Figure 241-10), when stress hyperglycemia develops prior to the first venipuncture of the day. Failure to recognize the effect of stress on blood glucose measurements may lead to the erroneous perception that the diabetic cat is poorly controlled, and insulin therapy is invariably adjusted, often by increasing the insulin dosage; repetition of this cycle eventually culminates in the Somogyi phenomenon, clinically apparent hypoglycemia, or referral for evaluation of insulin resistance.

Stress hyperglycemia should be suspected if the cat is visibly upset or aggressive or struggles during restraint and the venipuncture process. However, stress hyperglycemia can also be present in diabetic cats that are easily removed from the cage and do not resist the blood sampling procedure. These cats are scared, but rather than become aggressive, they remain crouched in the back of the cage, often have dilated pupils, and usually are flaccid when handled. Stress hyperglycemia should also be suspected when (1) a disparity exists between assessment of glycemic control based on the results of the history, physical examination, and stability of body weight and assessment of glycemic control based on the results of blood glucose measurements, or (2) the initial blood glucose concentration measured in the morning is in an acceptable range (i.e., 150 to 250 mg/dL), but subsequent blood glucose concentrations increase steadily throughout the day (see Figure 241-10). Once stress hyperglycemia develops, it is usually a perpetual problem, and blood glucose measurements can no longer be considered accurate.

Figure 241-10 Blood glucose curves in a 5.3 kg male cat receiving 2 U of recombinant human Ultralente insulin *(solid line-solid circles)* 2 weeks after initiation of insulin therapy; 2 U of recombinant human Ultralente insulin *(broken line)* 2 months later; and 6 U of recombinant human Ultralente insulin *(dotted line)* 4 months later. The insulin dosage had been gradually increased based on the blood glucose curve results. The owner reported minimal clinical signs regardless of the insulin dosage, the cat had maintained its body weight, and the blood glycosylated hemoglobin concentration was 2.2% at the 4-month recheck. The cat became progressively more fractious during each hospitalization, supporting a finding of stress-induced hyperglycemia as the reason for the discrepancy between the blood glucose values and other parameters used to evaluate glycemic control. ↑, Subcutaneous insulin injection and food. (From Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, 3rd ed. Philadelphia, WB Saunders, 2004, p 569.)



241.12.3 Recurrence or Persistence of Clinical Signs

Recurrence or persistence of clinical signs of diabetes is the most common “complication” of insulin therapy in diabetic dogs and cats. Recurrence or continuing clinical signs suggest insulin ineffectiveness, which is usually caused by problems with the biologic activity of the insulin or by owner technique in administering the insulin; problems with the insulin treatment regimen; or problems with responsiveness to insulin caused by

concurrent inflammatory, infectious, neoplastic, or hormonal disorders (i.e., insulin resistance). The most common problems with the insulin treatment regimen in the dog are insulin underdosage, the Somogyi phenomenon, short duration of effect of Lente insulin, and once a day insulin administration. The most common problems with the insulin treatment regimen in the cat are insulin overdosage, causing the Somogyi phenomenon; inadequate absorption of longer acting insulin preparations; short duration of effect of intermediate-acting insulin preparations; and once a day insulin administration.

Discrepancies in the parameters used to assess glycemic control, resulting in an erroneous belief that the diabetic dog or cat is poorly controlled, should also be considered. This situation usually is caused by erroneously high blood glucose concentrations that suggest insulin ineffectiveness; these high values may be stress induced and do not reflect the animal's responsiveness to insulin. In the evaluation of a diabetic dog or cat for suspected insulin ineffectiveness, it is important that all parameters used to assess glycemic control be critically analyzed, most notably the owner's perception of how the pet is doing in the home environment, physical examination findings, and changes in body weight. If the history, physical examination, change in body weight, and serum fructosamine concentration suggest poor control of the diabetic state, a diagnostic evaluation to identify the cause is warranted, beginning with evaluation of the owner's insulin administration technique and the biologic activity of the insulin preparation.

241.12.3.1 Insulin Underdosage

Control of glycemia can be established in most dogs and cats using less than 1 U of insulin per kilogram of body weight administered twice each day. An inadequate insulin dosage in conjunction with once a day insulin therapy is a common cause of persistence of clinical signs. In general, insulin underdosage should be considered if the insulin dosage is less than 1 U/kg and the dog or cat is receiving insulin twice a day. If insulin underdosage is suspected, the insulin dose should be gradually increased by 1 to 5 U per injection in dogs (depending on the size of the dog) and 0.5 to 1 U per injection in cats, per week. The effectiveness of the change in therapy should be evaluated by the owner's perception of clinical response and measurement of serum fructosamine or serial blood glucose concentrations. Other causes of insulin ineffectiveness (most notably the Somogyi phenomenon) should be considered if the insulin dosage exceeds 1 to 1.5 U/kg/injection, if insulin is being administered every 12 hours, and if control of glycemia remains poor.

241.12.3.2 Insulin Overdosage and Glucose Counter-Regulation (Somogyi Phenomenon)

The Somogyi phenomenon results from a normal physiologic response to impending hypoglycemia induced by excessive insulin. When the blood glucose concentration declines to less than 65 mg/dL or when the blood glucose concentration decreases rapidly regardless of the glucose nadir, direct hypoglycemia-induced stimulation of hepatic glycogenolysis and secretion of diabetogenic hormones, most notably epinephrine and glucagon, increase the blood glucose concentration, minimize signs of hypoglycemia, and cause marked hyperglycemia within 12 hours of glucose counter-regulation (Figure 241-11). The marked hyperglycemia that occurs after hypoglycemia is due in part to inability of the diabetic dog or cat to secrete sufficient endogenous insulin to dampen the rising blood glucose concentration. By the next morning, the blood glucose concentration can be extremely elevated (400 to 800 mg/dL), and the morning urine glucose concentration is consistently 1 to 2 g/dL as measured with urine glucose test strips. Unrecognized short duration of insulin effect combined with insulin dosage adjustments based on morning urine glucose concentrations is historically the most common cause of the Somogyi phenomenon in dogs.

Clinical signs of hypoglycemia are typically mild or are not recognized by the owner; clinical signs caused by hyperglycemia tend to dominate the clinical picture. The insulin dose that induces the Somogyi

phenomenon is variable and unpredictable. The Somogyi phenomenon is often suspected in poorly controlled diabetic dogs for which the insulin dosage is approaching 2.2 U/kg/injection but can also occur at insulin dosages less than 0.5 U/kg/injection. Toy and miniature breeds of dogs are especially susceptible to development of the Somogyi phenomenon with lower than expected doses of insulin. In cats, the Somogyi phenomenon can be induced with insulin doses of 2 to 3 U per injection; as a result, cats may receive 10 to 15 U of insulin per injection because veterinarians, interpreting the persistence of clinical signs and the high blood glucose and serum fructosamine concentrations as underdosage, increase the insulin dose, thereby perpetuating the problem.

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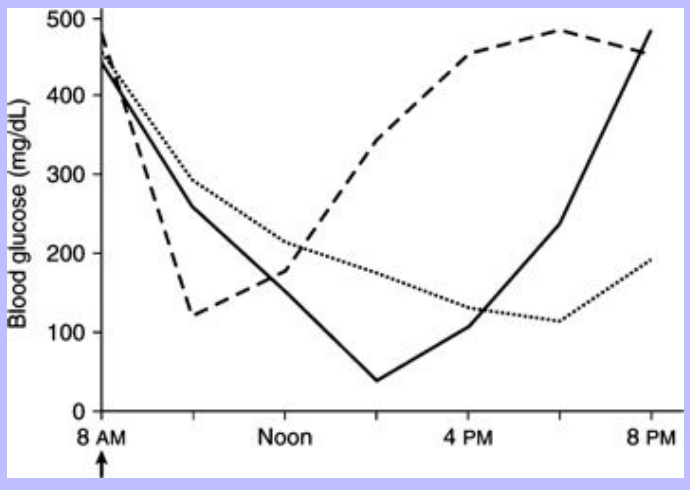
Figure 241-11 Blood glucose concentration curves from three dogs with poorly controlled diabetes that were treated with recombinant human Lente insulin twice a day, illustrating the typical blood glucose curves suggestive of the Somogyi phenomenon. In one dog *(solid line)*, the glucose nadir is less than 80 mg/dL and is followed by a rapid increase in the blood glucose concentration. In another dog *(dashed line)*, a rapid decrease in the blood glucose concentration occurs within 2 hours of insulin administration and is followed by a rapid increase in the blood glucose concentration; the rapid decrease in blood glucose stimulates glucose counter-regulation despite maintenance of the blood glucose nadir above 80 mg/dL. In the third dog *(dotted line)*, the blood glucose curve is not suggestive of the Somogyi phenomenon per se. However, the insulin injection causes the blood glucose level to decrease by approximately 300 mg/dL during the day, and the blood glucose concentration at the time of the evening insulin injection is considerably lower than the 8 AM blood glucose concentration. If a similar decrease in the blood glucose occurs with the evening insulin injection, hypoglycemia and the Somogyi phenomenon would occur at night and would explain the high blood glucose concentration in the morning and the poor control of the diabetic state. (From Nelson RW, Couto CG: Small Animal Internal Medicine, 3rd ed. St Louis, Mosby Inc, 2003, p 745.)



Diagnosis of the Somogyi phenomenon requires demonstration of hypoglycemia (a serum glucose concentration less than 80 mg/dL) followed by hyperglycemia (a serum glucose concentration greater than 300 mg/dL) after insulin administration. The Somogyi phenomenon should also be suspected when the blood glucose concentration decreases rapidly regardless of the glucose nadir (e.g., a drop from 400 to 100 mg/dL within 2 to 3 hours). If the duration of insulin effect is greater than 12 hours, hypoglycemia often occurs at night after the evening dose of insulin, and the serum glucose concentration is typically greater than 300 mg/dL the next morning (see Figure 241-11). Unfortunately, diagnosis of the Somogyi phenomenon can be elusive, partly because of the effects of the diabetogenic hormones on blood glucose concentrations after an episode of glucose counter-regulation. Secretion of diabetogenic hormones during the Somogyi phenomenon may induce insulin resistance, which can last 24 to 72 hours after the hypoglycemic episode. If a serial blood glucose curve is obtained on the day glucose counter-regulation occurs, hypoglycemia can be identified and the diagnosis established. However, if the serial blood glucose curve is obtained on a day when insulin resistance predominates, hypoglycemia will not be identified, and the insulin dose may be incorrectly increased in response to the high blood glucose values. A cyclic history of 1 or 2 days of good glycemic control followed by several days of poor control should raise suspicion for insulin resistance caused by glucose counter-regulation. Serum fructosamine concentrations are unpredictable but are usually increased (greater than 500 µmol/L); these results confirm poor glycemic control but do not identify the underlying cause.

Establishment of the diagnosis may require several days of hospitalization and serial blood glucose curves, an approach that eventually leads to problems with stress-induced hyperglycemia. An alternative approach, which the author prefers, is to arbitrarily reduce the insulin dosage 1 to 5 U and have the owner evaluate the dog's or cat's clinical response over the following 2 to 5 days. If clinical signs of diabetes worsen after a reduction in the insulin dosage, another cause of the insulin resistance should be pursued. However, if the owner reports no change or improvement in clinical signs, the clinician should continue to reduce the insulin dosage gradually. Alternatively, glycemic regulation of the diabetic dog or cat could be started over, using an insulin dosage of 0.25 U/kg (dogs) or 1 U/injection (cats) given twice daily.

241.12.3.3 Short Duration of Insulin Effect

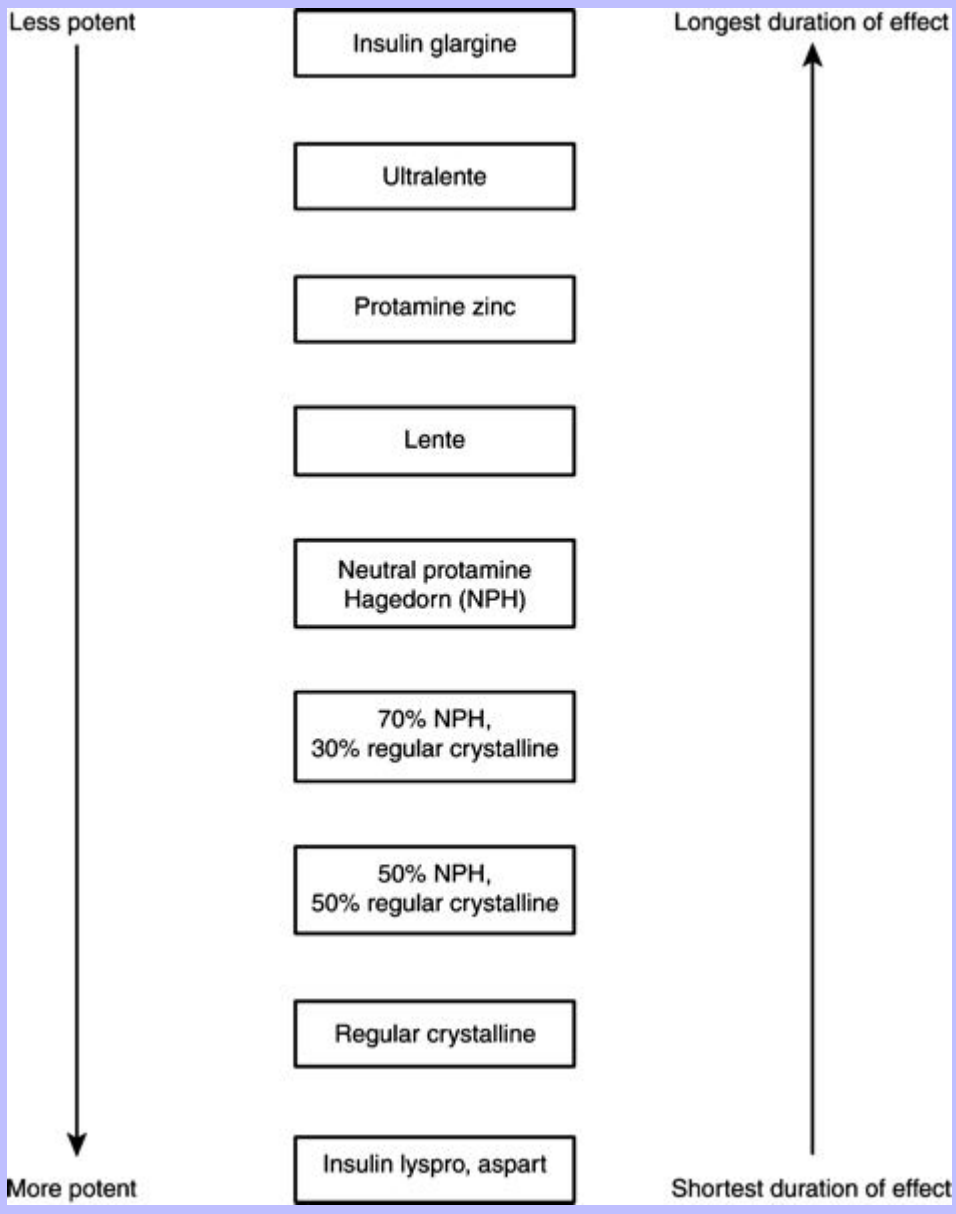
Short duration of insulin effect (i.e., less than 10 hours) is a common problem in diabetic dogs, and especially diabetic cats, despite twice a day insulin administration. In some diabetic cats, the duration of effect of NPH and Lente insulin is less than 8 hours. As a result, significant hyperglycemia (blood glucose concentration greater than 300 mg/dL) occurs for several hours each day, and the owners of these pets usually mention continuing problems with persistence of clinical signs or weight loss, or weakness caused by the development of peripheral neuropathy. Diabetic dogs with short duration of insulin have persistent morning glycosuria (greater than1 g/dL on urine glucose test strips). If the owners are adjusting the daily insulin dosage based on the morning urine glucose concentration, they usually induce the Somogyi phenomenon, because the insulin dosage is gradually increased in response to the persistent morning glycosuria. Serum fructosamine concentrations are variable but typically greater than 500 µmol/L. The diagnosis of short duration of insulin effect is made by demonstrating recurrence of hyperglycemia (blood glucose concentration greater than 250 mg/dL) within 6 to 10 hours of the insulin injection; also, the lowest blood glucose concentration is maintained above 80 mg/dL (see Figure 241-7). The clinician must evaluate multiple blood glucose concentrations obtained throughout the day to establish the diagnosis. The use of one or two afternoon blood glucose determinations consistently fails to identify the problem. Treatment involves changing to a longer acting insulin given twice a day (e.g., switching to PZI [cats], Ultralente, or

insulin glargine) or increasing the frequency of insulin administration (i.e., initiating three times a day therapy) if the duration of effect is less than 8 hours.

241.12.3.4 Prolonged Duration of Insulin Effect

In some diabetic dogs and cats, the duration of effect of Lente insulin or PZI is greater than 12 hours, and twice a day insulin administration creates problems with hypoglycemia and the Somogyi phenomenon. In these dogs and cats, the glucose nadir after morning administration of insulin typically occurs near the time of the evening insulin administration, and the morning blood glucose concentration is usually greater than 300 mg/dL (see Figure 241-11). Gradually decreasing blood glucose concentrations measured at the time of sequential insulin injections are another indication of prolonged duration of insulin effect. The effectiveness of insulin in lowering the blood glucose concentration varies from day to day, presumably because of varying concentrations of diabetogenic hormones, the secretion of which was induced by prior hypoglycemia. Serum fructosamine concentrations are variable but typically greater than 500 μmol/L. Effective treatment depends in part on the duration of effect of the insulin. A 24-hour blood glucose curve should be generated after administration of insulin once in the morning and with the dog or cat being fed at the usual times of the day. This allows the clinician to estimate the duration of effect of the insulin. If the duration of effect is less than 16 hours, a shorter acting insulin given twice a day or a lower dose of the same insulin given in the evening, compared with the morning insulin dose, can be tried. If the duration of effect is 16 hours or longer, switching to a longer acting insulin administered once a day or administering Lente insulin in the morning and regular crystalline insulin at bedtime (i.e., 16 to 18 hours after the morning insulin injection) can be tried. When different types of insulin are used in the same 24-hour period, the goal is to have the combined duration of effect of the insulins equal 24 hours. Differences in the potency of intermediate-and long-acting insulins versus regular crystalline insulin often necessitate the use of different dosages for the morning and evening insulin injections; regular crystalline insulin is more potent, and less is required to achieve the same glycemic effect, compared with Lente, NPH, PZI, and Ultralente insulins.

Figure 241-12 Categorization of types of commercial insulin based on potency and duration of effect. Note the inverse relationship between potency and duration of effect. (From Nelson RW, Couto CG: Small Animal Internal Medicine, 3rd ed. St Louis, Mosby, 2003, p 747.)



241.12.3.5 Inadequate or Impaired Insulin Absorption

Slow or inadequate absorption of subcutaneously deposited insulin is most commonly observed in diabetic cats receiving Ultralente insulin, a long-acting insulin that has a slow onset and prolonged duration of effect.[84,85] In approximately 25% of cats evaluated at our hospital, Ultralente insulin is absorbed from the subcutaneous site of deposition too slowly for it to be effective at maintaining acceptable glycemic control. In these cats, the blood glucose concentration may not decrease until 6 to 10 hours after the injection or, more commonly, it decreases minimally despite insulin doses of 8 to 12 U/cat given every 12 hours. As a consequence, the blood glucose concentration remains greater than 300 mg/dL for most of the day. We have had success in these cats by switching from Ultralente to Lente or PZI given twice a day.[85] When a change is made in the type of insulin, the insulin dosage is decreased (usually to amounts initially used to regulate the diabetic cat) to avoid hypoglycemia. The duration of effect of the insulin becomes shorter as the potency of the insulin increases, which may create problems with short duration of insulin effect (Figure 241-12). We have not yet identified similar problems with insulin glargine in diabetic cats, although our experience with this form of insulin is limited.

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Impaired absorption of insulin may also occur as a result of thickening of the skin and inflammation of the subcutaneous tissues caused by chronic injection of insulin in the same area of the body. Rotation of the injection site helps prevent this problem.

241.12.3.6 Circulating Insulin Antibodies

Insulin antibodies result from repeated injection of a foreign protein (i.e., insulin). The structure and amino acid sequence of the injected insulin relative to the native endogenous insulin influences the development of insulin antibodies. Conformational insulin epitopes are believed to be more important in the development of insulin antibodies than differences in the linear subunits of the insulin molecule per se.[86] The more divergent the insulin molecule from the species, the greater the likelihood that significant or worrisome levels of insulin antibodies will develop. Canine and recombinant human insulin are similar, and the development of insulin antibodies is uncommon in dogs treated with recombinant human insulin.[87] In contrast, canine and beef insulin differ, and serum insulin antibodies have been identified in 40% to 65% of dogs treated with beef/pork or beef insulin.[10,86,87] In the author's experience, the presence of serum insulin antibodies is often associated with erratic and poor control of glycemia, frequent adjustments in the insulin dose to improve control, and the occasional development of severe insulin resistance. Dogs treated with recombinant human insulin have more stable control of glycemia for extended periods compared with dogs treated with beef insulin. Although uncommon, insulin antibodies can develop in dogs treated with recombinant human insulin and should be suspected as the cause of poor glycemic control when another cause cannot be identified. Documentation of serum insulin antibodies should use assays that have been validated in diabetic dogs. A switch to porcine source insulin or to a purer form of insulin (i.e., regular crystalline insulin), or both, should be considered if insulin antibodies are identified in a poorly controlled diabetic dog.

Fortunately, insulin antibody formation is not common in diabetic cats treated with exogenous human insulin despite the differences between human and feline insulin.[88] Two studies identified an approximately equal frequency of positive serum insulin antibody titers in diabetic cats treated with beef insulin compared with diabetic cats treated with recombinant human insulin.[14,89] In the author's experience, insulin antibody

titers are weakly positive in most cats, the prevalence of persistent titers is low, and serum insulin antibodies do not appear to affect control of glycemia. Overt insulin resistance caused by insulin antibody formation occurs in fewer than 5% of cats treated with recombinant human insulin. Switching from recombinant human insulin to beef/pork source PZI may improve control of glycemia if insulin antibodies are the suspected cause of insulin ineffectiveness.

241.12.3.7 Concurrent Disorders that Can Cause Insulin Resistance

Insulin resistance is a condition in which a normal amount of insulin produces a subnormal biologic response. Insulin resistance may result from problems occurring before the interaction of insulin with its receptor, at the receptor, or at steps distal to the interaction of insulin and its receptor. Prereceptor problems reduce free metabolically active insulin concentrations; such problems include an increase in insulin degradation or in insulin-binding antibodies. Receptor problems include alterations in the insulin-receptor binding affinity and concentration and the development of insulin-receptor antibodies. Postreceptor problems are difficult to differentiate clinically from receptor problems, and the two types often coexist. In dogs and cats, receptor and postreceptor abnormalities are usually attributable to obesity or to a disorder that causes excessive secretion of an insulin-antagonistic hormone (e.g., cortisol, glucagon, epinephrine, growth hormone, progesterone, or thyroid hormone).

No insulin dose clearly defines insulin resistance. For most diabetic dogs and cats, control of glycemia can usually be attained using 1 U or less of intermediate-or long-acting insulin per kilogram of body weight given twice daily. Insulin resistance should be suspected if control of glycemia is poor despite an insulin dosage in excess of 1.5 U/kg, when excessive amounts of insulin (i.e., greater than 1.5 U/kg) are necessary to maintain the blood glucose concentration below 300 mg/dL, and when control of glycemia is erratic and insulin requirements must be constantly changed in an attempt to maintain control of glycemia. Failure of the blood glucose concentration to decrease below 300 mg/dL during a serial blood glucose curve is suggestive of but not definitive for insulin resistance. An insulin resistance–type blood glucose curve can also result from stress-induced hyperglycemia, the Somogyi phenomenon, and other problems with insulin therapy (Box 241-6), and a decrease in the blood glucose concentration below 300 mg/dL can occur with disorders that cause relatively mild insulin resistance. Serum fructosamine concentrations are typically greater than 500 µmol/L in animals with insulin resistance and can exceed 700 µmol/L if resistance is severe.

In general, any concurrent inflammatory, infectious, hormonal, or neoplastic disorder can cause insulin resistance and can interfere with the effectiveness of insulin therapy (see Box 241-6). In the author's experience, the conditions or disorders that most commonly cause insulin resistance in dogs are treatment with diabetogenic drugs (glucocorticoids), severe obesity, hyperadrenocorticism, diestrus, chronic pancreatitis, renal insufficiency, oral and urinary tract infections, hyperlipidemia, and the development of insulin antibodies in dogs treated with beef insulin. The disorders that most commonly cause insulin resistance in cats are severe obesity, chronic pancreatitis, renal insufficiency, hyperthyroidism, oral infections, acromegaly, and hyperadrenocorticism. Obtaining a complete history and performing a thorough physical examination constitute the most important step in identifying these concurrent disorders. Abnormalities identified on the physical examination may suggest a concurrent insulin-antagonistic disorder or an infectious process, which gives the clinician direction in the diagnostic evaluation of the animal. If the history and physical examination findings are unremarkable, other diagnostic tests should be pursued to further screen for concurrent illness, including a complete blood count, serum biochemical analysis, serum thyroxine concentration (cat), serum progesterone concentration (intact female dog),

abdominal ultrasound scan, and urinalysis with bacterial culture. The use of additional tests depends on the results of the initial screening tests (Box 241-7).

241.12 CHRONIC COMPLICATIONS OF DIABETES MELLITUS

Complications resulting from diabetes or its treatment are common in diabetic dogs and cats and include blindness and anterior uveitis resulting from cataract formation (dogs), peripheral neuropathy of the hind limbs, causing weakness, inability to jump, a plantigrade stance and ataxia (cats), chronic pancreatitis, recurring infections, hypoglycemia and ketoacidosis (see Box 241-5). Most of the devastating chronic complications of human diabetes (e.g., nephropathy, vasculopathy, and coronary artery disease) require 10 to 20 years or longer to develop and therefore are uncommon in diabetic dogs and cats. Diabetes mellitus is a disease of older dogs and cats, and most do not live beyond 5 years from the time of diagnosis.[12] In the author's experience, owners are usually willing to undertake the care of a diabetic pet once the fears related to chronic complications seen in human diabetics are alleviated.

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241.13.1 Box • 241-6 Recognized Causes of Insulin Ineffectiveness or Insulin Resistance in Diabetic Dogs and Cats

241.13.1.1 Cause: Insulin Therapy

Inactive insulin

Diluted insulin

Improper administration technique

Inadequate dosage

Somogyi effect

Inadequate frequency of insulin administration

Impaired insulin absorption (especially with Ultralente insulin)

Anti-insulin antibody excess

241.13.1.2 Cause: Concurrent Disorder

Diabetogenic drugs

- glucocorticoids
- megestral acetate
- progestagens

Hyperadrenocorticism

Diestrus (bitch)

Acromegaly (cat)

Infection (especially of the oral cavity or urinary tract)

Hypothyroidism (dog)

Hyperthyroidism (cat)

Renal insufficiency

Liver insufficiency

Cardiac insufficiency

Glucagonoma (dog)

Pheochromocytoma

Chronic inflammation (especially pancreatitis)

Pancreatic exocrine insufficiency

Severe obesity

Hyperlipidemia

Neoplasia

241.13.2 Cataracts

Cataract formation is the most common chronic complication of diabetes mellitus in the dog. A retrospective cohort study on the development of cataracts in 132 diabetic dogs referred to a university hospital found cataract formation in 14% of dogs at the time diabetes was diagnosed and a time interval of 25%, 50%, 75%, and 80% of the study population to develop cataracts of 60, 170, 370, and 470 days, respectively.[90] The pathogenesis of diabetic cataract formation is thought to stem from altered osmotic relationships in the lens induced by the accumulation of sorbitol and fructose; these sugars are potent hydrophilic agents that cause an influx of water into the lens, leading to swelling and rupture of the lens fibers and the development of cataracts.[91] Cataract formation is an irreversible process once it begins, and it can occur quite rapidly. Diabetic dogs that are poorly controlled and that have problems with wide fluctuations in the blood glucose concentration seem especially at risk for rapid development of cataracts. Blindness may be eliminated by removal of the abnormal lens. Vision is restored in approximately 75% to 80% of diabetic dogs that undergo cataract removal. Factors that affect the success of surgery include the degree of glycemic control and whether retinal disease or lens-induced uveitis is present.

241.13.2.1

Box • 241-7 Diagnostic Tests to Consider in the Evaluation of Insulin Resistance in Diabetic Dogs and Cats

- Complete blood count (CBC), serum biochemistry panel, urinalysis
- Bacterial culture of the urine
- Serum lipase and amylase activities (pancreatitis)
- Serum trypsin-like immunoreactivity, pancreatic lipase immunoreactivity (exocrine pancreatic insufficiency, pancreatitis)
- Adrenocortical function tests
  - Adrenocorticotropic hormone (ACTH) stimulation test (spontaneous or iatrogenic hyperadrenocorticism)
  - Low-dose dexamethasone suppression test (spontaneous hyperadrenocorticism)
- Thyroid function tests
  - Baseline serum total and free thyroxine (hypothyroidism or hyperthyroidism)
  - Endogenous thyroid-stimulating hormone (TSH) (hypothyroidism)
  - TSH stimulation test (hypothyroidism)
  - Thyroid-releasing hormone stimulation test (hypothyroidism or hyperthyroidism)
  - Triiodothyronine suppression test (hyperthyroidism)
- Serum progesterone concentration (diestrus in intact female dog)
- Plasma growth hormone or serum insulin–like growth factor I concentration (acromegaly)
- Serum insulin concentration 24 hours after discontinuation of insulin therapy (insulin antibodies)

Serum triglyceride concentration (hyperlipidemia)

Abdominal ultrasonography (adrenomegaly, adrenal mass, pancreatitis, pancreatic mass)

Thoracic radiography (cardiomegaly, neoplasia)

Computed tomography or magnetic resonance imaging (pituitary mass)

241.13.3 Lens-Induced Uveitis

During embryogenesis, the lens is formed within its own capsule, and its structural proteins are not exposed to the immune system; consequently, immune tolerance to the crystalline proteins does not develop. During cataract formation and resorption, lens proteins are exposed to local ocular immune systems, resulting in inflammation and uveitis. Uveitis that occurs in association with a resorbing, hypermature cataract may decrease the success of cataract surgery and must be controlled before surgery. Treatment of lens-induced uveitis focuses on reduction of the inflammation and prevention of further intraocular damage. Topical ophthalmic corticosteroids are the drugs most commonly used to control ocular inflammation. However, systemic absorption of topically applied corticosteroids may cause insulin antagonism and thus interfere with glycemic control of the diabetic state, especially in toy and miniature breeds. An alternative is topical administration of nonsteroidal anti-inflammatory agents (e.g., 0.03% flurbiprofen) or cyclosporine.

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241.13.4 Diabetic Neuropathy

Diabetic neuropathy is the most common chronic complication of diabetes in cats, with a prevalence of approximately 10% of cats with IDDM, but it is infrequently recognized in the diabetic dog. The cause of diabetic neuropathy is not known, although an alteration in polyol pathway activity may play a role in cats. The polyol pathway consists of two consecutive reactions: glucose first is reduced to sorbitol by aldose reductase and sorbitol subsequently is oxidized to fructose by sorbitol dehydrogenase. Aldose reductase is present in the Schwann cell, and accumulation of polyols (e.g., sorbitol, fructose) has been implicated in the pathogenesis of diabetic neuropathy. In a recent study, the severity of neurologic clinical signs and electrophysiologic abnormalities was best related to the blood glucose concentration; nerve water content was significantly elevated in diabetic versus healthy cats, nerve glucose and fructose were increased eightfold and twelvefold in diabetic versus healthy cats, respectively, and nerve myoinositol content in diabetic cats was reduced to 80% of the levels in healthy cats.[92] Myoinositol is a key element in many nerve cellular functions, and myoinositol depletion correlates with reduced nerve conduction velocity in diabetic nerves.[93,94] The role, if any, of other metabolic derangements, such as glycosylation of myelin, in the pathogenesis of diabetic neuropathy in cats remains to be determined.

Clinical signs of diabetic neuropathy include hindlimb weakness; impaired ability to jump; a plantigrade posture, with the cat's hocks touching the ground when it walks (see Figure 241-5); muscle atrophy, especially of the distal pelvic limb; depressed limb reflexes; deficits in postural reaction testing; and irritability on manipulation of the hindlimbs and feet.[92] Clinical signs may progress to include the thoracic limbs. Abnormalities on electrophysiologic testing, which are consistent with demyelination at all levels of the motor

and sensory peripheral nerves, include decreased motor and sensory nerve conduction velocities in the pelvic and thoracic limbs and decreased muscle action potential amplitudes.[92,95] Electromyographic abnormalities are usually absent but when identified are consistent with denervation. The most striking abnormality detected on histologic examination of nerve biopsies from affected cats is Schwann cell injury; axonal degeneration is identified in severely affected cats.

Currently, there is no specific therapy for diabetic neuropathy in cats. Aggressive glucoregulation with insulin may improve nerve conduction and reverse the posterior weakness and plantigrade posture in some diabetic cats (see Figure 241-5). However, the response to therapy is variable, and the risks of hypoglycemia increase with aggressive insulin treatment. Generally, the longer the neuropathy has been present and the more severe it is, the less likely improvement in glycemic control is to reverse the clinical signs.

241.13.5 Diabetic Nephropathy

Renal insufficiency and diabetes mellitus are common geriatric diseases that often occur concurrently, especially in older cats. Abnormal renal function may result from the deleterious effects of the diabetic state (i.e., diabetic nephropathy), or it may be an independent problem that develops in conjunction with diabetes in the geriatric pet. Histopathologic findings in diabetic nephropathy depend on the duration of the disease prior to evaluation of the dog or cat and on the degree of glycemic control; these findings include membranous glomerulonephropathy with fusion of the foot processes, glomerular and tubular basement membrane thickening, an increase in the mesangial matrix material, the presence of subendothelial deposits, glomerular fibrosis, and glomerulosclerosis. The pathogenic mechanism of diabetic nephropathy is unknown but is undoubtedly multifactorial. Clinical signs depend on the severity of glomerulosclerosis and the functional ability of the kidney to excrete metabolic wastes. Initially, diabetic nephropathy is manifested as severe proteinuria, primarily albuminuria, as a result of the glomerular dysfunction. As the glomerular changes progress, glomerular filtration becomes progressively impaired, resulting in the development of azotemia and eventually uremia. With severe fibrosis of the glomeruli, oliguric and then anuric renal failure develops. No specific treatment is available for diabetic nephropathy, apart from meticulous metabolic control of the diabetic state, conservative medical management of the renal insufficiency, and control of systemic hypertension.

241.14 PROGNOSIS

The prognosis for dogs and cats diagnosed with diabetes mellitus depends in part on the owners' commitment to treating the disorder, the ease of glycemic regulation, the presence and reversibility of concurrent disorders, and the avoidance of chronic complications associated with the diabetic state. The mean survival time for diabetic dogs and cats is approximately 3 years from the time of diagnosis, although survival time is somewhat skewed because dogs and cats are usually 7 years or older at the time of diagnosis, and the mortality rate during the first 6 months is relatively high because of concurrent life-threatening or uncontrollable disease (e.g., ketoacidosis, acute pancreatitis, renal failure).[12] Diabetic dogs and cats that survive the first 6 months can easily maintain a good quality of life for longer than 5 years with proper care by the owners, timely evaluations by the veterinarian, and good client-veterinarian communication.

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242 CHAPTER • 242 Hyperadrenocorticism

Claudia E. Reusch

242.1 HYPERADRENOCORTICISM IN DOGS

In 1932 Dr. Harvey Cushing, a neurosurgeon, documented the presence of small, basophilic pituitary adenomas in human patients with clinical signs of adrenocortical hyperfunction. Years later, it was found that these tumors produced excess adrenocorticotropic hormone (ACTH), with resultant bilateral adrenocortical hyperplasia. In humans as well as in dogs and cats, pituitary ACTH hypersecretion (Cushing's disease) is now recognized as the most common cause of naturally occurring hyperadrenocorticism (Cushing's syndrome). This condition must be distinguished from other natural causes, such as non-ACTH-dependent adrenocortical tumors and ACTH-secreting nonpituitary tumors (ectopic ACTH syndrome). The latter disorder has not been described in dogs and cats. It is also necessary to differentiate naturally occurring hyperadrenocorticism from iatrogenic causes, which result from chronic glucocorticoid therapy and probably constitute the majority of cases of hyperadrenocorticism.

242.2 HYPOTHALAMUS–ADENOHYPOPHYSIS–ADRENAL GLAND AXIS

Neurotransmitters from the central nervous system (CNS) modulate the release of hypophysiotropic hormones, such as corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), from neurons in the hypothalamus. Both CRH and AVP are considered the predominant stimulating neurohormones for ACTH secretion *in vivo*.[1] CRH consists of 41 aminoacids, and its structure is identical in humans, dogs, rats, and horses.[2] CRH and AVP are released into the hypothalamohypophyseal portal blood system and travel to the corticotropic cells in the anterior pituitary, where they stimulate the release of ACTH. ACTH is a single-chain polypeptide comprising 39 amino acids. The amino acid sequence of ACTH is highly conserved. In all mammals studied thus far, the first 24 amino acids are identical. Canine ACTH differs from human ACTH by only one amino acid residue, at position 37. It is synthesized from a well-characterized precursor molecule, pro-opiomelanocortin (POMC), which also gives rise to a variety of other peptides coreleased with ACTH.

In contrast to humans, the adenohypophysis of dogs and cats has a pars distalis and a discrete pars intermedia (Figure 242-1). The processing of POMC and the regulation of ACTH secretion differ between these two parts. The pars distalis produces mainly ACTH and beta lipotropin (beta-LPH). The pars intermedia contains two cell types and processes alpha melanocyte-stimulating hormone (alpha-MSH) and corticotropin-like intermediate lobe peptide (CLIP) in the predominant A cells. The B cells of the pars intermedia resemble the corticotrophs of the pars distalis, and cleavage of POMC is mainly into ACTH and beta-LPH (Figure 242-2). In the pars intermedia, the release of POMC-derived peptides is largely regulated by tonic dopaminergic inhibition.[3] It has long been assumed that the pars intermedia does not actively secrete ACTH into the circulation. However, the results of a recent study in dogs suggest that the pars intermedia may contribute to circulating ACTH concentrations.[4] The physiologic function of peptides processed from POMC is an exciting area of neuroendocrine research that requires further investigation.

In the adrenal cortex, ACTH stimulates the synthesis and secretion of several hormones, specifically glucocorticoids and androgenic steroids in the zona fasciculata and zona reticularis and mineralocorticoids in the zona glomerulosa. The effect of ACTH is rapid; within minutes, plasma levels of these hormones rise. Because aldosterone is mainly regulated by the renin-angiotensin system and plasma potassium concentrations and

because the amount of androgens produced is small, ACTH exerts its most important effect on glucocorticoids. The synthesis and release of glucocorticoids are almost exclusively controlled by ACTH. Cortisol is the major glucocorticoid, and this is the term used to describe glucocorticoids in the following section. Cortisol in turn inhibits ACTH release.

In summary, cortisol secretion is closely regulated by ACTH, and plasma levels of cortisol parallel those of ACTH.

Four mechanisms effect neuroendocrine control:

- Secretion of ACTH in an ultradian pulsatile fashion, which is influenced by the hypothalamus. The number of pulses ranges from six to 12 per 24-hour period.
- Stress responsiveness of the hypothalamus–adenohypophysis–adrenal gland axis. ACTH and cortisol are secreted within minutes after the onset of stress. Stress originates in the CNS and causes increased release of CRH and AVP.
- Feedback inhibition of ACTH by cortisol. Cortisol acts at multiple target sites, two of which have been identified: neurons in the hypothalamus that produce CRH and AVP, and corticotropic cells in the anterior pituitary. Two kinds of feedback are discussed: *fast feedback,* which occurs rapidly and inhibition of which affects stimulated but not basal secretion, and *slow feedback,* which depends on steroid levels and leads to a decrease in ACTH synthesis. Inhibition of slow feedback affects both basal and stimulated ACTH release.
- Release of interleukin-1, interleukin-6, tissue necrosis factor, and other cytokines associated with infection, which activates the hypothalamus–pituitary–adrenal gland axis.

242.3 ETIOPATHOLOGY

242.3.1 Cushing's Disease (Pituitary-Dependent Hyperadrenocorticism)

Approximately 80% to 85% of dogs with naturally occurring hyperadrenocorticism suffer from pituitary-dependent hyperadrenocorticism (PDH), which is characterized by overproduction of ACTH (Figure 242-3). In many cases the pituitary lesions are small adenomas, although in some dogs large tumors, usually adenomas, are found. Pituitary carcinomas, which appear to be rare in dogs, may invade surrounding structures.[5] In a small percentage of dogs with ACTH-dependent disease, corticotropic cell hyperplasia occurs rather than a tumor. Whether hyperplastic lesions occur exclusively or small pituitary tumors are missed during histopathologic examination is a matter of debate.

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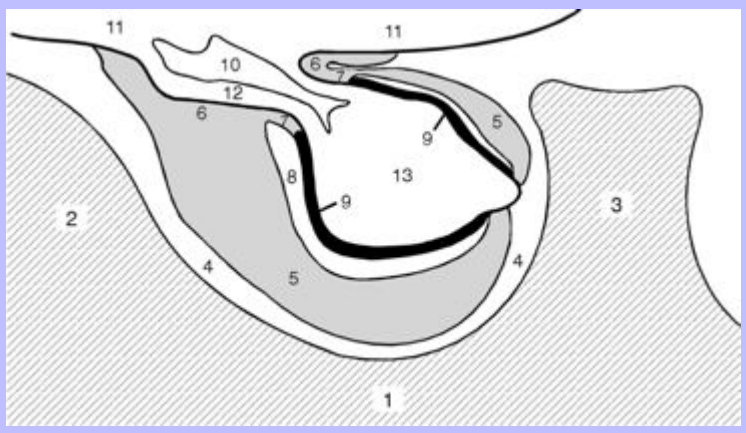
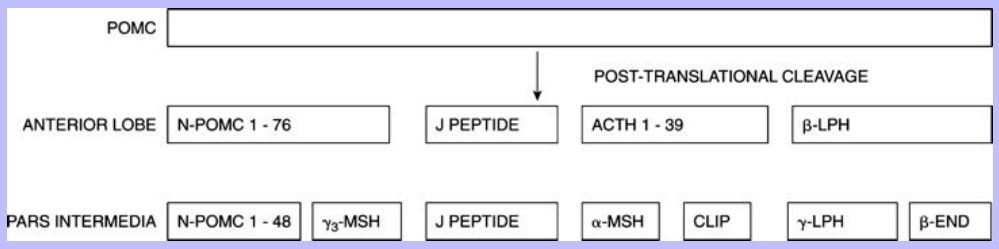
Figure 242-1 Schematic illustration of a median sagittal section through the canine pituitary gland. (Left is rostral, right is caudal.) *1,* Sphenoid bone; *2,* tuberculum sellae; *3,* dorsum sellae; *4,* pituitary fossa; *5,* pars distalis adenohypophysis; *6,* pars infundibularis adenohypophysis; *7,* transitional zone; *8,* hypophyseal cleft or cavity; *9,* pars intermedia adenohypophysis; *10,* third ventricle; *11,* hypothalamus (median eminence); *12,* pars proximalis neurohypophysis; *13,* pars distalis neurohypophysis. (From Meij B: Hypophysectomy as a treatment for canine and feline Cushing's disease. Vet Clin North Am Small Anim Pract 31:1021, 2001.)



In about 70% of dogs with PDH the tumors originate in the pars distalis, whereas in about 30% they arise either from the A cells or the B cells of the pars intermedia.[6]

Two hypotheses have been proposed for the pathogenesis of PDH. According to one hypothesis, the disease results from a defect at the hypothalamic level. Secretion of ACTH from the pars intermedia is controlled by tonic dopaminergic inhibition, and some evidence indicates that dopamine affects the pars distalis of the adenohypophysis. A decrease in the central dopamine concentration has been proposed to result in dysregulation of the hypothalamic–adenohypophysis–adrenal gland axis and, in turn, overproduction of ACTH and possible tumor formation.[7] According to the other hypothesis, PDH is caused by a primary pituitary defect, and increasing evidence substantiates this, such as the monoclonal character of corticotropic adenomas,[8] the occurrence of secondary adrenal insufficiency after selective resection of tumors,[9] and the low CRH concentration in the cerebrospinal fluid of dogs with PDH.[10] The current view is that corticotropic adenomas are the result of a complex, multistage process of tumorigenesis. The earliest stage may be an inherited aberration that plays an initiating or promoting role. A report of the occurrence of PDH in a family of seven Dandie Dinmont terriers supports the role of genetic factors.[11] Clonal expansion of the genomically altered cell may be caused by an intrinsic mutation that results in activation of cell replication; by extrinsic factors, such as intrapituitary growth factors; or by both these mechanisms.[12]

Figure 242-2 Processing of pro-opiomelanocortin (POMC) in the anterior lobe and in the pars intermedia of the pituitary gland. *J Peptide,* Joining peptide; *LPH,* lipoprotein; *MSH,* melanocyte-stimulating hormone; *CLIP,* corticotropin-like intermediate lobe peptide; *END,* endorphin.



Some reports have addressed pituitary tumor size in dogs. The most extensive tumor proliferation was encountered in dogs with a strong resistance to dexamethasone, therefore it was postulated that a pituitary tumor's growth potential depends on the degree of insensitivity to glucocorticoid feedback.[13] Whether large tumors are more likely to arise from the pars intermedia than the pars distalis has long been the subject of debate. Because the pars intermedia lacks glucocorticoid receptors and extensive tumors appear to be resistant to glucocorticoids, tumors originating in the pars intermedia may grow larger than those in the pars distalis. However, it has also been stated that pituitary tumors do not always maintain the characteristics of the cells of origin and that PDH cannot be simply divided into either pars distalis or pars intermedia type by plasma alpha-MSH levels or dexamethasone resistance.[14]

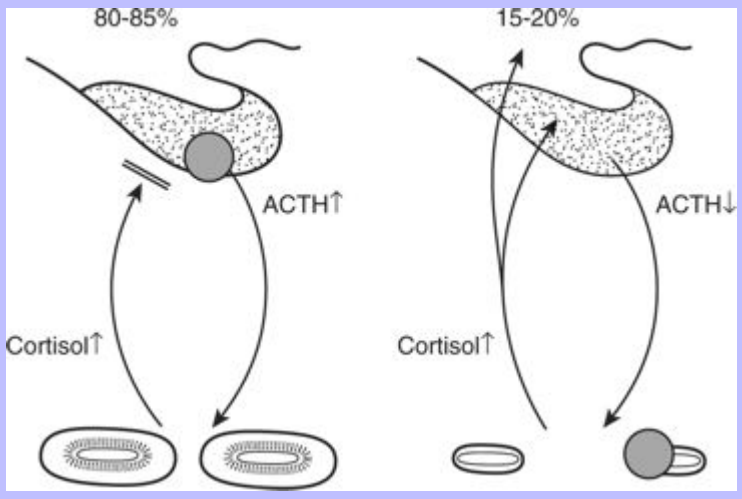
Another characteristic of corticotropic adenomas is their ability not only to produce ACTH but also to release excessive amounts of ACTH precursors. In dogs with PDH, the ACTH precursor concentration is significantly higher in animals with large pituitary tumors compared with those with small tumors.[15] It is important to be aware of this phenomenon as a clinician. ACTH precursors have low biologic activity, therefore dogs with (large) pituitary tumors may have only subtle or no clinical signs of hyperadrenocorticism.

PDH is also associated with alterations in the release of several pituitary hormones. It generally is agreed that glucocorticoids inhibit the release of AVP in dogs. A recent study found that, compared with controls, dogs with PDH had higher basal plasma levels of prolactin, lower levels of growth hormone (GH), and similar levels of luteinizing hormone (LH) and thyroid-stimulating hormone (TSH).[16]

242.3.1.1 Functional Adrenocortical Tumor

Among dogs and cats with naturally occurring hyperadrenocorticism, 15% to 20% have a functional adrenocortical tumor (FAT), which secretes cortisol independent of pituitary control. Cortisol in turn suppresses CRH in the hypothalamus and ACTH in the pituitary gland. The result of this chronic negative feedback is cortical atrophy of the uninvolved adrenal gland and atrophy of all normal cells in the involved adrenal gland (see Figure 242-3). 1593 1594

Figure 242-3 Simplified schematic of the pituitary-adrenal axis in dogs with pituitary-dependent hyperadrenocorticism *(left)* and with functional adrenal tumor *(right)*.



For many years it was assumed that adrenocortical tumors produced large amounts of hormone, more in fact than hyperplastic adrenal glands of dogs with PDH. However, the opposite appears to be true; in many dogs with an FAT, the hormone excess and subsequent clinical signs are only moderate. Therefore, even though adrenocortical tumors usually greatly exceed the size of the normal adrenal gland, the tumor tissue is only moderately active, and the neoplastic transformation results in a decreased degree of function per unit of volume.[17] It is also possible that the cortisol synthesis pathway in dogs with an FAT is not intact. In humans, adrenal carcinomas tend to produce large amounts of intermediates in the biosynthesis of cortisol, and a partial or complete deficiency of 11-beta-hydroxylase is common. The existence of a similar phenomenon in dogs has recently been suggested.[18]

In dogs with an FAT, the right and left adrenal glands are affected with equal frequency. Usually a unilateral, solitary adrenal mass is seen, although bilateral tumors are found in approximately 10% of cases.

Information in the literature on the incidence of adenomas and carcinomas varies, but the two tumor types probably occur with equal frequency. As with other endocrine tumors, it is difficult to distinguish between adrenal adenomas and adrenal carcinomas. Differentiation of adrenocortical tumors and pheochromocytoma may require a pathologist with experience in special immunohistochemical staining techniques. In some cases adrenocortical tumors that initially had been diagnosed as benign turned out to be malignant when metastases were discovered later.

Histologic differentiation between benign and malignant tumors is straightforward only when capsular or vascular invasion by the tumor has occurred. Otherwise, it is difficult to establish the biologic nature of the tumor, and distant metastasis may not occur.[19] Interestingly, it is not uncommon for adrenocortical tumors to be associated with pheochromocytoma.[17]

242.3.1.2 Simultaneous Occurrence of Pituitary and Adrenocortical Tumors

The co-existence of pituitary and adrenal tumors was recently described in 17 dogs with hyperadrenocorticism. Necropsy or surgery demonstrated unilateral adrenocortical adenoma with contralateral adrenal hyperplasia in 10 dogs; bilateral adrenal cortical adenoma in four dogs; and adrenal carcinoma with contralateral hyperplasia in three dogs. Pituitary lesions included a chromophobe microadenoma in 12 dogs; pituitary macroadenoma in four dogs; and pituitary carcinoma in one dog.[20] Two years later the study was revised, and it was speculated that some of these dogs actually may have had a condition similar to macronodular adrenal hyperplasia in humans.[21]

242.3.1.3 Adrenocortical Nodular Hyperplasia

In humans, bilateral nodular hyperplasia with hyperadrenocorticism has been identified as a sequel to several pathophysiologic conditions. Long-standing ACTH hypersecretion may result in nodular enlargement of the adrenal gland. Over time, these nodules may become autonomous or semiautonomous. Another type of nodular hyperplasia has been called *massive macronodular adrenal hyperplasia*. This type is ACTH independent and is characterized by bilateral large nodules that secrete excessive amounts of cortisol. This condition suggests that non-ACTH factors may induce cortisol secretion.[22] Recent studies indicate that receptors for various hormones may be abnormally expressed by the adrenal glands; for example, ectopic expression of the gastric inhibitory polypeptide receptor has been convincingly demonstrated.[23] This polypeptide stimulates the release of cortisol *in vivo* and *in vitro*. It is assumed that adrenocortical nodular hyperplasia also exists in dogs, although studies currently are lacking.

242.3.1.4 Clinical Findings

Hyperadrenocorticism, or Cushing's syndrome, is one of the most common endocrinopathies in dogs. The clinical signs and laboratory results in dogs with hyperadrenocorticism are largely attributable to chronic glucocorticoid excess and, to a much lesser extent, overproduction of adrenal androgens. In a few cases, symptoms are due to tumor growth, local invasion of tumors, or metastases.

242.3.1.5 Signalment

Dogs with naturally occurring hyperadrenocorticism are usually 6 years of age or older (the average age is 9 to 11 years). Of 100 dogs with Cushing's syndrome diagnosed in our clinic, only five were younger than 6 years, and all had PDH: two of the dogs were 5 years old (a German shepherd and a dachshund), one was 4 years old (a cocker spaniel), and two were 2 years old (a weimaraner and a puli). Dogs with an FAT tend to be older than dogs with PDH.[24]

A number of different breeds and mixed breeds with hyperadrenocorticism have been reported. The most commonly represented breeds are poodles, dachshunds, beagles, boxers, and various terrier breeds. Approximately 75% of dogs with PDH weigh less than 20 kg.[24] FAT most often occurs in poodles, German shepherds, dachshunds, Labrador retrievers, and various terrier breeds. Approximately 45% to 50% of dogs with an FAT weigh more than 20 kg.[24] Between 55% and 60% of dogs with hyperadrenocorticism are female.[24]

242.3.1.6 History and Physical Examination

Dogs with hyperadrenocorticism may have a number of dramatic clinical signs, although affected animals are usually in stable condition. Severe apathy, vomiting, diarrhea, muscle pain, and anorexia are not characteristic symptoms of Cushing's syndrome, therefore these signs indicate another disease or complications of hyperadrenocorticism (see below).

The clinical signs of hyperadrenocorticism are the sequelae to the combined gluconeogenic, immune-suppressive, anti-inflammatory, protein catabolic, and lipolytic effects of glucocorticoids exerted on various organ systems. PDH cannot be distinguished from FAT on the basis of the type or duration of symptoms. 1594 1595

Clinical signs, which may vary from mild to severe, depend on the duration of the disease and the degree of cortisol excess. Usually the course of hyperadrenocorticism is insidious and slowly progressive. Rarely, clinical signs are intermittent, with periods of remission and relapse in dogs with mild disease.[25] Fewer dogs are presented with severe clinical signs today than in years past, probably because of today's owners' heightened awareness of their pets' problems. Consequently, diagnosis of the disease may be more difficult in dogs with mild symptoms.

Typical symptoms include polydipsia, polyuria, polyphagia, truncal obesity or abdominal enlargement (due to hepatomegaly, muscle wasting and/or intra-abdominal fat accumulation), thin haircoat, failure to regrow shaved hair, alopecia (may or may not be bilaterally symmetric, usually sparing the head and extremities), thin skin, pyoderma, panting, muscle weakness, muscle atrophy and lethargy. Less common signs are heat intolerance, seborrhea, comedones, hyperpigmentation, calcinosis cutis, bruising, testicular atrophy, failure to cycle, clitoral hypertrophy, and facial paralysis (Table 242-1). In rare cases (five out of 800 dogs),[26] affected dogs develop a characteristic stiff gait, most often restricted to the pelvic limbs, called *myotonia* or *myotonia-like syndrome*.

It is important to note that the number and severity of these signs vary remarkably. Dogs with Cushing's syndrome may have only one sign or may have almost all the signs listed. In our clinic, 30% of the dogs with hyperadrenocorticism had only polydipsia and polyuria, and 10% had only dermatologic problems (Figure 242-4).

Dogs that develop Cushing's syndrome during the first year of life show weight gain and growth retardation in addition to more typical signs (i.e., polydipsia, polyuria, and alopecia).[26]

242.3.1.7 Clinicopathologic Findings

When the results of the clinical examination lead to a presumptive diagnosis of Cushing's syndrome, further diagnostic testing is required, including hematology, a biochemical profile, urinalysis, radiography and, when applicable, ultrasonography. These tests detect typical abnormalities associated with hyperadrenocorticism and rule out other diseases with similar signs, such as chronic renal failure, diabetes mellitus, liver diseases, hypothyroidism, diabetes insipidus, and the side effects of anticonvulsant drugs. Concomitant problems, such as urinary tract infection, can also be investigated. A definitive diagnosis of Cushing's syndrome necessitates specific tests.

242.3.1.7.1

Hemogram

Under the influence of increased glucocorticoids, most dogs develop a so-called stress leukogram, which is characterized by neutrophilia without a left shift, lymphopenia, eosinopenia, and monocytosis. Neutrophilia does not imply greater resistance to infection in affected dogs, because cell function is impaired. Not all changes are present in dogs with hyperadrenocorticism, but lymphopenia and eosinopenia are the most consistent abnormalities. It should be emphasized that a stress leukogram is a nonspecific finding that occurs in many sick dogs. In our clinic, 87% of the dogs with hyperadrenocorticism have thrombocytosis, with counts ranging from 403,000 to 1,140,000 platelets/μL.

242.3.1.7.2

Biochemical profile

About 85% to 95% of dogs with hyperadrenocorticism show increases in serum alkaline phosphatase (ALP) activity. This is partly due to the induction of a glucocorticoid isoenzyme, which is unique to the dog and is a hyperglycosylated form of the intestinal isoenzyme.[27] Some maintain that determination of the levels of this isoenzyme is a valuable test in the diagnosis of hyperadrenocorticism. Several methods, such as levamisole inhibition[28] and heat inactivation,[29] have been described. Although these tests have a high sensitivity, their lack of specificity makes them unsuitable as diagnostic tests. The increase in ALP activity may be dramatic; levels above 1000 U/L are frequently seen. However, no correlation exists between ALP activity and the severity of hyperadrenocorticism, the response to therapy, or the prognosis.[26]

Table • 242-1 Clinical Signs in Dogs with Hyperadrenocorticism

CLINICAL SIGN	INCIDENCE (% OF CASES)
Polydipsia/polyuria	80–91
Alopecia	60–74
Pendulous abdomen	67–73
Hepatomegaly	51–67
Polyphagia	46–57
Muscle weakness	14–57
Anestrus	54
Muscle atrophy	35
Comedones	25–34
Panting	30
Hyperpigmentation	23–30
Testicular atrophy	29
Calcinosis cutis	8–15
Facial nerve paralysis	7

Modified from Ling et al 1979; Peterson ME: Hyperadrenocorticism. *In* Peterson ME (ed): The Veterinary Clinics of North America, Small Animal Pracitce—Endocrinology. Philadelphia, WB Saunders, 1984, p 731; and unpublished data from the author. Not all symptoms were mentioned in all three studies, therefore the number of dogs varies among the symptoms. The total number of dogs in the three studies was 457.

*From the history and physical examination.

In 50% to 80% of dogs, a mild increase in alanine aminotransferase (ALT) activity is seen (less than 400 IU/L), which is attributed to hepatocellular leakage associated with cell swelling or minor necrosis. Mild to moderate increases in the cholesterol and triglyceride concentrations are common (50% to 90% of dogs) and are believed to be the result of increased lipolysis. Often affected dogs have alterations in

glucose metabolism, although only about 10% of dogs develop overt diabetes mellitus. Mild fasting hyperglycemia may be seen in 30% to 40% of dogs. The blood urea nitrogen and creatinine concentrations are low as a result of diuresis in about 30% to 50% of cases. Hypophosphatemia has been described in 38% of 300 dogs with hyperadrenocorticism.[30] Mild increases in the sodium concentration and mild decreases in the potassium concentration occur in few dogs with Cushing's syndrome.

Serum bile acids may be mildly elevated in up to 30% of cases.[31] When primary liver disease is considered a major differential diagnosis, this finding, together with an elevation in liver enzymes, may be confusing (Table 242-2).

242.3.1.7.3

Urinalysis

Urinalysis is an important part of the diagnostic workup. It is recommended that owners obtain a urine sample for determination of the specific gravity at home. Collection of a urine sample in hospitalized dogs with Cushing's syndrome is not recommended, because water intake often is decreased in a stressful environment. Most water-deprived dogs with hyperadrenocorticism are able to concentrate the urine, with specific gravities reaching 1.025 to 1.035. In 85% of dogs with Cushing's syndrome, the urine specific gravity of samples obtained at home is less than 1.015 to 1.020.[26] Glucosuria occurs in dogs with overt diabetes mellitus. Glucose is not found in the urine of dogs with hyperglycemia below the renal threshold. Many dogs with hyperadrenocorticism have proteinuria, which in some may be due to urinary tract infection. The urine protein/creatinine ratio in dogs with Cushing's syndrome usually ranges from 1.0 to 6.0 (normal is less than 1.0).

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Figure 242-4 **A,** Dachshund with pituitary-dependent hyperadrenocorticism showing truncal obesity, truncal alopecia, and sparse, fine remaining hair. **B,** Fox terrier with a functional adrenal tumor showing truncal obesity and truncal alopecia; the latter is less pronounced than in the dog in **A.** **C,** Terrier cross with pituitary-dependent hyperadrenocorticism showing ventral alopecia, thin skin, and prominent vasculature. **D,** Poodle with pituitary-dependent hyperadrenocorticism showing a stiff gait involving the pelvic limbs. This abnormality, called *myotonia-like syndrome,* occurs in only a few dogs. **E,** Dachshund with pituitary-dependent hyperadrenocorticism showing mild calcinosis cutis. **F,** Boxer with pituitary-dependent hyperadrenocorticism showing severe calcinosis cutis.

Table • 242-2 Frequently Encountered Clinicopathologic Abnormalities in Dogs with Hyperadrenocorticism

CINICOPATHOLOGIC FINDINGS	INCIDENCE (% OF CASES)
Increased ALP	85–95
Hyperlipidemia	50–90
Increased ALT	50–80
Decreased BUN	30–50
Fasting hyperglycemia*	30–40
Hypophosphatemia	38
Urine specific gravity <1.015–1.020	80
Proteinuria (UPC >1.0)	60–80
Urinary tract infection	40–50
Glucosuria	10

From Peterson ME: Hyperadrenocorticism. *In* Peterson ME (ed): The Veterinary Clinics of North America, Small Animal Practice—Endocrinology. Philadelphia, WB Saunders, 1984, p 731; Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, 2nd ed. Philadelphia, WB Saunders, 1996, p 187; and from unpublished data from this author.

ALP, Alkaline phosphatase; *ALT,* alanine aminotransferase; *BUN,* blood urea nitrogen; *UPC,* urine protein concentration.

* Only about 10% of dogs develop overt diabetes mellitus.

Long-term administration of glucocorticoids results in glomerular lesions and proteinuria in dogs.[32] The mechanisms by which glucocorticoids cause glomerular disease are not yet fully understood. Glucocorticoids may enhance the development of antigen excess by delaying clearance of immune complexes. Glomerular damage may also be caused by hypertension; many dogs with hyperadrenocorticism are hypertensive, and a relationship between hypertension and proteinuria has been postulated.[33] Proteinuria in dogs with hyperadrenocorticism does not lead to hypoalbuminemia.

Almost 50% of dogs with hyperadrenocorticism have a urinary tract infection,[34] and bacterial culture of a urine sample obtained by cystocentesis should be performed in all such dogs. As a result of immunosuppression and/or dilution, urinary sediment frequently is inactive despite bacterial infection, therefore sediment examination must not replace urine culture.

242.3.1.7.4

Thyroid function tests

More than 50% of dogs with hyperadrenocorticism have a total serum thyroxine (T_4) concentration below the reference range. Free T_4 is low in about 25% of cases.[35] Possible mechanisms include alterations in serum thyroid hormone binding and/or alterations in peripheral hormone metabolism. Glucocorticoids may also suppress TSH release from the pituitary. In dogs with clinical signs suggestive of both hyperadrenocorticism and hypothyroidism (alopecia, weight gain, lethargy), diagnosis may be difficult, and misdiagnosis may occur if the endocrine tests are not carried out in the correct order. In such cases, hyperadrenocorticism must be ruled out before tests for hypothyroidism are performed. Determination of the circulating thyroid-stimulating hormone (cTSH) concentration is not always helpful; although dogs with Cushing's syndrome usually have normal or decreased cTSH concentrations, about one third of dogs with hypothyroidism have low-normal cTSH concentrations.[36–38] Thyroid

hormone supplementation is thought to be unnecessary because thyroid hormone concentrations return to normal after successful treatment of hyperadrenocorticism.

242.3.1.7.5 Diagnostic imaging

242.3.1.7.5.1 Thoracic radiographs

Radiographic manifestations of hyperadrenocorticism include mineralization of the tracheobronchial tree and pulmonary parenchyma. Although these abnormalities appear to be significantly more common in dogs with hyperadrenocorticism, they are considered nonspecific.[39] Even though the clinical consequences have not been fully elucidated, pulmonary mineralization may contribute to the hypoxemia seen in dogs with hyperadrenocorticism.[40]

In dogs with an adrenal tumor, thoracic radiographs should be examined for metastases. Pulmonary thromboembolism is a potential complication of hyperadrenocorticism (see below). In dogs with sudden onset of dyspnea, radiographs should be carefully evaluated for abnormalities.

242.3.1.7.5.2 Abdominal radiographs

Radiographic findings associated with Cushing's syndrome are hepatomegaly, obesity, and good contrast and mineralization of the adrenal glands and other soft tissue structures. However, it was recently shown that hepatomegaly, obesity, and osteopenia are nonspecific and also may be seen in dogs with diabetes mellitus or hypothyroidism. The same study also reported that adrenal mineralization and calcinosis cutis were rarely seen and only in dogs with hyperadrenocorticism.[39] Approximately 50% of adrenal tumors are calcified, which allows good radiographic visualization. No difference is seen between adenomas and carcinomas regarding calcification; approximately 50% of both types undergo calcification.[41]

242.3.1.7.5.3 Ultrasonograph

An increase in experience among radiologists and improved resolution of imaging equipment have made visualization of the adrenal glands possible in almost all healthy dogs. However, a systematic approach is necessary for accurate identification and evaluation of the glands. Measurement of the dorsoventral dimension (thickness) appears to be the most accurate means of assessing size. Normal thickness has been reported to be 3 to 7.5 mm.[42,43] In dogs with PDH, the adrenal glands have a bilaterally symmetric appearance. It is important to remember that the absolute adrenal thickness is of limited diagnostic value because reference ranges have been established with limited numbers of dogs; different breeds may have different reference ranges; diseases other than hyperadrenocorticism may cause adrenomegaly (possibly stress related); and the measurement may be within the reference range of a dog population but may be enlarged for an individual dog. Ultrasonography, therefore, should not be used to diagnose Cushing's syndrome but rather to differentiate PDH from FAT. The shape and echogenicity of the adrenal glands in dogs with PDH are usually normal although focal areas of increased echogenicity and loss of the bilayer appearance are possible.

In comparison, the affected adrenal gland of a dog with an FAT often has an irregular, rounded shape with mixed echogenicity. In some cases the tumor appears as a homogenous nodule (Figure 242-5).

The size and shape of adrenal tumors are variable and do not allow differentiation between adenoma and carcinoma. In a study of a small number of dogs with an FAT, all tumors of a thickness greater than 4 cm were malignant.[44] Therefore the likelihood that an adrenal tumor is malignant may increase as its size increases. Other possible ultrasonographic findings include adrenal mineralization, renal displacement, and compression or invasion of the caudal vena cava (Doppler ultrasonography is a valuable tool for diagnosing compression or invasion). Both adrenal glands should always be visualized, for several reasons: (1) bilateral tumors do occur; (2) in quite a few dogs, the adrenal gland contralateral to an adrenal tumor is not decreased in size, and the diagnosis would be missed if only the normal gland is imaged[45]; and (3) concurrent FAT and PDH are possible.

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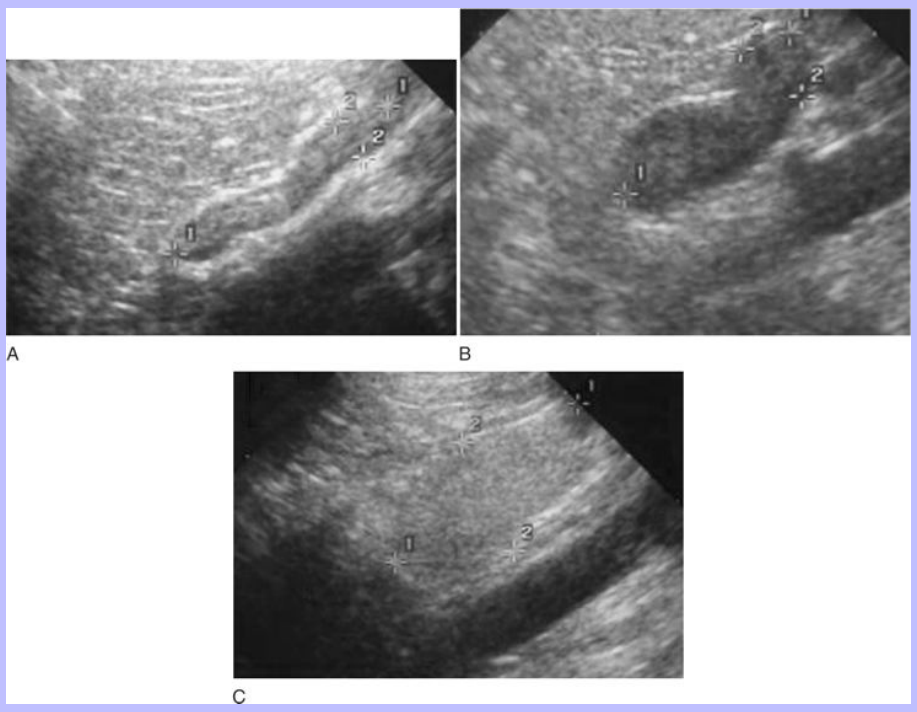
Ultrasonography is useful for detecting local invasion and distant metastases in dogs with an FAT and for revealing other abnormalities, such as urinary calculi and an enlarged renal pelvis (indicating pyelonephritis). In most dogs with hyperadrenocorticism, the liver is enlarged and has increased echogenicity. As with most diagnostic tools, ultrasonography has its limitations; it is difficult or impossible to differentiate between bilateral nodular hyperplasia and bilateral adrenal tumors, and between an FAT and other adrenal tumors (e.g., pheochromocytoma or metastatic tumor).

Figure 242-5 **A,** Longitudinal ultrasonographic view of the left adrenal gland of a healthy dog. The adrenal gland is peanut shaped and hypoechoic compared to the surrounding tissue. It is 2.9 cm long and 0.5 cm wide (thick). **B,** Longitudinal ultrasonographic view of the left adrenal gland of a dog with pituitary-dependent hyperadrenocorticism. The adrenal gland is still peanut shaped, but it is plumper than the one shown in **A.** This adrenal gland is 2.4 cm long and 0.8 cm wide (thick). It should be noted that measurements have limited diagnostic value, because the adrenal size of a variety of dogs with pituitary-dependent hyperadrenocorticism falls within reference ranges. **C,** Longitudinal ultrasonographic view of a right-sided adrenocortical tumor. The adrenal gland is seen as a rounded mass with increased echogenicity (length, 2.7 cm; width [thickness], 1.3 cm).



242.3.1.7.6 Specific endocrine testing

Further diagnostic workup of dogs suspected of having Cushing's disease is a two-step procedure. The first step is to confirm hyperadrenocorticism, and the second is to differentiate between PDH and FAT. Because the treatment protocols and risks are different for PDH and FAT, the second step should always be undertaken. In dogs with a unilateral adrenal tumor, adrenalectomy may be the treatment of choice, although owners should be informed of the risk of metastasis (approximately 50% of FATs are carcinomas). When mitotane is the chosen treatment, the dose usually is higher for dogs with FAT than for those with PDH. Therefore, if the etiology is unknown, dogs that have an FAT may not respond to a dose of mitotane tailored for treatment of PDH. In addition, it is important to diagnose an FAT correctly so that owners can be informed of the risk of tumor growth.

The screening tests used routinely in the diagnosis of hyperadrenocorticism are the urine cortisol to creatinine (C:C) ratio, the ACTH stimulation test, and the low-dose dexamethasone test. The question as to which of these is the best screening test is difficult to answer; each has advantages and disadvantages. For a sound interpretation of these tests, their accuracy, sensitivity, and specificity must be considered, as well as the prevalence of the disease. As a general rule, it is extremely important that dogs be carefully selected for testing and that the test be delayed if concomitant disease is a factor. Also, test results should be interpreted in relation to clinical signs.

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Differentiating tests for hyperadrenocorticism include the extended low-dose dexamethasone test, high-dose dexamethasone test, extended urine C:C ratio, measurement of the ACTH concentration, adrenal ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI).

242.3.1.7.7 Screening tests

242.3.1.7.7.1 Urine cortisol to creatinine ratio

Measurement of the urine C:C ratio is an easily performed test of adrenocortical function. In animals with hyperadrenocorticism, urine cortisol excretion increases as a reflection of augmented adrenal cortisol secretion.[46] Determination of the urine C:C ratio provides an integrated picture of glucocorticoid production by adjusting for fluctuations in plasma levels.[47] Numerous studies on the diagnostic value of the urine C:C ratio[48] have concluded that this test has a high sensitivity (up to 100%) but a low specificity (values as low as 20% are given) (Figure 242-6). Therefore determination of the urine C:C ratio has been advocated as a good test for ruling out hyperadrenocorticism.

Several important points should be considered when the urine C:C ratio is used. Most corticoid measured in the urine is free cortisol. However, depending on the assay used, varying amounts of cortisol metabolites may be detected. It is imperative, therefore, that each laboratory generate its own reference ranges. It is preferable that morning urine samples be submitted, although no consistent diurnal fluctuations have been demonstrated.[46] Also, urine samples for determination of the cortisol/creatinine ratio should be collected at home by the owner to avoid the influence of stress on glucocorticoid secretion.[49]

When the urine C:C ratios of 111 dogs with PDH were compared with those of 49 dogs with an FAT, the highest values were found in dogs with PDH. In dogs with a urine C:C ratio greater than 100×10^{-6} (reference range, less than 10×10^{-6}), the calculated probability of PDH is 90%.[50]

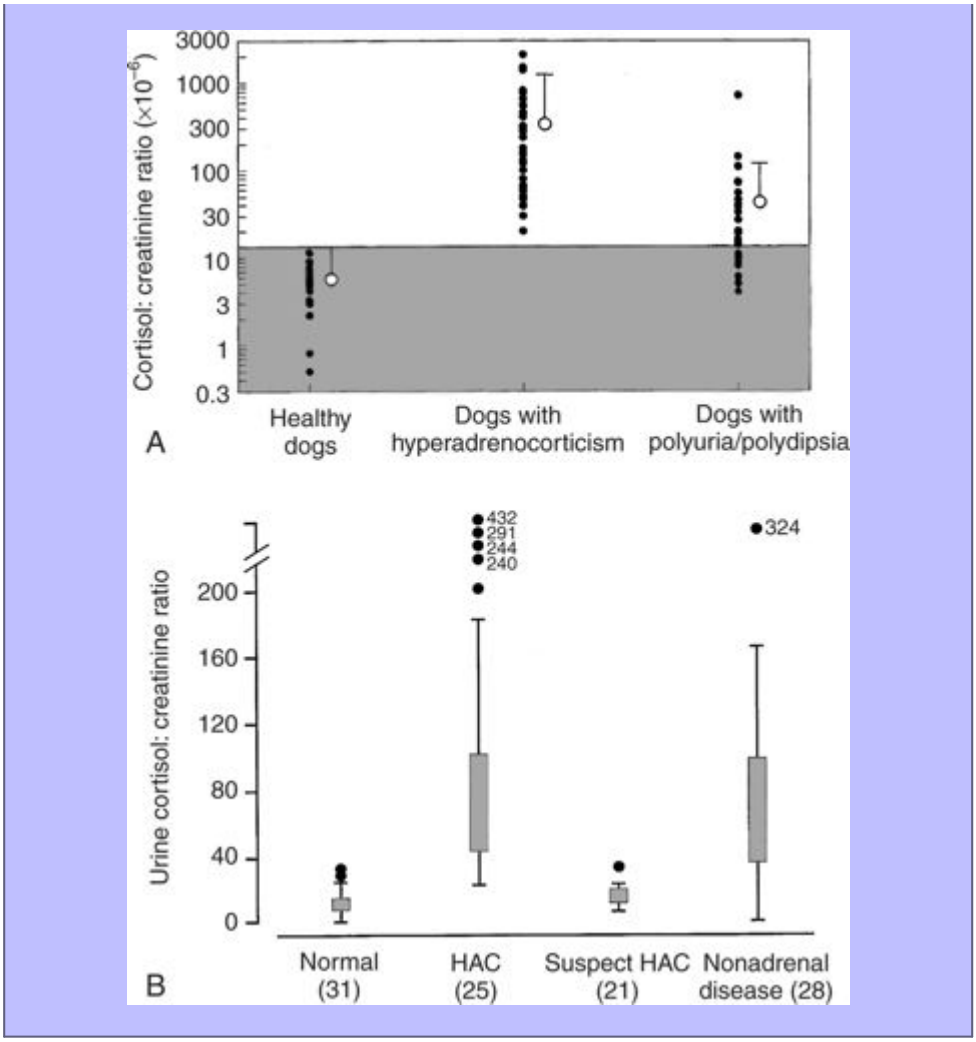
242.3.1.7.7.2

ACTH stimulation test

The ACTH stimulation test, which measures the response of the adrenal glands to maximal ACTH stimulation, is a test of adrenal gland reserve. The major function of this test is to diagnose or rule out hypoadrenocorticism. It has a sensitivity of 60% to 85% and a specificity of 85% to 90% (Figure 242-7). The sensitivity is higher (up to 85%) for the diagnosis of PDH than for the diagnosis of FAT (approximately 60%).[48] However, it is not possible to differentiate PDH from an FAT by means of the ACTH stimulation test on an individual case basis.

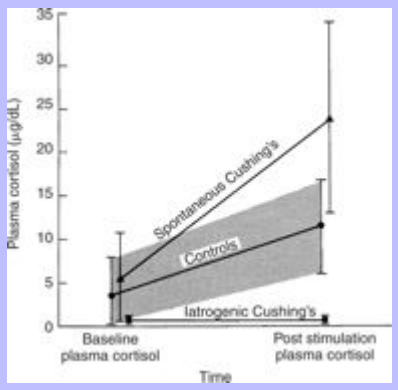
Several test protocols have been described that use either aqueous porcine ACTH gel (Acthar® Gel, Questcor Pharmaceuticals, Inc., Union City, USA; not available in certain countries) or a synthetic polypeptide containing the first 24 aminoacids of ACTH (Cortrosyn, Synacthen). Plasma samples are obtained before and 2 hours after intramuscular injection of 2.2 IU/kg of ACTH gel to determine the cortisol concentration. With the synthetic preparations, most protocols recommend collection of plasma before and 1 hour after intramuscular or intravenous[51] administration of 250 µg of synthetic ACTH. However, maximal stimulation of the adrenal glands can also be achieved with a dosage of 5 µg of synthetic ACTH per kilogram of body weight.[52] Reconstituted ACTH can be stored in plastic syringes at −20° C for 6 months.[53] The normal baseline cortisol concentration is 0.5 to 6 µg/dL, and the normal post-ACTH cortisol concentration is 6 to 17 µg/dL. Post-stimulation cortisol values between 17 and 22 µg/dL are considered borderline; values above 22 µg/dL are consistent with hyperadrenocorticism.

Figure 242-6 **A,** Urine cortisol to creatinine (C:C) ratios from healthy dogs, dogs with naturally occurring hyperadrenocorticism, and dogs with polyuria and polydipsia due to disorders other than hyperadrenocorticism. These values illustrate that the C:C ratio is a sensitive test for Cushing's syndrome, but it is not specific and should not be used as the sole test to confirm a diagnosis. **B,** Box plots of the urine C:C ratios found in normal dogs, dogs with hyperadrenocorticism (HAC), dogs in which hyperadrenocorticism initially was suspected but that did not have the disease (suspect HAC), and dogs with a variety of severe nonadrenal diseases. The number of dogs in each group is shown in parentheses. The box represents the interquartile range from the 25th to the 75th percentile (representing the middle half of the data). The horizontal bar through the box is the median. The "whiskers" represent the main body of data, which in most cases is equal to the range. Outlying data points are represented by the circles (exact values are given for these cases). These data illustrate that the urine C:C ratio is sensitive but not specific for the diagnosis of Cushing's syndrome. (**A** from Feldman EC, Mack RE: Urine cortisol: creatinine ratio as a screening test for hyperadrenocorticism in dogs. J Am Vet Med Assoc 200:1637, 1992; **B** from Smiley LE, Peterson ME: Evaluation of a urine cortisol: creatinine ratio as a screening test for hyperadrenocorticism in dogs. J Vet Intern Med 7:163, 1993.)



There are several reasons to use this test despite its relatively low sensitivity. First, it is the only test to differentiate between iatrogenic and naturally occurring hyperadrenocorticism. Second, because the test is frequently used to monitor medical therapy, it appears helpful to know the stimulation capacity of the adrenal glands prior to treatment. A possible third reason was recently revealed. It has been hypothesized that some dogs with hyperadrenocorticism that have normal ACTH stimulation results, in fact have a derangement of the steroid synthesis pathway; this would lead to abnormally increased precursor concentrations but normal concentrations of the end product, cortisol. Preliminary evaluations revealed that 17-hydroxprogesterone, one of the precursors, showed an exaggerated response to ACTH stimulation in dogs with Cushing's syndrome, which had abnormal or normal cortisol responses.[54] Further studies are needed to confirm whether the measurement of 17-hydroxprogesterone or other precursor concentrations is helpful in the diagnosis of canine Cushing's syndrome.

Figure 242-7 Mean radioimmunoassay (RIA) plasma cortisol concentrations (±2 SD) determined before and 1 hour after administration of synthetic ACTH in control dogs, dogs with spontaneous hyperadrenocorticism, and dogs with iatrogenic hyperadrenocorticism.



242.3.1.7.7.3 Low-dose dexamethasone suppression test

Dexamethasone is a synthetic glucocorticoid that does not cross-react with cortisol assays, therefore it can be used to evaluate the pituitary–adrenal gland axis. In normal dogs, the cortisol concentration decreases 2 to 3 hours after administration of dexamethasone and remains low for up to 24 to 48 hours. In dogs with hyperadrenocorticism, the pituitary–adrenal gland axis is abnormally resistant to the suppressive effects of dexamethasone and/or dexamethasone is metabolized more rapidly than normal. For the low-dose dexamethasone suppression (LDDS) test, blood samples are collected before and 4 and 8 hours after intravenous administration of dexamethasone at a dosage of 0.01 mg/kg. Either dexamethasone sodium phosphate or dexamethasone in polyethylene glycol may be used. In normal dogs the cortisol concentration is less than 1.4 μg/dL at 4 and 8 hours after dexamethasone administration. The cortisol concentration 8 hours after dexamethasone administration is used to detect hyperadrenocorticism; a concentration equal to or greater than 1.4 μg/dL is consistent with hyperadrenocorticism. The cortisol concentration at 4 and 8 hours after dexamethasone administration is also used as a differentiating test (see later). For the diagnosis of hyperadrenocorticism, the sensitivity of the test at 8 hours after dexamethasone administration is higher (85% to 95%) than the specificity (70% to 75%) (Figure 242-8).[48]

242.3.1.7.7.4 Misleading results

All three screening tests can have false-positive results in dogs suffering from nonadrenal disease,[55] therefore testing of such animals for hyperadrenocorticism should be avoided if possible. In general, a definitive diagnosis of hyperadrenocorticism should never be made solely on the basis of positive test results; the history and clinical findings should be considered carefully with each dog.

The extent to which phenobarbital treatment affects the results of screening tests is unclear. A review of the literature suggests that test results probably are not affected by this drug.

242.3.1.7.7.5 Glucocorticoid-induced alkaline phosphatase isoenzyme, liver biopsy, and combined dexamethasone suppression and ACTH stimulation tests

None of these tests give reliable results, therefore they are not recommended as screening tests for hyperadrenocorticism.

242.3.1.7.8 Differentiating tests

242.3.1.7.8.1 Extended low-dose dexamethasone suppression test

In dogs with an FAT, pituitary ACTH secretion is suppressed as a result of autonomous secretion of cortisol from the tumor. Administration of dexamethasone has no effect on the pituitary, and cortisol secretion therefore continues. Pituitary tumors have variable sensitivities to feedback inhibition, and the result is different response patterns after dexamethasone application.

The LDDS test can be used to identify dogs with PDH based on three criteria: a 4-hour cortisol concentration of less than 1.4 µg/dL; a 4-hour cortisol concentration of less than 50% of the basal cortisol concentration; and an 8-hour cortisol concentration of less than 50% of the basal cortisol concentration but equal to or greater than 1.4 µg/dL. When one or more of these criteria are met, the dog most likely has PDH.

Approximately 25% of dogs with PDH have a 4-hour cortisol concentration of less than 1.4 µg/dL; 60% have a 4-hour cortisol concentration of less than 50% of the basal concentration; and 25% have an 8-hour cortisol concentration of less than 50% of the baseline value. Overall, approximately 60% of dogs with PDH meet at least one of the three criteria. Dexamethasone resistance (none of the criteria are met) occurs in about 40% of dogs with PDH and in virtually all dogs with an FAT.[56] In such dogs another differentiating test must be used (see Figure 242-8).

A significant positive correlation was found between the size of the pituitary tumor and resistance to dexamethasone using the high-dose dexamethasone suppression test.[13] According to a preliminary study, similar results may be achieved with the LDDS test. Dogs with large pituitary tumors were significantly more often resistant to dexamethasone (according to the criteria cited above) than dogs with small tumors.[57]

242.3.1.7.8.2 High-dose dexamethasone suppression test

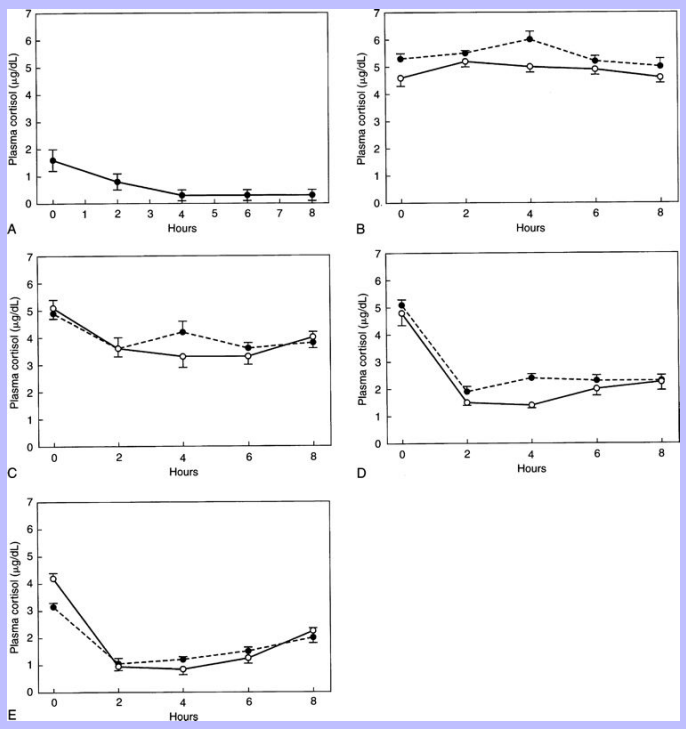
Traditionally, the high-dose dexamethasone suppression (HDDS) test has been used to differentiate PDH from an FAT. In dogs with an FAT, even large doses of dexamethasone should not suppress plasma cortisol levels. In contrast, administration of a large dose of dexamethasone should suppress ACTH secretion in most dogs with PDH. The test protocol is the same as that for the LDDS test except that a dexamethasone dosage of 0.1 mg/kg is used. Suppression is defined as a cortisol concentration less than 50% of the baseline concentration or less than 1.4 µg/dL at 4 or 8 hours after injection of dexamethasone. Suppression of the cortisol concentration occurs in approximately 75% of

dogs with PDH, whereas suppression virtually never occurs in dogs with an FAT. The HDDS test, therefore, is interpreted as follows: If the cortisol concentration is suppressed, a dog most likely has PDH; if no suppression of cortisol levels occurs, a dog may have either PDH or an FAT.

According to the results of one study,[13] if the cortisol concentration is not suppressed in the HDDS test, a dog with PDH may have large pituitary tumors.

Many dogs with PDH that show suppression of the cortisol concentration on the HDDS test also show cortisol suppression on the LDDS test. In one large study,[56] the HDDS test results provided additional information in only a small percentage of dogs (26 of 216 [12%]). It therefore appears useful routinely to perform an extended LDDS test in dogs suspected of having Cushing's syndrome. In dogs with dexamethasone resistance, rather than a HDDS test, it probably would be more efficient to perform one of the other differentiating tests, such as measurement of endogenous ACTH or adrenal ultrasonography.

Figure 242-8 Mean plasma cortisol concentrations before and after administration of a low dose of dexamethasone in (**A)** 27 normal dogs; **(B)** 48 dogs with adrenocortical tumors; **(C)** 130 dogs with pituitary-dependent hyperadrenocorticism (PDH); **(D)** the dogs among the 178 with Cushing's syndrome that had at least one plasma cortisol concentration less than 1.4 µg/dL after dexamethasone administration (total, 54; each had PDH); and **(E)** the dogs among the 178 with Cushing's syndrome that, after dexamethasone administration, had at least one plasma cortisol concentration less than 50% of the baseline concentration (total, 95; each had PDH). Note the two curves for graphs **B, C, D,** and **E.** These represent the use of dexamethasone sodium phosphate *(dashed line)* and dexamethasone in polyethylene glycol *(solid line)*. No significant difference in results is seen with these dexamethasone products. (From Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, 2nd ed. Philadelphia, WB Saunders, 1996, p 227.)



242.3.1.7.8.3

Extended urine cortisol to creatinine ratio

The extended urine C:C ratio combines a screening test (urine C:C ratio) with a differentiating test (a special form of the HDDS test). Urine samples are collected at home for 3 consecutive days for determination of the C:C ratio. After the second urine sample has been collected, the owner administers 0.1 mg/kg of dexamethasone, per os, at 8-hour intervals (three times). The mean is calculated from the first two urine samples and is used as baseline urine C:C ratio. Provided the baseline urine C:C ratio is elevated, a diagnosis of PDH is justified if the ratio of the third sample is less than 50% of the baseline value.[17]

The advantage of this test is that it can be performed at home. Disadvantages include the limited specificity of the urine C:C ratio and possible owner error associated with administration of the dexamethasone tablets. Little current information is available regarding the accuracy of this test.

242.3.1.7.8.4

Endogenous ACTH

Determination of the ACTH concentration is a reliable test for differentiating PDH from an FAT. In dogs with an FAT, the ACTH concentration is suppressed through negative feedback, whereas in dogs with PDH, the pituitary tumor secretes ACTH. Rapid processing of the sample is important because the hormone disappears quickly from fresh whole blood. Blood should be collected into a chilled plastic tube containing ethylenediamine tetra-acetic acid (EDTA) and immediately centrifuged at 4° C. The plasma should be stored at −20° to −70° C, then packed on dry ice and shipped to a laboratory. Addition of the protease inhibitor aprotinin (500 kallikrein inactivator units per milliliter of blood) to the EDTA tube may prevent rapid breakdown of ACTH.[58] Not all assays for human ACTH can be used in the dog, therefore validation is imperative.

The reference range for ACTH is 20 to 100 pg/mL. Concentrations of ACTH less than 20 pg/mL are strongly suggestive of an FAT, and concentrations greater than 45 pg/mL are consistent with a diagnosis of PDH. The range between 20 and 45 pg/mL is considered nondiagnostic. It should be noted that reference ranges and cutoff values may differ among laboratories. In one study, approximately 70% of dogs with an FAT had ACTH concentrations less than 20 pg/mL; in the remaining dogs, the ACTH concentration was in the nondiagnostic range.[24] In another study, 85% to 90% of dogs with PDH had ACTH concentrations greater than 45 pg/mL, and in the remaining 10% to 15%, the levels were nondiagnostic.[59] In dogs with a nondiagnostic test result, another sample should be submitted or another differentiating test performed (Figure 242-9).

242.3.1.7.8.5

Ultrasonographic examination of the adrenal glands

Adrenal ultrasonography is an extremely valuable tool for differentiating PDH from an FAT (see Ultrasonography, above).

242.3.1.7.9

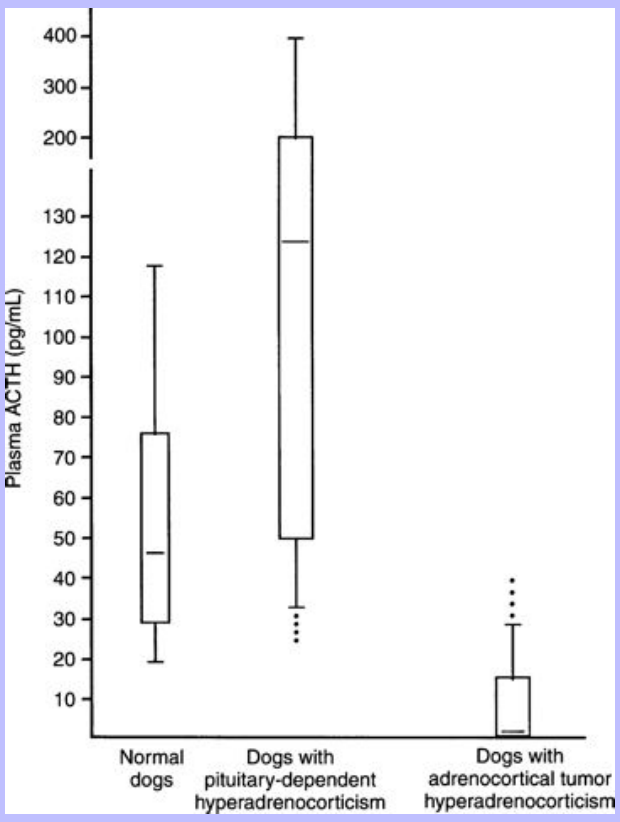
Advanced diagnostic imaging

Because the adrenal glands can be visualized so well with ultrasonography, advanced imaging techniques usually are not required. However, techniques such as CT and MRI are the only reliable

methods of evaluating the size of a pituitary tumor. Survey radiography of the skull does not aid in their diagnosis because pituitary tumors in dogs usually do not erode bone or invade the sphenoid bone.

Because the pituitary lacks a complete blood-brain barrier, contrast medium diffuses freely from the circulation into the interstitial space. Contrast enhancement of a pituitary tumor improves its detection and allows delineation of tumor from peritumoral edema and adjacent neural structures.

Figure 242-9 Endogenous plasma ACTH concentrations from clinically normal dogs, dogs with functioning adrenocortical carcinomas or adenomas, and dogs with pituitary-dependent hyperadrenocorticism (PDH). Each box represents the interquartile range from the 25th to the 75th percentile (the middle half of the data). The horizontal bar through the box is the median. The "whiskers" represent the main body of data, which in most cases is equal to the range. Outlying data points are represented by the circles. (From Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, 2nd ed. Philadelphia, WB Saunders, 1996, p 230.)



In dogs, pituitary tumors grow dorsally. The so-called suprasellar tumor extension is partly a reflection of the incomplete diaphragma sella, which provides minimal resistance. Growth may result in invagination into the third ventricle, and the tumor may eventually compress and/or invade the hypothalamus and thalamus and, when large enough, other brain structures. In contrast to humans with pituitary tumors, the optic chiasm in dogs is usually spared because of its more rostral location.

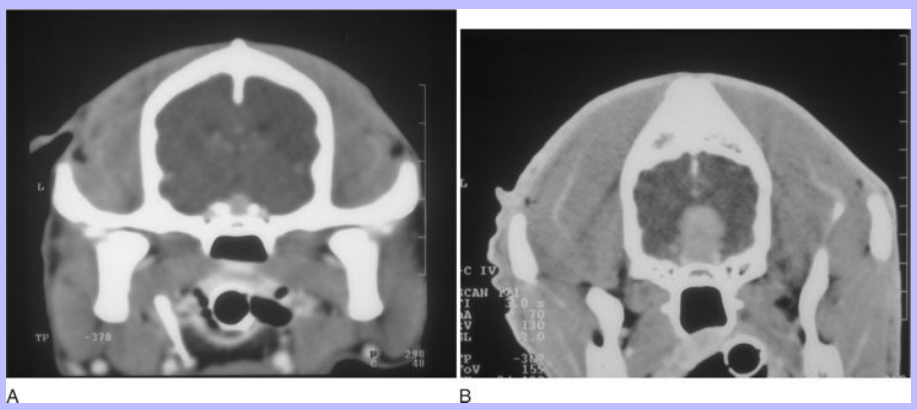
Currently we recommend that CT (or MRI) be performed in dogs with PDH because of the potential risk of a large tumor (see below). However, CT and MRI cannot replace endocrine function tests, because about half of pituitary tumors are not visible. In addition, CT and MRI do not differentiate between a functional and nonfunctional mass (Figures 242-10 and 242-11).

242.3.1.7.9.1

Computed tomography

The size of the pituitary gland varies among different breeds of dogs and among dogs of the same breed. In 35 healthy dogs, CT measurements of the pituitary gland ranged from 3.2 to 5.1 mm for height, 4.2 to 6.9 mm for width, and 3.6 to 7.2 mm for length.[60] The first sign of pituitary enlargement appears to be an increase in height (i.e., dorsal extension into the suprasellar region). The pituitary gland is considered to be enlarged when the dorsal contour of the pituitary protrudes above the suprasellar extension of the intercrural cisterns, which are easily recognized on CT images.[13] Alternatively, the ratio of the height of the pituitary gland to the area of the brain measured on an image through the center of the pituitary (P:B ratio) can be used to discriminate between enlarged (P:B greater than 0.31) and normal (P:B less than or equal to 0.31) pituitary glands.[60] Large tumors are easily detected on contrast-enhanced CT images because of their size and altered shape. In rare cases, tumors may be difficult to visualize without contrast. In 50% to 60% of dogs with PDH, a pituitary mass can be detected by CT. In the remaining 40% to 50% of cases, the disease is caused by a small tumor (less than 3 to 4 mm) that is not visible even with contrast. Newer CT techniques, using a series of transverse scans through the center of the pituitary during and after rapid intravenous injection of contrast medium (dynamic CT), reveal a difference in enhancement between the neurohypophysis and the adenohypophysis. This is due to variations in the blood supply; an early, strong enhancement of the central neurohypophysis (“pituitary flush”) is seen, as is a slightly delayed, weaker enhancement of the peripheral adenohypophysis. Displacement or distortion of the neurohypophyseal flush may reveal the existence of small tumors.[61]

Figure 242-10 Contrast-enhanced transverse computed tomographic images through the pituitary. **A,** Mixed-breed dog with signs of hyperadrenocorticism but no neurologic signs. The pituitary is enlarged (0.6 cm in height). **B,** Bergamasker with hyperadrenocorticism that had been treated with mitotane for 2 years, after which neurologic signs developed (i.e., disorientation, ataxia, aggressive behavior). The pituitary is grossly enlarged (2.1 cm in height).



242.3.1.7.9.2 Magnetic resonance imaging

Although CT and MRI are both effective at identifying large pituitary tumors, MRI is superior for defining the full extent and relationship of a tumor to surrounding structures and is probably more accurate in identifying small lesions. The size, signal, and contrast enhancement characteristics of the normal canine pituitary gland using MRI have been described.[62] In one study, in about 50% of dogs with PDH and no neurologic signs, a pituitary tumor was visible on MRI, and the tumors ranged in size from 4 to 12 mm.[63]

242.3.1.8 Treatment

The method of treatment must be carefully chosen based on the cause of the disease (PDH or an FAT), the age and condition of the dog, and whether concomitant disease is a factor. The cost and availability of treatment methods, as well as the frequency of follow-up evaluations, are also important considerations.

242.3.1.9 Surgery

242.3.1.9.1 Adrenal tumor

Surgical removal is the treatment of choice for adrenal tumors. Each dog must be assessed preoperatively for metastases or invasion of the tumor into surrounding tissues. Adrenalectomy is technically challenging and should be performed by a skilled surgeon. Approximately 50% of dogs develop severe postoperative complications, including pancreatitis, pneumonia, pulmonary thromboembolism, acute renal failure, sepsis, and hypoadrenocorticism due to insufficient steroid levels. The reported death rate after adrenalectomy varies greatly; in two large studies the rate was 27% and 34%.[19,26] It is not known whether dogs with an FAT that undergo long-term medical treatment before adrenalectomy have fewer postoperative complications and higher survival rates. In dogs in which tumor removal was incomplete, clinical signs persist, or hyperadrenocorticism recurs weeks to months after surgery.

Autonomous cortisol secretion results in atrophy of the cells of the zona fasciculata and zona reticularis and, in a few dogs, of the aldosterone-producing cells of the zona glomerulosa. Thus glucocorticoid substitution intraoperatively and postoperatively is necessary. Mineralocorticoid treatment is instituted when required.

Intravenous fluids (0.9% sodium chloride [NaCl] or Ringer's solution) should be administered at a maintenance rate at the start of anesthesia and during surgery and the postoperative period. When the tumor is located, dexamethasone should be given at a dosage of 0.1 mg/kg over a 6-hour period. The dose should be repeated two to four times per day, subcutaneously, until oral medication can be started.[59] An alternative to dexamethasone is hydrocortisone, which can be given intravenously during surgery at a dosage of 4 to 5 mg/kg, and thereafter at a dosage of 1 mg/kg given intravenously every 6 hours until oral medication is started. Compared to dexamethasone, hydrocortisone has the advantage of having both glucocorticoid and mineralocorticoid activity. Prednisolone is then administered orally according to the following schedule:

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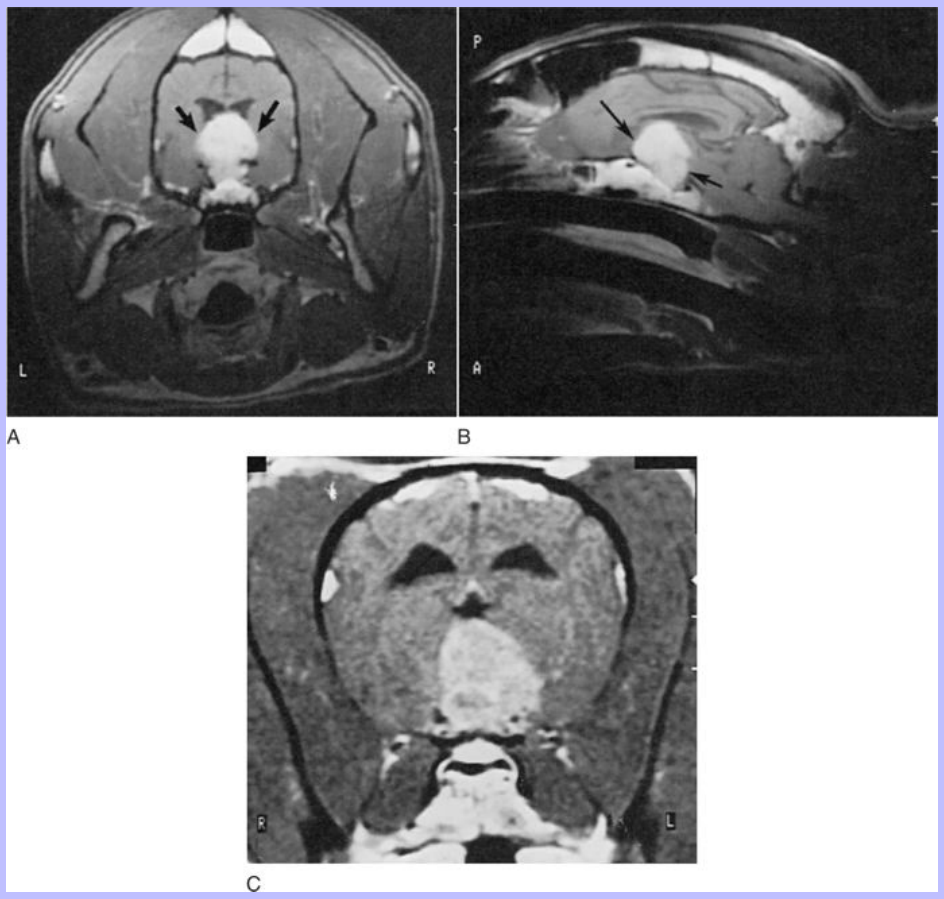
- 1 mg/kg twice daily for 2 to 3 days
- 0.5 mg/kg twice daily for 2 to 3 days
- 0.25 mg/kg twice daily for 3 weeks
- 0.25 mg/kg once a day for 3 weeks
- 0.25 mg/kg every other day for 3 weeks
- 0.25 mg/kg every 3 days

Figure 242-11 **A,** Transverse view of a post-gadolinium MRI scan of a 7-year-old bull terrier with pituitary-dependent hyperadrenocorticism (PDH) caused by a 2.4 cm mass *(arrows);* the dog developed signs of disorientation and ataxia. **B,** Midline sagittal view of the brain of the same dog (using MRI), showing the densely enhancing mass *(arrows)* arising from the pituitary fossa and causing compression of the floor of the overlying third ventricle. **C,** Post-gadolinium MRI scan of an 8-year-old Boston terrier with PDH and signs of disorientation, ataxia, and circling. (From Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, 2nd ed. Philadelphia, WB Saunders, 1996, p 237.)



Prednisolone usually can be discontinued after 2 to 3 months. The ACTH stimulation test is helpful for evaluating adrenal function. Intensive postoperative monitoring is essential for preventing or detecting potential complications. If hyperkalemia and/or hyponatremia occur, oral fludrocortisone (0.01 to 0.02 mg/kg/day) or parenteral desoxycorticosterone pivalate (DOCP; 2.2 mg/kg every 25 days) should be given. In most cases these electrolyte abnormalities, which reflect mineralocorticoid deficiency, last only a few days. Antibiotics, pain medication, and heparin should be used routinely. When bilateral adrenalectomy is performed (because of bilateral tumors), the dog needs lifelong supplementation with mineralocorticoids and glucocorticoids. 1604

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242.3.1.9.2 Pituitary tumor

242.3.1.9.2.1 Hypophysectomy

During the past decade, transsphenoidal pituitary surgery has become the treatment of choice for humans with PDH. Although hypophysectomy has been attempted numerous times in dogs, the procedure has only recently become feasible.[60,64] Hypophysectomy in dogs (and cats) is performed by a transsphenoidal approach. Of 84 dogs with PDH that underwent hypophysectomy,[65] six died within 4 weeks of surgery and were considered procedure-related mortalities. In another six dogs, the tumor was incompletely removed. The overall response rate was 86% (i.e., 72 of the 84 dogs went into remission). This compares favorably with the results of dogs with PDH treated medically with mitotane. Perioperative and long-term complications include mild transient hypernatremia, transient reduction or cessation of tear production, diabetes insipidus (persistent in 10% of cases), and secondary hypothyroidism (persistent in all cases). Hyperadrenocorticism recurred in 11 of 72 dogs (15%), 5 to 47 months after surgery. Thus far, only dogs with small or moderate-sized tumors (up to 10 mm in diameter) have been suitable candidates.

Pituitary surgery is possible only in a specialized veterinary institution and requires a team approach involving a neurosurgeon, an endocrinologist, and a radiologist.[65] Transsphenoidal hypophysectomy has the potential to become the treatment of choice for dogs (and cats) with PDH.

242.3.1.9.2.2 Adrenalectomy

Removal of both adrenal glands results in complete resolution of the clinical signs of hyperadrenocorticism. However, because the success rate of medical treatment is relatively high and treatment is fairly easy, the risk of surgery seems unwarranted.

242.3.1.10 Medical Management

Medical management of dogs with Cushing's disease may be questioned, because unlike adrenalectomy or hypophysectomy, it does not result in a cure. No studies have investigated the degree to which medical treatment increases the life expectancy of dogs with Cushing's syndrome. However, uncontrolled hyperadrenocorticism markedly affects the quality of life and can lead to a number of complications, including infection and life-threatening thromboembolism. For these reasons, treatment should be undertaken in most dogs with clinical signs of hyperadrenocorticism. Exceptions include very old dogs and those with concomitant disease in which appetite is sustained by excess cortisol. Dogs with laboratory values consistent with hyperadrenocorticism (increased ALP, positive screening test results) but without

clinical signs should not be treated. In cases in which the cause of the abnormal test results (e.g., primary hepatopathy) remains unknown, the dog should be re-evaluated a few weeks or months later.

Mitotane, trilostane and, to a lesser extent, ketoconazole are effective treatments for hyperadrenocorticism.

242.3.1.10.1 Mitotane

Mitotane (o, p'-DDD, Lysodren) is a potent adrenocorticolytic drug that causes necrosis of the zona fasciculata and zona reticularis (sites of glucocorticoid production). The zona glomerulosa (site of mineralocorticoid production) is less sensitive to this drug. Mitotane is fat soluble and should always be administered with a meal.

Depending on the dosage and duration of treatment, the adrenal cortex may be partly or completely destroyed. Currently, two main treatment regimens are based on this pretext.

242.3.1.10.2 Partial adrenocortical destruction

The goal of this treatment regimen is to partly destroy the zona fasciculata and zona reticularis so that excess cortisol production is stopped and synthesis is restricted to amounts needed for daily life. The zona glomerulosa should retain all of its function. Treatment consists of an induction phase and a maintenance phase.

242.3.1.10.2.1 Induction phase

For induction, mitotane is administered at a dosage of 50 mg/kg/day, divided, given twice a day at the end of a meal. It is difficult to determine when adrenocortical destruction is adequate to prevent the occurrence of hypoadrenocorticism by further treatment. Daily administration of mitotane should be stopped when (1) the dog's water intake decreases markedly; (2) the dog's appetite is reduced or the dog eats more slowly (thus the meal is offered before administration of mitotane); or (3) the dog has vomiting, diarrhea, or lethargy. For most dogs with Cushing's syndrome, a change in appetite is the most reliable indicator of effective treatment. When a change in the dog's appetite is noted, re-evaluation by the veterinarian and an ACTH stimulation test should be performed. Treatment is considered adequate when the post-ACTH plasma cortisol concentration is 1 to 4 μg/dL. The time required to achieve this varies among dogs. The average length of induction reported in the literature differs. We found that the target concentration of cortisol was achieved after 3 to 4 days of therapy in more than 50% of dogs with PDH.[66] Thus we routinely perform an ACTH stimulation test on the fifth day of treatment. When the post-ACTH plasma cortisol concentration is 1 to 5 μg/dL, maintenance therapy is started. Some dogs may need 1 or more days of induction therapy, and a second ACTH stimulation test may be required.

Another method of monitoring treatment involves daily phone calls by the veterinarian to the owner regarding the dog's condition, particularly appetite.[59] Appetite is the most important aspect of the monitoring of the response to treatment. Dogs with a poor appetite before the start of treatment should be carefully reassessed; either they do not have Cushing's syndrome, or they have concurrent disease, which must be treated first.

Even with careful treatment and monitoring, some dogs experience apathy, weakness, anorexia, vomiting, diarrhea, and/or ataxia. These symptoms may be due to (1) lower than normal plasma

cortisol concentrations (overdose), (2) a decrease in plasma cortisol levels to within the normal range (relative glucocorticoid deficiency, or *glucocorticoid withdrawal syndrome*); or (3) mitotane intolerance. With these dogs, owners are told to stop mitotane treatment and to administer prednisolone (or prednisone) at a dosage of 2 mg/kg per os. When the symptoms are attributable to decreased cortisol levels, dogs return to normal within a few hours. An ACTH stimulation test should be performed to differentiate overdose of mitotane from glucocorticoid withdrawal syndrome. In dogs with mitotane overdose (i.e., a post-ACTH cortisol level of less than 1 μg/dL), prednisolone is administered and tapered over 1 to 3 weeks. If the dog's condition is then stable without prednisolone, mitotane treatment can be restarted at a maintenance dosage. In dogs that do not tolerate mitotane, the daily dosage can be divided into smaller portions, or another drug can be used.

A few researchers advocate administration of both mitotane and prednisolone during the induction phase. We feel that mitotane overdose can be more rapidly recognized clinically when that drug is used alone.

242.3.1.10.2.2

Maintenance phase

Maintenance therapy starts with administration of about 50 mg/kg of mitotane per week (e.g., given on Wednesday and Sunday); the dose should be divided and given with meals. With time the dosage may need to be altered (some dogs require half the dose; others, double), therefore owners must be told to monitor the dog for signs of hypoadrenocorticism or recurrence of Cushing's symptoms. An ACTH stimulation test should be performed every 1 to 3 months during the early stages of maintenance treatment and then twice yearly. The goal of maintenance therapy is the same as that for induction: a post-ACTH plasma cortisol concentration of 1 to 5 μl/dL. Determination of the urine C:C ratio is not suitable for monitoring treatment, because overlap occurs between well-regulated and overdosed patients.

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Mitotane overdosage may occur at any time during treatment and usually manifests as a glucocorticoid deficiency. Rarely, a concomitant mineralocorticoid deficiency with electrolyte abnormalities may be seen. Treatment consists of cessation of mitotane therapy (transient in most cases) and administration of prednisolone. In dogs with complete adrenocortical insufficiency, a mineralocorticoid (fludrocortisone or DOCP) must also be administered. Permanent adrenocortical insufficiency rarely occurs and is seen in about 5% of cases. In a small number of dogs, mitotane induces CNS symptoms, such as apathy, ataxia, blindness, and head pressing. These clinical signs usually occur several months after the start of treatment and, because of their transient nature, disappear a few hours after administration of the drug. Dividing the dosage over multiple administrations is often helpful, but in some cases the dosage must be reduced. Similar symptoms occur with mitotane overdosage or an expanding hypophyseal tumor, therefore careful re-evaluation of the patient is required.

Approximately 50% of dogs have recurrence of symptoms at some point during treatment. The reasons are similar to those for recurrence during the induction phase: (1) the individual animal requires a higher dosage; (2) owner compliance is poor; (3) the drug is not given with food and thus is poorly absorbed; (4) a drug-associated decrease in intestinal fat absorption results in decreased mitotane absorption; (5) the dog has an FAT rather than PDH; (6) increased ACTH secretion by the hypophyseal tumor (possibly supported by a decrease in negative feedback) results in regeneration of the adrenal cortex; and (7) mitotane stimulates induction of microsomal liver enzymes for its own metabolism.

The partial adrenocortical destruction regimen results in a good to excellent response in about 80% of dogs with PDH. It can also be used to treat dogs with an FAT. It is important to remember that compared to hyperplastic cells, tumor cells frequently are more resistant to the cytotoxic effects of mitotane. About 50% of dogs with an FAT require an induction phase lasting longer than 2 weeks. On average, they also require a higher maintenance dosage of mitotane.[67] Because approximately 50% of dogs with an FAT have adrenal carcinomas, we use the following treatment regimen in those that do not undergo adrenalectomy.

242.3.1.10.2.3

Complete adrenocortical destruction

The goal of this treatment regimen is destruction of the entire adrenal cortex, with resultant iatrogenic hypoadrenocorticism, by long-term mitotane administration.[68]

Mitotane is administered at a dosage of 50 to 75 mg/kg/day (divided into three or four smaller doses given with food) for 25 days. Lifelong administration of fludrocortisone (0.01 mg/kg) and cortisone is started on the third day of mitotane administration. The cortisone dosage is 1 mg/kg given twice a day; then, 1 week after the discontinuation of mitotane treatment, the cortisone dosage is reduced to 0.5 mg/kg given twice a day. An equivalent dose of prednisolone (approximately 0.4 mg/kg and then 0.2 mg/kg) can be used instead of cortisone, because it is less expensive. In a number of dogs, daily mitotane administration must be stopped for a short period because of adverse side effects, such as anorexia, vomiting, diarrhea, weakness, and neurologic symptoms. In most dogs, mitotane administration can be resumed after a few days. This treatment regimen is easier to implement than that for partial adrenocortical destruction because it is not necessary to determine when the therapy takes effect. The side effects and complications are similar to those of other regimens using mitotane. However, the risk of unrecognized adrenal insufficiency is lower, because cortisone and mineralocorticoids are substituted.

The necessity of administering daily medication to prevent life-threatening hypoadrenocorticism must be emphasized to owners. The complete adrenocortical destruction regimen should be used only when the diagnosis is certain and owner compliance can be assured. Recurrence of initial symptoms can also occur with this regimen, therefore an ACTH stimulation test should be performed regularly (two to four times a year). Routine electrolyte evaluation (sodium, potassium) is recommended as for dogs with spontaneous Addison's disease. Clinical remission is reported to occur in 86% of dogs with PDH.[69]

We use complete adrenocortical destruction almost exclusively in dogs with inoperable adrenal tumors. In some dogs, this treatment regimen results in complete tumor remission and disappearance of metastases. For these patients, a modified treatment regimen is used: after the 25th day of daily therapy, mitotane is administered at a dosage of 50 to 75 mg/kg, given weekly (divided over two to four days) for life. An ACTH stimulation test is used routinely to ensure complete cessation of cortisol production, as indicated by a pre-ACTH and post-ACTH plasma cortisol concentration below the assay detection level.

For both protocols, the cortisol requirement in times of stress (illness, surgery) is increased and higher than the partly destroyed adrenocortex can produce or that is administered exogenously. Depending on the level of stress, up to 2 mg/kg of prednisolone may be given daily.

242.3.1.10.3 Trilostane

The use of trilostane for the treatment of canine PDH was first reported in 1998.[70] Since then the drug has gained wide popularity, especially in Europe. Two prospective studies that evaluated the effects of trilostane were recently published.[71,72] In the United Kingdom, trilostane is officially registered for use in dogs under the name of Vetoryl. The human preparation is available as Modrenal. Trilostane is an orally administered competitive inhibitor of 3-beta-hydroxysteroid dehydrogenase. This enzyme system mediates the conversion of pregnenolone to progesterone in the adrenal gland. Cortisol, aldosterone, and androstenedione are produced from progesterone via various biochemical pathways. Trilostane inhibits progesterone and blocks the synthesis of its end products (Figure 242-12).

We have used trilostane for nearly 4 years in the treatment of PDH and have found that about 80% of dogs have a good to excellent response. The time required for a noticeable response to trilostane is similar to that for mitotane. Improvements include a rapid decrease in polydipsia, polyuria, and polyphagia and a rapid increase in activity level, as well as delayed improvement in the haircoat, skin condition, and abdominal muscle tone. Some dogs may show transient worsening of dermatologic problems before clinical improvement becomes obvious; this may also occur with mitotane. The ACTH stimulation test determines adrenal reserve and therefore is suitable for evaluating the extent of enzyme inhibition during treatment and for calculating dosage adjustments (Figure 242-13).

We currently administer trilostane as follows: dogs weighing less than 5 kg receive 30 mg once a day; those weighing 5 to 20 kg receive 60 mg once a day; and those weighing more than 20 kg receive 120 mg once a day. Re-evaluations, which are performed after 1, 3, 6, and 13 weeks and 6 and 12 months, include the history, a physical examination, and an ACTH stimulation test. It appears important that, for each evaluation, testing be performed at the same time after drug administration. When the ACTH stimulation test is performed 2 to 6 hours after drug administration, the target range of the post-ACTH cortisol level is 1 to 2 µg/dL; this corresponds with the low end of the desired range for dogs treated with mitotane. Several of our dogs had post-ACTH cortisol levels between 0.5 and 1 µg/dL for months without showing signs of hypoadrenocorticism. Two explanations for this may be that (1) trilostane is known to decrease the cortisol concentration for only a few hours; and (2) steroid precursors, which have accumulated as a result of enzyme inhibition, may have certain glucocorticoid-like effects that prevent signs of hypocortisolism even when the cortisol concentration is low.

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Figure 242-12 Biosynthetic pathways of mineralocorticoids, corticosteroids, and androgens in the adrenal cortex. *3β-HSD,* 3β-Hydroxysteroid dehydrogenase, which converts pregnenolone to progesterone and dehydroepiandrosterone to androstenedione. This enzyme system is blocked by trilostane.

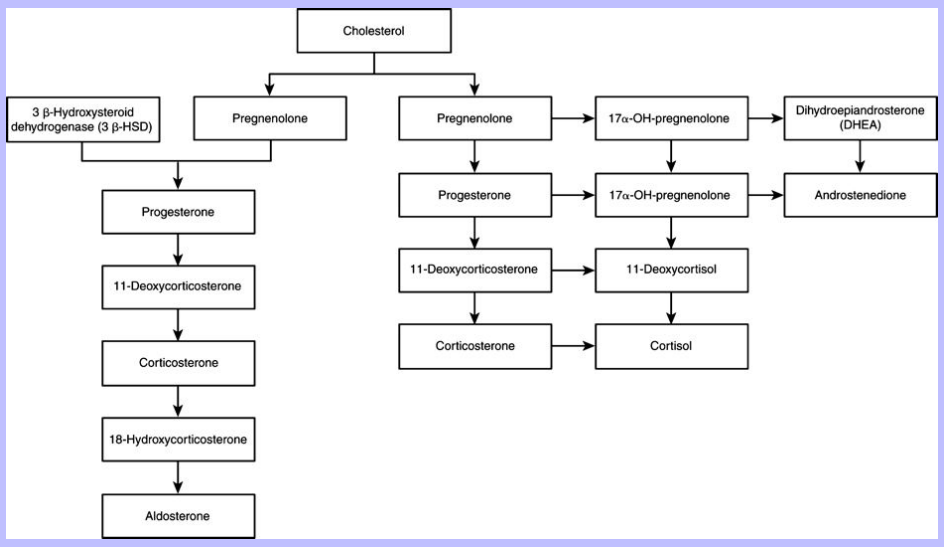
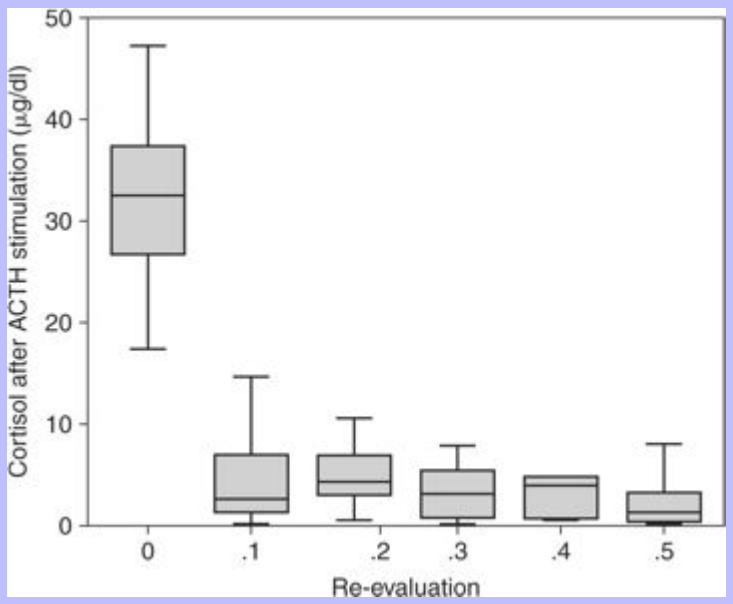


Figure 242-13 Cortisol concentrations after ACTH stimulation in dogs with PDH treated with trilostane. *0,* Prior to therapy; *1* to *5,* re-evaluations at 1, 3 to 4, 6 to 7, 12 to 16 and 24 to 28 weeks after initiation of treatment with trilostane. Data are presented as box plots; the boxes represent values from the 25th to the 75 percentile, the horizontal line in each box is the median, and the "whiskers" represent the range. (From Ruckstuhl NS et al: Results of clinical examinations, laboratory tests, and ultrasonography in dogs with pituitary-dependent hyperadrenocorticism treated with trilostane. Am J Vet Res 63:506–512, 2002.)



Frequent adjustments in the dosage of trilostane (both increases and decreases) are required, particularly during the first few weeks of treatment. Adjustments should be made in increments of 20 to 30 mg/dog. The effective dosage of trilostane differs markedly among dogs with PDH, possibly because of a significant variation among individuals in 3-beta-hydroxysteroid dehydrogenase activity in the adrenal glands. However, the response to treatment appears to stabilize over a period of time, after which dosage adjustments are seldom necessary.

Distinct changes in the ultrasonographic appearance of the adrenal glands were observed in our studies. In almost all dogs, a marked increase was seen in the thickness and echogenicity of the outer zone, which was assumed to be the adrenal cortex. This finding may reflect increased synthesis of precursors arising from an increase in ACTH secretion, or it may be the result of abolition of negative feedback normally exerted by cortisol. Studies are under way to verify this.

Overdosage of trilostane is possible and was assumed to be the cause of adverse symptoms in four of 88 dogs.[71,72] Three of the dogs survived with discontinuation of trilostane and institution of symptomatic treatment. Other problems attributed to the use of trilostane are rare and include lethargy, anorexia, vomiting, and diarrhea. These symptoms are usually mild and self-limiting. In a study of 78 dogs treated with trilostane,[72] it was not known whether the death of two dogs shortly after the start of treatment was related to the drug or to another illness. Postmortem examination of one dog revealed signs suggestive of terminal heart failure.

Our experience with trilostane is limited to treatment of canine PDH, which has entirely replaced mitotane at our hospital. It has been reported that trilostane can also effectively control hyperadrenocorticism caused by an FAT.

242.3.1.10.4 Ketoconazole

Ketoconazole, a fungistatic drug, also blocks several P-450 enzyme systems, effectively inhibiting the synthesis of glucocorticoids and androgens. Its effects on mineralocorticoids are negligible. Dogs are started at a dosage of 5 mg/kg given twice a day for 1 week. If the drug is well tolerated (i.e., no decrease in appetite or icterus is seen), the dosage is increased to 10 mg/kg given twice a day for 2 weeks. After this period, an ACTH stimulation test is performed. If the post-ACTH cortisol concentration is higher than the target range of 1 to 4 μg/dL, the dose should be increased to 15 mg/kg twice a day. Most dogs require a daily dose of 30 mg/kg for a long period for good clinical control. The disadvantages of ketoconazole are the expense, the requirement for twice daily administration for life, and the drug's lack of efficacy in up to 50% of cases. Possible side effects include anorexia, diarrhea, and increased hepatic enzyme activity. Hypocortisolism can also occur, but dogs respond rapidly to cessation of ketoconazole administration and administration of glucocorticoids. Before the introduction of trilostane, ketoconazole was primarily used in dogs that did not tolerate mitotane. Today, trilostane rather than ketoconazole would be chosen for such cases.

242.3.1.10.5 Selegiline hydrochloride

The use of selegiline hydrochloride (L-deprenyl) for the treatment of hyperadrenocorticism in dogs is controversial. L-deprenyl has been hypothesized to downregulate ACTH by enhancing the dopamine concentration, thereby controlling pituitary hyperadrenocorticism. For a number of years, various reports have described the efficacy of L-deprenyl in dogs with PDH, and aggressive advertising campaigns have been mounted. Interestingly, no scientific data were presented to substantiate these claims. A 6-month controlled clinical study revealed that of 10 dogs with PDH, treatment with L-deprenyl resulted in no clinical improvement in four dogs, worsening of symptoms in four others, and improvement in two. Several of the owners reported that dogs were more lively during treatment; this was assumed to be one reason for good owner compliance and for the improvement reported in the other studies. In those studies, evaluation of clinical signs was based on owner observations and not on scientific data. L-deprenyl is metabolized into substances with amphetamine-like structures, which may explain the improvement in the general condition and behavior of treated dogs. We do not recommend L-deprenyl for the treatment of canine PDH.[73]

242.3.1.10.6 Other drugs

A variety of other drugs (bromocriptine, cyproheptadine, metyrapone, aminoglutethimide) have been investigated for the treatment of hyperadrenocorticism; however, they have not produced favorable results.

242.3.1.11 Complications and Concurrent Disease Associated with Hyperadrenocorticism

242.3.1.11.1 Large pituitary tumors

Generally, dogs with PDH have a risk of pituitary tumor growth. Approximately 50% of dogs with PDH have a tumor that is visible on CT or MRI scans at the time of diagnosis, and in approximately 50% of all dogs with PDH, the tumor has a tendency to grow. Neurologic signs caused by expansion of a pituitary tumor are seen in about 15% to 20% of dogs with PDH.[74–76]

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Hypophyseal tumors are often categorized, according to their size, as macrotumors (equal to or greater than 10 mm in height) or microtumors (less than 10 mm in height). However, this categorization is useful for neither clinical nor imaging purposes. Tumors as small as 3 to 4 mm can be visualized using advanced imaging techniques. Neurologic symptoms occur in some dogs with tumors less than 10 mm but may not occur in others with tumors 10 mm or larger. It would appear more appropriate to use the term *macrotumor* to describe tumors visible by means of CT or MRI and the term *microtumor* to define masses that cannot be visualized. Pituitary tumors grow dorsally in the dog. The diversity of neurologic signs is due to involvement of different regions of the hypothalamus and thalamus and other brain regions.

The onset of neurologic signs may precede, coincide with, or follow (most often in clinical practice) the diagnosis of hyperadrenocorticism. Clinical signs are usually quite subtle at the start and can be recognized only by someone who knows the dog well. In most cases these signs constitute slight changes in the dog's behavior. Symptoms progress slowly to include dullness, listlessness, restlessness, loss of interest in normal activities, brief episodes of disorientation, anorexia, and weight loss. Later in the course of the disease, symptoms include ataxia, aimless pacing, and stupor. Some dogs may be misdiagnosed with blindness because mental dullness results in inappropriate responses to visual stimuli. Some symptoms, particularly anorexia, resemble those of hypocortisolism caused by medication overdose. For these reasons, careful re-evaluation, including an ACTH stimulation test, is necessary when suspicious symptoms develop.

Diagnosis of a pituitary tumor requires CT or MRI, and good correlation exists between tumor size and the severity of symptoms. In dogs with marked neurologic symptoms, tumors are frequently greater than 10 mm in height, although tumors with a height of only 0.7 to 0.8 mm may occasionally cause symptoms.[76,77] In addition to tumor size, the development of neurologic symptoms probably is related to the tumor growth rate, the size of the skull cavity, and whether peritumoral inflammation or edema is present. Radiation currently is the only treatment available. Most regimens use cobalt-60 teletherapy or a linear accelerator to administer 3.5 to 4 Gy three times a week for 4 to 6 weeks with the animal under general anesthesia. Complications are uncommon, and only rarely do dogs need to be treated with anti-inflammatory doses of steroids because of initial worsening of signs, which probably is related to

radiation-associated brain edema. Other problems include graying of hair at the entrance sites of the beam, scalp epilation, and otitis externa.

It is difficult to draw a final conclusion from the few reports available on radiation therapy, and the optimal treatment protocol has yet to be established. In our experience, hypophyseal tumors are relatively sensitive to radiation, and dramatic improvement may occur in some dogs with severe neurologic symptoms. Generally, the prognosis and severity of clinical signs are inversely related.[78] Dogs with severe neurologic symptoms and a tumor larger than 20 to 25 mm have a much poorer prognosis than dogs with mild to moderate symptoms and a tumor less than 20 mm. It is important to remember that some dogs improve during radiation therapy, whereas others require weeks for improvement or normalization. Therefore dogs should not be euthanized during or shortly after radiation treatment because of lack of improvement.

In most dogs, radiation has little or no effect or only a transient influence on the secretory nature of the tumor, and additional medical treatment is required. Recurrence of neurologic signs weeks to years later is possible, and in such cases deterioration may be rapid.

We currently recommend CT or MRI for every dog with PDH. For dogs with dexamethasone resistance (per LDDS or HDDS tests), we strongly recommend pituitary imaging. For dogs with tumors greater than 7 mm, we suggest radiation therapy regardless of whether neurologic signs are present.

242.3.1.11.1.1 Adrenal tumors.

Adrenal tumors may invade local tissues and vessels and may metastasize. Traumatic and nontraumatic rupture of the tumor may result in intra-abdominal or retroperitoneal hemorrhage or vena caval thrombosis, causing hindlimb edema.[79–81]

242.3.1.11.2 Pulmonary thromboembolism

Pulmonary thromboembolism is a potentially life-threatening complication of hyperadrenocorticism. However, because no systematic studies exist and a definitive diagnosis is often difficult, its incidence is not known. Dogs with hyperadrenocorticism that undergo surgery (e.g., adrenalectomy) are at increased risk of developing pulmonary thromboembolism. Thromboembolism may occur in other organs, but this is probably rare. It is generally accepted that hyperadrenocorticism leads to a state characterized by hypercoagulation. In humans with Cushing's syndrome, this state is thought to be related to an increase in plasma clotting factors, especially factor VIII and the von Willebrand factor complex, and to an impairment of fibrinolytic capacity.[82] Similar mechanisms are thought to occur in dogs. Recently it was shown that dogs with hyperadrenocorticism had elevated levels of factors II, V, VII, IX, X, and XII and of fibrinogen. Antithrombin was decreased, whereas thrombin-antithrombin complexes were increased.[83] Conditions such as hypertension and obesity may also play a role in the development of pulmonary thromboembolism.

An acute onset of respiratory distress (tachypnea, dyspnea, cyanosis) is characteristic of pulmonary thromboembolism, which may be difficult or impossible to diagnose definitively in veterinary patients. Pulmonary thromboembolism can result in a variety of radiographic patterns; in fact, a recent study found no radiographic abnormalities in 27% of 29 cases.[84] Therefore an animal with severe respiratory distress in which no radiographic changes are seen should be suspected of having pulmonary

thromboembolism. Abnormal radiographic findings include interstitial, alveolar, or mixed patterns; pleural effusion; increased diameter and blunting of pulmonary arteries; and decreased vascularity of affected lung lobes with increased vascularity of unaffected lobes. Echocardiography, including Doppler evaluation, is a helpful diagnostic tool in human medicine but needs further investigation in veterinary medicine. In most dogs, arterial blood gas analysis reveals hypoxemia (partial pressure of oxygen [PO_2] less than 70 mm Hg) and hypocapnia (partial pressure of carbon dioxide [PCO_2] less than 35 mm Hg). However, these are nonspecific findings of inefficient gas exchange and cannot be used alone for diagnosis. A definitive diagnosis may be obtained with pulmonary angiography or ventilation and perfusion scanning with radioisotopes. Because these procedures are either invasive or not widely available, a diagnosis often is made on the basis of clinical signs, radiographic findings, and blood gas analysis results.

Treatment is mainly empirical. In experimental conditions emboli begin to dissolve within hours of formation without treatment, and complete resolution has been documented within days. In naturally occurring disease, however, prothrombic tendencies persist. Therapy consists of general support and administration of oxygen and anticoagulants, such as heparin or warfarin. These drugs have no effect on existing emboli but are used to prevent further clot formation. One of several protocols used for heparin treatment involves an initial dosage of 200 to 300 IU/kg given every 8 hours. The dosage must be modified for each dog to maintain the activated partial thromboplastin time (aPTT) at 1.5 to 2.5 times normal. No information is available on the use of low-molecular-weight heparin. Warfarin is administered initially at a dosage of 0.1 to 0.2 mg/kg given orally every 24 hours. During the first few days, heparin should also be given to combat the initial prothrombic effects of warfarin. The warfarin dosage is then adjusted to achieve an aPTT of 1.5 to 2.5 times normal. 1609 1610

Thrombolytic agents, such as streptokinase, have the potential to dissolve clots. However, their effectiveness in naturally occurring disease has not been critically evaluated, probably because of the expense and the risk of life-threatening hemorrhage.

The prognosis in dogs with pulmonary thromboembolism is guarded to grave. Recovery, if it occurs, usually requires at least 7 to 10 days.

No studies have been done on the success of prophylactic treatment in animals at risk of developing pulmonary thromboembolism. In humans with Cushing's syndrome, it has been shown that thromboembolic complications after surgery can be significantly reduced by anticoagulant prophylaxis.[82] It may be advisable to start low-dose heparin therapy several days prior to surgery in dogs with hyperadrenocorticism and to continue administration for several days afterward.

242.3.1.11.3 Diabetes mellitus

Dogs with hyperadrenocorticism may develop diabetes mellitus because of insulin antagonism by glucocorticoids. Insulin resistance results either directly, because of a reduction in the number or efficacy of glucose transporters, or indirectly, because of an increase in the glucose concentration and resultant free fatty acid concentration. Approximately 30% to 40% of dogs with Cushing's syndrome show mild elevations in the glucose concentration, but only about 10% develop overt diabetes mellitus. Diagnosis of diabetes mellitus in a dog with previously diagnosed Cushing's syndrome usually is straightforward. However, it is much more difficult to diagnose Cushing's syndrome in a dog with established diabetes mellitus. It often is not possible to make a diagnosis based on clinical signs. Both diseases are characterized by polydipsia, polyuria, polyphagia, hepatomegaly, and sometimes weakness. Also, in

dogs with both endocrine diseases, skin and haircoat changes typical of Cushing's syndrome (bilateral symmetric alopecia, skin atrophy) may not occur or may be very mild. It may not be possible to make a diagnosis based on the results of routine laboratory tests, because a stress leukogram and increased hepatic enzyme activities occur in both diseases. The urine specific gravity in most diabetic dogs is greater than 1.025, whereas dogs with both Cushing's syndrome and diabetes mellitus often have hyposthenuria or isosthenuria. Dogs with diabetes mellitus often have false-positive results on screening tests for Cushing's syndrome, therefore the results of these tests must be interpreted carefully. To avoid false-positive results, we recommend that dogs suspected of having Cushing's syndrome and other severe illness should not undergo screening tests. Screening tests should be performed only after good glycemic control has been achieved; however, this is difficult to impossible in dogs with Cushing's syndrome. In such cases, therefore, positive results may be due to poor glycemic control or concurrent hyperadrenocorticism. Further management of such dogs must be considered carefully based on all clinical and laboratory findings.

242.3.1.11.4 Urinary tract infection, pyelonephritis, and calcium-containing uroliths

Nearly 50% of dogs with hyperadrenocorticism have a bacterial urinary tract infection. Dysuria and pyuria may not occur because of the anti-inflammatory and immunosuppressive effects of steroids. Hyperadrenocorticism may also predispose dogs to calcium-containing uroliths, because glucocorticoids increase renal calcium excretion.

242.3.1.11.5 Pancreatitis

Anecdotal reports indicate that hyperadrenocorticism may predispose dogs to pancreatitis. A recent study found that the risk of developing fatal acute pancreatitis was increased by hyperadrenocorticism, as well as by other factors.[85] The mechanism for this is unknown, but it may result from disturbed lipid metabolism.

242.3.1.11.6 Degenerative and immune-mediated diseases

The anti-inflammatory and immunosuppressive effects of cortisol can mask concurrent problems. The most common of these are degenerative arthropathy and skin allergy, which may become apparent once treatment is initiated and cortisol concentrations decrease.

242.3.1.11.7 Hypertension and glomerular disease

Systemic hypertension occurs in a large percentage of dogs with hyperadrenocorticism. Blood pressure can remain elevated despite resolution of hypercortisolemia. According to a recent study, aldosterone does not appear to contribute to hypertension in dogs with hyperadrenocorticism.[86] The major cause of hypertension may be excess cortisol, which enhances sensitivity to endogenous vasoconstrictors.

Hypertension may cause or contribute to glomerular damage and may lead to glomerulosclerosis. Glucocorticoids may also cause glomerulonephritis (see Chapter 261). Both types of glomerular lesions are associated with proteinuria.

242.4 HYPERADRENOCORTICISM IN CATS

Hyperadrenocorticism is an endocrine disorder not commonly recognized in cats. Over a 10-year period, one university clinic diagnosed Cushing's syndrome in more than 800 dogs and in only 34 cats.[26]

Similar to the incidence seen in dogs, 80% to 85% of cats have PDH, and 10% to 15% have an FAT. Adenomas and carcinomas occur with equal frequency. Adrenal tumors may secrete excessive amounts of steroids other than cortisol. Two recent case reports described cats with clinical signs of hyperadrenocorticism caused by a progesterone-secreting adrenal mass.[87,88]

242.4.1 Clinical Findings

Middle-aged to older cats are most commonly affected with hyperadrenocorticism. There does not seem to be a breed predilection; however, approximately 70% of feline cases are female. The most common clinical signs are polydipsia, polyuria, and polyphagia. Most authors have assumed that these symptoms are caused by diabetes mellitus, which develops in approximately 80% of cases, and that they therefore are late signs of hyperadrenocorticism. However, a recent case study described polydipsia and polyuria in two cats with hyperadrenocorticism that did not have concurrent diabetes mellitus and in one cat that had hyperadrenocorticism for 8 months before diabetes mellitus developed.[89] Other frequent findings include pendulous abdomen, generalized muscle wasting, lethargy, and obesity. Many cats have dermatologic symptoms, including hair loss; unkempt haircoat; truncal or patchy alopecia; fragile, thin skin prone to traumatically induced tears (so-called feline fragile skin syndrome); and secondary infections (including demodicosis). Hepatomegaly and weight loss occur less frequently.

Hyperglycemia is the most frequent laboratory abnormality. Only 10% of dogs with hyperadrenocorticism develop overt diabetes mellitus, whereas as many as 80% of cats with Cushing's syndrome are diabetic. Cats seem to be more sensitive to the diabetogenic effects of steroids than dogs, and in many cases it is only after diabetes mellitus has been diagnosed that hyperadrenocorticism is suspected. Insulin resistance is a typical feature of diabetes mellitus caused by hyperadrenocorticism. However, it should be noted that not all cats with Cushing's syndrome and concurrent diabetes mellitus are insulin resistant.

Other findings include hypercholesterolemia and an increase in ALT activity, which may be caused by hyperadrenocorticism or diabetes mellitus. Some cats have elevated ALP activity. Because the activity of a steroid-induced isoenzyme is not increased, this elevation is thought to be associated with diabetes mellitus (and hepatic lipidosis) rather than with hyperadrenocorticism.[90]

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242.4.1.1 Specific Endocrine Testing

A diagnosis of hyperadrenocorticism should be based on the results of one or more of the screening tests (urine C:C ratio, ACTH stimulation test, LDDS test). The endogenous ACTH concentration, an HDDS test, and adrenal ultrasonography can be used to differentiate PDH from an FAT in cats.

242.4.1.2 Urine Creatinine to Cortisol Ratio

Slightly more than 70% of cortisol (free cortisol and metabolites) is eliminated in the urine in dogs, whereas only 18% is eliminated in the urine of cats. Despite this difference, the urine C:C ratio of cats with

hyperadrenocorticism is significantly higher than that of healthy cats, and this test can be used in the diagnosis of Cushing's syndrome.[91] Urine should be collected by the owner at home. It is important to remember that false-positive results may be caused by other disease processes. Goosens et al.[91] reported a reference range of 2 to 36 × 10^{-6} based on the results of 42 healthy cats. Our reference range, using 31 healthy cats, was 0 to 4 × 10^{-6}. This discrepancy is possibly due to the different types of radioimmunoassay used. The amount of cortisol metabolites measured varies among assays, therefore it is critical that reference ranges be established for each assay.

242.4.1.3 ACTH Stimulation Test

In both dogs and cats, the ACTH stimulation test is mainly a test of adrenal reserve, and its major role is to rule in or rule out hypoadrenocorticism. The test's sensitivity is low, and because a variety of nonadrenal illnesses can cause abnormal test results, its specificity is also low. According to the test protocol most often used, blood samples for cortisol determination are taken before and 30 and 60 minutes after intramuscular administration of 125 µg/cat of a synthetic polypeptide containing the first 24 aminoacids of ACTH (e.g., Cortrosyn, Synacthen). The time to maximum peak cortisol response is longer and the maximum cortisol concentration is significantly higher after intravenous administration than after intramuscular administration. Therefore the protocol for intravenous administration is to collect blood samples before and 60 and 90 minutes after administration of ACTH. Because peak effect of cortisol is less consistent in the cat than in the dog, two post-ACTH samples are recommended. Reference ranges for the cat are slightly lower than those for the dog and should be established for the laboratory and protocol used. In our laboratory, the upper limit for the normal post-ACTH cortisol concentration using the intramuscular protocol is 13 µg/dL.[92] We consider levels between 13 and 16 µg/dL to be borderline, and a concentration above 16 µg/dL to be consistent with hyperadrenocorticism.

242.4.1.4 Low-Dose Dexamethasone Suppression Test

The degree and duration of adrenocortical suppression after dexamethasone administration is more variable in cats than in dogs. It appears that a dosage of 0.1 mg/kg of dexamethasone suppresses cortisol levels in healthy cats and cats with nonadrenal illness more reliably than 0.01 mg/kg of dexamethasone, which is the dosage used in dogs. Currently, the protocol most often used involves collection of blood samples for production of plasma or serum before and 4 and 8 hours after intravenous administration of 0.1 mg/kg of dexamethasone. Cortisol levels of less than 1 µg/dL at 4 and 8 hours are considered normal, levels between 1 and 1.4 µg/dL are borderline, and levels greater than 1.4 µg/dL are consistent with hyperadrenocorticism. Post-dexamethasone suppression of cortisol concentrations at 4 and 8 hours does not occur in cats with an FAT. Approximately 70% of cats with PDH show no or inadequate suppression.[90]

242.4.1.5 Measurement of Endogenous ACTH

Healthy cats may have very low ACTH concentrations, therefore the measurement of endogenous ACTH test can be used only after a diagnosis of hyperadrenocorticism has been made. Normal to elevated levels of ACTH support a diagnosis of PDH, and low to undetectable levels indicate an FAT. Sample handling is critical (see discussion earlier in this chapter).

242.4.1.6 High-Dose Dexamethasone Suppression Test

Compared with dogs, a higher dose of dexamethasone (1 mg/kg) has been advocated to differentiate between PDH and an FAT in cats; however, very limited information is available. Blood samples should be taken before and 4 and 8 hours after administration of dexamethasone. Suppression (less than 50% of baseline or less than 1.4 μg/dL) is consistent with PDH. No or insufficient suppression may be due either to an FAT or to PDH and cannot be used to differentiate between the two conditions.

242.4.2 Adrenal Ultrasonography

High-resolution transducers have made ultrasonographic visualization of the adrenal glands possible in cats, and reference ranges have been reported.[92] Symmetric adrenal glands of normal or enlarged size are suggestive of PDH, whereas unilateral enlargement or an adrenal gland with a masslike appearance suggests an FAT. Detailed information on the ultrasonographic appearance of the adrenal glands in cats with hyperadrenocorticism currently is limited.

242.4.3 Treatment

Hyperadrenocorticism is a debilitating disease in the cat. The deleterious effects of chronic hypercortisolism on skin fragility as well as on immune and cardiovascular function are frequently responsible for the death of untreated cats. Therefore treatment should be pursued, although compared to dogs, options are more limited and medical treatment is not as successful.

242.4.3.1 Adrenalectomy

Adrenalectomy (unilateral in cats with an FAT, bilateral in cats with PDH or bilateral FATs) appears to be the most successful of the treatment options available.[93] The surgical protocol and the medical management of cats during and after the procedure are similar to those followed in dogs. After discontinuation of intravenous steroids, oral prednisolone (2.5 mg twice daily) should be given. Mineralocorticoids (fludrocortisone, 0.1–0.2 mg/cat) should be administered to cats after bilateral adrenalectomy or to those that have hyperkalemia and/or hyponatremia after surgery. Serum electrolyte concentrations should be evaluated twice daily for several days after surgery. After bilateral adrenalectomy, cats require lifelong supplementation with both mineralocorticoids and glucocorticoids, whereas after unilateral adrenalectomy, supplementation generally can be weaned off over a 2-month period. Postsurgical complications are common and include sepsis, pancreatitis, thromboembolism, and hypoadrenocorticism. Surgery-related death occurs in about 30% to 40% of cases.

Successful adrenalectomy typically results in resolution or marked improvement of clinical signs within 2 to 4 months. In about 50% of cases, diabetes resolves, and in others the insulin requirement decreases.[89,93]

242.4.3.2 Hypophysectomy

Recently, transsphenoidal hypophysectomy for the treatment of PDH was described in seven cats.[94] Two cats died within 4 weeks of surgery. Remission was achieved in five cats, although relapse occurred in one of these 19 months after surgery. Diabetes mellitus resolved in two of the four cats that had the disease. In

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the future, transsphenoidal hypophysectomy may be the treatment of choice for cats with hyperadrenocorticism.

242.4.3.3 Radiation Treatment

The success rate for radiation treatment in cats has been variable at best. However, the number of cats treated with radiation is very small, therefore conclusions are difficult to draw.

242.4.3.4 Medical Treatment

A number of different medical protocols have been used in cats with hyperadrenocorticism. However, success rates are variable or poor, and long-term results are often disappointing. Medical treatment may be indicated for the presurgical management of hyperadrenocorticism and may improve the outcome of surgery.

242.4.3.4.1 Mitotane

The use of mitotane to treat hyperadrenocorticism has been discouraged in the past because of a perceived sensitivity of cats to chlorinated hydrocarbons. In addition, the success rate of mitotane treatment was reported to be poor.[26] One recent report describes successful long-term mitotane treatment in a cat with PDH.[95]

242.4.3.4.2 Ketoconazole

Treatment with ketoconazole (15 mg/kg given twice a day) resulted in clinical improvement in some cats and no response in others. Severe thrombocytopenia was reported in one cat and was thought to be due to an adverse drug reaction.

242.4.3.4.3 Metyrapone

Metyrapone has been successfully used as a treatment prior to bilateral adrenalectomy.[96,97] The optimal dose was 65 mg/kg given orally every 12 hours.

242.4.3.4.4 Trilostane

There are no published reports on the use of trilostane in cats with hyperadrenocorticism.

242.4.3.5 Prognosis

Hyperadrenocorticism in cats is a serious disease with a guarded to grave prognosis. Medical therapy has limited success, and the outcome of surgery is often hampered by the debilitated condition of the patient.

242.4.4 Hyperaldosteronism

Primary hyperaldosteronism, also called *Conn's syndrome* in human medicine, is a very rare disease in dogs and cats. It is usually caused by a unilateral adenoma or rarely by a carcinoma of the zona glomerulosa of the

adrenal gland. Bilateral adrenal hyperplasia in association with hyperaldosteronism has been reported in only one dog.[98] Aldosterone is the principal regulator of sodium and potassium balance and is important in the maintenance of normal intravascular fluid volume. It also plays a role in the control of acid-base equilibrium. In conditions involving excessive autonomous aldosterone secretion, sodium and water are retained, leading to expansion of the extracellular fluid volume and hypertension. The increase in sodium and water is usually limited by an "escape" mechanism. Nevertheless, hyperaldosteronism tends to be associated with extracellular volume expansion and arterial hypertension. The renin system is suppressed. Increased potassium excretion leads to progressive depletion of body potassium, development of hypokalemia, and hypokalemic metabolic alkalosis. Aldosterone also stimulates the excretion of phosphorus and magnesium. Other characteristics of hyperaldosteronism include resistance to vasopressin and disturbed vasopressin release.[99]

Clinical signs consist of weakness, which may be episodic; ventroflexion of the neck (in cats); stiff gait; myalgia; and lethargy. Hypertension may be present and may cause hypertensive retinopathy. Recently polydipsia and polyuria were described as the lead symptoms in a dog with an aldosteronoma.[99] Moderate to severe hypokalemia is the typical and most consistent finding. The sodium concentration may be normal or only slightly elevated. Definitive diagnosis requires demonstration of an inappropriately elevated aldosterone concentration with a low plasma renin concentration. Ultrasonography and CT are useful for localization and staging of the tumor. Initial treatment should be directed at alleviation of hypokalemia. Surgical intervention is the treatment of choice for tumors with no detectable metastases. For animals with metastases or in the rare case of bilateral hyperplasia, potassium supplementation and spironolactone, an aldosterone antagonist, can be given.

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243 CHAPTER • 243 Hypoadrenocorticism

Michael E. Herrtage

Hypoadrenocorticism is a syndrome that results from deficient production and secretion of glucocorticoids and/or mineralocorticoids by the adrenal cortices. Destruction of more than 90% of both adrenal cortices causes a deficiency of all adrenocortical hormones and the resulting clinical condition is termed *primary hypoadrenocorticism* (Addison's disease). Secondary hypoadrenocorticism is characterized by deficient production and secretion of adrenocorticotropic hormone, ACTH, which leads to atrophy of the adrenal cortices and impaired secretion of glucocorticoids. The production of mineralocorticoids, however, usually remains adequate because ACTH has only minor tropic effects on mineralocorticoid production. Primary and secondary hypoadrenocorticism differ not only in their pathophysiology but also in their clinical presentations.

243.1 ANATOMY AND PHYSIOLOGY

One adrenal gland is located craniomedial to each kidney, in retroperitoneal fat. The right adrenal gland lies between the medial surface of the cranial pole of the right kidney and the lateral aspect of the caudal vena cava at the level of the thirteenth thoracic vertebra. The right phrenicoabdominal vein crosses the ventral surface of the gland before joining the caudal vena cava. The left adrenal gland is found craniomedial to the border of the left kidney at the level of the second lumbar vertebra. Medially it is bounded by the descending aorta between the cranial mesenteric artery and the left renal artery.

Together, both adrenal glands from normal dogs weigh about 1 g. On cross-section, the adrenal cortex appears pale yellow whereas the medulla is dark brown. The cortex completely surrounds the medulla and consists of three distinct zones: the outer zona glomerulosa (arcuata) makes up about 25% of the cortex, the middle zona fasciculata makes up approximately 60%, and the inner zona reticularis accounts for the remaining 15% of the cortex. The medulla is adjacent to the zona reticularis, which makes up 10% to 20% of the total volume of the adrenal gland.

The adrenal cortex produces about 30 different hormones, many of which are believed to have little or no clinical significance (Figure 243-1). The hormones can be divided into three groups based on their predominant actions: *mineralocorticoids,* which are important in electrolyte and water homeostasis; *glucocorticoids*, which promote gluconeogenesis; and small quantities of sex hormones, particularly male hormones that have weak androgenic activity.

Aldosterone is the most important mineralocorticoid and is produced by the zona glomerulosa. The principal glucocorticoid, cortisol, and the sex hormones are produced in the zonas fasciculata and reticularis. Glucocorticoid and mineralocorticoid release are controlled by separate mechanisms (Figure 243-2).

243.1.1 Regulation of Glucocorticoid Release

Glucocorticoid release is controlled almost entirely by adrenocorticotrophic hormone (ACTH) secreted by the anterior pituitary, which in turn, is regulated by corticotrophin releasing hormone (CRH) from the hypothalamus (see Figure 243-2). CRH is secreted by the neurons in the anterior portion of the paraventricular nuclei within the hypothalamus and is transported to the anterior pituitary by the portal circulation, where it stimulates ACTH release. There is probably an internal or “short loop” negative feedback control by ACTH on CRH. ACTH secreted into the systemic circulation causes cortisol release with concentrations rising almost

immediately. Cortisol has direct negative feedback effects on (1) the hypothalamus to decrease formation of CRH and (2) the anterior pituitary gland to decrease the formation of ACTH. These feedback mechanisms help regulate the plasma concentration of cortisol.

243.1.2 Regulation of Mineralocorticoid Release

Aldosterone release is influenced primarily by the reninangiotensin system and by plasma potassium levels (see Figure 243-2). Renin is secreted into the blood by the cells of the juxtaglomerular apparatus within the kidneys. This apparatus consists of specialized cells in the wall of the afferent arteriole immediately proximal to the glomerulus as well as specialized epithelial cells of the distal convoluted tubule adjacent to that arteriole, the macula densa. Renin release may be stimulated by stretch receptors in the juxtaglomerular apparatus in response to hypotension, reduced renal blood flow, or by sodium and chloride receptors in the macula densa. Renin is also released by sympathetic nerve stimulation and is inhibited by angiotensin II, antidiuretic hormone, hypertension, and increased reabsorption of sodium by the renal tubules.

Renin is a proteolytic enzyme that splits circulating angiotensinogen, an alpha-2 globulin produced by the liver, into the decapeptide, angiotensin I. Angiotensin I is hydrolysed to the octapeptide, angiotensin II by angiotensin converting enzyme found almost exclusively in the pulmonary capillary endothelium. Angiotensin II is a powerful vasoconstrictor that also stimulates aldosterone secretion from the zona glomerulosa. Through its action on the distal convoluted tubule, aldosterone has negative feedback effects on the juxtaglomerular apparatus. Potassium has a direct stimulatory effect on the zona glomerulosa cells to release aldosterone. ACTH and sodium play less significant roles in aldosterone secretion. ACTH is necessary to maintain normal aldosterone output. In the absence of ACTH, the zona glomerulosa partially atrophies, causing mild to moderate aldosterone deficiency compared with almost total atrophy of the other zones.

The main function of aldosterone is to protect against hypotension and potassium intoxication. Aldosterone promotes sodium, chloride, and water reabsorption as well as potassium excretion in many epithelial tissues including the intestinal mucosa, salivary glands, sweat glands, and kidneys. Its main site of action is the renal tubule, where it promotes sodium and chloride reabsorption in the proximal convoluted tubule and sodium reabsorption by exchange with potassium in the distal convoluted tubule. It is one of the complex regulatory systems for the regulation of extracellular fluid electrolyte concentrations, extracellular fluid volume, blood volume, and arterial pressure.

243.2 PRIMARY HYPOADRENOCORTICISM (ADDISON'S DISEASE)

Primary hypoadrenocorticism results from progressive destruction of the adrenal cortices, which must involve more than 90% of the function before clinical signs become apparent. The condition is also referred to as Addison's disease, after the English physician, Thomas Addison, who in 1855 described the syndrome in humans. In those days, the most common cause was destruction of the adrenals by chronic tuberculosis.

Primary hypoadrenocorticism is rare in the dog although probably occurs more frequently than is recognized. Hypoadrenocorticism appears to be rare in cats with only one case series and a few case reports published.[1–3] The clinical signs, diagnosis, and treatment of hypoadrenocorticism are similar in the dog and cat.

243.3 PATHOGENESIS

243.3.1 Idiopathic Adrenocortical Atrophy

This is the most common cause in the dog and is thought to be the end result of immune-mediated destruction of the adrenal cortices. Immune-mediated destruction of the adrenal cortices is the most common cause of human primary hypoadrenocorticism and 21-hydroxylase (see Figure 243-1) is considered to be the major autoantigen.[4] The presence of antiadrenal antibodies in two dogs and characteristic histopathologic findings in another support the hypothesis of immune-mediated destruction.[5] The increased predisposition of primary hypoadrenocorticism in young to middle-aged female dogs is also suggestive of an immune-mediated disease. An immune-mediated etiology is also suspected in the cat.

In approximately 50% to 60% of humans with primary hypoadrenocorticism, the disease is associated with other immune-mediated disorders such as Hashimoto's thyroiditis, insulin-dependent diabetes mellitus, hypoparathyroidism, primary gonadal failure, and atrophic gastritis. Autoimmune polyglandular disease has also been recognized in the dog with hypoadrenocorticism and hypothyroidism being the most common combination, but diabetes mellitus and/or hypoparathyroidism may also occur concurrently.[6]

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Figure 243-1 Major biosynthetic pathways of adrenocortical steroid production. The zona glomerulosa produces mineralocorticoids. The zona fasciculata and reticularis produce glucocorticoids and sex hormones.

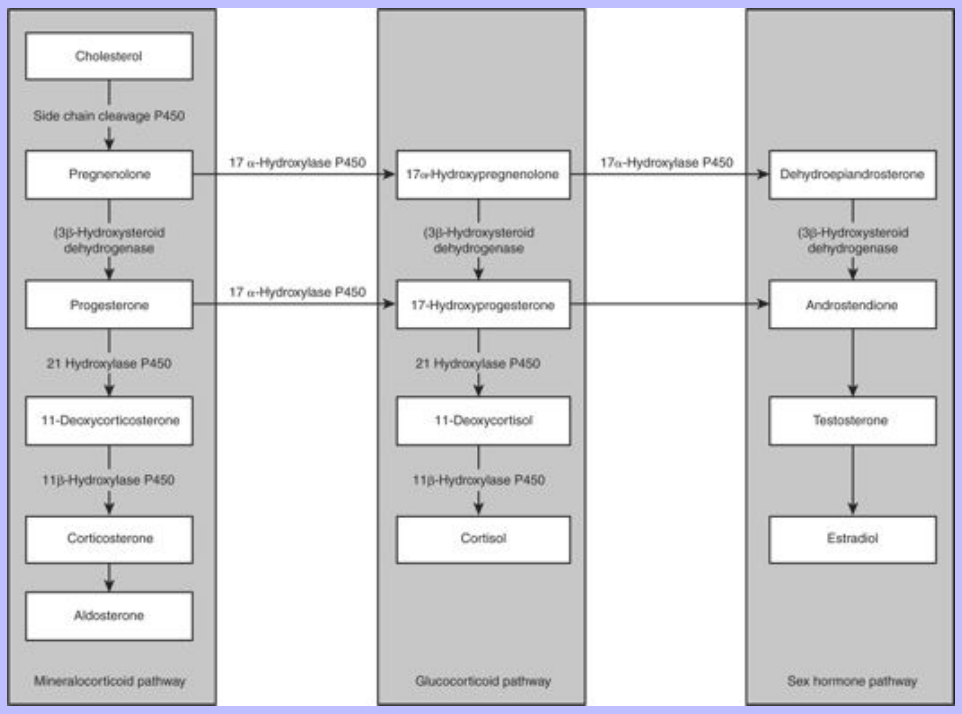
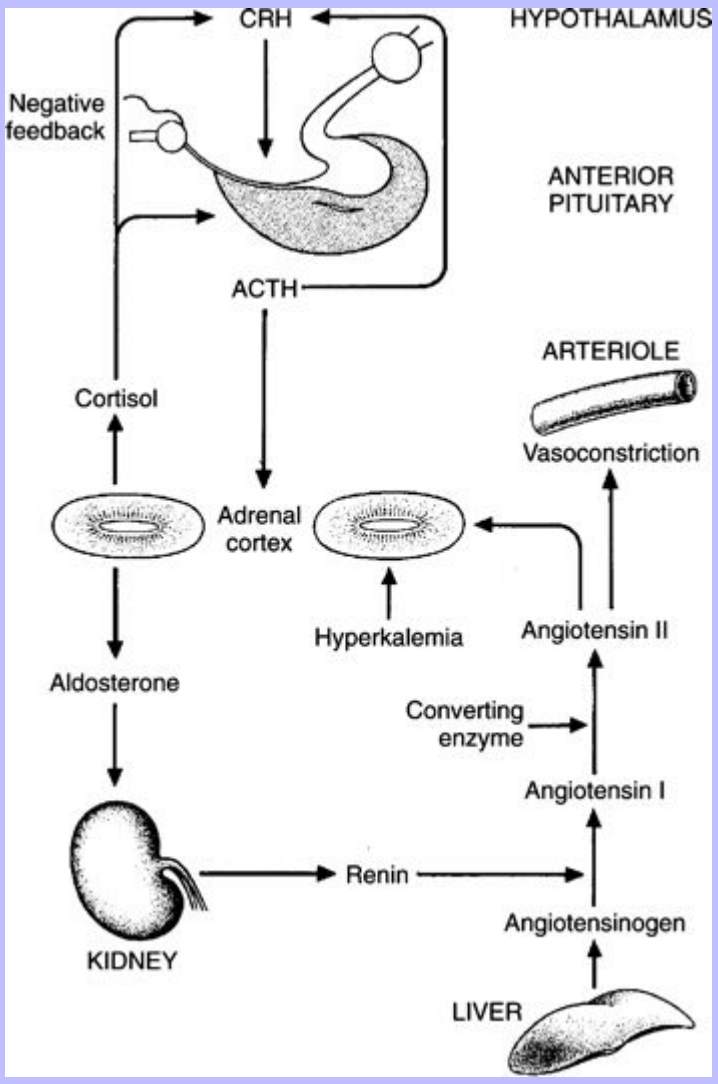


Figure 243-2 Regulation of glucocorticoid and mineralocorticoid release. Corticotrophin releasing hormone (CRH), adrenocorticotrophic hormone (ACTH)



243.3.2 Drug-Induced Adrenocortical Necrosis

Iatrogenic hypoadrenocorticism is a possible complication of mitotane therapy used in the treatment of canine hyperadrenocorticism (see Chapter 242). Although mitotane usually spares the zona glomerulosa and therefore mineralocorticoid secretion, cases of complete adrenocortical failure may occur in as many as 5% of treated dogs. In most of these dogs, the adrenal cortex does not recover when mitotane therapy is withdrawn and permanent mineralocorticoid and glucocorticoid replacement therapy is required. This is a separate entity from

transient glucocorticoid deficiency, which may occur following overdosage of mitotane during the induction or maintenance phase of therapy for hyperadrenocorticism.

Adrenocortical necrosis has also been reported following treatment of canine hyperadrenocorticism with trilostane.[7] Since trilostane is a reversible inhibitor the 3β-hydroxysteroid dehydrogenase enzyme system, which blocks adrenal synthesis of glucocorticoids, mineralocorticoids, and sex hormones (see Figure 243-1), this complication is not common. However, awareness of this possible complication is important because prompt treatment is required to correct this life-threatening situation.

243.3.3 Bilateral Adrenalectomy

The surgical removal of both adrenals has been used for the treatment of canine and feline pituitary-dependent hyperadrenocorticism. The surgery is technically difficult and there is a high morbidity and mortality rate even when performed by experienced surgeons. These dogs and cats must be treated for hypoadrenocorticism with replacement hormone therapy for the rest of their lives.

243.3.4 Other Possible Causes

Rarely, canine hypoadrenocorticism can be caused by hemorrhage or infarction of the adrenal glands, granulomatous or neoplastic involvement of the adrenal glands, amyloidosis of adrenal cortices, or following trauma to the adrenal glands.

243.4 PATHOPHYSIOLOGY

Adrenocortical pathology leads to mineralocorticoid and glucocorticoid deficiency. Aldosterone is the major mineralocorticoid and promotes sodium, chloride, and water reabsorption as well as potassium excretion in many epithelial tissues, including the intestinal mucosa, salivary glands, sweat glands, and kidneys. Its main site of action is the renal tubule, where it promotes sodium and chloride reabsorption in the proximal convoluted tubule and sodium reabsorption by exchange with potassium in the distal convoluted tubule. Deficiency of aldosterone causes impaired ability to conserve sodium and water and failure to excrete potassium leading to hyponatremia and hyperkalemia. Hyponatremia induces lethargy, depression, and nausea while causing development of hypovolemia, hypotension, reduced cardiac output, and decreased renal perfusion. Hyperkalemia causes muscle weakness, hyporeflexia, and impaired cardiac conduction. Glucocorticoid deficiency causes decreased tolerance of stress, loss of appetite, vomiting, diarrhea, abdominal pain, and lethargy.

243.5 SIGNALMENT

243.5.1 Breed

Many breeds of dog have been reported with hypoadrenocorticism, but great Danes, Portuguese water dogs, Rottweilers, standard Poodles, West Highland white terriers, and soft-coated Wheaten terriers appear to be at greater risk of developing hypoadrenocorticism compared with dogs of other breeds.[8] Evidence of familial occurrence and the possibility of an hereditary factor has been suggested in standard Poodles,[9,10] bearded collies,[11,12] and Leonbergers,[13] although the precise genetic mechanism responsible for inheritance of the disease remains undetermined.

No breed predisposition has been identified in the cat. Most reported cases of hypoadrenocorticism have been in domestic shorthaired and longhaired cats.

243.5.2 Age

Hypoadrenocorticism appears to be a disease of the young and middle-aged dog with an age range of 2 months to 14 years and a median age of 4 to 6 years. A similar age range has been noted in cats with hypoadrenocorticism.

243.5.3 Sex

Approximately 70% of dogs with naturally occurring hypoadrenocorticism are female and sexually intact females have been shown to have a significantly higher risk of developing hypoadrenocorticism than spayed females.[8] This is similar to autoimmune Addison's disease in humans and supports the hypothesis of an immune-mediated pathogenesis in most dogs. However, in the bearded collie and standard poodle, in which hypoadrenocorticism is considered to be highly heritable, both sexes are affected with equal probability.[10,12] No sex prediposition has been reported in cats.

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243.6 CLINICAL SIGNS

The clinical signs of primary hypoadrenocorticism vary from mild to severe with the progression being either acute or chronic. The chronic form of hypoadrenocorticism with clinical signs present for weeks to months is more common than the acute disease in the dog, although the distinction between these two syndromes is not always clear.

243.6.1 Acute Primary Hypoadrenocorticism

The clinical appearance of acute hypoadrenocorticism is that of hypovolemic shock (an Addisonian crisis). The animal is usually found in a state of collapse or collapses when stressed. Other signs include weak pulse, profound bradycardia, abdominal pain, vomiting, diarrhea, dehydration, and hypothermia. Bradycardia is an inappropriate response in a collapsed, hypovolemic patient and warrants immediate investigation. Acute hypoadrenocorticism is rapidly progressive, life threatening, and represents a true medical emergency. Symptomatic therapy with aggressive fluid therapy will help most afflicted dogs and cats by allowing more time to make a diagnosis.

243.6.2 Chronic Primary Hypoadrenocorticism

The clinical signs in the chronic form are often vague and nonspecific and may be exacerbated by stress (Box 243-1). The diagnosis should be considered in any dog or cat with a waxing and waning type of illness or that shows episodic weakness and collapse. The most consistent clinical signs include anorexia, vomiting, lethargy, weight loss, diarrhea, obtundation, depression, shaking or shivering, muscle fasciculations, severe muscle weakness, and polydipsia/polyuria. Less common signs such as regurgitation due to megaesophagus[14], painful muscle cramping[15], and hypoglycemic seizures[16] have been reported. The severity of each sign can vary during the course of the disease and may be interspersed with periods of apparent good health often following nonspecific veterinary therapy, usually consisting of cage rest, glucocorticoid therapy and/or parenteral fluid

administration. Hypoadrenocorticism can easily be mistaken for primary renal, gastrointestinal, or neuromuscular diseases.

Common findings on physical examination apart from obtundation and weakness include dehydration, bradycardia, weak femoral pulses, and prolonged capillary refill time. In a few cases, severe gastrointestinal hemorrhage with melena, hematochezia, and occasionally hematemesis can occur, resulting in profound anemia.[17] Since the history and clinical findings are not pathognomonic for hypoadrenocorticism, a high index of suspicion and a careful and critical evaluation of dogs and cats are necessary to arrive at the correct diagnosis.

243.7 CLINICOPATHOLOGIC FINDINGS

243.7.1 Hematology

Hematologic changes may include lymphocytosis, eosinophilia and mild normocytic, normochromic, nonregenerative anemia (Box 243-2). However, these findings are not as consistent as those changes seen in hyperadrenocorticism. Normal or increased eosinophil and lymphocyte counts in a sick animal with signs compatible with hypoadrenocorticism are significant, because the expected response to stress would result in eosinopenia and lymphopenia. A mild anemia may not be appreciated until the dog has been rehydrated because of the hemoconcentration effect of dehydration. Profound anemia (PCV<20%) is usually found in association with gastrointestinal hemorrhage.

243.7.1.1 Box • 243-1 Clinical Signs of Primary Hypoadrenocorticism (Addison's Disease)

Anorexia

Lethargy/depression

Weakness, usually episodic

Vomiting

Waxing and waning illness

Weight loss or failure to gain weight

Dehydration

Diarrhea or occasionally constipation

Polydipsia and/or polyuria

Collapse or syncope

Restlessness/shaking/shivering

Regurgitation

Painful muscle cramps

Melena

Weak pulse

Bradycardia

Abdominal pain

243.7.2 Biochemistry

The most consistent laboratory findings in hypoadrenocorticism are prerenal azotemia, hyponatremia, hyperkalemia, and mild to moderate metabolic acidosis. However, approximately 10% of dogs with primary hypoadrenocorticism have normal serum electrolyte concentrations and these cases are referred to as *atypical Addison's disease*.[18]

243.7.2.1 Blood Urea, Creatinine, and Urine Specific Gravity

Blood urea nitrogen (BUN) and serum creatinine concentrations are increased secondary to reduced renal perfusion and decreased glomerular filtration rate. Reduced renal perfusion results from hypovolemia, reduced cardiac output and hypotension, which in turn result from chronic fluid loss through the kidneys, acute fluid loss through vomiting, and/or diarrhea and inadequate fluid intake. This prerenal azotemia is often associated with hyperphosphatemia. Increases in BUN also result from gastrointestinal hemorrhage, which is common. This usually explains the discordant moderate-to-severe increase in BUN in a dog or cat with Addison's disease that has only a mild-to-moderate increase in serum creatinine concentration.

Prerenal azotemia is usually associated with concentrated urine (specific gravity >1.030) whereas the urine concentration in dogs and cats with primary renal failure is often isothenuric or only mildly concentrated (1.008 to 1.025). The urine specific gravity in dogs and cats with hypoadrenocorticism is variable but is usually between 1.015 and 1.030, which may cause confusion for the clinician as it is more dilute than would be expected in an animal with prerenal azotemia. This reduction in urine specific gravity develops in hypoadrenocorticism because of impaired concentrating ability secondary to chronic sodium loss reducing the renal medullary concentration gradient.[19] With appropriate fluid therapy, the blood urea and creatinine

concentrations in cases of hypoadrenocorticism will usually quickly return to normal confirming that the azotemia is prerenal.

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243.7.2.1.1

Box • 243-2 Routine Laboratory Findings in Primary Hypoadrenocorticism (Addison's Disease)

243.7.2.1.1.1

Hematology

Lymphocytosis

Eosinophilia

Relative neutropenia

Anemia usually a normocytic, normochromic, non-regenerative anemia, but can be blood loss anemia associated with gastrointestinal hemorrhage

243.7.2.1.1.2

Biochemistry

Azotemia

- Increased blood urea
- Increased creatinine
- Increased phosphate

Hyponatremia (<135 mEq/L)

Hyperkalemia (>5.5 mEq/L)

Reduced sodium: potassium ratio (< 25:1)

Reduced bicarbonate and total CO_2 concentrations

Hypochloremia

Hypercalcemia

Hypoglycemia

Hypoalbuminemia

243.7.2.1.1.3

Urinalysis

Specific gravity variable (usually 1.015 to 1.030)

243.7.2.2 Sodium and Potassium Concentrations

The serum sodium concentration is usually less than 135 mEq/L and the serum potassium concentration usually greater than 5.5 mEq/L. However, because of the variability of these two abnormalities, the ratio of sodium to potassium may be more reliable than the absolute values. The normal ratio varies between 27:1 and 40:1, whereas in dogs and cats with hypoadrenocorticism, the ratio is usually less than 25:1 and may be below 20:1. Serum chloride concentration is also reduced in association with sodium and frequently chloride concentrations below 100 mEq/L are found in animals with hypoadrenocorticism.

Concurrent hypovolemia, hyponatremia, and hyperkalemia may develop in other conditions apart from hypoadrenocorticism such as gastrointestinal disease, chronic blood loss, acute and chronic renal failure, chronic hepatic failure, chronic heart failure, repeated drainage of chylous and non-chylous pleural effusions, lymphangiosarcoma, and pregnancy (Box 243-3).[20–22] In a recent review of low sodium: potassium ratios in 34 dogs, renal failure or urinary tract disease leading to decreased urine excretion of potassium accounted for the low ratio in most of the dogs with sodium: potassium ratios of between 19.9 and 15.[23] These low ratios were more strongly associated with high serum potassium concentrations than with low serum sodium concentrations. Four of the dogs in that study had sodium: potassium concentrations ratios of less than 15 and each dog had hypoadrenocorticism. However, although *suggestive* of hypoadrenocorticism, a low sodium: potassium ratio of less than 15 is not *diagnostic* of hypoadrenocorticism. Pseudohyperkalemia, which is defined as a spurious increase in serum or plasma potassium concentration caused by in vitro changes, may be seen in hemolysed blood samples, especially from Akitas[24] and in dogs with thrombocytosis or extreme leucocytosis.[25]

243.7.2.2.1 Box • 243-3 Differential Diagnosis for Significant Hyperkalemia and/or Hyponatremia in Dogs and Cats

Renal or urinary tract disease

- Acute primary renal failure
- Chronic severe oliguric or anuric renal failure (rare)
- Urethral obstruction
- Uroabdomen (ruptured ureter, bladder, or urethra)
- Postobstructive diuresis
- Nephrotic syndrome

Hypoadrenocorticism

- Severe gastrointestinal disease
  - Parasitic infestations
    - Trichuriasis
    - Ascariasis
    - Ancylostomiasis
  - Salmonellosis
  - Viral enteritis
    - Parvovirus
    - Distemper
  - Gastric dilatation/volvulus
  - Gastrointestinal perforation
  - Severe malabsorption
  - Idiopathic hemorrhagic enteritis
  - Pancreatitic disease
- Severe hepatic failure
  - Cirrhosis
  - Neoplasia
- Severe metabolic or respiratory acidosis

Congestive heart failure

Massive release of potassium to the extracellular fluid

- Crush injuries
- Aortic thrombosis
- Rhabdomyolysis
  - Heat stroke
  - Exertional
- Massive infections
- Massive hemolysis (rare)

Chylous and non-chylous pleural effusions

Pregnancy

Lymphangiosarcoma

Pseudohyperkalemia

- Japanese Akitas and related breeds
- Severe leukocytosis (>100,000/mm^3)
- Severe thrombocytosis (>1,000,000/mm^3)

Diabetes mellitus

Primary polydipsia

Inappropriate ADH secretion

Drug-induced

Potassium-sparing diuretics

Nonsteroidal anti-inflammatory agents

Angiotensin-converting enzyme inhibitors

Potassium-containing fluids

Most of these diagnosis/conditions are rarely associated with abnormal electrolyte abnormalities.

References 20 through 25.

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Approximately 10% of dogs with primary hypoadrenocorticism have normal serum electrolyte concentrations at the time of initial examination. It is generally believed that these dogs with atypical Addison's disease have early or mild primary hypoadrenocorticism and that typical electrolyte abnormalities would develop with time. Rarely isolated primary hypocortisolemia has been reported in dogs that never develop serum electrolyte abnormalities.[26]

243.7.2.3 Calcium Concentration

Mild to moderate hypercalcemia is seen in about a third of dogs with hypoadrenocorticism. Usually these dogs are most severely affected by the disease. The mechanism by which hypercalcemia occurs in hypoadrenocorticism remains to be elucidated, but hemoconcentration, increased renal tubular reabsorption, and decreased glomerular filtration are thought to contribute. The differential diagnosis of hypercalcemia includes neoplasia, primary hyperparathyroidism, chronic renal failure, hypervitaminosis D, and granulomatous disease. In a study of 40 dogs with hypercalcemia, hypoadrenocorticism was the second most common cause and accounted for 25%.[27] In the same study, the degree of hypercalcemia was found to be significantly lower in dogs with hypoadrenocorticism (mean plasma calcium concentration 14.0 ± 1.6 mg/dL) than in lymphoproliferative disease (mean plasma calcium concentration 17.2 ± 2.8 mg/dL).

243.7.2.4 Blood Glucose Concentration

Theoretically, dogs with hypoadrenocorticism should have a tendency to develop hypoglycemia because glucocorticoid deficiency reduces glucose production by the liver and peripheral cell receptors become more sensitive to insulin. However, hypoglycemia is uncommon.[28] The potential for this complication should remain a concern for the clinician as rarely the severity of the hypoglycaemia may result in clinical signs of ataxia, disorientation, or seizures.[16]

243.7.2.5 Serum Albumin Concentration

Moderate to severe hypoalbuminemia has been noted in dogs with hypoadrenocorticism. The pathogenesis of hypoalbuminemia in primary hypoadrenocorticism is unknown, but gastrointestinal hemorrhage, impaired intestinal absorption of nutrients, and impaired albumin synthesis may be involved. The major causes of hypoalbuminemia include increased loss (for example, protein losing nephropathy or enteropathy, blood loss, severe exudation, or hemorrhage into body cavities) and decreased production (for example, severe malabsorption, maldigestion, or malnutrition or inadequate production in chronic liver disease). In one study, 39% of dogs with hypoadrenocorticism were found to have hypoalbuminemia.[29] However, other studies have shown the frequency of hypoalbuminemia to be considerably lower, between 6% and 12% of cases.[8,30] Some of the hypoalbuminomic dogs also have hypocholesterolemia, microhepatica, and/or ascites.

243.7.2.6 Liver Enzyme Concentrations

Mild to moderate increases in liver enzyme activities, such as alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, are found in some dogs with hypoadrenocorticism. Although the precise cause of these increases is unknown, reduced cardiac output and poor tissue perfusion probably play a role. Increased liver enzyme activities hypoalbuminemia, and hypoglycemia would raise the suspicion of primary hepatic disease in some dogs with hypoadrenocorticism and clinicians should be aware of this potential confusion.

243.7.2.7 Acid-Base Balance

Mild to moderate metabolic acidosis is common in dogs with hypoadrenocorticism. Total carbon dioxide concentrations and serum bicarbonate determinations are reduced. Acidosis develops because reduced aldosterone concentrations impair renal tubular secretion of hydrogen ions. Hypotension and poor renal perfusion are likely to contribute to the acidosis.

243.7.3 Electrocardiographic Findings

Hyperkalemia impairs cardiac conduction and may cause life-threatening arrhythmias. These changes can be assessed by electrocardiography (ECG) (Figure 243-3). Although the ECG changes do not correlate precisely with serum potassium concentrations, probably because of the influence of other electrolyte abnormalities particularly the cardioprotective effects of increased calcium, metabolic acidosis, and impaired tissue perfusion, the following guidelines have proved helpful:

>5.5 mEq/L	peaking of the T wave shortening of the Q-T interval
>6.5 mEq/L	increased QRS duration
>7.0 mEq/L	P wave amplitude decreased
	P-R interval prolonged
>8.5 mEq/L	P wave absent (sinoatrial standstill) severe bradycardia

In some cases, bizarre QRS complexes representing ventricular extrasystoles, paroxysmal ventricular tachycardia, or ventricular fibrillation may be seen and these are most likely the result of hypoxia and/or hyperkalemia.

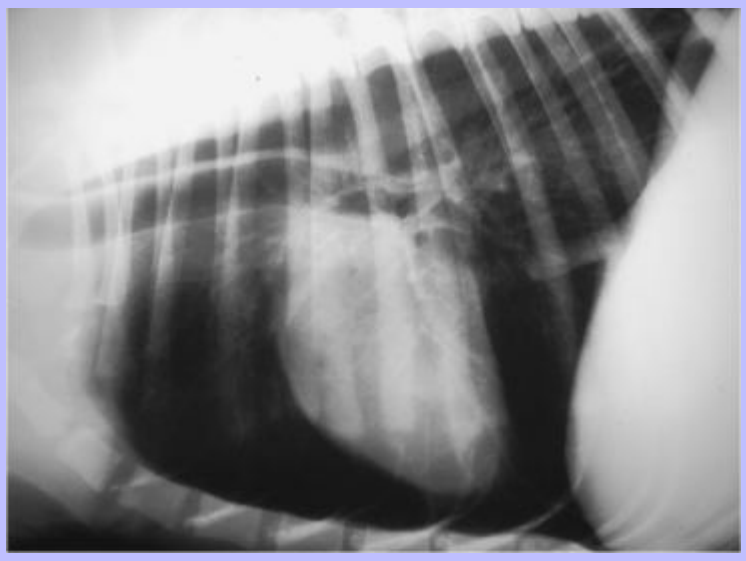
Electrocardiography can also be used for monitoring the response to treatment. An improvement in the ECG tracing suggests a reduction in serum potassium concentration.

243.7.4 Radiographic Findings

Dogs with hypoadrenocorticism may show radiographic signs of hypovolemia, which include: microcardia, decreased size of pulmonary vessels, reduced size of the caudal vena cava, and microhepatica (Figure 243-4). These changes, however, are not specific and only represent hypovolemia and dehydration regardless of the cause. The severity of these radiographic findings usually correlates with the degree of hypovolemia. 1618 1619

Figure 243-3 Electrocardiograms from a 4-year-old bearded collie dog with primary hypoadrenocorticism taken **(A)** before and **(B)** after supplementation with glucocorticoids and mineralocorticoids. Paper speed is 25 mm/sec and sensitivity is 1 cm = 1mV. **A,** The P waves are absent, the T waves are peaked, and there is profound bradycardia. The serum sodium concentration was 138 mEq/L and the serum potassium 9.5 mEq/L. **B,** ECG after treatment showing sinus arrhythmia. The serum sodium concentration was 142 mEq/L and the serum potassium 5.4 mEq/L.

Figure 243-4 Lateral thoracic radiograph of a standard poodle with primary hypoadrenocorticism showing the effects of hypovolemia, including microcardia, decreased pulmonary vasculature, and reduced caudal vena cava. The esophagus is dilated with air in the cranial thorax as evidenced by a dorsal tracheal stripe sign.



A few dogs with hypoadrenocorticism develop esophageal dilation or megaesophagus as a result of generalized muscle weakness and this can be seen on thoracic radiographs as an air-filled, dilated esophagus. Image-intensified fluoroscopy, using barium paste or barium mixed with food demonstrates a complete absence of esophageal peristaltic activity. The cause of esophageal dilatation in hypoadrenocorticism remains unclear but was considered to be attributable to the effect of abnormal sodium and potassium concentrations on membrane potential and neuromuscular function.[31] However, in some dogs with hypoadrenocorticism and megaesophagus, abnormal serum electrolyte concentrations were never documented, which suggests that the esophageal dilatation was associated with glucocorticoid deficiency.[14,32] The megaesophagus resolves rapidly with appropriate treatment for hypoadrenocorticism.

243.7.5 Ultrasonography

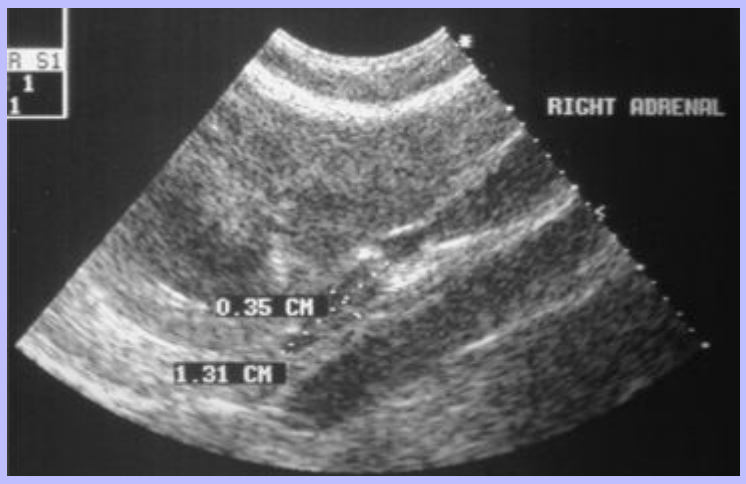
With high resolution ultrasound equipment, it is possible for an experienced ultrasonographer to image the adrenal glands of most normal and diseased dogs. Ultrasonographic examination of the adrenal glands has been performed in dogs with hypoadrenocorticism, and the adrenal glands were shown to be shorter (median values: left adrenal 12.1 mm; right adrenal 13.1 mm) and thinner (median values: left adrenal 2.4 mm; right adrenal 2.5 mm) than those of healthy dogs.[33] However, there is considerable variation in the normal measurements of canine adrenal glands with maximum dimensions (length × thickness) in the range 10 to 52 mm × 2 to 12 mm.[34,35] There is poor correlation between these dimensions and body weight and there are no published normal adrenal measurements for different breeds of dog. Although ultrasonography could not

distinguish between primary and secondary hypoadrenocorticism, the technique was considered to be a useful screening test especially in critically ill animals with acute disease (Figure 243-5).

243.7.6 Blood Pressure

Hypotension is present in nearly all humans with primary hypoadrenocorticism but is an uncommon finding in those with secondary hypoadrenocorticism. No large series of blood pressure measurements in dogs with hypoadrenocorticism have been published, but hypotension has been recorded in individual cases.[36]

Figure 243-5 A longitudinal sonogram of the right adrenal gland of a Labrador retriever with primary hypoadrenocorticism. The adrenal thickness (3.5 mm) and the adrenal length (13.1 mm) have been measured.



243.7.7 Endocrine Tests

243.7.7.1 ACTH Stimulation Test

The ACTH stimulation test is the gold standard test for providing a definitive diagnosis of hypoadrenocorticism. Intravenous synthetic preparations of ACTH, either cosyntropin (Cortrosyn, Organon) or tetracosactrin (Synacthen, Alliance), should be used. Absorption of depot products such as ACTH gel cannot be relied on, particularly if the animal is collapsed or severely hypotensive. The protocol is described in Box 243-4.

In dogs and cats with hypoadrenocorticism, the resting cortisol concentration will be low or undetectable with a subnormal or negligible cortisol response to ACTH. About 85% of dogs with naturally occurring hypoadrenocorticism have basal and post-ACTH cortisol concentrations of less than 1.0 µg/dL (30 nmol/L) and more than 90% of cases have cortisol concentrations that do not exceed 2.0 µg/dL (60 nmol/L) at any time during the test.[37] Similar low cortisol concentrations have been reported in cats with hypoadrenocorticism. The ACTH stimulation test, however, does not distinguish between primary

hypoadrenocorticism and secondary hypoadrenocorticism due to pituitary failure or iatrogenic glucocorticoid administration.

243.7.7.2 Endogenous Plasma ACTH Concentration

Plasma ACTH concentrations are useful in distinguishing primary from secondary hypoadrenocorticism, but stringent and meticulous sample handling is crucial since the activity of ACTH in the plasma will reduce rapidly resulting in falsely low values and incorrect interpretation (see Box 243-4). Dogs and cats with primary hypoadrenocorticism have extremely increased endogenous ACTH concentrations (>500 pg/mL), due to the lack of a negative feedback of cortisol on the pituitary, whereas those with secondary hypoadrenocorticism have low or even undetectable concentrations of ACTH (<5 pg/mL).

243.7.7.3 Plasma Aldosterone Concentrations

Basal aldosterone concentrations are of little or no diagnostic value. Plasma aldosterone concentrations should be measured in response to ACTH stimulation (see Box 243-4). Theoretically, plasma aldosterone concentrations should help differentiate between primary hypoadrenocorticism (with reduced cortisol and aldosterone concentrations) and secondary hypoadrenocorticism (with normal aldosterone and reduced cortisol concentrations). However, aldosterone assays are not widely available and few studies have reported.

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243.7.7.3.1 Box • 243-4 Protocols for Endocrine Tests for Hypoadrenocorticism

243.7.7.3.1.1 The ACTH Stimulation Test

- Collect 2 to 3 mL plasma or serum sample for basal cortisol concentration.*
- Inject 0.25 mg of synthetic ACTH (cosyntropin, Cortrosyn, Oganon: tetracosactrin; Synacthen, Alliance) intravenously to dogs or cats over 5 kg. Use only 0.125 mg in dogs or cats less than 5 kg.
- Collect a second sample for cortisol concentration 30 to 60 minutes later in the dog. In the cat, two samples should be collected at 60 and 90 to 120 minutes to ensure the peak response is measured.

243.7.7.3.1.2 Plasma Endogenous ACTH Concentration

- Blood (3 mL) is collected into a cooled plastic EDTA tube and centrifuged at 4° C immediately.
- The plasma should then be harvested and stored frozen (at less than −20° C) in a plastic tube.
- Samples must be transported to the laboratory frozen and must be kept frozen until assayed.
- Stringent and meticulous sample handling is crucial since hormone activity in the plasma will reduce rapidly resulting in falsely low values and incorrect interpretation.

- The endogenous ACTH assay must be validated for use in dogs and cats, otherwise the test may provide spurious results that could be misleading.

* The recent administration of glucocorticoids such as hydrocortisone, prednisolone, or prednisone may result in elevated cortisol concentrations due to cross-reactivity in many cortisol assays. For this reason glucocorticoids should be withheld for at least 24 hours before testing. There is no cross-reactivity with dexamethasone, but dexamethasone will suppress cortisol concentrations in animals with an intact hypothalamic-pituitary adrenal axis.

After stimulation with ACTH in normal dogs, plasma aldosterone concentrations should double, unless the basal concentration is already in the high-normal range.[38] In dogs suffering from primary hypoadrenocorticism with hypoaldosteronism, the basal aldosterone concentration is low with minimal or no increase in the post-ACTH aldosterone concentration. Some dogs with atypical Addison's disease have basal and post-ACTH aldosterone concentrations below the detectable limit of the assay despite the presence of normal serum sodium and potassium concentrations. Other dogs with atypical Addison's disease may have higher aldosterone concentrations than classical cases of hypoadrenocorticism both before and after ACTH stimulation, but concentrations are still abnormally decreased.

243.7.8 Treatment of Primary Hypoadrenocorticism

243.7.8.1 Acute Primary Hypoadrenocorticism

243.7.8.1.1 Intravenous saline

Hyperkalemia is life threatening in the acute Addisonian crisis but can be reliably treated with aggressive intravenous fluid therapy using normal saline (0.9% sodium chloride) at an initial rate of 60 to 80 mL/kg/hour for the first 1 to 2 hours. This treatment also helps in correcting the hypovolemia, hyponatremia, and hypochloremia. Urine output should be measured and if possible a central venous catheter should be used to monitor central venous pressure during fluid therapy. The response to treatment is often dramatic and other treatments for hyperkalemia such as glucose and insulin therapy or calcium administration are not usually required in animals with hypoadrenocorticism. The serum potassium decreases because of the dilution effect of the saline and the improvement in renal perfusion and glomerular filtration, which encourages further excretion of potassium into the urine. Although most cases respond quickly, generally within 12 hours, a few cases require intravenous fluid therapy over several days to correct the electrolyte imbalance and prerenal azotemia.

243.7.8.1.2 Intravenous glucose

If hypoglycemia is suspected, a 50% glucose solution should be added to the normal saline to produce a 5% dextrose solution. If hypoglycemia is known to be present, a bolus injection of 1 mL/kg of 50% glucose should be given intravenously initially before continuing with the 5% dextrose in 0.9% sodium chloride solution.

243.7.8.1.3 Glucocorticoid therapy

Glucocorticoid therapy should be used early in the treatment of the acute Addisonian crisis to correct hypocortisolemia. The glucocorticoids of choice in an acute crisis include the following:

hydrocortisone sodium succinate	10 mg/kg IV repeated every 3 to 6 hours or as a constant rate infusion at 0.5 mg/kg/hour[39]
prednisolone sodium succinate	5 mg/kg IV repeated every 3 to 6 hours
dexamethasone sodium phosphate	0.5 to 1.0 mg/kg IV given once

If possible, glucocorticoids should be withheld until after completion of the ACTH stimulation test since hydrocortisone and prednisolone have the potential to cross-react with cortisol in the assay falsely increasing the cortisol concentration. Dexamethasone can be used because it will not interfere with the cortisol assay and is recommended if glucocorticoid therapy cannot be delayed.

Mineralocorticoid preparations are not essential for treating an Addisonian crisis. However, mineralocorticoid therapy is recommended for any dog or cat suspected to have hypoadrenocorticism, once the ACTH stimulation test has been completed. As discussed, intravenous saline should help correct the hypovolemia, hyponatremia, hyperkalemia, and azotemia typical of this condition. No serious adverse reactions are associated with mineralocorticoid administration to non-hypoadrenal animals and the beneficial effects to those with the disease are complimentary to saline administration. Therefore it is recommended that desoxycorticosterone pivalate (DOCP; 2.2 mg/kg, IM) be administered. If the animal has hypoadrenocorticism, the drug will need to be given once again at 25 days, usually subcutaneously. The standard in management of these animals in crisis is administration of saline during completion of the ACTH stimulation test followed immediately by both glucocorticoid and mineralocorticoid therapy. Alternatives to DOCP have been tried. Hydrocortisone has been recommended as it possesses glucocorticoid and mineralocorticoid activities identical to those of endogenous cortisol.[39] Prednisolone also has some mineralocorticoid activity. Neither hydrocortisone or prednisolone have been shown to be superior to dexamethasone, which has no mineralocorticoid activity, in treating an Addisonian crisis (Table 243-1).

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Table • 243-1 Relative Potencies of Adrenal Steroids

COMPOUND	GLUCOCORTICOID EFFECT	MINERALO-CORTICOID EFFECT
Cortisol/hydrocortisone	1	1
Prednisolone/prednisone	5	0.8
Dexamethasone	37	Negligible
Betamethasone	40	Negligible
Desoxycorticosterone	Negligible	50
Fludrocortisone	10–20	150
Aldosterone	0	500

243.7.8.2 Chronic Primary Hypoadrenocorticism (Maintenance Therapy)

243.7.8.2.1 Mineralocorticoid therapy

Dogs and cats with primary hypoadrenocorticism that have the classic electrolyte disturbances of hyponatremia, hyperkalemia, and hypochloremia, require lifelong treatment with mineralocorticoids.

Use of mineralocorticoid supplementation in those with atypical Addison's disease, where the electrolyte concentrations are normal, is more complex. In one study, two dogs with atypical primary hypoadrenocorticism were discharged on glucocorticoid supplementation only and both dogs died within 9 days of a presumed Addisonian crisis.[40] However, rarely some dogs with atypical primary hypoadrenocorticism have an isolated glucocorticoid deficiency and normal mineralocorticoid concentrations; these respond well to just glucocorticoid replacement therapy as do those with secondary hypoadrenocorticism.[26] Certainly it is prudent to try and differentiate primary and secondary hypoadrenocorticism or isolated glucocorticoid deficiency with plasma ACTH concentrations and basal and post-ACTH stimulated plasma aldosterone concentrations. While awaiting test results, it is recommended to administer both mineralocorticoid and glucocorticoid replacement therapy to reduce the possibility of an acute Addisonian crisis developing.

There are two preparations used for mineralocorticoid supplementation, fludrocortisone acetate, and desoxycorticosterone pivalate.

243.7.8.2.2

Fludrocortisone acetate (Florinef, Squibb)

Fludrocortisone is a potent oral synthetic adrenocortical steroid with mainly mineralocorticoid effects, although it retains some glucocorticoid activity. It is available in 0.1 mg tablets. An initial dose of 15 µg/kg of fludrocortisone is administered once daily. The response is monitored and serum electrolytes measured after 5 to 7 days. The dose rate should then be adjusted until the serum sodium and potassium concentrations are within the normal range. Frequently the dose of fludrocortisone has to be increased during the first 6 to 18 months of therapy to maintain normal electrolyte concentrations and in a few of these cases, fludrocortisone may have to be administered twice daily. In one study, the daily maintenance dose of fludrocortisone increased from an initial median dose of 13 µg/kg to a final median dose of 23 µg/kg.[40] In the same study, the final dose of fludrocortisone administered to more than half the dogs ranged from 15 to 30 µg/kg/day.

Adverse effects develop in some dogs, particularly those receiving high doses of fludrocortisone to maintain serum electrolyte concentrations within the normal range. These include mild signs of iatrogenic hyperadrenocorticism (i.e., polyuria, polydipsia, polyphagia, and weight gain) due to the glucocorticoid effects of fludrocortisone (see Table 243-1).

243.7.8.2.3

Desoxycorticosterone pivalate (Percorten-V, Novartis)

Desoxycorticosterone pivalate is a long acting ester of desoxycorticosterone acetate, a synthetic corticosteroid with only mineralocorticoid activity and no glucocorticoid activity. It is formulated into a microcrystalline suspension for injection. This preparation is not available in all countries, but studies have shown it to be effective in replacing the mineralocorticoid deficiency in dogs with hypoadrenocorticism.[41] It is considered the drug of choice in the United States (editor's note). The recommended dosage is 2.2 mg/kg intramuscularly or subcutaneously every 25 days. In another study, lower doses of between 1.4 and 1.9 mg/kg were found to be effective in controlling electrolyte concentrations and this study also showed that the interval between injections varied among dogs, ranging from 14 days to 35 days.[40]

Signs of iatrogenic hyperadrenocorticism have not been associated with long-term use of desoxycorticosterone pivalate since it possesses negligible glucocorticoid activity (see Table 243-1).

However, some dogs developed anorexia and depression in the presence of normal electrolyte concentrations, which resolved promptly with glucocorticoid replacement therapy.

243.7.8.2.4 Glucocorticoid therapy

The majority of dogs treated with fludrocortisone do not require daily glucocorticoid supplementation for maintenance therapy after the initial period of treatment. Those treated with DOCP should also be given glucocorticoids. Glucocorticoids at replacement dosages are administered for the first 1 to 2 weeks of treatment until the animal is stable and then gradually reduced. If glucocorticoid therapy is discontinued, owners of dogs and cats with hypoadrenocorticism should always be provided with a supply of prednisolone tablets to be given if the pet appears unwell (depressed, anorexic, or vomiting). Prednisolone at a dose of 0.1 to 0.2 mg/kg daily should be sufficient as glucocorticoid replacement for those animals that do require glucocorticoids. Higher doses are more likely to produce signs of iatrogenic hyperadrenocorticism.

243.7.8.2.5 Salt supplementation

Sodium chloride tablets or salting of the food should be instigated at a dose 0.1 mg/kg/day initially to help correct hyponatremia but can be phased out and is not usually required long-term in most cases. Dogs requiring unusually high doses of fludrocortisone, however, may respond to a lower dose of fludrocortisone if concurrently provided with salt supplementation.

243.7.9 Prognosis

The prognosis with hypoadrenocorticism is excellent when appropriate maintenance therapy has been used together with thorough owner education. In one study, the median survival time for dogs with hypoadrenocorticism was 4.7 years with a range 7 days to 11.8 years.[40] In this study, age, breed, and sex were not shown to influence survival time and no significant difference was found in the survival time of dogs treated with fludrocortisone compared with desoxycorticosterone pivalate. The long-term prognosis also appears to be excellent in cats, although fewer cases have been studied.[2]

243.8 SECONDARY HYPOADRENOCORTICISM

Secondary hypoadrenocorticism is associated with a deficiency of glucocorticoids caused by a deficiency in ACTH production and/or release. The production of mineralocorticoids, although reduced, generally remains adequate to control serum sodium and potassium concentrations.

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243.8.1 Causes of Secondary Hypoadrenocorticism

Secondary hypoadrenocorticism can be associated with destructive lesions; for example, large nonfunctional tumors in the hypothalamus or pituitary. More commonly, however, it is an iatrogenic condition associated with prolonged suppression of ACTH by drug therapy with glucocorticoids or progestogens such as megestrol acetate.[42,43]

243.8.2 Clinical Signs

The clinical signs are variable, but may include depression, anorexia, occasional vomiting or diarrhea, weak pulse, and sudden collapse when stressed. If the secondary hypoadrenocorticism is associated with glucocorticoid therapy, then clinical signs of iatrogenic hyperadrenocorticism (Cushing's disease) are usually present.

243.8.3 Diagnosis

The diagnosis of secondary hypoadrenocorticism is based on a failure of the plasma cortisol concentrations to respond to ACTH stimulation together with low or undetectable endogenous plasma ACTH concentrations. If measured, the plasma aldosterone concentrations may be reduced, but basal concentrations will increase with ACTH stimulation.

243.8.4 Treatment

Glucocorticoid replacement, using prednisolone at a dose of 0.1 to 0.2 mg/kg daily is indicated for immediate correction of the clinical signs. Further treatment and the prognosis depend on the cause of the disease and whether it can be treated. Management of glucocorticoid therapy and the prevention of iatrogenic hyperadrenocorticism should be considered for all patients on long-term therapy with glucocorticoids or progestogens.

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244 CHAPTER • 244 Gastrointestinal Endocrine Disease

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244.1 GASTROINTESTINAL ENDOCRINOLOGY

244.1.1 Endocrine, Neurocrine, and Paracrine Activation

A gastrointestinal (GI) hormone is classically defined as a substance that (1) is found in gastrointestinal endocrine cells, (2) is released by physiologic stimuli (e.g., feeding), (3) circulates in blood, (4) binds to a cell receptor at a distant site, and (5) evokes a biologic response.[1,2] However, the characterization of an event as the physiologic result of a hormonal action may be exceedingly difficult. It is now clear that many substances previously classified as gastrointestinal hormones are neither confined to the gastrointestinal tract nor solely blood-borne. For example, many of the peptides localized in GI endocrine cells (e.g., cholecystokinin, substance P, neurotensin, and somatostatin) also may be found in GI neurons and act as neurocrine substances.[3] As enteric neuropeptides, these substances may evoke similar or different biologic responses.

Some of these same peptides (e.g., cholecystokinin, substance P, somatostatin) are also located outside the enteric nervous system in vagal afferent fibers or central nervous system neurons. Thus some GI hormones may also function as enteric or brain neuropeptides. A further complication is that some GI endocrine cells may release peptides into the extracellular fluid from which they diffuse to, and directly act on, neighboring cells. Thus a GI peptide may evoke a biologic response through a paracrine mechanism of activation that operates independent of, or in parallel to, an endocrine mechanism of activation. Finally, some substances (e.g., somatostatin) may evoke biologic responses through endocrine, paracrine, and neurocrine mechanisms: endocrine regulation of gastric acid secretion, paracrine regulation of antral gastrin secretion, and neurocrine regulation of smooth muscle contraction.

Although it is clear that some GI peptides evoke biologic responses through an endocrine mechanism, it is equally clear that other GI peptides activate cells through a multitude of cellular pathways: endocrine, neurocrine, and paracrine. The endocrine, neurocrine, or paracrine status of each well-established gastrointestinal peptide and other bioactive substances is reviewed in this chapter. An overview of endocrine, neurocrine, and paracrine mediators may be found in Table 244-1.

244.1.2 Endocrine Substances and Endocrine Cell Types

Gastrointestinal endocrinology has developed from a small subset of endocrinology consisting of three distinct peptides (secretin, gastrin, cholecystokinin) with local secretagogue effects, to a biologic discipline made up of more than 100 bioactive peptides, all of which are expressed in a controlled cell-specific manner. This chapter reviews only those GI hormones (and enteric neuropeptides and paracrine mediators) for which there are clearly defined biologic functions. Just as knowledge of bioactive peptides has proliferated in recent years, so too has knowledge of the cell types that produce these substances. More than 20 different endocrine cell types have been identified in the GI tract, and the number continues to grow. Differences in cell type and lineage have been addressed in recent reviews.

244.1.3 Gastrointestinal Hormones

244.1.3.1 Gastrin-Cholecystokinin Family

GI hormones[1,2,4] and related peptides have been divided into structurally homologous families, one of which consists of gastrin and cholecystokinin (CCK). Gastrin and CCK share five basic characteristics: (1) partial sequence homology; (2) similar, but not identical, biologic activities; (3) heterogeneity—each hormone exists in different molecular forms; (4) ubiquity—each hormone is synthesized in different cell types; and (5) differential principality—different molecular forms predominate in different tissues and cells.[1,4,5]

244.1.3.1.1 Gastrin

Gastrin exists in several molecular forms that contain 34, 17, and 14 amino acids, respectively. G-34, also known as *big gastrin*, is the most abundant form of gastrin in serum. G-17, known as *little gastrin*, is less abundant than G-34 in serum but is much more potent in stimulating gastric acid secretion. Mini gastrin (G-14) has little biologic effect. Endocrine cells (G cells) in the gastric antrum and duodenum secrete gastrin in response to protein meals and, to a lesser extent, gastric distension.[1,4,5]

Table • 244-1 Overview of Endocrine, Neurocrine, and Paracrine Mediators

SUBSTANCE	PHYSIOLOGIC RELEASE	SITE OF ACTION	EFFECT
GI Hormones			
Gastrin	Intra-gastric peptides, gastric distension	Gastric parietal and chief cells	H^+ and pepsinogen secretion
		Pancreatic acinar cells	Enzyme secretion
		Stomach, duodenum, pancreas	Growth
Cholecystokinin	Duodenal fatty acids, amino acids, H^+	Gallbladder	Contraction
		Sphincter of Oddi	Relaxation
		Pancreas	Enzyme secretion and growth
		Stomach	Inhibition of gastric emptyingHCO_3^- and water secretion
Secretin	Duodenal H^+, fatty acids	Pancreatic duct cells, biliary epithelium, duodenum	
Oxyntomodulin	Ileal/colonic glucose and lipid	Gastric parietal cells	Inhibition of H^+ secretion
GLP-1	Duodenal fatty acids	Pancreatic islet (β) cells	Stimulates insulin secretion (incretin during euglycemia)
	Ileal fatty acids	Stomach	Inhibition of gastric emptying (“ileal brake”)
GLP-2	Carbohydrates, lipids, SCFA	Small intestine, colon	Inhibits gastric emptying (ileal brake) and secretion
			Crypt cell proliferation, suppression of apoptosis
			Reduces gut permeability and bacterial translocation
Gastric inhibitory polypeptide	Fatty acids, glucose, amino acids	Duodenum, jejunum, ileum	Inhibition of gastric and intestinal motility
			Stimulates insulin secretion (incretin during euglycemia)
Somatostatin	Lipids, protein, and bile	Stomach, intestine, pancreas	Inhibition of gastric, intestinal, and pancreatic secretion
Motilin	H^+ and lipids	Stomach, duodenum, jejunum	Increases GES pressure, stimulates propulsive motility
			Stimulates gastric, pancreatic, and biliary secretion
Neurotensin	Fatty acids	Stomach, pancreas, gallbladder	Stimulation of gastric and pancreatic secretion
			Gallbladder contraction
Pancreatic polypeptide	Protein, cholinergic reflexes	Pancreas	Inhibition of pancreatic enzyme and fluid secretion

Peptide YY	H^+ and lipids	Ileum and colon	Ileal brake, proliferation of gut mucosa
		Stomach and pancreas	Inhibition of secretion (H^+, pancreatic enzyme)
5-Hydroxytryptamine	H^+	Intestine and colon	Stimulation of motility and secretion
Ghrelin	Dietary protein	Pituitary	Stimulation of growth hormone secretion
Enteric Neuropeptides			
Substance P	Luminal distension, H^+, hyperosmolarity	Stomach, intestine, colon	Sphincteric contractions, intestinal peristalsis
		Pancreas	Stimulation of pancreatic enzyme secretion
Vasoactive intestinal polypeptide	Vagal stimulation	Stomach, intestine, colon	Increased blood flow, stimulation of fluid secretion
		Stomach, intestine, colon Pancreas	Relaxation of smooth muscle Stimulation of fluid and bicarbonate secretion
Opioids	Intestinal distension	Stomach, intestine, colon	Inhibition of longitudinal smooth muscle contraction Stimulation of circular smooth muscle contraction Inhibition of water and electrolyte secretion
Bombesins (GRP and Neuromedin B)	Vagal stimulation	Stomach	Stimulation of gastric acid secretion
		Pancreas	Stimulation of pancreatic enzyme secretion
		Gallbladder	Stimulation of gallbladder contraction
Somatostatin	Lipids and protein	Stomach, intestine, pancreas	Descending inhibitory reflex of peristalsis
Gastrin/CCK	Intestinal distension	Ileum and colon	Ileal and colonic contractions
Neuropeptide Y	Intestinal distension	Intestine and colon	Inhibition of intestinal motility
5-Hydroxytryptamine	H^+ and hypertonic solutions	Stomach, intestine, colon	Regulation of migrating myoelectric complex
Paracrine Mediators			
Histamine	Vagal stimulation	Stomach	Stimulation of gastric acid secretion
Somatostatin	Lipids and proteins	Stomach	Inhibition of gastrin secretion
		Pancreas	Regulation of insulin and glucagon secretion

Prostaglandins	H^+, gastric distension	Stomach	Stimulation of bicarbonate and glycoprotein secretion Stimulation of epithelial cell renewal and blood flow Inhibition of prostanoid receptors

CCK, cholecystokinin; *GES*, gastroesophageal sphincter; *GLP-1*, glucagon-like peptide-1; *GLP-2*, glucagons-like peptide-2; *GRP*, gastrin-releasing peptide; *SCFA*, small chain fatty acids.

The most important biologic action of gastrin is the stimulation of gastric acid secretion by gastric oxyntic (parietal) cells. A substantial fraction of the gastric acid secretory response to protein meals is, in fact, mediated by gastrin. However, interactions between gastrin, acetylcholine (neurocrine stimulant), and histamine (paracrine stimulant) determine the final gastric acid secretory output.[6] Most evidence suggests that the gastrin effect occurs through the bindingof gastrin to gastrin receptors on oxyntic cells, although one study suggests that the gastrin effect might be indirectly mediated through gastrin receptors on gastric mucosal immunocytes.[7]

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Other important biologic actions of gastrin include stimulation of gastric pepsinogen secretion, gastric mucosal blood flow, antral motility, pancreatic enzyme secretion, and of pancreatic, gastric, and duodenal growth.[1,4,5,8] Pancreatic islet cells (delta cells) are a site of gastrin synthesis and secretion in fetal and neonatal animals.[8] Malignant transformation of these islet cells in adult animals results in functional gastrinomas. All but one of the gastrinomas that have been reported in the dog or cat have been of pancreatic origin (see Gastrinoma).

244.1.3.1.2

Cholecystokinin

Cholecystokinin (CCK) also exists in several molecular forms: CCK-63, CCK-58, CCK-39, CCK-33, CCK-12, CCK-8, and CCK-5. The predominant forms in serum are CCK-33, CCK-39, and CCK-58 and probably account for most of the GI hormone responses.[1,2,4] CCK-8 is the predominant form found in neurons and probably accounts for most of the enteric and central nervous system neuropeptide responses. Endocrine cells (I cells) in the duodenum and jejunum secrete CCK in response to intraduodenal fatty acids, amino acids, and H^+ ion.[1,2,4]

As a gastrointestinal hormone, CCK evokes several important biologic responses, most importantly, contraction of the gallbladder and stimulation of pancreatic enzyme secretion. Although CCK receptors have been demonstrated on both gallbladder smooth muscle cells and pancreatic acinar cells, it is now clear that CCK evokes gallbladder contraction and pancreatic enzyme secretion through activation of presynaptic cholinergic neurons at both sites.[4,8]

Other important endocrine actions of CCK include augmentation of pancreatic fluid secretion in the presence of secretin, relaxation of the sphincter of Oddi, inhibition of the gastric emptying of liquids, and stimulation of pancreatic growth.[1,4] Because CCK has trophic effects on pancreatic growth,[8] it has been suggested that canine juvenile pancreatic atrophy might result from CCK deficiency. However, CCK secretory deficiency was not observed in a group of young dogs with exocrine pancreatic insufficiency.[9] CCK has two important biologic actions as an enteric or brain neuropeptide (see Enteric Neuropeptides).

244.1.3.2 Secretin-Enteroglucagon-Gastric Inhibitory Polypeptide Family

Another structurally homologous group of GI hormones include secretin, enteroglucagon, gastric inhibitory polypeptide (GIP), as well as the enteric neuropeptides vasoactive intestinal polypeptide (VIP) and peptide histidine-isoleucine (PHI).

244.1.3.2.1 Secretin

Like gastrin and CCK, secretin exists in several molecular forms: 27-, 28-, 30-, and 71-amino acid polypeptides.[10] Acidification of the duodenum and jejunum by gastric H^+ is the most important stimulus for secretin secretion by endocrine cells (S cells) in the small intestine.[1,4] Intraduodenal lipid may also stimulate secretin release in some species. The most important biologic action of secretin is stimulation of secretion of a bicarbonate-rich pancreatic fluid from pancreatic ductal cells.[8,10] Pancreatic bicarbonate is important in neutralizing gastric acid delivered to the small intestine and in creating an alkaline environment that is close to the pH optimum of pancreatic lipase and colipase. Less important biologic actions of secretin are to stimulate secretion of bile bicarbonate and pancreatic enzymes.[1,8] The latter effect is observed only in the presence of CCK. Secretin has also been identified in brain neurons, but a functional role for secretin in these neurons has not yet been elucidated.

244.1.3.2.2 Enteroglucagon

Enteroglucagon and pancreatic glucagon arise from the same gene precursor through post-translational processing. Several molecular forms of enteroglucagon have been characterized, including enteroglucagon or oxyntomodulin, a 37 amino acid peptide; glicentin, a 69 amino acid, C-terminal extended form of oxyntomodulin; glucagon-like peptide (GLP)-1; intervening peptide-2; and GLP-2. Endocrine cells (L cells) in the terminal ileum and colon secrete enteroglucagon(s) in response to intraluminal glucose and lipid. The most important gastrointestinal action of the enteroglucagons is the inhibition of gastric acid secretion.[1,4] GLP peptides are also involved in the regulation of insulin secretion and glycemic control. GLP-1 is reported to stimulate proinsulin expression and to delay intestinal glucose absorption through inhibition of gastric emptying[11], thus acting as an incretin hormone during euglycemia to lower blood glucose. GLP-2 is a 33-amino acid peptide hormone released from intestinal endocrine cells following nutrient ingestion.[12] It exerts trophic effects on the small and large bowel epithelium via stimulation of cell proliferation and inhibition of apoptosis. GLP-2 also upregulates intestinal glucose transporter activity and reduces gastric motility and gastric secretion.[13]

244.1.3.2.3 Gastric inhibitory polypeptide (GIP)

GIP is a 54-amino acid peptide that exists in a single molecular form.[14] It is secreted by endocrine cells of the proximal small intestine in response to intraduodenal glucose, fatty acids, and amino acids. Two important biologic actions of GIP are inhibition of gastric acid secretion and stimulation of intestinal fluid secretion. The third, and likely most important, biologic action of GIP is the stimulation of pancreatic insulin release during hyperglycemia. It has been suggested that GIP and GLP-1 function as incretins and are the substances responsible for increased glucose disposal and enhanced insulin responses during intestinal absorption of glucose.[1,4,14]

244.1.3.3 Somatostatin

Somatostatin, or somatotropin release-inhibiting factor was originally isolated from the hypothalamus and found to inhibit growth hormone and thyrotropin release from the pituitary. Somatostatin was subsequently found in gut endocrine cells and gut neurons and shown to have endocrine, neurocrine, and paracrine biologic effects. Two molecular forms of somatostatin have been identified in gut endocrine cells: somatostatin-14 (SS-14), and somatostatin-28 (SS-28). Endocrine cells (D cells) throughout the GI tract secrete somatostatin in response to protein, lipid, and bile. As a GI hormone, somatostatin inhibits gastric acid and pepsin secretion, pancreatic enzyme and fluid secretion, gallbladder contraction, and intestinal amino acid and glucose absorption.[1,4] Synthetic forms of somatostatin (Sandostatin, Sandoz Pharmaceuticals) are available for the treatment of gastric acid secretory disorders.[15] In addition to its role as a gastrointestinal hormone, somatostatin also functions as an enteric neuropeptide (e.g., inhibition of intestinal motility) and as a paracrine substance (e.g., inhibition of gastrin secretion).

244.1.3.4 Motilin

Motilin is a 22-amino acid peptide found in endocrine cells of the proximal small intestine. Motilin secretion is stimulated by H^+ and lipid during the fed state. However, motilin secretion seems to be most important in the interdigestive (fasting) state. During fasting, motilin is episodically released into the serum and initiates phase III of the migrating motility complex (MMC, or interdigestive motility complex).[16] The MMC is a motility pattern that empties the stomach and small intestine of indigestible solids that accumulate during feeding. The cyclic release of motilin from the small intestinal mucosa during fasting is also thought to coordinate gastric, pancreatic, and biliary secretions with phase III of the MMC.[17] It has been shown that microbially ineffective doses of erythromycin (0.5 mg/lb or 1.0 mg/kg) initiate an MMC pattern that is indistinguishable from that induced by motilin. It has thus been suggested that erythromycin and other macrolide-like antibiotics might be useful gastric prokinetic agents.[18]

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244.1.3.5 Neurotensin

Neurotensin is a 13-amino acid peptide, isolated from dog ileal and jejunal mucosal endocrine cells (N cells), for which no definitive endocrine function has been established. Intraluminal lipid stimulates neurotensin release from these endocrine cells. Neurotensin has been shown to inhibit gastric secretion and emptying, stimulate pancreatic secretion, and stimulate gallbladder contraction. One of the most likely potential roles of neurotensin is that of a physiologic enterogastrone that mediates inhibition of acid secretion after fat ingestion.[1,4]

244.1.3.6 Pancreatic Polypeptide

Pancreatic polypeptide (PP) is a 36-amino acid peptide that shares sequence homology with the enteric neuropeptide known as neuropeptide Y (NPY). PP is found exclusively in pancreatic islet cells (F cells). PP release is stimulated by protein meals and by cholinergic reflexes. The most important biologic action of PP is the inhibition of pancreatic enzyme and fluid secretion.[1,4] Islet cell PP secretion likely autoregulates acinar and ductal cell secretions because of the islet-acinar portal venous system. Other possible endocrine

functions of PP include relaxation of gallbladder smooth muscle, mild stimulation of gastric acid secretion, and initiation of the MMC along with motilin.[17]

244.1.3.7 Peptide YY

Peptide YY is a 36-amino acid peptide with structural similarities to PP and to NPY. Peptide YY may function as a physiologic enterogastrone similar to neurotensin in inhibiting pancreatic and gastric secretions.[1,4]

244.1.3.8 5-Hydroxytryptamine

5-Hydroxytryptamine (5-HT or serotonin) is found in endocrine cells (i.e., enterochromaffin cells) and enteric neurons throughout the gastrointestinal tract of most animal species.[1,2,4] In some species, 5-HT is also found in intestinal mucosal mast cells, pancreatic islet cells, and bronchial endocrine cells. 5-HT secreted by enterochromaffin cells may act through an endocrine or paracrine mechanism to stimulate gastrointestinal smooth muscle contraction and intestinal electrolyte secretion.[2] Tumors of these enterochromaffin cells (see Carcinoids) may be associated with hypermotility and secretory diarrhea because of the effects of 5-HT on motility and secretion.

244.1.3.9 Ghrelin

Ghrelin is a 28-amino acid octanoylated peptide found most abundantly in endocrine cells of the stomach.[18,19] It stimulates pituitary growth hormone (GH) secretion. *Ghre* is the Proto-Indo-European root for the word “growth,” and the suffix-*relin* signifies “releasing substances.” Ghrelin administration also has been shown to stimulate appetite, body growth, and fat deposition. The post-prandial gastric expression of ghrelin suggests a gastrointestinal-hypothalamaic-pituitary axis that influences GH secretion, body growth, and appetite that is responsive to nutritional and caloric intakes. Ghrelin and leptin may be the “ying and the yang” of a system that relays peripheral information to the brain and directs the body in the appropriate maintenance of energy reserves and nutritional intake.

244.1.4 Enteric Neuropeptides

A substance may be defined as an enteric neuropeptide if (1) it can be demonstrated histochemically in enteric neurons, (2) mechanisms for its biosynthesis exist in enteric neurons, (3) it is concentrated in nerve terminals, (4) it is released from nerve terminals by depolarizing stimuli through a calcium-dependent mechanism, and (5) mechanisms for the breakdown, re-uptake, or removal of the substance exist.[3]

244.1.4.1 The Tachykinins

The tachykinin family is represented by substance P, substance K, neuromedin K, physalaemin, kassinin, and eledoisin. Substance P is probably the most important enteric neuropeptide of this group. Substance P is distributed in enteric neurons throughout the GI tract and pancreas, and it is released from these neurons in response to luminal distension or depolarization. Substance P has three important biologic actions as an enteric neuropeptide.[3] First, it causes contraction of GI smooth muscle through an indirect effect of mediating cholinergic transmission and a direct effect on smooth muscle during the peristaltic reflex.

Second, substance P is located in primary sensory afferent fibers and may be important, along with calcitonin gene-related peptide in pain input to the central nervous system. Finally, substance P neurons stimulate pancreatic enzyme secretion from pancreatic acinar cells.

244.1.4.2 Vasoactive Intestinal Polypeptide/Peptide Histidine-Isoleucine

The classic enteric neuropeptides VIP and PHI share sequence homology with one another and with the GI hormones secretin, enteroglucagon, and GIP. VIP and PHI have many similar biologic activities and are derived from the same biosynthetic precursor. VIP and PHI are released by vagal stimulation and have four important biologic actions:[3] (1) stimulation of pancreatic fluid and bicarbonate secretion, (2) stimulation of salivary and intestinal fluid secretion, (3) increasing intestinal blood flow, and (4) relaxation of GI smooth muscle. This last property of VIP/PHI is felt to be important in descending intestinal inhibition (along with somatostatin) and in sphincter relaxation. Functional tumors of VIP-producing cells produce a watery diarrhea syndrome (pancreatic cholera or Verner-Morrison syndrome) in humans. This syndrome has not yet been described in dogs or cats.

244.1.4.3 Opioids

Opioid neurons are distributed throughout the gastrointestinal tract, spinal cord, brain, and adrenal glands. Methionine-enkephalin, leucine-enkephalin, and dynorphin are the most representative members of the opioid enteric neuropeptide family.[3] At least three different types of binding sites for these opioid peptides can be distinguished in the gut (μ, δ, and κ) but there may be others (ε and σ). The binding sites for these opioids are located on other neurons, smooth muscle cells, and epithelial cells. Opioid binding results in (1) inhibition of contraction of longitudinal smooth muscle through inhibition of acetylcholine release from myenteric plexus neurons; (2) direct stimulation of circular smooth muscle contraction; and (3) inhibition of intestinal water and electrolyte secretion through inhibition of submucosal plexus neurons. These effects account for the potent antidiarrheal properties of morphine and other opiate alkaloids that have been recognized for centuries.[3]

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244.1.4.4 Bombesins

The bombesins are so-named because of their original isolation from the skin of the frog genus *Bombina*. The mammalian bombesins that have been identified as enteric neuropeptides are gastrin releasing peptide (GRP) and neuromedin B. GRP is released by vagal stimulation, and it stimulates gastrin release from antral G cells. Thus GRP acts a co-transmitter (along with acetylcholine) to stimulate gastrin release.[3,5] GRP also stimulates pancreatic acinar cell enzyme secretion.[3,8]

244.1.4.5 Somatostatin

In addition to its role as a gastrointestinal hormone, somatostatin (SS-14) has been identified as an enteric neuropeptide in neurons throughout the gastrointestinal tract. Somatostatin inhibits acetylcholine release from myenteric plexus neurons and may be involved in the descending inhibitory reflex of peristalsis.[3] Somatostatin neurons in the submucous plexus have a mucosal projection suggesting a further role for neuronal somatostatin in the control of mucosal function.

244.1.4.6 Gastrin-CCK

CCK-8 is an important enteric neuropeptide in the ileum and colon, especially in the cat. Intraluminal distension activates CCK-8-containing neurons, which then stimulate the release of acetylcholine from myenteric plexus neurons. CCK-8 thus acts as an excitatory transmitter in stimulating the peristaltic reflex in ileum and colon.[1,3] Brain CCK-8 neurons are involved in mediating the satiety response following feeding. Indeed, it has been suggested that human bulimia nervosa patients do not have normal satiety and have an impaired secretion of cholecystokinin in response to a meal.[20]

244.1.4.7 Pancreatic Polypeptides

A 36-amino acid peptide, NPY shares structural similarities with the GI hormones PP and peptide YY. Neurons that contain NPY decrease acetylcholine release from myenteric plexus neurons and hence inhibit small intestinal smooth muscle contraction.[3]

244.1.4.8 5-Hydroxytryptamine (5-HT or Serotonin)

In addition to its role as an endocrine/paracrine substance of the gastrointestinal tract, 5-HT is also found in enteric neurons, where it is believed to regulate the migrating myoelectrical complex and the intestinal peristaltic reflex.[3]

244.1.5 Paracrine Substances

A substance may be defined as having a paracrine mechanism of activation if (1) the substance is found within an effector cell, (2) receptors for the substance exist on an adjacent paracrine target cell, (3) the effector cell and paracrine target cell are in close proximity, and (4) the substance when applied to the paracrine target cell evokes a biologic response.[1,2] Histamine, somatostatin, adenosine, and prostaglandins have been shown to satisfy these criteria.

244.1.5.1 Histamine

Histamine is formed from the decarboxylation of histidine in mast cells found throughout the GI tract of dogs. In the dog, gastric mucosal histamine stores appear fully accounted for by mast cells, there being no evidence to indicate histamine is stored in endocrine cells.[6] Histamine released from mast cells diffuses into the interstitial milieu and is believed to bind parietal cell H_2 receptors to stimulate H^+ secretion.[6] A large body of evidence has accumulated in support of this idea, although one study suggests that the histamine effect might be indirectly mediated through histamine receptors on gastric mucosal immunocytes.[7] Regardless, H_2 receptor antagonists have been shown to be potent inhibitors of histamine, acetylcholine, and gastrin-stimulated H^+ secretion.

244.1.5.2 Somatostatin

The endocrine and neurocrine roles of somatostatin were discussed earlier in this chapter. As a paracrine substance, somatostatin has an important role in the inhibition of gastrin release. Somatostatin cells in the gastric antrum have long cytoplasmic processes that terminate adjacent to antral G cells. Paracrine release of somatostatin by these somatostatin cells is postulated to mediate the negative feedback inhibition of H^+ on gastrin release.[21] Somatostatin released from pancreatic islet cells (D cells) may also auto-regulate pancreatic insulin and glucagon secretion through a local paracrine mechanism.[22]

244.1.5.3 Prostaglandins

Prostaglandins are long chain fatty acids that are distributed throughout the GI tract. The role of prostaglandins as paracrine substances is perhaps best understood in the gastric mucosa, where they bind to inhibitory prostanoid receptors on gastric oxyntic cells. These receptors are coupled to inhibitory G proteins and subsequent inhibition of adenylate cyclase and H^+ secretion.[23] A "cytoprotective effect" of prostaglandins, separate from the direct inhibition of acid inhibition, has also been implied. Gastric prostaglandins, for example, stimulate mucosal bicarbonate and glycoprotein secretion, epithelial cell renewal, and mucosal blood flow. These effects are all central to the barrier properties of the gastric mucosa.[24] Synthetic forms of prostaglandins (Cytotec, Searle) are now available for the therapy of gastric mucosal barrier disorders.[25,26,27]

244.2 DISEASES OF THE GASTROINTESTINAL ENDOCRINE SYSTEM

In small animals, the major syndromes of gastrointestinal endocrine pathology are diabetes mellitus, pancreatic islet cell tumors, and intestinal carcinoid. The syndromes of glucagonoma, gastrinoma, carcinoid, and pancreatic polypeptidoma are reviewed.

244.2.1 Glucagonoma

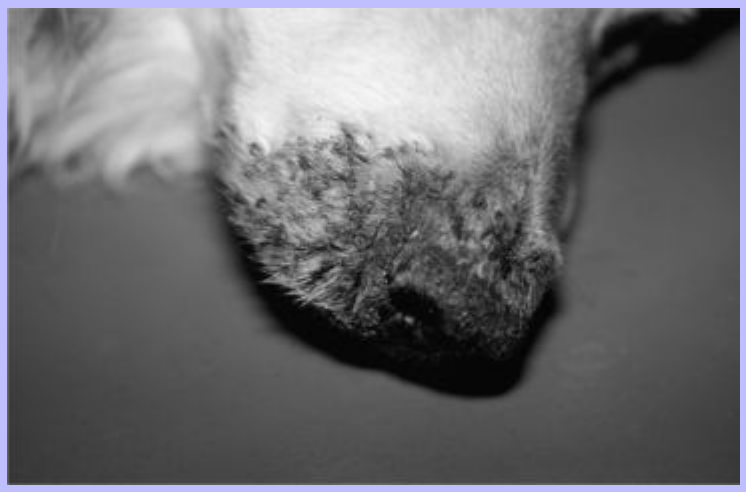
Glucagonoma is a rare tumor of the pancreatic alpha cells in dogs and humans. There are no reports of this disease in the cat. It is characterized by a crusting skin rash, termed *necrolytic migratory erythema* (NME) and glucose intolerance or overt diabetes mellitus (Figure 244-1). Increased serum glucagon concentrations stimulate hepatic amino acid turnover, gluconeogenesis, and glycogenolysis. In dogs, it is definitively diagnosed by immunohistochemistry of excised pancreatic tumor tissue.

244.2.2 Signalment and Clinical Signs

Eight dogs with presumptive or definitively diagnosed glucagonoma have been reported.[28–34] These eight dogs included seven breeds, four females, and four males, and their ages ranged from 5 to 13 years.

In human glucagonoma patients, NME is virtually pathognomonic for the disease. Although NME has been identified in all dogs with glucagonoma, it is more commonly associated with liver disease. Glucose intolerance or overt diabetes mellitus is also found in humans with glucagonoma and is caused by excess gluconeogenesis and glycogenolysis resulting from increased plasma glucagon concentrations. Other clinical signs in people include weight loss, anemia, diarrhea, stomatitis, and thromboembolic disease.

Figure 244-1 Necrolytic migratory erythema of the muzzle of a dog with glucagonoma. (Courtesy William H. Miller, Jr.)



Dogs with glucagonoma had 3-week to 16-month histories of crusting dermatologic lesions with or without ulceration or erosion at the time of presentation. Footpad lesions were present in all dogs with other affected sites including the elbows, hocks, nose, mucocutaneous junctions of the mouth or eyes, prepuce, vulva, scrotum, flank, ventral abdomen, and distal extremities. One dog also had oral ulcerations. Other clinical signs or physical exam findings at the time of initial presentation included lethargy, weight loss, decreased appetite, muscle atrophy, and peripheral lymphadenopathy. One dog also had palpable hepatomegaly.

244.2.2.1 Laboratory and Imaging Findings

Laboratory abnormalities included hyperglycemia (five dogs), nonregenerative anemia (three dogs), mild to moderately increased ALT activity (four dogs), mild to moderately increased ALP activity (three dogs), decreased albumin (two dogs), decreased globulin (one dog), decreased BUN (two dogs), decreased cholesterol (one dog), and glucosuria (two dogs). Liver function tests, including serum bile acid measurements (six dogs) and ammonia tolerance test (one dog), were normal. One dog had an ACTH stimulation test supportive of hyperadrenocorticism.

One or more imaging studies were performed in all dogs. Abdominal radiographs were unremarkable in all dogs. Abdominal ultrasound was normal in three dogs but revealed liver lesions in four dogs and a possible pancreatic mass in one dog. Liver abnormalities on ultrasound included a small liver with increased echogenicity of the portal and hepatic vein walls, diffuse hyperechogenicity, multiple small hypoechoic foci, and a single well-defined hyperechoic area. A mass in the left pancreatic limb was visualized by computed tomography in one case.

244.2.2.2 Diagnosis

Diagnosis in people is confirmed by demonstration of increased plasma glucagon concentrations and a pancreatic islet cell tumor that shows positive immunoreactivity for glucagon.

244.2.2.2.1 Glucagon measurement

Demonstration of increased circulating glucagon concentrations is important to establish the hypersecretion of glucagon by the tumor cells and to associate clinical signs with excess hormone secretion. Plasma glucagon concentrations of more than 1000 ng/L are considered diagnostic of the disease in people. Plasma glucagon concentrations were measured in six of the eight dogs reported in the literature. In all dogs plasma glucagon concentrations were increased, ranging from 1.6 to 10.1 times the upper limit of reference ranges. It is important to note, however, that syndromes other than glucagonoma may be associated with increased plasma circulating glucagon, including acute pancreatitis, hypercortisolism, hepatic failure, and renal failure. Because of the paucity of cases in the veterinary literature, it is difficult to determine plasma glucagon concentrations that are diagnostic of glucagonoma in the dog. The presence of concurrent disease, as noted above, should always be considered.

244.2.2.2.2 Plasma amino acid concentrations

Hypoaminoacidemia is often found in humans with glucagonoma and is thought to result from increased hepatic conversion of amino acid nitrogen into urea nitrogen by the excess glucagon.[35] Plasma amino acids were measured in three of the dogs reported and were decreased in all three (20 of 24, 13 of 18, and 4 of 5 amino acids determined). Arginine, histidine, and lysine concentrations were consistently decreased, although it must be noted that complete amino acid profiles were not measured in all cases.

244.2.2.3 Pathology

Most glucagon secreting tumors in people occur singly and are quite large (5 to 10 cm) at the time of diagnosis. Up to 82% are metastatic. In dogs, the diagnosis of glucagonoma has relied on demonstration of a primary pancreatic or metastatic tumor that stains positively for glucagon immunoreactivity. Pancreatic tumors were found in seven of the eight dogs reported. In one animal, serial sections of the pancreas failed to reveal neoplasia; diagnosis was instead based on positive glucagon immunoreactivity of metastatic tissue in the liver in conjunction with hyperglucagonemia. Location of pancreatic tumors included the right lobe (three dogs), left lobe (two dogs), body (one dog). As in the human, metastasis of glucagonoma is common in dogs and occurred in five of the eight cases. The liver was the most frequently affected site (four of the eight dogs) with one dog showing metastasis to a regional lymph node. Lymph node or liver tissue was not obtained in all cases so that the rate of metastasis may be higher than reported.

Glucagon immunohistochemical staining was performed on primary pancreatic and/or metastatic tumors. In most cases, tissue sections were also stained for immunoreactivity to somatostatin, gastrin islet amyloid polypeptide, insulin, pancreatic polypeptide, and/or synaptophysin, a marker for neuroendocrine cells.[36] In accordance with diagnostic criteria, all primary and metastatic tumors stained positively for glucagon immunoreactivity. In five dogs, primary tumor or metastatic tissue stained positively for one or more of above listed peptides. In some cases, metastatic tissue had different immunoreactivity than the primary tumor.

244.2.2.4 Therapy

Surgical resection or debulking is the treatment of choice for glucagonoma. In people removal of the glucagon-secreting tumor resolves the skin rash and other clinical signs. In the dogs with glucagonoma,

four had surgical resection of the pancreatic mass. Two of these animals were euthanized 3 days after surgery because of presumed acute pancreatitis. One dog with metastatic disease of a mesenteric lymph node had surgical resection of both the lymph node and pancreatic mass. Glucagon concentrations decreased into the reference range the day following surgery and remained normal for 3 months. Plasma amino acid concentrations also increased within 30 days, and cutaneous lesions resolved within 45 days of surgery. Nine months after surgery, the dog was euthanized due to the development of new skin lesions. A second dog with metastasis to the liver had mild improvement of skin lesions following surgical resection of the pancreatic mass. Plasma glucagon concentrations, however, remained increased 10 days following surgery, but the dog was well 4 months post surgery.

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Medical therapy should be considered as an adjunct for surgical resection in dogs with metastasis or for palliative therapy if surgery is not performed. Long-acting somatostatin analogues such as octreotide have been used to control plasma glucagon concentrations and clinical signs in humans. In one report, somatostatin was administered at a dosage of 6 μg/kg subcutaneously every 8 hours to a dog with metastatic disease, and marked improvement in skin lesions was reported within 14 days.[37] The treatment was not continued due to expense, and the dog was euthanized. Chemotherapeutic agents such as streptozotocin with 5-fluorouracil and dacarbazine have been somewhat successful in human treatment.[38] Intravenous amino acid therapy has also been helpful in some humans for the dermatologic abnormalities. There are no data on use of these agents in dogs.

Humans with glucagonoma often have concurrent diabetes mellitus. Some can be controlled by diet or oral hypoglycemic agents; however, many require insulin therapy.[39] Five of the eight dogs with glucagonoma had mild to moderate hyperglycemia with or without glucosuria. Two of these dogs were treated with insulin, one of which no longer required insulin 10 days after treatment was instituted. No long-term use of insulin in dogs with glucagonoma has been reported.

244.2.2.5 Prognosis

Because dogs have had metastatic disease at the time of diagnosis, prognosis is poor. Moreover, surgical outcome appears to be further complicated by the occurrence of pancreatitis. NME (also referred to as *superficial necrolytic dermatitis, hepatocutaneous syndrome,* and *metabolic epidermal necrosis*) is found more commonly in dogs with hepatic disease; glucagonoma accounts for less than 10% of the cases of NME. Therefore it is essential to assess liver function in dogs with NME so that a precise etiology may be determined and treatment options and prognosis correctly presented. Serum liver enzyme activities were abnormal in most dogs with glucagonoma; however, liver function tests were normal in all dogs tested.

Abdominal radiography and ultrasonography were found to be poor methods for detecting canine pancreatic glucagonoma. Computed tomography successfully identified the pancreatic glucagonoma in one dog and may prove more useful in the diagnosis of this disease. As clinical awareness and diagnostic testing improve, our understanding of the disease and treatment outcomes will undoubtedly improve as well.

244.2.3 Gastrinoma

In 1955 Zollinger and Ellison described a syndrome in people of gastric acid hypersecretion, severe peptic ulceration, and pancreatic islet cell tumor that was eponymously termed the *Zollinger-Ellison syndrome*. These islet cell tumors were subsequently demonstrated to secrete excessive amounts of gastrin and are now more appropriately called *gastrinomas*. Clinical signs result from excess plasma gastrin concentrations causing

gastric acid hypersecretion. Hypergastrinemia and gastric hyperacidity result in gastrointestinal inflammation and ulceration, maldigestion, and hypertrophy of gastric mucosa.

244.2.3.1 Signalment and Clinical Signs

Gastrinomas are uncommon and have been reported in 30 dogs and in three cats.[40–53] They occur in middle-aged dogs (average age 8.2 years; range 3.5 to 12 years). Cats ranged in age from 10 to 12 years. No breed predilection is noted, and females may be at slightly greater risk. The most frequent clinical signs have been vomiting and weight loss. Depression, lethargy, anorexia, and intermittent diarrhea are also commonly reported. Less frequent clinical signs include melena, abdominal pain, polydipsia, hematemesis, hematochezia, and obstipation. Physical examination findings are often nonremarkable in the early stages of the disease. However, abdominal pain, fever, tachycardia, pale mucous membranes, and dehydration may occur in extremely sick animals as a result of severe gastrointestinal ulceration or perforation. A palpable abdominal mass was reported in one cat.

Clinical signs result from gastrin-induced gastric acid hypersecretion and gastric mucosal hyperplasia. Hypersecretion and hyperplasia may result in gastric ulceration and gastric outflow obstruction. Gastroesophageal acid reflux may cause severe esophagitis and/or ulceration. Diarrhea and steatorrhea are caused by the large amount of acidic fluid entering the duodenum and jejunum and by the increased circulating concentrations of gastrin that reduce intestinal water and ion absorption.

244.2.3.2 Laboratory Findings

The CBC may reveal a regenerative anemia presumably due to gastrointestinal bleeding. Gastrointestinal inflammation may elicit a leukocytosis and neutrophilia with or without a left shift. One dog with concurrent myelofibrosis had a nonregenerative anemia. Biochemical abnormalities include hypoalbuminemia, hypoproteinemia, hypokalemia, hypochloremia, hyponatremia, metabolic alkalosis, hyperbilirubinemia, and mild increases in serum liver enzyme activities. Hypoalbuminemia and hypoproteinemia are due to loss of protein through an ulcerated gastrointestinal mucosa. Persistent vomiting in dogs and cats with gastrinoma results in hypokalemia, hyponatremia, hypochloremia, and metabolic alkalosis. Diarrhea and reduced food intake could also contribute to the hypokalemia. Hyper-and hypoglycemia have also been infrequently reported and may be due to concurrent hypersecretion of corticotropin or insulin, respectively; in one dog with hyperglycemia, extracts of the islet tumor revealed adrenocorticotropic hormone in addition to gastrin. Increases in serum liver enzyme activities and bilirubin may reflect tumor metastasis to the liver that is commonly found in these cases.

244.2.3.3 Imaging Findings

Survey abdominal radiographs are usually unremarkable or they may reveal loss of abdominal detail and/or ascites with gastrointestinal perforation. Contrast-enhanced radiographic studies may show evidence of gastroduodenal ulceration, prominent gastric rugal folds, thickened pyloric antrum, complete pyloric obstruction, or rapid small bowel transit time. Abdominal ultrasound may reveal gastric ulcer, thickened gastric wall or pylorus, or evidence of metastasis in the liver or regional lymph nodes. Gastrinomas are generally small in size and difficult to directly visualize by abdominal ultrasonography. Wider use of other imaging modalities such as endoscopic ultrasound, magnetic resonance imaging, and computed tomography undoubtedly increase diagnostic sensitivity;[54,55] however, no studies have been reported using these techniques on animals.

244.2.3.4 Endoscopic Findings

Endoscopy was performed on half of the dogs reported. Abnormalities noted were esophageal inflammation or ulceration, thickened gastric rugae, gastric ulceration or hemorrhage, excessive fluid in the stomach, hypertrophied pyloric antrum, and duodenal ulceration. Histological examination of endoscopically derived biopsy samples of thickened gastric mucosa or mural lesions may be relatively normal. In this case surgically obtained, full-thickness biopsy samples should be considered.

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244.2.3.5 Diagnosis

Clinical tests to support a diagnosis of gastrinoma include measurement of basal gastric acid secretion and serum gastrin concentration, provocative tests such as secretin and calcium stimulation, and somatostatin receptor scintigraphy. Demonstration of appropriate histopathological and immunohistochemical evidence from excised pancreatic tumor or metastatic tissue is necessary to confirm the diagnosis.

244.2.3.5.1 Basal gastric acid secretion

This test is commonly performed in humans and is abnormally increased in more than 80% of humans with gastrinoma.[38,56] This test has been performed in four dogs with gastrinoma. Gastric pH was low (pH = 0.99, 1.0, 1.0, 1.5) in all four dogs and was correlated with increased basal acid secretion in two of the dogs.

244.2.3.5.2 Basal serum gastrin concentration

This is considered the best screening test for gastrinoma in humans and is abnormal in more than 98% of those with gastrinoma. In dogs and cats with histologic evidence of gastrinoma, measured basal serum gastrin concentrations have been greater than three times the highest value in the reference range. However, other disease syndromes may be associated with increased basal serum gastrin concentrations including renal failure, gastric outflow obstruction, chronic gastritis, liver disease, and drugs that remove the negative feedback inhibition of acid on gastrin secretion, including antacids, H_2 receptor blockers, proton pump inhibitors, and glucocorticoids. Therefore this test cannot be relied upon as a sole diagnostic test, even if these other conditions can be ruled out. In humans with gastrinoma, basal serum gastrin concentrations more than 1000 ng/L combined with gastric pH less than 2.5 is diagnostic for gastrinoma without further testing. Due to the paucity of cases in the veterinary literature, basal serum gastrin concentrations diagnostic for gastrinoma (versus other diseases or drug therapy) have not yet been established.

244.2.3.5.3 Secretin stimulation

The preferred provocative test to diagnose gastrinoma in people is secretin stimulation. Secretin will stimulate gastrin secretion in patients with gastrinoma but not in healthy people. This test has been performed in three dogs with gastrinoma and one dog with pancreatic polypeptidoma, and therefore data regarding testing procedure and interpretation is limited. In dogs, serum samples should be collected before and 2, 5, 10, and 30 minutes following intravenous administration of 2 to 4 U/kg of secretin. The 2-and 5-minute samples are thought to be the most diagnostic. In humans a twofold or greater increase in serum gastrin following secretin administration is diagnostic for gastrinoma. In those animals that have

been tested, two dogs had a greater than twofold increase in gastrin and one dog had a 1.4-fold increase within 5 minutes of secretin administration. One dog diagnosed with pancreatic polypeptidoma had a transient fasting hypergastrinemia, but no response to secretin stimulation.

244.2.3.5.4 Calcium stimulation

Similar to secretin, calcium infusion stimulates an increase in serum gastrin concentrations in humans with gastrinoma, whereas serum gastrin concentrations are unchanged unaffected individuals. This test has been used in two dogs with gastrinoma and one dog with pancreatic polypeptidoma. Calcium is administered as an intravenous bolus of 2 mg/kg over 1 minute. Serum samples are collected before and 15, 30, 60, 90, and 120 minutes after calcium administration. Using this protocol, both of the gastrinoma dogs had a twofold increase in serum gastrin concentration in response to calcium infusion. Such an increase supports a diagnosis of gastrinoma in humans. The dog with pancreatic polypeptidoma, had normal serum gastrin concentrations after calcium infusion. Because of the dangers of intravenous calcium infusion, this test should be used with caution.

244.2.3.6 Pathology

A definitive diagnosis of gastrinoma requires the findings of hypergastrinemia, histopathologic evidence of pancreatic islet cell neoplasia, and immunohistochemical evidence of gastrin in neoplastic islet cells. The presence of hormones in endocrine tumor tissue alone does not necessarily guarantee their excessive secretion into the circulation. In dogs, gastrin-secreting tumors have been reported most frequently in the right lobe and body of the pancreas. Most animals had solitary nodules, but multiple masses have been reported. At the time of diagnosis, the gastrinoma had metastasized in 85% of cases, usually to the liver. Other metastatic sites included, spleen, lymph nodes, mesentery, omentum, peritoneum, and serosal surfaces of the duodenum and jejunum. The presence of gastrin in the tumors can be documented by immunohistochemistry or by radioimmunoassay of extracts from tumor tissue. Ultrastructural studies to detect unique intracytoplasmic granules can also be used to confirm gastrinoma; however, this requires electron microscopic techniques that may be cost prohibitive. Other pathological findings of dogs and cats with gastrinoma included perforating and nonperforating ulceration (95% of cases) of the esophagus, stomach, duodenum, and jejunum. Gastric hypertrophy, thyroid C-cell hyperplasia, thyroid follicular cell carcinoma, and adrenal hyperplasia have also been reported.

244.2.3.7 Therapy

Treatment of gastrinoma is directed toward surgical resection or reduction of the gastrinoma and/or metastases and medical control of gastrin secretion from the tumor cells. Adjunct medical therapy includes treatment of gastric acid hypersecretion, gastrointestinal ulceration, and fluid and electrolyte losses.[57]

244.2.3.7.1 Treatment directed at tumor cells

Surgical resection of gastrinomas can prove challenging since the primary tumors are small and difficult to localize. Tumor localization with imaging modalities such as endoscopic ultrasound, computed tomography, or magnetic resonance imaging are usually more sensitive than abdominal ultrasound and are used more successfully in humans. Somatostatin receptor scintigraphy, using a somatostatin analogues (e.g., ^{111}Indium octreotide or pentetreotide) to detect somatostatin receptors present on gastrinoma cells is a sensitive test used to localize tumors and metastases in people. Positive receptor

binding can also predict successful medical treatment of gastrinoma with somatostatin analogues. This technique has been reported in one dog in which 2 mCi of the octreotide analogue was used and images successfully generated by gamma camera imaging.[43] Careful digital palpation of the pancreas, liver, and surrounding areas should be performed if the tumor cannot be visualized at surgery; intraoperative pancreatic ultrasound may be beneficial. The pancreas should be handled carefully and pancreatic blood flow should be preserved to avoid postoperative pancreatitis. Because metastasis is common at the time of surgery, the liver, lymph nodes, spleen, duodenum, mesentery, and omentum should be inspected and biopsied as appropriate. Metastatic foci should also be resected, as possible, since this can provide palliation for the patient. As these tumors are slow growing, debulking may provide relief from clinical signs.

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Following pancreatic resection or manipulation, the animal should be managed as if it had acute pancreatitis, with fluid support, extensive monitoring, and restriction of food or water by mouth. Administration of octreotide, a somatostatin analogue, pre-and post-operatively has been suggested to decrease pancreatic gastrin and gastric acid secretion.[53]

244.2.3.7.2 Somatostatin analogues

Somatostatin inhibits gastrin and hydrogen ion secretion in gastrinomas and in gastric parietal cells. A long-acting somatostatin analogue, octreotide, has been used in two dogs with gastrinoma. Doses started at 2 μg/kg twice per day and were increased to 10 to 20 μg/kg three times per day. The dogs were maintained on this therapy for 10 to 14 months. One dog relapsed after the medication was discontinued. The other dog showed marked response to treatment after the dosing was increased to three times per day. At necropsy, one dog showed marked increase of tumor growth and metastasis. Unfortunately, the expense of this drug may limit its use. Successful treatment of gastrinoma with chemotherapeutic drugs has not been reported.

244.2.3.7.3 Adjunct medical therapy

244.2.3.7.3.1 Gastric hyperacidity

As gastrinomas are slow growing, medical therapy to control the major clinical signs of gastric hyperacidity and gastrointestinal ulceration may provide significant palliation for dogs and cats.[57] Because of the high rate of metastasis, gastrin secretion in most animals remain increased after surgery, and these dogs and cats suffer from continuing gastric hyperacidity. Adjunct therapy should be started immediately to prevent the development of perforating ulcers. The most common agents used to control gastric hyperacidity in veterinary medicine are the H_2 receptor antagonists such as cimetidine (Tagamet), ranitidine (Zantac), famotidine (Pepcid), and nizatidine (Axid). See Box 244-1 for dosages and dosing intervals. They are potent inhibitors of H^+ secretion in dogs and cats. Success with cimetidine therapy has been reported in several dogs and one cat with gastrinoma. It has been suggested that animals unresponsive to standard doses of gastric acid secretory inhibitors may respond to higher doses and/or dual agent therapy.[53]

Omeprazole (Prilosec) is an inhibitor of parietal cell H^+, K^+-ATPase and reduces gastric acid secretion with a long duration of action in normal dogs.[57] Two dogs with gastrinoma have been successfully treated with omeprazole. In one case, omeprazole controlled gastrointestinal signs that

were unresponsive to treatment with cimetidine and sucralfate. This dog remained asymptomatic for more than 2 years. Omeprazole may be the better choice for control of gastric hyperacidity either in place of or in addition to H_2 receptor antagonists but it should be emphasized that there is no evidence-based medicine in support of either drug classification.

244.2.3.7.3.2 Gastrointestinal ulceration

Treatment of gastrointestinal ulceration includes surgical resection and control of gastric hyperacidity as discussed. The use of diffusion barriers and cytoprotective agents is discussed here. Dosages and dosing regimes are presented in the Drug Index (see Box 244-1).

Sucralfate (Carafate) is an example of a diffusion barrier used to promote ulcer healing. It is a complex of sulfated sucrose and aluminum hydroxide that reacts with gastric acid and binds to necrotic tissue proteins. Misoprostol (Cytotec) is a 16,16-dimethylated synthetic prostaglandin that has cytoprotective properties in addition to its direct acid-inhibitory effect. Synthetic prostaglandins may be useful in restoring the protective properties of the gastric mucosal barrier in ulcer patients, although the beneficial effects of this classification of agents have not yet been unequivocally established in evidence-based medicine type studies.[57]

244.2.3.7.3.2.1 Box • 244-1 Drug Index

244.2.3.7.3.2.1.1 Histamine (H_2) Receptor Antagonists

Cimetidine (Tagamet-SmithKline Beecham), 2 to 4 mg/lb (5 to 10 mg/kg) PO, SQ, IV q6h or q8h

Ranitidine (Zantac-Glaxo), 0.5 to 1.0 mg/lb (1 to 2 mg/kg) PO, SQ, IV q8h or q12h

Famotidine (Pepcid-Johnson & Johnson, Merck Consumer), 0.1 to 0.5/mg/kg PO, IV q12h

Nizatidine (Axid-Eli Lilly), 1.0 to 3.0 mg/kg SQ, IM, IV q8h

244.2.3.7.3.2.1.2 H^+, K^+-ATPase Inhibitors

Omeprazole (Losec-MerckSharp & Dohme) 0.35 mg/lb (0.7 mg/kg) PO q24h

244.2.3.7.3.2.1.3 Diffusion Barriers

Sucralfate (Carafate-Marion), 1 g q8h for large dogs 0.5 g q8h for smaller dogs 0.25 to 0.5 g q8h to q12h for cats

244.2.3.7.3.2.1.4 Synthetic Prostaglandins

Misoprostol (Cytotec-Searle), 2 to 5 µg/kg PO q8-12 h

244.2.3.7.3.2.1.5 Somostatin Analogs

Octreotide (Sandostatin-Novartis), 2 to 8 µg/kg SC q8-12h

244.2.3.8 Prognosis

Long-term prognosis in dogs and cats with gastrinomas is grave since metastatic disease is present in 85% at the time of surgery. In animals that underwent surgery and medical management, survival times ranged from 1 week to 18 months. The prognosis is likely to improve with increased awareness and diagnostic techniques for tumor localization. The availability and affordability of anti-secretory drugs and therapies to reduce gastric hyperacidity and promote ulcer healing will also promote longevity in animals with gastrinoma.

244.2.4 Intestinal Carcinoid

Intestinal carcinoid is a rare tumor arising from enterochromaffin cells that can be found in the tracheobronchial epithelium, pancreatic ducts, biliary tree, genitourinary tract, stomach, and intestine. In people they are classified according to their location and ability to secrete vasoactive amines. People with carcinoid tumors can develop carcinoid syndrome that manifests as facial flushing, abdominal cramping, bronchoconstriction, and diarrhea. Clinical signs are related to the excessive secretion of 5-hydroxytryptamine (serotonin) from the neoplastic enterochromaffin cells.

Carcinoid tumors have been described in 25 dogs and four cats. In dogs this tumor has been found in the liver (15), stomach (1), duodenum (2), cecum (1), ileocecal junction (1), colon (2), rectum (2) and gall bladder (1).[58–64] In cats they have been localized to the stomach, pancreas, intestine, and liver.[65–68] Metastasis was common at the time of diagnosis with sites including liver, lymph nodes, lung, spleen, adrenal glands, and mesentery. A functional carcinoid syndrome as reported in humans has not been recognized in cats and dogs. Most animals had clinical signs relating to structural effects of the tumor or generalized disease related to neoplasia. The most common clinical signs were anorexia, vomiting, weight loss, and gastrointestinal bleeding. Diarrhea was less common.

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In veterinary medicine, diagnosis is confirmed by histopathologic and ultrastructural examination of the tumors. Diagnosis in people relies on several factors including measurement of plasma and urinary serotonin levels or its metabolites. Such tests have not been reported in veterinary patients. Most animals were diagnosed upon postmortem examination. Surgical resection was successful in a recent case report in a cat that remained disease free for 4 months before succumbing to an unrelated disease. Although these tumors are slow growing, metastasis is common at diagnosis; therefore prognosis is guarded.

244.2.5 Pancreatic Polypeptidoma

Pancreatic polypeptide is commonly found by immunohistochemical staining in human and canine pancreatic endocrine tumors that secrete other enteric hormones such as gastrin, glucagon, or insulin. The significance of its presence in these cells is unknown, and increased plasma pancreatic peptide concentrations have been documented rarely in humans. These patients do not display a characteristic clinical syndrome; however, secretory diarrhea and a macular rash may be associated with excess pancreatic polypeptide secretion from polypeptidomas. There has been one report in the veterinary literature implicating pancreatic polypeptidoma in clinical disease.[69]

In this case a 7-year-old FS cocker spaniel had chronic vomiting, hypertrophic gastritis, duodenal ulceration, and pancreatic adenocarcinoma with hepatic metastasis. Plasma PP concentrations were extremely high in this dog. Neoplastic tissues obtained at necropsy revealed positive immunohistochemical staining for pancreatic

polypeptide and insulin while there was no staining for gastrin, glucagon, or somatostatin. Clinical signs were thought to be due to high plasma PP concentrations since PP decreases pancreatic bicarbonate secretion and mildly increases gastric acid secretion. However, plasma PP may also be elevated in humans with other diseases including inflammatory diseases, renal failure, and laxative abuse; therefore further case reports are needed to characterize this syndrome.

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245 CHAPTER • 245 Pheochromocytoma

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Brian D. Husbands

Pheochromocytoma is a rare tumor that arises from the chromaffin cells of the adrenal medulla. Unlike the steroidogenic cells of the adrenal cortex, which are derived from mesoderm, chromaffin cells are embryologically derived from the neural crest as a part of the sympathetic autonomic nervous system.[1] The adrenal medulla is essentially a modified sympathetic ganglion that lacks postganglionic processes. In the fetus, chromaffin cells are widely distributed and form paraganglia. With the exception of the adrenal medulla, the paraganglia involute at birth.[1] Tumors arising from remnant paraganglia in adult animals are referred to as *paragangliomas* or *extra-adrenal pheochromocytomas*.

245.1 PATHOPHYSIOLOGY

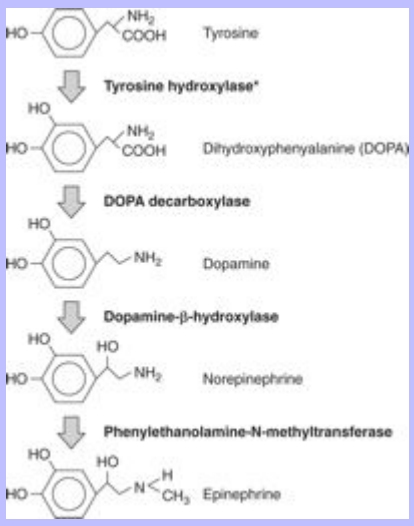
Consistent with the role of the adrenal medulla as a sympathetic ganglion, chromaffin cells are capable of producing, storing, and secreting a variety of neurotrans-mitters and neuropeptides.[2] Catecholamines are the primary secretary product of the adrenal medullary cells, however. Catecholamines, along with other products including ATP and chromagranin, are stored within cytoplasmic vesicles in the chromaffin cells. When the chromaffin cells are stimulated, vesicles are transported to the cell membrane and the contents are expelled via exocytosis.[3]

Catecholamines are synthesized from the amino acid tyrosine through a series of enzyme modifications (Figure 245-1). The first step in catecholamine synthesis involves the conversion of L-tyrosine to L-DOPA through the action of tyrosine hydroxylase. This hydroxylation reaction is the rate limiting step in the pathway and is subject to negative feedback regulation by norepinephrine.[1] In dogs and humans the end product of catecholamine synthesis in the adrenal medulla is predominantly epinephrine, whereas in the cat it is norepinephrine.[4] Pheochromocytomas may produce any of the catecholamines or other physiologically active peptides.

The half-life of catecholamines in circulation is short (minutes). Two enzymes mediate the catabolism: catecholamine-O-methyltransferase (COMT) and monoamine oxidase (MAO).[1,5] The sequential action of COMT and MAO on catecholamines results in the production of the predominant metabolite, vanillylmandelic acid (VMA)[1] (Figure 245-2). Catecholamines and metabolites are excreted in the urine.

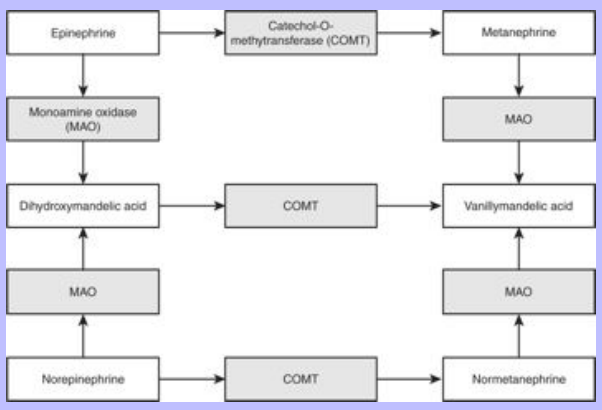
The normal adrenal gland is regulated through a combination of sympathetic innervation and circulating hormones.[2] There is an intricate regulatory connection between the adrenal cortex and medulla. Whereas the peptide products of the adrenal medulla influence steroidogenesis in cortical cells, the steroid hormones influence both differentiation and catecholamine production in the medullary chromaffin cells.[2] One of the hallmarks of neoplastic transformation is the loss of regulatory control, particularly those involved with growth and cell death. For endocrine tumors, such as pheochromocytoma, deregulation may also include loss of normal physiologic control of hormone production and secretion. Thus pheochromocytomas are often associated with increased levels of circulating catecholamines or other physiologically active products.

Figure 245-1 Catecholamine synthesis. *Tyrosine hydroxylase is the rate limiting enzyme and is subject to negative feedback control by norepinephrine.



The action of catecholamines is mediated by specific G protein coupled cell surface receptors[3] (Table 245-1). The receptors are subdivided into α and β types, which include the subtypes αl, α2, β1, β2, and the less prevalent β3. The binding of catecholamines to their receptors initiates cellular increases or decreases in second messengers, which, in turn propagate cellular signaling and affect the cellular response.[3] Epinephrine and norepinephrine have approximately equal affinity for the al, α2, β1 receptors, but epinephrine has higher affinity for β2 receptors.[1,3]

Figure 245-2 Catabolism of catecholamines. *COMT*, catecholamine-O-methyltransferase; *MAO*, monoamine oxidase. Shaded boxes indicate an enzymatic step.



245.2 ETIOLOGY

Cancer is a genetic disease in that inherited and acquired mutations drive the transformation of a normal cell to a tumor cell.[6,7] The cause of genetic mutations in most cancers is not understood and pheochromocytoma is no exception. Roughly 10% of human pheochromocytomas are considered hereditary, the rest, sporadic. Pheochromocytoma may be a feature of a number of distinct hereditary syndromes including multiple endocrine neoplasia type 2 (MEN-2), von Hippel-Lindau disease (VHL), and neurofibromatosis type I[8,9] (Table 245-2). Additional hereditary forms of pheochromocytoma are distinct from these syndromes. Some of the genes that predispose tumor development in the various hereditary disorders have been characterized[8,9] (see Table 245-2). These genes do not appear to play a role in the development of most sporadic pheochromocytoma. A number of chromosomal loci are consistently mutated in sporadic pheochromocytoma, which suggests that these regions contain genes important for pheochromocytoma carcinogenesis.

The role of genetic factors, hereditary or acquired, has not been evaluated in canine or feline pheochromocytoma. Many canine cancers do have a hereditary basis, however. There are reports of dogs with multiple endocrine tumors including a dog with a syndrome similar to MEN-2.[10,11] In addition, a large proportion of dogs diagnosed with pheochromocytoma also have another malignancy, some of these in endocrine tissue. In a search of the Veterinary Medicine Database (VMDB), which contains medical record data abstracted from 26 North American veterinary colleges, the diagnosis of pheochromocytoma was recorded for only 0.05% of canine patients evaluated between 1990 and 2002.

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Table • 245-1 The Biochemical Characteristics and Physiologic Effects of Catecholamine Receptors

RECEPTOR TYPE	α1	α2	β1	β2
Biochemistry				
Receptor affinity	Epi ≥ Nor	Epi ≥ Nor	Epi = Nor	Epi >> Nor G_s
G-protein subtype	G_q	G_i	G_s	G_s
Second messenger	↑IP3, DAG	↓cAMP	↑cAMP	↑cAMP
Physiologic Effects				
Ocular	Mydriasis			
Cardiovascular				
Heart			Increase heart rate, contractility, conduction velocity	
Arterioles	Constriction			Dilatation
Veins	Constriction			Dilatation, relaxation
Respiratory				
Bronchial smooth muscle				Relaxation
Gastrointestinal				
Motility	Decrease	Decrease		Decrease
Spincters	Contraction	Contraction		
Liver	Glycogenolysis	Glycogenolysis		Glycogenolysis
Pancreatic acini	Decrease secretion			
Adipose				Lipolysis

ENDOCRINE EFFECTS	ALPHA	BETA
Adrenal cortex	Decreased aldosterone secretion	(Both alpha and beta)
Pancreas		
Alpha cell		Increased glucagon
Beta cell	Decreased insulin	
D cell		Increased somatostatin
PP cell	Increased pancreatic polypeptide	
Gastric antrum		Increased gastrin
Kidney		Increased renin and erythropoietin
Parathyroid		Increased parathyroid hormone
Ovary		Increased progesterone
Testis		Increased testoterone

In the 277 dogs with pheochromocytoma identified in the VMDB, 129 (46%) were diagnosed with other tumors. This finding is consistent with previous reports.[4,12] The presence of multiple tumors in an individual is suggestive of hereditary predisposition.

Fifty-five different breeds were represented among the 277 cases of canine pheochromocytoma in the VMDB. Chi-square analysis comparing the frequency of pheochromocytoma in specific breeds to the frequency of pheochromocytoma in all dogs in the VMDB database revealed significantly increased relative risk of this tumor in seven different breeds of dogs (Table 245-3). Breed predisposition is suggestive of hereditary predisposition, but study of pedigrees is required to confirm this suspicion and to determine the mode of inheritance.

245.3 CLINICAL PRESENTATION

The average age of dogs diagnosed with pheochromocytoma is 10 to 11 years, with a range of 1 to 18 years.[4,12,13] Reports indicate that this is a disease of aged cats. No gender predilection is apparent in either species.[14–16] Although certain breeds may be predisposed to pheochromocytoma, any breed can be affected, including mixed breed dogs.

The clinical signs in dogs with pheochromocytomas are complicated by the high frequency of concurrent illnesses, including hyperadrenocorticism, diabetes mellitus, renal failure, and hepatic disease.[4] In humans with pheochromocytoma, the most common complaints include headache, palpitations, and sweating, which are not readily detectable in dogs and cats. In addition, roughly half of the pheochromocytomas diagnosed in dogs are incidental.

Table • 245-2 Familial and Sporadic Pheochromocytoma in Humans[9,22,32]

CLINICAL CHARACTERISTICS		FREQUENCY OF PEOCHROMOCYTOMA	GENES INVOLVED
MEN-2A	Bilateral medullary thyroid carcinoma; Parathyroid hyperplasia;	20% to 40%	RET
MEN-2B	Bilateral medullary thyroid carcinoma, Phenotypic abnormalities: Bony abnormalities, mucosal neuromas, marfanoid habitus, bumpy lips	60%	RET
VHL	Bilateral renal carcinomas and renal cysts; other tumors	18% to 25%	VHL
NF-1	Cafe-au-lait spots of the skin, Neurofibromas, Hamartomas of the iris, macrocephaly, bone dysplasia, learning disability, seizures, CNS tumors, other malignant tumors such as neurofibrosarcomas and leukemia	1%	NF-1
Sporadic	Older than with hereditary syndromes; Unilateral disease	100%	P53, RB, Others?

MEN, Multiple endocrine neoplasia; *VHL,* von Hippel-Lindau disease; *NF-1,* Nuerofibromatosis type 1, *Sporadic,* Nuerofibromatosis type 1, *Sporadic,* Nonhereditary.

The most common clinical signs in dogs with pheochromocytoma, in the absence of complicating disease, are weakness and collapse.[4] Other historical complaints may be associated with a variety of systems including gastrointestinal (anorexia, weight loss, vomiting, diarrhea), nervous (restlessness, pacing, depression, seizures), cardiopulmonary (exercise intolerance, lethargy), and miscellaneous complaints such as abdominal distension, polyuria, and polydipsia. In cats with pheochromocytoma, polyuria and polydipsia are consistently reported.[14–16]

Clinical signs associated with pheochromocytoma may be related to increased circulating catecholamines or directly associated with the tumor (Table 245-4). Although most pheochromocytomas occur in the adrenal gland, presentation may differ considerably with paraganglioma in extra-adrenal locations, such as the vertebral canal.[17]

Table • 245-3 Relative Risk of Pheochromocytoma in Purebred Dogs Identified in the VMDB Database (1990–2002)

BREED	NUMBER OF DOGS WITH PHEOCHROMOCYTOMA	NUMBER OF DOGS WITHOUT PHEOCHROMOCYTOMA	RELATIVE RISK	95% CONFIDENCE INTERVAL
Airedale terrier	6	1950	5.8	2.6–12.9
Basset hound	5	647	14.4	5.9–34.7
English springer spaniel	8	6639	2.3	1.1–2.5
Golden retriever	31	28,246	2.1	1.5–3.1
Puli	2	130	28.1	7.1–111.8
Weimaraner	5	2167	4.3	1.8–10.4
Wire hair fox terrier	6	1569	7.1	3.2–16.0
Mixed breed	70	109,850	1.2	0.9–1.6
All dogs 1990–2002	277	509,751	NA	NA

245.4 DIAGNOSTIC EVALUATION

245.4.1 Minimum Database

Abnormalities detected in dogs and cats with pheochromocytomas are nonspecific. The presence of concurrent disorders may be reflected in the complete blood count, serum chemistry profile, and urinalysis.[4] Often, the hemogram is normal.[4,13,18] Leukocytosis can be seen secondary to increased circulating catecholamines or stress. Mild anemia may be present secondary to chronic disease or hemorrhage. Thrombocytopenia or thrombocytosis may indicate acute or chronic bleeding, respectively.

Increases in serum liver enzyme activities have been reported in 10% to 25% of pets with pheochromocytoma.[4,13,18] The abnormal serum liver enzyme activities may be secondary to hypertension with changes in hepatic perfusion or can occur with concurrent disease such as hyperadrenocorticism. These abnormal liver enzymes do not correlate with the presence of hepatic metastases.[13]

1635 1636

Table • 245-4 Clinical Signs Associated with Canine Pheochromocytoma[4,12,13,18,33]

EXCESS CATECHOLAMINES	MASS EFFECT
Tachycardia/arrhythmia	Abdominal distention
Polypnea/panting	Weak femoral pulses
Coughing	Hemoabdomen
Ataxia/incoordination	Ascites
Episodic weakness	Pleripheral edema
Seizures	Collapse
Collapse	Budd-Chiari like syndrome*
Blindness (retinal hemorrhages)	
Polyuria/polydipsia	
Anorexia	
Vomiting	
Diarrhea	
Anxiety/pacing	

* Budd-Chiari like syndrome is the mechanical obstruction of the vena cava between the heart and the liver.

Proteinuria, resulting from hypertensive glomerulopathy or concurrent illness, is observed in as many 50% of dogs and cats with pheochromocytomas.[4,13] Hyposthenuria/isosthenuria may be present due to the inhibitory effect of circulating catecholamines on vasopressin secretion and activity.[4]

245.4.2 Blood Pressure

In dogs with pheochromocytoma, the presence of systemic hypertension (systolic pressure >160 mm Hg) is variable (25% to 86% of patients), which may reflect sporadic secretion of catecholamines resulting in intermittent hypertension.[4,13]

245.5 DIAGNOSTIC IMAGING

Imaging techniques are useful for localizing a mass and for determining the extent of disease, including whether the tumor is unilateral or bilateral, is invading local structures, or has metastasized to distant regions.[13] This information is valuable in planning surgical approach and in determining prognosis.

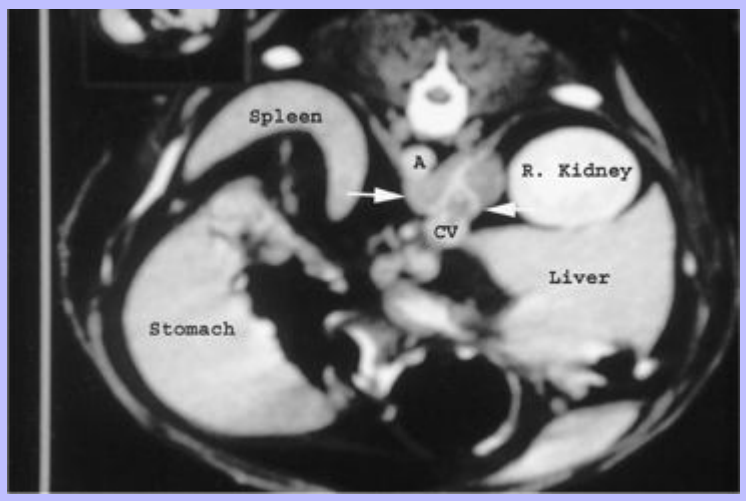
245.5.1 Radiography

Plain abdominal radiographs may reveal a mass or mineralization in the adrenal region.[4,12,13,19] Frequently, the adrenal lesion cannot be detected. Thoracic radiographs may reveal changes consistent with hypertension such as cardiomegaly, pulmonary congestion, or edema.[4,13,18] Contrast studies such as caudal vena cava or nonselective venography and excretory urography may be helpful in detecting caval invasion or thrombosis and renal integrity, respectively.[4,12,13,18,20]

245.5.2 Abdominal Ultrasound

Sonographically, pheochromocytomas appear as mass lesions of the adrenal gland with variable echogenicity.[19,21] Pheochromocytomas cannot be distinguished from other tumors in the adrenal gland based on the sonographic appearance. Other findings could include evidence of metastasis, invasion, or vascular involvement.

Figure 245-3 Transverse abdominal CT image in the cranial lumbar region of a dog with pheochromocytoma. *A*, Aorta; *CV,* caudal vena cava.



245.5.3 Computed Tomography

Computed tomography (CT) is sensitive for lesion localization and in assessment for local invasion and metastasis (Figure 245-3).[4,19] Hypertension secondary to intravenous contrast media (diatrazoate sodium meglumine or iothalamate meglumine) has been reported in humans with pheochromocytomas.[19,22] It is suspected that these medications precipitate catecholamine release. In dogs, hypertension subsequent to administration of contrast media has not been reported.

245.5.4 Magnetic Resonance Imaging

Although there are no reports describing the use of magnetic resonance imaging (MRI) in dogs or cats with a pheochromocytoma, this modality is considered highly sensitive in the detection of pheochromocytoma in humans.[19]

245.5.5 Nuclear Scintigraphy

Scintigraphic studies are used frequently in humans and are reported in the dog for localization of pheochromocytoma.[22–25] Radioactive iodine labeled meta-iodobenzylguanidine (MIBG) is structurally similar to norepinephrine and is taken up by chromaffin cells. This technique is less sensitive than CT for identification of pheochromocytoma in humans but is more specific and it may be useful in the identification of metastases.[25] Octreotide is a somatostatin analog that may be radioactively labeled and binds somatostatin receptors on the surface of neuroendocrine cells such as those in pheochromocytomas. Octreotide scanning may detect lesions in patients with normal MIBG scans.[25]

245.5.6 Positron Emission Tomography

Positron emission tomography (PET) using 6-(^{18}F) fluorodopamine has been helpful in humans when conventional testing is equivocal.[22,26,27] The use of this technique for localization of pheochromocytoma in the dog has been reported and shows promise.[26]

245.6 BIOCHEMICAL DIAGNOSIS

245.6.1 Catecholamine Measurement

Catecholamines, their metabolites, or other neuroendocrine products may be measured in plasma or urine. These techniques are infrequently used in dogs or cats because of limited availability, lack of reference ranges, expense, and complicated sample collection and handling.[4,20,26] In addition, the accuracy of these diagnostics is limited. False-positive results are associated with stress, excitement, certain dietary components, and medications. False-negative results are associated with intermittent secretion of catecholamines by the tumor and improper sample handling.[4,20,26]

245.6.2 Provocative Testing

Certain agents, including histamine, tyramine, metoclopromide, and glucagon, cause adrenal catecholamine release and can be used to screen individuals for pheochromocytoma.[4,20] Because of the risk of a hypertensive crisis, these tests are not recommended.

245.6.3 Clonidine Suppression Test

Clonidine is a centrally acting α-agonist that suppresses the release of catecholamines. In all patients, blood pressure and heart rate can decrease after administration. Lack of reduction in plasma catecholamines following administration of clonidine is consistent with pheochromocytoma.

245.6.4 Phentolamine Test

Phentolamine is an α-receptor antagonist, thus administration inhibits α-mediated vasoconstriction. In patients that are hypertensive secondary to excessive catecholamines, phentolamine results in vasodilation and decreased blood pressure within minutes of administration, an effect that lasts about 10 minutes. This test is not recommended due to potential for hypovolemic shock and difficulties in interpretation.

245.7 PATHOLOGY

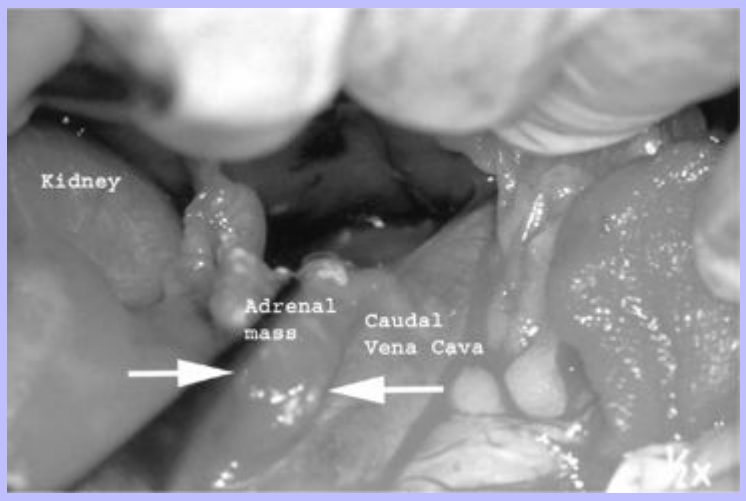
245.7.1 Cytology

Although there is some potential to induce a hypertensive crisis or hemorrhage, fine-needle aspiration can be performed with ultrasound or CT guidance. Cytologic features of pheochromocytoma are consistent with a tumor of neuroendocrine origin. Cytologic misdiagnosis has been documented.[13]

245.7.2 Histopathology

Microscopically, pheochromocytomas are composed of nests of polyhedral cells with lightly eosinophilic, granular cytoplasm that are separated by a fine fibrovascular stroma.[13,23,28] Immunohistochemical techniques may be useful in distinguishing pheochromocytoma from other tumors of the adrenal gland.[4,28] The distinction between benign and malignant tumors is unclear. In humans, presence of capsular or vascular invasion and nuclear pleomorphism do not correlate with behavior.[23]

Figure 245-4 Intraoperative photograph demonstrating a noninvasive pheochromocytoma in a dog.



245.8 TREATMENT

245.8.1 Surgery and Perioperative Management

Surgical excision of pheochromocytoma is the treatment of choice (Figure 245-4). Surgical and anesthetic complications are common, however. The surgical approach to adrenalectomy has been described.[29]

Pre-anesthetic goals include stabilization of hypertension and control of arrhythmias.[30] Treatment with α-receptor antagonists, such as phenoxybenzamine or prazosin, will normalize intravascular volume in individuals with chronic hypertension. Arrhythmias should be treated with β-adrenergic antagonists such as propanolol or esmolol. It may be prudent to normalize blood pressure and rhythm disturbances for 1 to 2 weeks prior to surgery in light of the high complication rate reported in dogs and cats.[18,30,31]

Medications that stimulate release of catecholamines or may precipitate arrhythmias (ketamine, morphine, and halothane) should be avoided. Anesthetic protocols used in humans include the use of thiopental, propofol, isoflurane, or sevoflurane.[30]

Careful monitoring of blood pressure, cardiac rhythm, and red cell volume is essential. Manipulation of a pheochromocytoma can induce catecholamine release with subsequent hypertension. Following resection, hypovolemia may occur as the circulating catecholamine concentrations decrease. Hypotension is best managed by administration of intravenous crystalloids. In dogs that have a poor response to fluid expansion, dopamine may be indicated. Postoperatively, monitoring must continue until the animal is stabilized. In one study of dogs undergoing surgical resection of pheochromocytoma, hospitalization time ranged from 3 to 12 days.[31]

245.8.2 Medical Management

Dogs or cats with nonresectable or metastatic pheochromocytoma may be treated medically. The goals of medical therapy are to control sequelae to elevated catecholamines (hypertension and arrhythmias) and control of the tumor (both primary and metastatic).

245.8.3 Chemotherapy

Chemotherapy has not been evaluated for treatment of pheochromocytoma in dogs or cats. Humans with malignant pheochromocytoma are often treated with protocols combining vincristine, cyclophosphamide, and dacarbazine, which prolongs survival in patients with metastatic disease.[23] In addition to typical chemotherapy related side effects, there is some risk of inducing a hypertensive crisis due to tumor cell lysis with release of stored catecholamines.[23]

245.8.4 Targeted Therapy

Radiolabeled MIBG, in addition to imaging applications, has demonstrated efficacy in the treatment of malignant pheochromocytoma in humans either alone or in combination with chemotherapy. Similarly, octreotide may be useful in people if octreotide scintigraphy demonstrates uptake. Neither of these techniques has been reported in the dog.

245.9 PROGNOSIS

Animals with surgically resectable pheochromocytoma can have prolonged survival times. The median survival time for six dogs with surgical resection was 15 months. For dogs surviving the immediate postoperative period, a range in survival from 2 to 40 months has been reported.[4] Prognosis in cats is probably similar. In the few reported cases of pheochromocytoma in cats, only one cat survived postoperatively. Metastasis has been reported in 13% to 50% of dogs with pheochromocytoma. Sites of metastasis include liver, regional lymph nodes, spleen, lungs, brain, and bone (femur and lumbar vertebral body). Metastasis of feline pheochromocytoma has not been reported.

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246 CHAPTER • 246 Estrous Cycle and Breeding Management of the Healthy Bitch

Auke C. Schaeferes-Okkens

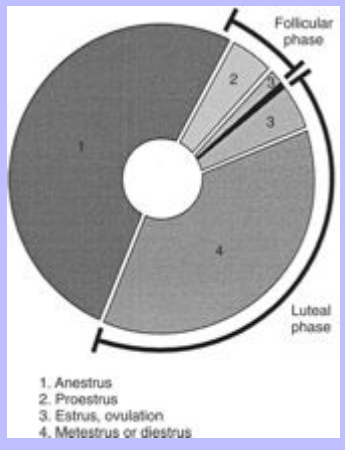
246.1 THE ESTROUS CYCLE

Onset of puberty in the healthy bitch occurs between 6 and 18 months of age. After each estrous cycle, which has a length of about 3 months, an anestrus with a variable duration occurs. The mean interval from onset of one estrous cycle to the next is about 7 months, with a range of 4 to 12 months. The interestrous interval may be regular or variable within individual bitches. After 8 years of age, the duration and frequency of the cycles become less regular and the interestrous interval increases.[1]

The stages of the estrous cycle are proestrus, estrus, and diestrus (metestrus) (Figure 246-1). The average duration of proestrus is 9 days, with a range of 3 to 17 days. Proestrus is defined as the period when the bitch is sexually attractive while rejecting the male's advances until the first willingness to accept the male. However, early behavioral signs are indistinct. Therefore it is common to use the onset of serosanguineous vaginal discharge and vulvar swelling to mark the first day of proestrus.

On average, estrus (the period of acceptance of the male) has a duration of 9 days, with a range of 3 to 21 days. During estrus the vulva begins to shrink and soften. The discharge usually persists, but generally diminishes. It may remain serosanguineous or turn straw-colored. Diestrus begins when the bitch will no longer accept the dog. It has an average duration of about 70 days if it is assumed to end when the plasma progesterone concentration initially declines to a level of less than or equal to 3 nmol/L (lnmol/L =0.315 ng/ml). In addition to this behavior-oriented classification of the cycle, it is also possible, and more appropriate, to concentrate on ovarian function and to classify the follicular phase, the phase of preovulatory luteinization and ovulation, the luteal phase and the anestrus (see Figure 246-1).

Figure 246-1 Diagram of the estrous cycle and anestrus in the dog. (From Schaefers-Okkens AC: The ovaries. In Rijnberk A: *Clinical endocrinology of dogs and cats*. Netherlands, 1996, Kluwer Academic Publishers.)



246.2 FOLLICULAR PHASE

As tertiary follicles develop in the ovaries they produce estradiol, leading to peak plasma levels of 180 to 370 pmol/l in late proestrus, 1 to 2 days before the preovulatory luteinizing hormone (LH) surge (Figure 246-2). On laparoscopic inspection, follicle development is not readily apparent on the ovary because of the ovarian bursa. Furthermore, until mid-proestrus, follicular development appears only as clear grayish areas with indistinct boundaries on the ovarian surface. These areas gradually develop into distinct fluid-filled vesicular follicles, which protrude distinctly above the ovarian surface.[2] The external signs of proestrus, such as hyperemia and edema of the vulva and bloody vaginal discharge, are caused by increased concentrations of estradiol (Figure 246-3). This also causes lengthening and hyperemia of the uterine horns, enlargement of the cervix (which can be palpated), and thickening of the vaginal wall.

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Figure 246-2 Diagram of estradiol, LH, and progesterone concentrations in plasma in relation to commonly observed estrus behavior of the bitch, and the optimal period for mating. (From Schaefers-Okkens AC: The ovaries. In Rijnberk A: *Clinical endocrinology of dogs and cats,* Netherlands, 1996, Kluwer Academic Publishers.)

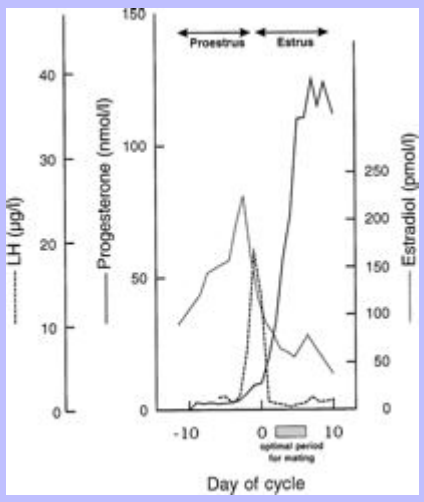
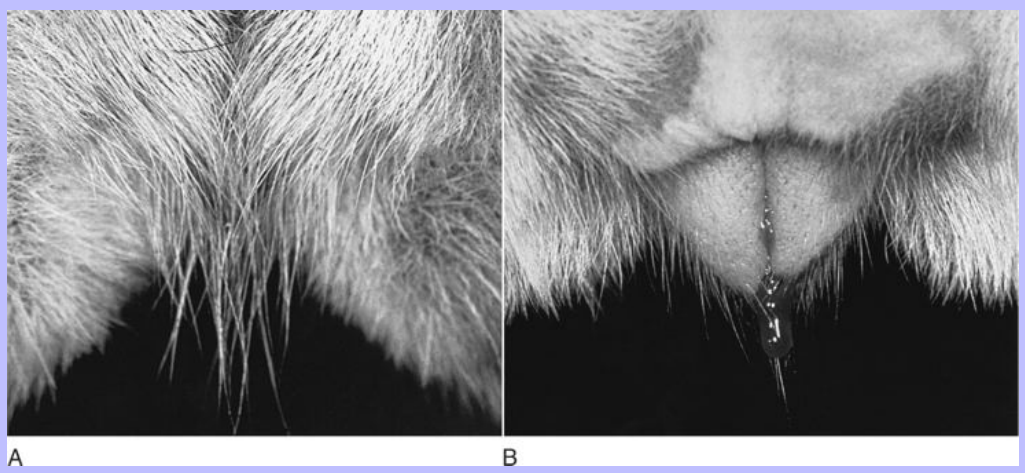
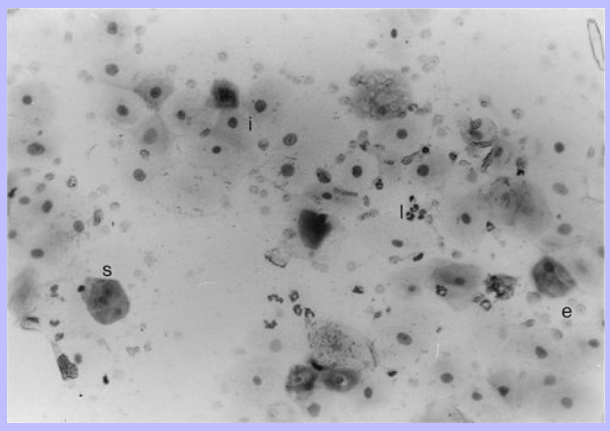


Figure 246-3 The vulva of a beagle bitch during **(A)** anestrus, and during **(B)** proestrus/estrus. (From Schaefers-Okkens AC: The ovaries. In Rijnberk A: *Clinical endocrinology of dogs and cats,* Netherlands, 1996, Kluwer Academic Publishers.)



The percentage of superficial cells in the vaginal smear increases and the percentage of parabasal and small intermediate cells decreases. Erythrocytes are numerous, and leukocytes are seen in the early follicular phase but disappear as cornification progresses (Figure 246-4). Superficial cells dominate as the follicular phase progresses (Figure 246-5). However, it should be realized that although vaginal cytology gives an indication of the stage of the cycle, it is not reliable for timing the preovulatory LH surge or ovulation.[3]

Figure 246-4 Vaginal cytology in the bitch at the onset of the follicular phase, showing primarily intermediate *(i)* cells, some superficial *(s)* cells, erythrocytes *(e)*, and leukocytes *(l)* (May Grünwald Giemsa, original magnification, 200).



With vaginoscopy it can be observed that the vaginal mucosal folds are swollen, are pale, and have smooth, rounded surfaces (balloons) (Figure 246-6). The increased concentrations of estradiol frequently cause hypertrophy of the floor of the posterior vagina, just cranial to the urethral orifice and therefore folding over and covering the urethral orifice (Figure 246-7). At the end of the follicular phase that is during the decline in estradiol and the rise in progesterone concentrations in plasma, shrinkage begins in response to reduced estradiol-dependent water retention. These cyclic changes are most marked in the dorsal median fold and precede those of the mid-vaginal mucosa (Figure 246-8).

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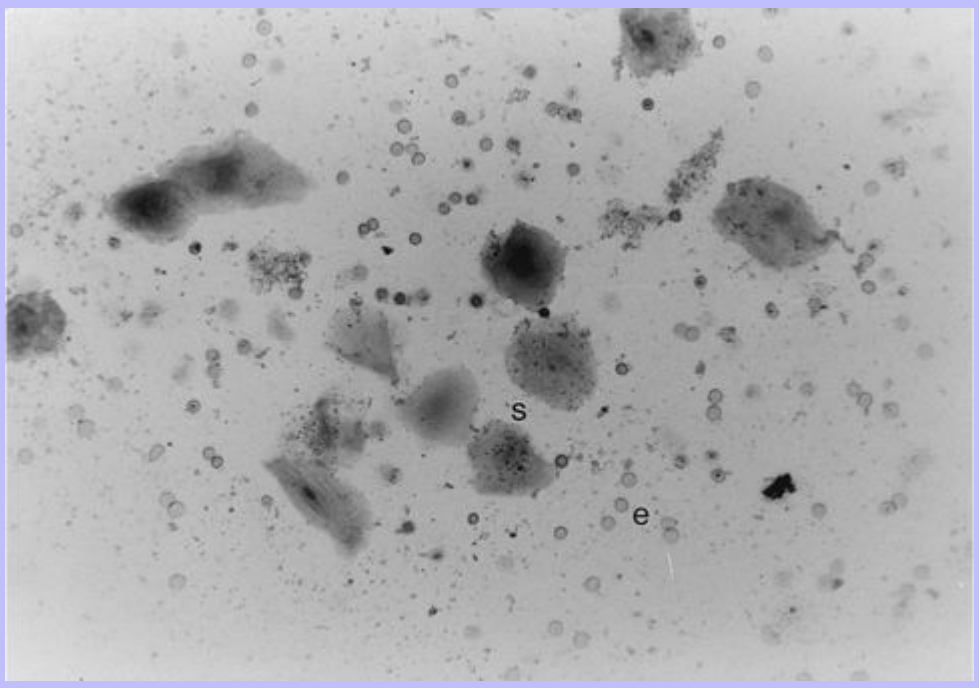
Figure 246-5 Vaginal cytology in the bitch during the second half of the follicular phase, at ovulation, and the onset of the luteal phase. This smear shows superficial cells (s) and erythrocytes (*e*). (May Grünwald Giemsa, original magnification 200)



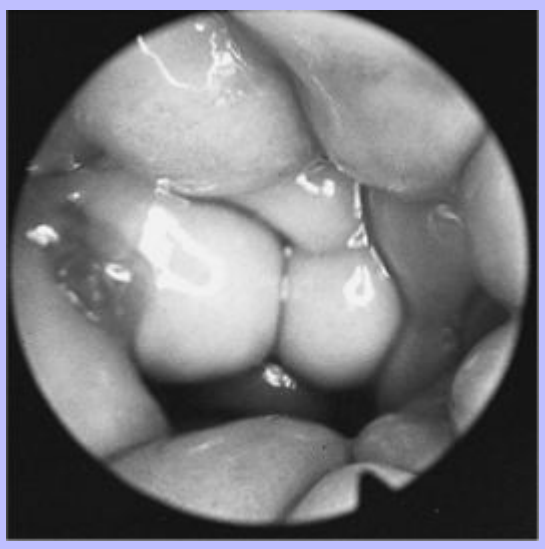
The basal plasma follicle-stimulating hormone (FSH) concentration is relatively low during the follicular phase, whereas the basal plasma LH concentration is higher than in different phases of the anestrus (Figure 246-9). The secretory pattern of LH is characterized by frequent increases of short duration.[4] Plasma progesterone concentrations initially remain low but fluctuate and increase during the second half of the follicular phase as a result of partial luteinization of the follicles.

246.3 PRE-OVULATORY LUTEINIZATION AND OVULATION

The pre-ovulatory surge of LH lasts 24 to 72 hours. It usually starts shortly after the estradiol peak and coincides with declining estradiol and rising progesterone concentrations in plasma (see Figure 246-2). Rapid and extensive

luteinization takes place during the preovulatory LH surge. Ovulating follicles therefore have many of the characteristics of rapidly developing corpora lutea. Most ova in the dog are ovulated in an immature state as primary oocytes. The process of ovulation can take up to 24 hours. In the first 2 to 3 days after ovulation the oocytes mature; that is, they undergo the first meiotic division and the extrusion of the first polar body, after which fertilization can occur.[5]

Figure 246-6 Vaginoscopy in the bitch at the onset of the follicular phase. Note the swollen, pale mucosal folds with smooth rounded surfaces (balloons) and the bloody secretion between the folds.



Plasma progesterone levels are 6 to 13 nmol/L at the time of the LH peak, and 15 to 25 nmol/L at the time of ovulation, 36 to 48 hours later. Concurrent with the LH peak, a pre-ovulatory surge in FSH occurs that reaches peak concentrations 1 to 2 days after the LH peak. Estrus behavior usually starts synchronously with the pre-ovulatory LH peak (see Figure 246-2), but some bitches initially demonstrate estrus behavior days before or after the LH peak.[6] Shrinkage of the vaginal mucosa starts about midway in the follicular phase and continues through the phase of pre-ovulatory luteinization and ovulation, when many longitudinal folds can be observed (Figure 246-10). 1642 1644

Figure 246-7 A modest vaginal hyperplasia which is observed quite often in the posterior vagina during the estradiol-influenced phase of the cycle (follicular, ovulation, fertilization phase). (From Schaefers-Okkens AC: The ovaries. In Rijnberk A: *Clinical endocrinology of dogs and cats,* Netherlands, 1996, Kluwer Academic Publishers.)

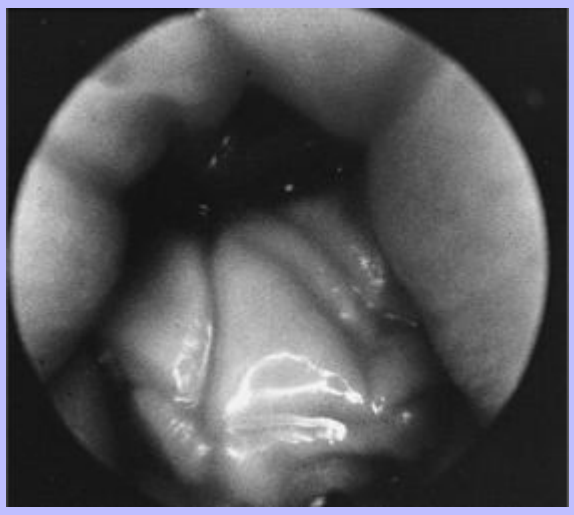
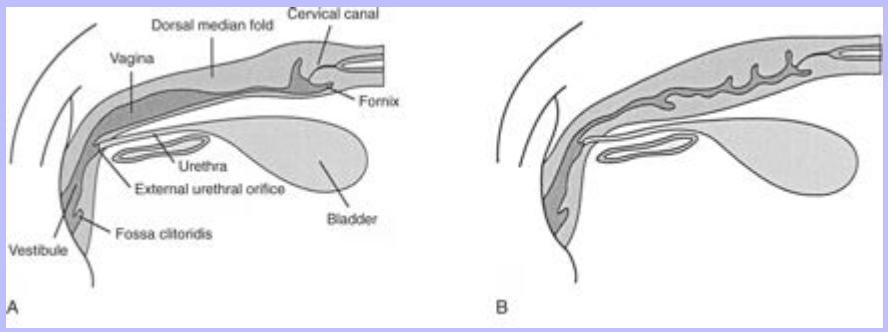


Figure 246-8 A sagittal section through the vestibule, vagina, and cervix of a bitch **(A)** during anestrus and **(B)** during the proestrus/estrus period. In this stage the vaginal wall is extremely folded. **C,** A close up of the cranial part of the vagina and the cervix during the anestrus period. Note the very short cervical canal. (From Schaefers-Okkens, AC: The ovaries. In Rijnberk A: *Clinical endocrinology of dogs and cats,* Netherlands, 1996, Kluwer Academic Publishers.)



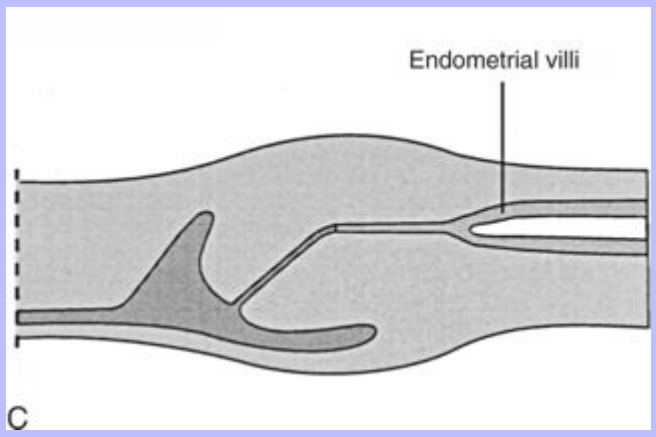


Figure 246-9 The mean (± SEM) plasma FSH and LH concentrations of the smoothed baseline in six beagle bitches during the follicular phase, the luteal phase, and during early, mid-, and late anestrus. *Indicates significant difference. (From Kooistra HS et al: Concurrent pulsatile secretion of luteinizing and follicle-stimulating hormone during different phases of the oestrous cycle and anoestrus in beagle bitches, *Biol Reprod* 60:65, 1999.)

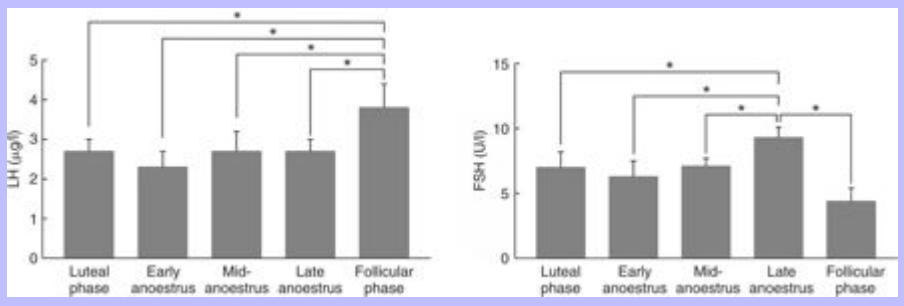
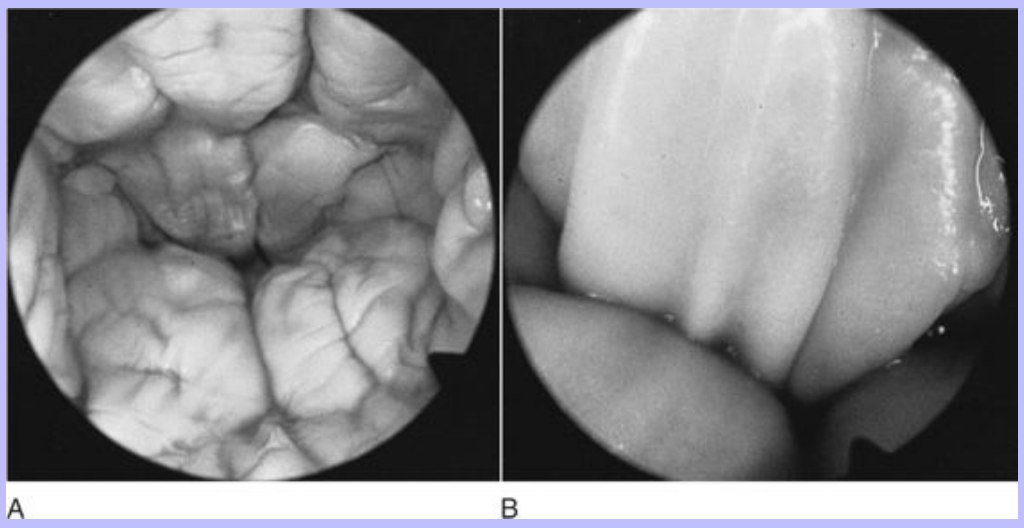


Figure 246-10 Vaginoscopy at the time of ovulation. The plasma progesterone concentration in this bitch was 22 nmol/l. **A**, The mucosal shrinkage leads to longitudinal folds. **B,** Close up of the shrinkage of the longitudinal folds of the dorsal median fold of the cranial vagina. (From Schaefers-Okkens AC: The ovaries. In Rijnberk A: *Clinical endocrinology of dogs and cats,* Netherlands, 1996, Kluwer Academic Publishers.)

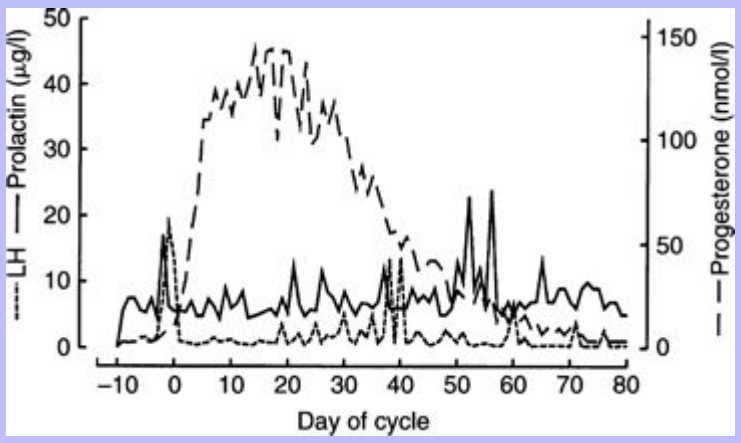


246.4 LUTEAL PHASE

Plasma concentrations of progesterone originating from the corpora lutea increase during the remainder of the estrus and during the onset of diestrus. Estrus behavior is thus seen during the period of a rising plasma progesterone concentration. Increased progesterone concentrations plateau at 10 to 30 days after the LH peak. Thereafter, in non-pregnant bitches, the progesterone secretion declines slowly and reaches a basal level of 3 nmol/l for the first time at about 75 days after the start of the luteal phase (Figure 246-11).

During the initial part of the luteal phase, the transition from estrus to diestrus takes place. In this period, the cytology of the vaginal mucosa changes from primarily superficial cells to mainly intermediate and parabasal cells and leukocytes (Figure 246-12). This change is an indication that the fertile period has expired. During oocyte maturation, shrinkage of the vaginal mucosa continues and increasing numbers of sharp edged summit profiles appear. In the transition period from estrus to diestrus, the mucosa thins and profiles become round. At the start of diestrus, a patchwork of red and white areas can be seen (Figure 246-13).

Figure 246-11 Mean LH, progesterone, and prolactin levels in plasma of three dogs during the follicular and luteal phase. The data have been synchronized on day 1, the day after the onset of the follicular phase on which the progesterone concentration in the peripheral blood had reached 16 nmol/l. (From Schaefers-Okkens AC: The ovaries. In Rijnberk A: *Clinical endocrinology of dogs and cats,* Netherlands, 1996, Kluwer Academic Publishers.)



The factors that are responsible for initiating the regression of the corpora lutea in the dog are still unknown. Prostaglandin $F_{2\alpha}$ originating from the endometrium is not the causative factor in the bitch as it is in the cow and sheep. This is demonstrated by the fact that hysterectomy does not influence the length of the luteal phase.[7]

Prolactin acts as a luteotropic factor in the second half of the luteal phase.[8,9] During the first half of the luteal phase the corpus luteum functions independent of pituitary support.[10] Thereafter, inhibition of prolactin secretion causes a sharp decrease in progesterone secretion (Figure 246-14). LH concentrations change little during the luteal phase, with the exception of a slight increase in the second half of the luteal phase (see Figure 246-11). There is no proof of direct luteotropic properties for LH in the cyclic bitch.[9,11]

Pseudopregnancy is a syndrome that in greater or lesser degree accompanies the extended luteal phase of all non-pregnant ovarian cycles in the bitch. If the nature of the syndrome is mild, it is generally referred to as a *physiologic* or *covert pseudopregnancy*. In contrast, overt or "clinical" pseudopregnancy includes obvious mammary development, changes that are not distinguishable from the changes of late pregnancy, or lactation are seen (see Chapter 247). Mammary gland development is influenced by prolactin and growth hormone (GH) and their secretion pattern is influenced by progesterone.[12] GH, produced in the mammary gland itself, may promote the physiologic proliferation and differentiation of mammary gland tissue during the luteal phase by local autocrine/paracrine effects, prolactin is important for lobuloalveolar development.[13]

In the start of the luteal phase, a higher basal GH secretion is present, with less GH being secreted in pulses than during the last part of the luteal phase, where the basal GH secretion is lower with more GH being secreted in

pulses. This phenomenon may be explained by partial suppression of pituitary GH release by progesterone-induced GH production in the mammary gland (Figure 246-15).[12] In most non-pregnant bitches the decline in plasma progesterone concentrations during the luteal phase is associated with a moderate but significant increase in prolactin secretion (see Figures 246-11 and 246-15).[12] In the overt pseudopregnant bitch, however, the plasma prolactin concentration may strongly increase, probably corresponding with the degree of "clinical" pseudopregnancy.[14]

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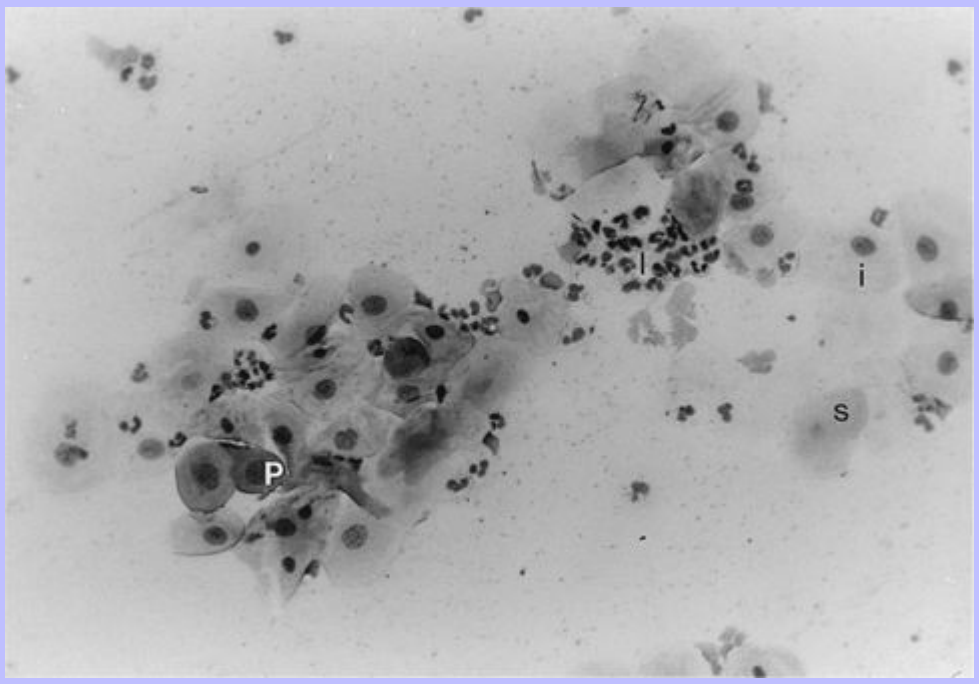
Figure 246-12 Vaginal cytology during diestrus, which starts 6 to 10 days after the preovulatory LH peak. This smear shows intermediate cells *(i)*, parabasal *(p)* cells, and leukocytes *(l)* (May Grünwald Giemsa original magnification, 200).

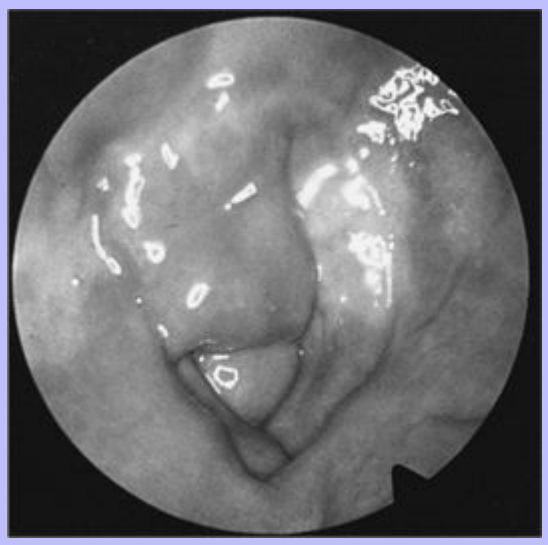


246.5 ANESTRUS

The time of the onset of anestrus depends on which criteria are being used to define the end of the luteal phase: for example, after 2 to 3 months when mammary development subsides, the first time that the plasma progesterone concentration reaches a level below 3 nmol/L, or the moment that the influence of progesterone on the endometrium is no longer evident. In any case, the transition from the luteal phase into anestrus is gradual and varies considerably among bitches. The transition from anestrus to follicular phase can begin at any time throughout the year and there appears to be little, if any, seasonal influence. Breed differences and strains within breeds can form the basis of variation in mean interestrous intervals. In the Collie, for instance, the mean interval is 36 weeks, and in the Alsatian, it is about 20 to 22 weeks. Some breeds such as the Basenji and Tibetan Mastiff, however, have a single annual estrous cycle, which may possibly be influenced by a photoperiod. Environmental factors can also affect the interestrous interval: an anestrous bitch placed in close proximity to a bitch in estrus

can show an advance of the onset of proestrus by several weeks. Furthermore, bitches housed together often have synchronous estrous cycles.

Figure 246-13 Vaginoscopy during diestrus. Note the rounded profiles and the patchwork of red and white areas.

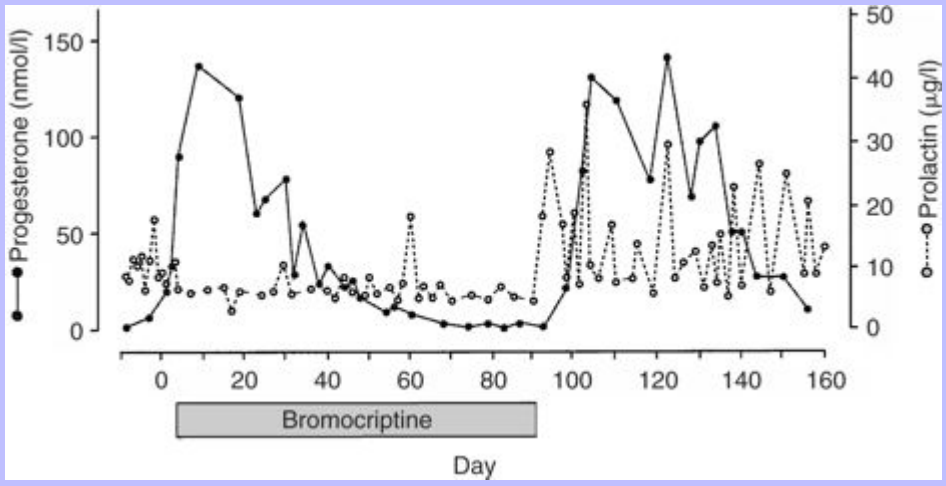


Progression from early to late anestrus is characterized by a greater amplitude and a higher number of GnRH pulses by the hypothalamus, an increase in the sensitivity of the pituitary to GnRH from early to late anestrus, and an increase in ovarian responsiveness to gonadotropins.[15,16] Furthermore, the increase in the basal plasma FSH concentration should be considered to be a critical event required for the initiation of folliculogenesis (see Figure 246-9).[4,17] In addition, a period of increased LH pulsatility is observed shortly before the onset of proestrus.[4,18,19] There is some evidence that factors that decrease opiodergic activity promote LH release and the termination of anestrus.[18] Finally, during the course of anestrus in the bitch, there is an increase in hypothalamic mRNA encoding for the estrogen receptor and the expression of the gene for P450 aromatase, which catalyzes estrogen biosynthesis.[20,21] Although sporadic elevations are observed, plasma estradiol concentrations are usually low and do not begin to rise until late anestrus.

Apart from these changes in the hypothalamic-pituitary-ovarian axis, there is an involvement of dopaminergic influences in the initiation of a new follicular phase in the bitch. Administration of the dopamine agonists bromocriptine and cabergoline shortens the anestrus and is associated with a decrease in the plasma prolactin concentration, which suggests that the shortened anestrus is the result of the suppression of prolactin secretion.[8,22] However, the anestrus of dogs treated with metergoline, a drug that in a low dose lowers the plasma prolactin concentration via a serotonine-antagonistic pathway, is not shortened, which indicates that not the decrease in the plasma prolactin concentration, but the dopamine-agonistic influence is a critical event in the transition to a new follicular phase.[23] Furthermore, a low dose of bromocriptine, which does not decrease the plasma prolactin concentration, prematurely induces a new follicular phase.[24] In addition, under physiologic conditions low plasma prolactin concentrations are found during anestrus and no obvious changes in the plasma

prolactin concentration have been observed in the bitch during the transition from anestrus to the follicular phase (see Figure 246-15).[4,25]

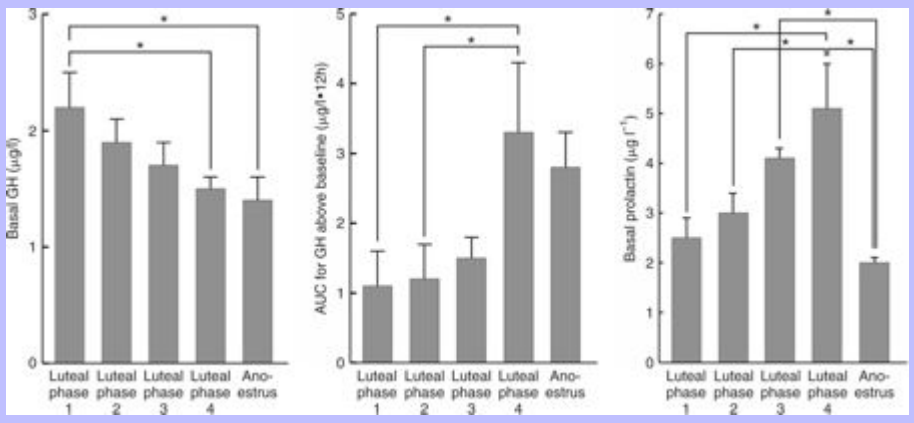
Figure 246-14 Progesterone and prolactin levels in the peripheral blood of one dog, treated with bromocriptine (bar) from ovulation in the first cycle until the onset of the next follicular phase. The luteal phase and especially the anestrus are considerably shortened. (From Schaefers-Okkens AC: The ovaries. In Rijnberk A: *Clinical endocrinology of dogs and cats,* Netherlands, 1996, Kluwer Academic Publishers.)



Bromocriptine-induced shortening of the anestrus is associated with a quick rise in the basal plasma FSH concentration without a concomitant increase in the basal plasma LH concentration[26], similar to what is observed during the physiologic late anestrus. This again indicates that in the bitch an increase in the circulating plasma FSH concentration is a critical event in the initiation of ovarian folliculogenesis.[4]

As a consequence of what is described, induction of a follicular phase may take place by pulsatile administration of GnRH. In a study, in which GnRH was administered in pulses of 15 to 500 ng/kg every 90 minutes for 7 to 9 days to 36 anestrous bitches, GnRH pulses resulted in proestrus, estrus, ovulation, and pregnancy in 26, 20, 16, and 12 bitches, respectively. Efficacy was dose dependent.[27] A fertile estrus could also be induced by administering a timed-release GnRH agonist, followed by a GnRH analogue on the first day of induced estrus.[28] Anestrus can also be terminated by treating bitches with porcine LH. In one study proestrus was induced in all bitches (n =16). Twelve bitches came in estrus, from which seven ovulated. Bitches, in which proestrus but not estrus occurred, were all treated in early anestrus.[29] The observed rapid increase of plasma estradiol concentration after LH treatment suggests that increased follicle steroidogenesis is a primary effect of LH. On the other hand the insufficient reaction to porcine LH of bitches in early anestrus may be due to a deficiency of FSH or FSH receptors in this stage of anestrus. Follicular aromatase in rats and most other species studied appears to be primarily under up-regulation control by FSH.[30]

Figure 246-15 The mean (± SEM) basal plasma GH concentration, the mean (± SEM) area under the curve (AUC) for GH above the baseline and the mean (± SEM) basal plasma prolactin concentration in six beagle bitches. Blood samples were collected at 10-minute intervals for 12 hours at four stages of the luteal phase (luteal stage 1 through 4, with mean plasma progesterone concentrations of 123, 56, 20, and 9 nmol/L, respectively) and during mid-anestrus. *Indicates statistically significant difference. (Modified from Kooistra HS, Okkens AC: Secretion of growth hormone and prolactin during progression of the luteal phase in healthy dogs: a review, *Mol Cell Endocrinol* 197:167, 2002.)



Anestrus can thus also be shortened considerably by administration of dopamine-agonists such as bromocriptine and cabergoline.[8,18,22,31] When bromocriptine treatment, twice daily 20 µg/kg, orally, is started during the luteal phase, the interestrous interval can be shortened from 245 days to 100 days (see Figure 246-14).[8] When started during the anestrus 100 days after the ovulation the next proestrus can be expected after a mean period of about 45 days.[31] The fertility of an estrus initiated by bromocriptine treatment appears to be normal.

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246.6 BREEDING MANAGEMENT OF THE HEALTHY BITCH

Breeding management starts with the determination if the bitch is healthy and if a normal fertility can be expected (Figure 246-16). For that reason the age and the breeding history of both the bitch and the male dog have to be considered. Thereafter, a complete gynecologic examination of the bitch is needed. Recurring examinations should be performed during the follicular phase, ovulation, and pregnancy. A decrease in fertility may be expected with increasing age. One of the reasons for this diminished fertility may be the development of cystic endometrial hyperplasia (CEH; see Chapter 251).

246.7 THE HISTORY CONCERNING THE REPRODUCTION DATA

The reproduction history of the bitch must be considered in the breeding management program. The age of the bitch at her first estrus and the length of the interestrous intervals are important. The bitch that has not experienced an estrus by 18 months of age is considered to have a primary anestrus. One of the major causes of primary anestrus is probably true hermaphroditism or pseudohermaphroditism. If a bitch has experienced estrus, an interval of more than 12 months or an interval that is double the usual interestrous interval for that individual bitch is considered to be a prolonged interestrous interval.

One reason for a prolonged anestrus can be hypothyroidism. However, it should be realized that less pronounced cases of hypothyroidism may result in prolonged or abbreviated proestrus or weak estrus symptoms instead of anestrus. Anestrus may also be induced with drugs such as progestagens or glucocorticosteroids. Glucocorticoids probably decrease levels of circulating gonadotropic hormones.[32] In bitches older than 8 years of age, the duration and frequency of the cycles become more irregular and the interestrous interval increases. An apparent prolonged anestrus can be present if the bitch has a silent estrus or if the owner did not observe the estrus properly. Shortened interestrous intervals (intervals of less than 4 months) may be caused by a split heat or are seen in combination with persistent estrus (see Chapter 247).

Attention must also be given to the length of estrous periods. The average length of proestrus and of estrus is 9 days each. The bitch is considered to have a persistent estrus, if ovulation has not occurred after about 25 days from the onset of proestrus. In that case the plasma progesterone concentration will be lower than 16 nmol/L, and estrus symptoms such as sanguineous discharge, estrus behavior, estradiol influence seen during vaginoscopy, and/or the presence of superficial cells in the vaginal smear are present. Plasma estradiol concentrations are not consistently elevated.[33] Persistent estrus can be caused by ovarian tumors and cysts (see Chapter 247).

Attention must also be given to attempts to mate the bitch and/or the results of matings in previous cycles, previous pregnancies and parturitions and how many puppies were born. There are a number of problems that can lead to an unsuccessful mating. One problem can be inexperience or behavioral problems from bitch and/or male dog. Also anatomic disorders may prevent a normal mating. Strictures, adhesions, septa, and hyperplasia, for example, are common in bitches.[34] They can be congenital or acquired as a result of local treatment of vaginitis with irritating drugs (see Chapter 253).

Another important reason for a failure to mate or a missed conception is mating at an improper moment. A large number of fertility problems are the result of inappropriate management of the bitch and are avoidable if a proper breeding program is used. Additionally, CEH or CEH-endometritis or infectious diseases such as canine brucellosis or herpesvirus infection may also lead to breeding problems. Infertility due to CEH without endometritis, in which case the bitch does not show signs of a systemic disease, may be diagnosed during an ultrasonographic examination.

Canine brucellosis is a contagious disease for which the clinical manifestations vary greatly. It is characterized in the bitch by generalized lymphadenopathy and by early embryonic death, abortion (mainly between the 45^{th} and 55^{th} day of gestation), and infertility.[35] Canine brucellosis must be considered whenever there is a history of abortion or poor reproductive performance in either sex. The diagnosis can, however, not be established based on clinical signs alone. Serologic tests are necessary to confirm the diagnosis of canine brucellosis.

Canine herpesvirus can cause a high percentage of dead puppies in the first weeks after parturition. Herpesvirus does not seem to lead to a decrease in fertility.

246.8 THE EXAMINATION OF THE BITCH

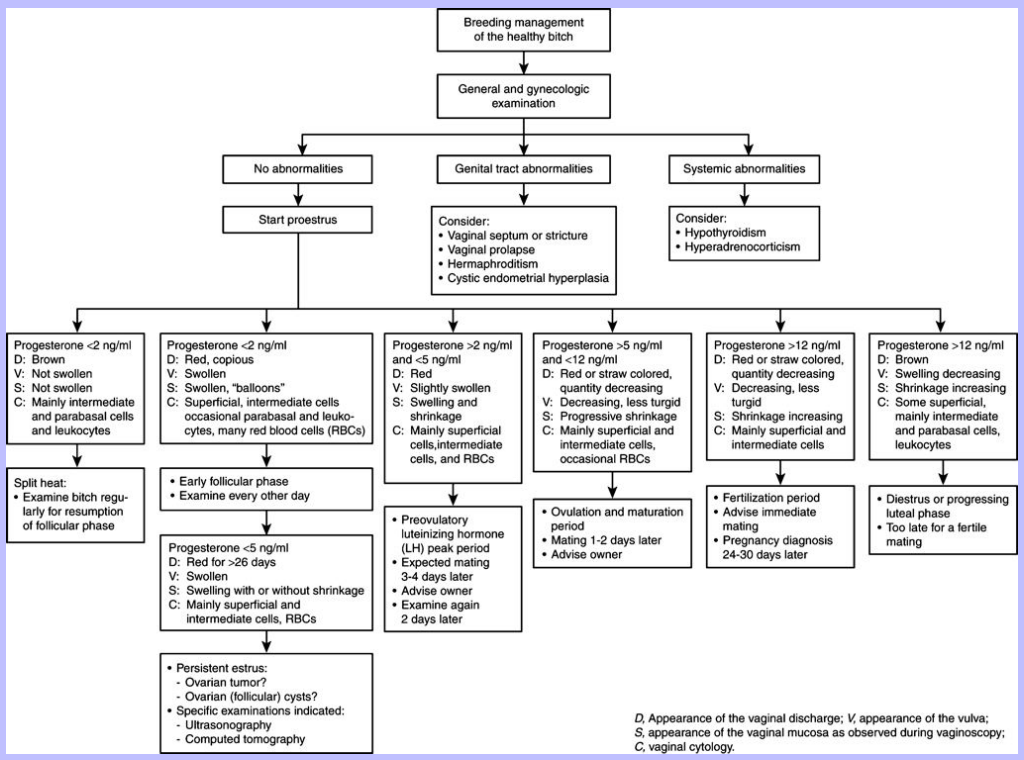
Breeding management starts with a general examination followed by sequential examinations. During the gynecologic portion of the first examination special emphasis should be given to palpation of the uterus and digital evaluation of the vagina. The following items should be examined every other day, starting 5 to 6 days after onset of proestrus: the vulva (size, swelling), vaginal discharge (quantity, color), and vaginoscopic, and cytologic findings. Furthermore, the owner should be asked to look for behavioral changes consistent with estrus. The start of estrus behavior usually occurs synchronously with the preovulatory LH peak (see Figure 246-2), but the first signs of this behavior can be observed several days before or after the LH peak or may never be seen. Repeated examinations are carried out to determine if the cycle is progressing normally (see Figure 246-16).

Vaginoscopic and cytologic observations not in agreement with the expected stage of the cycle may be a sign of a fertility disorder, which may or may not be serious. For example, a split heat is common in both younger and older healthy bitches. In cases of split heat, the follicular phase stops before ovulation and resumes after a few days or weeks. The vaginal discharge changes from red to brown; the smear shows intermediate cells, parabasal cells, and leukocytes and the swelling of the vaginal mucosal folds diminishes. It is probably caused by prematurely regressing follicles. Ovulation will generally occur if proestrus returns. Treatment is usually not necessary, but close monitoring of the cycle is essential for determining the appropriate mating period.

Sequential examinations should also be carried out to determine the ovulation period. Data concerning vulvar swelling, vaginal discharge, and vaginoscopic and cytologic findings have been described. Because of the variable length of proestrus and estrus, it should be clear that breeding a bitch on preset days of the cycle (e.g., 11 to 13 days after onset of proestrus bleeding) gives inconsistent results. Although breeding in accordance with estrus behavior will give better results, some bitches are nevertheless bred too early and others too late. Determination of the ovulation period is therefore of value. Several methods have been described to determine the ovulation period and the proper period for mating. The principal methods are measurement of the plasma progesterone concentration and vaginoscopy.

Plasma progesterone concentrations should, along with the other examinations, be determined every other day. 1647
At the onset of the follicular phase, determined through cytologic and vaginoscopic findings, the time between 1649
two determinations of plasma progesterone may be longer than in the progressing follicular phase. Use of an enzyme-linked immunosorbent assay (ELISA) or enzyme immunoassay kit for plasma progesterone determination may be less accurate, especially in medium (progesterone: >3 nmol/L, <16 nmol/L) plasma progesterone concentrations as compared with a plasma progesterone determination via a radioimmunoassay (RIA).[36,37] The RIA method is therefore the preferred method for progesterone determination. When frozen or chilled extended semen is being used, and sperm life span is expected to be shorter than in fresh semen, it is especially advisable to determine plasma progesterone concentrations by RIA to ensure accuracy in determining the ovulation day and the fertile period, therefore permitting use of a single insemination.

Figure 246-16 Algorithm for the breeding management of the healthy bitch.



Plasma progesterone concentrations increase slightly at the time of the preovulatory LH peak and rapidly at the onset of ovulation. At this time the plasma progesterone concentration exceeds 16 nmol/L. The onset of the optimal period for mating is 24 hours later and is based on the time needed for maturation of the oocytes, capacitation, and life span of the sperm.[38] With determination of the period for mating using a rapid RIA for the plasma progesterone concentration, it was found that 105 of 112 (94%) bitches with normal fertility became pregnant and 81 of 104 bitches (78%) with suboptimal fertility became pregnant. In the latter group, only 23% of previous matings without proper breeding management had been successful.[39]

Determination of the preovulatory LH peak would also provide an excellent parameter for the estimation of the ovulation time. In-hospital ELISA LH kits are available. However, more frequent blood sampling is required than for progesterone because of the risk of missing the preovulatory LH peak. Vaginoscopy can also be used to try to establish the ovulation period. The mucosal changes are, however, a response to hormonal changes and are therefore secondary changes. Additionally, interpretation of the changes is subjective.

Vaginoscopy is thus a less reliable method of estimation of the ovulation period than measurement of hormone levels. For experienced veterinarians, it can be a useful tool for monitoring the stage of the cycle, but mating advice based on vaginoscopy should include the recommendation to mate at least twice, with an interval of 48 hours. Vaginal cytology is useful in diagnosis of early proestrus, progressing proestrus-estrus, or diestrus. There are, however, no reliable changes in the smear indicative of the preovulatory LH surge or of ovulation.[3] Lastly, ultrasonography is not reliable for ovulation determination.[40]

246.9 ADDITIONAL EXAMINATIONS

In bitches with previous fertility problems, vaginal culture may be of use. A mixed bacterial flora, including *Pasteurella,* beta-hemolytic streptococci, and *Escherichia coli,* often inhabits the canine vagina and should not be considered a causative factor for infertility. In an examination of the aerobic bacterial flora of the genital tract of 59 bitches in four breeds during different stages of the cycle and pregnancy (all bitches whelped at least once during this study), culture results were negative in only 5%. Although the cultures in general showed a mixed flora, single species were obtained from 18% of the specimens. The aerobic bacterial flora consisted of common opportunistic pathogens.[41] Therefore bacterial culturing of vaginal swab specimens from bitches without signs of genital disease is of little value. Treatment is indicated in cases of suspected genital inflammation only if there are many bacteria (more than 100 colonies per culture) or the culture reveals only one species. Treatment may be systemic or local, but locally applied drugs alter the vaginal environment, are often spermicidal, and should therefore not be used shortly before breeding.

Pregnancy diagnosis is important within a breeding management program. Between 26 and 32 days after mating, pregnancy may be diagnosed by abdominal palpation. In some bitches an earlier diagnosis can be made depending on the degree of muscular guarding, thickness, and breed. The examination should, however, be repeated in case of a negative finding. In case of a negative or dubious finding, if vesicles of different size and elasticity are palpated, or if only one or two gestational vesicles are found, an ultrasonography is indicated. In the last two instances, fetal resorption has frequently been observed, which may warrant further examinations and sequential ultrasonographic examinations during the rest of the pregnancy. Furthermore, in cases of only one or two gestational vesicles the chance and risk of a prolonged pregnancy have to be discussed with the owner.

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247 CHAPTER • 247 Ovarian and Estrous Cycle Abnormalities

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Edward C. Feldman

Deviation from anticipated, typical estrous cycle events in a bitch intended for breeding can prompt owners to bring their dogs to a veterinarian for evaluation. The canine reproductive cycle is categorized into four distinct phases, each having particular behavioral, physical, and endocrinologic characteristics. Considerable variation exists within the normal canine reproductive cycle, breeders commonly interpret such variation as an indication that an abnormality exits. The clinician must differentiate bitches having normal estrous cycles with unexpected patterns from those with true abnormalities. Detection of individual variation within the normal range of events in a fertile bitch can be crucial to providing effective counseling concerning breeding management. Additionally, evaluation of the estrous cycle for actual abnormalities is an important component in assessing the apparently infertile bitch. Variations from normal estrous cycle events in the bitch can sometimes be traced to specific ovarian disorders.

247.1 THE NORMAL CANINE ESTROUS CYCLE

The interestrous interval normally varies from 4.5 to 10 months in duration, with 7 the average. The anestrus phase of the interestrous interval is marked by reproductive inactivity, uterine involution, and endometrial repair. The normal bitch is neither attractive nor receptive to male dogs. Minimal mucoid vaginal discharge is present, and the vulva is not swollen. Vaginal cytology is scant, characterized by small parabasal cells, with occasional non-toxic neutrophils and may have small numbers of mixed bacteria present. Viewed endoscopically, the vaginal mucosal folds are flat, thin, and pale red. The termination of anestrus (onset of proestrus) follows the pulsatile, hypothalamic gonadotropin-releasing hormone (GnRH) induced secretion of the pituitary gonadotropins, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Such pulsatile GnRH secretion is a physiologic requirement of gonadotropin release. Following GnRH stimulation during late anestrus, pituitary gonadotrophs release LH in a rapid, transitory pattern and FSH in a slow, sustained pattern. Mean levels of both FSH and LH rise moderately during late anestrus. At the termination of anestrus, the pulsatile release of LH increases, which precedes and likely amplifies ovarian folliculogenesis during proestrus. Estrogen levels are basal (5 to 10 pg/mL) and progesterone levels at nadir (<1 ng/mL) in late anestrus. Anestrus normally lasts from 1 to 6 months.[1,2]

During proestrus, the bitch attracts male dogs but is still not receptive to breeding. She may become more playful or passive concerning the male as proestrus progresses. A serosanguineous-hemorrhagic vaginal discharge of uterine origin is present and the vulva is mildly enlarged and turgid. The microscopic appearance of exfoliated vaginal epithelial cells shifts over a period of 4 to 7 days from small parabasal cells to small then large intermediate cells, superficial-intermediate cells, and finally superficial (cornified) epithelial cells. These changes in the vaginal cells reflect the degree of estrogen influence on the vaginal mucosa. The vaginal wall becomes thickened under the progressive influence of estrogen, in preparation for copulation. Red blood cells are usually but not invariably present on the vaginal smear.

Endoscopically, the vaginal mucosal folds appear edematous, pink and rounded. FSH and LH levels are low during most of proestrus, rising during preovulatory surges. Estrogen rises from basal anestrus levels to peak levels (50 to 100 pg/dl during late proestrus), while progesterone remains basal (<1 ng/mL) until rising (2 to 4 ng/mL) in conjunction with the LH surge. The LH surge generally lasts only 12 to 24 hours in the bitch. Occasionally, more than one LH surge occurs, the one associated with a concurrent rise in serum progesterone

level reaching 2 to 3 ng/mL is likely associated with ovulation. Proestrus lasts from 3 days to 3 weeks and averages 9 days. The follicular phase of the ovarian cycle coincides with proestrus and early estrus.[1,3]

During estrus, the normal bitch displays receptive or passive behavior with a male dog, which enables breeding. Serosanguineous to hemorrhagic vaginal discharge diminishes to variable degrees. Vulvar enlargement and edema tends to be maximal but the vulva is soft. Vaginal cytology usually consists of 80% to 100% superficial cells. Red blood cells tend to diminish but may persist throughout estrus. Endoscopically, vaginal mucosal folds become progressively wrinkled or crenulated, the degree correlating with oocyte maturation to a fertilizable stage. Plasma estrogen progressively declines to basal concentrations, achieved as estrus ceases. Progesterone concentrations steadily increase (usually 4 to 10 ng/mL at ovulation), marking the onset of the luteal phase of the ovarian cycle.

Estrus lasts 3 days to 3 weeks, with an average of 9 days. The receptive behavior of estrus may precede or follow shortly after the LH peak. Duration of receptivity is variable and may not coincide precisely with the fertile period. Receptive behavior reflects decreasing estrogen and increasing progesterone concentrations. Ovulation of primary (infertile) oocytes begins approximately 1 to 2 days after the LH surge; oocyte maturation occurs over the following 1 to 3 days. The life span of secondary (fertile) oocytes is 2 to 3 days. The resultant fertile window in the bitch, during which time breeding is most likely to result in conception, is between 3 and 7 days after the LH surge, or after the initial day progesterone reaches 2 to 3 ng/mL.[1–3]

During diestrus, the normal bitch becomes refractory to breeding and gradually less attractive to male dogs. Vaginal discharge diminishes, often becoming mucoid and mildly suppurative and odorous before disappearing, and vulvar edema turgid, then slowly regressing. Vaginal cytology is abruptly altered by the reappearance of parabasal epithelial cells and, frequently, neutrophils. Vaginal cytology on the first day of diestrus has less than 50% superficial cells. Endoscopically, vaginal mucosal folds appear flattened, pink, and flaccid. Plasma estrogen concentrations are low during diestrus, except for a mild rise reported in the pregnant bitch prior to parturition. Plasma progesterone concentrations steadily rise during the first few weeks of diestrus to a plateau of 15 to 80 ng/mL, before progressively declining in late diestrus. Progesterone secretion is dependent on both pituitary LH and prolactin secretion. Proliferation of the endometrium and quiescence of the myometrium occur under the influence of progesterone.

Diestrus usually lasts 2 to 3 months in the absence of pregnancy. Parturition terminates pregnancy 64 to 66 days after the LH peak (or the initial rise in progesterone), or 56 to 58 days after the onset of diestrus as determined by vaginal cytology. Gestational length may be related to litter size and parity.[4] Prolactin concentrations increase in a reciprocal fashion to declining progesterone concentrations as diestrus ends. Prolactin concentrations are higher in pregnant bitches. Mammary ductal and glandular tissues increase in response to prolactin, which makes lactation a normal event even in the non-pregnant state (pseudopregnancy).[1–3]

247.2 NORMAL VARIATIONS IN THE CANINE ESTROUS CYCLE

During evaluation of a bitch for estrous cycle abnormalities, the medical history, signalment, and husbandry of a bitch should be taken into account along with the specific reproductive history, physical examination findings, and results of clinical testing. Following the bitch over time, through one estrous cycle, is often necessary to reach a diagnosis.

247.2.1 Delayed Puberty

The onset of the first estrous cycle occurs after a bitch attains 70% of her adult height and body weight. Small breeds generally begin their first estrous cycle between 6 and 10 months of age, whereas large breeds may normally begin as late as 18 to 24 months. Family histories (dam and female siblings) can help predict the onset of reproductive activity. Efforts at differentiating delayed puberty from an actual failure to have reproductive cycles should be postponed until a bitch is at least 2 to 2.5 years old. Bitches with delayed puberty have normal reproductive cycles once initiated.

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247.2.2 Silent Heat Cycles

The occurrence of a silent heat cycle needs to be ruled out during evaluation of a bitch for a reported failure to have estrous cycles. Fastidious bitches with minimal vulvar swelling, vaginal discharge, or behavioral changes may have estrous cycles that escape human detection, especially in the absence of a male dog. Estrous cycles tend to become more apparent as the bitch ages. Performing weekly vaginal cytologies, housing the bitch near an intact male, or using white bedding can aid in prospective detection of a silent heat, permitting ovulation timing and breeding. Performing monthly progesterone assays permits retrospective identification of estrus but will not facilitate breeding that cycle. Silent heat cycles need to be differentiated from true primary anestrus. True primary anestrus in the bitch that fails to experience an estrous cycle is most likely due to a disorder of sexual development, and is uncommon.[3]

247.2.3 Split Heat Cycles

Bitches experiencing split heat cycles, in which proestrus and possibly early estrus occur without progression, may be thought to have abnormally short cycles, lack of sexual receptivity, or infertility if breedings were forced or artificial insemination performed. Waves of folliculogenesis with increased estrogen production but without ovulation occur in split heats. Follicular atresia follows, no luteal phase with progesterone production occurs, and normal sexual receptivity fails to develop. These cycles typically occur in young bitches and are characterized by periods of hemorrhagic vaginal discharge typical of proestrus, attractiveness to males, and usually no receptivity. In young bitches, split cycles are thought to be due to immaturity. These cycles may also occur in mature bitches with a history of normal past cycles, usually in association with stress. Increased endogenous cortisol levels associated with stress (travel, shipping, kenneling) may inhibit the LH surge and associated ovulation.

After a period of 2 to 10 weeks, another proestrus typically begins, which may or may not proceed to ovulation. Eventually, most young bitches experiencing split heats progress through a normal estrus to diestrus. The condition is not associated with reproductive pathology in the young or stressed bitch, and no treatment is recommended. Breeding the bitch thought to have been previously stressed in familiar surroundings is advised. Serial vaginal cytology documenting the influence of estrogen on vaginal mucosa early in the cycle, and progesterone assays performed 1 to 2 weeks later (<2 ng/mL) documenting folliculogenesis without ovulation or luteinization confirm the diagnosis of a split heat. Occasionally split cycles occur on a regular basis in mature individual bitches, making them difficult to breed, and likely associated with abnormalities of the hypothalamic/pituitary/ovarian axis.

247.2.4 Management Errors

Bitches examined because they have failed to permit breeding or to conceive after a forced breeding or artificial insemination during the perceived fertile period need to be evaluated for kennel management errors. The timing of receptive and fertile periods during estrus varies significantly among normal bitches and even in individual bitches during different estrous cycles. These periods may not correlate with the handler's choice of predetermined breeding dates, typically between days 10 to 14 after the onset of vaginal bleeding. Ovulation timing protocols utilizing serial vaginal cytology, repeated vaginoscopy, and serum progesterone and LH concentrations are useful in identifying the actual fertile period when breeding should occur.[5] Behavioral or physical problems can interfere with acceptance of a male for breeding. Dominant bitches exposed to an inexperienced male may not allow breeding even during the appropriate time. Vulvar or vaginal abnormalities such as strictures and septate bands, and vaginal hyperplasia may make natural breeding painful and result in a bitch refusing to permit copulation even when in estrus[6] (Figure 247-1). The pre-breeding veterinary examination permits early detection of such anatomic problems, enabling their correction or adjustment in breeding plans (artificial insemination versus natural) before the onset of proestrus.

247.3 PATTERNS OF ABNORMAL ESTROUS CYCLES

Abnormal estrous cycles can be categorized and simplified into several patterns that reflect either a prolongation or abbreviation of a phase of the cycle, or an alteration in the normal sequence of events. An owner's interpretation of a bitches behavior and physical characteristics may not equate with the actual physiologic events, which necessitates prospective documentation of the cycle through vaginal cytology, vaginoscopy, behavioral analysis, and assessment of serum progesterone and LH concentrations.

247.3.1 Prolonged Proestrus or Estrus

Prolonged proestrus or estrus occurs when a bitch displays vaginal bleeding (of uterine origin) for more than 21 to 28 consecutive days, accompanied by attractiveness to males. Greater than 80% to 90% superficial cells are found on vaginal cytology. Such bitches may or may not be receptive to breeding. Prolonged proestrus and/or estrus most likely results from persistent secretion of estrogens with or without small elevations in progesterone secretion. If secreted, progesterone enhances the presence of sexual receptivity.

Endogenous sources of prolonged estrogen exposure in the bitch, with or without progesterone, include ovarian follicular cysts and secretory neoplasias.[7] Secretory, anovulatory follicular ovarian cysts tend to be solitary, lined with granulosa cells and exceed normal preovulatory follicles in size, ranging from 1 to 5 cm in diameter (Figure 247-2). Bilateral follicular cysts may indicate a problem with the hypothalamic pituitary ovarian axis. Follicular cysts tend to occur in bitches less than 3 years of age. Ovarian neoplasias capable of producing estrogen occur and include tumors of epithelial origin (cystadenomas and adenocarcinomas) as well as tumors of gonadal-stromal origin (granulosa-theca cell tumors).[8] Ovarian neoplasia tends to occur in bitches older than 5 years of age. Ovarian tumors can occur unilaterally or, less commonly, bilaterally. Functional ovarian neoplasia and cystic ovarian pathology can occur simultaneously (Figure 247-3). Cysts found in the contralateral ovary, and endometrial hyperplasia that accompany a functional tumor occur most frequently with gonadal-stromal origin tumors.[9]

Figure 247-1 Vaginoscopic view of a septate band of tissue in the caudal vaginal of an estrus bitch exhibiting pain during breeding efforts. The band is retracted with a spay hook.

Figure 247-2 Functional, nonovulatory follicular ovarian cysts found in a Mastiff bitch that has been experiencing estrus for greater than 3 months.

There are few differential diagnoses for prolonged vaginal bleeding. Vaginal bleeding secondary to infection, inflammation or neoplasia of the genitourinary tract, a vaginal foreign body, or a coagulopathy should be differentiated from prolonged proestrus or estrus. Excessive exogenous administration of estrogen may be encountered when a bitch is treated for urethral sphincter incompetence with diethylstilbestrol (DES), or from attempts to prevent unwanted pregnancy using DES or estradiol cypionate. Recognized sequela to chronic estrogen exposure include bone marrow dyscrasias, predisposition to the cystic endometrial gland hyperplasia/pyometra complex, and the development of ovarian cysts.[7–9]

After confirmation of naturally occurring hyperestrogenism is obtained through vaginal cytologies (they can be confirmed with serum estrogen level measurement), abdominal ultrasonography is recommended in the attempt to identify an ovarian follicular cyst or functional neoplasia (Figure 247-4). Normal preovulatory follicles measure 4 to 9 mm in diameter, smaller than follicular cysts and most functional neoplasia.[10] Analysis of the estrogen and progesterone levels in fluid from abnormal cystic ovarian structures obtained via ultrasound guidance and histologic analysis of tissues obtained surgically can confirm the diagnosis.

Figure 247-3 Ovarian carcinoma, right ovary (ruler), accompanied by ovarian follicular cysts, left ovary, in a Boxer bitch that has been experiencing estrus for greater than 2 months.

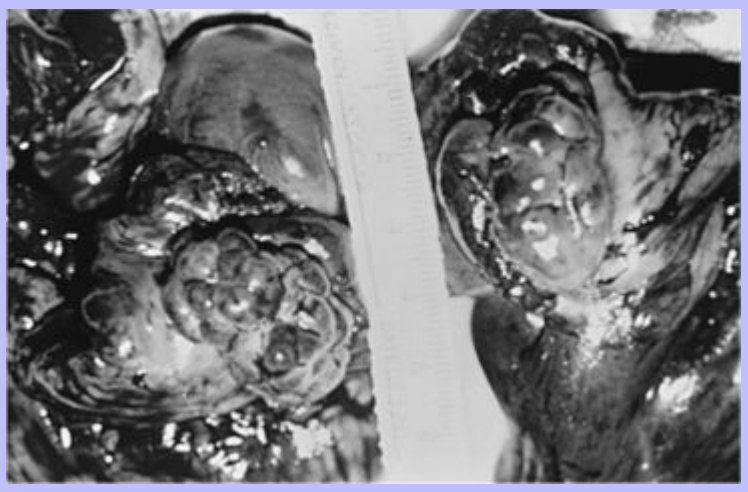
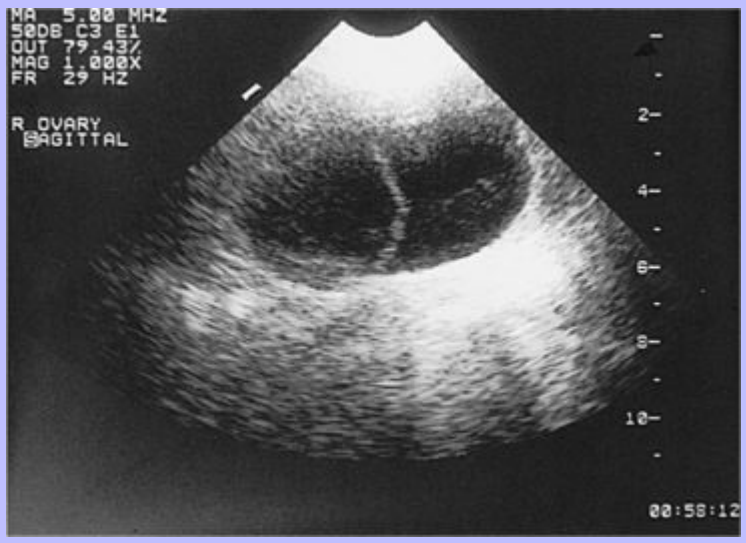


Figure 247-4 Ultrasonographic appearance of a functional, estrogen secreting, nonovulatory ovarian follicular cysts.



Because follicular cysts may spontaneously undergo atresia or luteinization, not all bitches experiencing prolonged proestrus or estrus require treatment. Progression of the follicular cyst to an atretic follicle or a corpora lutea can be monitored ultrasonographically, via vaginal cytologies, and by serum estrogen and progesterone levels. Therapy aimed at terminating prolonged proestrus or estrus becomes necessary if spontaneous regression fails to occur, vaginal bleeding is a continuing nuisance, estrus behavior and the attraction of males is unacceptable, or other complications develop (blood loss anemia, marrow dyscrasias, vaginal hyperplasia) (Figure 247-5). Medical and surgical options exist for treatment of persistent pathologic follicular cysts. Medical therapies should not place the reproductive health of the bitch at risk. Progesterone treatment of bitches with functional follicular cysts puts the bitch at increased risk for the development of cystic endometrial hyperplasia/pyometra, and is not advised. The use of GnRH (50 to 100 ug/bitch IM q24-48h for up to 3 doses) or human placental gonadotropin (H.C.G.; 11 IU/lb; 22 IU/kg, IM, q24-48h) has been advocated as affective in inducing cyst regression or luteinization, although reported success rates for either vary.[3,7] GnRH does not appear to be antigenic in the bitch and may be the preferred treatment. Successful induction of cyst regression or luteinization is reflected by a reduction in vaginal discharge, change in vaginal cytology reflecting reduced estrogen effect, diminished attractiveness to males, and normalization of behavior. Serum estrogen concentrations fall, and increased progesterone concentrations occur if luteinization results. Ultrasonographic monitoring of ovarian morphology shows regression of hypoechoic structures.

It has been suggested that failure of medical therapies to resolve prolonged proestrus or estrus indicates that ovarian neoplasia is more likely than a follicular cyst; this has not been our experience.[3,6] Medical treatment of prolonged proestrus or estrus is usually unrewarding and surgical removal of the cyst the most expedient means of managing the problem.[3] Removal of the cyst alone is optimal, but resection of the associated ovary is usually necessary. Histologic evaluation of the removed tissue confirms the diagnosis and, importantly,

permits evaluation for evidence of neoplasia that may warrant additional therapy and a much more negative prognosis (Figure 247-6).[11]

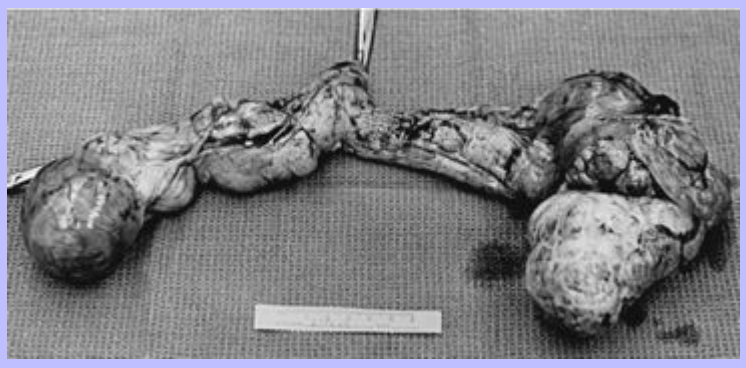
Figure 247-5 Vaginal hyperplasia, present for greater than 3 months in a Mastiff bitch that is experiencing prolonged proestrus/estrus secondary to follicular ovarian cysts.

247.3.2 Prolonged Interestrous Intervals

Bitches exhibiting prolonged interestrous intervals may have prolongation of either anestrus or diestrus. Prolonged anestrus occurs when no ovarian activity occurs for longer than 16 to 20 months in a bitch having previously experienced estrous cycles (secondary anestrus). An actual failure to continue to cycle must be differentiated from silent heats. Underlying disease and iatrogenic causes for failure to cycle should be ruled out by a careful history, physical examination and database. The mechanism by which anestrus is normally terminated in the bitch is not well understood. Dopamine inhibits prolactin secretion. Prolactin levels decrease from late diestrus to late anestrus. Both FSH and LH have been reported as the hormone initiating proestrus folliculogenesis. Dopamine agonists (cabergoline, bromocriptine) can be used to shorten anestrus in both the normal bitch, and in bitches with secondary anestrus of unknown etiology. The mechanism by which dopamine agonists induce proestrus may be a direct reduction in prolactin levels or a direct dopaminergic action on either the gonadotrophic axis or on ovarian gonadotrophin receptors.[12]

A bitch examined for evaluation of prolonged intervals between heat cycles may be under the influence of increased plasma progesterone concentrations (>2 to 5 ng/mL). When plasma progesterone concentrations remain elevated for longer than 9 to 10 weeks, prolonged diestrus is probable. The clinical behavior of the bitch cannot be differentiated from one with prolonged anestrus. The value of vaginal cytologies, serial plasma progesterone levels, and the ultrasonographic appearance of the ovaries and uterus becomes important in establishing a diagnosis.

Figure 247-6 Bilateral ovarian neoplasia.



Prolonged diestrus may occur secondary to the presence of a luteinized (progesterone-secreting) ovarian cyst. The progesterone causes negative feedback to the pituitary/hypothalamic axis, preventing the stimulation of normal ovarian activity. Luteinized cysts can be single or multiple, involving one or both ovaries.[3] Abdominal ultrasonography can identify hypoechoic structure(s) within the affected ovary(ies) (Figure 247-7). Abdominal radiography rarely provides diagnostic information because the cysts are relatively small. Serum progesterone levels greater than 2 to 5 ng/mL confirm the diagnosis. Treatment with prostaglandin F2alpha (PGF2α) usually causes only a transient decline in serum progesterone levels, indicating partial luteolysis. Surgical removal of the cyst(s) with histologic analysis is the recommended treatment. Separation of the cyst from the affected ovary is optimal but is technically difficult, necessitating ovariectomy.[3] Acquiring a uterine biopsy to evaluate the presence and extent of accompanying cystic endometrial hyperplasia is advisable, as it can provide valuable information to the owner concerning future fertility of the bitch (see Figure 247-7). Cystic endometrial hyperplasia, if present, may resolve partially after elimination of the cyst.

Nonfunctional ovarian cysts may cause failure to cycle due to their mass effect. Rete ovarii cysts and subsurface epithelial structure cysts are examples of nonfunctional ovarian cysts. Increases in plasma estrogen or progesterone concentrations will not be identified, although these cysts have the potential to produce a wide variety of other steroidal compounds without systemic effect.[3] The diagnosis, initially suspected using abdominal ultrasonography, is confirmed by histologic evaluation of surgically removed tissues.

Premature ovarian failure can result in permanent anestrus. Although the functional longevity of the ovaries of bitches is not known, on average the decline in function would not be expected before 7 to 10 years of age. Prolonged anestrus due to premature ovarian failure could be supported by documentation of markedly increased plasma FSH and LH concentrations as would be seen following ovariohysterectomy. Such increases indicate a lack of negative feedback to the pituitary and hypothalamus, without any other identifiable cause for anestrus.[13] Immune mediated oophoritis, diagnosed by ovarian histopathology, could result in prolonged anestrus. A mononuclear infiltrate predominated by lymphocytes, plasma cells and macrophages has been reported to occur in both ovaries in a bitch experiencing estrous cycle abnormalities.[13] This is an extremely rare disorder.

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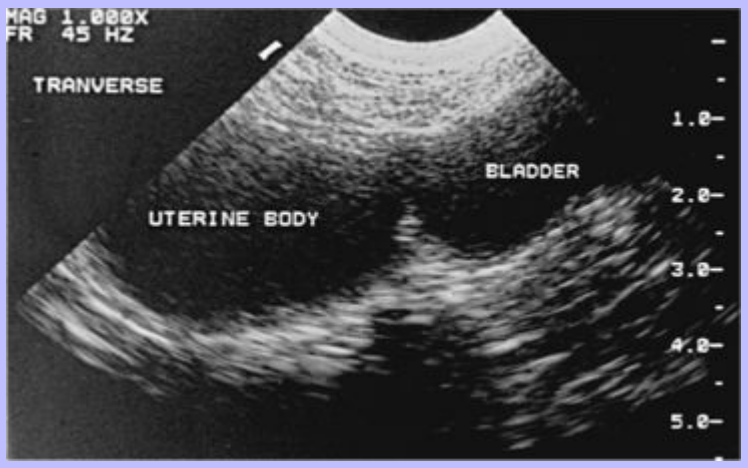
Figure 247-7 Ultrasonographic appearance of cystic endometrial hyperplasia and hydrometra in a Doberman bitch that is experiencing prolonged interestrous intervals, with elevated plasma progesterone concentrations for greater than 4 months, due to a luteinized ovarian cyst.



Hypothyroidism is a potential cause for failure to cycle, but the diagnosis should be well supported by other clinical signs (lethargy, weight gain, bilaterally symmetric alopecia) and clinical pathologic data (hypercholesterolemia, nonregenerative anemia), as well as confirmation of subnormal serum thyroid (total T4 and free T4 by equilibrium dialysis) levels, ideally supported by elevated endogenous TSH levels. Bitches with circulating antithyroid antibodies may have artificially elevated total T4 levels due to cross reactivity. Hypothyroid bitches placed on adequate replacement therapy should begin to cycle within 6 months of becoming euthyroid.[3,14–16] The presence of immune mediated thyroiditis is thought to have a genetic basis in some breeds and may occur with other immune mediated endocrinopathies. The breeding soundness of such bitches should be addressed with clients. Glucocorticoids can feedback on pituitary gonadotrophins FSH and LH, causing a failure to cycle.[16–17] Therefore administration of any steroid medication must be discontinued in a bitch with prolonged anestrus.

247.3.3 Shortened Interestrous Intervals

Bitches with short (less than 4.5 months) interestrous intervals can fail to conceive due to incomplete uterine involution and repair, precluding implantation.[3] Classically, bitches with shortened interestrous intervals are normal in other respects. Ovulation and luteinization occur, the secondary oocyte is fertilized but fails to implant successfully. Documentation of this disorder requires evaluation of serial vaginal cytologies during estrus and diestrus, and plasma progesterone concentrations during the luteal phase of at least two consecutive cycles. Currently, there is no reliable, commercially available, consistent pre-implantation method of confirming fertilization in the dog. The occurrence of folliculogenesis without ovulation (split heat) and hypoluteiodism (premature luteal failure) should be ruled out. Shortened interestrous intervals occur because anestrus is abbreviated. A defect in the hypothalamic-pituitary-ovarian axis may exist, which causes

interference with the normal maintenance of anestrus; an imbalance of dopamine versus prolactin levels has been theorized to contribute to this syndrome. Anestrus can be abbreviated clinically in the normal bitch by the administration of prolactin inhibitors such as cabergoline and bromocriptine.

Intervention should not take place unless the bitch is older than 3 years, because these abnormalities may naturally resolve with maturity. One suggested therapy consists of inducing anestrus through the use of mibolerone, a potent synthetic androgen causing negative pituitary and hypothalamic feedback and ovarian inactivity, for 6 months. Mibolerone must be compounded as it has been taken off the market due to the potential for abuse. The compound is started 6 to 8 weeks after the previous estrus. Potential and predictable side effects include clitoral hypertrophy, mucoid vaginal discharge, atrophy of the glandular endothelium, epiphora, and virilized behavior. The bitch should be bred on the first cycle after discontinuation of the drug, which can occur immediately, or be delayed from 6 to 9 months.[3] Unfortunately, many bitches experience infertility during the first cycle after mibolerone administration, likely due to endometrial atrophy, and then begin to cycle frequently again.

No controlled studies exist that document the efficacy of this protocol, and it is not recommended by the authors. The availability of better, reversible birth control medications for the bitch, with fewer side effects, will improve the ability to treat this disorder. A genetic basis is suspected, and bitches experiencing shortened interestrous intervals likely are not good breeding candidates.

247.3.4 Hypoluteoidism

The maintenance of canine pregnancy requires plasma progesterone concentrations of greater than 1 to 2 ng/mL. Hypoluteiodism, primary luteal failure occurring before term gestation is a potential but not documented cause of abortion in dogs.[3,13,17] Induction of abortion follows reduction of plasma progesterone levels below 2 ng/mL.[3,18] The diagnosis of gestational loss caused by premature luteolysis is difficult and requires documentation of inadequate plasma progesterone concentrations prior to abortion for which no other cause is found. Measurement of precise progesterone concentrations, especially in the critical 1 to 3 ng/mL range, is not accurate using currently available rapid in-house ELISA kits.

Plasma progesterone concentrations diminish in response to fetal death, thus documentation of a low value after an abortion does not establish the diagnosis of hypoluteiodism as the cause for reproductive failure. Administration of progesterone to maintain pregnancy in bitches with primary fetal abnormalities, placentitis, or intrauterine infection can cause continued fetal growth with the possibility of dystocia and sepsis. Administration of progesterone to maintain pregnancy in a bitch not actually requiring therapy can delay parturition, which endangers the life of the bitch and her fetuses and may masculinize, female fetuses.

Bitches with low plasma progesterone concentrations and historical late term loss of pregnancy with no apparent pathology should be evaluated for premature myometrial activity mid gestation, using uterine monitors. Elaboration of prostaglandins from the endometrium and placenta associated with premature myometrial activity can result in declining progesterone levels. Pharmacologic intervention to decrease myometrial activity may be indicated, using tocolytic agents such as terbutaline. Bitches experiencing premature myometrial activity in one pregnancy may or may not exhibit it during subsequent pregnancies. Exogenous progesterone supplementation for bitches with premature labor (not necessary in the authors' experience with appropriate tocolytic therapy) can interfere with normal parturition, and oral progesterone supplementation can be complicated by causing poor lactation (interference with prolactin production), dystocia, and fetal death.[19,20]

247.3.5 Exaggerated Pseudocyesis (Pseudopregnancy)

Nonpregnant bitches showing overt signs of term pregnancy are frequently brought to veterinarians because of concerns about parturition. Symptoms exhibited during overt pseudocyesis include weight gain, mammary gland hyperplasia and lactation, mucoid vaginal discharge, inappetence, restlessness, nesting, and mothering of inanimate objects. Abdominal palpation and ultrasonography can establish the presence or absence of fetuses. Alternatively, owners may be concerned about bitches showing overt signs of pseudocyesis because they find the behavior or physical symptoms objectionable in a bitch they know is not pregnant.

Pseudocyesis is an exaggeration of the normal physiologic phenomena experienced by any nonpregnant bitch completing the luteal portion of an estrous cycle. These signs are the result of progesterone concentrations declining and prolactin increasing. The clinical expression of pseudocyesis varies from indiscernible to (rarely) potentially serious. Clinical signs of pseudocyesis usually are reported from 6 to 12 weeks after estrus. Signs of pseudocyesis are often reported by owners when giving reproductive histories as if its occurrence indicates a reproductive disorder, when in fact, pseudocyesis probably establishes that the bitch has a normal hypothalamic-pituitary-ovarian axis and estrous cycle.

Bitches that exhibit signs consistent with a diagnosis of pseudocyesis are probably under the influence of prolactin. Similar concentrations can be demonstrated in bitches that have no clinical signs, suggesting that the former may have increased target organ concentrations or heightened peripheral sensitivity to the hormone.[3] The condition is self limiting, usually regressing in 1 to 3 weeks, and therapy is not recommended unless the signs are unusually prolonged or pronounced, such as causing mastitis. Unusually persistent cases of inappropriate lactation should be evaluated for hypothyroidism, in which excess TRH may, in turn, cause increases in prolactin.

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Table • 247-1 Drug Appendix

GENERIC	TRADE	DOSAGE	ROUTE	FREQUENCY	DESCRIPTION
GnRH	Cystorelan	50–100 ug	IM	q 24-48h ×3	Hypothalamic releasing hormone
h.c.g.	Gonamone	11 IU/lb (22 IU/kg)	IM	q 24-48h	Placental gonadotropin
PGF2α	Lutalyse	0.05-0.10 mg/lb (0.10-0.20 mg/kg)	SC	q 8h	Natural prostaglandin
Mibolerone	Pseudocyesis:	0.008 mg/lb (0.016 ug/kg)	PO	q 24h ×5	Synthetic androgen
Bromocriptine		0.005-0.05 mg/lb (0.01-0.10 mg/kg)		q 24h	Ergot alkaloid divided
Carbergoline		2.5 ug/lb (5.0 ug/kg)		q 24h or divided bid ×3–5	Ergot alkaloid

Therapy, when recommended, is usually directed at decreasing or eliminating lactation. Therapy is pursued to reduce the likelihood of mastitis occurring secondary to milk stasis, or to diminish lactation-induced household soiling. Minimal measures are recommended. Mammary stimulation, via licking, mothering behavior, or warm or cold compressing should be discontinued. Dopamine antagonists, of which phenothiazines are a class, enhance prolactin secretion and should not be administered. Mild sedation with a non-phenothiazine tranquilizer may be helpful.[3]

A variety of hormonal and medical therapies have been employed to reduce or stop lactation in pseudopregnant dogs. Side effects, in most cases, outweigh the benefit of these medications. Therapy with gonadal hormones, progesterone, estrogen, or testosterone is not recommended due to complications of repetitive cycles of pseudocyesis, symptoms of proestrus or estrus, and virilization behavior, respectively. The compounded synthetic androgen mibolerone, administered at 0.008 mg/lb (0.016 mg/kg) orally once daily for 5 days, has successfully abbreviated the signs of pseudocyesis in approximately 50% of treated cases, although this medication also may cause virilization.[21] Ergot alkaloids are potent prolactin inhibitors (dopaminergic) and can be used to abbreviate exaggerated pseudocyesis. Bromocriptine can be administered at 0.005 to 0.05 mg/lb/day (0.01 to 0.10 mg/kg/day) in divided doses until lactation ceases. Vomiting, depression and anorexia are commonly reported side effects, usually more problematic than the lactation. Carbergoline, administered at 2.5 ug/lb/day (5.0 ug/kg/day), given divided or once daily for 3 to 5 days effectively decreases prolactin concentrations and diminishes signs of pseudocyesis with fewer side effects, but is expensive and must be compounded for use in all but giant breeds. Permanent avoidance of clinical pseudocyesis requires ovariohysterectomy.

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248 CHAPTER • 248 Abnormalities in Pregnancy, Parturition, and the Periparturient Period

Catharina Linde-Forsberg

248.1 PREGNANCY

248.1.1 Physiologic Changes and Clinical Monitoring

Maternal physiologic alterations during pregnancy are due to increased metabolic demands. Blood volume increases by 40%, which provides an adequate reserve to compensate for the large quantities of blood and fluids lost at parturition. The volume increase is primarily plasma with a resulting hemodilution (the hematocrit is around 30% at term). An increase in cardiac output occurs, caused by enhanced heart rate and stroke volume. The functional residual capacity of the lungs is decreased by anterior displacement of the diaphragm by the gravid uterus, and oxygen consumption during pregnancy increases by 20%. Pregnant animals also have delayed gastric emptying due to decreased gastric motility and displacement of the stomach.

It is recommended to examine bitches and to obtain radiographs at about 45 days of gestation. This allows the veterinarian to assess the health of the bitch, confirm pregnancy, count fetuses, and answer questions. Ultrasound is less exact for determining the number of fetuses but is excellent for assessing fetal viability and can be performed with accuracy from the twenty-fourth day.

248.1.1.1 Gestation Length

Apparent gestation length in the bitch averages 63 days, with a variation from 56 to 72 days if calculated from the first mating.[1] This surprisingly large apparent variation is mainly due to the long and variable behavioral estrus period of the bitch. Gestation length is quite predictable when instead calculated either from the preovulatory surge of luteinizing hormone (LH) being 65 ± 1 days, from the day of ovulation being 63 ± 1 days, or from the time of fertilization being 60 ± 1 days.[2,3] There exists conflicting data in the literature regarding whether a correlation exists between breed or body weight, and/or litter size and length of gestation.

248.1.1.2 Prediction of Parturition Day

The ability to determine gestational age and to predict the day of parturition in the bitch is of considerable clinical importance, especially in case of threatening abortion, prolonged gestation, or when the bitch is scheduled for elective caesarean section or suffers from dystocia. B-mode ultrasonography has been used to assess the diameter of pregnancy structures and to estimate fetal size during pregnancy. Inner chorionic cavity diameter on the eighteenth to the thirty-seventh day from ovulation and fetal head diameter on the thirty-eighth day to parturition show the best correlation to gestational age and day of parturition.[4] Other fetal structures used to time pregnancies using ultrasonography are fetal limb buds, first detectable at the thirty-third to the thirty-fifth day; eyes, kidney, and liver at the thirty-ninth to the forty-seventh day; and intestine at the fifty-seventh to the sixty-third day.[1] Using radiography the fetal skeleton is rarely visible before the forty-second day; the skull on the forty-fifth to the forty-ninth day; pelvic bones on the fifty-third to the fifty-seventh day; teeth on the fifty-eighth to the sixty-third day.[1] Serum cortisol levels increase at the time of delivery and remain high for 12 hours to reach basal levels again after 36 hours.[5] Levels of

15-ketodihydro-prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) increase 24 hours before parturition and again at the onset of whelping.[5] In most bitches, parturition occurs 65 ± 1 days from the LH-peak, which coincides with the initial sharp rise in serum progesterone concentrations to greater than or equal to 4.5 nmol/L (≥ 1.5 ng/mL). The accuracy of parturition day prediction within an interval of ± 1, ± 2, and ± 3 days using prebreeding serum progesterone concentrations was 67%, 90%, and 100%, respectively, and was not influenced by body weight or litter size.[6] The fact that serum progesterone levels decrease significantly from 12 to 15 nmol/L (4 to 5 ng/mL) to below 6 nmol/L (2 ng/mL) starting 24 hours before the onset of whelping can also be used to predict parturition in the late gestational stage.

248.2 DISORDERS DURING PREGNANCY

248.2.1 Early Fetal Loss and Abortion

The incidence of early embryonic and fetal death (before 45 days of pregnancy) and spontaneous abortion in the bitch is not known and is difficult to determine because resorption of conceptuses may occur until the forty-fifth day of pregnancy without noticeable signs, or the bitch may consume aborted fetuses. However, early pregnancy diagnosis using ultrasonography, which is becoming increasingly popular, indicates that fetal resorption is a frequent occurrence in the bitch.

248.2.2 Infectious Agents

Hemorrhage from the genital tract often precedes abortion caused by a bacterial infection. This may be due to an effect of bacterial toxins on the placenta and a release of $PGF_{2\alpha}$ causing the uterus to contract and expel its contents. The underlying cause of the hemorrhage should be diagnosed. Antibiotics, anti-inflammatory or tocolytic drugs (e.g., terbutaline), or both should be administered in an attempt to prevent the abortion. It should be explained to the owner that the bitch can abort some fetuses but may carry the remainder of the litter to term; therefore the bitch should be examined for the presence of any remaining fetuses after cessation of treatment.

248.2.2.1 Brucella Canis

Abortion caused by *B. canis* usually occurs between 45 and 55 days of gestation and is accompanied by a highly contagious brown to greenish-gray vaginal discharge that lasts for 1 to 6 weeks. Infected bitches may not exhibit other clinical signs. *B. canis* may also cause conception failure, fetal death, and absorption in early stages of gestation or the birth of weak, infected puppies. The infection is chronic and mostly asymptomatic in adult animals. Infected animals have intermittent bacteremia and shed bacteria through body fluids. Diagnosis is most commonly based on serologic testing, bearing in mind that it can take several months after infection before antibody titers rise and that antibiotic treatment may create false-negative test results. Additionally, surface antigens of *B. canis* cross-react strongly with antibodies to several other nonpathogenic bacterial species. Blood cultures are therefore strongly recommended before declaring an animal infected.

248.2.2.2 Toxoplasma Gondii and Neospora Caninum

T. gondii and *N. caninum* are both tissue cyst-forming protozoan microorganisms that are vertically transmitted to puppies if a bitch is infected during pregnancy. Infected bitches usually remain clinically

normal, but the puppies are severely affected. Toxoplasmosis is known to cause fetal death and is a rare cause of abortion in dogs. Premature birth, stillbirth, and the birth of weak puppies have also been reported due to toxoplasmosis. Neosporosis causes fatal encephalomyelitis and polymyositis in neonatal puppies infected in utero and has experimentally been shown to cause fetal death and resorption.[7]

248.2.2.3 Canine Herpesvirus

The canine herpesvirus is species specific. In experimental studies it has been demonstrated that the effect of an infection is dependent on stage of pregnancy when infection occurs. Infection in early stages causes fetal death and mummification; in midpregnancy it may result in abortion and in later stages premature birth. More common in naturally occurring cases is that the puppies are born apparently healthy but become ill during the first 1 or 2 weeks and succumb within days. Often the whole litter is affected; however, some of the puppies may survive but develop defective vision, deafness, neuromuscular disorders, or kidney malfunction at 7 or 8 months of age. Normally immunity is incurred, and bitches that have lost a litter due to herpesvirus infection subsequently give birth to normal litters. Canine herpesvirus is presumed to be enzootic in dogs all over the world and the seroprevalence is as high as 46% in some European countries, the incidence not being higher in breeding kennels than among nonbreeding dogs.[8] Herpesvirus has been isolated from 67% of infertile and aborting bitches in those countries, but it is not clear whether it is the virus itself or a combination of several agents that cause the disturbances.

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248.2.2.4 Hypoluteodism

Inadequate progesterone production by the corpora lutea is a potential cause of fetal death and abortion in some species but has not unequivocally been proven to exist in the dog. A blood sample for progesterone taken at the time of an abortion often will show low concentration due to the luteolytic effects of the prostaglandin release during fetal expulsion; but, if repeated 1 week later, normal for stage levels of progesterone may be found. Any attempts at treating cases of imminent abortion with progestogens should only be done using a short-acting compound, because the bitch cannot deliver a litter when under the influence of high concentrations of progesterone.[1]

248.2.3 Insulin Resistance

The physiologic increased progesterone concentrations typical of diestrus or pregnancy stimulate growth hormone secretion, which in some individuals may cause down-regulation of insulin receptors and inhibition of postreceptor pathways. The condition is typically seen in middle-aged and older bitches that are pregnant or have recently been in estrus. The resulting type II diabetes is usually transient. Once blood progesterone concentration returns to anestrus levels and thus the stimulus for growth hormone secretion declines insulin resistance resolves.

Insulin resistance should be suspected in a bitch with supranormal blood insulin concentrations in the presence of a normal or increased blood glucose concentration.[9] Treatment should be initiated to prevent permanent damage to the pancreas. A poor prognosis exists for the fetuses, which sometimes become undernourished but sometimes instead grow excessively large (due to the excess in glucose), with a poor survival rate. In the bitch, acromegaly may develop as a result of excessive secretion of growth hormone by the progesterone-stimulated mammary gland. Edema, especially of the head, throat, and legs is seen in combination with excessive skin and wrinkling and an increase in interdental spaces. In advanced cases there

may be a change of voice, getting coarse from the edema of the throat. The condition may become life threatening for the bitch, and it is often necessary to interrupt a pregnancy.

248.2.4 Hypoglycemia

Preparturient hypoglycemia in the bitch is rare. Some hypoglycemic dogs may be incorrectly diagnosed as hypocalcemic because this is a more common condition and because they respond to treatment with calcium borogluconate. Affected bitches have been reported to be in late gestation and have a short history of muscle weakness, convulsions, or collapse. Blood testing demonstrates the hypoglycemia.[10–12] The condition improves dramatically after treatment with intravenous glucose solutions and resolves after parturition.

248.2.5 Premature Labor

Premature labor may have infectious causes, but can also occur in the clinically healthy bitch. Hypoluteoidism as a cause for premature uterine contractions has not been clearly demonstrated in the bitch. Short-acting progestational compounds may, however, be given in an attempt to maintain pregnancy. To adequately inhibit premature uterine contractions, tocolytic compounds such as terbutaline, a beta-adrenergic receptor antagonist, should also be administered orally or subcutaneously to effect and should be discontinued 48 hours before the anticipated day of delivery.

248.3 NORMAL PARTURITION

248.3.1 Litter Size

Litter size in dogs ranges from just one puppy in some of the miniature breeds to 15 or more in some of the giant breeds. Litter size is smaller in the young bitch and increases up to 3 to 4 years of age, decreasing again as the bitch gets older. A litter size of only one or two puppies predisposes to dystocia and thus fetal death, because of insufficient uterine stimulation and large puppy size (i.e., *single-puppy syndrome*).[13] This can be seen in dog breeds of all sizes. Breeders of the miniature breeds tend to accept small litters but should be encouraged to breed for litter sizes of at least three to four puppies to avoid this complication.

248.3.2 Physiology of Parturition

An understanding of the course and control of normal parturition (eutocia) is necessary for the diagnosis and treatment of abnormal parturition (dystocia). Studies of canine parturition and extrapolations from other species provide information on the physiologic and endocrinologic changes important for normal parturition. Stress produced by the reduction of the nutritional supply by the placenta to the fetus stimulates the fetal hypothalamic-pituitary-adrenal axis, resulting in release of adrenocorticosteroid hormone, and it is thought to be the trigger for parturition. An increase in fetal and maternal cortisol is believed to stimulate the release of $PGF_{2\alpha}$, which is luteolytic (from the fetoplacental tissue), resulting in a decline in plasma progesterone concentration. Withdrawal of the progesterone blockade of pregnancy is a prerequisite for the normal course of canine parturition; bitches given long-acting progesterone during pregnancy fail to deliver.[1] Concurrent with the gradual decrease in plasma progesterone concentration during the last 7 days before whelping, a progressive qualitative change occurs in uterine electrical activity. In addition, a significant increase in uterine activity takes place during the last 24 hours before parturition with the final fall in plasma progesterone concentration to below 6 nmol/L (2 ng/mL).[1,14] The change in the estrogen-to-progesterone ratio is probably a

major cause of placental separation and cervical dilation, although in the dog, estrogens have not been unambiguously shown to increase before parturition as they do in many other species. Estrogens sensitize the myometrium to oxytocin, which in turn initiates strong contractions in the uterus when it is not under the influence of progesterone. Sensory receptors within the cervix and vagina are stimulated by the distention created by the fetus and the fluid-filled fetal membranes. This afferent stimulation is conveyed to the hypothalamus and results in release of oxytocin during second-stage labor. Afferents also participate in a spinal reflex arch with efferent stimulation of the abdominal musculature to produce abdominal straining. Relaxin causes the pelvic soft tissues and genital tract to relax, which facilitates fetal passage. In the pregnant bitch, this hormone is produced by both ovary and placenta, increasing gradually over the last two thirds of pregnancy.[15] Prolactin, the hormone responsible for lactation, starts to rise 3 to 4 weeks after ovulation and surges dramatically with the abrupt decline in serum progesterone just before parturition.[1,5]

248.3.3 Signs of Impending Parturition

Relaxation of the pelvic and abdominal musculature is a consistent but subtle indicator of impending parturition. The most consistent change is the drop in rectal temperature caused by the final abrupt decrease in progesterone concentration. The last week before parturition the rectal temperature of the bitch fluctuates to drop sharply 8 to 24 hours before parturition and 10 to 14 hours after the concentration of progesterone in peripheral plasma has declined to less than 6 nmol/L (2 ng/mL).[1,13] To properly assess the prepartum drop in body temperature, measurements should be made every 1 to 2 hours while the temperature decreases and less frequently when the temperature is seen to increase again. The drop in rectal temperature is individual but also may depend on body size. Thus in miniature breed bitches, it can fall to 35° C (95° F), in medium-sized bitches to around 36° C, whereas it seldom falls below 37° C (96.8° F) in bitches of the giant breeds. This difference is probably an effect of the surface area-to-body volume ratio. Several days before parturition the bitch may become restless, seek seclusion, or become excessively attentive, and she may refuse all food. She may exhibit nesting behavior 12 to 24 hours before parturition, concomitant with increasing frequency and force of uterine contractions. Shivering may be an attempt to increase body temperature. In primiparous bitches, lactation may be established less than 24 hours before parturition, whereas after several pregnancies colostrum can be detected as early as 1 week prepartum.

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248.3.4 Stages of Parturition

Parturition is divided into three stages, with the last two stages being repeated for each puppy delivered.

248.3.4.1 First Stage

The duration of the first stage is usually 6 to 12 hours. It may last 36 hours, especially in a nervous primiparous animal; however, for this to be considered normal, the rectal temperature must remain low. Vaginal relaxation and dilation of the cervix occur during this stage. Intermittent uterine contractions, with no signs of abdominal straining, are present. The bitch may appear uncomfortable, and the restless behavior may become more intense. Panting, tearing up and rearranging of bedding, shivering, and occasional vomiting may be seen. Some bitches show no behavioral evidence of first-stage labor. The inapparent uterine contractions increase both in frequency and intensity toward the end of the first stage. During pregnancy the orientation of the fetuses within the uterus is 50% heading caudally and 50% cranially, but this changes during first-stage labor when the fetus rotates on its long axis, extending its head, neck, and limbs, resulting in 60% to 70% of puppies being born in anterior and 30% to 40% in posterior

presentation.[16,17] The fluid-filled fetal membranes are pushed ahead of the fetus by the uterine-propulsive efforts and dilate the cervix.

248.3.4.2 Second Stage

The duration of the second stage is usually 3 to 12 hours (in rare cases 24 hours). At the onset of second-stage labor the rectal temperature rises to normal or slightly above normal. The first fetus engages in the pelvic inlet, and the subsequent intense, expulsive uterine contractions are accompanied by abdominal straining. On entering the birth canal, the allantochorionic membrane may rupture and a discharge of some clear fluid may be noted. Covered by the amniotic membrane, the first fetus is usually delivered within 4 hours after onset of second-stage labor. Normally the bitch will break the membrane, lick the neonate intensively, and sever the umbilical cord. At times the bitch will need some assistance to open the fetal membranes to allow the newborn to breathe, and sometimes the airways will have to be emptied of fetal fluids. The umbilicus can be clamped with a pair of hemostats and cut with a blunt scissors to minimize hemorrhage from the fetal vessels, leaving about 1 cm of the umbilicus. In case of continuing hemorrhage the umbilicus should be ligated.

248.3.4.2.1 Diagnosing second-stage labor

It is crucial that the veterinarian is able to determine whether the bitch is in the second stage or still in first stage of labor. Inexperienced breeders tend to get nervous during a bitch's first-stage labor, not fully understanding the function of this preparatory stage of parturition during which uterine contractions, the softening of the birth canal, and the opening of the cervix take place.

Three signs indicate that the bitch has entered into second-stage labor:

1. The passing of fetal fluids (first water bag [allantois], bursts)
2. Visible abdominal straining
3. The rectal temperature returning to normal level

If one or more of these signs have been observed, the bitch is in second-stage labor.

In normal labor the bitch may show weak and infrequent straining for up to 2, and at the most 4, hours before giving birth to the first fetus. If the bitch is showing strong, frequent straining without producing a pup, this indicates the presence of some obstruction, and she should not be left for more than 20 to 30 minutes before seeking veterinary advice.

The bitch should be examined for the following reasons:

- If she has greenish discharge but no pup is born within 2 to 4 hours
- If fetal fluid was passed more than 2 to 3 hours previously, but nothing more has happened
- If she has had weak, irregular straining for more than 2 to 4 hours
- If she has had strong, regular straining for more than 20 to 30 minutes
- If more than 2 to 4 hours have passed since the birth of the last puppy and more remain

- If she has been in second-stage labor for more than 12 hours

248.3.4.3 Third Stage

The third stage of parturition, expulsion of the placenta and shortening of the uterine horns, usually follows within 15 minutes of the delivery of each fetus. Two or three fetuses may, however, be born before the passage of their placentas occurs. The bitch should be discouraged from eating more than one or two of the placentas because she may develop diarrhea and vomiting, with risk of aspiration pneumonia. Lochia (i.e., the greenish postpartum discharge of fetal fluids and placental remains) will be seen for up to 3 weeks or more but is most profuse during the first week. Uterine involution is normally completed after 12 to 15 weeks.

The bitch should be examined for the following reasons:

- If all placentas have not been passed within 4 to 6 hours (although placental numbers may be difficult to determine because of the bitch eating them)
- If lochia are putrid or foul smelling
- There is continuing continuing severe genital hemorrhage
- If the rectal temperature is higher than 39.5° C (101.3° F)
- If the general condition of the bitch is abnormal
- If the general condition of the puppies is abnormal

248.3.5 Interval Between Births

Expulsion of the first fetus usually takes the longest. The interval between births in normal uncomplicated parturition is from 5 to 120 minutes.[16,17] In almost 80% of cases the fetuses are delivered alternately from the two uterine horns.[16] When giving birth to a large litter a bitch may stop straining and rest for more than 2 hours between the delivery of two consecutive fetuses. The second-stage straining will then resume, followed again by the third stage, until all the fetuses are born.

248.3.6 Completion of Parturition

Parturition is usually completed within 6 hours after the onset of second-stage labor, but it may last up to 12 hours. It should never be allowed to last for more than 24 hours because of the risks involved both for the bitch and the fetuses.

248.4 DYSTOCIA

248.4.1 Definition

Dystocia is defined as difficult birth or the inability to expel the fetus through the birth canal without assistance.

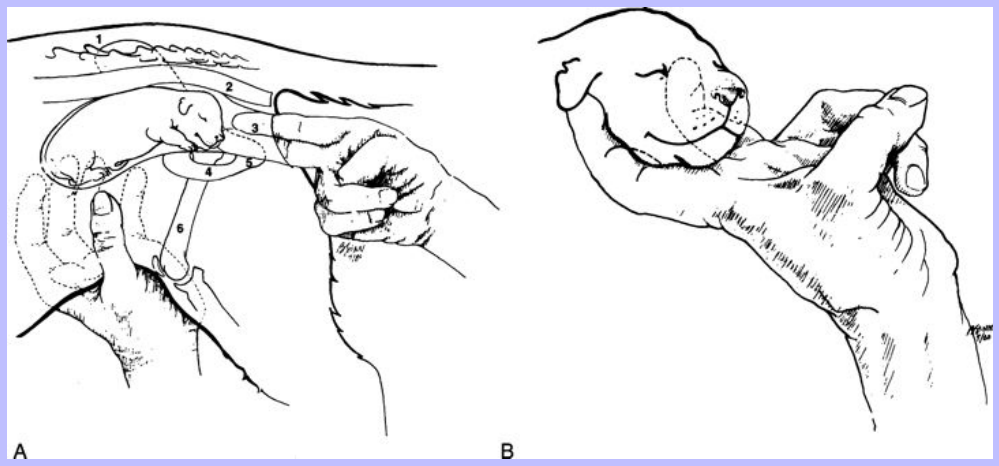
248.4.2 Frequency

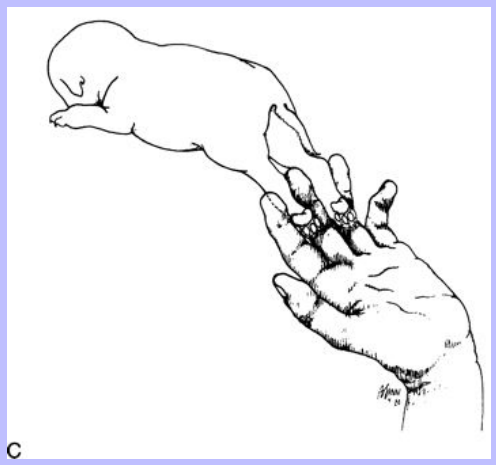
Dystocia is a frequent problem in the dog. The true average incidence of dystocia in the bitch is probably below 5%, but it may amount to almost 100% in some breeds of dogs, especially those of the achondroplastic type and those selected for large heads.[13,17,18]

248.4.3 Clinical Assessment

When a bitch with possible dystocia is examined, an accurate history and a thorough physical examination are important prerequisites for proper management. The three criteria for being in second-stage labor, namely, (1) passage of fetal fluids, (2) visible abdominal straining, and (3) temperature returned to normal, should be assessed. An evaluation of the bitch's general health status should be made and signs of any adverse effects of parturition noted. Observation should be made of the bitch's behavior and the character and frequency of straining, and the vulva and perineum should be examined, noting color and amount of vaginal discharge. Mammary gland development including congestion, distention, size, and presence of milk should be evaluated. Palpation of the abdomen, roughly estimating the number of fetuses and degree of distention of the uterus, should be carried out. Digital examination of the vagina using aseptic technique should be undertaken to detect obstructions and determine the presence and presentation of any fetus in the pelvic canal (Figure 248-1). In most bitches it is not possible to reach the cervix during first stage, but an assessment of the degree of dilation and tone of the vagina may give some indication of the status of the cervix and the tone of the uterus. Pronounced tone of the anterior vagina may indicate satisfactory muscular activity in the uterus, whereas flaccidity may indicate uterine inertia.[19] The character of the vaginal fluids also will indicate whether the cervix is closed, with the production of scant fluid volume that is sticky creating a certain resistance to the introduction of a finger. The cervix is likely open when fetal fluids lubricate the vagina, making the exploration easy. When the cervix is closed the vaginal walls also fit quite tightly around the exploring finger, whereas with an open cervix the cranial vagina palpates more open.

Figure 248-1 *A,* Determination of the fetal disposition when the head has entered the vaginal canal. The bitch should be standing for this procedure. 1, Right wing of ilium; 2, rectum; 3, lumen of vaginal vestibule; 4, right half of pubic symphysis; 5, right wing of ischium; 6, right femur. *B,* The index and middle fingers are used to guide the head and to exert moderate traction in a cranial presentation. *C,* Manual traction as applied in a caudal presentation. The fingers should be positioned proximal to the hocks for best results. (From Shille VM: Diagnosis and management of dystocia in the bitch and queen. *In*: Bojrab MJ [ed]: Current Techniques in Small Animal Surgery. Philadelphia, Lea & Febiger, 1983, p 338; used with permission.)





Radiographic examination is valuable to assess gross abnormalities of the maternal pelvis and number and location of fetuses, to estimate fetal size, and to detect congenital defects or signs of fetal death. In the dead fetus, intrafetal gas will appear 6 hours after death and can be detected radiographically, whereas overlapping of cranial bones and collapse of the spinal column will not be seen until 48 hours have passed after the death of the fetus. Ultrasound examination will determine fetal viability or distress, with normal heart rate being 180 to 240 beats per minute (bpm), decreasing in the compromised fetus. Some bitches brought to veterinarians for dystocia have already delivered all fetuses or were only pseudopregnant. Pseudopregnancy is most commonly diagnosed as lactation without pregnancy, but it may include abdominal contractions, nesting behavior, and changes in personality that convince an owner that the pet is pregnant.

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248.4.4 Diagnosis

The range of normal variations observed in dogs at parturition makes recognition of dystocia difficult, especially for the inexperienced observer. The following criteria for dystocia may assist in making the diagnosis:

- The rectal temperature has been down and returned to normal with no signs of labor.
- A green vulvar discharge is seen, but no fetuses have been delivered. (These discharges emanate from the marginal hematoma of the placentas and indicate that at least one placenta is beginning to become separated from the maternal blood supply. They are normal once birth is underway.)
- Fetal fluids were passed 2 to 3 hours earlier, but no signs of labor are noted.
- Labor is absent for more than 2 hours or is weak and infrequent for more than 2 to 4 hours.
- Strong and persistent nonproductive labor occurs for more than 20 to 30 minutes.
- An obvious cause of dystocia is evident (e.g., pelvic fracture or a fetus stuck in the birth canal and partially visible).
- Signs of toxemia (disturbed general condition, general edema, shock) are noted when parturition should be occurring.

Recently, systems for monitoring labor and delivery in the bitch have become commercially available (Veterinary Perinatal Services, Inc., Wheatridge, Colorado).[20] These systems are intended for use by veterinarians or by breeders at home with veterinary guidance. They consist of a uterine tocodynamometer and a fetal Doppler. Using this device the administration of calcium borogluconate and oxytocin can be monitored based on the individual uterine response of the bitch.

248.4.5 Maternal Causes of Dystocia

Traditionally, dystocia is classified as being of either maternal or fetal origin, or a combination of both (Table 248-1; Figures 248-2 and 248-3).

248.4.5.1 Uterine Inertia

Uterine inertia is by far the most common cause of dystocia in dogs. It is classified into *primary* and *secondary* inertia. In primary inertia the uterus may fail to respond to the fetal signals because only one or two puppies exist, which provide insufficient stimulation to initiate labor (the single-puppy syndrome), or because of overstretching of the myometrium by large litters, excessive fetal fluids, or oversized fetuses. Other causes of primary inertia may be an inherited predisposition, nutritional imbalance, fatty infiltration of the myometrium, age-related changes, deficiency in neuroendocrine regulation, or systemic disease in the bitch. Primary complete uterine inertia is the failure of the uterus to begin labor at full term. Primary partial uterine inertia occurs when enough uterine activity exists to initiate parturition, but it is insufficient to complete a normal birth of all fetuses in the absence of an obstruction. Secondary uterine inertia implies that some fetuses have been delivered and the remainder are in utero due to exhaustion of the uterine myometrium caused by obstruction of the birth canal; this condition should be distinguished from primary inertia.

Table • 248-1 Causes of Dystocia in Bitches (182 Cases)

	FREQUENCY (%)
Maternal causes	75.3
Primary complete inertia	48.9
Primary partial inertia	23.1
Birth canal too narrow	1.1
Uterine torsion	1.1
Uterine prolapse	—
Uterine strangulation	—
Hydrallantois	0.5
Vaginal septum formation	0.5
Fetal causes	24.7
Malpresentations	15.4
Malformations	1.6
Fetal oversize	6.6
Fetal death	1.1

(From Darvelid AW, Linde-Forsberg C: Dystocia in the bitch: a retrospective study of 182 cases. J Small Anim Pract 35:402–407, 1994.)

248.4.5.1.1 Management

In cases of primary uterine inertia, the owners should initially be instructed to try to induce straining by actively exercising the bitch, for instance, by running the dog around the house or up some stairs. A considerable number of puppies are born in the car on the way to the veterinarian. Most of these would probably have been delivered in the calm and quiet of home had the owners tried to induce straining themselves, thereby giving the puppies a better start in life and possibly also resulting in the whole litter being born without further intervention. Another means of induction of straining in the bitch with insufficient labor is by feathering of the dorsal vaginal wall. Feathering is accomplished by inserting two fingers into the vagina and pushing or "walking" with them against the dorsal vaginal wall, thus inducing an episode of straining (the Ferguson reflex). Feathering can also be effective in initiating labor after correction of the position or posture of a fetus. Nervous voluntary inhibition of labor due to psychologic stress may occur, mainly in a nervous primiparous animal. Reassurance by the owner or administration

of a low-dose tranquilizer may remove the inhibition.[21] Once the first fetus is born, parturition will usually proceed normally.

The bitch with complete primary uterine inertia is usually bright and alert, has a normal rectal temperature, and has no evidence of labor. The cervix is often dilated, and vaginal exploration is easy to perform owing to the presence of fetal fluids, but the fetus may be out of reach because of the flaccid uterus. Before initiation of medical treatment of uterine inertia, obstruction of the birth canal must be excluded.

Calcium solutions and oxytocin are the drugs of choice in cases of uterine inertia. Oxytocin has a direct action on the rate of calcium influx into the myometrial cell, essential for myometrial contraction. Many bitches do not respond to oxytocin alone but require prior administration of a calcium solution. Therefore some 10 minutes before the administration of oxytocin, 10% calcium borogluconate, 0.5 to 1.5 mL/kg body weight, should be given by slow intravenous infusion (1 mL/min) with careful monitoring of the heart rate. The calcium can also be administered subcutaneously, which eliminates the risk for arrhythmia but presents a small risk for granuloma formation at the injection site. Small breed bitches may be prone to hypoglycemia, particularly after prolonged straining. In such cases a dilute (10% to 20%) glucose solution can be added to the infusion or given intravenously in doses of 5 to 20 mL. The recommended dose of oxytocin for the bitch is 1 to 5 IU given intravenously or 2.5 to 10 IU intramuscularly, which can be repeated at 30-minute intervals. The response to treatment will be reduced with each repeated administration. Higher doses than recommended or too frequent administration may result in prolonged contracture of the myometrium, preventing fetal expulsion and impeding uteroplacental blood flow. The disadvantages of oxytocin administration include a tendency to cause premature induction of placental separation and cervical closure. If no response to treatment is seen after a second administration of oxytocin, the puppies should be delivered without further delay, either with the aid of obstetric forceps (if only one or two puppies remain and are within easy reach in the uterine corpus) or by cesarean section.

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Figure 248-2 Algorithm defining the various maternal causes for dystocia.

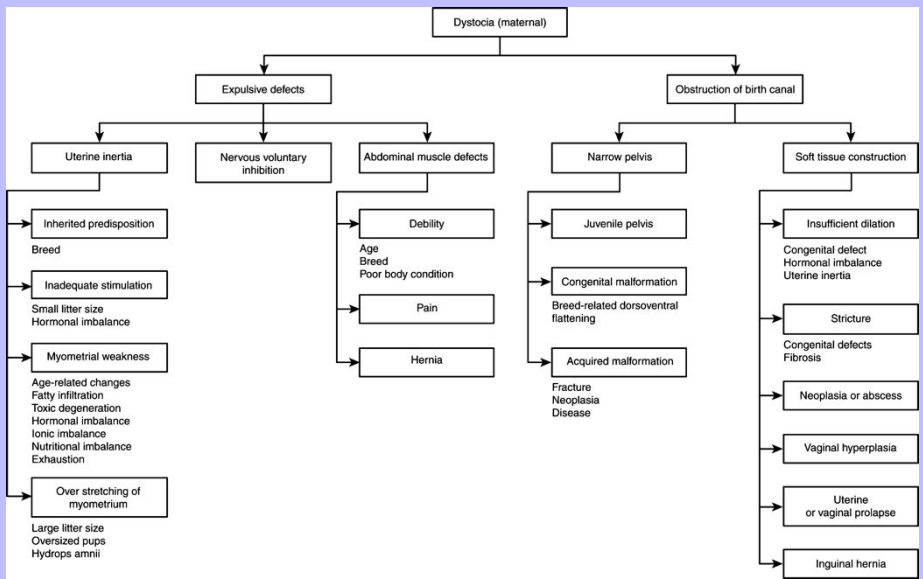
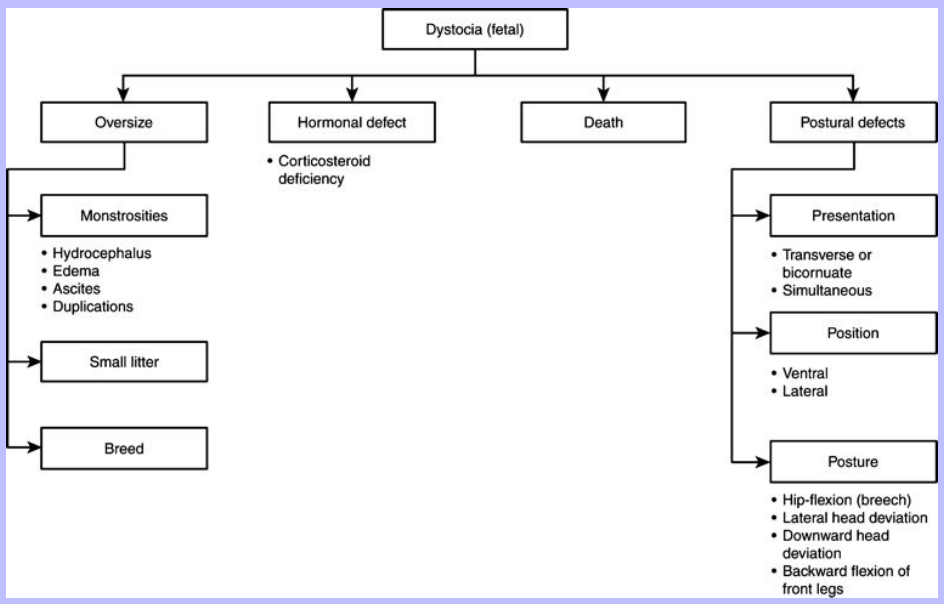


Figure 248-3 Algorithm defining the various fetal causes for dystocia.



The long-acting ergotamines should never be used in connection with parturition. The treatment regimen includes the following:

- The owner runs with the bitch and feathers the vaginal vault.
- A 10% solution of calcium gluconate is given slowly intravenously while carefully checking the bitch's heart rate.
- The bitch is given 30 minutes to respond to treatment. If straining begins, the treatment can be repeated if necessary or continued with oxytocin.
- If the calcium infusion has no effect within 30 minutes, oxytocin is given intravenously or intramuscularly.
- The bitch again is given 30 minutes to respond to treatment. If straining begins, the treatment can be repeated if necessary, although each additional administration will elicit a weaker response.
- If nothing happens within 30 minutes, it is not likely that further treatment will be successful. The fetuses should be delivered, either by forceps, if only one or two fetuses remain and are within easy reach, or by cesarean section.

248.4.5.2 Obstruction of Birth Canal

Obstruction of the birth canal may be of maternal or fetal origin. Some maternal causes for obstruction include:

- Uterine torsion and uterine rupture. These are acute, life-threatening conditions that can occur during late pregnancy or at the time of parturition. Sometimes a few fetuses are born before parturition stops, and the condition of the bitch may quickly deteriorate. Surgery is always required, and a quick diagnosis essential for survival.

- Uterine inguinal herniation usually is detected around the fourth week of pregnancy as the fetal uterine enlargements are growing and the contour of the abdomen is markedly abnormal. Sometimes the early stages may be mistaken for mastitis of the rear mammary glands. The condition is corrected by surgery, whereby the uterine horns are repositioned and the herniation sutured. In cases with circulatory disturbance and advanced tissue damage, the uterus will have to be removed. 1662 1663

- Congenital malformations of the uterus (e.g., partial or complete aplasia or hypoplasia of one or both uterine horns or of the corpus uteri) or the cervix are rare causes of maternal obstructive dystocia. Symptoms depend on the character and degree of the malformation. In cases of unilateral aplasia of an entire uterine horn, small litter size may be the only sign. Retained fetuses behind partial occlusions require surgery, and the final diagnosis is usually made during the operation.

- Soft tissue abnormalities such as neoplasms, vaginal septa, or fibrosis of the birth canal may cause obstructive dystocia. The prepartum relaxation of the vagina will often allow the passage of fetuses. Vaginal septa may consist of remnants from the fetal Müllerian duct system. However, they can also occur secondary to vaginal trauma or infection and, if extensive, may prevent the passage of the fetuses. Often, however, they are not so extensive, and vaginal relaxation may allow the fetuses to pass. Cervical or vaginal fibrosis usually is secondary to trauma or inflammatory processes and in severe cases will cause dystocia. Surgical intervention may save the puppies. Tumors and septa formations may be removed; but in the case of fibrosis, surgery is seldom successful because of new scar tissue formation during the healing process.

- Narrow pelvic canal causing obstructive dystocia may result from previous pelvic fractures, immaturity, or congenital malformation of the pelvis. The normal canine pelvis usually has a vertical diameter greater than the horizontal. Congenitally narrow birth canals exist in some brachycephalic and terrier breeds; in addition, their fetuses have comparatively large heads and wide shoulders. When achondroplasia exists, as in the Scottish terrier, dorsoventral flattening of the pelvis modifies the normal pelvic inlet, which creates a fetal obstruction. In a study using indirect pelvimetry, significant differences were found between Scottish terrier bitches whelping normally compared with those with dystocia owing to a too narrow birth canal, confirming the dorsoflattening and also demonstrating a shortening of the pelvis in the bitches with dystocia. The weight of the puppies was the same in both groups.[17] Boston terrier bitches were also studied, and again a significantly greater inner pelvic height was found in the normally whelping bitches; however, in this breed the size of the puppies was also of importance because the weight of the pup was related with the size of its head. In the bulldog the large, deep chest and pronounced waist causes the gravid uterus to drop down. At parturition, the fetuses are therefore presented at a relatively acute angle to the pelvic inlet. Bulldogs sometimes also have slack abdominal musculature, leading to insufficient uterine contractions and abdominal straining to lift the fetus up into the pelvic cavity.

248.4.6 Fetal Causes of Dystocia

Fetal obstructions may be caused by malpresentations, malorientations, or oversized fetuses as well as monstrosities including hydrocephalus, edema, or various duplications (see Figure 248-3). Simply being

oversized is a cause for malpresentation. Fetal death may result in dystocia due to malpositioning or inadequate stimulation for parturition to begin. A healthy fetus is active during expulsion, extending its head and limbs, twisting, and rotating to get through. In most breeds the greatest bulk of the fetus lies in its abdominal cavity, whereas the bony parts (the head and the hips) are comparatively small. The limbs are short and flexible and rarely cause serious obstruction to delivery in the normal-sized fetus.

248.4.6.1 Oversized Fetuses

A puppy weighing 4% to 5% of the weight of the bitch is considered the upper limit for an uncomplicated birth. In the absence of monstrosities, oversized fetuses are often associated with small litter size. In breeds in which miniaturizing exists, great disparity in fetal size within litters may occur, with some greatly oversized individuals. In brachycephalic breeds like the Boston terrier, dystocia occurs from the combination of a flattened pelvic inlet and puppies having a large head. Obstructive dystocia was found to occur already at pup weights of 2.5% to 3.1% of the adult weight in these breeds.[18] In dystocia due to an oversized fetus, sometimes a portion of the fetus may protrude from the vulva. In anterior presentation the head may be born and the shoulders and chest cause obstruction, whereas in posterior presentation the hind limbs and hips may protrude.

248.4.6.2 Posterior Presentation

Posterior presentation is considered normal in dogs, occurring in 30% to 40% of fetal deliveries.[14,16,17] Posterior presentations have, however, been related both to higher pup mortality[17] and to a predisposition for dystocia, because mechanical dilation of the cervix may be inadequate, particularly where this involves the first fetus to be delivered. In addition, expulsion is rendered more difficult because the fetus is being delivered against the direction of its haircoat and because the fetal chest, instead of being compressed, becomes distended by the pressure from the abdominal organs through the diaphragm. Occasionally the fetus may have the elbows hooked around the pelvic brim, preventing further expulsion. Should the fetus become lodged in the pelvic canal, pressure on the umbilical vessels trapped between the fetal chest wall and maternal pelvic floor may cause hypoxia and reflex inhalation of fetal fluids.

248.4.6.3 Breech Presentation

Breech presentation (i.e., posterior presentation with hind legs flexed forward) can be a serious complication, especially in medium-and small-sized breeds. Vaginal exploration will reveal a tail tip, maybe the anus, and the bony structure of the pelvis of the fetus.

248.4.6.4 Lateral or Downward Deviation of the Head

These are two of the most common malpositionings in the dog. Lateral deviation is most common with long-necked breeds such as rough collies, whereas downward deviation is seen in brachycephalic breeds and long-headed breeds such as Sealyham and Scottish terriers. In lateral deviation, vaginal exploration will demonstrate just one front leg, the one contralateral to the direction of the deviation of the head (i.e., when the head is deviated to the left, the right front paw will be found and vice versa). When the animal has a downward deviation of the head, either both front legs and sometimes the nape of the neck of the fetus can be palpated, or both front legs may be flexed backwards and only the scull of the fetus be reached.

248.4.6.5 Backward Flexion of Front Legs

This condition is especially common when the fetus is weak or dead and is sometimes seen in combination with deviation of the head, especially downward. For bitches of the larger or even medium-sized breeds, it may be possible to deliver a puppy with one or both front legs flexed.

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248.4.6.6 Transverse or Bicornual Presentation

Sometimes a fetus, instead of progressing from the uterine horn through the cervix to the vagina, will proceed into the contralateral uterine horn, possibly due to some obstruction. Another reason may be that the fetus was implanted close to the body of the uterus. These cases always require surgery, because no possibility for manual correction exists.

248.4.6.7 Two Fetuses Presented Simultaneously

Sometimes one fetus from each horn is presented at the same time, jamming the birth canal. When possible, if one is coming backwards, this one should be removed first, because it occupies more space.

248.4.6.8 Management of Fetal Malpresentations

If a fetus is present in the birth canal, manipulation by hand or by obstetric forceps may be attempted. In bitches of the giant breeds it may even be possible to insert one hand through the vagina into the uterus and thus extract the puppy. During natural birth the puppy will almost make a full somersault, emerging from the loop of the uterine horn, progressing upwards to pass through the pelvic canal, and then moving down through the long vestibulum of the bitch to reach the vulva placed some 5 to 15 cm below the level of the pelvic floor. Thus after the fetus is seized, a gentle traction in posteroventral direction is applied.

Fetal position must be assessed. If the fetus has advanced into and partly through the pelvic canal, it will create a characteristic bulge of the perineal region, below the tail. Easing the vulvar lips upward may reveal the amniotic sac and the position of the fetus. Vaginal exploration and radiographic examination will aid in making a diagnosis in the cases when the fetus has not advanced as far.

The narrowest part of the birth canal is within the rigid pelvic girdle. If external manipulation is to be attempted, the fetus that cannot be easily pulled out may have to be pushed forward to in front of the pelvic girdle, where corrections of its position or posture are easier to perform. This should be done between periods of straining of the bitch, never working against the uterine contractions. It should also be remembered that the widest part of the pelvic girdle usually is on the diagonal (see Figure 248-1); thus rotating the fetus 45 degrees may create sufficient room for passage. Generous application of obstetric lubricant (liquid paraffin, Vaseline®, or a sterile water-soluble lubricant) is helpful, especially if the bitch has been in second-stage labor for some time.

Depending on the position and posture of the fetus, a grip should be applied around its head and neck, from above or below whichever is most convenient, around its pelvis, or around the legs. Care should be taken because the neck and limbs of the fetus are easily torn when pulled. Correction of posture may be obtained by manipulation of the fetus through the abdominal wall with one hand and concurrent transvaginal manipulation with the other. A finger may be introduced into the mouth of the fetus to help correct a

downward deviation of the head. Should it be necessary to change the postures of the limbs, a finger should be inserted past the elbow or knee and the limb moved medially in under the fetus and corrected.

A gently applied alternating right-to-left traction of the puppy, gently rocking it back and forth or from side to side and possibly twisting it to a diagonal position within the pelvis, will help free the shoulders or the hips one at a time. A slight pressure applied over the perineal bulge may prevent the fetus from sliding back into the uterus again between strainings.

Obstetric forceps should only be used for assisted traction of a relatively oversized fetus when it is likely the rest of the puppies in the litter are smaller or when just one or two fetuses remain. The forceps is guided with a finger and never introduced further than to the uterine body because of the risk of getting part of the uterine wall within the grip, thereby causing serious damage. If the head of the fetus can be reached, the grip should be applied around the neck (Pålssons forceps) or across the cheeks. In posterior presentation the grip should be around the fetal pelvis. If the legs can be reached, the grip should be around those, not around the feet.

248.4.6.8.1 Outcome of obstetric treatment

A study[13] reporting on treatment outcome shows that digital manipulation, including forceps delivery, medical treatment for dystocia, or both, is successful in only 27.6% of the cases. Around 65% of bitches brought to the clinic because of dystocia thus end up having a cesarean section.

Fetal death increased from 5.8% in bitches brought in within 1 to 4.5 hours after the beginning of second-stage labor to 13.7% in the period between 5 to 24 hours. Overall fetal death was 22.3%.[13] Early diagnosis and prompt treatment is therefore crucial in reducing the puppy death rate in cases of dystocia.

248.4.6.9 Criteria for Cesarean Section

The indications for cesarean section include the following:

- Complete primary uterine inertia that does not respond to medical treatment
- Partial primary uterine inertia that is refractory to medical management
- Secondary uterine inertia with inadequate resumption of labor
- Abnormalities of the maternal pelvis or soft tissues of the birth canal
- Relative fetal oversize, if considered likely to be repeated in several fetuses
- Absolute oversize (single-puppy syndrome or fetal monstrosity)
- Excess or deficiency of fetal fluids
- Fetal malposition unamendable to manipulation
- Fetal death with putrefaction
- Toxemia of pregnancy and illness of the bitch

- Neglected dystocia
- Prophylactic (history of previous difficult deliveries)

Prophylactic cesarean section should be questioned on ethical grounds if it is performed to assist the propagation of a breed line that cannot reproduce successfully without intervention.

Once a decision has been made to deliver the litter by cesarean section, surgery should be carried out without delay. The bitch has often endured hours of more or less intensive labor and may be suffering from physical exhaustion, dehydration, acid-base disorders, hypotension, hypocalcemia, hypoglycemia, or a combination of these symptoms. The prognosis for both bitch and offspring is good if surgery is performed within 12 hours after the onset of second-stage labor; it continues to be fairly good for the bitch after 12 hours but guarded for the fetuses. If more than 24 hours have passed after the onset of second-stage labor, the entire litter is usually dead and further delay compromises the life of the bitch.

248.5 POSTPARTURIENT CONDITIONS

It is normal for the bitch to have a slightly elevated rectal temperature, up to 39.2° C (102.56° F), for a couple of days after parturition. It should, however, not exceed 39.5° C (103.1° F). Fever during this period usually emanates from conditions of the uterus or the mammary glands.

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248.5.1 Perinatal Loss

Based on a number of surveys, pup losses up to weaning age appear to range between 10% and 35%[17,20,22] and averages around 12%.[22–24] More than 65% of pup mortality occurs at parturition and during the first week of life; few neonatal deaths occur after 3 weeks of age. Inbreeding is said to be associated with a high incidence of fetal and neonatal mortality. Breed differences in pup mortality patterns have been reported.[17] The principal cause of pup mortality has been attributed to fetal asphyxia, accounting for 42.5% of the total mortality. The majority of these pups (82.2%) died during whelping or in the first 24 hours after birth. The death of just over half of these pups could be directly attributed to dystocia. The remaining pups were compromised during what appeared to be a normal whelping.[17]

248.5.2 Uterine Disorders

248.5.2.1 Hemorrhage

Some hemorrhage from the genital tract after parturition is normal, but maternal blood loss should never exceed a scant drip from the vulva. True hemorrhage should be distinguished from normal vaginal postparturient discharge. Excessive hemorrhage after parturition may indicate uterine or vaginal tearing or vessel rupture or may be evidence of a coagulation defect. The hematocrit should be checked, remembering that 30% is normal for the bitch at term. Inspection of the vulva and vagina should be performed in an attempt to locate the source of the bleeding. Oxytocin can be administered to promote uterine involution and contraction of the uterine wall. In more severe cases of uterine hemorrhage, an exploratory laparotomy may be necessary. The bitch should be monitored closely for signs of impending shock, and blood transfusion may be required while attempting to determine the cause of hemorrhage.

248.5.2.2 Retained Placentas and Fetuses

Retained placentas in the bitch may cause severe problems, especially when accompanied by retained fetuses or infection. Clinical signs of retained placenta include a thick dark vaginal discharge. Retained fetuses can be identified by palpation or radiographic or ultrasonographic examination. The examination should also encompass the corpus uteri and the vagina in search for partly expelled fetuses or fetal membranes. A retained placenta is often palpable in the uterus, depending on the size of the bitch and degree of uterine involution. Extraction of retained tissue, by careful "milking" of the uterine horn or by using forceps, is sometimes possible. Treatment with 1 to 5 IU oxytocin per dog subcutaneously or intramuscularly two to four times daily for up to 3 days can help expulsion of retained placentas. The long-acting ergot alkaloids should not be used because they may cause closure of the cervix. Antibiotic treatment is advisable if the bitch is showing signs of illness.

248.5.2.3 Acute Metritis

Acute metritis is an ascending bacterial infection of the uterus in the immediate postpartum period. Dystocia, obstetric manipulation, retained fetuses or placental membranes, or parturition in an unsanitary environment predispose to metritis. Metritis may rarely occur after normal parturition, natural or artificial insemination, or an abortion. Infection usually ascends through an open cervix and is often caused by gram-negative bacteria. Clinical signs include fever, dehydration, depression, anorexia, poor lactation and mothering, and a purulent or sanguinopurulent vaginal discharge. A doughy enlarged uterus may be palpated abdominally. Abdominal radiographic or ultrasonographic examination (or both) is indicated to evaluate the uterine size and uterine contents. A vaginal culture is recommended. Vaginal cytology will show large numbers of degenerate neutrophils, red blood cells (RBCs), bacteria, and debris. The complete blood count (CBC) often shows leukocytosis with a left shift. Therapy consists of immediate administration of intravenous fluids and antibiotics and evacuation of uterine contents. The latter may be accomplished by administering oxytocin or $PGF_{2\alpha}$. One high-dose regimen exists for administration of $PGF_{2\alpha}$ (0.1 to 0.25 mg/kg subcutaneously once or twice daily for 3 to 8 days) and one low-dose regimen (0.025 to 0.05 mg/kg subcutaneously six to eight times daily for 2 to 3 days). The high-dose alternative may cause adverse reactions such as abdominal pain and increases in pulse rate, respiratory rate, and salivary secretions. These reactions appear within 10 minutes of administration and normally disappear again after 30 minutes to 1 hour. It should be remembered, however, that the prostaglandins are not licensed for use in dogs. In more severe cases, ovariohysterectomy (OHE) is the recommended treatment.

248.5.2.4 Subinvolution of Placental Sites

In the postparturient period it is normal for the bitch to have a serosanguineous vaginal discharge for 3 to 6 weeks. Normally the uterine involution is completed within 12 weeks after whelping. Subinvolution of placental sites is suspected if a sanguineous vaginal discharge persists for longer than 6 weeks (Figure 248-4). The cause of this condition is unknown, and the bitch often shows no symptoms of illness. Vaginal cytology shows predominantly RBCs, with syncytial trophoblast-like cells being a useful confirmatory finding. Subinvolution of placental sites almost exclusively affects the young, primiparous animal, and in the majority of cases resolves spontaneously, with the prognosis for future pregnancy being good. Because of increased risk of anemia, secondary bacterial infection, or rupture of the affected placental sites with subsequent peritonitis, the bitch should be monitored until the disorder resolves. OHE is indicated in rare cases of profound permanent bleeding or uterine infection.

248.5.2.5 Uterine Rupture

Uterine rupture should be considered a possible but uncommon cause of illness in the postparturient period. Uterine rupture can occur when prostaglandins or oxytocin have been administered for induction of abortion or treatment of pyometra, metritis, or dystocia. The condition may occur as a result of dystocia or during an apparently normal parturition or may be due to injury occurring in late pregnancy. The clinical signs of uterine rupture include abdominal pain and distention and a rapid deterioration of the condition of the bitch. The diagnosis is confirmed by exploratory laparotomy, and OHE is the usual treatment combined with intravenous fluids and antibiotic therapy.

248.5.2.6 Uterine Prolapse

Uterine prolapse is an uncommon complication during parturition. It occurs in primiparous and multiparous bitches. The prolapse usually occurs immediately or within a few hours after delivery of the last pup. The prolapse can be complete, with both uterine horns protruding from the vulva, or may be limited to the uterine body and one horn. Treatments include manual reposition, reposition by means of laparotomy, and amputation. OHE is usually performed.

248.5.2.7 Toxic Milk Syndrome

The toxic milk syndrome is poorly documented. Pathologic conditions in the uterus of the bitch may cause toxins to be excreted in the milk. Suckling offspring that are affected by toxic milk syndrome become vocal and uncomfortable. Other signs are diarrhea, salivation, bloating, and a reddened anus. Treatment consists of removing the pups from the bitch and the administration of fluid therapy and oral glucose until bloating resolves. If the bitch is successfully treated for the uterine condition, the litter can be returned after 24 to 48 hours, otherwise hand rearing is necessary.

Figure 248-4 ***A***, Subinvolution of the placental sites. In the unopened left uterine horn the typical oval swellings of the placental areas can be observed. In the opened horn, the placentation zones and the hemorrhage emanating from those areas can be seen. ***B***, A hystographic picture of a bitch with subinvolution of the placental sites, 4 months after whelping. The placentation zones are seen as darker areas. Normal uterine involution is completed within 12 weeks in the bitch.

248.5.3 Mammary Gland Disorders

248.5.3.1 Agalactia

Agalactia, or absence of milk after parturition, may be due to a failure of milk production or milk letdown. True agalactia, failure of milk production, is uncommon but may occur repeatedly in some bitches. More commonly it may be observed after premature parturitions or cesarean sections. Treatment with metoclopramide 1 to 5 mg/kg subcutaneously or per orally every 6 to 8 hours for a maximum of 5 days may promote prolactin release and milk production in these cases. Failure of milk letdown may occur as a consequence of excessive secretion of epinephrine, resulting from fright or pain, which has a blocking effect upon the release of oxytocin. Oxytocin 0.5 to 2.0 IU per dose can be administered repeatedly for a

few days until milk flow has been established. Primiparous, nervous, or confused bitches may experience temporary agalactia. Reassurance by the owner and administration of low doses of acepromazine orally may help the bitch to settle down, and subsequent suckling by the puppies will enhance milk flow. Other causes of agalactia are physical exhaustion, undernourishment, shock, mastitis, metritis, systemic infections, and endocrine imbalances.

248.5.3.2 Galactostasis

Milk stasis (i.e., galactostasis) causes enlarged and edematous mammary glands that are firm and warm to the touch. The bitch shows signs of discomfort and pain and fails to let down milk. The condition should be differentiated from mastitis and agalactia. The cause is unknown in dogs, but it usually involves the two most caudal pairs of mammae in bitches with a high milk production, with few puppies, or with both. It can also occur in glands with malformed teats, which the offspring avoid suckling. Another cause can be that nursing comes to an abrupt end owing to death of the litter or sudden weaning. To relieve mammary congestion the owner can apply gentle massage and warm-water compresses to the mammary glands or perform careful milking to relieve some of the pressure. Sometimes it helps to put more aggressively nursing neonates to the bitch. Treatment includes reducing food intake and the administration of a mild diuretic. Neglected galactostasis may lead to mastitis or involution of the mammary gland. Cabergoline (Galastop vet.), a dopamine agonist, at 2.5 to 5 µg/kg/day orally for 4 to 6 days, reduces prolactin secretion and thereby lactation. The use of dopamine agonists should be restricted to bitches that have either lost their litter or have a litter old enough to be weaned.

248.5.3.3 Acute Mastitis

Acute mastitis in the bitch occurs from hematogenously spread bacterial infections or from bacteria ascending through the teat orifices. Predisposing factors include mammary gland congestion, trauma, and poor sanitary conditions. The mammary glands become hot, painful, and enlarged; the milk shows increased viscosity and changes in color from yellow to brown, depending on the amount of blood and purulent exudate present. Clinical signs include fever, anorexia, and depression in the bitch. The offspring may be restless and crying. Milk cytology reveals the presence of degenerate neutrophils, RBCs, and bacteria. Culture of the milk often shows growth of *Staphylococcus* spp., *Streptococcus* spp., or *Escherichia coli*. Treatment consists of adequate antibiotics, application of warm-water compresses, and massage of mammary glands. If abscessation of the glands occurs, surgical débridement and drainage is essential. Untreated acute mastitis may result in gangrenous mastitis and septic shock. Depending on the severity of the condition, the litter may stay with the bitch or has to be separated and hand reared.

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248.5.4 Miscellaneous Disorders

248.5.4.1 Puerperal Tetany

An acute decrease in extracellular calcium concentration is the cause of puerperal tetany (eclampsia). Eclampsia occurs most commonly in dogs of the small breeds, usually within the first 21 days after whelping, but occasionally during late pregnancy or at parturition. Early signs are restlessness, panting, pacing, whining, salivation, tremors, and stiffness. The symptoms aggravate to clonic-tonic muscle spasms, fever, tachycardia, miosis, seizures, and death. Treatment must be instigated immediately and consists of slow intravenous infusion of a 10% calcium borogluconate solution. The dose required varies depending on the degree of hypocalcemia and the size of the bitch. Careful cardiac monitoring for bradycardia and

arrhythmias is important. If arrhythmia or vomiting occurs, the infusion must be temporarily halted and then, if necessary, resumed at a slower rate. Because hypoglycemia may follow hypocalcemia, the intravenous administration of a 10% dextrose solution is recommended. The puppies should be removed from the bitch and hand fed a canine milk replacer for 24 hours. If the litter is 4 weeks old or more, it is advisable to wean them. Oral supplementation of the lactating bitch having experienced eclampsia with calcium carbonate at 100 mg/kg body weight per day, divided with meals, and vitamin D is recommended. Prophylactic calcium treatment during the course of pregnancy of bitches expected to develop eclampsia probably is contraindicated, because it may cause a disturbance of the calcium homeostasis.

248.5.4.2 Disturbances in Maternal Behavior

Maternal behavior involves hereditary factors, several hormones (e.g., estrogens, progesterone, oxytocin, and prolactin), previous experiences as a mother, and the stimulus of the neonate. Good maternal behavior includes nest building, nursing, and protecting. The period during which the bitch will form a bond with a pup is probably less than 24 hours. The bitch should spend most of the time with the litter for at least the first 2 weeks. Most bitches have strong maternal instincts, but their behavior depends strongly upon their hormonal balance, general health, and the environment. In some breeds a higher occurrence of bad mothering exists, and in other species several genes for maternal behavior have been identified. Sublimation (i.e., close emotional attachment to a human) may cause problems at parturition, when the bitch may manifest panic and reject her pups.[21] On the contrary, a bitch may resent human intervention, not accepting assisted birthing and cesarean-delivered offspring, and may sometimes even kill them. Major disturbing factors during and after parturition, mental instability, or pain may cause the mother to kill her neonates. Hypocalcemia should always be ruled out in cases of aggression in lactating bitches. Good health, quiet and familiar surroundings, and most important of all, presence of her young will promote normal maternal behavior.

248.6 REFERENCES

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249 CHAPTER • 249 Early Spay and Neuter

Margaret V. Root Kustritz

Prepuberal gonadectomy is castration or ovariohysterectomy of puppies or kittens 6 to 14 weeks of age. Performance of neutering of dogs and cats at the more traditional age of 6 months usually also occurs before puberty, so the term *early spay and neuter* is perhaps more correct. Early spay and neuter surgeries have been performed at humane organizations and universities in at least 17 states for as many as 13 years. The procedure is approved by many major veterinary professional and humane organizations, including the American Veterinary Medical Association.[1]

Surgical neutering of young puppies and kittens is of greatest advantage to humane organizations, because it circumvents the problem of noncompliance by adopters with spay and neuter agreements after adoption. It also permits placement of neutered animals while they are still young enough to benefit from socialization in the new home. Breeders may also benefit from the procedure, which allows placement of neutered pet-quality puppies and kittens while still young, precluding indiscriminate breeding of animals that do not meet the breed standard or that carry hereditary disorders.

In one survey, 57% of humane shelters surveyed could not provide young puppies and kittens that already had been neutered because of unavailability of a veterinarian to perform the surgeries.[2] In 1998 only 48% of 29 North American veterinary colleges responding to a survey reported teaching early spay and neuter surgeries to their students despite 90% having a working relationship with a local humane organization.[2] Students polled at a university after completing a rotation in which early spay and neuter surgeries were performed stated that performance of early spay and neuter surgeries increased their confidence in performing pediatric surgery and anesthesia in general.[3]

Pediatric anesthesia is complicated by the immature physiology and small body mass of the animals.[4] Hypothermia occurs readily in puppies and kittens. Fluids used for surgical preparation should be warm and water based as opposed to alcohol based. The animal should be maintained on a circulating warm-water pad, and anesthesia and surgery time should be minimized to prevent heat loss. Intravenous fluids to be administered intraoperatively also should be warmed.

Hypoglycemia occurs more readily in pediatric than in adult animals because of reduced glycogen stores in skeletal muscle and liver and slower rates of hepatic gluconeogenesis and glycogenolysis. Pediatric animals should be fasted for no more than 3 to 4 hours before anesthesia is induced. Dextrose may be provided in the intravenous fluids intraoperatively.

Pharmacokinetics of drugs administered are altered by immature pediatric renal and hepatic physiology, which do not approach adult levels until the animal is 12 to 14 weeks of age.[4] The overall effect of these physiologic changes is increased availability of anesthetic agents for a longer period of time due to decreased metabolization and slower rate of excretion; drug doses may need to be reduced in pediatric animals.

Anesthetic equipment should be of a size that minimizes resistance and dead space.[5,6] Masks should be tight fitting. Monitoring of anesthesia involves close observation of heart and respiratory rates. Pediatric animals cannot respond to hypoxia with increased stroke volume and do not respond readily to increased concentrations of carbon dioxide in blood with an increase in respiratory rate.[7]

Several anesthetic protocols for early spay and neuter of puppies and kittens have been reported. The optimal reported protocols, defined as those that minimized induction and recovery times and provided the smoothest induction and recovery and best depth of sedation, are listed in Table 249-1.[5,6]

Surgical procedures are as in older animals.[5,8,9] This is an elective procedure and should only be performed on those animals that are in good health, are free of internal and external parasites, and are vaccinated. General principles of surgery on pediatric animals should be observed. These include gentle tissue handling, decreasing surgery time to minimize intraoperative hypothermia, and maintaining meticulous hemostasis.

Castration in puppies is performed as in adult dogs. Both testes are removed through a single prescrotal incision. Both a *closed technique*, in which the tunic containing the spermatic cord and vessels are left intact, and an *open technique*, in which the tunic is opened, have been described.[5,9] Fine absorbable suture or hemostatic clips may be used for ligation of the spermatic cord and vessels. Closure is routine. Either subcuticular closure with absorbable suture or external interrupted or continuous nonabsorbable sutures may be used; external skin sutures have not been reported to bother puppies castrated prepuberally unless they are too tight.[9] Some reports exist of tissue glue used for skin closure after early spay and neuter surgeries, but this is not reported to work well in puppies.

Table • 249-1 Optimal Anesthetic Regimens for Early Spay and Neuter Surgeries in Puppies and Kittens*

	PUPPIES		KITTENS	
Males	Premed	Atropine (0.04 mg/kg IM) +oxymorphone (0.22 mg/kg IM)	Premed	—
	Induction	Propofol (6.5 mg/kg IV)	Induction	Tiletamine/zolazepam (11 mg/kg IM)
	Inhalant	Isoflurane as needed	Inhalant	Isoflurane as needed
Females	Premed	Atropine (0.04 mg/kg IM) +oxymorphone (0.11 mg/kg IV)	Premed	—
	Induction	Propofol (4.3 mg/kg IV)	Induction	Ketamine HCl (11 mg/kg IM) +midazolam (0.22 mg/kg IM)
	Inhalant	Isoflurane	Inhalant	Isoflurane

* From Faggella AM, Aronsohn MG: Evaluation of anesthetic protocols for neutering 6-to 14-week-old pups. J Am Vet Med Assoc 205:308–314, 1994; Faggella AM, Aronsohn MG: Anesthetic techniques for neutering 6-to 14-week-old kittens. J Am Vet Med Assoc 202:56–62, 1993.

Castration in kittens is performed as in adult cats.[6] Bilateral scrotal incisions are made. Both *closed techniques*, in which the spermatic cord and vessels within the tunic were either ligated or tied on itself, and an *open technique*, in which the spermatic cord and vessels were tied to each other, have been described. The scrotal incisions are left open to heal by second intention.

Ovariohysterectomy of puppies and kittens is as in adult animals. Serous fluid in the abdominal cavity is a not infrequent finding and is not associated with any known pathology.[5,8] Use of ovariohysterectomy (Snook) hooks is not recommended.[9] Carmalt clamps, with ridges perpendicular to the tissue enclosed within them, may be preferred to mosquito clamps for compression of the small ovarian vessels and uterine body.[7] Fine absorbable suture material or hemostatic clips may be used for ligation of the ovarian vessels and uterine body. Closure is routine. Subcuticular or external sutures may be used for closure of the skin.

Surgery time should be shorter for early spay and neuter surgeries than for similar surgery in older animals.[10] The animals recover quickly from anesthesia and should be fed a small meal as soon as possible to prevent hypoglycemia. Postoperative pain can be controlled by administration of butorphanol (0.11 to 0.22 mg/kg intravenously, intramuscularly, or subcutaneously);[10] most animals do not require postoperative pain management. External skin sutures can be removed in 10 to 14 days.

It is recommended that all puppies and kittens gonadectomized prior to 16 weeks of age be tattooed to prevent unnecessary surgical exploration to verify intact status later in life. Tattoos are recommended to be 1/2 to 3/4 inches in diameter, and should be placed in the prepubic area of females and the inguinal area of males; the preferred figure is the “male” or “female” symbol with an *x* across it (Figure 249-1).

A growing body of veterinary literature supports the safety of early spay and neuter surgeries. Short-and long-term complications hypothesized to occur include increased anesthetic and surgical morbidity and mortality, increased prevalence of infectious disease, obesity, stunting of growth, increased incidence of feline lower urinary tract disease, behavioral problems, and estrogen-responsive urinary incontinence. 1668 1669

Figure 249-1 Tattoo symbols recommended for placement in the prepubic area of female puppies and kittens and inguinal area of male puppies and kittens after early spay and neuter.

Short-term complications of anesthesia and surgery do not occur more commonly in animals neutered when young compared with those neutered when older. One study evaluating short-term effects of ovariohysterectomy and castration in 1213 dogs and 775 cats on which surgery was performed at less than 12 weeks, 12 to 24 weeks, or more than 24 weeks of age demonstrated that the short-term complication rate was highest in the group neutered at more than 24 weeks of age.[10]

Long-term complications of neutering also are not more common in animals undergoing early spay or neuter than in those animals neutered at more traditional ages, with the possible exception of predisposition to infectious disease in puppies.[11,12] In one study, incidence of parvovirus was higher in dogs neutered at less than 24 weeks of age compared with those neutered at more than 24 weeks of age.[12] This may have been due to the shelter from which the dogs originated, which had an overall higher incidence of parvovirus in young dogs than the other shelters in that study.

Obesity is a multifactorial problem. Retrospective studies have identified neutering as a risk factor for development of obesity. However, a study in dogs did not demonstrate an increase in body weight, food intake, or depth of back fat in those animals gonadectomized either at 7 weeks or 7 months of age, compared with those left intact.[13] That study was concluded when the animals were 15 months of age; predisposition to obesity may have become evident in the neutered animals at an older age. In cats, those neutered at either 7 weeks or 7 months of age had higher body weights and body condition scores and a larger falciform fat pad than did those left intact when evaluated at 24 months of age.[14,15] Metabolic rate has been demonstrated to be decreased in gonadectomized cats, regardless of age at time of surgery.[16]

Stunting of growth does not occur in animals gonadectomized when quite young. Closure of physeal plates is delayed in puppies and kittens gonadectomized at any time prior to puberty with subsequent increase in bone length.[13,14,17] Some question whether the delay in physeal closure may predispose these animals to growth plate fractures; no such correlation has been demonstrated.[18]

Feline lower urinary tract disease (FLUTD) has not been demonstrated to be more prevalent in cats gonadectomized when young. Urethral diameter is not significantly smaller or larger in male or female cats gonadectomized at either 7 weeks or 7 months of age, compared with intact cats at 22 to 24 months of age.[14,19]

Behavior problems have not been demonstrated to be more prevalent in animals gonadectomized when quite young. In addition, these animals are not less likely to be retained in homes after adoption than animals gonadectomized when older.[11,12,20] Service dogs neutered at 7 weeks of age are equally likely as dogs neutered at 7 months of age to be successfully trained and placed.[21]

Estrogen-responsive urinary incontinence has not been demonstrated to occur more commonly in animals gonadectomized when young. Estrogen-responsive urinary incontinence is, in fact, less commonly seen within 3 years of surgery in female dogs ovariohysterectomized before their first estrus than in female dogs ovariohysterectomized after their first estrus, with incidences of 9.7% and 20.1%, respectively.[22,23]

Early spay and neuter surgeries are safe and easy to perform. Performance of early spay and neuter surgeries allows veterinarians to sharpen their general skills regarding pediatric anesthesia and surgery and to provide a service to the humane organizations in their community and to the community at large.

249.1 REFERENCES

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250 CHAPTER • 250 Contraception and Pregnancy Termination in the Dog and Cat

Bruce E. Eilts

Contraception, or the prevention of pregnancy or estrus, is one of the most frequent requests made to veterinarians. Most often that request is for ovariohysterectomy (OHE), or spay, in the female or neutering (castration) in the male, which results in permanent sterilization. In addition to OHE, a permanent sterilization method is ovariectomy. Temporary estrus prevention has been achieved using several different drugs such as megestrol acetate, mibolerone, and testosterone. Immunologic methods to induce permanent or temporary sterility have been investigated but are not yet perfected. Often a client will request that an unwanted pregnancy be terminated. Pharmaceuticals such as estrogens, prostaglandin, prolactin inhibitors, dexamethasone, antiprogestogens, or combinations thereof have been used successfully in clinical situations to terminate pregnancy (Table 250-1). This chapter will present the most common techniques and drugs, including drug availability and drug cost at the time of writing, that are readily available. Techniques using drugs that are not available or in formulations not readily available in the United States will not be presented.

Table • 250-1 Drugs Used to Induce Pregnancy Termination in the Bitch

DRUG	VET. LABEL	DRUG NAME	MFG.	AVAILABILITY	UNIT	PACKAGE SIZE	COST/PACK ($)	MG DOSE	DAYS RX	RX/DAY	COST/DOSE ($)	COST/TREATMENT ($)	HOSPITAL	REF
Estradiol cypionate	Yes	ECP	Pfizer	US	2 mg/cc	50 cc bottle	22.66	0.044	1	1	0.099	0.099	No	11
Bromocriptine—oral only?		Parlodel	Geneva	US	2.5 mg tab	30 tab	26.45	0.0622	4	2	0.21	1.75	No	23
Cabergoline—oral only?		Dostinex	Pfizer	US	0.5 mg tab	8 tab/pack	148.57	0.005	7	1	1.857	12.99		24
Cloprostenol	Yes	Estrumate	Schering	US	250 µg/mL	20 mL	14.98	0.025	5	1	0.79	3.95	Yes	20
Dexamethasone		Various	Various	US	6 mg tab	100 tab	2.59	0.22	10	2	0.007	0.14	No	35
Mifepristone (RU 486)		Mifeprix	Danco	US	200 mg tab	3 tab/pack	1.350	2.5	1	1	56.25	56.25	No	29
Prostaglandin $PGF_2\alpha$	Yes	Lutalyse	Pfizer	US	5 mg/mL	30 mL	8.79	0.25	9	3	0.145	3.91	Yes	15
Tamoxifen		Taxol	Bristol Meyers	US	10 mg tab	60 tab	59.17	1	10	2	0.99	19.80	No	14
Epostane				Great Britain								0		
Aglepristone		Alizene	Virbac	France	5 mg/mL			100		21				

Tab, Tablet; Hospital, Hospitalization required; Ref, Reference; Vet. Label, Veterinary Label Available; Availability Unit, then the drug is packaged.

250.1 CANINE

250.1.1 Permanent Sterilization

250.1.1.1 Female

The most common contraceptive techniques in the dog are OHE for the female and neutering for the male. Advantages of OHE include permanent sterilization and prevention of estrual behavior, no remaining reproductive tract to incur future pathology, reduced incidence of mammary neoplasia in females, and decreased incidence of some prostatic disease in the male. Disadvantages include permanent sterilization, potential anesthetic complications (4.1% during OHE[1]), intra-and postoperative surgical complications

(7.3% for OHE[2]), pathology of reproductive tract remnants, urinary incontinence in the female, and obesity. Clients should be advised about side effects such as obesity and urinary incontinence. Although more females become obese after surgical sterilization than males, the causes of obesity are many and cannot be attributed solely to gonadectomy. Urinary incontinence exacerbated by low estrogen is a common side effect of gonadectomy in the bitch. The exact cause is unknown. The advantages and disadvantages of early spay and neuter are covered in Chapter 249. Although OHE is the most common technique used for permanent female sterilization in the United States, it has been shown that the long-term side effects associated with only performing ovariectomy are no different than when OHE is performed.[3,4] The advantages of performing ovariectomy include shorter surgery time, a smaller incision, and less abdominal trauma. Perhaps North American veterinarians should contemplate the advantages of ovariectomy over OHE. Tubal ligation, although rendering a female sterile, will not alleviate estrus and its associated unwanted behavior or reduce the incidence of mammary neoplasia.

250.1.1.2 Male

Neutering males is the most common technique available to consistently render males permanently sterile. Performing a vasectomy is uncommon. An attempt at intratesticular injections of glycerol to render males permanently sterile was not successful.[5] An intratesticular injection of zinc gluconate neutralized with arginine is now marketed as Neutersol. The company claims 99.6% effectiveness (with the need for anesthesia in only about 24% of dogs) when administered to puppies 2 to 10 months of age.[6]

250.2 TEMPORARY CONTRACEPTIVE TECHNIQUES

Before temporary contraceptive drugs are used, the client should be advised that only valuable breeding dogs should be left reproductively intact. Most dogs should have gonadectomies performed to sterilize them and remove sexual behavior. The most commonly available drugs to prevent estrus or pregnancy are megestrol acetate, mibolerone, and testosterone. Megestrol acetate has been marketed as Ovaban. To prevent estrus, the clinician should administer 0.5 mg/kg for 32 days starting at least 1 week before the next anticipated estrous cycle. The manufacturer approves a maximum of 32 days treatment. The next estrus will be in 4 to 5 months if estrus was imminent. If given during diestrus (for example, the client did not know the estrual stage) the next estrous cycle will occur at the regularly anticipated time. To stop estrus when the bitch is in the first 3 days of proestrus, the manufacturer recommends administering 2 mg/kg/day for 8 days. The next estrous cycle will be 4 to 6 weeks earlier than it normally would have been. It is recommended that the drug not be used during the first estrous cycle and that not more than two consecutive estrous cycles be suppressed. Side effects include increased appetite, weight gain, and (uncommonly) pyometra or mammary neoplasia. However, the drug is contraindicated in bitches with mammary neoplasia, diabetes mellitus, liver disease, uterine disease, or pregnancy. Apparently, it has no effect on post-treatment fertility. Ironically, the drug is not approved for breeding bitches.

Mibolerone was marketed as Cheque drops and is an androgen that blocks LH release, therefore preventing estrus. It is advised not to administer it before the first estrous cycle, because it will cause premature physeal closure. Treatment must be started at least 30 days before the next anticipated estrous cycle at an oral dose of 30 µg/day for dogs 0.5 to 12 kg, 60 µg/day for dogs 12 to 30 kg, 120 µg/day for dogs 25 to 50 kg, and 120 µg/day for dogs greater than 50 kg or German shepherd dogs. The manufacturer has approved administration for a maximum of 24 months, but the drug has been administered experimentally as long as 43 months without apparently causing problems. The next estrous cycle after stopping treatment will reportedly occur in 7 to 200 days (i.e., unpredictable) with normal fertility. If pregnancy does occur during treatment, any female pups will be masculinized. Side effects of mibolereone include clitoral hypertrophy, vaginal discharge, vaginitis,

aggressiveness, anal gland inspissations, musky body odor, and epiphora. It is also not recommended for breeding bitches.

Many Greyhound breeders may use testosterone to suppress estrus. Orally, methyl testosterone at 5 mg/wk (or divided, two times/wk) or parenteral testosterone propionate at a dose of 25 mg intramuscularly in the pectorals every 2 weeks prevents estrus. Clitoral hypertrophy or vaginal discharge may be side effects.

Many experimental methods such as antibody formation against GnRH[7] to prevent estrus or antibody formation against conception specific zona pellucida antigens[8] have been investigated; however, none have been consistently successful and none have been marketed.

Nothing that is effective for causing temporary infertility in the male is available. However, administration of leuprolide acetate (a GnRH agonist that down-regulates LH and therefore lowers testosterone concentrations) at a single dose of 1.0 mg/kg subcutaneously suppressed sperm production in 8 weeks and then persisted for 6 weeks.[9] The effects did reverse, leaving the hope that a drug may be available to cause temporary sterility in males.

250.3 PREGNANCY TERMINATION

250.3.1 Bitch

Only valued breeding animals should have pregnancy terminated in an effort to preserve future fertility. All other dogs should have an OHE performed to end the pregnancy. Drugs that can be administered during estrus to prevent pregnancy include estrogens and tamoxifen. If a request for pregnancy termination is made for a valued breeding animal, it must be decided if the bitch was actually in estrus and mated. A vaginal cytology examination will quickly determine if the bitch is in estrus. If the vaginal cytology slide is 90% to 100% cornified, the bitch is in estrus; and if the vaginal cytology slide does not contain cornified cells, the bitch is not in estrus (the bitch may have progressed into diestrus). Mating can be confirmed by the presence of sperm cells in the vaginal cytology; however, if no sperm cells are present in the vaginal cytology it cannot be assumed that the bitch was not mated. Sperm cells normally are not evident more than 24 hours after mating when doing routine vaginal cytology examinations. All bitches mated within 24 hours of obtaining a vaginal smear had sperm heads in the sample, and 75% that were mated within 48 hours had sperm heads when the vaginal cytology was prepared in the following manner.[10] A cotton swab moistened with saline is placed in the vagina for 1 minute, and then the tip of the swab is placed in a small tube containing 0.5 mL saline for 10 minutes. After 10 minutes the swab tip is squeezed dry into the tube and the fluid in the tube is centrifuged at 2000 × g for 10 minutes. The sediment is then stained using the same technique as a vaginal cytology.

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Few alternatives exist if the client insists on a therapeutic procedure being performed when the bitch is in estrus before a pregnancy examination is performed. The only true mismate drugs available for this time period are the estrogens. The estrogens commonly used for mismate include estradiol cypionate (ECP), estradiol benzoate, and diethylstilbestrol (DES). The administration of DES is not effective as a mismate therapy.[11] Estradiol benzoate when administered at 0.01 mg/kg intramuscularly at 3 and 5 days (and occasionally 7 days) after mating in 358 bitches resulted in 16 (4.5%) of the bitches actually whelping.[12] None of the bitches had bone marrow aplasia reported, but there was a 7.3% incidence of pyometra reported (the "normal" incidence was reported to be 2% to 10% in the study).[12] Using ECP at a dose of 44 µg/kg one time during estrus resulted in no (0/4) bitches becoming pregnant, no pyometras, and no evidence of aplastic

anemia at 25 days after treatment.[11] Estrogens must only be used during cytologic estrus and the owner must be warned of potential side effects. If estrogens are administered during diestrus by mistake, or because it is assumed that one must wait 3 to 5 days after mating for administration, then the potential for inducing a pyometra rises considerably.[11] Reports of infertility after estrogen administration[13] are not documented, and in practice situations it is common to see a bitch become pregnant again during the next estrus.

The only other drug that can be used at the time of mismate presentation is tamoxifen citrate (Taxol, Bristol-Meyers, Squibb, New York, NY.). Tamoxifen citrate is normally considered to be an antiestrogen, but in dogs it has estrogenic activity. It has been administered at a dose of 1 mg/kg orally twice a day for 10 days starting either in proestrus, estrus, or the second, fifteenth, and thirtieth days of diestrus.[14] The drug had a 100% (12/12) efficacy for preventing pregnancy when administration began before the fifteenth day of diestrus, but when administered on the fifteenth day of diestrus or later it was not effective at preventing pregnancy. Side effects of the drug included pyometra, endometritis, and cystic ovaries when administered during all stages of the estrous cycle except early diestrus. Half (2/4) of the bitches receiving the drug during proestrus developed pyometra.[14] Because of the poor efficacy and side effects, tamoxifen citrate has not been widely used or accepted as a mismate drug in the dog.

If the client decides to pursue alternative therapies other than OHE or estrogens, it is important to have a pregnancy examination performed before instituting therapy, because 38% of bitches presented for elective pregnancy termination may not actually be pregnant.[15] The pregnancy examination should be performed at least 30 to 40 days after the possible breeding to minimize a false-negative diagnosis caused by an error in calculating the gestation duration from a mating that occurred early in estrus. Pregnancy diagnosis with ultrasound is reliable 25 days after the LH peak (19 days after the first day of diestrus). If a bitch is truly not pregnant, the expense, side effects, and any potential risks associated with pregnancy termination therapy can be avoided (albeit the expense of the pregnancy examination will be incurred). If the bitch is pregnant, the owners may elect to allow the bitch to have that litter and avoid any complications associated with pregnancy termination.

The most common therapies to terminate pregnancy rely on luteal demise, because the bitch requires an ovarian luteal progesterone source to maintain pregnancy. Luteolysis results in a decline in serum progesterone and when serum progesterone drops below 2 ng/mL for 24 hours, abortion occurs.[15] Many clinicians[15–18] have shown prostaglandins to be luteolytic in the bitch. The most common prostaglandin is the natural prostaglandin ($PGF_{2\alpha}$; Lutalyse, Pfizer, New York, NY). A single dose of prostaglandin will not result in luteolysis in the dog. Side effects of prostaglandin therapy include vomiting and diarrhea, but these only last about 30 minutes and tend to wane as the treatment protocol continues. However, it is recommended by some authors that bitches should be hospitalized for the duration of the treatment[19] or for at least 30 minutes after each treatment. To minimize caloric loss it is best to feed the bitches at least 1 hour after treatment so that the food is not vomited and lost on a daily basis. The natural $PGF_{2\alpha}$ is given at a dose of 0.1 to 0.25 mg/kg administered subcutaneously two to three times a day. A protocol found to have the fewest side effects is $PGF_{2\alpha}$ administered at a dose of 0.1 mg/kg subcutaneously every 8 hours for 2 days and then 0.2 mg/kg subcutaneously every 8 hours until abortion is complete.[15] Abortion is usually complete within 9 days,[15] but some bitches will abort fetuses and still have live fetuses after 9 days. It is extremely important to continue the treatments until abortion is complete and to use ultrasound examination to ensure that all the fetuses are expelled. Bitches have had normal litters after abortion with $PGF_{2\alpha}$.[19] The main drawbacks to using $PGF_{2\alpha}$ are the side effects and the duration of treatment. Prostaglandins have not been approved for inducing abortion in the bitch, so it is important to obtain client consent and forewarn them of the potential complications,

prolonged treatments, and need for multiple abdominal ultrasound examinations that need to be performed. Because of the side effects of the natural prostaglandins, potent synthetic prostaglandins, with fewer side effects, were developed.

Synthetic prostaglandins have also been used to induce abortion in the bitch. Synthetic prostaglandins available for the bovine include cloprostenol, fluprostenol, and alfaprostol. These synthetic prostaglandins have a much greater affinity for the prostaglandin receptors and have a longer half-life than natural prostaglandins. The synthetic prostaglandins also cause fewer smooth muscle contractions, therefore reducing side effects. It is important to note that the dose of the synthetic prostaglandins is much lower than that of the natural prostaglandin and that an error in dose calculation may be fatal. Cloprostenol has been used at a dose of 1 to 2.5 µg/kg subcutaneously once daily for 4 to 5 days and was 100% effective at inducing abortion after a 4 to 7-day treatment regimen.[20] The once-daily treatments of cloprostenol provide an advantage over treatments with natural prostaglandin, which are required every 8 hours. At the low dose of 1 µg/kg, the side effects of cloprostenol were noted to be minimal to none.[20]

In an attempt to alleviate any side effects associated with prostaglandin administration, other drugs have been added to the treatment regime. These include atropine sulphate at a dose of 0.025 mg/kg, prifinium bromide at a dose of 0.1 mL/kg, and metopimazine at a subcutaneous dose of 0.5 mg/kg.[21] Administration 15 minutes before a 2.5 µ/kg dose of cloprostenol given every 48 hours for three doses prevented side effects in 58% (39/67) of the bitches.[21] After one cloprostenol treatment, 53 of the 67 bitches had aborted, and after a second treatment 2 days later, 62 of the 67 bitches had aborted.

Other drugs that cause serum progesterone to decline are the dopaminergic drugs, which are prolactin inhibitors. Because prolactin is luteotropic during the second half of gestation,[22] lowering the prolactin concentration will cause luteal demise and result in a pregnancy loss. Prolactin inhibitors currently available include bromocriptine (Parlodel, Sandaz, Bloomfield, CO) and cabergoline (Dostinex, Pfizer, New York, NY).

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Bromocriptine administered orally at a dose of 62.5 µg/kg twice daily to dogs at 43 to 45 days postovulation resulted in only two of four bitches aborting.[23] Side effects included two episodes of emesis in three of the bitches approximately 3 hours after treatment. Loose stools were also noted. Bromocriptine tabs can be crushed and dissolved in oil to ease dosing (because the compound is inactivated by water). Bromocriptine as a sole abortifacient does not appear to be a good choice in the bitch. It is more commonly used in combination with a prostaglandin product.

Cabergoline administered after 40 days of gestation at 60 µg orally once daily, given to a 32 kg German shepherd dog, resulted in abortion after 7 days with no side effects.[24] In contrast to Europe, only an oral 0.5 mg tablet of cabergoline is available in the United States. Cabergoline may be difficult to administer because the tablets are 0.5 mg and the dose for a 10 kg dog is only 0.05 mg. An oral solution, much like that done with bromocriptine, could be formulated. Expense may be a factor with this drug.

250.4 COMBINED STUDIES

In an effort to reduce the side effects and increase the efficacy of prostaglandins and prolactin inhibitors, a combination of the two has been used.[25] Cloprostenol at 1.0 or 2.5 µg/kg/day injected subcutaneously in combination with cabergoline at a dose of 1.65 µg/kg/day subcutaneously daily for 5 days from midgestation was 100% effective (5/5), and side effects were less severe than with cloprostenol alone. In the group treated with the low dose, no adverse side effects were noted.[25]

Oral cabergoline at a dose of 5 μg/kg/day given until 2 days after fetal death (mean: 9 days) combined with cloprostenol at a dose of 1 μ/kg every other day until fetal death (mean: 3 injections) starting at 25 days after the LH peak resulted in 100% (5/5) of bitches resorbing fetuses.[26] Fetal death was documented with ultrasound. There were no side effects of treatment when the cabergoline was administered 1 hour after the cloprostenol, but the bitches did have a serosanguineous discharge that lasted an average of 16 days. Combinations of cabergoline, bromocriptine, and cloprostenol have been used[26] and include treatments of cabergoline administered orally for 10 days at a dose of 5 μg/kg combined with a single subcutaneous injection of 2.5 μg/kg cloprostenol at the start of the treatment; cabergoline administered orally for 10 days at a dose of 5 μg/kg combined with two subcutaneous doses of 1 μg/kg cloprostenol administered on the twenty-eighth and thirty-second day after the LH surge; bromocriptine administered orally at a dose of 30 μg/kg three times a day for 10 days plus a single subcutaneous dose of 2.5 μg/kg cloprostenol; bromocriptine at a dose of 30 μg/kg three times a day for 10 days plus two doses of 1 μg/kg cloprostenol. These combinations were administered to groups of five bitches starting at 28 days after the LH surge, and treatment was successful at inducing fetal resorption without overt abortion in all bitches except one that was administered the cabergoline and 1 μg/kg cloprostenol on the twenty-eighth and thirty-second day after the LH surge. Some bitches that resorbed litters had red cells, neutrophils, and cellular debris in the vaginal cytology smears for 4 to 21 days after treatment. All treated bitches did become pregnant on the subsequent estrous cycle, which occurred sooner than normally anticipated. The side effects of treatment included those commonly seen with prostaglandin when the high dose of cloprostenol was used, but the signs were not seen when the lower dose of cloprostenol was administered.[26] Using either a combination of increasing amounts of bromocriptine mesylate (15 to 30 μg/kg orally, every 12 hours) and dinoprost tromethamine (0.1 to 0.2 mg/kg subcutaneously, every 24 hours), or bromocriptine mesylate (15 to 30 μg/kg orally, every 12 hours) and cloprostenol sodium (1 μg/kg subcutaneously every 48 hours) resulted in 100% success in inducing abortion in 25 bitches.[27] Side effects included pseudopregnancy and a mucoid sanguineous vulvar discharge for 3 to 10 days.

In an attempt to shorten the treatment period required to induce abortion with $PGF_{2\alpha}$, combination therapy with injectable $PGF_{2\alpha}$ and intravaginal PGE1 (misoprostol) has been used.[28] Prostaglandin was administered at a dose of 0.1 mg/kg subcutaneously three times a day for 2 days and then at a dose of 0.2 mg/kg subcutaneously three times a day to effect. Misoprostol (Cytotec, Pharmacia, Peapack, New Jersey) was administered at a dose of 1 to 3 μg/kg, deposited into the cranial vaginal vault once daily using a cat pilling device. The mean time to complete abortion in nine bitches using this combination was 5 days, as compared with a mean of 7 days previously reported for complete abortion induced with $PGF_{2\alpha}$ as a sole agent.

250.5 OTHER DRUGS

Drugs that have been investigated but are not commonly used to induce abortion in practice situations include isoquinolones, progesterone receptor antagonists, progesterone synthesis inhibitors, and progesterone blockers. The antiprogesterone compound mifepristone (Mifeprix, Danco, New York, NY), more commonly known as RU 486 or RU 38486 for its use in preventing human pregnancies, works by preventing the progesterone binding to uterine progesterone receptors and therefore preventing the action of progesterone from occurring. Oral administration of mifepristone at a dose 2.5 mg/kg twice daily for 4.5 days starting at the thirty-second day of gestation resulted in 100% (5/5) of the bitches having a decline in progesterone 2 days after treatment started and pregnancy loss with no side effects around 3 days after treatment initiation.[29] Four pregnancies were terminated in bitches that were at 35 to 39 days gestation using oral mifepristone.[30] Doses as low as 8.3 mg/kg and up to 20 mg/kg were administered orally for one or two treatments and abortion occurred within 2 to 11 days.[30]

Mifepristone is available as a 200 mg tablet in the United States but is not labeled to terminate pregnancy in the bitch. Expense may be a factor.

Aglepristone (Alizine) is another progesterone blocker that is available in France, Norway, and Sweden but not the United States to terminate pregnancy in the bitch. Two doses of 10 mg/kg given subcutaneously 24 hours apart from day zero to the twenty-fifth day or on the twenty-sixth day to the forty-fifth day after mating caused uncomplicated abortions within 7 days in 100% (35/35) and 95.7% (66/69) of bitches, respectively.[31] If the bitch was in midpregnancy, a brown mucoid vaginal discharge was seen 24 hours before fetal expulsion. Other side effects included slight depression, transitory anorexia, and mammary gland congestion. A clinical trial using 124 bitches had similar effects, and fetal resorption occurred within 7 days with no subsequent reproductive effects noted.[32] In a subsequent study using the same dose at the thirtieth day of gestation, all (5/5) bitches aborted with no apparent side effects other than a slight mucoid discharge 1 week after administration.[33] A single bitch was bred and became pregnant after treatment.

Epostane inhibits steroid synthesis by inhibition of 3β-hydroxysteroid dehydrogenase and Δ5–4 isomerase, thereby preventing progesterone synthesis.[34] Epostane was 100% (23/23) effective at preventing whelping (compared with a 100% whelping rate for controls) when administered orally for 7 days at doses of 50 or 300 mg (given to beagle bitches weighing about 10 kg) starting the first day of diestrus.[34] No side effects were seen, and subsequent fertility was not affected because 94.8% (127/134) of all the bitches treated conceived on the next estrous cycle.[34] Epostane is not available in the United States.

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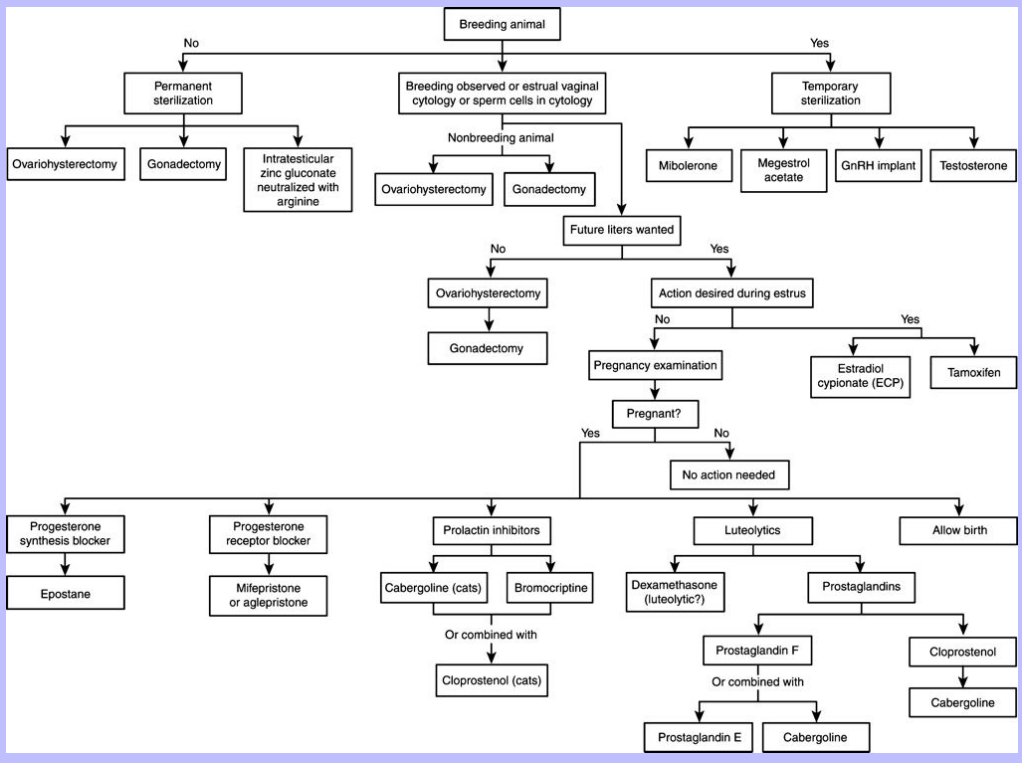
Figure 250-1 Algorithm for breeding.



250.6 DEXAMETHASONE

Two recent studies have been done using two different dose regimens of oral dexamethasone from 30 to 50 days of gestation.[35,36] The most effective dose regimen was the administration of oral dexamethasone using a 10-day dose schedule as follows: 0.2 mg/kg twice a day for 7 days, 0.16 mg/kg in the morning of the eighth day, 0.12 mg/kg in the evening of the eighth day, 0.08 mg/kg in the morning of the ninth day, 0.04 mg/kg in the evening of the ninth day, and 0.02 mg/kg the morning of the tenth day. A 10-day dose regimen was more effective than a shorter 7.5-day dose regimen in terminating pregnancies. At the author's institution a dose of 0.2 mg/kg twice a day for 10 days is used, with no tapering of the dose. The author and colleagues have observed no more than the anticipated side effects from not tapering the dose.

The initial fetal deaths with dexamethasone treatment were 5 to 9 days after initiation of the treatment; however, live fetuses were seen as long as 8 to 12 days after treatment started.[35] Pregnancies less than 40 days of gestation generally had no fetuses expelled, and the majority had no external signs of pregnancy loss.[36,35] A mild vaginal discharge was seen in only about 20% (26/75) of the bitches that resorbed fetuses. Abortion or resorption was generally complete 10 to 23 days after the treatment was initiated.[35] It is imperative that the pregnancy be re-examined with ultrasound and the drug continued until fetal death is noted. The treatment may fail if a treatment regimen is followed without checking for fetal loss. Although the exact mechanism of action is not known, dexamethasone may have a luteolytic effect. In the few bitches that had progesterone measured, the progesterone concentration fell to less than 1 ng/mL by the fourth day after treatment was initiated. If the initial treatment fails, a second treatment regimen may cause abortion, but most bitches treated a second time carried puppies to term.[35] Clinical failures have occurred using the recommended 10-day dose regimen. In the case of clinical failure, it may be advisable to treat with prostaglandin.

The main side effects of dexamethasone treatment include polydipsia and polyuria.[36,35] The polydipsia and polyuria usually began around 2 to 3 days after treatment started and were maximal 4 to 5 days later. The side effects generally subsided 3 to 4 days after the termination of treatment. Polydipsia and polyuria are not serious side effects but may be undesirable for dogs housed indoors in colder climates.

Successful pregnancies were obtained in 18 of 20 bitches bred during the first estrus after treatment and 2 of 2 on the second estrus. Therefore dexamethasone treatment appears to have no deleterious effects on future pregnancies and oral dexamethasone appears to be a safe, efficacious abortifacient in the bitch. Because dexamethasone is so readily available, inexpensive, has relatively minor side effects reported, does not require hospitalization, and is effective, it is the method recommended. Although not the ideal drug, it offers the most advantages of the ideal mismate drug when compared with all the other products available.

250.7 QUEEN

250.7.1 Permanent Sterilization

The same techniques applied to the canine can be applied to the feline, however much less information is available on the effects of OHE or ovariectomy on the queen. Toms are most commonly castrated; however, interest in sterilizing feral cats has led to some research on baited oral contraceptives. No intratesticular injections are approved for cats.

250.7.2 Termination of Pregnancy

The request for mismating or aborting queens is not common. Many of the same drugs can be used for mismate in cats as are used in dogs; however, the list is not nearly as inclusive. Pregnancy in the cat has similar aspects as the dog, in that the ovaries and corpora lutea are needed throughout pregnancy. Any drug altering luteal function will cause a queen to abort. The same strategy for determining pregnancy and the value of OHE can be used in the queen as in the bitch. The following drugs have been investigated for mismate in the queen.

250.7.3 Estrogen

Estrogen can be used shortly after copulation if an unwanted breeding was observed. Estradiol cypionate at a dose of 250 μg intramuscularly administered 6 days after coitus retarded embryo transport in the oviduct and also retarded ova development.[37] A single dose of 0.125 to 0.25 mg/cat of ECP given intramuscularly 40 hours after coitus has been suggested as an effective mismating regimen; however, no data is available on its efficacy.[38] Administration of ECP has the same potentially serious side effects in the queen as in the bitch (such as pyometra or aplastic anemia); however, the incidence is apparently less than the low incidence seen in the bitch.

250.7.4 Prostaglandin

Recent research investigating the period in gestation at which prostaglandin is most successful at inducing abortion in the queen confirmed that greater than or equal to 40 days appears to be a critical time for effectiveness.[39] Prostaglandin administration at doses associated with acceptable side effects before that time does not induce luteolysis. Despite the apparent resistance to abortion seen in other studies before the fortieth day of gestation, daily administration of 2 mg/cat $PGF_{2\alpha}$ subcutaneously for 5 days resulted in 100% (3/3) abortion when administered from the thirty-third day after mating.[40] However, queens exhibited nausea, vomiting, diarrhea, and prostration starting 10 minutes after treatment and continuing for an hour. All queens aborted fetuses within 6 days. This success before the fortieth day of gestation may be related to the timing of gestation from coitus. It is more difficult to measure the exact length of gestation in the queen compared with the dog, because estrus lasts about 8 days, regardless of the day of coitus. A subcutaneous dose of 0.2 mg/kg $PGF_{2\alpha}$ given twice the first day, followed by 0.5 mg/kg twice daily for up to 5 days was given to four queens at 30 days of gestation and four queens at 45 days of gestation.[39] One of four queens at 30 days aborted, whereas 75% (3/4) of queens at 45 days aborted. Queens that aborted had progesterone values less than 1.0 ng/mL, therefore verifying the eventual luteolytic effect of the prostaglandin.

250.7.5 Prolactin Inhibitors

Oral cabergoline at a dose of 5 to 15 μg/kg administered to feral cats 36 to 40 days of pregnancy for 4 to 9 days caused abortion in all (41/41) queens.[41] Combinations of prolactin inhibitors and prostaglandin have also been used to terminate pregnancy in the queen.[42] Cabergoline was administered orally at a daily dose of 5 μg/kg, and cloprostenol was administered subcutaneously every 2 days at a dose of 5 μg/kg starting at the thirtieth day after coitus. All (5/5) queens aborted after an average of 9 days of treatments. No side effects were seen, and queens that were bred subsequently became pregnant.

250.8 SUMMARY

Managing a mismate or pregnancy termination must be discussed with the client. Not using drugs and performing an OHE is usually the best alternative. If drugs are to be used, their use must be discussed with the client regarding safety, efficacy, convenience, compliance in treatment, side effects, and cost. As with most treatment regimens, familiarity with one treatment sometimes overrides using a superior method. It is therefore important to be aware of the most current literature available regarding protocols.

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251 CHAPTER • 251 Cystic Endometrial Hyperplasia and Pyometra

Margaret V. Root Kustritz

251.1 INTRODUCTION

Pyometra is a chronic disease process with acute manifestation most commonly observed during the luteal phase of the estrous cycle, within 8 weeks of standing heat or ovulation induction.[1,2] Pyometra (from Greek, literally, "pus in the uterus") occurs when bacteria colonize a uterus with progressive hormone-mediated cystic hyperplasia of the endometrium. An inflammatory component is present, but the term *pyometra* is preferred to other published terms including pyometritis, catarrhal endometritis, and chronic cystic endometritis.[2–4] At no time should pyometra be confused with postpartum metritis.[2,5]

Incidence of pyometra in dogs and cats in the United States is poorly described, largely because the majority of bitches and queens are spayed relatively early in life in the United States. Many fewer bitches and queens undergo elective ovariohysterectomy (OHE) in European countries. It was reported in a Swedish study that 23% to 24% of bitches develop pyometra by 10 years of age.[6]

251.2 PATHOGENESIS

Pyometra has a two-step pathogenesis. The primary insult is development of cystic endometrial hyperplasia (CEH). The secondary insult is bacterial infection. A recent publication attempting to separate pyometra from CEH was unable to demonstrate independent development of the two entities in clinically ill bitches.[7]

CEH is a hormone-dependent change that develops after repeated estrous cycles in the bitch or queen. This histopathologic change can be induced experimentally with administration of either estrogen or progesterone, with progesterone having a greater effect.[8–10] Experimentally, the condition develops most quickly if progesterone is administered after priming with estrogen, as occurs during the spontaneous estrous cycle in bitches and in queens induced to ovulate.[10] Dogs that develop pyometra have not been demonstrated to have higher endogenous serum progesterone concentrations than normal dogs.[11] However, the normal down-regulation of estrogen receptors in the presence of rising serum progesterone concentrations may not occur in dogs with CEH-pyometra.[12,13] The progesterone-dominated uterus is more susceptible to proliferative and inflammatory changes, as has been demonstrated in studies in which uterine biopsies, scarification of the endometrium, or infusion of bacteria from bitches with pyometra into the uterus of healthy bitches were performed during the luteal phase.[14–17]

Another hormone that may be involved is insulin-like growth factor I (IGF-I). It has been demonstrated that the number of receptors for mitogenic IGF-I is higher in the uterus of bitches with pyometra than in normal bitches.[18] Serum concentration of prostaglandin metabolites also has been demonstrated to be elevated in bitches with pyometra; significance of this is unknown.[19]

Cats are considered to be induced (reflex) ovulators. However, a relatively high incidence of uterine disease in cats housed alone or with no exposure to an intact tom cat has promoted research that has documented apparent

spontaneous ovulation to occur in as many as 39% to 40% of queens.[20–22] A tentative diagnosis of pyometra should not be discounted in queens with no known history of coitus.

Administration of exogenous hormones, especially estrogens (diethylstilbestrol [DES], estradiol cypionate [ECP]) and progestins (megestrol acetate, medroxyprogesterone acetate), may hasten development of CEH and subsequent pyometra in bitches and queens.[18,23,24] In one study of eight dogs with CEH-pyometra at the uncommonly young age of less than 3 years, six of eight had received exogenous ECP or megestrol acetate in the previous 6 months.[24]

Secondary bacterial infection is the next step in the pathogenesis of pyometra in bitches and queens. CEH can occur independent of infection or may be associated with formation of sterile intrauterine fluid (hydrometra or mucometra).[25,26] The most common bacterial organism isolated from the infected uterus of bitches and queens is *Escherichia coli*.[4,15,20,27] The biotype of *E. coli* associated with pyometra in a given bitch or queen has been identified to be virtually identical in most cases to that animal's biotype of fecal *E. coli*.[28,29] Other organisms that may be isolated include *Staphylococcus* spp., *Streptococcus* spp., *Proteus mirabilis*, and *Pseudomonas aeruginosa*.[4]

The development of pyometra in bitches and queens transpires thus: (1) development of CEH over repeated cycles; (2) movement of normal vaginal bacterial flora into the uterus during proestrus and estrus[30]; (3) functional closure of the cervix, decreased myometrial contractility, and increased secretory activity of uterine glands during the progesterone-dominated luteal phase; (4) colonization and overgrowth of coliform bacteria or other organisms with secondary endotoxemia (in coliform infections) and renal disease. Studies[15,31] have shown bitches with pyometra to be predisposed to lymphopenia and decreased lymphocyte function, as well as to neutrophil damage with subsequent decrease in phagocytic capacity of PMNs.

Conditions that may develop subsequent to pyometra include septic shock and renal failure. Lipopolysaccharide endotoxins released from the cell wall of Gram negative organisms stimulate release of cytokines, such as tumor necrosis factor (TNF), interleukins (Ils), and platelet activating factor (PAF), which cause vasodilation and subsequent decreased intravascular volume and tissue perfusion.[32] Cardiac arrhythmias may occur in animals with septic shock.[33] Hypoglycemia and hepatocellular damage commonly occur secondary to septicemia.[33]

Renal dysfunction secondary to pyometra is due to decreased renal tubular concentrating ability as the result of endotoxemia and possibly to glomerular changes.[3] Mild tubulointerstitial nephritis and other renal tubular changes have been reported to occur in as many as 38% of bitches with pyometra.[34] Glomerular filtration rate (GFR) has been demonstrated to be decreased in up to 75% of bitches with pyometra and azotemia; glomerular lesions were not demonstrated by histopathology in that study.[35] Other studies have reported glomerulonephritis development secondary to deposition of antigen and antibody complexes in the glomeruli.[2] Renal disease secondary to pyometra usually reverses with successful treatment for pyometra.

251.3 SIGNALMENT AND HISTORY

CEH develops after repeated cycles, so CEH-pyometra is usually a disease of older bitches and queens. CEH with minimal to no inflammatory component has been demonstrated to occur at an average age of 7.2 years in bitches.[9] Reported mean age at time of development of pyometra in bitches is 7.8 years, with a reported range of

1 to 15 years and a reported majority in bitches over 6 years of age.[4,24,36,37] Mean age at time of diagnosis of pyometra in queens is 5.3 years, with a majority of cases occurring in queens aged 5 to 6 years or more.[21,24,28]

Reported risk factors include breed, parity, and body condition. Breeds described to be at increased risk in two studies are the golden retriever, rough collie, rottweiler, and Cavalier King Charles spaniel.[6,37] Mongrels are at decreased risk.[37] In several studies, nulliparous animals have been described to be at increased risk of developing CEH-pyometra.[21,37] However, in queens, no correlation was noted between likelihood of developing pyometra and age at first breeding, or occurrence of breeding or queening.[38] One survey in bitches reported that less than 50% of bitches with pyometra were nulliparous.[23] Anecdotal reports suggest that pyometra may be more likely to occur in middle-aged to old queens that are morbidly obese than in older queens with normal body condition.[39]

Bitches with a history of false pregnancy (pseudocyesis) are not at increased risk for development of pyometra. Serum progesterone concentrations do not differ between normal bitches, bitches with a history of false pregnancy, and bitches with pyometra.[11] In a survey of dogs with pyometra compared with age-matched controls, the dogs with pyometra were significantly less likely to have a history of false pregnancy.[36]

Pyometra is usually diagnosed during the luteal (progesterone-dominated) phase of the estrous cycle. Reported mean interval from the last known standing heat in dogs to onset of clinical signs of pyometra is 7.1 weeks, with a range of zero to 15 weeks.[1,4,9,24,40] Reported mean interval from the last known heat in queens to onset of clinical signs of pyometra is 3.8 weeks.[24]

251.4 CLINICAL SIGNS

Dogs and cats with uncomplicated CEH or presence of sterile intrauterine fluid (hydrometra or mucometra) may be asymptomatic.[25,26,38] Clinical signs in bitches and queens with pyometra vary depending on patency of the cervix. As might be expected, cervical patency (open cervix pyometra) is associated with presence of vulvar discharge, and cervical impatency (closed cervix pyometra) is more commonly associated with abdominal distension (Table 251-1). Vulvar discharge is usually purulent; it is creamy, red-brown to green in color, and foul smelling. Onset of clinical signs may be acute or gradual; in general, more severe clinical signs are associated with cervical impatency.[5,9]

251.5 DIAGNOSIS

Definitive diagnosis of pyometra requires demonstration of presence of purulent fluid within the uterus. A tentative diagnosis is made by demonstration of uterine enlargement in a nonpregnant bitch or queen and usually is associated with clinical signs and physical examination findings of systemic disease and hematologic changes. A complete work-up for dogs and cats with possible pyometra includes a physical examination; radiography or ultrasonography of the abdomen; a complete blood count (CBC), serum chemistry profile and urinalysis; urine culture; and possibly measurement of progesterone in serum. Ancillary tests are performed as needed (e.g., culture of free abdominal fluid in pets with possible peritonitis and a coagulation profile in animals with overtly hemorrhagic discharge).

Physical examination findings often are unremarkable in dogs and cats with uncomplicated CEH. Severity of physical examination findings generally is greater in animals with closed cervix pyometra than in those with

open cervix pyometra. Uterine enlargement may or may not be palpable (Table 251-2). Caution must be used when palpating a potentially friable distended uterus in any animal with possible pyometra.

Table • 251-1 Reported Mean Prevalence of Clinical Signs in Bitches and Queens with Pyometra

	BITCHES (%)	QUEENS (%)
Purulent vulvar discharge	87	59
Lethargy	72	32
Anorexia	73	40
Abdominal distension	—	17
Polyuria/polydipsia (PU/PD)	28	9
Vomiting	36	16
Diarrhea	27	—

From Hardy RM, Osborne CA: Canine pyometra:pathophysiology, diagnosis and treatment of uterine and extra-uterine lesions. J Am Anim Hosp Assoc 10:245–268, 1974; Wheaton LG et al:Results and complications of surgical treatment of pyometra:a review of 80 cases. J Am Anim Hosp Assoc 25:563–568, 1989; Kenney KJ et al: Pyometra in cats:183 cases (1979–1984). J Am Vet Med Assoc 191:11301132, 1987.

Table • 251-2 Reported Prevalence of Physical Examination Findings in Bitches and Queens with Pyometra

	BITCHES (%)	QUEENS (%)
Palpable uterine enlargement	31–40	68
Purulent vulvar discharge	75	39
Dehydration	15–28	33
Fever (>102.5° F)	41–43	20
Hypothermia (<100.0° F)	3	—

From Hardy RM, Osborne CA: Canine pyometra: pathophysiology, diagnosis and treatment of uterine and extra-uterine lesions. J Am Anim Hosp Assoc 10:245–268, 1974; Wheaton LG et al: Results and complications of surgical treatment of pyometra:a review of 80 cases. J Am Anim Hosp Assoc 25:563–568, 1989; Kenney KJ et al: Pyometra in cats: 183 cases (1979–1984). J Am Vet Med Assoc 191:1130–1132, 1987.

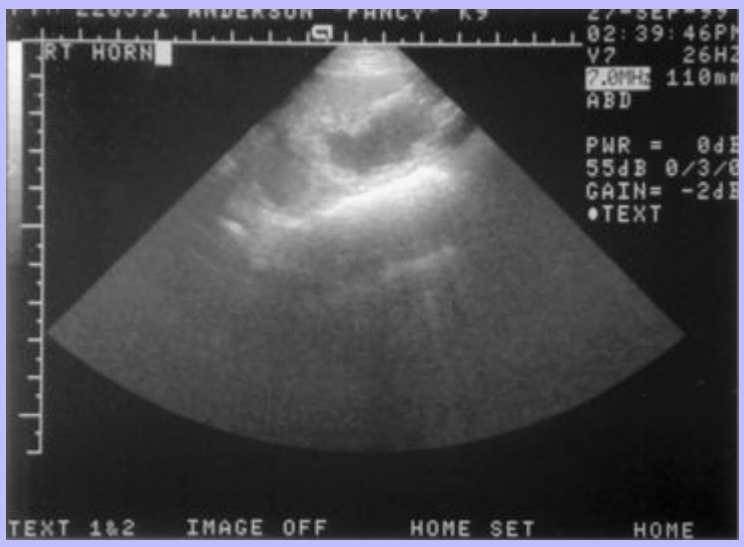
Cervical patency is inferred from presence or absence of vulvar discharge. A narrow diameter endoscope may be passed the length of the vagina to attempt to see the cervix but usually it is only the appearance of fluid moving into the cranial vagina that allows one to state that the cervix is functionally open.[30]

Nonreproductive abnormalities that may be detected by physical examination in dogs and cats with pyometra include dehydration, which occurs secondary to renal disease, fever, and anorexia; fever due to infection; hypothermia due to septicemia or shock; and abdominal pain, which may be evident in animals with uterine distension or peritonitis due to leakage of purulent material from the uterus (see Table 251-2).[4,24,27,41]

Uterine enlargement that cannot be assessed by physical examination may be detected by abdominal radiography or ultrasonography. Pyometra occurs during diestrus; radiographic demonstration of uterine enlargement prior to 42 to 45 days postestrus may not allow differentiation of pyometra from pregnancy. Abdominal ultrasound is a more definitive diagnostic technique. Ultrasonographically, CEH appears as a fluffy, irregular, mottled thickening of the endometrium on uterine horns viewed in cross-section (Figure 251-1). CEH may not be visible in animals with distension of the uterine horns caused by large volumes of intrauterine fluid. Fluid-filled uterine horns are observed without difficulty in dogs and cats with pyometra and can readily be differen-tiated from pregnancy by 24 to 25 days postbreeding (Figure 251-2).[2,42]

Hematologic changes reported in dogs and cats with pyometra include changes in white blood cell (WBC) number and anemia. Leukocytosis, often to greater than 30,000 cells/μL, is reported to occur in 62% to 68% of dogs and 66% of cats with pyometra.[24,27,31] A regenerative left shift and monocytosis may accompany the leukocytosis. These changes are characteristic of a suppurative and exudative inflammatory process such as pyometra.[43] Lymphopenia is reported to occur in 8% to 35% of dogs and 5% of cats with pyometra.[24,27,31] Anemia of chronic infection is reported to occur in 25% of dogs and 4% of cats with pyometra.[24,27,43] Thrombocytopenia is rarely reported in dogs with pyometra and may be a component of disseminated intravascular coagulation (DIC).[43] Erythrocyte sedimentation rate is reported to be elevated in bitches with pyometra compared with normal diestrual bitches; usefulness of this change as a diagnostic test is equivocal.[44]

Figure 251-1 Ultrasound image of cystic endometrial hyperplasia (CEH) in a bitch. Reader should note the fluffy, mottled lining of the uterine wall on cross section.



No changes are seen in the serum chemistry profile that are pathognomonic of pyometra in dogs and cats.[44] Azotemia due to dehydration and possible renal dysfunction is reported to occur in 18% to 26% of dogs and 12% of cats with pyometra.[4,27,35] Other changes that are present commonly include hyperproteinemia and increased alkaline phosphatase (ALP) and alanine transaminase (ALT).[2,27]

Urinalysis findings are suggestive of secondary renal disease. Proteinuria may or may not be present, regardless of presence of azotemia.[4,35] Urine specific gravity (USG) varies with hydration status and presence of polyuria due to renal disease subsequent to endotoxemia; in one study of 27 dogs with pyometra, 89% had USG less than 1.035.[35] In that same study, 22% of the dogs had concurrent urinary tract infection.[35]

Increases in serum progesterone concentration promote quiescence of the myometrium and may decrease efficacy of medical therapy. Although dogs and cats generally have clinical signs of pyometra while in diestrus,

16% to 38% of bitches and 20% of queens have been reported to have serum progesterone concentrations of less than 1 ng/mL at the time of diagnosis.[15,20,40] This may be due to release of endogenous prostaglandin from the diseased endometrium with subsequent luteolysis. Knowledge of serum progesterone concentration may alter course of treatment.

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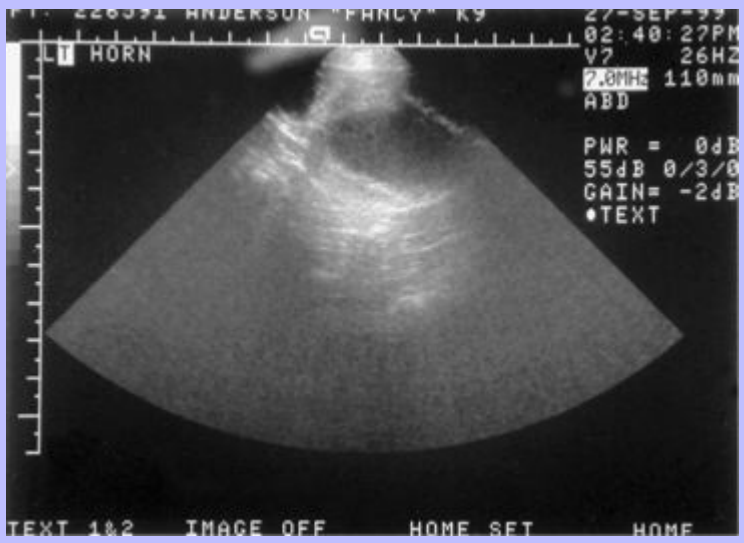
Figure 251-2 Ultrasound image of pyometra in a bitch. Reader should note the uterine horns distended with fluid.



251.6 TREATMENT

OHE is the best treatment of pyometra in dogs and cats. The underlying pathologic change, CEH, cannot be reversed with medical therapy. All animals with CEH are predisposed to pyometra after each subsequent estrus. Recurrence of secondary infection has been demonstrated to occur commonly with the biotype of organism that was causative of pyometra historically in a given animal, suggesting that medical therapy does not clear infection in all cases but rather decreases infection to a subclinical level.[45]

Complete OHE is always recommended. Caution must be used when handling the friable, distended uterus. Ovariectomy alone is reported to cause resolution of clinical signs of pyometra in dogs in 5 to 15 days.[9] This response probably is due to an iatrogenic decrease in serum progesterone concentration and is not a quick enough response to provide relief for critically ill animals.

Other surgical therapies reported involve placement of in-dwelling catheters transcervically to allow flushing of the uterus with antiseptic compounds or mucolytic agents.[4,46] Success with such techniques is not well described, and this mode of therapy is not recommended.

Medical therapy for pyometra is most appropriate for dogs and cats with a patent cervix. Medical therapy for animals with closed cervix pyometra has been reported.[23,43,47] Administration of ecbolic agents cause uterine contractions that propel purulent fluid against the internal cervical os and cause cervical dilation. However, in one survey of 30 dogs with pyometra, 13% had positive bacterial cultures of abdominal swabs despite lack of

uterine rupture, suggesting leakage of purulent material through the friable uterine wall or via the uterine tubes.[15] All reported cases of salpingitis (uterine tube inflammation) in dogs were in bitches with pyometra.[2] Finally, with no clear knowledge of viability of uterine tissue, it is impossible to know whether causing uterine contractions may not cause uterine rupture. For these reasons, medical therapy for animals with closed cervix pyometra is not recommended.

All dogs and cats with pyometra, whether treated by OHE or medically, must be treated with antibiotics. An appropriate antibiotic choice is made based on culture and sensitivity testing of vulvar discharge or intrauterine content at the time of OHE. Good empiric choices for use while culture results are pending are ampicillin (22 mg/kg per os three times daily) and amoxicillin-clavulanate (14 mg/kg per os two times daily). Antibiotics should be administered for 2 to 4 weeks after OHE and until vulvar discharge is no longer evident in those animals treated medically. The bacterial infection of pyometra may be difficult to eradicate because of inability of antibiotics to diffuse into the pool of intrauterine fluid and possibly because of spontaneous formation of a glycocalyx biofilm that may bind antibiotics, again preventing ability of the antibacterial agent to reach embedded bacterial cells.[46]

Medical therapy for dogs and cats with pyometra can be considered if (1) the cervix is open, evidenced by presence of vulvar discharge; (2) the animal is still of breeding age, generally 6 years of age or less for dogs and 8 years of age or less for cats; (3) the animal is a valuable component of a breeding program; and (4) no evidence exists of renal disease or other sequelae to the pyometra. The effect of medical therapy may not be evident for up to 48 hours after initiation of treatment.[5] The author feels it is unethical to prolong the animal's suffering unnecessarily if secondary disease is present.

Antibiotic therapy alone will not affect a cure in dogs and cats with pyometra. An ecbolic agent, which causes uterine contractions and promotes expulsion of the purulent fluid, must be administered concurrently. The best-described ecbolic agent for use in treatment of pyometra in small animals is prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). $PGF_{2\alpha}$ causes uterine contractions when administered once or twice daily and causes luteolysis when given twice daily. Because most animals with pyometra are in diestrus and may have increased serum progesterone concentrations, it may be beneficial to measure serum progesterone concentrations to determine if administration of luteolytic doses of $PGF_{2\alpha}$ is required. Prostaglandins cannot effect luteolysis in the first 5 days of diestrus in dogs at any dose and are not as effective a luteolytic agent in cats as in dogs. Analogues of $PGF_{2\alpha}$ such as cloprostenol, also are ecbolic and luteolytic in dogs and cats, but all doses described here refer to the native compound and should not be used with analogues.

$PGF_{2\alpha}$ is administered subcutaneously, at doses of 0.1 to 0.25 mg/kg.[23,47,48] Some authors recommend a gradual increase in dose over the first 48 to 72 hours of treatment to minimize side effects.[48] The lower end of the dose range generally is recommended for treatment of queens. Infusion of $PGF_{2\alpha}$ into the vaginal lumen also has been described in dogs.[49] $PGF_{2\alpha}$ is administered until the uterus nears normal size, as determined by abdominal palpation, radiography, or ultrasonography. In most cases, less than 7 days of treatment are required.[47]

Side effects of $PGF_{2\alpha}$ are referable to its causing contractions of the gastrointestinal (GI) tract and include hypersalivation, vomiting, and diarrhea. Queens may exhibit excessive grooming and restlessness. Side effects generally occur within 5 to 15 minutes of drug administration, subside within 30 to 60 minutes, and usually lessen in severity with each subsequent injection. The clinician can minimize side effects by using lower doses of $PGF_{2\alpha}$, by diluting the volume of $PGF_{2\alpha}$to be given with normal saline before administration, and by walking

dogs after it is given. Concurrent administration of atropine (500 mg/kg intramuscularly) also may be beneficial.[2] $PGF_{2\alpha}$ is not approved for treatment of pyometra in dogs and cats in the United States.

Progesterone receptor blockers, for example mifepristone and aglepristone, are reported to be efficacious for treatment of pyometra in dogs and cats, with minimal side effects.[50–52] These drugs are not available for veterinary use in the United States. Other compounds described for treatment of pyometra, none of which are recommended, include estrogen, androgens, oxytocin, and ergot alkaloid derivatives.[9,48]

Ancillary supportive therapy to be used includes intravenous fluid therapy and maintenance of normal body temperature. Other ancillary treatments reported for treatment of pyometra in dogs and cats include use of hypertonic saline with 60% dextran to combat septic shock and promote renal blood flow, use of hemoglobin glutamer-200 to enhance tissue delivery of oxygen in animals with poor oxygenation secondary to shock, and treatment with equine-derived antibodies against endotoxin to combat renal disease due to endotoxemia.[32,53,54]

At the subsequent estrus, a sample should be collected from as far forward in the vagina as possible early in proestrus (bitches) or estrus (queens), and appropriate antibiotic therapy should be administered for at least the duration of proestrus and estrus while the cervix is open and the uterus is vulnerable to infection with bacteria ascending from the vagina. Antibiotic therapy is recommended even if the bitch or queen will not be bred during that estrus. Because fertility is compromised and because the bitch or queen still has CEH and a predisposition to pyometra, she should be bred and all desired offspring obtained as quickly as is feasible. The dog or cat should then be spayed as soon as her breeding life is over or if pyometra recurs.

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251.7 PROGNOSIS

Spontaneous resolution of mild inflammatory changes overlying CEH has been reported to occur subsequent to plasma cell infiltration.[10,55] Animals with pyometra do not recover spontaneously.

Overall reported success rate for treatment of pyometra in dogs ranges from 46% to 100%; reported success rate for treatment of pyometra in one study was 92% in cats.[2] In general, those animals that do not recover have concurrent disease or complications due to sepsis or toxemia.[24]

After medical therapy, reported prevalence of recurrence of pyometra in bitches is 10% to 77% within 27 months of therapy.[2,45] Other reported long-term complications include persistent anestrus, failure to conceive, and spontaneous abortion.[23] In two studies evaluating fertility of bitches after medical treatment for pyometra, reported percentages of dogs bred that went on to whelp were 64% and 87%.[23,48] In the former study, prognosis for future fertility was best in those animals requiring less than 6 days of treatment with $PGF_{2\alpha}$.[23] Prognosis for future fertility generally is better in queens, with a reported queening rate of 90% in those queens bred after medical therapy for pyometra.[2]

251.8 UTERINE STUMP PYOMETRA

Pyometra of the uterine stump occurs rarely in dogs and cats. It is assumed to be associated with remnant ovarian tissue or administration of exogenous estrogen or progestins in most cases, because any remnants of endometrial tissue should be quiescent in the absence of hormonal stimulation. Clinical signs are as described for pyometra in intact animals. Diagnosis is best made by abdominal ultrasound; pyometra of the uterine stump appears as a

cystic mass near the bladder. Diagnosis of ovarian remnants is described in Chapter 247. Treatment includes systemic antibiotic therapy and surgical removal of the uterine stump and ovarian remnants, if any.

251.9 CONCLUSION

CEH is a hormone-mediated gradual change of the uterine lining. Presence of CEH predisposes the uterus to infection; infection overlying CEH with subsequent formation of intrauterine purulent fluid is pyometra. Nulliparous animals may be predisposed; those animals with a history of false pregnancy are not predisposed to pyometra. Diagnosis requires demonstration of uterine enlargement and presence of purulent intrauterine fluid. Neutrophilia with a regenerative left shift and monocytosis often are present. Secondary renal disease may occur subsequent to endotoxemia in dogs and cats with coliform infection. OHE is the treatment of choice in most cases. Medical therapy with $PGF_{2\alpha}$ may be attempted in young, valuable bitches and queens with a patent cervix and no evidence of secondary renal disease.

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252 CHAPTER • 252 Canine Female Infertility

Gary C.W. England

252.1 INTRODUCTION

Over recent years there has been increased awareness of canine female infertility, particularly in dogs bred for working and showing purposes. The true extent of infertility is unknown, although reproductive failure is common. It is with increasing frequency that breeders and managers of breeding colonies approach their veterinarian for help with reproductive problems. In some circumstances reduced fertility may not be fully appreciated because breeding is relatively infrequent when compared with other domestic species. In addition, wide breed variations exist (particularly in litter size) that make it difficult to compare animals of different breeds. Certain breeds appear to have an increased incidence of infertility.

The normal expectation of fertility in the bitch is a whelping rate of 70% to 80% after mating to a male with normal semen quality. Variations from this exist, depending in particular upon the age of the bitch. Average peak reproductive efficiency occurs at approximately 3 years of age, and a significant decline occurs in the number of pups born to bitches aged 7 years and older.[1]

The investigation of infertility is complicated by the fact that fertility problems may be difficult to recognize. Failure to conceive does not result in an immediate return to estrus. Furthermore, pseudopregnancy is a normal physiologic event and, in some bitches that do not whelp, the owner may have confused the signs of pseudopregnancy with pregnancy. However, the early diagnosis of pregnancy is now possible using ultrasonography, the detection of acute-phase proteins in serum, and the measurement of serum relaxin concentrations. Early pregnancy diagnosis helps allow prompt investigation into why an individual bitch fails to produce live offspring.

As with other species, the causes of infertility may be classified as structural (including congenital, acquired, and neoplastic diseases), functional (including endocrinologic abnormalities), infectious, or managemental. However, what is most helpful to the clinician is the way in which these cases are presented, namely (1) failure to cycle, (2) abnormal estrous cycles, (3) normal estrous cycles with failure of copulation, (4) normal estrous cycles with copulation (distant from ovulation) and conception failure, (5) normal estrous cycles with copulation (close to ovulation) but conception failure, or (6) normal estrous cycles and conception with subsequent pregnancy failure.[2]

252.2 INVESTIGATION OF INFERTILITY

Many cases of “infertility” are caused by a lack of owner understanding of normal canine reproductive physiology. For example, considerable normal variations exist in the onset of puberty between animals and in the timing of ovulation from the onset of proestrus.

The previous breeding history, including parity and litter size, together with information regarding the stud dog, are probably the most important factors (one of the common causes of infertility is related to the male). Additional information concerning the onset of puberty, present cyclicity, general medical history, and the administration of pharmaceutical compounds (steroids in particular) may also be useful. After a full clinical examination to rule out systemic disease, specific examination of the reproductive tract should be performed.

This should include inspection of the external genitalia, palpation of the mammary glands, digital examination of the vestibule and caudal vagina, and transabdominal uterine palpation.

Several other techniques are useful for the investigation of reproductive disease, including exfoliative vaginal cytology, vaginal endoscopy, transcervical collection of uterine cells to evaluate uterine disease, and ultrasound imaging of the ovaries and uterus. Laparoscopy and laparotomy may also be valuable for inspection of the uterus, uterine tubes, and ovaries but are infrequently used due to their invasive nature and the requirement for general anesthesia. Measurement of circulating hormone concentration has a number of indications. It can be used to confirm the presence of gonadal tissue, to detect hormone secreting neoplasms and cystic structures, and for the prediction and confirmation of ovulation.

252.3 CLINICAL PRESENTATIONS OF INFERTILITY

252.3.1 Failure to Cycle

Failure to cycle may be either primary (no estrus activity before 24 months [i.e., delayed puberty]) or secondary (no estrus activity within 12 months of a previous cycle [i.e., prolonged anoestrus]). In most cases a specific disease process may be responsible for this problem, and careful investigation for an underlying cause is important for appropriate treatment and prognosis. Estrus induction may be attempted with either primary or secondary failure when a specific cause has been identified.

252.3.1.1 Delayed Puberty

The age at puberty ranges between 6 and 24 months. Most bitches cycle within 1 to 6 months of attaining adult height and weight, and the age of puberty can be influenced by the breed, body weight, and environmental conditions. In general, bitches that do not reach puberty by 2 years of age are considered to have delayed puberty. It is common for there to be few signs associated with the first estrus and therefore some bitches which are thought to have delayed puberty may have simply had an unobserved estrus. Increased serum progesterone concentrations (> 2.0 ng/mL [6.5 nmol/L]) demonstrates that ovulation has occurred within the last 60 days (i.e., the estrus has been missed).

Investigation of delayed puberty involves collection of information on housing and diet (because poor environmental conditions and nutrition may be associated with failure to cycle) and a thorough clinical examination to rule out chronic debilitating disease.

An underlying chromosomal abnormality may also cause delayed puberty. Many of these bitches are phenotypically abnormal (having a small cranially positioned vulva and developing clitoral enlargement at puberty). A smaller propor-tion of bitches are phenotypically normal but have an abnormal complement of sex chromosomes that results in ovarian hypoplasia or ovarian dysgenesis. Establishing a karyotype usually demonstrates chromosomal abnormalities such as 77XO, 79XXX, 79XXY, and 78XX/78XY.[3] In normal bitches with no underlying disease, estrus induction can be attempted as described later.

252.3.1.2 Prolonged Anestrus

The average interestrus interval is 31 weeks; although some variation occurs around this mean value, this has no apparent effect on fertility. Certain breeds, for example the Basenji, cycle only once per year. The reason for these variations is unclear. Prolonged anestrus represents an interestrus interval greater than

anticipated for that particular animal (usually more than 12 months from the previous cycle). Failure of normal reproductive cyclicity has several causes. A common problem is the failure of observation of the signs of estrus, particularly in kenneled bitches. This may occur in fastidious bitches, which quickly remove any vulval discharge, or when the discharge is scant. Serum progesterone concentrations greater than 2.0 ng/mL (6.5 nmol/L) indicate a missed estrus and ovulation within the previous 2 months.

Initial investigations should include a thorough history and examination for chronic systemic disease and evaluation of the general body condition. Important factors in the history are any indications of chronic disease and any previous or concurrent treatments or medication. Drug-induced anestrus should be considered when the interestral interval is prolonged; pharmaceutical preparations that have the ability to prevent estrus include glucocorticoids, anabolic steroids, androgens, and progestogens. Investigation of thyroid function may also be useful because some evidence indicates a relationship between thyroid hormone insufficiency and abnormalities of the estrous cycle. Hypothyroidism has been associated with prolonged anestrus and infertility. The mechanism of this abnormality has not been fully established; however, prolactin is released after the injection of thyrotropin-releasing hormone (TRH). Therefore factors that affect endogenous TRH release probably affect prolactin and thyroid function. Low concentrations of serum thyroid hormones and failure to respond to a stimulation test may be used to confirm the condition, although clinically these animals usually have typical clinical signs associated with hypothyroidism. After replacement therapy most bitches return to estrus within 6 months. Interestingly however, hypothyroidism in greyhounds was not shown to be related to poor reproductive function[4] and a consistent relationship between thyroid disease and reproductive function has yet to be established. When no underlying disease is present, estrus induction may be attempted.

Progesterone-producing ovarian cysts have been described in the bitch, producing prolonged interestrus intervals and cystic endometrial hyperplasia. Ovarian cysts may be identified ultrasonographically and the diagnosis confirmed by serial measurement of serum progesterone concentrations. Medical treatment has not been successful, and usually the cystic ovary needs to be surgically removed. These cysts should not be confused with cysts originating from the ovarian bursa that are of no significance.

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In some cases, ovarian neoplasms that produce either progesterone or androgens result in a failure to return to cyclical activity. Such tumors are rare and are usually associated with chronic wasting and an abdominal mass effect with ascites. Treatment is surgical removal.

Some bitches have normal cyclical activity, including follicular growth and ovulation, without obvious external signs of proestrus or estrus. This is often called *silent estrus* (silent heat) and is common in certain breeds, greyhounds for example. The condition may be the reason the owner overlooks the signs of estrus. Ovulation may be confirmed by measurement of serum progesterone concentration as described previously. Alternatively, the weekly examination of exfoliative vaginal cytology will allow anticipation and monitoring of estrus.

Premature ovarian failure has been suggested as a rare but permanent cause of anestrus in previously normal bitches.[5] For an accurate diagnosis of these cases, investigation of the karyotype and measurement of serum concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid hormone should be undertaken.[3] In valuable breeding animals, estrus induction regimens may be contemplated; however, no information is available concerning the efficacy of these treatments in animals with premature ovarian failure.

252.3.1.3 Induction of Estrus

Estrus-induction may be attempted when no underlying abnormality has been detected in bitches older than 2.5 years with delayed puberty or in bitches with prolonged anestrus. A variety of agents may be used for this purpose, including prolactin inhibitors (cabergoline or bromocriptine), equine chorionic gonadotropin (eCG) with human chorionic gonadotropin (hCG), gonadotropin-releasing hormone (GnRH), and estrogens. Unlike other domestic species, it is not possible to induce estrus by shortening the luteal phase using prostaglandins because the luteal phase is followed by a variable, but prolonged, period of anestrus.

The most useful method of estrus induction is the administration of prolactin inhibitors (although these may have a variable effect in bitches with delayed puberty). Prolactin plays a role in the regulation of interestrous intervals, possibly by affecting gonadotropin secretion, ovarian responsiveness to gonadotropins, or both. When prolactin inhibitors are administered daily (cabergoline at 5.0 μg/kg/day) during prolonged anestrus, a rapid return to estrus occurs (usually within 30 days). If treatment is stopped once proestrus has begun, a high pregnancy rate usually occurs that is similar to that seen in natural cycles.

For bitches with delayed puberty it may be necessary to attempt estrus induction using gonadotropins, if the administration of prolactin inhibitors fail. Many protocols have used exogenous gonadotropins for the induction of estrus, and commonly low doses of eCG (20 IU/kg for 5 days) with a single administration of hCG (500 IU/bitch on the fifth day) are recommended.

Although several reports document the value of estrogens and GnRH (either in pulses or the use of a superagonist), such regimes are not commonplace in clinical practice because whelping rates are relatively low.

252.3.2 Abnormal Estrous Cycles

252.3.2.1 Split Estrus

A short interval (2 to 12 weeks later) between clinical signs of estrus is often described as a *split estrus*. This occurs most frequently at the pubertal estrus but can occur at any age. An initial phase of follicular growth and estrogen secretion occur, but the follicles regress and signs of estrus disappear. Subsequently a second follicular phase appears. In some cases this may be repeated several times until finally the bitch ovulates normally. This syndrome is confusing because it may be thought that the bitch has failed to ovulate or that fertilization with subsequent resorption or abortion has occurred. The recognition of split estrus syndrome is important to ensure that mating is achieved at the correct time. In some cases, induction of ovulation may be attempted using hCG, although it can be difficult to be certain at which point to administer this preparation. This is most successful when administered at the peak of vaginal epithelial cell cornification.

252.3.2.2 Ovulation Failure

The frequency of ovulation failure is approximately 1% of estrus cycles,[6] and clinicians commonly make the diagnosis by serial monitoring of serum progesterone concentrations. This condition is likely to have a similar cause to those bitches with split estrus (possibly caused by low concentration of LH or LH

receptor). Attempts to induce ovulation during estrus using 500 IU/kg hCG between 1 day before to 1 day after the first mating may be successful.

252.3.2.3 Prolonged Proestrus or Estrus

The time at which bitches ovulate after the onset of vulval bleeding is very variable. Usually this is between the sixth and twentieth day after proestrus began. For the average bitch, the surge in serum LH occurs on the tenth day; ovulation follows 2 days later. However, many normal bitches do not ovulate at this time, and most bitches with alleged prolonged proestrus are actually at the extremes of normality; they simply ovulate later in the cycle than anticipated. In some, normal ovulation occurs 30 days after the onset of proestrus.

These animals do not require treatment, but careful assessment of the optimum mating time, usually by evaluation of vaginal cytology or measurement of serum progesterone (see later). It is unlikely that the administration of hCG would produce normal ovulation earlier in the cycle; however, little data is available on such use of this agent.

Estrogen-secreting follicular cysts may produce persistent estrus. These bitches may be brought to a veterinarian because of the inconvenience; however, the persistent elevation of serum estrogen can also lead to bone marrow suppression with anemia and thrombocytopenia.

Ultrasonographically large (8 to 12 mm diameter) fluid-filled follicles may be identified. These must be carefully differentiated from normal follicles and early corpora lutea, both of which have central fluid-filled cavities. Some follicular cysts respond to alternate-day administration of hCG on three occasions. Failing this, cysts may respond to progestogen administration using drugs such as megestrol acetate. With the latter an increased risk of pyometra is seen, because the progestogen is administered after a prolonged period of estrogen priming. Ovariectomy may be required if no response to exogenous hormone therapy is seen. Cyst-like structures are frequently identified around the ovaries at routine surgery. These are often parabursal in origin and have no significance on cyclicity or fertility.

252.3.2.4 Ovarian Neoplasia

Ovarian neoplasms are not common in the bitch, accounting for approximately 1.0% of all neoplasms.[7] The mean age of occurrence is 8 years, although some bitches may develop neoplasia as early as 7 months of age. Tumors that release estrogen may produce signs of persistent estrus and bone marrow suppression, although clinical signs are also often related to a mass effect or ascites. Neoplasia may be most effectively diagnosed at ultrasound examination. The tumors may be germ cell, epithelial, or sex-cord stromal in origin. They do not commonly metastasize. Ovariohysterectomy is the treatment of choice; care should be taken not to rupture neoplasms during surgery because metastatic spread is often by transcoelomic seeding. *1682*

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252.3.3 Normal Estrous Cycle with Failure of Copulation

252.3.3.1 Behavioral Problems

Some bitches are frightened and traumatized by attempted breeding and may refuse subsequent mating. Other bitches may be “humanized” or are too familiar with the male and do not exhibit normal estrus behavior. Observation of the bitch at attempted mating should allow identification of typical behavior

patterns that may include marked submission or aggression. Careful management of the virgin bitch is important to ensure that behavioral abnormalities do not become established.

252.3.3.2 Vestibulovaginal and Vestibulovulval Abnormalities

Strictures of the caudal reproductive tract are common. Circular strictures or transverse bands are usually found at the junction of the vestibule and the vagina, although vestibulovulval strictures can also be identified. Vestibulovaginal abnormalities are often first noted during attempted mating when they cause pain or a failure to achieve intromission. Small constrictions and fibrous bands may be manually broken down under general anesthesia when the bitch is in proestrus or estrus. Mating may be allowed later during the same estrus. Surgical exploration via an episiotomy may be required for larger transverse bands.

252.3.3.3 Vaginal Hyperplasia

Vaginal hyperplasia is an accentuated response of the caudal vaginal floor to normal circulating estrogen concentrations. Usually the vaginal mucosa cranial to the external urethral orifice is involved and becomes edematous and thickened. This mass of tissue may result in pain at coitus in some bitches, and in others it may rapidly increase in size and protrude from the vulva preventing coitus. The latter condition is sometimes referred to as a *vaginal prolapse* (correctly, it is a prolapse of hyperplastic vagina). Occasionally the circumference of the vagina and not just the floor may be involved.

In most bitches the mass decreases in size at the end of estrus, therefore conservative management with local cleansing and lubrication are sufficient. Ovariohysterectomy during the subsequent anestrus will prevent recurrence. In bitches that are required for breeding, artificial insemination may be necessary or submucosal surgical resection of the tissue performed during early estrus before mating. A minority of surgically treated cases recur; however, the use of surgery has been questioned because a familial tendency has been reported in certain breeds.[8] Although rare, true prolapse of the nonhyperplastic vagina has been reported during estrus when it also may prevent mating.

252.3.3.4 Congenital Anomalies of the External Genitalia

Hypoplasia of the vulva has been described and may be associated with pain at coitus and often a perivulval dermatitis. Considerable breed variation is seen in the normal vulval anatomy; for example, the greyhound has small external genitalia.

Congenital abnormalities including vulvar atresia and vulvar agenesis are rare, and may cause chronic vaginitis.

252.3.3.5 Vaginal Hypoplasia and Aplasia

Segmental aplasia of the Müllerian duct system may be *partial*, producing vaginal hypoplasia, or *complete*, resulting in vaginal aplasia. The condition is rare and may cause the retention of uterine fluid with signs similar to pyometra. Diagnosis may be made by palpation or positive-contrast radiographic examination of the vagina.

252.3.4 Normal Estrous Cycle with Copulation (Distant from Ovulation) and Conception Failure

The most common reason for failure of conception is inappropriate timing of mating. This is often because mating is planned a set number of days after the onset of proestrus (often the twelfth to the sixteenth day). Although the majority of bitches ovulate between 10 and 14 days after the onset of proestrus, some ovulate as early as the fifth day or as late as the thirtieth day. Therefore should a bitch be mated on the twelfth to the sixteenth day this can be inappropriate and result in failure of conception. A further complication is that bitches are not necessarily consistent in the day on which they ovulate between subsequent estrus cycles. Detecting the time of ovulation is difficult because the behavioral signs of estrus do not always correlate with the changes in peripheral hormones, and often the dog and bitch are not allowed to display normal courtship behavior.

252.3.4.1 Fertilization Period and Fertile Period

Spontaneous ovulation occurs approximately 48 hours after the surge in serum LH. Eggs are released as primary oocytes that must reach the metaphase of the second meiotic division before fertilization can occur. This maturation takes 48 to 60 hours. Oocytes remain fertilizable for a further 2 to 3 days, therefore the time span over which fertilization may occur, termed the *fertilization period*, is between 4 and 7 days after the LH surge (i.e., between 2 and 5 days after ovulation).

Dog sperm can remain viable and fertile within the uterus and uterine tubes for at least 6 days. Therefore it is possible for matings that take place before the fertilization period to result in conception. A second term is therefore used, the fertile period, which encompasses the fertilization period and the time that sperm survive within the female reproductive tract before ovulation and oocyte maturation. The *fertile period* extends from 3 days before until 7 days after the preovulatory LH surge (i.e., between 5 days before and 5 days after ovulation).

The optimal time for mating is during, or immediately preceding, the fertilization period. The period of peak fertility ranges from 1 day before to 5 or 6 days after the LH surge.

252.3.4.2 Determination of the Optimal Time of Mating

252.3.4.2.1 Clinical and management assessments

In laboratory beagles a close association exists between the time of the LH surge and the onset of standing estrus. However, in many breeding bitches a marked variation exists in this relationship, with the LH surge occurring between 3 days before to 9 days after the onset of estrus. Teasing the bitch has little value in determining the fertile period. Assessment of the volume and color of the vaginal discharge is similarly unreliable.

One clinical assessment that may be useful is the timing of vulval softening. During proestrus, the vulva and perineal tissues become enlarged and increasingly turgid in response to increasing estrogen. At the time of the LH surge, serum estrogen concentrations begin decreasing at the same time that serum progesterone concentrations increase. With this change a reduction is seen in edema of the reproductive tract, with the consequence that a distinct softening of the vulva occurs. In cases where only clinical

assessments are available for the determination of the optimum time for breeding, a combination of the onset of standing estrus and the timing of vulval softening may be used. Each of these events occurs on average 1 or 2 days before ovulation. Therefore breeding should be planned commencing on the next day or so for natural mating or commencing 3 days later for preserved semen inseminations.

252.3.4.2.2 Hormone measurement

Measurement of peripheral serum concentrations of LH is a reliable and accurate method of determining the optimum time to mate. However, in many countries it is difficult to obtain reliable LH measures in clinical practice, because enzyme-linked immunosorbent assay (ELISA) kits are not always available. 1683 Serum progesterone concentrations begin to increase toward the end of proestrus at the time of the LH surge. 1684 Luteinizing follicles produce this increase in progesterone; therefore serial monitoring of serum progesterone concentrations allows anticipation of ovulation. Test kits designed to measure progesterone by ELISA are commercially available and have been shown to be useful for predicting the optimum mating time in the bitch. Breeding or insemination should be planned between 4 and 6 days after serum progesterone concentrations exceed 2.0 ng/mL (6.5 nmol/L) (the concentration typically observed at the time of the LH surge). Some reports suggest that breeding should commence 1 day after values exceed 8.0 to 10.0 ng/mL (25.0 to 32.0 nmol/L), which are commonly seen at the beginning of the fertilization period. Progesterone concentration may also be measured in whole blood or vaginal fluid.

252.3.4.2.3 Vaginal cytology

The examination of exfoliative vaginal epithelial cells is frequently used to monitor the estrous cycle. During proestrus, increased serum estrogen concentrations cause thickening of the vaginal mucosa, which becomes a keratinized squamous epithelium. Surface vaginal epithelial cells may be collected using either a moistened swab or by aspiration. The relative proportions of different types of epithelial cells can be used as a marker of the endocrine environment. Several methods for staining of cells and various indices of cornification and keratinization have been suggested. In general, the fertile period can be predicted by calculating the percentage of epithelial cells that appear cornified using a modified Wright-Giemsa stain. Breeding should be attempted throughout the period when more than 80% of epithelial cells are cornified. Although this is a useful guide, some bitches reach peak values of only 60% cornification, and in others there may be two peaks of cornification. Neutrophils are generally absent from the vaginal smear during estrus because the keratinized epithelium is impervious to these cells. Their reappearance during late estrus reflects the breakdown of this epithelium. The return of neutrophils to the vaginal smear has been used by some workers as an indicator of the time of optimum fertility.

Some bitches demonstrate poor cellular changes in the vaginal smear; in some, neutrophils may be found throughout estrus (the extent of these variations has not been quantified). Despite these variations, at the Guide Dogs for the Blind Association in the United Kingdom, mating based on vaginal cytology was found to increase the pregnancy rate and litter size of bitches compared with a similar group mated only based on the onset of proestrus.[9] Whelping rates have been consistently maintained above 90% over a 10-year period since the introduction of this technique.

252.3.4.2.4 Vaginal endoscopy

Endoscopic assessment of the vaginal epithelial contour and profile, mucosal color, and color of any vaginal fluid may be of use for estimating the time of the fertilization period. Enlarged edematous pink

or pinkish-white mucosal folds are present during proestrus and estrus. Progressive shrinking of these folds accompanied by pallor occurs during the preovulatory decline in estrogen. Subsequently, mucosal shrinkage is accompanied by wrinkling of the mucosal folds that become distinctly angulated and dense cream to white in color. These gross changes have been used to assess the fertile period. Jeffcoate and Lindsay[10] proposed a scoring scheme to allow description and recording of the vaginoscopic changes. These clinicians also suggested that vaginoscopy could be used to indicate the end of the fertilization period.

252.3.4.3 Evaluation of Cervicovaginal Secretions

Many workers have reported changes in the nature of the cervicovaginal secretions in relation to the fertile period. These include changes in electrical resistance, glucose concentration, and mucus crystallization patterns. None of these techniques has been subject to detailed validation or widely used in clinical practice.

252.3.5 Normal Estrous Cycle and Copulation (Close to Ovulation) with Conception Failure

252.3.5.1 Infertile Male

An important aspect of infertility is the influence of the male. Poor semen quality can reduce the litter size or result in conception failure. Knowledge of a comprehensive breeding soundness examination of the male is mandatory when investigating a female that might be infertile.

252.3.5.2 Uterine Disease

A common ultrasonographic finding in bitches that fail to become pregnant despite mating to a fertile male during the fertilization period is the presence of cystic endometrial hyperplasia.

Although the exact relationship between this observation and fertility is yet to be proved, the existence of under-lying endometrial disease may contribute to infertility by allowing persistence of commensal bacteria within the uterus (after introduction through the open cervix during estrus) or by interfering with normal placental development. Ultrasonographic detection of cystic endometrial hyperplasia is best achieved during the luteal phase. Cystlike lesions are observed most commonly in middle-aged and elderly bitches and anecdotally may precede the development of later pyometra. Treatment regimes to aid fertility have yet to be fully evaluated.

252.3.5.3 Aplasia of the Tubular Genital Tract

An uncommon cause of infertility is aplasia of one segment of the uterine horn, uterine tube, or both. Frequently this is a unilateral condition that does not influence fertility. Bilateral agenesis is associated with infertility, although the bitch may cycle, ovulate, and mate normally. Diagnosis may be made by positive contrast vagino-uterogram performed during estrus. Laparotomy is a more valuable diagnostic tool.

252.3.6 Normal Estrous Cycle and Copulation with Pregnancy Failure

252.3.6.1 Habitual Abortion

Some clinicians have implicated progesterone deficiency as a cause of repeated abortion in bitches.[11] Despite this contention, the minimum concentration of progesterone in serum required to support the pregnancy is only 2.0 ng/mL.[12] Measurement of progesterone concentration at the time of an abortion often reveals that concentrations are low; however, this is likely to be the result of the abortion rather than the cause of the abortion. Insufficient luteal function has been demonstrated after estrus induction regimens[13] and in one case of oophoritis.[14] Serum progesterone concentrations of bitches with habitual abortion are usually similar to those of normal pregnant bitches. Progesterone or progestogen supplementation during pregnancy may produce masculinized female pups and cryptorchid male pups, and it may possibly impair or delay parturition resulting in fetal death. Progestogen therapy should therefore be restricted to those cases in which a true luteal insufficiency has been diagnosed.

The majority of cases of abortion and resorption may be documented using real-time B-mode ultrasound. In some cases only a single conceptus is lost and the remaining pregnancy continues normally. Most cases of resorption and abortion are related to an abnormal uterine environment (cystic endometrial hyperplasia, see previous discussion), embryonic and fetal defects, or are the result of infectious agents.

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252.3.6.2 Infectious Causes of Pregnancy Loss

252.3.6.2.1 Canine herpesvirus

Canine herpesvirus may cause infertility, abortion, stillbirths, and genital lesions in the bitch.[15] In the pregnant bitch, placental lesions and infection of the fetus occurs. Experimental data suggests that infection during early pregnancy results in fetal death and subsequent mummification, infection during midpregnancy results in abortion, and infection during late pregnancy results in premature birth. The virus has also been recovered from vesicular lesions on the genitalia of bitches, and frequently these lesions are evident at the onset of proestrus, suggesting that venereal transmission is probably important. Viral recrudescence from the vesicular lesions may be stimulated by the stress of pregnancy and parturition. Canine herpes virus infection is becoming increasingly recognized within Europe. As a result of this, a vaccine has recently been licensed for use in breeding animals and is commercially available in France and the United Kingdom.

252.3.6.2.2 Brucella canis

This is the only bacterium known to be a specific cause of infertility in the bitch. Infection can produce abortion and infertility. Between 1.5 and 6.6% of dogs in the USA have antibodies to the organism. Brucella can be transmitted by contact with aborted fetal or placental tissue, contact with the vaginal discharge of infected bitches, venereal transmission or congenital infection.

Abortion occurs most commonly between the forty-fifth and fifty-fifth day of pregnancy; however, there may be embryonic resorption or the birth of stillborn or (more rarely) weak pups. The isolation of the bacterium from blood or aborted tissue is diagnostic of the disease; however, there may be prolonged

periods when the bitch is not bacteremic, and a negative blood culture does not rule out infection. Fortunately, diagnosis using the plate agglutination test for screening and tube agglutination for confirmation is not difficult. Treatment of the condition with a combination of streptomycin and tetracycline is often effective in clinical cases; however, antimicrobial treatment does not remove the organism from tissues. Because a carrier state can occur and these animals may be potential sources of infection, they are best neutered and removed from the breeding program.

252.3.6.2.3 Canine adenovirus

It is well established that infection with canine adenovirus during pregnancy can result in the birth of dead or weak pups that die within a few days after parturition. In most cases, however, the virus is ingested after parturition and causes neonatal mortality. Carrier bitches may act as a source of infection for pups.

252.3.6.2.4 Canine parvovirus

Canine parvovirus has been implicated by some breeders as a cause of infertility in their kennels. However, Meunier and colleagues[16] found that the conception rate, incidence of stillbirths, average litter size, or average number of pups weaned per litter did not change after the introduction of canine parvovirus to a kennel. Canine parvovirus may cause an acute generalized infection in pups less than 2 weeks of age, which can occur as a consequence of uterine infection or as a result of exposure to the virus soon after birth.

252.3.6.2.5 Canine distemper virus

Experimental exposure of pregnant bitches to canine distemper virus may produce either clinical illness in the bitch with subsequent abortion or subclinical infection of the bitch and the birth of clinically affected pups. Although the latter provides evidence for transplacental transmission, the frequency of this under natural conditions is unknown.

252.3.6.2.6 Toxoplasma gondii

Toxoplasma infection of the bitch may cause abortion, premature birth, stillbirth, and neonatal death. Surviving infected pups may carry the infection.

252.3.6.3 Normal Vaginal Bacterial Flora

A widespread belief exists among breeders and veterinarians that certain bacteria that inhabit the reproductive tract of the dog and bitch cause infertility, vaginitis, and fading puppy syndrome. This arose from the work in the 1930s that concluded that streptococci were responsible for infertility, abortion, anestrus, and weak pups. With the advent of virus isolation techniques, several specific viruses have been identified, and it seems likely that the earlier work overemphasized the importance of the streptococci. These bacteria are now considered to be part of the normal commensal flora and probably invade secondarily to viral damage or are contaminants.

Many aerobic and anaerobic bacteria normally inhabit the vestibule and vagina of the healthy bitch, and the bacterial flora is normally mixed. The aerobic bacteria isolated from normal bitches include *Escherichia*

coli, staphylococci, and streptococci, whereas the anaerobic bacteria include *Bacteroides* spp. and *Peptostreptococcus* spp. Mycoplasmas have been isolated from between 30% and 88% of normal bitches.

Several authors have examined the vaginal bacterial flora of normal bitches and compared them with those of infertile bitches. These studies were reviewed by van Duijkeren,[17] who found that the bacterial species cultured from infertile bitches did not differ significantly from healthy bitches. Therefore the results of microbiologic examination of the reproductive tract of the bitch must be treated with caution because the simple isolation of bacteria from the vagina does not constitute a diagnosis of reproductive disease. However, disease may result if the uterine or vaginal defense mechanisms are depressed, thereby allowing overgrowth of the normal commensals. Many of the normal vaginal inhabitants may become pathogens if a breakdown in local immunity occurs.

252.4 CONCLUSION

Infertility is an important and increasingly recognized condition in the bitch. Canine female infertility has a number of causes, the most common of which are inappropriate mating time, male factor infertility, and uterine disease. The approach to the infertile bitch should involve a logical investigation to determine the underlying cause, the optimal treatment, and prognosis. After collection of a detailed clinical history and a physical examination, the clinician should determine the typical presentation of the problem, followed by additional investigation to establish the cause. Although specific diseases can be significant causes of infertility, an understanding of the normal anatomy, physiology, and the wide range of variations that can occur is an important aspect of investigating canine female infertility in clinical practice.

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253 CHAPTER • 253 Vaginal Disorders

Beverly J. Purswell

253.1 ANATOMY

253.1.1 Embryologic Origins of the Posterior Reproductive Tract

In normal sexual development of female dogs and cats, the urogenital sinus, genital tubercle, and genital swellings become the vestibule, the clitoris, and the vulva, respectively.[1] The paramesonephric (mullerian) ducts give rise to the uterine tubes (oviducts), uterus, cervix, and vagina.[2] The caudal end of the vaginal canal opens into the vestibule by joining the urogenital sinus to the distal paramesonephric ducts at the vaginovestibular junction. Although both the paramesonephric ducts and the urogenital sinus probably contribute to the vaginal epithelium, the vaginal squamous epithelial cells are considered to originate from the urogenital sinus.[2] The urogenital sinus also gives rise to the urinary bladder and to the urethra, which enters the vestibule just caudal to the vaginovestibular junction.

253.1.2 Anatomic Relationship of the Vagina and the Vestibule

The *vestibule* is the common external opening of the urinary and reproductive tracts. Cranially, the vestibule ends at the vagina, where the narrowing of the vaginovestibular junction can be palpated digitally. The vestibule has a distinct ventral slope starting at the vaginovestibular junction and extending caudally to the ventral commissure of the vulva (Figure 253-l). The urethral opening is on the ventral floor of the vestibule approximately 0.5 cm distal to the vaginovestibular junction.

The *vagina* extends (caudal to cranial) from the vaginovestibular junction to the cervix. The bitch has a relatively long vagina, which places the cervix in the abdomen, not the pelvic canal. This length makes examination of the vagina in its entirety difficult without special equipment and impossible using only digital palpation. The anterior part of the vagina is quite narrow (5 to 7 mm), which makes visualization of the cervix and its external os difficult even endoscopically.

253.2 EXAMINATION OF THE VESTIBULE AND VAGINA

253.2.1 Vaginal Cytology

Vaginal cytology is the technique most widely used to evaluate the distal reproductive tract of the bitch and is valuable in the interpretation of the nature of vulvar discharges. Localization of a disease process may be facilitated by comparing cytology from the vestibule to that of the vagina. Vaginal cytology is indicated any time disease of the reproductive tract is suspected.

Neutrophils in low numbers are seen normally in vaginal cytology at any time except during the peak of the estrogenic phase of the estrous cycle (middle to late proestrus and all of estrus). Large numbers of neutrophils are seen in early diestrus; this influx of neutrophils is not associated with any disease process and is considered a normal phenomenon. The presence of large numbers of neutrophils during any other stage of the estrous cycle indicates an inflammatory process.

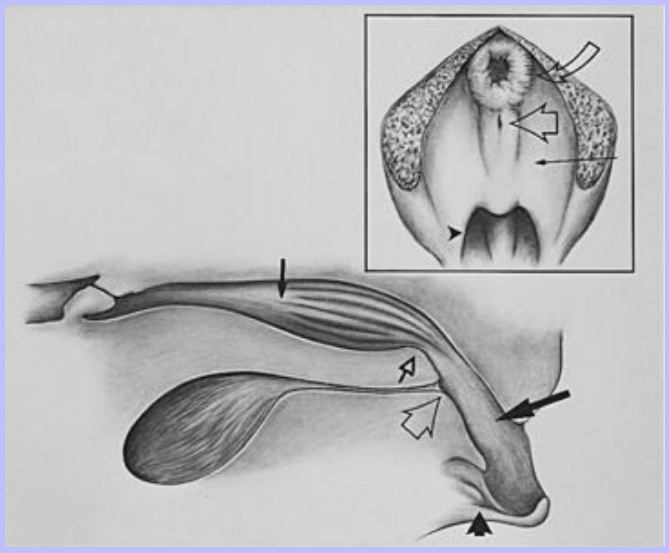
253.2.2 Visual and Digital Examination of the Vagina and Vestibule

Digital examination of the distal reproductive tract is valuable in the diagnosis of a variety of abnormalities. However, the animal's size may limit the examination. Because of the length of the distal reproductive tract, particularly that of the vagina, it is impossible to examine the vagina digitally in its entirety. Only the vulva, vestibule, urethral opening, and vaginovestibular junction can be adequately evaluated with a digital examination. Many of the abnormalities found in this area are best diagnosed with a digital examination and may remain undetected with other forms of inspection.

Vaginoscopy may be performed with an endoscope, a proctoscope, or any fiber-optic equipment long enough (15 to 20 cm) to allow inspection of the entire vagina. The procedure can be performed on the awake, standing bitch with sedation used as needed. Rigid equipment (e.g., proctoscope) tends to allow better visualization of the vagina than the flexible endoscopes because of the collapsing nature of the vaginal folds. When flexible fiber-optic endoscopes are used, insufflation of the vagina with air is necessary for a thorough examination. 1686

The outside diameter of the endoscope must be 5 mm or less for complete visualization of the anterior vagina and paracervical area.[3] This small diameter may also be helpful for traversing the narrowing at the vaginovestibular junction for examining small bitches (those weighing less than 9 kg). Body size does not always correlate with the vestibular and vaginal diameter, especially in the prepubertal or ovariectomized bitch. Equipment less than 5 cm in length (e.g., otoscopes) provide visualization only of the vestibule. 1687

Figure 253-1 Anatomic relationship of the vestibule and the vagina in the bitch. The insert shows the annular stricture at the vaginovestibular junction cranial to the urethral opening. Other structures shown are the urethral opening *(open arrow head),* the clitoral fossa *(solid arrow head),* the vaginovestibular junction *(open arrow),* the vagina *(solid arrow),* and the vestibule *(large solid arrow).*



253.2.3 Vaginal Bacterial Cultures

It has become common practice for clients to request vaginal cultures from bitches prior to breeding. The literature includes reports on vaginal flora in normal bitches and bitches with reproductive tract disease.[4,5] The species of bacteria isolated from the cranial and caudal vagina are similar in these two groups. The aerobic bacterial flora of the bitch's vagina consists of common opportunistic pathogens, the presence of which does not influence fertility.[5] Careful interpretation of culture results is mandatory in the evaluation of an area with normal flora. Culture of the vagina during an overt disease process is valuable in the selection of appropriate therapy. However, isolation of opportunistic aerobic pathogens, anaerobic bacteria, or mycoplasmas in an asymptomatic animal does not constitute evidence of infection.[4] Research shows that prophylactic use of antibiotics in apparently healthy breeding bitches may predispose the vagina to colonization by organisms that are known opportunistic pathogens.[6] Only a guarded swab technique should be used to obtain vaginal cultures.

253.3 VAGINAL ABNORMALITIES

253.3.1 Vaginitis

The term *vaginitis* describes an inflammatory process, not necessarily an infectious one. Inflammation can be identified easily with vaginal cytology and vaginoscopy. The clinical signs are those associated with irritation, such as licking, vulvar discharge, and attraction of male dogs. With vaginitis, vaginal cytology shows increased numbers of neutrophils in various stages of degeneration, with or without increased numbers of bacteria. Chronic vaginitis may induce the presence of lymphocytes and macrophages. Vaginoscopy reveals the presence and extent of hyperemia, exudate, and mucosal lesions, such as vesicles, ulcers, and lymphoid follicle hyperplasia. An attempt should be made to differentiate other systemic disorders that cause similar signs. Urinary tract problems should be ruled out as a cause of the vestibular irritation or attraction of male dogs. Lymphoid follicle hyperplasia is a common finding in the vestibule of bitches with urinary tract infections arising from chronic inflammation. Dermatologic lesions may be the cause of a perineal irritation and can prompt excessive licking. Comparison of vestibular cytology with vaginal cytology may aid in localization of the problem.

Juvenile (puppy) vaginitis is a common malady in prepubertal bitches. The most common sign is purulent vulvar discharge. Juvenile vaginitis may respond to systemic antibacterial therapy or to topical douching, but inevitably the signs return when treatment is discontinued. The condition resolves naturally after the first estrous cycle, if not before. Neutering of these animals should be postponed until signs have resolved or the first estrus has occurred. The vulvar area should be kept clean to prevent secondary skin problems. No other treatment is necessary.

Adult vaginitis can be caused by anatomic abnormalities that lead to accumulation of discharge or urine in the vagina. Accumulation of urine in the vagina may cause apparent urinary incontinence, with urine dribbling from the vulva when the bitch changes position. Bacterial or chemical vaginitis occurs secondary to the predisposing cause.

Strictures at the vaginovestibular junction are thought to cause problems in some individuals. Care must be taken to localize the area of inflammation before this diagnosis is made. These vaginovestibular strictures can be easily identified by a digital examination. Digital or surgical dilatation may be required to eliminate the problem, although recurrence is common. Vaginectomy may be required in persistent cases. Vaginoscopy,

contrast radiography, or other imaging modalities should be used to rule out foreign bodies, tumors, and uterine stump granulomas as predisposing causes (Figure 253-2). Contrast radiography may be helpful in identifying anatomic abnormalities or concurrent urinary tract disease, including acquired ectopic ureters after ovariohysterectomy.[7] A knowledge of the normal changes that occur in the vagina with the estrous cycle is critical in the interpretation of contrast radiographs (Figure 253-3). When vaginoscopy is performed in an animal with chronic inflammation, care must be taken not to perforate the vaginal wall.

Because systemic disease may predispose a bitch to vaginal infection, the animal's general health should be evaluated. If a predisposing cause is not identified, vaginal cultures should be performed and appropriate antibacterial therapy instituted. In some cases of chronic inflammation without any apparent predisposing cause, glucocorticoids may be useful for eliminating the inflammation. Initial lavage of the vagina may be beneficial for removing accumulated material.

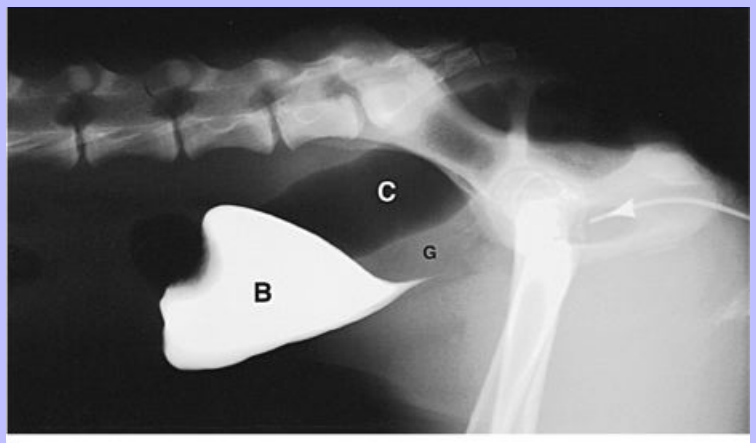
Viral vaginitis has been described in conjunction with canine herpesvirus infection. Genital infections of canine herpesvirus result in diffuse, multifocal, raised vesicular lesions on the vaginal mucosa that characteristically cause no clinical signs in the bitch.[8] No treatment is necessary, but it is advisable to separate the affected animal from any pregnant bitches or neonatal puppies.[9]

253.3.2 Anatomic Abnormalities

A variety of congenital abnormalities of the vagina and vestibule have been described. The exact incidence is unknown, but some of these abnormalities are common. Abnormal embryologic development is responsible for most of these conditions.

A persistent hymen occurs at the junction of the vagina and vestibule where the paramesonephric duct joins the urogenital sinus. Incomplete perforation of the hymen usually causes an annular stricture (see insert in Figure 253-1) or a vertical septum or band. Affected bitches most often have breeding difficulties, chronic vaginitis, or urinary incontinence unresponsive to conventional therapy because of urine pooling. Digital palpation is the preferred method of diagnosing these conditions. Vaginoscopy may bypass the affected area. If these anomalies are incidental findings in an asymptomatic animal, no correction is necessary. Digital dilatation can be attempted in either condition and may be successful, depending on the extent of the tissue involved. An episiotomy may be required to attain adequate exposure of the vaginovestibular junction for surgical manipulation. A vertical band is easily removed surgically, and correction of the presenting signs is usually complete. An annular stricture is more difficult to correct permanently. The stricture may be excised completely, with the mucosa closed perpendicular to the initial incision, in an attempt to enlarge the lumen. Another approach is to make a series of radial incisions perpendicular to the lumen. Both procedures may require frequent and repeated postoperative digital dilatation to prevent stricture recurrence. Clinical signs may persist after attempted surgical correction. Vaginectomy is an alter-native therapy that alleviates problems associated with the vagina.

Figure 253-2 Uterine stump granuloma in a 7-month-old spayed bitch presented for urinary incontinence. **A,** Lateral abdominal radiograph obtained after infusion of air into the colon *(C)* and iodinated contrast medium into the urinary bladder *(B)*. The uterine stump granuloma *(G)* is evident as a soft tissue mass compressing the neck of the urinary bladder. **B,** Transverse computed tomographic image obtained at the level of the cranial pelvic canal (sacrum *[S]* and femur *[F]*). The granuloma is compressing the left ureter at the trigone and indenting the left dorsolateral margin of the urinary bladder. (Courtesy Dr. Jeryl C. Jones, Virginia-Maryland Regional College of Veterinary Medicine, Blacksburg, VA.)



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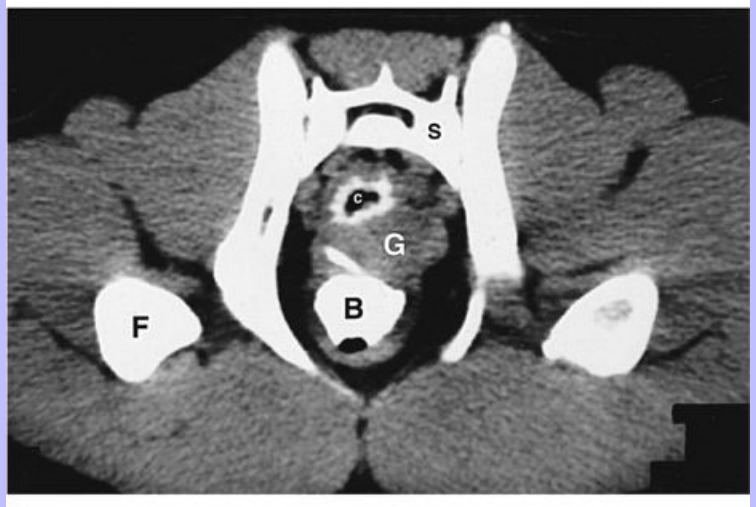

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Bitches with annular strictures may be bred artificially and re-evaluated immediately prior to parturition. Sufficient relaxation usually occurs to allow normal delivery of the puppies. Cesarean section or an episiotomy may be needed at parturition if relaxation is insufficient to allow whelping.

Vaginal anomalies arise as a result of problems associated with organogenesis of the paramesonephric duct. The external genitalia and vestibule are usually normal in these animals because of their separate embryologic origin. Incomplete fusion of the paramesonephric ducts results in a vertical septum in the vagina (double vagina).[10] Surgery is indicated if the bitch's intended use is breeding or if clinical signs are present. Concomitant anomalies must be ruled out prior to attempted correction of any abnormality. Segmental hypoplasia or aplasia of the vagina has been described in the bitch, and surgical correction is not possible. Vaginal diverticula may occur and can fill with debris, causing local inflammation. Surgical removal of the diverticula is indicated to resolve this condition. Contrast radiography and vaginoscopy are helpful in identifying and defining the extent of the various vaginal anomalies. Ovariohysterectomy may be indicated when the condition is extensive. A partial or total vaginectomy may also be indicated when the condition is causing secondary problems, such as chronic urinary tract infections.

Vulvar anomalies are occasionally identified in a bitch with breeding difficulties. Tight bands at the dorsal commissure are a common cause of painful copulation (dyspareunia) and are easily identified with digital palpation. If necessary, the bitch may be bred artificially and re-examined immediately prior to parturition to assess potential whelping difficulties. Relaxation of the vulva is usually sufficient to allow normal delivery.

Inverted vulvas may be found in prepubertal bitches. The vulva is inverted to the point of being hidden from view by skin folds. Vaginitis, perivulvar irritation, vulvar discharge, or urinary tract disease may occur secondary to the infolding of the vulva and distortion of the vestibule and urethral opening. Neutering of these bitches should be postponed until after the first estrus. Eversion of the vulva normally occurs during the first estrus, and the condition is self-correcting. In bitches neutered prior to puberty, episioplasty may be necessary to alleviate the chronic urinary tract infections and perivulvar dermatitis associated with an inverted infantile vulva.[11,12] Removal of the redundant skin folds around the vulva exteriorizes the vulva, which helps eliminate the perivulvar dermatitis. Exteriorization of the vulva results in less turbulence of urine during voiding, making ascending infections less likely (Figure 253-4).

Faulty urogenital sinus embryogenesis may lead to congenital problems in the vestibule, vulva, and perineum. Open vulvar clefts, perineal dysgenesis, and rectovaginal fistulas have been described in the bitch and require surgical correction. These distal abnormalities, which can be acquired or congenital, may be associated with other reproductive or urinary tract anomalies. Clitoral anomalies are usually associated with intersex conditions and take the form of clitoral enlargement with penislike anatomy (Figure 253-5). Surgical removal of the clitoris to prevent excoriation is advised if the clitoris protrudes from the vulva.

Figure 253-3 Variations in the normal appearance of the canine vagina after retrograde positive contrast vaginography. **A,** Anestrus. Note the smooth mucosal margination and absence of filling defects, as well as the closed cervix, which allows no contrast medium to ascend into the uterus. **B,** Estrus. Note the thickened rugae appearing as linear filling defects in the mucosal margins and the open cervix, which allows contrast medium to ascend into the uterus. (Courtesy Dr. Jeryl Jones, Virginia-Maryland Regional College of Veterinary Medicine, Blacksburg, VA.)

253.3.3 Vaginal Fold Prolapse, Vaginal Hyperplasia, and Vaginal Prolapse

Under the influence of estrogen, some young bitches develop an edematous ventral fold in the distal vaginal mucosa immediately cranial to the urethral opening (Figure 253-6); this fold may become large enough to protrude from the vulvar opening. Traditionally, this condition has been referred to as vaginal hyperplasia. Histologically, however, this tissue is no more hyperplastic than the rest of the vagina under the influence of estrogen. Pronounced edema is the major histologic lesion, with fibroplasia resulting from the edema. Prolapse of a vaginal fold occurs almost exclusively when the bitch is under the influence of estrogen; this may occur at

the first estrus or become evident during later estrous cycles. Once the condition manifests itself, it has a tendency to recur during each subsequent estrus. The condition usually is self-limiting and resolves once the estrogenic influence ends at the onset of diestrus or with ovariohysterectomy. Ovariohysterectomy resolves the condition permanently and is the treatment of choice for animals not intended for breeding. Surgical removal of the prolapsed tissue can be attempted and resolves the condition permanently in some animals. Artificial insemination can be performed in affected bitches, with resolution expected with the onset of diestrus. Occasionally vaginal fold prolapse fails to resolve after estrus, or it recurs at the end of pregnancy, when estrogen levels rise slightly.[13] The condition is not generally thought to be hereditary, although evidence indicates a hereditary predisposition in some family lines and some breeds.

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Figure 253-4 Episioplasty in a bitch with an inverted vulva, performed as treatment for chronic urinary tract infections and perivulvar inflammation. **A,** Presurgical appearance of the vulva and surrounding skin folds; the arrow indicates the ventral commissure of the vulva. **B,** Postsurgical appearance of the vulva after removal of redundant skin folds.

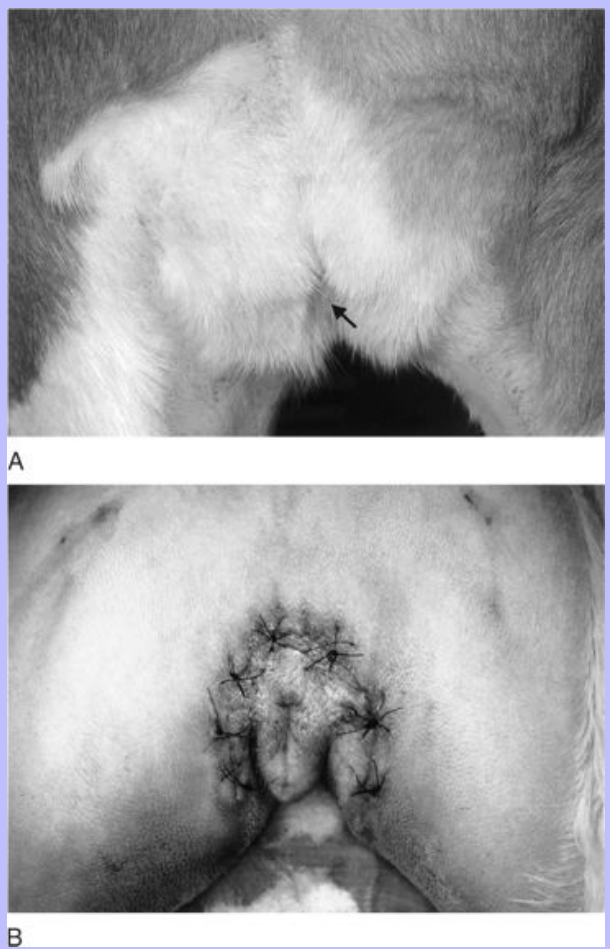
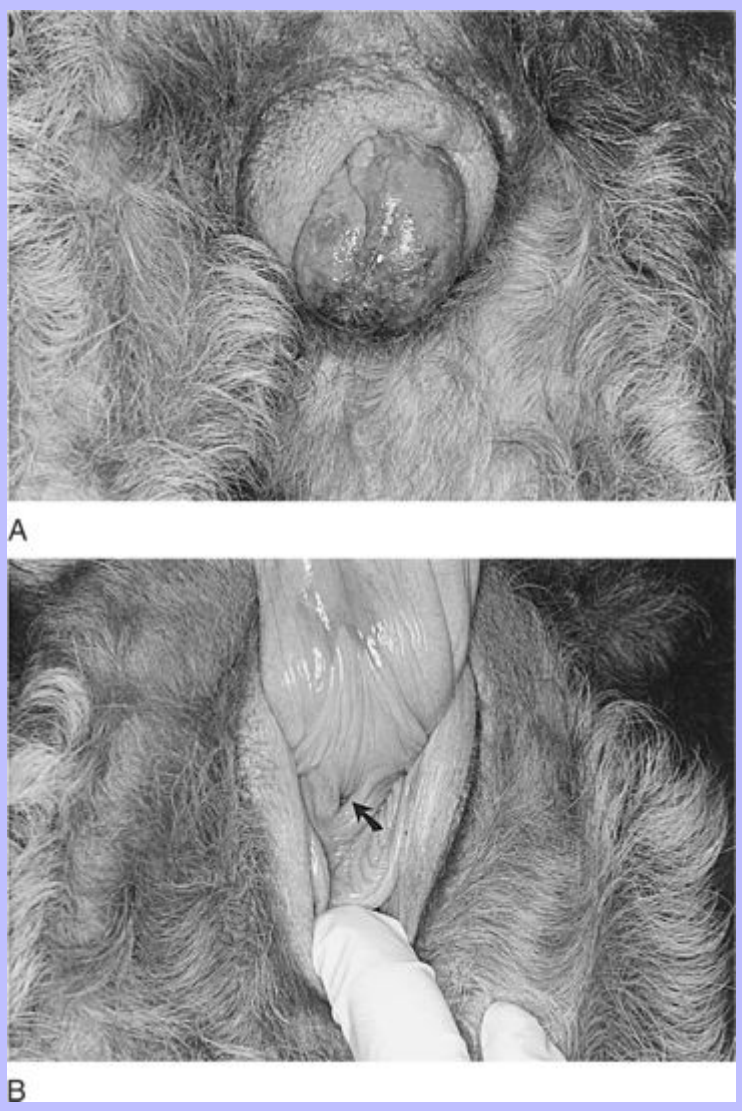


Figure 253-5 Clitoris of a male pseudohermaphrodite, showing penislike anatomy.

Figure 253-6 Vaginal fold prolapse (vaginal hyperplasia) in a bitch. **A,** Vaginal fold prolapse protruding from the vulva; excoriation is evident. **B,** Vaginal fold prolapse originating anterior to the urethral opening (arrow indicates urethral opening).



253.3.4 Miscellaneous Vaginal Disorders

Vaginal lacerations can occur during copulation, obstetric procedures, or vaginoscopy. Hemorrhage from the vulva is the primary sign. A bitch that bleeds from the vulva after breeding should be examined for vaginal

tears. The decision must be made whether suturing is necessary or possible. Systemic antibiotics should be administered to prevent infections, particularly dissecting pelvic infections.

Vaginal and vulvar neoplasia account for 2.5% to 3% of all canine tumors[14]; 70% to 80% of these tumors are benign. Signs may include perineal enlargement, a mass protruding from the vulva, vulvar discharge, tenesmus, or dysuria. Tumors prolapsing from the vulva must be differentiated from vaginal fold prolapse through evaluation of the stage of the estrous cycle and its relationship to the onset of signs, the location of the mass, and failure of the mass to regress at the onset of diestrus. Leiomyomas are the most common benign tumor and are often pedunculated. Leiomyosarcoma is the most common malignant vaginal tumor. Surgical excision is the treatment of choice for tumors. Transmissible venereal tumors are more common in younger animals and respond readily to chemotherapy. The prognosis for vaginal and vulvar tumors is good provided metastasis has not occurred with the malignant tumors. Ovariohysterectomy is recommended at the time of removal because of the possibility of hormonal influence on the incidence and possible recurrence rate.

Vaginal prolapse rarely occurs in the bitch or queen. It is usually associated with dystocia, tenesmus, or forced extraction of the male during the genital tie in the dog. Uterine prolapse may follow, depending on the cause. Treatment involves replacement of the affected structures. An abdominal approach may be necessary to replace the vagina. An ovariohysterectomy may be performed at the time of correction if so desired.

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254 CHAPTER • 254 Semen Evaluation, Canine Male Infertility, and Common Disorders of the Male

Mushtaq A. Memon

Kaitkanoke Sirinarumitr

254.1 SEMEN EVALUATION

The purposes of semen collection and evaluation are to assess an animal for breeding soundness; to perform artificial insemination; to preserve semen; to attempt to localize the site of disorder in some infertile dogs; and to determine treatment response for infertile dogs. Collection of the prostatic fluid and its submission for cytology and bacterial culture may help differentiate prostatic disorders from other problems. Semen evaluation may be performed before a dog is purchased, before he is first used for breeding, or if he shows signs of infertility. Semen collection and evaluation are relatively easy and can be done at any small animal practice. The results should be recorded on the canine Breeding Soundness Examination (BSE) form, which was devised by the Society for Theriogenology.

254.1.1 Semen Collection

254.1.1.1 Equipment

Semen from the dog is easily collected using an artificial vagina (AV), a device composed of a latex rubber cone (Reproduction Resources, Hebson, Illinois) connected to a 15 mL calibrated plastic centrifuge tube. The AV should be washed with plain tap water (no soap, detergent, or other cleansing agent is used), rinsed thoroughly with distilled water, and air dried. Gas sterilization, if available, may be used on the AV. Some dogs may ejaculate into other containers under the pressure of hand massage alone. However, semen is collected successfully from most dogs with an AV because the AV simulates the pressure normally felt by the male during copulation. The calibrated collection tubes used in the procedure should also be washed with tap water, rinsed with distilled water, and sterilized with gas or autoclaved before use to prevent the formation of formaldehyde residues, which are harmful to sperm.[1]

For optimum results, collection should be done in a quiet room with the dog on a nonslip surface and with the owner present. Semen may be collected before other examinations are performed, including the physical examination. For better responsiveness, the semen can be collected in the presence of a teaser bitch in proestrus or estrus. If a bitch in estrus is not available, a commercially available pheromone (Eau d' Estrus, International Canine Genetics, Malvern, Pennsylvania; or methylparaben; Sigma Chemical, Saint Louis, MO) or vaginal swabs from a disease-free estral bitch can be used. The top of the AV should be folded down, and a scant amount of lubricant should be applied to facilitate later removal of the device from the dog's erect penis.

254.1.1.2 Procedure

The male and female are brought on leashes into a collecting room and allowed to play for a few minutes. The semen collector, if right handed, kneels at the dog's left side and, holding the AV in the left hand, uses the right hand to move the prepuce up and down the penile shaft to achieve protrusion of the penis into the

AV. (Left-handed collectors may reverse the sides described above.) As the male begins to thrust the penis into the AV, the collector moves the sheath above the engorging bulbous glandis, keeping firm, steady pressure around the circumference of the penis to maintain the erection (Figure 254-1). Most male dogs ejaculate the presperm (clear) and sperm-rich fractions (cloudy) of the semen during pelvic thrusting; they then dismount and lift one hind leg as though trying to step over the bitch and achieve the tie. At this point the penis should be rotated 180 degrees, so that it is directed caudally, and held still, with tight pressure maintained around the circumference, until the third prostatic fraction of semen has been ejaculated. The prostatic fluid is ejaculated after a short pause in association with anal contractions and rhythmic pulsations of the penile urethra, which the collector can detect. After a few milliliters of prostatic fluid have been collected, the AV may be removed from the penis; the dog may continue to ejaculate prostatic fluid for some time after removal of the AV. The dog should not be kenneled or sent home until the erection has subsided completely and the entire penis is back in the preputial sheath. Normally, this takes about 5 to 10 minutes after semen collection.

254.1.2 Evaluation

Five parameters, in particular, should be evaluated and recorded for each semen collection (Table 254-1): the color and volume of the sample, and the motility, concentration/total number, and morphology of the sperm.

Figure 254-1 Latex rubber cone (artificial vagina) fitted over the penis during semen collection.

254.1.2.1 Color

The color of the sample is observed grossly in the collection tube. The first fraction should be clear, whereas the second (sperm-rich) fraction should be milky white. The third fraction (prostatic fluid) should be clear. Yellow discoloration may indicate urine contamination or the presence of purulent exudate. A red or brown color may indicate prostatic disease, trauma, urethritis, or ulceration.

254.1.2.2 Volume

The volume of semen can be read directly from the calibrated collecting tube. Volume varies among breeds and among individual dogs. Semen volume is not an important parameter with regard to the BSE, but it is necessary for determining the number of sperm per ejaculate. The separate volume for the prostatic fluid need not be recorded, because it varies according to the length of time the prostatic fluid is collected.

254.1.2.3 Sperm motility

Motility testing should be performed immediately after collection. The examiner places a drop of undiluted semen on a slide with a cover slip, examines the specimen at ×100 to ×200 magnification (because canine spermatozoa are resistant to cold shock, the slide need not be warmed), and estimates the percentage of sperm cells moving in a progressive and forward manner across the field (Figure 254-2). Although sperm motility estimation is not precise, it is a quick functional test.

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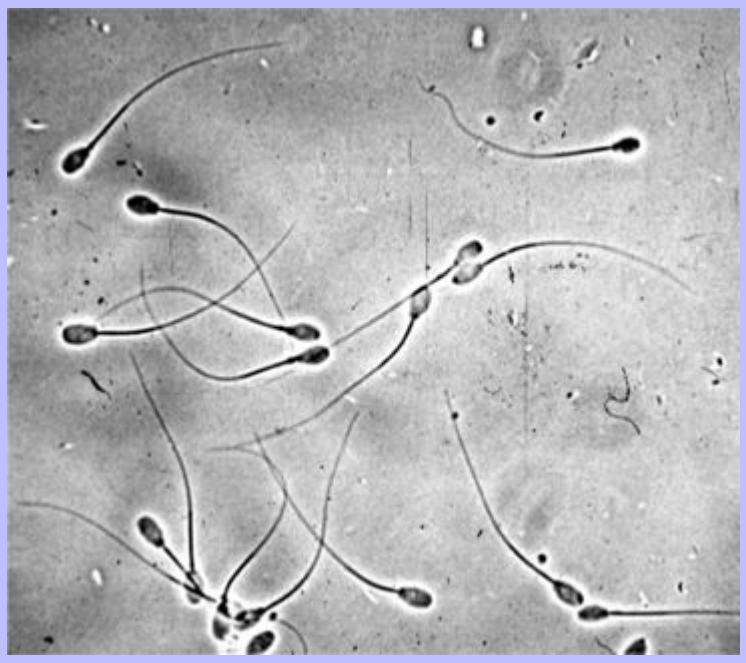
Table • 254-1 Characteristics of Normal Canine Semen

		SEMINAL FRACTION		
PARAMETER	UNFRACTIONED EJACULATE	1	2	3
Color	Opaque to white	Clear	Milky white	Clear
Volume (mL)	~30	0.1–2	0.1–4	1–25 +
pH	6.1–7.0	6.2–6.4	–	–
Sperm motility	>80 %	–	–	–
Morphologically normal sperm	>80 %	–	–	–

Figure 254-2 Estimation of the percentage of motile sperm (i.e., those moving in a progressive, forward manner) in a semen sample.



254.1.2.4 Concentration/total number of sperm

The total number of sperm in the ejaculate is more important than the concentration of sperm per milliliter, because the concentration changes dramatically depending on the amount of prostatic fluid collected. The sperm concentration can be measured with a commercial WBC Unopett system (Becton Dickinson, Rutherford, New Jersey) (Figure 254-3). The semen sample is stirred gently, drawn up into the capillary pipette (20 μL) provided with the kit, and dispensed into the diluent-containing reservoir chamber. Diluted semen then is dispensed into both chambers of a Neubauer hemocytometer (Becton Dickinson, Rutherford, New Jersey) (Figure 254-4), and the contents of the grid's 1-mm central square (composed of 25 small squares) are counted on each side of the hemocytometer and averaged.[2] (The central square fills the field of a light microscope when the ×10 objective is used.) The number of spermatozoa in the central square is the concentration in millions of spermatozoa per milliliter of semen. The total number of sperm in the ejaculate equals the concentration multiplied by the volume. The normal total number of sperm[1] ranges from 300 to 2000×10^6; large breed dogs ejaculate more sperm than small breed dogs.[3] (Direct cell counts done with the hematocytometer are time-consuming; quicker methods used to determine the sperm concentration are an electronic blood cell counter or spectrophotometer.) The total number of sperm may be decreased in quite young, old, and inbred dogs.

254.1.2.5 Sperm morphology

Sperm morphology is usually assessed by staining the semen sample and observing the sperm under oil immersion (×1000) objective. Various stain techniques may cause some artifactual changes in sperm morphology. Defects vary with the stain used, but the percentage of morphologically normal sperm should be fairly consistent regardless of method.[4] Eosin/nigrosin stain and Wright's Giemsa stain (Diff Quik) are the stains most commonly used. For staining with eosin-nigrosin, a drop of semen and a similar-sized drop of stain are placed on one end of a clean glass slide and mixed gently with a wooden applicator. A second slide then is used as a spreader slide. A thin film, similar to a blood smear, is made and air-dried. For staining with rapid Wright's Giemsa stain, the semen smear is made as for a blood smear, air-dried, and immersed in each of the three solutions for 5 minutes each. The slide then is rinsed and allowed to dry. One hundred sperm cells should be examined and the findings recorded, including normal sperm, primary abnormalities (all head defects, proximally coiled tails, proximal cytoplasmic droplets), and secondary abnormalities (detached heads, bent tails, and distal cytoplasmic droplets). Primary abnormalities are abnormalities that occur in the testis during spermatogenesis. Secondary abnormalities occur during epididymal transport or as a result of sample-handling techniques. Most dogs have greater than 80% normal sperm per ejaculation.[5]

Figure 254-3 WBC Unopett system, used to measure sperm concentration.

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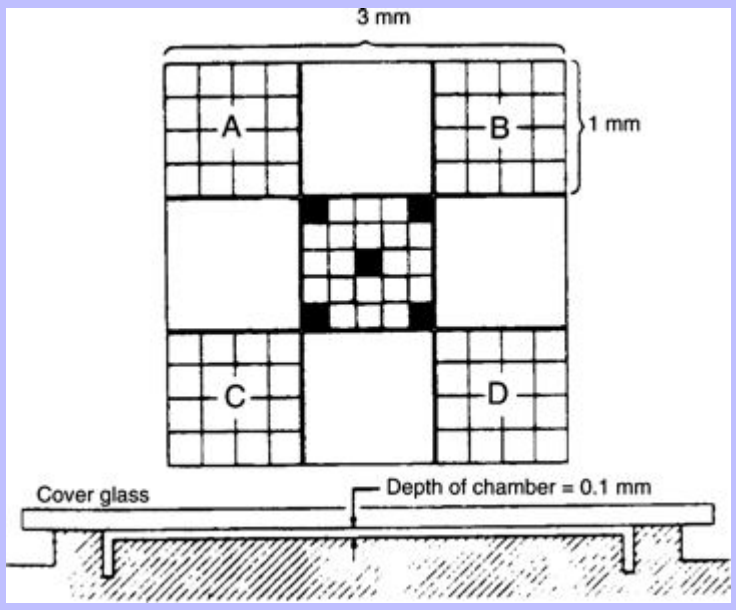
Figure 254-4 Neubauer hemocytometer, which is used to count sperm.



254.2 CANINE MALE INFERTILITY

Infertility in the male may result from infections, endocrinopathies, structural abnormalities, neoplasia, illness, or poor breeding management. Abnormalities of the genital tract, which includes the penis, prepuce, testes, epididymis, vasa deferentia, urethra, and prostate gland, may also result in infertility. These conditions may result in reduced libido or failure to achieve normal copulation. A thorough physical examination should be conducted after semen is collected.

254.2.1 History

A complete medical history of the male dog should be obtained, including information on vaccinations, diet, medications, past illnesses, and laboratory results, as well as a complete reproductive history. The record also should include a list of all breedings; the litter size from each breeding; the results of previous semen evaluations; and the breeding history of each bitch, including her estrous cycle, progesterone level, and conception rates from breedings with other males.

254.2.2 Physical Examination

A thorough physical examination should be performed. Abnormalities that may interfere with libido or ability to mount and achieve intromission include a persistent frenulum, hypospadias, disk disease, spondylosis, hip dysplasia, and a luxating patella. Dogs with heritable diseases should not be bred. The penis and prepuce should be inspected and palpated for any abnormalities. The erect penis can be examined after semen collection.

The scrotum and testes should be palpated for consistency and shape. Testicular degeneration, hypoplasia, or atrophy may result in softening of the testis, whereas testicular fibrosis or neoplasia may result in hardness of the testis. Although testicular size varies normally among breeds, the size should be measured with calipers and recorded. An abnormally enlarged scrotum or testis may indicate inflammation. Each epididymis, including the head, body, and tail, should be thoroughly palpated and the results recorded.[5]

The prostate is the major accessory sex gland and is responsible for seminal volume. It is an encapsulated, bilobed, bilaterally symmetric ovoid gland, located at the caudal pole of the bladder, that encircles the proximal urethra.

The prostate should be palpated by digital rectal examination after semen has been collected.

254.2.3 Additional Diagnostic Tests

Infertile dogs may require additional tests, including determination of the seminal plasma pH; aerobic and anaerobic bacterial cultures; culture for mycoplasmas and ureaplasmas; and semen cytology. Seminal fluid from samples that lack sperm should be evaluated for its alkaline phosphatase (ALP) concentration, which comes from the epididymis, to ensure a complete ejaculation.[2] Hormonal assays and epididymal aspiration, testicular biopsy, and chromosomal karyotyping may be considered in dogs with azoospermia. Ultrasonographic examination is a useful diagnostic procedure for detecting some abnormalities of the prostate, testes, and epididymis.

254.2.4 Azoospermia

Azoospermia is the ejaculation of seminal plasma without spermatozoa.[6] The causes of azoospermia may be classified as pretesticular, testicular, and post-testicular. Pretesticular causes in dogs include hypopituitarism, long-term high-dose steroid or antineoplastic therapy, hypothyroidism, inguinal and scrotal hernia, and fever. Testicular causes include intersex, germinal cell aplasia, bilateral cryptorchidism, testicular injury, irradiation, orchitis, autoimmune testicular disorders, and testicular neoplasia.[2,7] Phenotypic male dogs with chromosome abnormalities such as XXY or XX-male syndrome usually have aspermatogenesis. In dogs, XXY karyotype usually causes testicular hypoplasia and hypoplasia of tubular and accessory reproductive organs, along with azoospermia and sterility. Post-testicular causes of azoospermia include obstruction of the collecting ducts, epididymides, or ductus deferens, including epididymal segmental aplasia; sperm granulomas; spermatocele; acute inflammation; neoplasia; and previous vasectomy.[9] Some dogs may have azoospermia as a result of incomplete ejaculation.

254.2.4.1 Incomplete Ejaculation

Incomplete ejaculation may occur in normal, intact dogs that require the presence of a bitch in proestrus or estrus during semen collection. Some nervous or inexperienced dogs may also have an incomplete ejaculation. The dog may ejaculate only presperm fluid. More than one sample should be collected and evaluated before a diagnosis of azoospermia is made. Seminal fluid should be submitted for ALP measurement. The concentration normally is less than 5000 U/L for dogs that failed to have a complete ejaculation. Dogs with true azoospermia arising from causes other than bilateral blockage of the outflow tract usually have a seminal ALP concentration greater than 5000 U/L. If the seminal ALP concentration is

equivocal, another semen collection should be performed and the sample submitted for seminal ALP determination.[2]

254.2.5 Oligospermia

The term *oligospermia* refers to a low total number of spermatozoa in the ejaculate. Oligospermic dogs are not necessarily infertile. Causes of oligospermia reported in dogs include unilateral Sertoli cell tumor, orchitis, epididymitis, prostate diseases, incomplete ejaculation, retrograde ejaculation, overuse, and partial outflow obstruction.[2,9] Reported infectious causes of orchitis and epididymitis in dogs include *Brucella* sp., *Escherichia coli,* mycoplasma, and other aerobic organisms that make up the normal preputial flora.[2] Retrograde ejaculation has been reported in dogs.[10] The diagnosis of retrograde ejaculation may require collection of urine by cystocentesis after ejaculation and comparison of the number of sperm in the ejaculate with the number in the urine sediment. Retrograde flow of semen has been demonstrated in dogs sedated with xylazine.[11] Dogs with idiopathic oligospermia may be treated with a gonadotropin-releasing hormone (GnRH) agonist (1 µg/kg given subcutaneously), with or without subsequent treatment with human chorionic gonadotropin (HCG) (1600 IU given intramuscularly).

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254.2.6 Teratozoospermia and Asthenozoospermia

The term *teratozoospermia* refers to a low percentage of morphologically normal sperm (greater than 80% of sperm should be morphologically normal). Congenital causes of teratozoospermia in dogs include fucosidosis, a lysosomal storage disease that affects epididymal epithelial cell function, causing the retention of cytoplasmic droplets. Acquired causes reported are testicular tumors; orchitis; prostatitis; high fever; and obesity, which causes an increase in the intrascrotal temperature due to periscrotal fat. The causes of asthenozoospermia (progressive sperm motility less than 70%) are the same as those for teratozoospermia, as well as infection of the reproductive tract, use of contaminated collection equipment, and immotile cilia syndrome. Water-soluble lubricants, residues from the manufacture of latex or plastic AVs or collecting tubes, urine, and water can reduce the motility of sperm.[2,9] Sperm agglutination and reduced motility may be found in dogs that test positive for *Brucella* infection.

254.3 COMMON DISORDERS OF THE MALE DOG

254.3.1 Benign Prostatic Hypertrophy

Benign prostatic hypertrophy (BPH) is a naturally occurring, age-related condition in men and intact dogs. Most dogs with BPH are over 5 years of age. Dogs with BPH are predisposed to prostatic cysts, infections, and prostatic abscessation. An enlarged prostate may compress the descending colon or the rectum, or both.[2]

254.3.1.1 Pathogenenesis

The pathogenesis of BPH is not completely known. Dihydrotestosterone (DHT), testosterone, estradiol, and some growth factors are involved in prostatic growth.[12] The hormone DHT, a metabolized form of testosterone, plays a major role in the growth of both the stromal and glandular components of the prostate.[13]

254.3.1.2 Clinical Signs and Diagnosis

Clinical signs of BPH include constipation, dripping of a sanguineous discharge from the tip of the penis, blood-contaminated urine or semen, and difficulty urinating.[13] Dogs with BPH may or may not show any clinical signs related to BPH. Diagnosis of BPH requires determination of prostatic enlargement that is not caused by any other prostatic diseases. The prostate gland of dogs with BPH is symmetrically enlarged and moderately firm, and no signs of pain are associated with rectal palpation.[14] Dogs with BPH that also have a prostatic cyst may have asymmetrically shaped prostatic lobes.

Ultrasonographic examination demonstrates symmetrically enlarged prostatic lobes. The prostatic parenchyma is homogeneous in echogenicity with or without a cavitating cystic lesion. On radiographic films, enlargement of the prostate is suggested if the prostatic diameter on lateral radiographs is greater than 70% of the distance between the sacral promontory and the pubis.

Prostatic volume can be predicted using the following formula:

$$[1/2.6\ (L \times W \times D)] + 1.8$$

where *L* is the greatest craniocaudal measurement, *W* is the transverse measurement, and *D* is the dorsoventral measurement of the prostate, as measured using ultrasonography.[15] The results of a complete blood count in dogs with BPH are normal, and aerobic bacterial culture of prostatic fluid shows less than 10,000 colony-forming units (CFU) per milliliter.[13]

254.3.1.3 Treatment

The treatment goals for dogs with BPH are to reduce the size of the prostate and alleviate the signs related to BPH. In most dogs, castration is recommended for BPH. Medical treatment is suitable for valuable breeding dogs and for dogs with a high risk of adverse reactions to anesthesia or surgery. The recommended drug for BPH treatment is finasteride (Proscar), administered at a dosage of 0.1 to 0.5 mg/kg (or 1 tablet/dog weighing 1 to 50 kg), given orally every 24 hours for 1 to 4 months.[13] In dogs with BPH that were treated with finasteride, the prostate became involuted through programmed cell death, or apoptosis, rather than necrosis, therefore no inflammatory process arose in the involuted prostate.[16] Finasteride reduces prostatic volume and the serum DHT level but does not adversely affect the semen quality, libido, serum testosterone concentration, or fertility.[13,17,18]

254.3.2 Prostatitis

Bacterial prostatitis is common in sexually intact dogs and can be acute or chronic. The organism most commonly found in dogs with prostatitis is *E. coli,* followed by staphylococci and streptococci.[19]

254.3.2.1 Clinical Signs and Diagnosis

Clinical signs in dogs with acute prostatitis include fever; pain; depression; straining to urinate or defecate; stiff-legged gait; hematuria; edema of the scrotum, prepuce, or hindlimb; and pollakiuria. During rectal examination of the prostate, dogs with prostatitis show signs of pain. The prostate may be asymmetric if

abscessation is present. Dogs with chronic prostatitis may have clinical signs of infertility problems or lower urinary tract disease.[2] Dogs with prostatitis may have leukocytosis. The urine may contain blood, bacteria, and white blood cells. Prostatic fluid collected either by ejaculation or by prostatic massage contains a significant number of inflammatory cells, and the aerobic bacteria count is greater than 10,000 CFU/mL.[2] Prostatic abscesses detected by ultrasonography are usually discrete, hypoechoic or anechoic lesions with or without distant enhancement.

254.3.2.2 Treatment

Prostatitis with abscessation can be treated medically and/or surgically. Surgical correction of prostatic abscessation may be associated with a high percentage of adverse sequelae. Surgical techniques used include marsupialization, placement of a Penrose drain, drainage with omentalization of the cavities remaining, and partial prostectomy.[2] Medical treatment for prostatitis usually includes appropriate antimicrobial therapy. Finasteride therapy or castration should also be considered. Combination therapy with an antimicrobial and finasteride is more successful than treatment with an antimicrobial alone. Antimicrobial therapy should be based on bacterial sensitivity.

254.4 TESTICULAR PROBLEMS

254.4.1 Cryptorchidism

Cryptorchidism is the most common disorder of sexual development. It is defined as a lack of descent of one or both testes into the scrotum by 6 months of age.[8] In normal dogs, the testes usually have descended by 10 days of age. The incidence of cryptorchidism is higher in dogs (0.8% to 9.8%) than in cats (1.7%). The condition is more common in certain breeds (e.g., toy and miniature poodles, Yorkshire terriers, Chihuahuas, boxers, and miniature schnauzers). Cryptorchidism is considered a hereditary disorder, therefore an animal with this condition should not be used for breeding. The exact mode of inheritance is not known, but it is thought to be a sex-limited autosomal recessive type; therefore both males and females can carry the gene and pass it on to their offspring.

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The diagnosis is made on the basis of the physical examination findings. In the cat, the penis should be examined for androgen-dependent penile spines (Figure 254-5).[2,20] The penile spines atrophy by 6 weeks after complete castration. (Retained testes are atrophic and are generally not visible on abdominal ultrasound scans.) An animal with unilateral cryptorchidism (one testis in the scrotum) dog can produce sperm, whereas dogs that are bilaterally cryptorchid usually do not produce sperm. Because cryptorchidism does not affect testosterone production, a cryptorchid animal would show sexual desire and may be able to breed.

Hormonal analysis is the definitive diagnostic test for differentiating bilaterally cryptorchid animals from castrated animals. Baseline serum testosterone concentrations of less than 0.02 ng/mL indicate an absence of retained testicular tissue. In dogs with abdominally retained testes, the serum testosterone concentration usually is 0.1 to 1.2 ng/mL, whereas in adult dogs with one or two scrotal testes, the serum testosterone concentration usually is 1 to 5 ng/mL. However, testosterone is secreted in pulses throughout the day, therefore challenge testing may be more accurate than evaluation of a single sample. A hormonal stimulation test with HCG or GnRH can be used to demonstrate the presence and production of testosterone.[2,20,21] The incidence of Sertoli cell tumors is higher with abdominally retained testes. Although not a common

occurrence, torsion of an abdominal testis can occur, leading to sudden abdominal pain. This phenomenon occurs almost exclusively in dogs with testicular tumors.

Treatment of animals with cryptorchidism is limited to castration. In unilaterally cryptorchid dogs, both testes (scrotal and abdominal) must be removed. Medical treatment with hormones such as GnRH or HCG is not effective. Removal of carrier parents from the breeding population would result in a decrease in the incidence of this condition.

254.4.2 Scrotal Hernia

With a scrotal hernia, the abdominal contents pass through the inguinal canal into the scrotum. An incidence of less than 1% is reported, and the condition occurs primarily in young dogs ranging in age from 5 months to 4 years (the average age is 1.73 years).[2]

Figure 254-5 Spines on the penis of a cat.

Figure 254-6 Unilateral left side enlargement of the scrotum of a 3-year-old pug with a hernia.

Differential diagnoses include orchitis, testicular torsion, testicular neoplasia, sperm granulomas, and trauma. On physical examination, a common finding is a fluctuant enlargement of the scrotum; in some cases, unilateral enlargement (Figure 254-6) is associated with ipsilateral inguinal swelling. The definitive diagnosis is made by careful palpation of the scrotum. Ultrasonography of the scrotum provides excellent information on the type of contents (Figure 254-7). Treatment involves surgical removal or replacement of the herniated tissues.

Figure 254-7 Sonogram of the scrotum with a hernia. Note the oval-shaped gray testis. The white areas below the testis are part of the omentum that has herniated from the abdomen. The black area around the testis is fluid, which accumulated in the scrotum. The hernia was corrected by surgery.

254.4.3 Testicular Tumors

Testicular tumors are common in dogs and rare in cats. The three most common types are Sertoli cell tumors, seminomas, and interstitial cell tumors. The reported incidence of testicular tumors is 0.91%, and the age of affected dogs ranges 2 to 19 years. The tumors may be unilateral or bilateral. All three types are equally prevalent in descended testes.

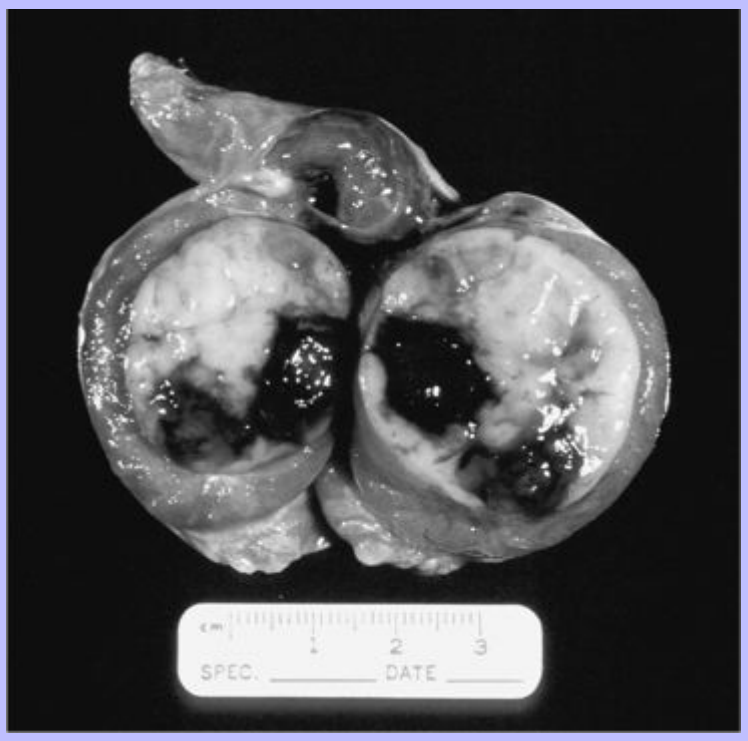
Dogs with testicular tumors most often have testicular enlargement without pain. A presumptive diagnosis is made by digital palpation and/or ultrasonographic examination of the scrotum. A neoplastic testis may or may not be significantly enlarged. Atrophy of the contralateral testis may have occurred as a result of hormone produced by the neoplastic testis or of an increase in the intrascrotal temperature. Nonpalpable tumors may be visualized sonographically, but the tumor type cannot be differentiated with this imaging modality.

Castration is the treatment of choice. Because of the high incidence of bilateral neoplasia and atrophy of the unaffected testis, removal of both testes is recommended. Unilateral orchiectomy may be considered in valuable breeding dogs. Sperm numbers decline 50% immediately after unilateral orchiectomy. Compensatory hypertrophy of the remaining testis, characterized by increased diameter of the seminiferous tubules, may be evident as early as 3 months after surgery.[2]

Sertoli cell tumors (SCTs) are more common in abdominally retained testicles. The scrotal testis that contains a SCT is usually enlarged and firm. Sonographically, the SCT is visible in the testicular parenchyma as a hypoechoic to anechoic area. SCTs commonly are associated with a feminizing paraneoplastic syndrome

caused by estrogen secretion, which may lead to estrogen-induced pancytopenia. Feminizing signs are reported in 24% to 39% of dogs with an SCT. The clinical signs of paraneoplastic syndrome include bilaterally symmetric alopecia of the trunk and flanks with hyperpigmentation of the inguinal skin; a dry, easily epilated coat; gynecomastia; a pendulous preputial sheath; attraction of male dogs; and bone marrow hypoplasia with nonregenerative anemia.[2] Signs of feminization resolve within 21 days of surgical removal of the SCT. The prognosis for dogs with bone marrow hypoplasia secondary to SCT is guarded. Exfoliated cytology of the preputial mucosa may be useful for confirming the presence or recurrence of hyperestrogenism in dogs with SCT. The epithelial cells show cornification similar to that seen in the vaginal cells of a bitch in estrus.

Figure 254-8 Testicular seminoma from an 8-year-old Dalmatian with an enlarged testis. Note the large areas of lobulated neoplasm and the areas of hemorrhage.



Seminomas (SEMs) are tumors of the spermatogenic cells. A higher incidence of these tumors is reported in older German shepherds (those over 10 years of age). Up to 10% of SEMs may metastasize to local or distant sites. Seminomas vary in size from 1 to 10 cm in diameter, are soft on palpation, and grossly are seen as homogenous or ovulated masses that are cream to pink-gray on the cut surface (Figure 254-8).

Interstitial (Leydig) cell tumors (ICTs), also called *interstitial cell adenomas,* arise from the endocrine cells of the testis. These tumors are small, usually less than 1 cm in diameter, and vary in color from yellow to brown on the cut surface. ICTs are the tumor of scrotal testes. Unlike the other two tumor types, ICTs are an incidental finding at the time of necropsy.

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255 CHAPTER • 255 Feline Reproduction

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255.1 REPRODUCTIVE TRACT ANATOMY

255.1.1 The Queen

255.1.1.1 Reproductive Tract

The reproductive tract of the queen is suspended in the abdominal cavity by the broad ligament, an extension of the peritoneum, which consists of the mesovarium, mesometrium, and the suspensory and proper ligaments of the ovary. The ovaries of the queen are mobile, oval, and typically 8 to 9 mm long.[1] The ovaries are attached cranially to the diaphragm by the suspensory ligament, which is attached to the abdominal wall by the mesovarium. The caudal pole of the ovary is attached to the tip of the uterine horn by the proper ligament. The lateral surface of the ovary is covered by an extension of the mesovarium, the mesosalpinx, and the medial surface is covered by the infundibulum of the uterine tube. The mesosalpinx in the queen is small and contains no fat, permitting excellent laparoscopic visualization of the ovary.

The uterine tube (oviduct) in the queen is 4 to 6 cm long and is visible as a tortuous structure within the mesosalpinx near the ovary. The uterus is bicornuate and extends from the uterine tubes cranially to the cervix caudally. The body of the uterus is 2 to 3 cm long, and each horn is 9 to 11 cm long and 0.3 to 0.4 cm wide. The mucous membrane of the uterus, which typically is reddish brown but may be focally pigmented (black), contains wide, spiral, longitudinal folds. Transabdominal palpation of the normal uterus and uterine horns typically is possible only during estrus or pregnancy.

The feline vestibule is 1 to 2 cm long, and the vagina is 2 to 3 cm long. The external urethral orifice is located ventrally at the vestibulovaginal junction. The feline cervix is approximately 45 mm cranial to the vulva. The cervix, vagina, and vestibule of the queen have a horizontal orientation. Examination of the cervix in the queen is difficult, because the vagina is narrower than the vestibule and nondistensible.[2] The intravaginal component of the cervix is papilliform and has the external uterine orifice. The queen has major mucous-producing vestibular glands (Bartholin's glands), 5 mm in diameter, in the lateral aspect of the vestibule.

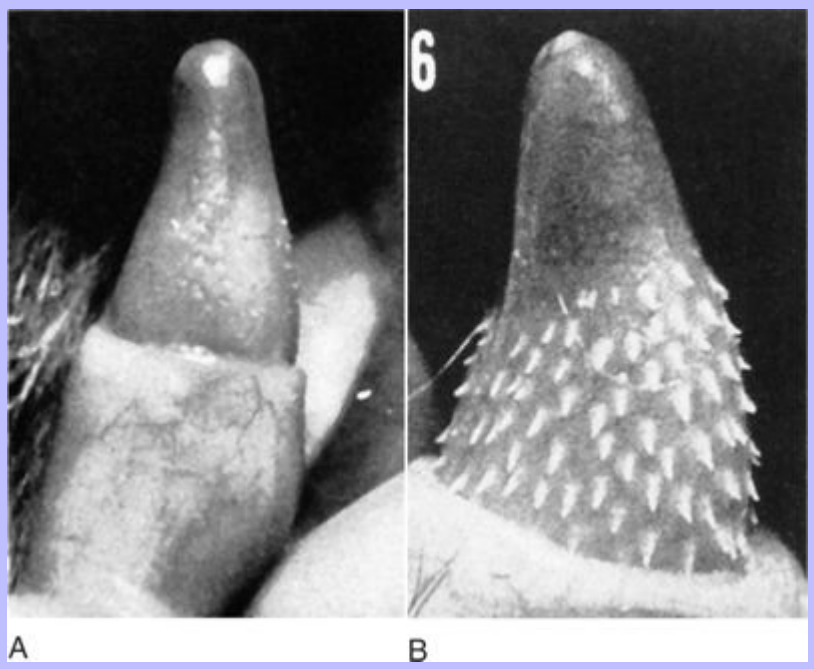
The vulva of the cat is covered with dense hair and does not vary during different stages of the estrous cycle because it is unresponsive to estrogen. The clitoris is small and protrudes slightly from the shallow fossa clitoridis; it is not normally visible.

255.1.1.2 Mammary Gland

The typical female cat has eight mammary glands arranged symmetrically in four pairs extending from the ventral thorax to the abdomen. The preferred nomenclature for glandular identification is numeric; from 1 to 4, left and right, with the cranial glands being numbered 1. Each mammary gland consists of multiple lobules drained by four to eight ducts, which open into each teat. The lymphatic drainage of the two caudal

teats is the superficial inguinal lymph node, whereas the two cranial mammary glands drain into the axillary lymph nodes. No lymphatic connections exist between the cranial and caudal segments of the mammary glands or across the midline, nor does lymphatic drainage from the mammary gland enter the abdomen or thorax.[3]

Figure 255-1 The smooth glands of a castrated male cat and penile spines of an intact male cat. (From Aronson LR, Cooper ML: Penile spines of the domestic cat: their endocrine behavior relations. Anat Rec 157:71–78, 1967.)



255.1.1.3 Placentation

Implantation occurs 12 to 13 days after ovulation in the cat. Fetuses are usually evenly distributed in the left and right horns as a result of embryo transmigration. The queen exhibits zonary, endotheliochorial placentation resulting from the loss of maternal endometrial epithelium and connective tissue. The fetal chorionic capillary epithelium is in direct contact with the maternal capillary endothelium, and placental transfer of maternal antibodies has been demonstrated in the queen.

255.1.2 The Tomcat

255.1.2.1 Reproductive Tract

The feline scrotum is ventral to the anus and lies dorsal to the caudally directed penis. The scrotum is densely covered with hair. The testes of the tomcat are ovoid to spherical and approximately 1.5 cm long

and are positioned obliquely so that the epididymis is craniodorsal.[4] The epididymis is not normally palpable because of its close attachment to the testes. The spermatic cord and the tubular tunica vaginalis, which covers it, are relatively long due to the distance between the scrotum and the superficial inguinal ring. The feline penis is structurally similar to the canine penis, having proximal cavernous and distal osseous components. The os penis is small (approximately 5 mm long) and is pointed distally. The prepuce is a thick fold with a caudally facing orifice. The penis is usually contained within the prepuce. The base of the penis is studded with six to eight rows of small, cornified, keratinized papilla (spines), which are present only under the influence of testosterone. Penile spines are considered a secondary sex characteristic in the domestic male cat (Figure 255-1).

The tomcat has two accessory sex glands, the prostate and the bulbourethral gland. The prostate of the tomcat is bilobed and consists of the pars compacta and the pars disseminata. The pars compacta, which is approximately 1 cm long, surrounds the dorsal and ventral urethra 2 to 3 cm caudal to the bladder. The pars disseminata consists of small lobules in the urethral wall extending from the bladder neck to the bulbourethral gland. The bulbourethral glands are small (5 mm long) and lie dorsolaterally on the urethra at the level of the ischiatic arch. 1697 1698

255.2 REPRODUCTIVE PHYSIOLOGY

255.2.1 The Queen

The queen is seasonally polyestrous. Ovarian activity is primarily under the influence of photoperiod and is stimulated by increasing hours of daylight. The true seasonal nature of the reproductive cycle of queens housed strictly indoors may not be evident. Cats maintained strictly indoors and exposed to artificial light for more than 14 hours a day may cycle at any time of the year and do not exhibit the typical seasonal breeding of their free-roaming counterparts. However, if these cats are returned to an outdoor environment, their ovarian activity becomes seasonal in nature. The queen exhibits induced, or reflex, ovulation. However, this is not an absolute phenomenon, and spontaneous ovulation occurs.[5]

255.2.1.1 Sexual Maturity and Pubertal Estrus

The queen typically reaches sexual maturity at 6 to 9 months of age. Two main factors influence the age of sexual maturity: body weight and exposure to light. The onset of ovarian activity and sexual maturity in the cat occurs as body weight approaches 2.5 kg; exposure to long photoperiod is essential. Queens exposed to outdoor light only typically exhibit estrus at the end of winter as day length increases. If a queen does not reach a body weight and age compatible with sexual maturity until late summer, when day length is decreasing, ovarian activity and sexual maturity most likely will be delayed until the following spring. The impact of breed on sexual maturity in domestic cats is small. As a general rule, oriental breeds are considered to exhibit pubertal estrus at an earlier age compared to long-haired breeds.

255.2.1.2 Estrous Cycle

In the absence of ovulation or pregnancy, repeated estrous cycles occur every 10 to 14 days during increasing photoperiod. The interval between repeated heat cycles is referred to as the *interestrous interval*. Other than the polyestrous cycle, which results in an interestrous interval, the queen has an estrous cycle that may be considered in four phases, which are similar to those in the dog: proestrus, estrus, diestrus, and anestrus.

Proestrus, the period of follicular development, is characterized by increasing serum estrogen concentrations. Queens do not permit mating during proestrus. The average duration of proestrus in the queen is 1 day. During this time, increased affection may be noted by the observant owner; however, proestrus is difficult to identify clinically. Under the influence of estrogen, the epithelial cells of the vaginal vault become cornified during proestrus and continue to cornify during estrus. In queens that permit vaginal cytology, vaginal smears may aid in the identification of proestrus.

Estrus, the period of sexual receptivity, is associated with follicle maturation and peak circulating serum concentrations of estrogen. In the queen, peak serum estrogen concentrations occur at the same time as maximal vaginal epithelial cornification. During estrus the queen permits copulation. The average duration of estrus in the queen is approximately 7 to 9 days regardless of coitus or ovulation.[6] There are few external physical signs of estrus in the queen. The female cat in estrus exhibits extreme affection, with a marked increase in head rubbing, vocalization, and frequent crouching of the thoracic limbs with rigid extension and treading of the pelvic limbs. Queens in estrus may also exhibit other signs, such as lordosis, and a laterally deviated tail. The presence of a male cat is not required to induce clinical signs of estrus. Queens subjected to stress may not exhibit behavioral estrus.

During copulation the male mounts the female and frequently bites the scruff of her neck. Male thrusting induces vocalization in the queen, which may be attributable to vaginal distention.[2] During the immediate postcoital period, the female exhibits a characteristic rolling and grooms the perineal region. Multiple copulations are common during estrus and may occur as frequently as every 15 to 20 minutes. The queen may exhibit mate preference towards particular tomcats.

After estrus the queen progresses through her estrous cycle, depending on the time of year, whether she experienced coitus, and her fertility. One of two outcomes follows estrus (Figure 255-2). One possible outcome is a nonovulatory cycle. Lack of ovulation typically occurs because of lack of copulation. If a queen does not ovulate, her estrous cycle will be 18 days long. This includes approximately 8 days of proestrus and estrus with a 10 day interestrous interval[5] (Figure 255-3). Anovulatory queens continue to exhibit signs of estrus every 18 days, providing they are exposed to increasing day length.

The other possible outcome is an ovulatory cycle. Estrogen priming of the reproductive tract is required to permit a surge in luteinizing hormone (LH) and ovulation in the queen. Historically, the release of gonadotropin hormone and ovulation in the cat were thought to occur only with stimulation of the vestibule and cervix associated with mating; however, spontaneous ovulation also occurs in the domestic cat.[2,5]

If the queen ovulates and forms functional corpora lutea, the rise in the serum progesterone concentration marks the start of *diestrus*. During diestrus, the serum estrogen concentration returns to baseline, and an increase in the serum progesterone concentration inhibits ovarian follicular development and return to estrus (Figure 255-4).

During an ovulatory nonpregnant cycle, the length of diestrus is determined by the life span of the corpora lutea. In the absence of pregnancy, the corpora lutea spontaneously regress after 35 to 37 days. At this time, the serum progesterone concentration returns to baseline, and the queen exhibits behavioral estrus approximately 10 days later. This results in an interestrous interval of about 45 days.

During an ovulatory pregnant cycle, the life span of the corpora lutea is prolonged and maintains the serum progesterone concentration above baseline for the duration of pregnancy. If the pregnancy is carried to term, gestation length is about 65 days. After queening, lactational anestrus typically delays the return to

heat for an additional 45 to 50 days. Lactational anestrus is caused by inhibition of the synthesis of gonadotropin-releasing hormone (GnRH) as a result of sensory input caused by suckling. The ovulatory pregnant interestrous interval in the queen is approximately 120 days if lactational anestrus occurs. Pregnancy loss after 35 days results in a variable interestrous length. Typically, signs of estrus are detected about a week after pregnancy loss.

The interestrous interval is defined as the interval between repeated heat cycles, during which the queen does not exhibit signs of estrus or permit coitus. In the absence of ovulation or pregnancy, the normal interestrous interval in the queen is approximately 10 to 14 days. At the end of the interestrous interval, the onset of behavioral estrus is associated with waves of ovarian follicular activity and increased estrogen production. Each estrus is not necessarily associated with a new follicular wave. Typically, during the interestrous interval, the serum estrogen concentration returns to baseline, and the subsequent estrous behavior is associated with a new follicular wave. However, in some cats, follicular waves may overlap, or the serum estrogen level may not return to baseline during the interestrous interval. Clinically, these individuals are identified by persistent behavioral estrus, prolonged estrus, or "nymphomania." This phenomenon is neither typical nor abnormal.

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Figure 255-2 Flow diagram depicting the possible outcomes after behavioral estrus in the queen.

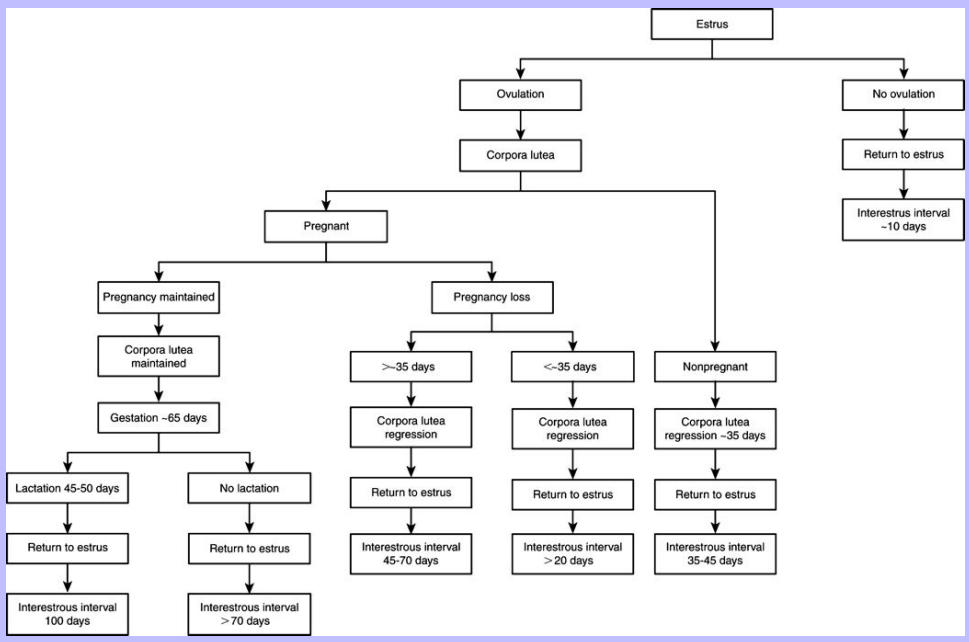
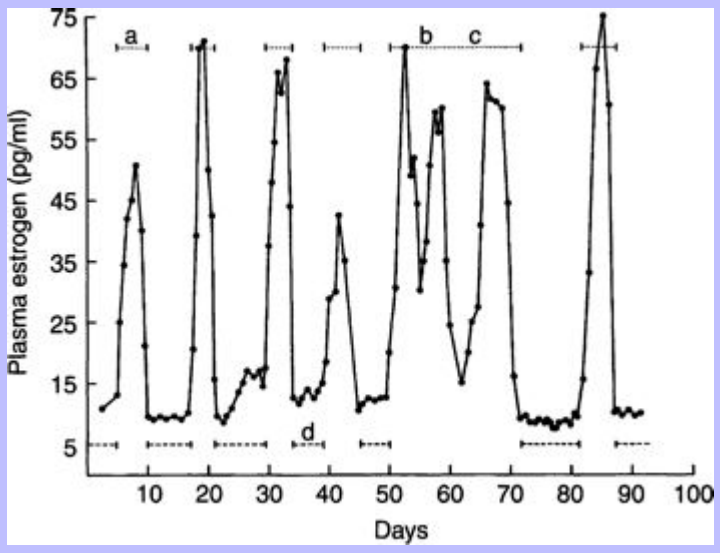
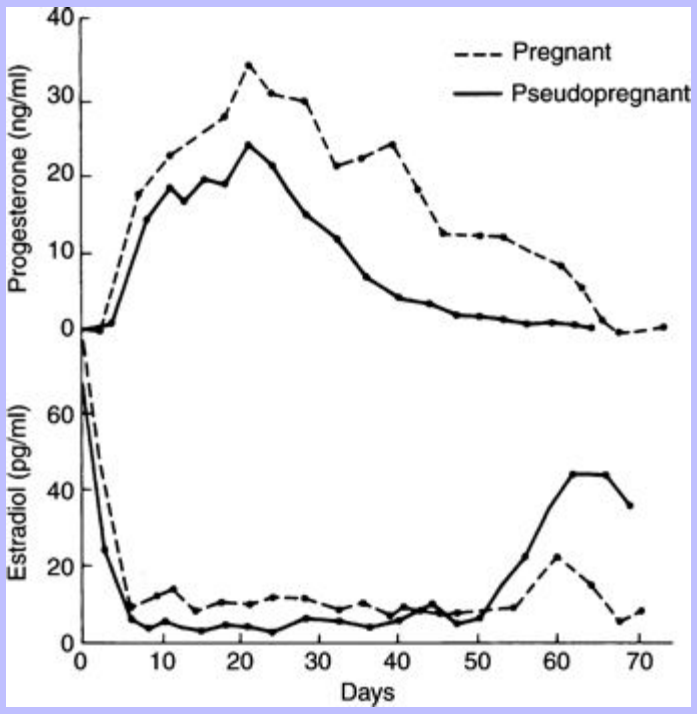


Figure 255-3 Schematic representation of the various estrogen secretion patterns that may occur during the estrous cycle of the cat. (From Feldman EC, Nelson R [eds]: Canine and Feline Endocrinology and Reproduction, 3rd ed. WB Saunders, 2001, pp 744 and 992.)



Anestrus is a time of ovarian quiescence, when there is no ovarian follicular activity or functional corpora lutea (CL). In the queen, anestrus occurs in association with a short photoperiod, when females are exposed to less than 4 to 6 hours of light per day. Outdoor queens typically enter anestrus during winter. Indoor queens may exhibit anestrus when exposed to less than 6 hours of light per day. Anestrus also results from exposure to continuous light due to ovarian hyperstimulation.

Figure 255-4 Average concentrations of progesterone and estrogen during ovulatory cycles in the queen. (From Feldman EC, Nelson R [eds]: Canine and Feline Endocrinology and Reproduction, 3rd ed. WB Saunders, 2001, pp 744 and 992.)



255.2.1.2.1 Hormone profile of the queen's reproductive cycle

Increased photoperiod is associated with decreased circulating plasma concentrations of melatonin in the queen. Serum prolactin and melatonin concentrations are thought to fluctuate in association with one another. The exact relationship between the serum prolactin and melatonin concentrations and ovarian activity is not well understood; however, during periods of ovarian activity (estrus), serum concentrations of both are low.[7]

Estradiol 17-beta is produced in association with the follicular phase of the ovarian cycle by the developing follicles. The serum estrogen concentration peaks during estrus, often exceeding 80 pg/mL. In the absence of ovulation, ovarian follicles regress, and the serum estrogen concentration typically decreases to baseline (less than 20 pg/mL) during the interestrous interval. As a new follicular wave develops, the cycle continues until cessation of the breeding season or induction of ovulation.

Induction of ovulation in the queen has historically been attributed to vaginal stimulation causing an LH surge. The amplitude and duration of each LH surge are influenced by the intensity and frequency of coital stimulation. An optimal LH surge is reported in association with four copulations within a 2-to 4-hour period. In some instances spontaneous ovulation occurs.

If ovulation occurs, the resulting corpora lutea induce an increase in the serum progesterone concentration within 24 to 48 hours. The serum progesterone level during diestrus may be as high as 60 ng/mL. In the nonpregnant female, the feline corpora lutea exhibit spontaneous regression after 35 to 37 days. A decline in the serum progesterone concentration is noted around day 25, with a return to baseline by day 40. In the pregnant animal, unknown mechanisms result in maintenance of the corpora lutea, with the serum progesterone concentration remaining greater than 2 ng/mL for the duration of gestation. The specific factors responsible for luteotropic support in the cat are unknown, but they may be associated with placental development, fetal development, or other, unidentified factors.

The serum relaxin concentration is detectable only in the pregnant queen. In early pregnancy (until day 25 of gestation), the serum concentration is low. Peak concentration (7 to 9 ng/mL) is reached around day 35 of gestation. During the last 15 days of gestation, a decline is noted, and the serum relaxin concentration is undetectable 24 hours prior to parturition.[8]

In the pregnant queen, the serum prolactin concentration begins to increase at day 35 of gestation and peaks prior to parturition. Prolactin is luteotropic in the pregnant queen and is the hormone responsible for mammary development and lactation. Administration of a dopamine agonist (e.g., cabergoline) results in a decrease in serum prolactin and a decline in serum progesterone. Serum prolactin concentrations are low during estrus.

255.2.1.2.2 Vaginal cytology during the estrous cycle

Vaginal cytology samples from the cranial vagina may be difficult to obtain in the conscious queen using a cotton tip applicator due to the narrowness of the vaginal vault. As an alternative, a small volume of saline (0.5 mL) can be flushed into and aspirated from the vagina to harvest vaginal epithelial cells. Vaginal cytology varies during the estrous cycle of the queen. During proestrus, the increasing serum estrogen concentration is reflected by an increase in the percentage of cornified vaginal epithelial cells. As queens enter estrus, mucous secretions thin, and debris is less visible in the background of vaginal smears; this is referred to as *clearing*.

An increase in keratinized anuclear squames is also noted on vaginal cytology during estrus in the queen.[7] Vaginal cytology during the interestrous interval is characterized by the predominance of nucleated superficial and intermediate squamous epithelial cells. The diestrus smear in the cat has a predominance of parabasal cells. During anestrus, vaginal cytology is similar to that during the interestrous interval, with a predominance of nucleated superficial and intermediate epithelial cells and much background debris.[7] Red blood cells are not noted during any phase of the reproductive cycle. Clinically, vaginal cytology in the queen may be used to detect the influence of estrogen in queens that fail to exhibit behavioral estrus or in those suspected of having ovarian remnant syndrome. Vaginal cytology is not a useful adjunct for ovulation timing in the queen nor is it useful for determining queening dates.

255.2.2 The Tomcat

The reproductive life span of the tomcat is reported to be more than a decade. In the absence of routine semen evaluation, information about reproductive performance is limited to litter production. Early declines in ejaculate quality typically remain undetected.

255.2.2.1 Sexual Maturity

Although spermatozoa may be evident in the spermatic cord of tomcats as early as 30 weeks of age, sexual maturity and the ability to mount, complete penile intromission, and ejaculate is rare prior to 12 months of age. Tomcats are typically sexually mature by 24 months of age. Persian and British breeds may mature later (3 years of age). Early characteristics associated with the development of sexual maturity in the tomcat include development of a rounded face and the onset of fighting, marking and mounting behaviors. Testicular descent is usually complete prior to birth. Spermatogenesis occurs in association with testicular weights greater than 1 g as body weight approaches 3 kg. The tomcat is capable of spermatogenesis year round; however, there is evidence of seasonal variation in sperm production and increased spermatozoa concentrations during long photoperiods.

255.2.2.2 Hormonal Profile of the Tomcat

The basal serum testosterone concentration in the intact male cat varies as a result of the pulsatile nature of the release of LH and follicle-stimulating hormone (FSH) from the pituitary. The serum testosterone concentration is an unreliable indicator of testicular function. In the domestic cat, penile spines develop under the influence of testosterone and provide a clinically useful bioassay for detection of circulating testosterone.

255.3 COMMON CLINICAL PROBLEMS

255.3.1 The Queen

255.3.1.1 Abnormal or Prolonged Estrous Behavior

Estrous behavior in a previously ovariohysterectomized female cat may indicate the presence of ovarian remnant syndrome. Alternatively, abnormalities of the zona reticularis of the adrenal cortex may be associated with sex hormone production. Ultrasonographic examination of the abdomen and evaluation of the serum sex hormone concentrations, along with stimulation of adrenocorticotrophic hormone (ACTH), may be useful for distinguishing between the two syndromes. Abnormal adrenal sex hormone production in the queen is uncommon.

255.3.1.2 Ovarian Remnant Syndrome

Ovarian remnant syndrome is the presence of functional ovarian tissue in a previously ovariohysterectomized animal. Functional residual ovarian tissue may produce enough follicular activity to trigger clinical signs of estrus in a female cat that had undergone ovariohysterectomy (OHE). Clinical signs of estrus generally occur months to years after OHE but can begin days after the surgery. The residual ovarian tissue is typically not in an abnormal location, and there appears to be no predisposition for the left or right ovary.[9] Accessory ovaries have been reported, but failure to remove ovarian tissue that extends into the mesovarium is more likely. Revascularization of free-floating ovarian tissue has been reported.[10]

The diagnosis of ovarian remnant syndrome is based on observation of appropriate clinical signs and confirmation of the presence of functional ovarian tissue through measurement of the serum estradiol

and/or progesterone levels. A serum estradiol concentration greater than 20 pg/mL is associated with clinical signs of estrus. Vaginal cytology is an inexpensive, convenient bioassay that can confirm the influence of estrogen (i.e., cornification of the vaginal epithelium). Provided that no adrenal pathology exists and that exogenous estrogens are not being administered, ovarian remnant syndrome is the most likely cause of cyclic estrous behavior in a cat thought to have been surgically neutered. Various techniques for confirming the presence of ovarian tissue through the use of GnRH or HCG have been described; however, this is seldom clinically justified.[11] An increased serum progesterone level (greater than 2 ng/mL measured 2 to 3 weeks after estrus) may be seen in association with luteinization of ovarian remnants.

Removal of residual ovarian tissue by exploratory celiotomy is curative. Surgery is recommended during estrus or diestrus, because the presence of ovarian follicles or corpora lutea aids the identification of residual ovarian tissue. Medical suppression of follicular ovarian activity with progestational or androgenic compounds is less desirable because of the side effects, such as diabetes mellitus.

255.3.1.3 Mucometra and Pyometra

Mucometra and pyometra may occur in the queen in association with cystic-endometrial hyperplasia or as separate clinical entities. Under the influence of progesterone, the intrauterine leukocyte response is suppressed, myometrial contractility is reduced, and endometrial gland development is stimulated. Uterine quiescence and endometrial gland secretions create an opportune environment for bacterial proliferation. Intrauterine bacterial contamination may occur via ascending the urogenital tract or by the hematogenous route, resulting in a pyometra. Alternatively, the uterus may become distended with mucus and may remain sterile, resulting in a mucometra. *E. coli* is the most common intrauterine bacterial isolate in feline pyometra. Exogenous progesterone administration and repeated heat cycles without pregnancy precipitate the development of pyometra.

The clinical signs associated with pyometra in the queen vary with cervical patency. Most queens with pyometra are ill at the time of examination, having clinical signs ranging from anorexia, lethargy, and weight loss to those of septic shock and peritonitis resulting from uterine rupture. Queens with an open-cervix pyometra typically exhibit a moist perineum and purulent vaginal discharge, and owners may report increased grooming behavior. Polyuria and polydipsia may be noted in association with open and closed pyometra as a result of the nephrogenic diabetes insipidus that occurs secondary to the effect of *E. coli* endotoxins on renal antidiuretic hormone (ADH) receptors.

Clinicopathologic evaluation most often reveals a neutrophilic leukocytosis and hyperglobulinemia. Hypoalbuminemia may be noted in association with sepsis, and a decreased blood urea nitrogen (BUN) may be noted with severe polyuria and polydipsia. The serum progesterone concentration at the time of diagnosis typically is greater than 5 ng/mL. Vaginal cytology is unreliable for the diagnosis of pyometra. 1701
However, cytologic specimens containing numerous degenerate neutrophils with intracellular bacteria are 1702
consistent with pyometra. Ultrasonographic evaluation of the uterine horns is a reliable method of diagnosing pyometra. The uterine lumen is typically distended with flocculent material of variable echogenicity (Figure 255-5). Cystic ovarian structures may be noted, but the ultrasonographic appearance of the ovary varies.

The treatment of choice for pyometra is medical stabilization with antimicrobials and intravenous fluids, followed by surgical ovariohysterectomy. Medical therapy with natural prostaglandins and antimicrobials may be considered for queens with mucometra or for some cats with pyometra. Successful treatment of mucometra and pyometra with prostaglandin$_2$-α (PGF_2-α) (Lutalyse; Pharmacia and Upjohn, Kalamazoo,

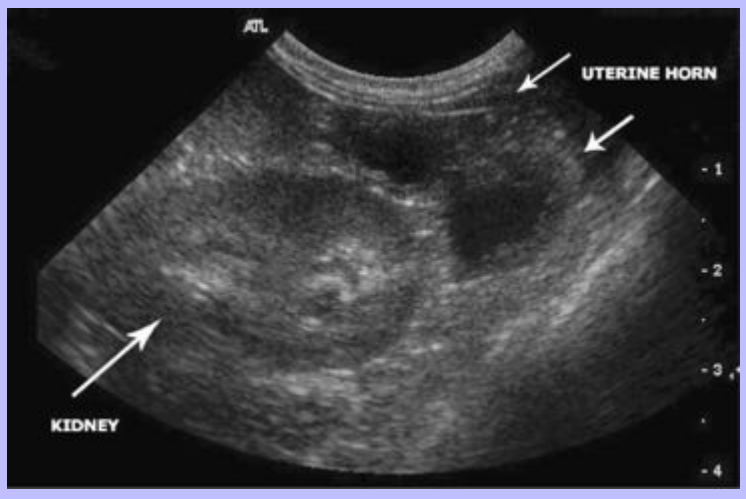
Michigan) results from the drug's effect on the uterine myometrium, cervix, and corpora lutea. In the queen, the corpus luteum is relatively resistant to the effects of exogenous prostaglandins. Repeated measurement of the serum progesterone concentration is advised prior to and during prostaglandin therapy to identify animals with persistent luteal function. Medical therapy should be considered only if an animal is of reproductive importance. Candidates for medical PGF_2-α therapy should be young (less than 6 years of age) and otherwise healthy, with evidence of a patent cervix (i.e., vaginal discharge). Contraindications for medical management of pyometra or mucometra include sepsis, peritonitis, significant organ disease, or old age, which is associated with an increased incidence of cystic endometrial hyperplasia. Concurrent administration of bactericidal broad-spectrum antimicrobials is advised.

PGF_2-α should be administered subcutaneously at a dosage of 0.1 mg/kg twice a day for 2 days, and increased to 0.2 mg/kg twice a day until abdominal ultrasound scans reveal no evidence of uterine enlargement, the complete blood count (CBC) has normalized, polyuria has improved, and the serum progesterone level is less than 5 ng/mL. Synthetic prostaglandins are available for use in Europe, and the dosage must be adjusted to account for the variation in potency. Side effects of prostaglandin therapy include restlessness, emesis, salivation, tenesmus, diarrhea, lordosis, and kneading. Administration of the prostaglandin at a reduced dosage for the first 48 hours should reduce the severity of side effects. Breeding at the next estrous cycle is recommended.

255.3.1.4 Pregnancy Termination

Please refer to Chapter 250.

Figure 255-5 Ultrasonographic image of dilated uterine horns in a cat with pyometra. (Courtesy Tom Baker, University of California, Davis.)



255.3.1.5 Abnormal Mammary Development not Associated with Pregnancy

Mammary development in a nonpregnant or spayed female is abnormal. Care must be taken to distinguish between mammary development, which typically involves more than one gland, and formation of a

mammary mass. Mammary development occasionally may occur in male or female cats in association with cessation of exogenous progestogen administration; however, the degree of mammary development is usually mild and transient.

In comparison, mammary hyperplasia (also known as *fibroadenomatous mammary hyperplasia*) is associated with dramatic enlargement of multiple mammary glands (Figure 255-6). The glands typically are painless, but they may become necrotic and subject to secondary infection. Usually no milk production occurs in these glands. Mammary hyperplasia is most frequently noted in young animals after their first estrous cycle. The condition appears to be associated with an increase in the serum progesterone concentration, and antiprogestins may be indicated.[12] Surgical mastectomy is indicated with severe necrosis or infection.

255.3.1.6 Mammary Masses

Mammary tumors are the third most common neoplasia in cats. Early ovariohysterectomy is associated with a decreased risk of mammary neoplasia. Most feline mammary tumors are malignant, and carcinomas are the most common tumor type.[13] Any detected mammary mass in the feline should be surgically removed with wide margins by an experienced surgeon and considered malignant until proven otherwise. Prior to surgical excision, ultrasonographic evaluation of the regional lymph nodes and radiographic evaluation of the thorax are advised to detect metastatic disease.

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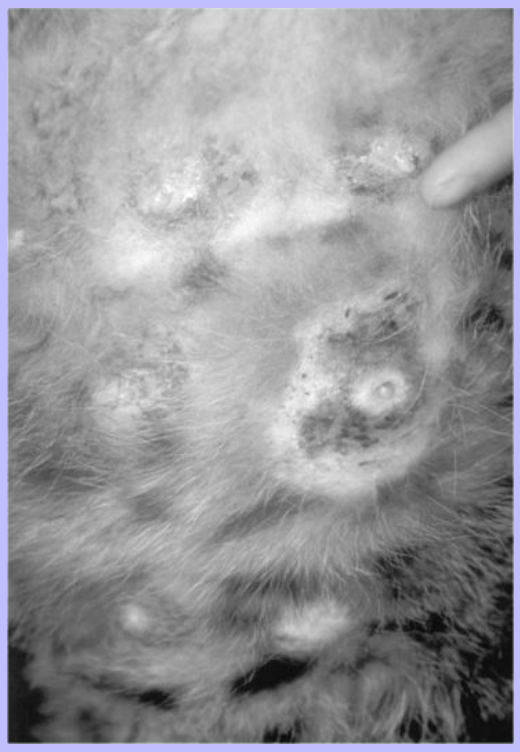
Figure 255-6 Mammary hyperplasia in a cat. (Courtesy Dr. Richard Nelson, University of California, Davis.)



255.3.1.7 Subfertility and Infertility

Valuable breeding queens are commonly brought to a veterinarian for evaluation as a result of failure to reproduce at an expected rate. It is essential that, in addition to ensuring that clients have realistic expectations, the clinician take a logical and thorough approach to evaluation of the animal's reproductive performance and health. *Subfertility* in the queen refers to failure to produce an expected number of live kittens successfully; this may occur as a result of failure to breed or conceive or failure to carry fetuses to term. *Infertility* refers to the absolute inability to reproduce. Prior to any examination, cattery and breeding management must be evaluated to ensure that true subfertility or infertility exists. Good husbandry has a significant impact on reproductive performance in any species. Stocking density must be low enough to reduce stress associated with social situations and crowded conditions. Noise pollution should be avoided. Transport of animals between cages, and properties should be minimal. An adequate plane of nutrition should be maintained. Prophylactic techniques for common conditions should be performed on a regular basis, including routine retrovirus evaluation, appropriate vaccinations, grooming, nail trimming, dental care, external and internal parasite control, and appropriate quarantine.

Cattery owners should have a basic understanding of feline reproductive physiology so that estrous behavior, mating, and queening can be accurately recorded. Queens should be mated with a proven tomcat prior to infertility evaluation and ideally should be 1 to 6 years of age.

After ensuring that breeding management is adequate, the clinician should take a complete history and perform a thorough physical examination. The queen should then be further categorized based on her reproductive status.

255.3.1.7.1 Failure to cycle

A combination of silent heat and spontaneous ovulation may lead an owner to believe that a queen has chronic anestrus. Regardless of whether the owner believes that the queen cycles, evidence for ovarian activity should be obtained. Vaginal cytology provides a convenient bioassay for the influence of estrogen during intervals of increasing photoperiod. Animals that fail to show signs of estrus during appropriate light exposure may be categorized as having prolonged anestrus.

Differential diagnoses for prolonged anestrus should include inadequate light exposure, prior gonadectomy, stress, abnormalities of sexual development, and drug administration. If all differentials have been excluded, attempts can be made to induce estrus by housing a tomcat nearby and increasing the day length. Where appropriate, pharmacologic induction through administration of dopamine agonists or FSH analogs can be attempted.

255.3.1.7.2 Prolonged estrus

As previously mentioned, overlapping waves of follicular activity in the queen may result in signs of persistent estrus. Other explanations include ovarian follicular cysts and exogenous estrogen administration. Abdominal ultrasound is useful for detecting ovarian cysts. The cysts are typically greater than 4 mm in diameter and are visible in the parenchyma of the ovary; however, they may be difficult to differentiate from follicles. Ovariohysterectomy is curative.

255.3.1.7.3

Failure to ovulate

Queens with ovulatory failure maintain an interestrous interval of approximately 10 days during the breeding season. Successful ovulation depends on the presence of mature follicles and an adequate LH surge, which is dependent on the frequency and number of copulations (if spontaneous ovulation does not occur). Failure to ovulate indicates that mating was incomplete or that it occurred too infrequently or at the wrong time. Breeding management should be re-evaluated.

255.3.1.7.4

Failure to conceive (prolonged interestrous interval) and pregnancy loss

An interestrous interval greater than 25 days indicates that ovulation likely occurred. Explanations for failure to conceive include true conception failure and early fetal resorption. Ovulation should be confirmed by measurement of an increased serum progesterone concentration 48 to 72 hours after cessation of mating. Abdominal ultrasonography may also be used to evaluate for implantation. Fetal resorption occurs most commonly in association with congenital defects, which may occur secondary to teratogen exposure. Feline leukemia virus is an important viral cause of embryonic death, fetal death, and abortion in the queen. Other infectious causes of fetal resorption include chlamydia, feline panleukopenia virus, feline coronavirus, and feline respiratory virus complex. *Toxoplasma* infection has been implicated in feline infertility. Bacterial infections (e.g., *Salmonella* spp.) are more likely to result in abortion than resorption.

255.3.1.7.5

Uterine monitoring for prevention of early pregnancy loss

Uterine monitoring may be used during gestation to evaluate for premature uterine contractions (Figure 255-7). Pregnancy loss as a result of hypoluteoidism has not been documented in the queen. It is more likely that any decrease in serum progesterone associated with premature contractions occurs secondary to endogenous prostaglandin release and destruction of the CL. Clinical signs associated with premature contractions are typically limited to an abnormal vaginal discharge (usually hemorrhagic) prior to term in the pregnant queen. Tocolytic agents (e.g., terbutaline) have been tried successfully in queens to reduce uterine contractions and carry pregnancy to term.

255.3.1.7.6

Abnormal sexual behavior

Infrequently, queens may exhibit intense dislike for particular males and refuse to allow breeding. Selection of an alternate male or artificial insemination resolves the problem. In queens that fail to show signs of estrus or that refuse to permit copulation, induction of ovulation followed by artificial insemination may be required.

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Figure 255-7 Pregnant queen with uterine monitor in place. (Courtesy Karen Copeley, Veterinary Perinatal Services, Colorado.)

255.3.1.7.7 Uterine pathology

Cystic endometrial hyperplasia may be associated with infertility in the older queen. Definitive diagnosis requires uterine biopsy. No effective treatment is available.

255.3.2 The Tomcat

Tomcats are not typically brought to the veterinarian for reproductive evaluation unless they have an external abnormality of the genital tract, are exhibiting poor libido, or show evidence of infertility.[14]

255.3.2.1 Abnormalities of the Genitalia

255.3.2.1.1 Trauma

Injury to the external genitalia and other parts of the body is common in tomcats as a result of intermale aggression and fighting behavior. Routine wound management, consisting of cleaning, debridement, and antimicrobial therapy, is appropriate. Animals not intended for breeding should be castrated.

255.3.2.1.2 Cryptorchidism

Testicular descent in the tomcat is usually complete at birth. However, because continued movement of the testicles in the inguinal canal is noted until puberty, it is wise to delay evaluation for cryptorchidism in the tomcat until 6 months of age. The incidence of cryptorchidism in the tomcat is low, and there appears to be no predilection for the left or right side. In one retrospective study, cats were more likely to be unilaterally cryptorchid.[15] In the cats with bilateral cryptorchidism, both testicles were in the

abdominal cavity. Persian cats were over-represented.[15] Medical therapy for the treatment of feline cryptorchidism cannot be advocated due to suspected heritability. Surgical castration is curative.

There is a single report of estrous behavior in a bilaterally cryptorchid tomcat in association with interstitial cell hyperplasia.[16] Feminizing syndromes in association with cryptorchid testicles and Sertoli cell tumors are extremely rare in the cat.

255.3.2.1.3 Testicular hypoplasia

Testicular hypoplasia is rarely reported in the tomcat, because most male cats are castrated. However, it has been detected in association with prepu-bertal panleukopenia infection, as a result of fever-induced germinal layer destruction, and in association with vitamin A deficiency.

255.3.2.1.4 Orchitis

Orchitis is rare in the tomcat and usually occurs secondary to a bite wound. It may also be the result of extension of peritoneal infection through the inguinal ring in association with feline infectious peritonitis. Cats are naturally resistant to *Brucella canis* infection.

255.3.2.1.5 Persistent penile frenulum

In the cat, breakdown of the penile and preputial mucosal surface adhesion is an androgen-dependent phenomenon. Persistent penile frenulum is associated with early castration (before 7 weeks of age).

255.3.2.1.6 Phimosis, paraphimosis, and priapism

Phimosis (constriction of the orifice of the prepuce) and *paraphimosis* (inability to retract the penis into the prepuce) are unusual in cats but may occur secondary to preputial trauma, or to entanglement of the hairs of the prepuce. *Priapism* (persistent erection) is also uncommon but has been reported in association with hemostasis, thrombosis, and failure of detumescence.[17]

255.3.2.2 Prostatic Disease

The prostate is rudimentary and generally of little clinical concern. However, both bacterial prostatitis and prostatic neoplasia have been reported in the cat.[18,19] Clinical signs include dyschezia and intermittent constipation and hematuria.

255.3.2.3 Urine Spraying and Masturbation

The tomcat sprays urine to identify territory, and this is considered normal behavior for an intact male. Castration resolves urine spraying in 80% of cats.[20] Urine spraying may persist in the castrated cat and is considered undesirable by most owners. It is important for the clinician to distinguish between urine spraying (typically on vertical surfaces) and inappropriate elimination. Selective serotonin reuptake inhibitors and tricyclic antidepressants are commonly used to reduce the occurrence of urine spraying in castrated males. There is a single case report describing the successful use of cyproheptadine for the treatment of urine spraying and masturbation in a tomcat.[20]

255.3.2.4 Infertility

Evaluation of the tomcat for infertility is uncommon. Limited data are available regarding common problems and their successful management. Reported reasons for reproductive evaluation of the tomcat associated with infertility include lack of libido, behavioral abnormalities, trauma, and infections. Tomcats infrequently undergo semen evaluation because of the reluctance of most owners to permit general anesthesia and electroejaculation to enable semen evaluation and because of the general lack of availability of this service in private practice. Evaluation of infertility in the tomcat should include cattery management evaluation as described for the queen. A complete physical examination should be performed and a routine clinicopathologic and infectious disease database should be obtained, in addition to evaluation of the genital tract for signs of trauma or abnormality.

255.3.2.5 Lack of Libido

Gonadal abnormalities or sexual immaturity may result in a lack of libido in the male cat. In breeds that are typically late maturing, the evaluation should be delayed until 3 years of age. The penis should be examined to document the influence of testosterone. Testicular palpation and measurement of testicular volume should be performed; however, currently, little published data correlate reproductive performance with testicular volume in the cat. Breeding management should be reviewed to ensure that husbandry or stress is not a contributing factor. If permitted, electroejaculation, semen evaluation, and artificial insemination are advised if the cat appears to be clinically normal and management problems have been excluded. Testosterone supplementation is not recommended in tom cats as it results in negative feedback on endogenous hormone production, thereby exacerbating the problem.

255.4 NEOPLASIA OF THE GENITAL TRACT

Please refer to Chapter 188.

255.5 PREGNANCY AND PARTURITION

Fertilization takes place in the uterine tube. Morulae enter the uterus approximately 5 days after coitus, and embryos are distributed evenly in the left and right uterine horns. Superfecundation is possible. The hormonal profile during pregnancy reveals increased serum progesterone and relaxin concentrations and a low serum estrogen concentration. The serum prolactin concentration increases in the latter half of gestation. The main source of progesterone support is the corpora lutea. Waves of ovarian follicular activity may occur during pregnancy, resulting in fluctuations in the serum estrogen concentration, which can result in estrous behavior during gestation.

Figure 255-8 Ultrasound image of a gravid uterine horn with an intraluminal fetus and fetal membranes. (Courtesy Tom Baker, University of California, Davis.)

Pregnancy diagnosis by means of transabdominal palpation in the queen is best performed during the second and third weeks of gestation. During this time, palpation of the uterus reveals grape-sized vesicles. Later in pregnancy, the segmental nature of the uterine lumen is lost, and transabdominal palpation is more challenging. Abdominal ultrasonography is the preferred technique for diagnosing pregnancy in the queen, because it is easy to perform during all stages of gestation and it provides information regarding fetal viability (Figure 255-8). The normal fetal heart rate in the cat exceeds 200 beats per minute, and heart rates are detectable as early as 25 days after mating. Radiographic detection of the fetal skeleton is possible at 45 days after breeding.

A mild, transient increase in the serum estrogen level is noted several days prior to parturition; this is associated with upregulation of oxytocin receptor expression in preparation for parturition.

255.5.1 Care of the Pregnant Feline

Metabolic requirements do not increase until the second half of gestation. The current recommendation is to feed pregnant queens a commercially prepared, AAFCO-approved kitten diet at the time of pregnancy diagnosis; to increase the amount of food by 25% for weeks 5 and 6 of gestation; and to make an additional 25% increase for weeks 7 and 8 of gestation. Food intake may be increased a further 25% in the final week of gestation. Commonly, cat breeders supplement pregnant queens with raw liver during early pregnancy because of concerns about hypovitaminosis A; this is not necessary when queens are fed commercial cat food. Pregnant cats should be weighed once weekly and kept indoors. Weight gains in the range of 5% of body weight are anticipated per week. Routine vaccinations should be avoided because of the risk of cerebellar hypoplasia with the modified-live panleukopenia vaccine. Griseofulvin and glucocorticoids are known teratogens in the queen, and their use should be avoided during pregnancy.

255.5.2 Clinicopathic Changes in the Pregnant Queen

Plasma volume expansion in the queen results in a mild normocytic-normochromic nonregenerative anemia during late gestation. Queens should be given access to a box prior to their anticipated due date. A private

cardboard box lined with towels provides the queen with a quiet, dark environment while also permitting observation. Reports of the length of gestation in the cat vary because of the inability to establish the time of ovulation accurately. As a general rule, parturition occurs 65 days from the first known breeding.

Some queens have a decrease in rectal temperature approximately 12 hours prior to the onset of parturition. Stage one labor (cervical dilatation) commences with the onset of uterine activity and ends with complete cervical dilatation. During this stage, nesting behavior, increased licking of the perineum, and restlessness may be noted. Queens typically choose to stay in the queening box at this time. Some cats that are particularly bonded to their owners may actively seek them.

Typically, visible abdominal contractions indicate the start of stage two labor. This stage is defined by coordinated uterine contractions and expulsion of the neonate. The first delivery should occur within 1 to 2 hours of visible contractions. Clear, blood-tinged fluid is generally expelled from the vulva prior to delivery of the first kitten. It should be noted that posterior presentation of the neonate is common and is not necessarily associated with dystocia. Queening is typically completed within 12 hours. Litter size is breed dependent and ranges from one to 10 kittens per litter.

Dystocia is less common in the queen than in the bitch. Uterine monitoring as described in the bitch has been used successfully in the queen to identify impending labor and to aid in evaluation of dystocia.[21] Medical therapy with oxytocin and calcium gluconate may be attempted without uterine monitoring. Uterine monitoring, when possible, may demonstrate the nature of the problem, and response to therapy can then be accurately judged. Uteroverdin (green discharge) present prior to presentation of a kitten; an interval longer than 1 hour between kittens; a sick queen; or stage one labor that lasts longer than 24 hours without the onset of stage two labor warrants examination of the queen by a veterinarian. The initial evaluation should consist of a physical examination, digital vaginal examination, radiography of the abdomen to establish the presence of kittens, and abdominal ultrasonography to ascertain fetal heart rates. Generally speaking, fetal heart rates less than 150 beats per minute indicate fetal distress, and cesarean section is advised to reduce neonatal mortality and queen morbidity. If available, uterine monitoring may be used to direct medical management of dystocia.

Colostrum is produced as long as 72 hours postpartum. Neonates should nurse within 1 hour of birth. The typical duration of lactation in the queen is 4 to 6 weeks, depending on the time of weaning. Lactational anestrus is typical in nursing queens; however, signs of estrus may occur as early as 2 weeks postpartum.

255.5.3 Care of the Partum Queen

During lactation the metabolic demand doubles. In the immediate postpartum period, many queens are reluctant to leave their kittens and may show transient anorexia. A continuous supply of palatable, easily digestible, calorie-dense food should be available, in addition to an ample supply of fresh water. If possible, the food and water should be placed in the queening box during the first week of lactation to encourage consumption. Postpartum lochial discharge is normal in the queen and should be scant and reddish brown. Nursing queens should be monitored closely for signs of illness, such as excessive or abnormal vaginal discharge (putrid odor, black or green color), fever, inappetence, vomiting, or diarrhea.

Involution in the queen varies between nursing and non-nursing queens. In the non-nursing queen, uterine size and tone return to those of a prepartum queen by 4 weeks postpartum. In the nursing queen, continued hyperinvolution occurs, resulting in a uterus similar in tone and thickness to that seen during ovarian quiescence.[22]

255.6 PARTURIENT AND PERIPARTURIENT PRESENTATIONS

255.6.1 Neonatal Care

Please refer to Chapter 256.

255.6.2 Uterine Torsion

There are several reports of uterine torsion in the queen (Figure 255-9). Uterine torsion should be considered a possible problem in any queen seen in late pregnancy or during parturition with dystocia, abdominal pain, or hypovolemic shock.[23] Medical stabilization is essential to reduce mortality. Intravenous colloids may be indicated for blood volume expansion. In addition, pain relief, antimicrobial therapy, and plasma products may be indicated. After stabilization, exploratory celiotomy permits definitive diagnosis, and surgical ovariohysterectomy is curative.

255.6.3 Retained Placenta

Any excessive, malodorous vaginal discharge in the postpartum queen is abnormal. Placental retention should be a considered in any queen with a fever and increased or purulent, foul-smelling vaginal discharge in the immediate postpartum period. The diagnosis of retained fetal membranes is best made by means of ultrasonographic evaluation of the uterus, because owner observations may be unreliable. In these cases, abdominal ultrasonography reveals uterine horn distension and focal hyperechoic intrauterine contents in association with a retained placenta. Medical therapy, consisting of administration of PGF_2-α (Lutalyse), 0.1 mg/kg given subcutaneously once a day for 3 to 5 days, is typically effective. Concurrent antimicrobial administration is indicated in queens with a fever or marked leukocytosis.

255.6.4 Metritis

Acute metritis may occur in association with retained fetal membranes or as a result of ascending bacterial infection in the immediate postpartum period. Clinical signs of metritis include anorexia, fever, vomiting, kitten neglect, decreased milk production, and a purulent, sanguineous vaginal discharge. Medical therapy with PGF_2-α (Lutalyse) and antimicrobials may be attempted, providing that the queen is stable and the cervix is open.

255.6.5 Prolapsed Uterus

Uterine prolapse has been reported in the queen (Figure 255-10). Queens suspected of having uterine prolapse should be examined promptly to reduce desiccation and trauma to the exposed tissue. Manual replacement of the uterus can be attempted; however, because repeated prolapse tends to occur, ovariohysterectomy is advised.

Figure 255-9 Torsion of a gravid uterine horn. (Courtesy Dr. Gerald Ling, University of California, Davis.)

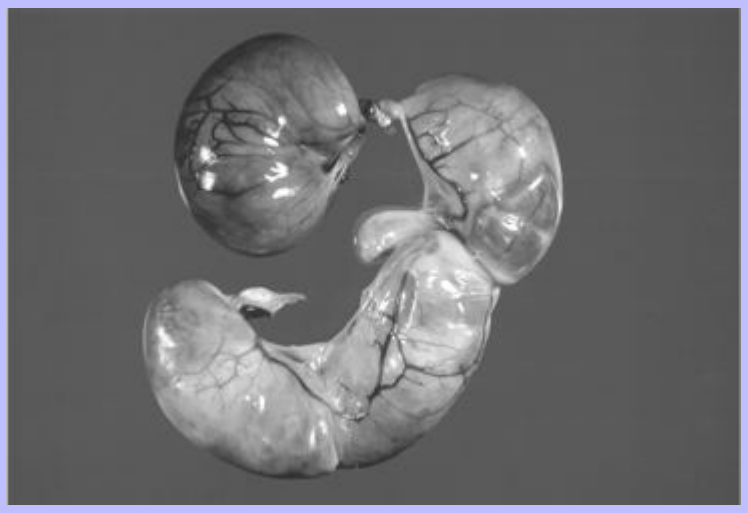

Figure 255-10 Uterine prolapse in a cat. (Courtesy Dr. Richard Nelson, University of California, Davis.)

255.6.6 Hypocalcemia

Hypocalcemia (eclampsia) may occur early in lactation as a result of the sudden increase in calcium loss associated with milk production. Clinical signs include incoordination, stiff gait, facial pruritus, muscle fasciculation, hyperthermia, and seizure activity. The diagnosis is based on clinical observations in the

lactating queen. Immediate medical therapy consists of slow intravenous administration of 2 to 5 mL of 10% calcium gluconate over 5 minutes. Repeated administration may be required to achieve resolution of clinical signs. The electrical activity of the heart should be monitored during intravenous calcium administration to evaluate for arrhythmia. Long-term therapy should include daily calcium carbonate supplementation (TUMS, 500 mg/day). If necessary, kittens should be prevented from nursing and should be hand raised after receiving colostrum.

255.6.7 Mastitis

Inflammation and subsequent bacterial infection of the mammary glands during lactation are common. Clinical signs include anorexia, lethargy, fever, and vomiting. Neonates may have diarrhea. Affected glands appear red and swollen and are warm and painful. Palpation may reveal firm areas associated with inflammation. The milk expressed from the affected glands may be grossly purulent and red or grayish, and the queen's body temperature may be increased. The most common bacterial isolates include *Enterobacter* sp., staphylococci, and streptococci. Medical treatment, consisting of warm compresses, stripping of the affected mammary glands, and administration of broad-spectrum antibiotics usually is curative. In severe cases, when inflammation results in tissue necrosis, surgical debridement may be required.

255.7 ASSISTED REPRODUCTION

255.7.1 Electroejaculation

Although male cats may be trained to ejaculate using an artificial vagina, most client-owned cats presented for semen collection are untrained. Semen collection and evaluation in the untrained tomcat are best achieved using electroejaculation techniques with the cat under general anesthesia. Many drugs commonly used for sedation in the cat interfere with urethral sphincter function. When electroejaculation is performed, urine contamination negatively affects the quality of the ejaculate. The preferred drug combination for electroejaculation in the cat is ketamine and xylazine. An alternate option, in a cooperative tom that permits placement of an intravenous catheter, is a constant-rate infusion of propofol. In a recent study, a propofol infusion was shown to have a minimal impact on urethral sphincter function in dog; however, studies in the cat have not been completed.[24]

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Once sedated, tomcats are placed in lateral recumbency, and a well-lubricated rectal electroejaculation probe of appropriate size is inserted into the rectum. The penis should be gently exteriorized and held in the normal caudal orientation for semen collection. For electroejaculation in the carnivore, probes with longitudinal electrodes are preferred.[25] The rectal probe is connected to a standard electroejaculator unit capable of measuring voltage and amplitude. The standard electroejaculation regimen uses a total of 80 electrical stimuli delivered in three series, consisting of 30 (series 1: 10 stimulations at 2, 3, and 4 V), 30 (series 2: 10 stimulations at 3, 4, and 5 V), and 20 (series 3: 10 stimulations at 4 and 5V) stimulations.[25]

Care should be taken to ensure light ventral pressure to maximize ejaculate yield. Semen should be collected in plastic supplies prewarmed to body temperature.

255.7.1.1 Semen Evaluation

Evaluation of the ejaculate should include determination of the semen volume, pH, and color, as well as the sperm count, percentage motility, progressive motility, gross morphology, and acrosomal integrity.[25] In comparison to the dog, cat ejaculate contains a higher concentration of spermatozoa (1.5 to 2×10^9/mL). Counts are best performed manually using a hemocytometer. The volume obtained varies with the skill of the person performing the electroejaculation; however, an ejaculate volume of 50 to 100 μL per series may be considered normal. The ejaculate should be cloudy. The normal pH of feline ejaculate is 7.4 to 8.3. Urine contamination is suggested by a yellow discoloration and is confirmed by a pH less than 7.4.

Immediately after collection, the ejaculate should be evaluated at body temperature for the percentage motility and progressive motility of sperm. Normal progressive motility of sperm in the cat is 50% to 80%. Sperm morphology is a commonly used indicator of fertility in the male. In general, lower fertility is thought to be associated with a higher percentage of morphologically abnormal spermatozoa and/or a lower percentage motility. However, studies evaluating the percentage of normal spermatozoa required for consistent fertility have not been completed.[26] The gross morphology of feline spermatozoa may be determined by fixing an ejaculate aliquot (20 μL) in 500 μL of glutaraldehyde (1% solution), followed by phase contrast light microscopic evaluation at ×1000.[25] If phase contrast microscopy is not available, morphologic assessment can be performed by staining an air-dried smear of ejaculate with Diff Quick. Some domestic cats consistently ejaculate a high proportion (greater than 50%) of morphologically abnormal spermatozoa without associated infertility.[27]

Evaluation of acrosomal integrity is a useful adjunct to semen evaluation because it is critical to the fertilization process. Examination of the unstained feline acrosome may be challenging because of the small size of spermatozoa (26 μm long). Acrosomal staining prior to evaluation may be done in the cat using the protocol described by Larson and Miller,[28] or it may be completed with phase microscopy if available.

255.7.2 Semen Freezing

Cryopreservation of feline semen is important for the preservation of genetically valuable animals. Although semen freezing in the cat is not routinely performed in private practice, electroejaculation and semen collection and evaluation for the tomcat are not difficult. Numerous protocols have been described for cryopreservation of feline spermatozoa, the details of which are outside the scope of this chapter.[29,30] Of importance is the susceptibility of feline spermatozoa to cold shock. To minimize damage, extreme care must be taken to ensure that everything that comes in contact with feline spermatozoa is at the same temperature as the sperm cells themselves. As a general rule, anything that is added to feline spermatozoa should be added slowly, with gentle mixing. Because of the high incidence of pyometra associated with feline artificial insemination, antimicrobials (commonly penicillin and streptomycin) typically are added prior to insemination.

255.7.3 Induction of Estrus and Induction of Ovulation in the Queen

Infrequently, induction of estrus may be required in the queen for artificial insemination with frozen semen or for queens that fail to exhibit clinically detectable signs of estrus. Induction of estrus in the sexually mature queen has been successfully achieved using exposure to long photoperiod or with administration of exogenous gonadotropins. Various protocols and dosing regimens have been described. Dosing regimens are described

per cat, because ovulatory response is not related to body weight. Typically, 100 to 200 IU of equine chorionic gonadotropin (ECG; Sigma Chemical Co., St. Louis, Missouri) is used to stimulate follicular development, and 100 to 150 IU of human chorionic gonadotropin (HCG; Sigma Chemical Co.) is used to stimulate final follicle maturation and ovulation.[31,32] Ovulation occurs approximately 24 to 36 hours after administration of HCG.

The authors' preferred protocol is ECG, 100 to 150 IU, given subcutaneously or intramuscularly on day 1, followed by HCG, 50 to 100 IU, given subcutaneously or intramuscularly 84 hours later. Insemination should be performed 2 to 3 days after HCG administration. Alternatively, cabergoline (5 µg/kg given orally every 24 hours) can be administered for a maximum of 15 days. Insemination should be performed on day 3 of estrus. Ovulation in the cat is compromised by preovulatory anesthesia. If artificial insemination is to be performed, it is important that ovulation occur prior to anesthesia or it may be inhibited. Because of the molecular size of exogenous gonadotropins, repeated administration may be associated with antibody formation and reduced ovarian response. The immunologic consequences of exogenous gonadotropin administration may be minimized by reducing the frequency and number of times they are used during an animal's reproductive life.

255.7.4 Artificial Insemination

Cervical patency varies during the feline estrous cycle. Vaginal insemination is readily achieved using a bulb-tipped, 20-gauge needle and 1 mL syringe. Blind transcervical catheterization under general anesthesia has also been described.[33] The suggested insemination dose for artificial insemination is 50 million progressively motile spermatozoa.

Laparoscopic insemination in felines is well described. The suggested insemination dose is 10 million progressively motile spermatozoa per uterine horn.

255.8 CONTRACEPTION

Please refer to Chapter 250.

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256 CHAPTER • 256 Care of the Neonate and Fading Pups

Gary C.W. England

The incidence of neonatal death is surprisingly high in domestic dogs born in pet homes and to private breeders. The incidence of stillbirth is 6% to 33% of all births, and the neonatal death rate ranges from 6% to 11%. Some of these cases can be attributed to genetic factors or dystocia, which can be difficult to avoid. However, in many such deaths, inappropriate or poor husbandry practices are the cause or a contributing factor. It is clear, however, that this need not be the case; in a survey of 1342 puppy births at the Guide Dogs for the Blind Association in the United Kingdom, the total rate for stillbirth and neonatal loss (up to 6 weeks of age) was less than 5%.

Understanding the challenges facing the fetus at the end of gestation and during parturition, as well as the normal biology of the neonate, enables the veterinarian and breeder to better deal with neonatal problems. This chapter discusses those challenges and methods that may be used to overcome them.

256.1 CHALLENGES TO THE FETUS AND NEONATE

A number of factors may affect the survival of the neonate by challenging (1) the fetus during late gestation, (2) the fetus at parturition, and (3) the neonate immediately after birth.

256.1.1 Fetal Challenges during Late Gestation

Any challenge that adversely affects fetal development and results in the birth of an underweight neonate is likely to influence the newborn's subsequent survival. In humans, low birth weight can result in immaturity of the cardiovascular system and other physiologic functions (Barker hypothesis),[1] and this likely is also true in the dog. Such influences may make the puppy more susceptible to subsequent challenges, such as hypoxia, hypothermia, and neonatal infections.

A small or underweight puppy may be the result of inappropriate nutrition or generalized debility of the dam, the parasite burden of the dam, specific or generalized placental lesions, or infection of the dam with agents that cross the placenta (e.g., canine herpes virus).

256.1.2 Challenges at Parturition

During the change from fetal to neonatal life, a number of significant challenges can arise that may compromise subsequent survival. For example, although uterine contractions are essential to propel the fetus into the birth canal, this process also creates the opportunity for a decrease in the placental blood supply, constriction of the umbilical vessels, and early placental separation. Most, if not all, pups are born with mild to moderate hypoxia and slight to severe acidosis. The acidosis is generally respiratory in origin, but a metabolic component also is often present. In an adult, acidosis usually results in increased respiratory effort to remove the excess carbon dioxide. However, this is not always observed in the neonate (which suggests that carbon dioxide is not such a potent stimulator of respiratory drive in the neonate as it is in the adult).

Also, body temperature declines rapidly after birth, because the wet neonate is born into an environment cooler than the maternal temperature. Although a brief period of hypothermia may actually be useful as a mechanism to protect against the effects of hypoxia, it is clear that persistence of hypothermia contributes to neonatal mortality. In the normal neonate, hypoxia and hypothermia are rapidly reversed and a stable state is

reached within 3 to 4 hours after birth. If the acid-base disturbance or hypothermia are maintained beyond this period, a fatal cycle of decline may ensue. Clearly, conditions such as dystocia (including, ultimately, cesarean operation) and poor mothering behavior prolong both hypoxia and hypothermia, resulting in increased neonatal mortality.

256.1.3 Neonatal Challenges

The common challenges met by the neonate are persistence of the previously mentioned hypoxia, as a result of a delay in the removal of fetal membranes or fluid by the dam; persistence of hypothermia, associated with a delay in drying of the neonate; and a cold or drafty environment. Poor mothering behavior by an inexperienced primiparous bitch may be the primary cause of both hypoxia and hypothermia.

Adequate intake of fluid is the next major hurdle for the neonate, not only because of the requirement to absorb colostrum (see discussion below) but also because adequate fluid maintenance is important for recovery from acidosis. Neonates have a relatively higher percentage of fluid in the extracellular space and relatively poorer renal function than do adults. This situation, combined with the neonate's ability to lose fluid because of a high surface area to body ratio, results in a greater susceptibility to changes in fluid balance for neonates compared to adults.

Furthermore, the neonatal immune system is incompletely developed until at least 10 days after birth, which makes newborns susceptible to bacterial and viral infection. The dog has an endothelial-chorial placenta that allows approximately 20% of passive immunity to be acquired by the fetus in the uterus. The remaining 80% of antibodies must be absorbed across the intestine within the first 24 to 48 hours of life. The absorption of immunoglobulin G (IgG) from colostrum decreases markedly after this time, because the ability of the intestinal wall to absorb intact proteins declines. Failure to consume sufficient colostrum during the interval when the intestinal wall is open to the absorption of intact protein seriously compromises the immune status of the neonate.

Neonates have limited reserves of body fat, and their ability to generate energy from precursors is poor. Also, because glycogen reserves are depleted shortly after birth (only limited storage of glycogen occurs), the neonate requires a prompt intake of energy. A short time without food can result in a significant hypoglycemia, particularly in neonates that have been hypoxic or hypothermic. In humans, it has been suggested that anoxia can reduce gut motility and result in abnormal uptake of ingested nutrients. Clearly, food intake can be restricted in its availability from the dam because of illness, poor mothering, poor milk production or letdown, or a large litter size. Several of these factors may occur concomitantly with hypoxia or hypothermia, compounding the problems.

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The neonate may also be faced with a number of challenges from potential pathogenic organisms. In many cases these are normally commensal bacteria that become pathogenic in a debilitated animal. In some cases, primary pathogenic organisms are involved (e.g., canine herpes virus, discussed later).

256.1.4 Characteristics of Normal Neonates

Neonatal pups are unable to stand at birth, although they are quite mobile, using their front limbs to crawl. They normally spend 90% of the time asleep and cry only when they are disturbed or hungry. During normal sleep, pups make frequent small movements of the limbs, characteristic of rapid eye movement (REM) sleep.

The normal rectal temperature for the first week after birth is 32° to 34° C. Respiration should be regular and even, usually 15 to 40 breaths per minute. The heart rate is usually 200 to 220 beats per minute (bpm), and heart murmurs may be functional. The capillary refill time is normally 1 to 1.5 seconds.

Normal birth weight varies according to breed, with pups of most medium breeds weighing 200 to 300 g at birth. The birth weight of healthy neonates increases by 5% to 10% per day, and failure to achieve this weight gain may indicate poor health.

Pups are born with their eyes closed; separation of the upper and lower lids, with opening of the eyes, occurs at approximately 10 to 14 days of life.

256.2 OPTIMIZING NEONATAL SURVIVAL

It is clear that during late pregnancy, parturition, and the early neonatal period, a number of significant challenges arise that, if not overcome, can result in the ultimate demise of the neonate. Having an understanding of these challenges allows the veterinarian or breeder to manage the pregnant, parturient, and nursing bitch and her litter so as to reduce subsequent mortality.

256.2.1 Care of the Bitch Before and During Pregnancy

Prior to mating, due consideration should have been given to routine anthelmintic treatment, although this does not necessarily reduce the potential for transplacental infection with *Uncinaria* sp. or transplacental and transmammary infection with *Toxocara* organisms. If a significant problem has been identified in a kennel, daily oral administration of 25 mg/kg fenbendazole from day 40 of gestation until 2 days past whelping may reduce transmission to the fetus.

During pregnancy, voluntary food intake usually increases; however, the body condition score of the bitch should be examined to ensure that she is not too fat or too thin. It is normal to increase the amount of food offered in the last 20 days of pregnancy, at which time a diet consisting of at least 30% protein, 18% fat, and 20% to 30% carbohydrate is suitable. At whelping the bitch will be eating 60% more food than usual. Obesity during pregnancy and poor nutrition both can contribute to poor neonatal survival, resulting in fetal oversize or lactational problems and fetal undersize, respectively.

One week prior to anticipated parturition, the bitch should be encouraged to accept a nest in a suitable environment. This should be a warm, clean, draft-and damp-proof room that can be heated. The room is best isolated from the main thoroughfare of the household. Ideally, the bed should be large enough to allow the dam to stretch, and it should provide sufficient room for a large litter. The sides should be high enough to prevent the puppies from escaping until they are approximately 4 weeks old.

In the last week of pregnancy, it is prudent to record the bitch's rectal temperature at least twice daily to detect the prepartum hypothermia that precedes the onset of parturition by 24 to 36 hours. This decline in body temperature is mediated by a sudden reduction in the serum progesterone concentration. The rectal temperature usually changes from approximately 39° C to less than 37° C.

256.2.2 Care of the Bitch at Parturition

Careful monitoring of the bitch at parturition can reduce neonatal mortality by reducing the risk of hypoxia and hypothermia and ensuring adequate intake of colostrum. Education of the whelping attendant is essential

to ensure that this individual understands the normal stages and time sequence of parturition. Uterine activity can be monitored by observation of the bitch's abdomen when she is relaxed, but monitoring is more accurate if external monitoring devices, such as a tocodynomometer, are used.[2]

Prompt veterinary attention should be sought if evidence of any form of dystocia arises. It is not possible to give definitive guidelines for every potential case of dystocia, but veterinary examination is warranted in certain situations, such as when the bitch (1) has exceeded 70 days from the last mating and has no signs of impending parturition; (2) is unsettled and strains forcefully but infrequently; (3) shows signs of straining, which then cease; (4) has a black/green vulval discharge with no signs of parturition; (5) shows a decline in rectal temperature but parturition has not commenced within 48 hours; (6) has been straining ineffectually for 1 hour or longer; (7) has produced the last pup more than 2 hours previously but still is restless; and (8) has produced the last pup more than 2 hours ago, and a larger litter is expected.

256.2.3 Care of the Neonate

The first essential steps after the pup's birth are to establish a clear airway, stimulate respiration, dry and warm it, and encourage it to suck. Normally this is achieved by the dam licking and nuzzling the pup. Young or maiden bitches may need help and encouragement with the immediate licking and cleaning. Failure of this behavior to occur, for whatever reason, can be catastrophic.

It is essential that a clear airway be established as soon as a fetus has been born. If human help is required, this involves removing the surrounding fetal membranes and clearing the mouth and nose of fetal fluid with either a dry towel or a small pipette. Gentle compression of the chest usually establishes respiratory effort. If this does not occur but the heart is beating, respiratory stimulation should continue by means of rubbing of the thorax and removal of more fluid by gently swinging the neonate in a small arc (however, the latter course should be avoided unless absolutely necessary because of the risk of brain trauma). In certain cases, administration of a respiratory stimulant (e.g., doxapram hydrochloride) may be efficacious, as may administration of oxygen. If respiration does not commence, artificial respiration can be attempted. This should be done carefully so as to induce only slight lung expansion and not overinflate the lungs. If the heart is not beating, external cardiac massage combined with artificial respiration may be attempted.

The umbilicus should be cut approximately 3 cm from the fetal abdomen; excessive bleeding can be prevented by application of a ligature.

Once regular respiratory efforts are maintained, the neonate may be placed in a prewarmed box or incubator until it is active, at which point it may be returned to the dam and encouraged to suck. Sucking normally occurs immediately after birth and at intervals of 2 to 3 hours for the first few days. 1709 1710

Hypothermia is a major cause of neonatal mortality, therefore the environmental temperature is a critical factor. Because neonates are unable to regulate their own temperature for the first week of life, they rely on the dam and other neonates for warmth. A chilled neonate does not respond normally or move properly, nor is it able to suck; this may cause the dam to neglect it, exacerbating the problem. The whelping area should be heated to 25° to 30° C for the first few days. This temperature may be almost unbearable for the dam, but it can be safely reduced to approximately 24° C after this time. It is most important that the litter be kept well away from any drafts.

The area where parturition and rearing are to take place is also a concern. Although it is important that this room not be near a thoroughfare, it is beneficial for socialization of the puppies if noise can be heard, such as

from a washing machine, a radio, or people talking. The room should be of sufficient size to allow the growing puppies to play and, where possible, to have access to an outside area.

256.2.4 Care of Older Neonates

During the first few weeks of life, the dam normally takes care of the needs of the litter. Nevertheless, the pups should be examined regularly. It is most important to assess for the general demeanor, weight gain, and general characteristics of healthy neonates described previously.

Normally the dam licks the neonate's perineal region to stimulate it to defecate and urinate. After the first 2 to 3 weeks, pups urinate and defecate voluntarily, which increases the amount of soiling in the whelping bed. The environment should always be kept clean, warm, and dry.

An important neonatal assessment is the correct rate of development. At 10 to 14 days, a pup's eyes should open, and it gradually should become able to focus on objects. It also should gain strength and begin to crawl around.

256.2.5 Artificial Rearing of Neonates

For a number of reasons, some or all of the litter may need to be reared artificially; such reasons include the death of the dam, the birth of a large litter, a sick dam, poor mothering ability, eclampsia, or inadequate milk production. When possible, artificial rearing is best avoided. A good alternative is to foster the pups onto another dam, such as a lactating bitch that has just whelped and lost its litter or a bitch with pseudopregnancy. With an excessively large litter, it may be possible to alternate some of the litter between artificial rearing and rearing by the dam. Whenever possible pups should remain in the nest with the dam to ensure normal socialization.

It is essential that all neonates receive colostrum from the dam to ensure an adequate uptake of immunoglobulins. If the dam has died, it may still be possible to express some colostrum from her as long as it is not contaminated with drugs or toxins. Colostrum from a different species may be used as an alternative to bitch colostrum, although the antibody protection offered is limited. Despite this, some nonspecific defense against infectious agents may be afforded by compounds such as lysozyme, lactoferrin, oligosaccharides, and lactoperoxidases.[3] Furthermore, some evidence indicates that the lipid-dependent antimicrobial activity present in bovine milk may be effective in the neonatal puppy.[3] Clearly, the best alternative is to store colostrum for such a possibility by freezing or to purchase a commercially available preparation. Some veterinarians claim reasonable success with the technique of subcutaneously injecting the neonate with serum from vaccinated dogs.[4]

With artificial rearing, consideration must be given to the nutritional requirements of the neonate. An important factor that is often overlooked is the changing composition of mammary secretions during lactation.

The optimum milk protein concentration, total lipid concentration, and milk fatty acid and amino acid composition vary markedly among the different species, and it is not appropriate to substitute milk from another species, at least on a long-term basis. The preferred option is to use a commercially manufactured milk replacer because of the quality and consistency of these products. The milk should be warmed to body temperature (approximately 34°C) and should be fed according to the manufacturer's instructions, with regard to the pup's body weight and age.

Artificial rearing is both demanding and time-consuming, especially if rearing is undertaken entirely without the bitch. Pups normally feed every 2 to 4 hours during the first 5 days of life, after which feeding declines to every 4 hours. Feeding can be achieved by using a commercial feeding kit, which contains a bottle and teat. This encourages normal sucking, but it can be time-consuming. The teat aperture should be large enough to prevent the pup from sucking in air but small enough to prevent the flow of excessive volumes of milk. Feeding can also be done with a dropper bottle or 2 mL syringe. In some cases it may be beneficial to use a stomach tube to feed the pups, especially during the first few days of life. This is especially useful for sick neonates or when the litter is large and the attendant faces time constraints.

As previously discussed, neonates do not voluntarily urinate or defecate until 2 to 3 weeks of age. In the absence of the dam, the perineal region must be stimulated every 3 to 4 hours with a moistened piece of cotton to ensure normal voiding.

256.3 SICK PUPPIES

256.3.1 Known Causes of Mortality

Pups may fail to thrive and ultimately die for many reasons, including poor husbandry, maternal factors (e.g., illness and poor nutrition, which usually result in low birth weight pups), congenital defects, problems at parturition (usually dystocia, resulting in anoxia or hypoxia), poor mothering behavior, trauma, immune insufficiency, and infection with viruses, bacteria, or parasites. These causes, most of which were described previously (except for infectious causes), account for approximately 45% of all cases of neonatal mortality.

Infectious organisms are often given much prominence as the cause of neonatal death, although they account only for about 20% of mortality cases, depending on the country. Some infectious agents are specific pathogens, whereas others are opportunistic organisms that can colonize a compromised neonate. Specific examples of agents that can cause neonatal death include canine herpes virus, canine parvovirus, canine distemper virus, and some protozoa.

Exposure of an immunologically naive bitch to canine herpes virus during late pregnancy can result in abortion or in neonatal death, usually 7 to 21 days after birth. Earlier demise of the pups does not occur, and on this ground alone herpes virus infection can be differentiated clinically from true fading puppy syndrome (see below). Canine parvovirus type 1 may cross the placenta if the bitch is exposed in early pregnancy; although such disease is rare, it may result in resorption of the fetuses or in acute neonatal death 7 to 21 days after parturition. Infection with canine parvovirus type 2 may cause myocarditis in neonates, although this now is uncommon. Similarly, congenital infection with canine distemper virus is rarely seen.

Interestingly, a number of bacteria have been isolated from dead pups with peritonitis, pneumonia, pleuritis, and enteritis. These include beta-hemolytic streptococci, staphylococci, *Pasteurella* sp., *Escherichia coli,* *Campylobacter* sp., *Salmonella* sp. and, less commonly, *Ureaplasma* and *Mycoplasma* organisms. Most of these organisms are part of the commensal flora of the bitch's genital tract, and they cause disease only when the neonate has succumbed to one of the previously mentioned challenges. The inherent vulnerability of a neonate puts it at risk for colonization by these organisms, which may result in rapid death with few initial clinical signs.

Transplacental infection with *Toxoplasma gondii* is uncommon, although experimental infection may result in neonatal death. Similarly, although the incidence of natural transplacental transmission of *Neospora caninum* is unknown, experimental infection results in stillbirth with evidence of myocarditis. *Toxocara canis* infection

usually causes disease in pups over 2 weeks of age, by which time the worms have grown large enough to cause gastrointestinal obstruction or to migrate up the biliary tract and cause hepatitis.

256.3.2 Unknown Causes of Mortality (True Fading Puppy Syndrome)

In approximately 55% of pups that die, no specific cause can be determined; these pups are correctly termed *fading puppies*. Such pups usually have a normal birth weight but appear depressed and show poor sucking with persistent crying. The condition progresses to generalized weakness and ultimately to death, usually between day 3 and day 5 after birth.[5] Fading puppies usually have no macroscopic lesions (except often a small liver), no identifiable congenital defects, and no histologic lesions, and they simply have an absence of contents within the large and small intestine. They constitute a distinct category, separate from most other causes of neonatal death. These other "known" causes ultimately result in puppies that "fade," but most often from day 7 after birth onward.

Interestingly, Blunden et al.[6] found that true fading puppies (those with no other known cause) had significantly lower phosphatidylcholine components of lung surfactant than pups that died of known causes. Lung surfactant is required for normal respiratory adaptation and maintenance after birth. A significant reduction of surfactant is observed in sudden infant death syndrome in humans, and the low values in fading puppies suggest that faulty production of surfactant may similarly be involved in the etiology of this condition. In the normal animal, increased respiratory effort tends to stimulate surfactant production; it may be that pups with true fading puppy syndrome are born marginally hypoxic and, because carbon dioxide stimulation of respiration is absent, they do not breathe deeply; they thereby enter a downward spiral of low surfactant, hypoxia, failure to thrive, failure to suck, hypothermia and, ultimately, death.

Despite the clear difference in clinical presentation between true fading puppies and puppies with identifiable causes of disease, it is common for any puppy that becomes ill to enter a downward course of failure to feed, resultant dehydration, and death. Many veterinarians use the term "fading puppy" to describe this demise regardless of its cause.

256.3.3 Clinical Signs of Sick or Fading Puppies

True fading puppy syndrome generally is observed from day 2 after birth onward, and most such pups die between day 3 and day 5. The pups usually show progressive weight loss, depression (or occasionally unusual restlessness early in the disease process), persistent crying, failure to suck, generalized weakness, dehydration, hypothermia and, ultimately, death.

In conditions in which the cause of the illness is identifiable, ill health usually results in frequent crying, restlessness, and hypothermia, progressing to clinical signs of diarrhea and/or dyspnea with resultant dehydration or cyanosis and, ultimately, death, usually later than 7 days after birth. In certain circumstances some neonates are more chronically affected and fail to grow as expected prior to the onset of obvious clinical disease.

256.3.4 Consequences of Disease in Canine Neonates

Whatever the initial challenge, the inherent susceptibility of the newborn results in its ultimate demise. Neonates have poor mechanisms of thermoregulation, which leaves them susceptible to hypothermia. They are unable to shiver and have poor reserves of brown adipose tissue. Puppies have approximately one fifth the glomerular filtration ability of adults and almost twice the water requirement, which makes them susceptible

to dehydration. At birth, they have high red and white cell counts, which decline rapidly over the first week, and immature liver enzyme systems. The neonate's ability to regulate blood glucose concentration also is immature, and the newborn relies almost entirely on hepatic glycogen reserves over the first 24 hours. With prolonged parturition or a prolonged interval to feeding, the reserves may be exhausted, and hypoglycemia may complicate hypothermia.

256.3.5 Treatment of the Sick Puppy

256.3.5.1 Minor Disease

Any neonate with minor signs of disease (lethargy, slowness to feed, lack of weight gain) requires early supplemental feeding. If the intake of colostrum is a concern, a source of frozen-thawed or replacement colostrum should be given, as discussed earlier, preferably before day 3 of life. Thereafter milk supplements should be fed by stomach tube every 2 hours. During this early phase, it is essential that the pup's body temperature be maintained at approximately 34° C and the temperature should be recorded every few hours. The environmental temperature should also be monitored using a thermometer placed adjacent to the neonates and maintained at 25° C to 30° C. Adequate hydration should be ensured and can be estimated from recordings of weight gain (measured three times daily), by evaluation of the skin's elasticity, and by examination of the urine. Because normal neonatal urine is colorless, the presence of color in the urine may be a useful and simple indicator of dehydration. General nursing care also is important and should include regular perineal stimulation to ensure urinary and fecal voiding.

The use of antimicrobials may be considered in an ill neonate, not necessarily because of a primary infectious cause of the illness, but rather because a sick neonate is highly susceptible to colonization from otherwise commensal organisms. A commonly used antibiotic is clavulanic acid–potentiated amoxicillin, administered at a dosage of 12.5 to 25 mg/kg given orally twice daily.

256.3.5.2 Significant Disease

In a neonate with anything other than mild clinical signs, rapid and aggressive treatment is essential, including oxygen administration, fluid therapy, and administration of broad-spectrum antimicrobial agents.[7] Despite such treatment, the mortality rate can be high. Absence of feeding, dehydration, or other clinical signs are indicators for immediate initiation of aggressive treatment.

If significant disease is suspected, it is important that a regimen of rigorous clinical examination and evaluation every 4 hours be established; it should include recording of the rectal temperature, assessment of the mucous membrane color and capillary refill time, recording of the respiratory and heart rates, and evaluation of skin elasticity and urine color. At specific points in time, evaluation of blood hematology and biochemistry may be useful. Many pups are hypoglycemic, and a rapid evaluation can be done by placing a drop of blood on a glucose reagent stick.

It is important that normal laboratory values be interpreted with respect to the age of the neonate (Table 256-1), because the hematologic and biochemical parameters of neonates differ significantly from those of adults.

An incubator or a homemade oxygen tent system can provide an oxygen-enriched environment for the pup. *1711*
Alternatively, a tracheal catheter can be placed, a technique that is especially useful for pups with *1712*

concomitant upper respiratory tract problems. Oxygen administration can help overcome hypoxia, and artificial ventilation may be useful for reversing acidosis and encouraging the production of lung surfactant.

Table • 256-1 Normal Hematologic and Biochemical Values for Neonatal Pups (Birth to 8 Weeks Old)

PARAMETER	0 TO 2 WEEKS	2 TO 4 WEEKS	4 TO 8 WEEKS
RBC ($\times 10^6$/uL)	3.4–6	3.5–4.8	4.5–6.8
Hb (g/dL)	9–12.6	8.5–8.9	8.4–9.5
PCV (%)	32–50	25–30	26–40
MCV (fL)	65–90	50–80	65–75
MCH (pg)	21–30	16–25	20–30
MCHC (%)	32–35	32–35	30–33
WBC ($\times 10^3$/uL)	9–25	8–16.5	10–18.9
ALT (IU/L)	20–300	10–30	10–50
AST (IU/L)	20–250	10–50	15–30
ALP (IU/L)	200–10,000	150–500	100–150
TP (g/dL)	3.5–5.5	3.5–4.5	4–5
Alb (g/dL)	1.5–3	1–2	2–3
Glucose (mg/dL)	50–150	60–150	60–250

RBC, Red blood cell concentration; *Hb,* hemoglobin concentration; *PCV,* packed cell volume; *MCV,* mean corpuscular volume; *MCH,* mean corpuscular hemoglobin; *MCHC,* mean corpuscular hemoglobin concentration; *WBC,* total white blood cell concentration; *ALT,* alanine aminotransferase; *AST,* aspartate aminotransferase; *ALP,* alkaline phosphatase; *TP,* total protein; *Alb,* albumin.

Pups with pale mucous membranes and a slow capillary refill time (greater than 2.0 seconds) usually are at least 10% dehydrated. This fluid deficit must be replaced, in addition to the ongoing maintenance requirement. Fluid requirements for general maintenance are approximately 60 to 180 mL/kg/day. In a small number of neonates, fluid may be replaced by oral administration of electrolytes; however, in most pups, fluids must be provided by intravenous, intraperitoneal, or intraosseus administration.

256.3.5.2.1 Intravenous catheter placement may be difficult in a dehydrated neonate.

An over-the-needle catheter should be used whenever possible, because this is the easiest type to keep in position for long periods. However, human neonatal scalp catheters may be technically easier to place in small vessels. It is always worthwhile to spend some time ensuring adequate venous access, and although surgical cut down onto a vein initially may seem to lengthen the procedure, in the long-term it often is the most sensible option. The cephalic vein is most often catheterized, although because of the short length of the neonate's leg, kinking of the catheter is common. Catheterization of the jugular vein is better. With catheter placement, care must be taken to perform appropriate sterile preparation of the site to avoid introducing organisms or providing a focus of infection.

In the consideration of which fluids are most suitable for administration, it is sensible in most cases to assume that acidosis is a factor. The safest fluid replacement, therefore, is lactated Ringer's solution (although the neonate has reduced hepatic function and may be unable to metabolize lactate into bicarbonate), which is given with added maintenance potassium (20 mmol/L). Ideally the acid-base and electrolyte status should be established, although this may be difficult. If the acidosis is likely to be severe, bicarbonate may be given; administration of 2 mmol/kg over 2 to 4 hours is recommended if specific acid-base data are not available.

Once the ideal fluid has been selected, it is important that ongoing maintenance and current deficits be estimated. Normal principles of the estimation of fluid deficit apply; as a rough guide for immediate replacement, 1.5 mL can be administered per 50 g of body weight. In many neonates the total fluid volume to be administered is small, and it may be useful to consider administration via a syringe pump to avoid overhydration. Intraperitoneal administration may be used if venous access is difficult or if ongoing monitoring to ensure successful intravenous administration is likely to be inadequate. The most appropriate intraperitoneal dosing scheme is to provide fluids in three boluses at approximately 8-hour intervals. The risk of accidental puncture of viscera is relatively small, although repeated needle placement poses a risk of sepsis. Despite the relative merits of this technique, intraperitoneal fluids may be relatively slowly absorbed, especially in hypovolemic neonates. In reality, it is preferable to ensure adequate venous access.

If access to a vein is not possible, fluids may be administered by the intraosseus route.[8] In the neonate, access normally is provided via the trochanteric fossa of the proximal femur or the flat medial aspect of the proximal tibia (distal to the tibial tuberosity). The hair should be clipped and the site prepared aseptically. A standard 18-to 20-gauge needle (size and length vary, depending on the pup's size) is used to push longitudinally into medullary cavity. In some cases the cortical bone is sufficiently soft to allow the use of an intravenous over-the-needle catheter. Repeated puncture is not advised, because holes in the cortical bone allow fluid leakage; however the catheter may be left in position for up to 72 hours. Thereafter a new catheter should be placed in a different bone. Fluid and drugs can be administered via the needle at rates similar to those for intravenous infusion.

In some neonates hypovolemia may be complicated by sepsis, and the resultant combination of problems can be catastrophic. Although the use of corticosteroids in neonates with hypovolemic and septic shock remains controversial, short-acting intravenous agents (e.g., methylprednisolone sodium succinate) are the drugs of choice. Septic shock may result in further depletion of glycogen reserves, increased peripheral use of glucose, and decreased gluconeogenesis, resulting in hypoglycemia. In such animals, additional bolus glucose therapy can be provided by using a 5% dextrose solution mixed 50:50 with the lactated Ringer's solution or by giving 1 to 2 mL of 10% glucose intravenously.[9]

In certain circumstances, specific drug therapy may be considered, including administration of vitamin K_1 for pups with signs of hemorrhage, or administration of doxapram hydrochloride for pups with poor respiratory effort (or in an attempt to increase surfactant production). In human neonates, it is common to administer a surfactant (phospholipids, neutral lipids, and hydrophobic surfactant–associated proteins B and C from calf lungs) via the intratracheal route in an attempt to modify alveolar surface tension and thus stabilize the alveoli.[10] This treatment is combined with conventional mechanical ventilation or high-frequency oscillatory ventilation. Because in dogs with true fading puppy syndrome there appears to be an abnormality of lung surfactant composition, a similar treatment may be useful but currently is untested.

Broad-spectrum antimicrobials frequently are administered to neonates with significant illness. In these cases it is not appropriate to wait for culture and sensitivity results; however, it is sensible to collect bacteriologic samples prior to drug administration to allow concomitant processing, which may result in a change in the selected antimicrobial once the results have been obtained. Culture of whole blood is recommended. When drug administration is considered, confusion often arises over products that are given to the dam and excreted in milk. A drug's concentration in milk depends on its lipid solubility,

blood protein binding capacity, and pKa; however, in general less than 5% of the maternal dose reaches the milk.

256.4 INVESTIGATION OF NEONATAL LOSS

It is important to ensure an accurate diagnosis of neonatal loss. All stillborn pups and those that die shortly after birth should undergo a detailed postmortem examination that includes appropriate bacteriologic, virologic, and histologic testing. The bodies should be chilled rather than frozen and then transported to an appropriate pathology facility.

256.5 PREVENTIVE HEALTH CARE PROGRAMS

A preventive health care program should be planned for the differing circumstances of each breeder.[11] In principle, this program should include broad-spectrum anthelmintic therapy, which commences at 3 weeks of age and is repeated 2 weeks later. Fecal examination to determine the parasite burden can modify the subsequent treatment regimen. Immunization of puppies with appropriate vaccines (canine distemper, parvovirus, adenovirus type II, and parainfluenza) should be initiated at 6 to 9 weeks of age. The precise choice of vaccine depends on the preference of the veterinarian and the particular circumstances of the client.

256.6 CONCLUSION

Acquiring an understanding of the common challenges facing the neonate may help the veterinarian and breeder to reduce perinatal loss. In the absence of detailed research work into the physiology of birth adaptation, generic management strategies should be followed to ensure the health of the bitch during pregnancy and the care of the neonate during parturition and the first few weeks of life. When neonatal problems occur, rapid and aggressive supportive therapy is mandatory, as is proper investigation of all cases of neonatal mortality.

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257 CHAPTER • 257 Renal Disease: Clinical Approach and Laboratory Evaluation

Stephen P. DiBartola

257.1 DEFINITIONS

Azotemia is defined as an increased concentration of nonprotein nitrogenous compounds in the blood, usually urea and creatinine. *Prerenal azotemia* is a consequence of reduced renal perfusion (e.g., severe dehydration, heart failure), and *postrenal azotemia* results from interference with excretion of urine from the body (e.g., obstruction, uroabdomen). *Primary renal azotemia* is caused by parenchymal renal disease. The term *renal failure* refers to the clinical syndrome that occurs when the kidneys are no longer able to maintain their regulatory, excretory, and endocrine functions, resulting in retention of nitrogenous solutes and derangements of fluid, electrolyte, and acid-base balance. Renal failure occurs when 75% or more of the nephron population is nonfunctional. The term *uremia* refers to the constellation of clinical signs and biochemical abnormalities associated with a critical loss of functional nephrons, including the extrarenal manifestations of renal failure (e.g., uremic gastroenteritis, hyperparathyroidism). The term *renal disease* refers to the presence of morphologic or functional lesions in one or both kidneys regardless of extent.

257.2 CLINICAL APPROACH

The clinician should try to answer the following questions:

- Is renal disease present?
- Is the disease glomerular, tubular, interstitial, or some combination of these?
- What is the extent of the renal disease?
- Is the disease acute or chronic, reversible or irreversible, progressive or nonprogressive?
- What is the current status of the animal's renal function?
- Can the disease be treated?
- What nonurinary complicating factors are present and require treatment (e.g., infection, electrolyte and acid-base disturbances, dehydration, obstruction)?
- What is the prognosis?

The diagnosis of renal disease begins with a careful evaluation of the history and physical examination findings.

257.2.1 History

A complete history should be taken, including signalment (age, breed, sex), presenting complaint, husbandry, and review of body systems. The history of the presenting complaint should include information about the onset (acute or gradual), progression (improving, unchanging, or worsening), and response to previous therapy. Information about husbandry includes the animal's immediate environment (indoor or outdoor), use

(pet, breeding, show, or working animal), geographic origin and travel history, exposure to other animals, vaccination status, diet, and information about previous trauma, illness, or surgery.

Questions relating to the urinary tract include those about changes in water intake and the frequency and volume of urination. The owner should be questioned about pollakiuria, dysuria, or hematuria. Care must be taken to distinguish dysuria and pollakiuria from polyuria and to differentiate polyuria from urinary incontinence. The distinction between pollakiuria and polyuria is important, because polyuria may be a sign of upper urinary tract disease, whereas pollakiuria and dysuria usually are indicative of lower urinary tract disease. Nocturia may be an early sign of polyuria but also can occur as a result of dysuria. Normal urine output ranges from 20–40 mL/kg/day in dogs and cats.

Information about the initiation of urination and the diameter of the urine stream may be helpful, because animals with partial urethral obstruction may have difficulty initiating urination or may have an abnormal urine stream. If hematuria is present, the owner should be questioned about its timing. Blood at the beginning of urination may indicate a disease process in the urethra or genital tract. Blood at the end of or throughout urination may signify a problem in either the bladder or the upper urinary tract (kidneys or ureters).

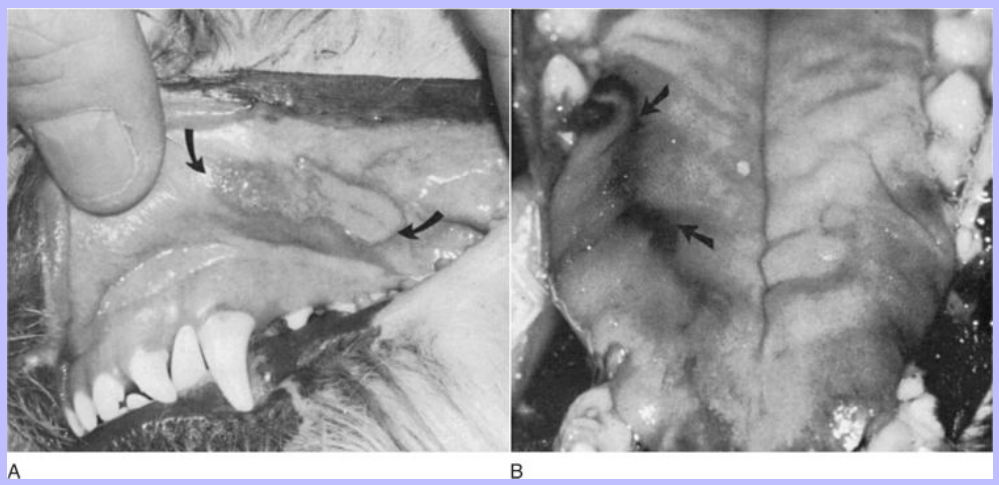
Polydipsia usually is more easily detected by owners than polyuria. Water intake should not exceed 60–80 mL/kg/day in dogs and 40 mL/kg/day in cats. It is helpful to describe amounts in quantitative terms familiar to the owner, such as cups (approximately 250 mL) or quarts (approximately 1 liter). The owner should be questioned about exposure of the animal to nephrotoxins, such as ethylene glycol in antifreeze, Easter lily (cats only), aminoglycosides (e.g., gentamicin), and nonsteroidal anti-inflammatory drugs (e.g., flunixin meglumine, ibuprofen). Also, it should be determined whether the animal has received any drugs that could cause polydipsia and polyuria (e.g., glucocorticoids, diuretics).

257.2.2 Physical Examination

A complete physical examination (including fundic and rectal examinations) should be performed. Careful attention should be paid to hydration status and to whether ascites or subcutaneous edema is present, because these may accompany nephrotic syndrome (i.e., glomerular disease). The oral cavity should be examined for ulcers, tongue tip necrosis, and pallor of the mucous membranes (Figure 257-1). The presence of retinal edema, detachment, or hemorrhage or of vascular tortuosity should be noted during fundic examination. Occasionally, severe hypertension secondary to renal disease results in acute onset of blindness due to retinal detachment. Young, growing animals with renal failure may develop marked fibrous osteodystrophy, characterized by enlargement and deformity of the maxilla and mandible (so-called rubber jaw), but this is rare in older dogs with renal failure.

Both kidneys can be palpated in most cats and the left kidney in some dogs. Kidneys should be evaluated for size, shape, consistency, pain, and location. Unless empty, the bladder can be palpated in most dogs and cats. The bladder should be evaluated for degree of distension, pain, wall thickness, and presence of masses, both intramural (e.g., tumors) and intraluminal (e.g., calculi, clots). In the absence of obstruction, a distended bladder in a dehydrated animal suggests abnormal renal function or administration of drugs that impair urinary concentrating ability (e.g., glucocorticoids, diuretics). The prostate gland and pelvic urethra are evaluated by rectal examination. The penis should be exteriorized and examined and the testes palpated. A vaginal examination is performed to evaluate for abnormal discharge and masses and to assess the appearance of the urethral orifice.

Figure 257-1 **A,** Buccal ulcer. Uremic ulcers often are found in tissue overlying teeth *(arrows)*. Oral ulceration is most commonly observed in dogs with primary (intrinsic) renal azotemia. **B,** Tongue margin necrosis. This lesion may occur in dogs with acute or chronic azotemia.



257.2.3 Differentiation of Acute from Chronic Renal Failure

Acute renal failure (ARF) sometimes can be difficult to distinguish from chronic renal failure (CRF). However, differentiation is crucial, because ARF potentially is reversible, whereas CRF is not. The history, physical examination findings, renal size, and hematocrit can be helpful in making this distinction. The kidneys are small (but can be normal sized and occasionally even enlarged) in CRF but are normal sized (or slightly enlarged) in ARF. A history of previous polyuria and polydipsia is often (but not always) found in patients with CRF. Physical examination findings such as weight loss and poor haircoat suggest CRF but are not always present. Likewise, nonregenerative anemia often but not always is found in patients with CRF.

Due to the development of renal secondary hyperparathyroidism in CRF, ultrasonography of the parathyroid glands may be helpful in the differentiation of CRF from ARF. In one study, the parathyroid glands of normal dogs and of dogs with ARF and CRF were evaluated using a 10 MHz linear-array, high-resolution transducer.[1] As expected, the maximal measured length of the parathyroid glands in dogs with CRF (3.9 to 8.1 mm) was greater than that for normal dogs (2 to 4.6 mm) and dogs with ARF (2.4 to 4 mm). Although measurements overlapped somewhat among groups, parathyroid gland ultrasonography may be helpful in the differentiation of ARF and CRF. Parathyroid gland size appeared to be related to the body weight of the dog.

Urea can dissociate into isocyanic acid, which in turn can react nonenzymatically with the terminal valine residue of hemoglobin to form carbamylated hemoglobin. The amount of carbamylated hemoglobin present is related to the severity and duration of azotemia. Carbamylated hemoglobin concentrations are higher in dogs with renal failure than in control dogs and higher in dogs with CRF than in those with ARF.[2,3]

257.3 LABORATORY EVALUATION OF RENAL FUNCTION

257.3.1 Glomerular Function

Evaluation of glomerular function is an essential part of the diagnostic approach in dogs and cats suspected of having renal disease, because the glomerular filtration rate (GFR) is directly related to functional renal mass. Determinations of the serum creatinine and blood urea nitrogen (BUN) concentrations are commonly used screening tests; the creatinine clearance test is useful in pets suspected of having renal disease that have normal BUN and serum creatinine concentrations. Plasma clearance of radioisotopes and renal scintigraphy are sophisticated techniques that may be used to determine the GFR and obtain information about kidney function but that do not require urine collection. Evaluation of urinary protein excretion allows assessment of primary glomerular disease (e.g., glomerulonephritis, glomerular amyloidosis).

257.3.1.1 Blood Urea Nitrogen

Urea is synthesized in the liver via the ornithine cycle from ammonia derived from amino acid catabolism. The amino acids used in the production of urea arise from the catabolism of exogenous (i.e., dietary) and endogenous proteins. Renal excretion of urea occurs by glomerular filtration, and the BUN concentration is inversely proportional to the GFR. Urea is subject to passive resorption in the tubules, and this occurs to a greater extent at slower tubular flow rates, which occur during dehydration and volume depletion. Thus urea clearance is not a reliable estimate of the GFR. With significant vascular volume depletion, decreased urea clearance may occur without a decrease in the GFR.

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The production and excretion of urea do not proceed at a constant rate. These two processes increase after a high-protein meal, therefore an 8-to 12-hour fast is recommended before measurement of the BUN concentration to avoid the effect of feeding on urea production. Gastrointestinal bleeding can increase the BUN concentration, because blood represents an endogenous protein load. In 52 dogs with hematemesis, melena, or both, the BUN concentrations and BUN to creatinine ratios were significantly higher than in age-matched control dogs; this suggests that gastrointestinal hemorrhage contributes to an increased BUN concentration in dogs as a consequence of increased gastrointestinal absorption of nitrogenous compounds.[4] Clinical conditions characterized by increased catabolism (e.g., starvation, infection, fever) also can increase the BUN concentration. Some drugs may increase the BUN concentration by increasing tissue catabolism (e.g., glucocorticoids, azathioprine) or by decreasing protein synthesis (e.g., tetracyclines), but these effects likely are minimal. On the other hand, the BUN concentration can be decreased by low-protein diets, anabolic steroids, severe hepatic insufficiency, or portosystemic shunting. These nonrenal variables limit the usefulness of the BUN concentration as an indicator of the GFR. The normal BUN concentrations are 8 to 25 mg/dL in the dog and 15 to 35 mg/dL in the cat.

257.3.1.2 Serum Creatinine

Creatinine is a nonenzymatic breakdown product of phosphocreatine in muscle, and daily production of creatinine in the body is determined largely by the muscle mass of the individual. Young animals have lower concentrations, whereas males and well-muscled individuals have higher concentrations. The serum creatinine concentration is not appreciably affected by diet. Creatinine is not metabolized and is excreted by the kidneys almost entirely by glomerular filtration. Its rate of excretion is relatively constant in the steady

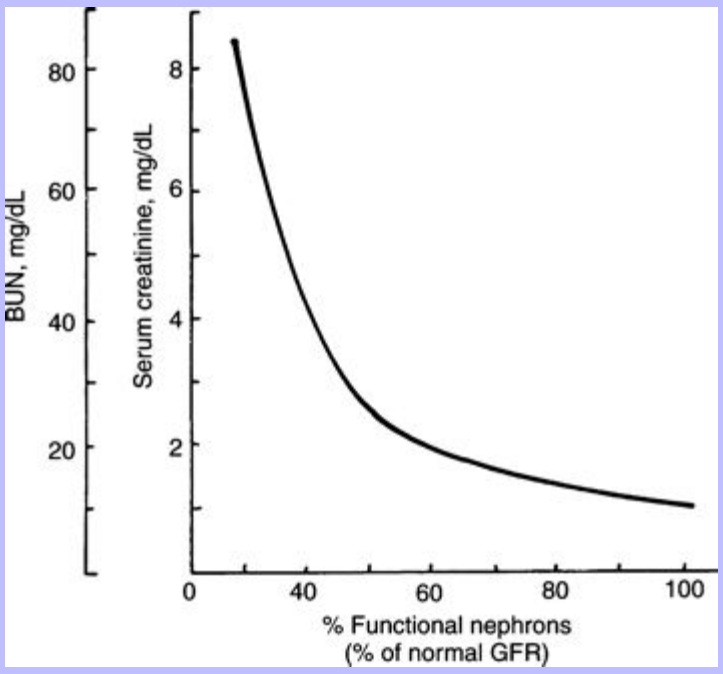
state, and the serum creatinine concentration varies inversely with the GFR. Thus *determination of creatinine clearance provides an estimate of the GFR*.

Creatinine is measured by the alkaline picrate reaction, which is not entirely specific for creatinine and which measures another group of substances collectively known as noncreatinine chromagens. These substances are found in plasma, in which they may constitute up to 50% of the measured creatinine at normal serum concentrations, but they normally do not appear in urine. As the serum creatinine concentration increases as a result of progression of renal disease and a declining GFR, the amount of noncreatinine chromagens remains unchanged and contributes progressively less to the total measured serum creatinine concentration. The normal serum creatinine concentrations are 0.3 to 1.3 mg/dL in the dog and 0.8 to 1.8 mg/dL in the cat.

The relationship of the BUN or serum creatinine concentration to the GFR is a rectangular hyperbola. The slope of the curve is small when the GFR is mildly or moderately decreased but large when the GRF is severely reduced (Figure 257-2). Therefore large changes in the GFR early in the course of renal disease cause small increases in the BUN or serum creatinine concentration, which may be difficult to appreciate clinically; on the other hand, small changes in the GFR in advanced renal disease cause large changes in the BUN or serum creatinine concentration. The inverse relationship between the serum creatinine concentration and the GFR is valid only in the steady state.

When nonrenal variables have been eliminated from consideration, an increase in the BUN or serum creatinine concentration above normal implies that at least 75% of the nephrons are not functioning (see Figure 257-2). Neither the cause nor the reversibility of this malfunction can be predicted from the increase in the BUN or serum creatinine concentration. Also, the increase in the BUN or serum creatinine concentration cannot be used to predict whether azotemia is prerenal, primary renal, or postrenal in origin, or to distinguish between acute and chronic, reversible and irreversible, and progressive and nonprogressive processes. The BUN/creatinine ratio in prerenal and postrenal azotemia may be increased as a result either of increased tubular resorption of urea at lower tubular flow rates or of easier absorption of urea than creatinine across peritoneal membranes in animals with uroabdomen. A decrease in the BUN/creatinine ratio often follows fluid therapy, reflecting a decrease in tubular resorption of urea rather than an increase in the GFR.

Figure 257-2 Relationship of blood urea nitrogen (BUN) or serum creatinine concentration to percentage of functional nephrons. (From Chew DJ, DiBartola SP: Manual of Small Animal Nephrology and Urology. New York, Churchill Livingstone, 1986.)



257.3.1.3 Cystatin C

Cystatin C is a small polypeptide protease inhibitor that is freely filtered by the glomeruli. It does not undergo tubular secretion, and filtered cystatin C is almost completely resorbed by the proximal tubular cells and catabolized to its constituent amino acids. Cystatin C is produced at a constant rate in all tissues, and its excretion is not dependent on age, gender, or diet. As a result, the serum concentration of cystatin C may serve as a useful marker of the GFR. Some concern exists that the serum cystatin C concentration may be affected by the presence of inflammation or neoplasia.

Recently, two studies evaluated normal dogs and dogs with renal failure using an immunoturbidometric assay designed to measure the serum concentration of human cystatin C.[5,6] The serum concentration of cystatin C in normal dogs was found to be approximately 1 mg/dL.

257.3.1.4 Creatinine Clearance

The renal clearance of a substance is that volume of plasma that would have to be filtered by the glomeruli each minute to account for the amount of that substance appearing in the urine each minute. The renal clearance of a substance that is neither resorbed nor secreted by the tubules is equal to the GFR. For such a

substance in a steady state, the amount filtered equals the amount excreted. Thus: GFR × P_x = U_x × V. Dividing both sides of the equation by P_x gives the familiar clearance formula (U_xV/P_x), which in this case is equal to the GFR.

Creatinine is produced endogenously and excreted by the body largely by glomerular filtration, and its clearance can be used to estimate the GFR in the steady state. Numerous studies in the dog and cat have shown that *endogenous* creatinine clearance in these species is 2 to 5 mL/min/kg. Values for glomerular function tests in the dog and cat are presented in Table 257-1.

In chronic progressive renal disease, urinary concentrating ability is impaired after two thirds of the nephron population have become nonfunctional, whereas azotemia does not develop until three fourths of the nephrons have become nonfunctional. Thus the main indication for determination of *endogenous* creatinine clearance is the clinical suspicion of renal disease in a pet with polyuria and polydipsia that has normal BUN and serum creatinine concentrations. The only requirements for determination of *endogenous* creatinine clearance are accurately timed urine collection (usually 12 or 24 hours), determination of body weight, and an assessment of the serum and urine creatinine concentrations. Failure to collect all urine produced erroneously reduces the calculated clearance value.

To eliminate the inaccuracy caused by noncreatinine chromagens, some investigators have advocated use of *exogenous* creatinine clearance. In this procedure, creatinine is administered subcutaneously or intravenously to increase the serum creatinine concentration approximately tenfold and to reduce the relative effect of noncreatinine chromagens. *Exogenous* creatinine clearance values exceed endogenous creatinine clearance values and closely approximate inulin clearance in the dog. In one study, the inulin and *exogenous* creatinine clearances were nearly identical in dogs. The creatinine/inulin clearance ratio was not altered by ablation of 50% to 94% of renal mass and was not affected by gender, dietary protein intake, or duration of time after renal ablation.[7] *Endogenous* creatinine clearance is a reliable estimate of the GFR only when methodology specific for true creatinine is used.[8] In cats, *exogenous* creatinine clearance may be slightly lower than inulin clearance.

257.3.1.5 Single Injection Methods for Estimating the Glomerular Filtration Rate

Single injection plasma clearance methods using inulin, iohexol, or creatinine have been used in dogs and cats with normal and reduced renal mass to estimate the GFR.[9–14] With these methods, the plasma clearance of a substance that is not bound to plasma proteins and is excreted only by glomerular filtration (e.g., inulin, iohexol, creatinine) is calculated as the quotient of the administered dose divided by the area under the plasma concentration versus time curve. This technique has the advantage of not requiring collection of urine, but its accuracy depends on the pharmacokinetic model used to calculate the area under the curve and the timing and number of samples used to make the calculation. The advantages and limitations of single injection plasma clearance methods for evaluation of the GFR were recently reviewed.[15]

Table • 257-1 Tests of Glomerular Function in Dogs and Cats

PARAMETER	DOG	CAT
Blood urea nitrogen (mg/dL)	8–25	15–35
Serum creatinine (mg/dL)	0.3–1.3	0.8–1.8
Serum cystatin C (mg/dL)	0.5–1.5	Not available
Endogenous creatinine clearance (mL/min/kg)	2–5	2–5
Exogenous creatinine clearance (mL/min/kg)	3–5	2–4
24-Hour urine protein excretion (mg/kg/day)	<20	<20
Urine protein to urine creatinine ratio (U_{Pr}/U_{Cr})	<0.4	<0.4

257.3.1.6 Radioisotopes

Radioisotopes (e.g., ^{125}I-iothalamate or ^{131}I-iothalamate, ^{51}Cr-ethylenediaminetetraacetic acid [EDTA], ^{99m}Tc-diethylenetriamine penta-acetic acid [DTPA]) also have been used to estimate the GFR in dogs and cats using both plasma clearance and dynamic renal scintigraphic methods. The plasma clearance approach has the same advantages and limitations as described above for iohexol or exogenously administered creatinine; procedures involving radioisotopes require technical expertise and equipment available primarily at referral institutions. Methods using ^{99m}Tc-DTPA to estimate the GFR are clinically useful because the short half-life of ^{99m}Tc (6 hours) allows the animal to be released within 24 to 48 hours after the procedure.

The percentage of an injected dose of ^{99m}Tc-DTPA extracted by the kidneys over a finite period correlates well with inulin clearance (the gold standard for estimation of the GFR). A major advantage of dynamic renal scintigraphy is that it provides information about individual kidney function; however, in dogs with renal disease, this method correlates less well with inulin clearance than does the plasma clearance method.[16] Renal scintigraphy is less accurate than plasma clearance methods for several reasons. A brief sampling period (usually 1 to 3 minutes after injection) is used in dynamic renal scintigraphy to avoid loss of radioactivity as urine is excreted from the kidneys into the ureters and bladder. In a recent study, the ideal time for counting radioactivity during ^{99m}Tc-DTPA renal scintigraphy in normal dogs was found to be 30 seconds to 2 minutes after injection.[17] Data acquired over such a short period may not accurately reflect the animal's steady state GFR. Other factors that contribute to potential inaccuracy include characteristics of the gamma camera itself (e.g., field uniformity, linearity, spatial resolution), the selection of renal and background regions of interest, and renal depth correction.[18] Partial obstruction can delay excretion of the tracer from the kidneys and lead to overestimation of the GFR. Despite these limitations, dynamic renal scintigraphy is helpful in clinical situations when information about individual renal function is important. Nuclear imaging with ^{99m}Tc-DTPA has been used to determine the GFR in normal dogs[19] and dogs with renal disease[20] and in normal cats and cats with renal dysfunction.[21,22]

Quantitative renal scintigraphy[23] and determination of plasma disappearance after single injection[24] using ^{99m}Tc-mercaptoacetyltriglycine have been used to estimate renal plasma flow in dogs. Hepatic uptake of ^{99m}Tc-mercaptoacetyltriglycine in cats may limit the value of this tracer for evaluation of renal plasma flow in this species.[25]

257.3.1.7 Urine Protein to Creatinine Ratio

In animals with persistent proteinuria on routine urinalysis, the severity of the proteinuria may be assessed by measuring 24-hour urine protein excretion or by performing a urine protein to urine creatinine ratio (U_{Pr}/U_{Cr}). A normal value for 24-hour urine protein excretion in dogs and cats is less than 20 mg/kg/day. 1719
Dogs with primary glomerular disease (e.g., glomerulonephritis, glomerular amyloidosis) often have markedly increased 24-hour urine protein excretion values, and those with amyloidosis generally have the highest 24-hour urine protein excretion values.[26,27] 1720

Determination of the U_{Pr}/U_{Cr} eliminates the necessity of a 24-hour urine collection and has been shown to correlate closely with 24-hour urine protein excretion in dogs[28] and cats.[29] Its value lies in the fact that, whereas both the urine creatinine and urine protein concentrations are affected by the total urine solute concentration, their ratio is not. The normal U_{Pr}/U_{Cr} in dogs and cats is less than 0.4. In dogs, U_{Pr}/U_{Cr} results are not affected by differences in gender, the method of urine collection, fasted versus fed states, or the time of day of collection.[30,31] Pyuria and marked blood contamination of urine samples can result in an abnormal U_{Pr}/U_{Cr} in the absence of glomerular disease.[32] Consequently, both the urine protein concentration and the U_{Pr}/U_{Cr} must be evaluated in conjunction with urinary sediment findings. Feeding of a high-protein diet or induction of renal failure increased 24-hour urine protein excretion and the U_{Pr}/U_{Cr} in cats,[33] and administration of prednisone to normal dogs increased the U_{Pr}/U_{Cr} from normal to a mean of 1.2 at 30 days and 0.9 at 42 days.[34] Values for 24-hour urine protein excretion and the U_{Pr}/U_{Cr} are presented in Table 257-1.

Dogs with proteinuria on screening urinalysis have been shown to have an increased U_{Pr}/U_{Cr}.[26,28,31,35] A high degree of overlap is found between dogs with glomerulonephritis and those with amyloidosis with regard to 24-hour urine protein excretion and the U_{Pr}/U_{Cr}.[26,27] Therefore renal biopsy remains the only reliable way to differentiate these two diseases.

257.3.1.8 Microalbuminuria

In humans, microalbuminuria is defined as excretion of 30 to 300 mg of albumin in urine per day, and its presence may be an early indicator of vascular endothelial damage.[36] Microalbuminuria is an established risk factor for progression of renal disease in humans with type 1 or type 2 diabetes mellitus.[37] Whether microalbuminuria is predictive of progressive renal disease in humans with essential hypertension is less certain, but it is associated with adverse cardiovascular events in this population.[38,39] Microalbuminuria in dogs has been defined as a urine albumin concentration of greater than 1 mg/dL but less than 30 mg/dL. Urine albumin concentrations in this range can be detected by an antigen-capture enzyme-linked immunosorbent assay (ELISA) (i.e., ERD-Screen Urine Test; Heska Corp., Fort Collins, Colorado).[40] In recent studies, the prevalence of microalbuminuria in normal healthy dogs was 19%, and the prevalence in a hospital population of dogs was 36%. Microalbuminuria has been detected in heartworm-infected dogs and in those with familial renal disease (e.g., soft-coated wheaten terriers with glomerular disease, male dogs with X-linked hereditary nephritis). The effect of pyuria on detection of microalbuminuria was found to be variable. It remains to be determined whether seemingly normal dogs with microalbuminuria are at

increased risk for the development of progressive renal disease. Sequential monitoring of dogs with documented microalbuminuria probably is warranted until this factor's prognostic value in otherwise normal dogs can be determined.

257.3.1.9 Bladder Tumor Antigen Test

The first-generation Bard bladder tumor antigen (BTA) test (i.e., V-BTA Test; Polymedco, Cortlandt Manor, New York) is a qualitative latex agglutination dipstick test run on voided urine that detects a glycoprotein antigen complex associated with bladder neoplasia in humans. In a prospective study of 65 dogs with transitional cell carcinoma and other urinary tract disorders, the Bard V-BTA Test had a sensitivity of 90% and a specificity of 78%.[41] False positives occurred in urine samples with marked proteinuria or glucosuria and in those with pyuria or hematuria. The high sensitivity of the test and its less reliable performance in the presence of pyuria and hematuria suggest that it would be most appropriately used as a routine screening test in geriatric dogs at risk for the development of transitional cell carcinoma.

In another study, the V-BTA Test reliably differentiated dogs with lower urinary tract neoplasia from normal dogs but did not reliably differentiate dogs with neoplasia from dogs with other abnormalities of the lower urinary tract.[42] The V-BTA Test is commercially available for veterinary use.

Second-and third-generation Bard BTA tests (BTA Stat and Bard Trak, respectively), as well as other tests that use monoclonal antibodies against human bladder tumor antigens, give false-negative results in dogs and should not be used.[41]

257.3.2 Tubular Function

The kidney is an organ of water conservation. Depending on the needs of the animal, the kidney can produce urine that is highly concentrated or quite dilute. Normal urinary concentrating ability depends on the ability of the hypothalamic osmoreceptors to respond to changes in plasma osmolality, the release of antidiuretic hormone (ADH) from the neurohypophysis, and the response of the distal nephron to ADH. In addition, medullary hypertonicity must be generated and maintained by the countercurrent multiplier and exchanger systems of the kidney, and an adequate number of functional nephrons must be present to generate the appropriate response to ADH. Laboratory tests of tubular function are summarized in Table 257-2.

257.3.2.1 Urine Specific Gravity and Osmolality

The total urine solute concentration is measured either by the urine specific gravity (USG) or the urine osmolality (U_{Osm}). The latter depends only on the number of osmotically active particles, regardless of their size. The *urine specific gravity* is defined as the weight of a solution compared with an equal volume of distilled water. It depends on both the number and molecular weight of the solute particles but has the advantage of requiring only simple, inexpensive equipment for measurement.

Table • 257-2 Tests of Renal Tubular Function in Dogs and Cats

TEST	DOG	CAT
Random urine specific gravity	1.001–1.070	1.001–1.080
Urine specific gravity after 5% dehydration	1.050–1.076	1.047–1.087
Urine osmolality after 5% dehydration (mOsm/kg)	1787–2791	1581–2984
Urine to plasma osmolality ratio after 5% dehydration	5.7–8.9	Not available
Fractional electrolyte clearance (%)		
Sodium	<1	<1
Potassium	<20	<24
Chloride	<1	<1.3
Phosphate	<39	<73

Modified from DiBartola SP: Clinical Evaluation of Renal Function. 16th Annual Waltham/OSU Symposium for the Treatment of Small Animal Disease. Vernon, California, Kal Kan Foods, 1992, p 10.

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Normally, urine is composed of solutes of relatively low molecular weight (e.g., urea, electrolytes), and a roughly linear relationship exists between the urine osmolality and the urine specific gravity. The range of urine osmolality that corresponds to a given USG, however, may be relatively wide. If the urine contains appreciable amounts of larger molecular weight solutes (e.g., glucose, mannitol, radiographic contrast agents), these substances have a proportionally greater effect on specific gravity than on osmolality.

The term *isosthenuria* (USG of 1.007–1.015, U_{Osm} of 300 mOsm/kg) refers to urine of the same total solute concentration as unaltered glomerular filtrate. The term *hyposthenuria* (USG less than 1.007, U_{Osm} less than 300 mOsm/kg) refers to urine of lower total solute concentration than glomerular filtrate. Although rarely used clinically, the term *hypersthenuria (baruria)* (USG greater than 1.015, U_{Osm} greater than 300 mOsm/kg) refers to urine of higher total solute concentration than glomerular filtrate. The normal range of the total urine solute concentration for dogs and cats is wide (USG of 1.001 to 1.080). In a study of normal pet dogs, USG values were found to vary widely (from 1.006 to greater than 1.050).[43] Samples obtained in the morning had higher USG values than those obtained in the evening, and urine concentration decreased with age, but no effect of gender on the USG was detected.

257.3.2.2 Water Deprivation Test

The water deprivation test (WDT) is a useful test of tubular function and is indicated in the evaluation of animals with confirmed polydipsia and polyuria for which the cause remains undetermined after initial diagnostic evaluation. An expedient safe alternative to the WDT is DDAVP (synthetic ADH) trial therapy. Please see Chapter 28 for a discussion on this approach.

The water deprivation test usually is performed in animals with hyposthenuria (USG less than 1.007) that are suspected of having central or nephrogenic diabetes insipidus or psychogenic polydipsia. A dehydrated animal that has dilute urine has already failed the test and should not be subjected to water deprivation. In such an animal, failure to concentrate urine likely is due to structural or functional renal dysfunction or to the administration of drugs that interfere with urinary concentrating ability (e.g., glucocorticoids, diuretics). The water deprivation test also is contraindicated in animals that are azotemic. It should be performed with extreme caution in animals with severe polyuria, because such pets may rapidly become dehydrated during water deprivation if they have defective urinary concentrating ability.

At the beginning of the water deprivation test, the bladder must be emptied and baseline data collected (e.g., body weight, hematocrit, plasma proteins, skin turgor, serum osmolality, urine osmolality, USG). Water then is withheld, and these parameters are monitored every 2 to 4 hours. The urine and serum osmolalities are the best tests to follow, but osmolality results often are not immediately available to the clinician. Thus the USG and body weight assume the greatest importance for decision making during performance of the test. An increase in the total plasma protein concentration is a relatively reliable indicator of progressive dehydration, but increases in the hematocrit and changes in skin turgor are not reliable. The serum creatinine and BUN concentrations should not increase during a properly conducted water deprivation test.

Maximal stimulation of ADH release occurs after the loss of 3% to 5% of body weight. The test is concluded when the dog or cat either demonstrates adequate concentrating ability or becomes dehydrated, as evidenced by loss of 3% to 5% or more of its original body weight. It is important when weighing the animal to use the same scale each time and to empty the bladder at each evaluation.

The time required for dehydration to develop during water deprivation varies. Dehydration usually becomes evident within 48 hours in normal dogs and cats but in rare cases may require a longer time. Dogs with diabetes insipidus and psychogenic polydipsia usually become dehydrated after a much shorter period of water deprivation (less than 12 hours and usually less than 6 hours). By the time dehydration is evident, the USG usually exceeds 1.045 in normal dogs and cats. Failure to achieve maximal urinary solute concentration does not localize the level of the malfunction, and a structural or functional defect may be present anywhere along the hypothalamic-pituitary-renal axis. Furthermore, animals with medullary solute washout may have impaired concentrating ability regardless of the underlying cause of polyuria and polydipsia.

If urine osmolality has increased less than 5% or the USG has changed less than 10% for three consecutive determinations, or if the animal has lost 3% to 5% or more of its original weight, 0.1 to 0.2 U/lb of aqueous vasopressin (Pitressin) (up to a total dose of 5 U) or 5 μg of DDAVP may be given subcutaneously and the parameters of urinary concentrating ability monitored 2 to 4 hours after ADH injection. A further increase in urine osmolality after administration of ADH should not exceed 5% to 10% in normal dogs and cats.

257.3.2.3 Gradual Water Deprivation

Gradual water deprivation can be performed to eliminate diagnostic confusion caused by medullary solute washout. The owner can be instructed to restrict water consumption to 120 mL/kg/day 72 hours before, 90 mL/kg/day 48 hours before, and 60 mL/kg/day 24 hours before the scheduled water deprivation test. In dogs with psychogenic polydipsia, this promotes endogenous release of ADH, increased permeability of the inner medullary collecting ducts to urea, and restoration of the normal gradient of medullary hypertonicity. An alternate approach is to instruct the owner to reduce water consumption by approximately 10% per day over a 3-to 5-day period (but not to less than 60 mL/kg/day). This approach should be used only for animals that are otherwise healthy on initial clinical evaluation, and the owner should provide dry food *ad libitum* and weigh the dog daily to monitor for loss of body weight.

257.3.2.4 Fractional Clearance of Electrolytes

The extent to which electrolytes appear in the urine is the net result of tubular resorption and secretion. The fractional clearance of electrolytes can be used to evaluate tubular function and is defined as the ratio of the clearance of the electrolyte in question to that of creatinine:

$$FC_x = (U_xV/P_x)/(U_{Cr}V/P_{Cr}) = (U_xP_{Cr})/(U_{Cr}P_x)$$

where FC_x = fractional clearance of X; U_x = urine concentration of X; P_x = plasma concentration of X; U_{cr} = urine concentration of creatinine; P_{cr} = plasma concentration of creatinine; V = urine flow rate.

This ratio usually is multiplied by 100, and the fractional clearance value is expressed as a percentage. The advantage of this measurement is that a timed urine collection is not necessary. In normal animals, the fractional clearances of all electrolytes are much less than 1 (100%), implying net conservation, but values are higher for potassium and phosphorus than for sodium and chloride. Unfortunately, fractional excretion values calculated from "spot" urine samples are variable and do not correlate well with values calculated using 72-hour urine samples.[44]

The fractional clearance of sodium may be useful in the differentiation of prerenal and primary renal azotemia. In animals with prerenal azotemia and volume depletion, sodium conservation should be avid and the fractional clearance of sodium low (less than 1%). In animals with azotemia caused by primary parenchymal renal disease, the fractional clearance of sodium is higher than normal (greater than 1%). 1721 1722

Values for fractional electrolyte clearances have been reported for normal dogs,[45] dogs with CRF,[46] normal cats,[47,48] and cats with experimentally induced CRF.[49] Normal values for urinary fractional clearance of electrolytes are summarized in Table 257-2.

257.4 ROUTINE URINALYSIS

Urine for urinalysis may be collected by voiding (midstream sample), catheterization, or cystocentesis. Cystocentesis is preferred because it prevents contamination of the sample by the urethra or genital tract, it is simple to perform when the bladder is palpable, the risk of introducing infection is negligible, and it is well-tolerated by both dogs and cats. In animals to be evaluated for hematuria, however, it may be helpful first to evaluate a sample collected by voiding, because other methods of urine collection may add red blood cells to the sample as a result of trauma.

For urinalysis, fresh urine should be examined whenever possible. Refrigerated urine should be warmed to room temperature before the urinalysis is performed. The technique used to collect the sample should be noted, because this may influence the interpretation. Urinalysis is divided into three parts: physical properties, chemical properties, and sediment evaluation.

257.4.1 Physical Properties

257.4.1.1 Appearance

Normal urine is yellow as a result of the presence of urochrome pigment. Concentrated urine may be deep amber, and dilute urine may be almost colorless. A red or reddish brown color usually is due to red blood

cells, hemoglobin, or myoglobin; a yellow-brown to yellow-green color may be due to bilirubin. Normal urine usually is clear. Cloudy urine often contains increased cellular elements, crystals, or mucus. The most common abnormal odor is ammoniac and is due to the release of ammonia by urease-producing bacteria.

257.4.1.2 Specific Gravity

As mentioned before, the USG reflects the total solute concentration of the urine, and the amount of any substance in urine must be interpreted in light of the specific gravity. For example, 4+ protein in 1.010 urine represents more severe proteinuria than 4+ protein in 1.045 urine. The USG should be obtained before any treatment is given, because fluids, diuretics, or glucocorticoids may alter the specific gravity.

257.4.2 Chemical Properties

257.4.2.1 pH

Urine pH varies with diet and acid-base balance. The normal pH of urine in dogs and cats is 5.0 to 7.5. Causes of an acidic urine pH include a meat protein–based diet, administration of acidifying agents, metabolic acidosis, respiratory acidosis, paradoxical aciduria in metabolic alkalosis, and protein catabolic states. Causes of an alkaline urine pH include urinary tract infection by urease-positive bacteria, a plant protein–based diet, urine allowed to stand exposed to air at room temperature, postprandial alkaline tide, administration of alkalinizing agents, metabolic alkalosis, respiratory alkalosis, and distal renal tubular acidosis.

257.4.2.2 Protein

Randomly obtained urine samples from normal dogs contain small amounts of protein (up to 50 mg/dL). Commonly used dipstick methods for protein determination are much more sensitive to albumin than globulin. In the evaluation of proteinuria, it is critical to localize the origin of the protein loss by means of the history, physical examination, and critical evaluation of the urine sediment. Persistent, moderate to heavy proteinuria in the absence of urine sediment abnormalities is highly suggestive of glomerular disease (e.g., glomerulonephritis, glomerular amyloidosis). If the sediment is active and proteinuria is mild to moderate, the possibility of inflammatory renal disease or disease of the lower urinary or genital tract should be considered.

257.4.2.3 Glucose

Glucose in the glomerular filtrate is almost completely resorbed in the proximal tubules and is not normally present in the urine of dogs and cats. Glucose appears in the urine *(glucosuria)* if the blood glucose concentration exceeds the renal threshold (approximately 175 to 225 mg/dL in the dog and 250 to 350 mg/dL in the cat). Most dipstick tests use a colorimetric test based on an enzymatic reaction (glucose oxidase) specific for glucose. Causes of glucosuria include diabetes mellitus, stress or excitement in cats, administration of glucose-containing fluids, and renal tubular diseases, such as primary renal glucosuria and Fanconi syndrome. Glucosuria also may be observed occasionally in dogs and cats with chronic renal disease, those with tubular injury caused by nephrotoxins, and in some dogs with familial renal disease.

257.4.2.4 Ketones

Beta hydroxybutyrate, acetoacetate, and acetone are ketones, the products of exaggerated and incomplete oxidation of fatty acids. They are not normally present in the urine of dogs and cats. The nitroprusside reagent present in dipstick tests reacts with acetone and acetoacetate but is much more reactive with acetoacetate. It does not react with beta hydroxybutyrate. Causes of ketonuria include diabetic ketoacidosis, starvation or prolonged fasting, glycogen storage disease, a low-carbohydrate diet, persistent fever, and persistent hypoglycemia. Ketonuria occurs more readily in young animals, and of the causes listed above, diabetic ketoacidosis is the most important cause in adult dogs and cats.

257.4.2.5 Occult Blood

Dipstick tests for blood are sensitive but do not differentiate erythrocytes, hemoglobin, and myoglobin. These tests are more sensitive to hemoglobin than to intact erythrocytes; the former causes a diffuse color change, whereas the latter causes spotting of the reagent pad. A positive test result must be interpreted in light of the urine sediment findings (i.e., presence or absence of red blood cells). Free hemoglobin (secondary to hemolysis) is the most common abnormal pigment found in urine. Potential causes of hemolysis include transfusion reaction, autoimmune hemolytic anemia, disseminated intravascular coagulation, postcaval syndrome of dirofilariasis, splenic torsion, and heat stroke. Myoglobinuria is less common but may be present if severe rhabdomyolysis occurs (e.g., status epilepticus, crushing injury). For proper interpretation, the occult blood reaction must be considered together with the urine sediment findings (e.g., hematuria).

257.4.2.6 Bilirubin

Bilirubin is derived from the breakdown of heme by the reticuloendothelial system. It is transported to the liver, where it is conjugated with glucuronide and excreted in the bile. Only direct-reacting or conjugated bilirubin appears in the urine. The canine kidney can degrade hemoglobin to bilirubin, and the renal threshold for bilirubin is low in dogs. Thus in dogs with liver disease, bilirubin may be detected in the urine before its serum concentration is increased. It is not unusual to find small amounts of bilirubin in concentrated urine samples from normal dogs, especially males. Bilirubin is absent from normal feline urine. The causes of bilirubinuria are hemolysis (e.g., autoimmune hemolytic anemia), liver disease, extrahepatic biliary obstruction, fever, and starvation.

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257.4.2.7 Leukocyte Esterase Reaction

Indoxyl released by esterases from intact or lysed leukocytes reacts with a diazonium salt and is detected as a blue color reaction after oxidation by atmospheric oxygen. This test is specific for pyuria in canine urine samples but has low sensitivity (produces many false-negative results).[50] In cats, the leukocyte esterase test was found to be moderately sensitive but highly nonspecific (produced many false-positive results) for the detection of pyuria.[51]

257.4.3 Urinary Sediment Examination

Depending on the criteria used for data analysis, as few as 3% or as many as 16% of dogs and cats with normal findings on physical and chemical evaluation of urine may have important urinary sediment

abnormalities (e.g., pyuria, bacteriuria, microscopic hematuria).[52] The sediment examination should be performed on fresh urine samples, because casts and cellular elements degenerate rapidly at room temperature. Urine should be centrifuged at 1000 to 1500 rpm for 5 minutes and the sediment then stained with Sedi-Stain (Becton Dickinson, Franklin Lakes, New Jersey) or examined unstained, depending on individual preference. In the evaluation of urine sediment, the method of urine collection must be kept in mind, because it influences the interpretation. The USG must also be kept in mind, because it influences the relative numbers of formed elements. The number of casts is recorded per low power field (lpf), and the numbers of red blood cells, white blood cells, and epithelial cells are recorded per high power field (hpf).

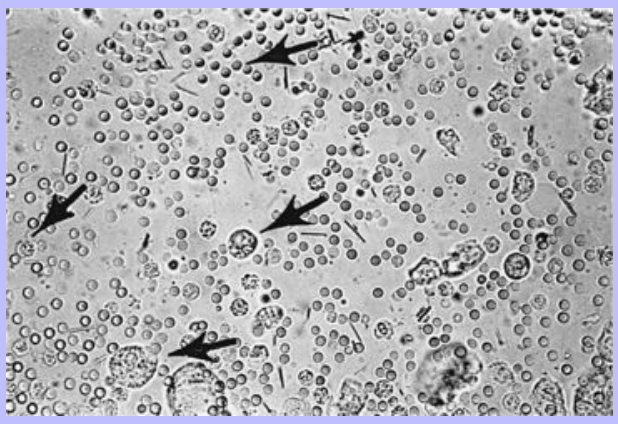
257.4.3.1 Red Blood Cells

Occasional red blood cells are considered normal in the urine sediment. Normal values are: voided sample, 0 to 8/hpf; catheterized sample, 0 to 5/hpf; and cystocentesis sample, 0 to 3/hpf. The presence of an excessive number of red blood cells in the urine is called *hematuria* (Figure 257-3), which may be microscopic or macroscopic. The causes of hematuria are summarized in Box 257-1.

257.4.3.2 White Blood Cells

Occasional white blood cells are considered normal in the urine sediment. Normal values are: voided sample, 0 to 8/hpf; catheterized sample, 0 to 5/hpf; and cystocentesis sample, 0 to 3/hpf. The presence of an increased number of white blood cells in the urine sediment is called *pyuria* (Figure 257-4) and, in an appropriately collected urine sample, is indicative of inflammation somewhere in the urinary tract. The presence of white blood cells does not help localize the lesion unless white cell casts are present, indicating renal origin. Urinary tract infection is the most common cause of pyuria, but genital tract contamination also may cause pyuria in voided or catheterized samples (Box 257-2).

Figure 257-3 Photomicrograph of an abnormal urine sample. Arrow at top indicates red blood cells (RBCs), arrow at left indicates a white blood cell (WBC), and central and bottom arrows indicate two different sizes of transitional epithelial cells. RBCs in urine may resemble those in blood or may shrink or swell in response to variations in urine osmolality.



257.4.3.2.1

Box • 257-1 Causes of Hematuria in Dogs and Cats

257.4.3.2.1.1

Urinary Tract Origin (Kidneys, Ureters, Bladder, Urethra)

Trauma

- Traumatic collection (e.g., catheter, cystocentesis)
- Renal biopsy
- Blunt trauma (e.g., automobile accident)

Urolithiasis

Neoplasia

Inflammatory disease

- Urinary tract infection
- Feline urologic syndrome (idiopathic feline lower urinary tract disease)
- Chemically induced inflammation (e.g., cyclophosphamide-induced cystitis)

Parasites

- *Dioctophyma renale*
- *Capillaria plica*

Coagulopathy

- Warfarin intoxication
- Disseminated intravascular coagulation
- Thrombocytopenia

Renal infarction

Renal pelvic hematoma

Vascular malformation

Renal telangiectasia (Welsh corgi)

Idiopathic renal hematuria

257.4.3.2.1.2 Genital Tract Contamination (Prostate, Prepuce, Vagina)

Estrus

Inflammatory, neoplastic, and traumatic lesions of the genital tract

257.4.3.3 Epithelial Cells

Both squamous and transitional epithelial cells may be found in the urine sediment, but they are often of little diagnostic significance. Squamous cells are large, polygonal cells with small round nuclei (Figure 257-5). They are common in voided or catheterized samples because of urethral or vaginal contamination. Occasional squamous cells are normal, and increased numbers may be present during estrus.

Transitional epithelial cells are variable-sized cells derived from the urothelium from the renal pelvis to the urethra (Figure 257-6). Although their size generally increases from the renal pelvis to the urethra, the finding of small transitional cells in the urine sediment does not have localizing value. Caudate cells are transitional cells with tapered ends thought to originate from the renal pelvis (Figure 257-7). Occasional transitional cells are normal, and increased numbers may be present with infection, irritation, or neoplasia of the urinary tract. Renal cells are small epithelial cells from the renal tubules, but their renal origin can be determined only if they are observed in cellular casts. Neoplastic epithelial cells are best identified using conventional blood cell stains (e.g., Wright-Giemsa).

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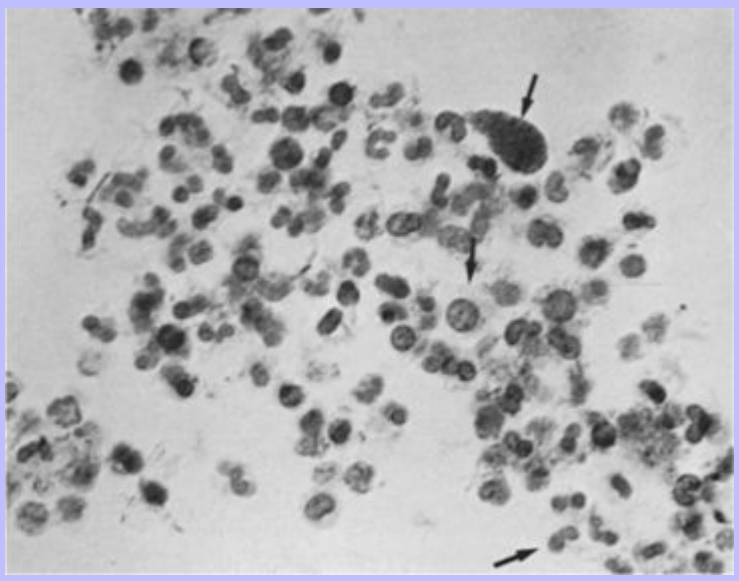
Figure 257-4 Photomicrograph of an abnormal urine sample. White blood cells (WBCs) in urine are subject to degenerative changes that may complicate their identification. They may shrink in concentrated urine or swell in dilute urine. WBCs usually are one and one half to two times the size of red blood cells. Clumps of WBCs often are associated with infection. Occasional transitional epithelial cells also are present in this field. The arrow at bottom right indicates a neutrophil with a swollen cytoplasm and easily identifiable polymorphonuclear nucleus. Occasional transitional epithelial cells also are present *(top arrow)*.



257.4.3.4 Casts

Casts are cylindric molds of the renal tubules composed of aggregated proteins or cells. They form in the ascending limb of Henle's loop and the distal tubule because of the maximal acidity, highest solute concentration, and lowest flow rate in this area. The presence of casts in the urinary sediment indicates activity in the kidney itself and thus is of localizing value. Occasional hyaline (Figure 257-8) and granular (Figure 257-9) casts per low power field are considered normal. No cellular casts should be observed in sediment from normal urine. Excretion of an abnormal number of casts in the urine is called *cylindruria*.

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257.4.3.4.1 Box • 257-2 Causes of Pyuria

257.4.3.4.1.1 Urinary Tract Origin (Kidneys, Ureters, Bladder, Urethra)

Infectious

- Urinary tract infection (e.g., pyelonephritis, cystitis, urethritis)

Noninfectious

- Urolithiasis
- Neoplasia
- Trauma
- Chemically induced (e.g., cyclophosphamide)

257.4.3.4.1.2 Genital Tract Contamination (Prostate, Prepuce, Vagina)

Figure 257-5 Photomicrograph of a squamous epithelial cell in the urine. Note the small nucleus, irregular cell shape, and folding of the cytoplasmic margins in some areas.

Figure 257-6 Photomicrograph of a raft of transitional epithelial cells in the urine.

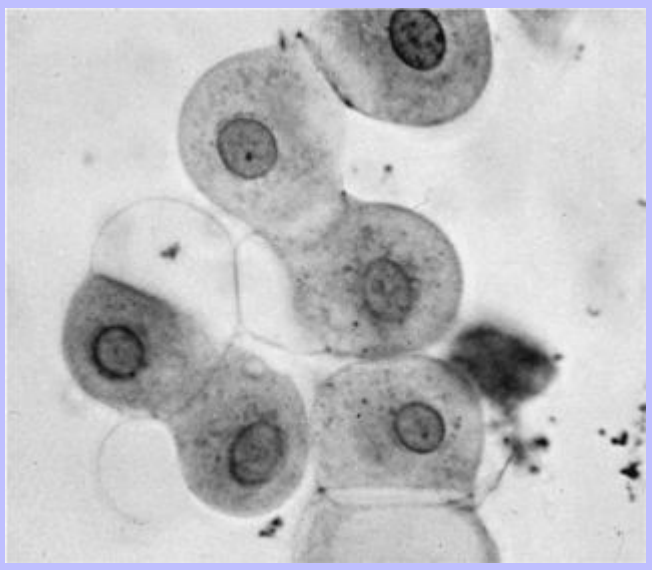


Figure 257-7 Photomicrograph of caudate epithelial cells in urine. The tails on these small epithelial cells suggest that they originated in the renal pelvis.

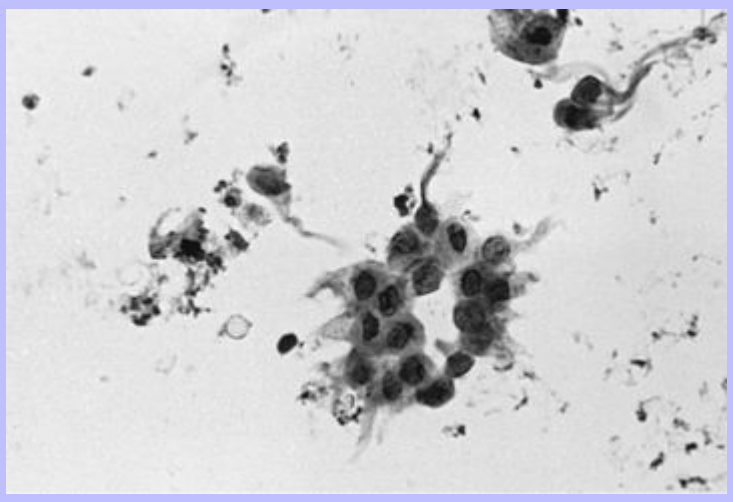
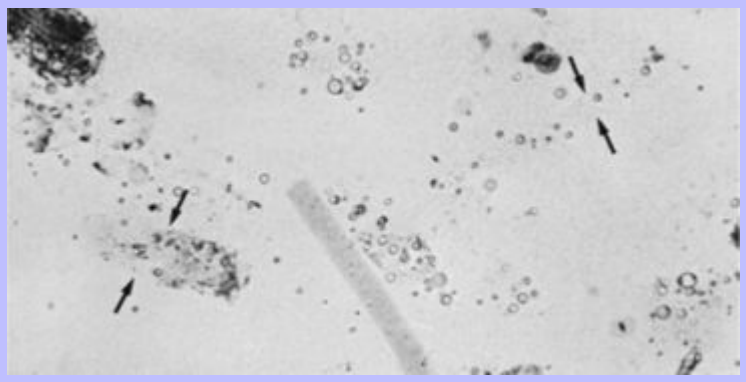


Figure 257-8 Photomicrograph of hyaline casts in urine. Note the transparent nature of these casts *(between arrows)*. The casts are easily missed because their optical density is very low, necessitating low illumination for optimal visualization. The darker cast in the center of the field is a waxy cast. Many lipid droplets are present in the background.



Casts observed in the urine sediment are categorized as hyaline, granular, cellular, or waxy. Hyaline casts are pure protein precipitates (Tamm-Horsfall mucoprotein and albumin). They are difficult to see and dissolve rapidly in dilute or alkaline urine. Small numbers of hyaline casts may be observed with fever or exercise. They are commonly seen in renal diseases associated with proteinuria (e.g., glomerulonephritis, glomerular amyloidosis).

Coarsely (Figure 257-10) and finely (see Figure 257-9) granular casts represent the degeneration of cells in other casts or precipitation of filtered plasma proteins and are suggestive of ischemic or nephrotoxic renal tubular injury. Fatty casts, a type of coarsely granular cast that contains lipid granules, may be seen in nephrotic syndrome or diabetes mellitus. Cellular casts include white cell or pus casts (suggestive of pyelonephritis) (Figure 257-11), red cell casts (fragile and rarely observed in dogs and cats), and renal epithelial cell casts (Figure 257-12) (suggestive of acute tubular necrosis or pyelonephritis). Waxy casts represent the final stage of degeneration of granular casts; they are relatively stable, and their presence suggests intrarenal stasis (Figure 257-13). They often are very convoluted and have cracks and blunt ends.

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Figure 257-9 Photomicrograph of a finely granular cast in urine.

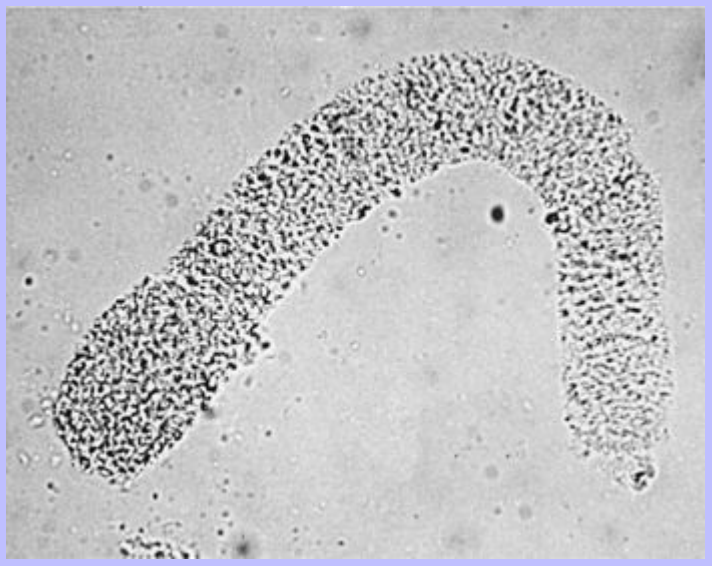


Figure 257-10 Photomicrograph of coarsely granular casts in urine. A "shower" of casts is seen in this field. The cast at the left contains coarse granules; the one on the far right is a cellular cast undergoing degeneration.

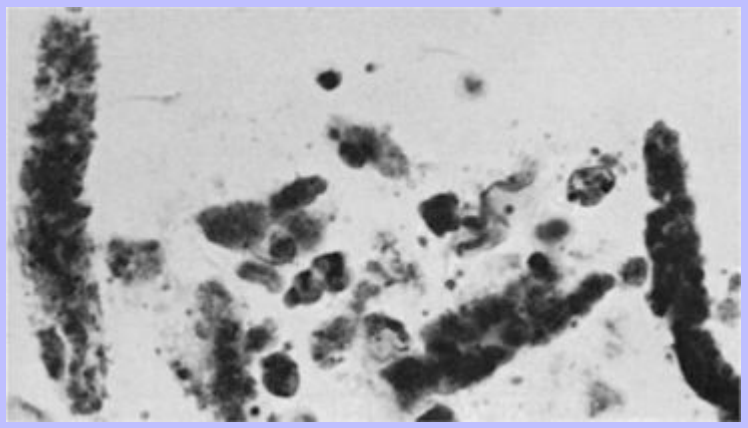


Figure 257-11 Photomicrograph of a white blood cell cast in urine. Neutrophils can be seen within this cast, and their presence suggests renal bacterial infection (i.e., pyelonephritis).

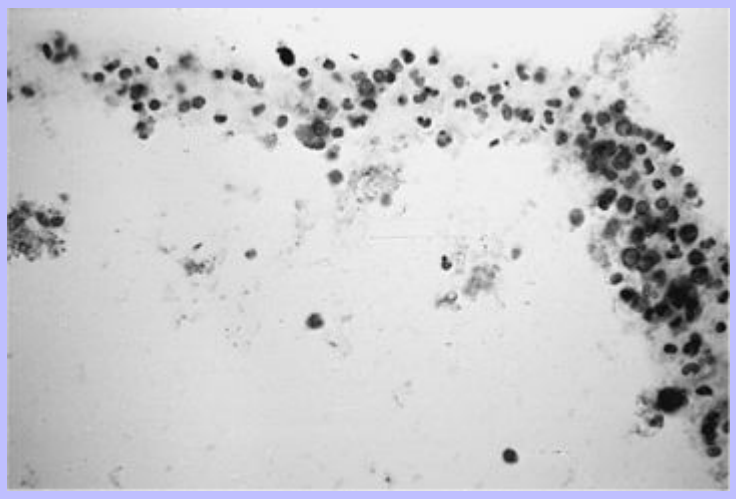


Figure 257-12 Photomicrograph of an epithelial cell cast in urine. Small renal epithelial cells can be identified in this cast *(white arrows)*. (Courtesy Nancy Facklam, nancy.facklam@gov.ab.ca)

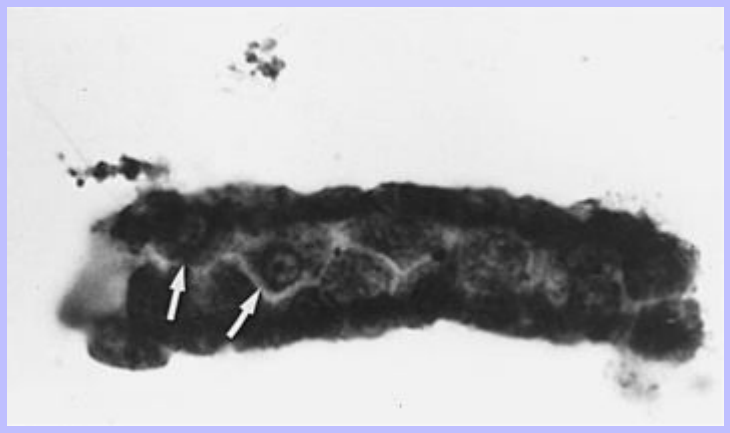
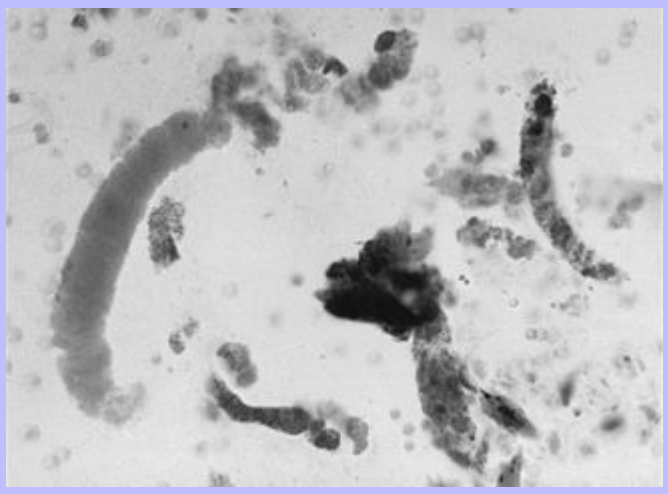


Figure 257-13 Photomicrograph of a urine sample containing waxy and granular casts. The cast at the left is waxy, whereas the others are granular. Note that the waxy cast is translucent, and the hyaline casts are transparent. Waxy casts are brittle and often have cracks or sharply broken ends.



257.4.3.5 Organisms

Normal bladder urine is sterile. The distal urethra and genital tract harbor bacteria, and voided or catheterized urine samples may be contaminated with bacteria from the distal urethra, genital tract, or skin. Contamination from the urethra in voided or catheterized specimens usually does not result in large enough numbers of bacteria to be visualized microscopically in the urine sediment. If allowed to incubate at room temperature, however, these contaminants may proliferate. For these organisms to be readily apparent microscopically, there must be more than 10,000 rods or more than 100,000 cocci per milliliter of urine. The presence of large numbers of bacteria in urine collected by catheterization or cystocentesis suggests a urinary tract infection (Figure 257-14). Usually accompanying pyuria is seen. Particulate debris in the sediment may be confused with bacteria and cause false-positive results. Also, the bottle of stain may be contaminated with bacteria. Microscopic absence of bacteria in the sediment does not rule out urinary tract infection. Yeast and fungal hyphae in the sediment usually are contaminants.

Figure 257-14 Photomicrograph of a urine sample containing bacteria. Chains of bacterial rods are present in this field, as are red blood cells *(arrows)* and a large struvite crystal. Bacteria are most readily identified in urine when they are rods; they often are observed in association with clumped white blood cells or within white blood cells.

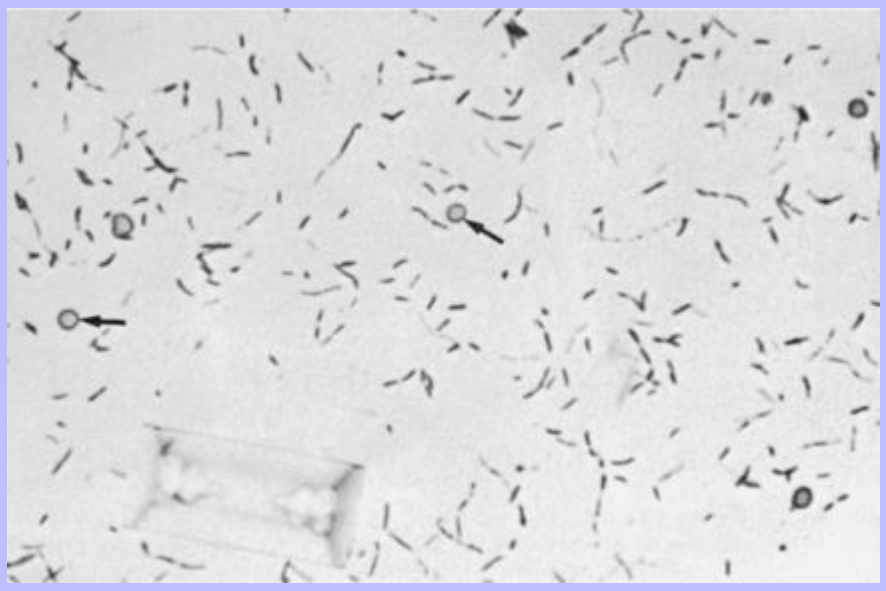
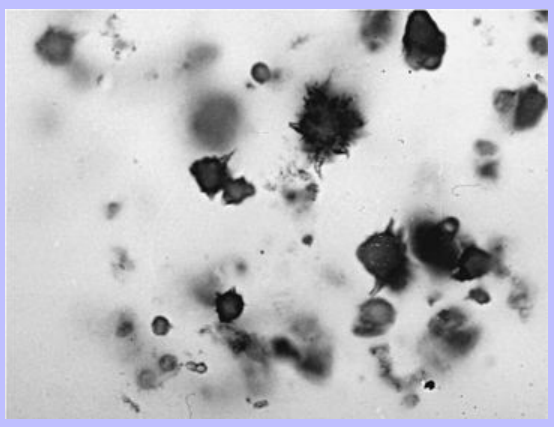


Figure 257-15 Photomicrograph of a urine sample containing ammonium biurate crystals. These crystals may be observed in normal Dalmatian dogs and in dogs with liver disease or portosystemic shunts.



257.4.3.6 Crystals

The solubility of crystals depends on the urine pH, temperature, and specific gravity. Crystals commonly are present in the urine of dogs and cats and often are of little diagnostic significance. Struvite, amorphous phosphates, and oxalates are examples of crystals that may be found in normal urine samples. Uric acid, calcium oxalate, and cystine typically are found in acidic urine, whereas struvite ($MgNH_4PO_4 \cdot 6H_2O$, or so-called triple phosphate), calcium phosphate, calcium carbonate, amorphous phosphate, and ammonium biurate typically are found in alkaline urine. Characteristic crystals also may be found in the urine sediment of animals receiving specific drugs, especially sulfonamides. Bilirubin crystals may be found in concentrated samples of normal dog urine. Urates are commonly observed in the urine of Dalmatians and may be seen in the urine of animals with liver disease or portosystemic shunts (Figure 257-15). Struvite crystals may be observed in the urine of cats with idiopathic lower urinary tract disease, in dogs and cats with struvite urolithiasis, or in the urine of normal animals (Figure 257-16). In oliguric ARF, the presence of calcium oxalate crystals (Figures 257-17 and 257-18) is highly suggestive of ethylene glycol intoxication. The presence of cystine crystals in the urine of dogs and cats is abnormal and suggestive of cystinuria (Figure 257-19).

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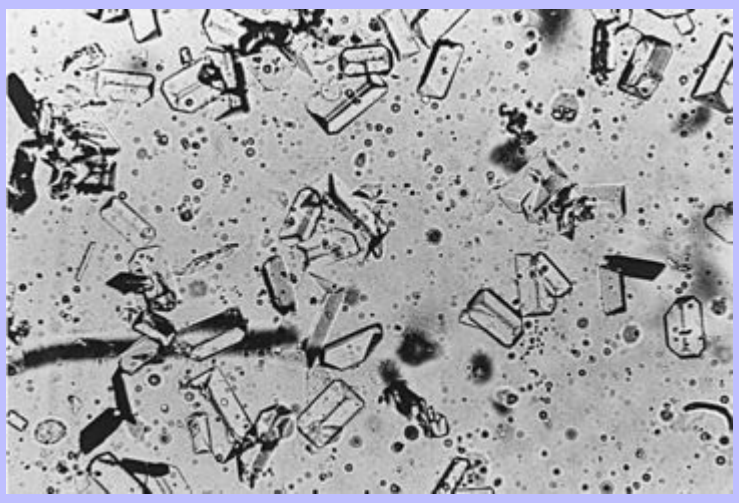
Figure 257-16 Photomicrograph of a urine sample containing struvite crystals. These crystals may be observed in the urine of normal dogs and cats and are common in alkaline urine.



257.4.3.7 Miscellaneous Findings

Sperm commonly are found in urine samples from normal intact male dogs. Rarely, parasite ova of *Dioctophyma renale* or *Capillaria plica* or microfilaria of *Dirofilaria immitis* may be observed in the urine sediment. Refractile lipid droplets may be seen with diabetes mellitus or nephrotic syndrome. They also may be observed in cats as a result of degeneration of lipid-laden tubular cells.

257.5 MICROBIOLOGY

Clinical signs and urinalysis findings provide supportive evidence, but microbiology is required to diagnose urinary tract infection (UTI) conclusively. The kidneys, ureters, bladder, and proximal urethra of normal dogs and cats are sterile, whereas a resident bacterial flora populates the distal urethra, prepuce, and vagina. Urinary tract infection occurs when bacteria colonize areas of the urinary tract that normally are sterile. Aerobic gram-negative bacteria account for most UTIs in dogs and cats, and the remainder are caused by gram-positive organisms. *Escherichia coli* is the organism most commonly implicated in urinary tract infections in dogs and cats. Other organisms isolated include *Proteus* spp., coagulase-positive staphylococci, and streptococci. *Pasteurella multocida* occasionally is isolated from cats with UTI. *Enterobacter* sp., *Klebsiella* sp., and *Pseudomonas aeruginosa* are observed less commonly in dogs and rarely in cats.

Figure 257-17 Photomicrograph of a urine sample containing calcium oxalate dihydrate crystals. These crystals may be observed in the urine of normal dogs as well as in those with calcium oxalate urolithiasis or acute renal failure caused by ethylene glycol ingestion. Note the typical “Maltese cross” appearance within a rhomboidal structure. These crystals can vary markedly in size.

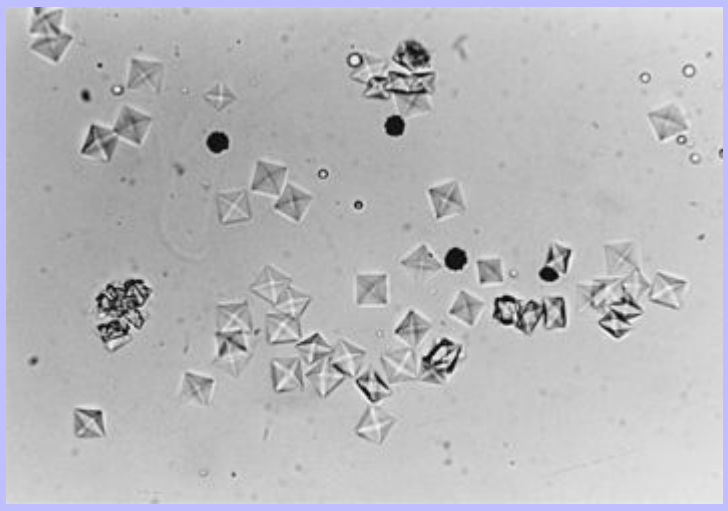


Figure 257-18 Photomicrograph of a urine sample containing calcium oxalate monohydrate crystals. Previously misnamed hippurate, these "picket fence"–and "dumbbell"–shaped crystals may be found in the urine of dogs with acute renal failure caused by ethylene glycol ingestion.

Results obtained with bacterial culture of urine depend on the method of urine collection. Voided urine has the greatest potential for bacterial contamination, and catheterization may inoculate the bladder with bacteria from the distal urethra. Urine collected by cystocentesis should be sterile in normal animals. Quantitative bacterial culture of urine allows determination of the number of bacterial colonies (colony-forming units [cfu]) that grow from 1 mL of urine (cfu/mL). Ideally, urine should be submitted for culture within 30 minutes of collection. If this is not possible, the sample may be refrigerated for up to 6 hours without significant loss of bacterial growth. Chemical preservation with a solution of boric acid, glycerol, and sodium formate, in combination with refrigeration, effectively maintained bacterial viability in canine urine samples for up to 72 hours.[53]

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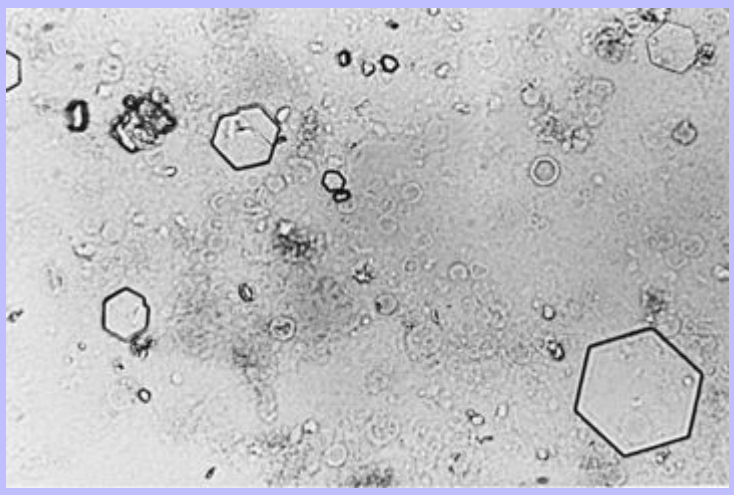
Figure 257-19 Photomicrograph of a urine sample containing cystine crystals. These crystals usually are found in acidic urine and are not present in normal animals. Their presence suggests cystinuria with or without cystine urolithiasis.



Bacterial culture of midstream-voided urine samples from normal dogs and cats often results in the growth of less than 1000 to greater than or equal to 100,000 cfu/mL. Therefore culture of voided urine is not recommended in evaluation of patients for UTI. If, however, no growth is obtained from a voided urine sample, UTI can be excluded as a diagnosis. Bacterial growth of greater than or equal to 100,000 cfu/mL may result from culture of urine obtained from catheterization in 20% of normal female dogs. Thus using a measurement of 100,000 cfu/mL as an indicator of UTI in female dogs results in a substantial number of false-positive results. Also, the urethral catheterization procedure itself may cause UTI in 20% of normal female dogs. Consequently, collection of urine by cystocentesis is recommended for establishing a diagnosis of UTI in female dogs. Isolation of bacteria from urine collected by catheterization from male dogs is uncommon, and a measurement of greater than 1000 cfu/mL is recommended for establishing a diagnosis of UTI using these urine samples. In both male and female cats, growth of greater than 1000 cfu/mL in samples collected by catheterization is considered compatible with a diagnosis of UTI.

Urine samples obtained by cystocentesis from normal dogs and cats should yield no growth, because this procedure bypasses the normal bacterial flora of the urethra and genital tract. Consequently, results obtained by cystocentesis are the standard against which results obtained using voided or catheterized samples are compared. A small number of organisms from the skin or environment occasionally contaminate samples obtained by cystocentesis, and growth of less than 1000 cfu/mL may be considered suggestive of contamination. Isolation of bacteria from urinary tissues obtained during surgery indicates UTI regardless of the number. Colony counts used to establish a diagnosis of UTI for different methods of urine collection are summarized in Table 257-3.

Microscopic examination of gram-stained urine smears also may be helpful in the diagnosis of UTI. In one study, one drop of uncentrifuged urine was allowed to dry, gram-stained, and examined under oil immersion. The presence of more than 2 organisms per field correlated with bacterial counts of greater than 1000 cfu/mL, whereas no organisms were visible in specimens with less than 1000 cfu/mL.[53]

257.6 RADIOLOGY

Radiography provides precise information about renal size that frequently cannot be obtained from the physical examination. To correct for variation in patient size and radiographic magnification, renal size is evaluated in reference to surrounding anatomic landmarks, usually the second lumbar vertebra (L2) on the ventrodorsal view. The left kidney normally is well visualized in the dog, but the right kidney often cannot be seen as well, especially its cranial pole. In the dog, the left kidney (near vertebra L2 to L5) is located caudal to the right kidney (near vertebra T13 to L3). In the cat, the kidneys lie near vertebra L3, with the right kidney positioned slightly cranial to the left. Renal size in dogs and cats can be assessed radiographically and compared to the length of vertebra L2. On the ventrodorsal view, the kidney to L2 ratio is 2.5 to 3.5 in dogs and 2.4 to 3 in cats.

Excretory urography is performed by taking sequential abdominal radiographs after intravenous administration of an iodinated organic compound. The contrast medium is filtered and excreted by the kidneys, and the quality of the study partly depends on the patient's GFR. Radiographs should be taken at appropriate intervals (e.g., less than 1 minute, 5 minutes, 20 minutes, and 40 minutes) to obtain maximum information about the renal parenchyma and collecting system. Excretory urography is useful for the evaluation of a number of abnormalities, including renal size, shape, or location; filling defects in the renal pelvis or ureters; certain congenital defects (e.g., unilateral agenesis); renomegaly; acute pyelonephritis; and rupture of the upper urinary tract. Excretory urography should not be performed in dehydrated patients or in those with known hypersensitivity to contrast media. Although excretory urography normally is a safe procedure, a decrease in the GFR may persist for several days after intravenous administration of contrast agents to normal dogs, and ARF has been reported in a dog after excretory urography.[54] The general technique and interpretation of excretory urography in dogs and cats have been reviewed elsewhere.[55] Ultrasound-guided percutaneous antegrade pyelography has been used to localize ureteral obstruction in dogs and cats.[56]

Table • 257-3 Assessment of Quantitative Urine Culture Results in Dogs and Cats

METHOD OF COLLECTION	SPECIES	SEX	COLONY COUNT INDICATIVE OF URINARY TRACT INFECTION (UTI)
Cystocentesis*	Dog	Male	$>10^2$ cfu/mL
		Female	$>10^2$ cfu/mL
	Cat	Male	$>10^2$ cfu/mL
		Female	$>10^2$ cfu/mL
Catheterization	Dog	Male	$>10^3$ cfu/mL
		Female	$>10^5$ cfu/mL†
	Cat	Male	$>10^3$ cfu/mL
		Female	$>10^3$ cfu/mL
Midstream voided	Dog	Male	Unreliable‡
		Female	Unreliable‡
	Cat	Male	Unreliable‡
		Female	Unreliable‡

* Growth of small numbers of a single organism ($\leq 10^2$ cfu/mL) from urine samples collected by cystocentesis is suggestive of skin contamination during collection. Growth of large numbers ($>10^3$

cfu/mL) of multiple organism from urine samples collected by cystocentesis is suggestive of needle puncture of bowel and contamination by intestinal flora.

† This guideline may result in erroneous diagnosis of UTI because $>10^5$ cfu/mL may be obtained from urine samples collected by catherization in 20% of normal female dogs. Also, the procedure of urethral catheterization itself may cause UTI in 20% of normal female dogs. Collection of urine by cystocentesis is recommended for establishing a diagnosis of UTI in female dogs.

‡ Culture of midstream-voided urine samples from normal dogs and cats may result in growth of $\geq 10^5$ cfu/mL. In the absence of prior antimicrobial therapy, a negative result on a voided sample excludes a diagnosis of UTI.

257.6.1 Ultrasonography

Renal ultrasonography is a noninvasive imaging technique that does not depend on renal function, has no known adverse effects on the patient, and allows characterization of internal renal architecture. The major advantage of ultrasonography is the ability to discriminate among the renal capsule, cortex, and medulla, the pelvic diverticula, and the renal sinus.[57–60] Normally, the kidney is less echogenic than the liver or spleen. Collagen and fat provide highly reflective acoustic interfaces and account for the observation that the renal capsule, diverticula, and sinus are the most echogenic structures in the kidney. The renal medulla normally is less echogenic than the renal cortex because of its higher water content and fewer acoustic interfaces.[59] The hyperechogenicity of the renal cortex relative to the medulla varies among normal cats and has been attributed to variations in the amount of fat in the proximal tubular cells.[61]

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Renal length and volume, as determined by ultrasonography, are linearly related to body weight in dogs.[62,63] In cats, renal length as determined by ultrasonography ranges between 3 and 4.3 cm.[64] Measurements of renal size determined by excretory urography exceed those obtained by ultrasonography.[57,64] This difference is due to osmotic diuresis and radiographic magnification effects during excretory urography and to indistinct renal margins and inaccurate choice of scanning planes during ultrasonography.[62,64]

Renal ultrasonography is useful for differentiating solid from fluid-filled lesions and for determining the distribution of lesions in the kidney (i.e., focal, multifocal, diffuse).[65] A pattern of multiple, anechoic cavitations is highly suggestive of polycystic kidney disease.[66,67] Cysts are smooth, sharply demarcated, anechoic lesions that demonstrate through transmission.[58] The renal pelvis is dilated with anechoic fluid in hydronephrosis, and the kidney is surrounded by an accumulation of anechoic fluid in cats with perinephric pseudocysts.[68,69] Organized hematomas, abscesses, and necrotic nodules present a pattern of mixed echogenicity. Focal or diffuse lesions of mixed echogenicity that disrupt normal anatomy often are tumors.[65] Poorly vascular tumors of homogenous cell type (e.g., lymphosarcoma) may produce hypoechoic lesions that occasionally may be misinterpreted as cysts.[65,66] Diffuse parenchymal renal diseases characterized by cellular infiltration with preservation of normal renal architecture (e.g., chronic tubulointerstitial nephritis) may produce diffuse hyperechogenicity but occasionally have a normal ultrasonographic appearance. Consequently, normal renal ultrasonographic results do not eliminate the possibility of renal disease.

Ethylene glycol intoxication also causes renal hyperechogenicity. Within 4 hours of ethylene glycol ingestion, renal cortical echogenicity exceeds that of the liver and approaches that of the spleen.[70,71] Medullary echogenicity increases to a lesser extent. Increased cortical and medullary echogenicity, with relative

hypoechogenicity of the corticomedullary junction and inner medulla, results in a “halo” sign that correlates with the onset of anuria. Renal hyperechogenicity in ethylene glycol intoxication is attributed to deposition of calcium oxalate crystals in the kidneys.

An echogenic line in the outer zone of the medulla and paralleling the corticomedullary junction (so-called medullary rim sign) has been observed in ethylene glycol intoxication but also in acute tubular necrosis, hypercalcemic nephropathy, granulomatous nephritis caused by feline infectious peritonitis, and chronic tubulointerstitial nephritis.[72,73] This lesion also has been observed in normal cats[61] and has been associated with mineralization of tubular basement membranes. In a study of 32 dogs with medullary rim sign, most of the dogs in which this feature was the sole ultrasonographic finding had no evidence of renal dysfunction, whereas those with other ultrasonographic abnormalities (e.g., reduced renal size, increased medullary echogenicity, pyelectasia) had clinical evidence of renal dysfunction.[74]

Intrarenal resistance to blood flow may be assessed during duplex Doppler ultrasonography and evaluated by calculation of the resistive index. The normal value for the renal resistive index in healthy, unsedated dogs is approximately 0.6.[75] Somewhat lower values have been reported in normal, sedated dogs[76] and cats.[77] Other studies have suggested an upper limit of 0.7 for the resistive index in normal, unsedated cats.[78,79] Higher than normal values for the resistive index have been reported in some renal diseases of dogs and cats[80] but not in experimentally induced aminoglycoside nephrotoxicosis.[81]

Renal ultrasonography also has been used to monitor the status of renal allografts in dogs[82] and renal autografts in cats.[78] A rapid increase in renal volume in the immediate postoperative period may signify rejection, but some enlargement normally occurs as a consequence of edema and renal hypertrophy. The renal volume and cross-sectional area, as monitored by ultrasonography, increased by 103% and 83%, respectively, as a result of hypertrophy and rejection by 17 days after allograft transplantation in dogs.[82] Changes in renal width were greater than changes in height or length, which suggests that the cross-sectional area measurement may be a useful parameter to monitor. In cats, renal autografts increased 50% in the cross-sectional area by 13 days after transplantation as a result of postoperative edema and hypertrophy, but no changes were seen in the resistive index.[78]

257.7 RENAL BIOPSY

Renal biopsy allows the clinician to establish a histologic diagnosis and should be considered when the information obtained is likely to alter patient management. Examples of such situations include differentiation of protein-losing glomerular diseases, differentiation of ARF from CRF, determination of the status of the tubular basement membranes in ARF, and determination of the patient's response to therapy or the progression of previously documented renal disease. A renal biopsy should not be performed until a thorough clinical evaluation of the patient has been completed.

Before renal biopsy, an intravenous catheter should be placed, and the animal's clotting ability should be evaluated by measurement of the buccal mucosal bleeding time and estimation of platelet numbers. The patient's hematocrit and plasma proteins should be determined before biopsy but after adequate rehydration with parenteral fluids. The hematocrit and plasma proteins may be monitored after biopsy to detect hemorrhage.

Several techniques can be used for renal biopsy, including blind percutaneous, laparoscopic, keyhole, open, and ultrasound-guided approaches. The choice of technique depends largely on the experience and technical skill of

the operator, the species to be biopsied, and the sample size required. The blind percutaneous technique works well in cats, because their kidneys can be readily palpated and immobilized. Laparoscopy allows direct visualization of the kidney and detection of hemorrhage but requires special equipment and expertise. The keyhole approach occasionally is used in dogs but is useful only if the operator is experienced with the technique. In one study of renal biopsy techniques in dogs, modifications of the keyhole technique and the use of laparoscopy did not improve the quality of the biopsy specimen obtained or reduce the complication rate.[83]

If the operator is relatively inexperienced with renal biopsy or if a larger sample is required, wedge biopsy by means of laparotomy is recommended. Laparotomy offers the operator the advantages of being able to inspect the kidneys and other abdominal organs visually, to choose the specific biopsy site, to take an adequately sized sample, and to observe the kidney for hemorrhage. Some techniques require general anesthesia for adequate patient restraint and analgesia, but needle biopsy specimens of the kidney can be obtained from dogs and cats under ultrasound guidance using one of several sedation protocols. In one study, the GFR (estimated by ^{99m}Tc-DTPA) was similar in dogs sedated with butorphanol and diazepam, acepromazine and butorphanol, and diazepam and ketamine, and the GFR of sedated dogs was not significantly different from that of awake dogs.[84]

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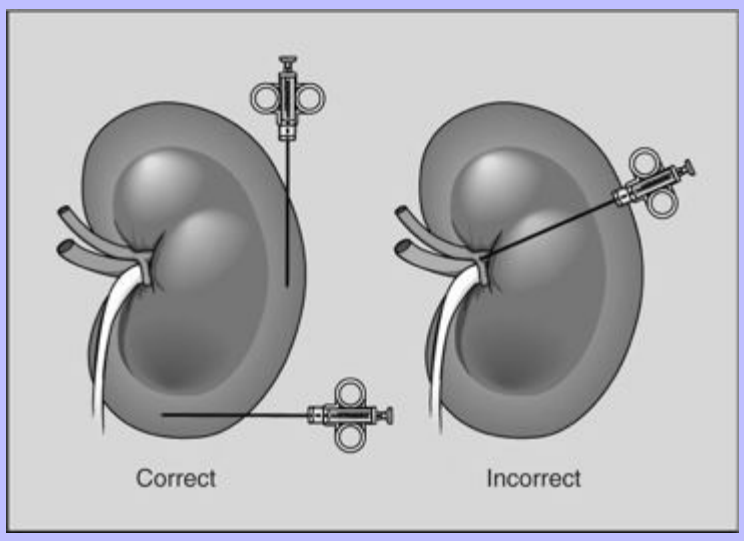
At our hospital, renal biopsy in dogs and cats currently is performed under ultrasound guidance using the Bard® Biopty biopsy instrument (Bard Biopty biopsy system; C.R. Bard, Covington, Georgia) and with the animal sedated with a combination of medetomidine, butorphanol, and atropine. This combination of drugs recently was evaluated for renal biopsy in dogs (using ^{99m}Tc-DTPA renal scintigraphy as an estimate of the GFR) and was found to have effects on the GFR similar to those observed with saline alone.[85] In another study, needle biopsy of the kidney in normal cats sedated with ketamine and acepromazine had minimal effect on the GFR as evaluated by ^{99m}Tc-DTPA renal scintigraphy.[25] Occasionally, the tissue architecture is less important (e.g., in renal lymphosarcoma and feline infectious peritonitis), and aspiration of the kidney using a 23-or 25-gauge needle may provide useful material for cytology.

The most commonly used biopsy instruments are the Franklin-modified Vim Silverman needle and the Tru-Cut biopsy needle. Excessive penetration of the kidney with the outer cannula of the Franklin-modified Vim Silverman instrument should be avoided to prevent retrieval of an insufficient amount of renal cortex. Care should be taken in directing the angle of the biopsy instrument to avoid the renal hilus and major vessels. Samples containing large amounts of medulla are more likely to contain large vessels and to lead to infarction of renal tissue. It therefore is recommended that the biopsy needle be directed along the long axis of the kidney, solely through cortical tissue (Figure 257-20). In cats, because of the small size of feline kidneys, it is common to obtain relatively large amounts of medullary tissue, and this has been associated with infarction and fibrosis.

After biopsy using the open approach or keyhole technique, the kidney should be digitally compressed for 5 minutes, and after release the abdomen inspected for hemorrhage. The sample may be dislodged from the biopsy instrument with a stream of sterile saline from a syringe or, alternatively, the biopsy instrument may be immersed directly in fixative. For routine histopathology, the sample should be fixed in buffered 10% formalin for at least 3 to 4 hours. For immunofluorescence studies, the sample can be preserved in Michel's transport medium. Immunopathology studies also may be performed by a peroxidase-antiperoxidase method using formalin-fixed samples, without the need for special preservation of the sample.

After renal biopsy, a brisk fluid diuresis should be initiated to prevent clot formation in the renal pelvis. The patient's hematocrit and plasma proteins should be monitored at appropriate intervals over the next 12 to 24 hours to detect serious hemorrhage.

Figure 257-20 Demonstration of renal biopsy technique showing correct and incorrect placement of the biopsy instrument in the kidney. (Drawing courtesy Dr. Shelly Vaden, North Carolina State University, Raleigh.)



The most common complication of renal biopsy is hemorrhage. Subcapsular hemorrhage commonly occurs at the site of biopsy, and many patients experience microscopic hematuria during the first 48 hours after biopsy. Macroscopic hematuria is less common. Severe hemorrhage into the peritoneal cavity is rare and usually is associated with improper technique. Such hemorrhage must be treated aggressively by compression bandage of the abdomen, fresh whole blood transfusion, and exploratory surgery if necessary.

Linear infarcts in the path of the biopsy needle are commonly observed after renal biopsy in both dogs and cats. These are small and superficial when the biopsy is limited to the renal cortex. However, if an arcuate artery is damaged by passage of the biopsy needle through the corticomedullary junction, a wedge-shaped infarct may occur. This complication is more common in cats because of the small size of the kidneys in relation to the length of the biopsy needle.

Hydronephrosis occasionally complicates renal biopsy. If the renal pelvis is penetrated by the biopsy needle, bleeding may occur, and clot formation can lead to obstruction of the kidney and hydronephrosis. This complication should be considered if the biopsy report indicates the presence of transitional epithelium at one end of the biopsy or if progressive renal enlargement is detected after renal biopsy. The risk of this complication can be minimized by limiting the biopsy site to the renal cortex and instituting a fluid diuresis afterward.

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258 CHAPTER • 258 Acute Uremia

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Thierry Francey

Acute uremia is a clinical condition in which the kidneys suddenly and often catastrophically fail to meet the excretory, metabolic, and endocrine demands of the body. This abnormality is induced by rapid hemodynamic, filtration, tubulointerstitial, or excretory injury to the kidneys or outflow system (or both), which results in accumulation of solutes (uremia toxins), metabolic dysfunction, and dysregulation of fluid, electrolyte, and acid-base balance. Acute uremia is, conceptually, a quickly developing disease to intrinsically normal kidneys. However, some animals have prerenal, renal parenchymal, or postrenal events superimposed on a pre-existing chronic renal injury that causes a similar clinical condition.

The term *acute renal failure* (ARF) does not standardize the classification of acute uremia relative to its severity, clinical course, response to therapy, or prognosis for recovery.[1,2] To date no specific biologic markers provide these distinctions. Numerous definitions of acute uremia exist that are based on changes in glomerular filtration rate (GFR), degree of azotemia, or urine production in humans. These criteria, however, are rarely applied to animals because the abruptness of their disease and changes in azotemia or volume of urine production are usually not known. Acute uremia in animals is generally a disease recognized later than in humans and with varying abruptness and azotemia. The diagnosis of ARF is established with high specificity but low sensitivity. Affected animals have a spectrum of functional and clinical deficiencies that should be considered in its classification, management, and outcome.

Acute uremia is associated with a rapid (hours to days) and progressive increase in serum concentrations of urea, creatinine, and phosphate. There may also be variable degrees of hyperkalemia, metabolic acidosis, or both. Progression of azotemia may not be recognized in animals being evaluated for the first time that are already in a late stage of disease or in those without previously obtained serial blood chemistry determinations. After azotemia is demonstrated, the acute condition must be differentiated from functional disturbances (prerenal azotemia) or chronic renal failure (CRF). Oliguria and anuria are characteristic of severe forms of acute uremia, but this feature is unpredictable. Nonoliguric forms of acute uremia are common and must be differentiated from polyuria associated with CRF. In contrast to CRF, acute uremia is potentially reversible if the animal survives until the underlying conditions resolve and natural recovery (repair) of the renal injury takes place. Throughout its progression, therapeutic opportunities exist to alter the outcome of the disease. If the diagnosis is missed or if the injury is too severe, the kidney will be incapable of morphologic repair. Thus delays in initiating therapy or failure to provide appropriate supportive therapy may result in irreversible renal damage and death.

The incidence of acute uremia is lower than that of CRF in both dogs and cats. The clinical signs associated with acute and CRF may be similar, and clinicians must distinguish between these conditions to administer appropriate therapy and render an accurate prognosis. Acute uremia frequently complicates other surgical or medical diseases and must be recognized as a serious complication of any condition.

258.1 CAUSE OF ACUTE UREMIA

Acute uremia can be categorized as prerenal azotemia, intrinsic ARF, postrenal azotemia, or some combination of these conditions.

258.1.1 Prerenal Azotemia

Prerenal azotemia is a hemodynamically mediated decline in GFR resulting from decreased renal blood flow, perfusion pressure, or increased renal vascular resistance. It represents a functional alteration in GFR that is completely reversible without morphologic consequences to renal parenchyma. Prerenal azotemia develops as a coordinated neural and humoral response to hemodynamic deficiencies in an attempt to preserve perfusion to vital organs. Filtration failure ensues when the renal perfusion pressure falls below the threshold for renal autoregulation (usually a mean arterial pressure [MAP] < 80 mm Hg).[3,4] As renal compensatory mechanisms are activated in response to hemodynamic failure (cardiogenic, septic, hypovolemic shock) or to decreased functional renal mass, even small additional impairments in renal perfusion or glomerular hemodynamics (nonsteroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers) can precipitate severe filtration failure.[5,6] Activation of the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system, and the release of antidiuretic hormone (ADH) in response to these hemodynamic events promote via salt and water conservation, urine concentration, and oliguria in an attempt to restore blood volume.

Mild azotemia (serum creatinine concentrations < 4 mg/dL, and blood urea nitrogen [BUN] concentrations < 80 mg/dL), increased urine specific gravity [USG], and decreased urine sodium excretion (urine sodium concentration < 20 mEq/L; fractional excretion of sodium < 1%) are hallmarks of prerenal azotemia. These parameters may be masked by the use of diuretics or by underlying conditions (CRF, adrenal insufficiency, hepatic failure, diabetes insipidus) that impair renal concentrating ability. Tubular reabsorption of urea can be increased disproportionately to creatinine at these low urine flow rates, causing variable increases in BUN/creatinine ratio.[7,8] A prerenal component is often superimposed on intrinsic renal failure, causing severe uremia. Prolonged renal hypoperfusion can result in structural alterations secondary to ischemic cellular injury that may induce intrinsic ARF. Vasculitis, pancreatitis, hypoproteinemia, heat stroke, liver failure, and gastric torsion are examples of disease states inducing hemodynamic disturbances with the propensity to cause progressive prerenal azotemia leading to intrinsic ARF.[9]

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258.1.2 Intrinsic Acute Renal Failure

Intrinsic ARF is the result of parenchymal damage to the kidney and can be categorized according to the initial site of injury as *primary vascular*, *glomerular, tubular*, or *interstitial*. This anatomic classification is arbitrary due to multiple interactions between these structures but may be helpful in understanding the pathophysiology of lesions observed in individual dogs and cats (Box 258-1). For clinical purposes, ARF may be categorized based on cause. With this classification, ARF can develop as a continuation of prerenal events, local ischemia (ischemic nephrosis), or as a consequence of exogenous or endogenous nephrotoxins (toxic nephrosis). Using a causative classification, primary renal diseases (pyelonephritis, toxic nephrosis) and systemic diseases with renal manifestations (pancreatitis, ischemic nephrosis) can induce ARF with mixed anatomic involvement.

Ischemia due to prolonged hypotension, hypovolemia, circulatory collapse, or excessive renal vasoconstriction predisposes a dog or cat to filtration failure and acute uremia as an extension of prerenal azotemia. Renal ischemia may also develop after renal arterial thrombosis, disseminated intravascular coagulation (DIC), or septic thrombi.

258.1.2.1 Box • 258-1 Causes of Intrinsic Acute Renal Failure

258.1.2.1.1 Renal Ischemia

Progression of prerenal azotemia

Renal vascular disease (avulsion, thrombosis, stenosis)

258.1.2.1.2 Nephrotoxicity

Exogenous toxins

Endogenous toxins

Drugs

258.1.2.1.3 Primary Renal Diseases

Infections: pyelonephritis, leptospirosis, infectious canine hepatitis

Immune-mediated disease: acute glomerulonephritis, systemic lupus erythematosus (SLE), renal transplant rejection

Neoplasia: lymphoma

Miscellaneous: "Alabama rot"[26]

258.1.2.1.4 Systemic Diseases with Renal Manifestation

Infections: Feline infectious peritonitis (FIP), borreliosis, babesiosis, leishmaniasis, bacterial endocarditis

Pancreatitis

Systemic inflammatory response syndrome, sepsis, multiple organ failure, disseminated intravascular coagulopathy (DIC)

Heart failure

SLE

Hepatorenal syndrome

Malignant hypertension

Hyperviscosity syndrome: polycythemia, multiple myeloma

Nephrotoxins are the primary cause of ARF in dogs. They can be of exogenous or endogenous origin and of diverse chemical classes including organic compounds and solvents, antimicrobials, vasoactive drugs, and miscellaneous therapeutics (Box 258-2).[10–12]

NSAIDs inhibit cyclooxygenase (COX)-dependent synthesis of vasodilatory prostaglandins that regulate renal blood flow when renal perfusion is compromised. Nonselective COX-1/COX-2 inhibitors (flunixin meglumine, ibuprofen, aspirin),[13] promote loss of counter-regulatory vasodilation to an ischemic insult, which intensifies vascular resistance and furthers hypoperfusion of the kidney.[14] Although species differences exist, newer NSAIDs with selective COX-2 inhibition (meloxicam, carprofen, deracoxib) also have the potential to be nephrotoxic.

The principal toxicity associated with NSAIDs use in animals is a nonoliguric ischemic nephrosis. Idiosyncratic tubulointerstitial nephritis, nephrotic syndrome, renal papillary necrosis, and hyporeninemic-hypoaldosteronism have also been described in humans.[15] The nephrotoxicity of NSAIDs is exacerbated in animals with congestive heart failure (CHF), nephrotic syndrome, renal insufficiency, hypertension, cirrhosis, and those undergoing anesthesia in which renal perfusion is compromised and renal vascular tone is increased.[14] Because of the ischemic nature of this nephrotoxicity, the lesions are generally reversible.

ACE inhibitors may induce ARF through alterations in glomerular hemodynamics, renal hypoperfusion, and tubular ischemia. Sodium depletion, diuretic abuse, and CHF may increase the nephrotoxic potential of these drugs. The risks of toxicity are magnified in animals with pre-existing CRF because basal GFR is dependent on increased postglomerular resistance mediated by angiotensin II.[6,16,17] ACE inhibitors with mixed renal and hepatic elimination may prove less toxic in animals with CRF when compared with ACE inhibitors that are excreted only through the kidneys.[18]

Clinicians may prevent ARF induced by NSAIDs or ACE inhibitors with judicious monitoring of serum creatinine concentrations before mitigating treatment, together with early (3 to 5 days) and frequent (biweekly) monitoring of serum creatinine concentrations after the start of therapy. If increased concentrations of serum creatinine are documented, treatment should be stopped or doses reduced. Special precautions should be taken when administering diuretics, ACE inhibitors, NSAIDs, or a combination of these medications concurrently due to their additive hemodynamic effects.

Ethylene glycol toxicosis is one of the most common causes of ARF and one of the most common toxicoses recognized in companion animals.[19] Automobile antifreeze is the usual source of exposure, and the toxicity develops by the direct actions of its metabolites on the tubular epithelium and deposition of calcium oxalate crystals in the tubular lumens and interstitium.

Plant-related intoxications represent a new category of acute uremia in dogs and cats with severe nephrosis. Exposure and ingestion of lilies has been reported to cause severe acute ARF in cats.[20,21] Similarly, ingestion of grapes or raisins has been recently associated with ARF in dogs.[22,23]

Aminoglycosides (gentamicin, amikacin, tobramycin, netilmicin, and neomycin) are potent nephrotoxins causing direct tubular injury or tubular dysfunction associated with wasting of filtered solutes.[24] Further, nearly all antimicrobials (including penicillins, cephalosporins, carbapenems, fluoroquinolones, macrolides,

tetracyclines, and sulfonamides) can cause tubular injury, tubular dysfunction, or intratubular obstruction.[15,24,25]

Amphotericin B is a polyene antifungal that complexes with sterol moieties of cell membranes forming pores that disrupt cellular integrity and increase membrane permeability.[26] Nephrotoxicity is the dose-limiting factor associated with use of this drug, and renal function should be closely monitored throughout its administration. The advent of lipid formulations, and particularly of liposome encapsulated amphotericin B, has markedly decreased the nephrotoxicity associated with amphotericin use and has allowed more aggressive application of this drug.[27–30]

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258.1.2.2 Box • 258-2 List of Substances with Nephrotoxic Potential

258.1.2.2.1 Therapeutic Agents

Antibacterial drugs

- Aminoglycosides
- Penicillins
- Nafcillin
- Cephalosporins
- Sulfonamides
- Fluoroquinolones
- Carbapenems
- Rifampin
- Tetracyclines
- Vancomycin
- Aztreonam

Antifungal drugs

Amphotericin B

Antiviral drugs

Acyclovir

Foscarnet

Antiprotozoal drugs

Pentamidine

Sulfadiazine

Trimethoprim-sulfamethoxazole

Dapsone

Thiacetarsemide

Cancer chemotherapeutics

Cisplatin, carboplatin

Methotrexate

Doxorubicin

Adriamycin

Azathioprine

Immunosuppressive drugs

Cyclosporine

FK506

- Interleukin (IL)-2
- NSAIDS
- Ace inhibitors
- Diuretics
  - Mannitol
- Miscellaneous therapeutic agents
  - Dextran 40
  - Allopurinol
  - Cimetidine
  - Apomorphine
  - Deferoxamine
  - Streptokinase
    - Aminocaproic acid
    - Lipid-lowering agents
    - Methoxyflurane
    - Penicillamine
    - Acetaminophen
    - Tricyclic antidepressants
  - Radiocontrast agents

258.1.2.2.2 Nontherapeutic Agents

Heavy metals

- Mercury
- Uranium
- Lead
- Bismuth salts
- Chromium
- Arsenic
- Gold
- Cadmium
- Thallium
- Copper
- Silver
- Nickel
- Antimony

Organic compounds

- Ethylene glycol
- Carbon tetrachloride
- Chloroform

Pesticides

Herbicides

Solvents

Miscellaneous agents

Gallium nitrate

Diphosphonates

Mushrooms

Grapes/raisins

Calcium antagonists

Snake venom

Bee venom

Lily

Illicit drugs

258.1.2.2.3 Endogenous Toxins

Pigment nephrosis

Hemoglobin

Myoglobin

Cisplatin is an alkylating antineoplastic agent concentrated within and excreted primarily by the kidney. Its administration leads to a dose-dependent, progressive, and irreversible nonoliguric ARF. Carboplatin, an analogue of cisplatin, is less nephrotoxic and has largely replaced cisplatin in clinical practice.[15]

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Primary renal diseases include infectious, immune-mediated, neoplastic, or degenerative conditions with primary expression in the kidney. When peracute or extensive, primary renal diseases produce an acute uremia that must be differentia-ted from traditional ischemic or nephrotoxic causes. Acute pyelonephritis develops from ureteral reflux of bacteria in the urine of animals with lower urinary tract (LUT) infection. It is an important cause of acute uremia in both dogs and cats.[11,31] The azotemia may be moderate or severe and associated with variable urine output. Suppurative nephritis is an infection arising from hematogenous dissemination of bacteria or septic embolization of the kidneys in animals with bacteremia or septicemia. Predisposing conditions include bacterial endocarditis, discospondylitis, and pyometra.

Leptospirosis is a specific infectious zoonosis of dogs with predominantly hepatorenal manifestation.[32–38] It was a well-characterized syndrome of acute hemorrhagic diathesis, subacute icterus, or subacute uremia caused by *Leptospira interrogans* serogroups *canicola* and *icterohaemorrhagiae*. Widespread use of a bivalent vaccine against these serogroups led to near extinction of leptospirosis in the canine population, until recently.[32,33,35,38] Retrospective studies in the United States and Canada have documented a regional re-emergence of the disease since the 1990s and a change in its epidemiology with *L. pomona, L. bratislava, L. grippotyphosa,* and *L. autumnalis* as the most commonly identified serogroups. The associated clinical syndrome has also changed, with ARF rather than hepatorenal or coagulation manifestations.[32,33,36,39] Possible explanations for the recently recognized re-emergence and clustering of leptospirosis could include urbanization of the canine population and encroachment of dogs into environments harboring reservoirs of the host species.[32,34,37] New, multivalent vaccines have emerged in response to these epidemiologic trends, but it remains to be seen whether vaccination will change the prevalence or biology of this disease. Because of its growing prevalence as a cause of acute uremia in dogs, leptospirosis should be included routinely in the differential diagnosis of all dogs with ARF, regardless of vaccination status.

A rapidly progressive form of ARF with severe azotemia, proteinuria, peripheral edema, and body cavity effusion has been associated with positive serology for *Borrelia burgdorferi*. This form of the disease is recognized routinely in dogs from endemic areas and, despite aggressive therapy, is invariably fatal.[40]

Systemic diseases including pancreatitis, sepsis, and hemolytic anemia (see Box 258-1) promote intrinsic ARF through secondary mechanisms associated with renal hemodynamics, systemic inflammatory responses, or drug toxicities associated with the underlying disease or diseases (see Pathophysiology, following). The ensuing ARF can exacerbate the course of the primary disease or dominate the clinical presentation of affected animals.

258.1.3 Postrenal Azotemia

Postrenal azotemia occurs with obstruction or diversion of urine and consequent retention of excretory products within the body. The most common causes of postrenal azotemia include partial or complete obstruction of the urethra or bladder by uroliths, mucous plugs, blood clots, or intra-or extraluminal mass lesions. Bilateral ureteral dilation should raise suspicion of a common outflow obstruction at the ureterovesical junction caused by a transitional cell carcinoma in the bladder neck or inadvertent ligation of the ureters during ovariohysterectomy. Bilateral ureteral obstruction or unilateral obstruction in a dog or cat with only one functioning kidney can be caused by calcium oxalate uroliths, solidified blood clots, mucous plugs, inflammatory debris, or stricture. These problems are being recognized with increased frequency as a leading cause acute uremia in cats.[41,42] Rupture of the urinary outflow tract diverts urine into the retroperitoneal space (ureteral), peritoneal cavity (ureteral, bladder, or proximal urethra), or pelvic canal (urethra), with consequent

development of oligoanuria and uremia. Correction of the outflow obstruction or rupture may represent a surgical challenge, but if successful it will resolve azotemia without the presence of permanent structural damage to the kidneys.

Protracted outflow obstruction for more than 7 days can result in renal parenchymal damage and intrinsic ARF. At this stage, recovery of renal function is unpredictable and influenced by the severity and duration of the obstruction, completeness of the surgical correction, postobstructive medical complications, and pre-existing renal disease. Intuitively, a successful outcome will be less likely and the animal will be subjected to greater structural damage or death from uremia if correction of the outflow impairment is delayed or incomplete.

258.2 PATHOPHYSIOLOGY OF ACUTE UREMIA

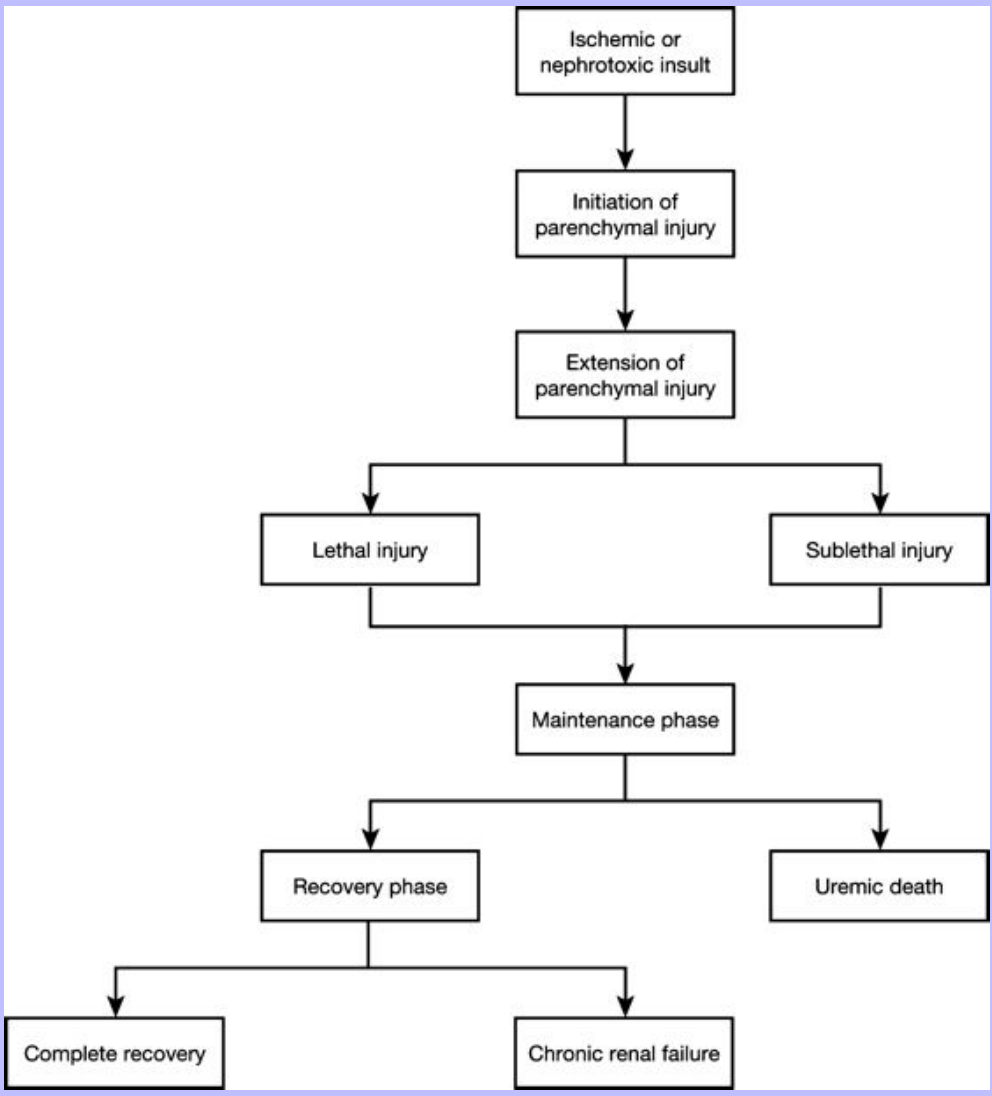
Ischemic and toxic insults to the kidney cause a state of acute tubular injury (ATI). At the cellular level, ATI can vary from sublethal cell damage to cellular necrosis or apoptosis. The term *ATI* is often equated with the older term, *acute tubular necrosis,* used to denote ARF; however, the two terms should be distinguished in the pathophysiologic description of the syndrome. The histopathologic changes in some kidneys are more subtle than necrosis, and the tubular injury may be sublethal, making ATI a more appropriate descriptor and providing better correlation between observed structural alterations and clinical correlates of renal dysfunction.[43] With ischemic and nephrotoxic ARF, the tubular injury is characterized by degenerative and less commonly necrotic foci of tubular epithelium distributed heterogeneously throughout the kidneys with minimal evidence of interstitial inflammatory infiltrates. The straight portion of the proximal tubule (S3 segment) shows the most severe degenerative changes after an insult and maximal mitotic activity during recovery. The convoluted proximal tubule (S1 and S2 segments), the segments in the inner medulla, the medullary thick ascending limb, and the collecting tubules are least severely affected or completely spared by ischemic or toxic damage.[43,44]

258.2.1 Phases of Intrinsic Acute Renal Failure

ARF classically proceeds through three clinical phases: (1) initiation, (2) maintenance, and (3) recovery.[45] The late stage of the initiation phase is now recognized as pathophysiologically distinct and this classical progression has been modified recently to include the *extension phase* as indicated in Figure 258-1.[2,46] The initiation phase is the period during which the animal is subjected to the renal insult. At this phase, parenchymal injury evolves, and the tubular epithelium undergoes sublethal but potentially reversible injury.[2,47] Early intervention during the initiation phase will often prevent progression to more severe injury.

During the extension phase the kidney is subjected to alterations in renal perfusion, continued hypoxia, secondary inflammation, and ongoing epithelial and endothelial injury. As a result of these sustained or cumulative insults, the cellular injury progresses to cell death by necrosis or apoptosis. The functional consequences are a progressive decline in glomerular filtration, loss of urine-concentrating ability, and development of oligoanuria (or nonoliguria) and azotemia. At this critical phase in the pathogenesis, clinical manifestations may not be apparent, but the injury may be unresponsive to therapeutic intervention. The combined initiation and extension phases may last from hours to days but remain unrecognized because the changes in GFR and USG are not clinically apparent.

Figure 258-1 Clinical phases of acute renal failure (ARF). In the initiation and extension phases, renal damage and sublethal cellular injury evolve, but renal failure is not evident. In the maintenance phase, the inciting events have ceased, cellular damage is established, and signs of uremia become apparent. The recovery phase involves tubular regeneration and repair and the partial or complete return of renal function.



The maintenance phase ensues after a critical amount of irreversible epithelial damage has occurred. GFR is decreased, the regulation of regional blood flow is altered, urine volume may decrease, and the complications

of uremia develop. Elimination of inciting factors at this phase will not alter existing damage or rate of recovery.[17,48] The maintenance phase lasts from days to weeks and when prolonged portends a slower rate of recovery and a likelihood of permanent renal impairment.

The recovery phase is the period where renal tissue undergoes regeneration and repair with restoration of renal function. Recovery may be associated with an increase in urine output and progressive resolution of the azotemia; however, molecular evidence of regeneration may be detected before these signs are apparent.[48] An increase in urine production at this phase may not correspond to meaningful improvement in GFR, so changes in the azotemia may lag behind evidence of tubular repair. Diuresis is a physiologic response to accumulated water, salt, and osmotically active solutes, immature tubular function, or diuretic therapy. Functional repair follows cellular recovery of the sublethally injured epithelium, removal of intratubular debris, and re-epithelialization of the tubule.[49] The renal injury induces growth factor production and alters gene expression to enable remnants of surviving epithelium to dedifferentiate, re-enter the cell cycle, replicate, repopulate the denuded tubule, and redifferentiate into a functionally mature tubular epithelium. These events are orchestrated by mitogens (stimulate cell proliferation), motogens (stimulate cell mobility), and morphogens (induce changes in multicellular architecture) including insulin-like growth factor-1 (IGF-1), epidermal growth factor (EGF), transforming growth factor (TGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), nerve growth factor (NGF), hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF).[50] These same repair factors may also contribute to fibrosis and other deleterious aspects of the pathogenesis and progression of renal damage. The recovery phase may last from weeks to months. With renal repair, some animals recover adequate or even normal renal function after weeks or even months of anuria that follows a severe renal injury like ethylene glycol intoxication.

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258.2.2 Outflow Obstruction

Acute urinary outflow obstruction transmits increased hydrostatic pressure to the renal pelvis, the tubular system, and Bowman space. Within glomerular capillaries, the ultrafiltration pressure is dissipated, causing a progressive decline in GFR. The heightened pressure in Bowman capsule and tubular lumen is counterbalanced by ongoing sodium and water reabsorption along the nephron, but this compensation is inadequate to prevent filtration failure. Renal blood flow is progressively altered with initial increases and subsequent decreases due to local vasodilation and increased interstitial hydrostatic pressure, respectively.

258.2.3 Pathogenesis of Acute Renal Failure

Four functional and pathologic alterations have been shown to participate to variable degrees in the initiation, extension, and maintenance phases of ARF on the basis of animal models of ischemic and nephrotoxic ARF: (1) reduction of the glomerular capillary ultrafiltration coefficient (K_f) and permeability, (2) intratubular obstruction, (3) back leak of filtrate across disrupted tubular epithelium, and (4) intrarenal vasoconstriction and renal medullary hypoxia.[45,49,51]

Decreased ultrafiltration coefficient (K_f) reduces GFR by either a decrease in hydraulic conductivity or effective surface area of glomerular capillaries. Transmission and scanning electron microscopy in animal models of ARF demonstrated both loss and fusion of normal foot processes and marked disruption of podocyte architecture.[52] Vasoconstriction initiated by angiotensin II and other vasoactive agents or contraction of the mesangium by ischemia, toxins, thromboxane A_2, endothelin, and platelet activating factor alter K_f by

reducing effective glomerular surface area. It is likely that conductivity and surface area are affected by both ischemic and toxic insults.[52–54]

Intratubular obstruction occurs when tubular casts produced by desquamated epithelial cells or cellular debris combine with intratubular proteins.[55,56] Tubular obstruction can also occur by precipitation of filtered heme pigments, crystal deposition (calcium oxalate, sulfonamides), or by extratubular compression (interstitial edema, inflammation). The impediment to tubular fluid flow increases intratubular hydrostatic pressure, decreases net ultrafiltration pressure, and halts single nephron glomerular filtration.

Back leak of tubular fluid across the disrupted epithelium further decreases urine formation and consequently the apparent ultrafiltration rate.[57,58]

Intrarenal vasoconstriction is a common participant in the pathogenesis of either hemodynamic or nephrotoxic injury. The resulting decrease in renal blood flow is transient and may occur in either the initiation or the extension phases. At the same time renal blood flow will be redirected preferentially to the cortex to maximize GFR and solute reabsorption at the expense of perfusion to the outer medulla. The redistribution creates profound hypoxia at the site of this oxygen-demanding segment.[3,51,59,60] Vasoconstriction is induced by altered regulation of competing dilatory and constrictive vasoactive processes that regulate and balance vascular resistance. Up-regulation of the renin-angiotensin system, impairment of renal autoregulatory capacity, enhanced adrenergic activity, and systemic or local release of vasoactive agents (thromboxane A2, leukotrienes C4 and D4, endothelin-1, adenosine, and endothelium-derived prostaglandin E_2) promote enhanced vasoconstrictive forces. The vasoconstriction frenzy is further exacerbated by vascular endothelial dysfunction to cause decreased production and release of vasodilator substances, including nitric oxide and prostaglandins.

258.2.4 Cellular Biology of Intrinsic Acute Renal Failure

Discovery of the cellular responses to ischemic and nephrotoxic injuries have improved our understanding of the clinical course of ARF. An extensive discussion of these mechanisms is beyond the scope of this review but are summarized in Figure 258-2 and reviewed in-depth elsewhere.[17,43,61]

Hypoxia secondary to poor perfusion of the outer medulla causes depletion of energy-dependent mechanisms within cells. Energy depletion alters cytosolic ionic concentrations (Na+, Ca++), loss of cellular polarity and vectorial cellular transport, disruption of tight junctions and the brush border membrane, and detachment of tubular cells from the basement membrane. In addition to these degenerative events, release of inflammatory cytokines (IL-l, TNF-), chemokines, heat shock proteins, nitric oxide, and reactive oxygen species induce a proinflammatory state that further compromises cellular oxygenation. Recognition of these hypoxic and inflammatory interactions provides opportunity for new therapeutic strategies to alter the course of ARF.

The kidney is exposed to high concentrations of endogenous and exogenous toxins, including drugs and their metabolites. This is intensified by regional hemodynamic, reabsorptive, and concentrating processes. In contrast to NSAIDs and ACE inhibitors, which induce ischemic lesions through alterations in blood flow in the glomerulus and the interstitium, other nephrotoxins, like aminoglycosides and ethylene glycol, cause direct epithelial injury and cellular damage (see discussion of cause ARF)[15,19]

258.3 CLINICAL CONSEQUENCES OF ACUTE UREMIA

The clinical consequences of acute uremia are the collective result of the excretory (water, potassium, phosphorus, nitrogenous waste products, medications), regulatory (fluid volume, electrolytes, acid-base, divalent cations, blood pressure), and endocrine (calcitriol and parathyroid hormone [PTH], erythropoietin) failure of the kidney. The clinical manifestations of acute uremia are the result of the multisystemic basis of the syndrome. Recent observations in dogs indicate that usually four or more organ systems are affected at presentation and in early stages of management. Ranking of organ system involvement (in percent of uremic dogs) revealed the following: gastrointestinal (GI) (93%), cardiovascular (80%), respiratory (52%), hematologic (40%), and neurologic (36%).[62] The multisystemic features of uremia per se become interspersed with the discrete symptomatology induced by the underlying cause, concurrent diseases, and therapy. An awareness and understanding of these collective manifestations of uremia is necessary to properly direct the therapeutic approach.

258.3.1 Disorders of Fluid Balance

At initial examination most animals are hypovolemic and dehydrated due to GI fluid losses, hemorrhage, and inadequate fluid intake. Dehydration at this stage of disease fosters renal hypoperfusion and leads to a prerenal azotemia. Extended hypovolemia promotes further impairment of renal perfusion, worsens the azotemia, and predisposes the kidneys to additional ischemia injury. Overaggressive fluid therapy predictably leads to hypervolemia and overhydration, causing peripheral and pulmonary edema, pleural effusion, systemic hypertension, and CHF. In dogs referred for severe ARF, nearly 70% were overhydrated when they arrived at the authors' hospital, some in excess of 25% of their body weight.

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Serial measurements of body weight and critical assessment of hydration at presentation and at regular intervals during therapy are essential to avoid this iatrogenic complication.

258.3.2 Inadequate Urine Production

Oliguria or anuria is both a hallmark and a critical feature of acute uremia. Whereas anuria constitutes essentially no urine production, no consensus exists on the exact definition of oliguria. Urine production less than 0.27 mL/kg/hr,[63] less than 0.48 mL/kg/hr[64,65] and less than 1 to 2 mL/kg/hr[66] have all been described. The authors interpret urine production less than 1 mL/kg/hr in a rehydrated, euvolemic, or hypervolemic dog or cat on intravenous fluids or receiving diuretics as pathologically oliguric. The concept of pathologic oliguria seems justified by the fact that animals with normal renal function would be expected to produce more than the lower limit of normal urine output under similar clinical conditions. Pathologic oliguria should be differentiated from physiologically appropriate oliguric states associated with prerenal disorders that are responsive to fluid administration.

Approximately one third of dogs with severe ARF are anuric, one third are oliguric, and one third are nonoliguric.[62] Severe renal injuries associated with nephrotoxins have a higher incidence of anuria. Solute retention, overhydration, hyperkalemia, and metabolic acidosis are exacerbated in oligoanuric animals compared with those with nonoliguric disease. Persistent oligoanuria prevents administration of essential therapies associated with large fluid volumes (enteral and parenteral medications, blood products, and nutrition). The conversion from an oliguric to a nonoliguric state may facilitate delivery of these therapies without concurrent improvement in GFR.

258.3.3 Electrolyte and Acid-Base Disturbances

Impaired excretory function of the diseased kidney leads to an array of electrolyte and acid-base disturbances. The most prominent disturbance is hyperkalemia, which can be further aggravated by inappropriate potassium administration in enteral or parenteral fluids and by metabolic acidosis. Hyperkalemia decreases the transmembrane potassium gradient, depolarizes cell membranes, and impairs excitation and conduction. When expressed at the sinus node and on myocardial cells, these perturbations cause classic electrocardiographic abnormalities associated with the severity of hyperkalemia. The cardiac effects lead progressively to bradycardia, atrial standstill, and cardiac arrest as the hyperkalemia worsens. These same electrophysiologic disturbances affecting skeletal muscle, smooth muscle, and peripheral nerves can cause profound weakness, flaccid paralysis, respiratory failure, GI hypomotility, and hyporeflexia. Hyperkalemia is a leading cause of death, failure of conventional therapies, and a specific indication for dialysis.

Abnormalities in serum sodium are frequently iatrogenic and induced by inappropriate fluid therapy and excessive use of sodium bicarbonate. Hyponatremia is an indication of excessive free water administration associated with hyponatric solutions (5% dextrose, TPN, or enteral formulations). Transient dilutional hyponatremia is seen after the administration of mannitol, hypertonic dextrose, or synthetic colloid solutions as free water shifts from the intracellular to the extracellular space. It may also be recognized with excessive losses of sodium associated with vomiting, pancreatitis, adrenal insufficiency, or diuretic administration.

Hypernatremia may be documented at initial examination and indicates excessive free water loss. In hospitalized animals, it is a common complication of isonatric crystalloid administration for maintenance fluid requirements. Hypernatremia is a complication of excessive administration of hypertonic saline or sodium bicarbonate.

Metabolic acidosis is a predictable feature of acute uremia due to the impaired acid excretion, decreased bicarbonate reabsorption, and decreased ammonia generation. Metabolic acidosis is worsened by additional acid loads generated by the underlying disorder (ethylene glycol, salicylate intoxication), decreased perfusion (lactic acidosis), hypercatabolism, and concurrent diseases (diabetic ketoacidosis). These abnormalities are attended by an increased anion gap, decreased serum bicarbonate, acidemia, and hyperkalemia. Severe metabolic acidosis produces tachypnea, Kussmaul's respiration, decreased cardiac contractility, cardiac arrhythmias, hypotension, and pulmonary congestion.[67] Neurologic sequelae include depression, lethargy, stupor, or coma due to impaired volume regulation in the brain.[68] Metabolic acidosis induces insulin resistance and increases protein catabolism, which further contributes to the azotemia and muscle wasting.[69]

Dehydration, intractable vomiting, or sodium bicarbonate therapy will occasionally cause metabolic alkalosis. Mixed acid-base disturbances are common in animals with impaired ventilation (pulmonary edema or hemorrhage, pleural effusion, pneumonia) or hyperventilation (pain, pulmonary thromboembolism).

258.3.4 Uremic Intoxications

Acute filtration failure causes the rapid accumulation of a spectrum of low (< 500 D) and middle molecular weight (500 to 15,000 D) uremia toxins. Collectively, uremia toxins contribute to the multisystemic features of acute uremia in direct proportion to their accumulation in the body. Conversion of urea to ammonia, decreased mucus production, hypergastrinemia, and central effects of uremia toxins contribute collectively to the GI manifestations. The GI signs include anorexia, nausea, vomiting, fetid breath, stomatitis, oral ulcerations, lingual necrosis, xerostomia, reflux esophagitis, gastritis, GI ulcers, hematemesis, GI bleeding, diarrhea,

enterocolitis, intussusception, and ileus.[70] As a subcomponent of the collective GI involvement, as many as 10% of dogs with severe ARF develop acute pancreatitis.[11,62]

Toxin-induced bleeding tendencies are promoted by impaired platelet-vessel wall and platelet-platelet interactions. Purpura, petechia, ecchymosis, bruising, bleeding from gum margins and venipuncture sites, epistaxis, and GI blood loss are characteristic. GI bleeding contributes to anemia and on occasion causes acute blood loss. In addition, uremia toxins cause or contribute to hypothermia, uremic pneumonitis, carbohydrate intolerance, and impaired immunity.

258.3.5 Cardiovascular Complications

Volume overload, cardiomegaly, heart failure, cardiac arrhythmias, and hypertension are common cardiovascular complications. Less commonly pericarditis, pericardial effusion, and tamponade may occur.[71] Bradycardia, supraventricular and ventricular premature contractions, and paroxysmal ventricular tachycardia are expected arrhythmias with severe uremia. Approximately 80% of the dogs with severe acute uremia have systemic hypertension. The severity of the hypertension is variably volume dependent and could be exacerbated by fluid therapy. If unresolved it may cause retinal detachment, hyphema, retinal hemorrhage, encephalopathy, and cerebrovascular hemorrhage.[72,73]

Uremic animals are at risk for cardiac arrest due to severe hyperkalemia and the collective metabolic, acid-base, and electrolyte disturbances associated with acute uremia. Bradycardia and vomiting pose additional risks for cardiac arrest secondary to increased vagal tone associated with the gastroenteritis.

258.3.6 Pulmonary Complications

Respiratory disease is seen in approximately half of dogs with severe uremia, is frequently life threatening, and is often refractory to conventional therapy. In order of frequency, pulmonary edema, pleural effusion, pneumonia, pulmonary hemorrhage, uremic pneumonitis, and pulmonary artery thromboembolism have been documented. Interstitial or alveolar edema and pleural effusion develop from excessive fluid administration and volume overload. The signs of fluid overload must be distinguished from those of CHF before appropriate therapy can be instituted. Aspiration pneumonia is a common sequelae to protracted vomiting. Severe generalized patchy interstitial to alveolar pulmonary infiltrates and associated pulmonary dysfunction is recognized in some dogs with leptospirosis.[74] Respiratory arrest may complicate all these respiratory disorders.[75]

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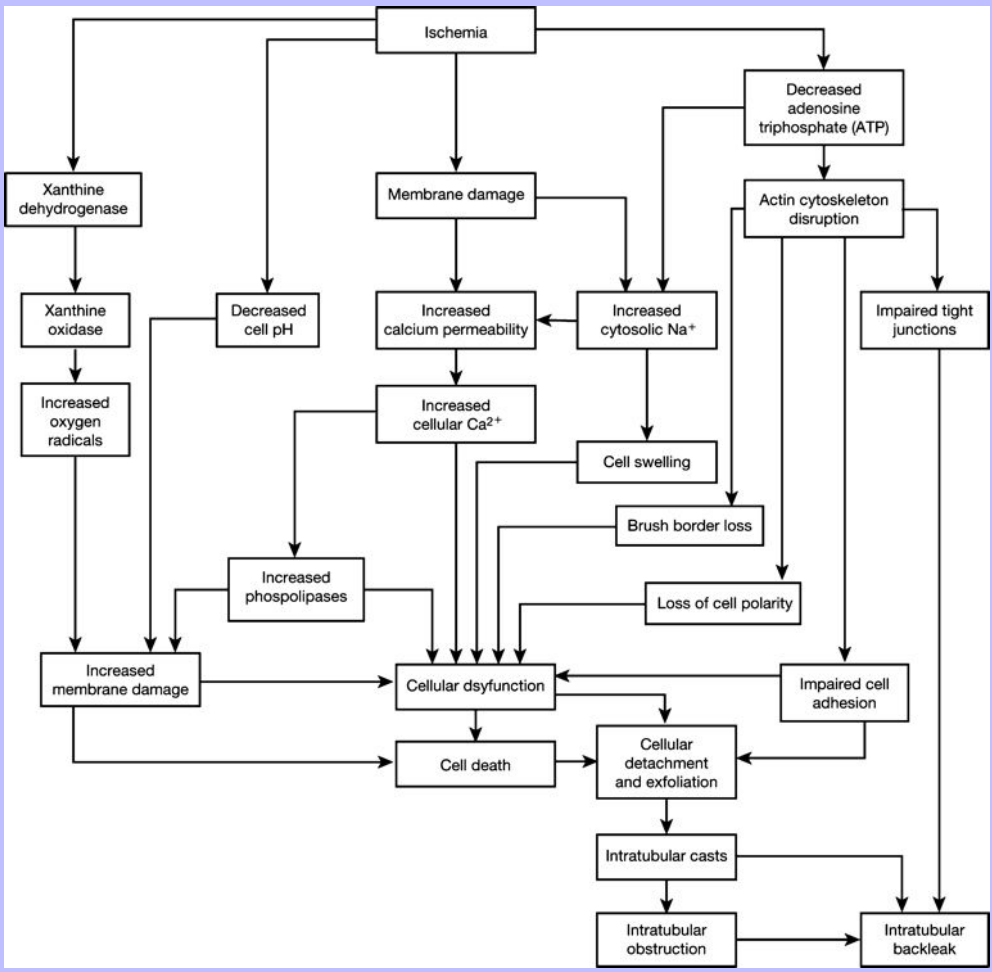
Figure 258-2 Cellular events in renal tubular epithelia in response to an ischemic insult. The diagram illustrates the multifactorial interactions that result ultimately in sublethal cellular dysfunction or cell death.



258.3.7 Neuromuscular Disorders

The underlying cause for neuromuscular dysfunction is multifactorial but includes intrinsic central nervous system (CNS) pathology (cerebral hemorrhage) and secondary manifestations of the uremic state (electrolyte and acid-base imbalances, hypertension). Resulting clinical signs are diverse and include fatigue, dullness, lethargy, impaired mentation, altered behavior, confusion, stupor, tremors, seizures, coma, peripheral neuropathies, myoclonus, muscular cramps, and muscular weakness. Ethylene glycol toxicosis causes specific CNS dysfunction before the onset of or in concert with the development of overt renal failure. Rapid

correction of the azotemia with hemodialysis can induce osmotic shifts of water in the brain, resulting in cerebral edema, seizure, cerebellar and brain stem herniation, coma, and death.

CNS side effects are associated with some medications (H_2 blockers, metoclopramide) when administered at conventional doses to animals with reduced capacity to eliminate such drugs. Animals with acute renal swelling display pain on abdominal palpation due to distension of the renal capsule. Prostration, dullness, or aggressive behaviors are typical manifestations of renal pain, especially in cats.

258.4 DIAGNOSIS OF ACUTE UREMIA

The clinical signs of acute uremia vary with the underlying cause and severity of disease, previously administered therapy, and comorbid diseases predisposing or compounding renal injury. A rapid and accurate differentiation of the possible syndromes resulting in acute uremia must be made to direct the therapeutic approach. These possible syndromes are (1) prerenal azotemia, (2) prerenal azotemia complicating CRF, (3) acute (parenchymal) renal failure (ARF), (4) prerenal azotemia complicating ARF, (5) chronic end-stage renal failure, and (6) postrenal azotemia. Each of these disparate azotemic conditions may appear quite similar. Because no specific biologic markers are available to predict the existence, severity, or recovery of renal parenchymal injury, the diagnosis of acute uremia is established from a comprehensive data base (which includes history, physical examination, laboratory testing, diagnostic imaging, histopathology, and special testing).

258.4.1 History

Acute uremia is characterized by a sudden onset of illness of less than 1 week's duration; however, animals with acute uremia secondary to underlying urinary or systemic diseases may have a longer duration of documented illness. Historical signs include listlessness, depression, anorexia, vomiting, diarrhea, and weakness. Less commonly, seizures, syncope, ataxia, and dyspnea may be reported. Potential exposure to nephrotoxic chemicals or plants (lily,[21] grapes or raisins[22,23]), new environmental conditions, ill animals, or traumatic events should be ascertained in the history. Recent surgery, diagnostic testing, travel, newly prescribed medications, or blood loss are potential risk factors for renal injury. Oliguria or anuria are consistent features of acute uremia, but a history of normal or increased urine production does not exclude its consideration. Historical weight loss, polyuria, polydipsia, nocturia or isosthenuria, or laboratory evidence of pre-existing renal insufficiency suggests underlying chronic renal disease. Renal function in animals with asymptomatic chronic renal insufficiency may decompensate suddenly after subtle insults including, fever, concomitant disease, vomiting, diarrhea, CHF, and drug administration, and they may develop a uremic crisis that is seemingly acute.

258.4.2 Physical Examination

Physical examination is an essential component of the diagnostic approach and may define the location and cause of the uremic state. Due to the acute nature of this condition, most animals in ARF have good body and coat condition. They have variable degrees of hydration. Depression, hypothermia, oral ulceration, “uremic breath,” bile-stained fur, scleral injection, cutaneous bruising, discoloration or necrosis of the tongue, tachycardia or bradycardia, tachypnea, muscle fasciculations, and seizures are present in proportion to the severity and duration of the azotemia. Bilaterally enlarged, firm, slightly resilient, or painful kidneys noted on abdominal palpation is indicative of acute nephritis or nephrosis or bilateral ureteral obstruction. Enlarged and firm kidneys on palpation are more suggestive of renal neoplasia, amyloidosis, or polycystic kidney disease. Asymmetry in kidney size is being recognized more frequency in cats with acute uremia due to the increasing

incidence of unilateral ureteral obstruction (Figure 258-3). The obstructed kidney is enlarged, and the contralaterally smaller kidney is frequently end-stage and nonfunctional. The size of the urinary bladder is variable on abdominal palpation, depending on the quantity of urine formation and the integrity of the outflow tract. An undetectable urinary bladder indicates profound oliguria or anuria or complete ureteral obstruction. An enlarged, firm, and painful bladder predicts outflow obstruction of the bladder.

In the absence of hemorrhage or hemolysis, mucous membranes are usually pink in dogs and cats with ARF. This is in contrast to the pale mucous membranes observed in animals with CRF. Most animals with ARF have evidence of dehydration when first evaluated, which may underscore prerenal causes or contributions. Prolonged capillary refill time, dry mucous membranes, decreased skin turgor, sunken eyes, tachycardia, poor pulse quality, and hypotension are consistent with the presence of dehydration and hypovolemia. Animals that have been given parenteral fluids may demonstrate signs of overhydration (wet mucous membranes, serous nasal discharge, increased skin turgor, peripheral edema, tachypnea, dyspnea, muffled heart sounds, hypertension, and ascites).

ARF is frequently layered secondarily on other diseases or even CRF. Manifestations of these other conditions may dominate findings of the physical examination and mask its characteristic features. Lameness, icterus, fever, discolored urine, back or flank pain, petechia, and dysuria are associated with some disorders. Uremic animals typically are hypothermic in proportion to the severity of the azotemia. The presence of a normal or slightly elevated body temperature is inappropriate for uremic animals and is consistent with fever associated with an underlying infectious or inflammatory state.

258.4.3 Laboratory Assessment

The initial diagnostic assessment should include a complete blood count (CBC), comprehensive biochemical profile (serum creatinine, urea, phosphate, calcium, bicarbonate, sodium, potassium, chloride, glucose, albumin, globulin, hepatic transaminases, and bilirubin) (Figure 258-4), urinalysis with sediment examination, and urine culture.

CBC results may reflect primary or comorbid conditions of diagnostic relevance. Normal or increased red blood cell (RBC) count, hematocrit, and hemoglobin concentrations are consistent with prerenal azotemia or acute uremia, whereas a nonregenerative anemia suggests CRF. The hemogram may be significantly influenced by the hydration status of the animal and may overestimate the actual RBC mass with dehydration and underestimate red cell mass with over hydration.

Progressive azotemia is part of the definition for acute uremia (Figure 258-4). In humans, the diagnosis is predicated on subtle daily increases in serum creatinine, but this feature is observed rarely in animals. Animals are usually evaluated when the azotemia is well established, and clinical signs are clearly apparent. Both serum creatinine and urea nitrogen will increase in direct proportion to the severity of the renal impairment or completeness of the outflow obstruction. The degree of functional impairment can be broadly categorized based on steady-state serum creatinine concentration given the inverse relationship between serum creatinine and renal function (GFR).[76] From this projection, the renal dysfunction can be staged as mild in animals with a serum creatinine concentration less than 2.5 mg/dL (>40% of normal function), moderate for those with a serum creatinine concentration between 2.5 mg/dL and 5.0 mg/dL (between 40% and 20% of normal function), severe for those with a serum creatinine concentration between 5 mg/dL and 10 mg/dL (between 20% and 10% of normal function), and extreme if the serum creatinine concentration is greater than 10 mg/dL (<10% of normal function). Reductions in lean body mass and overhydration can lower the serum creatinine concentration and cause overestimation of true renal function.

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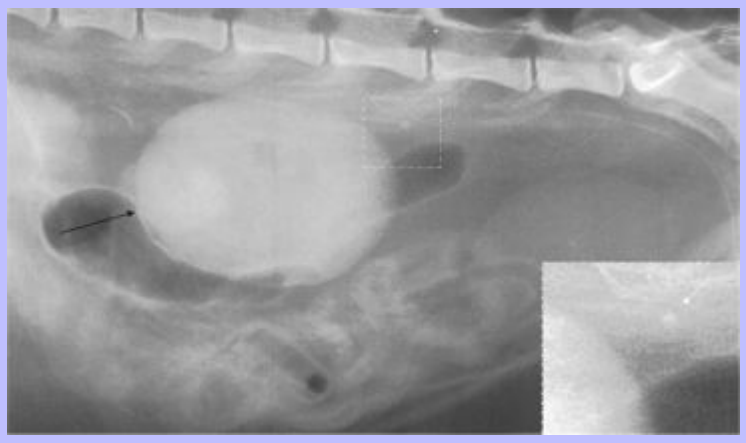
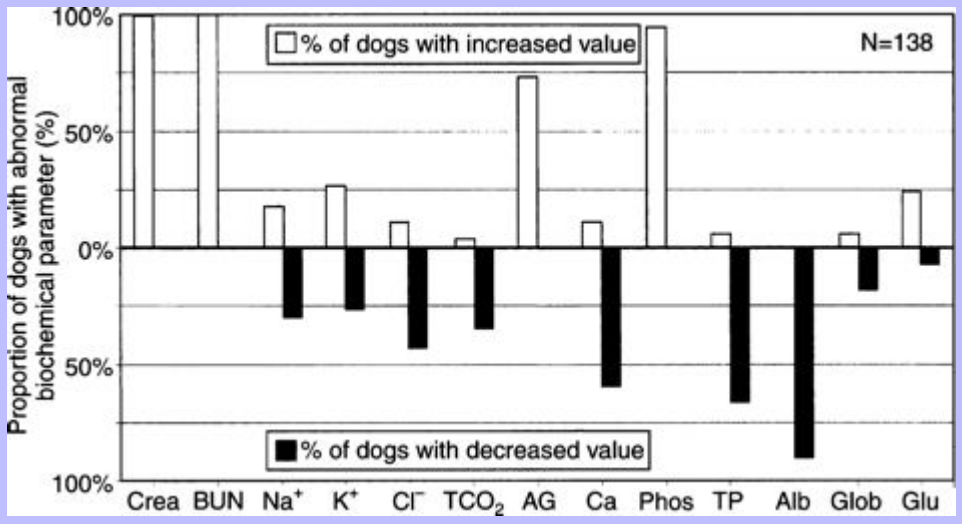
Figure 258-3 Lateral radiographic image of a cat abdomen illustrating extreme asymmetry in renal size characteristic of the "big kidney-little kidney" syndrome associated with ureteral obstruction. The right end-stage kidney *(black arrow)* is superimposed on the enlarged left kidney. The dashed box and insert highlight a radiodense calcium oxalate urolith in the left ureter *(white arrow)*.



Serum urea nitrogen (SUN) concentration also increases inversely with reductions in GFR and contributes to the developing azotemia. Unlike creatinine, urea is influenced by numerous extra renal parameters that make its concentration less specific as a marker of renal function. Urea appearance is closely linked with exogenous and endogenous nitrogen metabolism, hydration status, urine production, and diuretic therapy that make it a useful predictor of the clinical severity of the uremic state. Urea is also used as a surrogate for the production and removal of low molecular weight uremia toxins during dialysis.[77]

Figure 258-4 Incidence of serum biochemical changes in 138 dogs with severe ARF at the time of referral. The proportions of dogs with abnormally high (above zero line) and abnormally low (below zero line) values are shown for the following parameters: creatinine (Crea), BUN, sodium (Na^+), potassium (K^+), chloride (Cl^-), total CO_2 (TCO_2), anion gap (AG), calcium (Ca), phosphorus (Phos), total protein (TP), albumin (Alb), globulins (Glob), and glucose (Glu).



For comparable azotemia, animals with acute uremia usually have more profound alterations of serum mineral, electrolytes, and bicarbonate concentrations reflected on the biochemistry profile than animals with CRF (see Figure 258-4). In acute uremia, serum phosphate concentration generally exceeds that of creatinine and may be associated with mild to moderate hypocalcemia. Serum calcium concentration may be less than 5.0 mg/dL in animals with acute antifreeze intoxication. In contrast, serum calcium is usually normal or moderately elevated in proportion to serum creatinine and phosphate in animals with CRF.[78,79] Serum potassium concentration varies with the severity and cause of the uremia, extent of vomiting, and fluid and diuretic administration (see Figure 258-4). Serum potassium typically is increased (between 5.5 mEq/L and 9.0 mEq/L) in proportion to the degree of azotemia. It tends to be higher in animals with anuric ARF or urinary outflow obstruction. Serum bicarbonate concentration decreases with the severity of the renal failure such that bicarbonate deficits of 5, 10, and 15 mmol/L are associated with mild, moderate, and severe degrees of acute uremia, respectively.[80] Profuse vomiting or previous bicarbonate administration may cause metabolic alkalosis that is not consistent for the degree of azotemia.

Distinguishing animals with prerenal azotemia from those with intrinsic ARF can often be made from results of history, clinical findings, and USG. The presence of mild or moderate azotemia, clinical dehydration, hypovolemia or hypotension, and oliguria in conjunction with a concentrated USG or urine osmolality confirms the diagnosis of prerenal azotemia. Therapeutic confirmation of the diagnosis can be made by a rapid

resolution of the azotemia and oliguria with restoration of fluid balance and normalization of systemic hemodynamics. Numerous laboratory parameters including BUN/creatinine ratio, urine/plasma sodium (U/P_{Na}), and fractional sodium excretion (FE_{Na}) have also been used to distinguish oliguric animals with a prerenal condition from those with ARF. The discrimination is achieved by the increased reabsorption of urea and sodium in prerenal states compared with ARF. The utility of these tests becomes problematic in animals with coexisting diseases that impair concentration of the urine or after diuretic administration that increases urinary sodium excretion. Additionally, BUN/creatinine ratio has been shown to provide no localizing value in dogs with renal disease but may be more predictive of heightened catabolism or intestinal bleeding.[8,81] More recently, the fractional excretion of urea (FE_{urea}) has been shown to be highly sensitive for identification of humans with prerenal azotemia from those with prerenal azotemia and concurrent diuretic administration or others with intrinsic ARF (similar testing may be useful in animals).[82]

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The tubular epithelial enzymes, gamma-glutamyl transpeptidase (GGT) and N-acetyl-beta-D-glucosaminidase (NAG), can be measured in urine to predict cellular leakage as an early marker of tubular injury or necrosis.[83–87] Urinary enzymes have shown good sensitivity for early recognition of renal injury, but they have not been adopted widely in veterinary or human diagnostics. Carbamylated hemoglobin is a nonenzymatic and nonreversible reaction product of the urea metabolite, cyanate, with hemoglobin. The concentration of carbamylated hemoglobin reflects time exposure of blood to the azotemia and has been shown to differentiate dogs with acute azotemia from those with CRF.[88,89] Testing for carbamylated hemoglobin is becoming more readily available in human hospitals and is likely to find increased utility in uremic animals.

A complete urinalysis should be performed on every dog or cat with obtainable urine at initial examination prior to instituting therapy. Both renal concentrating and diluting capabilities become impaired in the early phases of intrinsic ARF resulting in a USG that is fixed in the range between 1.008 and 1.018. A USG greater than 1.030 for dogs or greater than 1.035 for cats in the presence of azotemia indicates prerenal filtration failure.[90] A USG between 1.012 and 1.029 (dogs) or 1.012 and 1.034 (cats) associated with azotemia is consistent with a prerenal component superimposed on intrinsic renal insufficiency (*prerenal-on-acute* or *prerenal-on-chronic* disease) or an underlying urine-concentrating defect. Glucosuria in the absence of hyperglycemia is present in 50% of dogs with severe ARF and is an important sign of proximal tubular dysfunction.[62] It predicts tubular necrosis and is a useful discriminator between intrinsic ARF and other types of acute or chronic uremia.[11] Qualitative (dipstick) proteinuria is detected in most uremic animals but has little discriminatory importance.[11] Overt proteinuria associated with a urine protein/creatinine ratio greater than six should alert the possibility of primary glomerular injury.

The urine sediment examination may demonstrate RBCs, white blood cells (WBCs), casts, crystals, yeast, fungi, or bacteria that aid the differential diagnosis and cause of the uremia and should be performed routinely on freshly obtained urine. The presence of granular and hyaline casts document active renal pathology with tubular epithelial shedding or necrosis and glomerular protein leakage. Casts are detected in approximately 30% to 40% of dogs with ARF, but their absence does not exclude a diagnosis of acute parenchymal injury.[11] Calcium oxalate crystalluria is indicative of hyperoxaluria associated with ethylene glycol intoxication and oxalate nephrosis (cats).[19,90–93]

Imaging of the urinary tract with survey radiography and ultrasonography is indicated in the evaluation of all animals with acute uremia. Ultrasonography is complementary to diagnostic radiography and is the preferred imaging modality for urinary disease. Ultrasonography is rapid, noninvasive, and provides greater delineation

of renal geometry, intrarenal architecture, parenchymal consistency, and outflow integrity. It provides a more definitive assessment of renal and abdominal pathology, including nephritis and nephrosis, pyelonephritis, urolithiasis, hydronephrosis, outflow obstruction, pancreatitis, abdominal neoplasia, prostatitis, and ascites. Ultrasonic imaging facilitates collection of diagnostic specimens for biochemical analysis, cytology, culture, and histology by incorporation of guided percutaneous needle aspiration or biopsy techniques.[94] Duplex Doppler sonography can be used to verify segmental blood flow in the kidney and to predict changes in vascular impedance associated with induction and resolution of some forms of renal injury and outflow obstruction.[95,96] The sonographic appearance of the kidneys can provide immediate verification for conditions like antifreeze poisoning, ureteral obstruction, and end-stage renal disease. Ethylene glycol intoxication, for example, is characterized by marked to intense increases in cortical echogenicity with variable degrees of hypoechoic intensity at the cortical medullary junction (halo sign)(Figure 258-5). However, the increased availability and utility of ultrasonography has curtailed the routine use of survey radiography to image the urinary tract. For the diagnosis of ureteral obstruction in cats, survey radiographs may be more sensitive and predictive than ultrasonography, if careful scrutiny is directed to barely perceptible radiodensities in the retroperitoneal space, and they are justified in all cats with acute uremia (see Figure 258-3).

Excretory urography, renal scintigraphy, computed tomography (CT), and magnetic resonance imaging (MRI) may have specific indications in selected animals, but these imaging modalities are not routinely available. Antegrade pyelography incorporating ultrasound-guided pyelocentesis has become increasingly useful to confirm the presence, degree, and location of ureteral obstruction in cats (Figure 258-6). In 20% to 30% of cats with ureteral obstruction, no discrete calcific material is identified with either sonographic or survey radiographic techniques. For these circumstances, and for cases with multiple sites of obstruction or stenosis, antegrade pyelography remains the best aid for identification and localization for surgical intervention.

The cause and course of the acute uremia can be determined for most animals from assessment of the history, physical findings, and contemporary diagnostic testing. Where these features cannot be predicted with certainty, renal histopathology can provide a specific morphologic and potentially causative basis for the disease, its potential reversibility, and chronicity. Details of the techniques, indications, and contraindications for renal biopsy have been described recently.[97,98] Percutaneous or laparoscopic needle techniques can be performed in both dogs and cats with minimal sedation, anesthesia, or invasiveness and obviate the need for surgically obtained renal specimens. Routine biopsy of animals with acute uremia is probably unjustified when balanced against the potential for complications and lack of scientifically documented assessment of risk versus benefit. Renal biopsy should be considered if the definitive cause, extent, and chronicity of the renal injury cannot be established with noninvasive diagnostic methods or if therapeutic decisions would be predicated on this information. Discretion should be used in extrapolating acute morphologic findings from the biopsy to the potential long-term reversibility of the functional deficiencies. The advent of hemodialysis has changed the clinical understanding of reversible and irreversible renal failure. Identification of severe pathology at acute stages of disease may not correspond to an unfavorable outcome if the potential (time) for renal repair is provided with finite periods of renal replacement.

Serologic testing for leptospirosis should be performed on all dogs with acute uremia without a confirmed cause. The evaluation should be expanded to include titers to *L. pomona, L. bratislava, L. grippotyphosa, L. autumnalis,* and *L. hardjo* in addition to *L. canicola* and *L. icterohaemorrhagiae*, because the distribution of infecting serovars differ geographically.* Strict criteria for serologic conformation of an active leptospiral infection have not been established, and the recent introduction of multivalent vaccines makes interpretation more difficult. A microscopic agglutination titer greater than 1:100 indicates positive serology, and a fourfold or greater rise in titer between paired sera separated by 7 to 14 days predicts active infection.[101,102] Ambiguity in the diagnosis arises when only a single titer is available for analysis. Previous retrospective studies

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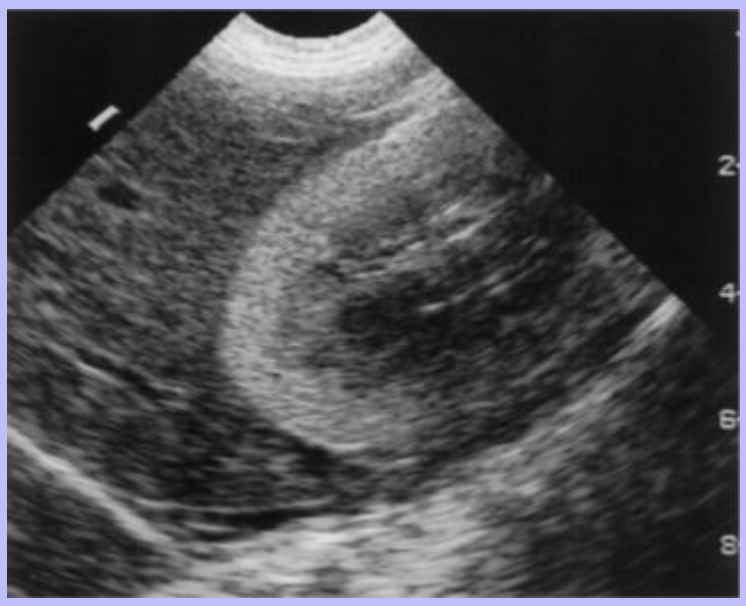
arbitrarily established single titers of greater than 1:800 and greater than 1:3200 to nonvaccinal serovars as criteria for a positive diagnosis of leptospirosis in dogs.[33,34,36] However, laboratory variation, differences in humoral responses to individual serogroups, vaccination, and background (asymptomatic) exposure make strict serologic criteria difficult to assign. Vaccination can produce titers greater than 1:1250 to serogroups, *icterohaemorrhagiae* and *canicola,* in dogs; however, vaccination should not produce titers to nonvaccinal serovars that exceed those of vaccinal agents.[103] A recent survey of nonselected dogs identified a surprisingly high percentage of nonvaccinated dogs with positive serology to leptospirosis serogroups indicating background population exposure.[39] Shedding of leptospiral DNA has also been recognized using a sensitive polymerase chain reaction (PCR) assay in both asymptomatic and symptomatic seronegative dogs.[104] These observations suggest some dogs have delayed seroconversion or fail to seroconvert despite being actively infected. This sensitive diagnostic technique will improve clinicians' ability to diagnose active infections and understanding of renal carriage, shedding, and risks of leptospirosis in the presence and absence of vaccination. Given the limitations of current diagnostic methods, clinical guidelines for a diagnosis of active infection include a single elevated titer (≥ 1:800) to a vaccinal serogroup accompanied by clinical signs consistent with leptospirosis; a single microscopic agglutination titer 1:800 for nonvaccinal serogroups; evidence of seroconversion in paired acute and convalescent sera; and presence of typical clinical signs of leptospirosis followed by a response to appropriate antimicrobial therapy.[32]

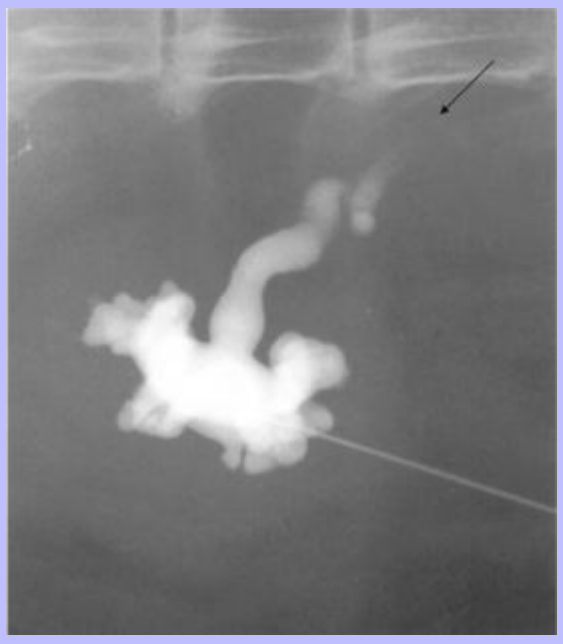
Figure 258-5 Ultrasonographic image of the kidney from a dog acutely poisoned with antifreeze. The renal cortex is markedly hyperechoic, compared with the ultrasonic density of the adjacent spleen. This sonographic feature is a consistent finding with ethylene glycol intoxication.



A diagnosis of ethylene glycol intoxication can be made presumptively by the presence of an increased serum osmolality, osmolal gap, profound metabolic acidosis, increased anion gap, hypocalcemia, the presence of

calcium oxalate crystalluria, and sonographic appearance of the kidneys (see Figure 258-5).[19,91,93] Confirmation of the diagnosis, documentation of the degree of intoxication, and response to therapy is best performed by chemical analysis of gastric fluid, serum, or urine for the presence of ethylene glycol or its toxic metabolites by commercial laboratories. Blood ethylene glycol and glycolic acid concentrations may persist for days at toxic concentrations despite therapy with alcohol or 4-methylpyrazole in affected animals with severe oliguria or anuria.[104,105]

Figure 258-6 Nephropyelogram of a cat kidney with a proximal ureteral obstruction. The figure highlights the ultrasound-placed needle in the renal pelvis and the extensive pelvic and ureteral dilation outlined by the injected contrast. The proximal ureter is dilated, torturous, and ends abruptly *(arrow),* despite the increased pressure associated with contrast injection. These findings are consistent with a radiolucent structure producing complete ureteral obstruction.



* References 32, 33, 37, 38, 99, 100.

258.5 MEDICAL MANAGEMENT OF ACUTE UREMIA

Medical management of acute uremia in animals remains founded on observations from animal models of ARF and recommendations extrapolated from human therapeutics.[4,106–108] Recommendations are prioritized to prevention of renal injury in predisposed or high-risk animals, to elimination of underlying or ongoing renal insults, and to amelioration of identified biochemical, metabolic and clinical consequences of established uremia. The mechanisms underlying the impaired glomerular hemodynamics, epithelial and vascular disruption, and

intratubular obstruction that mediate acute renal injury have been characterized in great detail in recent years (see Pathogenesis of Acute Renal Failure). Cellular energetics, vascular congestion, cytosolic calcium, oxidant stress, necrosis, apoptosis, nitric oxide, epithelial cytoskeleton, and growth promoters are but a few mediators recently recognized to participate in the pathogenesis of ARF. Novel therapies have emerged from each of these areas of discovery to counteract specific pathophysiologic events scientifically crafted in the experimental models. Despite the therapeutic promise of each of these areas of investigation to prevent or ameliorate development of ARF or to accelerate renal repair, none have become established in clinical therapeutics. This is to be expected in animals with naturally acquired disease that possess multifactorial risks and predispositions to acute uremia of diverse cause, severity, duration, and expression.

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Thus conventional approaches to management of acute uremia remain supportive for the predicted and documented clinical consequences that develop.

258.5.1 Prevention of Acute Renal Injury

The highest priority for the management of acute uremia is to recognize those dogs or cats highly predisposed to a uremic crisis and to intervene to prevent its development. Pre-existing renal disease, advanced age, dehydration, hypovolemia, hypotension, sepsis, fever, prolonged anesthesia and surgery, trauma, systemic disease, use of vasoactive or nephrotoxic drugs, high environmental temperatures, and nephrolithiasis are predispositions that pose an increased risk.[109] Risk factors are cumulative and predispose additive potential for renal injury. When predispositions coexist with ongoing or projected therapies having a potential for renal injury, the following procedures should be reviewed. Exposure to ischemia and toxic insults should be eliminated, and the dose of nephrotoxic drugs should be modified. Hemodynamic adequacy must be established, and life-threatening fluid, electrolyte, and acid-base imbalances corrected. Decontamination procedures (induced vomiting, gastric lavage, administration of activated charcoal, and cathartics) and treatment with specific antidotes should be instituted after acute exposure to known nephrotoxins. Table 258-1 illustrates these points in the therapeutic approach to acute antifreeze poisoning. The correction of existing fluid deficits and attention to ongoing fluid balance offers the best insurance to moderate ATI. Mild to moderate ECF volume expansion with isonatric fluids is beneficial before the administration of known nephrotoxic drugs (aminoglycosides, cisplatin, amphotericin B), anesthesia, or surgical intervention. Mannitol administered (see details, following) prior to exposure to hemodynamic or nephrotoxic insults will promote urine formation and a natriuresis but has shown only limited efficacy to protect against the development of ATI. The preventative use of other therapies has consistently failed to provide any advantage over judicious fluid management.[4,110–113]

258.5.2 Conventional Management of Established Uremia

Strategy for the management of existing ARF includes elimination of known causes of renal injury (see Prevention of Acute Renal Injury) and supportive therapies directed to the life-threatening consequences of acute uremia. Systemic infections such as leptospirosis should be treated aggressively with appropriate antimicrobial therapy, and hemodynamic deficiencies must be resolved rapidly to establish euvolemia and normotension. Animals with mild renal damage may regain adequate function within 3 to 5 days of initiating treatment. This may forestall progression to life-threatening uremia. Animals with moderate or severe renal damage may require weeks to achieve repair of the injury; yet most die from uremia within 5 to 7 days. The disparity between this window for effective medical therapy and the re-establishment of renal function underlays, in part, the high mortality and unfavorable outcome associated with ARF.

258.5.3 Systemic Hemodynamics and Body Fluids

Alterations in body fluid composition are classic causes and consequences of acute uremia. Fluid therapy remains the foundation of medical management. The fluid plan must restore deficiencies in fluid volume, correct abnormalities in fluid composition, and promote urine formation. Replacement fluids should mimic as closely as possible the composition of fluid deficits. Priority is given to restoration of intravascular and interstitial volume, normalization of arterial blood pressure and renal perfusion, and compensation for ongoing fluid losses. At *initial* examination most animals with ARF are dehydrated and hypovolemic due to active fluid losses (vomiting, diarrhea, and possibly hemorrhage). The fluid deficit should be corrected with 0.9% sodium chloride or balanced crystalloid solutions (lactated Ringer's) administered intravenously to replete vascular volume. The initial replacement volume (milliliter) to correct the extracellular deficit is calculated from clinical estimates of dehydration according to the formula:

$$\text{Volume Replacement (mL)} = [\text{body weight (kg)}] \times [\text{estimated deficit (\%)}] \times 1000$$

Table • 258-1 Therapeutic Approach to Acute Antifreeze Poisoning

THERAPEUTIC PLAN	THERAPEUTIC OPTIONS
Prevent ongoing exposure (<2 hours)	1. Induce vomiting 2. Perform gastric lavage 3. Administer activated charcoal
Correct ECF fluid deficits Correct dehydration	1. Correct ECF volume deficits (saline, lactated 2. Correct metabolic acidosis (if present) 3. Correct hypocalcemia if present) 4. Initiate maintenance fluids/ongoing losses
Document urine production/promote diuresis	1. Establish urinary catheter, monitor urine output 2. Administer mannitol, furosemide, or both after rehydration
Administer antidote	1. Ethanol (20%): 5.5 mL/kg IV q4h-5 Rx, then (dogs/cats) 5.5 mL/kg IV q6h-4 Rx or 2. Ethanol (30%): 1.3 mL/kg IV bolus, then (dogs/cats) 0.42 mL/kg/hr IV for 48 hours
Eliminate toxin/metabolites	3. 4-methyl pyrazole: 20 mg/kg IV, then (dogs) 15 mg/kg IV @ 12 & 24 hours, then 5 mg/kg IV @ 36 hours 4. Hemodialysis at earliest opportunity (dogs/cats)
Manage ARF/oliguria	1. Conventional medical therapy 2. Hemodialysis

The estimated deficit is a value between 5% and 15% determined from history, physical examination, and laboratory information or computed from known deviations from historical body weight. The rate at which the deficits are corrected is predicated on the hemodynamic stability of the animal and its tolerance for fluid administration. Mild or moderate fluid deficits (5% to 8%) in hemodynamically stable animals can be replaced within 6 to 8 hours. Moderate or severe fluid deficits (>8%) associated with evidence of hypovolemia must be corrected more aggressively. The hypovolemic component of the deficit should be administered as bolus infusions within 30 minutes to restore intravascular volume and prevent prolonged hypoperfusion of kidneys. The remainder of the deficit can then be delivered over 6 to 8 hours to correct the dehydration.

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Aggressive fluid replacement must be tempered in animals with cardiovascular disease to prevent circulatory congestion and heart failure. Serial monitoring of central venous pressure (CVP) can facilitate safe and

efficient fluid administration. An increase in CVP of 5 to 7 cm H_2O above baseline or an absolute CVP greater than 10 cm H_2O indicates an excessive rate or volume of fluid administration. Five percent dextrose in water or maintenance formulations (including half-strength saline and dextrose solutions) are not appropriate choices to replete the initial deficits and should be reserved to compensate insensible or maintenance losses later in the course of treatment.

Fluid deficits associated with profound hypovolemia and hypotension or severe blood loss must be replaced more rapidly with crystalloid solution (up to or greater than 90 mL/kg/hr) or with fluids targeted for blood volume expansion. Synthetic colloid solutions (Dextran-70 or Hetastarch) administered at 20 mL/kg will expand blood volume immediately by 17% to 24% and by approximately 35% within 60 minutes of administration.[114] Synthetic colloid solutions provide no replacement of extravascular volume necessitating concurrent administration of crystalloid solutions to replete the interstitial compartment. These solutions may be rational choices for support of vascular volume in clinical settings where oxygen-carrying capacity is less critical than volume restoration. Hypovolemia secondary to blood loss or hemorrhage may require administration of compatible whole blood, blood components, or synthetic hemoglobin products (Oxyglobin®, BioPure, Cambridge, Massachusetts).[115,116]

The production of urine at greater than 1.0 mL/kg/hr with fluid volume replacement suggests a significant prerenal contribution to the oliguria and azotemia. Failure to induce a significant diuresis after volume replacement indicates either that parenchymal damage is severe or that initial fluid deficits were underestimated. Additional fluid may be administered taking care to promote only mild volume expansion without overhydration.

After correction of the initial fluid deficits, subsequently administered fluid must reflect maintenance requirements and ongoing losses. Maintenance fluid should be limited to 5% dextrose in water to replace insensible free water losses (20 to 25 mL/kg/day) and balanced electrolyte solutions to replace measured or estimated urine, GI, and other sensible losses. Commercial maintenance formulations can be supplied if insensible and urinary losses are approximately equal. Animals that are provided only isonatric solutions (saline, lactated Ringer's) become depleted of free water and develop hypernatremia within 3 to 4 days. The severity of the hypernatremia may be amplified in animals with appreciable free water loses in the urine during the diuretic phase of ARF, post obstructive diuresis, or subsequent to treatment with osmotic diuretics like mannitol. In oliguric animals, the urinary replacement should be negligible and not prescribed at the same rate as in animals with normal urine production. Urinary losses should be measured or accurately estimated in nonoliguric animals to prevent underestimation of the urinary replacement. Nonoliguric animals in the diuretic phase of ARF or after relief of postrenal obstruction may produce greater than 10 mL/kg/hr of urine that will not be matched by estimates of normal urine production.

Supplementation of potassium in replacement or maintenance fluids must be prescribed on an individual case basis. Fluids containing supplemental potassium are generally contraindicated in oliguric animals or during rapid fluid replacement. If the supplemental load of potassium has no effective elimination route, it will quickly promote hyperkalemia. Animals in the diuretic phase of ARF may excrete excessive amounts of potassium and require supplementation to prevent potassium wasting; but potassium supplementation should always be provided cautiously and only with monitoring of daily serum potassium concentrations.

Fluids must be administered conscientiously to oliguric or anuric animals. Hypervolemia is a common complication of overzealous fluid administration or improper monitoring of fluid balance. Sixty to 70% of animals with moderate to severe acute uremia are overhydrated when referred to the authors' emergency service, or they become hypervolemic during the initial hospitalization period. Failure to induce an effective

diuresis (>1 mL/kg/hr) once the fluid deficits are replete predicts further fluid loading will be unproductive and predispose the animal to overhydration. Weight gain, tachypnea, harsh breath sounds, increased skin turgor, chemosis, serous nasal discharge, peripheral or pulmonary edema, circulatory congestion, ascites, and systemic hypertension are consistent indicators of overhydration and hypervolemia. The presence of dry oral mucous membranes in uremic animals does not reflect hydration status due to decreased salivary secretion (xerostomia). This finding may cause underestimation of true hydration and inappropriate fluid administration.

An excessive fluid load may be difficult or impossible to correct in animals with marginal urine formation. At the first evidence of overhydration, all fluid delivery should be curtailed appropriately or discontinued, and attempts should be made to induce a diuresis (see following). If the fluid burden cannot be managed successfully with diuretic administration, no medical options are available to resolve the overhydration and therapy must be directed to consequences of circulatory overload (systemic hypertension, peripheral and pulmonary edema, pleural effusion, CHF, and ascites). For life-threatening overhydration, fluid removal with hemodialysis or peritoneal dialysis is the only available therapeutic option (see Renal Replacement Therapy, following).

Cross-linked polyelectrolyte sorbents offer a promising and clinically applicable oral solution for overhydration in uremic animals. These materials can adsorb up to 50 times their intrinsic weight in GI water, providing an effective alternative for fluid elimination. At typical doses, orally administered sorbets could eliminate up to 1 L of daily fluid accumulation in a 30 kg dog. Additionally, these polymers can adsorb solutes dissolved in intestinal water, providing an alternative clearance for urea, creatinine, and potassium. Prototype materials have been used successfully in a uremic dog and are being developed for human administration.[117]

258.5.4 Inadequate Urine Production

The conversion from oligoanuric to nonoliguric renal failure has been a long-standing goal in the management of acute uremia. The routine use of diuretics and vasodilators has been advocated when fluid therapy alone is ineffective to promote diuresis.[4,110,111,118] Management benefits of an induced diuresis include (1) disclosure of less severe renal injury, (2) better regulation of fluid and electrolyte balance, (3) opportunity to provide parenteral nutrition, (4) increased toxin clearance, and (5) optimism for attending clinicians. Despite conventional endorsement of diuretic therapy in the management of ARF, this practice is losing credibility due to a lack of documented efficacy of pharmacologic agents to alter the course, morphology, or outcome of ARF. Empiric use of these drugs impose recognized risks.[4,107,110–112,118–121] A recent cohort evaluation of diuretic administration in human patients with ARF documented an increased risk of death and failure to recover renal function with diuretic use compared with its nonuse.[112,122] If delayed beyond a few hours from the initiation phase of the insult, the efficacy of diuretics becomes negligible. Their use should never supplant judicious fluid and hemodynamic support.[4,110,111,118,123]

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Hypertonic mannitol (an osmotic diuretic) is used commonly for the prevention and management of oliguric forms of ARF. Therapeutic effects include decreased vascular resistance and cellular swelling; increased renal blood flow (RBF), GFR, and solute excretion; protection from vascular congestion and erythrocyte aggregation; increased osmotic tubular fluid flow with dispersion of tubular debris, casts and obstructions; and scavenging of toxic free radicals.[4,110,124–126] Its use to promote urine formation in the early stages of acute oliguric renal failure has been recommended in animals but lacks evidence-based justification.[9,106,127] Mannitol (20% to 25% solution) is administered to fluid replete animals as a slow intravenous bolus at 0.25 to 1.0 g/kg. If an effective diuresis results within 30 to 60 minutes, a CRI at 1.0 to 2.0 mg/kg/min or intermittent boluses of 0.25 to 0.5 g/kg intravenously, every 4 to 6 hours, can be given to continue the diuresis for 24 to 48

hours. If an adequate diuresis is not established by 60 minutes, an additional 0.25 to 0.5 g/kg intravenous bolus can be repeated cautiously, but further administration is contraindicated due to the risks of volume expansion, hemodilution, hypervolemia, and mannitol toxicity.[9,106,127–129] Mannitol should not be given to animals with severe fluid overload, pulmonary edema, or CHF. The more established the onset of uremia, the lower the expectation mannitol will promote a diuresis or influence the course of the disease.

Furosemide is less effective than mannitol at improving renal function in experimental renal injury, but these observations have not been verified in clinical trials or in dogs and cats with naturally occurring forms of disease. Furosemide inhibits active sodium and chloride reabsorption in the distal nephron causing diuresis, natriuresis, and kaliuresis. It increases tubular fluid flow and osmolar clearance, similar to the effects of mannitol. Additionally, it causes vasodilation, increased RBF, and decreased tubular oxygen consumption in hypoxia-sensitive tubular segments.[4,110,126]

Overhydration, hyperkalemia, and toxin elimination are the established indications for the use of furosemide in animals or humans with ARF.[*] Furosemide is given initially at 2 to 6 mg/kg intravenously after existing fluid deficits have been corrected. If an adequate diuresis of greater than 1 mL/kg/hr is not achieved within 30 minutes, the initial dose can be repeated. If a diuresis is achieved, the dose can be repeated every 6 to 8 hours or given as a CRI at 0.25 to 1.0 mg/kg/hr to extend the diuresis for 24 to 48 hours. Diuretics should always be administered cautiously. The animal's fluid and electrolyte balance must be monitored to prevent depletion of ECF volume that might precipitate additional prerenal insults on the existing renal injury. Like mannitol, the diuresis induced by furosemide may not improve renal morphology or change the outcome or clinical course of animals with ARF. Predictable adverse effects are development of ECF volume contraction, sodium wasting, deafness, and delay to referral.

Dopamine is a catecholamine with diuretic properties caused by PGE_2-mediated renal vasodilation, increased RBF, increased GFR, decreased tubular sodium and water reabsorption, and decreased tubular oxygen consumption. The pharmacologic effects of dopamine are dose dependent and differentially mediated through dopaminergic and adrenergic receptors. In dogs, “renal” doses of dopamine between 0.5 to 3 μg/kg/min promote these responses primarily by activating dopamine-specific D_1-like and D_2-like receptors in the kidney and postganglionic sympathetic nerves. Doses between 5 and 7 μg/kg/min activate β_1-receptors to increase cardiac output; whereas higher doses stimulate alpha receptors causing undesired vasoconstriction, tachycardia, cardiac arrhythmias and potential for myocardial, intestinal and renal ischemia.[4,110,111,118,130] At doses between 0.5 to 3 μg/kg/min, dopamine may increase urine formation and facilitate conversion from an oliguric to a nonoliguric state. Higher doses promote renal vasoconstriction, tachycardia, cardiac arrhythmias, and are contraindicated in ARF. Problems arise with overlap in dose effects, variable dopamine elimination, and individual animal sensitivity and binding affinities. These variables predispose critical animals to untoward and unpredictable effects to standard dosing.

Studies in anesthetized cats document a different spectrum of dopaminergic effects that suggest a lack of dopamine-specific receptor activity in the kidneys of this species.[130–132] Low-dose dopamine infusion (1 to 3 μg/kg/min) causes no significant changes in mean arterial blood pressure, heart rate, urine output, or sodium excretion.[131,132] Only at doses greater than 10 μg/kg/min did dopamine infusion results in dose-dependent increases in urine output and sodium excretion; however, the diuretic response was coupled with variable decreases in GFR, renal vasoconstriction, and inconsistent changes in mean arterial blood pressure and renal blood flow most consistent with α-adrenoreceptors effects.[131] These differences in the actions of dopamine predict it is conceptually inappropriate for use in cats with oligoanuric ARF. Recently, D_1 receptors with a

high affinity to fenolodopam were identified in the kidney cortex of cats, suggesting alternative drug strategies to promote diuresis.[130]

Despite the early observational benefits ascribed to dopamine that have fostered its contemporary use, essentially no documented benefits exist to support its continued use in acute uremia, except for pressor control.[4,110,111,113,119] Dopamine has no propensity to improve renal function or alter outcome and can no longer be patently endorsed.

* References 4, 9, 106, 112, 119, 121, 122, 126–128.

258.5.5 Management of Electrolyte and Acid-Base Disorders

Hyperkalemia is a common and life-threatening electrolyte disorder in animals with acute uremia. Severity of hyperkalemia and its associated cardiac and neuromuscular disturbances dictate the therapeutic approach. Options for the management of hyperkalemia are to antagonize the increased resting potential in cardiac myocytes, redistribute potassium from the extracellular to the intracellular fluid compartments, and eliminate the potassium load from the body (Table 258-2).

Severe hyperkalemia (>8 mmol/L) is associated with life-threatening cardiac arrhythmias and conduction disturbances that are accentuated by rapid increases in serum potassium and the degree of hyponatremia. To immediately resolve these threats, calcium gluconate (10 % solution) can be administered at 0.5 to 1.0 mL/kg as a slow intravenous bolus over 10 to 15 minutes to increase the threshold potential for cardiac excitation (see Table 258-2).[133–135] Calcium chloride is not an appropriate substitute because of its potency, acidifying tendency, and irritation if injected extravascularly. Rapid injection of calcium solutions may cause hypotension and cardiac arrhythmias; therefore arterial blood pressure and electrocardiogram (ECG) monitoring should be established during calcium administration. The infusion should be halted temporarily if S-T segment elevation, Q-T interval shortening, progressive bradycardia, or hypotension is observed. The effects of calcium infusion on the myocardium are rapid in onset but short lived (approximately 25 to 35 minutes), and it has no effect on serum potassium concentrations. Calcium infusion should be regarded as a *stopgap* to counteract conduction disturbances until longer-lasting controls can be initiated.

Once the cardiotoxicity has been controlled, transient lowering of serum potassium can be achieved by promoting its translocation from the extracellular to the intracellular fluid compartment with sodium bicarbonate or insulin and glucose administration. During these temporary reprieves from the hyperkalemia, additional measures must be initiated to provide long-term regulation of serum potassium. 1745 1746

Table • 258-2 Management of Hyperkalemia in Acute Renal Failure

THERAPY	MECHANISM OF ACTION
Mild Hyperkalemia (<6.0 mEq/L)	
IV fluids (0.9% saline, lactated Ringer's)	Plasma volume expansion, dilutes K+, and increases GFR and renal potassium excretion
Kayexalate 2g/kg in 3–4 divided doses PO with 20% sorbitol; may also be given as retention enema without sorbitol	Exchanges K+for Na+across the intestinal mucosa
Moderate Hyperkalemia (6.0 to 8.0 mEq/L)	
Sodium bicarbonate 1–2 mEq/kg IV slowly over 20 minutes	Translocates K+to intracellular space in exchange for H+
Dextrose (20%-50%) 1.5 g/kg IV bolus	Stimulates insulin release, which promotes transcellular entry of K+into cells
Regular insulin and dextrose (20%-50%) Insulin @ 0.1–0.25 U/kg plus Dextrose @ 1–2 g/U IV	Promotes transcellular entry of K+ into cells
Severe Hyperkalemia (>8.0 mEq/L)	
Calcium gluconate (10%) 0.5–1.0 mL/kg over 10–15 minutes; monitor the ECG during administration	Specific antagonist of the cardiotoxic effects of K+
Hemodialysis/peritoneal dialysis	Whole-body clearance of excessive potassium load

Moderate hyperkalemia (6.0 to 8.0 mmol/L) may resolve naturally after induction of diuresis. If diuresis cannot be established or serum potassium cannot be controlled with furosemide administration, all potassium-containing parenteral fluids should be replaced with solutions devoid of potassium. Sodium bicarbonate should be given to correct any existing deficit. Sodium bicarbonate can be administered empirically at 1 to 2 mmol/kg intravenously over 20 minutes in the absence of serum bicarbonate measurements (see Table 258-2). Therapeutic effects begin within 10 minutes and may persist for 1 to 2 hours.[133–135] Bicarbonate administration increases extracellular pH, which translocates potassium into cells in exchange for hydrogen ions.[133,134] Sodium bicarbonate is contraindicated in animals with metabolic alkalosis and is risky in overhydrated animals. Sodium bicarbonate administration may lower serum calcium concentration and precipitate a hypocalcemic crisis in animals with pre-existing hypocalcemia. Recent studies have shown equal efficacy for either hypertonic sodium chloride or sodium bicarbonate to reduce serum potassium and cardiac toxicity in dogs with artificially induced hyperkalemia.[136,137]

Hypertonic (20%) glucose can be administered at 0.5 to 1.5 g/kg intravenously as an alternative to sodium bicarbonate. Glucose stimulates insulin release and promotes the transcellular uptake of potassium. Alternatively, regular insulin can be given at 0.25 to 1.0 U/kg intravenously in combination with intravenous glucose at 1 to 2 g/U of administered insulin.[133,134] The effects of bicarbonate and glucose and insulin are more sustained than the effects of calcium but must be repeated as clinical circumstances dictate until the potassium load is alleviated.

Mild hyperkalemia (<6.0 mmol/L) is rarely problematic but should be monitored at 8-to 12-hour intervals. Mild hyperkalemia generally resolves with initial (potassium free) replacement fluids and routine furosemide or bicarbonate administration (or both). For long-term control in pets with refractory hyperkalemia, sodium

polystyrene sulfonate resin (Kayexalate) may be given orally at 2 g/kg in 3 to 4 divided doses as a suspension in 20% sorbitol (to prevent constipation). The resin can also be used as a retention enema suspended in water in animals unable to tolerate oral administration. The resin exchanges sodium for potassium secreted into the intestinal lumen to promote increased intestinal potassium clearance. Exchange resins are effective at controlling low-grade hyperkalemia, but have little efficacy in the management of the associated cardiotoxicity. The acceptability of these preparations is low due to persistent side effects including nausea, constipation, GI ulceration, and necrosis.

If conventional therapy fails to provide an immediate or lasting resolution for the hyperkalemia, peritoneal or hemodialysis is indicated as alternative therapies (see Renal Replacement Therapy).

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258.5.6 Hypokalemia

Hypokalemia may develop during the diuretic stage of ARF if renal potassium losses exceed potassium intake. The use of diuretics, inadequate dietary intake, vomiting, and diarrhea contribute to its development. Hypokalemia is usually asymptomatic, but clinical signs may be noted if the serum potassium concentration is less than 2.5 mmol/L. Muscle weakness, fatigue, vomiting, anorexia, GI ileus, and cardiac arrhythmias may become apparent. Ventroflexion of the neck is observed commonly in cats.

Oral potassium supplementation at 1 to 3 mmol/kg/day is usually sufficient in animals that are able to eat. Guidelines for parenteral potassium supplementation are based on the severity of hypokalemia. Serum potassium rarely is less than 2.0 mmol/L in animals with acute uremia, and maintenance fluids containing potassium concentrations between 20 and 30 mmol/L are usually sufficient to restore normokalemia. Potassium supplementation, including that in maintenance fluids, should be provided cautiously in uremic animals. Serum potassium should be evaluated frequently to avoid hypokalemia or hyperkalemia.

258.5.7 Acid-Base Imbalances

Metabolic acidosis is the most common acid-base disorder in uremic animals. Mild metabolic acidosis (serum bicarbonate >16 mmol/L) will often resolve after fluid replacement and the onset of diuresis. Moderate to severe metabolic acidosis (serum bicarbonate <16 mmol/L) should be treated with intravenous sodium bicarbonate. Initial treatment should be directed at correcting serum pH and serum bicarbonate to approximately 7.2 and 14 to 16 mmol/L, respectively. The initial bicarbonate replacement dose (mmol) = [body weight (kg) ×0.3 × bicarbonate deficit (desired bicarbonate–measured bicarbonate)]. One half of the calculated replacement is administered intravenously over 20 to 30 minutes, and the remainder is provided with intravenous fluids over 2 to 4 hours if arterial pH is less than 7.2 after distribution (30 to 60 minutes) of the initial bolus.[108,134,138]

Full equilibration of the initial bicarbonate dose requires 2 to 4 hours, but most uremic animals have an ongoing requirement for sodium bicarbonate of approximately 80 to 90 mg/kg/day to offset production of metabolic acids. Consequently, bicarbonate should be reassessed after administration of the initial replacement dose and at least once daily to determine if therapy has been adequate or additional therapy to normalize serum bicarbonate concentration is required. Excessive sodium bicarbonate administration can promote metabolic alkalosis, volume overload, pulmonary edema, and hypertension. Serum potassium and ionized calcium concentrations may decrease precipitously with overcorrection of the acidemia causing secondary hypoventilation, hypercapnia, shift in oxyhemoglobin dissociation, reduced tissue oxygen delivery, and paradoxic cerebral acidosis after rapid increases in serum pH.[108,134,138] Alternative alkalizing agents,

including sodium acetate, sodium lactate, sodium or potassium citrate, and calcium carbonate, require hepatic metabolism to generate bicarbonate and offer no advantage to that of sodium bicarbonate.

Mild to moderate metabolic alkalosis (serum bicarbonate >26 and <35 mmol/L) resolves with administration of normal saline or balanced electrolyte solutions to correct the ECF fluid volume and chloride deficits and with the onset of diuresis. Protracted vomiting must be controlled with antiemetics to prevent persisting metabolic alkalosis. Respiratory acid-base disorders are seen in animals with concurrent pulmonary complications. Management of the respiratory component requires correction of the underlying pulmonary or pleural disease (or both) and appropriate regulation of ventilation and oxygenation. Sodium bicarbonate is not an appropriate therapy for the acidemia of respiratory origins.

258.5.8 Uremia Intoxications

Uremia toxins must be removed from the body by restoration of excretory function, intensive fluid diuresis, or dialysis to resolve the signs attributable to the azotemia. Immediate recovery of excretory function is rarely possible in advanced forms of acute uremia, and symptomatic therapies must be provided to ameliorate the uremic intoxications (Table 258-3).

258.5.8.1 Oral and Gastrointestinal Complications

Oral hygiene, uremic stomatitis, and oral ulcerations can be improved dramatically by rinsing the oral cavity every 6 to 12 hours with solutions or gels containing 0.1% to 0.2% chlorhexidine. This therapy reduces the bacterial contamination of the oral cavity, helps prevent and heal oral ulcers, and relieves the discomfort associated with the stomatitis and lingual necrosis. Pain from lingual necrosis or severe ulceration can be managed further with topical lidocaine preparations.

Antiemetic therapy is required to manage fluid and electrolyte imbalances, nutritional needs, and the discomfort associated with protracted vomiting. All oral fluids, medications, and food should be discontinued until vomiting ceases for 12 to 24 hours. H_2-receptor antagonists such as cimetidine, ranitidine, and famotidine have become mainstays for the management of gastritis, vomiting, and gastric ulceration (see Table 258-3).[70,139] They reduce gastric acid production by blocking the histamine receptor on gastric parietal cells and also reduce pepsin production, which may promote gastric ulcer formation. H_2-receptor antagonists undergo 50% to 70% renal elimination, and dosing should be reduced in proportion to the degree renal failure to prevent side effects. Omeprazole is a potent inhibitor of gastric acid secretion and acts by irreversible inactivation of H^+/K^+-ATPase activity to prevent secretion of hydrogen ions into the stomach.[139] Omeprazole reduces acid secretion in the dog for up to 24 hours; however, expense may limit its widespread application.

Oral antacids are of limited value to reduce gastric acidity due to their frequent dosing requirement. Their usefulness is limited further in animals with protracted vomiting. Sucralfate is a basic aluminum salt of sucrose octasulfate used to manage gastric ulceration. It binds tightly to exposed protein in gastric ulcers to form a protective barrier against pepsin, acid, bile, or pancreatic secretions. Sucralfate also stimulates mucus and bicarbonate secretion and mucosal prostaglandin production to improve microvascular integrity and mucosal blood flow. The efficacy of sucralfate is limited in animals that cannot tolerate oral medications. Medical therapy is typically continued for 2 to 3 weeks but may need to be extended in animals with severe gastritis after antifreeze ingestion or severe uremia. Management of the gastritis generally controls vomiting if excretory function can be restored quickly and the azotemia resolved.

Centrally acting antiemetic therapy should be considered if vomiting cannot be controlled by restricted oral intake and treatment of the gastritis (see Table 258-3). Metoclopramide is a D_2-dopaminergic antagonist that directly suppresses the chemoreceptor trigger zone.[139] It also has prokinetic effects on the stomach to promote gastric emptying, which is often delayed in uremic animals. Metoclopramide can be provided by either oral or parenteral routes and is most effective when administered as a constant intravenous infusion (see Table 258-3). Metoclopramide is excreted by the kidneys, and the dose needs modification in animals with severe uremia. Phenothiazine derivative antiemetics (chlorpromazine, prochlorperazine, acepromazine) suppress vomiting through antagonism of α-adrenergic receptors at the CRTZ and the emetic center. They are effective antiemetics in uremic animals but prone to sedative and hypotensive side effects. They should be considered for animals with intractable vomiting in which the adverse effects can be accepted. Serotonin receptor antagonists (ondansetron and dolasetron) provide central antiemetic effects at both the CRTZ and emetic center. They are highly effective for chemotherapy-induced vomiting and may be effective in acute uremia. Prokinetic agents can be used to treat delayed gastric emptying, uremic gastric paresis, and the persistent vomiting.

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Table • 258-3 Therapeutic Agents Used in the Management of Gastrointestinal Uremic Intoxications*

AGENT	INDICATION/MECHANISM	CONVENTIONAL DOSE
Chlorhexidine (CHX-Guard®)	Stomatitis, oral ulceration Bacteriocidal agent	
Cimetidine† (Tagamet® *Smith Kline French*)	Esophagitis, gastritis, gastric ulceration/hemorrhage	5–10 mg/kg PO, IM, IV q4-6h (dog)
	H_2-receptor antagonist	5–10 mg/kg PO, IM, IV q6-8h (cat)
Ranitidine† (Zantac® *Glaxo*)	Esophagitis, gastritis, gastric ulceration/hemorrhage H_2-receptor antagonist	0.5–2.0 mg/kg PO, IV q 8-12h
Famotidine† (Pepcid® *Merck Sharp Dohme*)	Esophagitis, gastritis, gastric ulceration/hemorrhage H_2-receptor antagonist	0.5–1.0 mg/kg PO, IM, IV q 12-24h
Omeprazole (Prilosec® *Merck Sharp Dohme*)	Esophagitis, gastritis, gastric ulceration/hemorrhage H+/K+-ATPase proton pump blocker	0.5–1.0 mg/kg PO q24h
Sucralfate (Carafate® *Marion*)	Esophagitis, gastritis, gastric ulceration/hemorrhage Cytoprotective agent	0.5–1.0 g PO q6-8h (dog) 0.25–0.5 g PO q8-12h (cat)
Misoprostol (Cytotec® *Searle*)	Esophagitis, gastritis, gastric ulceration/hemorrhage Cytoprotective agents-PGE, analogue	1–5 g/kg PO q6-12h
Chlorpromazine (Thorazine ® *Smith Kline French*)	CRTZ, emetic center antiemetic α_2-adrenergic, D_2-dopaminergic, H_1-histaminergic, M_1-cholinergic antagonists	0.2–0.5 mg/kg IM, SQ q6-8h
Prochlorperazine (Compazine® *Smith Kline French*)	CRTZ, emetic center antiemetic α_2-adrenergic, D_2-dopaminergic, H_1-histaminergic, M_1-cholinergic antagonists	0.1–0.5 mg/kg IM, SQ q8-12h
Acepromazine (PromAce® *Fort Dodge*)	CRTZ, emetic center antiemetic α_2-adrenergic, D_2-dopaminergic, H_1-histaminergic, M_1-cholinergic antagonists	0.01–0.05 mg/kg IM, SQ q8-12h
Ondansetron (Zofran® *Glaxo Wellcome*)	5-HT_3 receptor antagonist CRTZ, peripheral vagal nerve	0.1 mg/kg PO q12-24h 0.1–0.3 mg/kg IV q8-12h
Dolasetron (Anzemet® *Hoechst Marion Russel*)	5-HT_3 receptor antagonist CRTZ, peripheral vagal nerve	0.5 mg/kg PO, SQ, IV q24h
Metoclopramide† (Reglan® *Robins*)	CRTZ antiemetic, prokinetic agent D_2-dopaminergic antagonist, $5HT_3$-serotonergic antagonist	0.1–0.5 mg/kg PO, IM, SQ q 6-8h 0.01–0.02 mg/kg/hr CRI

Cisapride (Propulsid® *Jansen Pharmaceutica Inc*)	Prokinetic agent 5-HT_4 receptor agonist, 5-HT_1/5-HT_3receptor antagonist	0.1–0.5 mg/kg PO q8-12h

CRTZ, Chemoreceptor trigger zone; *5-HT,* 5-hydroxytryptamine.

* Most of these drugs have not been approved for use in the dog or cat.

† Agent undergoes renal excretion and the dose must be adjusted accordingly to prevent toxicity.

Uremic bleeding can be fatal if associated with CNS hemorrhage but more commonly causes GI bleeding and anemia. Uremic bleeding improves with resolution of the azotemia after intensive diuresis or dialysis. Transfusion of packed RBCs is indicated for animals with severe anemia and active bleeding and may reduce bleeding time through indirect effects on platelet function.[140] Transfusion of platelet-rich plasma will not improve platelet function or reduce bleeding time, because function of the transfused cells is altered upon exposure to uremic plasma.

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258.5.8.2 Impaired Immunity

Uremia imposes increased susceptibility to infection due to accumulation of toxins that impair immunity and cellular host defenses.[141,142] The deficiencies in host defenses are compounded by widespread breaches of mucosal integrity associated with GI ulceration, intravenous and bladder catheterization, parenteral medications and feeding, and intervention with hemodialysis, peritoneal dialysis, and immunosuppressive drugs.[141] Infection may be difficult to identify because uremia dampens the febrile response. Strict asepsis during catheter placement and meticulous catheter site care are mandatory for uremic animals. If infection is suspected, blood, urine, and catheter tip cultures should be obtained, and broad-spectrum antibiotic therapy initiated pending culture results. Prophylactic use of antibiotics may foster bacterial resistance or "superinfections" and should be prescribed with caution.

258.5.8.3 Pulmonary Signs

Respiratory complications arise mostly from overhydration, infection, and aspiration of gastric fluids during vomiting. Overhydration is treated by cessation of fluid delivery and diuretic administration to achieve an appropriate dry weight. Animals with severe pulmonary edema and oliguria may require removal of the fluid burden by peritoneal or hemodialysis. Bacterial pneumonia is managed with antibiotics and supportive pulmonary care. Aspiration pneumonia should be treated aggressively with antiemetic therapy, parenteral broad-spectrum antibiotics, and supplemental oxygen or ventilatory support, if required. Uremic pneumonitis is a complication of severe azotemia resulting in a respiratory distress syndrome, noncardiogenic pulmonary edema, and respiratory compromise or failure.[75] Uremic pneumonitis is treated supportively with supplemental oxygenation or mechanical ventilation. It has potential to improve with resolution of the azotemia and is an indication for dialysis. Dogs with leptospirosis frequently develop radiographic and clinical signs consistent with uremic pneumonitis that is independent of the severity of the azotemia. The lesions are induced by endothelial damage and vasculitis.[74]

258.5.9 Nutritional Management of Acute Renal Failure

Protein-calorie malnutrition is a component of the acute uremic syndrome. This includes impaired immune function, increased susceptibility to infection, delayed wound healing, decreased strength, and poor quality of

life. The imposed catabolism exacerbates the hyperkalemia, hyperphosphatemia, acidosis, and azotemia. It increases morbidity and mortality.[143,144] Anorexia, nausea and vomiting, comorbid diseases, uremic toxins, insulin resistance, and hyperparathyroidism contribute to the nutritional inadequacies. Metabolic acidosis is a major stimulus for breakdown of muscle protein and amino acid oxidation and contributes to the ongoing catabolism.[145,146]

An accurate assessment of nutritional status is necessary to guide nutritional therapy. Change in body weight is the simplest parameter to assess. This can be flawed by changes in hydration status, lean body mass, or fat stores. Body condition scoring is a useful index to document sequential changes in body composition, but it is only qualitative and subject to hydration errors and experience of the evaluator.[147,148] Bioelectrical impedance analysis is a new, safe, noninvasive, and reproducible method to precisely quantitate changes in total body water, extracellular fluid volume, and body cell mass with potential application in uremic animals.[149,150] Goals of nutritional therapy are to meet the energy and nutrient requirements of the animal; alleviate the azotemia; prevent alterations in fluid, electrolyte, vitamin, mineral, and acid-base balance; and aid the renal repair. The optimal nutritional regime for dogs and cats with ARF has not been defined, but a high-energy and moderate protein, potassium and phosphate formulation as prescribed for CRF is logical. Sufficient energy must be supplied to prevent catabolism of endogenous protein, spare lean body mass, and minimize azotemia. The illness energy requirement for animals with acute uremia is determined as the resting energy requirement times a stress factor (1.2 to 1.4 for uremic dogs and 1.2 for uremic cats). RER is determined according to the following formulae:

$$\text{RER (kcal/day)} = 70(\text{Wt}_{\text{kg}})^{0.75}$$

or

$$\text{RER (kcal/day)} = 70 + (30 \times \text{Wt}_{\text{kg}})$$

(where Wt_{kg} is the body weight in kilograms[151]

Carbohydrate and fat provide the nonprotein sources of energy required in the diet. Commercial diets, liquid enteral formulations, or parenteral solutions designed for the management of renal failure can be used. These formulations contain a relatively high fat content to increase energy density, and they should be introduced slowly to prevent GI complications, especially pancreatitis.

The optimal protein requirement for animals with acute uremia is not known and is likely to be influenced by underlying and coexistent clinical conditions. Consequently, the minimum protein requirements for normal dogs (1.25 to 1.75 g/kg/day; approximately 8% to 10% protein on a ME basis) and cats (3.8 to 4.4 g/kg/day; approximately 20% to 25% protein on a ME basis) are generally adopted for uremic animals. This degree of restriction may not be necessary or desired in animals with mild or moderate azotemia or greater catabolic stresses, where more liberal protein prescriptions may be needed. Phosphorus, sodium, potassium, and magnesium intake should be restricted to prevent accumulation of these minerals; however, intake must be modified according to the clinical and biochemical dictates of the animal.

Delivery of adequate nutrition is constrained by inappetence and the GI complications of uremia. Oral or enteral feeding may not be possible or recommended in the initial stages of ARF due to gastritis, pancreatitis, or uncontrolled vomiting. Peripheral parenteral nutrition or total parenteral nutrition is indicated under these circumstances to provide interim nutritional support.[152] Peripheral parenteral nutrition is formulated with isotonic solutions administered through a peripheral vein. However, complete nutritional requirements cannot be met by this technique. It should only be used as an adjunct to oral intake or to supply partial nutritional

support not to exceed 5 days. Total parenteral nutrition is formulated to provide all essential nutrients for indefinite periods but requires central venous administration due to the hypertonicity of the nutrient solutions.

Oral or enteral tube feeding is recommended in animals that are not vomiting but fail to achieve caloric requirements. The indications, complications, and technical aspects of enteral feeding have been reviewed recently.[151] Esophageal feeding tubes or percutaneous gastrostomy tubes are invaluable aids for the long-term nutritional support of animals that are likely to have prolonged recovery times. Caloric and protein requirements can be met readily by the intermittent or continuous administration of blended therapeutic diets or liquid enteral preparations formulated for the management of renal insufficiency.[151] The clinical benefits of enteral or parenteral nutrition cannot be overemphasized, but it may not be possible to supply the volume required to achieve the nutritional requirements in oliguric animals without dialysis to alleviate overhydration.

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258.5.10 Renal Replacement Therapy

ARF is the most common indication for dialytic intervention in dogs and cats, and modern dialysis equipment and procedures are well suited for uremic animals.[77,104,105] Medical therapies cannot approach the efficacy, efficiency, and clinical benefits that dialysis provides. Without dialysis, animals with severe uremia generally die within 5 to 7 days precluding sufficient opportunity for regeneration or repair of the renal injury. Dialysis extends the life expectancy of uremic animals facilitating their potential for recovery. Peritoneal dialysis uses the peritoneal lining as a dialytic exchange surface across which diffusive and osmotic forces transfer toxic wastes and excessive fluid from the blood to a dialysate solution instilled in the abdominal cavity.[104,108,153] It is a conceptually simple technique applicable in both general and specialty practice but can be a deceptively intensive and fraught with technical and clinical complications.[104,154] Continuous renal replacement therapy (CRRT) is a noninterrupted extracorporeal procedure using hemofiltration for solute and fluid removal. CRRT is less demanding technically than intermittent hemodialysis. It is generally provided in intensive care settings for patients with profound clinical and hemodynamic instability.[121,155] The technical and clinical lure of CRRT has captured the interest of veterinary critical care specialists for the management of acute uremia. Intermittent hemodialysis is the standard extracorporeal therapy for acute uremia in humans and animals. The fluid, electrolyte, and acid-base abnormalities are corrected, and the accumulated uremia solutes are removed from the body by diffusive and convective gradients between blood and the dialysate solution in the artificial kidney.[77,104,105] Hemodialysis has become a routine therapy for severe uremia in both dogs and cats.

Immediate renal replacement therapy is indicated when the clinical consequences of the azotemia, inadequate urine production, and the fluid, electrolyte, and acid-base disturbances cannot be managed with medical therapy alone. General guidelines for patient selection and indications for dialytic therapy are outlined in Box 258-3. Hemodialysis (and peritoneal dialysis and CRRT therapies) can resolve virtually all excretory deficiency of acute uremia.

258.5.10.1 Box • 258-3 Indications for Dialytic Therapy in Animals

258.5.10.1.1 Acute Uremia:

1. Anuria
2. Failure of fluid administration or diuretic therapy to initiate an adequate diuresis

3. Failure of conventional therapy to control the azotemia or the biochemical and clinical manifestations of acute uremia
4. Life-threatening fluid overload
5. Life-threatening electrolyte or acid-base disturbances
6. BUN > 100 mg/dL; serum creatinine > 10 mg/dL
7. Clinical course refractory to conservative therapy for 12–24 hours

258.5.10.1.2 Miscellaneous:

1. Severe overhydration; pulmonary edema; congestive heart failure (CHF)
2. Acute poisoning/drug overdose

To date, failure to recover renal function after 1 to 4 weeks of conventional medical support have been used as benchmarks to predict irreversible from reversible renal failure in animals. However, these criteria have been redefined with the advent of hemodialysis, and many animals with seemingly irreversible disease at the outset of medical management can recover renal function if supported by dialysis beyond the 4-week limit.

258.5.10.2 Azotemia

Even severe azotemia can be corrected completely with just a few hemodialysis sessions, but the expediency of its resolution must be tempered by the tolerance of the animal to rapid changes in serum solute concentrations. Both peritoneal dialysis and CRRT procedures produce a more gradual and continuous resolution of the azotemia throughout the first 2 to 3 days of therapy. For animals that do not recover within this time period, CRRT must be transitioned to intermittent hemodialysis for long-term support.

258.5.10.3 Electrolyte Disturbances

Dialysis is indicated in patients where medical treatments provide only transient resolution of the hyperkalemia and no relief of the excessive potassium load for long-term control. Life-threatening conduction disturbances are frequently corrected within minutes of starting hemodialysis despite the absence of perceptible changes in peripheral blood potassium concentration, thus providing both an immediate and prolonged solution to hyperkalemia.

Abnormalities of other electrolytes or minerals resulting from the uremia, comorbid diseases, or therapy, can be corrected by formulating the dialysate to approximate the serum concentration desired for each solute at the end of the dialysis session. The bicarbonate concentration of the dialysate can be increased above reference values to promote accrual of depleted buffer reserves and to supplement impaired renal bicarbonate generation.

258.5.11 Correction of Fluid Excesses

Excessive fluid load can be removed readily by ultrafiltration using intermittent hemodialysis or CRRT, or by osmotic gradients with peritoneal dialysis. Slow rates of ultrafiltration between 5 to 10 mL/kg/hr generally are tolerated. Increased rates of fluid removal are possible but require careful assessments of the animal's hemodynamic condition and use blood volume monitoring equipment.

258.5.12 Acute Intoxications

Hemodialysis should be considered for the immediate management of acute poisoning when the toxin is dialyzable, when antidotal therapy has been delayed, or when no specific antidote to the intoxication is available. Hemodialysis is indicated specifically for the treatment of common poisonings including ethylene glycol, methanol, salicylate, lithium, ethanol, phenobarbital, acetaminophen, theophylline, aminoglycosides, tricyclic antidepressants, and possibly metaldehyde.[77,104,105] Peritoneal dialysis and CRRT procedures may be capable of removing a variety of toxins, but these treatments are less efficient than hemodialysis and do not represent satisfactory substitutes.

Hemodialysis will rapidly eliminate ethylene glycol and its metabolites from animals poisoned with antifreeze (Figure 258-7). It should be initiated without any delay as the principal therapy to resolve the intoxication and to support the accompanying fluid, electrolyte, and acid-base disorders associated with the toxicosis.[77] For acute poisoning (within 5 to 6 hours), it is possible to remove all the toxin and prevent development of renal injury with a single dialysis treatment.[77,112] If the treatment is delayed beyond this window, renal injury may be expected, and a series of dialysis treatments must be provided to support the uremia and renal repair.

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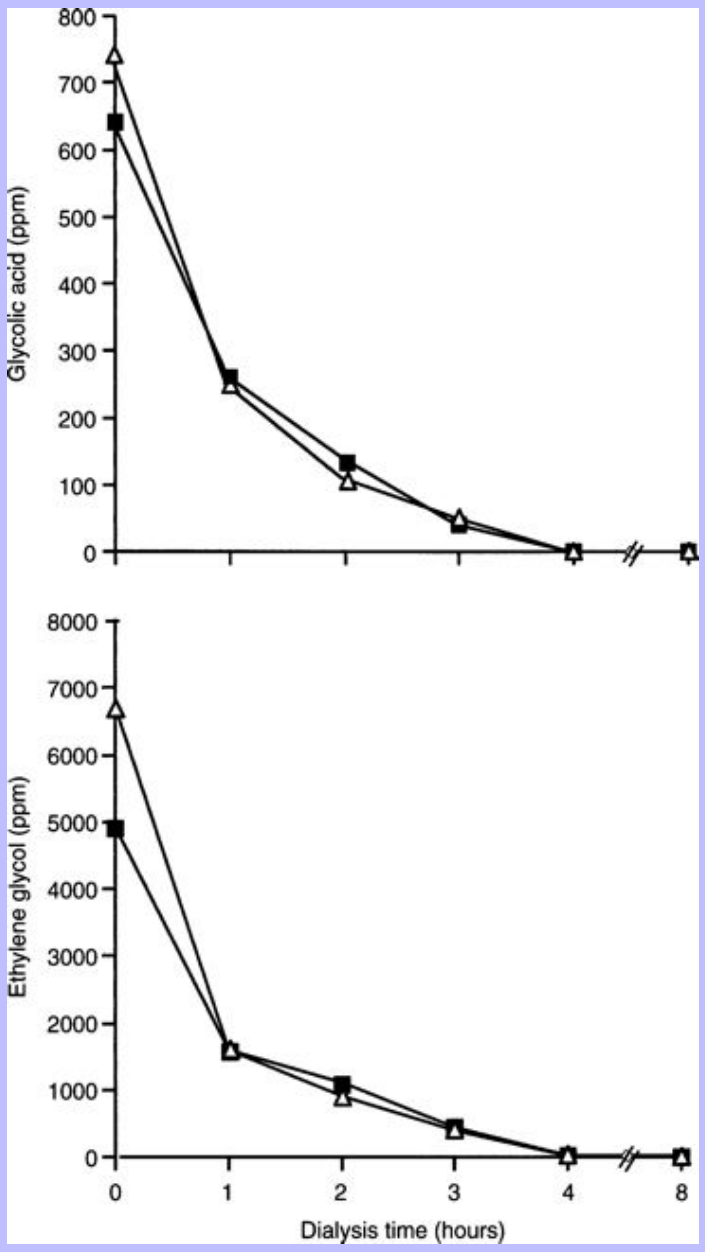
Figure 258-7 Changes in serum glycolic acid *(upper panel)* and ethylene glycol *(lower panel)* concentrations in two dogs treated with hemodialysis after simultaneous exposure to antifreeze 4 to 6 hours before presentation. Despite the extremely high initial concentrations of these toxins, both dogs recovered uneventfully with no evident renal injury after a single dialysis treatment.



Transplantation of renal allografts from unrelated dogs and cats has become more successful in the past 10 years and provides an alternative renal replacement option for animals that sustain irreparable renal injury.[156–159] Transplantation early in the course of severe renal injuries (antifreeze poisoning) may prove more cost-effective than a protracted course of dialysis.

258.5.13 Outcome and Prognosis

The prognosis for recovery from acute uremia depends on the cause, extent of damage, comorbid diseases, multiple organ involvement, and availability of diagnostic and therapeutic services. Little documentation exists in the veterinary literature to accurately predict the importance of these independent variables. A recent review of 99 cases of ARF in dogs produced by the usual causes documented a mortality of nearly 60% from death or euthanasia.[11] Nearly 60% of the surviving dogs subsequently developed CRF, and only 44% recovered normal renal function. Severity of the azotemia, hypocalcemia, anemia, proteinuria, specific cause (ethylene glycol intoxication), and comorbid systemic disease (DIC) were associated with failure to survive. In this series, 92% of dogs with a history of ethylene glycol ingestion died or were euthanatized due to the poor prognosis. In another series of 37 dogs with confirmed ethylene glycol intoxication, greater than 95% of those with initial azotemia died, whereas all nonazotemic dogs survived.[160] Survival for dogs with hospital-acquired ARF was reported as 38%, with age and initial urine production as significant predictors of mortality.[161]

In contrast to these outcomes in dogs, 9 of 15 (60%) cats with severe ARF secondary to pyelonephritis and ethylene glycol intoxication that were managed with hemodialysis or transplantation recovered with partial or normal renal function.[31] One hundred percent of cats with acute pyelonephritis survived. In these animals, as in other series, the magnitude of the azotemia at presentation did not predict survivability. Similar to previous reports, a recent review of 138 cases of severe ARF in dogs requiring hemodialysis revealed an all-cause mortality of nearly 60% from death or euthanasia.[62] For the majority of surviving dogs, renal function had been substantially recovered by the time of discharge. Survival from infectious (80%) and hemodynamic and metabolic causes (40%) is more favorable than survival from toxic causes (20%).[62] The outcome for dogs with acute leptospirosis is particularly favorable, with survival approaching 90% with either severe (dialysis dependent) or milder forms (medically managed) of ARF.[85]

ARF is a serious and frequently fatal disease in both dogs and cats. Recovery is best for animals with infectious causes and worst for animals with nephrotoxic causes or multiple organ failure. Early recognition, appropriate fluid therapy, and extended support with dialysis offer the greatest opportunity for a favorable outcome.

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259 CHAPTER • 259 Renal Transplantation

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Chronic renal failure is a progressive, debilitating, and terminal disease. Medical management, although effective initially, is not sufficient for cats with end-stage renal failure. Kidney transplantation offers an avenue of therapy when medical management fails. The first clinical feline renal transplantation was performed in 1987. Several centers now offer this procedure.

259.1 CANDIDATE SELECTION

Ideally, a feline candidate for kidney transplantation should have no medical problems other than kidney failure. Renal diseases appropriately treated with transplantation include acquired conditions (e.g., chronic interstitial nephritis, toxic nephropathy, membranous glomerulonephropathy) and congenital disorders (e.g., renal dysplasia, polycystic kidney disease). Amyloidosis, pyelonephritis, and obstructive nephropathy from calcium oxalate nephrolithiasis are relative contraindications because of potential effects on the transplanted kidney. To avoid injury to the transplanted kidney, cats with ethylene glycol–induced renal failure should not be considered for transplantation until the ethylene glycol and its metabolites have been completely eliminated from the body. Hemodialysis may be necessary to ensure elimination of these metabolites.

An extensive diagnostic evaluation (Box 259-1) should be performed prior to transplantation to identify contraindications to the procedure. These tests commonly are performed locally, especially if significant travel to a transplantation center otherwise would be necessary, to avoid needless travel and expense for the owners of cats that turn out to be poor candidates.

The immunosuppression necessary to prevent graft (renal) rejection in an animal that previously has had pyelonephritis, a bacterial urinary tract infection (UTI), or an indwelling catheter may “reactivate” a latent infection. Infection may cause pyelonephritis in the transplanted kidney and activation of the rejection process.[1] Also, these animals are predisposed to overwhelming systemic infection. Such cats therefore are not ideal candidates, and a 1-to 3-week “test” course of cyclosporine (CyA) and prednisone prior to transplantation is recommended.[2] If urine culture results are positive after such a trial, transplantation should not be performed.

Another potential contraindication to kidney transplantation is inflammatory bowel disease (IBD). The variability of absorption of CyA in cats with IBD increases the risk of rejection. Inflammatory bowel disease may also heighten immune system activation, making immunologic attack on the transplanted kidney more likely.[1] Cats infected with the feline leukemia virus (FeLV) or the feline immunodeficiency virus (FIV) should also be excluded as candidates because of their increased susceptibility to infection.

The immunosuppression associated with renal transplantation has resulted in activation of *Toxoplasma* tissue cysts and clinical disease in several cats. An attempt should be made to assess carefully both the donor and the recipient for toxoplasmosis. A positive toxoplasmosis titer does not determine whether active infection is present. A serologically positive recipient must be considered at higher risk. A seropositive donor should not be used for a seronegative recipient.

A thorough cardiac evaluation, including thoracic radiographs, an electrocardiogram (EKG), and an echocardiogram, should be performed prior to transplantation surgery. Because of the shortened anticipated life span associated with significant cardiac disease, cats with congestive heart failure or diffuse hypertrophy are eliminated as candidates. Intolerance of aggressive fluid therapy or focal hypertrophy are relative contraindications and must be evaluated in light of the entire clinical picture.[2]

Other conditions likely to affect renal function or patient longevity, including uncontrolled hyperthyroidism, diabetes mellitus, or neoplasia, should exclude any cat from consideration for renal transplantation. Hypertension affects about 30% of feline transplantation candidates.[3] Prior to transplantation, antihypertensive therapy should be titrated to control blood pressure.[2] Intensive handling is necessary, particularly in the immediate postoperative period, therefore fractious cats should not undergo transplantation, because they will not tolerate the level of care necessary for a good outcome.

Transplantation is appropriate when medical management fails to maintain the cat in satisfactory condition. It can be difficult to determine the point of decompensation, but good guidelines include weight loss, the development of anemia, or worsening azotemia. Some programs suggest transplantation when a certain creatinine level has been exceeded (e.g., 4 mg/dL). Despite the uncertainty involved in determining the best time for transplantation, a lengthy delay from decompensation to transplantation must be avoided. Severe debilitation with excessive weight loss (greater than 25%) and chronic uremia reduces the success rate of transplantation. Transplantation is not a salvage operation, and cats that are severely debilitated should not be considered for it. Attempts to reverse the debilitation in these cats with enteral nutrition via a feeding tube have been disappointing.[1] Hemodialysis to control azotemia and uremic symptoms has been quite successful, but peritoneal dialysis is not advised because of frequent complications, including peritonitis.

259.2 DONORS

Because sufficient renal function can be provided even by a portion of just one kidney, unilateral nephrectomy for kidney donation does not diminish the quality of life or life span of the donor.[4] Kidney donors should be young cats that have been screened to ensure their general health (i.e., complete blood count [CBC], chemistry panel, urinalysis, and urine culture) and lack of infectious disease (FeLV, FIV, toxoplasmosis).

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259.2.1 Box • 259-1 Diagnostic Testing for Candidates for Renal Transplantation

The following diagnostic tests should be performed for any animal being considered for renal transplantation:

- Complete blood count (CBC)
- Chemistry panel
- Thyroid level determination
- Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) testing (cats)
- Blood typing
- Electrocardiogram (EKG) and echocardiogram

- Thoracic radiographs
- Abdominal ultrasonography
- Toxoplasmosis titer
- Urinalysis and culture
- Blood pressure measurement

An intravenous pyelogram allows evaluation of renal structure. Donor cats ideally are the same size or bigger than the recipient, but no more than 0.5 kg smaller. Most programs require the recipient family to adopt the donor cat.

259.3 PREOPERATIVE MANAGEMENT

The cat that is to receive a new kidney (the recipient) should be admitted to the hospital several days prior to the scheduled transplantation surgery. The recipient is cross-matched to several potential donors, and any further evaluation of the donor or recipient should then be completed. Intravenous fluids are given at a rate that maintains hydration or that provides diuresis if the blood urea nitrogen (BUN) is greater than 100 mg/dL. If anemia has not been corrected by previous erythropoietin therapy, blood transfusions can be given to achieve a target packed cell volume (PCV) of 30% or higher. Cyclosporine (NeOral, 3 to 4 mg/kg given orally twice daily) is administered starting 1 to 2 days before surgery. Prednisone (1 mg/kg given orally twice daily) is started the day of surgery. Enteral nutrition is provided by feeding tube if the recipient cat is not eating voluntarily. Blood samples for determination of CyA concentrations are submitted the morning of surgery.

259.4 DONOR SURGERY

If kidney preservation methods are not used, anesthesia is induced in the donor cat approximately 30 minutes before induction in the recipient. The donor is given mannitol (0.25 to 1 g/kg) intravenously prior to harvesting the kidney to protect against acute tubular necrosis associated with warm ischemia.[5] The left kidney is preferred for transplantation because of the longer renal vein. If two renal veins are present, the smallest is ligated and the largest prepared for anastomosis. Kidneys with two renal arteries are usually avoided in cats because both would need to be preserved to ensure adequate renal blood flow. Preservation and anastomosis in dogs with two renal arteries has been reported.[6]

Once the recipient vessels have been prepared, the donor kidney is removed and flushed with ice-cold heparinized saline solution. The surgical team working with the donor closes the abdominal incision while the team working with the recipient performs the vascular anastomosis. If preservation methods are used, the donor kidney is removed, flushed with a storage medium, and stored in solution on ice until the recipient has been prepared. Hypothermic preservation of the harvested kidney has been reported in cats with storage times of up to 7 hours.[7] The advantages of cold preservation include the need for only one surgical team, the additional time available for vessel preparation after kidney harvest, and the longer time before ischemic injury occurs during anastomosis.[5,7]

259.5 RECIPIENT SURGERY

Magnification (×3 to ×10) is required for anastomosis of the vessels and ureters in small dogs and cats. In dogs, the left common iliac vein is sutured to the renal vein in an end-to-side manner, and the iliac and renal arteries are sutured end-to-end. This technique was also initially reported for use in cats; however, it has been associated with neuropraxia and lameness of the pelvic limb on the side of the anastomosis.[9] The technique currently preferred in cats is an end-to-side anastomosis of the renal vein to the caudal vena cava and of the renal artery to the aorta. The time from occluding blood flow to the kidney for harvesting to release of the vascular clamps after anastomosis (warm ischemia time) should be kept to less than 60 minutes.[8]

Several techniques have been described for implantation of the donor ureter into the recipient bladder. A drop-in technique initially was used in cats, because the small diameter of the feline ureter (0.4 mm) makes primary anastomosis technically difficult.[10] With this intravesical technique, a ventral cystotomy is performed, and the ureter is brought into the bladder through a small incision in the dorsal bladder wall. The distal end of the ureter is either attached to the inside of the bladder with a single suture or left free in the bladder lumen. Obstruction of the ureter by granulation tissue was a frequent complication of this technique, therefore it has been replaced by the mucosal appositional technique.[11]

For mucosal apposition, an operating microscope is used to allow visualization of the distal end of the ureter, which is incised longitudinally and then sutured to the bladder mucosa in a simple interrupted pattern. Ureteral obstruction is less common with this technique; however, partial obstruction may still be seen in the immediate postoperative period. An extravesical technique was recently described and may reduce the incidence and severity of postoperative obstruction. With this procedure, a seromuscular incision is made in the ventral surface of the urinary bladder, avoiding a large cystotomy, and a small incision is made in the mucosa at the caudal aspect of the seromuscular incision. The ureteral mucosa is sutured to the bladder mucosa, and the seromuscular layer is closed. In dogs either the intravesical or extravesical mucosal appositional technique can be used.[6]

Before the abdomen is closed, the transplanted kidney is stabilized to the body wall by suturing of the kidney capsule to a pocket in the retroperitoneal membrane or to a muscle flap created in the transversus abdominis muscle.[5,8] This helps prevent graft torsion and vessel avulsion in the postoperative period. In dogs, the native kidneys are usually removed to minimize systemic hypertension unless delayed graft function is suspected.[6] The native kidneys are usually preserved in cats. In all recipients, biopsy of one of the native kidneys should be performed.

259.6 PERIOPERATIVE MANAGEMENT AND COMPLICATIONS

Postoperative treatment should include fluid therapy, immunosuppressive drugs, analgesia, and careful monitoring of the hematocrit, electrolyte balance, and cardiovascular status.

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Blood pressure should be monitored every 1 to 2 hours after surgery for the first 48 hours. Hypotension in the postoperative period is dangerous to graft function because of decreased renal blood flow and an increased risk of vessel thrombosis. Hypertension is also dangerous in the postoperative period because it has been associated with central nervous system (CNS) disorders, including seizures.[12] The urine specific gravity and serum BUN and creatinine concentrations should be monitored daily, and these parameters usually improve within 12 to 72 hours after surgery.[8]

Complications seen in the immediate postoperative period may include vessel torsion, hemorrhage, or thrombosis; ureteral leakage or obstruction; malignant hypertension; neurologic abnormalities; and delayed graft function.[12,13] Delayed graft function associated with ischemia-reperfusion injury or partial ureteral obstruction results in lack of improvement in kidney function after surgery. If improvement is not seen within a few days of surgery, abdominal ultrasonography should be performed to assess blood flow in the renal vessels and to evaluate the transplanted ureter for dilatation, which may indicate obstruction. Complete ureteral obstruction or leakage of urine from the ureteroneocystostomy site would require additional surgery to correct the abnormality. Intestinal intussusception has been reported in dogs after transplantation.[6]

259.7 IMMUNOSUPPRESSION

Cyclosporine is a calcineurin inhibitor that blocks the transcription of interleukin-2 (IL-2), impairing T-helper and T-cytotoxic lymphocytes. CyA is not myelosuppressive and has no effect on nonstimulated lymphocytes, thus preserving nonspecific host resistance to infection. The decrease in IL-2 also results in a decrease in other mediators that cause rejection. Prednisone and CyA are synergistic and inhibit T-cell proliferation.

CyA is available as a microemulsified form (NeOral, Novartis Pharma AG, Switzerland; Gengraf, Sangstat Medical Corp., Cambridge, MA). The bioavailability of this formulation is greater and less variable than that of the nonmicroemulsified formulation (Sandimmune, Norvartis), primarily because of more reliable gastrointestinal (GI) absorption. These forms are not interchangeable. The oral form is bitter and should be put in a gelatin capsule. CyA is also available as an intravenous formulation. All forms of CyA must be protected from light.

CyA is cleared by the cytochrome p-450 system. Drugs that induce p-450 enzymes (e.g., phenobarbital) reduce CyA levels. Drugs that compete for clearance by p-450 (e.g., cimetidine, ketoconazole, erythromycin) increase CyA levels. Ketoconazole increases blood levels of CyA twofold in cats and twofold to threefold in dogs.[14,15] Although this reduces the dosage of CyA needed to maintain therapeutic levels, the individual variations in effect and the risk of hepatotoxicity are undesirable. Certain drugs, such as ranitidine, aminoglycosides, trimethoprim, or sulfamethoxazole, can potentiate renal damage.

Because of variations in absorption and metabolism and because the therapeutic window is relatively narrow, CyA blood levels must be closely monitored. The appropriate target range depends on the methodology, sample type, and time after transplantation. Whole blood levels are generally higher than plasma levels, because CyA is extensively bound to the red blood cells. High-performance liquid chromatography (HPLC) provides the most reliable results. Other methods, including immunoassays that use polyclonal or monoclonal antibodies, measure the parent compound and metabolites, which vary in their immunologic effect. Trough levels of 400 to 600 ng/mL as measured by HPLC in whole blood are recommended for the first month. After the first 1 to 3 months, the CyA dosage can be reduced to achieve trough levels of 350 to 450 ng/mL. Fluorescent immunoassay (TDx-FLx assay) yields whole blood levels 1.5 to 4.2 times higher.[5] If HPLC is not readily and reliably available, comparison of HPLC to TDx-FLx values in a minimum of three samples in an individual cat can provide a conversion relationship that allows correct clinical decisions to be made in many cats.[16]

An excess of circulating CyA can cause nephrotoxicity. In humans, values above 1000 ng/mL are associated with azotemia, but many cats tolerate higher levels (up to 3000 ng/mL) before renal toxicity becomes apparent.[17] In contrast, some cats have developed CyA nephrotoxicity at trough levels of 700 to 800 ng/dL.[5] The serum creatinine concentration rarely exceeds 2 to 3 mg/dL from CyA toxicity. Increases in the serum creatinine

concentration usually occur 1 to 2 days after the CyA level reaches high values and normally decline within 1 to 2 days of a decrease in the drug to acceptable levels.[5] Adverse effects of CyA in cats include mild GI signs. Dogs may exhibit gastrointestinal irritation, weight loss, gingival hypertrophy, papillomatosis, shedding, and hypertrichosis.

Prednisone is a standard component of transplantation immunosuppression. It inhibits production of some cytokines (IL-1, IL-6, gamma interferon) that are essential for T-cell production and function. Prednisone also inhibits production of local chemotactic factors, prostaglandins, thromboxanes, and leukotrienes. By 1 month after surgery, the initial dosage of 1 mg/kg given every 12 hours can be reduced to 0.5 to 1 mg/kg given orally every 24 hours. Other immunosuppressive drugs are rarely used in feline renal transplant recipients. Azathioprine (0.3 mg/kg given orally every 3 days) has been used in a few cases, but myelosuppression is a potential problem associated with this drug. In dogs, azathioprine has been used successfully with CyA and prednisone, but hepatotoxicity and pancreatitis are noted side effects. Leflunomide analogs are showing promise, but the expense makes this drug unlikely to become the first-line drug of choice.

259.8 MONITORING

Weekly examination is recommended for the first month after transplantation. At each examination the BUN, creatinine, cyclosporine levels, PCV, and body weight are evaluated. The owner should bring in a urine sample for assessment of the urine specific gravity; cystocentesis and urinary catheterization should be avoided to reduce the risk of inducing urinary tract infection. Each examination should be arranged so that a trough CyA level can be drawn. The owner should administer the next dose immediately after blood sampling to maintain the dosing schedule.

As the cat clinically improves and the CyA levels stabilize, examinations are reduced to every 2 weeks for a month, then monthly for 3 months. At that point, quarterly examinations are usually sufficient. Urine culture, complete chemistry panel, and CBC are performed two to four times a year, and a cardiac consultation should be done yearly. Monthly measurement of antibody titers to *Toxoplasma gondii* for the first 6 months has been recommended.[18]

259.9 COMPLICATIONS

259.9.1 Rejection

Hyperacute rejection from preformed antibodies occurs in the first several hours after transplantation and has not been reported in clinical cases. In the absence of immunosuppression, acute rejection results in destruction of the kidney in 5 to 8 days. Acute rejection is typically reported within the first 2 to 3 months or at any time CyA levels decline to subtherapeutic values. Early clinical signs, which may be vague, include general malaise, vomiting, anorexia, and depression; the serum creatinine concentration may not be elevated in early rejection. Aggressive antirejection therapy should be started with any suspicion of rejection to reduce the damage to the kidney. Intravenous CyA is administered over 4 to 6 hours (i.e., 6.6 mg/kg given every 24 hours, or 4 mg/kg given twice daily diluted in 20 to 100 mL of 0.9% saline or 5% dextrose).[1,5] Intravenous prednisolone sodium succinate (10 mg/kg given every 12 hours) is also administered. Intravenous fluid therapy is administered to maintain hydration. The BUN and creatinine concentrations should improve within 24 to 48 hours. Once these concentrations have normalized and the cat is taking food, intravenous medications can be changed to the oral form.

Chronic allograft nephropathy can be caused by chronic rejection or nonimmunologic factors. Arterial hyperplasia, which leads to graft ischemia, is the predominant lesion of chronic allograft nephropathy. Nonimmunologic factors, such as glomerular hyperfiltration due to small kidney size and a reduced number of nephrons, hypertension-induced vascular injury, and cyclosporine toxicity, have not been recognized as major problems in feline transplantation. Graft survival in cats with chronic allograft nephropathy is about 3 years.

259.9.2 Ureteral Obstruction

Ureteral obstruction caused by stricture formation occurs most commonly 7 to 14 days after surgery. Signs include an increase in the creatinine concentration, a decrease in the urine specific gravity, and a dilated renal pelvis and/or ureter on abdominal ultrasonography. Surgical revision of the neoureterostomy site is indicated. Use of a mucosal apposition surgical technique has markedly reduced the incidence of this complication. Obstruction secondary to retroperitoneal fibrosis, an uncommon cause, occurs at $1^{1}/_{2}$ to 5 months after surgery.

259.9.3 Neurologic Signs

A variety of neurologic signs can be encountered in the postoperative period, including seizures, disorientation, obtundation, or coma.[19] In humans, several potential causes have been identified, including infection, hypertension, CyA toxicity, hypomagnesemia, uremic encephalopathy, erythropoietin therapy, and underlying neurologic disease.[12] Cyclosporine has been associated with postoperative neurologic signs, although CyA levels have not been consistently increased in cats that showed neurologic abnormalities. An immediately functioning graft has been proposed to decrease solute concentrations rapidly, as in dialysis disequilibrium syndrome, a neurologic complication associated with rapid osmolar shifts. A BUN concentration greater than 100 mg/dL and a serum creatinine concentration greater than 10 mg/dL increase the risk of CNS disease by tenfold; preoperative hemodialysis should be considered in this population.[12] Control of hypertension postoperatively reduces neurologic signs, making hypertensive encephalopathy a plausible cause of such signs.[3]

259.9.4 Hypertension

Severe hypertension that occurs in the first 48 hours after surgery can lead to neurologic signs, ataxia, stupor, seizures, blindness, ocular hemorrhage, or retinal detachment. The exact reason for the development of postoperative hypertension is unknown. Preoperative hypertension does not predict postoperative hypertension, although volume expansion during surgery may play a role. Vasoactive substances generated in the transplanted kidney during the warm ischemia time may be released when the vascular clamps are opened, resulting in hypertension. Pain associated with the surgery may exacerbate the hypertension. Diligent blood pressure monitoring for at least 48 hours after surgery is advised. If hypertension develops, treatment with a fast-acting antihypertensive agent is indicated (e.g., hydralazine, 2.5 mg given subcutaneously).[3]

259.9.5 Infection

The immunosuppression necessary to prevent rejection predisposes recipients to infection. Over 50% of human transplant recipients develop infection in the first year, and bacterial UTI is the most common type. In humans, common infections (UTI, surgical wound infection, pneumonia) tend to occur more often in the first

month, corresponding to the highest levels of immunosuppression. In cats, bacterial UTI, viral upper respiratory infections, toxoplasmosis, and a variety of fungal infections have been reported.

Because CyA primarily interferes with cell-mediated immunity, unusual infections may arise. Toxoplasmosis has caused fatal infections in three cats and one dog.[18] Infections occurred 3 weeks to 6 months after surgery and were associated with administration of increased immunosuppressive medications in three of the four cases. Transmission of toxoplasmosis from the donor to the recipient was suspected in one case; reactivation of latent infection was suspected in the three with high levels of immunosuppression. Close monitoring of seropositive recipients after surgery is recommended, and treatment with clindamycin is advised if titers rise. Transplant recipients should avoid situations that might expose them to large numbers of other cats, including boarding kennels.

259.9.6 Neoplasia

Human renal transplant recipients on long-term immunosuppressive therapy have a higher rate of neoplasia compared to the general population. The rate of *de novo* cancer in feline renal transplant recipients is 9.5% to 14%. Lymphosarcoma is the most common neoplasm. Other reported malignancies include squamous cell carcinoma, malignant round cell tumors, hepatic carcinoma, bronchogenic adenocarcinoma, transitional cell carcinoma, and intestinal adenocarcinoma.[5,20]

259.9.7 Miscellaneous Complications

A variety of other complications have been reported. A hemolytic-uremic–like syndrome was reported in three cats[21]; it was characterized by hemolysis, thrombocytopenia, and thrombotic microangiopathy. Intrarenal thrombosis leads to renal cortical necrosis. In children, this syndrome is typically caused by *E. coli* O157:H7 endotoxin; other causes in renal transplant recipients include acute vascular rejection, malignant hypertension, and nephrotoxicity arising from CyA, tacrolimus, or antilymphocyte antibody administration. In cats, the outcome has been graft failure and death. Retroperitoneal fibrosis, characterized by the development of fibrous tissue around the ureter and renal capsule, has been encountered. Surgical debulking of this tissue can relieve ureteral obstruction and renal compression.[22] Hypercalcemia was reported in one cat as a result of primary hyperparathyroidism.[23] Prednisone and CyA have been implicated in the development of post-transplantation diabetes mellitus, which has been recognized in cats.[24]

259.10 OUTCOME

The outcome after transplantation has improved as veterinary surgeons have gained more experience with the procedure. Perioperative mortality is approximately 25%. For cats discharged from the hospital, the 6-month survival rate is 60% to 70%. Mortality is highest in the first 6 months after surgery. Older age at surgery (over 10 years) predicts a worse outcome, particularly in the first 6 months, but in one study these deaths were not attributed to age-related diseases.[12] The overall 3-year survival rate is 40% to 50%.[5,12] In one study, one third of deaths were due to allograft rejection.[12] CNS disease, neoplasia, viral upper respiratory infection, hemolytic-uremic syndrome, gastrostomy tube peritonitis, and a variety of other causes of death have also been reported.

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259.11 CANINE TRANSPLANTATION

Renal transplantation is not as well established in dogs as in cats. Problems with the efficacy and toxicity of immunosuppressive drugs in dogs make sufficient immunosuppression more difficult. Unacceptable GI toxicity of many immunosuppressive drugs precludes their routine use. Long-term survival in unrelated dogs using rabbit antidog antithymocyte serum, CyA, azathioprine, and prednisone have been reported, but antithymocyte serum is not commercially available.[6] Protocols involving leflunomide, CyA, and prednisone, or CyA, azathioprine, and prednisone are undergoing evaluation in unrelated dogs that are haplotype mismatched.

259.12 SUMMARY

Renal transplantation provides a method of treating end-stage renal disease in cats. Successful long-term outcomes are possible, with improved quality of life in addition to prolonged longevity. Careful patient selection is advised. Long-term immunosuppression is necessary. Multiple complications have been encountered, but improvements in surgical technique, management, and monitoring are gradually extending the average survival time of transplant recipients. The procedure is becoming more widely available, and more clients are requesting evaluation and referral of their pets.

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260 CHAPTER • 260 Chronic Kidney Disease

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260.1 OVERVIEW OF CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is the most common kidney disease in dogs and cats. Regardless of the cause or causes of nephron loss, CKD is characterized by irreversible structural lesions. After correcting any reversible primary diseases and prerenal or postrenal components of renal dysfunction, further improvement in kidney function should not be expected in patients with CKD, because compensatory and adaptive changes designed to sustain kidney function have largely already occurred. However, unless additional kidney injury occurs or CKD is very advanced, rapid deterioration of intrinsic kidney function is also unusual. The magnitude of kidney dysfunction typically remains stable or slowly declines over months to years.[1,2] However, it may not be necessary for the disease process responsible for the initial kidney injury to persist for progressive dysfunction to occur. Therefore irrespective of underlying causes, CKD is often described as an irreversible and progressive disease.

Patients with CKD often survive for many months to years with a good quality of life. Although as yet no treatment can correct existing irreversible kidney lesions of CKD, the clinical and biochemical consequences of reduced kidney function can often be ameliorated by supportive and symptomatic therapy. In addition, therapy may be designed to interrupt mechanisms that contribute to the self-perpetuation of progressive CKD.

260.1.1 Chronic Kidney Disease—Defined

Kidney disease is defined as the presence of functional or structural abnormalities in one or both kidneys. It is recognized by reduced kidney function or the presence of kidney damage. Kidney damage is defined as either (1) microscopic or macroscopic renal pathology detected by kidney biopsy or direct visualization of the kidneys or (2) markers of renal damage detected by blood or urine tests or imaging studies (Box 260-1).[3] The severity and clinical implication of kidney disease varies greatly depending on the magnitude of kidney involvement.

CKD is defined as (1) kidney damage that has existed for at least 3 months, with or without decreased glomerular filtration rate (GFR), or (2) a reduction in GFR of more than 50% from normal persisting for at least 3 months. The authors recommend that a duration of at least 3 months be used as the benchmark criterion for confirming the diagnosis of CKD based on the observation that renal compensatory hypertrophy and improvement in renal function may continue for up to 3 months after acute loss of nephrons.

260.1.2 Terms and Concepts Related to Kidney Disease, Kidney Failure, and Uremia

Use of the terms *kidney disease*, *kidney insufficiency, kidney failure, azotemia,* and *uremia* as synonyms may result in misdiagnosis and formulation of inappropriate or even contraindicated therapy. In addition, it may result in misinterpretation of epidemiologic data. For example, in the past, confusion has occurred in the

interpretation of statistics about the frequency of kidney lesions reported by pathologists. Some investigators misinterpreted data regarding the frequency of morphologic evidence of kidney disease and suggested that all cases with kidney disease had kidney failure.

260.1.2.1

260.1.2.1 Box • 260-1 Markers of Kidney Damage*

260.1.2.1.1 Blood Markers

Elevated blood urea nitrogen (BUN) concentration

Elevated serum creatinine concentration

Hyperphosphatemia

Hyperkalemia or hypokalemia

Metabolic acidosis

Hypoalbuminemia

260.1.2.1.2 Urine Markers

Impaired urine-concentrating ability

Proteinuria

Cylinduria

Renal hematuria

Inappropriate urine pH

Inappropriate urine glucose concentration

Cystinuria

260.1.2.1.3 Imaging Markers—Abnormalities in Kidney

Size

Shape

Location

Density

Number

* Markers must be confirmed to be of renal origin to be evidence of kidney damage.

Kidney disease should not be used synonymously with *kidney failure* or *uremia*. Depending on the quantity of renal parenchyma affected and the severity and duration of lesions, kidney disease or diseases may or may not cause kidney failure or uremia. The clinical relevance of the difference between kidney disease and kidney failure is emphasized by the fact that symptomatic and supportive therapies designed to correct fluid, electrolyte, acid-base, nutrient, and endocrine imbalances in patients with kidney failure typically are not appropriate for patients with kidney disease without kidney dysfunction.

Kidney disease may affect glomeruli, tubules, interstitial tissue, and vessels. Some kidney diseases may be associated with dysfunction (e.g., some forms of nephrogenic diabetes insipidus and some forms of renal tubular acidosis) or biochemical abnormalities (e.g., cystinuria) without detectable morphologic alterations. Others may be associated with morphologic kidney disease (anomalies, infections, endogenous or exogenous toxin-induced lesions, immune-mediated lesions, damage caused by hypercalcemia and other mineral imbalances, traumatic lesions) that affects one or both kidneys with variable effects on kidney function. The specific cause or causes of kidney disease or diseases may or may not be known; however, quantitative information about kidney function (or dysfunction) is not defined or implied by the term *kidney disease*.

Kidney function *adequate* for homeostasis does not require that *all* nephrons be functional. The concept that adequate kidney function is not synonymous with normal kidney function is of importance in understanding the difference between kidney disease and kidney failure; formulating meaningful prognoses; and formulating therapy. The term *kidney failure* is analogous to liver failure or heart failure in that a level of organ dysfunction is described rather than a specific disease entity. Similarly, the term *kidney insufficiency* implies kidney dysfunction, but at a level that is less severe than kidney failure. The kidneys perform multiple excretory, regulatory, and biosynthetic functions including selective elimination of waste products of metabolism from the body, maintenance of fluid, acid-base and electrolyte homeostasis, and synthesis of a variety of hormones. Failure to perform these functions may not be an *all or none phenomenon*. For example, in slowly progressive kidney diseases, failure to appropriately concentrate or dilute urine according to body need typically precedes failure to eliminate waste products of metabolism of such magnitude that it causes azotemia. In turn, laboratory detection of impaired ability to eliminate waste products of metabolism (such as urea and creatinine) and to maintain electrolyte and nonelectrolyte solute balance within normal limits typically precedes the onset of polysystemic signs of kidney dysfunction. Clinical signs and polysystemic disorders caused by abnormalities of water, electrolyte, acid-base, endocrine, and nutrient balance are not invariably present in patients with primary kidney failure (i.e., not all patients with primary kidney failure are uremic). This is related, at least in part, to the reserve capacity of the kidneys and the ability of unaffected nephrons to undergo compensatory hypertrophy and hyperplasia.

In dogs, acute loss of two thirds or more of functional nephrons is associated with loss of adequate urine-concentrating ability, whereas acute loss of three fourths or more of functional nephrons results in azotemia. However, over the subsequent weeks to months, urine-concentrating ability and excretory function improve as a consequence of compensatory hypertrophy and hyperplasia of surviving nephrons. As a consequence, 3 months after loss of three fourths of functioning nephrons, renal concentrating ability is often adequate and azotemia is no longer present. Chronic renal insufficiency therefore implies a 75% reduction in GFR that typically corresponds to a loss of substantially more than 75% of the functional nephrons.

Azotemia is defined as an abnormal concentration of urea, creatinine, and other nonprotein nitrogenous substances in blood, plasma, or serum. Azotemia is a laboratory finding with several fundamentally different causes. Because nonprotein nitrogenous compounds (including urea and creatinine) are endogenous substances, abnormally elevated concentrations in serum may be caused by an increased rate of production (by the liver for urea; by muscles for creatinine), or by a decreased rate of loss (primarily by the kidneys). Because

azotemia may be caused by factors that are not directly related to the urinary system and by abnormalities of the lower urinary tract (LUT) not directly related to the kidney, *azotemia* should not be used as a synonym for kidney failure or uremia. Although the concentrations of serum urea nitrogen (SUN) and creatinine are commonly used as crude indices of GFR, meaningful interpretation of these parameters depends on recognition and evaluation of prerenal, primary renal, and postrenal factors that may reduce GFR.

Uremia is defined as (1) abnormal quantities of urine constituents in blood caused by primary generalized kidney disease *and* (2) the polysystemic toxic syndrome which occurs as a result of abnormal kidney function. When the structural and functional integrity of both kidneys has been compromised to such a degree that 1757
polysystemic signs of kidney failure are clinically manifested, the relatively predictable symptom complex 1758
called *uremia* appears, regardless of underlying cause. In some instances, uremic crises may suddenly be precipitated by prerenal disorders or, less commonly, postrenal disorders in patients with previously compensated primary kidney failure. Uremia is characterized by multiple physiologic and metabolic alterations that result from impaired kidney function.

In summary, kidney disease may precede kidney insufficiency and failure, and likewise, kidney insufficiency and failure may precede uremia. In some situations, kidney disease may not progress to kidney insufficiency or failure. In others, prerenal events may precipitate a uremic crisis in patients with chronic kidney insufficiency or failure. In untreated patients with kidney disease, uremia is always accompanied by kidney failure and azotemia.

260.1.3 Staging Chronic Kidney Disease

Patients with CKD can be categorized into stages along a continuum of progressive kidney disease.[4] The value of staging CKD is to facilitate application of appropriate clinical practice guidelines for diagnosis, prognosis, and treatment. The International Renal Interest Society (IRIS) has proposed a four-tier system for staging CKD in dogs and cats (Box 260-2 and 260-3; Figures 260-1 and 260-2). Although the specific values used to categorize patients with CKD into these stages are inherently arbitrary, staging is nonetheless useful for establishing prognosis and managing patients with CKD.

The stage of CKD is assigned based on the level of kidney function. The level of GFR is accepted as the best measure of overall kidney function in health and disease.[3] Ideally, the stage of CKD would be assigned based on measured GFR values. However, because of technical and economic constraints, GFR is usually estimated in dogs and cats by serum (or plasma) creatinine concentration. Limitations on specificity and sensitivity of serum creatinine concentration as an estimate of GFR can lead to misclassification. Ideally, two or more serum creatinine values obtained when the patient is fasted and well hydrated should be determined over several weeks to stage CKD. Further, variations between laboratories, patient-specific characteristics (e.g., breed, age, gender, body condition, and lean body mass) and transient prerenal and postrenal events may influence serum creatinine values. Reduced muscle mass, a common manifestation of advanced CKD, may result in a substantial reduction in serum creatinine concentration relative to true GFR. Greyhounds reportedly have higher serum creatinine concentrations, presumably due to their athletic nature.[5] Because of these variations, published reference ranges for serum creatinine are often exceedingly broad. Using the staging system described here, some patients classified as having mild renal azotemia (stage 2) may have serum creatinine values within published reference ranges. As a consequence, the patient's overall clinical status should be considered when interpreting serum creatinine concentration and other laboratory tests and when planning patient management.

260.1.3.1 **Box • 260-2 Stages of Canine Chronic Kidney Disease**

260.1.3.1.1 **Stage 1 (Nonazotemic)**

Markers of renal disease present

Creatinine < 1.4 mg/dL (< 125 µmol/L)

Proteinuria: classify—(P/NP/BP)

Hypertension: classify—(Hc/Hnc/NH/BH/HND)

260.1.3.1.2 **Stage 2 (Mild Renal Azotemia)**

Markers of renal disease present

Creatinine 1.4–2.0 mg/dL (125–180 µmol/L)

Proteinuria: classify—(P/NP/BP)

Hypertension: classify—(Hc/Hnc/NH/BH/HND)

260.1.3.1.3 **Stage 3 (Moderate Renal Azotemia)**

Creatinine 2.1–5.0 mg/dL (181–440 µmol/L)

Proteinuria: Classify—(P/NP/BP)

Hypertension: Classify—(Hc/Hnc/NH/BH/HND)

260.1.3.1.4 **Stage 4 (Severe Renal Azotemia)**

Creatinine > 5.0 mg/dL (> 440 µmol/L)

Proteinuria: Classify—(P/NP/BP)

Hypertension: Classify—(Hc/Hnc/NH/BH/HND)

P, Proteinuria; *NP,* nonproteinuria; *BP,* borderline proteinuria; *Hc,* hypertension with complications; *Hnc,* hypertensive with no complications; *NH,* nonhypertensive; *BH,* borderline hypertensive; *HND,* hypertension not determined.

260.1.3.2 **Box • 260-3 Stages of Feline Chronic Kidney Disease**

260.1.3.2.1 **Stage 1 (Nonazotemic)**

Markers of renal disease present

Creatinine < 1.6 mg/dL (< 140 µmol/L)

Proteinuria: Classify—P/NP/BP

Hypertension: Classify—Hc/Hnc/NH/BH/HND

260.1.3.2.2 Stage 2 (Mild Renal Azotemia)

Markers of renal disease present

Creatinine 1.6–2.8 mg/dL (140–250 µmol/L)

Proteinuria: Classify—P/NP/BP

Hypertension: Classify—Hc/Hnc/NH/BH/HND

260.1.3.2.3 Stage 3 (Moderate Renal Azotemia)

Creatinine 2.8–5.0 mg/dL (251–440 µmol/L)

Proteinuria: Classify—P/NP/BP

Hypertension: Classify—Hc/Hnc/NH/BH/HND

260.1.3.2.4 Stage 4 (Severe Renal Azotemia)

Creatinine > 5.0 mg/dL (> 440 µmol/L)

Proteinuria: Classify—P/NP/BP

Hypertension: Classify—Hc/Hnc/NH/BH/HND

P, Proteinuria; *NP,* nonproteinuria; *BP,* borderline proteinuria; *Hc,* hypertension with complications; *Hnc,* hypertensive with no complications; *NH,* nonhypertensive; *BH,* borderline hypertensive; *HND,* hypertension not determined.

Stage 1 CKD includes dogs and cats with CKD that are not azotemic, whereas stage 2 CKD includes dogs and cats that are mildly azotemic (see Boxes 260-2 and 260-3). Patients in these stages of CKD typically do not have clinical signs of kidney dysfunction with the exception of polyuria and polydipsia. Occasionally cats with stage 2 CKD may have weight loss or selective appetites. However, patients may have clinical signs resulting from their kidney lesions (e.g., acute pyelonephritis, nephrolithiasis). Patients with marked proteinuria or systemic hypertension due to CKD may have clinical signs related to these aspects of kidney disease. Renal function is often stable for an extended period in nonproteinuric, nonhypertensive (NH) dogs and cats with stages 1 and 2 CKD. However, when progression does occur in this group of patients, it may occur largely as a consequence of their primary kidney disease.[4] Patients with stages 1 and 2 CKD should be evaluated with the goals of identifying and providing specific treatment for their primary kidney disease. In addition, renal function should be monitored to assess for possible progression of their kidney disease.

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Figure 260-1 Classification of canine chronic kidney disease (CKD) based on serum creatinine concentrations. Firm evidence of renal disease in stage 1 would generally be morphologic, such as abnormal renal architecture on survey radiographs, abnormal renal ultrasound findings, or biopsy diagnosis of renal disease. Classification of prerenal azotemia (generally due to dehydration or renal ischemia) or postrenal azotemia (generally due to ureteral obstruction, urethral obstruction, or a rupture of a portion of the urinary tract) is based on careful evaluation of the history and physical examination and other clinical or imaging findings. This determination may require additional tests. Classification of azotemia as renal is based on the presence of azotemia with no identifiable prerenal or postrenal causes and urine specific gravity (USG) less than 1.030. (Developed by the International Renal Interest Society, www.iris-kidney.com. Used with permission.)

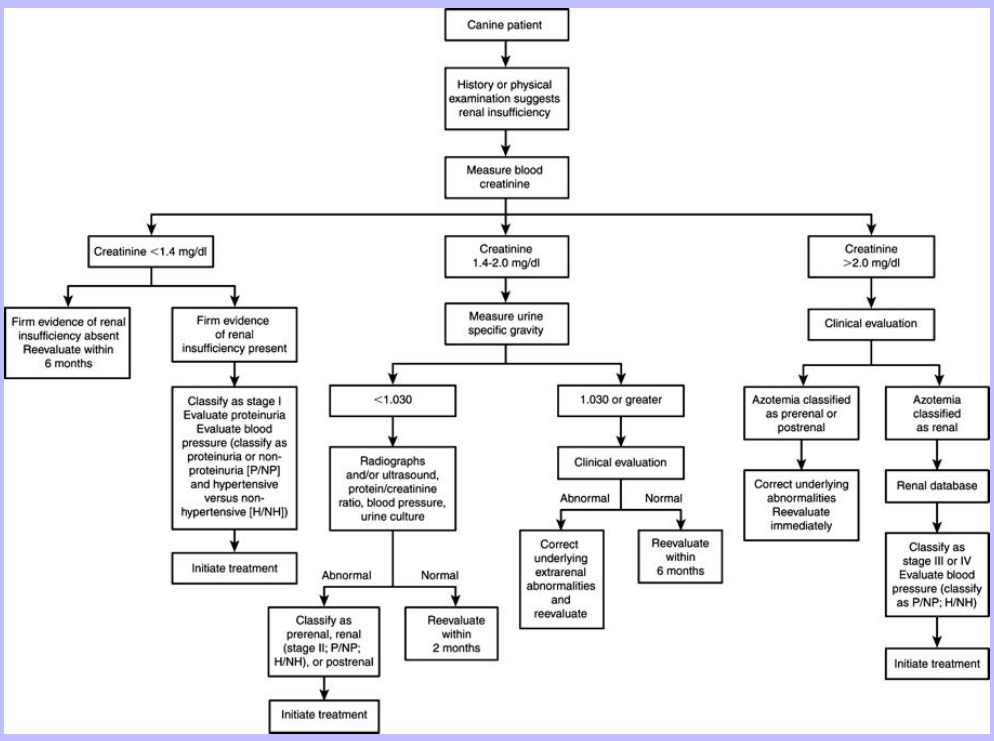
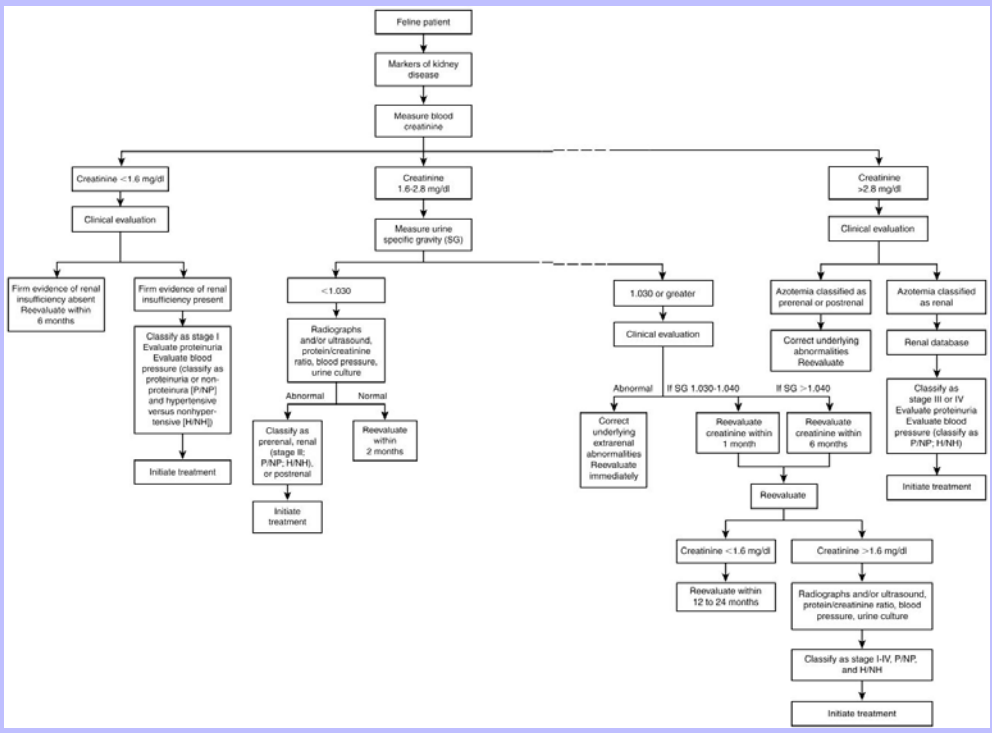


Figure 260-2 Classification of feline chronic kidney disease (CKD) based on serum creatinine concentrations. Firm evidence of renal disease would generally be morphologic, such as abnormal renal architecture on survey radiographs, abnormal renal ultrasound findings, or biopsy diagnosis of renal disease. Classification of prerenal azotemia (generally due to dehydration or renal ischemia) or postrenal azotemia (generally due to ureteral obstruction, urethral obstruction, or a rupture of a portion of the urinary tract) is based on careful evaluation of the history and physical examination and other clinical or imaging findings. Classification of azotemia as renal is based on the presence of azotemia with no identifiable prerenal or postrenal causes and urine specific gravity (USG) less than 1.040. (Developed by the International Renal Interest Society www.iris-kidney.com. Used with permission.)



Patients with moderate azotemia are classified as stage 3 CKD. Patients in this stage may have clinical signs referable to their loss of kidney function; however, with appropriate treatment, they typically do not have clinical signs of overt uremia. Patients with stage 3 CKD may progress due to inherent mechanisms of

spontaneous progression, as well as their underlying kidney disease. Therefore in addition to identifying and treating primary kidney disease, therapy designed to modify factors promoting progression of renal disease may be of benefit to these patients.

Stage 4 CKD includes dogs and cats with severe azotemia (serum creatinine values greater than 5.0 mg/dL). This stage is also called *chronic kidney failure* and is frequently associated with clinical signs that occur as a consequence of loss of kidney function. Diagnostic and therapeutic initiatives in this stage include those appropriate for stage 3 patients, as well as therapy designed to prevent or ameliorate signs of uremia.

It is useful to further subclassify patients according to their urine protein loss and systemic blood pressure. Proteinuria and hypertension may influence prognosis and may be amenable to therapeutic intervention. Classification of patients as proteinuric necessitates eliminating hemorrhage, inflammation, or both as the cause for proteinuria and determination of the urine protein/creatinine ratio. For both dogs and cats, patients are classified as proteinuric (P) when their protein/creatinine ratio exceeds 1.0. Values between 0.5 and 1.0 are classified as borderline proteinuric (BP). Values less than 0.5 are classified as nonproteinuric (NP). Patients with borderline proteinuria should be re-evaluated after 2 months to reassess classification. In some patients, classification of proteinuria may change due to the natural course of their disease or in response to therapy. The role of microalbuminuria in this classification scheme remains to be determined.

The lack of consensus as to what blood pressure values constitute hypertension in dogs and cats obfuscates any classification of patients as to their hypertension status. It is likely that "normal" blood pressure values for dogs and cats will change as more data become available. The IRIS has proposed the following hypertension classification system for dogs and cats: Patients may be classified as hypertensive with no complications (Hnc) when their systolic blood pressure exceeds 160 mm Hg and no extrarenal evidence of hypertension exists (i.e., ocular, neurologic, or cardiac changes consistent with hypertensive injury). Patients may be classified as hypertensive with extrarenal complications (Hc) when their systolic blood pressure exceeds 150 mm Hg and extrarenal evidence of hypertension is present. Patients may be classified as borderline hypertensive (BH) when their systolic blood pressure is between 150 mm Hg and 180 mm Hg and no extrarenal evidence of hypertension exists. Patients may be classified as NH when their systolic blood pressure is less than 150 mm Hg. If blood pressure has not been determined, the patient should be classified as hypertension not determined (HND).

260.1.4 Affected Population

CKD is a common cause for illness and death in dogs and cats. It is among the most common diseases recognized in older cats. The prevalence of kidney disease has been estimated to range between 0.5%[6] and 7%[7] in dogs and between 1.6%[6] and 20%[7] in cats.

Although frequently considered a disease of older animals, CKD occurs with varying frequency in dogs and cats of all ages. In a retrospective study of cats with CKD, 53% of affected cats were over 7 years old, but animals ranged in age from 9 months to 22 years.[8] In a study on age distribution of kidney disease in cats based on data submitted from 1980 to 1990 to the Veterinary Medical Data Base at Purdue University, 37% of cats with renal failure were less than 10 years old, 31% of cats were between the ages of 10 and 15, and 32% of cats were older than 15 years of age.[9] Similarly, in a study of cats with CKD reported in 1988, their mean age was 12.6 years with a range of 1 to 26 years.[10] Mean age among 45 control cats in this study was 10.0 years. During 1990, the prevalence of kidney disease among cats of all ages was reportedly 16 cases for every 1000 cats examined. During the same year, the prevalence of kidney disease among cats 10 years of age or

older was 77 per 1000 cats examined, and among cats older than 15 years, 153 per 1000.[8] Maine coon, Abyssinian, Siamese, Russian blue, and Burmese cats were disproportionately reported as affected.

Although renal failure apparently occurs less commonly in dogs than cats, its incidence increases similarly with age. Based on data submitted from 1983 to 1992 to the Veterinary Medical Data Base at Purdue University, 18% of dogs with renal failure were less than 4 years old, 17% of dogs were between the ages of 4 and 7, 20% of dogs were between the ages of 7 and 10, and 45% of dogs were older than 10 years of age. During this period, the prevalence of renal failure among dogs of all ages was nine cases for every 1000 dogs examined. The prevalence of renal failure among dogs 7 to 10 years of age was 12.5 per 1000 dogs examined; among dogs 10 to 15 years, 24 per 1000, and among dogs older than 15 years, 57 per 1000.

260.1.5 ## Causes of Chronic Kidney Disease

CKD may be initiated by a variety of different familial, congenital, or acquired diseases (Box 260-4). In a study of biopsy findings in 37 dogs with primary renal azotemia, chronic tubulointerstitial nephritis was observed in 58%, glomerulonephropathy occurred in 28%, and amyloidosis was observed in 6%.[11] In cats, tubulointerstitial nephritis was observed in 70%, glomerulonephropathy occurred in 15%, lymphoma was observed in 11%, and amyloidosis occurred in 2%. Unfortunately, the initiating cause or causes of CKD often cannot be identified at the time of diagnosis. The initiating causes of diseases thought to originate in the tubulointerstitium have been especially elusive. Although bacteria can cause tubulointerstitial lesions, in the authors' experience, a bacterial urinary tract infection (UTI) is more often a sequela of the immunocompromised condition associated with renal failure than the cause. In one retrospective study of renal failure cats, bacterial UTI was detected in 20% of the patients.[9] Glomerulonephropathies have been linked to a variety of neoplastic, metabolic, and infectious and noninfectious inflammatory processes.[12] Periodontal disease has been linked to microscopic renal lesions in dogs, but a cause-and-effect relationship has not been established.[13] Feline immunodeficiency virus (FIV) has been linked to renal disease in cats, although few cats with CKD are FIV positive.[14,15] Subcutaneous administration of feline herpesvirus 1 (FHV-1), calicivirus, and panleukopenia virus vaccines grown in feline tissue culture systems to kittens have been shown to induce production of antifeline renal tissue antibodies in serum (Lappin and colleagues).[16] This observation prompts the question as to whether repeated vaccinations play a role in development of chronic renal disease.

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260.1.5.1 ### Box • 260-4 Disorders That May Cause Chronic Renal Failure

Familial or Congenital

Dogs

Amyloidosis in Shar Pei and beagle dogs

Cystadenocarcinoma in German shepherd dogs

- Renal dysplasia in Shi Tzu, Lhasa apso, golden retrievers, Norwegian Elkhounds, Chow Chows, and others
- Glomerulopathy in English cocker spaniels, Doberman pinschers, bull terriers, soft-coated Wheaton terriers, Samoyeds
- Fanconi syndrome in Basenjis
- Polycystic disease in Cairn terriers

Cats

- Amyloidosis in Abyssinian cats and oriental shorthair cats
- Polycystic disease in Persian and Himalayans

Acquired

Infectious

- Bacterial
- Mycotic—blastomycosis
- Leptospirosis
- Leishmaniasis
- Feline infectious peritonitis (FIP)

Immune complex glomerulopathy (Consult Chapter 261 on glomerulopathies)

Amyloidosis

Neoplasia

- Lymphosarcoma
- Renal cell carcinoma
- Nephroblastoma
- Others

Sequela of acute renal failure

Bilateral hydronephrosis

- Spay granulomas
- Transitional cell carcinoma—bladder trigone location
- Nephrolithiasis

Polycystic

Hypercalcemia

- Malignancy
- Primary hyperparathyroidism

Idiopathic

Difficulty in detecting the inciting cause of CKD is associated with three phenomena related to the evolution of progressive renal diseases. First, various components of nephrons (glomeruli, peritubular capillaries, tubules, and interstitial tissue) are functionally interdependent. Second, the functional and morphologic responses of tissues comprising the kidneys to different causative agents are limited. Third, after maturation of nephrons, which occurs at approximately 1 month of age, new nephrons cannot be formed to replace others irreversibly destroyed by disease. Progressive irreversible lesions initially localized to one portion of the nephron are eventually responsible for development of lesions in the remaining but initially unaffected portions of nephrons. For example, progressive lesions (such as amyloid or immune complex disease) confined initially to glomeruli will subsequently decrease peritubular capillary perfusion. Reduced peritubular capillary perfusion will in turn result in tubular epithelial cell atrophy, degeneration, and necrosis. Recent

studies suggest that tubular epithelial cells may also be damaged as a consequence of glomerular proteinuria. Secondary tubular damage may be related, at least in part, to excessive tubular cell uptake of filtered proteins or protein-bound substances.[17] Studies showing that the rate of disease progression correlates with the amount of proteinuria, and that therapy designed to reduce proteinuria retards progression, support the concept that glomerular proteinuria damages tubules. The secondary processes of inflammation and fibrosis amplify these processes. An influx of T cells and macrophages into the interstitium may cause further tubular injury, and macrophages in particular produce profibrotic substances. Ultimately nephron destruction initiated by glomerular disease will simulate repair by substitution of functioning nephrons with nonfunctional connective tissue.

Similarly, generalized progressive interstitial disease initially caused by bacteria eventually destroys tubules and glomeruli and stimulates inflammation and fibrosis. Thus irrespective of the initiating cause, replacement of the majority of the damaged nephrons with collagenous connective tissue results in overall reduction in kidney size and impaired renal function.

Because of the structural and functional interdependence of various components of nephrons, differentiation of different progressive renal diseases that have reached an advance stage is often difficult. Functional and structural changes prominent during earlier phases of progressive generalized renal diseases may permit identification of a specific cause and localization of the initial lesion to glomeruli, tubules, interstitium, or vessels. With time, however, destructive changes of varying severity (atrophy, inflammation, fibrosis, and mineralization of diseased nephrons), superimposed on compensatory and adaptive morphologic and functional of remaining partially and totally viable nephrons, provide a functional and morphologic similarity to the findings associated with these diseases.

Despite the irreversibility of generalized renal lesions associated with CKD, it is important to formulate diagnostic plans to try to identify the underlying cause and to determine if it is still active. Although specific therapy directed at eliminating or controlling the primary cause will not substantially alter existing renal lesions, it is important in the context of minimizing further nephron damage. Renal diseases potentially amenable to specific therapy include bacterial pyelonephritis, chronic urine outflow obstruction, nephrolithiasis, renal lymphoma (particularly in cats), hypercalcemic nephropathy, and some immune-mediated diseases.

Acute onset of nonurinary disorders, especially those that interfere with compensatory polydipsia, may precipitate a uremic crisis in patients with asymptomatic CKD (so-called acute-on-chronic uremic crisis). However, if acute decompensation of CKD has been caused by reversible factors, correction of them will often result in recompensation of the CRF.

260.1.6 Prognosis of Chronic Kidney Disease

Cats with stages 2 and 3 CKD commonly survive 1 to 3 years, whereas dogs with stage 3 CKD typically survive about 6 to 12 months. However, many survive much longer. A host of factors influence prognosis of CKD, both favorably and unfavorably. Included among these factors are the quality of medical care provided to the patient and the level of owner commitment. The estimate of prognosis often influences the owner's decisions about treatment options in complying with recommendations for management of the patient. A comprehensive evaluation of the patient is the best way to establish a reasonably accurate prognosis.

Prognosis for patients with CKD is usually subcategorized according to the probability of immediate survival (short-term prognosis) and survival over the subsequent months to years (long-term prognosis). A guarded prognosis indicates that the chances for recovery are unpredictable. Fair, good, or excellent prognoses indicate

varying degrees of probable recovery, whereas poor or grave prognoses indicate that recovery is improbable or hopeless. Loss of renal function is irreversible in patients with CKD. In this context, recovery refers to improvement of biochemical deficits and excesses and amelioration of clinical signs rather than recovery of renal function.

Factors to be considered in establishing meaningful prognoses for patients with CKD include (1) the nature of the primary renal disease, (2) severity and duration of clinical signs and complications of uremia, (3) probability of improving renal function (reversibility—primarily of prerenal, postrenal, and newly acquired primary renal conditions), (4) severity of intrinsic renal functional impairment, (5) rate of progression of renal dysfunction with or without therapy, and (6) age of the patient. In addition, blood pressure and the magnitude of proteinuria are risk factors influencing prognosis in dogs with CKD.[18]

Severity of uremic signs is often a relatively good predictor of short-term prognosis. Patients with stable CKD without clinical signs of uremia usually have a good short-term prognosis. Untreated patients with severe clinical signs of uremia typically have a guarded to poor short-term prognosis. However, it is best to determine whether renal function and clinical signs can be therapeutically improved in such cases before establishing the short-term prognosis. A uremic crisis often occurs in patients that present with CKD as a consequence of superimposed acute renal failure or prerenal or postrenal conditions. Although CKD is an irreversible condition, improvement of renal function is potentially possible when uremia results from the sum effects of CKD and a potentially reversible cause of azotemia. If treatment results in improved renal function and ameliorates clinical signs of uremia, the short-term prognosis often becomes guarded to good.

Severity of renal dysfunction as determined by serum creatinine concentration or measurement of GFR provides a less accurate means of assessing short-term prognosis than does the clinical condition of the patient. The relationship between magnitude of renal dysfunction and clinical signs of uremia is often unpredictable. Therefore short-term prognosis should not be established based on a single measurement of the severity of renal dysfunction. In addition, a single determination of renal function is unreliable as an index of the potential for improvement in renal function.

Assessment of the severity of renal dysfunction is typically more useful in establishing long-term prognoses. In general, severe renal dysfunction is associated with shorter long-term survival and, often, a lower quality of life. This generalization is supported by findings of a recent study of cats with spontaneous CKD.[2] For cats with CKD without apparent clinical signs and having a mean plasma creatinine concentration of 2.6 mg/dL, mean survival was 397 days. For cats with CKD with one or more clinical signs attributable to CKD and a mean plasma creatinine concentration of 3.6 mg/dL, mean survival was 313 days. Uremic cats with a mean plasma creatinine concentration of 10.3 mg/dL survived less than 3 days. However, in a recent clinical trial in dogs with spontaneous CKD, mean serum creatinine concentration did not appear to influence survival when dogs were fed a renal diet. Median survival for 21 dogs with a mean serum creatinine concentration of 3.3 mg/dL was 615 days. Median survival for a subpopulation of dogs in this group with serum creatinine values between 2.0 and 3.1 mg/dL was also 615 days. However, among 17 dogs fed a maintenance diet in this study, median survival for dogs with a mean serum creatinine of 3.7 mg/dL was 252 days, whereas survival for the subpopulation with serum creatinine values between 2.0 and 3.1 mg/dL was 461 days. In summary, the prognosis should be established in the context of the clinical condition of the patient, rate of progression of renal dysfunction, response to therapy, cause of the underlying renal disease (if known), and other complicating factors (e.g., UTI, nephrotic syndrome).

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Systemic hypertension has been linked to progression of CKD in humans for decades.[19] Increased systolic blood pressure has been shown to increase risk of uremic crises and death in dogs with spontaneous CKD.[18] In

this study, systolic blood pressure values determined at the time of initial patient evaluation were compared with long-term outcome. Increased risk of developing a uremic crisis and of death was observed in the patients with the highest blood pressure values. In addition, a greater decline in renal function over time was observed in these dogs. Although this study was not designed to prove a cause-and-effect relationship between hypertension and progressive renal disease, it does indicate that initial blood pressure values should be considered in formulating a prognosis for dogs with CKD. The prognostic significance of blood pressure values in cats with CKD has yet to be established.

Results of a clinical trial from the University of Minnesota Veterinary Medical Center revealed that proteinuria is a risk factor for uremia and death in dogs with spontaneous kidney disease.[20] In this study, the risk of death associated with CKD increased by 60% for each unit of urine protein/creatinine ratio above 1.0. Whether proteinuria conferred this adverse risk as an independent mediator of renal injury or as a consequence of the biologic behavior of glomerular diseases is unclear. In dogs, glomerulopathies have been associated with poor long-term prognoses.[12] This may be related to the observation that proteinuria has been implicated in promoting progressive renal injury.[21] Therapeutic amelioration of proteinuria using angiotensin-converting (ACE) inhibitors may stabilize renal function in humans and dogs with glomerular disease, further suggesting a likely role for proteinuria in the progression of CKD.[22]

Compared with the rate of progression of CKD in middle-aged to older dogs with acquired renal disease, CKD often progresses at a much slower rate in dogs with congenital and familial nephropathies such as renal dysplasia. A comparably slower rate of progression has also been observed in young dogs with acquired CKD (e.g., after nephrotoxin exposure). Many of these patients appear remarkably resistant to developing clinical signs of uremia despite substantial elevations in serum creatinine and urea nitrogen concentrations.

260.2 CLINICAL CONSEQUENCES OF CHRONIC RENAL FAILURE

260.2.1 Uremia

Uremia is the clinical state toward which all progressive, generalized renal diseases ultimately converge. Diverse clinical and laboratory findings characterize uremia and emphasize the polysystemic nature of CKD (Box 260-5). The term *uremia* was adopted originally because of the presumption that all of the abnormalities result from retention in the blood of end-products of metabolism normally excreted in the urine. However, uremia involves more than renal excretory failure alone. A variety of metabolic and endocrine functions normally performed by the kidney are also impaired, resulting in anemia; malnutrition; impaired metabolism of carbohydrates, fats, and proteins; defective use of energy; alterations in immunity; and metabolic bone disease.

Urea, once thought to be “the” uremic toxin, is not a major cause of uremic toxicity, although it may contribute to some of the clinical abnormalities, including anorexia, malaise, and vomiting. Numerous nitrogenous compounds with a molecular mass of 500 to 12,000 D (so-called middle molecules) are retained in CKD and appear to contribute to morbidity and mortality in uremic subjects.[23] In addition to impaired excretion, many middle-sized molecules along with various cytokines and growth factors accumulate in CKD because the kidney's capacity for catabolizing many substances is also impaired. Further, plasma levels of many polypeptide hormones, including parathyroid hormone (PTH), insulin, gastrin, glucagon, luteinizing hormone (LH), and prolactin, increase in patients with CKD because of impaired renal catabolism and enhanced glandular secretion.

260.2.2 Gastrointestinal Consequences

Gastrointestinal (GI) complications are common and prominent clinical signs of uremia. Anorexia and weight loss are nonspecific findings that may precede other signs of uremia in dogs and cats. The patient's appetite may be selective for certain foods, and it may wax and wane throughout the day. Factors promoting weight loss and malnutrition include anorexia, nausea, vomiting and the subsequent reduction in nutrient intake, hormonal and metabolic derangements, and catabolic factors related to uremia, particularly acidosis.

Anorexia appears to be multifactorial in origin. Recent research, using a rodent model, has suggested that an *anorectic factor* in the plasma of uremic patients that can suppress appetite.[24] It appears to be a middle molecule in size and may be a peptide. Elevated serum leptin concentrations have also been implicated as a factor contributing to anorexia.[25]

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260.2.2.1 Box • 260-5 Complications and Comorbid Conditions in Chronic Kidney Disease

260.2.2.1.1 Complications of Chronic Kidney Disease (CKD)

Anemia

Arterial hypertension

Dehydration

Hyperparathyroidism

Hyperphosphatemia

Hypocalcemia and hypercalcemia

Hypokalemia

Malnutrition

Metabolic acidosis

Uremic signs

260.2.2.1.2 Comorbid Conditions

Cardiac disease

Degenerative joint disease

Dental and oral diseases

Hyperthyroidism (cats)

Nephroliths and ureteroliths

Urinary tract infections (UTIs)

Vomiting is a frequent, but inconsistent finding in uremia. It results from the effects of as yet unidentified uremic toxins on the medullary emetic chemoreceptor trigger zone and from uremic gastroenteritis. The severity of vomiting correlates crudely with the magnitude of azotemia. Because uremic gastritis may be ulcerative, hematemesis may occur. Vomiting may be a more frequent complaint in uremic dogs than cats. Nonetheless, vomiting is reportedly found in one quarter to one third of cats with clinical signs of uremia.[2] Vomiting may impair compensatory polydipsia, enhancing the risk of dehydration and exacerbating prerenal azotemia and clinical signs of uremia.

Uremic gastropathy is characterized microscopically by glandular atrophy, edema of the lamina propria, mast cell infiltration, fibroplasia, mineralization, and submucosal arteritis. Elevated gastrin levels have been implicated in development of uremic gastropathy.[26] Gastrin induces gastric acid secretion directly by stimulating receptors located on gastric parietal cells and by increasing histamine release from mast cells in the gastric mucosa. Enhanced histamine release may also promote GI ulceration and ischemic necrosis of the mucosa through a vascular mechanism characterized by small venule and capillary dilatation, increased endothelial permeability, and intravascular thrombosis.[27] Because up to 40% of the circulating gastrin is metabolized by the kidneys, reduced renal function may promote hypergastrinemia.

Elevated gastrin levels have been documented in cats with spontaneous CKD.[26] Although the prevalence of hypergastrinemia appeared to increase as renal dysfunction became more severe, there was great variability of gastrin levels among cats with similar degrees of renal dysfunction, suggesting that additional factors (in addition to the degree of renal impairment) likely affect serum gastrin levels in CKD.

Gastrin-induced gastric hyperacidity may lead to uremic gastritis, GI hemorrhage, nausea, and vomiting. Back diffusion of hydrochloric acid and pepsin into the stomach wall may lead to hemorrhage, inflammation, and release of histamine from mast cells. Thus the cycle may be perpetuated as mast cell–derived histamine causes further stimulation of parietal cells to produce hydrogen ions. However, gastric hyperacidity is not universally found with uremic gastritis. Some human uremic patients have hypochlorhydria. Thus hypergastrinemia is not the only reason for uremic gastritis. Other factors implicated in the genesis of uremic gastropathy include psychologic stress related to illness, an increase in proton back diffusion caused by high urea levels, erosions caused by ammonia liberated by bacterial urease acting on urea, ischemia caused by vascular lesions, decreased concentration and turnover of gastric mucous, and biliary reflux due to pyloric incompetence (which may be an indirect consequence of elevated gastrin levels).

In a recent study of 80 cats with spontaneous CKD, dysphagia and oral discomfort occurred in 7.7% of uremic cats and 38.5% of cats with end-stage renal failure.[2] Periodontal disease was observed in 30.8% of uremic and 34.6% of end-stage CKD cats in the same study. Halitosis was reported in 7.7% of cats in both groups. Moderate to severe CKD may result in uremic stomatitis characterized by oral ulcerations (particularly located on the buccal mucosa and tongue), brownish discoloration of the dorsal surface of the tongue, necrosis and sloughing of the anterior portion of the tongue (associated with fibrinoid necrosis and arteritis), and uriniferous breath. The mucous membranes may also become dry (xerostomia). Degradation of urea to ammonia by bacterial urease may contribute to many of these signs. Poor oral hygiene and dental disease may exacerbate the onset and severity of uremic stomatitis.

Uremic enterocolitis, manifested as diarrhea, may occur in dogs and cats with severe uremia, but it is typically less dramatic and less common than uremic gastritis. Owners of 80 cats with spontaneous CKD did not report

diarrhea.[2] However, when present, uremic enterocolitis is often hemorrhagic. Considerable GI hemorrhage may initially escape clinical detection. Intussusception may occasionally complicate uremic enterocolitis. Constipation is a relatively common complication of CKD, particularly in cats. Primarily it appears to be a manifestation of dehydration, but it can occur as a complication of intestinal phosphate-binding agents.

260.2.3 Impaired Urine-Concentrating Ability, Polyuria, Polydipsia, and Nocturia

Among the earliest and most common clinical manifestations of CKD is onset of polyuria, polydipsia, and sometimes nocturia due to reduced urine-concentrating ability. Polydipsia was the single most commonly reported clinical sign reported in a study of 80 cats with CKD. Cat owners recognized polydipsia over twice as often as polyuria. Although urine specific gravity (USG) values of cats in stages 2, 3, and 4 CKD are usually below 1.035, the authors have seen cats that have remained persistently (up to 18 months) azotemic prior to losing adequate concentrating ability (i.e., specific gravity >1.040).

A decrease in adequate urine-concentrating ability results from several factors including increased solute load per surviving nephron (solute diuresis), disruption of the renal medullary architecture and counter-current multiplier system by disease, and primary impairment in renal responsiveness to antidiuretic hormone (ADH). Loss of renal responsiveness to ADH may result from an increase in distal renal tubular flow rate, which limits equilibration of tubular fluid with the hypertonic medullary interstitium. Additionally, ADH-stimulated adenyl cyclase activity and water permeability in the distal nephron may be impaired in uremia.[28] Polydipsia is of course a compensatory response to polyuria. If fluid intake fails to keep pace with urinary fluid losses, dehydration will ensue because of the inability to conserve water by concentrating urine. Dehydration subsequent to inadequate fluid intake is a common problem in cats with CKD.

260.2.4 Arterial Hypertension and Cardiovascular Consequences

Hypertension may be either a cause or consequence of CKD. When present, it may adversely affect long-term prognosis.[18] It is a common complications of CKD, reportedly occurring in up to 66% of cats with CKD.[29] Although one recent study suggested that hypertension may be unusual in dogs with CKD,[30] other studies have reported incidences of from 30% to 93% of dogs with CKD.[18,30] Dogs with glomerular diseases are at increased risk for hypertension.

The pathophysiology of arterial hypertension and its complications is described in Chapters 129 and 130.

260.2.5 Neuromuscular Consequences

260.2.5.1 Encephalopathies and Neuropathies

Metabolic encephalopathies and peripheral neuropathies may occur in dogs and cats with uremia.[31,32] It is reported that as many as 65% of dogs and cats with primary renal insufficiency or renal failure have neurologic manifestations. Of dogs with neurologic signs, altered consciousness (31% of patients) and seizures (29% of patients) were the most common signs.[32] In the authors' experience, acute onset of altered mentation is an important neurologic finding in dogs and cats with CKD that typically heralds a poor short-term prognosis. Other common signs include limb weakness, ataxia, and tremors. Patients may develop what has been described as the *twitch-convulsive* state, wherein the simultaneous combination of tremor, myoclonus, and seizures is seen. In advanced CKD, patients may have neurologic signs that are

cyclical and episodic, varying from day to day. The severity and rate of progression of neurologic signs appears to vary directly with the rapidity with which uremia develops.

The pathogenesis of uremic neurologic signs remains unclear, but important roles for PTH and the uremic environment are suspected.[31] Both the sodium potassium adenosine triphosphate pump and several of the calcium pumps are altered in uremia. Alterations in the calcium pumps have been thought to be due at least in part to PTH acting through monophosphate-independent pathways. Calcium pumps are particularly suspected of playing a role in uremic encephalopathy because they mediate neurotransmitter release and information transfer at nerve terminals. Clinical signs of tremors, myoclonus, and tetany may develop due to hypocalcemia. Arterial hypertension may also lead to neurologic signs in patients with otherwise well-controlled renal failure. Clinical signs are acute in onset and may include seizures, behavioral changes, dementia, isolated cranial nerve deficits, and death. In the authors' experience, many of the patients with acute onset of neurologic signs also had hypertension.

Imbalances of neurotransmitter amino acids within the brain have also been implicated in uremic encephalopathy. Analysis of cerebrospinal fluid (CSF) in humans with uremic encephalopathy has shown decreased levels of glutamine and GABA, as well as increased levels of glycine, dopamine, and serotonin.

260.2.5.2 Myopathies

Hypokalemic polymyopathy is occasionally observed in association with CKD, primarily in cats. Because of the influence of potassium on resting cell membrane potentials, potassium imbalances typically manifest clinically as neuromuscular dysfunction. Hypokalemia increases the magnitude (i.e., increases electronegativity) of the resting potential, thereby hyperpolarizing the cell membrane, making it less sensitive to exciting stimuli. The cardinal and most dramatic sign of hypokalemia, regardless of cause, is generalized muscle weakness. In hypokalemic polymyopathy, muscle weakness and pain present clinically as cervical ventroflexion and a stiff, stilted gait.[33] Mild cardiac rhythm disturbances may also occur. Serum creatinine kinase and other muscle enzyme activities may be elevated, and in severe instances, rhabdomyolysis may occur.

Muscle dysfunction unrelated to serum potassium concentrations may also occur in uremia. In humans with CKD, accumulation of a dialyzable uremic toxin derived from dietary protein has been shown to promote abnormalities in sarcolemma ion flux leading to reduced muscle membrane potential.

260.2.6 Hematologic Consequences

260.2.6.1 Anemia

The anemia of renal failure is usually characterized by normochromic and normocytic red blood cells (RBCs). Usually hypoplasia of the erythroid precursors in the bone marrow occurs, with little or no interference with normal leukopoiesis and megakaryocytopoiesis. On blood smears, spiculed and deformed red cells (burr cells or echinocytes) may be noted. Although affected by the patient's age, species, specific renal diagnosis, and concurrent diseases, the severity and progression of the anemia correlates with the degree of renal failure and worsens with progressive renal failure in both dogs and cats.[34]

The hematocrit may become profoundly low. At these low hematocrits, compensatory mechanisms such as increased levels of 2,3 DPG; lowered peripheral vascular resistance; and an elevated cardiac output (in the

absence of previous cardiac disease) help maintain tissue oxygenation. Clinical signs of anemia include pallor of the mucous membranes, fatigue, listlessness, lethargy, weakness, and anorexia.

Anemia in patients with CKD is multifactorial and may be exacerbated by concurrent illness. Although experimental and clinical evidence exists for the supporting roles of shortened red cell life span, nutritional abnormalities, erythropoietic inhibitor substances in uremic plasma, blood loss, and myelofibrosis, erythropoietin deficiency has clearly emerged as the principal cause of anemia in humans and animals with CKD. The peritubular fibroblasts of the renal cortex appear to be the major source of erythropoietin synthesis. It may also be produced by renal interstitial fibroblasts. The kidneys synthesize erythropoietin on demand in response to intrarenal tissue hypoxia due either to decreased oxygen-carrying capacity (anemia) or decreased oxygen content (hypoxia). Many CKD patients have a relative, rather than absolute, erythropoietin deficiency in that plasma levels exceed the normal range.[35] However, when compared with equivalently anemic but nonuremic patients, plasma erythropoietin concentrations are lower. Anemic CKD cats have been reported to have plasma erythropoietin concentrations similar to normal cats.[36] Erythropoietin deficiency of CKD has been hypothesized to result from decreased renal mass resulting in an insufficient cellular capacity for new hormone synthesis.

Other clinically important causes for anemia in dogs and cats with CKD are iron deficiency and chronic GI blood loss. In most patients, iron deficiency can only be detected by measuring serum iron, staining bone marrow biopsy samples for iron content, or through response to iron supplementation. Chronic GI hemorrhage may occur even in the absence of characteristic color changes in the feces. It can be suspected based on a hematocrit level that is unexpectedly low relative to the magnitude of renal dysfunction, and an elevation in the SUN/serum creatinine ratio.

260.2.6.2

Hemorrhagic Consequences of Uremia

Uremia may be associated with a hemorrhagic diathesis that is characterized by bruising, GI hemorrhage with hematemesis or melena, bleeding from the gums, or hemorrhage subsequent to venipuncture. GI hemorrhage can be an important route of blood loss leading to anemia and exacerbating azotemia and uremia. In renal failure, bleeding results from an acquired qualitative platelet defect, abnormalities in the interaction of platelets and the vessel wall, and biochemical and rheologic abnormalities in the blood itself.[37] Uremic platelet dysfunction appears to be multifactorial in origin. The platelet count is usually within the normal range or mildly decreased. Abnormal platelet aggregability, diminished thromboxane-A_2 production, abnormal intracellular calcium mobilization, and increased intracellular cAMP have been described in uremic platelets.[37] Abnormal glycoprotein function may impair platelet adhesiveness to the subendothelium. In addition, uremia may be associated with increased release of prostacyclin and nitric oxide, which may also impair adhesion of platelets to the endothelium. The largest polymers of von Willebrand's factor, which predominate in the platelet adhesion process, are decreased in uremia. Uremic toxins have also been implicated in impairing platelet function. For example, elevated levels of plasma guanidinosuccinic acid, interfere with activation of platelet factor III by ADP, thus leading to abnormal platelet function. Administration of desmopressin acetate (DDAVP) has been shown to shorten bleeding times and improve clinical bleeding in uremic humans.[37] DDAVP is thought to stimulate release of large multimeric von Willebrand's factor complexes from endothelial cells and platelets.

Unfortunately, development of tachyphylaxis often limits usefulness of DDAVP after 2 or 3 doses. Alternative therapies have included administration of cryoprecipitates or conjugated estrogens, which may have similar effects. Increasing hematocrit values to above 30 by transfusion or administration of

erythropoietin has also been shown to improve bleeding times in humans. Increasing hematocrit may improve bleeding times by a rheologic effect or by increasing hemoglobin concentrations that may in turn inactivate the platelet-inhibiting effects of nitric oxide. 1766 1767

260.2.7 Renal Secondary Hyperparathyroidism

260.2.7.1 Incidence and Pathophysiology

In a recent study of cats with spontaneous CKD, the overall prevalence of renal secondary hyperparathyroidism was 84%.[38] Hyperparathyroidism occurred in 100% of cats with end-stage CKD and 47% of asymptomatic cats with only biochemical evidence of CKD. Hyperparathyroidism was even detected in some cats with normal serum calcium and phosphorous concentrations. Plasma PTH concentrations have been reported to increase as serum creatinine concentrations increase.[39]

The pathogenesis of hyperparathyroidism in CKD is multifactorial. Renal secondary hyperparathyroidism occurs in association with phosphorous retention, hyperphosphatemia, low circulating 1,25-dihydroxyvitamin D (calcitriol) levels, reduced blood ionized calcium concentration, and skeletal resistance to the calcemic action of PTH. However, in early to moderate renal failure, it is difficult to dissect out the specific factors responsible for hyperparathyroidism because the increase in PTH serves to prevent hypocalcemia, hyperphosphatemia, and the decrease in calcitriol formation.[40] Phosphorous retention and hyperparathyroidism develop early in CKD, although serum calcium and phosphorus concentrations remain within normal limits.[41] Phosphorous retention is intimately related to development of secondary hyperparathyroidism.[42,43]

Relative or absolute deficiency of calcitriol has been hypothesized to play a pivotal role in development of renal secondary hyperparathyroidism.[44] Calcitriol, the most active form of vitamin D, is formed by 1α-hydroxylation of 25-hydroxycholecalciferol in renal tubular cells. PTH promotes renal 1α-hydroxylase activity and formation of calcitriol. In turn, calcitriol limits PTH synthesis by feedback inhibition. Phosphrous retention inhibits renal 1α-hydroxylase activity. Early in the course of CKD, the inhibitory effects of phosphorus retention on renal tubular 1α-hydroxylase activity limits calcitriol production. Because calcitriol normally inhibits PTH synthesis, reduced calcitriol synthesis promotes renal secondary hyperparathyroidism. Initially, the resultant hyperparathyroidism increases 1α-hydroxylase activity despite continued phosphorous retention, thereby restoring calcitriol production toward normal. However, normalization of calcitriol production occurs at the expense of persistently elevated plasma PTH activities—a classic example of the *trade-off hypothesis*. As renal failure progresses, loss of viable renal tubular cells ultimately limits renal calcitriol synthetic capacity and calcitriol levels subsequently remain low. Deficiency of calcitriol leads to skeletal resistance to the action of PTH and elevates the set point for calcium-induced suppression of PTH secretion. Skeletal resistance to PTH limits skeletal release of calcium, whereas elevating the setpoint for PTH secretion allows hyperparathyroidism to persist even when plasma ionized calcium concentrations are normal or elevated.[39,44]

Recent evidence suggests that phosphorous retention may also play a primary role in promoting hyperparathyroidism. Phosphorous has been shown to stimulate PTH secretion in parathyroid cell cultures.[45] Further, phosphorous restriction in dogs and humans with CKD has been shown to decrease PTH secretion without changing serum calcitriol levels.[46,47] In untreated human patients with mild to moderate CKD (serum creatinine concentration ≤3.0 mg/dL), serum phosphorus concentrations correlated

directly with PTH, independent of serum calcium and 1,25-dihydroxyvitamin D levels.[48] Interestingly, this correlation was present despite the fact that most patients had serum phosphorous concentrations within the normal range. Notably, in both humans and cats, overt hyperphosphatemia may not be a prerequisite for phosphorous to have an effect on PTH secretion.[38,48] It has been suggested that high phosphorous intake may accentuate uremia-induced abnormal phosphorous metabolism causing increased parathyroid cell phosphorous concentration.[48] *In vitro* studies have suggested that parathyroid glands exposed to elevated phosphorous levels respond by increasing PTH secretion.[45] Reduced 1,25-dihydroxycholecalciferol may have a permissive effect, may have an additional direct effect on PTH secretion in this setting, or it may have both.[48]

In more advanced renal failure, only serum calcium concentration correlated with serum PTH activity.[48] Impaired intestinal absorption of calcium due to low serum calcitriol levels likely plays an important role in hyperparathyroidism in these advanced renal failure patients. Blood ionized calcium concentrations are often reduced in cats with spontaneous CRF; in one study, over 50% of cats with advanced end-stage CKD were hypocalcemic.[38]

260.2.7.2

Clinical Consequences

Although renal secondary hyperparathyroidism and renal osteodystrophy, are well-documented effects of CKD, clinical signs associated with renal osteodystrophy are uncommon in dogs and cats. In dogs, it most often occurs in immature patients, presumably because metabolically active growing bone is more susceptible to the adverse effects of hyperparathyroidism. For unexplained reasons, bones of the skull and mandible may be the most severely affected and may become so demineralized that the teeth become moveable and fibrous changes are obvious, particularly in the maxilla. Marked proliferation of connective tissue associated with the maxilla may cause distortion of the face. Jaw fractures can occur but are uncommon. Other possible but uncommon clinical manifestations of severe renal osteodystrophy include, cystic bone lesions, bone pain, and growth retardation.

Although excessive levels of PTH affect bones and kidneys, it affects the function of other organs and tissues, including brain, heart, smooth muscles, lungs, erythrocytes, lymphocytes, pancreas, adrenal glands, and testes as well.[49] Toxicity of PTH appears to be mediated through enhanced entry of calcium into cells with PTH or PTH2 membrane receptors. Sustained PTH-mediated calcium entry leads to inhibition of mitochondrial oxidation and production of ATP. Extrusion of calcium from cells is reduced because of the impairment in ATP production and disruption of the sodium-calcium exchanger. Persistently increased basal cytosolic calcium levels promote cellular dysfunction and death.[39]

Potential nonskeletal clinical consequences of hyperparathyroidism include mental dullness and lethargy, weakness, anorexia, and an increased incidence of infections due to immunodeficiency.[39] Hyperparathyroid-induced cellular dysfunction may lead to carbohydrate intolerance, platelet dysfunction, impaired cardiac and skeletal muscle function (due to impaired mitochondrial energy metabolism and myofiber mineralization), inhibition of erythropoiesis, altered red cell osmotic resistance, altered B cell proliferation, synaptosome and T cell dysfunction, and defects in fatty acid metabolism.[39,50] Excess PTH levels may also promote nephrocalcinosis and consequent progressive loss of renal function.[39]

Renal secondary hyperparathyroidism may be associated with substantial enlargement of the parathyroid glands. This finding may be of clinical importance in cats because of frequent coincident hyperthyroidism

that may be suggested by the presence of a thyroid nodule palpable in the cervical region. In a recent report, hyperplastic parathyroid glands were palpable as paratracheal masses in 11 of 80 cats with spontaneous CKD.[2] Care should be taken to confirm hyperthyroidism prior to treatment because both hyperparathyroidism and hyperthyroidism can lead to paratracheal masses.

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Plasma PTH concentrations should be determined by methods that measure intact PTH using a two-site immunoradiometric or immunochemiluminometric assay. The two-site method uses antibodies directed against two different regions of the intact PTH molecule. A commercially available two-site immunoradiometric assay (Allegro Intact PTH, Nichols Institute Diagnostics, San Juan Capistrano, CA) has been validated for use in dogs and cats. Only intact PTH will be recognized because it will be the only form of the peptide to have both determinants. Older PTH assays typically detect those species of hormone that contain amino acids located in the midregion (43 to 68) of the PTH molecule.

However, because renal insufficiency and failure results in reduced renal clearance of the nonbiologically active midregion PTH fragments, these methods do not accurately reflect parathyroid glandular secretion. Thus renal secondary hyperparathyroidism is best monitored by use of a two-site assay for intact hormone.

260.2.8 Laboratory Findings

260.2.8.1 Metabolic Acidosis

Metabolic acidosis is a common manifestation of CKD. It results primarily from the limited ability of failing kidneys to excrete hydrogen ions, because of reduced ammoniagenesis, decreased filtration of phosphate and sulfate compounds, and decreased maximal renal tubular proton secretion.[51] Impaired renal tubular reabsorption of filtered bicarbonate may also contribute to acidosis. Bicarbonate wasting and chloride retention results in hyperchloremic (normal anion gap) acidosis. When phosphorous and organic acid (uric acid, hippuric acid, lactic acid) retention is sufficient, high anion gap acidosis results.

A combination of tubular reabsorption of filtered bicarbonate and excretion of hydrogen ions with ammonia and urinary buffers, primarily phosphorous, maintains normal acid-base balance. As renal function declines, hydrogen ion excretion is maintained largely by increasing the quantity of ammonium excreted by surviving nephrons. However, at some level of renal dysfunction, the capacity to further increase renal ammoniagenesis is lost and metabolic acidosis ensues. Decreased medullary recycling of ammonia due to structural renal damage may also contribute to impaired ammonium excretion.

Chronic metabolic acidosis may promote a variety of adverse clinical effects including anorexia, nausea, vomiting, lethargy, weakness, muscle wasting, weight loss, and malnutrition. Alkalization therapy is often of value in reversing these signs. In addition, chronic mineral acid feeding to dogs has been shown to increase urinary calcium excretion and progressive bone demineralization, the magnitude of which depends on age and dietary calcium levels. Studies on the effects of dietary acidification in cats have revealed that chronic metabolic acidosis can cause negative calcium balance and bone demineralization or negative potassium balance, which may in turn promote hypokalemia, renal dysfunction, and taurine depletion.[52]

Severe acidemia may result in decreased cardiac output, arterial pressure, and hepatic and renal blood flows and centralization of blood volume.[53] Centralization of blood volume results from peripheral arterial vasodilatation and central venoconstriction. Decreases in central and pulmonary vascular compliance may predispose patients to pulmonary edema during fluid administration, an effect that may be particularly

important in patients with acute uremic crises requiring intensive fluid therapy. Acidemia also promotes re-entry arrhythmias and a reduction in the threshold for ventricular fibrillation. Severe acidosis may also influence carbohydrate and protein metabolism, serum potassium concentrations, and brain metabolism.

Chronic acidosis may promote protein malnutrition in patients with CKD. Protein catabolism is increased in patients with acidosis to provide a source of nitrogen for hepatic glutamine synthesis, glutamine being the substrate for renal ammoniagenesis.[54] The combined effects of reduced protein synthesis due to uremia and accelerated proteolysis due to acidosis promote elevations in blood urea nitrogen (BUN), increased nitrogen excretion, and negative nitrogen balance typical of uremic acidosis. Altered branched chain amino acid metabolism appears to be involved. Chronic metabolic acidosis increases the activity of muscle branched chain keto acid dehydrogenase, the rate-limiting enzyme in branched chain amino acid catabolism. This is important in that branched chain amino acids are rate limiting in protein synthesis and play a role in regulation of protein turnover. Alkalization therapy effectively reverses acidosis-associated protein breakdown. Clinicians speculate that changes in intracellular pH accompanying acidosis lead to alterations in gene transcription which increase the activity of the cytosolic, ATP-and ubiquitin-dependent protein degradation pathway. Severe chronic metabolic acidosis has the potential to induce a cycle of progressive protein malnutrition and metabolic acidosis. Excessive protein catabolism may lead to protein malnutrition despite adequate dietary intake. This process may then accelerate breakdown of endogenous cationic and sulfur-containing amino acids, thus promoting further acidosis.

Acidosis poses a particularly vexing problem for CKD patients consuming protein-restricted diets. Dietary protein requirements appear to be similar for normal humans and humans with CKD unless uremic acidosis is present. When acid-base status is normal, adaptive reductions in skeletal muscle protein degradation protect patients consuming low-protein diets from losses in lean body mass. Metabolic acidosis blocks the metabolic responses to dietary protein restriction in two ways: (1) it stimulates irreversible degradation of the essential, branched chain amino acids; and (2) it stimulates degradation of protein in muscle.[54] Thus acidosis may limit the ability of patients to adapt to dietary protein restriction. Metabolic acidosis also suppresses albumin synthesis in humans and may reduce the concentration of serum albumin. These findings have not yet been confirmed in dogs and cats.

260.2.8.2 Azotemia

Azotemia is defined as an excess of urea or other nonprotein nitrogenous compounds in the blood. Loss of renal function leads to accumulation of a wide variety of nonprotein nitrogen-containing compounds, including urea and creatinine. Many waste products of protein catabolism are excreted primarily by glomerular filtration. Thus patients with primary renal failure have impaired ability to excrete proteinaceous catabolites because of marked reduction in GFR. Retention of metabolic waste may be further aggravated by impaired tubular secretion, and by extrarenal factors that promote renal hypoperfusion and increased catabolism of body tissues. Although accumulation of wastes is largely the result of decreased renal excretion or increased protein catabolism, production of some compounds may also be increased (e.g., guanidine). Because these compounds are derived almost entirely from protein degradation, their production increases when dietary protein increases.

Urea is synthesized using nitrogen derived from amino acid catabolism. Urea may be excreted by the kidneys, retained in body water, or metabolized to ammonia plus carbon dioxide by bacteria in the GI tract. Ammonia produced in the GI tract is recycled to urea in the liver yielding no net loss of nitrogen or urea. Regardless of whether urea per se is toxic, BUN concentrations are typically directly related to the protein content of the diet. Further, in patients with renal failure, BUN concentrations tend to correlate reasonably

well with clinical signs of uremia. For practical purposes, BUN may thus be viewed as a marker of retained *uremic toxins*.

In addition to increasing protein intake and declining renal function, BUN concentrations may also be increased by GI hemorrhage, enhanced protein catabolism, decreasing urine volumes (due to prerenal factors such as dehydration), and certain drugs (e.g., glucocorticoids). Urea nitrogen concentrations may decline with portosystemic shunts, hepatic failure, and low protein diets. Reduced BUN concentration may also indicate protein calorie malnutrition. Because many extrarenal factors may influence BUN concentration, creatinine is often used as a more reliable measure of GFR in patients with CKD. 1768 1769

BUN concentrations should be interpreted with knowledge of simultaneously obtained serum creatinine values, particularly in patients consuming reduced protein diets. The ratio of BUN/serum creatinine concentration should decline when dietary protein intake is reduced. In patients consuming reduced protein diets, an increase in the ratio of BUN/serum creatinine concentrations may suggest poor dietary compliance, enhanced protein catabolism, GI hemorrhage, dehydration, anorexia or declining muscle mass.

260.2.8.3 Hyperphosphatemia

The kidneys play a pivotal role in regulating phosphorus balance because they are the primary route of phosphorus excretion. Renal phosphorus excretion is the net of glomerular filtration less tubular reabsorption of phosphorus. If dietary phosphorus intake remains constant, a decline in GFR will lead to phosphorus retention and ultimately hyperphosphatemia. However, during the early stages of renal failure, serum phosphorus concentrations typically remain within the normal range because of a compensatory decrease in phosphorous reabsorption in the surviving nephrons. This renal tubular adaptation is largely an effect of renal secondary hyperparathyroidism. Increased PTH levels promote renal excretion of phosphorous by reducing the tubular transport maximum for phosphorous reabsorption in the proximal tubule via the adenyl cyclase system. When GFRs decline below about 20% of normal, this adaptive effect is no longer is able to prevent hyperphosphatemia.

In dogs with CKD, serum phosphorus concentrations typically parallel SUN concentrations. Thus hyperphosphatemia is common in azotemic patients but unexpected in patients with nonazotemic renal disease. The primary consequence of hyperphosphatemia is development and progression of secondary hyperparathyroidism. Increases in serum PTH activities in dogs and humans with CKD are closely associated with the degree of hyperphosphatemia.[39,48] Hyperphosphatemia was found to be 72% efficient in predicting hyperparathyroidism in cats with CKD.[38]

The combination of hyperphosphatemia and a normal plasma calcium concentration produces an elevated calcium-phosphate product ($Ca \times PO_4$ in units of mg/dL). If the calcium-phosphate product exceeds approximately 70, a tendency exists for calcium phosphate to precipitate in arteries, joints, and soft tissues. This process is commonly called *metastatic calcification*. Calcification is especially prominent in proton-secreting organs, such as the stomach and kidneys, in which basolateral bicarbonate secretion results in an increase in pH that promotes calcium hydrogen phosphate (brushite) precipitation.[55] However, myocardium, lung, and liver are also commonly mineralized in patients with CKD.

Hyperphosphatemia has been directly linked to increased mortality in humans and dogs with CKD.[56,57] In humans with CKD receiving hemodialysis therapy, the adjusted relative risk of mortality was stable in patients with serum phosphorous concentrations below 6.5 mg/dL, but increased significantly above this

level.[56] Patients with serum phosphorous in the 6.6 to 7.8 mg/dL range had 13% higher mortality than patients in the reference range (4.6 to 5.5 mg/dL). Patients in the 7.9 to 16.9 mg/dL range had a relative mortality risk 34% higher than patients in the reference range. Mild hyperphosphatemia (5.0 to 6.5 mg/dL) was not associated with an elevated mortality risk.

The calcium × phosphorous product showed a mortality risk trend similar to that seen for phosphate with patients with Ca × PO_4 products greater than 72 having a relative mortality risk of 1.34 relative to products between 42 and 52 mg^2/dL^2.[56] Mortality risk associated with hyperphosphatemia appeared to be independent of elevated PTH levels, which alone appeared to have only a weak association with mortality. However, the statistical association between PTH and mortality may have been impaired by use of multiple methods for PTH assay in the patients studied. Analysis of calcium revealed no correlation with relative risk of death.[2]

260.2.8.4 Hypercalcemia, Hypocalcemia, and Hypermagnesemia

Hypocalcemia is a common disorder of calcium found in patients with renal failure. In a recent report, ionized hypercalcemia was detected in 6% and ionized hypocalcemia in 26% of 80 cats with spontaneous CKD.[38] Further, mean blood ionized calcium concentration was significantly lower in CKD cats in this study than in normal control cats, and over half of the cats with advanced end-stage CKD were hypocalcemic. However, when these same 80 cats were evaluated using total serum calcium concentrations, hypercalcemia was found in 21% of the cats, whereas hypocalcemia was detected in only 8%. Clearly, serum total calcium concentrations do not reliably reflect ionized calcium concentrations in cats with CKD. Similar discrepancies have been observed in dogs with CKD.[58] The mechanism of serum total hypercalcemia in the face of normal to reduced blood ionized calcium concentrations is unclear but may be related to increased concentrations of calcium complexed to retained organic and inorganic anions such as citrate, phosphate, or sulfate.

In patients with hypercalcemia, it is important to ascertain whether hypercalcemia is the cause, rather than result of CKD. Hypercalcemia due to malignancy or hypervitaminosis D is most likely to induce renal failure. One way of discriminating the cause-and-effect relationship between hypercalcemia and renal failure is to determine the patient's blood ionized calcium concentration. Only ionized hypercalcemia promotes renal failure. However, true ionized hypercalcemia may occur in patients with CKD as a consequence of excessive doses of calcitriol or calcium-containing intestinal phosphate-binding agents or in patients with severe renal secondary hyperparathyroidism with marked hyperplasia of the parathyroid glands. The authors have also observed small increases in ionized calcium concentrations in dogs with early to moderate CKD that are not receiving calcitriol or calcium therapy and do not have advanced hyperparathyroidism. The mechanism of ionized hypercalcemia in these dogs is unclear.

Hypermagnesemia is common in CKD because the kidneys are primarily responsible for magnesium excretion.[38] Typically in CKD, the protein binding of magnesium is normal, complexed magnesium is usually increased, and ionized magnesium may be increased, normal, or decreased. Although the homeostatic mechanisms involved in the control of magnesium are not well documented, they appear to rely on the bone, gut, and kidney, as found with calcium and phosphorous control.

260.2.8.5 Hypokalemia

An association between CKD and hypokalemia has been recognized in cats by several investigators.[59,60] In contrast, hypokalemia appears to be an uncommon finding in untreated dogs with CKD, occurring primarily as an iatrogenic complication of fluid therapy in this species. A particularly intriguing concept is that hypokalemia may be a cause of CKD in cats, rather than simply a consequence of it. In a recent uncontrolled study of the long-term effects of feeding a potassium-restricted, acidifying diet, evidence of renal dysfunction developed in three of 9 cats; renal lesions consisting of lymphoplasmacytic interstitial nephritis and interstitial fibrosis were observed in five of the 9 cats.[60] However, it is not clear whether potassium depletion or hypokalemia preceded the onset of renal failure. In another study, four of seven cats with induced CKD fed a diet containing 0.3% potassium developed hypokalemia, whereas four cats with normal renal function fed the same diet did not develop hypokalemia.[61] Interestingly, muscle potassium content decreased in normokalemic cats with spontaneous CKD, indicating that a total-body deficit of potassium may develop well before the onset of hypokalemia.[62] These findings support the concept that reduced renal function precedes development of hypokalemia.

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The mechanism of hypokalemia in cats with CKD has remained elusive, but inadequate intake and increased renal losses appear to be likely candidates. Inadequate intake of potassium could reflect decreased appetite or insufficient dietary potassium content. Dietary risk factors for hypokalemia include acidifying ingredients, reduced magnesium content, and high protein content. It has yet to be established that renal potassium wasting occurs in cats with CKD.

Normally the kidneys closely regulate potassium. Although large quantities of K+ appear in glomerular filtrate, essentially all is reabsorbed before reaching the distal tubules. The majority of potassium appears in urine as a result of potassium secretion from tubular cells into the lumen in the distal nephron. Potassium excretion in these segments of the nephron is sensitive to tubular flow rates; rapid urine formation promotes potassium secretion, whereas slow urine formation limits potassium secretion. Distal potassium secretion is modulated by potassium reabsorption by the intercalated cells in the cortical and outer medullary collecting tubules. Thus in potassium depletion, net potassium absorption rather than secretion may occur in the distal nephron.

In patients with CKD, the residual nephrons maintain potassium balance by increasing distal tubular secretion of potassium. GI secretion of potassium (primarily in the colon) also appears to increase in CKD and may play an important role in modulating potassium balance. Because of these adaptations, most dogs and cats with CKD are able to tolerate normal dietary potassium intake (about 0.6% dry matter) until renal dysfunction is very severe. However, the ability to rapidly excrete a potassium load may be impaired in CKD resulting in transient hyperkalemia.

Although hypokalemia continues to be detected with some regularity in cats with CKD, its neuromuscular manifestations are uncommon. Presumably this change is the result of an increase in the potassium content of feline diets that has occurred over the past decade in response to the problem of hypokalemia in cats with CKD.

Although generalized muscle weakness has been described as the cardinal sign of hypokalemia, decreased renal function and anorexia are probably more common manifestations of hypokalemia in cats with CKD. In many cats with CKD and hypokalemia, renal function improves after potassium supplementation and restoration of normokalemia, suggesting that hypokalemia may induce a reversible, functional decline in

GFR. Recently, renal function was shown to be adversely affected in normal cats when an acidified, potassium-restricted diet was fed.[63] Potassium depletion and acidosis appeared to have additive effects in impairing renal function in this study. Based on these results, it was hypothesized that in cats with CKD, a self-perpetuating cycle of excessive urinary potassium losses and whole-body potassium depletion may develop that is likely to further decrease in renal function. Feeding acidified diets or dietary acidifiers to cats with CKD was suggested to exacerbate their tendency develop potassium depletion.

Potassium imbalances may disrupt a variety of cell functions. Hypokalemia-impaired protein synthesis has been hypothesized to promote weight loss and poor hair coat.[33] Marked potassium depletion has also been linked to polyuria resulting from decreased renal responsiveness to ADH. This antagonism to ADH appears to be due to interference with generation and action of cyclic AMP and to impairment of the countercurrent mechanism. Locally generated prostaglandins may mediate at least part of this effect.

260.2.9 Progression of Chronic Kidney Disease

A progressive decline in kidney function typically occurs over months to years in dogs and cats with naturally occurring kidney diseases.[64] It is logical to assume that CKD progresses as a consequence of continuing renal damage induced by the disease process that initiated CRF. Although this assumption may be at least partially correct for some patients, the initiating cause cannot be identified at the time of diagnosis of CKD in most patients. Instead, renal lesions observed in progressive nephropathies of diverse origins typically include focal segmental glomerulosclerosis and tubulointerstitial lesions (including tubular dilation and interstitial inflammation and fibrosis). Glomerular lesions accompanied by varying levels of proteinuria are typical of progressive kidney diseases including primary tubulointerstitial diseases. In humans, both the decline in GFR and long-term prognosis are more closely related to the extent of associated tubulointerstitial lesions than glomerular lesions.[65]

In rodents, loss of a critical mass of functional renal tissue invariably leads to failure of the remaining nephrons, suggesting that CKD may progress through mechanisms independent of the initiating cause.[66] For example, removal of approximately three quarters or more of the nephrons in rats by surgical resection, infarction, or a combination of these techniques, results in a syndrome of progressive azotemia, proteinuria, arterial hypertension, and eventually death due to uremia. Lesions that develop in the remaining kidney remnant include focal segmental glomerulosclerosis and tubulointerstitial lesions, including tubular dilation and interstitial inflammation and fibrosis. Progressive renal injury and loss of renal function occurs in this rodent model of kidney failure, despite the fact that the remaining kidney remnant was initially normal.

Numerous studies have been performed in an attempt to determine if findings obtained in partially nephrectomized rodents are relevant in dogs and cats. Reducing renal mass in dogs and cats resulted in mild proteinuria, glomerulopathy, and tubulointerstitial renal lesions.[61,67,68] Although these findings are consistent with observations in rats, reducing renal mass by seven eighths or less did not consistently result in a progressive decline in GFR. In studies performed at the University of Georgia, progressive decline in GFR was detected in dogs in which renal mass had been reduced by fifteen sixteenths.[57] These findings confirm that progressive renal disease develops in dogs; however, a marked reduction in renal mass may be necessary to initiate this process in an otherwise normal remnant kidney.

The preponderance of clinical and experimental evidence suggests that in dogs and cats with stages 3 and 4 CKD, progression of renal disease may result, at least in part, from factors unrelated to the activity of the

inciting disease.[4,69,70] These factors may include intraglomerular hypertension, glomerular hypertrophy, hypertension, proteinuria, tubulointerstitial disease, and intrarenal precipitation of calcium phosphate.

260.2.9.1 Intraglomerular Hypertension and Glomerular Hypertrophy

Long-term elevations in intraglomerular pressure, resulting from transmission of systemic pressures, glomerular hemodynamic processes, or both, appear to be deleterious over time. Intraglomerular hypertension, with consequent glomerular hyperfiltration, occur as a compensatory event designed to maintain the total GFR as nephrons are lost to disease. In glomerular diseases, intraglomerular hypertension may also occur as a compensatory adaptation to reduction in permeability of the glomerular capillary wall 1770
to small solutes and water. In this setting, the fall in GFR is minimized by elevating intraglomerular 1771
pressure. Primary renal vasodilatation may occur in some diseases such as diabetes mellitus. A compensatory increase in glomerular size may also occur in all of these settings.

The mechanisms by which intraglomerular hypertension and hypertrophy injure glomeruli are incompletely understood, because multiple factors are involved. Intraglomerular hypertension may directly injure endothelial cells of the glomerular capillaries. In addition, increased glomerular diameter and increased capillary wall stress may cause detachment of glomerular epithelial cells from the glomerular capillary walls. The consequent focal areas of denudation permit increased flux of water and solutes through the glomerular capillary wall. However, macromolecules cannot cross the glomerular basement membrane and are trapped in the subendothelial space.

The result is formation of characteristic *hyaline deposits* in glomeruli that progressively narrow the capillary lumens, thereby decreasing glomerular perfusion and filtration. Increased strain on mesangial cells can stimulate them to produce cytokines and extracellular matrix. The release of cytokines, such as transforming growth factor-β (TGF-β) and platelet-derived growth factor, may mediate the rise in matrix synthesis.[71] The consequent expansion of mesangial matrix further encroaches on the capillary surface area.

Although these effects lead to the characteristic glomerular lesions of progressive nephropathies, intraglomerular hypertension also impairs glomerular permselectivity leading to proteinuria. Proteinuria is thought to be an important pathophysiologic link between glomerular injury, tubulointerstitial injury, and progression of renal disease.

260.2.9.2 Systemic Hypertension

In humans, the association between systemic hypertension and kidney disease is well established. The Multiple Risk Factor Intervention Trial (MRFIT) identified systemic hypertension as a significant risk factor for development of end-stage kidney disease.[72] A similar association has recently been identified in dogs.[18] Further, in the Modification of Diet in Renal Disease (MDRD) study, the level of systemic blood pressure was linked to progression of kidney disease among black and proteinuric human CKD patients.[73]

Systemic hypertension leads to progression of kidney disease, at least in part, through unopposed transmission of systemic hypertension to the glomerular capillary bed resulting in glomerular injury. This event occurs particularly in patients with CKD because autoregulation of blood flow, which normally protects glomerular capillaries from excessive pressure, is impaired. Studies in dogs and cats have confirmed that reduced kidney function is associated with an adaptive preglomerular vasodilatation that permits transmission of systemic hypertension to the glomerular capillaries.[70,74]

260.2.9.3 Proteinuria

Proteinuria itself may contribute to progressive renal injury.[20] Proteinuria is a strong, independent risk factor for progression to end-stage CKD in humans.[75] Studies performed at the University of Minnesota Veterinary Medical Center have shown proteinuria to be a risk factor for uremia and death in dogs with naturally occurring CKD. Proteinuria has also been reported to be related to progression of renal disease in dogs with induced renal failure.[69] A relationship between proteinuria and progression of renal disease has not yet been established in cats. Proteinuria may promote progressive renal injury in several ways. Some proposed mechanisms include mesangial toxicity, tubular overload and hyperplasia, toxicity from specific proteins such as transferrin containing iron, and induction of proinflammatory molecules such as monocyte chemoattractant protein-1. Excessive proteinuria may injure renal tubules via toxic or receptor-mediated pathways or via an overload of lysosomal degradative mechanisms. Abnormally filtered proteins accumulate in the renal proximal tubular lumens where, after endocytosis into proximal tubular cells, they contribute to renal tubulointerstitial injury through a complex cascade of intracellular events. These events include up-regulation of vasoactive and inflammatory genes such as the endothelin-1 (ET-1) gene, the monocyte chemoattractant protein-1 (MCP-1) gene, which encodes for an inflammatory peptide involved in macrophage and T-lymphocyte recruitment, and the RANTES (regulated on activation, normal T cell expressed and secreted) that encodes for a chemotactic molecule for monocytes and memory T cells.[76] Formed in excessive amounts, these molecules are secreted toward the basolateral side of tubular cells and incite an inflammatory reaction. In addition, complement components escaping through glomerular capillary walls may initiate interstitial injury. Small lipids bound to filtered proteins may also be liberated during resorption. Inflammatory or chemotactic properties of these lipids may promote tubulointerstitial disease. Finally, inspissation of filtered proteins due to tubular reabsorption of water in the distal nephron may lead to formation of casts that obstruct nephrons.

260.2.9.4 Tubulointerstitial Disease in Glomerulopathies

In humans, primary glomerular diseases are typically associated with varying degrees of tubulointerstitial lesions. Remarkably, it is the intensity of the accompanying or evolving injury in the tubulointerstitium, rather than injury in glomeruli, that is the most reliable overall predictor of decline in renal function.[77] In contrast, primary tubulointerstitial diseases as a group are the more indolent and slowly progressive of all human nephritides. Although the etiopathogenesis of canine and feline nephropathies is often uncertain, current evidence suggests that a substantial portion of canine CKD results from primary glomerulopathies, whereas the majority of feline CKD appears to be of tubulointerstitial origin.[11,78] The indolent course of CKD commonly observed in cats may be related to the tubulointerstitial origin of their disease, whereas many dogs experience a more aggressive decline in renal function, perhaps as a consequence of the glomerular origin of their primary renal disease.

Glomerular diseases have the capacity to incite tubulointerstitial disease. Although the mechanisms underlying the development of tubulointerstitial disease in this setting are not incompletely understood, multiple factors have been hypothesized to contribute.[77] As described previously, proteinuria is an important factor.[79] Additional factors include tubular ischemia related to decreased postglomerular blood flow; loss of tolerance with subsequent tubulointerstitial damage secondary to immune mechanisms of glomerular injury; seeping of inflammatory mediators from inflamed glomeruli; renal deposition of calcium phosphate; and enhanced tubular ammoniagenesis leading to complement-mediated injury of the

tubulointerstitium.[77] Evidence indicates that an active immunologic process may be involved in the tubulointerstitium of patients with glomerulonephritidies beginning early in the course of disease. In some instances this process appears to represent an extension of the inflammation in glomeruli.[77] In some models of renal disease, corticosteroids or other immunosuppressive therapy can ameliorate the tubulointerstitial damage without effect on glomeruli.[80]

260.2.9.5 Intrarenal Precipitation of Calcium Phosphate

Phosphate retention begins early in the course of CKD and has been implicated in promoting progressive renal injury in several species, including dogs and cats.[57,70,81] A role for phosphorus in promoting progressive CKD is based on the observation that dietary phosphorus restriction limited renal-related mortality in dogs and renal mineralization in cats. Phosphorus may promote progression of CKD, at least in part, by precipitation with calcium in the renal interstitium. This renal mineralization may then initiate an inflammatory reaction, resulting in renal interstitial fibrosis and tubular atrophy.

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260.2.9.6 Other Factors

260.2.9.6.1 Lipids and progression

Experimental studies in rodents indicate that hyperlipidemia may promote progression of renal disease.[82] This association is based on the observation that cholesterol loading enhanced glomerular injury, whereas reducing lipid levels with drugs such as lovastatin slowed the rate of progressive injury. Factors responsible for these effects are incompletely understood. Exposing glomerular and tubular cells to low-density lipoprotein and its oxidized variant stimulates their proliferation, induces injury and apoptosis, and stimulates them to produce extracellular matrix contributing to fibrosis.[19] An additive effect of hyperlipidemia and proteinuria has been described in humans with CKD.[83] Although hypercholesterolemia is common in dogs and cats with CKD, the clinical applicability of these findings in other species is unclear. Evidence that lipid reduction is beneficial in humans with CKD is conflicting. However, a meta-analysis of 13 prospective controlled studies indicated that lipid reduction was associated with a lower rate of decline in kidney function and decreased proteinuria.[84]

260.2.9.6.2 Metabolic acidosis

Metabolic acidosis has been theorized to enhance progression of renal failure by activation of the alternative complement pathway as a result of enhanced renal ammoniagenesis.[77] In human patients with CKD, reducing renal ammoniagenesis and renal tubular peptide catabolism was accompanied either by reduced renal tubular injury or by tubular hyperfunction. However, recent studies in rats have failed to confirm a role for acidemia and enhanced renal ammoniagenesis in renal injury and progression of renal failure.[85] Longer-term studies have suggested that effects initially attributed to enhanced renal ammoniagenesis may have been transient or related to the timing of therapeutic intervention in the previous study. These researchers concluded that metabolic acidosis neither causes nor exacerbates chronic renal injury. Further, the renal protective effect of alkali therapy is unproven in humans with CKD. Studies performed by the authors in cats with induced CKD have likewise failed to identify an adverse effect of chronic acidosis on renal structure or function.

260.2.9.6.3 Chronic hypoxia

It has been hypothesized that chronic oxygen deprivation to the tubulointerstitial compartment contributes to scarring in the tubulointerstitium.[86] Chronic hypoxia is thought to result from compromise of blood flow to the interstitial capillary network downstream from inflamed glomeruli. Concurrently, the peritubular capillary network downstream from other vasodilated glomeruli may be damaged subsequent to transmission of systemic blood pressures to this normally low-pressure capillary network. The resultant tubulointerstitial hypoxia is hypothesized to promote fibrosis by regulating gene expression of a broad spectrum of molecules including growth factors, hormones, vasoactive compounds, and enzymes. For example, *in vitro* studies have indicated that hypoxia is a profibrotic stimulus for tubular epithelial cells, interstitial fibroblasts, and renal microvascular endothelial cells. Hypoxia has been shown to induce a wide variety of growth factors, including many implicated in the pathogenesis of progressive renal disease, such as TGF-β1 and platelet-derived growth factor (PDGF).

The apparent beneficial role for ACE inhibitors in minimizing progressive renal diseases is consistent with the proposed role for chronic hypoxia. In theory, ACE inhibition could protect the kidneys by enhancing interstitial oxygen delivery through dilating the efferent arterioles, reducing vascular resistance, and improving microvascular flow through the interstitium.

260.3 DIAGNOSTIC EVALUATION

Patients with CKD should be evaluated to determine their diagnosis (type of kidney disease), severity, complications, comorbid conditions (concurrent diseases unrelated to CKD), and risk for continued loss of kidney function.[3] Morphologic diagnoses usually require evaluation of kidney biopsy samples. However, renal biopsies are indicated only when the benefits of renal biopsies (e.g., the results are likely to substantially change the prognosis or treatment) outweigh the associated risks.

Severity of CRD is classified based on the level of renal function. Serum creatinine concentration is the most commonly used measure of severity of renal dysfunction and is the basis for staging CKD (see Box 260-2). To optimize accuracy of staging of CRD, serum creatinine concentrations used to stage CRD should be evaluated when the patient is well hydrated. Multiple measurements are desirable to establish accuracy and stability of renal dysfunction. However, renal function may be more accurately measured using plasma clearances of iohexol, inulin, or other substances excreted exclusively by glomerular filtration.[87–91] Plasma clearance studies are indicated in at least three settings. First, they provide an accurate measure of renal dysfunction in stages 1 and 2 patients where serum creatinine determinations may be insensitive.

Second, they provide a basis for dose adjustments for drugs that are potentially toxic and are excreted primarily by the kidneys. Third, they are an excellent means of assessing progression of CKD. Because body muscle mass commonly declines as CKD progresses through stages 3 and 4, endogenous production of creatinine from muscle creatine may decline, confounding interpretation of serial serum creatinine values.

Appropriate management of complications and comorbid conditions may improve patient quality of life, as well as short-term and long-term survival (see Box 260-5). Diagnostics necessary to identify complications and comorbid conditions associated with CKD are outlined in Box 260-6. The prevalence of complications of CKD is mainly related to the level of renal function as reflected in the stage of CKD. CKD is typically characterized by alterations in a variety of kidney functions in addition to impaired GFR. These may include impairment of the (1) filtration barrier for plasma proteins (resulting in albuminuria and proteinuria), (2) reabsorption or secretion of

water or specific solutes, and (3) various endocrine functions (anemia due to erythropoietin deficiency, calcitriol deficiency, and renal secondary hyperparathyroidism). These functional derangements are the basis of most complications of CKD.

Comorbid conditions are concurrent diseases other than CKD. Because patients with CKD are typically middle-aged to older, they often have a substantial number of comorbid conditions. Comorbid conditions of particular frequency and concern for dogs and cats with CKD include UTIs, urolithiasis, urinary obstruction, degenerative joint diseases, dental and other oral diseases, and cardiac disease. In addition, hyperthyroidism and upper urinary tract uroliths are common and important comorbid conditions in cats with CKD. In a survey of 48 cats with CKD, the authors found that 27 had upper urinary tract stones. Comorbid conditions may have an important influence on prognosis and treatment.

The level of kidney function tends to decline over time for most patients with CKD. It is important to assess the risk for loss of kidney function so that therapy may be designed to minimize progressive decline in GFR can be initiated. The risk of progression of kidney disease is affected by diagnosis and by modifiable and nonmodifiable factors. Some of these factors can be assessed even before the decline in GFR (Box 260-7). Therapies designed to slow progression of CKD may be specific for the diagnosis (e.g., antibiotics for bacterial pyelonephritis), whereas others are supportive (e.g., dietary intervention, antihypertensive therapy and angiotensin-converting enzyme [ACE] inhibitors). 1772 1773

260.3.1

Box • 260-6 Problem-Specific Data Base for Patients with Chronic Renal Failure

1. Medical history including medication review
2. Physical examination including retinal examination
3. Urinalysis with urine sediment
4. Quantitative urine culture
5. Complete blood count (CBC)
6. Urine protein/creatinine ratio (if indicated by urinalysis)
7. Serum urea nitrogen (SUN) concentration
8. Serum creatinine concentration
9. Serum (or plasma) electrolyte and acid-base profile including:
    a. Sodium, potassium, and chloride concentrations
    b. Blood gas analysis or total serum CO2 concentrations
    c. Calcium, phosphorus, and albumin concentrations
10. Arterial blood pressure
11. Kidney-bladder-urethra survey radiographs
    a. Kidneys—size, shape, location, number

b. Uroliths or masses affecting kidneys, ureters, or urethra

c. Urinary bladder—size, shape, location, uroliths

12. Clinician should consider:

a. Additional imaging studies as indicated (clinician should rule out urinary obstruction, renal uroliths, pyelonephritis, renal cystic disease, perinephric pseudocysts, and renal neoplasia):

i. Renal ultrasound

ii Intravenous urography

b. Determining glomerular filtration rate (GFR)

i. Plasma clearance of iohexol, inulin, creatinine, or other

ii Classical clearance methods or scintigraphic methods

c. Determining parathyroid hormone (PTH) and ionized calcium levels for managing renal secondary hyperparathyroidism

d. Skeletal radiographs for evidence of renal osteodystrophy, measurement of carbamylated hemoglobin concentration, or parathyroid gland ultrasonography when the distinction between acute and chronic kidney disease (CKD) remains unresolved

e. Renal biopsy

f. Prior to initiating therapy, clinician should consider freezing aliquots of serum (or plasma) and urine for additional diagnostics that may be desired later

260.4 TREATMENT OF CHRONIC KIDNEY DISEASE

260.4.1 Overview of Treatment

Treatment of CKD should generally include specific therapy, prevention and treatment of complications of decreased kidney function, management of comorbid conditions, and therapy designed to slow loss of kidney function.[3] To this end, a clinical action plan should be developed for each patient based on their diagnosis, stage of CKD, existing complications and comorbid conditions, and risk factors for progression of their kidney disease.

260.4.1.1 Box • 260-7 Risk Factors That May Promote Progression of Renal Failure

260.4.1.1.1 Risk Factors for Acute Decline in Renal Function:

Volume depletion

Urinary obstruction

Potentially nephrotoxic drugs:

- Antibiotics
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-2 receptor blockers
- Intravenous radiographic contrast agents

260.4.1.1.2 Risk Factors for Long-Term Decline in Renal Function

Active renal disease

Urinary tract infection (UTI)

Nephrolithiasis and ureterolithiasis

Systemic hypertension

Proteinuria

Inappropriate diet

Specific therapy for CKD is based on a renal diagnosis. Treatment is directed at the etiopathogenic processes responsible for the patient's primary renal disease. Because the renal lesions of CKD are irreversible, they cannot be completely reversed or eliminated by specific therapy. Nonetheless, progression of renal lesions may be slowed or stopped by therapy designed to eliminate active renal diseases. Specific therapies are described in the chapters of this text on glomerular diseases, bacterial infections, familial renal diseases, and renal tubular disease. Unfortunately, a renal diagnosis amenable to specific therapy is not obtained for most patients.

Treatment directed at the complications of decreased kidney function is often termed *conservative medical management*. It consists of supportive and symptomatic therapy designed to correct deficits and excesses in fluid, electrolyte, acid-base, endocrine, and nutritional balance thereby minimizing the clinical and pathophysiologic consequences of reduced renal function. Conservative medical management also includes therapy designed to limit the progressive loss of renal function.

The goals of conservative medical management of patients with chronic primary renal failure are to (1) ameliorate clinical signs of uremia; (2) minimize disturbances associated with excesses or losses of electrolytes, vitamins, and minerals; (3) support adequate nutrition by supplying daily protein, calorie, and mineral requirements; and (4) modify progression of renal failure.[92] These goals are best achieved when recommendations regarding conservative medical management are individualized to patient needs based on clinical and laboratory finding. Because CRF is progressive and dynamic, serial clinical and laboratory assessment of the patient and modification of the therapy in response to changes in the patient's condition is an integral part of conservative medical management.

260.4.2 Dietary Therapy

260.4.2.1 Dietary Modifications in Renal Failure

Diet therapy has been a mainstay in the management of canine and feline CKD for decades and it continues to be the most commonly recommended treatment for these patients. In the past, the emphasis has been on reducing protein content. Although protein content continues to play an important role in diet formulation, other diet modifications are also important in managing renal failure patients. Diets recommended for dogs and cats with renal failure are modified from typical maintenance diets in several ways, including reduced protein, phosphorus, and sodium content; increased B-vitamin content and caloric density; and a neutral effect on acid-base balance. Feline renal failure diets are typically supplemented with additional potassium. Canine renal failure diets may have an increased omega-3/omega-6 polyunsaturated fatty acid (PUFA) ratio. Diets may also have added fiber designed to enhance GI excretion of nitrogenous wastes. Of these diet modifications, only phosphate, omega-3 PUFA, and protein have been extensively examined.

260.4.2.1.1 Diet phosphate

Renal diets are limited in phosphorus content to limit phosphorus retention, hyperphosphatemia, renal secondary hyperparathyroidism, and progression of renal disease. Phosphate balance results largely from the interaction between dietary intake and renal excretion. Ingested phosphate is cleared from blood by glomerular filtration, and then total excretion is adjusted by modifying proximal tubular reabsorption. As renal function declines, renal tubular reabsorption of phosphorus declines (increasing renal excretion) in an attempt to compensate for the reduction in glomerular filtration, thereby maintaining phosphorus balance. However, if phosphorus intake continues unabated, the renal adaptive capacity soon becomes overwhelmed and phosphorus retention and hyperphosphatemia develop.

Although phosphorus retention and hyperphosphatemia probably do not cause clinical signs, they may promote renal secondary hyperparathyroidism and renal mineralization that enhances progressive decline in renal function. Dietary phosphorus restriction has been shown to enhance survival and a slow decline in renal function in dogs with induced renal failure.[57] In cats, dietary phosphorus restriction has been shown to limit renal mineralization.

Available evidence supports a recommendation for dietary phosphate restriction for dogs and cats in stages 3 and 4 CKD. Because protein is a major source for phosphate, it is usually necessary to limit dietary protein to limit diet phosphate content.

260.4.2.1.2 Omega-3 polyunsaturated fatty acid

Dietary supplementation with omega-3 PUFA have been shown to be beneficial in dogs with induced CKD. Compared with dogs fed diets high in saturated fats or omega-6 PUFA, dogs consuming a diet supplemented with omega-3 PUFA had lower mortality, better renal function, fewer renal lesions, less proteinuria, and lower cholesterol levels.[93] In dogs fed the omega-3 PUFA diet, renal function actually increased and remained above baseline over 20 months of study. Lesions of glomerulosclerosis, tubulointerstitial fibrosis, and interstitial inflammatory cell infiltrates were also diminished in dogs fed the omega-3 PUFA diet. A variety of effects attributed to omega-3 PUFA supplementation may have contributed to the favorable renal effects observed, including their tendency to reduce

hypercholesterolemia, suppress inflammation and coagulation (by interfering with the production of proinflammatory, procoagulant prostanoids, thromboxanes, or leukotrienes), lower blood pressure, favorably influence renal hemodynamics, provide antioxidant effects, or limit intrarenal calcification. A subsequent study supported possible roles for altered lipid metabolism, glomerular hypertension and hypertrophy, and urinary eicosanoid metabolism in the beneficial renal effects of omega-3 PUFA.[94]

Available evidence supports a recommendation for dietary supplementation with omega-3 PUFA for dogs in stages 3 and 4 CKD. The optimum quantity of omega-3 PUFA supplementation and ratio of omega-3/omega-6 PUFA appropriate for renal diets have not been conclusively established. Additional omega-3 PUFA supplementation may not be appropriate for dogs already consuming a renal diet enhanced with omega-3 PUFA. Currently, no evidence supports a recommendation for or against omega-3 PUFA supplementation for cats with CKD.

260.4.2.1.3 Diet protein

Although the ideal quantity of protein to feed dogs and cats with CKD remains unresolved, a general consensus of opinion supports the fact that reducing protein intake ameliorates clinical signs of uremia in CKD and is therefore indicated for stage 4 CKD. BUN can be used as a crude measure of compliance with dietary recommendations because it declines as dietary protein intake is reduced. Although not generally regarded as an important uremic toxin, BUN is a surrogate marker for retained nonprotein nitrogenous waste products and typically correlates better with clinical signs than serum creatinine concentration.

The concept of reducing dietary protein intake in CKD patients that do not have clinical signs of uremia has been questioned. Limiting protein intake has been advocated for these patients to slow progression of CKD. This suggestion derives from studies in rats indicating that dietary protein restriction limits glomerular hyperfiltration and hypertension and slows the spontaneous decline in kidney function that follows reduction in kidney mass.[66] Studies in humans have supported the concept that protein restriction slows progression of CKD, albeit this effect may be small.[95] In contrast, multiple studies have failed to confirm a beneficial role for protein restriction in limiting progression of kidney disease in dogs or cats.[92] When not excessive, limiting protein intake does not appear to have any adverse effects, and it may be easier to initiate treatment with renal diets before the onset of clinical signs of uremia. In addition, protein restriction may delay onset of clinical signs of uremia as renal disease progresses. Although a role for protein restriction in slowing progression of canine and feline CKD has not been entirely excluded, available evidence fails to support a recommendation for or against protein restriction in patients with stage 3 CKD.

260.4.2.2 Diet Therapy—Evidence from Clinical Trials

The effectiveness of diet therapy in minimizing uremic episodes and mortality in dogs with naturally occurring stage 3 and stage 4 CKD has been established in a double-masked, randomized, controlled clinical trial.[1] The study compared a renal diet to a prototypical canine maintenance diet. The renal diet was characterized by reduced quantities of protein, phosphorus, and sodium compared with the maintenance diet, and it was supplemented with omega-3 PUFA. In this study the risk of developing an uremic crisis was reduced by approximately 75% in dogs fed the renal diet compared with dogs fed an adult maintenance diet, and the median interval before development of uremic crisis in dogs fed the renal diet was twice as long as that observed in dogs fed the maintenance diet. Further, the risk of death irrespective of the cause

was reduced by at least two thirds when dogs were fed the renal diet, and renal death risk was reduced by 70%.

Dogs fed the renal diet survived at least 13 months longer than dogs fed the maintenance diet. In addition, owners of dogs fed the renal diet reported significantly higher quality of life scores for their dogs than owners of dogs consuming the maintenance diet. The delay in development of uremic crises and reduced mortality observed in dogs fed renal diet was associated, at least in part, with reduction in the rate progression of renal failure.

The effectiveness of diet therapy in cats has been tested in a prospective study comparing a renal diet characterized by protein and phosphorus restriction to no diet change.[64] Cats that would not accept the renal diet, either due to pet or owner issues, continued to eat their regular diet. Therefore this study was neither randomized nor blinded, but it nonetheless yielded results similar to those observed in the canine study. Cats fed the renal diet (median survival time [MST], 633 days) survived substantially longer than cats that continued to consume their regular diet (MST, 264 days). In addition, plasma urea nitrogen, phosphorus, and PTH concentrations were reduced in cats that consumed the renal diet.

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260.4.2.3 Indications for Diet Therapy

In the past, criteria for timing of dietary intervention in dogs and cats with spontaneous CKD have been based on empiric observations. An often-cited guideline has been to initiate dietary therapy when serum creatinine exceeds 2.5 mg/dL or the SUN exceeds 60 to 80 mg/dL. More recently, one investigator recommended a staged approach whereby dietary phosphorus restriction and omega-3 PUFA dietary supplementation be implemented in dogs with serum creatinine values below 4.0 mg/dL with dietary protein restriction recommended only in dogs with serum creatinine values exceeding 4.0 mg/dL.[4] However, the clinical trial data available to date have demonstrated a benefit of dietary intervention in both stage 3 and stage 4 CKD. In a randomized, controlled clinical trial in dogs with naturally occurring CKD, diet therapy significantly reduced the risk of uremic crises and death in dogs with serum creatinine concentrations between 2.0 and 3.0 mg/dL.[1] These studies did not selectively determine the benefits of modifying individual dietary components, but rather report the results of a *diet effect*. Although studies on individual dietary components have been reported in dogs and cats with induced renal failure, the potential interactions between components have not been examined, nor have the results of these studies been confirmed in clinic patients.

Currently available data supports recommending therapy with appropriately modified diets in dogs and cats in stages 3 and 4 CKD. The value of diet therapy in stages 1 and 2 CKD has not been established; therefore no evidence supports a recommendation for or against diet therapy in these patients.

260.4.3 Drugs—Medication Review and Dose Modification

A review of current medications should be performed at each clinic visit, including dose adjustment based on level of kidney function, detection of potential adverse effects on kidney function or complications of CKD, detection of drug interactions, and, where indicated, therapeutic drug monitoring.[3] The clinician should ensure that all current medications are still necessary and that new medications have specific indications and do not pose a risk of drug interaction.

Because the kidneys are responsible for elimination of many drugs from the body, renal drug clearance is reduced as renal function declines, causing the half-life of the drug to be prolonged. In addition, distribution, protein binding, and hepatic biotransformation of drugs may be altered. For example, two protein-binding defects are seen in renal failure.[50] One group of primarily acidic drugs shows decreased binding leading to increases in free, active drug fractions in plasma (e.g., theophylline, methotrexate, diazepam, digoxin, salicylate). The effect of this change in binding is that lower doses of drugs are required to achieve therapeutic levels, but conventional doses may result in toxic levels. Basic drugs, such as propranolol or cimetidine, have increased binding leading to a decrease in free drug levels, thus diminishing the therapeutic effect. Increased total drug levels may be required to achieve the desired therapeutic effect with these drugs. However, these effects may be complicated by decreased renal clearance of the drugs.

Further, accumulation of active drug metabolites may augment drug potency or toxicity.

The sum effect of these changes is that for many drugs normally excreted by the kidneys, a tendency exists for drugs to accumulate in patients with renal failure. Excessive drug accumulation promotes an increased rate of adverse drug reactions and nephrotoxicity. If drugs requiring renal excretion must be administered to patients with renal failure, dose regimens should be adjusted to compensate for decreased organ function. However, dose adjustments may not be appropriate for drugs that are administered to a physiologic endpoint or effect such as antihypertensive agents.[96]

Because drug accumulation in patients with reduced kidney function is primarily a result of reduced renal drug clearance, dose adjustments should be made according to changes in drug clearance. Net renal excretion of a drug is a composite of glomerular filtration, tubular secretion, and tubular reabsorption. Generally it is assumed that these three factors all decline in parallel. Therefore drug clearance may be estimated by measuring GFR, either by plasma disappearance rate (e.g., iohexol disappearance rate) or classical clearance studies. Drug dose may then be adjusted according to the percentage reduction in GFR (i.e., the ratio of patient GFR/normal GFR), also known as the dose fraction (K_f):

$$K_f = (\text{patient GFR}/\text{normal GFR})$$

Dose regimens can be adjusted by increasing the normal dose interval or decreasing the normal dose in direct proportion to K_f.[97] The interval extension method is particularly useful for drugs with wide therapeutic ranges and long plasma half-lives in patients with renal impairment. Interval lengthening will result in wide swings of the plasma drug concentrations from peak to trough levels. If the range between the toxic and therapeutic levels is too narrow, either toxic or subtherapeutic plasma concentrations may result. For drugs excreted 100% unchanged by the kidneys, a precise increase in dose interval may be calculated by dividing the normal dosing interval by K_f:

$$\text{Modified dose interval} = (\text{normal dose interval}/K_f)$$

For example, if a drug is normally administered every 8 hours and the patient's GFR is 25% of normal (i.e., $K_f = 0.25$), then the appropriate dosing interval is (8 hrs ÷ 0.25) or 32 hrs. The calculated dose interval should be rounded to a convenient time schedule.

Alternatively, the size of the individual doses can be reduced while maintaining the normal time interval between doses. Decreasing the individual doses reduces the difference between peak and trough plasma concentrations. This effect is important for dugs with narrow therapeutic ranges and short plasma half-lives in

patients with renal dysfunction and is recommended for drugs for which a relatively constant blood level is desired. Dose reduction may be determined by multiplying the normal dose by K_f:

$$\text{Modified dose reduction} = (\text{normal dose} \times K_f)$$

For example, if the normal dose is 10 mg/kg given every 8 hours and the patient's GFR is 25% of normal (i.e., $K_f = 0.25$), then the appropriate dose is (10 mg/kg × 0.25) or 2.5 mg/kg given every 8 hours. Even using the reduced dose, normal interval method, the first dose of drug should be administered at the usual dose to initiate therapeutic drug concentrations in tissues and blood.

There have been no controlled clinical trials to establish the efficacy of the two methods for drug dose alteration in patients with CKD. Prolonging the dose interval is usually more convenient and less expensive. A combination of interval prolongation and dose size reduction may also be convenient and effective.

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Dose of antimicrobial drugs may be modified according to three general patterns, depending on the fraction of the drug eliminated by the kidneys (Table 260-1): (1) doubling the dosing interval or halving the drug dose in patients with severe reduction in renal function, (2) increasing the dose interval according to ranges of creatinine clearance values, and (3) precise dose modification as described previously. Drugs in the first category are relatively nontoxic. The second class includes drugs requiring dose modification according to GFR values because they are more likely to be toxic. For drugs in this class, dosing interval is increased twofold when GFR is between 1.0 and 0.5 mL/min/kg, threefold when GFR is between 0.5 and 0.3 mL/min/kg, and fourfold when GFR is less than 0.3 mL/min/kg. Drugs in the third class include relatively toxic antimicrobial drugs that are excreted solely by glomerular filtration (particularly aminoglycoside antibiotics). They require precise dose modification according to Kf. For these drugs, increased interval, fixed dose regimens appear to result in less nephrotoxicity than reduced dose, fixed interval methods. A combination of dose reduction and interval extension has been recommended for animals with markedly reduced kidney function (GFR < 0.7 mL/min/kg).

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Table • 260-1 Drug Dose Modifications for Patients with Renal Insufficiency and Failure

DRUG	ROUTE(S) OF EXCRETION*	NEPHRO-TOXIC?	DOSE ADJUSTMENT IN RENAL FAILURE†
Amikacin	R	Yes	Pr
Amoxicillin	R	No	D/I
Amphotericin B	O	Yes	Pr
Ampicillin	R, (H)	No	D/I
Cephalexin	R	No	C_{cr}
Cephalothin	R, (H)	No (?)	C_{cr} or D/I
Clindamycin	H, (R)	No	N
Chloramphenicol	H, (R)	No	N, A
Cyclophosphamide	H, (R)	No	N
Corticosteroids	H	No	N
Dicloxacillin	R, (H)	No	N
Digoxin	R, (O)	No	Pr
Doxycycline	GI, (R)	?	N
Enrofloxacin	R	No	I
Furosemide	R	No (?)	N
Gentamicin	R	Yes	Pr
Heparin	O	No	N
Kanamycin	R	Yes	Pr
Neomycin	R	Yes	C/I
Nitrofurantoin	R	No	C/I
Orbaloxacin	R	No	I
Penicillin	R, (H)	No	D/I
Propranolol	H	No	N
Streptomycin	R	Yes	C_{cr}
Sulfisoxazole	R	Yes	C_{cr}
Tetracycline	R, (H)	Yes	C/I
Tobramycin	R	Yes	Pr
Trimethoprim/sulfamethoxazole	R	Yes	C_{cr}, A

* Routes of excretion: R, Renal; H, hepatic; GI, gastrointestinal; O, other (minor route in parentheses).

† Dose modification: N, Normal; D/I, half dose or double dose interval (in severe renal dysfunction); C cr, adjust according to Ccr (see text); Pr, precise dose modification (see text—clinician should adjust it according to Kf); C/I, contraindicated; A, clinician should avoid in advanced renal failure.

Although GFR is the preferred measure of renal dysfunction for modifying drug therapy, serum creatinine concentration is a more universally available measure of renal dysfunction. A regression equation relating serum creatinine concentration to GFR in dogs has been established.[98]

Although the relationship between serum creatinine concentration and GFR is not linear, the reciprocal of serum creatinine concentration may be used to approximate GFR when serum creatinine concentration is less than 4 mg/dL. This rule of thumb will overestimate GFR when serum creatinine concentration exceeds 4 mg/dL. Despite increased expense and effort involved, it is recommend that GFR be used as the basis for modifying drug dose schedules whenever possible. This recommendation is particularly relevant when a potentially nephrotoxic drug must be administered.

Patients with preexisting renal disease and renal failure may also be predisposed to nephrotoxicity. For this reason, nephrotoxic drugs and drugs requiring renal excretion should generally be avoided in patients with renal failure. Where possible, less nephrotoxic drugs should be chosen. If nephrotoxic drugs are unavoidable, therapeutic drug monitoring and serial evaluation of renal function is essential.

So-called complementary medications (sometimes called *herbal medicines*, *naturopathic remedies*, and *phytomedicines*) are becoming increasingly popular. The potential for interactions with prescribed medications or simple adverse consequences in patients with reduced kidney function should be considered for patients receiving these medications. Herbal products that should be avoided in patients with renal dysfunction include aristolochic acid, barberry, buchu, Chinese herbal drugs, juniper, licorice, and noni juice.[96]

260.4.4 Phosphorus Retention, Hyperphosphatemia, and Renal Secondary Hyperparathyroidism

Serum phosphorus concentrations represent the net balance between dietary intake and renal excretion of phosphorus. Therefore maintaining serum phosphorus concentrations within the normal range as renal function is lost requires modification of phosphorus intake. In theory, optimum control of hyperphosphatemia would be achieved by reducing dietary phosphorus intake *in proportion* to the decrease in GFR.

Without treatment, phosphorus retention, hyperphosphatemia and renal secondary hyperparathyroidism occurs in most dogs and cats with stage 3 or stage 4 CKD.[39,99] Although hyperphosphatemia has been linked to pruritus, conjunctivitis, renal osteodystrophy, and soft-tissue calcification in humans, hyperphosphatemia *per se* is rarely linked to clinical signs in dogs and cats with CKD. Rather, minimizing phosphorus retention and hyperphosphatemia is an important therapeutic goal in patients with CKD because it appears to limit renal secondary hyperparathyroidism and prolong survival.[57,99]

The first step in correcting hyperphosphatemia is to restore hydration and correct prerenal hyperphosphatemia. Minimizing long-term phosphorus retention and hyperphosphatemia may be accomplished by limiting dietary phosphorus intake, oral administration of agents that bind phosphorus within the lumen of the intestines, or a combination of these methods. The usual approach is to start with diet therapy and add phosphorous binding agents if diet therapy alone fails to normalize serum phosphorous concentrations. Diet therapy with or without phosphate-binding agents normalizes serum phosphorus levels in most patients. However, phosphorus restriction alone appears to be insufficient to normalize serum PTH levels in some patients.[39,99] In such patients, a combination of limiting phosphorus intake combined with administration of calcitriol has been recommended.[39] Nagode and colleagues[39] have suggested that normalization of PTH levels using calcitriol therapy may provide clinical benefits that cannot be achieved by phosphorus restriction alone, including amelioration of many clinical signs associated with CKD. However, clinical trials of long-term calcitriol therapy are needed to establish the value of this therapy in dogs and cats with CKD. Calcitriol therapy is described later in this chapter.

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260.4.4.1 Dietary Phosphorus Restriction

Dietary phosphorus restriction is an important and effective intervention for normalizing phosphorus balance. It may be effective in normalizing serum phosphorus concentrations in most stage 3 and some stage 4 CKD patients. It will also decrease the dose of intestinal phosphorus-binding agents needed to bind dietary phosphorus in patients with more severe hyperphosphatemia. Dietary phosphorus restriction is

clearly indicated for patients with hyperphosphatemia. However, because phosphorus retention and hyperparathyroidism may occur before serum phosphorus concentrations exceed normal limits, and because fasting serum phosphorus concentrations may not accurately reflect overall phosphorus balance, phosphorus restriction may be indicated before the onset of overt hyperphosphatemia.[100]

Because proteins are a major source of dietary phosphorus, manufactured and homemade renal diets are usually restricted in both protein and phosphorus content. Typical commercial dog foods contain approximately 1% to 2% phosphorus on a dry matter basis and provide about 2.7 mg/kcal or more phosphorus. Modified protein diets designed for dogs with renal failure may contain as little as 0.13% to 0.28% phosphorus on a dry matter basis and provide about 0.3 to 0.5 mg/kcal of phosphorus. Typical commercial cat foods contain from 1% to 4% phosphorus on a dry matter basis and provide about 2.9 mg/kcal or more phosphorus. Modified protein diets designed for cats with renal failure may contain as little as 0.5% phosphorous on a dry matter basis and provide about 0.9 mg/kcal of phosphorus.

Phosphorus retention in CKD appears to occur in multiple compartments. As dietary phosphorus restriction reduces serum phosphorus levels, phosphorus leaches out of tissues, delaying the overall reduction in serum phosphorus concentration. Thus the overall efficacy of dietary phosphorus restriction in reducing serum phosphorus concentrations may not occur until the patient has been consuming the phosphorus-restricted diet for several weeks. In a study in cats with renal insufficiency and failure, the effect of restricting dietary phosphorus intake was apparent after 28 to 49 days.[99] Samples obtained for determinations of serum phosphorus concentration should be collected after a 12-hour fast to avoid postprandial effects. Sample hemolysis should be avoided because canine RBCs contain substantial quantities of phosphorus.

The minimum goal of therapy is to bring serum phosphorus concentration to within the normal range, although concentrations between 4.0 and 6.0 mg/dL may be preferred. Although PTH levels generally decline as serum phosphorus levels decline, normalization of serum phosphorus concentrations is not always accompanied by normalization of PTH concentration. In a recent clinical study of cats with chronic renal insufficiency and failure, dietary phosphorus restriction was associated with a normal serum phosphorus concentration in 12 of 13 cats, whereas PTH concentration was normalized in only eight of these 13 cats.[99] It is unclear whether further reducing serum phosphorus concentration within the normal range or using normalization of PTH levels as the preferred therapeutic endpoint would be of any clinical benefit.

Hypercalcemia was reported to develop in two cats managed with dietary phosphorous restriction.[99] The significance of the relationship, if any, between dietary phosphorus restriction and hypercalcemia in these two cats is unclear.

Unfortunately, as renal failure becomes more advanced, dietary phosphorus restriction alone may be insufficient to prevent hyperphosphatemia. When hyperphosphatemia persists despite dietary phosphorus restriction, administration of intestinal phosphorus-binding agents should be considered.

260.4.4.2 Intestinal Phosphorus-Binding Agents

Phosphorus-binding agents should be used in conjunction with dietary phosphorus restriction when dietary therapy alone fails to reduce serum phosphorus concentrations to the normal range. Dietary phosphorus intake should be reduced before initiating therapy with intestinal phosphorus-binding agents to minimize the quantity of phosphorus that must be bound. High dietary phosphorus content may greatly limit the effectiveness of phosphorus-binding agents or substantially increase the dose required to achieve the

desired therapeutic effect.[101] Administration of 1500 to 2500 mg of aluminum carbonate to dogs with moderate CKD failed to consistently correct hyperphosphatemia when dogs were fed diets containing greater than 1.0% phosphorus on a dry matter basis.[102]

Currently available phosphorus-binding agents include aluminum-based and calcium-based exchange compounds that liberate varying amounts of their associated cation (e.g., aluminum, calcium) as dietary phosphorus is bound. Factors that may influence selection of a specific phosphorus-binding agent include availability, palatability, and the associated cation. Aluminum-based binding agents have generally been preferred for dogs and cats because they are effective, inexpensive, and seemingly have few side effects. However, concern about the potential toxic effects of aluminum in humans has caused many aluminum-containing drugs to be removed from the market. Encephalopathies, microcytic anemia, and bone disease (particularly osteomalacia) related to aluminum toxicity have been extensively reported in human patients treated with these drugs. The potential for toxicity of aluminum salts in dogs and cats has been confirmed, but little evidence suggests that use of these drugs leads to clinically important aluminum toxicity in dogs and cats. Calcium-based drugs have the potential to promote hypercalcemia, particularly when administered between meals or used in combination with calcitriol.

Aluminum-containing intestinal phosphorus-binding agents include aluminum hydroxide, aluminum carbonate, and aluminum oxide. Initial doses of 30 to 100 mg/kg/day have been recommended for these aluminum-based phosphorus-binding agents. They are available over-the-counter in liquid, tablet, or capsule forms from most pharmacies as antacid preparations. In humans, capsules and tablets are less effective than liquids, but liquid preparations may be unpalatable to some dogs and cats. Sucralfate, a complex polyaluminum hydroxide salt of sulfate used primarily for treatment of GI ulcerations, may also be effective in binding phosphorus within the intestine.

Calcium-based phosphorus-binding agents include calcium acetate, calcium carbonate, or calcium citrate. Because calcium-based products may promote clinically significant hypercalcemia, it is recommended that serum calcium concentrations be monitored intermittently when using these drugs. They should not be used in hypercalcemic patients. When indicated, they may be used between meals as a source of additional dietary calcium. Calcium supplementation may increase the efficacy of phosphorus restriction in normalizing renal secondary hyperparathyroidism.

Reduced doses of calcium carbonate and calcium acetate may be used concurrent with aluminum-based binding agents to limit risks of both hypercalcemia and aluminum toxicity. However, calcium citrate may promote absorption of aluminum and should therefore not be used in concert with aluminum-based binding agents. Calcium acetate is the most effective calcium-based phosphorus-binding agent and the agent least likely to induce hypercalcemia because it releases the least amount of calcium compared with the amount of phosphorus it binds.[101] Initial doses of 60 to 90 mg/kg/day have been recommended for calcium acetate and 90 to 150 mg/kg/day for calcium carbonate. Some calcium carbonate preparations may not be effective because they fail to dissolve well in the GI tract; clinicians may investigate this by examining the stool or obtaining radiographs of the abdomen for evidence of radiodense tablets that have failed to dissolve.

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The most recent addition to the phosphorus-binding armamentarium is the cationic polymer agent sevelamer hydrochloride (Renagel® Tablets and Capsules, Genzyme Corp., Cambridge, MA). The primary advantage of this drug is that it does not promote hypercalcemia or absorption of aluminum. However, it is more expensive than older phosphorus-binding agents. In addition, concerns have been raised over its potential for inducing vitamin-K deficiency and hemorrhage. In preclinical studies in rats and dogs, sevelamer hydrochloride reduced vitamin D, E, K, and folic acid levels when given at doses of six to 100

times the recommended human dose. In clinical trials in humans, no evidence of reduction in serum levels of vitamins was seen; however, patients in this study were receiving vitamin supplements. Scant information exists on the safety, effectiveness, or dose of sevelamer in dogs and cats. Based on extrapolating the recommended dose from humans, an initial dose of 30 and 135 mg/kg per day divided and given with meals may be considered. Because the contents of Renagel® (Genzyme Corp.) expand in water, the manufacturer recommends that tablets and capsules should be swallowed intact and should not be crushed, chewed, broken into pieces, or taken apart prior to administration. Sevelamer reportedly lowers total and low-density lipoprotein cholesterol concentrations and elevated high-density lipoprotein cholesterol levels in humans.[103] Consideration should be given to monitoring clotting ability using the prothrombin time (PT) if this drug is used in dogs or cats with CKD.

Intestinal phosphorus-binding agents render ingested phosphorus and the phosphorus contained in saliva, bile, and intestinal juices unabsorbable. Because the primary goal is limiting absorption of phosphorus contained in the diet, administration of phosphorus-binding agents should be timed to coincide with feeding. These agents are best administered with or mixed into the food, or just prior to each meal. It is particularly important that calcium-based phosphorus-binding agents be administered with meals both to enhance the effectiveness of phosphorus binding and to minimize absorption of calcium and the risk of hypercalcemia.

Dose of phosphorus-binding agents should be individualized to achieve the desired serum phosphorus concentration. The effectiveness of therapy should be assessed by serial evaluation of serum phosphorus concentrations at about 2-to 4-week intervals. Dose of calcium-based phosphorus-binding agents should be decreased if serum calcium concentrations exceed normal limits; additional aluminum-based agents should be used in these patients if hyperphosphatemia persists.

260.4.5 Dehydration

Fluid balance in patients with polyuric renal failure is maintained by compensatory polydipsia. If water consumption is insufficient to compensate for polyuria, dehydration is the result. This may occur as a consequence of lack of intake or lack of access to fresh, clean, unadulterated water. Cats and some dogs with chronic kidney disease (CKD) fail to consume sufficient water to prevent chronic or recurrent dehydration. In addition, acute GI fluid losses resulting from renal or nonrenal causes may lead to extracellular fluid volume depletion.

Dehydration and volume depletion promote renal hypoperfusion and prerenal azotemia that may exacerbate the clinical and laboratory abnormalities of chronic renal insufficiency and failure. In addition to prerenal azotemia, dehydration may be associated with electrolyte disturbances such as hyperphosphatemia, hyperkalemia, and metabolic acidosis. Clinical signs characteristic of dehydration include decreased appetite, lethargy, and constipation. In some patients, prerenal azotemia may precipitate uremic crisis. Further, if dehydration and decreased renal blood flow are allowed to persist, additional ischemic renal damage may occur.

Patients that develop recurrent episodes of signs consistent with dehydration are candidates for intermediate-to long-term subcutaneous fluid therapy to be administered at home by the owner. The principal benefits of subcutaneous fluid therapy include improved appetite and activity and reduced constipation. The decision to recommend administration of subcutaneous fluids should be made on a case-by-case basis. Not every patient with chronic kidney disease and failure requires or will benefit from fluid therapy. Although a substantial number of cats with CKD appear to benefit from subcutaneous fluid therapy, proportionately fewer dogs

require fluid therapy. In addition, home administration of subcutaneous fluids is not appropriate for all owners. Although it is inexpensive, it does require time and may cause stress on the owner-pet relationship. It also has the potential to promote hypokalemia, hypertension, and fluid overload. Although a risk of subcutaneous infections exists, this appears to be an uncommon complication when owners are taught proper technique.

Normal saline or lactated Ringer's solution are the fluids most commonly used for home subcutaneous fluid therapy. They are well tolerated by most cats and dogs and appear to be reasonable choices for most patients. However, chronic administration of lactated Ringer's solution or normal saline as the principal maintenance fluid source may cause hypernatremia because they fail to provide sufficient electrolyte-free water. Ideally, fluids selected for chronic parenteral administration should provide free water and electrolytes for maintenance. A solution containing 0.45% saline and 2.5% glucose supplemented with 20 mEq/L of potassium chloride meets these requirements. Unfortunately, fluids containing dextrose may be irritating when administered subcutaneously, and their use should be discontinued if the patient indicates discomfort when they are given. A typical cat or small dog receives approximately 75 to 150 mL of fluids given daily or as needed. Chronic subcutaneous fluid therapy can result in fluid overload in some patients, particularly when fluid volumes in excess of those recommended here are used. The authors have seen several cats have severe dyspnea due to pleural effusion given large quantities of fluid (200 to 400 mL/day). This condition can usually be avoided by reducing the volume of fluids administered.

Response to long-term subcutaneous fluid therapy should be monitored by serially assessing hydration status, clinical signs, hematocrit, total serum protein concentrations, blood pressure, and SUN, creatinine, phosphorus, potassium, total CO_2, sodium, and chloride concentrations.

260.4.6 Hypokalemia and Potassium Depletion

Potassium depletion and hypokalemia are common in cats with CKD. Estimates of the prevalence of hypokalemia in this population of cats are in the range of 20% to 30%.[2,8,9] Total body potassium depletion is likely to be even more common than hypokalemia.[62] In contrast, hypokalemia is rarely recognized as a complication of canine CKD. The mechanisms underlying development of hypokalemia in cats with CKD remain unclear, but inadequate potassium intake coupled with increased urinary and fecal losses (or both) have been hypothesized to play a role.

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Although increasing the potassium content of renal diets has reduced the incidence of overt clinical signs of hypokalemia, hypokalemia remains a common laboratory finding in cats with renal insufficiency and failure. The antihypertensive agent amlodipine may promote hypokalemia in cats with chronic renal insufficiency and failure.[104]

Hypokalemia and potassium depletion may affect the kidneys or muscles of cats with CKD. Diets low in potassium and high in acid content have been implicated in impairing renal function and promoting development of lymphoplasmacytic tubulointerstitial lesions in cats.[33,60–63] Potassium depletion may result in reduced renal blood flow and GFR as a consequence of angiotensin II and thromboxane-mediated renal vasoconstriction. In addition, hypokalemia may promote polyuria by impairing renal responsiveness to ADH and by stimulating the brain thirst centers through increased levels of angiotensin II. Hypokalemic polymyopathy, characterized by generalized muscle weakness and cervical ventroflexion, is a well-recognized complication of chronic renal insufficiency and failure in cats.

Oral supplementation of potassium has been recommended for cats with renal insufficiency and failure to treat or prevent renal and muscular consequences of potassium depletion and hypokalemia. Although a consensus

of opinion suggests that cats with hypokalemia should receive potassium supplementation, the justification for *prophylactic* potassium supplementation in normokalemic cats is not well established. Although potassium supplementation is unlikely to be medically harmful to polyuric, normokalemic cats, administration of an oral medication may impose an unnecessary burden on both the cat and the cat owner. Patient acceptance may be a limitation due to the unpleasant flavor of potassium salts that is difficult to mask.

Oral replacement is the safest and preferred route for administering potassium. Parenteral therapy is generally reserved for patients requiring emergency reversal of hypokalemia or for patients that cannot or will not accept oral therapy. Potassium chloride may be added to fluids administered subcutaneously up to 30 mEq/L.

Potassium may be supplemented orally as the gluconate or citrate salts. Potassium chloride is not recommended because of its lack of palatability and acidifying nature. Potassium gluconate may be administered orally as tablets, flavored gel, or in a palatable powder form (Tumil-K, Virbac Corp., Fort Worth, TX). Depending on the size of the cat and severity of hypokalemia, potassium gluconate is given initially at a dose of 2 to 6 mEq per cat per day. Acidosis is a major risk factor for development of hypokalemia and therefore should be rectified early in the management of hypokalemia. Potassium citrate solution (Polycitra®-K Syrup, Baker Norton, Miami, FL) is an excellent alternative that has the advantage of providing simultaneous alkalinization therapy. Potassium citrate is initially given at a dose of 40 to 60 mg/kg/day divided into two or three doses. If muscle weakness is present, it usually resolves within 1 to 5 days after initiating parenteral or oral potassium supplements. Potassium dose should thereafter be adjusted based on the clinical response of the patient and serum potassium determinations. Serum potassium concentration should initially be monitored every 7 to 14 days and the dose adjusted accordingly to establish the final maintenance dose. In patients with hypokalemic polymyopathy, it may be necessary to monitor serum potassium concentrations every 24 to 48 hours during the initial phase of therapy. It is unclear whether all cats require long-term potassium supplementation; however, preliminary evidence suggests that such therapy is likely to be required by at least some older cats with chronic kidney disease.

Routine supplementation of low oral doses of potassium (2 mEq/day) has been recommended for all cats with chronic kidney disease.[59] This recommendation appears to be based on the as yet unproved hypothesis that in some cats with CKD, hypokalemia and potassium depletion might promote a self-perpetuating cycle of declining renal function, metabolic acidosis, and continuing potassium losses. It is proposed that supplementation may stabilize renal function before potassium depletion exacerbates the disease. Some investigators have observed positive responses to potassium supplementation in several normokalemic cats that had chronic renal insufficiency and failure. However, results of a recent clinical trial suggested that in cats with chronic renal insufficiency and failure that initially had normal serum potassium concentrations, daily supplementation for 6 months with 4 mEq of potassium gluconate was not demonstrably superior to providing sodium gluconate in restoring muscle potassium stores.[62] However, there were only a small number of cats enrolled in this clinical trial. In addition, median muscle potassium content did increase in the potassium supplemented cats from 328 to 402 mEq/kg, a value close to the value of 424 mEq/L established for normal cat muscle. Thus although the value of providing supplemental potassium to cats with chronic kidney disease having normal serum potassium concentrations has not been established, it is clear that muscle potassium, and probably total body potassium stores, are likely to be reduced in cats with chronic kidney disease, increasing the risk for developing hypokalemia. Further, evidence from this study indicates that chronic supplementation of 2 to 4 mEq/day of potassium is unlikely to be associated with significant adverse events. Based on current data, a recommendation cannot be made for or against routine supplementation of potassium.

Diets that are acidifying and restricted in magnesium content may promote hypokalemia. Therefore they should generally be avoided in cats with CKD. Intensive fluid therapy during uremic crises, particularly with

potassium-deficient fluids, may promote hypokalemia in cats or dogs that were not previously hypokalemic. Therefore serum potassium concentrations should be monitored during fluid therapy, and maintenance fluids should be supplemented with potassium chloride to prevent iatrogenic hypokalemia (concentrations of 13 to 20 mEq/L are appropriate for maintenance fluids). Potassium given intravenously should not be administered at a rate exceeding 0.5 mEq/kg/hr.

260.4.7 Metabolic Acidosis

Alkalinization therapy designed to correct metabolic acidosis plays an important role in management of patients with CKD. Potential benefits of alkalinization therapy in these patients include (1) ameliorating signs of uremic acidosis, including anorexia, lethargy, nausea, vomiting, muscle weakness, and weight loss; (2) minimizing the catabolic effects of metabolic acidosis on protein metabolism[54]; (3) enhancing the patient's capacity to adapt to additional acid stress resulting from such factors as diarrhea, dehydration, or respiratory acidosis; (4) limiting skeletal damage (demineralization and inhibited skeletal growth) resulting from bone buffering; and (5) rectifying adverse effects of severe acidosis on the cardiovascular system (impaired myocardial contractility and enhanced venoconstriction).[105]

Although data are unavailable for dogs, a recent study in cats with chronic renal insufficiency and failure indicated that metabolic acidosis occurred in less than 10% of cats with stage 3 CKD, but it approaches 50% of cats in uremic crisis.[2] Based on this data, it appears that only a minority of cats with clinically stable CKD are likely to benefit from routine alkalinization therapy. Thus the decision to intervene with alkalinization therapy should be based on a laboratory assessment of the patient's acid-base status. Unfortunately, no clinical data provides an obvious intervention threshold for treating metabolic acidosis in dogs and cats. However, in studies performed at the authors' research center, clinicians have been unable to demonstrate any adverse clinical effects of mild to moderate chronic metabolic acidosis in cats with induced chronic renal insufficiency and failure. In absence of clear clinical data, the authors recommend considering alkalinization therapy for dogs and cats with stable chronic renal insufficiency and failure when blood gas analysis confirms plasma bicarbonate values remain below 15 mmol/L on more than one determination. However, for patients with metabolic acidosis associated with a blood pH below 7.10, immediate parenteral intervention with sodium bicarbonate should be considered to increase the blood pH above this value.[105]

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Because serum total CO_2 measurements are of questionable accuracy and yet remain the most common tool for establishing acid-base status for most dogs and cats, the authors recommend that blood gas analysis be performed to confirm metabolic acidosis whenever total CO_2 declines below 15 mmol/L. Low serum or plasma total CO_2 values obtained by autoanalyzer techniques should be confirmed by blood gas analysis because falsely low total CO_2 readings may occur when blood collection tubes are not fully filled or are exposed to air while awaiting analysis.[106] In addition, there may be a substantial systematic difference between blood bicarbonate concentrations determined by blood gas analysis and serum total CO_2 concentrations determined on autoanalyzers due to inherent differences in the analytic methods. Appropriate reference ranges are equipment and method specific.

Treatment options for alkalinization therapy include diet, sodium bicarbonate, and potassium citrate. Most renal diets are neutral to slightly alkalinizing in effect and are an appropriate first step in mitigating metabolic acidosis. When several weeks of diet therapy alone fails to ameliorate the metabolic acidosis, alkalinization therapy should be considered.

Oral sodium bicarbonate is the most commonly used alkalinizing agent for patients with metabolic acidosis of chronic renal insufficiency and failure. Because the effects of gastric acid on oral sodium bicarbonate are unpredictable, the dose should be individualized for each patient. A suggested initial dose of sodium bicarbonate is 8 to 12 mg/kg body weight given every 8 to 12 hours. Unfortunately, many dogs and cats find sodium bicarbonate distasteful unless given as tablets. Sodium bicarbonate is available as 5-and 10-grain tablets.

Potassium citrate may offer the advantage, especially in cats, of allowing for the simultaneous treatment of both hypokalemia and acidosis with a single drug. Metabolic acidosis, when accompanied by potassium depletion or magnesium depletion, may respond poorly to alkali therapy alone. However, in that potassium doses required for adequate correction of hypokalemia may exceed the citrate dose required to correct acidosis, a risk exists for excessive alkalinization. Starting doses of 40 to 60 mg/kg every 8 to 12 hours are recommended.

Regardless of the alkalinizing agent chosen, administration of several smaller doses is preferred to a single large dose to minimize fluctuations in blood pH. The patient's response to alkalinization therapy should be determined by performing blood gas analysis 10 to 14 days after initiating therapy. Ideally, blood should be collected just prior to administration of the drug. Dose of the alkalinizing agent should be adjusted to maintain blood bicarbonate concentrations within the normal range. Because urine pH is often insensitive as a means of assessing the need for or response to treatment, it is not recommended for this purpose.

260.4.8 Arterial Hypertension

260.4.8.1 Rationale for Treatment

CKD is the most common recognized cause for arterial hypertension in dogs and cats. In these species, hypertension has been linked to renal, ocular, neurologic, and cardiac complications. In dogs with naturally occurring chronic renal insufficiency and failure, higher initial blood pressure has been reported to be a risk factor for uremic crisis and mortality.[18] In addition, retinopathy and hypertensive encephalopathy were detected in three of 14 dogs with blood pressure values exceeding 180 mm Hg in this study. However, firm evidence that pharmacologically lowering blood pressure will prevent or ameliorate the renal and extrarenal complications of arterial hypertension in dogs is lacking.

Lethargy, blindness, retinal hemorrhage and detachment, cerebral hemorrhage, seizures, stupor, and ventricular hypertrophy have been reported in cats with hypertension.[107–109] Although it is likely that elevated blood pressure promotes progressive renal injury in cats, as yet no reported evidence confirms this relationship. However, in contrast to dogs, studies exist that support the clinical value of therapeutic intervention for hypertension in cats. Subcutaneous administration of the antihypertensive drug hydralazine was reported to reduce the prevalence of seizures that developed as a consequence of hypertension after renal transplantation.[108] In a recent study using a surgically induced model of hypertensive renal insufficiency, only two of 10 cats receiving the antihypertensive agent amlodipine developed evidence of hypertensive retinal lesions, whereas these lesions developed in seven of 10 cats receiving placebo.[107]

260.4.8.2 Indications for Treatment

Unless evidence for hypertension-related organ injury is seen (e.g., retinal lesions, neurologic signs) or the systolic blood pressure is greater than 200 mm Hg, the decision to initiate antihypertensive therapy is not an emergency. Before initiating therapy for arterial hypertension, the patient's blood pressure should be established based on blood pressure determinations performed at three successive clinic visits. Every effort should be made to minimize the risk that measured elevations in blood pressure represent a transient “white coat” effect, rather than a sustained elevation in blood pressure.[110]

Patients with blood pressure values exceeding 160/100 mm Hg should be considered for treatment. Although specific values for diagnosis of arterial hypertension have not been established for dogs and cats, current evidence suggests that concurrent CKD may place them at increased risk for sustaining additional renal injury or developing complications associated with elevated blood pressure.[18,107–109] Findings in two studies suggested that ocular lesions associated with elevated blood pressure occurred in cats with systolic blood pressure values exceeding about 160 mm Hg. Similarly, in a study in dogs with naturally occurring CKD, the risk for uremic crises and increased mortality was reported to be increased in a group of dogs with systolic blood pressure values above 160 mm Hg.[18] However, this cut off point was arbitrarily chosen in this study and therefore should not be interpreted as defining the lower limit of hypertension.

260.4.8.3 General Goals and Guidelines for Treatment

The optimum endpoint for antihypertensive therapy has not been established for dogs and cats with CKD. In the absence of such information, treatment for arterial hypertension should be initiated cautiously with the goal of reducing blood pressure to at least below 160/100 mm Hg. Except in patients with acute, severe ocular or neurologic lesions, rapid reduction in blood pressure is not necessary. Particularly in dogs, it may take weeks to months to achieve satisfactory blood pressure control.

ACE inhibitors, such as enalapril and benazepril, and calcium channel blocking (CCB) drugs, such as amlodipine, have potential renoprotecitve benefits and are therefore appropriate options for renal patients with hypertension.[111] ACE inhibitors generally produce a relatively small reduction in blood pressure.[112,113] However, because of their beneficial role in altering intraglomerular hemodynamics, proteinuria, and the profibrotic effects of the intrarenal renin-angiotensin system, ACE inhibitors may have renoprotective effects even in absence achieving adequate blood pressure control. In a recent study the ACE inhibitor, enalapril, reduced the severity of renal lesions that develop in dogs with surgically reduced renal mass.[112] Further, in dogs with naturally occurring glomerulopathies, enalapril significantly reduced proteinuria and may have been beneficial in stabilizing renal function.[22] Based on this, they appear to be the preferred antihypertensive agent for dogs with CKD. However, the role of the renin-angiotensin-aldosterone system (RAAS) and ACE inhibitor therapy in cats with CKD and hypertension is more controversial.[114–117] Evidence that activation of the RAAS is consistently central to the genesis of hypertension in cats is contradictory, and ACE inhibitors have not been found to be consistently effective in lowering blood pressure in cats with CKD. Therapy using either benazepril or enalapril may be initiated in dogs or cats with CKD at a dose of 0.5 mg/kg given orally every 24 hours.

Calcium channel blockers preferentially antagonize preglomerular vasoconstriction, which theoretically, should not reduce glomerular hypertension. However, CCBs appear to have additional renoprotective

properties.[111] They may prevent renal injury by limiting renal growth, by reducing mesangial entrapment of macromolecules, and by attenuating the mitogenic effects of diverse cytokines and growth factors (e.g., PDGF, platelet-activating factor). In addition, amlodipine inhibits the *in vitro* proliferation of mesangial cells. However, clinical trials in humans have provided conflicting results as to the renoprotective effect of CCB beyond their antihypertensive effects. Controlled studies on the renoprotective effects of amlodipine in dogs and cats have not been published. In the authors' clinical experience, CCBs have been effective antihypertensive agents in dogs and cats with CKD. Because it is usually highly effective, has few side effects, and has a relative rapid onset, the long-acting dihydropyridine calcium antagonist amlodipine is the antihypertensive of choice for most cats with CKD. Amlodipine is prescribed at a dose of 0.625 mg for cats less than 4 kg and 1.25 mg for cats greater than 4 kg. In cats with CKD, amlodipine typically reduces systolic blood pressure by about 30 to 50 mm Hg within the first 1 to 2 months of therapy.[107,118] General principles of management of hypertension are described in Chapter 130, Hypertension.

260.4.9 Treatment of Anemia of Chronic Renal Failure

260.4.9.1 General Guidelines for Minimizing Anemia

An obvious but often overlooked consideration is minimizing iatrogenic blood loss. Iatrogenic loss is especially likely to occur in hospitalized cats and small dogs because of repeated sampling for diagnostic tests and monitoring. Therefore the quantities of blood collected from these patients should be recorded and monitored.

Chronic low-grade GI blood loss can also result in moderate to severe anemia in patients with CKD that would otherwise have sufficient endogenous erythropoietin production to maintain their hematocrit values in the low-normal range. These patients may lack overt GI signs or melena. Iron deficiency, microcytosis and an elevation in BUN/creatinine ratio above what is expected in context of the patient's diet may provide indirect evidence of occult GI blood loss. Because of difficulty in confirming GI hemorrhage, a therapeutic course with histamine H_2-receptor antagonists and sucralfate may be considered. Improvements in hematocrit, appetite, or both indicate a positive response.

Iron deficiency is a relatively common problem in dogs and cats with CRF. In a recent study, the serum iron concentrations of 3 of 6 CRF dogs and 3 of 7 CRF cats were below the reference range (transferrin saturations less than 20%).[119] Whether this is related primarily to inadequate intake and absorption of iron or increased losses of iron due to GI blood loss is unclear. Unfortunately, iron status can be difficult to assess in dogs and cats. Serum iron levels can be used to screen for both iron deficiency and anemia of chronic inflammatory disease as contributing factors in the diagnostic evaluation of anemia. In dogs, serum iron levels may not reflect body iron stores in that normal values can occur in patients with iron deficiency. However, determining stainable iron content in bone marrow is helpful in assessing body iron stores and may detect problems not identified by serum iron levels or transferrin saturation. When low serum iron levels reflect true iron deficiency, bone marrow stainable iron levels will be low; in those with anemia of chronic inflammatory disease, bone marrow levels will be normal or high reflecting sequestration. The distinction is important because anemia of chronic inflammatory disease will not improve in response to iron supplements and may even result in iron overload. It is necessary to identify and remove the concurrent inflammatory disease to treat anemia of chronic inflammatory disease. Transferrin saturation (estimated by dividing serum iron by total iron binding capacity) may be useful for assessing the ability of the mobilizable iron stores (perhaps independent of total tissue iron stores) to meet the demands of

erythropoiesis and, thus is particularly useful in evaluating patients during periods of increased erythropoiesis such as during recombinant human erythropoietin (rHuEPO) therapy.

Oral supplementation with ferrous sulfate is the preferred therapy for treatment of iron deficiency anemia and also for prevention of iron-deficient erythropoiesis in patients starting erythropoietin replacement therapy. Alternatively, iron dextran may be administered by intramuscular injection. However, parenteral administration of iron is associated with a small risk of anaphylaxis, shunting of iron to reticuloendothelial storage, and iron overload. Although serum iron levels and transferrin saturation should be monitored to adjust therapy, starting doses of iron sulfate of 50 to 100 mg/day for cats and 100 to 300 mg/day for dogs have been recommended. Oral iron supplements may be associated with GI upset and diarrhea, so small divided doses may be preferable.

In addition to iron deficiency, other nutritional abnormalities may contribute to anemia in patients with CKD. Protein malnutrition and its attendant changes in plasma amino acid and hormone concentrations is known to cause suboptimal erythropoiesis and anemia. Similar changes occur in human patients and may reflect mild protein/calorie malnutrition commonly present in advanced CKD. Although they have not been examined in dogs and cats, deficiencies in riboflavin (vitamin B_2), cobalamin (vitamin B_{12}), folate, niacin, or pyridoxine (vitamin B_6) might theoretically induce nutritional anemia. Vitamin status cannot be easily determined in dogs and cats; however, deficiencies should be suspected in patients with persistent anorexia, protein and calorie malnutrition, or GI malabsorption. In addition, some drugs may predispose the patient to nutritional anemia even when dietary intake is normal. For example, therapy with trimethoprim or methotrexate may interfere with cellular folate metabolism. Hypersegmentation of the polymorphonuclear leukocytes may provide a clinical indication of vitamin B_{12} or folate deficiency.

Risk of nutritional deficiencies can be minimized through timely initiation of proper diet modifications and, if necessary, use of dietary supplements. In addition to minimizing renal anemia, preventing protein and calorie malnutrition may reduce morbidity. B vitamins, folate, and niacin can be provided as an oral supplement often with iron.[33] Care must be taken with multivitamins not to oversupplement the fat-soluble vitamins A and D.

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RBC life span is decreased in advanced CKD. Proposed mechanisms for this mild hemolytic tendency include a malfunctioning of the membrane Na+-K+-ATPase pump and impaired regeneration of reduced glutathione needed to prevent hemoglobin oxidation. Cat hemoglobin appears to be especially prone to oxidative stress as evidenced by the frequent observation of Heinz bodies in their RBCs. Cats with CKD having large numbers of Heinz bodies tend to be more anemic. Drugs and foods (e.g., onions, propylene glycol, methylene blue, sulfonamides) that promote formation of Heinz bodies should be avoided in uremic pets whenever possible.

PTH has been postulated to play a role in the pathogenesis of anemia of CRF. PTH inhibits growth of all bone marrow cell lines *in vitro*. However, leukopenia and thrombocytopenia are not characteristic of CKD, arguing against an important role for PTH-induced bone marrow suppression. In a clinical series of canine CKD patients with anemia, the authors found no correlation between PTH levels and the degree of anemia.[34]

It has been postulated that increased serum phosphorus leads to increased intracellular red cell phosphorus. This in turn increases red cell 2,3 DPG levels, a noteworthy finding in anemic CRF patients.[34] Increased 2,3 DPG levels cause a rightward shift in the oxyhemoglobin dissociation curve, improving tissue oxygenation and decreasing the stimulus for erythropoietin synthesis.

260.4.9.2 Anabolic Steroids

Anabolic steroids were at one time the mainstay of therapy for anemia associated with CKD. Although controlled safety and efficacy studies in dogs and cats are lacking, clinical experience with anabolic steroids has been disappointing. With the advent of rHuEPO therapy, androgens have largely fallen out of favor for treatment of renal anemia in human and veterinary medicine. Based on studies in human patients and clinical experience with veterinary patients, androgens appear to work in only a small percentage of patients (usually those mildly affected), have a long delay to onset of action, and may be associated with undesirable side effects. Administration of anabolic steroids for treatment of dogs and cats with anemia of CKD should probably be limited to those patients with symptomatic anemia in which all other factors adversely affecting erythropoiesis (nutritional deficiencies, blood loss, hemolysis, concurrent disease) have been eliminated and other treatment options (erythropoietin, transfusion) are unavailable or have been exhausted.

260.4.9.3 Blood Transfusion

Transfusions of packed RBCs or whole blood may be indicated for anemic CKD patients who need rapid correction of their anemia, as in preparation for surgery. For some patients, repeated transfusions can be used for long-term maintenance of hematocrit. However, several drawbacks have limited the use of this therapy in dogs and cats, including lack of availability and expense of blood products, increasing risk of transfusion reactions with multiple transfusions, risk of immunosuppression, risk of transfer of infectious agents, and decreased life span of transfused cells in uremic patients. Even for the first transfusion, only compatible blood products (as determined by cross-matching) should be used in both dogs and cats. The post-transfusion target hematocrit should be the low end of the normal range. This should be adequate to reverse the anorexia and fatigue associated with the anemia while minimizing the complications of too rapid an increase in blood volume and viscosity such as circulatory overload, hypertension, and seizures.

260.4.9.4 Hormone Replacement Therapy

Hormone replacement therapy using rHuEPO has become the treatment of choice for anemia of CKD in cats and dogs when hematocrit values decline below about 20% and clinical signs are attributable to the anemia. Administration of rHuEPO causes a dose-dependent increase in hematocrit.[119] Correction of hematocrit to low normal takes approximately 2 to 8 weeks, depending on the starting hematocrit and dose given. As the anemia is corrected, most clients report that their pets show increases in appetite, body weight, energy level, and sociability.[119] Initially, erythropoietin is usually administered at a dose of 50 to 150 U/kg subcutaneously three times weekly. Most dogs and cats should be started at 100 U/kg administered three times weekly. Hematocrit is monitored weekly or biweekly until a target hematocrit of approximately 30% to 40% for cats and 37% to 45% for dogs is achieved.[119] When anemia is severe (hematocrit < 14%) but does not require transfusion, daily therapy with 150 U/kg may be preferred for the first week. In the presence of hypertension or when anemia is not severe, a dose of 50 U/kg three times per week may help to prevent increases in blood pressure and iron-deficient erythropoiesis. When a hematocrit at the low end of the target range is reached, the dosing interval should be decreased to twice weekly. Most animals require 50 to 100 U/kg two to three times weekly to maintain their hematocrit in the target range; however, the dose and dosing interval required to maintain individual patients in the normal range is highly variable.

Ongoing monitoring of hematocrit will be necessary to allow adjustments in dose and dosing interval. Animals requiring more than 150 U/kg three times weekly should be evaluated for erythropoietin resistance. Because of the lag time between dose adjustment and effect on hematocrit, patience must be exercised so as not to adjust the dose too frequently. Frequent dose adjustments will result in rapid, unpredictable changes in hematocrit and an inability to find a stable dosing regimen. In general, dose should not be changed any more often than once monthly. Avoiding iatrogenic polycythemia is especially important.

The basis for individual differences in response to rHuEPO is incompletely understood. Several causes of blunted response or failure to resolve renal anemia with rHuEPO therapy have been identified, including functional or absolute iron deficiency, anti-rHuEPO antibody formation, ongoing GI blood loss or hemolysis, concurrent inflammatory or malignant disease, and aluminum overload (not documented in veterinary patients). Owner errors related to drug storage, handling, or administration may account for some instances of poor response to rHuEPO therapy.

The demand for iron associated with stimulated erythropoiesis is high, and human patients without pre-existing iron overload will exhaust iron storage during rHuEPO therapy. The same appears true of dogs and cats. Iron supplementation is therefore recommended for all patients receiving rHuEPO therapy.

Adverse effects related to rHuEPO therapy in dogs and cats may include systemic hypertension, seizures, local reactions at the injection site, and development of antibodies directed at erythropoietin.[119] Hypertension may develop or increase in severity with rHuEPO therapy. Increased peripheral vascular resistance secondary to improved oxygen delivery and reversal of the vasodilation induced by chronic hypoxia may contribute to this effect. Increased blood viscosity associated with the increased hematocrit is thought to be only a minor contributor. Seizures have been observed in human, canine, and feline patients being treated with rHuEPO that have no prior history of a seizure disorder.[119] In dogs and cats, they have been reported in the setting of moderate to severe azotemia. Although hypertension, anemia, and uremic encephalopathy may be contributory, in humans, seizures are thought to be related to compensatory adaptations to increases in RBC mass. Seizures are not thought to be directly related to rHuEPO.

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Allergic reactions, including cutaneous or mucocutaneous reactions or cellulitis sometimes with fever and arthralgia, were uncommonly observed in both dogs and cats early in the course of rHuEPO therapy.[119] Lesions generally resolved within a few days and some did not recur when therapy was reinstated.

The most important complication associated with use of rHuEPO is refractory anemia and hypoplasia of the erythroid bone marrow associated with formation of neutralizing anti-rHuEPO antibodies.[119] In some affected patients, the severity of anemia was worse than before initiation of rHuEPO treatment. This observation suggested that the anti-rHuEPO antibodies were effective in interfering with the erythropoietin effects of rHuEPO and endogenous erythropoietin. The rHuEPO protein appears to be immunogenic in many, but not all, dogs and cats with antibody titers developing at variable times from several weeks to months after the onset of therapy. After cessation of therapy, antibody titers declined. In the absence of a widely available anti-EPO antibody assay, bone marrow myeloid/erythroid ratios provide the best method to ascertain if rHuEPO resistance is due to antibody formation. After therapy is stopped and antibody titers decline, suppressed erythropoiesis may be reversible and pretreatment levels of erythropoiesis are attained.

The relatively high prevalence of anti-rHuEPO antibody production prompts the question of when to initiate rHuEPO therapy. Premature initiation of erythropoietin therapy with subsequent development of

antierythropoietin antibodies may deprive the patient of the clinical benefits of this therapy when clinical signs of anemia eventually do develop and rHuEPO can be of greatest clinical benefit. When hematocrit values are below 20%, anemia likely contributes to adverse clinical signs characteristic of uremia. In addition, degree of azotemia, expected rate of progression of kidney failure, appetite and willingness to eat therapeutic diets, and rate of progression of anemia must all be considered in the risk-benefit analysis of when to start therapy. The advantages and disadvantages of rHuEPO therapy should be discussed with the owners when anemia appears to be contributing to the patient's deteriorating quality of life. Many pet owners may consider quality of life to be as or more important than quantity of life.

260.4.9.5 Future Treatment Directions

Future options for treatment of anemia of CKD may include development of species-specific erythropoietin and gene therapy.[120] Although not commerci-ally available, recombinant canine and feline erythropoietin have been developed.[121] They offer the hope of erythropoietin replacement therapy in dogs and cats without concern for antierythropoietin antibody formation. If concern for antibody formation can be eliminated, erythropoietin therapy could be initiated earlier in the course of chronic renal insufficiency and failure. It also has been demonstrated that gene therapy can be used to induce extrarenal production of erythropoietin in cats.[122]

260.4.10 Calcitriol Therapy

260.4.10.1 Rationale for Calcitriol Therapy

An undesirable consequence of reduced renal production of calcitriol is renal secondary hyperparathyroidism. Calcitriol (1,25-dihydroxyvitamin D), the most active metabolite of vitamin D, results from renal hydroxylation of 25-hydroxyvitamin D. Normally, calcitriol inhibits PTH synthesis and release and parathyroid gland growth, an effect mediated by the vitamin D receptor in the parathyroid gland. As functioning renal mass declines, renal production of calcitriol declines. In addition, phosphorus retention also inhibits renal hydroxylation of 25-hydroxyvitamin D to calcitriol and directly stimulates PTH release. By reducing PTH levels, calcitriol therapy minimizes abnormalities associated with renal secondary hyperparathyroidism. The effectiveness of calcitriol therapy in reducing PTH levels in dogs and cats with CKD is well established.[39] Although PTH has been proposed as a potential uremic toxin responsible for many constitutional signs or uremia, the clinical benefits of reducing PTH levels have not been conclusively documented. Nagode and colleagues[39] published results of a survey of veterinarians that use calcitriol in management of dogs and cats with CKD. Results of this survey reveal a high level of enthusiasm for calcitriol among veterinarians using the drug. Clinical impressions concerning use of calcitriol in dogs and cats suggest that patients seem (1) to be brighter and more alert and interactive with owners, (2) to have an improvement in appetite, (3) to be more physically active than before treatment, and (4) to have longer life spans. Further, these authors provide pathophysiologic support for the purported benefits of calcitriol therapy through referenced studies from multiple species. In contrast, Finco and colleagues,[123] using parathyroidectomy combined with an experimental model of renal failure, concluded that increased PTH levels do not contribute importantly to clinical signs of uremia in dogs. However, this study was not designed to directly address the effectiveness of calcitriol therapy in managing clinical signs of dogs and cats with CKD.

Despite reported favorable impressions concerning use of calcitriol, its role in managing dogs and cats with CKD should be confirmed by randomized, controlled clinical trials. Routine clinical practice is never *blind*, because owners and veterinarians know when active treatment is being received. Interpretation of uncontrolled studies is confounded by the desire of pet owners and clinicians for success, as well as the placebo effect, which can cause both parties to overestimate efficacy. In addition, calcitriol has the potential to promote hypercalcemia and renal injury if improperly used. A recommendation for or against routine use of calcitriol awaits results of properly designed controlled clinical trials.

260.4.10.2 Guidelines for Using Calcitriol

The primary goal of calcitriol therapy is to prevent or correct renal secondary hyperparathyroidism and its consequences. However, the decision to use calcitriol must be made with caution because hypercalcemia is a potentially serious complication. Sustained calcitriol-induced hypercalcemia will likely result in reversible or irreversible reduction in GFR. Although hypercalcemia reportedly occurs in 30% to 57% of humans treated with calcitriol, hypercalcemia appears to be an uncommon side effect in dogs treated with doses in the range of 2.5 to 3.5 ng/kg/day.[44] Hypercalcemia is likely to occur when calcitriol therapy is combined with calcium-containing phosphorus-binding agents, particularly calcium carbonate.

Serum phosphorus concentrations must be reduced to 6.0 mg/dL or lower before initiating calcitriol therapy (see discussion of management of hyperphosphatemia in this chapter). Serum phosphorus concentrations greater than 6.0 mg/dL may inhibit the effectiveness of calcitriol therapy and enhance the tendency for calcitriol to promote renal mineralization and injury. In addition, phosphorus restriction and calcitriol therapy are likely additive in reducing plasma PTH activities. Thus serum calcium and phosphorus concentrations should be carefully monitored in patients receiving calcitriol.

Calcitriol rapidly and effectively suppresses renal secondary hyperparathyroidism. An important advantage of calcitriol over other forms of vitamin D therapy in CKD is that calcitriol does not require renal activation for maximum efficacy. Dogs and cats appear to require much lower doses of calcitriol than those recommended for humans calculated on the basis of body weight.[39] Nagode and colleagues[39] have recommended a dose of 2.5 to 3.5 ng/kg body weight per day given orally to dogs and cats with CKD. The optimum maintenance dose for calcitriol must be determined for each patient based on serial evaluation of serum calcium and phosphorus and plasma PTH concentrations. The recommended endpoint of calcitriol therapy is normalization of PTH activity in absence of hypercalcemia. When the dose of calcitriol necessary to normalize PTH levels is associated with hypercalcemia, the daily dose may be doubled and given every other day. This approach is thought to be less likely to induce hypercalcemia because the effect of calcitriol on intestinal calcium absorption is related to the duration of exposure of intestinal cells to calcitriol.

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When plasma PTH concentration is markedly elevated or when standard therapy with calcitriol fails to normalize plasma PTH levels, pulse calcitriol therapy has been recommended.[39] In this approach, patients are given 20 ng/kg of calcitriol twice per week in the evening on an empty stomach. Pulse therapy is usually used no longer than 1 to 2 months to suppress resistant hyperparathyroidism. If successful, calcitriol is then given at the standard daily dose. Because it enhances intestinal absorption of calcium and phosphorus, calcitriol should not be given with meals. Custom-made capsules or liquid preparations containing appropriate doses of calcitriol for use in dogs and cats are available from compounding pharmacies. Compounded calcitriol preparations should contain appropriate preservatives to prevent oxidation.

Early detection of hypercalcemia is indicated to limit the extent of renal injury. However, the onset of hypercalcemia after initiation of vitamin D therapy is unpredictable (i.e., it may occur after days to months of treatment). Therefore continued monitoring of serum calcium, phosphorus, and creatinine concentrations is necessary to detect hypercalcemia, hyperphosphatemia, or deteriorating renal function before irreversible renal damage ensues. Serum calcium, phosphorus, urea nitrogen, and creatinine concentrations should be monitored 1 week and 1 month after initiating calcitriol therapy, and monthly to bimonthly thereafter. The product of serum calcium and phosphorus concentrations should not exceed 60; the goal is to attain values between 42 and 52.[48] Calcitriol's rapid onset (about 1 day) and short duration of action (half-life less than 1 day) permits rapid control of unwanted hypercalcemia. If hypercalcemia develops, it is advisable to stop treatment completely rather than reduce the dose. Therapy may be reinstituted with a reduced dose when serum calcium concentration returns to normal and serum phosphorus concentration is less than 6.0 mg/dL.

260.4.11 Minimizing Progression of Renal Failure

All patients with CKD are at risk for progressive kidney disease. Progression may occur as a consequence of their primary renal disease, in association with a variety of secondary factors that may promote progressive renal disease, or both. An important therapeutic goal for managing patients with CKD is to minimize or prevent progressive loss of renal function. Treatment designed to limit progression of kidney disease may involve a variety of interventions including diet therapy, controlling hypertension, minimizing proteinuria, and modulating the renin-angiotensin-aldosterone system.

Clinical and experimental evidence indicates that dietary intervention may be effective in preserving renal structure and function and prolonging survival. In a randomized controlled clinical trial in dogs with naturally occurring CKD, dietary intervention significantly prolonged survival and slowed decline in renal function.[1] Dogs consuming the renal diet survived an average 593 days, whereas dogs consuming a maintenance diet survived an average 188 days. This beneficial effect applied over a range of serum creatinine values encompassing both stages 3 and 4 CKD. Renal function declined in both groups, but the decline was significantly greater in the dogs consuming the maintenance diet. The specific mechanisms underlying the beneficial effects of the diet were not determined. However, it is likely that at least dietary phosphorus restriction and omega-3 PUFA supplementation contributed to the favorable effect.[1,57,93,94] It is also likely that once the dogs progressed to a more advanced level of renal dysfunction, dietary protein restriction provided an additional period of symptomatic relief, thereby prolonging survival further.

Similarly, in a nonrandomized clinical trial, cats fed a renal diet survived significantly longer than cats that continued to consume their usual diet (633 days versus 264 days).[64] It was not possible to establish the differences between diets used in this study, but the therapeutic renal diet was reduced in protein and phosphorus content. The renal diet was shown to be beneficial in lowering serum phosphorus and PTH concentrations, and it was suggested that the beneficial effect of the diet may have been related to this effect.[99]

Treatments designed to limit hypertension and proteinuria may also be of value in slowing progression of kidney disease and kidney failure. Hypertension and proteinuria are a well-established risk factors for progression of renal disease in humans.[19,124] Similarly, studies at the University of Minnesota Veterinary Medical Center have shown that elevated blood pressure and proteinuria are risk factors for uremic crises and increased mortality in dogs with stages 3 and 4 CKD.[18] The effects of blood pressure and proteinuria on progression of feline CKD have not been established.

Experimental and clinical evidence has confirmed the beneficial effect of blood pressure control on slowing progression of diabetic and nondiabetic nephropathies in humans.[19,125] In one large clinical trial, the renoprotective effect of antihypertensive therapy was further enhanced by maintaining blood pressure below the usual target value.[126] As a consequence, the "ideal" blood pressure to attain using antihypertensive therapy in human patients with CKD remains unresolved. Patient factors such as the presence or absence of proteinuria may also influence the goals of therapy. Antihypertensive therapy was most effective in limiting progression of kidney disease in patients with proteinuria. A greater reduction in blood pressure appears to be necessary for equivalent renoprotection in patients with greater levels of proteinuria.[19,126] Further, independent of blood pressure control, reducing proteinuria has been shown to have a favorable influence on kidney disease progression.[127]

Evidence supporting the renoprotective value of antihypertensive therapy in dogs and cats with naturally occurring CKD is lacking. However, studies performed in dogs with induced CKD indicate that administration of the ACE inhibitor, enalapril, limited glomerular and systemic hypertension, proteinuria, and glomerular and tubulointerstitial lesions.[112] Interestingly, enalapril was renoprotective in this study, despite the fact that the dogs had only mild hypertension and relatively modest proteinuria. Enalapril has also been reported to ameliorate proteinuria and stabilize renal function in dogs with naturally occurring glomerulopathies with protein/creatinine ratios greater than 3.0.[22] Enalapril therapy was associated with a reduction in proteinuria of over 50%. Over the 6 months of study, serum creatinine increased by more than 0.2 mg/dL in 13 of 14 dogs receiving placebo, but only three of 16 dogs receiving enalapril. In this study, enalapril significantly reduced systolic blood pressure from a mean of 154+/–25 before therapy to 142+/-19 after 6 months of treatment.

In humans, ACE inhibitors are generally considered to be the antihypertensive drugs of choice in patients with CKD, particularly when proteinuria is evident, because they lower both systemic and intraglomerular pressures and proteinuria.[19] Further, ACE inhibitors are indicated for patients with proteinuric CKD for the purpose of reducing proteinuria, regardless of whether the patient is hypertensive. It appears appropriate to consider ACE inhibitor treatment for dogs with CKD when systolic blood pressure values are proven to remain above 160 mm Hg and when the urine protein/creatinine values exceed 1.0.

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ACE inhibitors reduce blood pressure and proteinuria in cats; however, their unique renoprotective value has yet to be established in this species.[113] As a consequence, recommendations concerning use of ACE inhibitors in cats with CKD remain unresolved. The dihydropyridine calcium-channel blocker amlodipine is the antihypertensive drug of choice for most cats. However, in humans, dihydropyridine calcium-channel blockers appear to be associated with a greater risk of progression of kidney disease.[126] Although clinical impression suggests this is not the case in cats with CKD, the effect of amlodipine on progressive renal disease has not been critically examined in cats. It has been suggested that combining amlodipine with an ACE inhibitor might have greater renal-sparing potential. Studies into the clinical value of this drug combination are needed in cats with spontaneous renal failure.

The renoprotective effects of ACE inhibitors cannot be explained entirely by their effects on blood pressure. It is likely that renoprotection results in part from suppressing renal levels of angiotensin II. Angiotensin II may adversely affect the kidneys in several ways (Box 260-8).[125] Because of the role of angiotensin II in progression of CKD, angiotensin receptor blockers have also been considered for humans with CKD.[128] Angiotensin receptor blockers and ACE inhibitors differ in the mechanism by which they inhibit angiotensin II. The ACE inhibitors block conversion of angiotensin I to angiotensin II. However, angiotensin II formation

is not completely inhibited because it can also be generated by a nonACE-dependent pathway such as by the enzyme chymase. In addition, because bradykinin is normally degraded by ACE, ACE inhibitor therapy is associated with elevated bradykinin levels. Bradykinin is a vasodilator that may have renoprotective effects by stimulating nitric oxide production. Angiotensin receptor antagonists block the type 1 receptor but leave type 2 receptor effects unopposed, which appears to be important in vasodilation. In rats with nephropathy, angiotensin II antagonism has been reported to normalize proteinuria, eliminate inflammatory cell infiltration, and ameliorate glomerular and tubular structural changes.[129] A combination of an angiotensin receptor antagonist and ACE inhibitor has been suggested as a way to maximize blockade of the renin-angiotensin system by affecting both the bioavailability of angiotensin II and also by affecting its activity at the receptor level.[130] Each type of drug has been shown to be effective in reducing proteinuria and slowing progression of renal disease. However, in experimental models and clinical models in humans, combination therapy has proven more effective than either drug alone.[128] In humans there does not appear to be an increase in toxicity or adverse events with combination therapy.[125]

260.4.11.1 Box • 260-8 Potential Adverse Effects of Angiotensin II on the Kidneys

Glomerular hypertension

Impaired glomerular permselectivity

Mesangial cell proliferation

Induction of TGF-β, thereby increasing production of extracellular matrix

Increased aldosterone production

Macrophage activation; activation of inflammation-related transcription factors

Increased production of plasminogen activator inhibitor-1

Modified from Rosenberg ME: Chronic kidney disease: progression. NephSAP 2(3):94, 2003.

Whether combination therapy is safe, effective, and provides a therapeutic advantage needs to be determined for dogs and cats with CKD.

Blockade of the renin-angiotensin system limits both angiotensin II and aldosterone while retarding progression of renal disease. Recent studies have implicated aldosterone as an important pathogenic factor in this process.[131,132] Selective blockade of aldosterone, independent of renin-angiotensin blockade, reduces proteinuria and glomerular lesions in rats with experimental kidney disease. Where blockade of the renin-angiotensin system ameliorates proteinuria and glomerular injury, selective reinfusion of aldosterone restores proteinuria and glomerular lesions despite continued blockade of the renin-angiotensin system. This observation suggests an independent pathogenic role for aldosterone as a mediator of progressive renal disease. Aldosterone appears to promote progressive renal injury through both hemodynamic effects and direct

cellular actions.[131] It appears to have fibrogenic properties in the kidneys, perhaps in part by promoting production of the profibrotic cytokine TGF-β.[132] Experimental studies have shown that the aldosterone-receptor antagonist eplerenone may attenuate proteinuria and renal damage, independent of its effect on blood pressure. Although ACE inhibitors initially cause an acute reduction in aldosterone concentration, this effect is not sustained. It has been proposed that use of aldosterone-receptor antagonists in addition to ACE inhibitors will have additional benefits toward protecting the kidneys.[131] However, the role of this form of therapy has yet to be established.

Vasopeptidase inhibitors are agents that inhibit both ACE and neutral endopeptidase, an enzyme involved in the breakdown of natriuretic peptides, adrenomedullin, and bradykinin. They decrease angiotensin II production and increase accumulation of the previously mentioned vasodilators. In experimental renal disease, they appear to have a greater renoprotective effect than ACE inhibitors.[133] Studies on these agents have not been reported in dogs and cats with CKD.

Inflammation is a prominent feature of progressive renal diseases. Future therapies are likely to include novel inhibitors of specific profibrotic or proinflammatory cytokines and growth factors. The immunosuppressive agent mycophenolate mofetil has been shown to be renoprotective in remnant kidney rats.[134] Pirfenidone, an antifibrotic agent, has been shown to attenuate renal fibrosis.[135]

260.5 PATIENT MONITORING

Response to treatment should be monitored at appropriate intervals so that treatment can be individualized to the specific and often changing needs of the patient. The data base obtained before initiating therapy or after correcting an overt uremic crisis should be used as a baseline for comparison of the patient's progress. This evaluation should be repeated at appropriate intervals. Evaluations every 2 to 4 weeks are suggested until the initial response to therapy can be established. However, the frequency of evaluation may vary depending on severity of renal dysfunction, complications present in the patient, and response to treatment. Patients receiving therapy with erythropoietin or calcitriol require frequent, life-long monitoring. After the initial response to therapy has been established, dogs and cats in stages 1 and 2 CKD may require evaluation as infrequently as every 6 to 12 months. However, patients with substantial proteinuria may require monitoring much more frequently, depending on the course of their disease. Cats and dogs in stages 3 and 4 CKD should be re-evaluated about every 2 to 4 months, depending on the stability of their renal function. Specific recommendations for monitoring are described in the various treatment sections.

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261 CHAPTER • 261 Glomerular Diseases

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Glomerular diseases are a leading cause of renal disease and renal failure in dogs.[1] In randomly selected dogs, the incidence of glomerular lesions is as high as 43% to 90%,[2] and the incidence appears to increase with age.[3] Glomerular diseases also occur in cats, although they are less common. It has been accepted that amyloidosis and glomerulonephritis are the most common glomerular diseases of dogs and cats (Box 261-1). However, to make progress toward improved diagnosis and management of dogs and cats with glomerular disease, veterinarians must come to consider the different forms of glomerulonephritis as specific entities: membranous glomerulopathy, membranoproliferative glomerulonephritis and proliferative glomerulonephritis (including the subclass of IgA nephropathy). The proposed pathogenesis of each entity is somewhat different; in humans this leads to different clinical features and specific treatment recommendations for each disease.[4,5] Hereditary nephritis and minimal change disease are less common glomerular diseases in dogs and cats.

261.1 NORMAL GLOMERULAR STRUCTURE AND FUNCTION

The glomerulus is a modified capillary bed that functions as a filter, across which an ultrafiltrate of the plasma is formed.[4,5] The filtration barrier is composed of three layers: the fenestrated endothelium, the glomerular basement membrane (GBM), and the visceral epithelial cells, or *podocytes* (Figure 261-1). This complex structure is freely permeable to water and small dissolved solutes but retains cells and most macromolecules, such as proteins. The major determinant of passage into the filtrate is molecular size. Small molecules, such as inulin (5000 daltons), pass freely through the filter. Substances are retained with increasing efficiency as they increase in size to approximately 60,000 to 70,000 daltons; only small amounts of substances larger than this are filtered. Although the issue currently is a matter of dispute, many believe that ionic charge also influences filtration, and that negatively charged proteins are retained to a greater extent than would be predicted by size alone.[6] The podocyte foot processes and the slit diaphragms between them, as well as the basement membrane and the endothelium, are rich in negatively charged glycoproteins, creating this charge barrier. These polyanions are believed to play an important role in the maintenance of normal glomerular permeability and visceral epithelial cell shape. Albumin, a negatively charged protein with a molecular weight of 69,000 daltons, is normally largely excluded from the filtrate.

Despite this complex filtration system, small amounts of albumin and other proteins are normally found in the filtrate. Substantial degradation of these proteins occurs, resulting in excretion only of peptide fragments, which are not detected by routine total protein assays. Proteins and peptide fragments may also undergo resorption in the nephron distal to the glomerulus.[6]

261.2 CLINICAL FINDINGS IN GLOMERULAR DISEASE

261.2.1 Signalment

Glomerular disease can develop in a dog of any age but appears to be most common in middle-aged to older dogs. The prevalence of microalbuminuria, a marker of increased glomerular permeability, increases as dogs age, with more marked increases seen beyond 6 years of age.[7] The average age of 375 dogs with a variety of glomerular diseases reported in five studies was 8.3 years.[1,8–11] Male and female dogs were equally

represented. However, the average age and gender predilection seen with specific glomerular diseases varies somewhat from the overall averages. Glomerular diseases often occur secondary to another disease process. Infectious and noninfectious inflammatory diseases may be more likely in young and middle-aged animals, whereas neoplasms are more common causes of glomerular disease in older patients. Familial glomerular diseases often are manifested at an early age. Several breeds of dogs are known to have familial glomerular diseases (Table 261-1). Labrador retrievers and golden retrievers may have a higher incidence of glomerular disease; however, the possibility that this increased representation reflects the popularity of these breeds requires further evaluation.[8,12]

261.2.2 History

The clinical signs associated with glomerular disease vary considerably, depending on the severity of proteinuria and the presence or absence of renal failure.[8,9,13] Many animals with glomerular disease are asymptomatic, and proteinuria is detected during routine health screening. Alternatively, animals may manifest specific signs related to an underlying inflammatory, infectious, or neoplastic condition (Boxes 261-2 and 261-3). Signs of glomerular disease may be nonspecific (e.g., weight loss, lethargy) or consistent with chronic renal failure or uremia (polyuria, polydipsia, anorexia, vomiting, and malodorous breath). Acute renal failure is a less common presentation for animals with glomerular disease. When urinary protein losses are severe, signs of fluid retention (e.g., abdominal enlargement consistent with ascites, peripheral edema) or thromboembolism (e.g., dyspnea, loss of limb function) may be present. Hypertensive damage to the central nervous system, eyes, or heart may induce a variety of clinical signs.

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261.2.2.1 Box • 261-1 Glomerular Diseases Described in Dogs and Cats

- Amyloidosis
- Focal segmental glomerulosclerosis
- Glomerulonephritis
  - Crescentic type (rare)
  - Membranoproliferative form
    - Type I (mesangiocapillary)
    - Type II (dense deposit disease)?
  - Proliferative glomerulonephritis (mesangial and endocapillary)
- IgA nephropathy

Glomerulosclerosis

Hereditary nephritis

Lupus nephritis

Membranous glomerulopathy*

Minimal change glomerulopathy

* Membranous glomerulopathy is the most common glomerular disease in cats; other glomerular diseases appear to be uncommon in cats.

Figure 261-1 Electron micrograph of a glomerular capillary wall showing the filtration barrier composed of the fenestrated endothelium, the glomerular basement membrane, and the visceral epithelial cell (podocyte). (Courtesy J.C. Jennette, Chapel Hill, NC, School of Medicine, University of North Carolina.)

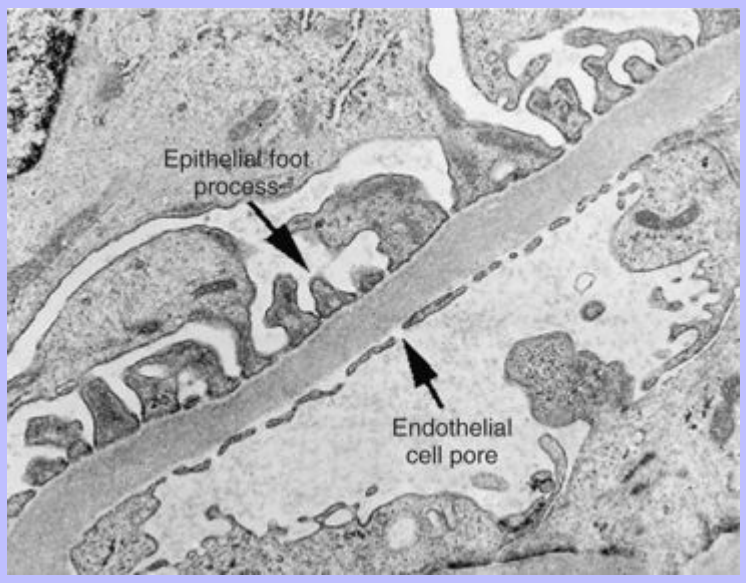

Table • 261-1 Breeds of Dogs with Familial Glomerulopathies

BREED	GLOMERULAR DISEASE
Beagle	Amyloidosis
Bernese mountain dog	Mesangiocapillary glomerulonephritis
Bull terrier	Hereditary nephritis
Cocker spaniel (especially English)	Hereditary nephritis
Dalmatian	Hereditary nephritis
Doberman pinscher	Glomerulosclerosis, cystic glomerular atrophy
English foxhound	Amyloidosis
Greyhound	Glomerular vasculopathy and necrosis
Newfoundland	Glomerulosclerosis
Rottweiler	Atrophic glomerulopathy
Samoyed (rare)	Hereditary nephritis
Shar Pei	Amyloidosis
Soft-coated wheaten terrier	Proliferative and sclerosing glomerulonephritis

261.2.2.2 Box • 261-2 Diseases Reported in Association with Glomerular Disease in Dogs

261.2.2.2.1 Systemic Disease (Glomerular Disease)

Infectious

Bacterial

Borreliosis (MPGN)

Bartonellosis (G)

Brucellosis (G)

Endocarditis (G)

Pyelonephritis (A)

Pyometra (A, G)

Pyoderma (A, G)

Other chronic bacterial infections (A, G)

Protozoal

Babesiosis (MPGN)

Hepatozoonosis (G)

Leishmaniasis (A, MPGN, MN, P-E and M)

Trypanosomiasis (G)

Rickettsial

Ehrlichiosis (G)

Viral

Canine adenovirus type 1 (P-M)

Parasitic

Dirofilariasis (A, MPGN, MN)

Fungal

Blastomycosis (A)

Coccidioidomycosis (A, G)

Inflammatory

Chronic dermatitis (A, G)

Inflammatory bowel disease (G)

Pancreatitis (A, G)

Periodontal disease (A, G)

Polyarthritis (A, G)

Systemic lupus erythematosus (A, MPGN, MN, P-E and M)

Other immune-mediated diseases (G)

Neoplastic

Leukemia (G)

Lymphosarcoma (A, G)

Mastocytosis (G)

Primary erythrocytosis (MCD?)

Systemic histiocytosis (G)

Other neoplasms (A, G, MN)

Miscellaneous

Corticosteroid excess (G)

Trimethoprim-sulfa therapy (G)

Hyperlipidemia (?)

Chronic insulin infusion (A)

Congenital C3 deficiency (MPGN)

Cyclic hematopoiesis in gray collies (A)

Familial (see Table 261-1)

Idiopathic (A, G, MPGN, MN, MCD, P-E or M)

A, Amyloidosis; *G,* glomerulonephritis, uncharacterized; *MPGN,* membranoproliferative (mesangiocapillary) glomerulonephritis; *MN,* membranous nephropathy; *MCD,* minimal change disease; *P,* proliferative (*E,* endocapillary or *M,* mesangial).

261.2.2.3 Box • 261-3 Diseases Reported in Association with Glomerular Disease in Cats

261.2.2.3.1 Systemic Disease (Glomerular Disease)

Infectious

Bacterial

- Chronic bacterial infections (G)
- Mycoplasmal polyarthritis (G)

Viral

- Feline immunodeficiency virus (G)
- Feline infectious peritonitis (MN)
- Feline leukemia virus (G, MN)

Inflammatory

- Pancreatitis (G)
- Cholangiohepatitis (G)
- Chronic progressive polyarthritis (G)
- Systemic lupus erythematosus (MN)
- Other immune-mediated diseases (G)

Neoplastic

- Leukemia (MN)

Lymphosarcoma (MN)

Mastocytosis (G)

Other neoplasms (G)

Miscellaneous

Acromegaly (?)

Mercury toxicity (MN)

Familial (MN)

Idiopathic (MN)

G, Glomerulonephritis, uncharacterized; *MN,* membranous nephropathy.

261.2.3 Physical Examination Findings

The physical examination is often unremarkable in dogs with glomerular disease.[8,9,13] Nonspecific evidence of systemic disease may be present, such as poor body condition or poor haircoat. Dogs with advanced renal failure may have oral ulcerations, pale mucous membranes, or dehydration. Subcutaneous edema or ascites, or both, is sometimes noted. Occasionally dogs have physical evidence of thromboembolic disease, such as dyspnea or a decreased or absent peripheral pulse. Evidence of a predisposing inflammatory, infectious, or neoplastic process may be detected during the physical examination. The kidneys of affected animals are variable in size. Animals with chronic renal failure often have small, firm, irregularly shaped kidneys, whereas those with milder disease often have normal-sized or, occasionally, enlarged kidneys.

261.2.4 Clinicopathologic and Imaging Findings

Proteinuria is the hallmark of glomerular disease and is discussed in Chapter 32. A urine protein to creatinine ratio (UPC) greater than 0.5 in a urine sample free of evidence of inflammation and macroscopic hematuria is abnormal. With respect to the UPC, no magic number or range of numbers is diagnostic for any one renal disease, and the overlap in expected ranges is too broad to be clinically reliable. In general, dogs with amyloidosis or membranous nephropathy have the highest UPCs, and those with tubulointerstitial disease have lower values.[14] Glomerular lesions have been identified in dogs without proteinuria.[15,16] In three studies of urine albumin in canine models of glomerular disease, microalbuminuria was detected prior to increases in the UPC, and the magnitude of microalbuminuria increased over time in dogs that eventually developed an increased UPC.[17–19] It therefore seems reasonable to conclude that a dog with persistent microalbuminuria of increasing magnitude should be assessed as having an injurious process to the glomerular filtration barrier and may eventually develop overt proteinuria.

Isosthenuria is a variable finding in dogs and cats with glomerular disease. In one study of dogs with glomerulonephritis, 37% had urine specific gravities in excess of 1.035, and isosthenuria was detected in only 29%.[9] However, dilute urine (i.e., a urine specific gravity less than 1.016) was more common in dogs with amyloidosis, occurring in 63% of dogs, whereas only 5.1% were able to concentrate above 1.035.[13] The presence of renal azotemia and an intact concentrating ability, called *glomerulotubular imbalance,* is indicative of glomerular disease. Cylindruria is common in dogs with glomerular disease; casts are most often hyaline but can be granular, waxy, or fatty. It is believed that proteins are packaged into casts to protect the renal tubular epithelium from their damaging effects. Renal hematuria develops with glomerular injury in humans and is more common in specific diseases (e.g., IgA nephropathy, mesangial proliferative glomerulonephritis), but it appears to be less common in dogs with glomerulopathies.[5] Erythrocytes that have passed through the abnormal glomerular capillary bed are often misshapen; the morphology of urine erythrocytes can be used to differentiate hematuria of glomerular origin from that due to other causes.

Hypoproteinemia due to hypoalbuminemia develops in many dogs and cats with glomerular disease and is more likely in animals with heavy proteinuria. Hypoalbuminemia occurred in 60% and 70% of dogs with glomerulonephritis or amyloidosis, respectively.[9,13] Azotemia, hyperphosphatemia, and metabolic acidosis, consistent with renal failure, may be present in dogs with severe disease. Of dogs with glomerulonephritis or amyloidosis, 53% and 26% respectively, were not azotemic.[9,13] Nonregenerative anemia that develops secondary to renal failure or to a systemic disease is observed in many affected animals. Other hematologic abnormalities also may reflect concurrent and possibly underlying systemic diseases. Thrombocytosis and hyperfibrinogenemia are common findings in dogs with glomerular disease.

The nephrotic syndrome of hypoalbuminemia, proteinuria, hypercholesterolemia, and edema, although pathognomonic for glomerular disease, was present in only 15% of dogs with glomerulonephritis in one study.[9] Incomplete nephrotic syndrome (i.e., without edema or ascites) was more common, occurring in 49% of the dogs.[9] Nephrotic syndrome is expected to occur more commonly in dogs with amyloidosis, membranous nephropathy, hereditary nephritis, and minimal change disease because of the heavy proteinuria associated with these diseases.[5,14]

On abdominal radiographs, the kidneys may appear normal or small and irregular. Some animals may actually have enlarged kidneys. Similar changes in shape and size can be seen with ultrasonographic scans, on which increased echogenicity of the cortex and loss of corticomedullary distinction may also be noted. The renal pelvis may be mildly dilated if polyuria is present or if fluids are being administered.

Dogs and cats with proteinuria should be thoroughly evaluated for underlying infectious, inflammatory, or neoplastic diseases (see Boxes 261-2 and 261-3). This evaluation should include a thorough physical examination, and diseases of the oral cavity and skin should not be overlooked as potential underlying diseases. Aspiration cytology should be performed on all cutaneous and subcutaneous masses. Serologic testing for regional infectious diseases, as well as antinuclear antibody testing, should be performed. During radiographic or ultrasonographic evaluation of the abdomen, attention should be given to other organs to detect any other disease process. Thoracic radiographs should also be evaluated in middle-aged to older dogs.

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261.2.5 Histologic Diagnoses

Renal biopsy provides a definitive diagnosis of glomerular disease but may not be needed if treatment of a potential underlying disease leads to resolution of the proteinuria or if end-stage renal disease is already

present. When evaluated appropriately, renal biopsy specimens can provide important clinical information about the type and severity of lesions in dogs and cats with glomerular disease. In fact, obtaining an accurate histologic diagnosis may be one of the more important factors in successful management of the dog or cat with glomerular disease. Clinical decisions regarding the diagnosis, treatment, and prognosis can be made from the information obtained through renal biopsy.

261.2.5.1 Procurement and Processing of the Renal Biopsy Specimen

The procedure used to obtain a renal biopsy specimen is discussed in Chapter 84. When a specimen is to be used for evaluation of glomerular disease, only cortical tissue should be obtained, because biopsy of the medulla is not needed and is associated with a greater risk of hemorrhage, infarction, and fibrosis. The use of general anesthesia is associated with an ability to obtain better quality specimens. An adequate sample of cortex has a minimum of five glomeruli when examined by light microscopy, although one glomerulus may be all that is needed to make a definitive diagnosis.

If a percutaneous method is used to obtain a renal biopsy specimen from a patient with glomerular disease, at least two quality samples of renal cortex should be obtained, using either a 16-or 18-gauge needle. A dissecting microscope can be used to verify that two adequate biopsy samples have been obtained. One sample should be placed in formalin, and the other should be divided into two smaller pieces containing glomeruli. One piece is put into a fixative suitable for electron microscopy (EM) (e.g., 4% formalin plus 1% glutaraldehyde in sodium phosphate buffer), and the other piece is frozen for immunofluorescent microscopy (IFM). An alternative to freezing is to immerse the tissue in ammonium sulfate-N-ethylmaleimide fixative (i.e., Michel's solution), which preserves tissue-fixed immunoglobulins. Wedge biopsies should be divided in a similar fashion; tissue for EM should be minced appropriately.

Thin sections (2 to 4 μm) of paraffin-embedded tissue should be used for light microscopy because standard sections of 5 to 6 μm are too thick for adequate assessment of glomerular cellularity and capillary loop thickness.[4] Hematoxylin and eosin staining can be used for initial assessment of the general appearance of the specimen. However, periodic acid–Schiff (PAS), which stains glycoproteins, is the preferred stain of many nephropathologists and is particularly useful for demonstration of interstitial and glomerular scarring and for assessment of the GBM. Methenamine silver specifically stains the basement membrane of the tubules, glomeruli, and Bowman's capsule. Trichrome is useful for evaluation of the mesangium and is also the best light microscopic stain for visualization of immunoglobulins. Congo red can be used to demonstrate the presence of amyloid.

EM of renal biopsy specimens has not been used frequently enough in dogs and cats to determine the diagnostic merit in groups of patients with varying presentations; however, in humans, EM appears to be most helpful in the evaluation of individuals with renal hematuria, a familial history of renal disease, or proteinuria with normal renal excretory function. Nevertheless, a sample should be collected for EM in nearly all dogs and cats undergoing renal biopsy, because the exact diagnosis is most likely unknown. IFM or immunohistochemistry should include at a minimum stains for immunoglobulin M (IgM), IgG, IgA, and C3.

261.2.5.2 Evaluation of the Renal Biopsy Specimen

Whenever possible, specimens should be evaluated by a pathologist with expertise in nephropathology. Renal biopsy specimens from proteinuric dogs and cats should be evaluated by light microscopy, EM, and IFM. Limiting the evaluation to light microscopy alone often allows for only a subjective interpretation of

the glomerular lesion, leaving too much room for error. Although many reports have described glomerular lesions in dogs and cats, the use of different nomenclature and different morphologic criteria among pathologists sometimes makes interpretation and comparison of the data difficult at best. A standard classification system for the characterization of glomerular lesions in dogs and cats needs to be embraced. The World Health Organization (WHO) criteria for the classification of human glomerulopathies have proved to be applicable to glomerular diseases in dogs.[11] General acceptance of this system would lead to a better understanding of the natural history, pathogenesis, and response to treatment in the various glomerular diseases in dogs and cats.

The normal glomerulus contains four to eight lobules, each composed of capillaries supported on a centrilobular core of mesangial matrix (Figure 261-2).[4,5] The GBM is thin, delicate, PAS-positive, and argyrophilic. The glomerular capillary lumen is normally widely patent and lined with eosinophilic endothelial cell cytoplasm (Figure 261-3). There should be only one or two nuclei per mesangial cell region. Parietal epithelial cells, visceral epithelial cells, endothelial cells, and mesangial cells comprise the normal glomerulus and can easily be identified by EM (see Figure 261-1). The flattened parietal epithelial cells line the inner surface of Bowman's capsule. The visceral epithelial cells (podocytes) line the outer surface of the capillary loops and rest on the GBM. The podocytes, which are characterized by their foot processes, form the outermost layer of the capillary wall. The endothelial cells line the inner surface of the capillary loops, with the nuclei disposed centrilobularly, toward the mesangium. The fenestrations of the endothelial cell cytoplasm can be visualized easily. The normal GBM should be approximately the same thickness as the base of a foot process turned 90 degrees.

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Figure 261-2 Schematic diagram showing the composition of each lobule in a normal capillary. (Courtesy J.C. Jennette, Chapel Hill, NC, School of Medicine, University of North Carolina.)

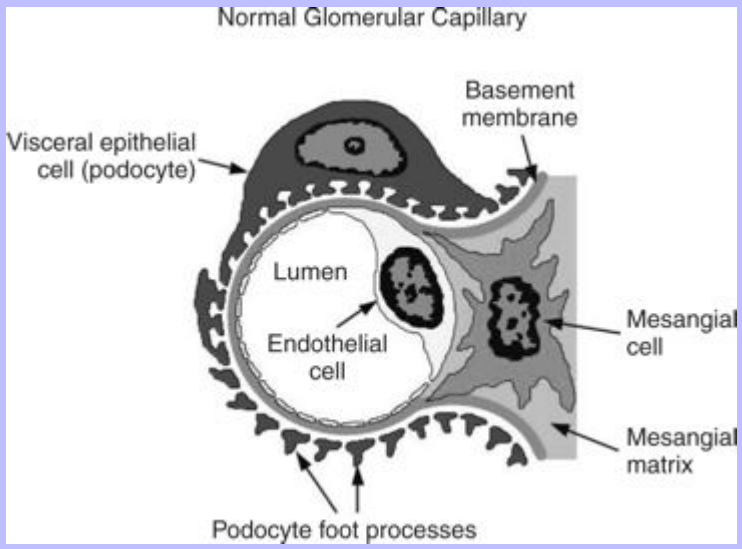
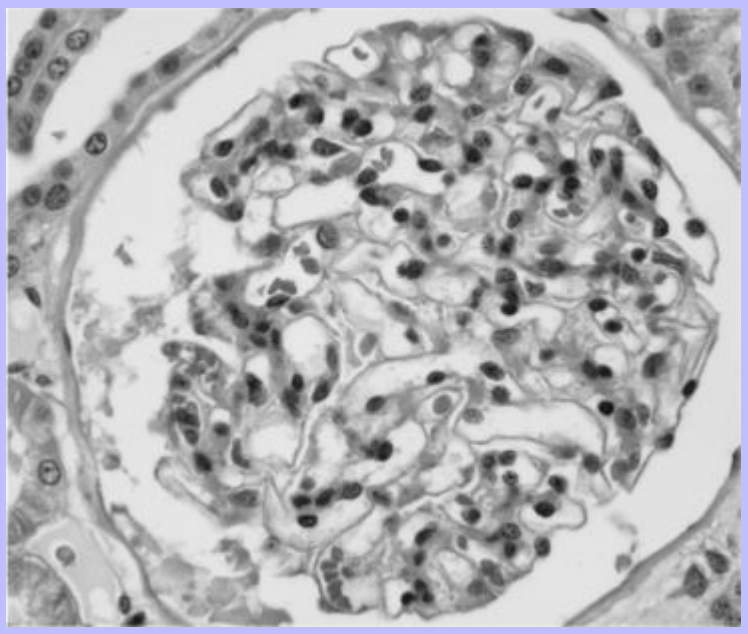


Figure 261-3 Normal glomerulus from a dog. Note that the capillary lumens are widely patent and the capillary loops are thin, often appearing discontinuous. Hypercellularity is not present.



When glomerular lesions are present, if nearly all of the glomeruli are affected, the disorder is *generalized*. The disorder is *focal* if less than half of the glomeruli are affected. When evaluating individual glomeruli, if the entire glomerulus is affected, the pattern is *diffuse,* or *global*. The lesion is *segmental* or *local* if only a few lobules within affected glomeruli are involved. Descriptions of each of the pathologic findings in the varying glomerular diseases are provided below. Lupus nephritis can be associated with several glomerular lesions and, when active, may have an interstitial infiltrate of mixed inflammatory cells and acute damage to the tubules.[5] *Crescents* can loosely be defined as two or more layers of cells in Bowman's space and are suggestive of severe injury. Crescentic glomerulonephritis, which is diagnosed when crescents are present in 50% or more of the glomeruli, appears to be uncommon in dogs and cats.

Immunofluorescent staining should be positive in dogs or cats with either *in situ* immune complex formation, as is believed to occur with primary membranous glomerulopathy, or with deposition of circulating complexes, as may occur with type I membranoproliferative glomerulonephritis and proliferative glomerulonephritis.[4,5] Because true anti-GBM GN has not been documented in the dog or cat, the expected immunostaining pattern is discontinuous, occurring either in the capillary loops or in the mesangium. The mesangium plays a role in the clearance of macromolecular debris from the glomerular capillary wall. As such, it is possible that some of the immunoglobulin present in the glomeruli of some dogs is not specific in nature and not associated with clinically relevant immunologic injury. Therefore the prevalence and relevance of positive immunofluorescent staining in dogs without glomerular disease needs further investigation.

261.3 GLOMERULAR DISEASES

Many glomerular diseases affect dogs; fewer appear to affect cats. Many of these diseases historically have been lumped under the umbrella of "glomerulonephritis" (see Box 261-1). As a profession, veterinary medicine needs to move beyond this generalization and begin to characterize each disease as a separate entity. The historical approach of combining diseases characterized as glomerulonephritis into one group has led to limited information on the natural history and effective treatment of the individual diseases in dogs and cats. In human medicine, the characterization of each glomerular disease as a specific entity has led to an advanced understanding of the pathogenic events leading to the specific glomerular disease. This enhanced understanding is forging the way to the development of optimized and specific therapeutic approaches for the individual glomerular diseases and to more clearly defined prognoses.[4,5] This section outlines what is known about the individual diseases in dogs and cats, with additional information garnered from the wealth of knowledge on these diseases in humans.

Acquired glomerular injury is the result of damage sustained after immune complex formation or deposition (e.g., membranous nephropathy, membranoproliferative glomerulonephritis, proliferative glomerulonephritis) or of damage caused by systemic factors that affect the glomerulus (e.g., amyloidosis, focal segmental glomerulosclerosis, minimal change disease). Although the effects of systemic factors vary, some general statements can be made regarding the pathogenesis of the immune complex–mediated glomerulonephropathies.[20] Immune complexes that are deposited in the glomerulus or that form *in situ* initiate glomerular damage. Cell-mediated immune mechanisms also take part in the pathogenesis of glomerular inflammation. Once glomerular damage has been initiated, other processes contribute to glomerular injury, including activation of complement and of the coagulation cascade and resident cells; influx of neutrophils, monocytes, and platelets; release of proteolytic enzymes; synthesis of cytokines or other growth factors; generation of proinflammatory lipid mediators; and alteration of hemodynamic factors. The mechanisms that determine whether progressive renal damage or resolution of the process occurs are unclear.

261.3.1 Membranoproliferative Glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN) may be the most common glomerular disease in dogs, accounting for 20% to 60% of dogs in various studies.[1,21] However, glomerular lesions are most likely to be called MPGN when they have not undergone thorough evaluation, including the use IFM and EM; the incidence of MPGN is most certainly overestimated in dogs. On the other hand, MPGN is more common in humans living in underdeveloped countries, where exposure to harmful environmental agents, including infectious disease, may be greater than in those living in developed countries.[5] MPGN therefore may be the glomerular lesion expected to be most common in dogs, but it probably is less common than currently reported.

261.3.1.1 Clinical Features

The mean age of dogs with MPGN in one study was 10.5 years.[11] Males and females appear to be equally affected. Even though the disease is common, no thorough study of MPGN as a distinct glomerular disease has been done in dogs. In humans the disease is characterized by a slowly progressive course, and about 50% of those affected develop nephrotic syndrome.

MPGN has been identified as a familial disease in Bernese mountain dogs. A unique, rapidly progressive form of MPGN that is accompanied by tubular necrosis and interstitial inflammation and is uniformly fatal

has been reported in association with *Borrelia burgdorferi* infection in dogs.[12] The average age of affected dogs was only 5.6 years. Labrador retrievers and golden retrievers were significantly predisposed to developing this lesion.

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261.3.1.2 Pathogenesis

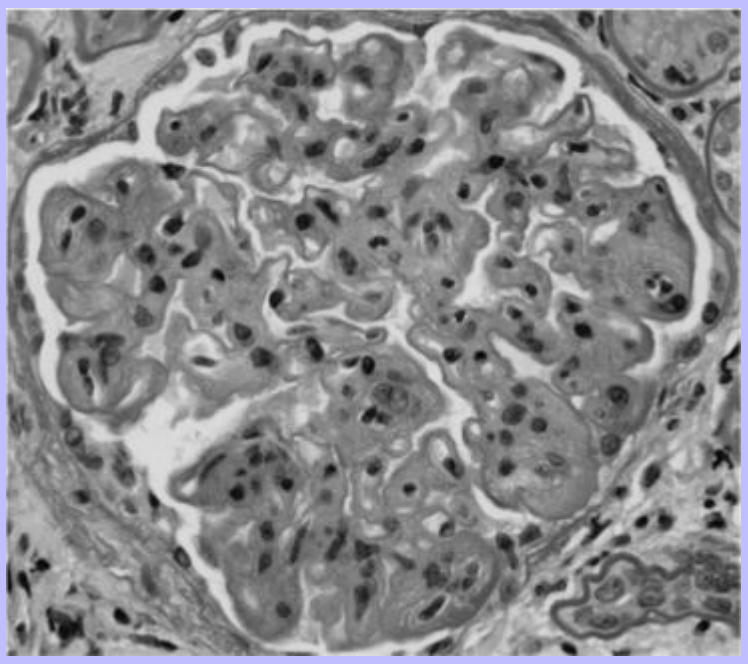
There are two types of MPGN.[4,5] Type I MPGN, also called mesangiocapillary GN, is often induced by infectious diseases and is characterized by immune complex accumulation on the subendothelial side of the GBM. The intramembranous dense deposits that characterize type II MPGN, also called *dense deposit disease,* are not immune deposits but are of undefined origin; type II MPGN is not associated with infectious diseases and seems to be uncommon in dogs. Renal lesions appearing to be type I MPGN have been associated with a variety of infectious diseases in dogs (see Box 261-2 and Box 261-3). The accumulation of immune complexes or dense deposits leads to cytokine-mediated activation and expansion of the mesangium and an inflow of leukocytes. In type II MPGN, activation of the alternate pathway of complement predominates, whereas in type I MPGN activation of the classic pathway occurs.

In humans with MPGN, hypocomplementemia is so common that this disease is sometimes called *hypocomplementemic GN*. Hypocomplementemia appears to develop either from increased consumption secondary to immune complex activation of the classic pathway or from the presence of anticomplement autoantibodies known as *nephritic factors*. Interestingly, type I MPGN also occurs in Brittany spaniels and in humans with congenital C3 deficiency.[15] The pathogenic role of hypocomplementemia is not understood.

261.3.1.3 Histopathologic Characterization

MPGN is diagnosed when both thickened capillary loops and mesangial hypercellularity (more than three nuclei per mesangial region) are present (Figure 261-4).[4,5,11] The glomerulus may become enlarged and segmented or lobular in appearance. The activated mesangium expands the capillary walls and extends into the subendothelial space, causing the double contour, or “railroad,” appearance of the GBM that can be seen with light microscopy. With IFM, immune complex deposition can be identified in type I MPGN as granular deposits of C3 in combination with IgG, IgM, or IgA, or combinations thereof, in the GBM or mesangium or both. With EM, type II MPGN can be differentiated from type I by the identification of intramembranous dense deposits. EM also is used to identify the immune deposits in type I MPGN.

Figure 261-4 Glomerulus from a dog with membranoproliferative (mesangiocapillary) glomerulonephritis. Note the thickened capillary loops and the mesangial hypercellularity, which result in the segmented and lobular appearance.



261.3.1.4 Specific Treatment

Effective treatment of the underlying infectious, inflammatory, or neoplastic disease is the cornerstone of management of patients with MPGN. Because activation of platelets appears to be involved in the pathogenesis of this disease, antiplatelet drugs also should be given.[5]

261.3.1.5 Prognosis

Specific data regarding the prognosis of MPGN in dogs is lacking. In people, azotemia, severe proteinuria, systemic hypertension and marked tubulointerstitial lesions at presentation are the most significant predictors of an unfavorable outcome.[5]

261.3.2 Membranous Nephropathy

Membranous nephropathy (MN) is probably the second most common glomerular disease in dogs, accounting for up to 10% to 45% of reported cases.[2,11,22–24] It is the most common glomerular disease of cats, in which other forms of glomerular disease are uncommon.[25,26] Because there is rarely evidence of an inflammatory

response in the glomeruli or interstitium, the disease is more correctly called a glomerulopathy or nephropathy, rather than glomerulonephritis.

261.3.2.1 Clinical Features

As in humans, MN appears to be more common in male dogs and cats (approximate male to female ratios are 1.75:1 in dogs and 6:1 in cats). The mean age of affected dogs from four studies was 8 years, but there was considerable range (1 to 14 years). The disease is more common in younger cats, with an approximate mean age of only 3.6 years (range, 1 to 7 years).[25] There does not appear to be any breed predilection, although a preponderance of Doberman pinschers was seen in one report. Interestingly, four of five of these Dobermans were 3 years of age or younger, which may suggest a familial pattern.[23]

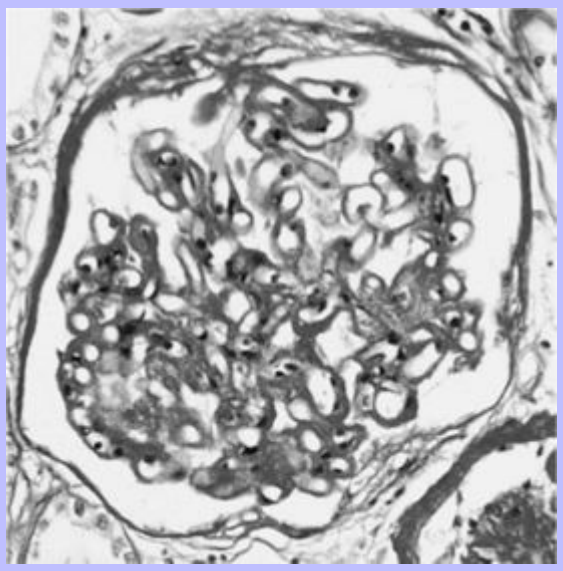
Proteinuria in animals with MN may be massive, often as high or higher than that which occurs in dogs with amyloidosis.[14] Because of this heavy proteinuria, many animals present with nephrotic syndrome. Microhematuria is reported in 30% to 40% of humans with MN but has not been systematically studied in dogs and cats.[5] Cats and dogs with MN may present with signs of renal failure. Many cats have normal to enlarged kidneys at presentation.

Membranous nephropathy has four ultrastructural stages that correlate with the temporal evolution of the disease and the clinical presentation in dogs, cats, and humans.[4,5,23,25] There is some suggestion that these stages also correlate with therapeutic outcomes in humans with MN, in that people may be more likely to respond to appropriate management if they are in one of the first two stages. More advanced stages in cats and dogs have been shown to correlate with more severe azotemia, whereas animals with milder disease were more likely to have nephrotic syndrome.[23,25]

261.3.2.2 Pathogenesis

In humans, MN is considered to be either primary (i.e., idiopathic) or to occur secondary to another disease process; primary disease is most common.[5] In primary MN, immune complexes are found mainly in the subepithelial spaces of the capillary loops. Secondary MN can be distinguished from the primary form by the presence of immune complexes in the mesangium or subendothelial space (or both) and in the subepithelial space. The finding of antibodies on the subepithelial side is unique to MN and suggests that 1791
binding occurs on the urinary side of the GBM. The subsequent activation of complement and cytokine 1792
responses may be reduced, because the site of reaction is distant to the circulation, which contributes to the lack of inflammation associated with MN.

Figure 261-5 Glomerulus from a dog with membranous nephropathy. Note the thickened, rigid-appearing capillary loops and the lack of hypercellularity. (Courtesy of J.L. Robertson, Blacksburg, VA, Virginia Maryland Regional College of Veterinary Medicine.)



Although the exact pathogenesis of this disorder is unknown, it is considered to be an immune complex–mediated disease. There is evidence to support both *in situ* formation of immune complexes and trapping of circulating immune complexes. However, in humans with primary MN, the weight of evidence supports the *in situ* reaction of unbound antibody with fixed antigens, perhaps intrinsic GBM or glomerular visceral epithelial cells antigens. In this regard, primary disease may be a true autoimmune disorder.

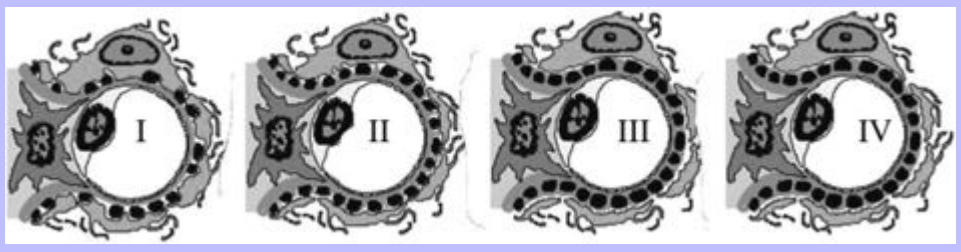
Circulating immune complexes most likely play a larger role in patients with secondary disease. Proteinuria probably develops through a complement-dependent mechanism, independent of inflammatory cells. The terminal complement complex (C5b-9 membrane attack complex) has been implicated in the pathogenesis of this disease. Increased urinary concentrations of the membrane attack complex have been demonstrated in some, although not all, individuals with MN. Demonstration of this complex may be more likely early in the disease process, when active immune deposit formation occurs. Myriad immune system irregularities have been reported in association with MN in humans (e.g., altered CD4+ to CD8+ ratio, Fc receptor dysfunction, and impaired lymphocyte and suppressor cell function), which supports a pathogenic role for an underlying immunologic defect. These irregularities are perhaps based on a genetic susceptibility, a theory supported by familial clustering of MN in humans.[4,5]

261.3.2.3 Histopathologic Characterization

The normally lacey-appearing GBM becomes uniformly thickened and more rigid as a result of the deposition of immune complexes in the subepithelial spaces in MN (Figure 261-5).[4,11] New basement membrane material accumulates around the immune deposits. Because the deposits do not become

impregnated with silver, “spikes” may be identified on the outside of the GBM when an appropriate silver stain is used. Advanced cases may show irregular thickening and distortion of the capillary walls with occasional widening of the mesangium. Immunofluorescent microscopy is useful in determining the site of immune complex deposition. Staining of the immune complexes produces a beaded appearance along the GBM and can be so heavy that it may be difficult to differentiate from a linear pattern. In secondary cases, the mesangial spaces are also positive. In dogs with MN, IgG and C3 have most commonly been identified, although there have also been reports of finding IgM and IgA.[11,21] Several studies have reported affected dogs and cats in which positive staining was identified only in the glomerular capillary loops, which suggests the presence of primary, or idiopathic, disease in these animals.[21–23,25]

Figure 261-6 Ultrastructural stages in the progression of membranous nephropathy. (Courtesy J.C. Jennette, Chapel Hill, NC, School of Medicine, University of North Carolina.)



Electron microscopy should be used to confirm the location of the immune deposits and to characterize the stage of disease progression (Figure 261-6).[4,23,25] Deposition of immune complexes, progressive engulfment of the complexes by the surrounding GBM, and eventual resolution of the deposits characterize the stages. Stage I is characterized by subepithelial dense immune deposits without adjacent projections of basement membrane material and only minimal thickening of the GBM. Projections of adjacent GBM material, or spikes, are identified in stage II. In stage III, these projections surround the immune deposits. In stage IV, the GBM is markedly thickened, and electron-lucent zones have replaced some or all of the electron-dense deposits. In advanced stage IV disease, sometimes referred to as stage V, there is variable thickening of the GBM and apparent resolution of the electron-dense deposits. In some affected animals, staging is difficult because several stages of disease may be present simultaneously.

261.3.2.4 Specific Treatment

In addition to identification of potentially inciting disease processes and nonspecific management of proteinuria, immunosuppressive therapy may be warranted in dogs or cats with persistent proteinuria caused by MN, particularly if they appear to have idiopathic, or primary, disease and are not azotemic. Affected humans with similar clinical pictures may respond to immunosuppressive therapy with corticosteroids combined with an alkylating agent (i.e., cyclophosphamide or chlorambucil).[5] The approach that has proven most beneficial is alternation of methylprednisolone and chlorambucil every other day for 6 months. Cyclosporine is considered a valid therapeutic option for patients not responding to corticosteroids and alkylating agents. Even when treatment is effective, relapses may occur. The use of immunosuppressive therapy in dogs and cats with membranous nephropathy needs to be studied more carefully.

261.3.2.5 Prognosis

Although MN appears to be progressive in some dogs and cats, the progression may be slow enough that many animals can lead relatively normal lives. In a study of 24 cats with MN, four (17%) survived 4 to 10 months and eight (33%) had long-term survival of 2.5 to 6 years; clinical remission occurred in seven (29%) of the cats. Corticosteroids were administered to three of the eight long-term survivors. However, 11 cats (46%) died or were euthanized due to nephrotic syndrome or renal failure shortly after diagnosis.[26] Long-term survivors had only IgG deposition, C3 deposition, or both; cats that also had deposition of IgM or IgA had a shorter survival period. Stage III and stage IV disease, defined by the presence of intramembranous deposits, was associated with a poorer prognosis.[26]

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Survival data for dogs is more difficult to extract from prior reports, although it appears to be similar to what has been reported in cats. Survival in dogs has ranged from 4 days to greater than 3 years.[23] Spontaneous remissions have been reported. Spontaneous remission occurs in 20% to 30% of humans with MN, whereas 20% to 40% of cases progress to renal failure.[5] The risk of progression in humans appears to correlate with the magnitude of proteinuria and renal function impairment; patients with the highest degree of proteinuria and azotemia are more likely to have more rapid progression compared with other patients.

261.3.3 Proliferative Glomerulonephritis

Proliferative glomerulonephritis, caused by endocapillary or mesangial proliferation, accounted for 2% to 16% of glomerular lesions in dogs in two studies.[11,21] In humans a complete pathologic diagnosis requires both a morphologic description (e.g., focal mesangial proliferative glomerulonephritis) and a specific disease designation (e.g., IgA nephropathy, lupus glomerulonephritis).[4,5] With the exception of IgA nephropathy, proliferative glomerulonephritis in dogs has not included the specific disease designation.[27,28] It therefore is difficult to correlate the diseases that have been described in dogs with the wealth of information regarding pathogenesis and treatment known for the specific diseases in humans.

261.3.3.1 Clinical Features

Dogs with proliferative glomerulonephritis reported in two studies were on average between 7 and 9 years of age.[11,10] Proteinuria and renal failure are the most common presenting signs in affected dogs. Renal failure may be mild or moderate and acute or chronic. Humans with mesangial proliferative glomerulonephritis often have microscopic or macroscopic hematuria; the presence of hematuria has not been thoroughly evaluated in dogs.[5]

261.3.3.2 Pathogenesis

Proliferative glomerulonephritis is an immune complex–mediated disease. Anti-GBM disease causes proliferative glomerulonephritis in humans but has not been described in the dog or cat. Postinfectious glomerulonephritis of humans, characterized by endocapillary proliferation, most commonly occurs after a streptococcal infection but has also been identified with other infections (e.g., staphylococcal infection).[5] Interestingly, this pattern of disease is usually caused by infections of limited duration that often have

resolved prior to the emergence of clinical signs of glomerular disease. Persistent infections are more likely to cause MPGN or MN.[4]

261.3.3.3 Histopathologic Characterization

Mesangial proliferative glomerulonephritis is characterized by mesangial cell hyperplasia, defined as four or more cells per mesangial area.[4,11] This is often accompanied by an increase in mesangial matrix (Figure 261-7). Endocapillary proliferative glomerulonephritis occurs with a proliferation of glomerular endothelial cells and may be accompanied by an increase in mesangial cellularity. An influx of mononuclear cells accounts for some of the increase in cellularity. Evaluation by IFM reveals fine granular deposits of IgG or IgM or both in the GBM and mesangium. EM can be used to characterize further the location of the immune complexes. Because the proliferative glomerulonephropathies often develop secondary to systemic diseases, immune complexes are often identified in the mesangium, although some complexes may be found in the capillary walls. Subepithelial “humps” can be identified in humans with postinfectious glomerulonephritis.[4]

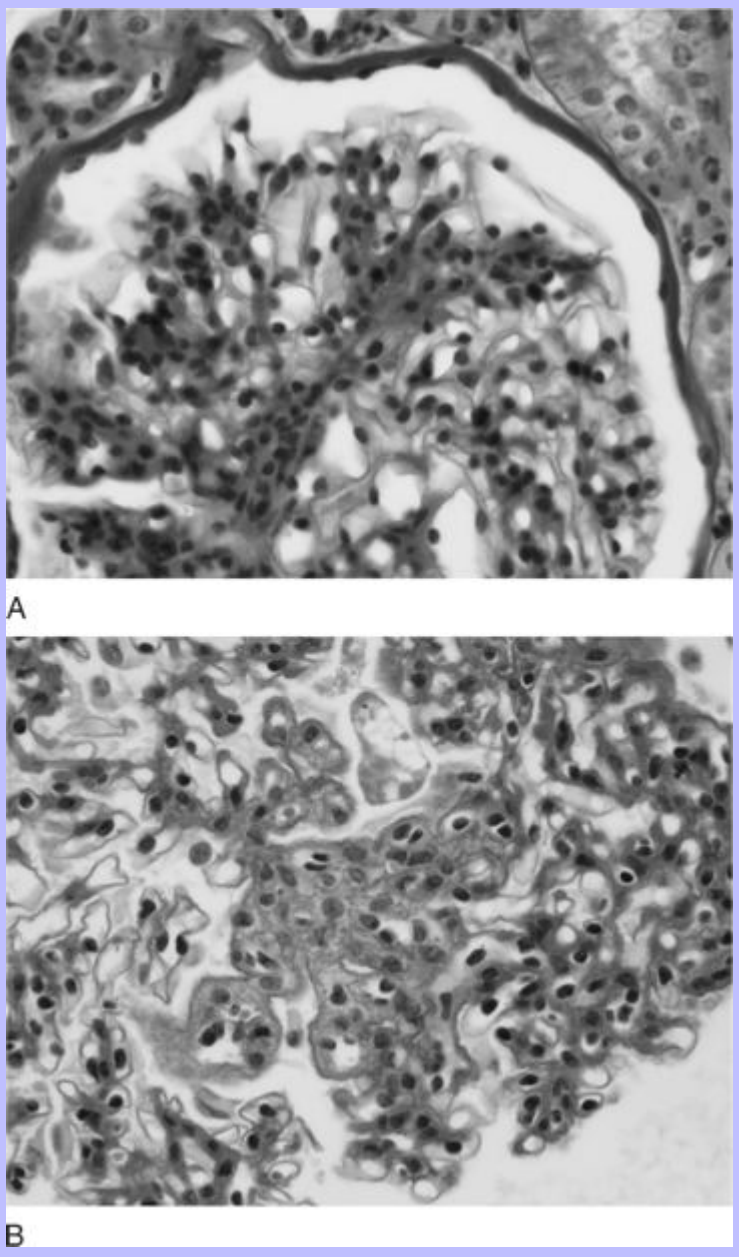
261.3.3.4 Specific Treatment

Because this category probably encompasses several disease entities, there are no specific treatment recommendations. The potential source of immune complexes should be removed, and nonspecific management of glomerular diseases should be followed.

261.3.3.5 Prognosis

The prognosis for this specific group of diseases has not been evaluated in dogs. The presence of chronic renal failure or the formation of crescents, or both, is most likely associated with a poorer prognosis.

Figure 261-7 Glomeruli from dogs with proliferative glomerulonephritis. **A,** Focal mesangial proliferative glomerulonephritis. **B,** Endocapillary proliferative glomerulonephritis.



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261.3.3.6 Immunoglobulin A Nephropathy

In several studies of canine glomerular disease, IFM has demonstrated mild to moderate frequency of IgA positivity, suggestive of IgA nephropathy.[27,28] However, because IgA is predominantly polymeric in dogs, it may be nonspecifically trapped in the mesangium, more so than monomeric IgA, the predominant form in humans. The diagnosis of IgA nephropathy requires a predominance of IgA positivity on IFM evaluation; codeposits of IgG, IgM, or C3 may be present but should be less intense than IgA. Mesangial proliferative glomerulonephritis is the expected light microscopic lesion; some humans do not have any apparent glomerular lesions. In one study of clinically normal dogs with glomerular lesions, 85% had IgA deposits.[16] In another study of 100 dogs with and without renal disease, 47 had IgA deposition, and in six dogs IgA was the only immunoglobulin detected.[28] Increased deposition of IgA was associated with increased cellular proliferation. Dogs with enteric or hepatic diseases had the highest incidence of IgA deposition. Excessive IgA immune complex formation due to enteric disease or decreased clearance of IgA complexes in association with liver disease have been proposed in the pathogenesis of secondary IgA nephropathy in humans.[5]

In people, IgA nephropathy is more common in young adults, with males outnumbering females; the prevalence varies substantially throughout the world.[5] In a report of three dogs with apparent IgA nephropathy, the dogs were male and young to middle aged (4 to 7 years).[27] The dogs had episodes of microscopic and macroscopic hematuria, as well as proteinuria and varying degrees of renal failure. Although the dogs were housed together in a blood donor facility, predisposing environmental factors were not identified. The dog most severely affected had uncontrolled hypertension and codeposits of IgG or IgM, both of which are negative prognostic indicators in humans.

Treatment of patients with secondary IgA nephropathy should be directed at treatment of the associated systemic disease. Control of hypertension should be considered a cornerstone of therapy. Fish oil rich in omega-3 fatty acids administered to affected humans resulted in slowed progression of renal disease but did not lead to a reduction in proteinuria.[5]

261.3.4 Amyloidosis

The term *amyloidosis* refers to a diverse group of diseases that have in common the extracellular deposition of fibrils formed by polymerization of proteins with a beta-pleated sheet conformation.[29] Several different proteins may be deposited to form amyloid in humans, but the number of proteins involved in domestic animals appears to be limited. Many of these proteins display specific tissue tropisms that lead to characteristic clinical syndromes. The dog is the domestic animal most commonly affected by amyloidosis. With the exception of the Chinese Shar Pei, amyloid is deposited primarily in the glomeruli of affected dogs.[13,30] In fact, amyloidosis is one of the most common glomerular diseases in dogs, accounting for 23% of dogs with glomerular disease in one study.[8]

261.3.4.1 Clinical Features

Reactive amyloidosis is the most common form of amyloidosis in dogs and cats. Renal amyloidosis is more common in older dogs. The mean age of affected dogs was 9.2 years in one study, in which 85% of affected

dogs were 7 years of age or older.[13] Females appear to be affected more often than males (the male to female ratio is 1:1.7). Beagles, collies, and Walker hounds may be at increased risk for amyloidosis.[13] Renal amyloidosis may be familial in beagles and English foxhounds.[31]

The most common clinical signs of renal amyloidosis in dogs are those common to other glomerular diseases. Because proteinuria associated with amyloidosis may be massive, many animals brought to the veterinarian are in nephrotic syndrome. In one study of proteinuria, six of seven dogs with amyloidosis had nonselective proteinuria, suggesting a marked loss of the size-selective properties of the glomerular capillary wall.[16] Although other organ systems may be involved (liver, spleen, adrenal glands, gastrointestinal tract), clinical signs associated with amyloid deposition in these organs are rare in dogs. Chronic infectious and noninfectious inflammatory diseases and neoplasia have been reported in association with reactive amyloidosis in 32% to 53% of affected dogs; however, many dogs and cats with reactive amyloidosis do not have an identifiable inflammatory process at the time of presentation.[8,13]

Renal amyloidosis in the Shar Pei develops at an earlier age (mean age 4.1 years) than in other dogs with amyloidosis, but like other breeds, the disease is more common in females (male to female ratio of 1:2.5).[13] In Shar Peis, amyloid is most commonly deposited in the renal medulla; only 64% of Shar Peis had glomerular involvement in one report.[30] As a result, as few as 25% to 43% of affected Shar Peis have proteinuria. Affected dogs may have signs of involvement of other organs, particularly the liver. Many Shar Peis have a history of recurrent fever and swelling of the tibiotarsal joints (commonly called *Shar Pei fever* or *Shar Pei swollen hock syndrome*) prior to the development of renal amyloidosis. Affected Shar Peis may be an animal model of familial Mediterranean fever in humans.

Amyloidosis is relatively uncommon in the cat, with the exception of Abyssinians and Siamese (especially the Oriental shorthair color variant).[32] In Abyssinians, amyloid is deposited primarily in the medulla, although glomerular involvement has been described. This pattern of deposition results in medullary fibrosis and papillary necrosis and leads to chronic renal failure as the most common clinical manifestation; marked proteinuria is not common. Siamese and Oriental shorthair cats have a predilection for deposition of amyloid in the liver, leading to hepatic rupture and hemorrhage. Diagnosis of renal amyloidosis in affected cats is based on a high index of suspicion and exclusion of other renal diseases or on postmortem examination; biopsy of the renal medulla is associated with too high a degree of risk to be warranted.

261.3.4.2 Pathogenesis

The primary protein involved in the formation of amyloid deposits in dogs and cats is amyloid A protein (AA), which is formed by the polymerization of the amino terminal portion of serum amyloid A protein (SAA), an acute-phase reactant.[29] SAA is synthesized and released by hepatocytes after they have been stimulated by macrophage-derived cytokines (e.g., interleukin-1 (IL-1), IL-6, tumor necrosis factor). Because of the association of amyloid A with inflammatory diseases, this form of amyloidosis has been termed *reactive,* or *secondary,* amyloidosis.

Concentrations of SAA increase 100-to 1000-fold after tissue injury. Although concentrations decrease to baseline by 36 to 48 hours after removal of the inflammatory stimulus, they remain increased if inflammation persists.[29] Chronic inflammation and persistent or prolonged increases in SAA concentrations are required for the development of reactive amyloidosis. Humans with familial Mediterranean fever, a disease similar to that reported in Shar Peis, have defective formation of pyrin, a protein involved in the

downregulation of mediators of inflammation.[33] Because only a small percentage of animals with chronic inflammation develop amyloidosis, other factors must be involved in the pathogenesis.[29] There are multiple polymorphs of SAA, and certain polymorphs perhaps are more amyloidogenic. There may be inherited and acquired variations in the ability to degrade SAA, a two-step process that involves cell surface–associated proteases contained in monocytes. A defect in the second step of this process may predispose some individuals to the development of amyloidosis. It has been demonstrated that the AA-degrading property of normal serum is decreased in humans with reactive amyloidosis. This activity correlated with serum albumin concentrations; hypoalbuminemia associated with the inflammatory process or amyloidosis may contribute to decreased AA-degrading activity. Increased concentrations of other acute-phase reactants that are protease inhibitors (e.g., antitrypsin and antichymotrypsin) also may contribute to the pathogenesis of amyloidosis.

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SAA concentrations are increased during the predeposition phase, before the appearance of tissue amyloid deposits, but may persist during the deposition phase. Abyssinians with renal amyloidosis have increased SAA concentrations.[29] Chinese Shar Peis with renal amyloidosis have increased serum concentrations of IL-6, a cytokine that stimulates SAA synthesis and release.[34] The deposition phase, during which amyloid deposits appear in the tissue, is subdivided into two phases. The rapid phase is characterized by rapid increases in the amount of amyloid, whereas the plateau phase is a time when little net change occurs in tissue deposition.

261.3.4.3 Histopathologic Characterization

The beta-pleated conformation is responsible for the characteristic staining properties of the amyloid deposits.[4] When the kidney is evaluated by conventional light microscopy, amyloid deposits in the glomeruli appear as acellular material that expands the mesangium and glomerular basement membranes and stains homogeneously eosinophilic with hematoxylin-eosin (Figure 261-8). Glomerular deposits are most often diffuse and global but occasionally are focal and segmental. Deposits sometimes can be found in the walls of small blood vessels, tubular basement membranes, and interstitial tissues. When stained with Congo red and evaluated by conventional light microscopy, amyloid deposits take on various shades of red, depending on the amount of amyloid and the thickness of the section. Deposits stained with Congo red and evaluated by polarizing microscopy are birefringent and have an apple green color (Figure 261-9). Reactive amyloidosis can be confirmed by decolorization of the Congo red–stained amyloid deposits by potassium permanganate oxidation. Electron microscopy is not needed to confirm a diagnosis of amyloidosis.

261.3.4.4 Specific Treatment

The beta-pleated sheet configuration of amyloid fibrils leads to their insolubility and resistance to proteolysis, making specific treatment relatively ineffectual. In humans with familial Mediterranean fever, colchicine prevented the development of renal amyloidosis even in patients who continued to have recurrent febrile episodes.[33,35] This led to the recommendation that colchicine be used in the management of Shar Peis with renal amyloidosis. Ideally this drug is administered during the predeposition phase, which in Shar Peis is presumably characterized by recurrent fevers and swollen hocks. However, colchicine administration may lead to remission of proteinuria even after the appearance of amyloid deposits. No evidence supports the effectiveness of colchicine once amyloidosis has resulted in renal failure. Although the effects of the drug in the treatment of amyloidosis are not fully known, colchicine does impair the release of SAA from hepatocytes by binding to microtubules and preventing secretion. In addition,

colchicine may prevent the production of amyloid-enhancing factor. The dosage of colchicine used is 0.01 to 0.03 mg/kg given orally every 24 hours. Gastrointestinal upset is the primary side effect.

Figure 261-8 Glomerular amyloidosis in a canine renal biopsy section stained with hematoxylin-eosin. (Courtesy S.P. DiBartola, Columbus, OH, College of Veterinary Medicine, Ohio State University.)

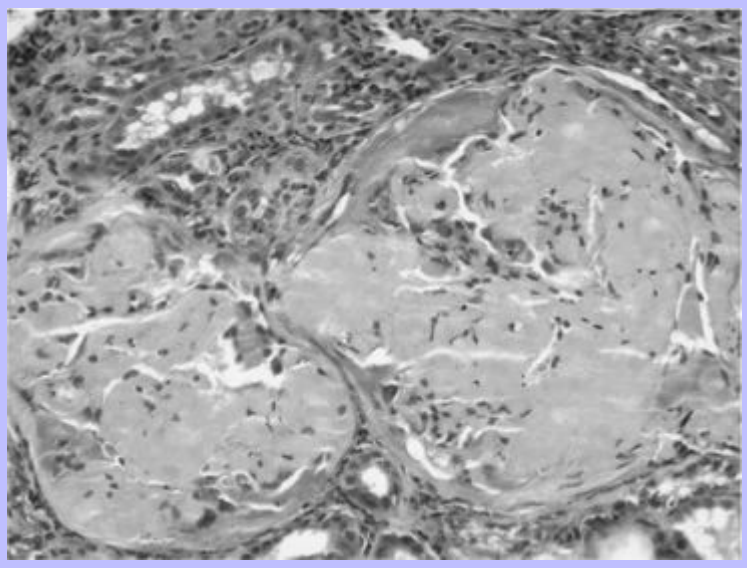
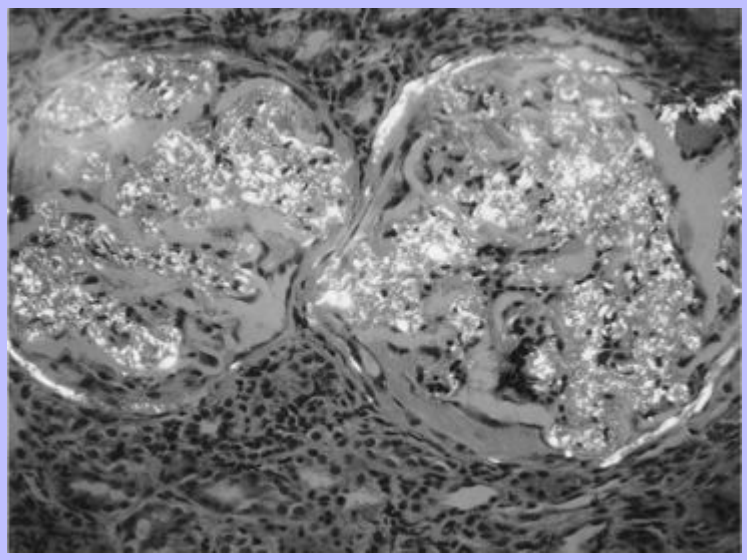


Figure 261-9 Section stained with Congo red, showing typical birefringence of glomerular amyloid deposits. (Courtesy S.P. DiBartola.)



Dimethylsulfoxide (DMSO) has been shown to be beneficial in a limited number of dogs with renal amyloidosis, although the exact benefit remains controversial.[35] If given during the rapid deposition phase, DMSO leads to a decrease in SAA concentrations and resolution of tissue deposits. However, the amount of amyloid deposited in the kidneys of humans was unchanged after DMSO administration, which lends support to the current belief that DMSO does not solubilize amyloid fibrils. The anti-inflammatory effects of DMSO may account for some of the beneficial effects. Reduction of interstitial fibrosis and inflammation may lead to improved renal function and reduced proteinuria. DMSO has an unpleasant odor that may lead to poor owner compliance. Furthermore, this drug may contribute to signs of nausea and anorexia seen in some dogs. The recommended dosage is 90 mg/kg given orally or subcutaneously three times weekly. DMSO should be diluted 1:4 with sterile water before injection to limit the pain associated with injection. Neither DMSO nor colchicine is effective once the plateau phase of deposition has been reached.

261.3.4.5 Prognosis

The prognosis for dogs and cats with renal amyloidosis is generally poor. In one study of dogs with amyloidosis, 58% died or were euthanized at the time of diagnosis. In the remaining dogs, survival ranged from 2 to 20 months; survival of a year or longer was reported in only 8.5%.[29] The longest survival was observed in a dog treated with DMSO.

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261.3.5 Hereditary Nephritis

The term *hereditary nephritis (HN)* refers to a diverse group of inherited glomerular diseases that are the result of a defect in basement membrane collagen (type IV).[36] These diseases are discussed in Chapter 264. A brief discussion of hereditary nephritis is included in this chapter because it should be considered as a differential diagnosis for any dog presenting with proteinuric renal disease, particularly if the dog is young.

261.3.5.1 Clinical Features

Hereditary nephritis has been reported in several breeds of dogs. An autosomal recessive form of the disease occurs in English cocker spaniels, whereas bull terriers and Dalmatians develop an autosomal dominant form.[36–39] An X-linked dominant form of HN has been described in Samoyeds and mixed-breed dogs; carrier females may have mild disease.[37] The report in the Samoyeds is of a single kindred; the disease is not considered to be common in this breed. HN is characterized by proteinuria, renal hematuria, and progressive glomerular disease. Concurrent hearing and ocular abnormalities, as described in humans with HN, appear to be uncommon in affected dogs, with the exception of anterior lenticonus, which occurs in some bull terriers.[38]

261.3.5.2 Pathogenesis

HN is the result of a genetic mutation or deletion in type IV collagen, the primary protein constituent of the GBM.[4,36] The presence of defective collagen leads to premature deterioration of the GBM and progressive glomerular disease.

261.3.5.3 Histopathologic Characterization

Prior to electron micrographic studies of English cocker spaniels, the renal lesions were described as renal cortical hypoplasia or membranoproliferative or sclerosing glomerulonephritis. Electron microscopy is required to make the diagnosis of HN. Multilaminar splitting and fragmentation of the GBM are seen, often with intramembranous, electron-dense deposits.

261.3.5.4 Specific Treatment

No specific treatment is available for affected dogs. Use of a diet formulated for renal failure and administration of angiotensin-converting enzyme (ACE) inhibitors have proved beneficial in affected dogs. Early detection of HN through screening of dogs of relevant breeds for microalbuminuria allows early therapeutic intervention, which may slow disease progression.[17]

261.3.5.5 Prognosis

The rate of progression is predictable in Samoyeds and English cocker spaniels, with terminal renal failure generally developing before 2 years of age.[36] However, disease progression is more variable in bull terriers and Dalmatians, with some dogs surviving for as long as 10 years.[38–39]

261.3.6 Minimal Change Disease

Although uncommonly described in dogs and cats, minimal change disease (MCD) is a common cause of nephrotic syndrome in humans, especially children.[5,40] Because EM is required for diagnosis, the disease most likely is underdiagnosed in dogs and perhaps in cats. In humans this disease is sometimes referred to as *nil disease, lipoid nephrosis,* or *idiopathic nephrotic syndrome*.

261.3.6.1 Clinical Features

There have been isolated reports of dogs that appear to have MCD; we have seen a few dogs in which we suspected this disease at North Carolina State University College of Veterinary Medicine. However, there is only one well-described case report of MCD in a dog presenting with nephrotic syndrome.[40] Proteinuria is likely to be of heavy magnitude with this disease, and nephrotic syndrome is common.

261.3.6.2 Pathogenesis

In humans, MCD is usually idiopathic, although secondary disease also occurs. Increased production of lymphokines by dysfunctional T cells is believed to be responsible for an increase in GBM permeability.[5] The primary change is loss of anionic charge in the glomerular capillary wall, leading to collapse of the podocyte foot processes. This loss of charge selectivity is the crucial event leading to proteinuria. The resultant proteinuria is highly selective; albumin is the primary protein lost.

261.3.6.3 Histopathologic Characterization

Animals with MCD have a lack of light microscopic lesions in the glomerulus.[4] Occasionally, slight hypercellularity is present, as evidenced by three or four nuclei in the mesangial region. Some lipid droplets may be present in the renal tubules, but there should not be any evidence of tubular atrophy or interstitial fibrosis. With IFM, immunoglobulin deposition is absent; however, there may be increased staining of vimentin, a marker for visceral glomerular epithelial cells. The diagnosis is confirmed with EM by identification of marked foot process effacement (Figure 261-10). MCD belongs to the WHO classification of minor glomerular abnormalities. In one study of glomerular lesions in dogs, 28 of 115 dogs fell into this classification, but only one of these dogs had MCD.[11] Therefore identification of only minor glomerular abnormalities in a dog or cat with proteinuria does not make a diagnosis of MCD.

261.3.6.4 Specific Treatment

An important reason to include MCD on the list of differential diagnoses for dogs with nephrotic syndrome is the disease's seemingly exquisite response to corticosteroids; the expected response rate in humans with MCD is 80% to 90%.[5]

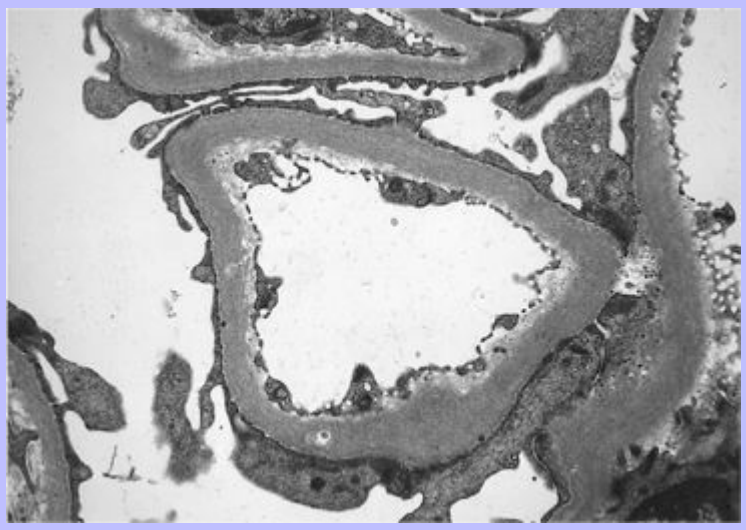
261.3.6.5 Prognosis

The prognosis for MCD in dogs is unknown. One or more relapses are seen in 75% to 85% of affected humans.[5]

261.3.7 Glomerulosclerosis

Glomerulosclerosis often develops as an end-stage lesion in response to glomerular injury.[4] Focal or global sclerosis may be a primary or concurrent lesion in animals with glomerular disease. The incidence of glomerulosclerosis increases with age, although the percentage of glomeruli expected to be sclerotic in dogs of advancing age groups has not been fully characterized. Glomerulosclerosis is a common finding in diabetic nephropathy of humans. Although glomerulosclerosis and proteinuria can develop in dogs with diabetes mellitus, the clinical relevance of this is unknown. Glomerulosclerosis can also develop after hypertensive renal damage.

Figure 261-10 Electron micrograph of a glomerular capillary loop in a dog with minimal change disease. Effacement of the foot processes has occurred.



Focal segmental glomerulosclerosis (FSGS) is a specific glomerular disease that has been identified, but poorly characterized, in dogs (Figure 261-11).[4,11] FSGS is a common glomerular disease in humans, accounting for up to 35% of nephrotic syndrome in adults. The disease is most likely underdiagnosed in dogs and often mischaracterized as MPGN. FSGS was the diagnosis rendered in 10% of dogs with glomerular disease in one study.[11] Males and females were equally represented, and the average age was 8.5 years. FSGS is diagnosed in the proteinuric patient that has segmental glomerulosclerosis in a glomerulus that is otherwise normal, without other glomerular lesions present to explain the sclerosis. IFM evaluation should be negative in affected patients; however, nonspecific trapping of immunoglobulins and C3 can occur in sclerotic areas.

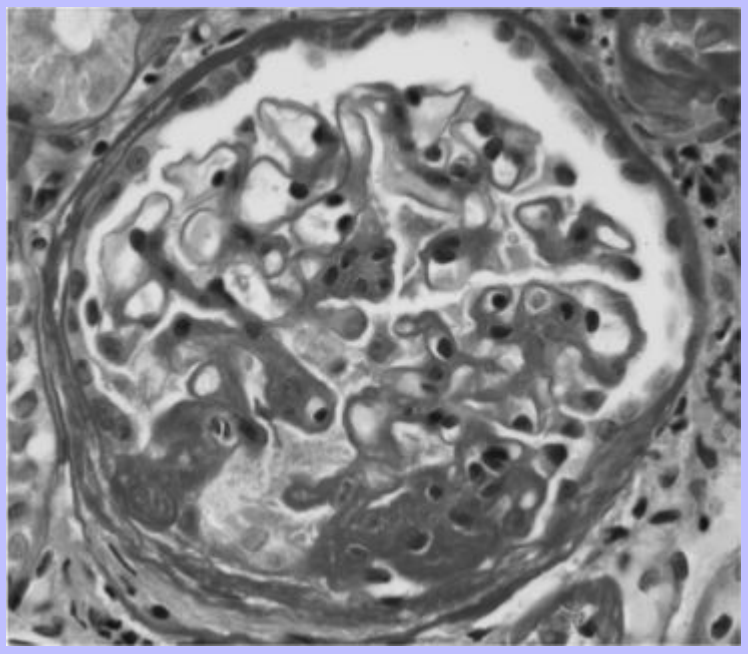
Five subtypes of this disease have been described in humans: perihilar, cellular, tip, collapsing and "not otherwise specified."[4] The clinical features of these subtypes vary somewhat, but the course is generally one of progressive proteinuria and renal failure. Permeability factor, a transferable circulating factor that promotes increased *in vitro* glomerular permeability to albumin and other plasma proteins, has been implicated in the pathogenesis of FSGS in humans.[5] Although the exact identify of this permeability factor is unknown, it is not an immunoglobulin or an immune complex. It is likely that several factors eventually will be identified that are capable of inducing increased glomerular permeability and eventual sclerotic lesions.

261.3.8 Tubulointerstitial Lesions Associated with Glomerular Disease

Proteinuria induces tubular damage, leading to progressive nephron loss.[41] Evidence in support of this includes the correlation between heavy proteinuria and a negative patient outcome in humans with various glomerular diseases; also, rodents with albumin-induced overload proteinuria develop renal injury and fibrosis, and the urine of proteinuric humans shows mediators of renal inflammation and fibrosis, some of

which are produced by renal tubules exposed to various proteins.[41] However, albumin may not be the culprit. Rodents with albumin-induced overload proteinuria develop altered glomerular permselectivity, with urinary loss of proteins in addition to albumin. Rats and humans with highly selective proteinuria appear to be at lower risk of eventual tubulointerstitial damage.

Figure 261-11 Glomerulus from a dog with a lesion resembling focal segmental glomerulosclerosis. Note the relatively normal appearance of the glomerular sections that are not sclerotic.



Some damage occurs secondary to obstruction of the tubules by protein casts.[42] However, the proteins themselves are also toxic to the tubular epithelial cells and lead to increased interstitial inflammation, fibrosis, and cell death. Proteinuria necessitates increased resorption of proteins through tubular cells by means of lysosomal processing. Ruptured lysosomes lead to cytoplasmic damage. Interstitial inflammatory cells, initially recruited in response to injury, contribute to the development of interstitial fibrosis. Other factors that may be involved in the genesis of interstitial inflammation and fibrosis induced by proteinuria include osteopontin, monocyte chemoattractant protein-1, urinary iron, endothelin-1, transforming growth factor-β, and tumor necrosis factor-alpha.[42] A direct link has not been established between proteinuria and progressive renal damage in dogs, but it probably exists to some extent. Because proteinuria may be a major factor responsible for progressive renal failure in patients with glomerular disease, aggressive management of the proteinuria should be considered a cornerstone of the treatment of dogs and cats with glomerular disease.

261.4 NONSPECIFIC MEDICAL MANAGEMENT OF GLOMERULAR DISEASE

In addition to specific management that might be implemented with the various glomerular diseases, nonspecific management is indicated. This therapy can be divided into three major categories: (1) treatment of potential

underlying diseases processes, (2) reduction of proteinuria, and (3) management of uremia and other complications of generalized renal failure (discussed in Chapter 260).

Many glomerulopathies in dogs are believed to develop secondary to a systemic infectious, inflammatory, or neoplastic disease process. However, the inciting agent may not be obvious at first presentation because the offending disease is no longer present or is occult. Continued observation and scrutiny are necessary, because the causative disease process may become obvious in the ensuing months after presentation. The initial step in the management of a persistently proteinuric dog or cat is to treat and eliminate, if possible, any potential predisposing diseases. The dog should be subsequently evaluated for resolution of the proteinuria, which may occur slowly over a period of months. If proteinuria does not resolve or worsens, a renal biopsy to determine the specific glomerular disease present may be warranted.

Enalapril significantly reduced proteinuria and delayed either the onset or the progression of azotemia in dogs with glomerulonephritis.[43] Treatment of dogs with glomerular diseases with ACE inhibitors is now considered a standard of care.[43] ACE inhibitors may reduce proteinuria and preserve renal function by several possible mechanisms. The decreased efferent glomerular arteriolar resistance effected by ACE inhibitors leads to decreased glomerular transcapillary hydraulic pressure and decreased proteinuria. Other proposed mechanisms include reduced loss of glomerular heparan sulfate, decreased size of the glomerular capillary endothelial pores, improved lipoprotein metabolism, slowed glomerular mesangial growth and proliferation, and inhibition of bradykinin degradation.[43] Typically enalapril (0.5 mg/kg given orally) is administered once a day. If no reduction in proteinuria is seen after 2 to 4 weeks, the frequency should be increased to twice daily (approximately half of the dogs may eventually need twice daily administration).[43] Although the serum creatinine concentration should be monitored, it is uncommon for dogs to have worsening of azotemia due to enalapril administration alone. Adequate blood pressure control of hypertensive dogs may also lead to a reduction in proteinuria and slow the progression of disease. Because ACE inhibitors are relatively weak antihypertensive agents, additional antihypertensive agents (e.g., amlodipine) may be needed if hypertension (i.e., systolic blood pressure greater than 170 mm Hg) persists after the initiation of ACE inhibitor therapy.

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Platelets and thromboxane may play an important role in the pathogenesis of glomerulonephritis. Thromboxane is an inducer of platelet aggregation and a chemotactic factor for neutrophils. Neutrophils induce damage to the GBM through release of proteolytic enzymes. Thromboxane release may lead to a reduction in the glomerular filtration rate by inducing vasoconstriction and mesangial cell contraction. Thromboxane synthetase inhibitors have been shown to decrease proteinuria in dogs with experimentally induced glomerulonephritis.[44] Aspirin is a nonspecific cyclo-oxygenase inhibitor that may be used to reduce glomerular inflammation and inhibit platelet aggregation, which may have an added benefit of preventing thromboembolism. In theory, very low doses of aspirin (0.5 mg/kg given orally once or twice daily) may selectively inhibit platelet cyclo-oxygenase without preventing the beneficial effects of prostacyclin formation.

Dietary protein restriction may be useful in the management of dogs with glomerulopathies. Humans and rats with glomerular disease demonstrate a reduction in proteinuria without a change in serum albumin concentrations with restriction of dietary protein. Diets should not be supplemented with protein, because this aggravates urinary protein losses. The enhanced omega-3 to omega-6 polyunsaturated fatty acid ratio and restriction in salt and phosphorus found in canine renal diets may also be of benefit to dogs with glomerulopathies. Omega-3 fatty acid supplementation has been shown to be renoprotective in dogs with renal failure and to mitigate hypertension and reduce serum triglyceride and cholesterol concentrations in humans with nephrotic syndrome.[45] These positive effects are in part mediated through generation of the 3-series prostaglandins. Sodium restriction is beneficial in the control of hypertension and fluid retention. Provision of adequate exercise may help reduce the formation of

edema or ascites. Because plasma volume is often reduced in animals with hypoalbuminemia and edema, the use of diuretics should be avoided unless these drugs are needed to control respiratory distress.

The use of immunosuppressive drugs in the treatment of both dogs and humans with glomerular disease is controversial. No controlled study has been done on the use of corticosteroids in dogs with glomerular diseases. Proteinuria has been demonstrated in dogs with corticosteroid excess and may induce glomerular lesions.[9,46] Furthermore, prednisolone administration was shown to reversibly increase proteinuria in dogs with hereditary nephritis.[47] The use of immunosuppressive agents is generally limited to dogs that have developed glomerulonephritis secondary to a steroid-responsive disease, such as systemic lupus erythematosus, but it should also be considered in animals with primary membranous nephropathy or MCD. Cyclosporine, the only drug that has been studied prospectively in dogs with glomerular disease, was found to be of no benefit.[48] However, dogs with idiopathic disease were included in this study regardless of which specific glomerular disease they had. In the future, the use of immunosuppressive drugs needs to be systematically studied in dogs with primary membranous nephropathy, MCD, or lupus nephritis. Until the results of such a study are available, immunosuppressive agents should be used only with caution and careful patient monitoring.

The UPC, urinalysis, body weight, body condition score, and serum albumin and creatinine concentrations should be evaluated monthly whenever modifications in the therapeutic plan are being made, or every 3 to 6 months if the dog's clinical signs are stable and therapeutic changes are not being made. Slight day-to-day variations in the UPC can occur; changing proteinuria is most accurately measured by assessing trends in the UPC over time. The systemic blood pressure should be measured at least every 3 to 6 months and more frequently if hypertension is unregulated. If the dog no longer has the ability to produce concentrated urine, a urine sample should be submitted for bacterial culture and susceptibility testing every 6 months. Because histologic lesions do not necessarily resolve even though renal function may improve, repeat biopsies generally are not needed. A reduction in proteinuria (ideally greater than 50%) as measured by the UPC without an increase in the serum creatinine concentration indicates improvement or response to therapy.

261.5 COMPLICATIONS OF GLOMERULAR DISEASE

Complications of severe proteinuria include edema formation, systemic hypertension, hypercoagulability and thromboembolism, hyperlipidemia, increased risk for infection, altered pharmacokinetics, malnutrition, muscle wasting, and endocrine abnormalities.[42] Edema formation, systemic hypertension, and hypercoagulability are the complications most frequently recognized in dogs, and less commonly in cats, with glomerular disease.

261.5.1 Edema Formation

Several factors contribute to the formation of edema in patients with nephrotic syndrome.[42] In severe forms of nephrotic syndrome, decreases in the plasma oncotic pressure allow for transudation of fluid into the interstitial spaces. The resultant decrease in effective plasma volume leads to increased renin-angiotensin-aldosterone activity and retention of water and sodium and worsening of edema. However, most humans with nephrotic syndrome do not have reduced blood volumes or increased plasma renin or aldosterone activities. Thus primary sodium retention must also be involved in the pathogenesis of edema in these patients. Proposed mechanisms in primary renal sodium retention include a reduced single nephron glomerular filtration rate with enhanced proximal tubular resorption and cytokine-induced modification of distal resorption, leading to resistance to natriuretic factors, including atrial natriuretic peptide. In humans it is believed that mechanisms of primary renal sodium retention are the most important determinants of edema formation until the serum albumin concentration decreases below 2 g/dL. Below this concentration, the plasma

oncotic pressure is sufficiently reduced to allow for transudation of fluid from the vascular compartment into the interstitial space.[42] Dogs may be more resistant to the formation of edema, which does not generally occur until the serum albumin concentration is below 1.5 g/dL. Plasma volume may be reduced at this point, making the use of diuretics in the management of edema relatively ineffective and also dangerous because of the increased risk of acute renal failure and thromboembolism.[42]

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261.5.2 Hypertension

Systemic hypertension has been reported in up to 80% of dogs with glomerular disease. The frequency of hypertension in each form of glomerular disease has not been established in dogs but does vary in humans. Hypertension appears to be most common in people with FSGS and membranoproliferative glomerulonephritis, whereas it is uncommon in association with MCD and does not occur higher than control populations in humans with membranous nephropathy.[5] The primary mechanism of hypertension in association with nephrotic syndrome is believed to be expansion of the plasma volume in association with primary renal sodium retention. However, generation of several vasoactive factors (e.g., renin, angiotensin II, endothelin) is increased in human patients with nephrotic syndrome and may contribute to hypertension. Nitric oxide deficiency may also play an important role in the development of hypertension.[42]

Target organs of hypertensive injury include the kidneys, the central nervous system, the eyes, and the heart. Blindness may be the presenting complaint in animals with hypertension, most commonly due to retinal detachment. However, retinal hemorrhage, edema, vessel tortuosity, and degeneration; hyphema; and secondary glaucoma may also occur. Hypertensive encephalopathy may be manifested as lethargy, altered mentation, altered behavior, seizures, or balance disturbances. Cardiac changes in dogs and cats with hypertension include systolic murmurs, gallop rhythms, and left ventricular hypertrophy. The blood pressure should be measured in all dogs and cats with glomerular disease, because uncontrolled hypertension is a risk factor for progressive renal injury.

261.5.3 Thromboembolism

Thromboembolism, perhaps the most serious complication of glomerular disease, was reported in 5% of dogs with glomerulonephritis, 14% of dogs with amyloidosis, and 13% of dogs with all forms of glomerular disease.[8,9,13] Because emboli may be difficult to detect, the prevalence of thromboembolism in dogs with glomerular disease may be higher than indicated by these studies. The risk of thromboembolism is highest in dogs with diseases most likely to cause nephrotic-range proteinuria (e.g., membranous nephropathy, amyloidosis). Pulmonary thromboembolism is most common, but emboli may also lodge in other arteries (e.g., mesenteric, renal, iliac, brachial, coronary) or the portal vein.

Although urinary loss of antithrombin III (AT III) has gained the most attention in veterinary medicine, the pathogenesis of the hypercoagulable state is multifactorial.[42] AT III is a serine protease inhibitor that modulates fibrin generation; heparin catalyses these reactions. AT III (65,000 daltons) is similar in charge and size to albumin (69,000 daltons); serum AT III activity closely correlates with the serum albumin concentration. This close correlation allows one to predict an increased risk of thromboembolism in patients with a serum albumin concentration less than 2 g/dL, when serum AT III activity would be expected to be less than 75% of normal.[8] However, AT III activity levels do not always correlate with the development of thromboembolism; other factors are involved.

Albumin binds to arachidonic acid, which, if unbound, would stimulate platelet aggregation through the generation of prostaglandins (i.e., thromboxane B_2); hypoalbuminemia is associated with increased platelet aggregation.[42] Hypercholesterolemia contributes to platelet hypersensitivity by influencing the membrane-associated enzyme and receptor activity through alteration of the membrane composition. The role of platelet hypersensitivity in the development of hypercoagulability may be enhanced by thrombocytosis, which occurs in many animals with glomerular disease. Increased fibrinogen concentrations (i.e., above 300 mg/dL), which are often present in patients with nephrotic syndrome, lead to increased fibrin complex formation and platelet hyperaggregation. The risk of thromboembolism may be further enhanced by increased concentrations of alpha$_2$ macroglobulin; alpha$_2$ antiplasmin; procoagulant cytokines; coagulation factors V, VII, VIII, and X; increased plasma viscosity and interstitial pressure; decreased plasma plasminogen concentrations; decreased plasma volume and blood flow; endothelial injury; and infections.[42]

Coumadins and aspirin have been used in the prevention of thromboembolism in at-risk dogs. However, warfarin is highly protein bound. It is very difficult to titrate the dose adequately to prolong the prothrombin time appropriately (i.e., 150% of baseline) in dogs with hypoalbuminemia, and its use is not recommended. Alternatively, low-dose aspirin is inexpensive, easy to administer, and has the added benefit of potentially reducing proteinuria.

261.5.4 Hyperlipidemia

Hypercholesterolemia was reported in 79% of dogs with glomerulonephritis and 86% of dogs with amyloidosis.[9,13] Cholesterol concentrations as high as 749 mg/dL have been reported, although the mean concentration was 312 mg/dL in 69 dogs with glomerulonephritis and 350 mg/dL in 23 dogs with amyloidosis.[8,9] Increases in total plasma cholesterol, very-low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) occur.[49] Hyperlipidemia is variably seen in humans with nephrotic syndrome and has not been fully studied in dogs. The pathogenesis of hyperlipidemia in association with nephrotic syndrome is complex.[49] Hypoalbuminemia stimulates hepatic protein synthesis, including the synthesis of lipoproteins, leading to hypercholesterolemia.[42] The serum albumin concentration and plasma oncotic pressure inversely correlate with the magnitude of hypercholesterolemia. It is unclear whether hypoalbuminemia or the decreased plasma oncotic pressure, or both, induce the increased synthesis. Alterations in lipid catabolism also contribute to the development of hyperlipidemia. Orosomucoid, which plays an important role in the maintenance of glomerular permselectivity, is lost in the urine of patients with glomerular disease. Urinary losses of orosomucoid exacerbate proteinuria but also contribute to hyperlipidemia by indirectly causing decreased hepatic production of heparin sulfate, a cofactor needed in normal lipoprotein lipase function.[49]

Some evidence supports the theory that uncontrolled hyperlipidemia contributes to glomerular and tubulointerstitial injury. LDL and oxidized LDL may alter mesangial cell function and increase the synthesis of mesangial matrix, thereby accelerating the formation of glomerulosclerosis.[42] Glomerular and tubulointerstitial lipoprotein deposition and lipoprotein-induced cytotoxicity also contribute to renal injury. Interestingly, glomerular lesions have been identified in cats with lipoprotein lipase deficiency and in miniature schnauzers with hyperlipidemia.[50]

261.6 PROGNOSIS FOR GLOMERULAR DISEASE

The prognosis for dogs and cats with glomerular disease is variable and probably based on a combination of factors. The prognosis is expected to differ with the various diseases, as discussed earlier in the chapter. Although progressive disease can be expected to occur in a large percentage of animals with glomerular disease, spontaneous remission and response to specific therapy can also be expected. Furthermore, disease progression can be slow enough for the animals to lead relatively normal lives, especially when the diagnosis is established early in the disease process. In humans, azotemia, severe proteinuria, systemic hypertension, and marked tubulointerstitial lesions at presentation are the most significant predictors of an unfavorable outcome in most forms of glomerular disease. Clinical impressions would suggest that these same variables affect the prognosis in dogs and cats.

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Dogs with glomerulonephritis that were azotemic at first evaluation survived less than 3 months.[9] The median survival of 53 dogs with glomerulonephritis and amyloidosis that were not dead or euthanized shortly after presentation was only 28 days, although individual dogs survived for more than 3 years; survival times did not correlate with any biochemical parameter in these dogs.[8] Both of these studies are inherently biased toward death by the inclusion of dogs from which renal tissue samples were collected during postmortem examination. More study is needed to characterize the natural history and prognosis of the various glomerular diseases in dogs and cats.

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262 CHAPTER • 262 Urinary Tract Infections

Joseph W. Bartges

A urinary tract infection (UTI) develops when a breach (either temporary or permanent) occurs in host defense mechanisms and a virulent microbe in sufficient numbers is allowed to adhere, multiply, and persist in a portion of the urinary tract. UTIs typically involve bacteria, although fungi and viruses also may infect the urinary tract. Infection may predominate at a single site, such as the kidney (pyelonephritis), ureter (ureteritis), bladder (cystitis), urethra (urethritis), prostate (prostatitis), or vagina (vaginitis), or it may be present at two or more of these sites. Because a UTI may involve more than one location, it may be relevant to identify the infection anatomically; that is, upper urinary tract (kidneys and ureters) or lower urinary tract (bladder, urethra, and prostate or vagina). UTIs may or may not produce clinical signs.

The reported incidence of bacterial UTI in dogs and cats is variable. Bacterial UTI is estimated to affect 14% of all dogs during their lifetime,[1] and it is more common in females.[2–5] In cats, bacterial UTIs occur more often in animals older than 10 years, and the incidence increases with age.[6–9] Fungal UTI is believed to be uncommon.[10–13] The incidence of viral UTI is unknown, but viruses have been implicated as a cause of lower urinary tract disease in cats (see Chapter 266).[14–18]

The pathogenesis of urinary tract infections represents a balance between uropathogenic infectious agents and host resistance. UTIs should be treated with antimicrobial agents; however, the status of host defense mechanisms is important in the development, treatment, and prevention of these infections.

262.1 DEFINITION OF CONCEPTS AND TERMS

262.1.1 Urinary Tract Infection

A *urinary tract infection* is defined as adherence, multiplication, and persistence of an infectious agent in the urogenital system. Infections often involve a bacterial organism that is present normally in the distal urogenital tract.

262.1.2 Microburia

Microburia refers to the presence of microbes, typically bacteria, in the urine.

262.1.3 Bacteriuria

Bacteriuria refers to the presence of bacteria in the urine. However, identification of bacteria in the urine is not synonymous with UTI. The presence of bacteria may represent contamination of a urine sample, particularly if the sample was collected by voiding or catheterization. Bacteria in the distal urogenital tract may appear in urine collected by these methods, or the urine may be contaminated after collection. *Significant bacteriuria* is the term used to describe bacteriuria that represents a UTI. A high bacterial number in a properly collected and cultured urine sample is indicative of a bacterial UTI. Small numbers of bacteria obtained from untreated pets usually indicate contamination. *Asymptomatic bacteriuria* refers to significant bacteriuria that is not associated with clinical signs of UTI. This often occurs in animals with compromised

host defenses, such as those with glucocorticoid excess, diabetes mellitus, or feline immunodeficiency virus infection.

262.1.4 Funguria

Funguria refers to the presence of fungi in the urine. Fungi are not normally present in the urogenital system, and identification of these organisms indicates the presence of an infection, regardless of whether clinical signs are seen.

262.1.5 Pyuria

Pyuria refers to the presence of white blood cells (WBCs) in the urine. Pyuria is defined as (1) more than 3 to 5 WBCs (neutrophils) per high-power field in urine sediment prepared from a 5 mL aliquot of urine collected by cystocentesis, or (2) more than 5 to 10 WBCs per high-power field in urine sediment prepared from a 5 mL aliquot of urine collected by catheterization or voiding. Pyuria is not synonymous with UTI; it only implies inflammation.

262.1.6 Inflammation versus Infection

The presence of inflammation is not synonymous with UTI. Many disease processes result in urinary system inflammation, characterized by hematuria, pyuria, and/or proteinuria. The presence of one or more of these conditions does not indicate the etiology or location of the disease process in the urogenital system. To identify the etiology of the inflammation, additional testing must be performed, such as imaging studies, urine culture, renal function tests, endoscopy, urodynamic studies, or biopsy.

262.2 ETIOPATHOGENESIS

262.2.1 Normal Host Defenses

Most UTIs are the result of ascending migration of pathogens from the distal urogenital tract into otherwise normally sterile locations. A resident population of bacteria that is normally present in the lower urogenital tract may decrease establishment of an uropathogen or may emerge as a uropathogen if normal host defenses are altered (Table 262-1).

Although the urinary tract communicates with the microbe-laden external environment, most of the urinary tract is normally sterile, and all of it is resistant to infection. Mechanisms of host resistance to UTIs may be divided into two categories: (1) natural inherent resistance factors and (2) acquired or induced resistance factors activated by the onset of a UTI (Box 262-1). Systemic host defenses play a role in the prevention of hematogenous spread of pathogens to and from the urinary tract; however, local host defense mechanisms are the initial defense in the prevention of ascending infection (Box 262-1).[19] There also appears to be a difference in host defense mechanisms between the upper and lower urinary tracts. For example, induction of diuresis is beneficial for preventing experimental induction of bacterial pyelonephritis in rats[20]; however, dilute urine appears to increase the susceptibility of animals to bacterial infection of the lower urinary tact.[7,21]

Table • 262-1 Bacteria Detected in the Urogenital Tract of Normal Male and Female Dogs

GENUS	DISTAL URETHRA OF MALES	PREPUCE	VAGINA
Acinetobacter		+	+
Bacteroides			+
Bacillus		+	+
Citrobacter			+
Corynebacterium	+	+	+
Enterococcus			+
Enterobacter			+
Escherichia	+	+	+
Flavobacterium	+	+	+
Haemophilus	+	+	+
Klebsiella	+	+	+
Micrococcus			+
Moraxella		+	+
Mycoplasma	+	+	+
Neisseria			+
Pasteurella		+	+
Proteus		+	+
Pseudomonas			+
Staphylococcus	+	+	+
Streptococcus	+	+	+
Ureaplasma	+	+	+

From Barsanti JA, Johnson CA: Genitourinary infections. *In* Greene CE (ed): Infectious Diseases of the Dog and Cat, 2nd ed. Philadelphia, WB Saunders, 1990, pp 157–183.

262.2.1.1

Box • 262-1 Natural and Acquired Host Defenses of the Urinary Tract

1. Normal micturition
    a. Adequate urine volume
    b. Frequent voiding
    c. Complete voiding
2. Anatomic structures
    a. Urethral high-pressure zones
    b. Surface characteristics of urothelium
    c. Urethral peristalsis
    d. Prostatic secretions (antibacterial fraction and immunoglobulins)
    e. Length of urethra
    f. Ureterovesical flap valves

g. Ureteral peristalsis

h. Glomerular mesangial cells (?)

i. Extensive renal blood supply and flow

j. Others (?)

3. Mucosal defense barriers

a. Antibody production

b. Surface layer of glycosaminoglycans

c. Intrinsic mucosal antimicrobial properties

d. Exfoliation of urothelial cells

e. Bacterial interference by commensal microbes of distal urogenital tract

f. Others (?)

4. Antimicrobial properties of urine

a. Extreme high and low of urine pH

b. Hyperosmolality

c. High concentration of urea

d. Organic acids

e. Low-molecular-weight carbohydrates

f. Tamm-Horsfall mucoproteins

g. Others (?)

5. Systemic immunocompetence

a. Cell-mediated immunity

b. Humoral-mediated immunity

From Osborne CA, Lees GE: Bacterial infections of the canine and feline urinary tract. *In* Osborne CA, Finco DR (eds): Canine and feline nephrology and urology. Baltimore, Williams & Wilkins, 1995, pp 759–797.

262.2.2 Microbial Factors

Not all microbes, particularly bacteria, are pathogenic. For example, of the more than several hundred serotypes of *Escherichia coli,* fewer than 20 account for most bacterial UTIs.[22] Because *E. coli* is the most common bacterial uropathogen in humans, dogs, and cats, its virulence (uropathogenicity) has been studied extensively.[22–33] Less is known about the uropathogenicity of other pathogens (Box 262-2). Uropathogens typically have more than one virulence factor, therefore the absence of one factor does not necessarily result in loss of uropathogenicity. Likewise, bacteria that are nonpathogenic in a normal pet may become pathogenic in one with altered host defenses.

262.2.3 Microbial Isolates

The bacteria that commonly cause UTIs are similar in dogs and cats. Infections caused by *E. coli* are most common, and this pathogen accounts for one third to one half of all organisms isolated from urine. Gram-positive cocci are the second major group of uropathogens. Staphylococci, streptococci, and enterococci account for one fourth to one third of isolates recovered. Bacteria that cause the remaining one fourth to one third of bacterial UTIs include *Proteus, Klebsiella, Pasteurella, Pseudomonas, Corynebacterium,* and *Mycoplasma* spp.; however, infection caused by any of these bacteria is uncommon.[6,7,11,34–37]

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262.2.3.1 Box • 262-2 Some Factors That May Enhance the Virulence (Uropathogenicity) of Bacteria Causing Urinary Tract Infection

1. *Escherichia coli*
    a. Certain O (somatic) antigens
        i. Outer polysaccharide portion of bacterial envelope
        ii Smooth colony morphology on culture plate
        iii Indirect marker of virulence (human studies)
    b. Certain K (capsular) antigens
        i. Capsule surrounds bacterium.
        ii May inhibit phagocytosis and complementmediated bactericidal activity
        iii Increased resistance to inflammation favors persistence of bacteria in tissue.
    c. Adhesive fimbriae (pili)
        i. Proteinaceous filamentous organelles that protrude from the surface of the bacterium
        ii Specific types of fimbriae (p-fimbriae) enhance the ability of a bacterium to remain adherent to uroepithelium despite cleansing action of urinary system.
    d. Hemolysin

i. Increases amount of free iron available for bacterial growth

ii May cause tissue damage

e. Aerobactin

i. Iron-binding protein

ii Facilitates bacterial growth

f. R-plasmids

i. Promote resistance to antimicrobial agents

g. Resistance to serum bactericidal activity

h. Short generation time in urine

2. *Proteus, Staphylococcus*, and some *Klebsiella* spp.

a. Adherence factors

b. Urease

i. Bacterial enzyme that hydrolyzes urea to ammonia

ii Ammonia directly injures uroepithelium.

iii Urease fosters production of magnesium ammonium phosphatase uroliths.

c. R-plasmids

3. *Pseudomonas* sp.

a. Heavy mucoid polysaccharide capsule

i. Prevents antibody coating

b. R-plasmids

Approximately 75% of bacterial UTIs in dogs are caused by a single species of pathogen, approximately 20% are caused by two species, and approximately 5% are caused by three species.[11] A similar pattern is found in cats.[7,8]

262.2.4 Routes of Infection

The majority of UTI occur as a consequence of ascending migration of pathogens through the genital tract and urethra to the bladder, ureters, and one or both kidneys. Rectal, perineal, and genital bacteria serve as the principal reservoirs for infection.[38–42] Although the intrinsic motility of some bacteria, including *E. coli* and *Proteus* spp., may aid their retrograde migration from the distal urogenital tract, brownian movement is the

primary mechanism for ascending infection.[41] In addition to gaining access to the urinary tract, microbes must adhere to and colonize the urothelial surface. Thus the establishment of a UTI depends on the number and virulence of microbes and their interaction with host defenses.

The upper urinary tract is most commonly infected by ascending microbes rather than through hematogenous seeding caused by systemic infection.[44–46] Because blood must pass through glomerular capillaries in the renal cortex before it reaches the medulla, most hematogenous bacteria do not reach the renal medulla. Apparently, renal cortical tissue is more resistant to infection than medullary tissue. Urinary tract obstruction or trauma increases the risk of hematogenous seeding of the urinary tract by interfering with the renal microcirculation.[47]

262.3 CLINICAL FINDINGS

262.3.1 Historical Information and Physical Examination Findings

Dogs and cats with UTI may or may not be symptomatic. Clinical signs associated with UTI are variable and depend on the interaction of (1) the virulence and numbers of the uropathogen, (2) the presence or absence of predisposing causes, (3) the body's compensatory response to infection, (4) the duration of infection, and (5) the site or sites of infection (Table 262-2). Pollakiuria, stranguria, dysuria, and inappropriate urination may be observed with lower urinary tract infections. Animals with upper urinary tract infections may show pain localized to one or both kidneys, hematuria, septicemia, or renal failure (with resultant clinical signs if both kidneys are infected). If the UTI is associated with a predisposing condition (e.g., diabetes mellitus, hyperadrenocorticism, or bladder neoplasia), clinical signs associated with that condition usually predominate. Female dogs with abnormalities of the vulva, perivulvar dermatitis, or vaginal stenosis may have an increased risk for UTI.[48] Male cats with perineal urethrostomies also have an increased risk for UTI.[49] Some animals may have infection of both the upper and lower urinary tracts, especially if renal failure is present.

262.3.2 Laboratory Results

Unless septicemia or renal failure is present, the results of complete blood cell counts are normal. If septicemia is present, leukocytosis and a left shift may be seen. Lower urinary tract infection does not cause changes in blood work unless another disease process is present. With upper urinary tract infections, serum biochemical analysis may be normal or may indicate renal failure (if both kidneys are diseased). If the UTI is associated with another disease, changes in laboratory parameters may reflect the associated condition. In cats, feline leukemia virus and feline immunodeficiency virus infections increase the risk of UTI.[7]

262.3.3 Results of Imaging Studies and Endoscopy

In many dogs and cats with a UTI, the results of imaging studies are normal. Survey abdominal radiography may reveal uroliths, renomegaly, or small kidneys, or other defects that may predispose the animal to the development of a UTI. Some dogs may have pelvic displacement of the urinary bladder (so-called pelvic bladder), which can be associated with urinary incontinence and UTI, although it also is observed in dogs without disease.[50] If no abnormalities are found by survey abdominal radiography, ultrasonography or contrast radiography should be performed. The upper urinary tract may be evaluated by excretory urography, and the lower urinary tract may be evaluated by contrast cystourethrography, double contrast cystography, and contrast vaginourethrography. A potential complication of contrast radiography of the lower urinary tract is

induction of a UTI. Ultrasonography is a noninvasive technique that is useful for evaluating the echotexture and architecture of the urinary tract except for the distal urethra. In humans, nuclear scintigraphy using technetium-99m–labeled dimercaptosuccinic acid (DMSA) may be useful for evaluating for pyelonephritis; however, this diagnostic aid has not been used in dogs.[51,52]

Table • 262-2 Abnormalities that Help Localize Urinary Tract Infections

SITE OF INFECTION	HISTORY	PHYSICAL EXAMINATION FINDINGS	LABORATORY FINDINGS	IMAGING STUDIES
Lower urinary tract	Dysuria, pollakiuria	Small, painful, thickened bladder	*Complete blood count (CBC):*	Normal kidneys
	Urge incontinence	Palpable masses in urethra or bladder	Normal Urinalysis: Pyuria, hematuria, proteinuria, bacteriuria	Structural abnormalitiesof lower urinary tract
	Signs of abnormal detrusor reflex (overflow incontinence, large residual volume)	Flaccid bladder wall, large residual volume	Urine culture: Significant bacteriuria	± Urocystoliths and/orurethroliths
	Gross hematuria at end of micturition	Abnormal micturition reflex ± Palpation of uroliths		± Thickening of bladder wall and rregularity of mucosa
	Cloudy urine with abnormal odor			Rarely, intraluminal gas formation (emphysematous cystitis)
	No systemic signs			
	Recent catheterization or urethrostomy			
Upper urinary tract	Polyuria, polydipsia	± Detectable abnormalities	CBC:± Leukocytosis	Renomegaly
	± Signs of systemic infection	± Fever and other signs of systemicinfection	Urinalysis: Pyuria, hematuria, proteinuria, bacteriuria, white	± Abnormal kidney shape
	± Renal failure	± Abdominal (renal) pain	blood cell or granular castsImpaired urine concentration	± Nephroliths, ureteroliths
		Kidney(s) normal or increased in size	± Azotemia and other findingsof renal failure	± Dilated renal pelves, dilated pelvicdiverticula
				± Evidence of outflow obstruction
Acute prostatitis or prostatic abscessation	Urethral discharge independent of micturition	± Fever and other signs of systemic infection	CBC:± Leukocytosis	± Indistinct cranial border of prostate
			Urinalysis: Pyuria, hematuria, proteinuria, bacteriuria	± Prostatomegaly
	Signs of systemic infection	± Painful prostate and/or painful abdomen	Prostate cytology: Inflammation and infection	± Prostatic cysts
	± Reluctance to urinate or defecate	± Prostatomegaly or asymmetric prostate		± Reflux of contrast medium into prostate
Chronic prostatitis	Recurrent urinary tract infections	Often no detectable abnormalities	CBC: Normal	± Prostatomegaly
	Urethral discharge independent of urination	± Prostatomegaly or asymmetric prostate	Urinalysis: Pyuria, hematuria, proteinuria, bacteriuria	± Prostatic cysts
	± Dysuria			± Prostatic mineralization

Endoscopy of the lower urinary tract may be useful for identifying mucosal and intraluminal lesions that may predispose an animal to UTI. In one cat, a urolith not visible by survey radiography was visualized by cystoscopy.[53] Disadvantages of cystourethroscopy include induction of anesthesia to perform the procedure, contamination of and trauma to the lower urogenital tract, and difficulty performing the procedure in male cats.

262.4 DIAGNOSIS

262.4.1 Urinalysis

A urinalysis should be performed as a routine part of a minimum database. A complete urinalysis involves determination of the urine specific gravity (USG) using a refractometer, chemical analysis using analytic test pads on dipsticks, and sediment examination. Cystocentesis is the best method of collecting urine when evaluating a dog or cat for UTI. If infectious prostatitis or vaginitis is suspected, these anatomic areas should be evaluated using different techniques (see Chapters 253 and 263).

With urinary tract infection the USG is variable, depending on whether the infection involves the upper urinary tract or an associated disease. Dipstick analysis often, but not always, reveals hematuria and proteinuria. Leukocyte esterase (WBCs) and nitrite (bacteria) test pads are not reliable in dogs and cats and should not be used.[54]

Examination of urine sediment should be a routine part of a complete urinalysis. The presence of a significant number of WBCs (more than 0 to 5 per high-power field) associated with hematuria and proteinuria in a properly collected urine sample suggests inflammation. Detection of significant microburia with pyuria indicates active inflammation associated with an infection. Bacteria and fungi may be difficult to identify in dilute urine, making a diagnosis of UTI problematic. UTI, especially a bacterial UTI, may be present without concurrent inflammation if host defenses are compromised (e.g., as in hyperadrenocorticism or feline leukemia virus infection).[7,12,55–59]

Rod-shaped bacteria may be identified in unstained preparations of urine sediment if more than 10,000 bacteria/mL are present, but they may not be consistently detected if present in fewer numbers. Cocci are difficult to detect in urine sediment if their numbers are less than 100,000 bacteria/mL.[2] Although detection of bacteria on urine sediment examination suggests bacterial UTI, this finding should be verified by urine culture. Urine sediment may be stained with Gram's stain or new methylene blue to aid in detection of microbes; however, urine culture is the gold standard for confirmation of UTI. Failure to detect bacteria on examination of urine sediment does not exclude their presence or rule out a UTI.

262.4.2 Urine Collection

For urine culture, urine should be collected by cystocentesis. With lower urinary tract disease, collection of a sample by this method may be difficult, and it may be necessary to collect urine by catheterization or, less desirably, voiding. These techniques require cleansing of the pet's external genitalia, and the perivulvar fur may require clipping to prevent contamination. Although urinary catheterization of dogs is usually accomplished without chemical restraint, cats require sedation or anesthesia. A sterile catheter and collection container (a syringe or a collection cup with a tight-fitting lid) are used. If the results of quantitative culture of urine samples obtained by catheterization or midstream voiding are equivocal after serial cultures, urine should be collected by cystocentesis.

The presence of bacteria, even in low numbers, in urine collected aseptically by cystocentesis indicates a UTI; however, false-positive results may occur if a loop of intestine is penetrated with the hypodermic needle during the procedure or if the sample is contaminated during handling. Contamination usually involves recovery of more than one organism.

262.4.3 Urine Culture

As mentioned previously, urine culture is the gold standard for diagnosis of a UTI. A diagnosis of UTI based only on clinical signs, hematuria, and/or urinary tract inflammation is a misdiagnosis that may result in inadequate or inappropriate treatment. Under some circumstances, antimicrobial therapy may be initiated without first obtaining the results of urine culture (see Empiric Antimicrobial Treatment, below); however, samples for urine culture should be collected before drug therapy is started. If antimicrobial therapy has been started, it should be discontinued for 3 to 5 days prior to performance of a urine culture to minimize inhibition of microbial growth.

A urine culture is the most definitive means of diagnosing a bacterial UTI. Fungal culture should be considered when yeast or fungi are identified on urine sediment examination. Care must be taken to collect, preserve, and transport the urine sample so as to avoid contamination, proliferation, or bacterial death.[60] Urine specimens for aerobic bacterial culture should be transported and stored in sealed, sterilized containers, and processing should begin as soon as possible. If laboratory processing is delayed by more than 30 minutes, the specimen should be refrigerated at 4°C.[61] At room temperature, bacterial counts may double every 20 to 45 minutes. Multiplication or destruction of bacteria may occur within 1 hour of collection.

If samples cannot be processed immediately for urine culture, several alternatives are available. Blood agar and MacConkey's agar plates may be inoculated and incubated for 24 hours. A calibrated bacteriologic loop or a microliter mechanical pipette that delivers exactly 0.01 or 0.001 mL of urine to the culture plates should be used. The urine is streaked over the plates by conventional methods. Blood agar supports the growth of most aerobic uropathogens, and MacConkey's agar provides information that aids the identification of bacteria and prevents “swarming” of *Proteus* spp. The plates are incubated or placed under an incandescent light.[62] If bacterial growth occurs on the plate after 24 hours, the plates may be submitted for identification and determination of antimicrobial sensitivities, or antimicrobial susceptibility may be determined using the agar disk diffusion method.[62,63] If no growth occurs after 24 hours, the plates may be discarded.

Commercially available urine culture collection tubes containing preservative, combined with refrigeration, may be used to preserve specimens for up to 72 hours.[64] More recently, in-house urine culture and susceptibility kits have become available (IndicatoRx; IDEXX Laboratories, Westbrook, Maine).

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262.4.3.1 Qualitative urine culture

A qualitative urine culture involves the isolation and identification of bacteria in urine; it does not include quantification of bacterial numbers. Although urine in the bladder is normally sterile, urine that passes through the distal urogenital tract often becomes contaminated with resident flora (see Table 262-1). Therefore the presence of bacteria in urine collected by catheterization or voiding is often difficult to interpret, even with quantification of bacteria (Table 262-3). For this reason, a diagnostic urine culture should include quantitation of bacterial numbers in addition to identification of the organism and antimicrobial susceptibility.

262.4.3.2 Quantitative urine culture

A quantitative urine culture includes isolation and identification of the organism and determination of the number of bacteria (i.e., colony-forming units [cfu] per unit volume). Quantitation allows interpretation of the significance of bacteria present in a urine sample. However, caution should be exercised in the interpretation of quantitative urine cultures obtained by midstream voiding or manual expression of the bladder. Although urine obtained from most dogs without a UTI is either sterile or contains less than 10,000 cfu/mL (see Table 262-3), counts of 100,000 cfu/mL or higher have occurred with sufficient frequency to make collection of urine by midstream voiding or manual expression unsatisfactory.[65] The definition of significant bacteriuria in cats involves lower numbers of organisms, because cats appear to be more resistant to UTI than dogs.

262.4.4 Antimicrobial Susceptibility Testing

Administration of antimicrobial agents is the cornerstone of treatment for UTI. The antimicrobial agent selected should be (1) easy to administer, (2) associated with few, if any, side effects, (3) inexpensive, (4) able to attain tissue or urine concentrations that exceed the minimum inhibitory concentration (MIC) for the uropathogen by at least fourfold, and (5) unlikely to affect the pet's intestinal flora adversely.[2] The antimicrobial agent chosen should be based on antimicrobial susceptibility testing.

262.4.4.1 Agar disk diffusion technique

Antimicrobial susceptibility testing is often done using agar disk diffusion (Kirby-Bauer technique),[66] which is adequate for most bacterial UTIs. The agar disk diffusion method consists of Mueller-Hinton agar plates that have been inoculated with a standardized suspension of a single uropathogen. Paper disks impregnated with different antimicrobial drugs are placed on the plate. After 18 to 24 hours' inoculation at 38° C, antimicrobial susceptibility is estimated by measuring zones of inhibition of bacterial growth surrounding each disk. The zones of inhibition are then interpreted in light of established standards and recorded as resistant, susceptible, or intermediately susceptible. Because of differences in the ability of various antimicrobials to diffuse through agar, the antimicrobial disk surrounded by the largest zone of inhibition is not necessarily the drug most likely to be effective. Also, because the concentration of antimicrobial (except nitrofurantoin) in the paper disks is comparable to the typical serum concentration of the drug, drugs that are found to be resistant by the agar disk diffusion method may be effective in the urinary tract if they are excreted in high concentrations in urine (e.g., ampicillin and cephalexin).

Table • 262-3 Interpretation of Quantitative Urine Cultures in Dogs and Cats*

	SIGNIFICANT		SUSPICIOUS		CONTAMINANT	
SAMPLE TYPE	DOGS	CATS	DOGS	CATS	DOGS	CATS
Cystocentesis	≥1000	≥1000	100 to 1000	100 to 1000	≤100	≤100
Catheterization	≥10,000	≥1000	1000 to 10,000	100 to 1000	≤1000	≤100
Midstream voiding	≥100,000†	≥10,000	10,000 to 90,000	1000 to 10,000	≤10,000	≤1000
Manual compression	≥100,000†	≥10,000	10,000 to 90,000	1000 to 10,000	≤10,000	≤1000

From Lulich JP, Osborne CA: Bacterial urinary tract infections. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine, 4th ed. Philadelphia, WB Saunders, 1999, pp 1775–1788.

* Values are given in colony-forming units per milliliter of urine (cfu/mL). Data represent generalities. Occasionally, bacterial UTI may be detected with fewer organisms (i.e., false-negative results).

† Because the contamination level of midstream samples may be 10,000 cfu/mL or higher (i.e., false-positive result), these samples should not be used for routine diagnostic culture.

262.4.4.2 Antimicrobial dilution technique

Antimicrobial dilution susceptibility tests are designed to determine the minimum concentration of an antimicrobial drug that will inhibit the growth of the uropathogen (i.e., the MIC). After inoculation and incubation of uropathogens into wells containing serial twofold dilutions of antimicrobial drugs at concentrations achievable in tissues and urine, the MIC is defined as the lowest antimicrobial concentration (or highest dilution) that allows no visible bacterial growth. The MIC is several dilutions lower than the minimum bactericidal concentration of drugs. In general, the antimicrobial agent is likely to be effective if it can achieve a concentration four times that of the MIC (Table 262-4). Many antimicrobial drugs that are excreted through the kidneys reach concentrations in urine that are 10 to 100 times greater than the serum concentration.

262.5 TREATMENT

262.5.1 Prevention

Normal host defense mechanisms are effective in preventing UTIs; however, they are not impenetrable. For example, normal host defenses may be overwhelmed if large quantities of a virulent uropathogen are introduced into the urinary tract during diagnostic and therapeutic procedures. Iatrogenic UTI is a common complication of indwelling urinary catheters, especially if an open-ended system is used. Bacterial UTI developed in 20% of healthy adult female dogs after intermittent catheterization; in 33% of male dogs during repeated catheterization; and in 65% of healthy male cats within 3 to 5 days of open indwelling catheterization. In a clinical study, bacterial UTI developed in 52% of dogs and cats with indwelling urinary catheters; the risk of UTI increased with the duration of catheterization.[67] The use of indwelling urinary catheters during diuresis or corticosteroid administration is particularly dangerous, and the problem is compounded if the dog or cat has preexisting urinary tract disease.

Table • 262-4 Average Canine Urine Concentrations of Some Antimicrobial Agents

DRUG	DAILY DOSAGE (mg/kg)	ROUTE OF ADMINISTRATION	MEAN URINE CONCENTRATION (SD)
Amikacin	5	SQ	342 ± 143 µg/mL
Amoxicillin	11	PO	202 ± 93 µg/mL
Ampicillin	26	PO	309 ± 55 µg/mL
Cephalexin	18	PO	500 µg/mL
Chloramphenicol	33	PO	124 ± 40 µg/mL
Enrofloxacin	5	PO	40 10 µg/mL
Gentamicin	2	SQ	107 ± 33 µg/mL
Hetacillin	26	PO	300 ± 156 µg/mL
Kanamycin	4	SQ	530 ± 151 µg/mL
Nitrofurantoin	4.4	PO	100 µg/mL
Penicillin G	36,700 U/kg	PO	295 ± 211 µg/mL
Penicillin V	26	PO	148 ± 99 µg/mL
Sulfisoxazole	22	PO	1466 ± 832 µg/mL
Tetracycline	18	PO	139 ± 65 µg/mL
Trimethoprim/sulfadiazine	13	PO	55 ± 19 µg/mL
Tobramycin	2.2	SQ	66 ± 39 µg/mL

From Ling GV: Therapeutic strategies involving antimicrobial treatment of the canine urinary tract. J Am Vet Med Assoc 185(10):1162–1164, 1984; and Lulich JP, Osborne CA: Bacterial urinary tract infections. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine, 4th ed. Philadelphia, WB Saunders, 1999, pp 1775–1788.
SD, Standard deviation; *SQ,* subcutaneous; *PO,* per os (by mouth).

Iatrogenic UTI may be prevented by (1) avoiding indiscriminate use of urinary catheters, (2) using a closed collection system for indwelling urinary catheters, (3) using indwelling urinary catheters cautiously when pets are undergoing diuresis, (4) avoiding the use of indwelling catheters in immunosuppressed pets or those receiving immunosuppressive medications (e.g., glucocorticoids), (5) appropriately using antimicrobials with urinary catheterization, and (6) using diagnostic and therapeutic techniques that minimize trauma and microbial contamination of the urinary tract.[2] Although it would seem logical to administer antimicrobial agents while an indwelling urinary catheter is in place so as to decrease the chance of iatrogenic UTI, the practice is discouraged. Concomitant oral or parenteral administration of antimicrobial agents during indwelling urethral catheterization reduces the frequency of development of a bacterial UTI; however, it promotes the development of UTI caused by multidrug-resistant bacteria.[67]

262.5.2 Eradication of Underlying Causes

Although antimicrobial agents are the cornerstone of treatment of UTI, they should be used in a logical fashion. Overuse and misuse of antimicrobial agents may result in the emergence of resistant organisms, a situation that has implications for veterinary and human health. A UTI occurs in association with compromise of host defense mechanisms, which may be transient or permanent. Transient compromise often results in the development of a simple, uncomplicated UTI; however, permanent compromise results in the development of complicated UTI. Evaluation for and correction or control of the compromise or compromises in host defense mechanisms are important in the treatment of UTI, especially if these infections are recurrent (Figure 262-1). For example, recurrent bacterial UTI may occur in female dogs with a recessed vulva; vulvoplasty may help prevent future infections.[68,69]

262.5.2.1 Bacterial Urinary Tract Infection

262.5.2.1.1 Uncomplicated UTI

Uncomplicated UTIs are those in which no underlying structural, neurologic, or functional abnormality is identified. Dogs and cats with an uncomplicated UTI are usually successfully treated with a 10-to 14-day course of an appropriate antimicrobial agent (see Figure 262-1). If the proper antimicrobial is chosen and administered at the appropriate dosage and frequency, clinical signs should resolve within 48 hours. Also, the results of a complete urinalysis should improve within this same time frame. If possible, a urine culture should be performed 5 to 7 days after cessation of antimicrobial therapy.

262.5.2.1.2 Empiric antimicrobial treatment

Treatment of uncomplicated bacterial UTI of acute onset may be undertaken without the results of antimicrobial susceptibility testing, provided (1) that the dog or cat has not been given antimicrobial agents within the last 4 to 6 weeks and (2) that this is an initial or infrequent occurrence. In such situations, the antimicrobial should be chosen for its known properties and with knowledge of bacteria that commonly cause UTI (Table 262-5). Identification of bacteria on examination of urine sediment, especially if Gram's staining is performed, increases the likelihood of empirically choosing an appropriate antimicrobial. For example, *E. coli* is the most common cause of bacterial UTI in dogs and cats and is a gram-negative rod associated with aciduria. Staphylococci, on the other hand, are gram-positive cocci associated with alkaluria because they produce urease, which metabolizes urea to ammonia, resulting in an alkaline urine pH.

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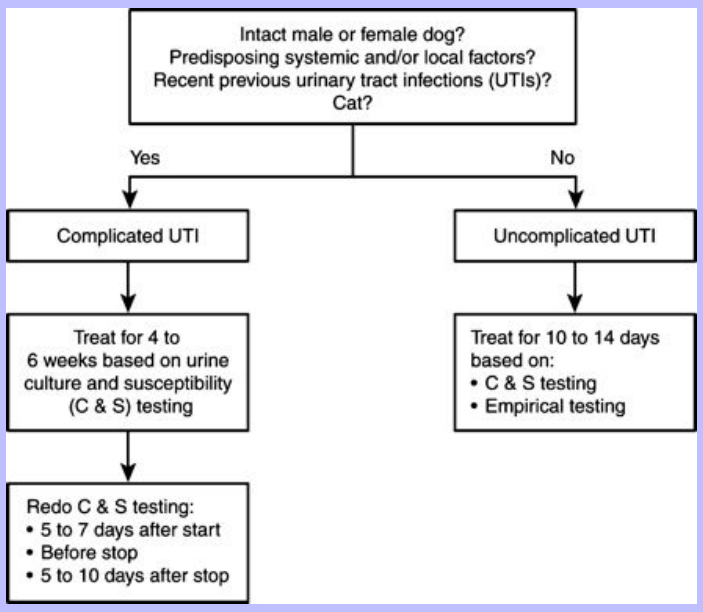
Figure 262-1 Algorithm for treatment of urinary tract infection (UTI) in dogs and cats. *C & S,* Urine culture and susceptibility testing.



The use of fluoroquinolones for empiric treatment of bacterial UTI is discouraged because of the inherent resistance of many gram-positive organisms and the developing resistance of many gram-negative organisms, especially *E. coli*, to this class of antimicrobials.[26,70]

Table • 262-5 Estimate of Susceptibility of Uropathogens to Commonly Used Antimicrobial Agents

UROPATHOGEN	DRUGS OF CHOICE	ALTERNATIVES
Enterobacter spp.	Trimethoprim-sulfadiazine	Cephalosporins (first and second generation), gentamicin, nitrofurantoin
*Escherichia coli**	Trimethoprim-sulfadiazine	Cephalosporins (first and second generation), fluoroquinolones, gentamicin
Klebsiella spp.*	Cephalosporins (first generation)	Amikacin, gentamicin, trimethoprim-sulfadiazine, cephalosporins (second and third generation)
Mycoplasma,* *Ureaplasma*	Fluoroquinolones	Tetracyclines
Proteus spp.*	Amoxicillin, ampicillin, amoxicillin-clavulanate	Cephalosporins (first and second generation), gentamicin, nitrofurantoin, trimethoprim-sulfadiazine
*Pseudomonas aeruginosa**	Fluoroquinolones	Tetracyclines, gentamicin, cephalosporins (first, second, and third generation)
Staphylococcus spp.*	Amoxicillin, ampicillin, amoxicillin-clavulanate	Cephalosporins (first generation), nitrofurantoin, trimethoprim-sulfadiazine
Streptococcus spp., *Enterococcus* spp.	Amoxicillin, ampicillin, amoxicillin-clavulanate	Cephalosporins (first generation), nitrofurantoin, trimethoprim-sulfadiazine

From Osborne CA, Lees GE: Bacterial infections of the canine and feline urinary tract. *In* Osborne CA, Finco DR (eds): Canine and feline nephrology and urology. Baltimore, Williams & Wilkins, 1995, pp 759–797.

* Prior treatment with antimicrobials may alter the susceptibility of uropathogens to these drugs.

262.5.2.1.3 Complicated UTI

Reproductively intact dogs, all cats, and animals with identifiable predisposing causes for UTI (e.g., renal failure, hyperadrenocorticism, and diabetes mellitus) should be considered to have a complicated UTI (see Figure 262-1). Pyelonephritis and prostatitis are examples of complicated UTI. Treatment with antimicrobials for longer than the routine 10 to 14 days may be indicated, and the drugs are usually administered for 4 to 6 weeks. The urine should be evaluated in the first week of treatment for response to therapy and also before discontinuation of therapy. Prophylactic antibiotic treatment may be necessary to control bacterial UTIs that are difficult to eradicate or that recur frequently.

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262.5.2.1.4 Recurrent UTI

262.5.2.1.4.1 Relapse

A *relapse* is defined as recurrence of a UTI caused by the same organism. Relapses usually occur within days to weeks of discontinuation of antimicrobial therapy. Possible causes of relapse include use of an inappropriate antimicrobial agent; administration of an appropriate antimicrobial agent at an inappropriate dosage, frequency, or duration; and complicating factors. A urine culture should be

evaluated prior to reinstitution of antimicrobial therapy, and further diagnostic evaluation for predisposing causes is indicated.

262.5.2.1.4.2

Reinfection

Reinfection is defined as infection with a different organism than that initially present. Reinfections usually occur some time after cessation of antimicrobial therapy. Although predisposing risk factors may be present, many animals that become reinfected do not have identifiable risk factors. If reinfection occurs infrequently, each episode may be treated as an uncomplicated UTI. However, if reinfection occurs more often than three times a year, the animal should be treated as having a complicated UTI. Additionally, prophylactic antimicrobial therapy may be indicated.

262.5.2.1.4.3

Superinfection

A *superinfection* occurs when a second bacterial organism is isolated while an animal is receiving antimicrobial therapy. This organism often displays a high degree of antibiotic resistance. A UTI that occurs in animals receiving antimicrobial therapy that also have an indwelling urethral catheter is an example of a superinfection.[67]

262.5.2.1.4.4

Prophylactic antimicrobial treatment

No good studies have evaluated prophylactic antimicrobial therapy in animals that have frequent reinfections. When prophylactic therapy is undertaken, urine culture and susceptibility testing should be done to ensure that the bacterial UTI has been eradicated. A drug should be selected that is excreted in high concentration in the urine and that is unlikely to cause adverse effects. Often a fluoroquinolone, cephalosporin, or beta-lactam antimicrobial is chosen. The antimicrobial should be given at approximately one third the therapeutic daily dose immediately after the pet has voided, and when the drug and its metabolites will be retained in the urinary tract for 6 to 8 hours. This is typically done at night. The drug is administered for a minimum of 6 months. Urine samples are collected, preferably by cystocentesis (not by catheterization, because this may induce a bacterial UTI) every 4 to 8 weeks for urinalysis and quantitative urine culture. If no evidence of bacterial UTI is found, prophylactic therapy is continued. If a bacterial UTI is identified, the active (break-through) infection is treated as a complicated bacterial UTI. If a break-through bacterial UTI does not occur after 6 months of prophylactic antimicrobial therapy, the therapy may be discontinued and the pet monitored for reinfection.[71,72]

262.5.2.1.4.5

Ancillary therapy

Many forms of ancillary therapy have been developed to aid in the treatment of UTI. Ancillary therapy includes urinary acidifiers, urinary antiseptics, local instillation of antimicrobial agents into the urinary bladder, alteration of urine volume, and the use of pharmacologic agents to affect the storage and voiding phases of micturition. Although the activity of antimicrobial agents is affected by the urine pH, rarely is alteration of the urine pH undertaken in an effort to increase activity. An exception is induction of aciduria when methenamine, a urinary antiseptic, is used.

Instillation of antimicrobial agents into the urinary bladder is ineffective and may be associated with complications. For example, instillation of gentamicin into a compromised urinary bladder may result

in absorption and attainment of toxic serum levels. If antimicrobial therapy is required, antimicrobials should be administered orally or parenterally. An instance when instillation of a pharmacologic agent into the urinary bladder may be beneficial is the use of a cystostomy catheter. A cystostomy catheter is inserted directly into the urinary bladder and exits the ventral abdominal wall. Instillation of Tris-EDTA through the cystostomy catheter into the urinary bladder after the bladder has been emptied of urine may decrease the incidence of bacterial UTI.[74]

262.5.2.2 Fungal Urinary Tract Infection

Fungal UTIs are rare in dogs and cats. They often are associated with glucosuria of diabetes mellitus but may also occur in animals that do not have diabetes. In one study of 20 dogs and cats with *Candida* spp. UTI, concurrent diseases or nonantifungal drugs administered within 1 month of isolation included antibiotics, corticosteroids, diabetes mellitus, nonurogenital neoplasia, and noncandidal urogenital disease. All animals had sources of local or systemic immune compromise that likely predisposed to infection.[12] Treatment of animals with a fungal UTI involves correction or control of the predisposing cause or causes, urinary alkalization, and administration of antifungal drugs. In animals without clinical signs, administration of urinary alkalinizing agents (e.g., potassium citrate or sodium bicarbonate) or the use of diets that induce alkaluria may result in successful eradication of the fungal UTI.[10] Fungal growth is inhibited in an alkaline medium. In animals with active disease, however, antifungal drugs that are excreted renally in an active form should be administered. Although amphotericin B is renally excreted and achieves high concentration in urine, it is not often used because it is parenterally administered and is nephrotoxic. Fluconazole is a good choice and is orally administered. Itraconazole may also be a good choice, but it has not been evaluated for the treatment of fungal UTIs in dogs and cats. Antifungal agents must be administered for several months in association with induction of alkaluria. Correction and/or control of the predisposing underlying disease is paramount in the treatment and prevention of fungal UTI.

262.5.2.3 Viral Urinary Tract Infection

Although viruses are associated with urinary tract disease in humans, their role in urinary tract disease in dogs and cats is unknown.[75,76] Viral infection of the lower urinary tract may be a cause of lower urinary tract disease in cats.[15,16]

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263 CHAPTER • 263 Prostatic Diseases

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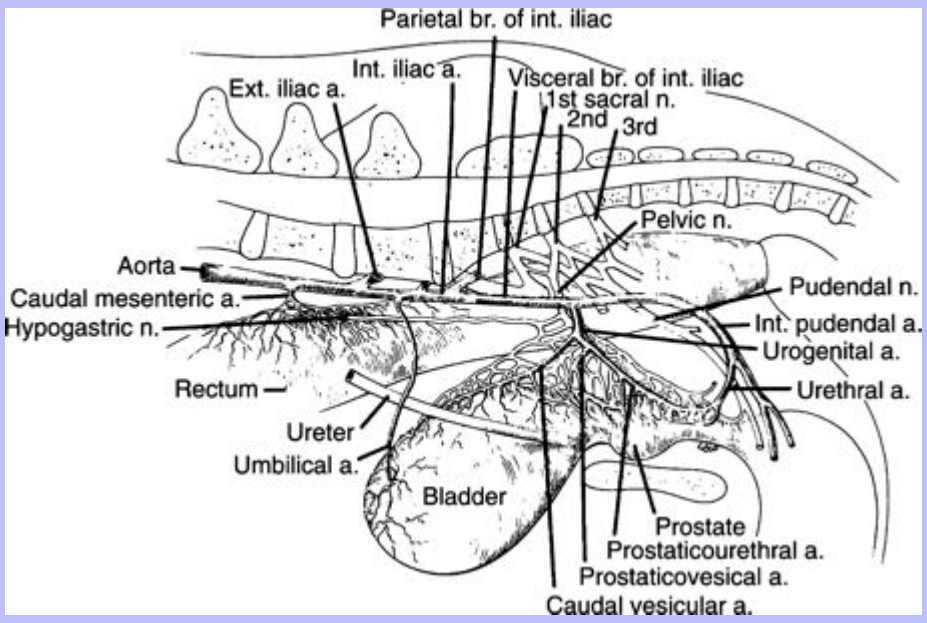
Amy Yeager

263.1 DEVELOPMENT AND ANATOMY

The embryologic development of the prostate begins from multiple outgrowths of the urethral epithelium.[1] During fetal development, testosterone secreted from the testes is reduced to dihydrotestosterone (DHT) in cells in the urogenital sinus, stimulating the formation of the prostatic lobes in the retroperitoneal space caudal to the urinary bladder (Figure 263-1).[2,3] Age, androgenic stimulus, disease, and the degree of urinary bladder distention affect the prostate's position. The gland is intra-abdominal in fetuses and pups less than 2 months old because of the urachal attachment that maintains the bladder in a cranioventral position.[4] The urachal remnant breaks down at about 2 months of age, at which time the prostate moves into an intrapelvic position.[3] Beginning about 8 months of age, androgenic stimulation arising from sexual maturity results in prostatic enlargement; the prostate is repositioned cranially over the pelvic brim as it increases in size, to a total or partial intra-abdominal position.[4] After castration, the prostate atrophies and returns to the intrapelvic position. The degree of urinary bladder distention also affects the prostate's position; specifically, a full bladder displaces the prostate intra-abdominally, whereas an empty bladder facilitates an intrapelvic position.[5]

The prostate is a bilobed, musculoglandular organ that completely encircles the proximal urethra between the membranous portion of the urethra and the neck of the urinary bladder. A capsule surrounds the prostate, and a prominent median septum divides the gland into two ovoid lobes that are dorsally flattened, with the ventral surface covered in a layer of fat.[3] Well-developed arrays of smooth muscle fibers from the capsule extend down into the parenchyma to blend with the smooth muscle of the urethra.[6] Numerous ducts open into the prostatic urethra at the colliculus seminalis, a central portion of the dorsal longitudinal urethral crest.[1] The deferent ducts enter the craniodorsal surface of the prostate and continue caudoventrally to open on each side of the colliculus seminalis.[1]

Figure 263-1 Diagram of the normal anatomic relationship of the prostate to other structures in the caudal abdomen. (Adapted from Miller ME et al: Anatomy of the Dog. Philadelphia, WB Saunders, 1964.)



The urogenital artery, a branch of the internal pudendal artery, supplies blood to the prostate via several prostatic branches through the dorsolateral surfaces (see Figure 263-1).[7] Several prostatic branches originate from the urogenital artery and enter the prostate gland at the dorsolateral surfaces. These branches tunnel beneath the capsule and further divide into smaller parenchymal arteries.[7] Venous drainage occurs via the urethral vein that accompanies the urethra or through small venules that follow the capsular arteries.[7] Lymphatic drainage is to the middle iliac lymph nodes.[3] The hypogastric and pelvic nerves provide sympathetic and parasympathetic innervation to the prostate (see Figure 263-1).[3] Parasympathetic stimulation during erection increases the rate of prostatic fluid production, and sympathetic stimulation during ejaculation ejects the fluid into the prostatic urethra.[8]

263.2 PHYSIOLOGY

In the dog, the prostate is the only accessory sex gland, and its secretory function is androgen dependent. Although both testosterone and DHT stimulate prostatic glandular activity, DHT is far more biologically active in that it binds to the androgen receptor with two times the affinity of testosterone and has a fivefold slower rate of dissociation.[9] In sexually mature dogs, the prostate comprises the compound tubular alveolar glands that radiate from the urethral duct openings.[10] In castrated and sexually immature dogs, the prostate comprises a branching ductular system with poor alveolar development.[10] Elimination of the androgenic stimulus, either pharmacologically or by castration, results in glandular and parenchymal atrophy of the prostate.[11] In addition to

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androgens, locally produced growth factors (i.e., endothelin-1, basic fibroblast growth factor, transforming growth factor-beta, interleukin-6, and interleukin-8) act to modulate prostatic alveolar development and function.[12]

Prostatic fluid makes up the first and third fractions of the ejaculate; it increases the volume of the ejaculate and possibly aids in sperm transport.[1] Prostatic fluid accounts for greater than 97% of the total ejaculate volume.[13] When neither micturition nor ejaculation is occurring, prostatic fluid is constitutively secreted and expelled into the prostatic urethra, from which it drains into the urinary bladder. Normal prostatic fluid is thin and clear. The major secretory product of the prostate is arginine esterase, which constitutes greater than 90% of the protein in the seminal plasma.[14] Prostate-specific antigen (PSA), the major seminal plasma protein in humans, is not detectable in canine serum or seminal plasma.[15] However, arginine esterase and PSA are both serine proteases and have similar molecular weights and hormonal regulation.[16] The canine prostate also secretes prostatic acid phosphatase.[15]

263.3 SIGNALMENT AND CLINICAL SIGNS

Most prostatic diseases are associated with prostatomegaly. Prostatic size correlates with body weight and age[17] (Table 263-1) as well as breed.[18] Scottish terriers are reported to have prostates four times larger than those of dogs of other breeds of similar weight and age.[18] Doberman pinschers and German shepherds were the breeds most commonly represented in a review of 177 cases of prostatic disease.[19]

Clinical signs associated with prostatic disease vary, depending on the degree of prostatomegaly and the specific disorder. Prostatic enlargement is common in dogs more than 5 years old. The most common clinical signs associated with prostatic disease are urethral discharge, hematuria, and tenesmus. However, patients with prostatic disease may be asymptomatic. The urethral discharge may be clear, purulent, or hemorrhagic. In a 14-year retrospective study of prostatic disease, hemorrhagic urethral discharge, which could be exacerbated by sexual arousal, was the only clinical sign observed in 23% of cases.[20] The source of the hemorrhage may be dilated prostatic urethral veins, which can be visualized with cystoscopy.[21] Greatly increased vascularity associated with hyperplasia, infection, or neoplasia in the prostatic parenchyma may be an additional source of hemorrhage.[22] Although widely described as a clinical sign associated with prostatic disease, tenesmus is present only when the prostate is morbidly enlarged. In one report, constipation developed after mineralization of a grossly enlarged paraprostatic cyst.[23] Additional clinical signs associated with prostatic disease include fever, cachexia, abnormal hindlimb gait, and caudal abdominal pain.

Table • 263-1 Formula for Calculation of Maximum Prostatic Measurements from Ultrasonographic Examination of Healthy Male Intact Dogs

DIMENSION	DEFINITION	FORMULA
Length	Diameter along urethral axis	(0.055 ×BW) +(0.143 ×A) +3.31
Width	Diameter perpendicular to axis of height^{T}	(0.047 ×BW) +(0.089 ×A) +3.45
Height^{S} (H^{S})*	Diameter perpendicular to axis of length	(0.046 ×BW) +(0.069 ×A) +2.68
Height^{T} (H^{T})†	Diameter along line separating two lobes	(0.044 ×BW) +(0.083 ×A) +2.25
Volume	[1/2.6 ×(Length ×Width ×[(H^{S} +H^{T})/2])] +1.8 cm^{3}	(0.867 ×BW) +(1.885 ×A) +15.88

Modified from Ruel Y et al: Vet Radiol Ultrasound 39:212, 1998; and from Kamolpatana K et al: Vet Radiol Ultrasound 41:73, 2000.
BW, Body weight; *A*, age.

* Height as measured from the sagittal view.

† Height as measured from the transverse view.

263.4 EXAMINATION OF THE PROSTATE AND PROSTATIC FLUID

263.4.1 Prostate

A cursory examination of the prostate can be performed by concomitant rectal and abdominal palpation. Rectal palpation permits examination of only the dorsal or dorsocaudal aspect of the prostate.[24] Concomitant abdominal palpation not only allows examination of the cranial aspects of the prostate, it also facilitates better palpation per rectum because the prostate can be pushed into or near the pelvic canal.[1] During palpation, the prostate should be evaluated for size, symmetry, surface contour, movability, and pain. The normal prostate is bilobed, symmetric, smooth, movable, and pain free.

Transabdominal ultrasonography is the best imaging modality for evaluation of the prostate because it is a safe, noninvasive method that allows for precise measurements as well as evaluation of the prostatic parenchyma. Dogs can be imaged in dorsal, dorsal oblique, or lateral recumbency. Because the haircoat is thin in the suprapubic area, clipping usually is not necessary. However, hair may be clipped from the ventral abdomen between the cranial aspect of the prepuce and pubic bone from the midline to the inguinal fold to facilitate imaging. Alcohol and/or coupling gel is applied to the skin to improve contact. A 5 to 10 MHz convex or sector transducer is recommended because of its 90-degree or greater field of view and because the transducer head can follow the body contour of the caudal abdomen better than that of a linear array transducer. To image the prostate, the transducer is placed against the ventral abdominal wall cranial to the pubis. The prostate should be imaged in both the sagittal (longitudinal) and transverse planes to ensure that all areas of the prostate are visualized. The true sagittal plane can be confirmed by observation of the hypoechoic urethral tract.

Prostate dimensions should be measured on both the sagittal and transverse planes (Figure 263-2). Prostate length and height should be measured on the sagittal images. Length is defined as the maximum prostatic diameter along the urethral axis, and height is defined as the maximum prostatic diameter perpendicular to the axis of the length. The transverse image of the prostate is then obtained by rotating the transducer 90 degrees. From the transverse image, height is defined as the prostatic diameter separating the two lobes, and width is defined as the maximum prostatic diameter perpendicular to the axis of the height. In a study of 100 healthy, intact male dogs, the maximum prostatic dimensions were reported, and the maximum predicted values of

prostate size were found to vary by age and body weight.[25] Formulas for calculating the maximum prostatic dimension in a normal, intact dog are presented in Table 263-1. Normal prostatic height on sagittal plane views for a dog castrated before 1 year of age is about 1 cm (Figure 263-3).

Figure 263-2 Sagittal **(A)** and transverse **(B)** ultrasonographic images of a normal prostate from an intact dog. The prostatic parenchyma is uniformly of medium texture and is moderately hyperechoic compared with surrounding structures, and the prostatic urethra *(U)* is hypoechoic. Note the anechoic bladder neck *(B)* and pubic bone shadow *(S)* on the sagittal image.

The ultrasonographic appearance of a prostate from a normal, intact dog should be uniformly fine-medium texture and moderately hyperechoic, an appearance similar to that of the spleen, with a capsule that is echoic and has smooth margins.[26] The urethra, which runs lengthwise through the middle of the two lobes, generally is hypoechoic compared with the prostatic parenchyma. In contrast, the ultrasonographic appearance of a

prostate from a castrated dog is slightly hypoechoic compared with surrounding fat and adjacent structures, such that the urethra is more difficult to visualize (see Figure 263-3). The echogenicity within the prostate should be assessed for focal, multifocal, or diffuse changes in echotexture. Increased echogenicity and coarse echotexture is associated with hyperplasia, inflammation, infection, and neoplasia. A more echogenic, butterfly-shaped hilar region may be imaged in the center of the prostate in the intact male dog (see Figure 263-2); this corresponds to collagen and epithelial tissue in the wall of the prostatic urethra and periurethral ducts.[27] The hilar echo may be masked by increased echogenicity caused by hyperplasia, inflammation, infection, and neoplasia. However, imaging of the hilar echo may be unreliable because of technical artifact.

Figure 263-3 Sagittal ultrasonographic image of a normal prostate from a castrated dog. Note the small size of the prostate (0.92 cm) and the slightly hypoechoic parenchyma compared with adjacent structures.

Ultrasonography also allows the examiner to determine whether cysts are present (or absent) in the prostate. The size, number, and location of the cysts should be characterized. The relative echogenicity of the luminal contents of the cysts should be characterized as hypoechoic or anechoic. Parenchymal mineralization may also be observed and is frequently associated with neoplasia. However, mineralization occasionally may develop with chronic inflammation.

Although ultrasonography can detect enlargement and changes in the internal prostatic architecture, these features are not pathognomonic for a specific disease. The ultrasonographic appearance of the prostate does not correlate well with culture results, nor does the presence and number of cysts factor into the incidence or type of infection encountered.[28] However, compared with radiography, ultrasonographic imaging is more sensitive for assessing focal or regional parenchymal disease.[29,30] Ultrasonography has also proved to be a useful technique for evaluating the response to pharmacologically induced prostatic involution.[31]

Ultrasonographic evaluation for prostatic disease should include evaluation of adjacent structures, including the urethra and urinary bladder. Primary urinary tract disease (e.g., infection, calculi, transitional cell carcinoma) may complicate or mimic prostatic disease. The sublumbar (medial iliac and hypogastric) lymph nodes should be evaluated. Enlargement and/or altered echogenicity may represent extension of prostatic disease into the regional lymph nodes. In addition, the smooth contour of the caudal lumbar vertebrae may

become irregular with metastasis of prostatic neoplasia, which may be more accurately diagnosed with a radiograph. In rare cases, when prostatic disease extends beyond the capsule, adjacent fat may become hyperechoic from edema, inflammation, fibrosis, or necrosis. Peritoneal fluid may be visible, and if so, analysis of the fluid may aid in the diagnosis of treatment.

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The location, size, and contour of the prostate can be evaluated with caudal abdominal radiography. A normal prostate does not displace the colon and bladder from their normal positions. Radiographically, the prostate has a soft tissue opacity, and its identification is influenced by the differential subject opacity of surrounding tissues. Radiographic diagnosis of prostatomegaly can be made when the prostate dimensions exceed 70% of the pubic-promontory distance on a lateral radiograph (Figure 263-4)[30] or 50% of the width of the pelvic inlet on a ventrodorsal radiograph.[32] However, neither of these methods accounts for the effects of age on prostate size. Often the exact dimensions of the prostate cannot be determined because of superposition of osseous structures or because of lack of abdominal serosal detail as a result of lack of fat, the presence of ascites, or focal peritonitis associated with prostatitis.[33] The ability of radiography to identify parenchymal changes associated with disease is limited to identification of mineralization, which may be insignificant or may be indicative of neoplasia or, less frequently, chronic inflammation. With caudal abdominal radiography, enlargement of sublumbar lymph nodes (medial iliac and hypogastric lymph nodes) may be observed, because it would cause ventral displacement of the colon. In addition, obvious lytic bone lesions involving the lumbar vertebral bodies and pelvic bones may be identified (Figure 263-5).

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Figure 263-4 Lateral radiograph of the caudal abdomen of a dog with marked prostatomegaly. The bladder is indicated by the cranial arrows and the prostate by the caudal arrows. (From Barsanti JA, Finco DR: Canine prostatic diseases. *In* Ettinger SJ [ed]: Textbook of Veterinary Internal Medicine, 3rd ed. Philadelphia, WB Saunders, 1989, p 1864.)

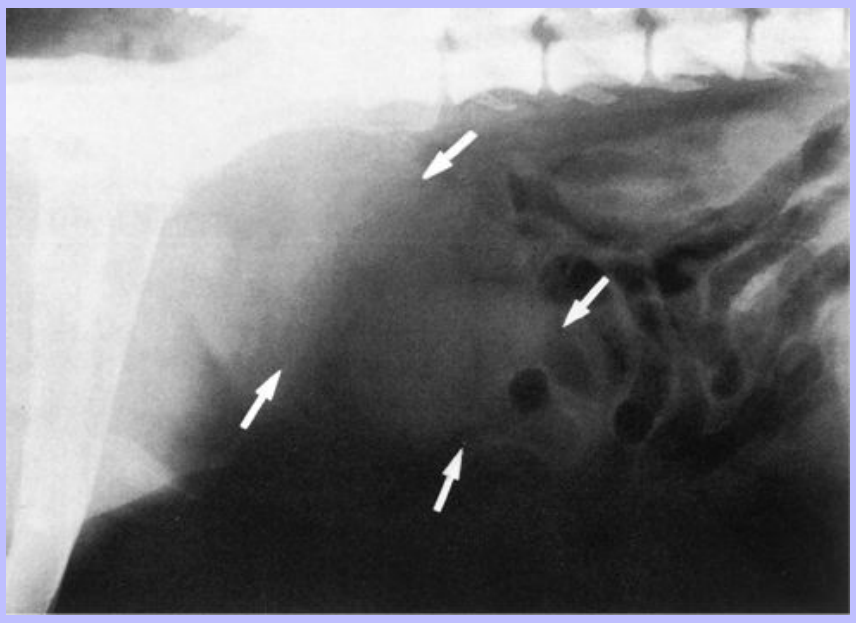
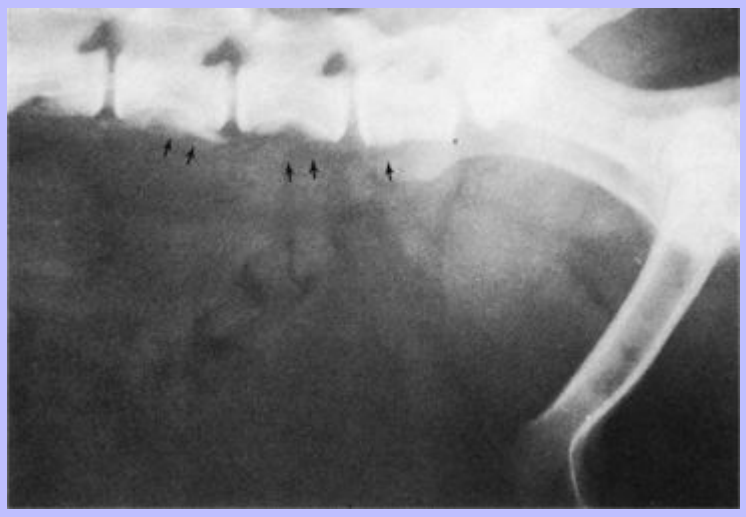


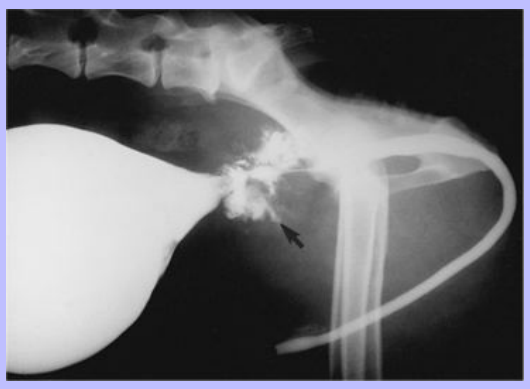
Figure 263-5 Early radiographic changes caused by prostatic adenocarcinoma. Proliferative changes *(arrows)* are indicative of early metastasis (L5-L7). (From Greiner TP, Johnson RG: Diseases of the prostate gland. *In* Ettinger SJ [ed]: Textbook of Veterinary Internal Medicine, 2nd ed. Philadelphia, WB Saunders, 1983, p 1474.)



Distention retrograde contrast urethrocystography (DRCU) has been described as a method for determining prostatic integrity. In a normal prostate, minimal positive contrast is identified in the prostatic parenchyma near the urethra (urethroprostatic reflux) (Figure 263-6).[34] However, accumulation of larger volumes of contrast material in the prostatic parenchyma (intraprostatic reflux) has been reported with all types of prostate diseases.[1] Irregularity or an undulant pattern to the prostatic urethral surface has been associated with benign prostatic hyperplasia, chronic bacterial prostatitis, and neoplasia (Figure 263-7).[30] Narrowing of the prostatic urethral diameter during DRCU has been reported to occur in association with benign prostatic hyperplasia, prostatic abscessation, and neoplasia.[30] Because the prostatic urethral diameter varies among normal dogs with the degree of bladder distention, changes in prostatic diameter must be interpreted cautiously.[35] In addition, the absence of positive results on contrast studies does not rule out the presence of prostatic disease.[30] In most cases, ultrasonography is a better method than DRCU for imaging prostatic integrity.

Figure 263-6 Distention retrograde contrast urethrocytogram from a normal dog. Note the small quantity of urethroprostatic reflux *(arrow)*. (From Root Kustritz MV, Klausner JS: Prostatic diseases. *In* Ettinger SJ, Feldman EC [eds]: Textbook of Veterinary Internal Medicine, 5th ed. Philadelphia, WB Saunders, 2000, p 1689.)

Figure 263-7 Distention retrograde contrast urethrocytogram from a dog with adenocarcinoma. Note the prostatomegaly and intraprostatic reflux of contrast agent (arrow). (From Root Kustritz MV, Klausner JS: Prostatic diseases. *In* Ettinger SJ, Feldman EC [eds]: Textbook of Veterinary Internal Medicine, 5th ed. Philadelphia, WB Saunders, 2000, p 1695.)

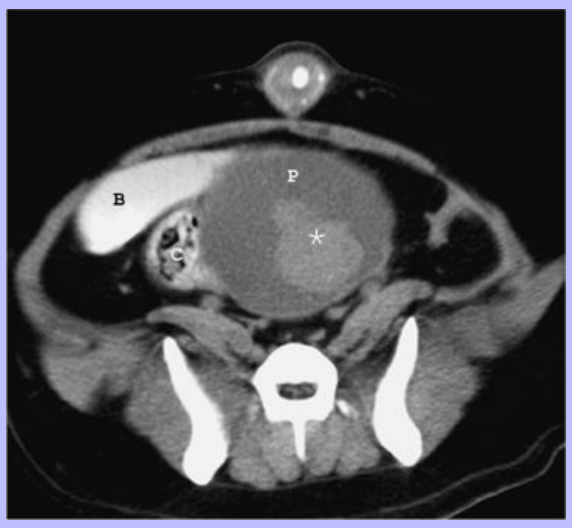


Computed tomography (CT) (Figure 263-8) and magnetic resonance imaging (MRI) are excellent modalities for imaging both the prostate and adjacent structures, where metastasis may be a concern. In humans, MRI is an accurate means of assessing changes in prostatic volume that is highly correlated with the weight of the excised prostate.[36] However, the veterinary literature has little information about the value of CT or MRI in the diagnosis of prostatic disease in the dog. Both of these imaging modalities are expensive, and both require immobilization of the dog with general anesthesia. Bone scintigraphy may be helpful for imaging osseous metastatic lesions before they can be identified by radiography.[37]

263.4.2 Prostatic Fluid

With any dog suspected of having prostatic disease, the prostatic fluid should be assessed by cytologic evaluation and quantitative bacterial culture. Prostatic fluid may be obtained either by ejaculation (collection of the third fraction) or by prostatic wash; the former method is preferred, especially when bacterial infection and concomitant cystitis are suspected. To ejaculate a dog, the prepuce is retracted caudally, and digital pressure is applied to the base of the penis, proximal to the bulbus glandis (Figure 263-9). Intense pelvic thrusting occurs with ejaculation. Prostatic fluid can be collected aseptically by ejaculation as long as care is taken (1) to change collection containers after the combined first and second fractions have been collected and (2) to ensure that the tip of the penis does not touch the inside of the sterile collection container. The combined first and second fraction sample should be saved for semen evaluation if indicated. Cytologic evaluation of the prostatic fluid aids in the determination of whether contamination occurred during ejaculation; specifically, the presence of squamous epithelial cells with gram-positive cocci in conjunction with an absence of neutrophils indicates that contamination occurred during collection.[38]

Figure 263-8 Transverse computed tomograph of the caudal abdomen of a dog with profound prostatomegaly *(P)* displacing the colon *(C)* and bladder *(B)*. Positive contrast was introduced into the bladder prior to examination. Note the irregular, high attenuating mass in the prostate *(*)*.



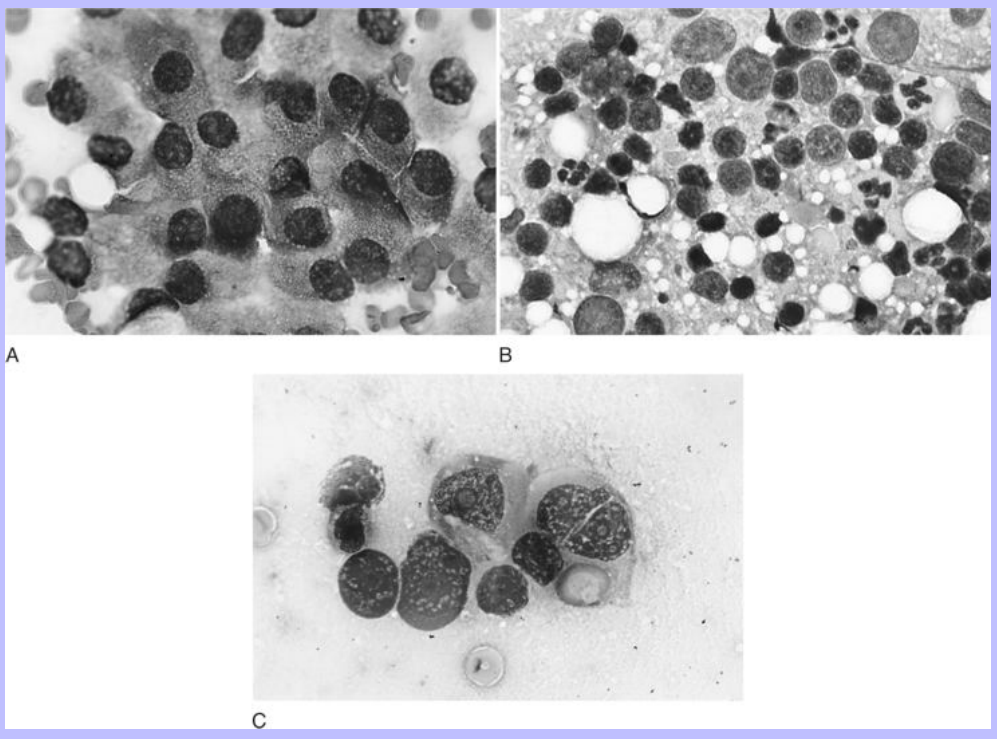
If the dog will not ejaculate, a prostatic wash should be performed (see Chapter 84). Using aseptic technique, the bladder is catheterized, and urine is removed. The bladder then is flushed with 5 mL of sterile saline, and this sample is saved (PM-1).[38] The catheter subsequently is retracted so that the tip is distal to the prostate. The prostate then is massaged per rectum for about 1 minute to express a quantity of prostatic fluid into the urethra, where it can be collected with a urinary catheter. Sterile saline (5 mL) is slowly injected while the urethral orifice is occluded. The catheter is advanced into the bladder as aspiration is performed, and the sample (PM-2) is collected. The prostatic wash sample should be fixed on a glass slide, stained with hematoxylin-eosin, and evaluated for cellularity (Figure 263-10). Comparison of the cytologic examination and quantitative bacterial culture results from both prostatic wash specimens (PM-1 and PM-2) allows the precise location of the problem to be determined.[1] If lower urinary tract infection is present, before the prostatic wash is performed, the dog should be treated with an appropriate antibiotic (e.g., ampicillin) that does not penetrate the prostate. After the infection has been successfully treated, the wash may be performed. Prostatic massage is not with-out risks. In cases of acute prostatitis or prostatic abscess, there is a risk of creating a septicemia by forcing bacterial organisms into the blood stream or of causing peritonitis.[1] Also, uncertainty exists as to whether prostatic fluid has been expressed.

Figure 263-9 Collection of prostatic fluid (third fraction) by means of ejaculation.

Fine needle aspiration may also be used for collecting prostatic fluid samples.[1] For this technique, the skin surface through which the needle is to be inserted should be clipped and surgically scrubbed. Once the needle enters the prostate, aspiration should be performed as the needle is redirected several times within the gland. Negative pressure is then slowly released, and the needle is withdrawn. In some cases, fine needle aspirate samples are nondiagnostic. If prostatic neoplasia is suspected, a prostatic biopsy, rather than a fine needle aspirate, may be necessary.[39] In one study, complications associated with fine needle aspiration included hematuria and periprostatic hemorrhage.[38,40] In another report, a sterile intraprostatic cyst was aspirated and

developed into a prostatic abscess.[41] Fine needle aspiration therefore may pose an increased risk of complications in febrile animals or those with leukocytosis or before examination of prostatic fluid obtained by ejaculation or prostatic massage.[1]

Figure 263-10 Prostatic wash samples from a normal dog **(A)**, a dog with adenocarcinoma **(B)**, and a dog with transitional cell carcinoma **(C)**. (×100 magnification.)



Cytologic examination of prostatic fluid can identify inflammation but cannot be used in place of bacterial culture to identify infection.[42] Low numbers of neutrophils (fewer than 5 per high-power field) can normally be found in voided urine and in an ejaculate.[1] Prostatic inflammation and infection are well correlated with the appearance of macrophages in prostatic fluid.[42] However, the severity of inflammatory infiltrate is well correlated with the type or number of bacteria present.[28] Quantitative bacterial cultures yielding equal to or greater than 2 $\log_{10}$ of one or more bacterial species in prostatic fluid samples, compared with the number of colonies of the same species in paired urethral or urine samples, is indicative of prostatic infection.[43] Urine bacterial culture results are well correlated with prostatic fluid culture results, such that cystocentesis is a safer alternative than fine needle aspiration of the prostate if prostatic fluid cannot be collected by ejaculation or prostatic wash.[42]

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The prostatic fluid pH in dogs with experimental prostatic infection (pH 6.3) did not significantly differ from that in dogs without infection (pH 6.25).[42] It is unclear whether prostatic fluid arginine esterase levels would

be useful in the diagnosis prostatic disease. In one study, serum arginine esterase levels were significantly higher in dogs with benign prostatic hyperplasia compared with normal dogs, dogs with bacterial prostatitis, and dogs with prostatic neoplasia.[44] In another study, although dogs with benign prostatic hyperplasia had higher arginine esterase levels than normal dogs, the levels were not significantly different from those in dogs with bacterial prostatitis or prostatic neoplasia.[15] Serum and seminal acid phosphatase levels showed no difference when normal dogs were compared with those with prostatic diseases or among different prostatic disorders.[15]

Careful selection and preparation of dogs for biopsy are essential. Prostatic biopsies are not recommended if bacterial prostatitis is suspected unless neoplasia is also suspected or the existence of chronic bacterial prostatitis can not be confirmed by other tests.[1] Antibiotics should be started 48 hours before a prostatic biopsy is performed if bacterial infection is suspected. A fluid-or air-filled urethral catheter can be passed before prostatic biopsy samples are taken to avoid damage to the prostatic urethra.[40] The biopsy site should be clipped and prepared aseptically. “Blind” prostatic biopsies are not recommended. Ultrasonographic guidance should be used for a prostatic biopsy because it provides continuous, real-time imaging of biopsy instrument placement; this reduces the risk of postbiopsy complications (hematuria, dissemination of infection, laceration of major blood vessels, urethral fistulation, orchitis, inadvertent puncture of adjacent organs).[1] In addition, ultrasonographic guidance increases the diagnostic yield of the biopsy sample, because the needle can be directed into what appears to be diseased tissue. The ultrasound transducer should be covered with a sterile sleeve, and sterile acoustic coupling gel should be used (Figure 263-11). The biopsy instrument can be introduced with a clip-on ultrasound guide or by freehand. The clip-on guide ensures that the needle remains in the plane of the sound beam. However, the guide limits the maneuverability of the biopsy instrument and may itself be awkward. The biopsy instrument should be directed tangentially to avoid the central prostatic urethra.[45] We prefer to use the spring-loaded Tru-Cut biopsy instrument.

Figure 263-11 Ultrasonographic guidance during biopsy minimizes the risk of complications and maximizes the diagnostic value of the sample.

263.5 BENIGN PROSTATIC HYPERPLASIA

Benign prostatic hyperplasia (BPH) is the most common prostate abnormality in intact male dogs and is estimated to occur in 100% of old, intact dogs.[6] Androgens are essential for the development and maintenance of BPH. However, with age, a modest decrease in the serum testosterone concentration, combined with no change in the serum estradiol-17-beta concentration, results in a relative decrease in the serum androgen to estrogen ratio.[10] This altered hormonal milieu is believed to contribute to the pathogenesis of BPH by increasing androgen receptor expression.

Histologic evidence of BPH develops at an early age. In a study of beagles, 16% had evidence of BPH at 2 years of age, and 50% had evidence of BPH at 4.1 to 5 years of age.[46] Electron microscopic analyses revealed that the volume densities of rough endoplasmic reticulum and secretory granules were significantly lower in the prostatic epithelial cells from dogs less than 1.5 years of age compared with older dogs.[47] After 4 years of age, intraparenchymal cyst formation may accompany BPH as a result of obstruction of parenchymal ducts that causes accumulation of prostatic secretions. In intact male dogs with no clinical evidence of urologic problems, the prevalence of intraparenchymal cyst formation is 14%.[25,48] The histologic pattern of BPH with intraparenchymal cyst formation shows areas of glandular hyperplasia, foci of atrophy, and chronic inflammation (lymphocytes and plasmocytes) in the stroma.[10] Intraparencymal cyst formation may predispose the prostate to bacterial infection.

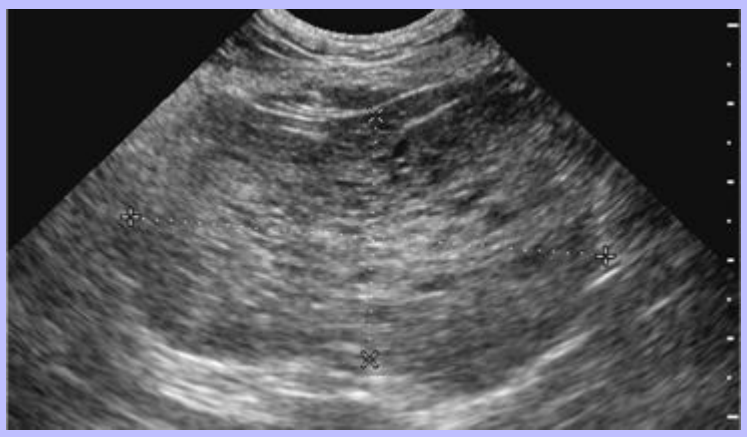
The diagnosis of BPH is made indirectly by elimination of other types of prostatic disease. A definitive diagnosis of BPH requires histopathologic confirmation.[19] However, it is difficult to justify a prostatic biopsy when the results of less invasive methods strongly support the diagnosis of BPH and the absence of more sinister prostatic diseases.[38] A presumptive diagnosis of BPH is based on the history, clinical signs, prostatic imaging, and prostatic fluid cytology and culture. Clinical signs associated with BPH include hemorrhagic urethral discharge, hematuria, hemospermia, and tenesmus. In one study in which hemorrhagic urethral discharge was the only sign of prostatic disease, 95% of the dogs had only BPH.[20] However, it is important to mention many dogs with BPH show no clinical signs. In a study on prostatic disease in 177 dogs, nearly half of the histologically confirmed cases of BPH had no clinical signs.[19] BPH may only become a clinical problem once it results in pressure on the colon or if it encroaches on the muscles and nerves in the pelvic canal.

On palpation, BPH produces a symmetrically enlarged prostate with a normal contour, although intraparenchymal cyst formation may result in some degree of asymmetry.[49,50] The ultrasonographic appearance of a prostate from a dog with BPH typically is moderately enlarged with symmetric, smooth margins and normal to slightly increased echogenicity.[51] The central hilar echo may be absent, and small, anechoic cysts in the parenchyma may be present.[52] (See Figure 243-12.) Cytologic evaluation of prostatic fluid from dogs with BPH reveals epithelial dysplasia without significant inflammation or any neoplastic changes.[53] If inflammatory cells are present, most of them (greater than 80%) are mononuclear cells (lymphocytes and plasmocytes).[54] Quantitative bacterial culture from prostatic fluid should be fewer than 100 bacteria per milliliter.[15]

For nonbreeding males, the recommended treatment for BPH is castration. Prostatic size significantly decreases within 7 to 10 days after castration.[55] Medical treatments are not as effective as castration in reducing prostatic size,[20,56] but they do offer an alternative for owners who decline surgery. Finasteride (Proscar®, Merck), a

5-alpha-reductase inhibitor, prevents conversion of testosterone to DHT[57,58] and produces a dose-dependent regression in prostate size.[59] At a daily oral dose of 0.1 to 0.5 mg/kg (5 mg of Proscar® per 10 to 50 kg body weight), finasteride reduces prostatic volume and secretory function by 43% in 16 weeks without adversely affecting semen quality.[60] However, the effects of finasteride are reversible within less than 8 weeks of discontinuation of treatment.[61] Finasteride is potentially teratogenic to male fetuses if pregnant females are exposed to the drug during the first third of gestation.

Figure 263-12 Transverse ultrasonographic image of a prostate with benign hyperplasia. Note the enlarged size, absence of hilar echo, and presence of many small cysts (too numerous to count) with anechoic luminal contents.



Several antiandrogenic drugs (chloradinone acetate,[58] osaterone acetate,[62] delmadinone acetate,[53] flutamide,[31] and megestrol acetate[50,63]) are effective at reducing prostatic size but can adversely affect gonadal function and are not recommended for use in breeding animals. Estrogens have also been used to treat BPH; however, because of the risk of myelosuppression and prostatic abscess formation, they are no longer a recommended treatment. The liposterolic extract of saw palmetto plant berries or the American dwarf palm tree *(Serenoa repens)* reportedly improves urinary flow rates in humans with BPH. However, treatment with *S. repens* for 91 days had little effect (positive or negative) in dogs.[64] In humans, BPH originates from the transition zone, a unique inner region of the prostate to this species, where its growth can impinge upon the urethra.[65] This differs from dogs, in which BPH is a diffuse process that develops from the peripheral terminal glands, expanding away from the urethra,[66] which may explain the differences observed with *S. repens* therapy.

263.6 CHRONIC BACTERIAL PROSTATITIS

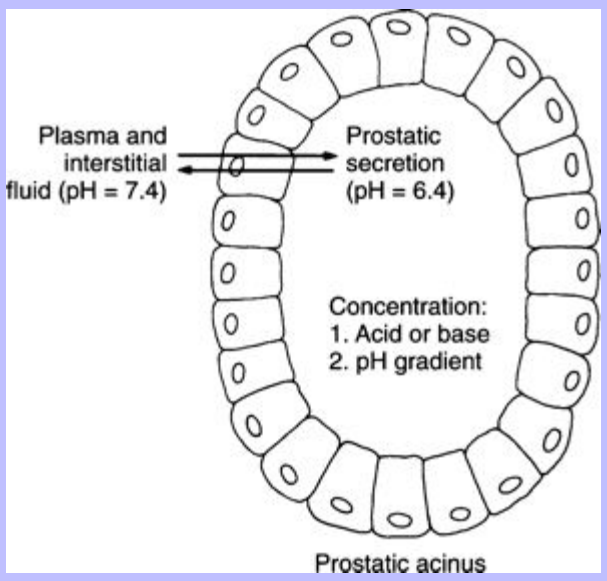
Chronic bacterial prostatitis (CBP) is the second most common prostate disorder in intact male dogs. It often occurs in conjunction with BPH. Bacterial infection of the prostate may arise by extension of bacteria from the urethra or by a hematogenous route. The pathogenic agent is usually common to the distal urinary tract (e.g., *Escherichia coli, Pseudomonas* and *Proteus* spp., staphylococci, and streptococci). *Brucella canis* may also cause CBP. However, gram-negative enteric organisms, particularly *E. coli*, are the most common cause.[67]

Clinical signs associated with CBP include recurrent urinary tract infection, hematuria, purulent or sanguineous urethral discharge, tenesmus, and constipation. Recurrent urinary tract infection caused by the same pathogen is a hallmark of CBP, because the pathogen persists in the prostate during antimicrobial therapy for the bacteriuria. Although the urine can be sterilized and the signs controlled during therapy, discontinuation of treatment leads to reinfection of the urine and recurrence of clinical signs.[68] Constant or intermittent dripping of sanguineous or purulent exudate from the penis independent of urination, another common finding with CBP, is attributed to an increase in the secretory rate of prostatic fluid induced by infection.[1] Constipation may occur secondary to CBP, because the dog may attempt to avoid pain induced by defecation.[1]

The diagnosis is based on the history, clinical signs, prostatic imaging, and prostatic fluid cytology and culture. The ultrasonographic appearance of a prostate from a dog with CBP (i.e., coarsely hyperechoic throughout the parenchyma) may be indistinguishable from that of BPH.[51] Regions of heterogenous echotexture and dystrophic mineralization, caused by fibrosis and chronic inflammation, may be indistinguishable from neoplasia.[52] Cytologic evaluation of prostatic fluid reveals degenerative neutrophils. Quantitative bacterial culture results show more than 10,000 bacteria of a single species per milliliter of seminal plasma.[15] In contrast to humans, the prostatic fluid pH, specific gravity, and cholesterol zinc concentrations are not reliable indicators for CBP.[69]

Chronic bacterial prostatitis is difficult to treat because most antimicrobial agents useful against the pathogens diffuse poorly into prostatic fluids (blood-prostate barrier). If left untreated, CBP can extend through the capsule into the abdomen, resulting in peritonitis.[33] In the absence of a specific secretory or active transport mechanism, an antimicrobial's ability to cross an epithelial membrane depends on its pKa and its lipid solubility (Figure 263-13). The pKa is the pH at which a drug exists equally in both ionized and nonionized forms. Only nonionized forms can cross epithelial membranes. Basic drugs (e.g., trimethoprim-sulfamethoxazole, erythromycin, clindamycin) diffuse easily from blood (pH 7.4) to prostatic fluid (pH less than 7.0).[42,68,70] Both chloramphenicol and enrofloxacin readily cross epithelial membranes; however, ciprofloxacin does not penetrate the prostate well.[71] Drugs with low lipid solubility do not cross epithelial membranes (e.g., ampicillin, penicillin, cephalothin). Antibiotics should be continued for 4 to 6 weeks, regardless of earlier disappearance of clinical signs. Prostatic fluid should be recultured 3 to 7 days after discontinuation of the antibiotics. Adjunctive treatment for CBP includes elimination of BPH. In one study in which CBP was experimentally induced with *E. coli,* castrated dogs cleared the infection within 4.2 weeks, compared with 9.5 weeks for intact dogs.[72] Because 5-alpha-reductase inhibitors also reduce prostate size and secretory function, medical treatment with finasteride should be included if owners decline surgery.

Figure 263-13 Factors determining the diffusion and concentration of antimicrobial drugs across the prostatic acinar epithelium. (From Stamey TA: Pathogenesis and Treatment of Urinary Tract Infections. Baltimore, Williams & Wilkins, 1980.)



263.7 PROSTATIC CARCINOMA

Prostatic carcinoma arising from the glandular or ductal epithelial cells occurs in intact and castrated dogs and is the most common prostate disorder in castrated dogs.[6] Castration at any age has not shown a sparing effect on the development of prostatic carcinoma[73]; however, the influence of early age castration (less than 8 weeks of age) has not been evaluated. Prostatic carcinoma is seen primarily after 6 years of age. Benign prostatic neoplasia has not been reported, and metastasis is common, usually developing in the sublumbar lymph nodes, lumbar vertebral bodies (see Figure 263-5), and lungs.

The diagnosis of prostatic carcinoma is made based on the history, clinical signs, and results of prostatic imaging, fluid analysis, and histopathology. Clinical signs of prostatic carcinoma were reported from 76 dogs and included hematuria, stranguria, and incontinence (62%); tenesmus associated with prostatomegaly (30%); musculoskeletal system involvement (36%); and weight loss and anorexia (42%).[74] In intact dogs, prostatic carcinoma is not always associated with prostatomegaly. However, in castrated dogs, prostatomegaly is highly associated with prostatic carcinoma (Figure 263-14). On palpation, the prostate may be normal in size but may feel firm and asymmetric and adhered to the pelvic canal. Ultrasonographically, a prostate from a dog with prostatic neoplasia typically appears large and irregularly shaped with hyperechoic and heterogenous foci (Figure 263-15).[51,52] Additional ultrasonographic findings from prostatic neoplasia may include areas of mineralization, parenchymal cysts (Figure 263-16), involvement of the bladder neck, capsular disruption with extension into adjacent fat and the peritoneal cavity, irregular contour of caudal lumbar vertebral bodies, and large, heterogenous sublumbar

lymph nodes (Figure 263-17). The appearance of neoplastic cells on prostatic fluid cytologic examination is diagnostically significant, but not finding neoplastic cells does not eliminate the possibility of neoplasia.

Figure 263-14 Necropsy specimen of a prostate *(P)* and bladder *(B)* with adenocarcinoma. Note the irregular contour and cyst formation *(arrow)*.

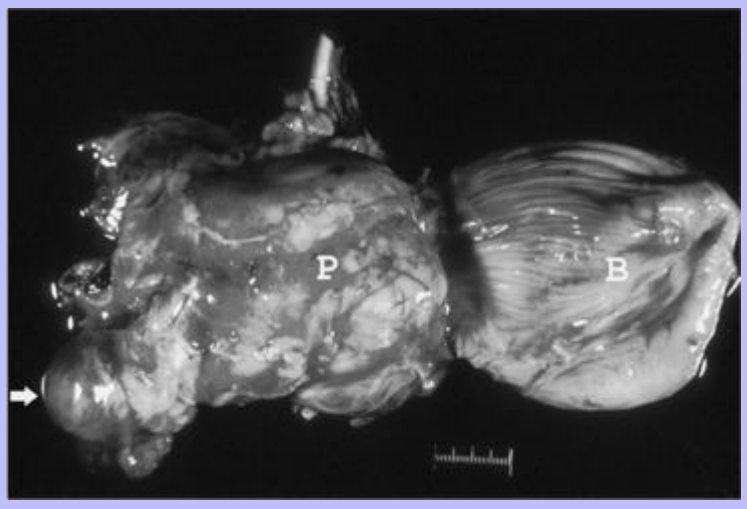


Figure 263-15 Sagittal ultrasonographic image of a prostate with adenocarcinoma. Note the hyperechoic and hypoechoic areas and irregular capsule typical of this lesion. (From Root Kustritz MV, Klausner JS: Prostatic diseases. *In* Ettinger SJ, Feldman EC [eds]: Textbook of Veterinary Internal Medicine, 5th ed. Philadelphia, WB Saunders, 2000, p 1696.)

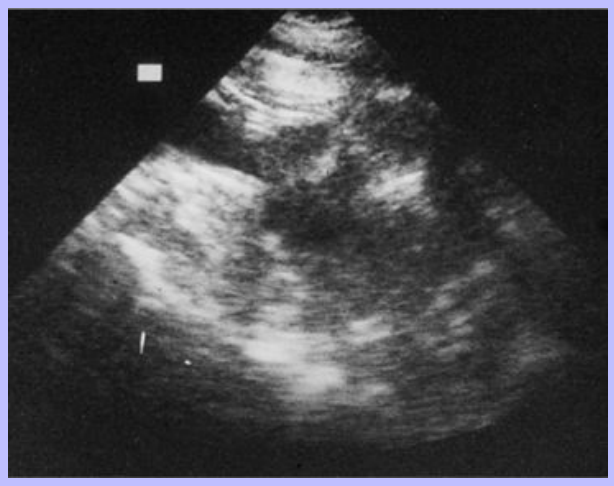


Figure 263-16 Sagittal **(A)** and transverse **(B)** ultrasonographic images of a prostate with adenocarcinoma. Note the enlarged size of the prostate for a castrated male dog, and the increased echogenicity and presence of large, coalescing cysts with hypoechoic luminal contents. The ultrasonographic appearance of a prostatic cyst or abscess may be similar to that of a prostatic carcinoma, and the diagnosis should be confirmed by prostatic fluid analysis and/or prostatic biopsy.

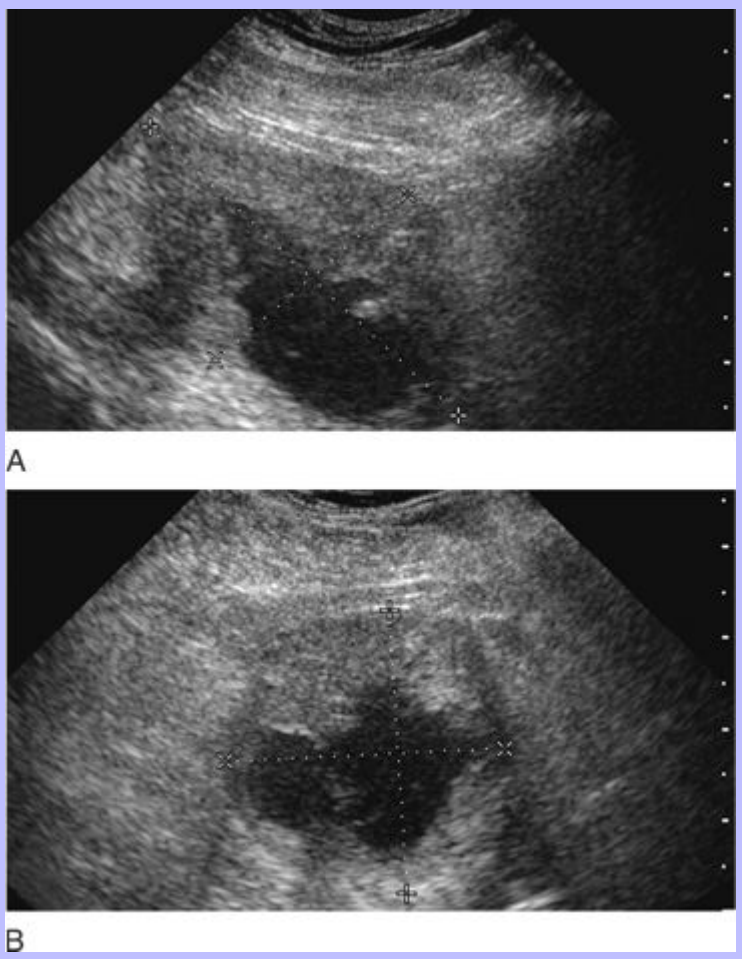


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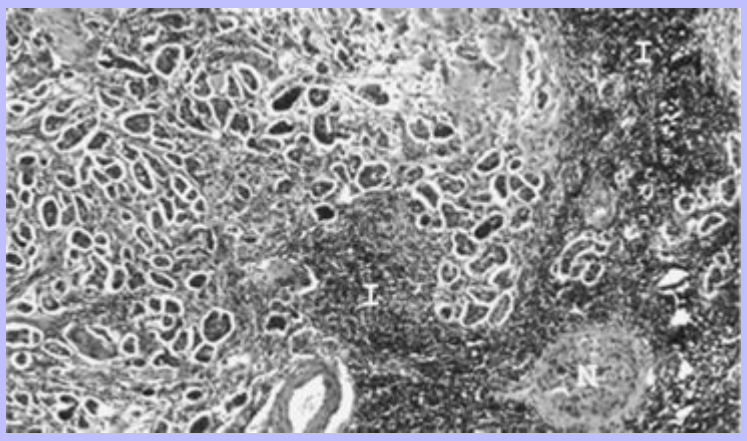
Figure 263-17 Sagittal ultrasonographic image of a mildly enlarged and abnormally hypoechoic medial iliac lymph node *(LN)* from the dog in Figure 263-13 with prostatic adenocarcinoma.

Adenocarcinoma is the most frequent histologic type of prostatic neoplasia, although more than half show intratumoral heterogeneity.[74] Histologic features of prostatic carcinoma include variation in glandular acinar size, shape, and spacing, with acinar cells containing enlarged nuclei and prominent nucleoli (see Figure 263-18).[74] Prostatic intraepithelial neoplasia (PIN), a common precursor prostatic neoplasia in humans, has been reported in the prostates of older dogs with and without neoplasia.[75] In dogs with prostatic neoplasia, the occurrence of PIN (7% to 66% of dogs with prostatic neoplasia) is too variable to be clinically useful.[74–76] Tumor markers frequently used in human medicine, such as PSA and prostatic acid phosphatase, are not useful in the diagnosis of prostatic neoplasia in the dog.[77]

The prognosis for dogs with prostatic neoplasia is poor. Treatment is primarily palliative and includes complete or partial resection of the prostate. There is no evidence that canine prostatic neoplasia is androgen dependent. Castration is recommended, however, because BPH can occur concurrently and may contribute to clinical signs associated with prostatomegaly.

Intraoperative orthovoltage radiotherapy (radiation therapy to surgically exposed prostate tumors) is currently the best adjunctive treatment for dogs without evidence of metastases, because it has the longest survival times (longer than 9 months).[78] Daily treatments (Monday through Friday) with external beam radiation therapy (43 to 54 Gy in 2.7 to 3.3 Gy fractions for 19 to 28 days) are reported to have limited success, with the complication of colitis developing in 56% of cases.[79] The use of radiation potentiators, such as cisplatin (OPLA-Pt), in conjunction with external beam radiation therapy reportedly increases survival times.[79]

Figure 263-18 Histopathology from the prostate in Figure 263-14. Note that, compared with the normal prostatic epithelial cells *(N),* the neoplastic epithelial cells are irregularly arranged and are not bordered by a basement membrane. Inflammatory infiltrate *(I)* is also evident.



Piroxicam, a specific cyclo-oxygenase-1 (COX-1) inhibitor, administered at a dosage of 0.3 mg/kg given orally once a day, has been used successfully to reduce the size of several canine carcinomas.[80–82] In one study, combining cisplatin treatment (60 mg/m^2 given intravenously every 21 days) with piroxicam therapy resulted in complete or partial tumor remission in 71% dogs, compared with no tumor remission with cisplatin therapy alone.[83] *In vitro* experiments suggest that piroxicam treatment will be effective in the treatment of prostatic adenocarcinoma.[84]

Treatment options currently under investigation include endothelin receptor antagonists and tyrosine kinase inhibitors. Atrasentan, a selective endothelin A receptor antagonist, significantly delayed the progression of metastatic, androgen-refractory prostatic neoplasia in humans at a dosage of 10 mg given orally once a day.[85] Tyrosine kinase inhibitors (CEP-751, CEP-701) inhibit the growth of prostatic neoplasia in rats regardless of androgen sensitivity and metastatic ability.[86] Another potential treatment option for prostatic carcinoma is photodynamic therapy (PDT). Researchers have investigated the biologic responses of the prostate and adjacent vital structures to two photosensitizers, meso-tetra-(m-hydroxyphenyl) chlorin and aluminum disulfonated phthalocyanine, but the completeness of treatment and long-term therapeutic effectiveness in prostate cancer have yet to be determined.[87]

263.8 ACUTE BACTERIAL PROSTATITIS AND PROSTATIC ABSCESS

Acute bacterial prostatitis and prostatic abscesses are uncommon in dogs. The occurrence of prostatic abscesses has been associated with BPH[88] and administration of estrogen.[1] Clinical signs associated with acute bacterial prostatitis and prostatic abscesses include anorexia, fever, depression, vomiting, gait abnormalities, and caudal abdominal pain. Neutrophilia with a left shift is also seen. The ultrasonographic appearance of acute bacterial

prostatitis is that of a normal-sized prostate with a hypoechoic parenchyma containing small cysts, whereas the ultrasonographic appearance of a prostatic abscess is that of prostatomegaly and one or more large anechoic cysts.[52]

Although the clinical signs may be similar, therapeutic differences between these two diseases make the treatment of acute bacterial prostatitis and prostatic abscess distinctly different. Acute bacterial prostatitis can be treated with an appropriate antimicrobial, as determined by culture and sensitivity, because the prostatic-blood barrier has been breached by infection.[89] Prostatic abscesses, on the other hand, do not resolve with antimicrobial treatment alone. Traditionally, prostatic abscesses have been treated by drainage through a capsulectomy incision via celiotomy. Marsupialization through the abdominal wall has been described but is associated with many complications, including prolonged recovery time, recurrent abscessation, dysuria, urinary incontinence, and septic peritonitis. Alternatives to marsupialization, reportedly associated with a lower risk of complications, include a modified Penrose drain technique[90] or omentalization (inserting omentum through the capsulectomy).[91,92] Surgery texts should be consulted for a more complete description of the techniques. Nonsurgical methods for treating prostatic abscesses have also been reported, with results showing varying efficacy. Antimicrobial therapy in conjunction with castration has been ineffective at resolving prostatic abscesses.[91] However, percutaneous, ultrasonographically guided drainage followed by alcoholization of the cavity was effective at resolving a prostatic abscess in one dog.[88]

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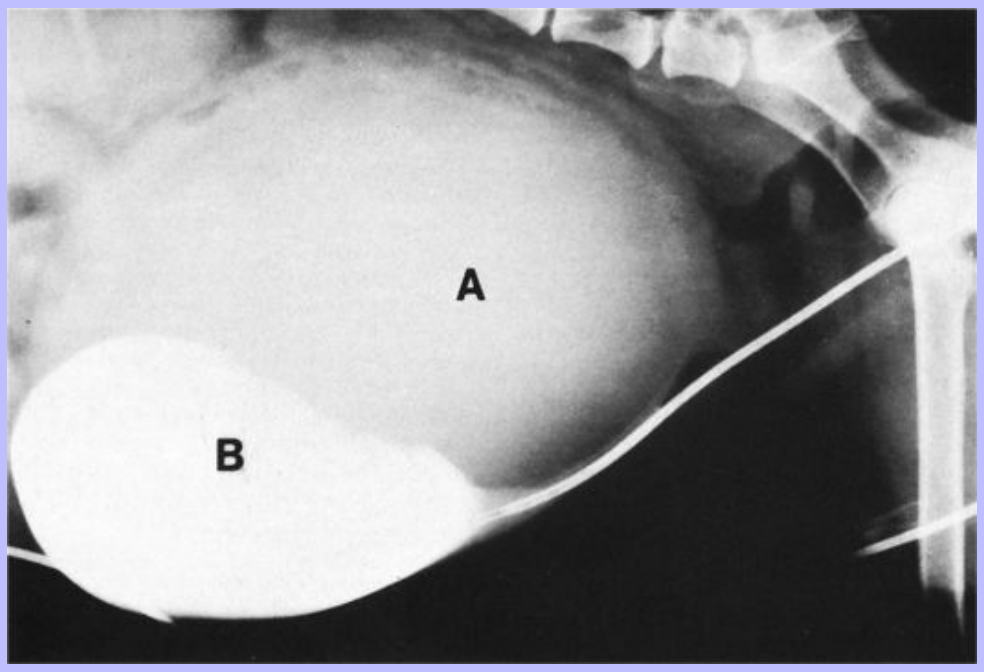
Figure 263-19 Large paraprostatic cyst *(A)* demonstrated with use of contrast material to outline the bladder *(B)*. (From Greiner TP, Johnson RG: Diseases of the prostate gland. *In* Ettinger SJ [ed]: Textbook of Veterinary Internal Medicine, 2nd ed. Philadelphia, WB Saunders, 1983, p 1477.)



263.9 PARAPROSTATIC CYST

The etiology of paraprostatic cysts is unknown. These large cysts, located outside the prostatic parenchyma, have a stalk that connects to the prostate. They may result from dilated paramesonephric duct remnants or from retention cysts.[26] Paraprostatic cysts are uncommon and are often not clinically discernible until their size is sufficient to impinge on the colon or urethra, or unless secondary infection occurs and an abscess develops.[93] Paraprostatic cysts vary in size, shape, and location. Most cysts are located cranial or dorsal to the prostate and urinary bladder.[93] The ultrasonographic appearance of a paraprostatic cyst is that of a well-circumscribed, ovoid structure with anechoic or hypoechoic contents.[93] However, a pyometra of the uterine masculinus can occur secondary to infection without hormonal influence and appears as multiple, convoluted, tubular cavitations.[52] Radiographically, a paraprostatic cyst appears as a "second" bladderlike structure (Figure 263-19). Occasionally, paraprostatic cysts have calcified walls. Fine needle aspiration of a paraprostatic cyst yields fluid varying from clear and yellow to turbid and brown.[1] The recommended treatment for paraprostatic cysts that cause symptoms of prostatic disease is surgical removal.[94]

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264 CHAPTER • 264 Familial Renal Disease in Dogs and Cats

Stephen P. DiBartola

Most familial renal diseases result in chronic renal failure at a young age (less than 5 years), but some are characterized by renal tubular defects (e.g., Fanconi syndrome in the basenji) or morphologic abnormalities that result in hematuria (e.g., renal telangiectasia in Pembroke Welsh corgis). A *familial* disease is one that occurs in related animals with a higher frequency than would be expected by chance. *Congenital* diseases are present at birth and may be genetically determined or may result from exposure to adverse environmental factors during development. In many familial renal diseases of dogs, the kidneys are thought to be normal at birth but undergo structural and functional deterioration early in life. Some familial renal diseases of dogs probably are examples of renal dysplasia. The term *renal dysplasia* refers to disorganized development of renal parenchyma as a result of abnormal differentiation; the condition is characterized by the presence of structures in the kidney inappropriate for the stage of development of the animal. Lesions suggestive of renal dysplasia include asynchronous differentiation of nephrons (indicated by persistence of immature or "fetal" glomeruli) and persistent mesenchyme (usually in the medullary interstitium).[1] Persistent metanephric ducts, atypical tubular epithelium, and dysontogenic metaplasia are observed less frequently.

Many familial renal diseases are variable in severity and rate of progression among individual animals. Most of these diseases are progressive and ultimately fatal, and therapy usually is limited to conservative medical management of chronic renal failure. The mode of inheritance and specific pathogenesis for many of these diseases are unknown. The primary nature of the renal disease and its mode of inheritance, when known or suspected, are listed in Table 264-1.

264.1 SIGNALMENT

Familial renal disease has been reported in many dog breeds (see Table 264-1) and may occur sporadically in mixed-breed animals. The clinician should consider the possibility of familial renal disease whenever chronic renal failure occurs in immature or young adult animals. In cats, familial amyloidosis has been characterized in Abyssinian, Siamese, and Oriental shorthair cats, and polycystic kidney disease (PKD) is common in the Persian breed.

In most of these diseases there is no clear sex predilection. In Samoyeds, however, hereditary glomerulopathy arises from an X-linked dominant trait. The age of onset of familial renal disease usually is 6 months to 5 years, with many animals developing signs before 2 years of age. Renal amyloidosis in beagles and English foxhounds, suspected glomerular basement membrane disease in beagles,[2] and telangiectasia of the Welsh corgi occur in older dogs (≥5 years), whereas PKD in cairn and West Highland white terriers is detected at a young age (5 to 6 weeks).

264.2 HISTORY AND PHYSICAL FINDINGS

The most common historical findings in dogs and cats with chronic renal failure due to familial renal disease are anorexia, lethargy, stunted growth or weight loss, polyuria and polydipsia, and vomiting. Other less common client complaints are poor haircoat, diarrhea, foul breath, and nocturia. In the Pembroke Welsh corgi with renal telangiectasia, the most common client complaints are hematuria, dysuria, and apparent abdominal pain. Hematuria also has been reported in German shepherds with multifocal renal cystadenocarcinomas.[3]

Dogs and cats with chronic renal failure due to familial renal disease may be thin and dehydrated. On oral examination, pallor of the mucous membranes, foul odor, and uremic ulceration may be noted. The kidneys usually are small and irregular, with the exception of cairn and West Highland white terriers and Persian cats with PKD, in which the kidneys often are markedly enlarged. Signs of fibrous osteodystrophy, such as “rubber jaw” or pathologic fractures, usually are detected in young growing dogs with renal failure. Signs of renal osteodystrophy rarely are apparent in older dogs with renal failure. The blood pressure should be measured and a fundic examination performed to evaluate for complications of hypertension (e.g., retinal hemorrhage, retinal detachment).

264.3 LABORATORY FINDINGS

The most common laboratory findings in dogs with familial renal disease resulting in chronic renal failure are azotemia, hyperphosphatemia, isosthenuria, and nonregenerative anemia. The serum calcium concentration in dogs may be normal, decreased, or increased. Hypercalcemia may be more common in young versus older dogs with renal failure. Compensated metabolic acidosis also may be observed. The presence of hypercholesterolemia and proteinuria should lead to suspicion of primary glomerular disease. Beagles with glomerular amyloidosis and Bernese mountain dogs with membranoproliferative glomerulonephritis develop nephrotic syndrome and proteinuria; however, proteinuria is variable and depends on the extent of glomerular involvement in Shar Peis and Abyssinian cats with familial amyloidosis. Glucosuria is found in Norwegian elkhounds and basenjis with primary renal tubular disorders.

Juvenile renal disease in the basenji is an animal model of Fanconi syndrome and is characterized by glucosuria, proteinuria, isosthenuria, and amino aciduria. Affected basenjis may also have decreased fractional resorption of phosphate, sodium, potassium, and urate. They may develop hypokalemia and metabolic acidosis with a normal anion gap (hyperchloremic metabolic acidosis). In Welsh corgis with renal telangiectasia, the major laboratory finding is hematuria, but urinary tract infection may also be present. Blood loss anemia is more common than nonregenerative anemia because of the large amounts of blood that may be lost in the urine. Affected Welsh corgis may develop nephrocalcinosis and calculi, and hydronephrosis may occur if a blood clot or calculus obstructs the ureter.

264.4 PATHOLOGIC FINDINGS

Familial renal disease is characterized by the presence of primary dysplastic lesions, compensatory lesions, and degenerative lesions.[1] In many cases the secondary degenerative lesions overshadow the underlying primary dysplastic lesions, making correct diagnosis difficult. Primary dysplastic lesions that have been observed in some familial renal disease of dogs include immature or “fetal” glomeruli, hyperplasia or adenomatoid proliferation of the medullary collecting ducts, and persistent mesenchyme in the renal medulla. Such changes are most prominent in the Lhasa apso, Shih Tzu, soft-coated wheaten terrier, standard poodle, chow chow, and miniature schnauzer. Juvenile renal diseases in the Samoyed, English cocker spaniel, and bull terrier result from abnormalities of type IV collagen in glomerular basement membranes and represent animal models of X-linked dominant, autosomal recessive, and autosomal dominant hereditary nephritis in humans, respectively.

Secondary degenerative lesions commonly observed in familial renal disease include interstitial fibrosis, interstitial infiltration by mononuclear inflammatory cells, dystrophic mineralization, and cystic glomerular atrophy.

The pathologic features of several individual familial renal diseases are presented below.

264.4.1 Abyssinian Cat

Abyssinian cats with familial amyloidosis usually develop clinical signs between 1 and 5 years of age. Male and female cats are affected. Amyloid deposits first appear in the kidneys between 9 and 24 months of age, and in many cats amyloid deposition leads to chronic renal failure within the first 3 years of life. Amyloid deposition in the kidney may be mild, and some affected cats may live to an advanced age without detection of the amyloid deposits. Proteinuria is a variable clinical finding and reflects the severity of glomerular involvement. Difficulty determining the mode of inheritance arises from the variability in severity and progression of amyloidosis among affected Abyssinian cats, but the disease appears to be inherited as an autosomal dominant trait with variable penetrance. Amyloid deposits in the kidneys of affected Abyssinian cats contain amyloid protein AA.[4]

Table • 264-1 Familial Renal Diseases of Dogs and Cats

BREED	DISEASE	AGE AT PRESENTATION	INHERITANCE	PROGRESSIVE RENAL FAILURE?
Beagle	Amyloidosis	5 to 11 yr	Unknown	Yes
English foxhound	Amyloidosis	5 to 8 yr	Unknown	Yes
Shar Pei	Amyloidosis	1 to 6 yr	Unknown	Yes
Abyssinian cat	Amyloidosis	1 to 5 yr	Autosomal dominant (incomplete penetrance)*	Yes
Oriental shorthair cat	Amyloidosis	<5 yr	Unknown	Variable; also, severe liver involvement
Siamese cat	Amyloidosis	<5 yr	Unknown	Variable; also, severe liver involvement
Basenji	Tubular dysfunction (Fanconi syndrome)	1 to 5 yr	Unknown	Variable
Norwegian elkhound	Tubular dysfunction (renal glucosuria)	Not reported	Unknown	No
Beagle	Unilateral renal agenesis	Incidental finding	Unknown	No
Bull terrier	Basement membrane disorder	<1 to 10 yr	Autosomal dominant	Yes
Doberman pinscher	Basement membrane disorder	<1 to 6 yr	Unknown	Yes
English cocker spaniel	Basement membrane disorder	<2 yr	Autosomal recessive	Yes
Samoyed	Basement membrane disorder	<1 yr	X-linked dominant (males)	Males
NAV dogs†	Basement membrane disorder	<1 yr (males) 1 to 3 yr (females)	X-linked dominant	Males and females
Bernese mountain dog	Membranoproliferative glomerulonephritis	2 to 5 yr	Autosomal recessive*	Yes
Brittany spaniel	Membranoproliferative glomerulonephritis (C3 deficiency)	4 to 9 yr	Autosomal recessive	Variable
Rottweiler	Glomerular disease	≤1 yr	Unknown	Yes
Norwegian elkhound	Periglomerular fibrosis (primary lesion unknown)	<1 to 5 yr	Unknown	Yes
Soft-coated wheaten terrier	Glomerular disease (membranoproliferative glomerulonephritis)	2 to 11 yr	Unknown	Yes
Beagle	Glomerular disease (basement membrane disorder?)	2 to 8 yr	Unknown	Yes
Cairn terrier	Polycystic kidneys	6 wk	Autosomal recessive*	Not reported
West Highland white terrier	Polycystic kidneys	5 wk	Autosomal recessive*	Not reported
Bull terrier	Polycystic kidneys	<1 to 2 yr	Autosomal dominant	Yes; also, valvular heart disease
Persian cat	Polycystic kidneys	3 to 10 yr	Autosomal dominant	Yes

* Suspected.

† Dogs from Navasota, Texas.

The principal pathologic lesions in the kidneys of Abyssinian cats with familial amyloidosis are medullary amyloid deposits, papillary necrosis, chronic tubulointerstitial nephritis characterized by lymphoplasmacytic infiltration and fibrosis, and variable glomerular amyloid deposits. Glomerular amyloidosis is mild and often difficult to detect in many affected cats but occasionally can be severe. Medullary amyloid deposition was found in all affected Abyssinians, whereas glomerular deposits were found in 75%.[5] Medullary interstitial amyloid deposits interfere with blood flow to the renal papilla, resulting in papillary necrosis and secondary interstitial medullary fibrosis and mononuclear inflammation.[6] Amyloid deposition is not restricted to the kidneys in Abyssinian cats with amyloidosis; deposits frequently are found in other organs (e.g., adrenal glands, thyroid glands, spleen, stomach, small intestine, heart, liver, pancreas, and colon).[5] However, amyloid deposits in these other organs do not appear to make an important contribution to the clinical syndrome, which is that of chronic renal failure. In Siamese and Oriental shorthair cats, however, severe deposition of amyloid in the liver can result in hepatic rupture and hemoabdomen. The amino acid sequence of the amyloid AA protein in affected Siamese cats differs slightly from that found in affected Abyssinian cats, and this difference may explain the predilection for hepatic deposition in affected Siamese cats.[7,8]

1821 1822

264.4.2 Alaskan Malamute

Chronic renal failure in three sibling malamute pups (4 to 11 months of age) was associated with histologic evidence of renal dysplasia.[9] The lesions observed included immature ("fetal") glomeruli, cystic glomerular atrophy, glomerular sclerosis, periglomerular fibrosis, adenomatoid hyperplasia of tubules, and persistent mesenchymal tissue.

264.4.3 Basenji

Histologic findings in the kidneys of basenjis with Fanconi syndrome are not consistent. Nonspecific findings include tubular atrophy and interstitial fibrosis. One morphologic marker for this disease may be enlarged, hyperchromatic nuclei in renal tubular cells (renal tubular cell karyomegaly). Affected animals may deteriorate rapidly and die of acute renal failure with papillary necrosis or pyelonephritis.

264.4.4 Beagle

A family of adult beagles developed glomerular amyloidosis and nephrotic syndrome characterized by proteinuria, hypercholesterolemia, and renal failure.[10] Some dogs had mild medullary deposition of amyloid. The amyloid deposits were sensitive to permanganate oxidation, suggesting the presence of amyloid protein AA. In another study, a family of beagles with proteinuria, late-onset renal failure, and multilaminar splitting of the glomerular basement membranes was described.[2]

264.4.5 Bernese Mountain Dog

Membranoproliferative glomerulonephritis resembling membranoproliferative glomerulonephritis type I in humans was described in young (2-to 5-year-old) male and female Bernese mountain dogs.[11,12] Affected dogs had typical laboratory abnormalities of renal failure, as well as marked proteinuria, hypercholesterolemia, and hypoalbuminemia. Pedigree analysis suggested an autosomal recessive mode of inheritance. Ultrastructural lesions included a double-layered glomerular basement membrane and electron-dense deposits, primarily in a subendothelial location. Immunoglobulin M and the third component of complement were identified by

immunofluorescence in glomeruli of affected dogs. Most of the dogs had high serologic titers against *Borrelia burgdorferi,* but the organism could not be detected immunohistochemically in the tissues of affected dogs. Membranoproliferative glomerulonephritis also has been reported in Brittany spaniels with deficiency of the third component of complement.[13]

264.4.6 Bull Terrier

Familial renal disease leading to chronic renal failure has been reported in bull terriers 1 to 8 years of age.[14,15] Both male and female dogs are affected, and the disease is inherited as an autosomal dominant trait.[16] It may represent an animal model of the dominant form of Alport syndrome in human beings.[17] Proteinuria, an early manifestation, correlated with underlying glomerular lesions in affected bull terriers.[18] Repeated urine protein to creatinine (UPC) ratios greater than 0.3 are considered supportive evidence of the disease in suspect bull terriers over 2 years of age that do not have overt evidence of renal failure.[15,18]

Light and electron microscopy of affected bull terriers shows thickening and splitting of glomerular basement membranes and involvement of tubular basement membranes.[14,16,18,19] Familial PKD that occurs in association with nodular thickening of the mitral and aortic valves and mitral dysplasia also has been reported in bull terriers.[20] Affected dogs did not have hepatic cysts.

264.4.7 Cairn and West Highland White Terriers

Autosomal recessive polycystic disease in the cairn terrier is characterized by the presence of multiple cysts throughout the liver and kidneys. Autosomal recessive PKD also has been reported in young (5-week-old) West Highland white terriers.[21]

264.4.8 Chow Chow

Chronic renal failure in six young, related chows chows (five male and one female) was suggestive of renal dysplasia.[22] Renal failure developed in four dogs by 6 months of age and in two dogs after 1 year of age. Renal dysplasia was suspected based on the presence of immature (“fetal”) glomeruli and pseudostratified columnar epithelium in the renal tubules of some dogs.

264.4.9 Doberman Pinscher

Diffuse thickening or multifocal irregular thickening with lamellation of the lamina densa has been observed in the glomerular basement membranes of Doberman pinschers with glomerulopathy.[26] Occasionally, deposits of immunoglobulins have been detected in the glomerular capillary wall, but these are thought to result from nonspecific trapping of immune complexes in basement membranes with some underlying structural defect. Unilateral renal aplasia has been observed in some affected female Doberman pinschers. Additional glomerular lesions include lobular accentuation of glomerular capillary loops, increased mesangial matrix, hypercellularity, intraglomerular adhesions, fibroepithelial crescent formation, and periglomerular fibrosis.[26]

264.4.10 English Cocker Spaniel

Juvenile renal disease in the English cocker spaniel is an animal model of autosomal recessive hereditary nephritis in humans.[23–25] Mutations have been identified in genes for the alpha-3 (COL4A3) and alpha-4 (COL4A4) chains of type IV collagen on chromosome 2 in affected human patients, and these loci are candidate genes for the disease in the English cocker spaniel.

The disease affects both male and female English cocker spaniels and manifests itself between 6 and 24 months of age. The earliest detectable abnormality (5 to 8 months of age) is proteinuria followed by reduced growth rate, impaired urinary concentrating ability, and azotemia (7 to 17 months of age).[24] The primary lesion is thickening and multilaminar splitting of the glomerular basement membrane. This lesion is identical to that observed in Samoyeds with X-linked hereditary nephritis and is similar to lesions observed in bull terriers with hereditary nephritis. The disease ultimately leads to diffuse glomerular sclerosis and periglomerular fibrosis with secondary tubulointerstitial disease; it is invariably fatal.

264.4.11 English Foxhound

Renal amyloidosis was reported in related adult English foxhounds.[27] The disease was associated with acute illness, renomegaly, and papillary necrosis in some affected dogs. Amyloid deposits were sensitive to permanganate oxidation, suggesting the presence of amyloid protein AA.

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264.4.12 German Shepherd

German shepherds with bilateral, multifocal renal cystadenocarcinomas are usually 5 to 11 years of age when they develop nonspecific signs such as anorexia, weight loss, polydipsia, and gastrointestinal disturbances.[3,28,29] The renal lesions are accompanied by cutaneous and subcutaneous nodules (dermatofibrosis) and multiple uterine leiomyomas in affected female dogs. The disorder is thought to be inherited as an autosomal dominant trait.

264.4.13 Golden Retriever

Chronic renal failure has been reported in young golden retrievers (less than 3 years of age).[30,31] Hypercholesterolemia was a common finding despite lack of other evidence of primary glomerular disease in most affected dogs. Hypercalcemia also was common and was attributed to an increased serum complexed calcium concentration. Cystic glomerular atrophy and periglomerular fibrosis were common histologic lesions, whereas immature (“fetal”) glomeruli were uncommon. Adenomatoid proliferation of the collecting ducts suggestive of primitive metanephric ducts, observed in several dogs, supports a diagnosis of renal dysplasia. Pyelonephritis occasionally complicates the disease in affected dogs.

264.4.14 Lhasa Apso and Shih Tzu

In the Lhasa apso and Shih Tzu, microscopic findings include a reduced number of glomeruli, glomerular atrophy, and small, immature (“fetal”) glomeruli that are hypercellular and that have inconspicuous capillary lumens. Tubular changes include atrophy, dilatation, and epithelial hyperplasia. Interstitial fibrosis is particularly severe in the renal medulla, but interstitial inflammation is minimal. To a certain extent, increased

interstitial medullary tissue may be persistent mesenchyme and, along with the immature glomeruli, is evidence of a primary renal dysplasia.

264.4.15 Miniature Schnauzer

Chronic renal failure suggestive of renal dysplasia was reported in eight related miniature schnauzers ranging in age from 4 months to 3 years.[32] Immature ("fetal") glomeruli, glomerular sclerosis, and severe interstitial fibrosis were observed.

264.4.16 Norwegian Elkhound

In the Norwegian elkhound, periglomerular fibrosis is an early histologic lesion that may be detected in some dogs before the onset of azotemia. Pathologic findings in dogs with more advanced disease consist of generalized interstitial fibrosis with glomerular sclerosis and atrophy. Hyperplasia of the collecting ducts also has been observed and may represent a primary dysplastic change, but immature ("fetal") glomeruli have not been observed. Norwegian elkhounds may also develop primary renal glucosuria that is not associated with chronic renal failure.

264.4.17 Persian Cat

PKD is inherited as an autosomal dominant trait in Persian cats.[33,34] The prevalence of PKD has been observed to be 35% to 57% in Persian cats surveyed by ultrasonography.[35–37] Cysts originate from both the proximal and distal tubules, they occur in both the renal cortex and the medulla, and they increase in number and size over time.[38] They can be detected by ultrasonographic examination of affected kittens as early as 6 to 8 weeks of age, but the absence of cysts at this early age does not preclude their development at a later age. In one study, ultrasound examination had a sensitivity of 75% and a specificity of 100% when performed at 16 weeks of age and a sensitivity of 91% and specificity of 100% when performed at 36 weeks of age.[34] Although common in human patients with PKD, hypertension has been absent or mild in cats with PKD that have been evaluated.[39,40] Affected Persian cats usually do not develop renal failure until later in adult life (average, 7 years), and renomegaly may be an incidental finding on physical examination. Occasionally, cysts may be found in the liver.[41,42]

264.4.18 Rottweiler

Chronic renal failure was reported in four related rottweilers (three females and one male) ranging in age from 6 to 12 months.[43] Hypercholesterolemia and an abnormally increased UPC ratio were consistent with a diagnosis of primary glomerular disease. Histologically, cystic glomerular atrophy and irregular thickening of glomerular basement membranes were observed.

264.4.19 Samoyed

Male Samoyeds with hereditary nephritis develop proteinuria, glucosuria, and isosthenuria by 2 to 3 months of age and azotemia by 6 to 9 months of age; death from renal failure usually occurs by 12 to 16 months of age.[44] Mesangial thickening, glomerular sclerosis, and periglomerular fibrosis are observed by light microscopy in affected males by 8 to 10 months of age.[45] Affected females develop proteinuria at 2 to 3 months of age but

remain clinically normal, other than failing to achieve normal adult body weight. This difference in the clinical course is a consequence of the X-linked dominant inheritance pattern and results from normal random inactivation of one X chromosome in each cell of the female embryo during development.[46]

Juvenile renal disease in the Samoyed is a hereditary glomerulopathy arising from a single nucleotide substitution in the gene (COL4A5) for the alpha-5 chain of type IV collagen on the X chromosome.[47] At birth, the glomerular basement membranes of affected male Samoyeds are morphologically normal, but reduplication and bilaminar splitting of the lamina densa are detected by electron microscopy at 1 month of age and progress to multilaminar splitting, thickening, and glomerular sclerosis by 8 to 10 months of age.[48] Affected females have only focal splitting of glomerular basement membranes and do not develop progressive disease.

Proteinuria and progressive renal disease presumably result from damaged glomerular basement membranes weakened by abnormal cross-linking of type IV collagen.[49] Deterioration of basement membranes and the onset of renal failure in affected males can be delayed but not prevented by feeding a diet low in protein and phosphorus beginning at 1 month of age.[50] Treatment of affected dogs with angiotensin-converting enzyme (ACE) inhibitors[51] or cyclosporine[52] has slowed progression of the disease. An X-linked dominant form of hereditary nephritis also has been described in dogs from Navasota, Texas (NAV dogs).[53] This disorder was characterized by earlier onset of renal failure in affected females, and alpha-3, alpha-4, and alpha-5 chains of type IV collagen were absent from the glomerular basement membranes in affected dogs. However, no mutation was found in exon 35 of the COL4A5 gene in affected dogs; consequently, this disease appears to result from a different mutation in the COLA5 gene.

264.4.20 Shar Pei

Familial amyloidosis resulting in chronic renal failure at a young age (mean, 4 years) occurs in male and female Shar Peis.[54] Proteinuria and laboratory evidence of nephrotic syndrome (e.g., hypoalbuminemia, hypercholesterolemia) may be present, depending on the severity of glomerular involvement. Some affected Shar Peis had a previous history of episodic joint swelling (usually the tibiotarsal joints) and high fever that resolves within a few days, regardless of treatment.[55,56] Recurrent fever and joint swelling that culminate in renal failure due to reactive systemic amyloidosis in young Shar Peis may represent an animal model of familial Mediterranean fever in humans. Some evidence indicates that amyloidosis in the Shar Pei is inherited as an autosomal recessive trait.[57]

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Affected Shar Peis have moderate to severe renal medullary deposition of amyloid, but only two thirds have glomerular involvement. These findings are similar to those seen in Abyssinian cats with familial amyloidosis. The remaining renal lesions are those of end-stage renal disease. Amino acid sequence analysis has demonstrated that the amyloid deposits in affected Shar Peis contain amyloid A protein.[58] In addition to the kidney, amyloid deposits may be observed in many other organs (e.g., liver, spleen, gastrointestinal tract, thyroid gland). Icterus, hepatomegaly, and occasionally hepatic rupture with hemoabdomen may occur in Shar Peis with severe deposition of amyloid in the liver.[59]

264.4.21 Soft-Coated Wheaten Terrier

Pathologic findings in some soft-coated wheaten terriers (SCWTs) with juvenile renal disease are suggestive of renal dysplasia.[60,61] Histologic lesions include interstitial fibrosis, periglomerular fibrosis, cystic glomerular atrophy, decreased numbers of glomeruli, and the presence of immature ("fetal") glomeruli. Adenomatous proliferation of the collecting duct epithelium also is a prominent feature.

SCWTs also are predisposed to protein-losing enteropathy (PLE), protein-losing nephropathy (PLN), or both.[62] Food hypersensitivity and increased gut permeability presumably lead to immune complex glomerulonephritis that progresses to end-stage renal disease. The results of gastroscopic food sensitivity testing and dietary challenge support the hypothesis of food hypersensitivity,[63] but gluten hypersensitivity does not seem to be involved.[64] The disease is thought to be present in 10% to 15% of SCWTs and affects middle-aged to older dogs, with a slight predilection for females. The mode of inheritance is uncertain. Clinical findings include polyuria, polydipsia, vomiting, and weight loss in dogs with PLN; proteinuria, hypoalbuminemia, hypercholesterolemia, azotemia, hyperphosphatemia, and nonregenerative anemia are common laboratory findings. Hypertension occasionally develops, and thromboembolism complicates the disease in 12% of SCWTs with PLN.[62] Renal lesions consist of membranous to membranoproliferative glomerulonephritis that progresses to glomerular sclerosis, periglomerular fibrosis, and chronic interstitial nephritis. Mesangial deposition of immunoglobulin A (IgA), IgM, and complement has been detected by immunofluorescence, which suggests that renal disease in the SCWT may be an animal model of IgA nephropathy or IgM mesangial nephropathy.[65] The disease is progressive, treatment is palliative, and the prognosis is poor. Thus familial renal disease in the SCWT may take the form of renal dysplasia or membranoproliferative glomerulonephritis.

264.4.22 Standard Poodle

In affected standard poodles, cystic glomerular atrophy and large numbers of immature ("fetal") glomeruli are observed, especially in dogs presented at 3 to 4 months of age. The cortical interstitium contains segmental areas of fibrosis, whereas more diffuse lesions occur in the medulla.

264.4.23 Welsh Corgi

Welsh corgi dogs with renal telangiectasia have red to black nodules in the kidneys, especially in the renal medulla adjacent to the corticomedullary junction. Clotted blood often is identified in these lesions and in the renal pelvis. Hydronephrosis (presumably caused by ureteral obstruction) occurs in almost half of affected dogs. Similar nodular lesions may be identified in other tissues, including the subcutis, spleen, duodenum, anterior mediastinum, thoracic wall, retroperitoneal space, and central nervous system. Histologically these lesions are cavernous, blood-filled spaces lined with endothelium, and thrombosis is a frequent finding in the sinuses. These sinuses, with their simple endothelial linings, may represent vascular malformations rather than benign tumors of vascular origin.

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265 CHAPTER • 265 Renal Tubular Diseases

Marie E. Kerl

The renal tubules are responsible for absorption of various components of the blood that has been filtered through the glomerulus. Among the filtered components that are reabsorbed into the blood are glucose, amino acids, and electrolytes. The tubules are also responsible for secretion of drugs and electrolytes, regulation of acid-base balance, and maintenance of fluid balance. Tubular defects occur regionally or globally and are either congenital or acquired. The glomerular filtration rate (GFR) is the main determinant of renal function, but the tubules are responsible for the final composition of the urine. Indicators from biochemical profiles, blood gas analysis, and urinalysis can be monitored to assess tubular function.

The renal tubules can be described according to function and anatomic location. The proximal convoluted tubule, loop of Henle, distal convoluted tubule, collecting tubule, and collecting duct are each responsible for various functions. The proximal tubule receives ultrafiltrate from Bowman's space and reabsorbs 60% to 65% of the filtrate. Absorption is accomplished by active transport of sodium (Na^+), which in turn promotes passive resorption of other solutes. The proximal tubule also actively secretes some solutes (e.g., organic anions, cations, and hydrogen ions [H^+]).[1] Solutes are not reabsorbed uniformly; virtually all filtered glucose and amino acids are reabsorbed, whereas lesser amounts of bicarbonate (HCO_3^-), Na^+, and chloride are reabsorbed. The loop of Henle, with the characteristic hairpin configuration central to the kidney's ability to excrete concentrated urine, is divided into four segments, having different absorption characteristics. The main function of the loop of Henle is to reabsorb approximately 30% of filtered sodium chloride (NaCl) against a concentration gradient to create an ultrafiltrate that is hyposmolar to plasma.[2] The distal tubule and the collecting tubule and duct are responsible for fine control of electrolytes including Na^+, potassium, and calcium; final regulation of acid-base balance; and water resorption to produce a concentrated urine.[3] Clinical manifestations of renal tubular disorders include formation of cystic calculi, metabolic acidosis, glucosuria, aminoaciduria, electrolyte disorders, and failure of urine concentration.[4,5]

265.1 CYSTINURIA

Cystinuria is caused by an inherited proximal tubular defect in which resorption of particular amino acids fails. Of these amino acids, cystine is relatively insoluble in urine, resulting in the formation of cystic calculi in acidic urine.[6–8] Plasma concentrations of cystine are normal in affected animals. The exact nature of the defect remains unknown; some breeds have cystine loss only, whereas other breeds fail to reabsorb a variety of amino acids.[7]

Many dog breeds have been reported with cystinuria, and occasional reports have been made for cats.[9,10] Commonly affected dog breeds include English bulldogs, Australian cattle dogs, dachshunds, mastiffs, basset hounds, Newfoundlands, Staffordshire bull terriers, and French bulldogs. Mixed-breed dogs are also affected.[8,11,12] The mode of inheritance in various breeds is sex linked or autosomal recessive, but cystinuric dogs do not always develop calculi.[8] The mean age of calculus formation is 4.5 years. The degree of cystinuria can vary among individuals and may decrease with age.[6] Males are over-represented for clinical cystine calculi, but cystinuria without calculi formation has been reported in females. Newfoundlands appear to have a more severe form of cystinuria, with calculi formation occurring in both males and females and at a younger age than for other breeds.[8]

Clinical signs associated with cystine calculi formation include stranguria, pollakiuria, and hematuria. Male dogs may develop secondary urethral obstruction. Evaluation of urine sediment reveals cystine crystalluria in some affected dogs, but a complete blood count and serum biochemical analysis do not aid diagnosis. Imaging studies may identify calculi, but the size, shape, and radiographic density of calculi vary. The radiographic density of larger calculi is similar to that of soft tissue, which allows them to be visualized on plain film radiographs; small calculi may not be visualized by this technique. Ultrasonography and contrast cystourethrography may be diagnostic if plain film radiography is unrewarding.[8]

Treatment involves mechanical removal or medical dissolution of calculi and long-term medical management to prevent recurrence. Surgical management is indicated in animals with urethral obstruction. Quantitative calculi analysis provides a definitive diagnosis. Bacterial urinary tract infection should be resolved with appropriate antibiotic therapy. Dissolution and prevention strategies include exclusive feeding of protein-restricted diets. Cystine is twice as soluble at a pH of 7.8 as at 6.5, therefore urinary alkalization is desired.[5] Some protein-restricted diets (Prescription Diet Canine u/d, Hill's Pet Nutrition, Topeka, Kansas) result in the formation of an alkaline urine, but if dietary therapy does not maintain the urine pH at the desired level, oral potassium citrate is recommended.[8] Induction of diuresis (e.g., by feeding canned, low-protein food or adding water to dry food) is likely to be beneficial.[6,8]

Drug therapies to reduce the formation of cystine calculi include the thiol drugs D-penicillamine and 2-mercaptopropionylglycine (2-MPG). Cystine is formed by a disulfide bond between two cysteine molecules. Thiol drugs form a disulfide bond with cysteine to form a more soluble cystine-thiol drug complex. Although both drugs are effective, metal chelation and gastrointestinal side effects of D-penicillamine make it a less desirable choice.[7] 2-MPG, administered at a dosage of 30 to 40 mg/kg of body weight, divided and given orally twice daily, is the treatment of choice, in combination with dietary modifications for dissolution and prevention of cystine calculi.[6–8,13]

265.2 CARNITINURIA

Carnitine is a sulfur-containing nonessential amino acid that functions as an enzyme cofactor necessary to transport energy-generating fatty acids from the cytosol to the mitochondrial matrix. Continued deficiency, which has been reported in dogs with dilated cardiomyopathy, may result from defective biosynthesis, defective tissue uptake or retention, or excessive renal excretion.[14,15] Carnitinuria has been reported in dogs with cystinuria.[16] Although high-fat, low-protein diets are recommended for the management of cystinuria, high-fat diets increase renal carnitine excretion in humans. Healthy dogs that consume low-and high-fat diets excrete similar amounts of carnitine; however, cystinuric dogs with altered amino acid resorption might excrete an excessive amount of carnitine if they consume a high-fat diet.[15] Chronic carnitine excretion in these animals eventually may result in carnitine deficiency, leading to cardiomyopathy.

265.3 HYPERURICOSURIA

Abnormal purine metabolism or excretion accounts for hyperuricosuria in dogs of certain breeds or those with underlying hepatic disease. The purine portions of nucleic acids undergo metabolism to form hypoxanthine and xanthine, which are oxidized to uric acid by xanthine oxidase (XO). Uric acid is hepatically metabolized by the enzyme uricase. Most mammals excrete allantoin almost exclusively, but humans and higher apes excrete mostly uric acid.[17]

Two subsets of dogs commonly develop purine urolithiasis: Dalmatians and dogs with primary hepatic disease. Dalmatians are intermediate between dogs of other breeds and humans with regard to purine metabolism, excreting approximately one half to two thirds as much allantoin as urate. Differences exist between Dalmatians and non-Dalmatian dogs in both hepatic and renal management of urates. The enzyme uricase, which converts uric acid to allantoin, is stored in hepatic peroxisomes.[18] Uric acid must be transported into hepatocytes before conversion to allantoin can occur. Dalmatians have normal amounts of uricase compared with non-Dalmatian dogs, but Dalmatians have abnormal uric acid transport across the hepatic membrane.[19] Also, both Dalmatians and non-Dalmatian dogs secrete and reabsorb urates in the proximal tubules, but Dalmatians appear to have less proximal tubular resorption. In addition, they have active distal tubular secretion of urates as a result of a membrane transport defect.[17,20,21] Although all Dalmatians have high urine uric acid levels, only a small percentage develop calculi. Certain breeds, such as English bulldogs, have been reported to have an increased frequency of urate calculi without obvious hepatic disease. These dogs might have a metabolic defect that predisposes to urate calculi formation, but the mechanism is unknown.[20,22]

Dogs with primary hepatic disease have reduced conversion of uric acid to allantoin and of ammonia to urea. These metabolic defects cause hyperuricuria and hyperammonuria.[23] Portal vascular anomalies and hepatic microvascular dysplasia have been most commonly associated with urate calculi formation, although any severe hepatic dysfunction could predispose to calculi formation.[24] Cats have been reported with urate urolithiasis.[10]

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The clinical signs of urate urolithiasis are consistent with lower urinary tract disease. Male dogs can develop urethral obstruction. Young to middle-aged dogs are more commonly affected than older dogs.[25] For Dalmatians, males are more frequently affected with urinary calculi than females. Dogs with primary hepatic disease have no gender predisposition for calculi formation. Definitive diagnosis of cystic calculi depends on calculi retrieval and quantitative analysis. Urate calculi are radiolucent on plain film radiography. Abdominal ultrasonography or double-contrast cystography is helpful for identifying calculi. Hepatic function studies are appropriate for non-Dalmatian dogs and for cats. Urate calculi are typically small and smooth and vary in color from yellow to green to black.[20]

Treatment consists of calculi removal or dissolution, followed by long-term medical management to prevent recurrence. Dissolution therapy includes a calculolytic diet, medication with XO inhibitors, alkalization of the urine, elimination of secondary infections, and induction of isosthenuria.[20] A purine-restricted diet that is low in claculogenic minerals (e.g., Prescription Diet Canine u/d; Hill's Pet Nutrition, Topeka, Kansas) is recommended.[20,21,26,27] The synthetic XO inhibitor allopurinol is used to treat and prevent urate urolithiasis because it can reduce the serum and urine uric acid concentrations.[28] Allopurinol should be administered only to dogs consuming a purine-restricted diet to avoid the formation of xanthine calculi.

Urine alkalization reduces renal tubular production of ammonia, thereby diminishing the production of urinary ammonium ions that complex with urate to form calculi. Alkalizing agents (e.g., oral sodium bicarbonate [$NaHCO_3$] and potassium citrate) should be administered at a dosage that maintains the urine pH near 7.0 to 7.5.[20,27] Dilute urine production is accomplished by feeding protein-restricted diets that reduce renal medullary concentrating ability.

Mechanical calculi removal should be considered in animals with urethral obstruction or in those that do not respond to dissolution therapy. The average time to dissolution of urate calculi is approximately 3.5 months (range, 1 to 18 months).[20,27] Dissolution sometimes occurs with definitive repair of a portovascular anomaly, but

calculi do not resolve without resolution of underlying hepatic defects.[23] Because the causes of urate stones differ, allopurinol therapy is not recommended for dogs with hepatic defects.[20,23]

The prognosis is fair to guarded for calculi recurrence in Dalmatians and depends on the owner's commitment to ongoing management and expense. In dogs with underlying liver disease, the prognosis is good if definitive therapy for the liver disease exists but guarded in dogs with irreparable liver disease.

265.4 HYPERXANTHINURIA

Xanthine calculi are rare. Xanthine is derived from dietary purines and is metabolized to uric acid by activity of XO. Reduced enzymatic conversion increases urinary excretion of xanthine, which has a solubility similar to that of uric acid in urine.[29] Most dogs that form xanthine-containing calculi are receiving allopurinol, an XO inhibitor, for urate calculi.[22,25,29] Congenital xanthinuria has been reported in a family of Cavalier King Charles spaniels and in a wirehaired dachshund.[30,31] Prevention consists of monitoring for xanthine crystalluria in dogs receiving allopurinol to prevent urate calculi.

265.5 RENAL GLUCOSURIA

Under normal conditions, glucose is freely filtered at the glomerulus and reabsorbed in the proximal tubules by facilitated diffusion in a cotransport mechanism with Na^{+}.[1] The transport mechanism has a maximum capacity, which is exceeded at a blood glucose concentration of 180 to 220 mg/dL in dogs and 260 to 310 mg/dL in cats.[4] When hyperglycemia (e.g., stress hyperglycemia, diabetes mellitus) exceeds the transport maximum, glucosuria occurs. Proximal tubular defects caused by tubular damage or inherited disorders can result in glucosuria in the absence of hyperglycemia.[32,33]

Primary renal glucosuria is rare but has been reported in Scottish terriers, basenjis, Norwegian elkhounds, and mixed-breed dogs.[4,34] Persistent glucosuria typically causes polyuria and polydipsia from osmotic diuresis, although some dogs are asymptomatic. Evaluation of serial blood glucose measurements or the serum fructosamine concentration should be considered to diagnose renal glucosuria definitively by ruling out hyperglycemia as a cause for glucosuria.[35] Because bacterial or fungal urinary tract infections occur frequently with persistent glucosuria, regular monitoring and appropriate antibiotic therapy are important. There is no cure for primary renal glucosuria, but the long-term prognosis is good with appropriate fluid intake and control of urinary infections. In some dogs, renal glucosuria is the initial sign of Fanconi syndrome.

265.6 FANCONI SYNDROME

In humans, Fanconi syndrome is an inherited proximal tubular defect that results in glucosuria, aminoaciduria, proteinuria, phosphaturia, and hypophosphatemia. Fanconi syndrome has also been reported in dogs, and basenjis are most commonly affected. Fanconi syndrome is thought to be inherited in 10% to 30% of all basenjis, but the mode of inheritance is uncertain. Idiopathic and inherited Fanconi syndrome has been reported rarely in other dog breeds.[4,32] Acquired Fanconi syndrome has been reported in association with gentamicin administration, ethylene glycol toxicity, and primary hypoparathyroidism.[4,33]

Fanconi syndrome causes abnormal fractional excretion of many solutes.[36] Abnormal glucose absorption, resulting in glucosuria and osmotic diuresis, is the most obvious sign. Amino acid resorptive abnormalities vary

from one individual to another but generally include abnormal absorption of cystine. Abnormal absorption of bicarbonate, sodium, potassium, and urate also occur. Isosthenuria sometimes occurs prior to glucosuria and osmotic diuresis as a result of nephrogenic diabetes insipidus.[4,36]

The onset of clinical signs in affected basenjis typically occurs by 4 to 8 years of age, with females outnumbering males 3:1.[32] Clinical signs typically include polyuria, polydipsia, weight loss, poor haircoat, weakness, and dehydration. Diagnostic testing reveals glucosuria, euglycemia, and isosthenuria. As the disease progresses, hyperchloremic metabolic acidosis and renal failure occur. Clinically significant hypokalemia might contribute to muscle weakness. Progression is variable; some affected dogs develop renal failure within a few months of the onset of clinical signs, whereas others remain stable for years.[4]

Treatment is supportive, because there is no cure for the tubular defects. Monitoring for metabolic acidosis, urinary tract infections, and azotemia should be performed regularly. Veterinarians are frequently asked to participate in a management protocol developed by basenji breed enthusiasts. This protocol involves oral administration of sodium bicarbonate to manage chronic metabolic acidosis, which exacerbates bicarbonaturia. Urinary alkalization with potassium citrate does not cause bicarbonaturia and provides potassium supplementation. The goals of alkalization should be to maintain the serum HCO_3^- concentration above 12 mEq/L and the potassium concentration at 4 to 6 mEq/L.[4] Renal failure should be managed with dietary protein restriction, fluid therapy, histamine-2 receptor antagonists, and treatment of hypertension. Treatment for acquired Fanconi syndrome should be directed at resolving the underlying cause of the disorder and providing supportive care. The prognosis for short-term management is guarded to good, depending on the severity of azotemia at the time of diagnosis. The long-term prognosis is guarded to poor.

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265.7 RENAL TUBULAR ACIDOSIS

The renal tubules regulate acid-base homeostasis through two processes: (1) resorption of 80% to 90% of filtered HCO_3^- in the proximal renal tubule, and (2) excretion of acids by means of titration of urinary buffers and excretion of ammonium in the distal renal tubule.[37] The term *renal tubular acidosis (RTA)* describes rare tubular disorders that lead to hyperchloremic metabolic acidosis. Various types of RTA have been described based on the area of the affected renal tubules. Proximal RTA (type II) occurs as a result of inability of the proximal tubules to prevent loss of HCO_3^-, and distal RTA (classic, or type I) occurs as the result of inability of the distal tubule to excrete H^+. Type IV RTA is distal RTA and hyperkalemia secondary to hypoaldosteronism or aldosterone deficiency. Unique diagnostic criteria exist for each type of RTA.[38]

A defect in the basolateral membrane Na^+-HCO_3^- cotransporter, with leakage of HCO_3^- into the tubular lumen, results in proximal RTA.[39] This disorder can occur alone or as part of another clinical tubular defect (e.g., Fanconi syndrome).[38] Ongoing loss causes a reduced plasma bicarbonate concentration, but the associated metabolic acidosis is self-limiting because of the distal tubule's ability to excrete acid. If oral sodium bicarbonate ($NaHCO_3$) is prescribed to normalize the plasma bicarbonate concentration, the amount of HCO_3^- presented to the distal tubule increases and overwhelms the distal buffering system, resulting in marked bicarbonaturia.[38]

Table • 265-1 Clinical Features of Proximal and Distal Renal Tubular Acidosis (RTA)

FEATURE	PROXIMAL RTA	DISTAL RTA
Hypercalciuria	Yes	Yes
Hyperphosphaturia	Yes	Yes
Urinary citrate	Normal	Decreased
Bone disease	Less severe	More severe
Nephrocalcinosis	No	Possible
Nephrolithiasis	Not usually	Yes
Hypokalemia	Mild	Mild to severe
Potassium wasting	Worsened by alkali therapy	Improved by alkali therapy
Alkali required for treatment	>11 mEq/kg/day	<4 mEq/kg/day
Other defects of proximal tubular function*	Yes	No
Reductions in plasma bicarbonate (HCO_3^-)	Moderate	Variable
Fractional excretion of HCO_3^- with normal HCO_3^- concentration	>15%	<15%
Urine pH during acidemia	<6.0	>6.0
Urine pH after ammonium chloride administration	<6.0	>6.0

From Bartges JW: Disorders of renal tubules. *In* Ettinger SJ, Feldman EC (eds): Textbook of Veterinary Internal Medicine, 5th ed. Philadelphia, WB Saunders, 2000, p 1704.

* Decreased resorption of sodium, potassium, phosphate, uric acid, glucose, and amino acids.

The diagnosis of proximal RTA is based on an acid urine pH and hyperchloremic metabolic acidosis, with a normal GFR but increased urine pH and fractional excretion of HCO_3^- (greater than 15%) after normalization of the plasma HCO_3^- concentration with alkali administration. Identification of concurrent proximal tubular defects (e.g., euglycemic glucosuria, aminoaciduria) also helps localize proximal RTA.[38] Bicarbonate wasting makes metabolic acidosis from proximal RTA difficult to correct, and alkali therapy exacerbates potassium wasting. Potassium citrate is better suited for chronic use than sodium bicarbonate.[38] One 540 mg tablet of potassium citrate provides 5 mEq of potassium and 1.7 mEq of citrate, and its metabolism yields 5 mEq of HCO_3^{-5}.

Distal RTA causes impairment of urinary acidification as a result of impaired H^+ secretion in the distal tubule.[37,38] Consequently, the kidneys are unable to maximally acidify urine in response to systemic metabolic acidosis. Under normal conditions, the distal tubule is able to excrete H^+ ions against a steep concentration gradient because of a hydrogen ion–adenosine triphosphatase (H^+-ATPase) pump. These tubular segments have tight junctions that resist backleak of acid, and they are able to generate ammonia to capture H^+ ions by forming ammonium ions, which are subsequently excreted.[39]

Type IV distal RTA is associated with hypoaldosteronism or aldosterone antagonism. Acidosis most likely results from loss of aldosterone stimulation of H^+-ATPase and decreased distal Na^+ absorption. This syndrome has not been characterized in veterinary medicine but should be considered in animals with hyperchloremic metabolic acidosis and hypokalemia.[37,38]

Characteristics useful in the diagnosis of distal RTA include hyperchloremic metabolic acidosis with an increased urine pH (greater than 6.0). In contrast to proximal RTA, with relatively mild systemic metabolic acidosis, distal RTA can have a more severe metabolic acidosis, because the distal tubule does not provide

buffering ability. Clinical characteristics seen in humans with distal RTA include nephrolithiasis, nephrocalcinosis, bone demineralization, growth retardation, and hypokalemia.[37,39] Distal RTA has been reported in cats with pyelonephritis and in one cat with hepatic lipidosis.[4,38] The diagnosis may be made by failure to acidify urine with an ammonium chloride challenge test. This test is performed by measuring the urine pH before and at hourly intervals for 6 hours after oral administration of 110 mg/kg of ammonium chloride. Normal dogs should acidify to a urine pH of 5.0, and cats to a pH of 5.5.

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Treatment for distal RTA consists of administration of an alkali source. A combination of potassium and sodium citrate, at a dosage range of 1 to 5 mEq/kg/day, orally, divided into 2 doses, may be preferred over HCO_3^- as the alkali source. Characteristics of proximal and distal RTA are presented in Table 265-1.[5,38]

265.8 NEPHROGENIC DIABETES INSIPIDUS

The term *nephrogenic diabetes insipidus (NDI)* describes any disorder in which the urinary concentrating mechanism is unable to respond to antidiuretic hormone (ADH) to produce concentrated urine. ADH is produced in the hypothalamus in response to hyperosmolarity or hypovolemia. Upon release, it attaches to receptors at the basolateral membrane of the collecting tubules and collecting ducts, causing the tubular luminal surface to become permeable to free water and resulting in the formation of urine that is more concentrated than plasma. Acquired NDI is a common cause of polyuria, because it can result from receptor interference caused by toxins (e.g., *Escherichia coli* endotoxin), drugs (e.g., glucocorticoids, chemotherapeutics), metabolic conditions (e.g., hypokalemia, hypercalcemia), tubular injury or loss (e.g., renal cystic disease, bacterial pyelonephritis), or alterations in the medullary concentration gradient (e.g., medullary washout).[40]

Congenital NDI is a rare disease caused by a deficiency of ADH receptors. Clinical signs, apparent soon after birth, include severe polydipsia and polyuria and a hyposthenuric urine (specific gravity of 1.001 to 1.005; osmolarity less than 200 mOsm/kg). The diagnosis is based on failure to concentrate urine after modified water deprivation testing, failure to respond to exogenous ADH, and exclusion of more common causes of NDI.[4]

Treatment for acquired NDI should be directed at resolving the underlying cause. Congenital NDI therapy consists of free-choice water consumption, dietary sodium and protein restriction, and/or thiazide diuretics (chlorothiazide, 20 to 40 mg/lb given orally every 12 hours; or hydrochlorothiazide, 2.5 to 5 mg/lb given orally every 12 hours). Dietary sodium and protein restriction reduces the amount of solute presented to the kidney that must be excreted in the urine each day, further reducing obligatory water loss.[41] The addition of diuretic therapy to dietary restrictions results in mild dehydration, increased fluid and sodium uptake in the proximal tubule, and 20% to 50% reduction of urine output.[41] If medical management is not an option for the client and polyuria can be tolerated, the animal can be maintained on free-choice water consumption alone.

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266 CHAPTER • 266 Feline Lower Urinary Tract Diseases

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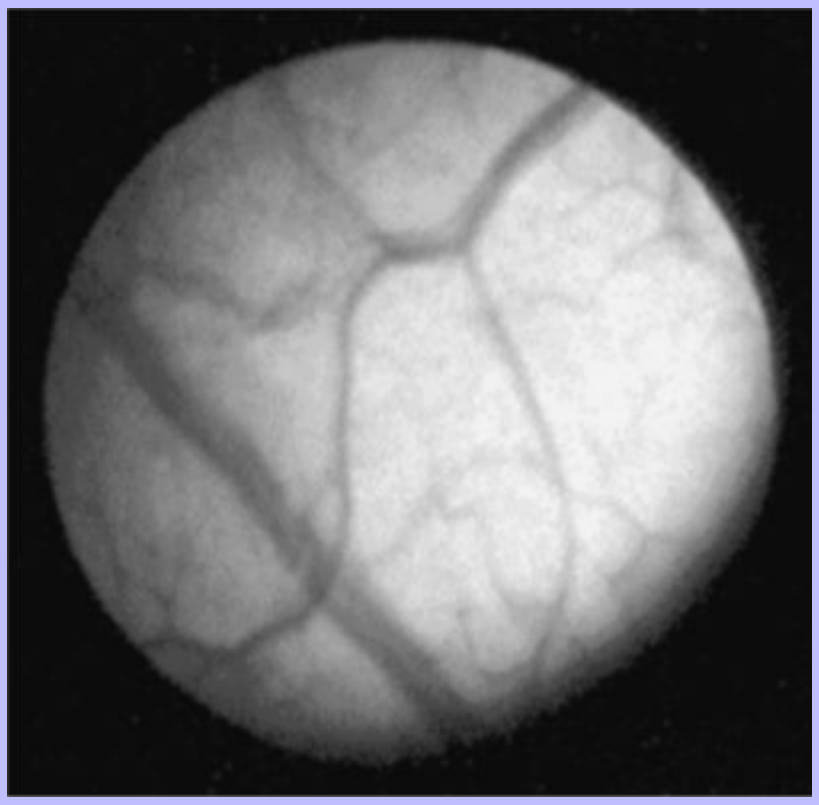
The terms *feline urologic syndrome* (FUS) and *feline lower urinary tract disease* (FLUTD) have served as shorthand descriptions for the well-known signs of straining, hematuria, pollakiuria (frequent passage of small amounts of urine), and periuria (urinations in inappropriate locations) in cats.[1] In 1925 an accurate clinical description of cats with lower urinary tract (LUT) signs described the disorder as common.[2] The roles of confinement and highly nutritious food were discussed, and the common occurrence of the problem in Persian cats was identified. In 1970, the term *FUS* was coined by Osbaldiston and Taussig[3] to describe a problem, "characterized by dysuria, urethral obstruction, urolithiasis (although no stones were reported), and hematuria." During the 1980s, Osborne and colleagues[4] suggested that FUS should be considered synonymous with FLUTD.

No diagnosis for the clinical signs of irritative voiding can be determined in approximately two-thirds of cats with LUT signs, and they are classified as having feline idiopathic cystitis (FIC). If a cystoscopy is performed and characteristic submucosal petechial hemorrhages are seen,[5] a diagnosis of feline interstitial cystitis can be made (Figures 266-1 and 266-2). This term was chosen because of the similarities between cats and humans with interstitial cystitis, an idiopathic pelvic pain syndrome that is characterized by difficult, painful, and frequent urinations without a diagnosable cause. Two forms of interstitial cystitis exist in humans: (1) nonulcerative and (2) ulcerative.[5] Cats with FIC generally have the nonulcerative form, however, the "classic Hunner's ulcers" have been described rarely in cats.[6] The name *FIC* will be used in this chapter for cats with idiopathic lower urinary tract disease. The term *LUT signs* will be used when referring to all possible causes of LUT disorders.

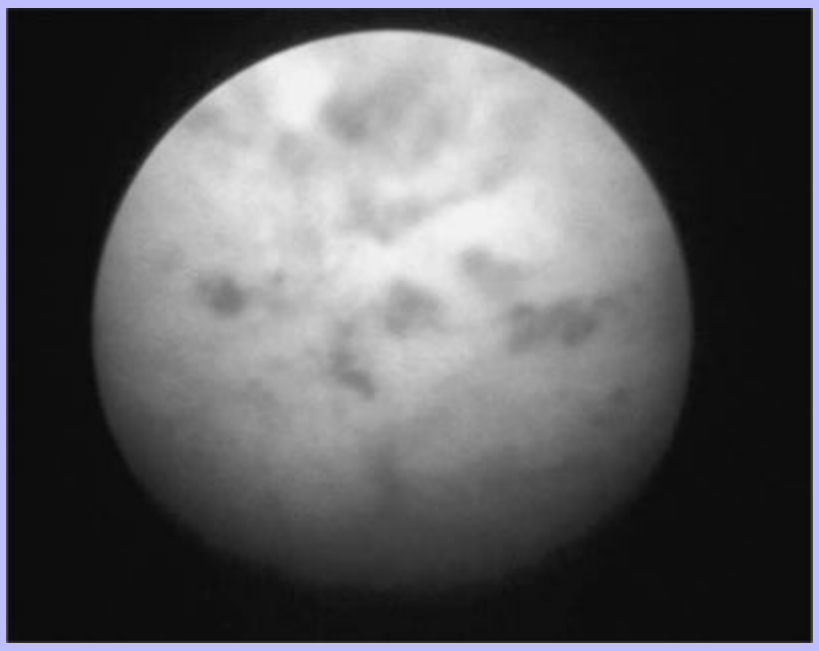
Approximately 4 million cats are destroyed annually in the United States for "elimination problems," the majority of which are related to the urinary tract.[7] Estimates of the prevalence of LUT signs were approximately 1.5% when private practices were evaluated.[8] Results of university-based studies during the past 40 years suggest that most (55% to 69%) cats presented for evaluation of nonobstructive LUT disorders have FIC; some 13% to 28% have uroliths.[9,10] Other less common problems such as urinary tract infections (UTIs), anatomic defects, behavioral problems, neoplasia, and obstructive uropathy (reflex dyssynergia) account for most other definable disorders referable to the LUT.

Figure 266-1 Cystoscopic appearance of blood vessels in a normal bladder from a healthy cat using liquid distention to 80 cm water pressure.



When cats present for periuria (but not spraying) as the only reported clinical sign, it can be difficult to decide if they should be classified as FIC or a behavioral problem. On cystoscopy in cats with only periuria, more than half had abnormalities in their bladder such as increased vascularity, edema, or glomerulations (submucosal petechial hemorrhages).[10] Cats with FIC may have a behavioral component simultaneously, and as many as 40% of cats with periuria have had a previous diagnosis of cystitis.[11] Regardless of the presence or absence of cystoscopic lesions, we treat cats with periuria similarly to cats with FIC.

Figure 266-2 Cystoscopic appearance of a bladder from a cat with feline idiopathic cystitis (FIC). Multiple small submucosal petechial hemorrhages (glomerulations) are present, as well as edema.



266.1 EPIDEMIOLOGY

The ratio of LUT cases to all cases seen in a clinic or hospital is called the *proportional morbidity rate*. Proportional morbidity differs from incidence because its denominator is biased toward sick animals owned by clients who are willing and able to bring their pets to a veterinarian, as well as the clinical interests of veterinarians involved in the study. Proportional morbidity estimates of LUT signs in cats have ranged from 1% to 6%,[12] and a recent study reported a rate of approximately 1.5%.[8] Recurrence rates for LUT signs are high. In one study, 45% of male cats experienced recurrence within 6 months of an initial episode of LUT obstruction.[13] In another study, the recurrence rate for affected cats without obstruction was 39% within 1 year.[14] A slightly higher recurrence rate (approximately 55%) was reported in another study.[15]

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A case-control study of cats with LUT signs was conducted recently in New Zealand (1991 to 1993).[16] One hundred ninety-three affected cats were compared with 189 case-matched (sex and age) and 189 random control cats from 13 private veterinary practices. No difference in age, gender or neuter status was identified between cases and controls. Increased risk of LUT signs was found for use of a litter tray only for elimination (cat unable to leave the house to eliminate), confinement indoor greater than or equal to 21 hours per day, sleeping inside, a move to a new house during the past 3 months, *ad libitum* feeding of dry cat food, and dry cat food feeding with low fluid intake. An increased incidence occurred during winter months, and further analysis identified a highly significant association with rainy days during the previous month. Access to outdoor prey was found to be protective.

Other studies have also reported an increased risk for LUT signs in cats fed exclusively dry food. A recent analysis of these data suggested increased risk with increased dry food consumption.[12] We found a 1-year recurrence rate of 39% in nonobstructed cats with FIC fed the dry formulation of a commercial food, whereas the recurrence rate in cats fed the canned formulation was 11%.[17] In another study, risk increased with the number of meals fed per day and was greater with periodic feeding than with *ad libitum* feeding.[12]

These studies support previous studies that found the risk for LUT signs to be highest in indoor-restricted cats that predominantly eat dry food.[12] Risk factors, however, must be kept in perspective. The proportional morbidity of LUT signs in the cat population is approximately 1.0%, although many cats are kept indoors and fed dry food exclusively.[18] The reformulation of many commercial cat foods (based on earlier epidemiologic studies) apparently has not reduced the role of dry food as a risk factor for LUT signs in cats. This circumstance suggests that environmental factors may unmask an underlying predisposition to LUT signs in some cats. The exact nature of this predisposition remains to be determined. The identification of differences in breed susceptibilities suggests that internal and environmental factors can influence disease risk in cats. Willeberg,[12] in a 1984 review, concluded that Siamese cats had a reduced risk of LUT signs, whereas Persians were at an increased risk. Jones and colleagues[16] reported an increased risk of LUT signs among long-haired but not purebred cats.

LUT signs can occur at any age but are unusual in cats less than 1 year of age and most frequent in cats 2 to 6 years of age. When clinical signs are considered without regard to obstruction, no difference in risk between males and females is observed. Adjustment for age is important because both neutering and LUT signs are age related. When adjusted for age, risk is greater for castrated males and spayed females than for intact cats,[12] but the age at neutering does not seem to be important.[19]

Excessive body weight and decreased activity have been associated with increased risk for LUT signs in some studies. When evaluating husbandry, the data concerning risk for LUT signs are mixed, indicating variously no effect[12,16] or increased risk.[20] If an increased risk exists in multiple-cat households, it could be associated with feeding and husbandry practices, territorial conflict, or horizontally transmitted infectious agents that could play a role in the development of LUT signs. Lack of a difference between affected and control cats in upper respiratory disease and the increase in risk associated with increasing amounts of time spent *indoors* seem to argue against infection as a causative factor in LUT signs of cats.[16]

266.2 FELINE IDIOPATHIC CYSTITIS

266.2.1 Pathophysiology

A variety of abnormalities have been found in the bladders, nervous system, hypothalamic-pituitary-adrenal axis, and other body systems in cats with FIC. FIC in cats is similar to interstitial cystitis in human beings. Humans serve as a useful model for cats with FIC, and vice versa.[5] Cats are classified as having *feline interstitial cystitis* if cystoscopy is performed and characteristic glomerulations are seen. Cats with feline interstitial cystitis meet all of the inclusion criteria, and exclusion criteria for diagnosis of interstitial cystitis that can be applied to animals.[21] Thus (allowing for species differences), cats with feline interstitial cystitis meet the National Institutes of Health (NIH) criteria for humans. Feline interstitial cystitis primarily resembles nonulcer interstitial cystitis in humans, although ulceration and inflammatory infiltrates occasionally have

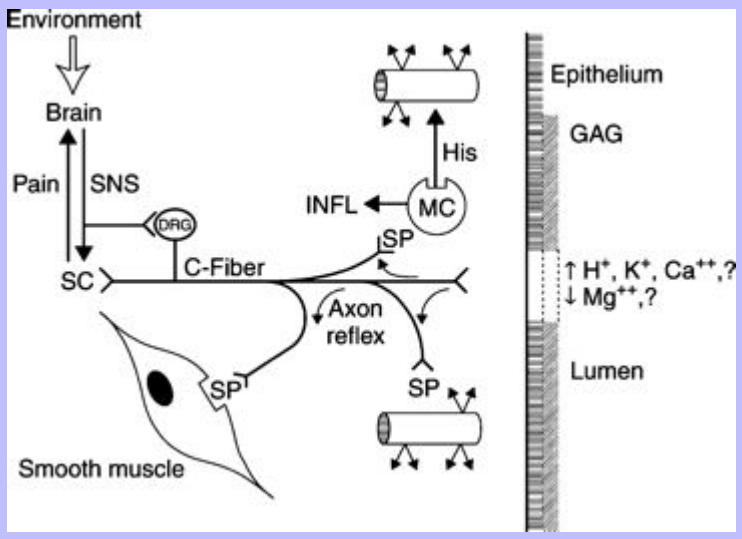
been observed in cats. Abnormalities of local bladder factors, sensory (afferent) neurons, central nervous system (CNS), and sympathetic (efferent) neurons occur in cats as they do in humans.[22]

Gender distribution seems to be different between affected males and females of cats and humans. In cats, both genders are affected roughly equally, whereas 90% of humans are women.[23] One reason for the gender discrepancy may be related to differences in diagnoses rather than diseases. For further details, the reader is referred to a recent review on similarities between cats and humans and to other models of interstitial cystitis.[21]

Both humans with interstitial cystitis and cats with FIC seem to excrete smaller amounts of both total urinary glycosaminoglycan[25] (GAG) and a specific GAG (GP-51)[26,27] than do normal individuals. GAG and GP-51 contribute to the surface mucus covering the urothelium that is believed to inhibit bacterial adherence and urothelial injury from the constituents of the urine. A defective GAG layer or damaged urothelium could permit hydrogen, calcium, potassium ions, or other constituents of urine to come into contact with sensory neurons innervating the urothelium. These ions can stimulate local release of neurotransmitters and result in neurogenic bladder inflammation[28] (Figure 266-3). Sensory neurons reach the bladder via the pelvic and hypogastric nerves, and the central processes of these nerves synapse in the dorsal horn of the sacral and lumbar spinal cord, respectively.[29] These neurons include unmyelinated nociceptive fibers, commonly referred to as *C fibers*. In one study of normal cats, only ~2.5% of C fibers responded to bladder distention. However, more than 10% of these fibers responded after infusion of an irritant into the bladder lumen. This increase was attributed to activation of normally "silent" C fibers, which respond only to noxious stimuli.[30]

Histologic changes associated with FIC are generally nonspecific and may include an intact or damaged urothelium with submucosal edema, dilation of submucosal blood vessels with marginated neutrophils, submucosal hemorrhage, and sometimes increased mast cell density[5] (Figure 266-4). Bladder mastocytosis appears to be involved in the pathogenesis of interstitial cystitis in some human patients and also in some cats with FIC[31–33] (Figure 266-5). Scanning electron microscopy of bladders in cats with FIC revealed patches devoid of superficial epithelial cells (so-called umbrella cells of the urothelium)[34] and disruption of tight junctions that worsened after hydrodistention (Figure 266-6). No correlation between histology, cystoscopic lesions, and clinical signs appears to exist in cats. In fact, owners have reported complete remission of LUT signs in cats with FIC, but visualization of their bladder revealed glomerulations and other abnormalities.[35] Similar studies have been documented in humans with interstitial cystitis.[36] Because of these findings, the authors do not routinely use cystoscopy or histopathology to monitor response to therapy.

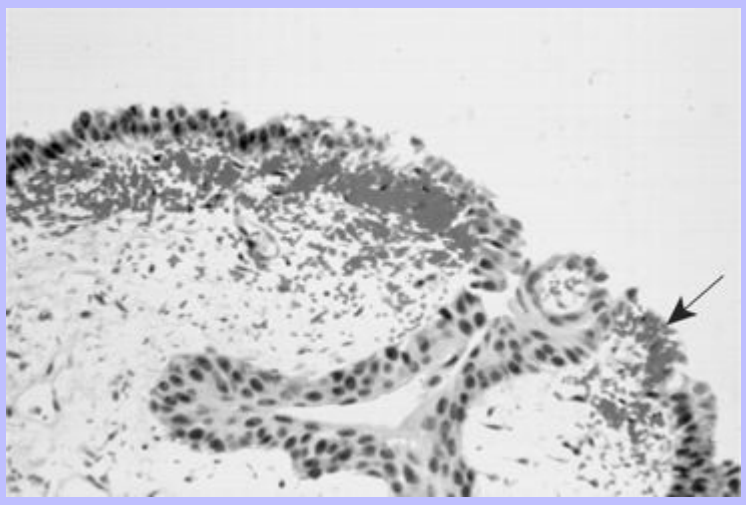
Figure 266-3 Conceptual model of bladder response to noxious stimuli. Damage of malfunction of glycosaminoglycan *(GAG)* layer or urothelium may permit urine constituents to activate sensory neurons *(C fiber)* in submucosa, which transmit action potentials to the spinal cord *(SC)* that are perceived as painful by the brain. Sensory fibers can also generate local axon reflex without propagating action potential. Axon reflex results in release of peptide neurotransmitters, such as substance P *(SP),* by nerve endings. Interaction of SP with receptors on vessel walls results in vascular leakage, which can be augmented by SP-induced release of histamine *(HIS)* by mast cells *(MC)*. These actions may give rise to submucosal petechial hemorrhages observed at cystoscopy. SP receptors also occur on smooth muscle, which when activated stimulate muscle contraction. In addition to luminal insults, increased vascular permeability and desquamation of superficial cells of urothelium can also results from systemic and environmental stimuli, and activate C fibers and mast cells. *SNS*, Sympathetic nervous system; *INFL*, inflammation; *DRG*, dorsal root ganglia.



Studies in cats with FIC have shown increased leakage of ions across the urothelium and urea leakage in nonhydrodistended bladders. Marked increases in permeability after hydrodistention were also present.[34] Bladder permeability is reported to be increased in cats with FIC. Bladder permeability to sodium salicylate was increased in an *in vivo* study of cats with FIC.[37] Additionally, *in vitro* bladder epithelial urea permeability

was significantly increased from normal in both undistended and distended bladders, water permeability was significantly increased in distended bladders, and transitional cell desquamation was identified in cats with FIC.[34] Cyclophosphamide-induced cystitis in rats and other animal models of cystitis have increased bladder permeability.[38] Therefore it is likely this finding is not specific to FIC but an underlying problem that might affect the nerves in the urothelium causing a perpetuation of clinical signs.

Figure 266-4 Histopathologic section of a bladder biopsy from a cat with feline idiopathic cystitis (FIC). Usually, cats with this disease have a very mild cellular infiltrate. Blood and edema can "pool" under the urothelium, and breaks in the urothelium can be seen. Submucosal hemorrhages would appear as a glomerulations when viewed cystoscopically. (H&E; × 40.)



Substance P (SP), an 11 amino acid peptide neurotransmitter, has been identified in the bladder C fibers of cats with FIC. The authors have observed a modest increase in SP immunoreactivity (IR) in the bladder of cats with FIC.[39] Significant increases in the SP receptor density (NK-1 receptors) in the bladder of humans with interstitial cystitis and cats with FIC also have been reported.[41,42] Unfortunately, clinical trials of the analgesic properties of SP antagonists in humans have been disappointing.[43,44] SP antagonists have not been investigated in cats with FIC.

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Figure 266-5 Histopathologic section of a bladder from a cat with feline idiopathic cystitis (FIC) stained with toluidine blue to visualize mast cells. Bladder mastocytosis may contribute to the pathophysiology of FIC in some cats, but mast cell stabilizing drugs do not appear to be beneficial in most cases.

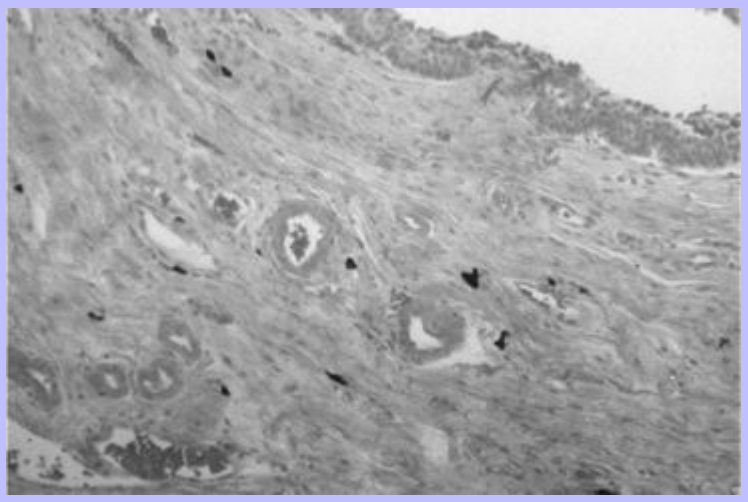


Figure 266-6 Scanning electron microscopy analysis of hydrodistended bladders from normal and feline idiopathic cystitis (FIC) cats. **A,** Low-magnification view of control bladder. **B,** High-magnification view of control bladder showing individual umbrella cells. **C,** Low-magnification view of FIC bladder demonstrating region where umbrella cell layer is disrupted. **D,** Close-up of area enclosed by box in **C. E,** Low-magnification view of FIC bladder showing regions where the urothelium is denuded from the underlying connective tissue. **F,** Close-up of area enclosed by box in **E**. (From Lavelle JP et al: Urothelial pathophysiological changes in feline interstitial cystitis: a human model. Am J Physiol Renal Physiol 278(4):540–553, 2000. Used by permission.)

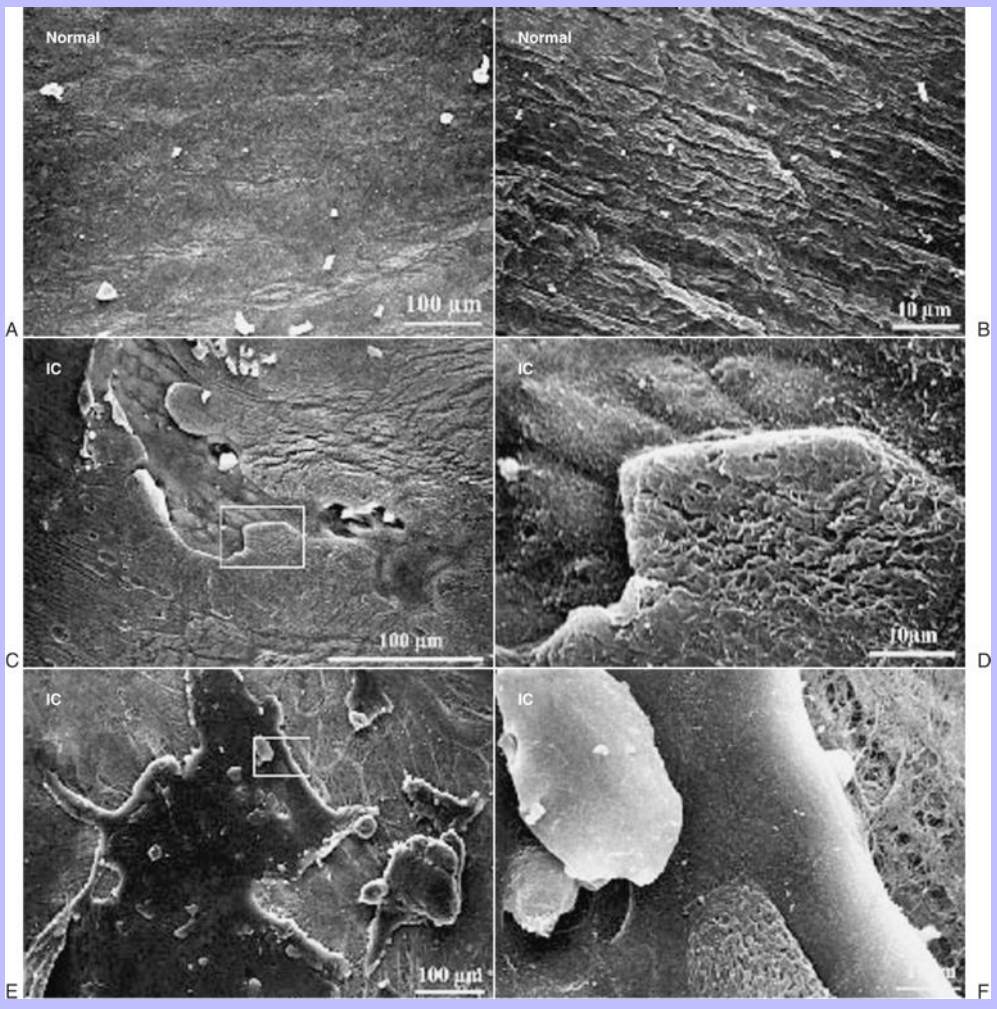
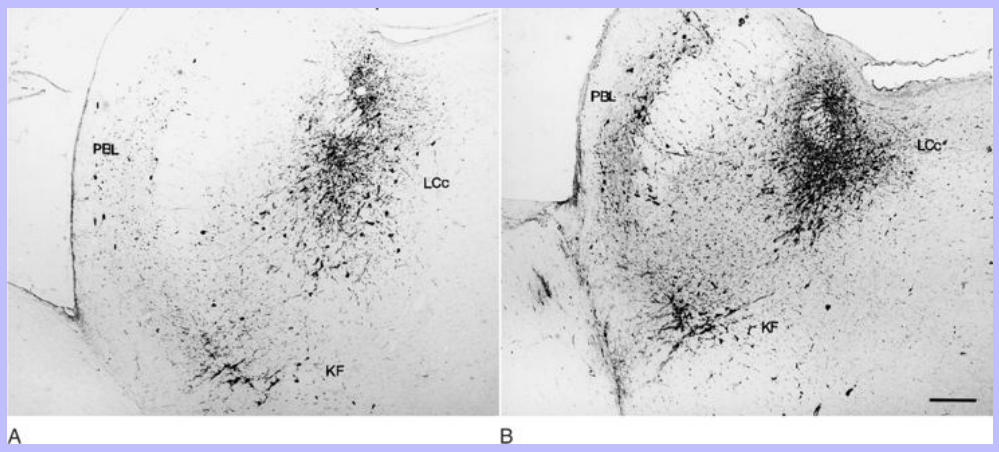


Figure 266-7 Photomicrographs of coronal sections of locus coeruleus *(LC)* of normal cat **(A)** and a cat with FIC **(B)**, immunostained for tyrosine hydroxylase *(TH)*. Reader should note increased staining density in LC complex *(LCc)*, parabrachial lateral *(PBL)*, and Kolliker-Fuse *(KF)* nuclei of cat with FIC compared with normal cat. Scale bar: 20 µm.



A significant increase in tyrosine hydroxylase (THIR) has been identified in the locus coeruleus (LC)[45] and in the paraventricular nucleus of the hypothalamus in cats with FIC[46] (Figure 266-7). TH is the rate-limiting enzyme of catecholamine synthesis. Bladder distention stimulates neuronal activity in the LC, and the LC (Barrington's nucleus) is the origin of the descending excitatory pathway to the bladder.[47] Moreover, chronic stress can increase TH activity in the LC,[48] with accompanying increases in autonomic outflow.[49] The LC contains the largest number of noradrenergic neurons and is the most important source of norepinephrine (NE) in the feline and human CNS. It is involved in such global brain functions as vigilance, arousal, and analgesia and appears to mediate visceral responses to stress.[50] The increased THIR observed in the LC of cats with FIC may provide a clue to the observation that clinical signs of FIC follow a waxing and waning course, and that they can be aggravated by environmental stressors.[28,51]

In addition to increased LC activity, cats with FIC also have increased plasma NE concentrations.[52] Increased plasma and CSF catecholamine concentrations and their metabolites compared with healthy cats have been measured during stressful situations. The stress studies included removing food 12 hours prior to testing, moving the cats to different cages, and abruptly changing their diets. As the healthy cats acclimated to the stress, their plasma catecholamine concentrations decreased, whereas cats with FIC demonstrated even higher concentrations of plasma NE, epinephrine, and their metabolites.[53] Enhanced stimulus-induced local NE release from the bladder,[61] and functional desensitization of central alpha-2 adrenoceptors (α-2 AR) have been reported in cats with FIC.[55] In the LC, α-2 agonists inhibit NE release, whereas in the spinal cord they inhibit transmission of nociceptive input to the brain.[56,57] Although spinal α-2 AR activation can inhibit nociceptive

input acutely, the receptors can become desensitized or down-regulated after chronic stimulation (i.e., by continuously elevated NE).[58,59]

In the bladder, α2-ARs are found primarily in the urethral submucosa and bladder mucosa (not the muscle), suggesting a role in the regulation of blood flow and urethral lubrication.[60] In this study, no α2-ARs were found in the bladder muscle, implying these receptors are not involved in bladder contraction. However, the α2-ARs can modulate NE outflow and may alter bladder contractility. Decreased sedation after clonidine administration intramuscularly and decreased mydriasis after medetomidine, a more selective α2 agonist, was found in cats with FIC, suggesting decreased α2-AR responsiveness *in vivo*. The reason for this is unclear, but it could be caused by receptor down-regulation due to persistent elevation in NE. In the presence of elevated NE, presynaptic α2-ARs could become down-regulated and unable to inhibit NE release. Electrical field stimulation studies of bladder strips from FIC cats revealed that atipamezole, an α2 antagonist, did not alter the relaxing effect of NE, further suggesting that α2-ARs are down-regulated in this disease.[61]

Based on history, physical examination and clinical signs, pelvic pain is a feature in cats with FIC. Abnormalities in the α2-ARs could be detrimental to patients because postsynaptic spinal α2-ARs possess antinociceptive properties and the α2a-AR subtype has been documented to play the major role in the control of spinal nociceptive responses.[62]

In addition to the sympathetic nervous system (SNS), abnormalities in the hypothalamic-pituitary-adrenal axis (HPA) have also been observed in cats with FIC. After a high dose (125μg) of synthetic adrenocorticotropic hormone (ACTH) was administered, cats with FIC had significantly decreased serum cortisol responses compared with healthy cats.[64] Using computed tomography (CT) and gross histopatholgic evaluation, the adrenal volume (both absolute and per kilogram body weight) were significantly lower in FIC cats, but no correlations could be found between adrenal size and cortisol production.[65] Although no obvious histologic abnormalities were identified, the areas consisting of the zonae fasciculata and reticularis were significantly smaller in sections of glands from cats with FIC than from healthy cats. Therefore it appears that although the sympathoneural system is fully activated in this disorder, the HPA axis is not. The significance of this finding is not known.

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Based on the identified sensory abnormalities in cats with FIC, the authors have begun to measure response to acoustic startle. These studies are designed to evaluate the observed anxiety-related behaviors. The acoustic startle response (ASR) is a brain stem reflex that responds to unexpected, loud stimuli. The magnitude of the response can be altered by a variety of experimental manipulations and is affected by many pathologic conditions. These attributes have led to use of the ASR to study neurologic dysfunctions of sensorimotor information processing. Given the role of neural abnormalities in cats with FIC,[52] it was speculated that their ASR responses might be abnormal, and initial results revealed the magnitude of ASR to 105 dB averaged more than double that of healthy cats.

The pathophysiology of FIC is not fully understood and may involve complex interactions between a number of body systems. Abnormalities are not localized just to the bladder, but are present in the nervous,[52] endocrine,[65] and cardiovascular systems.[67] How these systems communicate and manifest as FIC in some cats but not in others remains to be determined. To better treat their patients, it is important for clinicians to understand that this syndrome is not just a “bladder disease” amenable to simple diet or drug therapies.

266.2.2 Approach to the Patient

In humans with interstitial cystitis, various assays for urine markers have been evaluated to attempt to properly identify a marker unique to this disease.[68] Of all the factors evaluated, the recently identified *antiproliferative factor* had the least crossover with healthy controls and could be used to aid in the diagnosis of this disease. This and other assays have not been studied and are not readily available for human or feline patients. Therefore the diagnosis of FIC still remains a *diagnosis of exclusion.* An algorithm to aid clinicians in the diagnostics and treatment of FIC is presented in Figure 266-8. Because some two thirds of cats with LUT signs have FIC, and it appears that approximately 85%[69] of cats with FIC resolve their clinical signs in 2 to 3 days without treatment, it is debatable whether any diagnostics should be performed for a young cat in its first presentation of LUT signs. The basic tests are listed, and the clinician must decide based on the cat's signalment and clinical signs which tests will yield the most benefit for each individual patient.

266.2.2.1 Radiography

A plain abdominal radiograph that includes the entire urinary tract (including urethra) can be a useful diagnostic tool in cats with LUT signs. Approximately 15% of cats with stranguria, hematuria, pollakiuria, or a combination of these conditions will have radiographic evidence of cystic calculi. If only one diagnostic test can be performed, survey abdominal radiography is likely to provide information that is most clinically relevant. Contrast studies of the bladder and urethra in cats with FIC are usually unremarkable, though 15% have diffuse or asymmetrical thickening of the bladder wall.[70] A contrast cystogram and urethrogram can be helpful to evaluate for nonradiopaque calculi and other lesions such as mass lesions, blood clots, and strictures in cats with recurrent episodes. Contrast studies are especially indicated in elderly cats (> 10 years of age) where FIC is not as likely.

266.2.2.2 Urinalysis and culture

Less than 2% of young (<10 years of age) cats have true bacterial cystitis, so urine culture is a low-yield test.[1,10] Quantitative urine culture should be performed in all cats with recurrent (>2 episodes) LUT signs. The possibility of a UTI increases with age, perineal surgery, cystic calculi, or dilute urine.[71] A quantitative urine culture should be performed in cats with LUT signs older than 10 years of age, with a urine specific gravity (USG) less than 1.030, which has undergone perineal urethrostomy, or after a urinary catheter has been placed.

Urinalysis findings such as hematuria, proteinuria, and crystalluria are not specific for any particular type of bladder disease or even a specific stone type. For example, one can see pyuria if a true UTI is present, but mild pyuria can also be present in sterile cystitis upon occasion. Crystalluria can be found in many cats with no signs referable to their LUT. A baseline urinalysis is valuable to exclude polyuria. If submaximal urine concentration is present (<1.035 for cats eating solely dry food; <1.025 for cats eating primarily canned foods), it is possible that increased urine volume contributed to the condition. Therefore a serum biochemical profile and thyroid evaluation should be obtained.

When radiographic findings are negative and a urine culture reveals no growth in cats with no other identifiable abnormalities, the diagnosis of FIC is likely. However, if clinical signs persist after proper environmental and drug therapy have failed, the veterinarian should consider a referral to a specialty clinic for cystoscopy.

266.2.2.3 Cystoscopy

Cystoscopy is performed at referral practices when LUT signs fail to resolve after standard therapy in those cats with negative findings from radiography and urine cultures. This tool allows one to visualize the urethra and bladder at low and high pressures. Small cystic calculi, urachal diverticula, ectopic ureters, and small polyps all can be visualized (Figures 266-9 and 266-10). The authors do not use cystoscopy to "rule in" FIC, but rather to exclude less common diseases. Occasionally, increased vascularity and glomerulations have been noted in stressed, otherwise healthy cats; such lesions may remain in affected cats without clinical signs following treatment.[35]

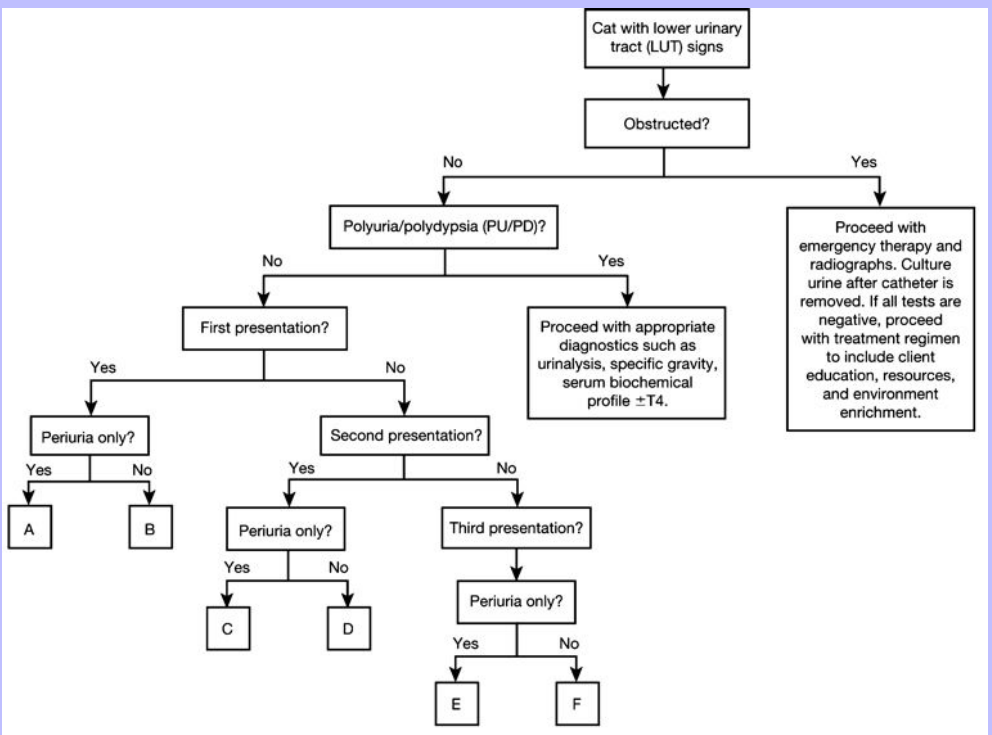
266.2.3 Treatment of Feline Idiopathic Cystitis

Having the proper tools to help owners understand FIC is important in maintaining client satisfaction when beginning any treatment regimen. It is not yet possible to predict which cats with FIC will relapse, so clients should be told what they can do to help decrease the risk of another episode. Clinical signs resolve spontaneously in as many as 85% of cats within 2 to 3 days, regardless of treatment. About 40% to 50% of these cats will have another episode within 12 months.[15,73] Some cats will have multiple recurrences, whereas a smaller population will never have complete resolution of clinical signs.

The underlying cause of this disorder is unknown, so current treatment recommendations must be tentative. The current goals of therapy for cats with FIC are not to "cure" them, but to decrease the severity of signs and to increase *interepisode* intervals, especially for severely affected cats.

Enhanced stress response system activity seems to be central to maintaining the chronic inflammatory process. Any treatment strategy to decrease SNS outflow may be important in reducing inflammation. Reduction of the noxiousness of urine or normalizing bladder permeability may also prove useful. An overarching premise is that FIC is not just a bladder disorder but involves complex interactions of the nervous and endocrine systems.[65] The development of chronic FIC requires the presence of a susceptible cat in a provocative environment. The challenge is to identify what is provoking the susceptible cat in hopes of preventing future bouts. Analgesia, changes in diet and water intake, discussion of feeding practices, litter box management, cleaning of soiled areas, restoration of normal cat behaviors and activities, and drug therapy all are considered as part of the authors' current approach to therapy.

Figure 266-8 Algorithm for lower urinary tract signs in the cat.



A **Diagnostic:** None are usually necessary.
Treatment: Litter box management and cleaning of soiled areas should be addressed.
Medications: No medications are recommended.

B **Diagnostic:** A radiograph should be considered, especially if hematuria is present.
Treatment: If the radiograph is negative, therapy should include analgesia for 2 to 3 days during the acute episode. Litter box management and cleaning of soiled areas should be addressed.
Medications: No medications are recommended.

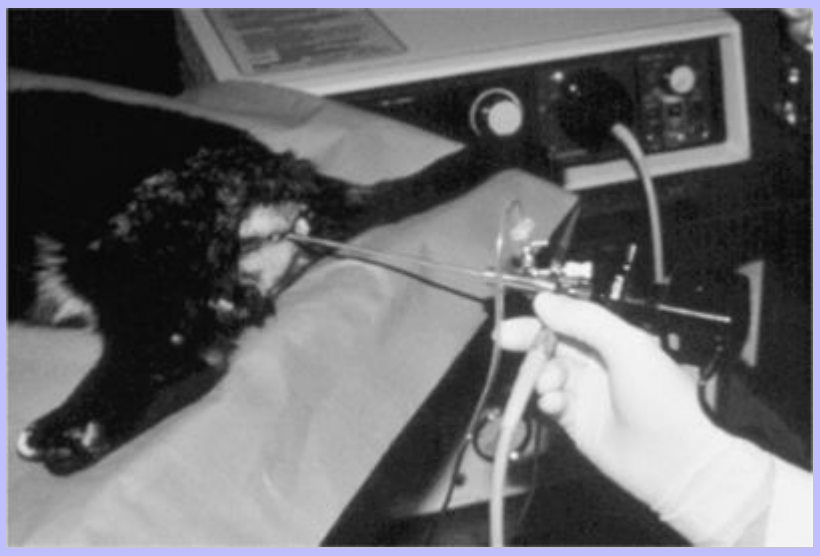
C **Diagnostic:** A urinalysis is recommended. If submaximal urine-specific gravity is present, then appropriate diagnostics are needed.
Treatment: If diagnostic tests are negative, then the resource checklist should be reviewed and additional areas that were not previously addressed should be incorporated.
Medications: Phermonotherapy is recommended.

D **Diagnostic:** A radiograph, urinalysis, and urine culture are recommended.
Treatment: If all tests are negative, analgesia should be provided for 2 to 3 days during acute episode. Canned food is encouraged for the cat in addition to litter box management and cleaning of soiled areas. The cat's urine-specity gravity is monitored for 3 to 4 weeks to assess the cat's water intake.
Medications: Phermonotherapy is recommended.

E **Diagnostic:** A urinalysis should be performed if it has not already been done. Radiographs, urine culture, and biochemical profile are also recommended.
Treatment: If all tests are negative, then the resource checklist is formally reviewed and those areas that have not already been addressed should be incorporated. Further information for cleaning soiled areas should be provided. Additional resources (web sites, books) on how to provide an enhanced indoor environment for cats should be provided to clients. Intercat conflict issues should also be addressed.
Medications: Phermonotherapy should be used in conjunction with behavior-altering medications such as tricyclic antidepressants (TCAs) or buspirone. The medication should be taken for 4 weeks; if no improvement is seen, a referral for further diagnostics and consultation should be considered.

F **Diagnostic:** A radiograph, an urinalysis, and a urine culture should be performed. A complete blood count (CBC) and biochemical profile should also be submited. If all tests are negative, a contrast study or abdominal ultrasound of the bladder and urethra should be condered to rule out nonradiopaque calculi and other mass lesions.
Treatment: If all diagnostics are negative, analgesia should be provided for 2 to 3 days during acute episode. In addition to canned food, the sheet on "Increasing your cat's water intake" should be reviewed. Water should be viewed as a "drug," and the cat's urine-specific gravity should be monitored to evaluate water intake. The resource checklist should be formally reviewed, and those areas that have not already been addressed should be incorporated. Additional resources (web sites, books) on how to provide an enhanced indoor environment for cats should be provided to clients. Intercat conflict issues should also be addressed. Follow up and support for clients are essential.
Medications: Phermonotherapy should be used in conjunction with behavior-altering medications such as TCAs or anxiolytics. Medication should be taken for 4 weeks; if no improvement is seen, a referral for further diagnostics such as a cystoscopy should be considered.

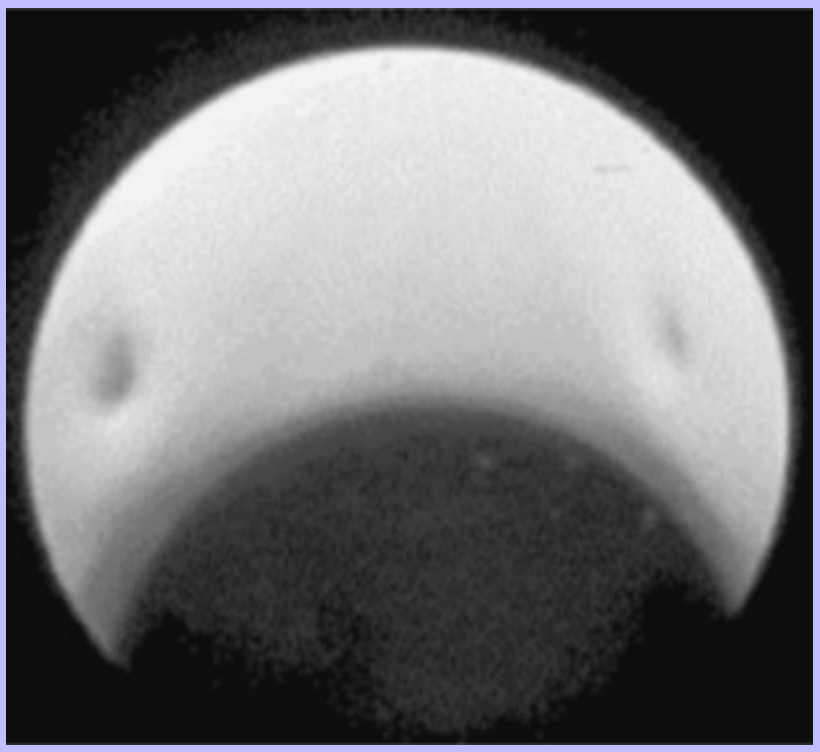
Figure 266-9 Cystoscopy of an anesthetized female cat using a 9F rigid cystoscope.



Using strategies from the literature,[74] the authors have found that clients will report a positive outcome (regardless of how well their cat responds to recommended therapies) if the client feels:

1. Listened to.
2. They receive an explanation for the problem that makes sense to them.
3. They feel care and concern being expressed by the caregivers and others in the clinic.
4. They gain an enhanced sense of mastery or control over the cat's illness or its symptoms.

Figure 266-10 Cystoscopic view of the right and left ureteral openings in a cat. They often appear to be in the proximal urethra when the bladder is not fully distended.



Because FIC can be a chronic, frustrating disease, the authors have found that keeping these four points in mind when communicating with clients benefits the client, pet, and clinician. The authors have also established a technician program whereby staff members follow a cat's progress as often as necessary to be sure that problems are explained thoroughly and that client gains enough understanding of the disease process to feel comfortable with managing the cat's disease.

266.2.3.1 Provisional Recommendations (Environmental Changes and Resources Available for Cats with FIC)

A list of necessary resources for indoor-housed pet cats has not yet been validated, but some recommendations are available.[75–78] Cats appear to benefit from appropriate access to resources, control of interactions with owners, and a tolerable level of conflict with other animals. The authors have assembled a provisional list for use by owners to guide consideration of some of these parameters (Box 266-1).

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The following tentative recommendations are organized to follow Box 266-1; more comprehensive suggestions are available in the many available publications about pet cats. Owners should try to institute environmental modifications slowly, one at a time, and in such a way that the cat can express its like or

dislike for the change.[79] The clinician should follow a staged approach to therapy that begins with client education and environmental enrichment. If a cat relapses, these topics are thoroughly reviewed and pheromonotherapy or drug therapy may then be instituted in conjunction with environmental strategies.

There should be enough litter boxes in different locations throughout the house. A rule that many find helpful is 1+1: *one* for each cat of a household plus *one*—and placing litter boxes in quiet, convenient locations. If different litters are provided, it may be preferable to offer them in separate boxes, because individual preferences for litter type have been documented.[80] Cats with a history of LUT problems reportedly prefer, unscented clumping litter.[11] Litter boxes should be cleaned regularly and replaced; some cats seem quite sensitive to dirty litter boxes. Litter box size and whether or not it is open or covered also may be important to some cats.[81]

Research has demonstrated that blowing an innocuous puff of air into a cat's face while it eats can lead to behavioral abnormalities.[82] This suggests that cats should be fed individually in a quiet location where they will not be startled by other animals, sudden movement, or activity of an air duct or appliance that may begin operation unexpectedly. Although canned food may be preferable for cats with FIC due to the increased water content, some cats may prefer dry foods;[83] offering choices in separate, adjacent containers rather than replacing the usual food with a new food permits cats to express their preferences. Feeding behavior also includes predatory activities. These may be simulated by hiding small amounts of food around the house, or by putting dry food in a container from which the cat has to extract individual pieces[84] or move to release the food pieces (if such interventions appeal to the cat).[77] Cats also seem to have preferences for water that can be investigated. Consideration may be given to freshness, taste, movement (water fountains, dripping faucets, or aquarium pump–bubbled air into a bowl), and shape of container (some cats seem to resent having their vibrissae touch the sides of the container when drinking). Food and water bowls should be cleaned regularly unless individual preference suggests otherwise.

The physical environment should include opportunities for climbing, scratching, hiding, and resting. Cats seem to prefer to monitor their surroundings from elevated vantage points; provision of climbing frames, hammocks, platforms, raised walkways, shelves, or window seats have been recommended.[77,78] Playing a radio to habituate cats to sudden changes in sound and human voices also has been recommended,[85] and videotapes to provide visual stimulation are available.[77]

Some cats may prefer to be petted and groomed, whereas others may prefer play interactions.[86] Play interactions with cats may include lures or laser pointers.[76,77] Cats also may enjoy playing with toys, particularly those that are small, move, and that have characteristics of natural prey.[87,88] For cats that prefer novelty, a variety of toys should be provided and rotated or replaced regularly.[87]

In multicat houses, cats also interact with each other. Because cats housed in groups do not appear to develop distinct dominance hierarchies or conflict-resolution strategies, they may attempt to circumvent agonistic encounters by avoiding others or decreasing their activity.[89] Unrelated cats housed together in groups appear to spend less time interacting with one another than related ones.[83] These cats may prefer to have their own separate food and water sources, litter boxes, and resting areas to avoid competition for resources and to avoid unwanted interactions.[89] Published guidelines for introducing new cats into a home are available and may be recommended to clients adding cats to their households.[76] Because of the dearth

of controlled trials, it is not currently possible to prioritize the importance of these suggestions or to predict which would be most appropriate in any particular situation.

266.2.3.2 Dietary Treatment

Dietary modifications may reduce the risk of recurrence of LUT signs in affected cats. Struvite crystals do not appear to damage normal urothelium, and efforts to acidify the urine to reduce struvite crystalluria by dietary modification are often *not* necessary. Efforts to acidify the urine using dry foods have no demonstrated value in treatment of FIC. Clinical experience suggests that diet change can result in recurrence of FIC signs in some cats. Moreover, with the advent of many similarly formulated prescription and commercial foods marketed for use in cats with urolithiasis or to "promote urinary tract health," changing diets can still result in recurrence of signs associated with FIC. It is not recommended to frequently change diets. It is encouraged to increase water intake, and consumption of a canned food is one way to accomplish this. To avoid the potential stress of being confronted with an unfamiliar diet, it is recommended to begin feeding new canned food alongside the original diet.

In studies from the United States and New Zealand, cats with idiopathic cystitis were significantly more likely to be fed dry food exclusively.[10–16] LUT signs recurred in only 11% of affected cats during 1 year of feeding canned formulation of a dietary product. Recurrence occurred in 39% of cats fed the dry formulation of the same food, suggesting that both constancy and consistency (i.e., increased water intake) may be important. Both diets contained similar potential renal solute load and resulted in a similar urine pH. The average USG of cats fed the dry formulation was 1.050, whereas that of the cats fed the canned formulation was 1.030. It appears that the canned form protected nearly 90% of cats against recurrence of LUT signs for up to 1 year, constancy of diet protected about 60%, and 10% were offered no protection from recurrence by diet. In addition to water contained in food, the suggestions the authors provide owners to encourage increased water intake by their cats are presented in Box 266-2 and 266-3.

266.2.3.3 Pheromonotherapy

Pheromones are fatty acids that seem to transmit highly specific information between animals of the same species. Although the exact mechanisms of action are unknown, pheromones reportedly induce changes in both the limbic system and the hypothalamus that alter the emotional state of the animal.[90] Five facial pheromones have been isolated from the cat (Table 266-1). A cat deposits the F3 fraction of facial pheromones on prominent objects (including humans) by rubbing their head against the object when the cat feels safe and at ease.[90] Feliway® (Ceva Sante Animale, Libourne, France), a synthetic analogue of this naturally occurring feline facial pheromone, was developed in an effort to decrease anxiety-related behaviors of cats. Although not specifically tested in cats with FIC, treatment with this pheromone has been reported to reduce the amount of anxiety experienced by cats in unfamiliar circumstances, a response that may be helpful to both cat and owner. Increased grooming and food intake in hospitalized cats[91] also has been reported with the use of Feliway®. Others have reported decreased spraying in multicat households,[92] decreased marking,[93] and a significant decrease in scratching behavior.[90] Although, Feliway® is not a panacea for unwanted cat behaviors or FIC, it has been used successfully in combination with environmental enrichment, drug therapies, or both.

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266.2.3.3.1

Box • 266-1 A Resource Checklist for Cat Owners

Enhanced stress response system activity seems to be central in exacerbating clinical signs in cats with feline idiopathic cystitis (FIC). Any treatment strategy to decrease sympathetic nervous system (SNS) outflow may be important in reducing these signs. By altering the environment of a cat that has had previous episodes of FIC, it is the authors' experience this can decrease clinical signs and increase the interepisode intervals. The authors provide this list to clients and tailor these resources on a case-by-case basis. Although most cats do not require all suggestions from this list, a detailed history obtained from the owner will dictate which areas seem to be most relevant for each patient. If drug therapy is necessary in the patient, it should be used in conjunction with the environmental strategies listed following.

Litter Box Management	Yes	No
Boxes are located on more than one level in multilevel houses.	_	_
Boxes are located so that another animal cannot sneak up on the cat while it uses it.	_	_
Boxes are located away from appliances or air ducts that could come on unexpectedly while the cat uses them.	_	_
The litter is kept clean, scooped as soon after use as possible (at least daily).	_	_
Boxes are washed regularly (at least weekly) with a mild detergent (e.g., dishwashing liquid), rather than strongly scented cleaners.	_	_
Unscented clumping litter is used.	_	_
The brand or type of litter purchased is changed infrequently (less than monthly).	_	_
If a type of litter is offered, it is put in a separate box so that the cat can choose to use it if it wants to.	_	_
Each cat has its own litter box in a convenient, well-ventilated location that still gives the cat some privacy while using it.	_	_
Food and Water		
Each cat has its own food and water bowl in a convenient location that provides some privacy while eating or drinking.	_	_
Bowls are located such that another animal cannot sneak up on the cat while it eats.	_	_
Bowls are located away from appliances or air ducts that could come on unexpectedly while the cat eats or drinks.	_	_
Food and water is kept fresh (daily).	_	_
Bowls are washed regularly (at least weekly) with a mild detergent.	_	_
The brand or type of food purchased is changed infrequently (less than monthly).	_	_
If a new food is offered, it is put in a separate dish next to the familiar food so that the cat can choose to eat it if it wants to do so.	_	_
Environmental Considerations		
Scratching posts are provided.	_	_
Toys are provided, rotated, or replaced regularly.	_	_
Each cat has the opportunity to move to a warmer or cooler area if it chooses to do so.	_	_
Each cat has a hiding area where it can get away from threats if it chooses to do so.	_	_
Each cat has its own space that it can use if it chooses to do so.	_	_
Rest		
Each cat has its own resting area in a convenient location that still provides some privacy.	_	_
Resting areas are located such that another animal cannot sneak up on the cat while it rests.	_	_
Resting areas are located away from appliances or air ducts that could come on unexpectedly while the cat rests.	_	_
If a new bed is provided, it is placed next to the familiar bed so that the cat can choose to use it if it wants to do so.	_	_
Movement—each cat has the opportunity to move about freely, explore, climb, stretch, and play if it chooses to do so.	_	_
Social contact—each cat has the opportunity to engage in play with other animals or the owner if it chooses to do so.	_	_

266.2.3.3.2

Box • 266-2 Increasing a Cat's Water Intake

Another important aspect to treat cats with feline idiopathic cystitis (FIC) and urolithiasis is to increase the cat's water intake. The authors have compiled a list of ways for clients to increase water intake. These “tricks” can be used by themselves or in combinations.

1. Switch from a dry diet to a canned formulation. See Box 266-4 for recommendations on how best to acclimate a cat to its new diet.

2. Add water to the food, whether it is dry or canned. Start slowly, and proceed as the pet's appetite permits. If food is available all the time, feeding the pet two meals a day before beginning to add water could help it accept the water more readily.
3. Place water next to the food. Some animals prefer a full, shallow dish; others seem to like reaching down into a container.
4. Add “wet” foods to the cat's food, like water-packed tuna, clam juice, and (low salt) gravy mixes.
5. Offer distilled or bottled water.
6. Try a pet “fountain” that can be purchased from pet stores and magazines.
7. Leave some water in the bottom of a sink, bathtub, or shower. Putting a shallow bowl under a slow drip ensures a drink of fresh water whenever the cat might want one.
8. Make ice cubes out of meat or fish broth. Bring the contents of a 6 oz can of tuna or salmon, or a cup of ground meat, to boil in 2 cups water, simmer for 10 minutes, and strain through cheesecloth into an ice tray. A broth cube in the pet's water bowl will flavor it and increases water intake in some cats.

A urine specific gravity (USG) should be obtained after 4 weeks of “water therapy” and should be approximately 1.030 if clients are successful.

Feliway® is sold as both a spray and room diffuser, and there has been success in the management of some FIC cats using Feliway®. The spray can be used to treat areas of the house where the cat is urinating by use of a single spray to the affected spot for 30 days. The authors also have found Feliway® to be beneficial to decrease anxiety associated with traveling. Clients can spray the cat carrier 15 minutes prior to the trip and then place the cat in the carrier to help decrease the stress and anxiety most cats associate with travel. The treated areas should be sprayed at least 15 minutes prior to the cat encountering the area, because the vehicle (ethanol) for this pheromone is offensive to most cats. The room diffuser can be placed in a room where the cat inappropriately urinates. One room diffuser is reported to cover approximately 650 square feet and to last for 30 days. This method of administration of the pheromone is new, and controlled trials are needed to make recommendations.

Table • 266-1 Chemical Components of the Facial Scent Gland Secretions in Cats

SECRETION	COMPONENTS	FUNCTION
F1	Oleic acid, caproic acid, trimethylamine 5-aminovaleric acid, *n*-butyric acid, α-methylbutryic acid	Unknown
F2	Oleic acid, palmitic acid, propionic acid, *p*-hydroxyphenylacetic acid	Sexual facial marking in tomcats
F3	Oleic acid, azelaic acid, pimelic acid, palmitic acid	Facial marking on items, antagonist of urine marking and scratching
F4	5β-choestan acid 3β-ol, oleic acid, pimelic acid, *n*-butyric acid	Allomarking, antagonist of territorial or irritative aggression
F5	Palmitic acid, isobutyric acid, 5-aminovaleric acid, *n*-butyric acid, α-methylbutyric acid, trimethylamine, azelaic acid, *p*-hydroxyphenlacetic acid	Unknown

Used with permission from MacDonald DW: The carnivores: order. Carnivora. *In* Brown RE, MacDonald DW (eds): Social odours in mammals. Oxford, Clarendon Press, 1985, p 619–622.

266.2.3.4 Drug Therapy

266.2.3.4.1 Analgesics

A lack of objective information exists to guide analgesic treatment of animals with chronic visceral pain. Amitriptyline (please see following discussion for further details) appears to provide analgesia for some cats, but use of this drug is usually reserved for cats with severe, recurrent FIC. Providing analgesia with nonsteroidal anti-inflammatory agents such as carprofen and ketoprofen, butorphanol, or more potent opioids such as fentanyl (patches) has been suggested; however, no studies have been reported to date, and many drugs are not approved for these uses. Breaking the chronic pain-inflammation cycle may be important in the management of at least some cats with severe disease. During acute flare-ups, some form of analgesia, such as butorphanol (Table 266-2), should be combined with a short-term tranquilizer such as acepromazine. Alternatively, buprenorphine can be used subcutaneously and, anecdotally, per os (a syringe can be used to squirt the injectable form into the cat's mouth). The effects of buprenorphine can last longer than butorphanol because of its high affinity toward mu receptors in the CNS.[94] It is generally easier for clients to give injections to their cats as compared with oral formulations. Because stress has been documented to perpetuate clinical signs, the least invasive approach for the cat should be attempted first, so routes of medication should be tailored for individual cats.

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Table • 266-2 Drugs Commonly Used to Treat and Manage Cats with Lower Urinary Tract Disease

DRUGS COMMONLY USED FOR ANALGESIA	CLASS	MECHANISM OF ACTION	INDICATION FOR USE	DOSE	POTENTIAL SIDE EFFECTS
Butorphanol (Torbugesic® or Torbutrol®)	Synthetic partial opiate agonist	Kappa and Sigma receptor agonist; analgesic effects in the limbic system	Analgesia for acute episode of FIC	0.2–0.4 mg/kg PO, SQ BID-TID	Sedation
Buprenoprhine (Buprenex®)	Synthetic partial opiate agonist	Partial mu receptor agonist	Analgesia for acute episode of FIC	0.01–0.02 mg/kg BID-TID; 0.015 mg/kg PO BID to TID (anecdotal)	Sedation
Fentanyl (Duragesic®)	Opiate agonist	Mu and opiate agonist	Analgesia for acute episode of FIC	25 g/hr	Respiratory depression; bradycardia
Drugs Commonly Used To Alter Bladder/Urethral Contractility					
Acepromazine (PromAce®)	Phenothiazine neuroleptic agent	Block postsynaptic central dopamine receptors; varying degrees of anticholinergic, antihistaminic, antispasmodic and alpha-adrenergic blocking capabilities	For sedation and antispasmodic for urethral obstruction	0.05 mg/kg SQ BID-TID	Hypotension; sedation
Prazosin (Minipress®)	Alpha-adrenergic antagonist	Inhibits α-1 adrenergic receptors	For sedation and antispasmodic for urethral obstruction	0.5 mg/kg PO BID	Hypotension; sedation
Phenoxybenzamine (Dibenzyline®)	Alpha-adrenergic antagonist	Inhibits α-adrenoceptors	For sedation and antispasmodic for urethral obstruction	2.5 mg PO BID	Hypotension; sedation
Bethanechol (Urecholine®)	Synthetic parasympathomimetic	Stimulates primarily muscarinic receptors	Detrusor atony	2.5–5.0 mg PO BID	Vomiting, diarrhea, and salivation
Drugs Commonly Used for the Treatment of FIC					

Amitriptyline (Elavil®)	Tricyclic antidepressant (TCA)	NE reuptake inhibition; central and peripheral anticholinergic activity; antagonism of the H1 receptor; 5-HT reuptake inhibition; glutamate and Na channel receptor antagonist	Chronic FIC	5.0–12.5 mg PO SID-BID	Sedation; weight gain; urine retention; urolith formation
Clomipramine (Anafranil® [human], Clomicalm® [veterinary])	TCA	NE and serotonin reuptake inhibition	Chronic FIC; urine spraying	0.5 mg/kg PO SID	Sedation; anticholinergic effects
Buspirone (BuSpar®)	A nonbenzodiazepine anxiolytic agent	Mixed dopaminergic agonist/antagonist; other mechanisms not well understood	Chronic FIC; urine spraying; anxiety	2.5–5.0 mg PO BID	Rare, but sedation or other neurologic effects
Fluoxetine (Prozac®)	Antidepressant	Selective serotonin reuptake inhibitor	Chronic FIC; urine spraying	1 mg/kg PO SID	Decrease food intake; vomiting and lethargy rare
Pentosan polysulfate sodium (Elmiron®)	GAG replacer	Unknown	Chronic FIC	50 mg PO BID	Diarrhea and vomiting rare
F3 fraction of feline facial pheromone (Feliway®)	Synthetic pheromone	Alter the emotional state of the animal via the limbic system and hypothalamus	Anxiety related behaviors; chronic FIC	1 spray in affected area SID or room diffuser	None reported
Drugs Commonly Used to Manage Urolithiasis					
DL-methionine	Sulfur-containing amino acid	Methionine metabolized and sulfate excreted in urine as sulfuric acid, thereby acidifying urine	For urine acidification when dietary management fails	0.5–1.0 g PO on food once daily	Gastrointestinal (GI) distress; metabolic acidosis
Ammonium chloride	Acid forming salt	Administration results in a decrease in serum bicarbonate and decrease in blood and urine pH	For urine acidification when dietary management fails	20 mg/kg PO BID	Metabolic acidosis; GI distress
Potassium citrate (Uracit-K®)	Alkalinizing salt	Citrate oxidized to bicarbonate; citrate chelates calcium, forming a more soluble salt	To reduce risk of calcium oxalate formation	100–150 mg/kg/day	GI

Allopurinol	Xanthine oxidase inhibitor	Inhibits the enzyme xanthine oxidase, which is responsible for the conversion of oxypurines to uric acid	For prevention/dissolution of ammonium urate stones	9 mg/kg/day	Xanthine stones; rarely used incats so side effects and safety unknown
2-MPG	Sulfhydryl compound related to penicillamine	Undergoes thiol-disulfide exchange with cystine to form a more water-soluble compound	For prevention and treatment of cystine urolithiasis	No studies performed in cats	No information available in cats; anemia in dogs is reported
FIC, feline ideopathic cystitis; SQ, subcutaneously; BID, twice a day; TID, three times a day; PO, oral administration					

We have used amitriptyline, (a tricyclic antidepressant [TCA]) in uncontrolled trials to successfully decrease clinical signs of severe, recurrent FIC.[35] Amitriptyline (Elavil®), may provide analgesia by inhibition of NE reuptake at noradrenergic nerve terminals[95] and possibly due to inhibition of a wide range of nociceptive neurons in the spinal trigeminal nucleus.[96] The beneficial effects of amitriptyline treatment on pain appear to be independent of its effect on depression in human beings.[97] This point is important when considering this drug for cats, because analgesia can occur at lower doses, which potentially could decrease the unwanted side effects such as weight gain and lethargy. Other actions of amitriptyline include the ability to stabilize mast cell membranes (by antagonism of the H1 receptor), serotonin (5-HT) reuptake inhibition, and antagonism of both glutamate receptors and sodium channels.[98] Urine retention through anticholinergic effects of the TCAs may result. Findings in a series of cats with severe FIC showed that the clinical signs of some cats were reduced during amitriptyline treatment during a 12-month period. Improvement in clinical signs was not always accompanied by improvement in the cystoscopic appearance of the bladder. Controlled studies of the safety and efficacy of amitriptyline in cats with FIC are not available, but it has been used with apparent safety by animal behaviorists for more than 10 years.

The drug should be given orally once daily before the owner retires for the night. The dose should then be adjusted to produce a barely perceptible calming effect on the cat (usually 2.5 to 12.5 mg). The reduction in severity of clinical signs can be dramatic in some cats; but in others little or no beneficial effect is observed. If no improvement is seen within 2 to 4 months, the medication should be gradually tapered and then stopped.

Clomipramine hydrochloride (Clomicalm®, veterinary label; and Anafranil®, human label) is also a tertiary amine like amitriptyline, but has more selectivity for blocking the reuptake of 5-HT. It has been reported to provide a beneficial effect (in combination with environmental strategies) for psychogenic alopecia in cats.[99] The authors have prescribed this in recurrent cases of FIC with anecdotal improvement in some cats. Complete blood count (CBC) and serum biochemical profile are recommended before treatment and at 1 and 3 months to ensure no untoward effects of therapy during the use of any TCA.

The selective serotonin reuptake inhibitor, fluoxetine (Prozac®),[100] has been reported to help cats with inappropriate urinations with variable success rates. Fluoxetine was used to help decrease the rate of urine marking after environmental alterations such as litter box hygiene and appropriate cleaning strategies. The nonbenzodiazepine anxiolytic, buspirone (BuSpar®) has been used to decrease high

arousal and reduce anxiety in intercat aggression.[101] Because cats with FIC have exacerbation of clinical signs associated with stressful situations, we have also prescribed buspirone for this disease with some success. Diazepam (Valium®) is a benzodiazepine that is used for behavioral disorders and has sedative, anticonvulsant, and anxiolytic effects. The most serious side effect encountered with the use of oral diazepam in cats is that of idiosyncratic hepatic necrosis,[102] which removes this drug from consideration for long-term therapy. Other benzodiazepines such as alprazolam and temazepam have not been reported to be associated with hepatic toxicity,[103] but experience with the use of these drugs in cats with FIC have not been reported.

We do not recommend amitriptyline for acute treatment of FIC because it has been shown to have minimal to no benefit in the short-term resolution of signs.[15] The authors reserve all the TCAs and the selective serotonin reuptake inhibitors for recurrent, severe cases. These drugs need to be used only after environmental strategies, diet changes (if necessary), and behavior modifications have failed. Furthermore, it is the authors' opinion that these drugs should then only be used in conjunction with the previously mentioned therapeutic strategies for optimal effects.

Amitriptyline (and TCAs) should not be discontinued abruptly, but tapered slowly over 2 to 3 weeks to avoid any possible withdrawal responses that cause exacerbation of clinical signs. The TCAs are extensively metabolized by the cytochrome P450 enzyme system and, although specific drug interactions and safety trials have not been evaluated in animals, caution is recommended when prescribing TCAs with other drugs known to affect drug metabolism.[103]

The act of medicating a cat can be stressful for some cats and owners. Transdermal delivery systems for drugs are available that make the administration of the drug much easier, but no clinical trials compare the plasma concentration, safety, and efficacy of the transdermal preparations to their oral counterparts. The authors are reluctant to recommend transdermal preparations until the pharmacokinetics and pharmacodynamics of compounds administered by this route have been investigated in affected cats.

266.2.3.4.2

Glycosaminoglycans

GAG replacement treatment has been used with some success in humans with interstitial cystitis[104] but usually does not provide long-term relief. The untested assumption is that exogenous GAG will attach to the defective urothelium, thereby decreasing bladder permeability. In addition, GAG can exert analgesic and anti-inflammatory effects that might prove useful. A study in humans reported that pentosanpolysulfate, a synthetic, branched polysaccharide that resembles the natural proteoglycan chondroitin sulfate, appeared to inhibit allergic and nonimmune mast cell stimulation and decrease intracellular calcium ion concentrations, which suggests another alternative for the benefit of this drug in some human patients.[105] However, there may be differences in the relative efficacy of the various available GAG. GAG replacers, such as Elmiron® can be tried. Side effects in humans can include gastrointestinal (GI) side effects (diarrhea) and hematologic abnormalities. Other veterinary marketed GAG replacers such as Cosequin® and Adequan® can be tried, but no evidence exists as to their efficacy in FIC.

266.3 UROLITHIASIS, URETHROLITHS, AND URETHRAL PLUGS

266.3.1 Urethral Obstruction

Urethral plugs are the most common cause of obstruction in male cats. In one series from the 1980s,[9] urethral plugs occurred in 60% of cats, no cause was found in 30%, uroliths alone were documented in only 10%, and uroliths with bacterial UTI were observed in 2%. Occasionally stricture and rarely neoplasia cause the obstruction. Urethral obstruction due to calcium oxalate urethroliths appears to be more common currently as compared with the early to mid-1980s.

It is unlikely for the urethra of female cats to become obstructed, but male cats have a narrow penile urethral lumen and are predisposed to obstruction with a urolith or urethral plug. Currently, it is unknown what causes the matrix of urethral plugs to form and is probably the outcome of several mechanisms. Many urethral plugs are composed of struvite with a proteinaceous matrix[9] (Figure 266-11). Struvite urethroliths were the sole type reported in cats from the 1980s, but calcium oxalate urethroliths occur more commonly now.

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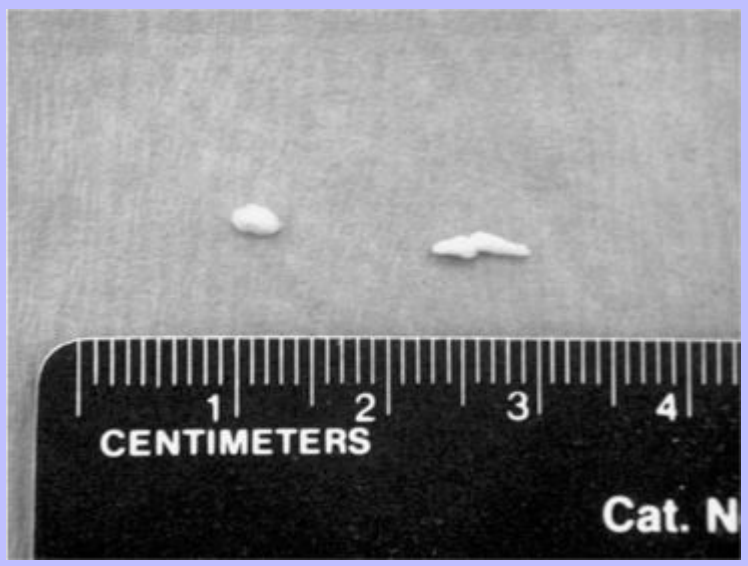
Figure 266-11 Fragments of urethral plugs obtained in a male cat after digital manipulation of the distal urethra and manual compression of the bladder.



It has been hypothesized that the concomitant occurrence of UTIs and crystalluria may lead to formation of matrix-crystalline plugs that obstruct various portions of the urethra, especially in male cats.[106] It was hypothesized that Tamm-Horsfal mucoprotein (THP) is contained within urethral plugs. Once this coalesces together with the crystals, white blood cells (WBCs), and red blood cells (RBCs), it can be surrounded by amorphous material and then obstruct the urethra. No evidence of THP in urethral plugs obtained from obstructed cats was identified in one group of cats we evaluated. However, the eletrophoretic pattern of some plugs resembled that of albumin and its degradation products, suggesting that the plug resulted from

precipitated serum proteins. The authors hypothesize that vasodilatation and leakage of plasma proteins from the suburothelial capillary plexus (*bladder weeping*) and secondary urethritis, which can be seen cystoscopically in cats with FIC, may trap crystals within the lumen of the male cat urethra and may result in obstruction. It is likely that oozing of plasma proteins into urine during active inflammation increases the urinary pH that contributes to the precipitation of struvite crystals that participate in urethral plug formation. Though conventional wisdom indicates that urethral plugs form in the urethra, the authors have observed with cystoscopy what appear to be plugs in the bladder. It is interesting that the mineral components of urethral plugs continue to be predominantly composed of struvite despite the apparent increase in frequency of calcium oxalate urolithiais. This may be due to the narrow range of *metabolic supersaturation* of struvite in urine. These and other hypotheses are not mutually exclusive, and plugs may form by different mechanisms, depending on a variety of factors present at any particular instance.

Regardless of the underlying cause or causes, relief of obstructions, re-establishment of urine flow, and correction of fluid, electrolyte, and acid-base imbalances associated with obstruction and postrenal azotemia are the first steps in proper management. Decompressive cystocentesis is a recommended first step, prior to attempts to pass a urinary catheter. A small (22-or 23-gauge) butterfly needle inserted into the lateral bladder wall midway between the apex and urethral outflow works well for this procedure and aids in the removal of urine without reinsertion of the needle. Alternatively, if a longer needle is necessary, it can be attached to an extension set and urine removed with a syringe in a similar manner. The bladder should be continuously palpated during the drainage and further pressure exerted on the bladder to allow nearly complete evacuation of urine. Complications are rare but include extravasation of urine into the peritoneal cavity and damage to the bladder wall.

Cats with urethral obstruction should be managed aggressively with medical treatment unless recurrent obstructions occur. A perineal urethrostomy surgery may be needed to prevent future episodes of urethral obstruction. This surgery carries some risks or complications such as bacterial UTIs and postoperative strictures.[107] Furthermore, clients need to be made aware that this surgery does not correct the underlying problem. Recurrent uroliths and FIC episodes can still occur. It is reported that the frequencies of feline urethrostomies performed at the University of Minnesota Veterinary Teaching Hospital has declined over the past 20 years, which is due, in part to a decrease in urethral plugs that are diagnosed.[108] The 50% decrease in occurrence of urethral obstruction could be due to the widespread use of urinary acidifying diets because struvite is the most common component to the urethral plug. Other factors that could have contributed to the decrease in perineal urethrostomy surgery could include more such surgeries done by private practitioners in primary or referral practices. Although the decline in urethral obstructions was halved, the frequency of urethrostomies decreased by 90%, suggesting that clinicians at this institution are now managing urethral obstruction successfully by nonsurgical methods.

For most obstructed cats (other than neurogenic obstruction), medical management with analgesics, antispasmodics (α1 adrenoceptor antagonists), and appropriate fluid therapy can be rewarding. Serum biochemistry, CBC, and urinalysis should be obtained, though is not necessary to evaluate such results prior to obstruction relief. Cats that are moribund should be resuscitated with intravenous fluids and correction of serious electrolyte and acid-base disturbances before anesthesia for placement of a urinary catheter. Specific rescue from the cardiotoxic effects of severe hyperkalemia (calcium salts, glucose, or insulin + glucose) may be necessary even before specific values for serum potassium return from the laboratory. An electrocardiagraphic assessment of all systemically ill cats with urethral obstruction should be performed. Only 12% of cats with urethral obstruction had severe hyperkalemia (> 8.0 mmol/L) in one recent report.[109]

Anesthesia is needed to allow proper manipulation of the cat's penis and passage of the urinary catheter. Isoflurane gas anesthesia can be administered by facemask to provide sedation and urethral relaxation. Alternatively, propofol infusion can be given for anesthesia. The combination of ketamine and Valium given intravenously to effect has been used for many years but does not provide adequate relaxation for some cats. After decompressive cystocentesis, the clinician should relieve the obstruction by catheterization and retropulsion with hydraulic forces using a sterile physiologic solution. Any urethral plug or urolith that is retrieved should be submitted for quantitative analysis. An indwelling catheter is not always needed once the obstruction is removed but is advised for cats with pronounced azotemia, those with a poor urine stream after advancing a catheter, and for those with an extremely large bladder volume at the time of obstruction relief because they are more likely to develop detrusor atony.

Urine output should be monitored frequently in severely ill cats. Cats recovering from severe postrenal uremia often have substantial postobstructive diuresis. Urine output is expected to be greater than 2.0 mL/kg/hr shortly after relief of obstruction and intravenous infusion of rehydration fluid volumes. Urine output can be marked, making it essential to ensure the amount of intravenous fluid volume infused is adequate to replace urine volume lost. Diuresis usually subsides as the waste products are excreted, which typically lasts 2 to 5 days. In some instances, the amount of intravenous fluids administered continues to drive the diuresis. The intravenous fluid infusion rate may be decreased by 25% to see if urine volume declines in concert. If so, continued tapering of intravenous fluids is recommended. Tapering of intravenous fluids can also be initiated after there has been resolution of azotemia. The magnitude of postobstructive diuresis is usually parallel to the magnitude of azotemia. Cats with minimal azotemia are not expected to have much, if any, diuresis.

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Nearly all cats treated for urethral obstruction at a university referral hospital survived initial treatment and stabilization.[109] Death can occur due to consequences of severe dehydration, hyperkalemia, metabolic acidosis, and hypocalcemia. Rarely, cats have a ruptured bladder secondary to long-standing urethral obstruction. Prognosis for survival in these cats is much worse.

Analgesics such as butorphanol, hydromorphone, and fentanyl (patches) can be used to alleviate pain. α-adrenoceptor antagonists (e.g., phenoxybenzamine, prazosin) and the phenothiazine derivative, acepromazine, can be used to help prevent smooth muscle urethral spasms that can occur after obstruction relief. Urethral spasms are a primary reason for cats to reobstruct once a plug or urethrolith has been removed. Preemptive therapy with antispasmodic medications may help prevent the recurrence of obstruction and help avoid need for perineal urethrostomy surgery. If detrusor atony is suspected, bethanechol can be added to the regimen provided the urethra is patent. After the cat has been successfully managed in the short term, care similar to that given to cats with FIC should be given.

266.3.2 Uroliths

Uroliths are organized concretions found in the urinary tract that contain primarily organic or inorganic crystalloid (ionic component of crystals) and a much smaller amount of organic matrix. When 70% or more of the urolith is composed of one type of crystal it is named for that crystal. Secondary crystalloids can comprise up to 30% of the total weight. Urine is commonly supersaturated with crystalloids, and observation of individual crystals in the urine does *not* mean the cat is at risk for urolithiasis. Crystalluria is not a disease, and no particular treatment is necessary unless a urolith is present, or a urolith or urethral plug has formed in the past. Supersaturation of urine with crystalloids depends on the interaction of dozens of crystalloid species formed by common mineral elements in the urine derived from the amount of each solute ingested and excreted in the volume of urine produced.[110] Moreover, these complex calculations do not take into account

potential organic molecule contributions, such as protein inhibitors or promoters of crystallization.[111] Urine pH also affects crystal formation. Struvite, calcium carbonate, and calcium phosphate are less soluble in alkaline urine; cystine and uric acid are less soluble in acid urine, but urate is less soluble in alkaline urine. Urine pH *per se* does not appear to have a major effect on the solubility of calcium oxalate; however, most calcium oxalate stones occur in cats with acid urine. Factors that predispose to urinary stasis play an important role in urolithiasis, because crystals must reside in the urinary tract for a sufficient time for a urolith to form.

266.3.3 Struvite Urolithiasis

The chemical composition of struvite is $MgNH_4PO_4$-$6H_2O$. Calcium phosphate (apatite) sometimes is present in small amounts (2% to 10%). The presence of three cations (Ca^{2+}, Mg^{2+}, and NH_4^+) detected by earlier qualitative methods led to the name *triple phosphate* previously used for these stones. Struvite uroliths are spherical, ellipsoidal, or tetrahedral in shape and may be present singly or in large numbers of varying sizes. The bladder is the most common site of struvite uroliths, although they may occur at any site in the urinary tract. In cats, struvite stones usually form in sterile urine. More than 90% of dogs, in contrast, have struvite stones associated with a urease-producing bacterial infection. Struvite solubility is reduced in urine of pH greater than 6.7. Struvite urolithiasis and urethral obstruction have been induced experimentally in healthy cats by feeding diets containing three to ten times the amount of magnesium found in commercial cat foods.[112] These studies led to the conclusion that magnesium was a primary cause of naturally occurring struvite urolithiasis in cats. It subsequently was learned that struvite stones in the bladder of healthy cats fed large quantities of magnesium dissolved when the urine pH was reduced to approximately 6.0.[112] These results suggested that magnesium's effect on struvite formation depended on the urine pH—an idea supported by the finding that the form of magnesium used in previous studies had increased the urine pH.[113] Therefore factors that may be associated with alkaline urine (e.g., family history of struvite stones, diet based on vegetable proteins [rare in cats], distal renal tubular acidosis) should be considered.

Lekcharoensuk and colleagues,[114] evaluated the association between dietary factors and struvite formation (Table 266-3). They reported that diets low in sodium or potassium or formulated to maximize urine acidity had a decreased risk for struvite urolith formation. Diets with the highest magnesium, phosphorus, calcium, chloride, or fiber contents, moderate protein content, and low fat content were associated with increased risk of magnesium ammonium phosphate urolith formation. However, these differences may also have been confounded by the many correlations between the dietary components and is compatible with the nutrient profile of relatively low-quality cat foods. In addition to nutrients, ingredients, and their combinations, breed, age, sex, body condition, and living environment were also significantly different between case and control cats (which were adjusted for in the multivariate logistic regression). The many interacting variables demonstrate the complexity of the process of stone formation.

It has been reported that spayed female cats have a higher risk of developing struvite uroliths,[115] but a more recent study[116] found a slightly higher risk only for *male* cats. When reproductive status was evaluated in this same study, neutered animals were three and a half times as likely to develop struvite uroliths compared with sexually intact cats. Cats with struvite uroliths were significantly younger than cats with calcium oxalate uroliths in the same study; however, when evaluating age, cats 4 years of age or older and 7 years of age or less had the highest risk for developing struvite urolithiasis. Breeds at risk were reported to be the Foreign Shorthair, Ragdoll, Chartreux, Oriental shorthair, domestic shorthair (DSH), and Himalayan. The Rex, Burmese, Abyssinian, Russian blue, Birman, Siamese, and mixed breed cats had a significantly lower risk of developing struvite uroliths.

266.3.3.1 Management of Urolithiasis

Patients who have had cystic calculi initially should be monitored every 2 to 3 months for recurrence. Uroliths larger than 3 mm will usually be evident with a plain abdominal radiograph. A double-contrast study or abdominal ultrasound may also be necessary for stones that are not radiodense (e.g., urate). If "sand and debris" or even very small stones (3 to 5 mm) are seen in the urinary bladder, surgery may not be necessary and voiding urohydropropulsion may be used to remove the stones (Figure 266-12, *A* and *B*). For a complete review of this technique, the reader is referred to the literature.[117] Stones as large as 5 mm can sometimes be removed from female cats by this method, but one should be prepared for surgical removal of stones that are not successfully removed with voiding urohydropropulsion.

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Table • 266-3 Differences in Content of Various Dietary Components and Predicted Urine pH for Diets Fed to Cats With Calcium Oxalate (CaOx) or Magnesium Ammonium Phosphate (MAP) Uroliths and to Control Cats Without Any Urinary Tract Diseases

	DIFFERENCE FROM CONTROL		COMPONENT RANGES*		
	CaOx	MAP	UNITS	CaOx	MAP
Protein	6% ↓	1% ↓	g/100 kcal	8.0–8.8; 10.5–13.8	
Carbohydrate	13% ↑	12% ↑	g/100 kcal	–	–
Fat	2% ↓	9% ↓	g/100 kcal	–	5.0–5.2
Fiber	4% ↑	7% ↓	g/100 kcal	–	Avoid >0.3
Calcium	11% ↓	7% ↑	mg/100 kcal	–	Avoid >205
Phosphorus	12% ↓	10% ↑	mg/100 kcal	–	Avoid >176†
Magnesium	11% ↓	15% ↑	mg/100 kcal	–	Avoid >26
Sodium	9% ↓	12% ↑	mg/100 kcal	78–370	Avoid >77†
Potassium	5% ↓	5% ↑	mg/100 kcal	181–320	Avoid >181‡
Chloride	5% ↓	6% ↑	mg/100 kcal	–	Avoid >167
Water	33% ↓	11% ↓	%	10.1–81.2	–
pH	1% ↓	1% ↑	pH	6.3–6.9	Avoid >6.5§

Data from table obtained from Lekcharoensuk C et al: Association between dietary factors and calcium oxalate and magnesium ammonium phosphate urolithiasis in cats. J Am Vet Med Assoc, 219:1228, 2001.

* Ranges over which significant differences in risk for affected cats were identified by multivariate analysis. Ranges with increased risk are denoted by "avoid." Reader should see reference for details and limitations of such interpretations.

† May be related to phosphorus salt used.

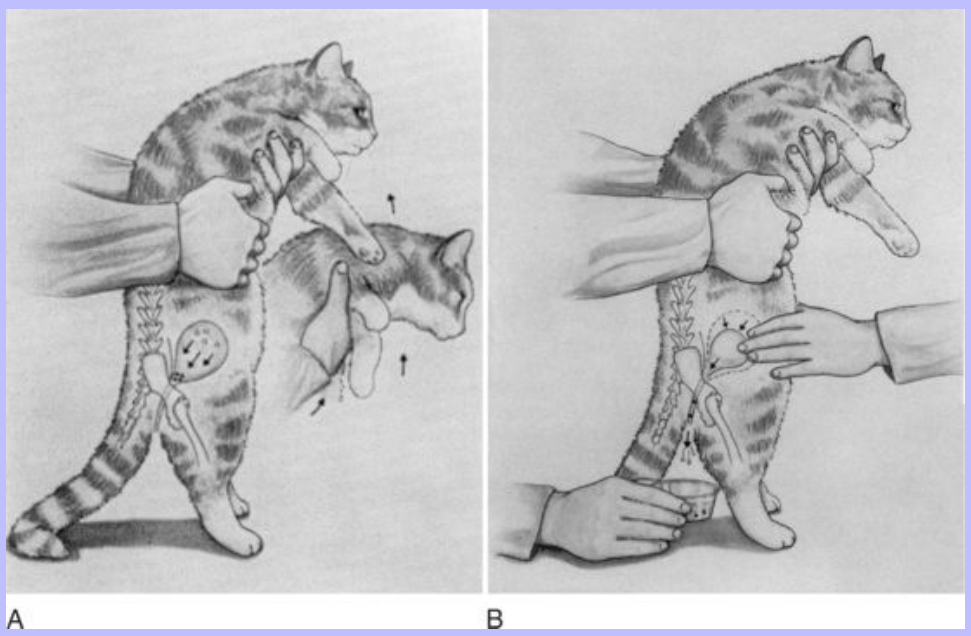
‡ Not considered biologically significant by authors.

§ Urine pH less than 6.3 could result in metabolic acidosis.

Once a urolith has been removed, the cat should be fed a canned diet, if possible, to decrease the urine concentration of stone mineral precursors. If a cat will not accept the new diet, water intake can be increased by the use of drinking fountains, flavored juices (e.g., ham, tuna), and the addition of ice cubes to

the cat's water (see Box 266-1 for further suggestions). Increasing water consumption is the cornerstone of therapy for urolithiasis in human[118] and veterinary medicine. When a urolith is diagnosed, the cat should be encouraged to consume enough water in canned or moistened foods to increase the urine volume until the USG is decreased to less than 1.030. Clients are advised that the urine should be clear, colorless, and odorless. USG should be monitored at periodic re-evaluations.

Figure 266-12 **A** and **B,** To remove urocystoliths by voiding urohydropropulsion, the patient is positioned so that the longitudinal axis of the vertebral column is approximately vertical. As a result, uroliths move from the ventral portion of the urinary bladder to the bladder neck. To expel urocystoliths, voiding is induced by applying steady digital pressure to the urinary bladder. (From Lulich JP, Osborne CA: Management of urocystoliths by voiding urohydropropulsion. Disorders of the feline lower urinary tract II. Diagnosis and therapy. Vet Clin North Am 26(3):631–632, 1996. Used with permission.)



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266.3.3.2 Struvite Urolithiasis Management

In cats with struvite urolithiasis without a UTI, urinary acidifiers played a more important role until most commercial cat foods were reformulated to reduce urine pH. Urine acidifiers should only be given to cats with urine pH greater than 6.5 measured under *ad libitum* feeding conditions. Ideally, urine should be collected from the cats in their own environment, and the sample brought to the hospital for assessment of

pH and specific gravity. A urinary pH meter is reported to be more accurate than urine dip strips.[119] Although the addition of D, L-methionine and ammonium chloride decreases the struvite activity product and sediment in the urine of healthy cats, this supplementation failed to reduce the urinary concentration of the HCL-insoluble fraction that may be a candidate for the matrix of struvite uroliths.[120] Ingestion of large quantities of urinary acidifiers can cause anorexia and systemic acidosis. A number of veterinary diets to help prevent the recurrence of struvite stones are available (Table 266-4 and Box 266-3); although these diets may be of benefit, none have evidence-based outcomes documenting their effectiveness in prevention of recurring struvite urolithiasis. Feeding patterns also may influence the development of struvite uroliths due to an increase in pH (postprandial alkaline tide) that may occur after a meal in meal-fed cats, depending on diet composition.[121] Therefore *ad-libitum* feeding in cats with struvite uroliths seems prudent.

Table • 266-4 Restricted Mineral Diets for Cats

Cat				**Amount Per 100 kcal**										
Diet **CANNED**	***Mfg.***	***Weight g***	***Energy kcal/can***	***Protein g***	***Fat G***	***CHO g***	***Fiber g***	***Ca mg***	***P mg***	***Na mg***	***K mg***	***Mg mg***	***Cl mg***	***pH range***
Average Values*				11	6	3	0.4	325	280	200	180	20	260	NA
Struvite	0													
c/d-S	*HIL*	156	164	9.9	5	6	0.5	143	114	133	191	13	286	6.2–6.4
s/d	*HIL*	156	215	8.8	7.1	3.3	0.4	130	109	181	196	9	348	5.9–6.1
Low pH/S	*IAM*	170	198	9.5	6.2	3.5	0.2	242	190	95	181	21	138	5.9–6.3
UR	*PUR*	156	217	8.6	7.6	3.4	0.02	190	170	90	200	10	290	5.9–6.3
S/O Control pH	*WAL*	165	175	7.5	8	1.9	0.2	170	210	210	210	15	180	6.3–6.5
Oxalate	0													
c/d-Oxl	*HIL*	156	162	9.5	4.5	7.4	0.2	154	125	67	202	20	115	6.6–6.8
Mod pH/O	*IAM*	170	198	9.1	5.9	3.2	0.2	233	173	99	267	21	147	6.3–6.9
S/O Control pH	*WAL*	165	175	7.5	8	1.9	0.2	170	210	210	210	15	180	6.3–6.5
0														
Diet **DRY**	***Mfg.***	***Weight g***	***Energy kcal/cup***	***Protein G***	***Fat G***	***CHO g***	***Fiber g***	***Ca mg***	***P mg***	***Na mg***	***K mg***	***Mg mg***	***Cl mg***	***pH range***
Average Values*				8.5	3.8	10	0.6	280	260	180	105	25	180	NA
Struvite														
c/d-S	*HIL*	76	285	8.5	4.1	10.3	0.2	197	184	106	210	15	258	6.2–6.4
s/d	*HIL*	122	521	7.4	5.8	6.6	0.2	233	165	151	193	16	329	5.9–6.1
Low pH/S	*IAM*	102	441	7.8	3.9	8	0.4	236	203	112	198	18	191	5.9–6.3
UR	*PUR*	227	366	8.3	2.7	10.7	0.3	260	200	60	200	20	260	5.9–6.3
S/O Control pH	*WAL*	NA	390	8.8	4.7	8.3	0.5	170	210	220	230	15	510	6.3–6.5
Oxalate														
c/d-Oxl	*HIL*	76	286	8.5	4.1	10.2	0.3	196	162	85	209	20	244	6.6–6.8
Mod pH/O	*IAM*	105	451	7.6	3.9	8	0.4	238	205	104	305	19	151	6.3–6.9
S/O Control pH	*WAL*	NA	390	8.8	4.7	8.3	0.5	170	210	220	230	15	510	6.3–6.5
SEMI-MOIST		***g***	***kcal/cup***	***g***	***G***	***g***	***g***	***mg***	***mg***	***mg***	***mg***	***mg***	***mg***	***range***
Struvite														
UR Formula	*PUR*	42	120	9.7	3.7	6.5	0.3	370	400	60	190	30	130	5.8–6.2

Diets listed in alphabetic order by manufacturer. Common veterinary diets restricted in mineral contents and formulated to be acidifying or maintain a neutral pH. Although dry foods are listed for completeness, canned food is recommended for cats with a history of urolithiasis.

* Average values of commercial and specialty foods. *Mfg*, Manufacturer; *HIL*, Hills Pet Food Company; *IAM*, Iams Company; *PUR*, Nestle's Purina Petcare Company; *WAL*, Waltham; *CHO*, carbohydrate.

266.3.3.2.1

Box • 266-3 Suggestions to Help Clients Change their Cats' Diets

Changing a cat to a new food may not seem easy or convenient at first, but it may be necessary for some cats with feline idiopathic cystitis (FIC) and urolithiasis. To help clients and their cats through this process, the authors offer the following suggestions, collected from clients and cats that have successfully made the change.

1. Before starting to change diets, be sure that the cat is at home, feeling better, and eating its usual diet normally. Never begin the recommended diet while the animal is still hospitalized.
2. A simple way to start is to offer the new food in the cat's usual feeding bowl next to the old diet in a different bowl. Putting both foods in similar bowls can make the change somewhat easier. If the cat eats the new diet readily, then old food can be removed. If the cat does not eat the new diet after 1 hour, take it up until the next feeding. At the next feeding, repeat the process, always providing fresh new food. Once the new diet becomes familiar to the cat (usually in 1 or 2 days), it should start eating it readily. When this occurs, start to decrease the amount of the old diet offered by a small amount (about 25%) each day until the change is complete. Using this strategy, the change should be completed over a period of 1 to 2 weeks.
3. If necessary, small quantities (less than a tablespoon per cup or can of food) of the cat's favorite food, or meat or fish juices can be mixed with the new food initially to make it more appealing.
4. Cats should be fed in a quiet environment where it will not be distracted or startled by humans or other pets.
5. If a cat has food available all the time and refuses the new diet, it may be easier to start by changing its feeding schedule to meal feeding by only leaving food out for 1 hour at each feeding time. If the cat does not eat all its food every day, this may be normal. No more than a 10% loss of weight should occur during this transition. If the inappetence continues, offer the cat's regular favorite diet once again. After 3 to 4 weeks a different diet may be tried once again. Fortunately, several diets are available for certain diseases, and certain cats might prefer one over the other.

If a struvite urolith was diagnosed with a recurrence, feeding a canned form of a calculolytic diet has been reported to induce dissolution of struvite calculi in female cats.[122] Calculoylysis usually occurs within 1 month. Caution should be observed when considering use of calculolytic diets; the diets should not be fed to growing kittens or to pregnant or lactating queens.

266.3.4

Calcium Oxalate Urolithiasis

Calcium oxalate stones are the most common stone type in people, and their incidence has been increasing in cats during the past 15 years.[114] These stones are composed of calcium oxalate monohydrate (whewellite) or calcium oxalate dihydrate (weddelite). Oxalate frequently is not detected by qualitative analysis, and quantitative analysis is necessary for diagnosis. Calcium oxalate calculi usually are white and hard. They often have sharp, jagged edges and may be single or multiple in number (Figure 266-13). Although they are found

most often in the bladder and urethra, when stones appear in the kidneys they are most likely calcium oxalate. 1847
Calcium oxalate uroliths frequently recur. If a UTI is present, it is usually a complication rather than a 1848
predisposing factor to oxalate urolithiasis.

The research implicating magnesium as a potential cause of struvite urinary stone disease in cats seems to have led cat food manufactures to restrict the magnesium content of diets, and add ingredients to promote more acidic urine in an attempt to minimize the struvite-promoting potential oftheir products. Unfortunately, an increase in the frequency of calcium oxalate urolithiasis appears to have occurred since these modifications began. Between 1984 and 1995 the proportion of calcium oxalate stones submitted to the University of Minnesota Urolith center increased from 2% to 40%.[123] Studies assessing the diet risk factors in cats with urolithiasis have reported that diets formulated to decrease risk of struvite uroliths by reducing pH reciprocally increased risk of calcium oxalate uroliths.[114] Other dietary risk factors for cats with calcium oxalate urolithiasis were evaluated in this study, and the reader is referred to Table 266-3.

Figure 266-13 Calcium oxalate stones obtained from a cat after a cystotomy.

Results have shown that differences in breed, age, sex, and reproductive status did not contribute to the apparent reciprocal relationship between occurrences of calcium oxalate and struvite uroliths in cats.[116] Indoor housing has also been reported to be an independent risk factor for calcium oxalate urolithiasis.[121] It has been suggested that indoor cats could void less often and allow a longer period for urolith-forming products to aggregate in the bladder.

Although urinary acidifiers can enhance the solubility of struvite crystals in cats, if acidosis occurs, they also promote release of calcium carbonate from bone, resulting in hypercalciuria.[124] Acidosis may be associated with decreased urinary citrate excretion and thus may predispose to calcium oxalate stone formation in humans.[125] Citrate forms a soluble complex with calcium and may normally be an inhibitor of calcium oxalate formation in humans, but this has not been studied in cats. Oxalate is derived both from the diet and endogenously from the metabolism of ascorbic acid (vitamin C) and the amino acid glycine. In human beings, increased dietary oxalate, increased colonic absorption of oxalate secondary to fat malabsorption, vitamin B_6 deficiency, and inherited defects of oxalate metabolism may predispose to the formation of calcium oxalate

stones. What, if any, role these and other diet-related factors play in naturally occurring oxalate urolithiasis in cats is not known.

Breeds reported to be at risk for calcium oxalate uroliths include ragdoll, British shorthair, foreign shorthair, Himalayan, Havana brown, Scottish fold, Persian, and exotic shorthair cats. The Birman, mixed breed, Abyssinian, and Siamese cats had significantly lower risks for developing calcium oxalate uroliths.[116] As mentioned previously, cats with calcium oxalate urolithiasis are generally older than cats with struvite urolithiasis. Cats 7 to 10 years of age are reported to be 67 times as likely to develop calcium oxalate uroliths as cats between the ages of 1 and 2 years.[116] Male cats were reported to be one and a half times as likely to develop calcium oxalate uroliths and neutered cats were seven times as likely compared with sexually intact cats.

Cats with calcium oxalate uroliths should have their serum analyzed to evaluate for the presence of hypercalcemia, a risk factor for stone formation. Correction of hyper-calcemia is important to prevent recurrent stone formation. Early intervention could prevent subsequent complications, such as renal failure. Altered calcium metabolism may play a role in development of oxalate urolithiasis in some cats. Mild hypercalcemia was reported from the University of Minnesota Urolith Center in 35% of cats with calcium oxalate uroliths.[123] In a recent study of hypercalcemic cats,[126] calcium oxalate urolithiasis was noted in 11 of 16 (69%) with LUT signs. Of these, 73% had calcium oxalate urolithiasis. In a series of case reports, five cats with hypercalcemia and calcium oxalate urolithiasis presented for evaluation of LUT signs also had been fed an acidifying diet or received urinary acidifiers (D, L-methionine).[127] Seven of 20 cats (35%) had urolithiasis in a series of cats with idiopathic hypercalcemia.[128] In four cats that were evaluated, all had elevated urinary fractional excretions of calcium (Figure 266-14). Calcium oxalate urolithiasis has also been reported in a cat with a functional parathyroid adenocarcinoma.[129]

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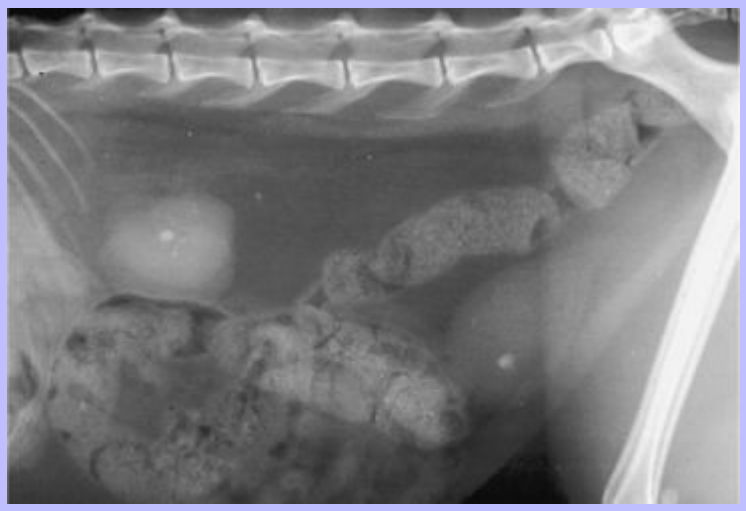
266.3.5 Calcium Oxalate Management

Attempts to dissolve calcium oxalate stones have not been successful, and surgery or voiding urohydropropulsion is required to remove stones. Postoperatively, a diet restricted in calcium and oxalate seems logical, but no evidence-based studies in cats with naturally occurring disease are available to support this recommendation. Moreover, high intake of dietary calcium appears to decrease risk for symptomatic kidney stones in humans, whereas intake of supplemental calcium may increase risk. Thus the timing and association with intake of other nutrients may also influence the role of calcium and other nutrients on stone formation, and these effects may be different in animals with naturally occurring disease than in healthy cats. Reducing only one of these minerals could increase the availability of the other. Dietary phosphorus should not be excessively restricted because reduced phosphorus could result in increased activation of vitamin D_3 to calcitriol by 1-α-hydroxylase in the kidney and cause increased intestinal absorption of calcium. In addition, urinary pyrophosphate derived from the diet may function as an inhibitor of calcium oxalate formation. Magnesium intake should not be restricted because it may serve as an inhibitor of calcium oxalate formation. Although dietary salt supplementation has been controversial to manage LUT signs (by increasing water consumption), due to a potential for increased urinary calcium excretion, the overall diuretic effect appears beneficial. Studies in healthy dogs reported a decreased relative supersaturation for calcium oxalate urolithiasis with sodium chloride supplementation (Steveson AE et al: Effect of dietary moisture and sodium content on urine composition and calcium oxalate relative superasaturating in healthy miniature Schnauzers and Labrador retrievers, Res Vet Sci 74:145-151, 2003). No studies are available in cats. Salt supplementation should not be used in cats with impaired renal function, cardiovascular disease, or hypertension. Avoidance of

Vitamin C is recommended because ascorbic acid is a metabolic precursor of oxalate, but no stones have been reported to develop in cats due to use of vitamin C.

Figure 266-14 Radiograph of a cat with calcium oxalate stones in the renal pelvis and ureter. The cat was subsequently diagnosed with idiopathic hypercalcemia.



Administration of citrate as potassium citrate (Urocit-K®) could be helpful because urinary citrate may act as an inhibitor of calcium oxalate formation, although no data are available from clinical studies. Beyond this effect, therapeutic manipulation of urine pH is not known to be beneficial because oxalate solubility is relatively unaffected by a wide range of urine pH. The recommended dose of potassium citrate is 100 to 150 mg/kg/day but it is unclear if this dose will actually increase urinary citrate in cats. A number of commercial diets that have been used in attempts to prevent recurrence of oxalate stones are available and listed in Table 266-3, but no evidence-based outcomes of their use have been published.

266.3.6 Urate Urolithiasis

When evaluating mineral composition of 20,343 feline uroliths at the University of Minnesota Urolith Center, only 5.6% were composed of uric acid and urate.[132] The University of California-Davis Stone Analysis Laboratory reported that 6.4% of stones from cats over the past 10 years were uric acid. Urate stones in cats are composed of uric acid and the monobasic ammonium salt of uric acid (ammonium acid urate). Calcium oxalate may be a secondary component of some urate stones, and those found in cats with portosystemic shunts often contain struvite in addition to urate.[123] Often times, the cause or causes of urate urolith formation are unknown. Urate calculi are small, brittle, spherical stones with concentric laminations. They usually are multiple in number and light yellow, brown, or green in color. They are found most often in the bladder and urethra, and the recurrence rate may be as high as 30% to 50%. When it occurs, UTI is a complication of urate urolithiasis rather than a predisposing cause.

266.3.6.1 Urate Management

Attempts to dissolve urate stones have not been successful, and surgery or voiding urohydropropulsion is required to remove stones. The cat should be evaluated for liver abnormalities (e.g., portosystemic shunts) and if present, the underlying cause should be corrected. Dissolution and prevention protocols for *dogs* include some combination of urine dilution, low-purine diet, alkalinization of urine, and allopurinol. Dissolution of an ammonium urate stone in a cat was reported to occur using a combination of allopurinol and a diet relatively low in purine precursors.[132] Although allopurinol will reduce the formation of uric acid, xanthine uroliths can occur, and the efficacy and potential toxicity of allopurinol in cats are not known.

266.3.7 Cystine Urolithiasis

When evaluating mineral composition of 20,343 feline urolith at the University of Minnesota Urolith Center, only 0.2% were composed of cystine.[132] Approximately two thirds of the stones were located in the bladder, and slightly more than one fourth of them were voided. Cystine uroliths are usually identified in middle-aged to older cats.[133] Most cats with cystine uroliths are DSH, but Siamese cats appear slightly over-represented. Bacterial UTIs are usually a consequence of cystine uroliths and not a cause. Although the cause of cystine uroliths is unknown, cystinuria results from a hereditable defect in renal tubular transport of cystine and other dibasic amino acids (ornithine, lysine, and arginine). Not all animals with cystinuria develop cystine uroliths; therefore the crystals appear to be a predisposing factor rather than a cause.

266.3.7.1 Management of Cystine Urolithiasis

In addition to increasing urine volume in cats with cystine uroliths, cystine becomes more soluble as the pH increases. Therefore a nonacidifying canned food seems appropriate. (2-mercaptoproplonyl-glycine) glycine (2-MPG), which decreases the concentration of cystine by a thiol-disulfate exchange reaction resulting in a more soluble compound, has been reported to be of benefit in preventing recurrent cystine uroliths in a cat.[132] No adverse effects were documented in this one cat. Potassium citrate can be used to further alkalinize the urine if necessary. Sodium bicarbonate is not recommended because dietary sodium may enhance cystinuria.

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266.3.7.2 Bacterial and Viral Cystitis

When interpreting the urinalysis, caution should be taken when reporting bacteria from the sediment. These “bacteria” are likely the result of cellular breakdown products in the urine that exhibit brownian motion and look similar to bacteria. Antimicrobials should be administered based on quantitative urine cultures and sensitivities. Bacterial UTIs are rare in cats but are more common in those with defenses that are compromised due to other diseases or treatments. Cats with previous urinary catheterizations, perineal urethrostomies, and tube cystostomies are more susceptible to infections.[71] Cats over 10 years of age with LUT signs have been diagnosed with bacterial UTIs in greater than half of the cases, often in association with renal failure.[134] The bacteria that cause UTIs in cats are similar to other species with *Escherichia coli* being the most common isolate. The gram-positive cocci such as staphylococci and streptococci account for the next most common isolates.[135]

Investigation of viruses as a causative agent of LUT signs began in the 1960s. Virus-like particles (suspected to be calicivirus) were identified in the matrix of urethral plugs from some male cats with urinary obstruction.[123] The isolation of feline calicivirus, bovine herpesvirus 4, and feline syncytia-forming virus from cats with naturally occurring LUT signs has also been reported.[136] Most recently, Rice and colleagues[137] documented feline caliciviruses (FCVs) from one female cat with FIC and one male cat with obstructive FIC in the 40 cats they evaluated. These viruses (FCV-U1 and FCV-U2, respectively) were genetically distinct from other known vaccine and field strains of FCV. What if any relationship viruses play in the etiopathogenesis in LUT sign in cats remains unknown.

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267 CHAPTER • 267 Canine Lower Urinary Tract Diseases

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267.1 ANATOMY AND PHYSIOLOGY OF THE LOWER URINARY TRACT

The function of the urinary bladder and urethra is storage and voiding of urine. The urinary bladder acts as a low-pressure reservoir for storage of urine until voiding occurs. The urinary bladder consists of the detrusor muscle (smooth muscle), submucosa, mucosa (composed of transitional epithelium), and serosa. The ureters enter the urinary bladder on the serosal surface and tunnel though the bladder wall obliquely to the mucosal surface. The oblique path of the intramural ureter results in a valvelike effect termed the *vesicoureteral valve*. The vesicoureteral valve, along with ureteral peristalsis and a compliant bladder, promotes unidirectional flow of urine to aid in prevention of ascending infection or urine reflux to the kidneys. A protective glycosaminoglycan layer coats and protects the bladder urothelium, which if defective may increase bladder permeability.[1]

The detrusor muscle is continuous with the smooth muscle of the urethra and helps form the internal urethral sphincter. The internal urethral sphincter is not an anatomically distinct sphincter; rather, it is a functional sphincter involving the proximal urethral and bladder neck.

The innervation of the lower urinary tract (LUT) includes sympathetic, parasympathetic, and somatic innervation. The internal urethral sphincter is innervated by sympathetic (α-adrenergic) innervation from the lumbar spinal cord (L1-L4) via the hypogastric nerve. The external urethral sphincter is composed of skeletal muscle and receives somatic innervation from S1-S3 via the pudendal nerve. The detrusor muscle of the urinary bladder receives parasympathetic innervation from S1-S3 via the pelvic nerve (causing contraction) and sympathetic innervation (β-adrenergic) from L1-L4 via the hypogastric nerve (facilitating relaxation). Afferent (sensory) information from stretch receptors in the bladder wall travels via the pelvic nerve to the spinal cord. Sensory information is also transmitted via the hypogastric nerve when overdistension of the bladder occurs. Afferent information from the urethra is transmitted via the pudendal nerve.

267.2 CLINICAL SIGNS OF LOWER URINARY TRACT DISEASE

Dogs with LUT disease most commonly have signs of inflammation or irritation of the bladder and urethra (such as dysuria, pollakiuria, or stranguria), discolored urine (due to hematuria), urinary incontinence, or inability to effectively void urine. Refer to Chapters 29 to 31 for an overview of these clinical syndromes. Dogs with clinical signs that suggest localization to the LUT (e.g., dysuria, pollakiuria and stranguria) may also have disease of the upper urinary tract such as extension of lower urinary tract infection (UTI) to the ureter, renal pelvis, and renal parenchyma.

Animals with rupture of the bladder or urethra often have systemic signs of uremia (anorexia, lethargy, vomiting, and diarrhea), along with indications of fluid accumulation in the abdomen or subcutaneously. Subcutaneous urine leakage may cause tissue necrosis and sloughing of the overlying skin.

267.3 DIAGNOSTIC APPROACH TO LOWER URINARY TRACT DISEASE

The reader is referred to Chapter 257 for an overview of the diagnostic approach to dogs with urinary tract disease and Chapter 188 for neoplasia of the urinary tract. For dogs with signs of LUT disease, the *minimum* diagnostic evaluation should include history, physical examination, and urinalysis. If possible, the initial evaluation should also include urine culture, complete blood count (CBC), serum biochemistry profile, abdominal radiographs, and ultrasound of the urogenital tract. A thorough history should include frequency and volume of urination, estimated daily water intake, color of urine, any abnormal odor of the urine, evidence of straining or pain during urination, and evidence of urinary incontinence including age of onset, when incontinence occurs (awake, asleep, or continuous), and frequency of incontinence. The physical examination of dogs with signs of LUT disease should include abdominal palpation, digital rectal examination, visual and digital examination of the external genitalia, and neurologic examination of the pelvic limbs and perineal region.

267.3.1 Cystoscopy

If a cause of LUT disease has not been determined from routine diagnostic evaluation, transurethral cystoscopy (also termed *urethrocystoscopy*) should be considered. Cystoscopy is becoming an integral part of the diagnostic evaluation of dogs with recurrent or persistent LUT disease.[2] Although minimally invasive, cystoscopy does require general anesthesia to minimize movement. Cystoscopy is more sensitive than excretory radiography for identification of ectopic ureters and associated anatomic defects (Figure 267-1).[3] Cystoscopy is also useful for diagnostic evaluation of dogs with recurrent urinary tract infection (UTI) to evaluate for anatomic defects and to obtain biopsies for cytology, histopathology, and microbiologic culture.

Cystoscopy is useful for documenting the extent and location of LUT neoplasia and for obtaining biopsies for cytology and histopathology from lesions within the bladder or urethra. Using cystoscopy allows the source of gross hematuria to be localized to the genital tract, urethra, bladder, and left or right kidney and ureter with more certainty than by attempting to predict the source of hematuria based on when this is noted during voiding. Box 267-1 lists indications for cystoscopy.[4]

267.3.1.1 Diagnostic Imaging

Abdominal radiographs are an integral part of the diagnostic evaluation of dogs suspected of having LUT disease. Abdominal radiographs should include the entire urinary tract from the diaphragm to the caudal most portion of the urethra. Although the common anatomic landmark for distal collimation of abdominal radiographs is the coxofemoral joint, this is inadequate for evaluation of the urethra caudal to the pelvis, especially in male dogs (Figure 267-2). Failure to include the entire urethra may result in failure to diagnose uroliths in the urethra and potentially ineffective therapy such as incomplete surgical removal of uroliths. Abdominal ultrasound examination of the urogenital tract is a useful complement to abdominal radiographs when available to the practitioner although this modality has the limitation that, unless transrectal ultrasonography is also preformed, the urethra will not be visualized.

Figure 267-1 Cystoscopy showing an ectopic ureter opening in the proximal urethra along with abnormal urethral confirmation.

267.3.1.1.1

Box • 267-1 Indications for Cystoscopy

Localization of source of hematuria

Urinary tract neoplasia

Determine extent and location of neoplasia

Obtain biopsy for cytology and histopathology

Recurrent urinary tract infections (UTIs)

Conduct examination for anatomic abnormalities uroliths

Obtain biopsies for cytology, histopathology, and culture

Urinary tract trauma

Examine for perforations, ruptures, and patency of urinary tract

Urinary incontinence

Examine for ectopic ureters and/or urethral anomalies

Give periurethral injection of bulk-enhancing agents for treatment

Urolithiasis

Confirm and remove small uroliths from bladder or urethra

Obtain uroliths for quantitative analysis and culture

Retrieve uroliths from bladder or urethra using stone forceps or stone basket

Fragment urocystoliths with electrohydraulic or laser lithotripsy

Flush bladder using Ellik evacuator to remove small uroliths or urolith fragments

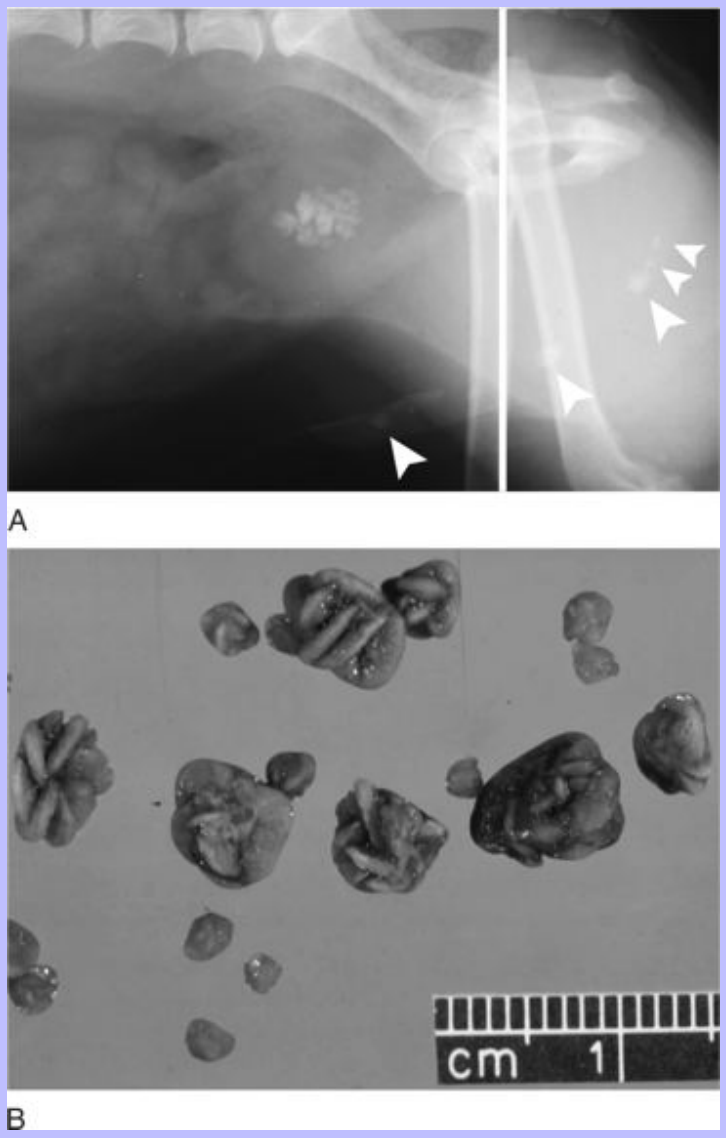
Abdominal ultrasound examination of the urogenital tract (combined with cystoscopy) reduces the use of contrast radiographic evaluation of LUT disease. However, contrast radiographs are still required for evaluation of some animals. Positive-contrast urethrocystography is the preferred technique for urethral defects such as delineating the extent and location of urethral strictures or extramural compressive lesions that preclude passage of the cystoscope. Positive-contrast urethrocystography is the preferred technique for diagnosis of pelvic bladder and rupture of the LUT (if cystoscopy is not available). Double-contrast cystography is the preferred technique for evaluation of the bladder for detection of radiolucent uroliths and mass lesions.

267.3.1.2 Urodynamics

Urodynamic evaluation is indicated for evaluation of dogs with refractory urinary incontinence, although urodynamic equipment is only available at selected referral hospitals. Urethral pressure profilometry can confirm a diagnosis of urethral incompetence.[5,6] Cystometrography may be used to diagnose detrusor instability (so-called overactive bladder), which may be due to a variety of inflammatory diseases of the LUT or may be idiopathic.[7] Some dogs with refractory urinary incontinence may have mixed incontinence

caused by both urethral incompetence and concurrent detrusor instability. Urodynamic testing allows for identification of the type and severity of urethral or detrusor dysfunction.[5]

Figure 267-2 **A,** Abdominal radiographs from a dog with calcium oxalate urocystoliths and urethroliths. Reader should note that if the radiographs were collimated at the coxofemoral joints *(solid white line)*, only one of the five urethroliths *(arrowheads)* would have been detected. **B,** Calcium oxalate uroliths from the dog in **A**. Uroliths were removed by retrograde urohydropropulsion and cystotomy.



267.4 UROLITHIASIS

267.4.1 Urolith Kinetics—Formation and Growth of Uroliths

A prerequisite for urolith formation is that urine is supersaturated, at least intermittently, with that compound. The point at which saturation of water with the pure chemical components of the crystal occurs is referred to as the *thermodynamic solubility product* (K_{sp}). However, the concentration of most urolith components in urine is actually greater than this, which can only be accomplished because urine contains inhibitors of crystal formation, which allow higher concentrations of solute to be held in solution. These solutions are described as being metastable (Figure 267-3). As the concentration rises still further, a point is reached at which the substance can no longer be held in solution; this is the formation product for the crystal (K_f). Because the concentrations of most urolith components in urine are in the metastable range, the question we should ask is not why some animals form uroliths, but why most do not. The ability of urine to hold more solute in solution than pure water is due to the many interacting ions that form soluble complexes, effectively reducing the free ionic concentration of each of the components.

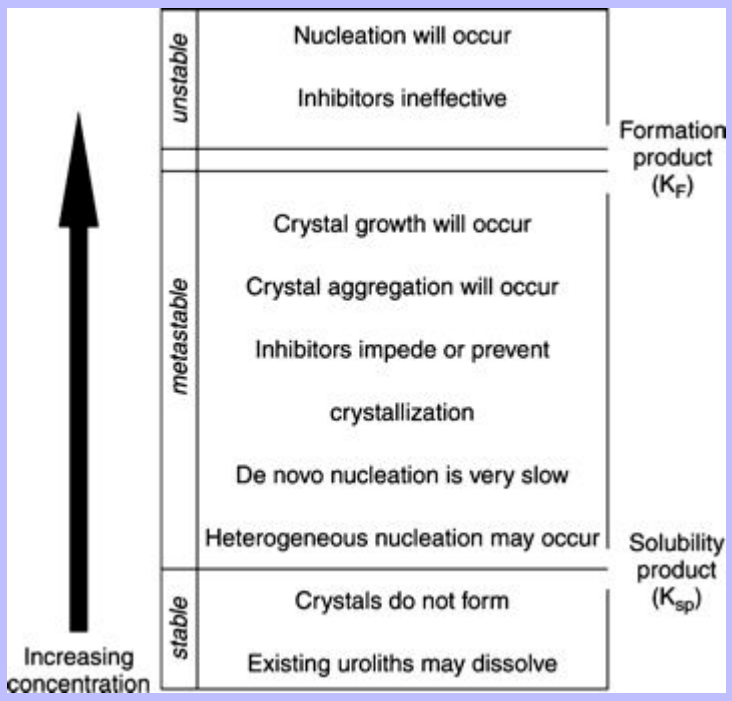
Urolith formation is initiated by the precipitation of a submicroscopic crystal nucleus in the form of a mineral lattice. If the crystal forms from a pure solution, this event is termed *homogeneous nucleation*. It is, however, probably more common for heterogeneous nucleation to occur in urine, with the crystal nucleus forming on existing surfaces (such as cell debris, urinary casts, or other crystals) because this requires a lesser degree of supersaturation.[8] If the growth of one type of crystal occurs on the surface of another, this is termed *epitaxial growth*.

Once a crystal nucleus has formed it has the potential to develop into a urolith of the same composition, with direct crystal growth occurring whenever the urine is supersaturated for that substance. Crystal growth requires a lesser degree of supersaturation than crystal nucleation. Direct crystal growth is a relatively slow process and unlikely to account for the development of most uroliths, particularly nephroliths, which must form in the time that it takes the urine to pass along the renal tubule. It is proposed that a combination of crystal growth and crystal aggregation occurs in most humans that develop uroliths.[8] In contrast to direct crystal growth, aggregation of crystals can occur rapidly. Humans that develop nephroliths excrete large crystal aggregates, whereas the urine of nonstone formers contains only small crystals.[9]

A final important factor in the development of uroliths is the retention of crystals or aggregates of crystals within the urinary tract. Crystalluria is a normal phenomenon in dogs; the exit of crystals from the urinary tract must be delayed for uroliths to develop.

In summary, the known causes of urolith formation can be divided into those that favor nucleation; those that promote crystal growth, aggregation, or both; and those that retain the urolith within the urinary tract so that further growth may occur. The importance of each of these mechanisms depends on the type of the urolith that is forming. Formation of some types of uroliths occurs principally (although not exclusively) because the concentration of solutes in urine is much higher than normal (e.g., struvite, cystine, and urate uroliths). Prevention of these types of uroliths is primarily directed at reducing the amount of solute excreted and promoting its solubility in urine (e.g., by manipulating urine pH). On the other hand, formation of calcium-containing uroliths (principally calcium oxalate) is much more complex.

Figure 267-3 States of saturation related to the formation of crystals in urine.



Urine is probably always supersaturated with respect to these compounds. Although increased urinary excretion of calcium or oxalate does play a role in the pathogenesis of urolithiasis, factors that complex calcium or oxalate in solution, reducing their effective concentrations (e.g., citrate) and that inhibit growth or aggregation of crystals (e.g., Tamm-Horsfall mucoprotein) are of much greater importance in preventing urolith formation. These individual mechanisms are discussed in more detail in the section on calcium oxalate formation.

267.4.2 Role of Matrix

Uroliths are composed of a crystalline component and variable quantities of matrix. The exact role of matrix in urolith formation in humans and dogs is unknown. Although numerous proteins and glycosaminoglycan have been detected in human nephroliths, it is unknown which ones may contribute to urolith formation versus simply being trapped in layers of the growing urolith. Occasionally, canine uroliths develop that are composed solely of matrix.[10]

267.4.3 *In Vitro* Assessment of Urolith Formation

The *gold-standard* assessment of dietary or other therapeutic interventions involves a clinical trial measuring the rate of *in vivo* formation or dissolution of uroliths. However, the protracted time course of such trials and the difficulty in studying the effect of a single intervention in isolation has resulted in the development of *in vitro* methods for evaluating the effects of urine composition on urolith formation or dissolution. The two

methods that have been used most frequently in veterinary medicine are the determination of relative supersaturation (RSS) and activity product ratios (APRs).

RSS is determined by measuring the concentration of various analytes (including calcium, oxalate, sodium, potassium, magnesium, ammonium, citrate, phosphate, pyrophosphate, and sulphate) in the urine, together with the urine pH, and then entering these values into a computer program that calculates a value for the ion activity product in the urine sample. The ratios of these activity products to the *thermodynamic solubility products* (K_{sp}) of their respective salts yield the RSS values. A RSS value less than one represents a urine sample that is undersaturated, whereas a RSS value greater than one represents a sample that is oversaturated, with respect to the compound being evaluated. Limitations of this method are that the computer program was optimized for calculations using human urine and that influence of promoters and inhibitors of crystal formation, growth, and aggregation on the measured free ion concentration cannot be included in the calculations. This technique has been applied to the analysis of urine from both dogs and cats.[11]

APRs are obtained by calculating ion activity products in the urine using a computer program in a similar manner to that used for determination of RSS. The difference with this method is that the measurements are made before and after incubation, with a seed crystal of the urolith type being investigated. The activity products will increase or decrease with incubation of the seed crystal depending on whether the urine is supersaturated or undersaturated with respect to the mineral being evaluated.[12]

267.4.4 Crystalluria

By convention, microscopic mineral precipitates within urine are called *crystals*, and macroscopic precipitates are called *uroliths* or *calculi*. The presence of crystalluria is not synonymous with disease, although it does signify that the urine is supersaturated with the mineral compound and is evidence that a risk exists for the development of uroliths. However, crystals may be found in the urine of dogs that do not have, and never develop, uroliths. This is particularly true of struvite and calcium oxalate crystals in all breeds and urate crystals in dalmatians. Conversely, some crystal types are not a normal finding and warrant further investigation even in the absence of uroliths. These include cystine, xanthine, and (in breeds other than dalmatians) urate crystals.

Crystals that were not present *in vivo* while the urine was in the excretory pathway, often form *in vitro* as the urine cools below body temperature.[13] Ideally, urinalysis should be performed as soon as possible without refrigeration of the sample when attempting to determine if crystalluria is present.

In dogs with urolithiasis, the type of crystals found in urinalysis may be helpful for predicting the mineral composition of the uroliths, although several caveats exist. If the dog's diet has been changed between the time of urolith formation and diagnosis, the crystals present at the time of diagnosis may be different from the mineral component of the urolith. Likewise, development or resolution of UTI with urease-producing organisms during the urolith formation and growth can change the type of crystal present in the urine.

267.4.5 Diagnosis of Urolithiasis

Uroliths are usually diagnosed based on results from radiography or ultrasonography. Occasionally, dogs have a history of voiding uroliths. Although uroliths may be palpated in the bladder or urethra, palpation is not a sensitive technique for ruling out urolithiasis. When uroliths are detected anywhere in the urinary tract, the entire urinary tract should be imaged with radiographs and ultrasound (or contrast radiography) to determine if uroliths are present in other locations (see Figure 267-2). Palpation of the external portion of the urethra and

digital rectal examination of the pelvic urethra should also be performed to examine for urethroliths. Although most uroliths are radiopaque and are visible on survey abdominal radiographs, some uroliths are radiolucent (or strictly speaking have the same radiopacity as the surrounding soft tissues), and some radiopaque uroliths are too small to be detected. In one *in vitro* study, failure rates for detection of uroliths by survey radiography were between 2% and 27%, depending on the size and composition of the uroliths.[14] In contrast, the radiographic procedures with greatest sensitivity were pneumocystography, double-contrast cystography, and ultrasonography using a 7.5 MHz transducer with false-negative results of 11%, 10%, and 6%, respectively.[14] Therefore precise determination of the location, presence or absence of uroliths requires either ultrasonography or contrast radiography. Ultrasonography is preferred, if available, because of relative ease, lack of requirement for urethral catheterization, and it also permits simultaneous evaluation of the upper urinary tract for nephroliths or ureteroliths.

Once the number and location of uroliths is determined, the next step is to attempt to determine the type of urolith present to formulate a treatment plan. Catheter-assisted retrieval of uroliths or mechanical removal during cystoscopy provides urocystoliths for quantitative analysis. Because qualitative analysis methods are unreliable, the preferred quantitative analysis methods are optical crystallography, x-ray defraction, and infrared spectroscopy.[10,15]

If uroliths are not available for analysis (or pending the result of quantitative analysis), the chemical composition can often be correctly predicted from signalment, and results of urinalysis, urine culture, and radiographs (Table 267-1).[16,17] Two additional imaging approaches for determining urolith composition can be used. Weichselbaum and colleagues[18,19] reported an *in vitro* method of comparing urolith opacity to various concentrations and depths of iodinated contrast solutions to predict urolith composition.

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Table • 267-1 Characteristics of Common Canine Uroliths

COMPOSITION	RADIOGRAPHIC DENSITY	SURFACE CHARACTERISTICS	URINE pH	CRYSTALLURIA	URINARY TRACT INFECTION	COMMONLY AFFECTED BREEDS*	OTHER
Calcium oxalate monohydrate (COM) and/or calcium oxalate dihydrate (COD)	Moderately to markedly radiopaque (see Figure 267-2)	Sharp projections, mulberry shaped or smooth round uroliths (see Figure 267-2); COD may appear jackstone shaped	Acidic to neutral	Calcium oxalate dihydrate crystals (square envelope) or calcium oxalate monohydrate crystals (dumbbell or picket-fence shapes)	None or secondary urinary tract infection (UTI) with common uropathogens	Miniature schnauzer, Lhasa Apso, Yorkshire terrier, Bichon frise, Pomeranian, Shih Tzu, Cairn terrier, Maltese, miniature poodle, Chihuahua	Often multiple small uroliths in bladder; multiple nephroliths if present
Struvite (magnesium ammonium phosphate hexahydrate)	Moderately to markedly radiopaque; larger uroliths appear more radiopaque (see Figure 267-7)	Single—may be smooth or speculated, may assume shape of bladder lumen (see Figure 267-8); multiple—smooth surfaces where uroliths contact each other, often pyramidal shape	Alkaline	Struvite or "triple phosphate" crystals ("coffin lid" appearance)	Urease-producing organisms *Staphylococcus*, *(Proteus*, mycoplasma); sterile struvite uroliths in cocker spaniels	Miniature schnauzer, Shih Tzu, Bichon frise, miniature poodle, cocker spaniel, Lhasa Apso	Uroliths >10 cm diameter are likely to be struvite; nephroliths are often staghorn shaped
Urate/xanthine	Radiolucent to faintly radiopaque	Multiple smooth uroliths	Acidic	Ammonium urate crystals (yellow-brown "thorn apple" or spherical shapes) or amorphous urate crystals	None or secondary UTI with common uropathogens; rarely, urease-producing organisms	Dalmatian, English bulldog, miniature schnauzer, Shih Tzu, Yorkshire terrier	PSS or other liver dysfunction; yellow-green urolith color
Cystine	Faintly to moderately radiopaque	Multiple smooth round uroliths in bladder and/or urethra; nephroliths may be staghorn shaped if present	Acidic	Cystine crystals (hexagonal shape) Cystine crystalluria always abnormal	None or secondary UTI with common uropathogens	Mastiff, Australian cattle dog, English bulldog, Staffordshire bull terriers, Newfoundland, dachshund	Positive urine cyanide-nitroprusside test; metabolic screening of urine available; males >> females
Calcium phosphate	Moderately to markedly radiopaque	Hydroxyapatit—multiple small uroliths with variable shape; brushite—multiple smooth round or pyramidal uroliths	Alkaline to neutral pH for hydroxyapatite, acidic for brushite	Amorphous phosphates or calcium phosphate crystals (thin prisms)	None or secondary UTI with common uropathogens	Yorkshire terrier, miniature schnauzer, Bichon friese, Shih Tzu, springer spaniel, Pomeranian, miniature poodle, cocker spaniel	Hypercalcemia is a predisposing factor

Silica	Moderately radiopaque	Classic jackstone appearance	Acidic to neutral	None	None or secondary UTI with common uropathogens	German shepherd, Old English sheepdogs, Labrador retriever, golden retriever, miniature schnauzer, cocker spaniels, Shih Tzus, Bichon frises	Males >> females

The breeds listed are those from which uroliths are most frequently submitted for mineral analysis; due to differences in breed popularity, this is not necessarily the same as the breeds that are at increased risk for stone formation.

Information from computerized tomography (CT) may eventually provide more objective means of predicting urolith composition in dogs. The peak attenuation measurements (termed *Hounsfield units*) of canine uroliths determined *in vitro* by noncontrast CT was significantly correlated with chemical composition in one study, confirmation of these findings *in vivo* is required.[20] In humans, CT has become the gold standard imaging technique for detection of uroliths,[8] and urolith composition can often be predicted from attenuation values obtained by micro CT scans *in vitro* and helical CT *in vivo*.[21]

267.4.6 Urolith Removal Techniques

Uroliths that may be medically dissolved include struvite, urates, and cystine.[22–24] For dissolution to occur, the urolith should be surrounded by undersaturated urine to allow the crystals to go back into solution. Therefore the location also affects the ability to medically dissolve uroliths; urocystoliths and nephroliths are amenable to dissolution but ureteroliths and urethroliths are not.[24] Urethroliths may be flushed back into the urinary bladder by retrograde urohydropropulsion for medical dissolution or mechanical removal.[25]

267.4.6.1 Cystotomy

Surgical removal of uroliths by cystotomy is the traditional method of mechanical removal of canine urocystoliths. However, use of newer, nonsurgical techniques for removal of smaller urocystoliths is increasing. It is notable that open surgical removal of uroliths is used in only 0.3% to 4% of human patients.[26]

267.4.6.2 Laparoscopic-Assisted Cystotomy

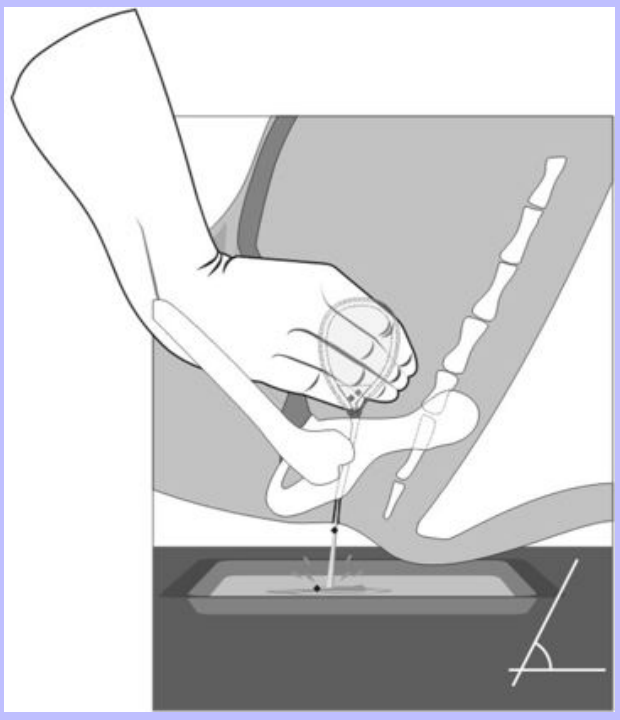
A recent report demonstrated that laparoscopic-assisted cystotomy may be used to remove urocystoliths that are too large to pass though the urethra.[27] This approach minimizes surgical trauma and may become more commonly used as veterinarians become more familiar with laparoscopic surgery.

267.4.6.3 Voiding Urohydropropulsion

Voiding urohydropropulsion is the removal of smaller urocystoliths by inducing voiding while the dog is positioned vertically so that urocystoliths pass with the voided urine (Figure 267-4).[28] Although the technique may be performed with the dog awake, general anesthesia facilitates complete urethral relaxation,

preventing development of high intravesicular pressures that could cause iatrogenic trauma to the bladder wall. Cystoscopy may be performed immediately prior to voiding urohydropropulsion to evaluate the urethra for strictures that would interfere with urolith passage. If the bladder is not distended with urine, it is distended with sterile saline via cystoscopy or urethral catheterization. The dog is positioned so that the spine is roughly 25 degrees caudal to a line perpendicular to the effects of gravity, such that a line drawn through the urethra into the bladder is vertical (see Figure 267-4). The bladder is agitated, and time is allowed for the urocystoliths to settle in the trigone. The bladder is palpated, and the intravesicular pressure is gradually increased by manual compression of the bladder to initiate a detrusor contraction. Once voiding begins, the bladder is compressed more firmly to attempt to maintain maximum urine flow rates, dilate the urethra, and flush out the urocystoliths. The bladder is refilled with sterile saline through a cystoscope or urinary catheter and the process is repeated until no urocystoliths are passed with the expelled fluid. Then postprocedural radiographs or cystoscopy are performed to confirm complete removal of the urocystoliths. Although periprocedural antibiotics are sometimes recommended to prevent iatrogenic UTI, this is not required provided proper aseptic technique is observed. If significant urethral leakage occurs when the dog is positioned vertically, inadequate bladder distention may prevent effective voiding of the uroliths. If this occurs, a Foley catheter is placed in the urethra with the balloon used to obstruct the trigone and the bladder is distended with saline. After agitation of the bladder to allow the urocystoliths to settle in the trigone, the Foley catheter balloon is deflated, the catheter is removed, and voiding urohydropropulsion is performed as described previously.

Figure 267-4 Diagram of a dog positioned for voiding urohydropropulsion. Reader should note that the trigone of the bladder is perpendicular to the effects of gravity, whereas the spine is approximately 25 degrees caudal this perpendicular line.



267.4.6.4 Retrograde Urohydropropulsion

Retrograde urohydropropulsion is the flushing of urethroliths into the urinary bladder, usually performed to relieve urethral obstruction.[25] General anesthesia is usually required for successful retrograde urohydropropulsion. If necessary, the dog or cat should be treated by decompressive cystocentesis and fluid therapy to correct acid-base and electrolyte imbalances before anesthesia to minimize the anesthetic risk. If the urinary bladder is overdistended, the bladder is gently decompressed by cystocentesis using a 22-gauge needle connected to a 60 mL syringe by extension tubing and a three-way valve. This lowers the urethral pressures proximal to the urethroliths to allow their retrograde movement. The largest urinary catheter possible is gently passed to the level of the distal calculus. An assistant compresses the urethra against the pubis via rectal palpation. A 2:1 mixture of sterile saline and sterile aqueous lubricant is rapidly flushed into the urethra distal to the obstructive calculus while compressing the urethral orifice around the catheter to prevent fluid leakage from the penis. An estimate of the total volume of flush required is 5 mL/kg of body weight or 60 mL, whichever is less. Once the urethra begins to dilate, the proximal (rectal) compression is released while flushing continues. If the urethroliths pass retrograde, the catheter is gently advanced to the trigone. If the calculus does not move retrograde, the degree of bladder distention should be assessed prior to repeating retrograde urohydropropulsion. If necessary, the bladder may be decompressed by cystocentesis before repeating the process. Subsequent retrograde flushes are done with sterile saline alone, because the urethra is well lubricated from the first attempt and saline can be more rapidly flushed through the catheter. Successful retrograde movement of all urethroliths should be confirmed by cystoscopy or radiography.

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The aim of retrograde urohydropropulsion is to flush the uroliths into the bladder, not to push them with the urinary catheter. Pushing against urethroliths with rigid polyethylene catheters may result in excessive mucosal trauma, the catheter being forced through the wall of the urethra, or the catheter being passed round the urolith providing a route for temporary urine drainage but without moving uroliths back into the bladder. Catheter-induced trauma predisposes the dog to future urethral stricture formation.

267.4.6.5 Catheter-Assisted Retrieval

Catheter-assisted retrieval of uroliths may be used to collect small urocystoliths for mineral analysis.[29] A urinary catheter is placed with the tip located within the trigone and the bladder is distended with urine or sterile saline. Next the bladder is vigorously agitated to suspend the smaller uroliths in the urine while rapid aspiration through the urinary catheter results in removal of the suspended uroliths along with the urine. If the dog tolerates urethral catheterization, this procedure may be performed without sedation or anesthesia.

267.4.6.6 Ellik Evacuator

During cystoscopy with a rigid cystoscope the telescope is removed, leaving the cystoscope sheath in place in the urethra with the tip of the sheath just inside the trigone. An Ellik evacuator is attached to the cystoscope sheath, and the bladder is rapidly lavaged to flush sterile saline into and out of the bladder using the bulb attachment. The design of the Ellik evacuator allows the aspirated uroliths to gravitate to the bottom chamber while fluid in the top chamber is flushed into and out of the bladder several times (Figure 267-5). This technique can be used to collect uroliths smaller than the diameter of the cystoscope sheath, and thus it allows for removal of larger uroliths than a standard urinary catheter. This technique may be

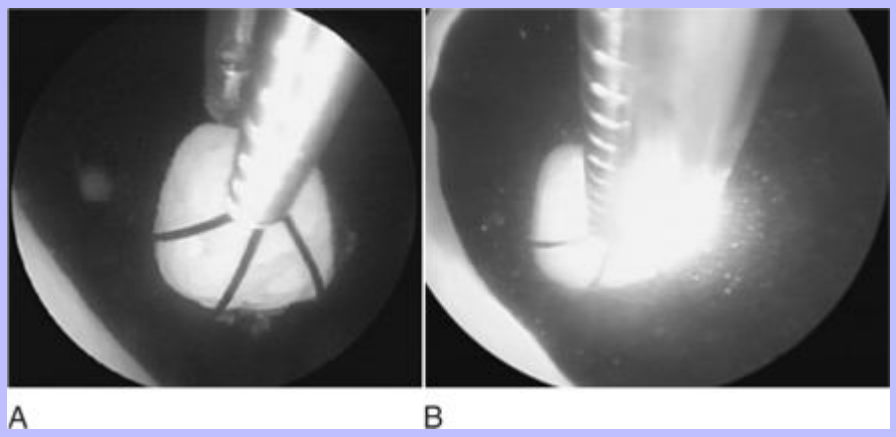
used to completely remove small uroliths from the urinary bladder or to obtain smaller uroliths for quantitative analysis and culture.

267.4.6.7 Stone Baskets

Stone baskets may be used to remove uroliths from the LUT provided the uroliths are smaller than the dilated urethra. Stone baskets are usually passed through the working channel of the cystoscope, the basket is opened, and once the urolith is engaged in the basket, the basket is closed around the urolith and positioned at the end of the cystoscope (Figure 267-6, *A*). The cystoscope and basket containing the urolith are then slowly withdrawn through the urethra with direct visualization to ensure the urothelium does not bulge around the urolith edges, which may indicate the urolith is becoming wedged in the urethra. This technique may be safely used to remove some uroliths that will not readily pass during voiding urohydropropulsion; however, caution is required to avoid getting the urolith wedged in the urethra.

Figure 267-5 An Ellik evacuator attached to a cystoscope sheath used for flushing small uroliths from the bladder. Reader should note the uroliths in the bottom chamber.

Figure 267-6 Fragmentation and removal of calcium oxalate monohydrate urocystoliths by electrohydraulic lithotripsy (EHL). **A,** Urocystolith held in a stone basket for fragmentation by EHL. The electrohydraulic electrode is visible dorsal to the basket. **B,** The electrohydraulic electrode has been activated generating a spark on the surface of the urolith.



267.4.6.8 Electrohydraulic Lithotripsy

Electrohydraulic lithotripsy (EHL), the fragmentation of urinary uroliths with hydraulic shock waves generated within the bladder lumen, has been successfully used to fragment and remove urocystoliths in dogs (see Figure 267-6).[30] The procedure requires an EHL generator and cystoscopic equipment with a 5F working channel for the electrohydraulic electrode. The average treatment time is more than 1 hour to adequately fragment urocystoliths, which are then removed by use of an Ellik evacuator. Large urocystoliths may take several hours to completely fragment by EHL.

267.4.6.9 Laser Lithotripsy

In humans, laser lithotripsy using the holmium laser has become the lithotrite of choice for fragmentation of large bladder calculi, ureteroliths, and nephroliths.[26,31,32] In humans, holmium laser lithotripsy has largely replaced EHL because it is faster and safer than EHL. The holmium laser is absorbed in 0.5 mm of fluid, allowing it to safely fragment uroliths within the urethra or ureter.[26,31] Also, because of the small diameter of the laser fibers, laser lithotripsy can be performed through small-diameter flexible endoscopes. Recent *in vitro* studies confirm that the holmium laser can efficiently fragment uroliths from dogs regardless of chemical composition.[14] Implanted urethroliths in male dogs were safely fragmented by laser lithotripsy using a holmium laser.[8] As holmium lasers become more widely available in veterinary medicine, this technique may replace cystotomy and urethrotomy for removal of uroliths.

267.4.6.10 Extracorporeal Shock Wave Lithotripsy

Extracorporeal shock wave lithotripsy (ESWL) is fragmentation of uroliths using shock waves that are generated outside the body. Although ESWL is better suited for fragmentation of uroliths fixed in one location such as nephroliths or ureteroliths, urocystoliths have been successfully fragmented using ESWL. Because the urocystoliths tend to move out of the focal spot of the lithotriptor, uniform fragmentation does not occur consistently. In treating 14 dogs using ESWL, urocystoliths were fragmented into pieces small enough to be removed through the urethra in 8 of the dogs in one ESWL session. If the fragments are too large to be removed through the urethra, ESWL may be repeated or a secondary procedure may be required to remove larger urocystolith fragments.

267.5 CALCIUM OXALATE UROLITHIASIS

Calcium oxalate uroliths are usually composed of 100% calcium oxalate, although some also contain varying amounts of calcium phosphate.[35,36] Calcium oxalate is a common component of many compound uroliths. Calcium oxalate occurs as two crystalline forms: (1) calcium oxalate monohydrate (whewellite) or (2) calcium oxalate dihydrate (weddellite). Calcium oxalate monohydrate occurs more commonly than calcium oxalate dihydrate in canine uroliths. Some dogs have both forms in different layers of the same urolith.[10] The only clinically relevant difference between these forms is that calcium oxalate dihydrate uroliths are more easily fragmented by shock waves than calcium oxalate monohydrate uroliths.[26,37] Calcium oxalate uroliths are radiopaque and often occur as multiple smaller uroliths in the LUT (see Figure 267-2). The surface characteristics vary; uroliths may be smooth, mulberry-shaped, or have sharp projections (see Figure 267-2). Although calcium oxalate uroliths are not caused by infection, they may be associated with secondary UTIs because the presence of uroliths may interfere with host defenses against infection and contribute to recurrent infections. In one study, 52% of female dogs and 32% of male dogs with uroliths that contained calcium oxalate had positive urine or urolith cultures.[38] However, compound uroliths that were made up of less than 50% calcium oxalate were included in the study, and only about half of the uroliths were cultured, which may have resulted in an overestimation of the prevalence of UTI. Other studies do not support an association of calcium oxalate uroliths with UTI.[39]

267.5.1 Epidemiology of Calcium Oxalate Urolithiasis

The percentage of canine uroliths submitted to the Minnesota Urolith Center that are composed of calcium oxalate has increased from approximately 5% in 1981 to 35% in 1997, making it the second most common urolith in dogs.[10,40] This is similar to the increased incidence of calcium oxalate uroliths and decreased incidence in struvite uroliths in cats over the same time period[10] and in humans over the last 50 years.[8] The exact reasons for the shift in prevalence of calcium oxalate uroliths in dogs is unknown. Better medical management of struvite uroliths may be decreasing the percentage of struvite uroliths, but this does not adequately explain the shift because a concurrent relative increase has not occurred in the percentage other types of uroliths.[10] Alternatively, increased use of diets designed to minimize the risk for struvite uroliths maybe increasing the risk for calcium oxalate uroliths (see section on diet, following). In humans, calcium oxalate uroliths occur most commonly in the upper urinary tract, whereas in dogs and cats they occur much more commonly in the LUT.[8,41]

Calcium oxalate uroliths occur more commonly in male dogs (68% to 71% of calcium oxalate uroliths submitted to two urolith centers) than female dogs (26% to 32%).[40,42] Similarly, in humans, men are affected three times more often than women; this has been hypothesized to be due to estrogen-induced reduction in urinary oxalate and increase in urinary citrate excretion in females.[8] Neutered male dogs have increased risk of calcium oxalate uroliths compared with intact dogs.[43] Obese dogs are more likely to form calcium oxalate uroliths, which is similar to cats and humans.[8,43] Breeds at increased risk for calcium oxalate uroliths include the miniature schnauzer, Lhasa Apso, Yorkshire terrier, Bichon frise, Pomeranian, Shih Tzu, Cairn terrier, Maltese, miniature poodle, and Chihuahua.[42–44] In one study, golden retrievers, German shepard dogs, and cocker spaniels had decreased risk of calcium oxalate uroliths.[43] Dogs that produce lower urine volumes and urinate less often may be more likely to have calcium oxalate urolithiasis.[45]

267.5.2 Etiopathogenesis of Calcium Oxalate Urolithiasis

Excessive urinary calcium excretion (hypercalciuria) or oxalate (hyperoxaluria) results in increased risk of calcium oxalate urolith formation. Calcium oxalate may precipitate on existing surfaces such as epithelial cells, cell debris, or other crystals (e.g., uric acid, calcium phosphate). This process, known as *heterogenous nucleation*, occurs at lower urine saturation for calcium oxalate than is required for homogenous nucleation. In humans, increased uric acid excretion (hyperuricosuria) often contributes to formation of calcium oxalate urolithiasis.

Urinary excretion of uric acid was slightly higher in miniature schnauzers with calcium oxalate urolithiasis than normal beagles[46]; however, because dogs have much lower serum and urine uric acid concentrations than humans (with the exception of dalmatians and English bulldogs),[22] hyperuricosuria is less likely to contribute to calcium oxalate urolith formation in dogs.

267.5.2.1 Hypercalciuria

Increased urinary excretion of calcium (hypercalciuria) is a common contributing factor to calcium oxalate urolithiasis in humans.[8] Hypercalciuria is also a common finding in dogs with calcium oxalate urolithiasis.[46–48] Hypercalciuria is proposed to occur by one of three mechanisms: (1) *absorptive hypercalciuria,* characterized by increased intestinal absorption of calcium; (2) *renal-leak hypercalciuria,* characterized by a primary renal leak of calcium; and (3) *resorptive hypercalciuria,* characterized by increased bone demineralization.[8,49] Humans and dogs with *absorptive hypercalciuria* have increased intestinal absorption of calcium with the excess calcium excreted in the urine (hypercalciuria).[8] The mildly increased serum calcium (from increased intestinal absorption) causes an increased filtered load of calcium in the glomerular filtrate and reduced tubular reabsorption of calcium due, in part, to suppression of parathyroid hormone (PTH) levels by high normal serum calcium concentrations. The combination of increased filtered calcium and reduced tubular reabsorption causes hypercalciuria. The increased intestinal absorption occurs in the jejunum and is accompanied by increased intestinal absorption of oxalate, which contributes to concurrent hyperoxaluria. Approximately 50% of humans with absorptive hypercalciuria have increased concentrations of 1,25-dihydroxycholecalciferol, causing increased intestinal calcium absorption.[8,50] In one study, five of six miniature schnauzers with calcium oxalate urolithiasis were classified as having absorptive hypercalciuria.[46]

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Renal-leak hypercalciuria is due to impaired renal tubular reabsorption of calcium.[8] Renal calcium loss reduces the serum ionized calcium, which causes increased PTH and 1,25-dihydroxycholecalciferol. Increased 1,25-dihydroxycholecalciferol causes increased intestinal absorption of calcium (and phosphorus), which returns the serum calcium to normal. The increased PTH also causes increased mobiliza-tion of calcium from bone, which could contribute to bone demineralization over time if dietary calcium intake is not adequate. Humans and dogs with renal-leak hypercalciuria have high serum PTH concentrations, normal serum calcium concentrations, and high fasting urinary calcium excretion.

Resorptive hypercalciuria and *hypercalcemic hypercalciuria* are closely related. Resorptive hypercalciuria is a subtle, normocalcemic version of primary hyperparathyroidism, whereas serum calcium is elevated with hypercalcemic hypercalciuria.[8] In humans, the most common cause of hypercalcemic hypercalciuria resulting in calcium oxalate urolithiasis is primary hyperparathyroidism. Other causes in humans include malignancy-associated hypercalcemia, hyperthyroidism and sarcoidosis, and other granulomatous diseases, although these have not been reported associated with calcium oxalate urolithiasis in dogs. In dogs, calcium oxalate uroliths have been reported secondary to primary hyperparathyroidism.[51,52] Dogs with hyperparathyroidism may form calcium phosphate, calcium oxalate, or mixed calcium oxalate and calcium phosphate uroliths.[51,53]

267.5.2.2 Hyperoxaluria

Urinary concentration of oxalate is an important factor in calcium oxalate crystallization and urolithiasis, because on a molar basis, increases in urine oxalate concentration have a greater effect on urinary saturation of calcium oxalate than equivalent increases in urinary calcium concentration.[8,48] Oxalate is freely filtered at the glomerulus and undergoes bidirectional transport in the renal tubules with net tubular secretion. Urinary oxalate is derived mainly from endogenous production in the liver from metabolism of ascorbic acid, glyoxylate, and glycine with lesser amounts from dietary intake of oxalate. Dietary meat protein intake contributes the amino acids hydroxyproline and tryptophan, which are metabolized to oxalate. In humans, rats, and pigs, some of the normal dietary oxalate is degraded in the intestines by normal bacterial flora including *Oxalobacter formigenes*.[8] Some humans with calcium oxalate nephrolithiasis have deceased intestinal *Oxalobacter formigenes*, which may be caused by chronic antibiotic therapy for concurrent medical conditions.[54] The potential role of a paucity of intestinal *Oxalobacter formigenes* in calcium oxalate urolithiasis in dogs has not been evaluated.

Varying degrees of hyperoxaluria is present in up to 50% of humans with calcium oxalate urolithiasis;[8] however, hyperoxaluria has not been detected in dogs with calcium oxalate urolithiasis.[46] Primary hyperoxaluria is a rare genetic disorder of humans that causes either oxalate nephrosis or recurrent calcium oxalate urolithiasis. Primary oxaluria has been reported in both dogs and cats, but was associated with oxalate nephrosis rather than calcium oxalate urolithiasis.[55,56]

267.5.2.3 Water Source

The mineral content of water may be a potential factor in calcium oxalate urolithiasis in humans, although the data are conflicting.[8] It has been proposed that increased sodium or calcium content or absence of trace minerals such as zinc, which chelates calcium, might increase risk of calcium oxalate urolithiasis. In one epidemiologic study in cats, the source of water (e.g., bottled, municipal) did not appear to affect the risk of

calcium oxalate urolithiasis.[57] No reports exist on the effects of mineral content of water on calcium oxalate urolithiasis in dogs.

267.5.2.4 Modifiers of Calcium Oxalate Crystal System

In humans the degree of saturation of urine for calcium oxalate overlaps between normal subjects and those who form uroliths. The reason some humans form uroliths and others do not is that urine normally contains several natural inhibitors of urolith formation and growth. Inhibitors are either organic or inorganic substances in urine that inhibit crystal formation, aggregation, or growth and if defective or deficient, may contribute to urolith formation. In humans, inhibitors of calcium oxalate include citrate, magnesium, pyrophosphate, glycosaminoglycans, nephrocalcin, and Tamm-Horsfall mucoprotein.[8] Although little is known about these inhibitors of calcium oxalate in dogs, they may play a similar role in dogs in determining which dogs form uroliths and which do not.

Two important inorganic inhibitors of calcium oxalate are (1) citrate and (2) magnesium. In urine, citrate forms complexes with calcium that are more soluble than calcium oxalate, lowering the ionic calcium concentration. Citrate inhibits both spontaneous and heterogenous nucleation of calcium oxalate crystals.[8] In humans, citrate is filtered by the kidneys and approximately 75% is reabsorbed by the tubules, with the major determinant of the amount reabsorbed being the acid-base status. Metabolic acidosis reduces urinary citrate excretion by augmenting tubular reabsorption of citrate, whereas metabolic alkalosis decreases tubular reabsorption and increases urinary citrate excretion.[8,58] In dogs, urinary citrate excretion is much lower than humans with less than 1% of filtered citrate normally excreted in the urine, although urinary citrate excretion increases dramatically with metabolic alkalosis.[58] Hypocitraturia has been reported in 15% to 63% of humans who form calcium oxalate nephroliths, with metabolic acidosis being the most important cause of decreased urinary citrate excretion.[8,59] In dogs, mean urinary citrate excretion was not significantly different between six miniature schnauzers with calcium oxalate urolithiasis and normal beagles; however, some individual miniature schnauzers appeared to have decreased urinary citrate excretion compared with the normal beagles.[46] Because hypocitraturia only affects 15% to 63% humans with calcium oxalate nephroliths, and because too few dogs have been evaluated to accurately define what level of daily urinary citrate excretion constitutes hypocitraturia in dogs, a role for hypocitraturia in calcium oxalate urolith formation in some dogs is possible, although unproven.

Similar to citrate's role with calcium, magnesium complexes with oxalate, reducing the urine saturation for calcium oxalate.[8] Deficient urinary magnesium concentration results in more oxalate being available to combine with ionic calcium; therefore lower dietary magnesium may predispose to calcium oxalate urolithiasis, a proposal which was supported by two recent epidemiologic studies.[39,60] Citrate and magnesium play complimentary roles by complexing calcium and oxalate respectively and lowering the urine saturation for calcium oxalate.

Pyrophosphate in the urine is another inhibitor of calcium oxalate. The amount of pyrophosphate in the urine is related to dietary phosphorus intake. Although the role of pyrophosphate in canine urine is unknown, diets low is phosphorus have been shown to increase the risk for calcium oxalate urolithiasis in dogs, which could be due to lowering of urinary pyrophosphate along with other factors (see Role of Diet, following).[39,60]

Nephrocalcin, synthesized by renal proximal tubular cells and the medullary thick ascending limb, is a potent inhibitor of calcium oxalate monohydrate crystal aggregation.[61] Urine from humans who form calcium oxalate uroliths contains nephrocalcin that lacks γ-carboxyglutamic acid and is tenfold less effective at inhibiting calcium oxalate monohydrate crystal aggregation than nephrocalcin from normal urine.[61] Lulich and colleagues[40] reported that urine from dogs with calcium oxalate contained different fractions of nephrocalcin than urine from normal beagles, which could also support a role for lack of this inhibitor in the pathogenesis of calcium oxalate urolith formation in dogs.

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Tamm-Horsfall mucoprotein, synthesized by the medullary thick ascending limb and the distal tubule, is another potent inhibitor of calcium oxalate aggregation.[8,62] The self-aggregated form of Tamm-Horsfall mucoprotein, which is the predominant form of this protein in the urine from humans with calcium oxalate nephroliths, is a less effective inhibitor of calcium oxalate crystal aggregation and may even promote calcium oxalate crystallization.[63] The role of Tamm-Horsfall mucoprotein in dogs with calcium oxalate uroliths is unknown.

267.5.2.5 Concurrent Medical Conditions

Hyperadrenocorticism is associated with calcium oxalate urolithiasis in humans and dogs.[8,64] In humans, glucocorticoid excess leads to hypercalciuria secondary to increased mobilization of calcium from bone.[8] Glucocorticoids may also decrease tubular resorption of calcium, resulting in hypercalciuria and increasing the risk of calcium oxalate urolithiasis. Chronic metabolic acidosis may contribute to calcium oxalate urolithiasis in humans and dogs.[8,65] The proposed mechanism is buffering of excess hydrogen ions by bone phosphorus and carbonates. The calcium concurrently released from the bone during buffering is excreted in the urine, resulting in hypercalciuria. Acidosis also reduces the urinary excretion of citrate, a potent inhibitor of calcium oxalate.

267.5.3 Treatment of Calcium Oxalate Urolithiasis

Calcium oxalate uroliths are not amenable to medical dissolution; therefore they must be mechanically removed from the urinary tract (see previous section for details). Once urolith removal is performed, postprocedural radiographs or cystoscopy should be performed to document complete urolith removal so that the efficacy of preventative measures can be accurately assessed. Incomplete surgical removal of uroliths has been reported in up to 20% of dogs in one series.[66]

267.5.4 Prevention of Calcium Oxalate Urolithiasis

Calcium oxalate uroliths tend to recur in most dogs, with recurrence rates of up to 50% within 3 years of initial diagnosis.[67,68] Therefore preventative measures such as diet and medications should be used to reduce the risk of recurrence. Once all uroliths have been removed and before initiation of preventative measures, a baseline database should be obtained, including serum biochemistry profile (to examine for hypercalcemia, metabolic acidosis, or support for concurrent hyperadrenocorticism) and urinalysis (to determine urine specific gravity [USG], pH and crystalluria). Dietary changes should be attempted, and the clinician should add medications if persistence of calcium oxalate crystalluria or recurrence of calcium oxalate urolithiasis is noted.

267.5.4.1 Role of Diet

Increased water intake though feeding a canned diet or by adding water to the diet may be the most important recommendation to help prevent recurrence of calcium oxalate urolithiasis in dogs.[39,40,42] Increased water intake is also a long-standing recommendation for prevention of urolithiasis in humans.[8] Increased water intake results in dilution of calculogenic substances in the urine and increases the frequency of voiding, which helps remove any free crystals that form in the urinary tract. In normal miniature schnauzers, increasing dietary moisture from 7% to 73% increased net daily water intake and reduced urine calcium oxalate RSS, which is suggested to reflect decreased risk of calcium oxalate urolithiasis.[69] In an epidemiologic study, canned canine diets significantly reduced the risk for calcium oxalate urolithiasis compared with dry diets.[39,60] Addition of water to the diet or changing to a predominantly canned diet should be implemented as the first step in prevention of calcium oxalate urolithiasis in dogs.

The ideal diet for prevention of calcium oxalate urolithiasis in dogs is unknown, and most dietary recommendations have been made based on surrogate end points (such as changes in urine concentration of calcium, 24-hour urinary calcium and oxalate excretion or calcium oxalate RSS), rather than reduction of urolith recurrence rates. The dietary factors thought to contribute to calcium oxalate urolithiasis in dogs are undergoing substantial change, with several conflicting recommendations in the literature. Previously, dietary factors hypothesized to decrease the risk of calcium oxalate urolithiasis in dogs included reduced dietary levels of protein, sodium, and oxalate precursors and higher dietary water, calcium, phosphorus, and potassium content.[16,42] In contrast, recent epidemiologic studies indicate that dietary factors in dogs associated with an decreased risk of calcium oxalate urolithiasis included increased dietary water, protein, calcium, phosphorus, magnesium, sodium, potassium, chloride and decreased dietary carbohydrate content.[39,60] In addition, dry diets that resulted in increased acidification of the urine were associated with an increased risk of calcium oxalate urolithiasis.[39,60] These were epidemiologic studies of commercial diets; thus there may have been significant confounding effects such that an apparent benefit from one factor, such as increased dietary protein, could actually have been due to other factors, such as increased phosphorus or potassium content of the diet rather than the protein content per se, because diets high in protein also tend to be high in phosphorus and potassium. Likewise, these associations do not prove cause and effect.[70]

Although diets designed for dogs with renal failure have been recommended previously for prevention of calcium oxalate urolithiasis, because these diets are phosphorus restricted, the authors do not recommend their use for this purpose. Reduced dietary phosphorus was associated with increased risk of calcium oxalate urolithiasis in dogs.[39,60] Dietary phosphorus restriction promotes increased intestinal absorption of calcium, with the excess calcium excreted in the urine. The increased intestinal calcium absorption occurs because dietary phosphorus binds calcium making it less available for absorption. Deficient dietary phosphorus also increases renal production of calcitriol, which promotes intestinal absorption of calcium and phosphorus.[40] Additionally, increased dietary intake of phosphorus is thought to increase urinary excretion of pyrophosphate, an inhibitor of calcium oxalate crystallization.[40]

Because humans and dogs with absorptive hypercalciuria have reductions in urinary calcium when dietary calcium is restricted, it was previously recommended to restrict dietary calcium. However, recent studies in humans and dogs indicate that dietary calcium restriction actually increases the risk of calcium oxalate

urolithiasis.[39,60,71] The proposed mechanism for this apparent paradox is that reduced dietary calcium results in increased dietary absorption of oxalate because less calcium is present in the intestinal lumen to bind oxalate. Increased intestinal oxalate absorption causes greater urinary oxalate excretion, which increases the risk of calcium oxalate urolithiasis. Therefore calcium oxalate preventative diets should not be calcium restricted. Although diets should be replete in calcium, calcium supplements between meals should be avoided because they may promote hypercalciuria and increase the risk of calcium oxalate urolithiasis.[72]

Because dry diets designed to maximize urine acidity were associated with a threefold greater risk of calcium oxalate urolithiasis and some authors have reported an association of acidic urine pH with calcium oxalate urolithiasis,[39,42,60] calcium oxalate preventative diets should not be maximally acidifying. Some diets recommended for prevention of calcium oxalate urolithiasis (e.g. Prescription diet u/d, Hill's Pet Nutrition) contain potassium citrate for the purpose of alkalinizing the urine, whereas other diets do not (e.g., Waltham® Canine S/O Lower Urinary Tract Support Diet, Waltham). Some authors have recommended targeting a urine pH of 6.5 to 7.5,[42,65] whereas others suggest urine pH of 5.5 to 6.0.[47] The solubility of calcium oxalate is not greatly influenced by urine pH, but because of the potential for acidosis promoting hypercalciuria, the authors currently recommend a target urine pH of at least 6.5 to 7.0. Urine pH greater than 7.5 may promote formation of calcium phosphate uroliths and should be avoided.[53]

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Currently the ideal protein content of diets for prevention of calcium oxalate urolithiasis in dogs is not known. Although dietary protein restriction has been recommended in the past,[65] the recent epidemiologic association of higher levels of dietary protein with decreased risk of calcium oxalate urolithiasis has caused re-evaluation of this recommendation.[39,60] The apparent benefit of increased dietary protein could have been due to other factors in the higher protein diets such as higher phosphorus content. In humans, increased dietary protein intake increases the risk of calcium oxalate urolithiasis through increased urinary uric acid excretion and contributes to increased bone buffering of acid derived from catabolism of the excess amino acids, thus promoting hypercalciuria.[8] Because dogs have lower urine uric acid concentrations and because the net acidification of canine diets can be controlled independent of protein content, dietary protein may not have the same effects on recurrence of calcium oxalate urolithiasis in dogs compared with humans.

The ideal dietary sodium content for prevention of calcium oxalate urolithiasis is also controversial. Dietary sodium restriction has previously been recommended based on the hypothesis that minimizing natruresis would concurrently minimize hypercalciuria.[65] However, recent epidemiologic studies associated higher dietary sodium with decreased risk of calcium oxalate urolithiasis.[39,60] In another study using normal dogs, increased dietary sodium (0.3 g of sodium per 100 kcal) reduced urine calcium oxalate RSS, compared with a low sodium diet (0.05 g of sodium per 100 kcal).[47,69] These authors have suggested that calcium oxalate preventative diets should not be sodium restricted or overly sodium supplemented. In a different study in normal dogs, increased dietary sodium increased total urinary calcium and sodium excretion per day, but it decreased the urinary calcium *concentration* because of the diuretic effects of increased dietary sodium.[60] Because crystallization risk is more affected by urinary concentration of calcium and oxalate than the amount excreted per day, the dilutional effects of higher dietary sodium may offset the tendency toward hypercalciuria.

The commercial diets most often recommended to reduce the risk of calcium oxalate urolithiasis include Waltham® Canine S/O Lower Urinary Tract Support Diet and Hill's Prescription diet u/d®.[47,65,67,73] Diets with high fat content such as Prescription diet u/d® should be avoided in dogs with history of pancreatitis,

obesity, diabetes mellitus, or hyperlipidemia. An alternative diet suggested for these animals is Hill's Prescription diet w/d® with supplementation of oral potassium citrate to achieve a urine pH of 6.5 to 7.0.[67] Urine RSS was substantially reduced when 17 dogs with calcium oxalate urolithiasis were fed Waltham® Canine S/O Lower Urinary Tract Support Diet.[73] Reduced RSS is suggested to reflect decreased risk of calcium oxalate urolithiasis; however, this is a surrogate end point with the ideal end point being an actual reduction in the urolith recurrence rates. Clinical trials demonstrating reduction of recurrence rates of calcium oxalate urolithiasis are needed to verify efficacy of currently recommended diets.

267.5.4.2 Medications

Dietary therapy alone will not uniformly prevent calcium oxalate urolith recurrence. If calcium oxalate uroliths recur despite dietary therapy, if calcium oxalate crystalluria is persistent, or if both occur, medications should be considered.

267.5.4.3 Thiazide Diuretics

Thiazide diuretics are proven to reduce urinary calcium excretion and reduce the recurrence of calcium oxalate urolithiasis in humans.[8,74] In normal dogs, administration of chlorothiazide did not reduce urinary calcium excretion, although these dogs were water loaded, which may have prevented the hypocalciuric effects.[75] In contrast, administration of hydrochlorothiazide decreased urinary calcium excretion and urine calcium concentration in dogs with calcium oxalate urolithiasis.[76] The reduction in urinary calcium was greatest in dogs with the highest pretreatment urine calcium concentrations and when combined with dietary therapy using Prescription diet u/d®.

Hydrochlorothiazide (2 mg/kg orally every 12 hours) should be considered in dogs that have persistence of calcium oxalate crystalluria or recurrence of calcium oxalate urolithiasis despite diet therapy. Thiazide diuretics cause subclinical volume depletion resulting in increased proximal tubular reabsorption of sodium and calcium.[76] This effect may be blunted or prevented by increased dietary sodium content and increased water intake. Therefore the benefit of hydrochlorothiazide needs to be evaluated in conjunction with canned diets with higher sodium content.

267.5.4.4 Potassium Citrate

Potassium citrate supplementation has been shown to reduce recurrence of calcium oxalate uroliths in humans either when given specifically for hypocitraturia or when done empirically without 24-hour urine collection to determine if hypocitraturia is present.[59] In humans, oral potassium citrate increases urine pH, which causes decreased tubular resorption of citrate, thus increasing urinary citrate excretion.[8]

In the veterinary literature, conflicting opinions exist concerning the utility of potassium citrate for prevention of calcium oxalate urolithiasis in dogs. Potassium citrate supplementation has been recommended at a dose of 50 to 75 mg/kg orally every 12 hours if the urine pH is acidic or if calcium oxalate crystals are still present despite dietary therapy.[42,77] In one study with normal dogs, potassium citrate supplementation did not significantly increase the mean urinary citrate excretion; although in three miniature schnauzers, supplementation did increase urinary citrate excretion and lowered the urinary relative calcium oxalate supersaturation.[78] In another study, potassium citrate also did not increase mean

urinary citrate concentration but it did cause a dose-dependent increase in urine pH.[77] Potassium citrate supplementation would be expected to have the greatest effect on urinary citrate excretion in dogs with hypocitraturia or metabolic acidosis; however, this has not been reported. The effectiveness of potassium citrate supplementation for reducing recurrence of calcium oxalate urolithiasis in dogs has also not been reported. Nonetheless, once dietary and hydrochlorothiazide therapy have been implemented, if calcium oxalate crystalluria is persistent or calcium oxalate uroliths recur, the authors recommend potassium citrate given to effect to achieve a urine pH of 6.5 to 7.0 using a starting dose of 50 to 75 mg/kg orally, every 12 hours. If the urine pH is already above 7.0 to 7.5, then potassium citrate should not be added. The serum potassium should be initially monitored monthly during potassium citrate supplementation and the dose reduced if hyperkalemia occurs.

267.5.4.5 Vitamins

Supplementation of vitamin C or vitamin D should be avoided in dogs with calcium oxalate urolithiasis. Because vitamin C is converted to oxalate, excessive vitamin C may contribute to hyperoxaluria and increased risk of calcium oxalate urolithiasis.[8] Vitamin D supplementation increases intestinal absorption of calcium, thereby promoting hypercalciuria and increased risk of calcium oxalate urolithiasis.[8,67] Although vitamin B_6 has been recommended, no data support any benefit from vitamin B_6 for prevention of calcium oxalate urolithiasis in dogs.

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267.5.4.6 Management of Recurrent Calcium Oxalate Urolithiasis

Because calcium oxalate uroliths recur in approximately 50% of dogs within 3 years,[68] appropriate surveillance methods should be used to document recurrences before the uroliths become too large to pass through the urethra. If recurrent urocystoliths are diagnosed early enough, many recurrences may be managed using nonsurgical methods. Although some dogs with recurrent calcium oxalate urocystoliths may be asymptomatic for extended periods of time, removal of urocystoliths is recommended to prevent urethral obstruction.

267.6 STRUVITE UROLITHIASIS

Struvite uroliths are usually composed of 100% magnesium ammonium phosphate hexahydrate, although some also contain varying amounts of calcium phosphate (termed *calcium apatite*) or calcium carbonate phosphate (termed *carbonate apatite*).[10,24,79] Struvite uroliths are commonly referred to as *infection stones* or *urease stones* because they are usually caused by UTI with urease producing organisms.[8,24] Struvite uroliths are moderately to markedly radiopaque (Figure 267-7). Although struvite uroliths may assume multiple shapes (e.g., smooth spherical, discoid) or conform to the shape of the bladder or renal pelvis, they are often faceted or pyramidal when multiple urocystoliths are present because the adjacent surfaces are smooth and flattened (see Figure 267-7; Figure 267-8). Large urocystoliths are most commonly composed of struvite. Large solitary urocystoliths may have sharp spiculated projections and assume the shape of the bladder lumen (see Figure 267-8).

267.6.1 Epidemiology of Struvite Urolithiasis

Although the incidence of calcium oxalate urolithiasis in dogs continues to increase, struvite remains the most common urolith type in dogs.[10] In 1997, 45% of all uroliths submitted to the Minnesota Urolith Center were

composed of struvite and 35% were composed of calcium oxalate.[10] Struvite uroliths are more commonly located in the LUT (95%) than the upper urinary tract (5%).[24] Struvite uroliths occur more commonly in female dogs (71% to 85% of struvite uroliths submitted to two urolith centers) than male dogs (15% to 29%).[24,42] Female dogs are affected more commonly because they are more likely to have UTIs than males.[24] Breeds most commonly affected with struvite uroliths include mixed breed dogs, miniature schnauzers, Shih Tzus, Bichon frises, miniature poodles, cocker spaniels, and Lhasa Apsos.[24] It is notable that all of these breeds except cocker spaniels and mixed breed dogs are also predisposed to calcium oxalate urolithiasis.

Figure 267-7 Abdominal radiographs from a dog with struvite urocystoliths. Reader should note the smooth surfaces where the urocystoliths contact each other.

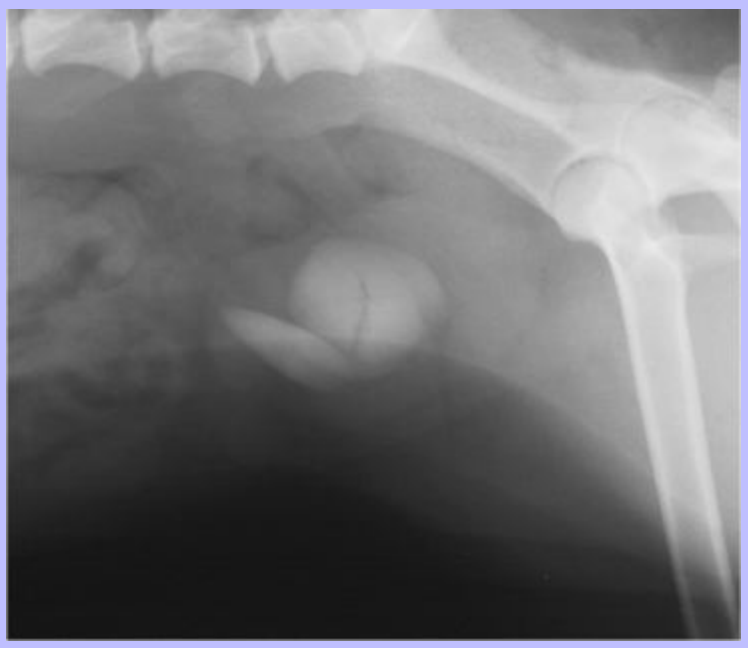
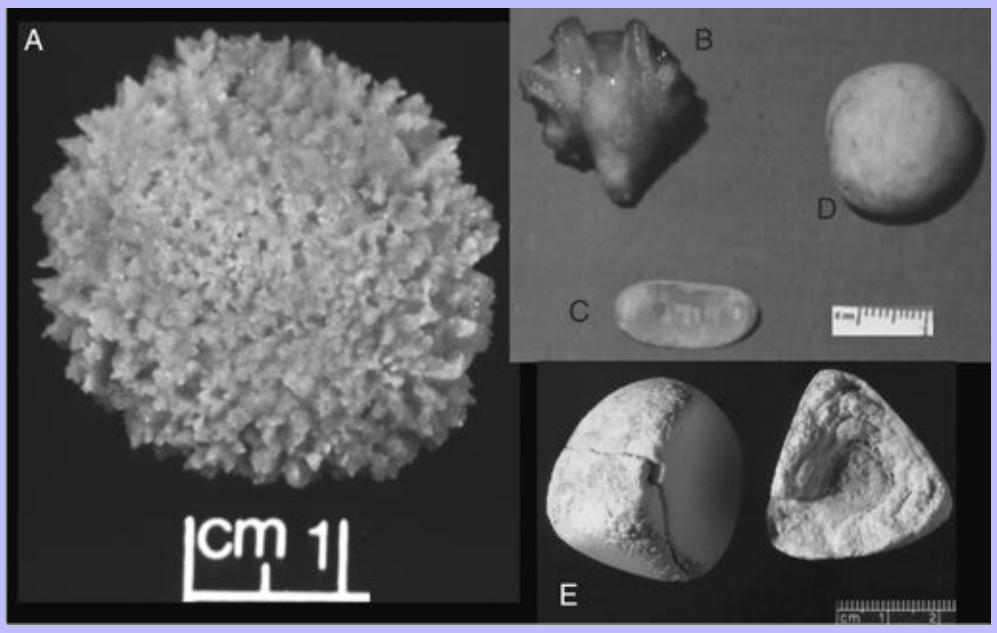


Figure 267-8 Examples of canine struvite uroliths. **A,** Spiculated solitary urocystolith. **B,** Staghorn nephrolith. **C,** Wafer-shaped urocystolith. **D,** Smooth solitary urocystolith. **E,** Pyramidal-shaped urocystoliths with smooth flat adjoining surfaces and distinct layers.



267.6.2 Etiopathogenesis of Struvite Urolithiasis

Most struvite uroliths in dogs are caused by UTI with urease-producing organisms.[24] Although recurrent, sterile struvite urolithiasis has been reported in related cocker spaniels,[80] sterile struvite uroliths are uncommon in dogs. In dogs, *Staphylococcus* spp. are the most commonly urease-producing organisms causing struvite uroliths, whereas *Proteus* spp. are the most common cause in humans.[8,24] Other urease-producing organisms that infrequently cause struvite uroliths include *Pseudomonas* spp. and *Klebsiella* spp.[24] Urease-producing mycoplasmas (termed *ureaplasma*) such as *Ureaplasma urealyticum* may also cause struvite urolithiasis.[24]

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Urease cleaves urea (which is abundant in urine) to form ammonia and bicarbonate. The ammonium is available to combine with magnesium and phosphate, which are normally present in the urine, to form magnesium ammonium phosphate hexahydrate (struvite) crystals. The bicarbonate increases the urine pH, which decreases the solubility of struvite crystals. The ammonium also damages the urothelial glycosaminoglycan coating. This allows struvite crystals and bacteria to attach to the urothelium and may promote production of an organic matrix for crystal-matrix interaction. Attached crystals have more time to aggregate and grow into uroliths before being flushed from the urinary tract with the urine; therefore damage to the glycosaminoglycan layer promotes struvite urolith formation. Increased dietary protein increases the

urine concentration of urea and phosphorus. However, unlike in cats where struvite uroliths may occur solely due to diet, UTI with a urease-producing organism is required in most dogs.[24]

Viable bacteria are trapped in the interstices of the layers of infection-induced struvite uroliths as they grow.[8,24] Bacteria have been cultured from the core of struvite uroliths that have been stored in formalin for years.[8] Therefore dissolution or fragmentation of struvite uroliths release viable bacteria into the urinary tract and will cause reinfection unless appropriate antimicrobials are used.[8,24] Antimicrobial penetration into struvite uroliths is limited; therefore as long as struvite uroliths are present anywhere in the urinary tract, resolution of UTI is unlikely and relapses usually occur within days of discontinuation of antibiotic therapy.

267.6.3 Treatment of Struvite Urolithiasis

Treatment options for struvite urolithiasis include medical dissolution or mechanical removal. The reader is referred to the section on urolith removal techniques. It is important that the underlying UTI be controlled with appropriate antimicrobials prior to manipulation or fragmentation of infection induced struvite uroliths to minimize the risk of urosepsis. Medical dissolution of urocystoliths in male dogs is associated with a risk of urethral obstruction once the urocystoliths are small enough to pass into the urethra. Therefore the clinical signs of urethral obstruction should be thoroughly explained to the owner if medical dissolution is used. The risks and benefits of mechanical removal versus medical dissolution should be discussed with the owner before concluding which approach is best for the individual patient.

Medical dissolution of struvite urocystoliths requires a combination of appropriate antimicrobial and calculolytic dietary therapy. Antimicrobial selection should be based on urine culture and antibiotic-susceptibility testing from urine obtained by cystocentesis prior to antimicrobial therapy. Antimicrobial therapy must be given throughout the entire dissolution period because viable bacteria are contained within the interstices of each layer of struvite uroliths. Two commercial calculolytic diets are available for dissolution of struvite uroliths in dogs: (1) Hill's Prescription diet s/d® and (2) Waltham® Canine S/O Lower Urinary Tract Support Diet. Hill's Prescription diet Canine s/d® has been proven to be effective for dissolution of struvite uroliths in dogs.[24] Waltham® Canine S/O Lower Urinary Tract Support Diet was effective for dissolution of canine struvite uroliths in an *ex vivo* model, although *in vivo* efficacy has not been reported.[81] Antimicrobial and dietary therapy should continue approximately 1 month beyond radiographic resolution of struvite urolithiasis because uroliths too small for radiographic detection may still be present.

Five to 7 days after initiation of antimicrobial therapy, urine should be obtained by cystocentesis for urinalysis and culture. Urinalysis should reveal decrease of the urine pH to less than 7.0, and the urine culture should be negative for bacterial growth. If the UTI is persistent, antimicrobial therapy should be changed based on antibiotic-susceptibility testing. Monitoring of dissolution therapy should consist of abdominal radiographs and urinalyses every 4 weeks. If bacteriuria, pyuria, or inappropriate alkaline urine pH are present, the urine should be cultured for aerobic bacteria and mycoplasma. If Hill's Prescription diet Canine s/d® is being fed, several changes on the serum biochemistry profile are common. Because of the low-protein content of this diet, serum urea nitrogen (SUN) concentrations should be low or low-normal, which confirms owner compliance with the dietary recommendations. Mild decreases in serum albumin and phosphorus concentrations are commonly present within 1 month of dietary therapy.[82] Mild increases in serum alkaline phosphatase activity have also been reported in some dogs consuming this diet.[24] These changes in the serum biochemistry profile are not expected with Waltham® Canine S/O Lower Urinary Tract Support Diet.

Average time for dissolution of canine infection-induced struvite urocystoliths is approximately 3 months.[24] Even large struvite urocystoliths may be medically dissolved, although larger urocystoliths take longer to dissolve than smaller uroliths because they have less surface area relative to their volume. Many of the symptoms of LUT inflammation (dysuria and pollakiuria) resolve during the first 10 days of therapy despite the presence of the urolith, which is likely attributable to control of the UTI.[24]

A common cause of failure to effectively dissolve struvite uroliths is inadequate control of the UTI. Therefore if therapeutic attempts fail or cease, urinalysis and urine culture should be repeated. Another common cause of dissolution failure is that if the struvite urolith contains layers of calcium apatite, carbonate apatite, or calcium oxalate, this may prevent dissolution of the struvite component of the urolith.[24,42] If any of the layers of the urolith contain more than 20% of nonstruvite minerals, dissolution is unlikely to occur.[42] Another common cause of failure to dissolve suspected struvite uroliths is that the urolith is composed of another mineral other than struvite.[24,42] If medical dissolution is unsuccessful, mechanical removal of the urolith should proceed with quantitative analysis of the retrieved uroliths.

Sterile struvite urocystoliths in dogs have been successfully dissolved using calculolytic dietary therapy alone or using urinary acidifiers without calculolytic diets.[24,80] Antibiotic therapy is not required for dissolution of sterile struvite uroliths. Sterile struvite uroliths dissolve more quickly (3 to 6 weeks) than infection-induced uroliths.[24,80]

267.6.3.1 Medications

Acetohydroxamic acid (AHA; Lithostat®) is a competitive and noncompetitive enzyme inhibitor of urease. Inhibition of microbial ureases prevents the breakdown of urea to form ammonium and bicarbonate, thereby lowering the urine pH and the concentration of ammonium. AHA has been used as an adjunct to dietary and antimicrobial therapy to promote dissolution of refractory struvite uroliths at a dose of 12.5 mg/kg orally, every 12 hours. However, AHA commonly causes side effects in dogs including hemolytic anemia, anorexia, vomiting, hyperbilirubinemia, and bilirubinuria.[24] Therefore the authors do not recommend AHA therapy unless mechanical removal of the struvite uroliths also poses a significant risk. Because AHA is renally excreted, it should not be administered to dogs in renal failure. In addition, AHA should not be administered to pregnant dogs because it is teratogenic.[24]

Urinary acidifying agents such as ammonium chloride are not necessary in management of struvite urolithiasis provided a calculolytic diet and antimicrobials are used. Persistence of an inappropriately alkaline pH of the urine is usually due to failure to control the urease-producing bacterial infection. Therefore the addition of urinary acidifying drugs to the dietary therapy is unlikely to reduce the urine pH and may cause metabolic acidosis.

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One report exists of dissolution of sterile struvite nephroliths in two dogs using an amino acid preparation, most likely through production of acidic urine pH.[83] Dissolution of struvite urocystoliths in dogs using this amino acid preparation has not been reported.

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267.6.4 Prevention of Struvite Urolithiasis

The key to prevention of infection-induced struvite urolithiasis is resolution of the underlying UTI and prevention of recurrent UTI. Antibiotic therapy should be continued for 3 to 4 weeks after mechanical removal or radiographic evidence of urolith dissolution. Then urine culture should be repeated 5 to 7 days after discontinuation of antibiotic therapy. If the urine culture is negative, another urine culture should be obtained 3 to 4 weeks later to confirm resolution of the UTI. If recurrent UTIs occur, prophylactic therapy with antibiotics administered at bedtime may prevent reinfection. The reader is referred to Chapter 262 for treatment of UTI.

The role of dietary therapy for prevention of struvite urolithiasis in dogs is complex. For dogs with sterile struvite urolithiasis, dietary therapy should be used long-term to prevent urolith recurrence; however, sterile struvite uroliths are uncommon in dogs. For dogs with infection-induced struvite urolithiasis, dietary therapy designed to prevent recurrence of struvite is likely unnecessary.[42] Prevention and control of recurrent UTI is usually effective regardless of diet.[42] Many of the breeds predisposed to struvite urolithiasis are also predisposed to calcium oxalate urolithiasis. In these breeds, dietary therapy to prevent struvite urolithiasis that includes urinary acidification and magnesium restriction could potentially contribute to formation of calcium oxalate urolithiasis later in life. Diets currently available for prevention of struvite urolithiasis in dogs include Waltham® Canine S/O Lower Urinary Tract Support Diet and Hill's Prescription diet c/d®. The authors only recommend struvite preventative diets such as Hill's Prescription diet c/d® for approximately 1 month after removal or dissolution of struvite uroliths while the UTI is monitored for recurrence. Once the UTI has been resolved, the dog can be changed to a commercial adult maintenance diet. Alternatively, Waltham® Canine S/O Lower Urinary Tract Support Diet may be fed long-term in breeds predisposed to both calcium oxalate and struvite urolithiasis because it is theoretically designed for prevention of both struvite and calcium oxalate urolithiasis.

267.6.5 Dogs with Calcium Oxalate and Struvite Urolithiasis

Certain breeds of dogs are predisposed to both calcium oxalate and struvite urolithiasis including miniature schnauzers, Shih Tzus, Bichon frises, miniature poodles, and Lhasa Apsos.[24,40,43] Some of these dogs form compound uroliths with different layers composed of both calcium oxalate and struvite. Other dogs form struvite uroliths in one urolith episode and then form calcium oxalate uroliths later in life or vice versa. In both of these situations, the struvite urolith usually forms as a result of UTI with urease-producing bacteria, whereas the calcium oxalate urolith forms due to patient metabolic predispositions such as hypercalciuria. Therefore management of these dogs is by control of the struvite component via control of the UTI and designing the long-term dietary and medication recommendations to prevent calcium oxalate urolith recurrence. It has been hypothesized that these dogs may be deficient in some inhibitors of crystal formation, aggregation, or both, which predisposes them to both urolith types.[24]

267.7 PURINE UROLITHIASIS

Naturally occurring canine purine uroliths consist of uric acid (and its various salts) and xanthine. Xanthine and uric acid are successive biodegradation products in the metabolism of purines (Figure 267-9). Purine uroliths may be of pure (100%) composition, or less commonly, may contain varying amounts of other minerals. For the purposes of the following discussion, unless otherwise stated, the term *urate* includes uric acid, ammonium urate,

and the other salts of uric acid (principally sodium acid urate, sodium calcium urate, and ammonium calcium urate).

Ammonium urate is, however, by far the most commonly encountered of the urate uroliths, accounting for 86% of these uroliths,[10] and so recommendations for diagnosis, treatment, and prevention are skewed toward the management of this urolith type.

Urate uroliths are typically small, smooth, round or ovoid uroliths that are greenish-brown in color. Frequently multiple urate uroliths are present. Cutting urate uroliths in cross-section reveals concentric laminations. Xanthine uroliths are typically similar in size and shape to urate uroliths; however, they are usually yellow to brown in color. The majority of urate (97%) and xanthine (94%) uroliths that are submitted for analysis have been removed from the LUT[22]; however, nephroliths and ureteroliths may be underrepresented due to the difficulty in removing uroliths from the upper urinary tract. The size and smoothness of purine uroliths explains the relative frequency with which they cause urethral obstruction.

Urate and xanthine uroliths are generally characterized as radiolucent or only slightly radiopaque on survey radiographs (see Table 267-1). Positive-contrast studies may be required to visualize these uroliths: using an *in vitro* model, approximately 20% of ammonium urate and sodium urate uroliths were not detected on survey radiographs, although detection rates were improved if uroliths less than or equal to 1 mm in diameter were excluded from the analysis.[14] Detection rates using high-frequency (5 or 7.5 MHz) sector ultrasound scanning are better than with survey radiographs, although enumeration of uroliths is poor.[14]

267.7.1 Epidemiology of Purine Urolithiasis

Purine uroliths (predominantly ammonium urate) accounted for 8.0% of canine uroliths analyzed at the Minnesota Urolith Center between 1981 and 1997, making it the third most common type of urolith in dogs.[10] Purine uroliths may be retrieved from dogs of any age but are most frequently found in young to middle-aged animals; the average age of dogs with urate uroliths is reported to be approximately 4 years.[22] Naturally occurring xanthine uroliths are rare; most xanthine uroliths are retrieved from dogs that have been treated previously with allopurinol. Urate uroliths are most frequently retrieved from dalmatian dogs, in a recent study 61% of ammonium urate and 91% of sodium and calcium urate uroliths submitted for analysis were from dogs of this breed.[22] Pure urate uroliths occur more often in males than females.[22,35,84] This may at least in part be due to their propensity for causing urethral obstruction; it is possible that some urate uroliths are voided by bitches without being detected.

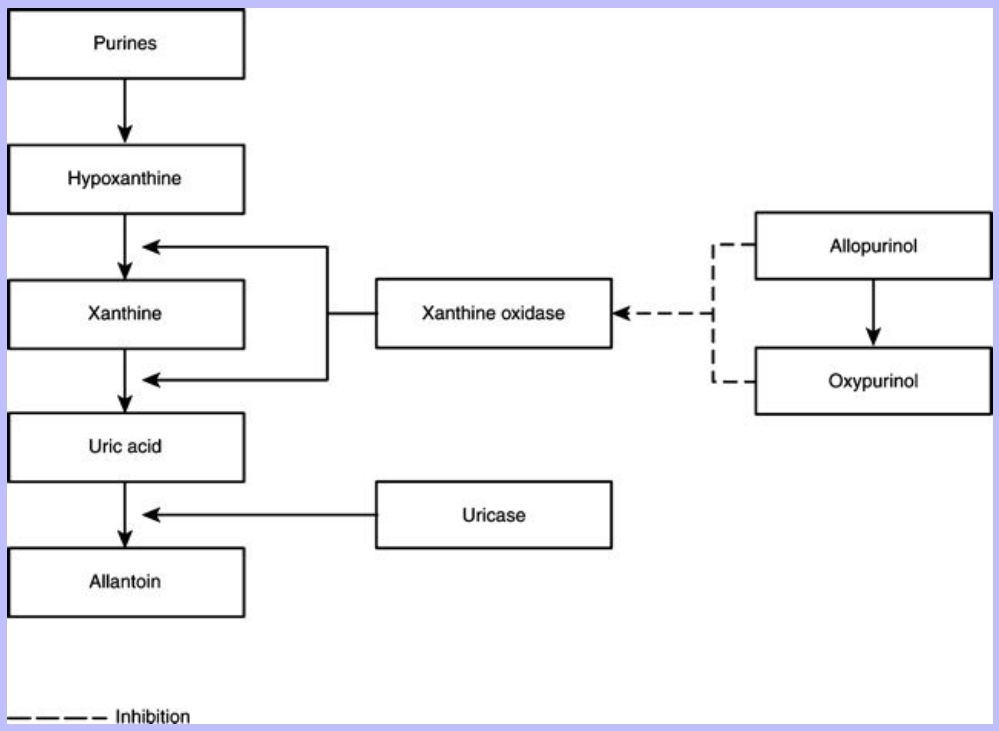
267.7.2 Etiopathogenesis of Purine Urolithiasis

The solubility of the purine metabolites, uric acid and xanthine, is much lower than that of allantoin. If urine is oversaturated with these substances, uroliths may form. Formation is promoted by a high dietary intake of purines and purine precursors and by the production of acidic urine. Production of alkaline urine decreases the risk of urate urolith formation by two mechanisms; increased solubility of uric acid and decreased production of ammonium ions.[85,86]

In human beings, infection with urease-producing bacteria may promote the formation of urate uroliths, due to the increase in ammonium ion concentration that results from hydrolysis of urea.[87] Although infection with urease-producing bacteria has been reported to occasionally contribute to formation of urate urolithiasis in

dogs, in most dogs, UTIs probably occur as a result of urolith-induced trauma or as a consequence of urinary catheterization, rather than as the cause of urolith formation.[22]

Figure 267-9 Metabolic pathway of purine degradation to allantoin showing site of action of allopurinol.



267.7.3 Dalmatian Dogs

Dalmatian dogs are predisposed to the development of urate urolithiasis due to the reduced rate at which they convert uric acid to allantoin compared with other breeds of dog, which results in 10 to 60 times greater daily urinary excretion of uric acid.[88] The uricase enzyme responsible for conversion of uric acid to allantoin is present in the liver of dalmatians in amounts comparable to those found in other breeds.[89] It is hypothesized that the reduced purine metabolism in dalmatians occurs because of a defective hepatic cell membrane transport system for uric acid.[90] The excretion of uric acid by dalmatians is increased further due to a reduced proximal tubular reabsorption of uric acid compared with other dogs.[91] Although all dalmatians excrete relatively large quantities of uric acid in their urine, not all form urate uroliths. Whether the risk for urolith formation in dalmatian dogs is solely related to the concentration of uric acid in the urine, or whether additional factors such as decreased crystallization inhibitors play a role, has yet to be definitively established. In one study, stone-forming dalmatian dogs had significantly lower urinary concentrations of Tamm-Horsfall protein than dalmatian dogs that had not formed uroliths.[92]

267.7.4 Hepatic Dysfunction

Severe hepatic dysfunction due to any cause may result in urate uroliths formation; however, the incidence of urate urolithiasis appears to be higher in dogs with portal vascular anomalies than with other causes of hepatic dysfunction.[93] Urate urolithiasis has also been reported in three miniature schnauzers with microvascular dysplasia.[22] The predisposition of dogs with hepatic dysfunction to urolith formation is presumably due to hyperammonuria and hyperuricuria, which result from a reduced ability to convert ammonia to urea and uric acid to allantoin, respectively.

267.7.5 Non-Dalmatian Dogs

Approximately 30% to 60% of urate uroliths submitted for analysis are retrieved from dogs other than dalmatians.[22,44] Many of these dogs do not have detectable hepatic dysfunction, and the reasons for lithogenesis are unknown. The breeds of dogs that, in addition to the dalmatian, are reported to have an increased incidence of urate urolith formation are English bulldogs, miniature schnauzers, Shih Tzus, and Yorkshire terriers.[44,84,94]

267.7.6 Xanthine Uroliths

The most common cause of xanthine uroliths in dogs is therapy with allopurinol, particularly if the dietary consumption of purines is high.[95,96] Xanthine is an intermediary in purine metabolism that is converted to uric acid by the action of the enzyme xanthine oxidase. This enzyme, which also catalyzes the conversion of hypoxanthine to xanthine, is inhibited by allopurinol (see Figure 267-9). Hereditary xanthinuria is a rare disorder that occurs in human beings with a deficiency in xanthine oxidase. Spontaneously occurring xanthine uroliths have been described in Cavalier King Charles spaniels and dachshunds, which were suspected, but not proven, to have a deficiency of xanthine oxidase activity.[97,98]

267.7.7 Treatment of Purine Uroliths

Urate uroliths are amenable to medical dissolution; however, in some circumstances this will not be the most appropriate mode of therapy, and direct surgical or nonsurgical removal of the uroliths is preferable. Obstruction of the urinary tract (if present) has to be relieved before medical dissolution can be attempted, and owners must be counseled that the risk of reobstruction is high.

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267.7.8 Dietary Modification

Dietary modification may promote dissolution of urate uroliths in four ways: (1) decreasing the urinary excretion of uric acid, (2) decreasing the urinary excretion of ammonium ions, (3) urinary alkalinization, and (4) augmentation of urine volume. Reduced excretion of uric acid is achieved by feeding a diet that has a very low content of purine and purine precursors. Diets designed for urate dissolution are therefore restricted in protein content and more specifically contain no fish or glandular organs, which are particularly high in purine content. Protein sources that are relatively low in purine precursors include eggs and dairy products. Restricting protein content also reduces ammonium ion excretion by decreasing the amount of urea generated. In one study in normal beagles, increasing the protein content of the diet by adding casein, a protein source

low in purines, doubled the urine saturation with ammonium urate.[99] Diets containing very low-protein content are unsuitable for feeding to growing, pregnant, or lactating animals. Homemade diets[22] and modifications of commercially available diets[100] have been published and may be more appropriate for feeding to growing animals, but the effectiveness of these diets in dissolving urate uroliths has not been systematically evaluated.

Alkaline urine contains very low concentrations of ammonia and ammonium ions, thus reducing the risk of ammonium urate formation. Production of alkaline urine is favored by eating a diet that is low in protein content.[101] The target urine pH for dissolution of urate uroliths is approximately 7.0. To achieve this goal, in addition to consumption of a low-protein diet, urinary alkalinizing agents are generally required. The agents that are most often used are sodium bicarbonate (25 to 50 mg/kg every 12 hours) and potassium citrate (50 to 150 mg/kg every 12 hours) with the dose titrated to produce the desired urine pH. Producing urine that has pH greater than 7.5 is not desirable because this may favor the formation of calcium phosphate uroliths.

For dissolution of urate uroliths, as with all urolith types, feeding a canned diet in preference to dry, or adding supplemental water to the diet is likely to be beneficial due to the resulting increase in urinary volume. Feeding a protein-restricted diet also impairs urine-concentrating capacity by decreasing the medullary concentration gradient (due to the low urea concentration). Other methods for augmenting urine volume are controversial. Adding salt to the diet increases urine output but has not been routinely recommended due to concerns that it increases urinary calcium excretion and may promote the formation of calcium-containing uroliths; however, recent studies refute this view (see the section on calcium oxalate urolithiasis).

Only one commercial diet is marketed specifically for the dissolution of urate uroliths: Prescription Diet Canine u/d®; Hill's Pet Nutrition. This diet has very low-protein content (10% to 13% dry matter, 2.4 to 2.8 g/100 kcal of metabolizable energy) and contains potassium citrate and calcium carbonate for urinary alkalinization, resulting in a urine pH of 7.0 to 7.5. Further alkalinization of this diet is generally not required. In a clinical study of 25 dogs with ammonium urate uroliths fed this diet and treated with allopurinol according to a previously published protocol,[102] complete dissolution occurred in nine dogs (36%), partial dissolution in eight dogs (32%), and no dissolution occurred in eight dogs (32%).[22] Similar results were reported when this diet was used for dissolution of sodium urate uroliths. Feeding of this diet has infrequently been associated with the development of dilated cardiomyopathy in dalmatians.[103]

The risk for development of cardiomyopathy may be increased in some non-dalmatian breeds of dogs, particularly English bulldogs, perhaps through development of carnitine deficiency.[22] Until further information is available, severely protein-restricted diets should only be used cautiously and fed for as short a period as possible in English bulldogs.

267.7.9 Xanthine Oxidase Inhibitors

Allopurinol is a synthetic isomer of hypoxanthine that inhibits the action of xanthine oxidase resulting in decreased uric acid production (see Figure 267-9). Allopurinol has a dose dependent half-life of 2.5 to 3.0 hours in dogs, although its major metabolite, oxypurinol, which is also an effective inhibitor of xanthine oxidase, has a longer half-life of 3 to 5 hours.[104,105] The bioavailability of allopurinol is not altered by administration with food.[104] The recommended dose of allopurinol for the dissolution of urate uroliths is 15 mg/kg every 12 hours.[106] Allopurinol and its metabolites are excreted via the kidney, so the dose should be reduced in patients with renal failure.

A variety of adverse reactions to allopurinol have been reported in humans. These are commonly minor and self-limiting, including gastrointestinal (GI) disturbances, pruritus, and development of a rash, but occasionally a life-threatening hypersensitivity reaction develops, characterized by fever, eosinophilia, hepatitis, renal failure, and erythema multiforme or toxic epidermal necrolysis.[107] Most human patients that develop the hypersensitivity syndrome have evidence of renal impairment prior to treatment with allopurinol, so this drug should be used cautiously in dogs with known renal insufficiency. Rare reports of adverse reactions in dogs receiving allopurinol exist, including hemolytic anemia and trigeminal neuropathy in one dog[108] and cutaneous erythema in a dalmatian receiving allopurinol and ampicillin.[22] Discontinuation of the ampicillin but not the allopurinol resulted in resolution of the skin lesions.[22]

The most commonly reported adverse effect of allopurinol therapy in dogs is development of xanthine uroliths, either in pure form or due to an outer shell of xanthine forming around pre-existing urate uroliths.[96,106] Xanthine urolithiasis is likely to occur if dogs are treated with allopurinol while receiving a nonpurine-restricted diet. Clinicians can sometimes dissolve xanthine uroliths by discontinuing allopurinol and instituting a low-purine diet.[106]

267.7.10 Portal Vascular Shunts

The surgical amelioration of portal vascular anomalies is expected to resolve hyperuricuria and hyperammonuria with the resultant dissolution of ammonium urate uroliths. However, no systematic studies have been performed to determine how frequently dissolution occurs after surgical correction of portovascular shunts. Similarly, although anecdotal reports of dissolution of uroliths in dogs with portovascular shunts fed low-protein diets exist, no controlled studies have determined how frequently dietary therapy alone is successful.

267.7.11 Evaluating Response to Medical Therapy

Owner compliance with dietary therapy can be evaluated by checking urine pH (should be ≥7.0), USG (should be <1.015), blood urea nitrogen (BUN) concentration (<10 mg/dL in previously nonazotemic animals), urine sediment examination (no urate crystals should be seen) and monitoring urolith size and number. Use of urine uric acid/creatinine ratios in randomly collected urine samples is not recommended because the measurements correlate poorly with 24-hour uric acid excretion.[109]

267.7.12 Prevention of Purine Urolithiasis

Urate uroliths recur frequently after urolith removal or dissolution. Preventative therapy after dissolution of uroliths is directed at minimizing the urine concentration of ammonia and uric acid by feeding a low-protein diet and by urinary alkalinization. The risk of urate urolith formation may decline with age. Prophylactic treatment with allopurinol is not recommended routinely due to the risk of xanthine urolith formation.

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Although the feeding of prescription diets to all dalmatian dogs in the absence of a documented episode of urate urolithiasis is not recommended, it is prudent to ensure that diets that favor uric acid and ammonium ion excretion (such as those high in protein, particularly fish and meat, or that are acidifying) are routinely avoided in this breed of dog.

267.8 CYSTINE UROLITHIASIS

Cystine is composed of two molecules of the amino-acid cysteine, linked by a disulfide bond. Dogs that develop cystine uroliths have cystinuria, a disease in which increased amounts of cystine (and to a variable extent other amino acids), are excreted in the urine. The solubility of cystine in the urine is low; therefore dogs with cystinuria are predisposed to urolith formation. Most canine cystine uroliths are pure, but a few contain other minerals, including struvite, urate, silicate, oxalate, or calcium apatite.[10,110,111]

Cystine urocystoliths are typically ovoid and smooth, and light-yellow to reddish-brown in color. The size of cystine uroliths is variable, but they are often small, and multiple uroliths may be present.[23] Cystine uroliths that are submitted for analysis have generally been removed from the LUT, and this urolith type is relatively frequently associated with urethral obstruction.[23] It is reported that Newfoundlands have a relatively high incidence of cystine nephroliths,[112] although this urolith type does not appear to be over-represented in nephrolith submissions as a whole.[23,113]

Although the *in vitro* radiopacity of cystine uroliths is similar to that of struvite and silica; small cystine uroliths are often difficult to visualize in giant breed dogs. If cystine uroliths are of sufficient size, they can be detected by survey radiography. Small uroliths are detected more reliably by double-contrast cystography or ultrasonography.[14]

267.8.1 Epidemiology of Cystine Urolithiasis

The prevalence of cystine urolithiasis is highly dependent on geographic location. The prevalence in the United States is only 1% to 2%,[10,110] whereas the prevalence in Europe is reportedly as high as 8% in Sweden and 26% in central Spain.[111,114]

Cystine urolithiasis occurs predominantly (98%) in male dogs,[23] although cystinuria may occur in dogs of either gender.[112] The typical age at which cystine uroliths are first diagnosed is 3 to 8 years.[115] Somewhat surprisingly, cystine uroliths are not common in very young dogs.[10] Cystine uroliths have been reported in many breeds of dog, those that are reportedly over-represented include Mastiffs, Australian cattle dogs, English bulldogs, Chihuahuas, Newfoundlands, pit bull terriers, and dachshunds.[84,110] Cystine uroliths are also found frequently in mixed breed dogs, although they are not over-represented.[23,110]

267.8.2 Etiopathogenesis of Cystine Urolithiasis

In the normal animal, cystine is freely filtered at the glomerulus and then actively reabsorbed in the proximal tubules; in cystinuric animals the carrier proteins responsible for reabsorption are defective. The disease in dogs is quite heterogeneous; with differences in both the type and quantity of amino acids excreted in the urine. The dibasic amino acids that may be lost, in addition to cystine, are ornithine, lysine, and arginine (COLA).[116] Although absorption of these amino acids from the intestine may also be reduced, this does not appear to be of any practical consequence, and clinical signs are limited to those of urolithiasis.

The mode of inheritance for cystinuria is reported to be autosomal recessive in Newfoundlands.[112] In Newfoundlands the molecular basis of the defect has been identified as a nonsense mutation in exon 2 of the

SLC3A1 (amino acid transport) gene.[117] However, in other breeds of dog with cystinuria this defect was not observed, indicating that the molecular pathogenesis of cystinuria in the dog is heterogeneous, similar to humans. Some forms of cystinuria in humans are incompletely recessive, resulting in a complex pattern of inheritance.

Cystinuria may be suspected by detection of characteristic crystals in urine, which are flat, colorless, and hexagonal, although these are not always present. If the concentration of cystine in urine is sufficiently high, the colorimetric cyanide-nitroprusside test may be used to confirm the diagnosis. The Metabolic Screening Laboratory, Section of Medical Genetics, University of Pennsylvania will perform this test on urine samples and will perform genetic screening in Newfoundlands using ethylenediamine tetra-acetic acid (EDTA) blood samples.

267.8.3 Treatment of Cystine Urolithiasis

Cystine uroliths are amenable to medical dissolution. This may be accomplished by maneuvers to reduce the concentration of cystine in the urine and to increase cystine solubility. As with all uroliths, augmenting urine volume is likely to be beneficial. Additionally, the solubility of cystine can be increased by increasing the urine pH to approximately 7.0 to 7.5, either by dietary therapy or by treatment with potassium citrate.

Feeding of a diet that is markedly protein restricted (Hill's Prescription diet canine u/d®) has been recommended because, among other potentially beneficial effects (alkalinization, sodium restriction, reduced urine concentration), this results in a 20% to 25% decrease in cystine excretion, presumably due to a reduced content of cystine precursors.[23] Feeding high-protein diets, particularly those rich in methionine, a cystine precursor, should be avoided in cystinuric dogs. However, the degree of protein restriction that is advisable is controversial because of the risk of carnitine deficiency and associated dilated cardiomyopathy in cystinuric dogs fed low-protein diets.[118] Dissolution of cystine uroliths has been reported without dietary protein restriction.[115]

Thiol-containing drugs react with cystine, resulting in its conversion to a more soluble compound by a disulfide exchange reaction; essentially, the drug is substituted for one of the cysteine residues of the cystine molecule. The prototypical thiol-containing drug used for this purpose is D-penicillamine, but this is associated with a high incidence of side effects, which effectively limits its use. Instead, the drug N-(2-mercaptopropionl)-glycine (2-MPG, Thiola; Mission Pharmacal Co, San Antonio, Texas), also known as *tiopronin*, is now more frequently used. Treatment with this drug at a dose of 20 mg/kg twice daily resulted in dissolution of approximately 60% of uroliths in one study, with the time required for urolith dissolution ranging from 1 to 3 months.[115] Unfortunately, a relatively high incidence of side effects has also been reported with this drug, including behavioral aggression, myopathy, proteinuria, anemia, thrombocytopenia, elevations of liver enzymes, and dermatologic changes.[23,115]

267.8.4 Prevention of Cystine Uroliths

Cystine uroliths frequently recur after surgical removal, with times to recurrence ranging from 1 to 36 months.[23,115] Recurrence is reportedly more likely to occur if the amount of cystine excreted is particularly high.[115] Treatment with 2-MPG, at a dose of 15 mg/kg twice daily, was successful in preventing the reformation of cystine uroliths in 76 of 88 (86%) of dogs in one study.[115] Urinary alkalinization and moderate protein restriction is likely to also be of benefit in preventing recurrence of cystine uroliths. Preventative

therapy may be titrated to maintain a negative cyanide-nitroprusside test result.[23] Because the tendency for cystine uroliths to develop decreases with increasing age, it may be possible to discontinue preventative therapy in older dogs, particularly if it has been several years since uroliths were detected.[23,115]

A few dogs receiving treatment to prevent cystine uroliths reforming have developed struvite uroliths.[115] This possibility should be considered if a urolith forms while a dog is receiving preventative therapy, particularly if it is unresponsive to 2-MPG or if UTI is present.

267.9 CALCIUM PHOSPHATE UROLITHIASIS

Most pure calcium phosphate uroliths in dogs are composed of hydroxyapatite; brushite (calcium hydrogen phosphate dehydrate) is less common and whitlockite (calcium orthophosphate) is rare.[53] Hydroxyapatite is also a common component of uroliths predominantly composed of struvite, with the hydroxyapatite either mixed throughout the urolith or as a distinct layer (sometimes an outer shell) within the urolith. Brushite uroliths tend to occur as multiple smaller urocystoliths with either a smooth round surface or a pyramidal shape (see Table 267-1), whereas hydroxyapatite occur as multiple small uroliths with variable surface characteristics. Calcium phosphate uroliths are moderately to markedly radiopaque on abdominal radiographs, thus they can be readily diagnosed with high-quality abdominal radiographs. Because of their size and shape, they often cause urethral obstruction.

267.9.1 Epidemiology of Calcium Phosphate Urolithiasis

Pure calcium phosphate uroliths are uncommon in dogs, comprising only 0.3% to 0.6% of uroliths submitted to the Minnesota Urolith Center per year.[10,53] Breeds most commonly affected with calcium phosphate uroliths include the Yorkshire terrier, miniature schnauzer, Bichon friese, Shih Tzu, Springer spaniel, Pomeranian, miniature poodle, and cocker spaniel.[53] For pure brushite uroliths, male dogs (75%) are more commonly affected than female dogs (24%), whereas with hydroxyapatite, male dogs are only slightly more commonly affected (52%) than female dogs (48%).[53]

Although pure calcium phosphate uroliths are uncommon, calcium phosphate occurs as a part of many uroliths that are predominantly composed (>70%) of struvite or calcium oxalate.[35] Viewed in this manner, calcium phosphate–containing uroliths are the third most common type of urolith.[35] However, the majority of uroliths that contain minor amounts of calcium phosphate are usually classified based on their major crystalline component of struvite or calcium oxalate.[8,10]

267.9.2 Etiopathogenesis of Calcium Phosphate Urolithiasis

Calcium phosphate saturation in the urine is affected by the concentrations of calcium and phosphate, the urine pH, and inhibitors of the calcium phosphate crystal system.[8,53] Alkaline urine pH decreases the solubility of hydroxyapatite and may contribute to calcium phosphate urolith formation. Excessive urinary alkalinization (>7.5) in an attempt to prevent calcium oxalate or other type of uroliths in dogs may contribute to the formation of calcium phosphate uroliths. Excessive urinary excretion of calcium (hypercalciuria) and phosphate (hyperphosphaturia) also results in an increased risk of calcium phosphate urolith formation.

Calcium-containing uroliths have been reported to occur in 30% to 40% of dogs with primary hyperparathyroidism.[51,52] Primary hyperparathyroidism results in hypercalcemia, hypophosphatemia, hyperphosphaturia, hypercalciuria, and alkaline urine pH.[51,52] The combination of increased urinary excretion of calcium and phosphate increases the degree of saturation of calcium phosphate predisposing to urolith formation. The increase in urine pH lowers the solubility of calcium phosphate. Uroliths from dogs with primary hyperparathyroidism may be composed of either calcium phosphate, calcium oxalate, or mixtures of calcium oxalate and calcium phosphate, with calcium phosphate being most common.[51,53]

In humans and cats, chronic hypercalcemic disorders other than primary hyperparathyroidism may cause hypercalciuria, thereby predisposing to calcium oxalate or calcium phosphate uroliths.[8,119–121] However, hypercalcemic disorders, other than primary hyperparathyroidism, that cause hypercalciuria rarely result in calcium-containing uroliths in dogs. Similarly, almost all humans with hypercalcemia who form uroliths have primary hyperparathyroidism.[8] Hypercalciuria in dogs without primary hyperparathyroidism more commonly results in calcium oxalate urolithiasis.

Although renal tubular acidosis is a common contributing factor to formation of calcium phosphate uroliths in humans, this has not been documented in dogs.[8,53,122] Struvite urolithiasis has been reported in two dogs with renal tubular acidosis.[122]

Dogs with urinary tract hemorrhage may develop blood clots that become mineralized with calcium phosphate.[53] These may not be true calcium phosphate uroliths even though the mineral component is composed of calcium phosphate, because they probably do not contain the same matrix proteins or ultrastructure as typical calcium phosphate uroliths.

267.9.2.1 Inhibitors of Calcium Phosphate

Urine contains substances that act to inhibit precipitation or growth of calcium phosphate crystals including pyrophosphates, citrate, magnesium, and nephrocalcin.[53] In urine, citrate forms complexes with calcium that are more soluble than calcium phosphate, lowering the ionic calcium concentration. The reader is referred to Inhibitors of Calcium Oxalate in this chapter for additional information on these inhibitors.

267.9.3 Treatment of Calcium Phosphate Urolithiasis

Calcium phosphate uroliths have been reported to dissolve in a few dogs after parathyroidectomy for treatment of primary hyperparathyroidism.[53] How frequently this occurs is unknown. Because calcium phosphate uroliths are frequently multiple small uroliths, waiting for spontaneous resolution of urocystoliths does carry an inherent risk of urethral obstruction. Therefore urolith removal by surgical or nonsurgical methods should also be considered.

267.9.4 Prevention of Calcium Phosphate Urolithiasis

The emphasis in prevention of calcium phosphate uroliths should initially be to diagnose and treat any underlying or predisposing conditions. The patient should be evaluated for evidence of primary hyperparathyroidism, hypercalcemia, hypercalciuria, hyperphosphaturia, or inappropriately alkaline urine pH. If dietary therapy, potassium citrate therapy, or sodium bicarbonate therapy have been used previously to

alkalinize the urine and prevent another type of urolith, a neutral urine pH should be the target. However, the urine should not be acidified because this increases the risk of calcium oxalate urolith formation, which is more common in dogs.

The optimal preventative diet for prevention of calcium phosphate uroliths in dogs is unknown. As with all urolith types, increasing net water intake through feeding a canned diet is likely to be the most important dietary factor. At present, the authors offer similar dietary recommendations to those for prevention of calcium oxalate urolithiasis for dog with calcium phosphate uroliths. The main caution is to avoid excessive alkalinization of the urine, which may occur with some diets used for prevention of calcium oxalate uroliths.

267.10 SILICA UROLITHIASIS

Silica (silicon dioxide) uroliths are relatively infrequently diagnosed, accounting for just 0.9% of specimens submitted to the Minnesota Urolith Center.[10] The mean age of affected dogs was 7.2 ± 3.1 years (range 1 to 17 years) and most (93%) of the affected dogs were male. Silica-containing nephroliths are rarely encountered in dogs from the United States,[10,113,123] although a very high prevalence of silica-containing nephroliths without accompanying cystoliths has been reported to occur in native Kenyan dogs.[124] Although many silica uroliths are pure, some are composed of multiple distinct layers, with oxalate and struvite being the most common additional minerals.[123] This observation has relevance when breed risks are considered; German shepherd dogs and Old English sheepdogs are at increased risk for developing silica uroliths, and when these develop they are typically pure, whereas additional breeds that are over-represented (including the miniature schnauzer, Shih Tzu, Lhasa Apso, and Yorkshire Terrier) are recognized to be at high-risk for development of uroliths generally, and they commonly form uroliths that are multilayered and incorporate other mineral types.[123]

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Most silica uroliths have a “jackstone” configuration unless an outer layer of mineral (typically struvite) masks their characteristic appearance.[125] Multiple uroliths are often present. On cross-section, silica uroliths are distinctly laminated. The radiopacity of silica uroliths is similar to that of struvite.[17]

267.10.1 Etiopathogenesis of Silica Urolithiasis

It is proposed that the development of silica uroliths occurs due to an increase in dietary intake of this mineral. Animal protein contains very low concentrations of silica. Therefore dietary sources are likely to be of plant origin or due to ingestion of soil either directly or by contamination of crops during harvesting. The plant sources that have been implicated in the pathogenesis of silica uroliths include rice and soybean hulls, which may be added to diets to provide bulk and thus aid in the management of obesity, and corn gluten feed, which is added to some poor quality pet foods as a cheap source of protein.[125] The high prevalence of silica-containing nephroliths in native dogs in Kenya is proposed to be due to either consumption of maize meal or due to a high silica content in the local groundwater.[124] Silica uroliths develop in humans that consume large quantities of antacids containing magnesium trisilicate, and this has been replicated experimentally in a beagle dog.[125]

267.10.2 Treatment and Prevention of Silica Urolithiasis

Effective protocols for the dissolution of silica-containing uroliths have not been identified. The risk of silica uroliths reforming is not well documented; in one study of silica uroliths, 12% of dogs had had a previous

episode of urolithiasis, but in most cases it was not known whether the previous urolith was also composed of silica.[123] The empiric recommendations for reducing the risk of silica uroliths reforming are to change the diet to one in which the vegetable content is limited and to avoid the ingestion of soil.[125] As with all uroliths, increased water intake should be promoted to decrease the resulting concentration of calculogenic material in urine.

267.11 UNCOMMON UROLITHS

Drugs and drug-metabolites may form uroliths of pure, mixed, or compound composition. The class of drugs that is most commonly incorporated into uroliths is the sulfonamides, although this is still a rare occurrence.[35,95] In addition, there have been single reported cases of ciprofloxacin, primidone, and tetracycline uroliths developing in dogs receiving these drugs.[95,126] A urolith composed of potassium, magnesium, and pyrophosphate (*perserite*) has been reported in a collie dog and four Persian cats.[127] The composition of this urolith is unexpected inasmuch as inorganic pyrophosphate is generally considered to be an inhibitor of urolith formation. The authors of the report speculate that formation of pyrophosphate-containing uroliths results from an enzymatic dysfunction similar to the recognized human condition of hypophosphatasia, leading to pyrophosphate supersaturation of the urine.[127]

267.12 MIXED AND COMPOUND UROLITHS

Many uroliths are impure. In fact, in one study, only 29% of specimens in females and 61% of specimens in males were composed of a single mineral substance.[35] If uroliths do not contain a predominant mineral (typically defined as >70%), they may be classified as mixed; mixed uroliths comprised 1.9% of uroliths submitted to the Minnesota Urolith Center, with an additional 6.6% of uroliths being described as compound in composition.[10] Compound uroliths are those in which distinct layers are present, with each layer having a different mineral composition. Management of compound uroliths is challenging. In principle, dissolution of compound uroliths may be achieved by first instituting protocols designed to dissolve the mineral that is predicted to form the outer layer of the urolith and then altering the protocol according to the predicted composition of the inner layer or layers. In practice, the probability that the mineral composition of each layer will be successfully predicted, and that all mineral layers will be of a type amenable to medical dissolution is quite low, thus most compound uroliths are treated surgically or removed by other nonsurgical techniques. After removal of a compound urolith, a strategy needs to be implemented to try to prevent recurrent urolithiasis. In general, the strategy is to try to prevent the reformation of whatever mineral composed the core of the removed urolith, because the outer layer or layers may not have formed had there not been a mineral substrate present on which heterogeneous nucleation could occur. Specific strategies designed to prevent the recurrence of compound uroliths of varying composition were reviewed recently.[128] The reader is also referred to the section on compound calcium oxalate and struvite urolithiasis in this chapter.

267.13 URETHRAL OBSTRUCTION

Urethral obstruction may occur due to mechanical or functional causes. Functional obstruction results from failure of coordination of urethral relaxation with detrusor contraction (reflex dyssynergia).[129,130] The reader is referred to Chapter 29 for the diagnostic approach to dogs with urinary retention.

Urethral obstruction is life threatening when complete. Dogs with urethral obstruction should be evaluated for hyperkalemia and metabolic acidosis because these may be life threatening. Common causes of urethral obstruction include urethroliths, blood clots, urethral strictures, one-way valve effects from proliferations of the urothelium such as neoplasia or proliferative urethritis, urinary bladder entrapment in perineal or inguinal hernias, and penile fractures.[25,131,132]

Urocystoliths small enough to fit into the urethra may become lodged in the urethra and are termed *urethroliths*. Blood clots causing urethral obstruction may originate from bleeding in the kidney or bladder.[131] Several types of neoplasia may cause urethral obstruction, including transitional cell carcinoma (most common), prostatic adenocarcinoma, leiomyoma, leiomyosarcoma, squamous cell carcinoma, myxosarcoma, and lymphoma.[133–136] The reader is referred to Chapter 188 for additional information.

Urethral strictures may form secondary to previous urethral injury from surgery, urethroliths, external trauma, or iatrogenic trauma from prior urethral catheterization. Firm polypropylene urinary catheters should not be used as indwelling urethral catheters because they often cause mucosal trauma and irritation that may lead to stricture formation.[16] Documentation of the site and extent of urethral strictures is best accomplished by positive-contrast urethrography. Although urethral strictures are often treated surgically, they may also be dilated using balloon dilation catheters in male dogs or using urethral or ureteral dilation sets in female dogs (Figure 267-10).

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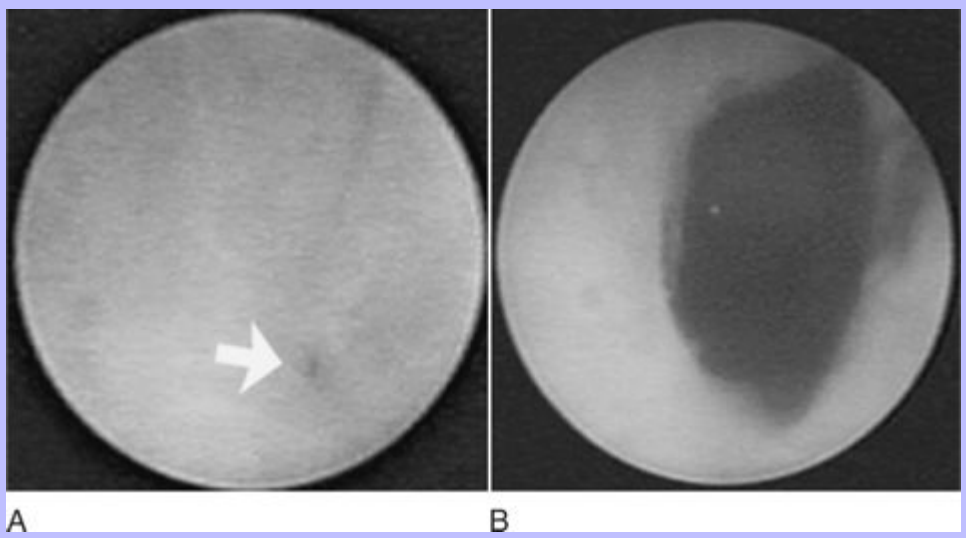
Figure 267-10 Dilation of a urethral stricture. **A,** Cystoscopic view of a urethral stricture in the proximal urethra with a diameter of less than 1 mm *(arrow)*. **B,** Cystoscopic view of the proximal urethra after dilation of the stricture to 5 mm.



Chronic inflammatory conditions (e.g., UTI, urolithiasis) may cause mucosal thickening and proliferation, which has been termed *granulomatous urethritis* or *proliferative urethritis*.[2,132] Proliferative urethritis is a more accurate description of the disease because the mucosa does not contain a granulomatous inflammatory infiltrate in all dogs, and proliferation of the urethral mucosa is commonly observed during urethrocystoscopy. The

mucosal proliferations are often bands of tissue that are connected to the urethral mucosa on each end, unlike the papillary projections of transitional cell carcinoma.[2] The mucosal proliferations cause a one-way valve effect that causes outflow obstruction but often permits retrograde passage of urethral catheters. Digital rectal palpation of dogs with proliferative urethritis reveals a thickened and firm urethra. The site of obstruction can be confirmed by voiding contrast urethrography or urethrocystoscopy. Proliferative urethritis should be differentiated from urethral neoplasia by cytology and histopathology.

Treatment of proliferative urethritis requires effective control of the UTI if this is the underlying cause. If the lesions fail to regress with adequate control of the UTI, immunosuppressive therapy with prednisone (2.2 mg/kg orally, every 12 hours) with or without cyclophosphamide may be added to antimicrobial therapy.[132] However, immunosuppression may exacerbate the underlying infection and is not consistently effective for resolving the lesions. The efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) for treatment of proliferative urethritis has not been reported. Prognosis is guarded in dogs with urethral obstruction from proliferative urethritis because some dogs fail to respond to the immunosuppressive therapy, and immunosuppression may prevent resolution of the underlying UTI. Urinary diversion via an indwelling urethral catheter or tube cystostomy may be required during initial medical therapy to bypass the urethral obstruction until the dog is able to void urine.[137,138] Surgical resection of a distal urethral obstruction and vaginourethroplasty was successful in treating proliferative urethritis in one dog.[136]

267.14 URINARY TRACT TRAUMA

Trauma to the urinary tract may be caused by blunt force (particularly in association with pelvic fractures), accidental incision during celiotomy, penetrating abdominal or perineal wounds, iatrogenic injury from improper cystocentesis technique or from rigid instruments (rigid cystoscopes, polypropylene or metal catheters), or from overdistension of the urinary bladder. Potential types of injury include contusions of the bladder or urethra, urethral tears, rupture or avulsion, urinary bladder rupture, and penile fracture.

Clinical signs of urinary tract trauma depend on the location of the trauma, duration and extent of urinary leakage, and the presence or absence of concurrent UTI. Contusions of the LUT may be asymptomatic or may cause hematuria, dysuria, and pollakiuria. Dogs with bladder or urethral rupture or urethral avulsion may be unable to urinate or may pass small amounts of bloody urine. Persistent intra-abdominal leakage of urine from a ruptured urinary bladder causes chemical peritonitis and postrenal azotemia manifested by lethargy, anorexia, vomiting, dehydration, abdominal distention, or pain on abdominal palpation. Transient urinary leakage caused by cystocentesis of an overdistended bladder, or from small rents in the urinary bladder wall as a result of overdistension during contrast cystography, does not usually cause clinical signs unless concurrent UTI is found. Bacterial peritonitis may result from even transient leakage of infected urine into the abdominal cavity.

The potential for concurrent damage to the urinary tract should be considered in all dogs with abdominal, pelvic, or perineal trauma. Diagnosis of the extent and location of traumatic injury is accomplished by either positive-contrast retrograde urethrocystography or urethrocystoscopy. During contrast urethrocystography, urinary tract rupture is confirmed by either direct visualization of leakage of contrast material from the urinary tract or by increased radiopacity of the abdominal cavity compared with radiographs obtained before injection of contrast (Figure 267-11). Passage of firm polypropylene urinary catheters should be avoided if urethral tears or lacerations are suspected because the catheter tip may enlarge urethral tears. Likewise, the ability to pass a urinary catheter and obtain urine from the bladder is insufficient to rule out urethral or bladder rupture. Urethrocystoscopy allows direct visualization of the location and extent of LUT injury, but the cystoscope should only be advanced under direct visualization of the lumen. If abdominal fluid is present, determination of the creatinine concentration of the fluid and comparison to the serum creatinine concentration is recommended rather

than measurement of urea nitrogen concentrations because urea rapidly equilibrates across the peritoneum. Urinary leakage can be confirmed by finding abdominal fluid creatinine concentrations more than one and a half to twofold higher than the serum concentration.

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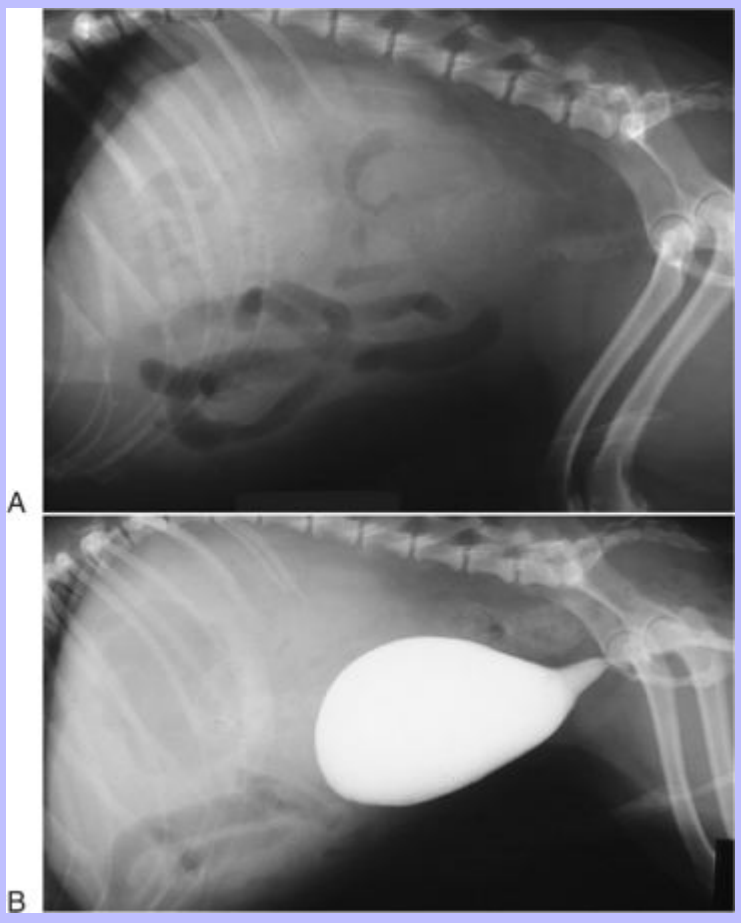
Figure 267-11 Contrast urethrocystography confirming urinary leakage secondary to traumatic cystocentesis of an overdistended urinary bladder. **A,** Abdominal radiographs showing loss of intra-abdominal detail secondary to uroabdomen. **B,** Positive-contrast urethrocystogram failed to demonstrate a leak from the urinary bladder; however, the intra-abdominal fluid is more radiopaque than before filling the bladder with contrast media, confirming urinary leakage.



Surgical repair is required for treatment of large rents in the urinary bladder, urethral avulsion, and large urethral lacerations. Small tears in the urethra or bladder wall may be treated conservatively by urinary diversion using an indwelling urethral catheter or by tube cystostomy.[137,138] Such small tears usually heal within 5 to 10 days. The

healing process can be re-evaluated by positive-contrast radiography or urethrocystoscopy. Likewise, contusions of the LUT heal within 3 to 5 days and do not require specific therapy.

267.15 INFLAMMATORY CONDITIONS OF BLADDER AND URETHRA

Inflammation of the bladder and urethra are termed *cystitis* and *urethritis*, respectively. Most conditions causing inflammation of the LUT affect both the bladder and urethra. Clinical signs of LUT inflammation include dysuria, stranguria, pollakiuria, and hematuria. By far the most common inflammatory condition of the canine LUT is bacterial infection of the bladder and urethra. (The reader is referred to Chapter 262 for additional information about bacterial UTI.) Dogs with chronic UTI may have follicular cystitis characterized by multiple small mucosal follicles seen in the bladder, urethra, and vaginal vestibule, which are visible during cystoscopy. These follicles contain lymphoid infiltrates and they regress spontaneously with control of the UTI. Follicular cystitis must be differentiated from polypoid cystitis and neoplasia.

Fungal UTI is less commonly diagnosed than bacterial UTI, with the most common isolate being *Candida albicans*.[139] In one study, all affected dogs had concurrent illnesses or received medications that were likely to have predisposed to fungal UTI.[139] Potential reasons for development of fungal UTI in dogs include surgery or instrumentation of the urinary tract, corticosteroid administration or hyperadrenocorticism, chemotherapy, and chronic antibiotic therapy. Persistent funguria should be documented before concluding that fungal UTI is present to exclude the possibility that contamination of the sample occurred *ex vivo*. Spontaneous resolution of fungal UTI occurred in two of 13 dogs in one study.[139] Oral fluconazole, flucytosine, or both may be effective for treatment of fungal UTI caused by *Candida* spp. Although both fluconazole and flucytosine are renally excreted, some stains of *Candida* are resistant to these drugs. Unfortunately, *in vitro* susceptibility testing for antifungal drugs is not readily available. Intravesical infusions of clotrimazole may be required to resolve candidiasis of the LUT in some dogs.[140] Effective management of the underlying condition that predisposed the dog to fungal UTI is required for long-term control of infection.

Polypoid cystitis is a relatively uncommon disease of the bladder characterized by inflammation, epithelial proliferation, and development of a polypoid mass or masses without histopathologic evidence of neoplasia.[141] Polypoid cystitis probably develops due to a hyperplastic inflammatory reaction secondary to chronic irritation of the bladder from recurrent UTI or urolithiasis. Dogs with polypoid cystitis have clinical signs of hematuria or LUT inflammation such as dysuria, stranguria, and pollakiuria. Female dogs are much more commonly affected than male dogs.[141] Ultrasonographic evaluation reveals single or multiple polypoid projections into the bladder lumen without distortion of the layers of the bladder wall (Figure 267-12). Diffuse thickening of the bladder wall may occur in some cases. Cystoscopy reveals polypoid projections in the bladder, which are sometimes difficult to definitively differentiate from transitional cell carcinoma (Figure 267-13). Papillary mucosal proliferative lesions with large blood vessels that extend to the tip of the projection are more characteristic of TCC than polypoid cystitis. Polypoid cystitis occurs more commonly in the cranioventral portion of the bladder, whereas transitional cell carcinoma occurs more commonly in the trigone of the bladder; however, the location and appearance of polypoid masses alone is insufficient for differentiating these diseases. Therefore biopsies of all polyps and papillary masses should be obtained for cytology and histopathology.

Figure 267-12 Ultrasonographic image of polypoid cystitis in a dog showing multiple polypoid projections *(arrows)* along the cranioventral portion of the bladder.

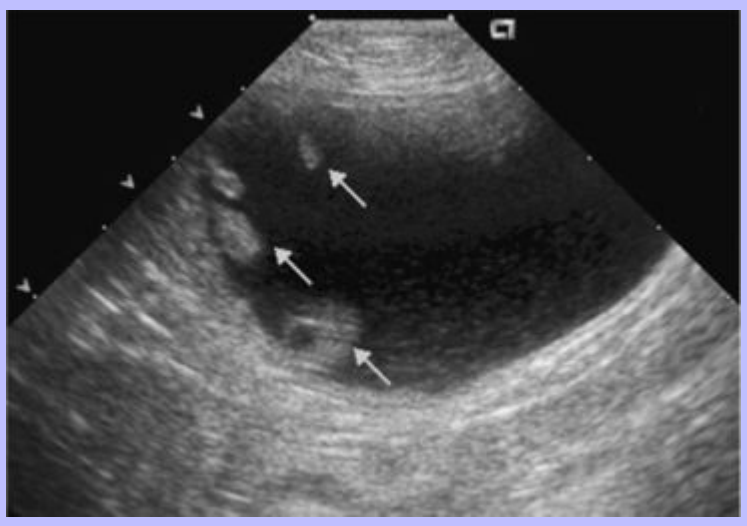


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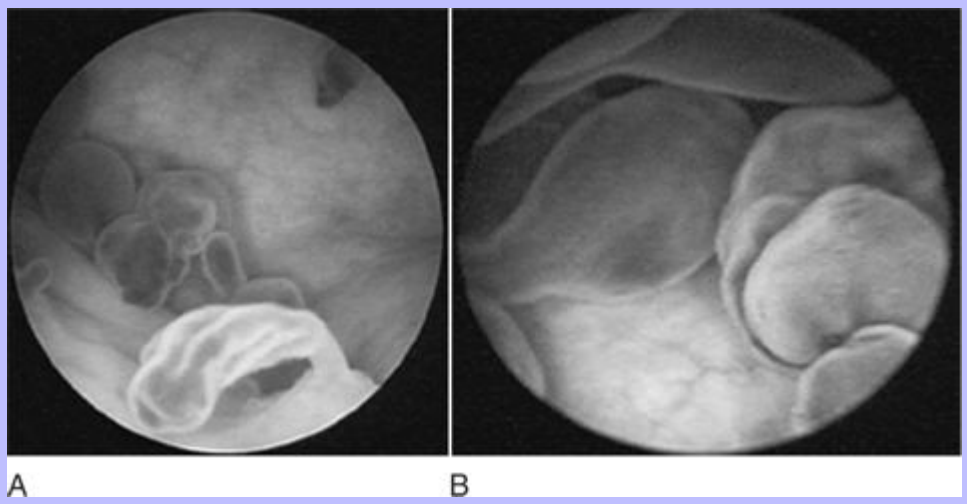
Figure 267-13 Polypoid cystitis and transitional cell carcinoma of the urinary bladder are sometimes difficult to differentiate visually. **A,** Cystoscopic image of polypoid cystitis from the dog in Figure 267-12. **B,** Transitional cell carcinoma of the urinary bladder of a dog.



Although effective management of UTI may result in spontaneous resolution of polypoid cystitis in a few cases, removal of the polyps by surgery or cystoscopy is required in most dogs. Surgical options include excisional biopsy of the polypoid masses or partial cystectomy of areas that are diffusely affected.[141] Cystoscopic resection of the isolated polyps may be performed using biopsy forceps, electrocautery loops, or the holmium laser.

Emphysematous cystitis is an uncommon form of bacterial cystitis characterized by gas production within the layers of the bladder wall. Emphysematous cystitis usually occurs from intramural gas production from bacterial fermentation of glucose in dogs with UTI and glucosuria. Diagnosis is made based on gas accumulation in the bladder wall visible of abdominal radiographs. Treatment involves effective treatment of the UTI and control of glucosuria.

Cyclophosphamide-induced cystitis is a sterile hemorrhagic cystitis caused by urinary excretion of acrolein, a metabolite of cyclophosphamide. Administration of furosemide concurrently with cyclophosphamide reduces the risk of cystitis developing.[142] Thiazide diuretics should not be used for this purpose because they may potentiate the myelotoxic effects of cyclophosphamide.[142] Treatment consists of discontinuation of cyclophosphamide therapy, short-term symptomatic therapy (e.g., narcotics for analgesia), and treatment of secondary UTI. Parasitic cystitis, caused by mucosal or submucosal invasion by the adult stage of *Capillaria plica*, is an uncommon disease in dogs. Capillariasis may be associated with clinical signs of dysuria, stranguria, and pollakiuria. Capillariasis is diagnosed by identification of the double-operculated ova during urinalysis. Treatment with ivermectin (0.2 mg/kg subcutaneously) eliminates the infection and improves clinical signs. In dogs that cannot be treated with ivermectin, an alternative therapy is fenbendazole (50 mg/kg orally, daily for 5 days).

267.16 URINARY INCONTINENCE

Urinary incontinence is defined as loss of voluntary control of urination resulting in leakage of urine from the urinary system to the exterior of the body. Urinary incontinence occurs either when intravesicular pressure is greater than urethral pressures (due to decreased detrusor compliance or poor urethral pressures) or due to anatomic abnormalities that bypass the normal continence mechanisms (e.g., ectopic ureters). Urinary incontinence must be differentiated from inappropriate urination associated with dysuria and pollakiuria. The reader is referred to Chapter 30 for the clinical signs and diagnostic approach to urinary incontinence. Box 267-2 lists common causes of urinary incontinence in dogs.

267.16.1 Urethral Incompetence in Female Dogs

Urethral incompetence (also called *urethral sphincter mechanism incompetence*) is the most common cause of incontinence in adult female dogs and usually occurs months to years after neutering. Congenital anatomic or functional abnormalities of the urethra may also result in urethral incompetence. Urethral incompetence frequently occurs concurrently in dogs with ectopic ureters due to malformation of the urethra (see Figure 267-1) and can result in treatment failure after surgical correction of ectopic ureters.[143]

Urethral incompetence may be confirmed by documenting decreased urethral closure pressure by urethral pressure profilometry; however, urodynamic equipment is only available at some referral hospitals. Although urodynamic confirma-tion is unnecessary in most cases, urodynamic evaluation should be considered for dogs with urinary incontinence that is unresponsive to standard treatment.[144,145] Alpha-adrenergic agonists (phenylpropanolamine, ephedrine, or pseudoephedrine) or estrogen (diethylstilbestrol or estriol) are recommended for treatment of urethral incompetence in female dogs. Phenylpropanolamine (1.1 to 1.5 mg/kg

orally, every 8 hours) is effective in approximately 85% to 90% of female dogs with urethral incompetence.[6,146] Estrogen therapy increases urethral closure pressure by increasing the density and responsiveness of α-adrenergic receptors in urethral smooth muscle. Estrogen therapy is effective in approximately 50% to 65% of female dogs with urethral incompetence.[147] Excessive doses of estrogen may cause severe bone marrow suppression; therefore owners should be cautioned not to exceed recommended doses and CBCs should be monitored in dogs receiving estrogen therapy. Diethylstilbestrol is administered at 0.1 to 0.2 mg/kg orally, daily (maximum dose 1 mg/dog) for 5 days, followed by the same dose once to twice a week. The maximum maintenance dose of diethylstilbestrol is 0.2 mg/kg/wk. The minimum effective dose should be used for maintenance.

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Box • 267-2 Causes of Urinary Incontinence

Urethral incompetence

Ectopic ureters

Neurologic disorders

Urge incontinence (secondary to urinary tract infection [UTI] or uroliths)

Idiopathic detrusor instability

Paradoxic (overflow) incontinence

Ureterocele

Pelvic bladder

Ureterovaginal or urethrorectal fistula

Patent urachus

Low-dose daily estrogen using estriol has recently been suggested as an alternative to diethylstilbestrol.[148] Estriol is administered at a dose of 2 mg orally, daily for 1 week, then the dose is reduced at weekly intervals to the minimal effective dose (typically 0.5 to 2.0 mg/dog given daily or every other day). In one study of 129 dogs, there was no evidence of bone marrow toxicity when estriol was administered for 42 days.[148] Although some authors suggest that low-dose daily estrogen therapy may be more effective than weekly therapy with diethylstilbestrol, the long-term safety of low-dose daily estrogen has not been reported.

Because estrogen up-regulates the α-adrenergic receptors that phenylpropanolamine stimulates, combination therapy with these medications is synergistic. Therefore female dogs that are refractory to either medication

alone may respond to combination therapy. For dogs that are refractory to combination therapy, urodynamic evaluation is recommended. Alternative therapies for dogs with refractory urinary incontinence due to confirmed urethral incompetence include cystoscopic injections of bulk-enhancing agents (glutaraldehyde cross-linked collagen) or surgical methods to increase urethral resistance.[149–151] Periurethral injection of collagen narrows the urethral lumen and allows for more effective closure of the urethra by existing urethral pressure. Periurethral injection of collagen resolved urinary incontinence in 53% of dogs with an additional 22% that were improved with concurrent administration of phenylpropanolamine.[150] In the authors' experience, repeat cystoscopic injections of collagen are required in some dogs weeks to months after initial injections. Surgical methods for treatment of refractory urinary incontinence include colposuspension and urethropexy.[149,151,152] Surgery resolves incontinence in approximately 50% of dogs, with an additional 25% to 40% being continent with concurrent administration of phenylpropanolamine.[149,151,152] However, improvement may not be sustained with a 1-year response rate of only 14% in one study.[149]

An additional medical treatment for urinary incontinence that has been reported recently is the use of gonadotrophin-releasing hormone (GnRH) analogues.[153] Improved continence was noted for several months after the subcutaneous administration of GnRH depot preparations, even though the bitches that were treated had not responded well to other treatments. This approach was investigated because of the observation that spayed bitches have very high concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) compared with intact bitches, and the treatment was shown to decrease the concentration of these hormones.

267.16.2 Detrusor Instability and Urge Incontinence

Although urethral incompetence is the most common cause of urinary incontinence, this may also occur due to detrusor contraction during storage of urine or due to low compliance of the detrusor muscle, which may be confirmed by cystometrography.[7,145] When decreased detrusor compliance occurs secondary to inflammatory conditions affecting the LUT (e.g., urolithiasis, UTI), this is termed *urge incontinence* (see Box 267-2). Clinical signs of dogs with urge incontinence may also include pollakiuria, stranguria, and dysuria. If no identifiable cause of decreased detrusor compliance is identified, this is termed *idiopathic detrusor instability*.[7] In one study of 77 dogs with refractory urinary incontinence, 10 dogs had poor bladder storage function alone and 15 dogs had both detrusor dysfunction and concurrent urethral incompetence.[145]

Treatment of detrusor instability is by anticholinergic medications (oxybutynin, imipramine, or dicyclomine) to decrease detrusor contractions during storage of urine.[7,154] Although oxybutynin (0.2 mg/kg orally, every 8 to 12 hours) has been most commonly recommended, dicyclomine appeared to have a greater effect on detrusor compliance in normal dogs than oxybutynin.[154] Clinical effectiveness of dicyclomine has not been reported in dogs with idiopathic detrusor instability. Imipramine is a tricyclic antidepressant medication that has anticholinergic effects to facilitate urine storage and also increases urethral closure pressure. Therefore imipramine may be effective for dogs with mixed incontinence due to detrusor dysfunction and concurrent urethral incompetence.[154]

267.16.3 Urinary Incontinence in Male Dogs

Urinary incontinence occurs much less commonly in male than female dogs and urethral incompetence is a less common cause in male dogs.[155] In one study, only five of 38 incontinent males dogs had urethral

incompetence.[156] Surgical procedures involving the proximal urethra and prostate are a common iatrogenic cause of urinary incontinence in male dogs, because the proximal urethra is integral in maintaining continence in male dogs.[155] Urethral incompetence in male dogs may be treated with α-adrenergic medications (phenylpropanolamine: 1.1 to 1.5 mg/kg orally, every 8 hours) or testosterone cypionate (2.2 mg/kg intramuscularly, every 30 days). Testosterone has potential side effects including prostate disease and behavioral aggression; therefore some authors discourage use of testosterone for treatment of urethral incompetence. Unfortunately, less than 50% of dogs with urethral incompetence are responsive to phenylpropanolamine.[155] Therefore surgical correction by vasopexy is recommended in male dogs with urethral incompetence that are unresponsive to phenylpropanolamine.[157] The authors have diagnosed several male dogs with idiopathic detrusor instability that were responsive to oxybutynin; therefore urodynamic evaluation is recommended prior to surgical therapy.

267.16.4 Ectopic Ureters

The reader is referred to the chapter on Diseases of the Ureter for discussion of ectopic ureters. Ectopic ureters are commonly associated with anatomic and functional abnormalities of the bladder and urethra.[3,143,158] Urodynamic evaluation of nine dogs with ectopic ureters revealed that four of nine dogs had decreased detrusor compliance and seven of nine had poor urethral function.[143] Therefore urodynamic evaluation is recommended prior to surgical correction of ectopic ureters to aid in predicting whether the dog will be continent after surgery. Anatomic abnormalities of the urethra and vaginal vestibule are common in dog with ectopic ureters (see Figure 267-1).[3] Ureteral troughs, fenestrations, and the intramural ureter in the dorsal urethral wall may all affect the ability of the urethra to generate adequate closure pressure. Therefore some authors have suggested removal of the submucosal ureteral remnants from the trigone and urethra with reconstruction of the muscular defect caused by the resection in addition to surgical correction of the location of the ureteral opening.[158] Urinary continence is improved by this more aggressive surgical approach in dogs with multiple anatomic abnormalities.[158]

267.17 ANATOMIC ABNORMALITIES

267.17.1 Ureterocele

A ureterocele is a cystic dilatation of the terminal portion of the ureter which often protrudes into the bladder lumen.[159–161] Ureteroceles are classified as either *orthotopic* (also called *intravesical*), if the ureter opening is in a normal trigonal location, or *ectopic*, if the ureter opening is distal to the normal trigonal position. Ureteroceles may cause a variety of clinical signs depending on their size and whether or not the ureter is ectopic. Urinary incontinence is the most common clinical sign of ureteroceles.[159,160] Ureteroceles may place pressure on the bladder and proximal urethra resulting in functional urinary retention, or they may cause signs of dysuria, stranguria, and pollakiuria. Dogs with ureteroceles may also present for recurrent UTI. Although ureteroceles are congenital abnormalities, some dogs with ureteroceles do not develop clinical signs until later in life.[159] Ureteroceles may be associated with developmental or acquired abnormalities of the upper urinary tract or LUT, including moderate to severe hydroureter and hydronephrosis, ectopic ureters, and urethral anomalies. Ureteroceles are diagnosed by excretory urography or ultrasonography.[160,162]

Treatment of ureteroceles depends on the type and extent of concurrent anomalies and whether or not the ureteral opening is ectopic. Excision of the ureterocele with reimplantation of the ureter is recommended for ectopic ureteroceles or ureteroceles associated with ureteral obstruction.[159] Orthotopic ureteroceles may be incised cystoscopically or by cystotomy; however, this often results in vesicoureteral reflux that could contribute to pyelonephritis if UTI is also present.

267.17.2 Urethral Prolapse

Prolapse of the urethral mucosa through the external urethral orifice is an acquired disease of male dogs, most common in English bulldogs (Figure 267-14).[163] The proposed causes for urethral prolase include excessive sexual excitement or stranguria associated with UTI or urolithiasis.[16,163] Although small urethral prolapses may resolve spontaneously in some dogs,[16] surgical correction is required in most cases. A recently reported urethropexy technique was successful in three of three dogs and is less invasive than surgical resection of the prolapsed tissue with apposition of the urethral and penile mucosa.[163]

267.17.3 Vesicourachal Diverticula

Vesicourachal diverticula are remnants of the urachal canal between the apex of the bladder and the umbilicus. Vesicourachal diverticula usually appear as an out pouching of the bladder wall near the bladder apex that can be diagnosed by contrast cystography or cystoscopy. Dogs with vesicourachal diverticula are predisposed to recurrent UTI, presumably from incomplete emptying of the urine in the dead space of the diverticula.[164,165] Vesicourachal diverticula may resolve spontaneously if the underlying cause can be corrected.[165] Surgical removal of urachal diverticula is recommended for dogs with persistent or recurrent UTIs and for dogs undergoing surgical removal of urocystoliths.

267.17.4 Urethrorectal or Ureterovaginal Fistula

Fistulas between the urethra and the rectum or between the ureter and vagina are uncommon conditions in dogs that may be congenital or acquired.[166–169] Ureterovaginal fistulas usually form as a result of ovariohysterectomy when the ureter is accidentally included in a ligature around the vaginal stump. Urethrorectal fistulas may be congenital or may be acquired after pelvic trauma. Clinical signs of urethrorectal fistulas include passing of urine from the anus during voiding or recurrent infections of the *urogenital tract*.[168,169] Urinary incontinence is the most common clinical sign of ureterovaginal fistulas in dogs.[166,167] Surgical correction of urethrorectal or ureterovaginal fistulas is recommended; however, surgical correction of urethrorectal fistulas may be complicated by intrapelvic location and by concurrent infection. Resolution of secondary UTI is essential after surgical correction of urethrorectal fistulas and may require prolonged antimicrobial therapy.

Figure 267-14 Urethral prolapse showing eversion of the distal urethral mucosa.

267.17.5 Persistent Urachus

Persistent urachus is an uncommon congenital abnormality in dogs where the entire urachal canal remains patent from the apex of the bladder to the umbilicus. The clinical signs are dribbling of urine through the umbilicus, and secondary UTI and omphalitis are common sequela. The diagnosis can be confirmed by performing contrast radiography by gently injecting iodinated contrast into the umbilicus. Treatment of persistent urachus is by surgical removal of the urachal canal.

267.17.6 Pelvic Bladder

Pelvic bladder is a term describing urinary bladders that have a blunt-shaped trigone, with the trigone located in an intrapelvic location associated with a shortened urethra.[170] Pelvic bladder is controversial as to whether or not it is a cause of urinary incontinence or an artifact of how contrast urethrocystography is performed.[170–172] The normal urinary bladder trigone tapers and connects to the urethra in an intra-abdominal location. The degree of distention affects the location of the trigone; therefore the bladder should be properly distended during contrast urethrocystography before diagnosing pelvic bladder. Pelvic bladder may also be associated with increased incidence of UTI, although this association has not been definitively proven.[170] Although some dogs with pelvic bladders do not have urinary incontinence[171,172]; other dogs with pelvic bladders have refractory urinary incontinence without any other identifiable cause. [170,173] Diagnosis of pelvic bladder is usually made by contrast urethrocystography, although the abnormal shape of the trigone can also be detected during cystoscopy, raising suspicion of the diagnosis. The authors' approach to dogs with radiographic evidence of pelvic bladder is to rule out other abnormalities that might cause urinary incontinence (e.g., urethral incompetence, ectopic ureters). If concurrent urethral incompetence is present, combination medical therapy with estrogen and α-adrenergic agonists should be attempted prior to surgical

intervention. If the dog is refractory to medical therapy, urethropexy or colposuspension are recommended to move the bladder neck cranially.[149,151,152]

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268 CHAPTER • 268 Ureteral Diseases

Lori L. Ludwig

268.1 ANATOMY AND FUNCTION

The ureters are fibromuscular ducts that carry urine from the renal pelves to the bladder. The course of the ureters is retroperitoneal, adjacent to the caudal vena cava and aorta and ventral to the psoas muscle. The ureters reach the dorsolateral surface of the bladder through the lateral ligaments and turn from a caudal to a cranial direction before they enter the bladder at the cranial border of the trigone. The degree of curvature of the ureters at the trigone depends on the degree of bladder distension. Recognition of this curvature is important in the evaluation of contrast radiographic studies and for catheterization of the ureters during surgery. Upon entering the bladder, the ureters course obliquely in the submucosa toward the bladder neck. This path through the bladder wall facilitates closure of the distal ureter when the bladder is distended with urine, preventing retrograde flow of urine from the bladder (vesicoureteral reflux).

The ureteral wall is composed of an outer adventitial layer, a muscular layer, submucosa, and a mucosa of transitional epithelium. The muscular wall of the ureter consists of an outer longitudinal, middle circular, and inner longitudinal muscle layer except at the ureterovesical junction, where only longitudinal fibers are present. During diuresis, stretching of these muscle layers can result in a seventeenfold increase in the ureteral luminal diameter.[1] The normal width of the ureteral lumen in dogs is reported to be 0.07 times the length of the second lumbar vertebra.[2]

The blood supply to the ureter arises from the renal artery cranially and from the prostatic or vaginal arteries caudally. These vessels anastomose at the level of the adventitia in the ureteral wall. The ureteral veins follow the same path as the arteries. The ureters are innervated by autonomic fibers, but this innervation is not responsible for ureteral peristalsis.[2] Ureteral peristalsis occurs when urine enters the ureter, initiating electrical impulses to be conducted between smooth muscle cells. If the peristaltic activity is initiated in the renal pelvis, urine is propelled toward the bladder. However, if peristaltic waves begin when urine enters the distal ureter because of an incompetent ureterovesical junction, urine moves toward the kidney. Because ureteral peristalsis is myogenic (not neurogenic) in origin, ureteral peristalsis persists with transplantation.

Ureteral contractions in normal dogs occur three to six times per minute.[2] The frequency of contractions increases with diuresis to a maximum point. Once the maximum frequency has been reached, the ureter dilates, and urine stasis occurs. Ureteral peristalsis also is impaired by transection and anastomosis of the ureter. Two weeks after surgery, conduction of peristaltic waves returns across the surgery site.[3] In addition, physical ureteral obstruction and some bacterial toxins can inhibit ureteral peristalsis.[4]

268.2 VESICOURETERAL REFLUX

Vesicoureteral reflux is flow of urine in a retrograde direction, from the urinary bladder into the ureters, that occurs when the intraluminal bladder pressure exceeds intraluminal ureteral pressure. This condition may result in transmission of lower urinary tract infection to the kidney.[2] It may also perpetuate lower urinary tract infection, because infected urine from the bladder refluxes into the ureter and then recontaminates the bladder when it returns from the ureter. In addition, renal parenchymal damage may result from increased intrapelvic

pressure associated with ureterectasis and transmission of voiding pressure to the renal pelvis during reflux.[2] Vesicoureteral reflux is prevented in normal animals by the long, submucosal/intravesical portion of the ureter (ureterovesical valve), which collapses as pressure in the bladder increases. Factors that may affect the functioning of the ureterovesical valve include the length, diameter, pliability, and ratio of length to width of the intravesical portion of the ureter; ureteral peristalsis, detrusor muscle function, and intraluminal pressure of the ureters or urinary bladder.[2,4]

Primary vesicoureteral reflux occurs in young dogs (7 to 12 weeks old) and may be related to intrinsic maldevelopment of the ureterovesical junction.[2] The process is usually self-limiting, because the submucosal portion of the distal ureter elongates as the dog grows. Primary vesicoureteral reflux is rare in adult dogs. Secondary vesicoureteral reflux is acquired and may occur with inflammation of the vesicoureteral junction, lower urinary tract obstruction, surgical damage, neurogenic disease of the bladder, and ectopic ureters.[2]

Maximum distension and voiding cystourethrography are the techniques most commonly used to diagnose vesicoureteral reflux. A catheter is placed in the membranous or prostatic urethra, and iodinated contrast material is infused into the catheter until the bladder is distended enough to stimulate contraction of the detrusor muscle. Alternatively, external pressure can be applied to the bladder to express urine. Lateral radiographs are taken at the beginning of voiding of the contrast agent from the bladder, or voiding is monitored fluoroscopically. Vesicoureteral reflux may be seen during contrast filling of the bladder, during voiding, or both. Reflux can also be detected cystoscopically by filling the bladder with a colored dye and then watching for this dye to be excreted from the ureters after the bladder is emptied and filled with clear fluid.[2]

Treatment of patients with vesicoureteral reflux should be aimed at eradication of urinary tract infections. Surgery may be indicated to treat predisposing factors such as obstructive lesions or ectopic ureters. Vesicoureteral reflux in young dogs is usually self-limiting and therefore requires no treatment.

268.3 CONGENITAL ANOMALIES

268.3.1 Ectopic Ureter

A ureter that enters the bladder distal to the trigone is considered ectopic. Ectopic ureters result from an embryologic abnormality of the ureteral bud of the mesonephric duct. The degree of deviation of the ureteral bud from the normal position determines the location of the ectopic ureteral opening, which can be anywhere along the urethra or in the vagina or uterus. Ectopic ureters may be unilateral or bilateral and extramural or intramural. Extramural ectopic ureters bypass the urinary bladder entirely and insert at a distal location. Intramural ectopic ureters appear externally to enter the bladder at the normal dorsolateral location; however, instead of opening in the trigone, the ureter traverses below the mucosa and opens in the bladder neck, urethra, or vagina. Reported variations to the intramural ectopic ureter include ureteral troughs, double ureteral openings, multiple fenestrated openings, and two intramural ureters opening in a single orifice.[5] Ectopic ureters commonly are associated with other abnormalities of the urogenital tract, including agenesis, hypoplasia, or irregular shape of the kidneys; hydroureter; ureterocele; urachal remnants; pelvic bladder; vulvovaginal strictures; and persistent hymen.[6,7]

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The diagnosis of an ectopic ureter is usually made in young females.[5,7] It is possible that males with ectopic ureters remain undiagnosed because the length of the urethra and external urethral sphincter may prevent urine dribbling. Intramural, bilateral ectopic ureters are most commonly reported.[7] A genetic basis for this disease

has been suggested by the documentation of ectopic ureters in litter mates and a report of a parent-offspring transmission.[7] Breeds reported to be at greater risk for ureteral ectopia include the Siberian husky, Labrador retriever, golden retriever, Newfoundland, English bulldog, West Highland white terrier, fox terrier, Skye terrier, and miniature and toy poodles.[7] Ectopic ureters have been rarely reported in cats.

Dogs and cats with ureteral ectopia most commonly present with a history of continuous or intermittent incontinence since birth or weaning. The incontinence may be more severe when the animal is in a recumbent position. Normal urine voiding may also occur. On physical examination, the perineum may be soaked or stained with urine, or perivulvar dermatitis may be noted. Male cats may have a constricted preputial orifice with dilatation of the sheath caused by urine accumulation. The results of hematologic studies and a serum biochemistry profile usually are normal unless concurrent renal disease is present. Bacterial urinary tract infections have been reported to occur in 64% of patients with ectopic ureters.[5] These patients may be at greater risk of developing infection as a result of lack or dysfunction of the vesicoureteral valve, impaired ureteral peristalsis, or stasis of urine in the lower urogenital tract.

Several modalities have been used to diagnose ureteral ectopia. Traditionally, contrast radiography has been recommended. Excretory urography allows evaluation of the size and morphology of the kidneys and ureters. To improve the accuracy of evaluation of the ureteral insertion, excretory urography should be combined with pneumocystography. The bladder should be distended with carbon dioxide or room air, which provides negative contrast around the ureter as it enters the bladder. Elevation of the caudal abdomen and oblique or dorsoventral views may be helpful for identifying the ureteral opening. Fluoroscopy can be useful in discriminating the path of the ureter as it enters the bladder. A dilated ureter is the abnormality most frequently detected with excretory urography.[6] Ureteral dilatation may result from obstruction to urine flow caused by a stenotic ureteral orifice or by functional obstruction that occurs with contraction of the urethral sphincter at the site of insertion of the ectopic ureter. In patients with infection, ureteral dilatation may also be a result of inhibition of ureteral peristalsis caused by *Escherichia coli* endotoxin.[6] In addition, a primary neuromuscular abnormality has been proposed as a cause of hydroureter. These changes may not be limited to the affected side, because chronic ascending infection and pyelonephritis may result in dilatation of the contralateral ureter and renal pelvis. Dilatation of the ureter may not be present if the ureter is only mildly displaced or has a troughlike opening. If the ureter appears to be straight as it enters the bladder, rather than forming the normal J shape, an ectopic location should be suspected.[6] An intramural ectopic ureter may appear to bypass the bladder on these studies and may be confused with an extramural ectopic ureter. Other diagnostic techniques may be required to confirm an ectopic opening because of superimposition of pelvic bones, the gastrointestinal tract, or contrast medium in the bladder and urethra. Lack of opacity of the distal ureter as a result of peristalsis or poor renal excretion may also result in a nondiagnostic study.

Other contrast radiographic procedures that have been described for the diagnosis of ureteral ectopia are retrograde urethrography and vaginourethrography.[4,7] The presence of a catheter in the urethra may obstruct the ectopic ureteral orifice, prohibiting a diagnosis with urethrography. Insertion of a Foley catheter into the vestibule and distension of the vagina and urethra with contrast may result in filling of the ectopic ureter with contrast medium, which confirms the diagnosis.

Ultrasonography has been reported to be an accurate means of determining ureteral anatomy.[4] The ureterovesicular junction is visible as a small, convex structure on the dorsal aspect of the bladder. Flow of urine from this area (“ureteral jet”) can be observed in dogs with normally positioned bladders. Distension of the bladder with fluid or administration of a diuretic may aid visualization. Reduced or absent urine flow from the distal ureter into the bladder indicates an ectopic ureter. In addition, dilatation of the ectopic ureter or renal

pelvis and thickening of the ureteral wall may be noted. One study that compared ultrasonography to contrast radiography for the diagnosis of ectopic ureters found that both techniques were accurate, with correct identification of 91% of the ectopic ureters.[4]

Direct visualization of the ureteral orifice with vaginoscopy and cystoscopy is a specific means of making the diagnosis of an ectopic ureter and for identifying abnormalities of the vagina and lower urinary tract. The vestibule and vagina can be visualized with a speculum, although ideally a rigid or flexible endoscope is used for complete evaluation of these structures, in addition to the bladder and urethra. Fluid insufflation aids visualization. The normal ureteral opening has a horseshoe-shaped, slitlike appearance when viewed endoscopically. Urine flow should be observed intermittently arising from these openings in the trigone region of the bladder. Inability to identify the normal ureteral openings should raise suspicion of an ectopic ureter. The urethra and vagina should be carefully evaluated for single or multiple ureteral openings and for a submucosal tunnel, which may appear as a slightly raised tube below the mucosal surface.

Cystometrographic studies and urethral pressure profilimetry can be used to identify functional abnormalities of the bladder and urethra in patients with ectopic ureters and may provide prognostic information.[7,8] The urethral pressure profile provides information about the pressures generated along the length of the urethra. This is often combined with the cystometrogram, which evaluates bladder capacity and compliance, and the strength of the detrusor reflex. In one study that evaluated the results of preoperative urodynamic measurements in nine dogs with ectopic ureters, reduced bladder capacity was detected in four dogs and urethral incompetence was found in six dogs.[8] Lack of response of urethral incompetence to phenylpropanolamine treatment before surgery was highly predictive of a poor postoperative outcome.[8]

Surgery is recommended for the treatment of patients with an ectopic ureter. The type of procedure performed depends on the morphology of the ureter and the functioning of the associated kidney. If the kidney is determined to be nonfunctional by preoperative evaluation, it should be removed with the ectopic ureter. Incontinence will likely persist after nephroureterectomy in patients with an ectopic intramural ureter unless the intramural segment is also removed.[7] The traditional treatment for intramural ectopic ureters has been to ligate the distal submucosal ureteral segment and create a new ureteral opening in the trigone of the bladder. Recently it was suggested that the intramural segment of ureter disrupts the functional anatomy of the internal urethral sphincter mechanism.[7] Therefore it has been recommended that the intramural segment be resected from the bladder neck and urethra and that the overlying mucosa and smooth muscle layers be apposed. A neoureterostomy is then performed by suturing the ureteral mucosa to the bladder mucosa in the region of the trigone. This trigonal and urethral reconstruction technique has been reported to result in less postoperative incontinence.[7] Extramural ectopic ureters are treated by ligating the distal end of the ureter at its attachment to the urethra, vagina, or uterus and reimplanting it into the bladder between the apex and the trigone. Because of the frequency of infection in patients with ectopic ureters, a urine culture from the bladder or renal pelvis should also be performed at surgery.

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The most common complication after surgical correction of an ectopic ureter is persistent urinary incontinence, which occurs in 44% to 67% of patients.[7,9] Reasons proposed for persistent incontinence include the presence of a submucosal ureteral remnant in the trigone or urethra, primary sphincter mechanism incompetence, other congenital abnormalities of the urogenital tract, or urinary tract infection. Urine culture should be performed in patients with persistent or recurrent incontinence and infection treated based on susceptibility results. Some patients with postoperative incontinence respond to alpha-adrenergic drugs (phenylpropanolamine or ephedrine). Additional procedures that have been proposed for treatment of persistent incontinence include endoscopic submucosal injection of glutaraldehyde cross-linked collagen

within the urethra and additional surgical procedures, such as colposuspension and cystourethropexy.[7] Partial or complete resolution of hydroureter and hydronephrosis may be seen after surgical correction of ectopic ureters even if the dilatation was severe before surgery.[10]

268.3.2 Ureterocele

A cystic dilatation of the submucosal segment of the distal ureter near the ureteral orifice is called a *ureterocele*. The proposed embryogenic mechanisms that result in the formation of a ureterocele include persistence of the membrane that separates the ureter from the lumen of the urogenital sinus; stenosis of the ureteral orifice, resulting in obstruction and ureteral dilatation; delayed ureteral migration, resulting in retention of the dilated distal ureteral segment; and embryonic arrest of myogenesis of the distal ureter.[4] Ureteroceles are classified as orthotopic or ectopic, depending on the location of the ureterocele and the associated ureteral orifice. An orthotopic ureterocele is located in the trigone of the bladder with an opening at the normal position of the ureterovesicular junction. Ectopic ureteroceles occur in conjunction with an ectopic ureter and have an opening within or distal to the bladder neck. A grading system for canine ureteroceles was recently proposed.[11] Grade 1 ureteroceles have no evidence of associated upper urinary tract disease. Grade 2 ureteroceles are associated with ipsilateral hydroureter, hydronephrosis, or chronic renal disease, and the condition is bilateral in grade 3 ureteroceles.

Orthotopic ureteroceles may go undiagnosed unless they are large enough to cause obstruction of the urethra or of the ipsilateral or contralateral ureter or unless they are associated with infection. Clinical signs associated with large orthotopic ureteroceles include abdominal pain, hematuria, stranguria, and pollakiuria. Incontinence is seen if the ureterocele is ectopic. The diagnosis is made with contrast radiography, ultrasonography, or uroendoscopy. Excretory urography combined with pneumocystography may reveal a contrast-filled dilatation of the ureter in the bladder or urethra; this is referred to as the *cobra head sign*.[4] If the kidney associated with the ureterocele has impaired function, a filling defect is seen as contrast accumulates within the bladder or urethra. On ultrasonographic evaluation, the ureterocele appears as a rounded, thin-walled, fluid-filled cystic structure in the bladder.[4]

Cystoscopic incision is commonly used to treat ureteroceles in humans and may also be effective in dogs with orthotopic ureteroceles.[11] In addition, ureteroceles may be treated by open resection. Ectopic ureteroceles should be treated as ectopic ureters by resection of the ureterocele, neoureterocystostomy, and reconstruction of the bladder neck and urethra. Unless renal dysfunction is present prior to surgery, the prognosis for correction of an orthotopic ureterocele is good. Incontinence has been reported to persist in 33% to 50% of patients treated for an ectopic ureterocele.[11,12]

268.3.3 Agenesis or Duplication

Ureteral agenesis results from failure of development of the ureteral bud. Segmental absence of the ureter or lack of a lumen may occur in combination with other congenital abnormalities.[4] Renal agenesis may be associated with ureteral agenesis, because the ureteral bud induces the embryonic metanephric kidney to proliferate and differentiate. Unilateral ureteral and renal agenesis is usually asymptomatic unless the opposite kidney is compromised. Ureteral duplication has also been reported and occurs when more than one ureteral bud develops from the same mesonephric duct or if an abnormality exists in division of the ureteral bud.[13] A duplex kidney results as renal parenchyma is formed around each developing ureter. The ureter draining the

lower part of the duplex system enters the bladder in the normal location, whereas the ureter draining the upper part is ectopic, terminating in the urethra.

268.4 ACQUIRED DISEASES

268.4.1 Ureteral Trauma

Ureteral injury can result from blunt abdominal trauma, penetrating wounds, or iatrogenic damage during surgery. Trauma to the ureters has been rarely reported in dogs and cats. Ureteral injury resulting from blunt trauma accounted for only 0.01% of the small animal hospital population in a recent report.[14] In humans, ureteral injuries, which usually result from gunshot wounds, are also uncommon, representing 5% of all patients with genitourinary trauma.[15]

The diagnosis of ureteral injury is often delayed for 3 or more days because of the rarity of this condition and the nonspecific clinical signs, which are often masked by hypovolemic shock, pain, and multiple organ injuries caused by the traumatic incident.[13] If the retroperitoneum is intact, urine accumulation is confined to this space, and several days may pass before an increase in the serum creatinine or potassium concentration is detected. Uroabdomen is present if retroperitoneal disruption occurs or with injury at the ureterovesicular junction. Uroabdomen may also result from concurrent urinary bladder rupture. Hematuria is not consistently present in patients with ureteral trauma alone.[14,15] If hematuria, abdominal pain, or uroabdomen is present, further evaluation of the urinary tract is indicated. Although the diagnosis of ureteral injury may not be made for days, this delay in humans has not been associated with increased mortality, loss of renal function, or the necessity for ureteronephrectomy.[15]

Radiography may reveal loss of peritoneal or retroperitoneal detail. Increased density, widening, and streaking of the retroperitoneum are indications of fluid accumulation but are not specific for urine.[4] Excretory urography can be performed if the patient is hydrated, normotensive, and not significantly azotemic. Extravasation of contrast medium from the site of rupture and renal pelvic or ureteral dilatation may be seen in affected animals. One report of ureteral trauma in small animals found excretory urography to be diagnostic in all four animals in which it was used; however, in humans with ureteral trauma, it has been reported to be less than 50% accurate.[14,15] Potential reasons for inaccuracy included poor urine output, a poor quality study, and radiographs taken at only one time period. Ultrasonography may demonstrate fluid accumulation in the retroperitoneal space but does not allow differentiation between a hematoma and extravasation of urine. Additional diagnostic tests that may be helpful include retrograde pyelography, computed tomography (CT), or magnetic resonance imaging. The diagnosis of ureteral trauma can be made at surgery, but direct inspection of the ureters after a traumatic incident is often complicated by the presence of retroperitoneal blood and fluid. Catheterization of the ureter from the bladder may aid identification of the site of ureteral rupture. In addition, intravenous injection of methylene blue increases visualization of urine coming from the proximal ureteral segment; however, this technique should be used with caution, because it has been associated with Heinz body anemia and renal failure. If intraoperative fluoroscopy is available, excretory urography can also be performed at surgery.

The goal of initial treatment should be to stabilize the patient for definitive surgery. Hypovolemic shock, hyperkalemia, and respiratory compromise must be treated prior to administration of anesthesia. If uroabdomen is present and the patient is not stable for surgery, a large-gauge, fenestrated catheter (e.g., peritoneal lavage catheter) can be placed intra-abdominally for drainage.

Definitive surgical treatment of the injured ureter depends on the severity and location of the injury and the functioning of the contralateral kidney. Ureteronephrectomy has been reported as the most common treatment in small animal patients.[14] This likely is due to the severity of ureteral damage and the technical difficulties of ureteral surgery. The prognosis with ureteronephrectomy is good if the other kidney is functional; however, ureteronephrectomy is considered a salvage procedure in humans and should not be performed if doubt exists about the function of the remaining kidney.

Successful ureteral anastomosis requires an adequate blood supply, good apposition of ureteral ends, and minimal tension. Urine diversion via a nephrostomy catheter or ureteral stent may also be helpful. A ureteral wound less than 50% the circumference of the ureter seals in 48 hours with adequate urine diversion.[3] Injuries to the proximal one third of the ureter may be treated by primary anastomosis. Injuries to the middle or distal one third may be treated by primary anastomosis or reimplantation of the ureter into the bladder (ureteroneocystostomy). If the ureter is reimplanted, the bladder may be advanced cranially (psoas cystopexy) or the kidney freed and moved caudally (renal descensus) to alleviate tension. Risks of primary repair and reimplantation include urine leakage, dehiscence, and stricture formation. Additional surgical techniques that have been described include bladder flap ureteroplasty and transureteroureterostomy.[13]

268.4.2 Iatrogenic Injury

Injury to the ureters can result from iatrogenic damage, which occurs most commonly during ovariohysterectomy. Inadvertent ligation and transection of the ureters has been reported.[16] The most common location for inadvertent ligation is near the uterine body. This may result in complete obstruction, with associated hydronephrosis, hydroureter, and eventually permanent renal damage if not corrected within 7 days.[13,16] An additional complication that has been reported to occur as a result of incorporation of the ureter into a uterine or vaginal ligature is ureterovaginal fistula.[17] The fistula may develop within 1 to 2 weeks of ovariohysterectomy and is associated with urinary incontinence. Treatment of ureterovaginal fistula involves ligation of the fistula and ureteral reimplantation into the bladder or ureteronephrectomy. Pyelonephritis is another complication that can occur with ureteral ligation and excision during ovariohysterectomy.

268.4.3 Urinoma

A paraureteral pseudocyst, or urinoma, forms when urine that has leaked from a ureter into the retroperitoneum becomes encapsulated in a thick, fibrous wall. The proposed mechanism of formation involves chronic, low-grade urine leakage from the ureter after trauma or obstruction, which causes necrosis of the surrounding fat and infiltration of round cells.[18] This inflammatory reaction results in the creation of a fibrous capsule over 3 to 6 weeks. A paraureteral pseudocyst was recently reported in a cat 3 weeks after an automobile-related accident.[19] Inadvertent ureteral transection during ovariohysterectomy was also reported to cause urinoma in a dog.[18] A preoperative diagnosis of a paraureteral pseudocyst is made by the identification of contrast accumulation in the pseudocyst during excretory urography or by visualization of hydronephrosis and hydroureter with a fluid-filled cavitary mass on ultrasonography.[4] Ureteronephrectomy has been the reported treatment.[18,19]

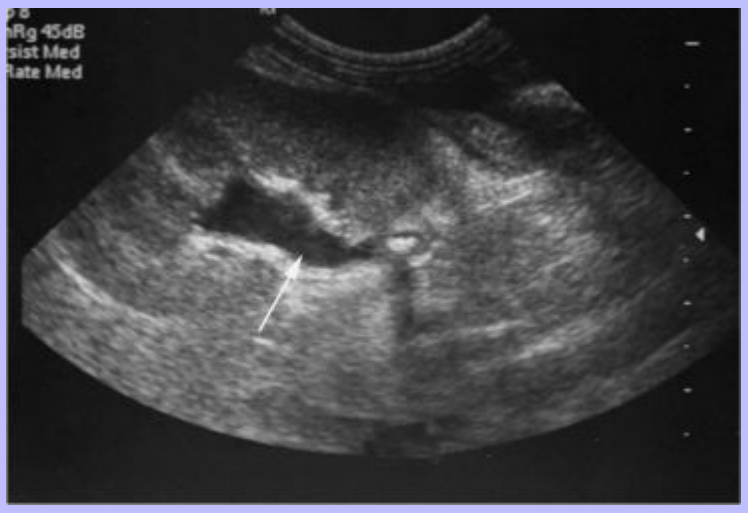
268.4.4 Ureteral Obstruction

Ureteral obstruction can result from intraluminal, intramural, or extramural causes. Intraluminal obstruction can occur as a result of a blood clot or calculus. Intramural fibrosis, stricture, or neoplasia may also obstruct urine flow. Extramural compression may occur from a retroperitoneal mass or bladder neoplasm or from a ligature placed inadvertently during surgery. Clinical signs of obstruction may not be apparent unless bilateral obstruction or concomitant infection of the urinary tract is present. Clinical signs may be mild, including dysuria, abdominal pain, vomiting, anorexia, and lethargy. On the other hand, patients with complete, bilateral obstruction are anuric and may be collapsed at presentation. Complete, bilateral obstruction that persists for 3 days or longer is fatal without appropriate treatment.[13]

It may be difficult to distinguish between obstructing and nonobstructing causes of ureteral dilatation. However, this distinction is important, because pyelonephritis may cause ureteral dilatation and would not warrant surgery. Conversely, an obstructing calculus or mass would necessitate early surgical intervention. Obstructing ureteral calculi in cats may be small and difficult to visualize on plain radiographs. Excretory urography is helpful for identifying ureteral dilatation to the point of obstruction and may show a filling defect or stricture if the associated kidney is functional and the patient is not severely compromised. With severe compromise of renal function, opacification of the kidneys and ureters is poor, resulting in a nondiagnostic study.[4] In addition, adverse systemic reactions and the potential for further damage to the kidney make this procedure less than ideal in dehydrated or severely azotemic patients.[4,13]

Percutaneous antegrade pyelography is an accurate diagnostic test for patients in which excretory urography is nondiagnostic, or when concern exists about the adverse effects of systemic contrast administration (Figure 268-1).[20] Fluoroscopy or ultrasonography can be used to guide needle or catheter placement into the dilated renal pelvis. Urine is aspirated from the renal pelvis and submitted for analysis and culture. Iodinated contrast material is then injected into the needle or catheter at a volume equal to one half the aspirated urine volume. *1878* The flow of contrast is monitored with fluoroscopy or with radiographs taken immediately after contrast *1879* injection. This technique is easily performed and has minimal complications, such as hematuria and leakage of contrast material or urine into the abdomen. Fluid diuresis is recommended with this procedure to prevent blood clot formation, which may result in obstruction.[20]

Figure 268-1 Percutaneous antegrade pyelography. Under ultrasound guidance, a needle was placed into the renal pelvis of a cat presenting with azotemia and anuria. Injection of contrast material allowed the diagnosis of complete, bilateral, distal ureteral obstruction by ureteroliths that were not evident on plain radiographs.



Ultrasonography is noninvasive, allows limited morphologic assessment of the renal parenchyma, and may allow diagnosis of ureteral obstruction. Although ureteral dilatation alone is not a specific sign of obstruction, visualization of focal hydroureter to the level of obstruction can be diagnostic.[4] In some patients it may be difficult to follow the entire course of the ureter because of its size and because of interference by other organs. In these cases, absence or reduced amplitude and duration of ureteral flow at the ureterovesicular junction can be used as an indirect sign of obstruction.[4] Additional noninvasive imaging that can be used to evaluate patients with ureteral obstruction are CT and renal scintigraphy. Renal scintigraphy allows evaluation of renal function in dogs with ureteral obstruction but does not predict what function will be after the obstruction has been relieved.[21]

Once the diagnosis has been made, rapid surgical intervention is indicated, because recovery of renal function is inversely related to the duration of obstruction.[13] If patency of a completely obstructed ureter is restored within 7 days of obstruction, renal function can return to normal.[13,21] If the obstruction persists for 2 weeks prior to correction, the affected kidney will regain approximately 50% of its preobstruction function. Complete loss of renal function does not occur until complete ureteral obstruction is present for longer than 4 weeks. If the patient is not stable for definitive surgical correction, a nephropyelostomy catheter can be placed to divert urine flow and preserve renal function. If hemodialysis is available, it can be useful for stabilization of severely uremic patients before they undergo long surgical procedures to remove the source of obstruction. The definitive surgical treatment depends on the cause and duration of obstruction.

268.4.5 Calculi

Calcium oxalate calculi are the most common type of uroliths found in the kidneys and ureters of cats.[21] Potential risk factors for the formation of these stones include hypercalcemia, feeding a urine-acidifying diet or a single brand of cat food, an indoor only environment, and being of the Persian breed.[22] Struvite and calcium oxalate calculi most frequently cause ureteral obstruction in dogs.[23] If ureteral calculi are diagnosed by plain radiography and are not associated with significant obstruction, serial radiographs should be taken to monitor calculi movement. Medical dissolution of ureteroliths is unlikely to be successful, because calculi in the ureter are not continually bathed in urine, and calcium oxalate calculi are not amenable to dissolution. Intravenous fluid diuresis, with or without diuretics, may encourage movement of calculi to the bladder. Failure of calculi to progress down the ureter on subsequent radiographs is an indication for surgical intervention. Currently there is no recommendation on the appropriate amount of time for which patients should be monitored for the passage of ureteroliths. An experimental study of artificial calculi in dogs has shown that solid spheres 2.8 mm in diameter become firmly impacted in the ureter; however, spheres 2.3 mm in diameter pass within 1 to 24 hours.[13] A clinical report of 11 cats with ureteroliths found that the calculi did not move toward the bladder in any patient monitored for a mean of 19 days.[21] Furthermore, fibrosis of the ureteral wall and ulcers of the ureteral epithelium at the site of obstruction demonstrated that the stones were immobile in these patients. Because even partial obstruction of the ureter results in decreased renal blood flow, decreased renal function, and potentially irreversible renal damage, early surgical intervention is indicated if there is evidence of obstruction.[21]

Options for surgical treatment of ureteroliths include ureterotomy; retrograde flushing of calculi into the renal pelvis, followed by pyelolithotomy; resection of the affected portion of the ureter, followed by primary anastomosis or reimplantation into the bladder; and ureteronephrectomy. Complications of ureteral surgery include urine leakage, dehiscence, and stricture formation. Placement of a nephrostomy catheter after surgery may be helpful for diverting urine flow until the ureter heals.

Extracorporeal shock wave lithotripsy (ESWL) is an alternative treatment for nephrolithiasis and ureterolithiasis in dogs. ESWL was reported to be effective in two dogs with ureterolithiasis and in one dog that developed ureteroliths after treatment for nephrolithiasis.[23] In humans, ESWL is reported to be less effective for ureteroliths than for nephroliths because of attenuation of shock wave energy by surrounding muscle and bone, difficulty with patient positioning, difficulty identifying ureteroliths by fluoroscopy or ultrasonography, and adherence of the ureterolith to the ureteral mucosa, which prevents fragments from passing during lithotripsy.[23] Disadvantages of ESWL in dogs include lack of availability, the need for general anesthesia, and the potential need for multiple treatments. ESWL is contraindicated in patients with coagulopathies, pacemakers, pregnancy, and obstruction distal to the calculi, which prevents removal of urolith fragments. Lithotripsy was reported to be successful in only one of five cats treated for ureterolithiasis.[21]

268.4.6 Neoplasia

Primary ureteral neoplasia is rare in dogs and has not been reported in cats. Transitional cell carcinoma has been the most frequently reported tumor type and is seen most commonly in females.[24] Other tumor types

include leiomyoma, leiomyosarcoma, and benign papillomas.[13,24] In a small number of patients, a good prognosis was reported for ureteronephrectomy of neoplasms confined to the ureter.[24]

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269 CHAPTER • 269 Problem-Oriented Differential Diagnosis of Autoimmune Skin Diseases

Karen A. Moriello

Immune-mediated skin diseases are uncommon in clinical veterinary practice; they accounted for fewer than 1.5% of all skin diseases seen in a university referral dermatology service (Figure 269-1). Nonetheless, they are problematic to the clinician because they can appear similar to other skin diseases that are more common.

Immune-mediated skin diseases are divided into two major categories: *primary autoimmune diseases,* in which the disease is the result of attack against self-antigens, and *secondary immune-mediated diseases,* in which the disease is the result of an attack against a foreign antigen. The most common foreign antigens are drugs, bacteria, and viruses that trigger an immunologic reaction, causing tissue damage. This chapter provides an overview of the more common autoimmune skin diseases and highlights key features that may narrow the list of differential diagnoses or may answer the question, “Should I be thinking of an autoimmune skin disease?”

269.1 CLINICAL CLUES IN THE HISTORY AND PHYSICAL EXAMINATION FINDINGS

Two major clinical presentations are seen in pets with autoimmune skin diseases (ASDs). One is the textbook presentation of the disease, which includes an acute onset of severe lesions. These patients are rarely problematic to the clinician with regard to diagnosis, because suspicion is high from the onset. The clinician suspects something serious, and an aggressive diagnostic evaluation is shortly underway. In the other clinical presentation, the disease manifests itself in a less obvious way, waxes and wanes, partially responds to treatment for a different disease, is a mild form of the ASD, or occurs concurrently with another chronic skin disease (e.g., atopic patients that develop pemphigus). The following points should raise suspicion of a possible immune-mediated skin disease:

269.1.0.1 Historical Clues

- Any severe skin disease with an acute or rapid onset
- Reports that the lesions wax and wane, especially in relatively short cycles of 7 to 10 days
- Intermittent episodes of depression, fever, and anorexia, especially if they coincide with the development of lesions
- Lack of response to seemingly appropriate therapy. For example:
  - A routine case of otitis externa that does not respond to therapy, with evidence emerging of primary lesions on the inner pinnae
  - Patients that continue to develop pustular lesions despite appropriate antibiotic therapy, especially if therapy has continued for longer than 3 weeks
  - Continued development of oral lesions on gums after appropriate dental therapy
- Difficulty eating or drinking (an early historical finding in dogs with oral ulcers)

269.1 Suspicious Physical Examination Findings

- Pruritus (variable in ASD, and its presence does not rule out ASD; evidence of pruritus may come from the history or may be obvious on examination [e.g., excoriations, observed self-trauma])
- Symmetry of skin lesions
- Skin disease (mild or moderate) with concurrent signs of systemic illness (fever, depression, anorexia)
- Large numbers of easily found, intact primary lesions all in the same stage, especially pustules, vesicles, or bullae
    - Intact or recently ruptured pustules on the inner pinnae
    - Intact pustules near the mammae of cats
    - Intact, flaccid pustules spanning several hair follicles, often yellow-green in color
- Thick, adherent crusting on the body
    - Crusting only on the face and/or footpads
    - Crusting that includes the face, footpads, and body
- A strong, offensive odor, with exudation and serum accumulation on the trunk, causing matting of the haircoat, especially if oily seborrhea is not present
- Ulcerations or erosions. For example:
    - Oral ulceration and/or erosions with or without halitosis and drooling
    - Mucocutaneous ulcerations and/or erosions, matting of the haircoat in these areas, and odor (often prominent findings)
    - Ulcerations and erosions in the axillary and/or inguinal region
- Depigmentation of the nose or mucocutaneous junctions

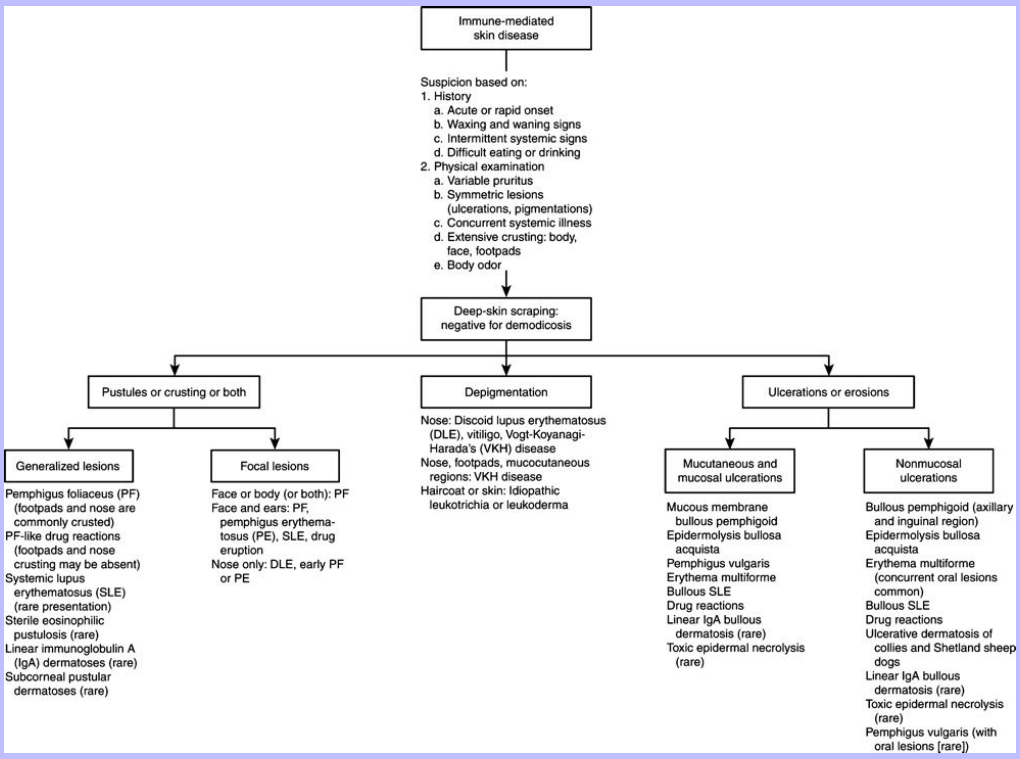
269.2 PROBLEM-ORIENTED APROACH TO DIFFERENTIAL DIAGNOSIS

The dermatologic problems most commonly associated with ASD are pustular eruptions, crusting and scaling, mucocutaneous ulcerations, nonmucocutaneous ulcerations, depigmentation, and miscellaneous problems, such as noninflammatory focal alopecia. Box 269-1 presents a problem-oriented list of differential diagnoses for autoimmune skin disorders. Because of the variation in clinical signs, some diseases fit into several categories.

Box 269-2 is a summary of the key diagnostic findings for skin biopsy and immunologic tests in various ASDs that help confirm the diagnosis. Skin scrapings and dermatophyte cultures should be negative in ASD. However, mite infestations and/or dermatophytosis can develop secondary to immunosuppressive disorders and occasionally occur concurrently. Adult-onset demodicosis can precede the development of an autoimmune skin

disease. In a "classic" ASD case, bacterial cultures of intact pustules should be reported as "no growth" or "scant" growth. If heavy growth of bacteria is found, this may indicate that the pustular disease is bacterial in origin, that bacteria have colonized skin lesions caused by the ASD, or that staphylococcal bacteria from the clinician's fingers contaminated the culture. In some cases skin biopsies are diagnostic, and in other cases a trial of antibiotic therapy or a review of previous therapies may answer the question. Cytologic specimens may also show concurrent *Malassezia* overgrowth. It is important to rule out candidiasis in patients with mucocutaneous or ulcerative dermatoses. This is best done by fungal culture at a reference laboratory (a swab is submitted) and by cytologic examination of exudate (unfixed, unstained slides of debris scraped from the lesion margins are submitted).

Figure 269-1 Algorithm for diagnosis of immune-mediated skin disease.



269.2.1 Box • 269-1 Differential Diagnosis of Autoimmune Skin Diseases

269.2.1.1 Generalized Pustular Eruptions and/or Crusting Dermatoses (Involving the Body, Head, Face, or Feet)

- Pemphigus foliaceus (PF) (footpad and nose commonly are crusted)
- Pemphigus-like drug reactions (nasal and footpad crusting may be absent)
- Systemic lupus erythematosus (rare presentation)

- Sterile eosinophilic pustulosis (rare disease)
- Linear IgA pustular dermatosis (rare disease)
- Subcorneal pustular dermatosis (rare disease)

269.2.1.2 Focal Pustular Eruptions and/or Focal Crusting

- Face and/or footpads: PF
- Face and ears only: PF (early), pemphigus erythematosus (PE), drug eruptions, lupus erythematosus
- Nasal only: Discoid lupus erythematosus, PE (early), PE

NOTE: Pustules are quite transient, and many of the generalized pustular diseases also present as generalized, malodorous, crusting dermatoses. The major differential diagnoses here are bacterial pyoderma, dermatophytosis, severe seborrhea, and zinc deficiency. Bacterial pyoderma rarely affects the head, and dermatophytosis is a nonsymmetric skin disease. Most cases occur in young animals (dermatophytosis) or sled dogs (zinc deficiency). Severe, oily seborrhea may also appear as a crusting dermatosis and can mimic PF if nasal and digital hyperkeratosis is present; the major differentiating factor is that primary seborrhea starts out at a young age. Zinc-responsive skin diseases may present as widespread or focal crusting dermatoses and can mimic PF.

269.2.1.3 Mucocutaneous and Mucosal Ulcerations

- Pemphigus vulgaris (may also have oral ulcerations)
- Mucous membrane bullous pemphigoid
- Epidermolysis bullosa acquisita
- Erythema multiforme (target lesions, cutaneous ulcerations also may be present)
- Bullous systemic lupus erythematosus
- Drug reactions
- Linear IgA bullous dermatosis (rare)
- Toxic epidermal necrolysis (rare)

Note: The primary lesions in these diseases are vesicles and bullae, which are quite transient and rupture, leaving erosions and ulceration. The adjacent haircoat becomes matted and odorous. The major differential diagnoses of concern are candidiasis, ulcerative mucocutaneous bacterial pyoderma, and cutaneous lymphoma.

269.2.1.4 Nonmucosal Ulcerations (Axillae, Inguina, Pinnae, or Other Haired Areas)

- Bullous pemphigoid

- Epidermolysis bullosa acquisita
- Linear IgA bullous dermatosis
- Bullous systemic lupus erythematosus
- Canine vesicular cutaneous lupus erythematosus (also called idiopathic ulcerative dermatosis of collies and Shetland sheepdogs)
- Erythema multiforme
- Toxic epidermal necrolysis
- Drug eruptions
- Pemphigus vulgaris (with concurrent mucocutaneous lesions)

NOTE: The primary lesions are vesicles and/or bullae, which are quite transient. These patients commonly present with fever, pain, a matted haircoat, and exudation. The major differential diagnoses of concern are deep bacterial pyoderma, deep pyoderma caused by demodicosis, and cutaneous deep and intermediate mycoses.

269.2.1.5 Depigmenting Skin Diseases

- Nasal only: Discoid lupus erythematosus, vitiligo-like syndrome, uveodermatologic syndrome, early PF or PE
- Nose, footpads, lips, eyelids, and mucocutaneous regions: Uveodermatologic syndrome (these animals have concurrent uveitis)
- Haircoat or skin: Idiopathic leukotrichia or leukoderma

269.2.1.6 Miscellaneous

- Focal alopecia: Alopecia areata, rabies vaccine, focal vasculitis
- Widespread noninflammatory alopecia: Alopecia areata, pseudopelade
- Erythematous target lesions: Erythema multiforme
- Nodular ulcerative lesions: Nodular panniculitis
- Purpura, hemorrhage, “punched out” lesions: Vasculitis
- Ear margin necrosis, pineal erosions: Vasculitis
- Dependent edema with erythema: Vasculitis

269.2.2 Box • 269-2 Key Diagnostic Findings in Common Autoimmune Skin Diseases

269.2.2.1 Skin Biopsy

- *Pemphigus vulgaris:* Suprabasilar acantholysis with cleft and vesicle formation; basal cells attachment to basement membrane resembles a row of tombstones.
- *Pemphigus foliaceus:* Intragranular or subcorneal pustules with acantholysis.
- *Pemphigus erythematosus:* Intragranular or subcorneal pustules with acantholysis with a lichenoid reaction.
- *Bullous pemphigoid, epidermolysis bullosa acquisita, linear IgA bullous dermatosis, mucous membrane pemphigoid,* and *bullous systemic lupus erythematosus:* Subepidermal cleft and vesicle formation, no acantholysis, and possible lichenoid reaction.
- *Systemic* or *discoid lupus erythematosus (DLE) (the histologic findings for both systemic and discoid lupus erythematosus are identical, except that pigmentary incontinence may be more prominent in DLE):* Hydropic and/or lichenoid interface dermatitis of the epidermis and possibly of the outer root sheath of the hair follicles, apoptosis of basal cells and, less commonly, subepidermal vesicles.
- *Erythema multiforme (EM) (the histologic findings with EM vary greatly; a key finding is apoptosis of keratinocytes throughout the epidermis):* Interface dermatitis with prominent single cell apoptosis of keratinocytes throughout the epidermis and outer root sheath of the epidermis.
- *Toxic epidermal necrolysis:* Hydropic degeneration of basal cells, full-thickness coagulation necrosis of the epidermis, and minimal dermal inflammation.
- *Uveodermatologic syndrome:* Lichenoid interface dermatitis with large histiocytes, as well as prominent pigmentary incontinence; hydropic degeneration of epidermal basal cells is rare.

269.2.2.2 Antinuclear Antibody Testing

- *Pemphigus erythematosus:* Weak positive titer may be seen.
- *Systemic lupus erythematosus:* Strong positive titer.
- **Direct Immunofluorescence Testing**
- *Pemphigus complex:* Positive intercellular fluorescence.
- *Pemphigus erythematosus:* Positive intercellular and basement membrane fluorescence.
- *Bullous pemphigoid (50% to 90% of cases), epidermolysis bullosa acquisita, linear IgA dermatosis, mucous membrane pemphigoid, systemic or cutaneous lupus erythematosus (50% to 90% of cases):* Positive basement membrane fluorescence.

NOTE: Direct immunofluorescence testing usually is negative in the other autoimmune skin diseases, however, this is not always the case, and nonspecific staining may be seen.

269.2.2.3 Indirect Immunofluorescence Testing

- Indirect immunofluorescence testing using a salt split-skin as a substrate is a relatively new method of differentiating the autoimmune subepidermal bullous diseases.

Cytologic examination of the contents of an intact pustule may be extremely valuable for making a diagnosis. This diagnostic test may be helpful for corroborating a diagnosis of pemphigus foliaceus (PF). Intact pustules are rare in cats, and if found, especially on the inner pinnae and near the mammae, are almost always caused by pemphigus foliaceus. In dogs, it is rare to easily find large numbers of intact pustules. The pustules of pemphigus are large, flaccid, and filled with a copious amount of pus. The specimen should be stained and examined for acanthocytes, which are round, deeply basophilic epidermal cells often present as rafts (i.e., numerous cells adhered together). In dogs these cells tend to be found in PF and in cases of severe bacterial pyoderma. Cytologic specimens should be carefully examined for eosinophils. In dogs, eosinophils can be seen in pustular specimens from PF. A finding of eosinophils should prompt the clinician to consider other differential diagnoses, such as allergic disease (small numbers of eosinophils), sterile eosinophilic pustulosis (almost pure fields of eosinophils), or parasitic diseases (variable). In cats, a finding of large numbers of eosinophils requires some thought on the part of the clinician, because many allergic skin diseases of cats can mimic ASDs.

270 CHAPTER • 270 Regenerative Anemias Caused by Blood Loss or Hemolysis

Urs Giger

Anemia is not a diagnosis in itself but is a common clinical sign and laboratory test abnormality in companion animals. Thus anemia may indicate a specific erythrocyte problem or can be associated with other organ disorders. Anemia and other hematologic abnormalities occur so frequently that a complete blood cell count (CBC) is generally requested in the diagnostic assessment of any ill dog or cat. Anemia is defined as a decrease in the red blood cell (RBC) mass as expressed by a reduction in number of circulating RBCs, hematocrit, and hemoglobin. Clinical signs of anemia result from decreased oxygen-carrying capacity, reduced blood volume, underlying disease, and the adjustments made to increase the efficiency of the erythron. Severity of clinical signs depends on the rapidity of onset, the degree and cause of anemia, and the extent of physical activity. A logical approach to the cause of anemia is usually fruitful. Anemias are classified by pathophysiologic mechanisms, bone marrow response, and RBC indices. This chapter reviews regenerative anemias caused by blood loss or hemolysis. Non-regenerative anemias will be covered in the next chapter (271) and additional details on hematologic aspects are provided in *Schalm's Veterinary Hematology* and other clinical pathology texts.[1–3]

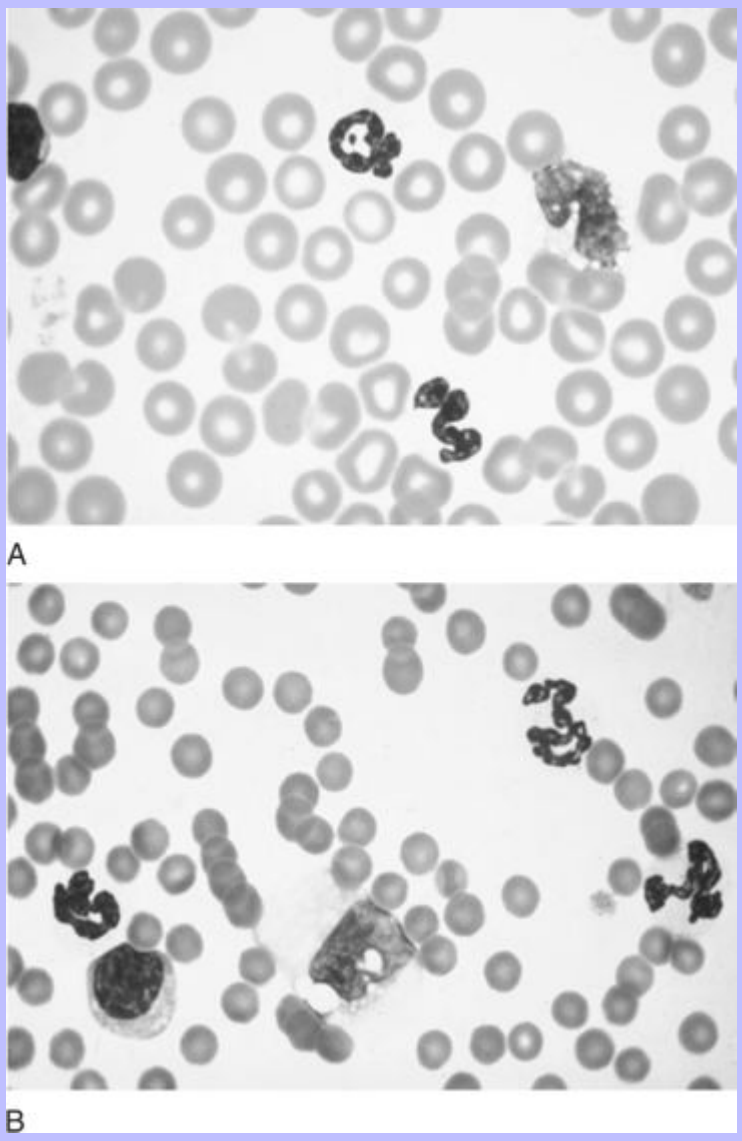
270.1 REGENERATIVE BONE MARROW RESPONSE

The number of circulating erythrocytes is the result of a dynamic equilibrium between the production and delivery of erythrocytes (Figure 270-1) and their destruction or loss. The normal homeostatic mechanisms of the body bring about recovery from anemia by accelerating erythropoiesis. The erythroid bone marrow response is primarily regulated by erythropoietin, a lineage-specific hematopoietic growth factor. Erythropoietin synthesis in the renal cortex is induced by anemia, although the actual sensor measures oxygen tension and renal hypoxia. It acts predominantly on erythroid precursor cells of the bone marrow known as *burst-forming units-erythroid* (BFU-E) and particularly colony-forming units-erythroid (CFU-E). At maximal stimulation, the bone marrow is capable of producing erythrocytes at tenfold to fiftyfold the normal rate. Erythropoietin also contributes to the maturation from the early committed erythroid precursors to fully hemoglobinized erythrocytes, which takes normally approximately 1 week.[1,3]

270.1.1 Reticulocytes

The most useful marker of accelerated erythropoiesis is an increased number of circulating reticulocytes.[1,3,4] Reticulocytes form after extrusion of the pyknotic nucleus from normoblasts and continue to mature, finally to erythrocytes, in the bone marrow and peripheral blood. Reticulocytes normally reside within the marrow for almost 2 days before they are released into the circulation. They continue to synthesize hemoglobin as long as they have functional messenger RNA, which is usually 1 day in circulation. However, during accelerated erythropoiesis, reticulocytes may be released prematurely from the marrow. The so-called stress or shift reticulocytes are macrocytic, less developed, and therefore require a longer time to mature to erythrocytes in circulation. In hemolytic disorders they contain high pyruvate kinase (PK) activity.[4] Because they contain residual RNA, which can be precipitated into a reticulum network and stained by certain supravital dyes, such as new methylene blue or brilliant cresyl blue, reticulocytes can be readily enumerated. The latter stain is particularly suitable as it is relatively free of precipitates. On a stained blood smear, the number of reticulocytes is counted per 500 to 1000 erythrocytes, and the reticulocyte result is reported as a percentage of cells examined (number per 100 cells). Some hematology instruments provide a specific count.

Figure 270-1 Normal canine **(A)** and feline **(B)** blood smear, Wright's-Giemsa staining. Reader should note the smaller size of feline erythrocytes.



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Because canine reticulocytes contain strong aggregates, they are relatively easy to count (Figure 270-2). In contrast, cats produce two types of reticulocytes: (1) aggregate and (2) punctate. Aggregate reticulocytes correspond to the reticulocytes seen in dogs and indicate an active regenerative response. After a short maturation time of less than 1 day, these aggregate forms become punctate reticulocytes. On a blood smear stained for reticulocytes, they contain up to 10 individual blue dots, which do not coalesce. As punctate

reticulocytes circulate over a period of 1 to 2 weeks and represent a cumulative response, they can reach high percentages. It is therefore best to report either the aggregate reticulocytes only, or both separately, in cats.

The upper limit of a normal reticulocyte count is often stated as 1%; however, healthy small animals generally have less than 0.4% reticulocytes per 100 erythrocytes. This number is not only increased by enhanced hematopoiesis but also affected by anemia, because it depends on the number of circulating erythrocytes and the duration of reticulocyte maturation in circulation. Therefore various "adjustments" to reticulocyte counts are used. If the erythrocyte count is available, the absolute reticulocyte count can be calculated and is less than 40,000/µL in a healthy animal:

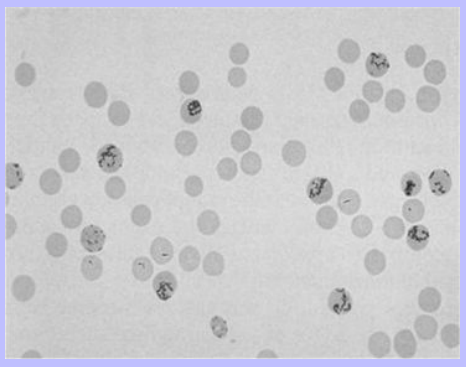
$$\frac{\%\ \text{reticulocytes} \times \text{RBC}/\mu\text{L}}{100} = \text{recticulocytes}/\mu\text{L}$$

The absolute reticulocyte count has now been adopted as the preferred expression of erythroid regeneration. Several automated hematology analyzers have incorporated staining to detect reticulocytes and provide absolute reticulocyte counts; however, some such counts may be falsely increased in the presence of Heinz's bodies, Howell-Jolly bodies, and punctate reticulocytes. If the erythrocyte count is not known, correction for anemia can be made based on the dog or cat's hematocrit compared with the average normal packed cell volume (PCV) value (dogs 45%; cats 37%) and is normally less than 0.4%.

Finally, the reticulocyte production index (RPI) also takes into consideration the extended maturation of stress or shift reticulocytes in circulation. This parameter is no longer applied clinically.

An increase in absolute reticulocyte count or corrected reticulocyte percentage provides the best evidence for a regenerative response. Although not as accurate, other hematologic manifestations such as mean cell volume (MCV) and red cell distribution width (RDW) may be used to indicate increased erythropoiesis when a reticulocyte count is not available. On a blood smear stained with Wright's stain or Diff-Quik, polychromatophilic cells represent erythrocytes recently released from the bone marrow (Figure 270-3). Because their blue-gray tint is due to the presence of RNA, their numbers correlate with the reticulocyte count. When more than one polychromatophilic cell is recognized per microscopic oil immersion field, accelerated erythropoiesis is likely. Polychromatophilic erythrocytes are often macrocytic, which indicates that these cells are released prematurely from the marrow, thereby contributing greatly to the high MCV and RDW, as well as anisocytosis of regenerative anemias. It should be noted that macrocytic anemia is not always regenerative but may indicate a maturation problem such as feline leukemia virus (FeLV) infection or folate deficiency in cats.[5,6]

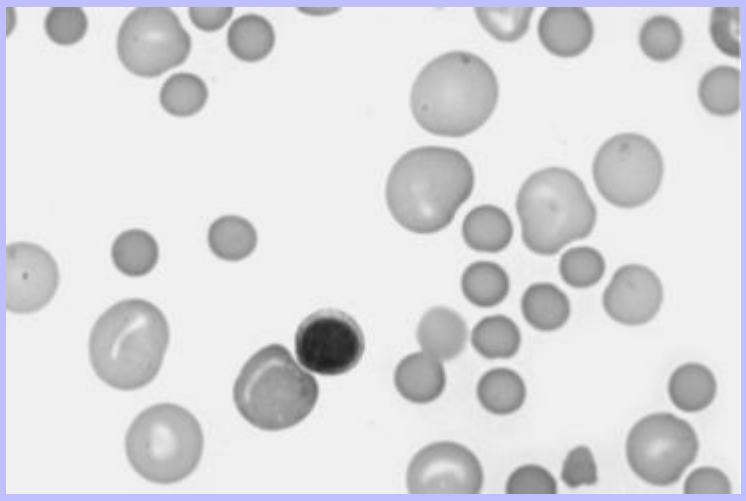
Figure 270-2 Canine reticulocytes as visualized by brilliant cresyl blue stain.



Nucleated erythrocytes (Figure 270-3) also known as *normoblasts* or *metarubricytes* with variably shrunken nuclei are rarely found in blood of healthy animals (less than 1 per 100 white blood cells [WBCs]). Depending on the hematology instrument, they may not be counted or may be under the WBCs. Large numbers may accompany a marked regenerative response in anemic pets. However, nucleated RBCs may also be seen in animals without reticulocytosis and regenerative response because of a breakdown of the barrier between marrow and vasculature. The highest numbers of normoblasts, for example, are observed in acute lead poisoning in the absence of anemia. Mild to moderate normoblastosis with nonregenerative anemia may be seen with myeloproliferative disorders, dyshematopoiesis, extramedullary hematopoiesis, hemangiosarcoma, and sepsis. Thus, normoblastosis should not be equated with a regenerative marrow response without confirmation by a reticulocyte count.

If an anemia is characterized as regenerative based on a reticulocytosis, bone marrow examination is rarely indicated. In regenerative anemia, the bone marrow cellularity is increased and the ratio of myeloid to erythroid elements in the bone marrow is generally below one. The earliest morphologically recognizable erythroid cell is a pronormoblast. An exponentially increasing number of round erythroid precursors that decrease in size to the pyknotic normoblast and are progressively more hemoglobinized indicate normal maturation. Although the erythropoietin response is lineage specific, independent stimulation of thrombopoiesis (e.g. iron deficiency) or granulopoiesis (e.g. immune-mediated hemolytic anemia [IMHA]) may also be present. Bone marrow examination rarely provides helpful information about an underlying cause or marrow iron deposition in animals with regenerative anemia that would otherwise remain undetected. 1887 1888

Figure 270-3 Polychromasia and anisocytosis with spherocytes and metarubricytes.



270.2 BLOOD LOSS ANEMIA

Blood loss anemia occurs whenever a disease process damages vascular integrity sufficiently for RBCs to escape from the intravascular space. Blood loss may be localized to one site and caused by trauma, surgery, tumor, gastrointestinal (GI) disorders, or parasites. Blood loss may be generalized in association with a hemorrhagic tendency. Surface bleeding such as petechiae and epistaxis suggests a platelet problem, whereas hematomas and

cavity bleedings indicate a coagulopathy. These primary and secondary hemostatic disorders are discussed in other chapters (see Chapters 272–274). Regardless of the cause, clinical manifestations of blood loss anemia depend on the volume of blood loss and onset (i.e., whether it is acute or chronic). Both acute and chronic blood loss are regenerative, although in the first few days after acute blood loss and in late stages of severe iron deficiency due to blood loss, such anemias are poorly regenerative.

270.2.1 Acute Blood Loss

Rapid blood loss of major proportions represents a double threat, because it decreases the total blood volume and oxygenation of tissue.[7,8] The total blood volume of dogs and cats is 8–10% and 6–8% of the body weight, respectively. Blood donations for transfusion of 4.4 mL/lb body weight, representing less than 20% of the blood volume of healthy animals, are generally well tolerated. However, when hemorrhage exceeds 20%, cardiovascular signs occur. Initial physiologic adjustments are peripheral vasoconstriction and tachycardia. Regional blood flow to skin and spleen is curtailed to protect perfusion of the brain, heart, and viscera. Thus pallor in acute blood loss anemia is caused not by thinness of blood but by reduced perfusion of the skin and is associated with a prolonged capillary refill time and dry mucous membranes. Besides the redistribution of blood to areas most vulnerable to hypoxemia, the heart rate is increased in an attempt to maintain cardiac output. This high-velocity flow is well tolerated because of the reduced viscosity of anemic blood and vasodilatation in the central and cerebral vascular beds into which most blood is diverted. As the blood loss exceeds 30% to 40% of the original blood volume, cardiac output decreases and hypotension with cardiovascular collapse ensues. The animal becomes immobile and exhibits a rapid, thready pulse, as well as cold skin and extremities. Acute blood loss exceeding 50% of the vascular volume within hours results in shock and eventually death before any changes in hematocrit and plasma protein are observed.[8,9]

If the acute blood loss is gradual, restoration of the plasma volume can occur, which in turn lowers the hematocrit. Unless fluid is administered, plasma volume expansion is a relatively slow process. After a sudden, single hemorrhagic event, albumin-containing fluid is mobilized from the extravascular space over a period of 2 to 3 days. This fluid shift reduces the skin turgor until the fluid deficit is replenished by oral or parenteral fluid intake. Because the associated fall in hematocrit is gradual, the severity of the hemorrhage may be markedly underestimated.

As the anemia is initially normocytic-normochromic and nonregenerative, it could be mistaken for a defective hematopoietic problem. Within a few hours, serum erythropoietin levels are, however, increased and erythropoiesis is stimulated. After 3 days the anemia becomes macrocytic and regenerative. A maximal reticulocyte response is seen within 4 to 7 days. The corrected reticulocyte count may reach 3% to 10% or several hundred thousands per microliter, which is somewhat less than with hemolytic anemias. In acute anemia, adequate iron stores are generally present but the marrow response may be hampered by limited iron mobilization. In cats, the transient rise in aggregated reticulocytes is followed by a marked sustained increase in punctate reticulocytes over a few weeks.

A stress leukogram may also be associated with acute blood loss. Although platelets are being consumed at the site of injury, this does not result in a clinically significant thrombocytopenia; to the contrary, after a slight dip to no less than 60,000/μL, acute blood loss is accompanied by a mild reactive thrombocytosis. In case of external blood loss, a concomitant loss of plasma proteins occurs that includes albumin and globulins. Thus the triad of anemia, hypoproteinemia, and reticulocytosis is considered a hallmark of acute external blood loss. Other test abnormalities depend on the cause of bleeding. Besides typical clinical signs of hemorrhage, examination of a blood smear for platelets and schistocytes and evaluation of an activated clotting time and

buccal mucosal bleeding time may suggest a hemostatic defect that can be confirmed by appropriate laboratory tests.

Four main objectives exist in the management of acute blood loss anemia: (1) fluid replacement, (2) prevention of further bleeding, (3) blood transfusion support, and (4) treatment of the underlying disorder. With sudden hemorrhage, the immediate effects of volume depletion are more important than the loss of circulating RBCs. Thus the first requirement is to maintain an adequate blood volume by intravenous infusion of crystalloid fluids (electrolytes), colloid solutions of plasma, hydroxyethylstarch, hemoglobin solution (Oxyglobin®), or whole blood. Fluid choice depends on the clinical setting, particularly the severity and rate of hemorrhage. With major hemorrhage leading rapidly to shock, losses are primarily from the intravascular space with little change in extra-and intracellular fluid compartments. Crystalloid fluids (isotonic saline or Ringer's lactate) are the first choice. Because crystalloids are rapidly distributed between the intra-and extravascular compartments, they need to be infused in a volume of two to four times the estimated loss. An infusion of crystalloids can rapidly restore circulation, thereby normalizing many hemodynamic parameters.

Within days, intra-and extracellular fluids shift into the intravascular space. For adequate resuscitation of a pet with hemorrhagic hypotension and shock, much larger fluid volumes must be given quickly to replete the fluid compartments and restore circulation. Colloid fluids such as 6% hydroxyethylstarch or dextran 70 solutions produce a volume expansion slightly larger than that infused and can maintain this effect for as long as a day. Because species-specific albumin solutions are not available for small animals, plasma, or whole-blood transfusions may be used for replacement therapy. Their use should, however, be discouraged unless clotting factors are needed or, because of anemia due to major blood loss, an oxygen carrier is deemed necessary. A bovine hemoglobin solution (Oxyglobin®) has become commercially available for dogs that provides oncotic pressure and an oxygen transporter. It can prove useful in the emergency management of acute blood loss and lacks immunologically important reactions and in dogs even after repeated administration.[10–12]

The depletion of RBC mass after acute blood loss may be difficult to estimate because of concurrent plasma loss and the hematocrit decreases only after total blood volume returns to normal. Thus the “transfusion trigger” can be particularly difficult to define in a hemorrhaging pet. Although a healthy normovolemic anemic animal at rest may tolerate a hematocrit as low as 5% to 10%, signs of hypoxia develop much earlier in a hypovolemic anemic animal. Thus small animals with precipitous blood loss may be deemed in need of a blood transfusion at hematocrits above 20%. Ten milliliters of whole blood per pound body weight increases the hematocrit by 10%, but fluid shifts and concomitant replacement of fluids may diminish the response. It should be noted that except for isotonic saline, fluids have to be administered through a catheter other than that used for transfusion. If venous access cannot be obtained in severely hypotensive animals, the intraosseous route may be used because RBCs and fluids rapidly reach the intravascular space. Because canine stored blood or packed RBCs have low 2,3-diphosphoglycerate (DPG) concentrations, which may hamper the oxygen release, some clinicians have advocated the use of fresh blood. However, DPGs are rapidly replenished in canine erythrocytes; therefore this may be more of a theoretic concern. Because the hemoglobin-oxygen affinity of feline erythrocytes is not DPG dependent, this is not a problem in cats; however, closed blood collection systems and blood component preparation for storage of feline blood are a problem. When hemorrhage has ceased, the recovery of the red cell mass to normal usually occurs within 1 to 2 weeks. Animals with acute blood loss anemia have adequate iron stores and generally do not require supplemental iron to reach an appropriate erythroid bone marrow response.

270.2.2 Chronic Blood Loss Anemia-Iron Deficiency Anemia

Animals have approximately 9 to 22 mg iron per lb body weight, and most of the iron is located in erythrocytes as hemoglobin (1 mg iron in 2 mL of blood).[3,13] In addition, muscle myoglobin and many important enzymes contain heme iron (e.g., cytochromes). Iron is also stored in various tissues, particularly spleen, liver, and bone marrow, as a soluble mobile fraction (ferritin) or insoluble fraction (hemosiderin), depending on the amount available. Transferrin represents the iron transport protein in the plasma and is normally 20% to 60% saturated with iron. As under physiologic conditions, iron losses through gut, urine, and skin are negligible, amounting to less than 1 mg/day in small animals. Iron balance is regulated by iron absorption. Iron is absorbed in the ferrous (Fe^{2+}) form as heme iron or nonheme iron by the mucosal cells of the proximal small intestine. The exact control mechanisms have not been elucidated, but absorption increases with diminished storage and increased erythropoietic activity. However, the maximal absorption remains rather limited—only a few milligrams per day.[14,15]

Chronic external blood loss is the major cause of iron deficiency anemia in small animals and is associated with a regenerative anemia. Iron deficiency denotes a deficit in total body iron, which occurs in varying degrees. Iron depletion is present when iron stores are depleted but serum iron and blood hemoglobin concentrations remain normal. In iron-deficient erythropoiesis, serum iron levels are also low but the anemia is only mild. *Iron deficiency anemia* refers to the most advanced stage, characterized by absent iron stores, low serum iron concentration, low transferrin saturation, and low hemoglobin and hematocrit values.

Chronic external blood loss may result from GI hemorrhage, parasitism, chronic bleeding neoplasia, and even chronic inflammatory bowel disease (IBD).[16–22] Severe flea infestation can cause substantial blood loss and mortality, particularly in kittens and puppies, because 100 fleas could potentially consume 1 mL of blood daily. Similarly, the quantity of blood loss caused by hookworms and rarely whipworms is proportional to the worm burden and may reach 100 mL/day. Hookworms burrow their heads deeply into the small intestinal wall and suck blood by peristaltic pumping. Chronic or intermittent GI blood loss may also result from hemorrhaging GI neoplasia, including leiomyoma, carcinoma, and lymphoma; bleeding intestinal aneurysm; and ulcerogenic drugs such as glucocorticosteroids, salicylates, and nonsteroidal anti-inflammatory agents. As each regular blood collection (450 mL) removes approximately 200 mg of iron from the body, overzealous blood donations and frequent phlebotomies for diagnostic purposes in small dogs and cats may lead to iron deficiency states.

In young animals the iron needed for growth may exceed the supply available from diet and body stores. Thus they are particularly at risk for developing an iron deficiency anemia. Because milk is low in iron, nursing animals may become iron deficient. However, with the general use of balanced commercial diets for growing animals, iron deficiency related to inadequate intake alone is rare. Intestinal malabsorption syndromes, such as IBD in Shar Peis, can be associated with iron deficiency states.

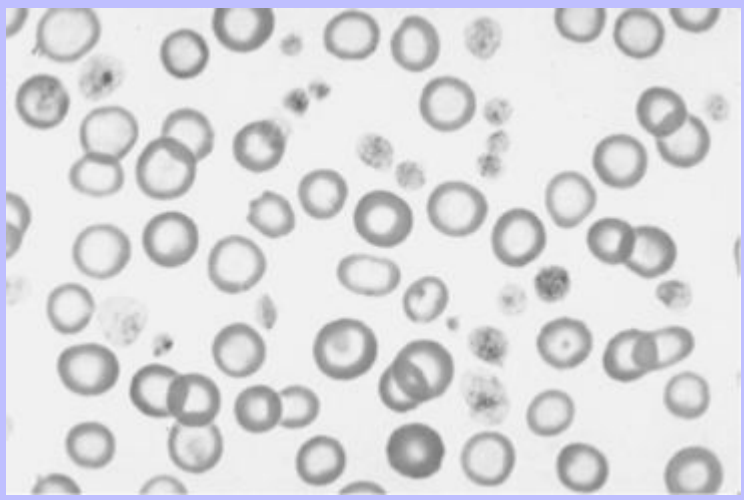
Iron deficiency anemia develops over weeks and is almost always insidious, allowing remarkably effective adaptation. Clinical signs are nonspecific and depend more on the rate of progression than the extent of anemia. Even when the hematocrit falls below 5% to 10%, clinical signs of anemia, besides pallor, may not be obvious at rest. The animals may become increasingly fatigued and exercise intolerant and, when stressed, may suddenly decompensate and die. Clinical manifestations include extremely pale mucous membranes, bounding pulses, gallop rhythm, and a systolic flow murmur. Reduced blood viscosity, vascular resistance (decreased afterload), and increased left ventricular filling (increased preload) maintain the cardiac output. Thus chronic anemia causes cardiomegaly through cardiac hypertrophy and dilation and may eventually lead

to congestive heart failure (CHF).[20] In contrast, tachypnea and dyspnea are not typical features of anemia unless the animal has pulmonary disease that impairs oxygen uptake. Pica, the craving to eat, chew, or lick unusual substances such as dirt, clay, feces, and metal, is a classical manifestation of iron deficiency. Because iron deficiency is most commonly caused by GI blood loss, melena is likely to be present, but occasionally it is intermittent or detected only by the occult fecal blood test. A positive test result for an animal receiving a commercial diet is probably clinically significant. Typical blood sweat and laboratory test abnormalities may provide the first clue to an iron deficiency anemia and possibly an occult intestinal malignancy.

Iron deficiency can produce clinical manifestations independent of anemia because depletion of iron-containing compounds in nonerythroid tissue results in impaired proliferation, growth, and function. These include reduced muscle activity, abnormal behavior, and skin and nail changes.

Severe iron deficiency anemia is characterized by a hypochromic microcytic anemia caused by decreased synthesis of hemoglobin and delayed cell maturation and extra mitosis.[1,7,16,23] On a blood smear the hypochromic cells are readily recognized by the increased central pallor (Figure 270-4) and are reflected by a decreased mean corpuscular hemoglobin concentration (MCHC). In advanced states the red cell corpuscles represent mere rings. Microcytosis is less well appreciated on a blood smear, because cell diameter is less affected than cell thickness; these flat, poorly stained cells are called *leptocytes* and have a reduced MCV. 1889
Anisocytosis is also a recognizable morphologic change and can be quantified by an increased RDW as 1890
determined by particle size counters. In addition, iron-deficient erythrocytes appear stiffer and less deformable, presumably because of oxidative damage of membrane proteins. Thus erythrocyte fragmentation, increased mechanical fragility, and accelerated lysis may occur, thereby affecting the various erythrocyte indices. However, in the osmotic fragility test, the red cells may be more resistant to destruction in hypotonic salt solutions because of their increased capacity to expand their volume.[1,14]

Figure 270-4 Hypochromasia and thrombocytosis in a dog with severe chronic blood loss anemia.



In humans, iron deficiency anemia is non-or poorly regenerative[14]; in contrast, iron deficiency in small animals is usually associated with a pronounced reticulocytosis.[16] The reticulocyte counts may reach

500,000/μL (10% corrected), presumably because of their delayed maturation. This reticulocytosis greatly contributes to the degree of anisocytosis and increased RDW.

The leukocytes are usually normal in number, but slight neutropenia may occur, whereas eosinophilia is seen in parasite-induced blood loss anemia. Interestingly, the platelet count is commonly increased to about twice normal, but may exceed $1 \times 10^6/\mu L$.[9]

Thrombocytosis associated with acute and chronic blood loss is considered reactive, but the exact mechanism remains unexplained. A search for occult blood loss is highly warranted in anemic animals with thrombocytosis. In uncomplicated iron deficiency anemia, the chemistry screening test results are unremarkable except for a low total protein related to concomitant intestinal losses of albumin and globulin.

The bone marrow is characterized by mild to moderate erythroid hyperplasia with nuclear distortions. The normoblasts appear small and have scant cytoplasm. After staining the bone marrow aspirate or biopsy section with Prussian blue, one sees dark-blue granular material scattered throughout the marrow. In iron deficiency anemia, no stainable iron in the form of deep-blue granules is found (hemosiderin appears in the unstained marrow smear as golden refractile granules). However, healthy cats normally store only small amounts of ferritin and hemosiderin in macrophages of their marrow; thus a lack of positive Prussian blue staining is not diagnostic for iron deficiency in cats, but Prussian blue–positive deposits in marrow exclude iron deficiency.

Serum iron concentrations are usually low, ranging from 5 to 60 μg/dL compared with a normal range of 60 to 230 μg/dL, depending to some extent on the method used.[13] However, serum iron concentrations are subject to many variables that may cause normal or even high results, including hemolyzed samples, iron supplementation, and recent transfusions. The iron-binding capacity is a measure of the amount of transferrin in circulating blood and may be slightly increased in iron deficiency states; thus the transferrin saturation is markedly decreased to below 20% (normal 20% to 60%). Serum ferritin concentrations would be expected to be low, but because ferritin is an acute phase protein, values are often increased by coexisting inflammation. Iron parameters can also be affected by transfusions, iron supplements, and glucocorticoid administration.

Management of chronic blood loss anemia is directed toward correction of the anemia, the iron deficiency, and treatment of the underlying disease. Transfusions with packed RBCs or whole blood are indicated only in cases of severe anemia or in preparation for anesthesia and surgery to correct the GI hemorrhage (PCV less than 15% to 20%) and clinical signs of tissue hypoxia. Because these animals are normovolemic and have increased cardiac output, transfusion volumes and rates should be conservative to avoid cardiac failure. Volume overload occurs more commonly in cats than in dogs. Correction of the anemia also results in resolution of cardiomegaly within several weeks. Although ulcerogenic drugs can be withdrawn immediately, control of ecto-and endoparasites (as well as any surgical corrections) should be undertaken only when the pets has been stabilized. Leiomyomas and leiomyosarcomas are frequent small intestinal tumors in older dogs, and their complete resection is often rewarding.

Once critical care has been provided and the underlying condition has been corrected, iron supplementation should be initiated to replenish iron stores. Iron is highly effective in treating iron deficiency. It has, however, no other legitimate therapeutic use, because it exerts no beneficial effects for other forms of anemia and may be harmful (exception: animals with chronic renal failure may in fact also experience an iron deficiency). Iron can be administered orally and parenterally. The oral route is the safest and least expensive. Ferrous sulfate in tablet or liquid form at a dose of 5 mg/lb daily along with a meal is effective, although the exact iron requirements have not been established for small animals. Iron fumarate and gluconate may be substituted, but other iron preparations are likely not to be effective, may cause gastric irritation, and hence are not

recommended. Treatment has to be continued for weeks to months to correct the iron deficiency state, but iron stores may never be completely replenished.

If oral iron replacement is deemed inappropriate or insufficient or a GI disorder prevents iron absorption, parenteral iron may be administered. Iron dextran complex containing 50 mg iron per milliliter can be given intramuscularly. After a small dose is injected deep into the muscle to test for hypersensitivity reaction, a maximal dose of 2 mL is administered daily; two thirds of the iron is absorbed from the injection site within days. Ferrous chloride is potentially available in intravenous form. As 2 mL of blood contains 1 mg iron, blood transfusions also provide an excellent source of iron, but they should be restricted to severely anemic animals.

270.3 HEMOLYTIC ANEMIAS

Once the erythrocyte has lost its nucleus and ribosomes, it can no longer synthesize proteins. Nevertheless, it survives hundreds of miles of hazardous travel through large and tiny blood vessels with its limited equipment. It is capable of sustaining adequate energy levels through anaerobic glycolysis, maintaining ionic composition, reducing methemoglobin and oxidized glutathione, and resealing its membrane if portions are lost. Despite these capacities, erythrocytes have a finite life span that may be shortened when the environment becomes hostile or when the cell's ability for self-repair becomes impaired. Accelerated erythrocyte destruction is the major mechanism in hemolytic disorders and plays a minor role in many other common anemias.[24]

The normal life span of erythrocytes averages approximately 100 to 120 days in dogs and 70 to 78 days in cats.[2,3] Although it is rarely done in clinical practice, the erythrocyte life span can be measured directly by two labeling methods. The cohort method depends on the incorporation of an isotopically labeled chemical such as radioactive iron or glycine into newly formed cells. In contrast, the random labeling methods use tracers that bind with all erythrocytes in the circulation and include radiolabeled chromium or cyanate, as well as nonradioactive biotin.[25] Because chromium elutes from cells readily, the apparent half-life is much shorter (i.e., 20 to 30 days instead of 60 days for normal canine erythrocytes and only 6 to 14 days instead of 37 days for feline erythrocytes).[26] If needed, the nonradioactive biotin-labeling method should be considered.

Although the concept of erythrocyte aging and death is well established, the precise mechanisms involved in normal cell senescence are still not clearly defined. No single marker exists to identify aged erythrocytes, but the following factors may contribute to the finite life span of erythrocytes: declining enzyme activities, change in calcium balance, diminished negative membrane charge, repeated oxidative injuries, and binding of complement or naturally occurring autoantibodies against membrane band 3 protein and galactosyl-containing glycolipid.[24,25] 1890 1891

The erythrocyte life span may be shortened as a result of some intrinsic defect, such as an erythroenzymopathy, or because of some extrinsic mechanism that leads to premature erythrocyte removal, such as antibodies against erythrocytes. These can be distinguished experimentally by cross-transfusion studies. When erythrocytes from a healthy animal are transfused to one with an extrinsic cause for hemolysis, the donated cells are destroyed as rapidly as the pet's own cells. However, if an animal's corpuscles are removed from the unfavorable environment, they survive normally. In contrast, erythrocytes with an intrinsic defect would be disposed of rapidly in either the affected animal or a healthy recipient. Such survival studies are generally not required in the evaluation of hemolytic anemias in clinical practice.

Erythrocyte destruction may take place either extra-or intravascularly.[1,3] Extravascular hemolysis predominates and is assumed to be the mode of destruction of senescent erythrocytes in healthy animals. Extravascular

destruction refers to erythrophagocytosis by macrophages of spleen, liver, and bone marrow. Damaged or senescent erythrocytes are prone to enhanced sequestration in these organs. Erythrophagocytosis may be either complete (culling) or partial (pitting). In particular, splenic environment with its low glucose concentration, mild hypoxia, hypercapnia, and relatively low pH can be deleterious to erythrocytes. Based on its structure, the canine spleen is more efficient than the feline spleen in removing erythrocytes. Macrophages destroy ingested erythrocytes through proteolytic and lipolytic enzymes.

The heme oxygenase system responsible for hemoglobin degradation is located primarily in phagocytic cells. The globin is broken down to amino acids, which are reused. In heme catabolism, iron becomes liberated, recirculates bound to transferrin in plasma back to the marrow for erythropoiesis, and the protoporphyrin ring opens. Carbon monoxide is split off, exhaled, biliverdin forms, and is subsequently reduced to bilirubin.

Unconjugated bilirubin is then released into the plasma; it is water insoluble and reversibly binds to albumin (indirect-reacting bilirubin). The albumin-bound bilirubin is readily absorbed by hepatocytes. In the liver, bilirubin is conjugated with glucuronic acid to form bilirubin diglucuronide, also known as *direct bilirubin*. The conjugated bilirubin is excreted via the bile canaliculi into the duodenum, but in the presence of massive heme breakdown, conjugated bilirubin leaks back into the plasma and is also excreted in the urine. Intestinal bacteria in the colon convert the bilirubin to urobilinogens. Most of the urobilinogen is excreted in the feces, but a small amount is reabsorbed. The reabsorbed urobilinogen is readily re-excreted by the liver (enterohepatic recirculation), with a small portion lost in the urine.

The serum bilirubin concentration is an important marker of the rate of hemoglobin metabolism and of hepatobiliary function. Normal serum values, measured by colorimetric methods, do not exceed 0.4 mg/dL, and jaundice is not appreciated until the serum bilirubin exceeds 2 mg/dL. One might predict that hemolytic disorders are associated with a greater rise in indirect bilirubin, whereas hepatic failure leads to a larger increase in direct bilirubin. However, because the process to conjugated bilirubin is highly efficient and rapid in small animals, the differential bilirubin determination in serum has not proved helpful in distinguishing hemolytic from hepatic causes of hyperbilirubinemia. Hyperbilirubinemia and hemoglobinemia can affect accurate measurements of serum liver and other chemistry screen parameters. Liver function tests are often indicated, because hemolysis may be associated with a hepatopathy. Heme can be metabolized by alternative pathways in other tissues (e.g., kidney in dogs). In any case, a rise in heme degradation results in hyperbilirubinuria because of increased urinary excretion of conjugated bilirubin. Bilirubin is readily identified by the diazo-reaction on the urine dipstick. Small amounts of bilirubin are normally found in urine from healthy dogs but not cats. Hemoglobinuria may make the bilirubin readings invalid. Bile pigment gallstones, seen in humans with hemolysis, are not observed in small animals.

Less commonly, erythrocytes are lysed within the systemic circulation as a consequence of membrane permeability changes or cellular fragmentation. With intravascular hemolysis, hemoglobin is directly released into the blood, from which it is removed by several mechanisms. Hemoglobin breaks into two alpha-beta dimers and binds to haptoglobin in plasma or further dissociates into heme to form hemopexin and methemalbumin. After these complexes are taken up by macrophages and hepatocytes, hemoglobin and heme are metabolized as described earlier in relation to extravascular hemolysis. Binding prevents excretion of hemoglobin into the urine, but during intravascular lysis, haptoglobin becomes easily depleted. Unbound plasma hemoglobin and heme may be removed by the liver or excreted through the renal glomeruli.

Proximal tubular cells reabsorb and catabolize most filtered hemoglobin and heme.

Hemoglobinuria ensues when the amount filtered exceeds the limited capacity of the tubular cells to resorb dimers. Although heme pigments may precipitate and form casts in the distal renal tubules, hemosiderinuric

tubular necrosis and acute renal failure are rarely observed in small animals with severe or chronic hemoglobinuria.

Intravascular lysis can be readily recognized by the presence of hemoglobinemia, depletion of plasma haptoglobin, and hemoglobinuria. Plasma hemoglobin levels of 10 to 20 mg/dL give plasma an amber coloration, and at 50 to 100 mg/dL the plasma appears reddish. The hemoglobinemia has to be distinguished from artifactual increases in plasma hemoglobin caused by blood collection methods that directly cause hemolysis, as well as delayed plasma separation. Plasma hemoglobin concentrations can be quantitated spectrophotometrically by an accurate and simple hemoglobinometer (HemoCue).[27] Hemoglobinuria imparts a red-brown color to the urine, reflecting both hemoglobin and methemoglobin. Because the urine dipstick identifies only heme (labeled "blood"), hemoglobinuria has to be differentiated from hematuria (whole erythrocytes) by microscopic examination after urine sedimentation. Myoglobinuria associated with massive muscle necrosis can also cause a positive test result but hardly ever occurs in small animals.

Based on the preceding mechanisms of erythrocyte destruction, the clinical features and laboratory test abnormalities of the various hemolytic disorders are similar. Besides the general signs of anemia such as pallor and weakness, characteristic signs of hemolysis are jaundice and pigmenturia. Jaundice is first appreciated on mucous membranes (gingiva and sclera) when serum bilirubin concentration exceed 2 mg/dL, whereas skin becomes icteric at slightly higher concentrations. Milder and chronic forms of hemolysis may not be associated with jaundice. Pigmenturia caused by hemolysis may be due to hyperbilirubinuria and hemoglobinuria. Hyperbilirubinuria persists in dogs with hemolytic disorders, whereas in cats it is not constant. Hemoglobinuria and hemoglobinemia are hallmark features of intravascular hemolysis and often indicate a more severe disorder.

The terms *hemolytic anemia* and *hemolytic disorder* are limited to conditions in which the rate of erythrocyte destruction is accelerated and the ability of the bone marrow to respond to the stimulus is unimpaired. As indicated in the introduction, hemolytic anemias are generally associated with accelerated erythrocyte production that is unrestricted by iron availability. In fact, the highest reticulocyte counts and most severe erythroid hyperplasias are observed in animals with hemolytic anemias. Thus hemolytic anemias are regenerative and macrocytic-hypochromic, although in the early stages and in some complicated acquired forms the erythroid response may be poor (e.g., immune-mediated hemolytic anemia). In addition, a number of common complex anemias related to insufficient erythrocyte production have a component of accelerated erythrocytic destruction such as the previously mentioned advanced iron deficiency anemia.

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The division of hemolytic anemias into acute and chronic forms is of limited usefulness, because acute crises may develop during the course of chronic disorders. Classification based on the site of hemolysis, predominantly within the circulation (intravascular) or within tissue macrophages (extravascular), is of some help, because only a few are associated with overt intravascular hemolysis. However, intravascular lysis may occur only transiently; therefore the unique manifestations of hemoglobinemia and hemoglobinuria may be missed. Excessive destruction of erythrocytes may occur either because of an intrinsic defect in the cell itself or because of the action of extrinsic factors on normal erythrocytes. Intrinsic defects are generally inherited and extrinsic are acquired. The division into intrinsic and extrinsic or inherited, and acquired forms is of pathogenic importance and is most useful as hereditary hemolytic anemias gain greater recognition. Furthermore, some hemolytic processes are associated with acquired disorders of other organs and are covered elsewhere.

270.3.1 Inherited Erythrocyte Defects

Several hereditary erythrocyte defects (Table 270-1) have been described in dogs and cats.[19] The mode of inheritance is autosomal recessive for all described erythrocyte defects, with the exception of feline porphyria,

in which at least one defect is inherited as a dominant trait. This is a large heterogeneous group of disorders, and most occur rarely. Through inbreeding practices (popular sire, line breeding), some erythrocyte defects have become common in certain breeds. Unless the affected breeds are closely related, a particular disease is probably caused by different mutations of the same gene. Erythrocyte-induced defects vary from mild compensated hemolytic to life-threatening anemia. Accurate laboratory tests are now available for many erythrocyte defects to detect affected and carrier animals.

Some defects represent hematologic curiosities without clinical signs (such as in Akitas and miniature poodles with inconsequential microcytosis and macrocytosis, respectively). Hereditary erythrocyte disorders have been classified into three groups: (1) heme defects and hemoglobinopathies, (2) membrane abnormalities, and (3) erythroenzymopathies.[28] Hereditary production and maturation defects of erythrocytes and other hematopoietic cells are discussed in Chapter 271.

270.3.2 Hemoglobin and Related Disorders

Dogs and cats apparently have embryonic but no fetal hemoglobin.[2] With the exception of some Japanese dog breeds, only one adult hemoglobin has been found in dogs. Historically, two major adult hemoglobins were described in cats with a large variation of the hemoglobin A/hemoglobin B ratios. Later studies, however, revealed only one alpha globin, but six different beta globins were found.[29] With each cat having one to four different beta globins, at least 17 hemoglobin patterns were recognized. In contrast to the common occurrence of thalassemia and sickle cell anemia in humans, no hemoglobinopathies have been documented in anemic dogs and cats.

Physiologically or pathologically generated methemoglobin contains heme in the ferric form (Fe^{3+}) and therefore cannot carry oxygen. It is reduced to the ferrous form (Fe^{2+}) by the methemoglobin or cytochrome b_5 reductase system. Isolated cases of methemoglobinemia associated with methemoglobin reductase deficiency were found among dogs of various breeds and several domestic shorthair cats (DSH).[3,30–32] Affected animals have cyanotic mucous membranes but generally do not exhibit any other clinical signs of hypoxemia unless vigorously exercised. The blood remains dark after air exposure because of the presence of 13% to 52% methemoglobin. In contrast to those with other erythrocyte defects, these animals are not anemic but rather develop a mild erythrocytosis and can have a normal life expectancy. Reducing agents such as methylene blue could be used but are generally not needed.

Defects of heme synthesis known as *porphyrias* have been reported in anemic Siamese cats and nonanemic DSH cats with pigmented and pink-fluorescent teeth and bones.

270.3.3 Erythrocyte Membrane–Related Abnormalities

The erythrocyte membrane consists of a bilayer affixed to a membrane skeleton, which determines cell shape and deformability. Owing to proteolysis, canine and feline erythrocytes lose their Na^+, K^+-adenosine triphosphatase (Na^+,K^+-ATPase) during late maturation in the bone marrow and reticulocytes.[33] Therefore erythrocytes have high-sodium and low-potassium concentrations similar to those of serum electrolyte values. Consequently, hyperkalemia generally does not occur after intravascular hemolysis unless stress reticulocytes are lysed. Erythrocytes from Sheba, Inus, Akitas, and some mongrel dogs in Korea and Japan represent an exception, because they keep their erythrocytic Na^+,K^+-ATPases and therefore have high-potassium and low-sodium concentrations in erythrocytes. Because Akitas' erythrocytes are leaky *in vitro*,

pseudohyperkalemia may occur if the plasma and serum are not readily separated from erythrocytes and its clot.[34]

Elliptocytosis and microcytosis related to cytoskeleton protein band 4.1 deficiency has been described in an inbred, nonanemic mongrel dog.[35,36] Other erythrocyte membrane defects are far less well defined but are generally characterized by increased osmotic fragility (Figure 270-5). Stomatocytes are overhydrated, cup-shaped macrocytes that are recognized by a slitlike pallor on a blood film. In the Alaskan malamute, stomatocytosis is associated with a chondrodysplastic dwarfism.[37] Miniature and middle schnauzers with stomatocytosis had no skeletal abnormalities, and both breeds had only mild regenerative anemia on the basis of hemoglobin measurements with high MCV and low MCHC indices[38,39] (Figure 270-6). Furthermore, stomatocytosis and hypertrophic gastritis have been reported in the Drentse partrijshond dog breed (Dutch breed) and a lipid disorder is suspected on the basis of abnormal erythrocyte membrane and plasma phospholipids.[40] A hereditary spherocytosis has been described in some golden retrievers.[41] A marked osmotic fragility of erythrocytes associated with recurrent anemia, severe splenomegaly, weight loss, lymphocytosis, and hyperglobulinemia but a negative Coombs' test has been observed mostly in Abyssinian and Somali cats.[42] Their erythrocytes are so fragile that the lysis is clearly evident once the ethylenediaminetetraacetic acid (EDTA) tube is left in the refrigerator overnight. Although the cause has not been identified, affected cats with marked splenomegaly may benefit from prednisone treatment and splenectomy. This may reduce the degree of *in vivo* phagocytosis of damaged erythrocytes; however, the *in vitro* osmotic fragility of erythrocytes does not appear to improve after treatment. This osmotic fragility has also been seen in Siamese and DSH cats.

270.3.4 Erythroenzymopathies

Devoid of a nucleus and mitochondria, erythrocytes generate energy almost exclusively through anaerobic glycolysis, also known as the *Embden-Meyerhof* pathway. Phosphofructokinase (PFK) and PK are two key regulatory enzymes of this pathway, but their deficiency results in two distinctly different forms of anemia in dogs. The Embden-Meyerhof pathway also plays an important role in an ancillary pathway. The *Rapoport-Luebering* pathway is responsible for the synthesis of DPG, which influences the oxygen affinity of canine but not feline hemoglobin. Erythrocyte DPG concentrations are low in cats.[3,43]

Table • 270-1 Inherited Erythrocyte Defects

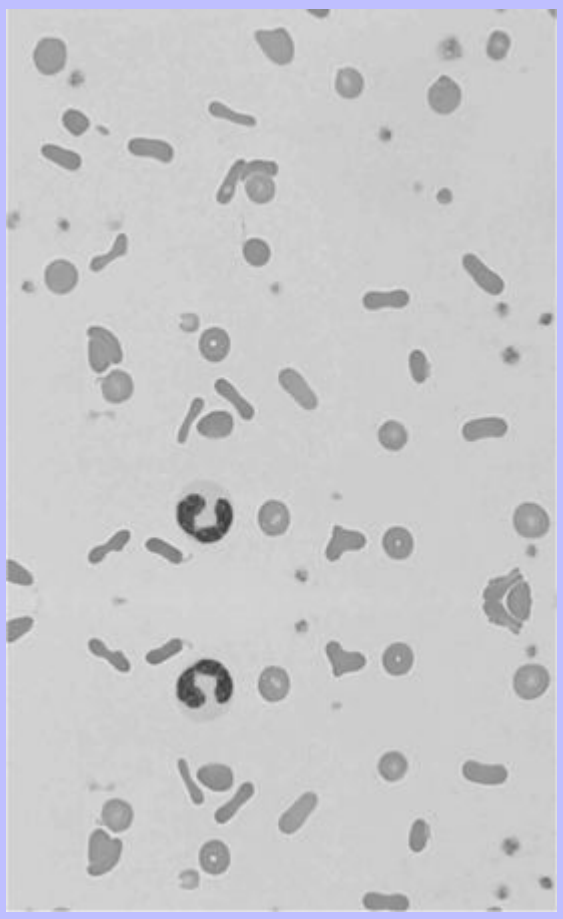
DEFECTS	BREEDS	INHERITANCE	PACKED CELL VOLUME (PCV) (%) RANGE	RETICULOCYTE (%) (CORRECTED)	ERYTHROCYTE HALF-LIFE (DAYS)	ERYTHROCYTE MORPHOLOGY	SPECIFIC TESTS	CLINICAL FEATURES
Erythroenzymopathies								
Pyruvate kinase (PK) deficiency	Basenji*, beagle*, West Highland white* and cairn terrier, miniature poodle, dachshund*, toy Eskimo*, pug	AR	11–29	5–95	4–9	Polychromasia, ecchinocytes	DNA test, abnormal M-PK, PK kinetic, stability, and glycolytic intermediates	Hemolytic anemia, myelofibrosis, osteosclerosis
	Abyssinian*, Somali*, DSH cats*	AR	10–33	1–33	U	Polychromasia	DNA test PK activity <20%	Intermittent hemolytic anemia
Phosphofructokinase (PFK) deficiency	English springer spaniel*, cocker spaniel*, mixed breed dog*	AR	11–48	5–23	4	Polychromasia	DNA test PFK activity, 8%–22%	Inducible hemolytic crises, mild myopathy, pigmenturia
Hemoglobin Synthesis Defects								
Hemoglobinopathies	None							
Cytochrome-b_5 reductase (Cb_5R) deficiency	Many isolated cases in dogs and DSH cats	U	High	N	U	Unremarkable	Cb_5R activity, 10%–30%; methemoglobin >10%	Cyanosis, no anemia, but polycythemia, exercise intolerance
Porphyria	Siamese	AD	10–25		U	Unremarkable	Porphyrins in urine and erythrocytes	Anemia, discolored teeth
	DSH	AD	N	N to 5	U	Unremarkable	Porphobilinogen deaminase deficiency (?)	Discolored teeth, ± anemia
Membrane and Other Abnormalities								
Elliptocytosis (band 4.1 deficiency)	Mixed breed dog*	AR	34	2	16–23	Elliptocytes	Membrane protein electrophoresis	None
Stomatocytosis	Alaskan malamute, miniature & middle schnauzer	AR	N	3–7	6–18	Stomatocytes, macrocytes, polychromasia	Stomatocytes, increased osmotic fragility	Chondrodysplasia in malamutes, none in schnauzers
Increased osmotic fragility	English springer spaniel, mixed breed dogs	U	N	2–5	U	Polychromasia, poikilocytosis	Increased osmotic fragility, unknown	Exercise-induced hyperthermia
Increased osmotic fragility	Abyssinian, Somali	U	8–35	1–4	U	Macrocytosis	Increased osmotic fragility	Intermittent anemia, splenomegaly
High-potassium erythrocytes	Akita, Japanese mongrels	U	N	N	U	Unremarkable	Increased erythrocyte and serum potassium	None, pseudo-hyperkalemia
Nonspherocytic hemolytic disorders	Beagle	AR	29–12	8–23	7–15	Polychromasia	Calcium ATPase pump (?)	None, mild anemia

Poikilocytosis	DSH cats	U	7–12	10–30	U	Severe poikilocytosis	Poikilocytosis	Severe anemia
Familial microcytosis	Akita	U	N	N	U	Microcytosis	Erythrocyte indices	None
Familial macrocytosis and dyshematopoiesis	Poodle (miniature and toy)	U	N	N	U	Macrocytes, hypersegmented neutrophils	Macrocytosis, normal osmotic fragility	None, gingivitis

Data collected from references and author's unpublished observations.
N, Normal; *U*, unknown; *AR*, autosomal recessive; *AD*, autosomal dominant; *DSH*, domestic shorthair.

* Molecular defect known.

Figure 270-5 Severe hereditary poikilocytosis in a 1-year-old domestic shorthaired (DSH) cat.

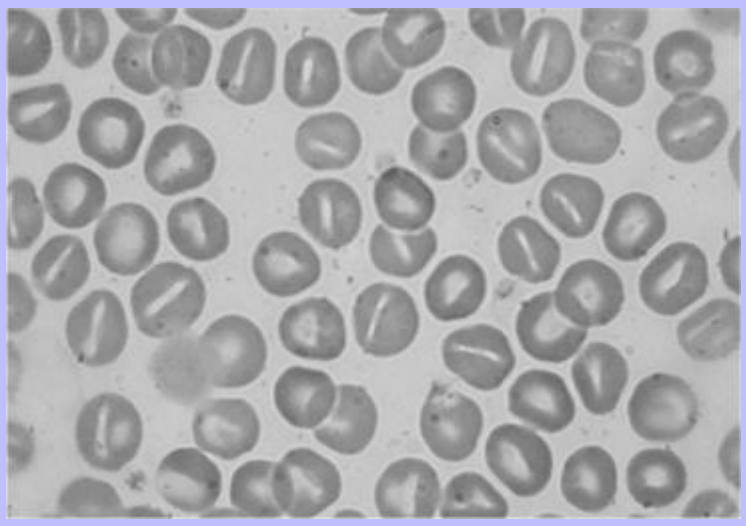


270.3.4.1 Phosphofructokinase Deficiency (PFK)

PFK deficiency is characterized by a chronic hemolytic disorder accentuated by hemolytic crises and an exertional myopathy.[44–47] After episodes of excessive panting and barking, extensive exercise, and high temperatures, affected dogs develop dark brown-red urine because of hemoglobinuria and hyperbilirubinuria. These sporadic events are associated with hyperventilation and elevated body

temperature, and the ensuing slight alkalemia results in intravascular lysis of PFK-deficient erythrocytes because these cells are more alkaline fragile than normal canine erythrocytes. During these crises, affected dogs may become severely anemic, icteric, lethargic, anorexic, and develop a fever that usually resolves within days with supportive care. If situations that trigger hemolytic crises are avoided, PFK-deficient dogs may not have problems and can reach a normal life expectancy. However, they have persistent hyperbilirubinuria and reticulocytosis despite a normal hematocrit because of ongoing hemolysis and a high hemoglobin-oxygen affinity because PFK-deficient erythrocytes contain low DPG levels and therefore lead to a relative tissue hypoxia. Furthermore, because affected dogs totally lack PFK activity in muscle, they have a metabolic myopathy characterized by exercise intolerance, occasional muscle cramps, and mildly increased serum creatine kinase activity; thus they perform poorly as field trial dogs.[44]

Figure 270-6 Stomatocytosis in a miniature schnauzer without anemia.



This glycolytic enzyme deficiency is common in field trial English springer spaniels in the United States, Great Britain, and Denmark, but has also been reported in bench English springer spaniels, as well as a cocker spaniel and a mixed breed dog.[43,48] Although the true prevalence remains unknown, a 1% to 4% prevalence among championed breeding bench and field English springer spaniels has been documented in a randomized survey in the United States.[49] PFK deficiency is caused by a missense mutation of the muscle-type PFK gene that results in truncation and instability of the enzyme, thereby leading to a complete muscle-type PFK deficiency.[50] A simple polymerase chain reaction (PCR)-based DNA test accurately diagnoses PFK-deficient and carrier dogs. A small blood sample, buccal swab, or semen is an appropriate source for DNA testing and requires no special handling or shipping. English springer spaniels (and cocker spaniels) with suspicious clinical signs or before field training and breeding should be DNA tested for PFK deficiency. In other breeds with suspicious signs, an enzymatic PFK test could be performed.

270.3.4.2 Pyruvate Kinase Deficiency (PK)

The classic erythrocytic PK deficiency initially reported in Basenjis is now seen in several other breeds including beagles, West Highland white and cairn terriers, miniature poodles, toy Eskimos, pugs, and

dachshunds.[43,44,51–54] Despite a persistent hemolytic anemia, the clinical signs, except for pallor, are often mild. The anemia ranges from about 10% to 32% and is highly regenerative with numerous circulating metarubricytes and reticulocyte counts that can be as high as sometimes approaching 95%. An unexplained progressive myelofibrosis and osteosclerosis of the bone marrow develops at about 1 year of age, although some West Highland white terriers may not show evidence until several years of life. Furthermore, it appears likely that previously described nonspherocytic hemolytic anemia and osteosclerosis in miniature poodles were caused by a PK deficiency.[55] PK-deficient dogs usually die because of anemias and generalized hemosiderosis with associated hepatic failure before 8 years of age. Splenectomy and prednisone treatment appear unhelpful in dogs. Erythrocytes completely lack the adult erythrocyte isozyme form of PK known as *R-PK*. Instead, they express a fetal or leukocyte M-PK form that is dysfunctional in erythrocytes *in vivo*. Molecular genetic screening tests are available for the identification of the PK mutation of affected and carrier Basenjis, beagles, dachshunds, toy Eskimos, and West Highland white and cairn terriers, but not yet for others.[56–58] A cumbersome PK enzyme activity test with isozyme characterization is required to define PK deficiency in other breeds. Carriers do not express the M-PK form and have approximately half-normal PK activity; however, differentiation between carriers and homozygous normal dogs based on enzyme activity may not be accurate.

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Feline erythrocytic PK deficiency has also been described in the Abyssinian and Somali breeds and few DSH cats.[59] Affected cats have chronic intermittent hemolytic anemia and mild splenomegaly but no osteosclerosis. The anemia is moderately regenerative and no poikilocytosis is seen. Erythrocyte PK activity is severely reduced, and no M-type PK expression occurs. A deletion caused by a splicing mutation in the R-PK gene has been identified, and a molecular screening test has been made available. Intermittent prednisone therapy and splenectomy appear to ameliorate the clinical signs of intermittent anemia. The oldest living cat reached 13 years of age.

270.3.5 Immune-Mediated Hemolytic Anemia (IMHA)

IMHA arises when an immune response targets erythrocytes directly or indirectly and hemolytic anemia ensues. Until the antierythrocytic antibodies are identified and the pathogenesis is better understood, the nomenclature and classification of IMHA remain imprecise and sometimes confusing.[46,60,61] In primary IMHA no inciting cause can be identified, hence the synonyms *idiopathic IMHA* and *autoimmune hemolytic anemia*. In contrast, secondary IMHA is associated with an underlying condition. "*Alloimmune*" hemolytic anemias such as neonatal isoerythrolysis (NI) and hemolytic transfusion reactions are caused by antierythrocytic alloantibodies.

270.3.5.1 Immune Mechanisms

Regardless of the underlying cause, IMHA results from a breakdown in immune self-tolerance. The process of clonal deletion for central tolerance is not capable of completely eliminating all potential self-reacting B cell clones *in utero*. Clonal anergy, another central control mechanism, is not totally efficient in the inactivation of B cells designed to respond to self-antigens. Therefore an immune response against erythrocytes may occur.[62] Because some erythrocyte antigens are hidden or cryptic, the appropriate B cell may encounter the antigen only after membrane damage exposes the antigen. An inflammatory or infectious process can also release new antigens into the circulation that cross-react with erythrocyte antigens or attach to the erythrocyte membrane. Furthermore, the appropriate T cell must find the matching B cell and bind via receptor-ligand pairs to activate the respective cell. However, during infection and

inflammation, nonspecific activation of lymphocytes can occur, so self-reacting antibodies may be nonspecifically induced. Finally, impairment of the down-regulation mechanisms such as activated B-cell death by apoptosis through a Fas ligand signal from T cells may allow an active autoimmune response to develop.[63–65]

The binding of immunoglobulin G (IgG) or IgM antibodies and complement to the surface of erythrocytes initiates immune destruction of the erythrocytes. Under most clinical circumstances, immune destruction is an extravascular process that depends on recognition of erythrocytes opsonized with IgG, complement, or both by specific receptors on reticuloendothelial cells.

IgG-coated erythrocytes can be destroyed without complement activation because tissue macrophages express receptors that recognize the Fc portion of the IgG molecule. IgG binding by Fc receptors on macrophages can mediate complete phagocytosis, particularly in the red pulp of the spleen. Macrophages with engulfed erythrocytes may be noted by cytologic examination of tissue aspirates. Alternatively, phagocytes remove only a portion of the membrane, leaving erythrocytes with a reduced surface area/volume ratio and thereby forming spherocytes. Because the deformability of spherocytes is impaired, these rigid cells are trapped in the spleen and are subsequently destroyed. Erythrocyte-bound IgG1 and IgG3 antibodies have a strong affinity for Fc receptors. Erythrocytes that become heavily coated with IgG can also bind complement. In as much as macrophages also have receptors for complement components C3b and iC3b, the attachment of complement component C3b, iC3b, or both via CR1 and CR3 receptors together with IgG enhances the phagocytic process, particularly of hepatic macrophages (Kupffer's cells). In addition, erythrocytes heavily coated with IgG may activate so much complement that intravascular cytolysis occurs.[60,66]

In contrast, macrophages do not have receptors for the Fc portion of IgM, and thus the destruction of IgM-coated erythrocytes is mediated by complement. The pentameric structure of IgM is readily able to induce binding and activation of complement on erythrocytes. High IgM antibody titers can generate the cytolytic complex via the classical complement system and, thereby, intravascular hemolysis ensues. However, the IgM antierythrocyte antibodies are more commonly present in sublytic concentrations, and inhibitory regulatory proteins prevent full complement activation. Nevertheless, some C3b and iC3b are bound to the cell surface, resulting in extravascular destruction of complement-sensitized erythrocytes. Alternatively, erythrocyte-bound complement may be inactivated to C3dg, which no longer impairs erythrocyte survival. Antierythrocytic antibodies inducing hemolysis are generally reactive at body temperature. Only in exceptional cases do cold-acting antibodies (at 4° to 37°C thermoamplitude) contribute to *in vivo* hemolysis and erythrocyte agglutination in cooler, peripheral vasculature.

270.3.5.2 Underlying Conditions and Predispositions

Historically, in most dogs with IMHA, no underlying condition was ever identified, and thus it was considered to be primary or idiopathic IMHA.[67] However, in later studies of autoimmune hemolytic anemia, probably reflecting more intense clinical investigations, an underlying disease process or trigger could be identified, including drug exposures, emerging infections, bee stings, neoplastic processes, and other immune disorders (Box 270-1).[68–70] Best exemplified in babesiosis and hemobartonellosis, hemolysis is severely exaggerated by immune processes. Many chronic infections including abscesses, discospondylitis, pyometra, and pyelonephritis can induce secondary immune disorders including IMHA. A temporal association between vaccination and onset of IMHA has also been suggested. In a limited retrospective study, one quarter of all dogs with IMHA of unknown cause were vaccinated within 1 month

of onset of clinical signs.[71] As this correlation was associated with modified and killed vaccines against common infectious diseases from different manufacturers, it appears likely that vaccines may trigger or enhance a smoldering immune process rather than be the underlying cause. Although a number of anecdotal reports support a temporal relationship between vaccination and IMHA, no significant association was found in a large-scale retrospective survey of animal health insurance records from Britain.[72] The higher rate of IMHA during the warmer months from May through August reported in some studies, but not in others, may also suggest an infectious cause including tick-borne disorders and allergen exposure during the warmer months.[73] The seasonality may vary geographically. The association of IMHA with other immune disorders, including hypothyroidism and immune-mediated thrombocytopenia (ITP), lends support to the hypothesis of a general immune disturbance. IMHA and ITP occurring concurrently are known as *Evans' syndrome*.[52,74] In contrast to humans, IMHA in dogs is often associated with inflammation and necrosis, suggesting again an underlying mechanism to trigger an immune response.

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270.3.5.2.1

Box • 270-1 Examples of Underlying Disorders and Triggers of Immune-Mediated Hemolytic Anemia

270.3.5.2.1.1

Infectious

Viral: FeLV, FIV, FIP infection, transient or chronic persistent upper respiratory or gastrointestinal (GI) viral diseases

Bacterial: leptospirosis, hemobartonellosis, various acute and chronic infections (e.g., abscess, pyometra, discospondylitis)

Parasitic: babesiosis, leishmaniasis, dirofilariasis, ehrlichiosis, ancylostoma caninum

Other emerging infectious diseases (e.g., bartonellosis), bee stings

270.3.5.2.1.2

Drugs

Sulfonamides

Cephalosporin

Penicillin

Vaccines

Propylthiouracil (cats)

Methimazole (cats)

Procainamide

270.3.5.2.1.3

Neoplasia

Hemolymphatic: leukemias, lymphoma, multiple myeloma

Solid tumors

270.3.5.2.1.4

Immune Disorders

SLE

Hypothyroidism

Primary and secondary immunodeficiencies

270.3.5.2.1.5

Genetic Predisposition

American cocker spaniel (one third of all cases)

English springer spaniel

Old English sheepdog

Irish setter

Poodle

Dachshund

FeLV, Feline leukemia virus; *FIV,* feline immunodeficiency virus; *SLE,* systemic lupus erythematosus.

IMHA is the most common reason for hemolytic anemias in dogs. A genetic predisposition is evident in some dogs by the breed predilection and familial occurrence. Thus they should no longer be grouped with the idiopathic form.[67,73] American cocker spaniels may represent one third of all dogs with IMHA. In other canine breeds predisposition is less well documented and may vary geographically. Certain histocompatibility leukocyte antigens have been associated with the occurrence of IMHA in humans. The previously reviewed hereditary erythrocyte defects, particularly the common occurrence of PK and PFK deficiency and osmotic fragility problems, should also be considered as an important differential diagnosis whenever IMHA is suspected in breeds documented to have these erythrocytic defects. As with other immune disorders, female dogs appear slightly predisposed, even when spayed. Primary IMHA is relatively rarely documented in cats, but IMHA may be secondary to FeLV or *Haemobartonella* infections, inflammation, or antithyroidal medication[75,76] No breed, gender, or other association has been found in cats.

270.3.5.3

Clinical Signs of Immune-Mediated Hemolytic Anemia

IMHA may present at any age but is most commonly encountered in young adult to middle-aged dogs. The clinical history is generally brief and vague. An underlying condition may be identified. A brief episode of vomiting or diarrhea may precede the typical signs of anemia (lethargy, weakness, exercise intolerance, pallor) and hemolysis (pigmenturia, icterus).[59–73] Some animals may be febrile, presumably because of erythrocyte lysis or an underlying infectious or inflammatory disease process. Others develop dyspnea, indicating pulmonary problems either as cause of the underlying disease or as a thromboembolic complication of IMHA.[77] Physical examination may also reveal mild splenomegaly and, less commonly, mild hepatomegaly and lymphadenopathy, which again suggest a secondary cause of IMHA. A

normal-sized spleen does not rule out a massive hemolytic process. Furthermore, signs attributable to their underlying disease may predominate, whereas chronic or recurrent signs of IMHA suggest a primary form.

In the rare case of cold-reacting antierythrocytic antibodies, peripheral skin lesions characterized by acrocyanosis and gangrenous necrosis of ear, nose, tail tip, and nail beds may be the obvious problem without any evidence of hemolysis.

270.3.5.4 Routine Laboratory Test Results

IMHA can be a mild to life threatening condition. The hematocrit may drop precipitously at any time because of active hemolysis. Although a regenerative, macrocytic-hypochromic anemia would be expected, as many as one third of all pets with IMHA have a nonregenerative anemia when first examined.[73,78,79] The disease course may have been peracute, not yet allowing time to mount a regenerative response. Alternatively, antibodies may be directed against erythroid precursors, thereby removing metarubricytes and reticulocytes, or the IMHA disease process may change the microenvironment of the bone marrow and thereby impair erythropoiesis. Evidence of ineffective erythropoiesis and erythrophagocytosis may be found on cytologic examination of a bone marrow aspirate.[80] Autoagglutination of erythrocytes and spherocytosis are typical findings on blood smears (Figures 270-7 to 270-9).

Besides erythroid abnormalities, a leukocytosis is often present and can exceed 100,000/μL, mostly because of a mature neutrophilia, but degenerative left shifts have also been observed. The degree of leukocytosis and toxic neutrophil changes has been correlated with the amount of necroses at necropsy.[81] Because high WBC counts are not generally encountered with other forms of anemia, this probably reflects a unique cytokine-mediated response to inflammation and necroses specific for IMHA, but concomitant infection and steroid-induced leukocytosis should also be considered. Thus concurrent hyperplasia of erythroid and myeloid cells may be present in the bone marrow. Furthermore, thrombocytopenia related to a concomitant ITP (Evans' syndrome) or other consumptive processes, such as with disseminated intravascular coagulation (DIC), may occur.[73] Dogs with IMHA often have coagulation test abnormalities with increased plasma fibrinogen and D dimer and FSP concentrations suggesting a DIC like syndrome.[82]

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Figure 270-7 Spherocytosis with polychromasia and anisocytosis.

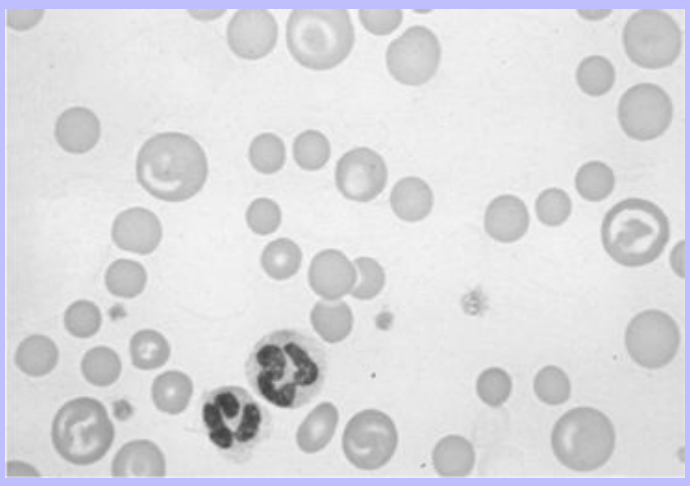
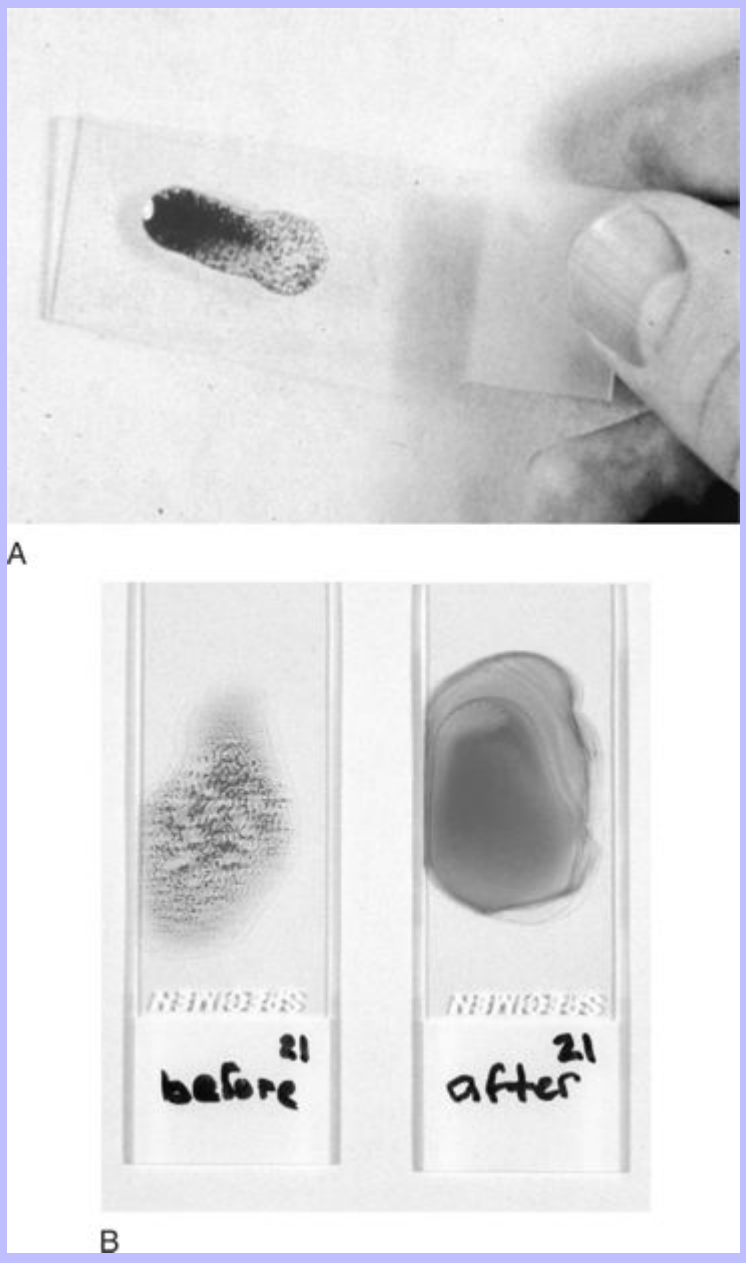


Figure 270-8 Macroscopic agglutination on slide **(A).** Agglutination of regular and washed blood. Reader should note macroscopic agglutination disappeared **(B)**.



Serum analysis may reveal a hyperbilirubinemia, and a serum bilirubin concentration above 10 mg/dL has been associated with a grave prognosis.[73] However, serum bilirubin values may be only slightly increased

in chronic cases, presumably because of highly efficient and accelerated bilirubin metabolism. Thus increased serum bilirubin concentrations could also indicate a concomitant hepatopathy. Dogs with IMHA often have increased serum liver enzyme activities even before steroid therapy. Pathologic examination has revealed major hepatic and other tissue necroses and inflammation in dogs with severe forms of IMHA.[81] The degree of hemoglobinemia (a sign of intravascular hemolysis) can vary drastically and rapidly and is associated with hemoglobinuria. Hyperbilirubinuria is expected as with any other hemolytic anemia; in cats, any degree of bilirubinuria is considered important, whereas larger amounts of bilirubin are generally present in urine of dogs with IMHA. There may also be evidence of a bacterial cystitis, which may indicate an underlying infectious disease or may occur secondarily because of immunoderegulation or immunosuppressive therapy.

Various imaging studies may be indicated to reveal underlying disease processes, such as neoplasia, and complications of IMHA. Evidence of thromboemboli may be detected on chest radiographs and abdominal ultrasonography, as well as at the site of catheters.[77,82]

270.3.5.5 Diagnostic Laboratory Test Results

A diagnosis of IMHA requires demonstration of accelerated immune destruction of erythrocytes. Thus besides documenting a hemolytic anemia, a search for antibodies or complement or both directed against erythrocytes is required; that is, one or more of the following three hallmarks has to be present to reach a definitive diagnosis of IMHA:

1. Marked spherocytosis
2. True autoagglutination
3. Positive direct Coombs' test

270.3.5.5.1 Spherocytosis

Spherocytes (Figure 270-3 and 270-7) are spherical erythrocytes that appear microcytic with no central pallor. They result from either partial phagocytosis or lysis. Such cells are rigid and extremely fragile in the erythrocyte osmotic fragility test. Because spherocytes have lost some membrane, they do not have any reserves to expand in hypotonic solution. Large numbers of spherocytes are highly suggestive of IMHA and are present in approximately two thirds of dogs with IMHA, but small numbers may be seen with hypophosphatemia, zinc intoxication, and microangiopathic hemolysis. Hereditary spherocytosis related to various membrane defects in humans has only been reported in one dog. In cats, spherocytes are difficult, if not impossible, to identify owing to the small size and lack of central pallor of normal feline erythrocytes.

270.3.5.5.2 Autoagglutination

Antierythrocytic IgM and, in large quantities, IgG antibodies may cause direct autoagglutination (Figure 270-8). Agglutination may be visible to the naked eye when blood (at low hematocrit) is in an EDTA tube or placed on a glass slide (macroscopic agglutination) (Figure 270-9), or it may become apparent as small clumps of erythrocytes on a stained blood smear or in a saline wet mount (microscopic agglutination). Autoagglutination has to be distinguished from rouleaux formation (Figure 270-9C), in which erythrocytes stack up on top of each other. For unexplained reasons, canine erythrocytes have a

tendency to agglutinate unspecifically in the presence of plasma, particularly at lower temperatures in EDTA. Mixing one drop of blood with one drop of saline may not break up this unspecific form of agglutination. It is therefore important to determine whether the agglutination persists after "saline washing," which has been termed *true autoagglutination*. This is accomplished by adding three times physiologic saline solution to blood (in a ratio of 3:1 to 5:1) after repeated centrifugation and removal of supernatant including the plasma. It should be noted that autoagglutination can interfere with the direct Coombs', crossmatch, and blood typing tests. Thus the simultaneous use of the so-called autocontrols is imperative.

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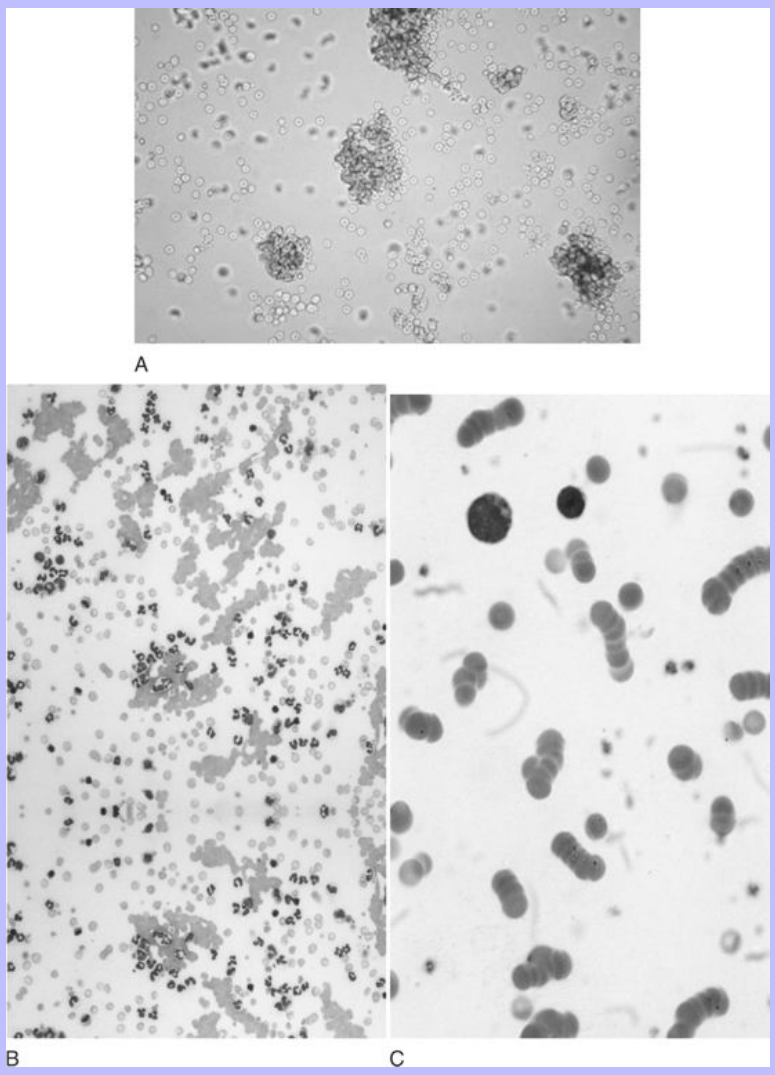
Figure 270-9 Microscopic agglutination wet mount **(A)** and Wright-Giemsa stain **(B)**. Reader should also note leukocytosis. Autoagglutination should not be confused with rouleaux formation **(C)**.



270.3.5.5.3

Direct Coombs test

The direct Coombs' test, also known as the *direct antiglobulin test (DAT)*, is used to detect antibodies, complement on a dog or cat's erythrocyte surface, or both, when the antierythrocyte antibody strength or concentration is too low (subagglutinating titer) to cause spontaneous autoagglutination.[83–85] The so-called incomplete antibodies on erythrocytes, together with species-specific antiglobulins against IgG, IgM, and C3b (Coombs' reagents), allow antibody bridging and thereby agglutination or lysis of coated erythrocytes (or both). Separate IgG, IgM, and C3b, as well as polyvalent Coombs' reagents, are available for dogs and cats. They are added at varied concentrations after washing the patient's erythrocytes free of plasma. The mixture is generally incubated at 37°C, then centrifuged, and supernatant and pellet are analyzed for hemolysis and agglutination, respectively. Performance of the direct Coombs' test at lower temperatures (4° and 20°C) is rarely indicated, because cold agglutinins and hemolysins are rarely strong enough and rarely active at near-normal body temperatures (30°C) to cause hemolysis. Cold agglutinins and hemolysins of clinical importance are generally IgM antibodies at high titer with a thermal amplitude that reaches 30°C. Because the same erythrocyte washing procedure is used in the direct Coombs' test as in the true autoagglutination test and the end point of the Coombs' reaction is agglutination and lysis of erythrocytes, true autoagglutination precludes the performance of a direct Coombs' test.

Positive direct Coombs' test results are reported as +1 to +4 or in the form of dilutions of the Coombs' reagent that cause in vitro agglutination, lysis, or both; the strength of the Coombs' reaction does not necessarily predict the severity of hemolysis seen clinically. Most dogs are IgG positive, some are IgG and IgM positive, and a few are only IgM positive.[86] To reach a definitive diagnosis of IMHA, the direct Coombs' test should be positive, but this does not discriminate between primary and secondary IMHA. Dogs with negative Coombs' test results should be re-evaluated for other causes of hemolytic anemia. However, a small proportion of dogs may have IMHA despite a negative Coombs' test result. False-negative Coombs' test results may occur because of insufficient quantities of bound antibodies on erythrocytes and for many technical reasons (inappropriate reagents or dilutions). Various techniques have been used to enhance the sensitivity of the direct Coombs' test, but none of them have gained wide acceptance in human and veterinary medicine. Furthermore, the test result may be negative in the absence of an inciting agent (e.g., drug). Negative results are also obtained for animals in which the disease is in remission; however, a few days of immunosuppressive therapy are not likely to reverse test results (i.e., in the presence of anemia and hemolysis the Coombs' test should be positive in a dog or cat with IMHA). Some treated animals have positive Coombs' test results long after the hemolytic anemia resolves. False-positive Coombs' test results occur only rarely, for example, early after an incompatible transfusion or because of technical problems. Furthermore, some animals may have a positive Coombs' test result without evidence of hemolysis and anemia; this has also been observed in healthy human blood donors.

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Little is known about the usefulness of the indirect Coombs' or antiglobin test in which the presence of antierythrocyte antibodies in the patient's serum is evaluated with random erythrocytes. Clearly, the indirect Coombs' test would remain negative if the antibody is directed against a cryptic or new (drug, parasite) antigen on the erythrocyte surface. Alternatively, a false-positive test result may occur in a dog that has previously been transfused and developed certain alloantibodies.

270.3.5.6 Therapy of Immune-Mediated Hemolytic Anemia

Because the severity of IMHA ranges from an indolent to a life-threatening disease, therapy has to be tailored for each pet and depends, in part, on whether the IMHA is primary or secondary. Removal of the triggering agent or treatment of the underlying condition can bring the IMHA under control. Thus if the IMHA is thought to be secondary to an infection, treatment with antiprotozoals, antirickettsials, or antibiotics should be instituted. Because of the potential for underlying occult infection and the predisposition to infection related to the immunoderegulation associated with IMHA and immunosuppressive therapy, antibiotic therapy is generally indicated. In addition, surgical correction of abscesses or other infections may be considered. Nonessential drugs, particularly those that might cause an immune reaction, should immediately be withdrawn. Despite these interventions, transfusion and immunosuppressive therapy are probably still required in the initial control of secondary IMHA.

Rehydration of the severely ill animal is pivotal to improve organ perfusion even when it lowers the hematocrit. If hypoxia due to severe anemia and a rapidly dropping hematocrit to critical levels ensues, packed RBC transfusions are beneficial. The increased oxygen-carrying capacity provided by transfused cells may be sufficient to maintain the animal for the few days required for other treatment modalities to become effective. The notion that transfusions are especially hazardous in animals with IMHA has been overemphasized and is not supported by retrospective studies in dogs and humans. Because the antierythrocytic antibody in IMHA is not an alloantibody, the destruction of transfused cells is no higher than that of autologous erythrocytes. However, autoagglutination may hamper accurate dog erythrocyte antigen (DEA) 1.1 blood typing and cross-matching tests even after RBC washing; hence, only DEA 1.1-negative blood should be transfused in autoagglutinating, untyped dogs. If compatible blood is not available, the ultrapurified bovine hemoglobin solution recently approved by the Food and Drug Administration can be administered and provides increased oxygen-carrying capacity and plasma expansion. In the original randomized study for Food and Drug Administration approval, this hemoglobin solution reduced the need for blood transfusions in the initial management of dogs with severe IMHA.[10] Some retrospective studies, however, suggested that this therapy was not beneficial if it was used as a last effort. With adequate transfusion support, animals with IMHA rarely die because of anemia, but they die because of overwhelming hemolysis and secondary complications such as thromboemboli and infections. Oxygen inhalation therapy is of little benefit unless the animal is suffering from pulmonary disease such as pulmonary thromboemboli.

The main goal in the treatment of IMHA is to control the immune response by reducing phagocytosis, complement activation, and antierythrocytic antibody production.[87] Glucocorticosteroids are the initial treatment of choice for IMHA. They interfere with both the expression and function of macrophage Fc receptors and thereby immediately impair the clearance of antibody-coated erythrocytes by the macrophage system. In addition, glucocorticosteroids may reduce the degree of antibody binding and complement activation on erythrocytes and, after weeks, diminish the production of autoantibodies. Oral prednisone or prednisolone at a dose of 0.5 to 1 mg/lb twice daily is the mainstay treatment. Alternatively, oral or parenteral dexamethasone at an equipotent dose of 0.3 mg/lb daily can be used but is probably not more beneficial. A response reflected by a stabilized or even rising hematocrit, appropriate reticulocytosis, and less autoagglutination and spherocytes can be expected within days. As glucocorticosteroid therapy is associated with well-known side effects, the initial dose is then tapered by reducing the amount by one quarter to one third every 7 to 14 days. Generally the faster the response to treatment the more rapidly the tapering is done. Within weeks to months, a low-dose alternate-day therapy may be reached with minimal steroid side effects. In secondary IMHA with appropriate control of the underlying disease, the tapering can

be accomplished more rapidly. Because of the potential for GI ulceration by steroids, treatment with sucralfate or other similar GI drugs may be considered, although none have been documented to be effective.

Despite apparent recovery as judged by reaching a normal hematocrit, animals, particularly those with primary IMHA, may continue to have a positive Coombs' test for weeks to months and could obviously have relapses. Such relapses may be controlled by the same treatment as initially used, but a more gradual tapering regimen may be used in which the animal receives prednisone (preferably every other day) or other immunosuppressive therapy for months.

Other immunosuppressive therapy is warranted when prednisone fails, controls the disease only at persistently high doses, or causes unacceptable side effects. Cytotoxic drugs are usually given with prednisone but may eventually be used independently. These cytotoxic drugs inhibit lymphocytes and thereby suppress the antierythrocyte antibody production only after weeks. They are therefore probably not effective in the acute management of IMHA but may have a place in the long-term control of refractory and relapsing cases. Cyclophosphamide, an alkylating and potent myelosuppressive agent, has been advocated in cases of fulminant IMHA. However, a randomized limited prospective clinical trial comparing prednisone with a combination of prednisone and cyclophosphamide did not find any beneficial effects of cyclophosphamide in the acute management of IMHA.[88] Retrospective studies with cyclophosphamide, azathioprine (an antimetabolite), or both were similarly disappointing, but overall assessment of these and other immunosuppressive agents is difficult based on retrospective and small case studies.[89–92] In addition to the strong myelosuppressive effects of these cytotoxic drugs, leading to reticulocytopenia, neutropenia, and thrombocytopenia, cyclophosphamide can induce a sterile hemorrhagic cystitis and secondary neoplasia. A potential regimen for the long-term management of dogs with IMHA might include azathioprine at 1 mg/lb once a day or every other day, but dogs need to be carefully monitored for cytopenias.[90] Hence, the risk/benefit ratio should be carefully considered when using these drugs.

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Several other immunosuppressive agents have been used on a limited basis in conjunction with prednisone, and anecdotal success has been reported in dogs and rarely in humans. Because some of these agents interfere with antibody action and macrophage function, they can elicit more immediate effects. Cyclosporine, an expensive but potent immunosuppressive agent most commonly used in preventing graft rejection and graft-versus-host disease in transplant patients, may be beneficial in controlling the immune response in dogs with IMHA. A dose regimen of 5 mg/lb once a day may be used initially, but blood concentrations should be monitored periodically to achieve an effective but safe level. Leflunomide and mycophenolate are in a class of agents similar to that of cyclosporine and have been used in a few cases with anecdotal success. Danazol, an androgen derivative, at a dose of 5 mg/lb once a day, may inhibit binding of antibodies and phagocytosis. However, a retrospective study in dogs with IMHA was disappointing; furthermore, danazol is expensive and may be hepatotoxic.[93] Intravenous human immunoglobulin (IVIG) may be helpful in the short-term treatment of dogs with IMHA, although its mode of action remains unresolved.[94–96] IVIG can block Fc receptors on macrophages (thereby reducing Fc-mediated phagocytosis of IgG-coated erythrocytes), interfere with complement action, and suppress antibody production. Human IVIG binds to canine lymphocytes and monocytes and inhibits erythrocyte phagocytosis.[96] A single IVIG dose of 0.25 to 1 g/lb has been beneficial in some refractory cases as indicated by a rising PCV and reticulocytosis within days, but the response has often been only temporary. More recently two 0.5 g/lb doses of IVIG 1 day apart has resulted in good responses. Anecdotally, plasmapheresis has also been used as an adjuvant therapy, but is currently not available for companion animals.[97]

Splenectomy may be considered in IMHA dogs and cats that do not respond to prednisone and other immunosuppressive therapy, that require long-term high-dose therapy to remain in remission, or that have intractable drug-induced side effects. The spleen is a major site of autoantibody production, as well as sequestration and destruction of erythrocytes coated with IgG, but probably does not directly affect the clearance of IgM-coated cells. In addition, histologic examination of the spleen may provide evidence of an underlying disease. The response to splenectomy has recently been described in a few dogs with IMHA, but an objective assessment based on a randomized trial has not been completed.[98] A risk exists of developing overwhelming infections after splenectomy. Splenectomy should not be considered in pets receiving immunosuppressive therapy aside from prednisone.

Thromboemboli and DIC-like syndromes are serious complications of IMHA that greatly contribute to morbidity and mortality. Although the pathogenesis remains unknown, venipuncture, catheters, and glucocorticosteroid therapy represent potential predisposing conditions. No study has documented any successful prevention or management protocol for these life-threatening problems, which represent rare complications in humans with IMHA. Predisposing factors should, whenever possible, be limited. Adequate perfusion and oxygenation of tissue should be provided with fluids and transfusions. Generally, anticoagulant therapy is instituted only after some evidence or suspicion of thromboembolism exists. Heparin at a dose of 5 to 250 IU/lb subcutaneously every 6 hours or by continuous infusion is the most commonly used drug, and other antithrombotic agents are being evaluated.[99] However, none of them have been documented to be effective and safe in dogs or other species in the control of thrombotic complications. Fresh frozen plasma (5 mL/lb every 12 hours) may be administered to replenish dangerously low plasma antithrombin III concentrations, but its efficacy has not been demonstrated.[100] Other complications may also be related to drug therapy.

Despite appropriate implementation of these therapeutic strategies, the mortality rate remains high. An impression exists that the fulminate form of IMHA is more frequently encountered today. Depending on the type of practice (primary to tertiary), mortality rates from 20% to 75% have been reported. Negative prognostic indicators are a rapid drop in PCV, highly increased serum bilirubin concentrations, nonregenerative anemia, intravascular hemolysis, persistent autoagglutination, and thromboembolic complications.[101]

270.3.6 Alloimmune Hemolytic Anemias—Neonatal Isoerythrolysis and Hemolytic Transfusion Reactions

Erythrocyte alloantibodies, also known as *isoantibodies*, are specific antibodies directed against erythrocyte antigens (blood types) from the same species but not from the individual producing the antibody.[2] Depending on the species and blood group system, these alloantibodies occur naturally (cats) or are produced only after sensitization with a mismatched blood transfusion (dog) and are responsible for NI (cats) and acute or delayed hemolytic transfusion reactions (dogs and cats). Additional information can be found in Chapter 127 on transfusion medicine.

In cats, only the AB blood group system has been recognized; it consists of three blood types: type A, type B, and type AB.[2] The inheritance pattern of these blood types is unique and of considerable importance to breeders. The A allele is dominant over the B allele. Thus only homozygous b/b cats express the type B antigen on their erythrocytes. Type A cats are either homozygous (a/a) or heterozygous (a/b).[102] The rare AB blood type, seen in certain families, is inherited separately as a third allele that is recessive to A and

codominant with B.[103] Simple in-practice blood typing cards are available, and other methods are being developed. Because a reaction in both test wells could be caused by autoagglutination, type AB test results should be confirmed after saline washing and in a reference laboratory using another method.[104] The prevalence of feline blood types varies geographically and among breeds.[102] Whereas purebred Siamese cats have all type A blood, Turkish Van and Angoras have equal numbers of type A and type B cats. All type B cats develop strong naturally occurring anti-A antibodies with high hemolysin and agglutinin titers (>1:32) after a few weeks of age, whereas type A cats generally develop only weak anti-B antibodies. Type AB cats have no alloantibodies. Thus acute life-threatening hemolytic transfusion reactions occur during the first mismatched transfusion (as little as 1 mL of blood), and NI is seen in type A and AB kittens born to primiparous type B queens.

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Feline NI is caused by maternal anti-A alloantibodies that gain access to the circulation and destroy type A and type AB erythrocytes.[2,105–107] Thus type A and type AB kittens from matings between a type B queen and a type A or AB tom are at risk. The proportion of kittens at risk for NI varies from zero to 25%, depending on the frequency of type B cats, and therefore represents a major and now preventable cause of the neonatal kitten complex in purebred cats.[102] The low-titer anti-B alloantibodies of type A queens have not been associated with NI. Cats (and dogs) have an endotheliochorial placenta that is impermeable to immunoglobulins from the mother's serum. However, feline colostrum and milk contains high maternal concentrations of immunoglobulins that pass the GI tract and are absorbed intact only during the first 16 hours of life.

Thus type A or type AB kittens produced by type B queens are born healthy. Upon ingestion of colostrum or milk containing anti-A antibodies, the kittens at risk can develop clinical signs during the first few days of life. They may die suddenly without obvious clinical signs during the first few hours of life. They can develop severe pigmenturia, which is readily visible when stimulating the neonates to urinate with a moist cotton ball. These kittens fail to thrive, are reluctant to nurse, become anemic and icteric, and rarely survive the first week of life. Some kittens at risk may have a subclinical course or slough their tail tip at 1 to 2 weeks of age, presumably because of an agglutinin-induced occlusion. The severity of clinical signs depends on the amount of colostral antibodies ingested before the kitten's ability to digest proteins and closure of the gut to the absorption of intact proteins, which varies from kitten to kitten, between queens and litters, and even within a litter. NI can be confirmed by typing the queen and kitten or the tom if the kitten died with suspicious signs.

Because of the acute disease course, treatment of NI is rarely successful. Foster nursing by a type A queen, who delivered recently, or with milk replacer, transfusion, and supportive care may be attempted. During the first day, when anti-A alloantibodies could still be absorbed, washed type B blood may be preferred, but thereafter type A blood is appropriate and may be best administered by the intraosseous route. However, NI can be readily prevented by (1) blood typing queen and tom and mating type B queens only to type B toms or (2) foster nursing type A and AB kittens born to type B queens for the first 24 hours. This can be accomplished by placing the kittens at risk with a type A queen (exchanged only if the type A queen's kittens are older than 1 day) or feeding a commercial milk replacer at least four times a day. Either all kittens of a litter at risk should be removed from the type B queen, or umbilical cord blood or blood from the jugular vein of the kittens (0.5 mL) can be typed with the typing card or cross-matched with anti-A plasma from the queen, thereby providing an opportunity to leave the type B kittens with the type B queen. Although maternal passive immunity does not appear to be essential in most cattery situations, 1 to 3 mL of serum from a type A cat (which lacks harmful anti-A antibodies) may be given orally during the first few hours of life or intraperitoneally or subcutaneously to kittens receiving a milk replacer.

More than a dozen blood group systems have been described in dogs and are referred to as *DEA* followed by a number.[2,104,108] For all blood groups other than the DEA 1 system, erythrocytes from a dog can be either positive or negative (e.g., DEA 4 positive or negative). The DEA 1 system, however, has at least two subtypes: DEA 1.1 (also known as A_1) and DEA 2 (A_2). Thus the dog's erythrocytes can be DEA 1.1 positive or negative, and DEA 1.1-negative erythrocytes can be DEA 1.2 positive or negative. The most antigenic and therefore most important blood type is DEA 1.1, for which simple blood typing cards are available. Typing of both blood recipient and donor for DEA 1.1 is recommended. An autoagglutination test card has been added, because autoagglutinating samples appear like DEA 1.1 positive.[104] True autoagglutination precludes typing. Typing for DEA 1.2, 3, 4, 5, and 7 is provided only by Midwestern Blood Services, but this extended blood typing has not be proven helpful in preventing blood type incompatibility reactions. In contrast to cats, dogs do not have clinically important naturally occurring alloantibodies but can develop them after mismatched transfusions, particularly anti-DEA 1.1 antibodies in DEA 1.1-negative dogs. Thus NI is not a clinical problem in dogs unless the bitch has previously received blood products. Similarly, acute hemolytic transfusion reactions are encountered only when a dog receives a blood transfusion 4 or more days after the first transfusion.[108–109] Careful history should indicate prior transfusions. These reactions can be prevented by cross-matching all dogs that have been previously transfused even when using the same donor. Furthermore, delayed hemolytic transfusion reactions characterized by a more rapid than anticipated drop of the hematocrit may be observed 1 to 2 weeks after a (first) transfusion because of the development of new antibodies. Because most reactions are directed against the DEA 1.1 antigen, DEA 1.1-negative (as well as untyped) dogs should never receive any blood products from DEA 1.1-positive donors. The only other acute hemolytic transfusion reactions were documented against a missing common antigen and DEA 4 in a DEA 4-negative dog, thus questioning the term *universal donor* for DEA 4-positive but otherwise negative dogs. However, a matched DEA 1.1 transfusion with crossmatching for a subsequent transfusion is practical and safe. Furthermore, some acute hemolytic reactions may be caused by use of expired, inappropriately stored, and contaminated blood. In case of acute hemolytic transfusion reactions, the transfusion should be stopped immediately and supportive therapy provided. Glucocorticosteroid administration has not been proven to be effective in preventing or treating hemolytic transfusion reactions.

270.3.7 Infection-Associated Hemolysis

Hemolytic anemia may develop after exposure to several parasitic, bacterial, and viral agents because of the direct action of the infectious agent or its products on erythrocytes. Few rickettsial and protozoal organisms are capable of infecting erythrocytes directly and causing severe hemolytic anemia (Table 270-2). Other infectious agents may induce a hemolytic component indirectly along with other major clinical signs. Thus any infection may trigger the production of humoral antibodies against host erythrocytes and together with an activated complement and phagocytic system, the rate of erythrocyte destruction may be markedly accelerated. Cats in particular have an inflammation-associated shortened survival of erythrocytes caused by an abscess, surgery, or trauma.[110] Furthermore, during bacterial (e.g., *Leptospira, Clostridium, Streptococcus, Staphylococcus*) septicemia, specific hemolysins can be produced. For instance, alpha toxin released during clostridial sepsis is a lecithinase that can attack erythrocyte membrane lipids, leading to erythrocyte fragmentation. Additional information on these infectious diseases can be found in Section VIII.

270.3.7.1 Hemobartonellosis

Hemobartonellosis in cats, also known as *feline infectious anemia*, is caused by an epicellular rickettsial organism of erythrocytes.[111,112] *H. felis* is classified in the family Anaplasmataceae, is distinctly different

from *Bartonella*, but is genetically similar to *Mycoplasma*. Hence *H. felis* has been renamed as *Mycoplasma haemofelis*, the large and more pathogenic form, and *M. haemominutum*, the small form. The natural transmission of these mycoplasmas still remains unclear, although bloodsucking ectoparasites are considered to be major vectors. Iatrogenic infection can occur via blood transfusion from carrier cats. In addition, they may be transmitted by oral ingestion of infected blood or from queens to their newborns. Finally, because cat bite abscesses often precede hemobartonellosis by a few weeks, particularly in male cats that roam outdoors, this may represent another form of transmission.

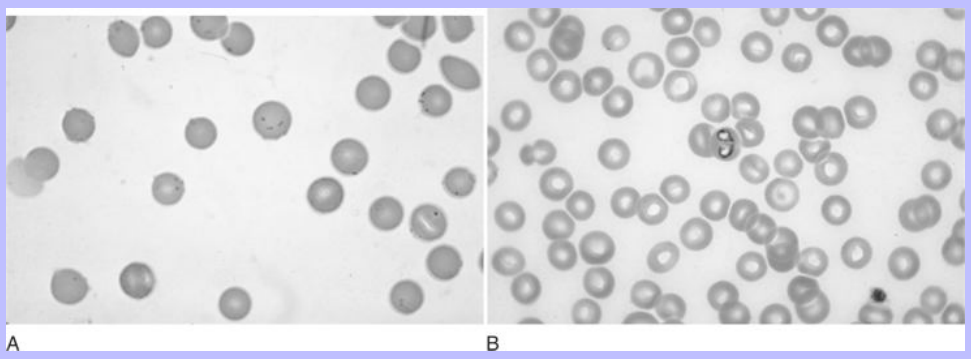
It is considered an opportunistic organism that causes illness only under predisposing conditions. Approximately half of the cats with hemobartonellosis were FeLV positive and infection with both agents exaggerates the severity of the anemia, whereas concurrent infection with feline immunodeficiency virus (FIV) does not appear to worsen the anemia. Although viral infections, abscesses, systemic illnesses, and trauma (including surgery) are apparent predisposing factors, such conditions are not always identifiable.[113,114]

The pathogenesis of hemobartonellosis can be divided into parasitic incubation, acute parasitemia, and recovery or carrier stage.[115] One week to months after infection, cats, when stressed, develop an acute parasitemic phase that results in mild to severe anemia. This stage is characterized by cyclic parasitemia and often lasts for weeks to months unless death caused by massive parasitemia and anemia ensues earlier. Parasitized erythrocytes lose their deformability and elicit an immune response and are therefore rapidly sequestered and phagocytized in spleen and other tissues. However, sequestered erythrocytes may shed the parasites and re-enter the blood circulation. Although cats may recover by mounting an immune response against the parasites, they cannot completely clear the infection and thus they remain carriers indefinitely by harboring organisms in macrophages.

Feline hemobartonellosis is associated with a gradual to precipitous drop in hematocrit that results in clinical signs of anemia. Cats are lethargic, weak, and inappetent, and cyclic fevers occur during the transient periods of parasitemia. Icterus is rare, but pale mucous membranes are common. Splenomegaly and weight loss may develop gradually.

No serologic tests are presently available, but PCR-based tests to detect the mycoplasma-DNA have greatly aided in the detection of these infections.[116] However, not every cat positive for *M. haemominutum* is anemic or experiences hemolysis. These organisms may be incidentally discovered in carrier cats with other diseases. A diagnosis of feline hemobartonellosis can also be made by recognizing the organisms on erythrocytes in a blood smear (Figure 270-10A). Blood needs to be collected before treatment and sometimes repeatedly. Blood smears should be prepared shortly after collection because organisms may detach. Any Romanowsky-type blood stain (e.g., Wright's-Giemsa, Diff-Quik) may be used. Organisms appear as blue-staining ring, rod, or coccoid forms on the surface of erythrocytes. They need to be differentiated from Howell-Jolly bodies, other parasites, basophilic stippling, and staining artifacts. New methylene blue and reticulocyte stains are inappropriate, because organisms may be confused with punctate reticulocytes and Heinz bodies; fluorescent stains provide no advantages. Parasitized erythrocytes become spherical. Erythrophagocytosis by monocytes and tissue macrophages (e.g., bone marrow, splenic aspirates), as well as autoagglutination of parasitized erythrocytes may be observed, and the direct Coombs' test at 37°C is often positive, supporting the major role of immune destruction. Because of the cyclic nature of the parasitemia, absence of organisms does not rule out an infection.

Figure 270-10 Hemobartonellosis in a cat **(A)** and babesiosis in a dog **(B)**.



Infected cats should be treated with tetracycline products for 3 weeks.[111] Doxycycline at a dose of 2.5 mg/lb twice a day is the preferred product because it needs to be administered only twice daily and appears to cause fewer side effects such as fever, anorexia, and hepatopathy. Enrofloxacin at a dose of 2.5 mg/lb once a day, orally, alone is a good alternative. Use of the two drugs in combination may be helpful in refractory cats. Parasitemia typically resolves quickly, and a clinical response is seen within days. None of the tetracyclines clear the infection completely; thus treated cats remain carriers, although relapses appear uncommon and have not been documented experimentally. Severely anemic cats may also benefit from blood transfusion from a blood type-compatible donor. Furthermore, because of the immune-mediated mechanism involved, treatment with prednisone at 0.5 to 1.0 mg/lb twice a day is indicated, particularly to inhibit the erythrophagocytosis.

In contrast to cats, dogs rarely have hemobartonellosis. It is caused by *Haemobartonella canis*, which can be transmitted by the brown dog tick (which also serves as a reservoir) and infected blood.[117] Unless dogs are splenectomized or have other serious illness and splenic dysfunction, infected dogs do not develop clinical signs of anemia. On stained blood smears *H. canis* differs from *H. felis* in that *H. canis* often forms chains across the surface of erythrocytes. Infected dogs with anemia are treated as described for cats and probably also remain latently infected.

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270.3.7.2 Cytauxzoonosis

Cytauxzoonosis has been sporadically reported in cats in south central and southeastern states of the United States and in Africa.[118,119] It is caused by *Cytauxzoon felis*, a piroplasm of the family Theileriidae. In *C. felis's* life cycle schizonts develop to merozoites in mononuclear phagocytes, whereas the erythrocytic piroplasms are the terminal chronically infected stage. Wildcats, particularly the bobcat *(Lynx rufus)*, appear to be the natural reservoir for *C. felis* in North America, and ticks probably serve as vectors. Thus cats with access to tick-infected wooded areas during the summer months are mostly at risk.

After an incubation period of days to weeks, the course of illness is rapidly progressive and leads to death in less than 1 week. Affected cats develop fever, anemia, icterus, pigmenturia, and dyspnea. The rapid multiplication of the protozoa in tissue and destruction of parasitized erythrocytes result in organ dysfunction, particularly of lungs, and hemolytic anemia, respectively, leading to hypoperfusion, hypoxia, and DIC. Only extremely rarely does a cat recover from the acute illness. A diagnosis is reached by

documenting the protozoa in erythrocytes on a Wright's-Giemsa-stained blood smear. They appear classically as signet ring–shaped blue forms, although other oval, tetrad, and dot forms may also be observed. Up to 5% of the erythrocytes may be parasitized, each with one piroplasm. Serologic and direct fluorescent antibody tissue tests have been developed but are not commercially available. Supportive fluid therapy and administration of the compound diminazene or imidocarb may be attempted, but cytauxzoonosis remains a disorder with a high degree of mortality.

270.3.7.3 Babesiosis

Whereas *Haemobartonella* and *Cytauxzoon* are important infectious agents in cats, babesiosis (see Chapter 168) is a major cause of acute hemolytic anemia in dogs.[120] *Babesia canis* and *B. gibsoni* are the only two hematozoan species that infect dogs, but strains of *B. canis* have been proposed on the basis of geographic range and pathogenesis. In the United States, canine babesiosis occurs most commonly in the southern states, but endemic areas have also been found farther north.[121–123] *B. gibsoni* has also been documented in California. Babesia infection is endemic in greyhounds and pit bulls. Puppies younger than 8 months of age and greyhounds appear to be more susceptible to *Babesia* infection; depending on the degree of tick control, few to all of the greyhounds in a kennel may be seropositive. Feline babesiosis has not been reported in the United States.

Ticks such as *Haemophilalis bispinosa* and *H. longicornus,* as well as *Rhipicephalus sangineus,* likely serve as major vectors, although transplacental transmission and transfer via blood transfusion have also been documented.[124] Ticks must feed a minimum of 2 days to pass sporozoites via saliva into the circulation of the host. *Babesia spp*. are engulfed by erythrocytes, in which they multiply into merozoites that infect other erythrocytes. A host immune response is elicited that may clear the infection. Most infected dogs in the United States do not become ill but remain carriers.

After a 10-to 12-day incubation period, infected dogs may develop severe hemolytic anemia, hypotensive shock, and a multiple organ dysfunction syndrome.[121–127] Although direct parasite damage contributes to the anemia, a oxidative damage and secondary IMHA appears more important. Autoagglutination and a positive direct Coombs' test result are commonly encountered.[128,129] Furthermore, infected dogs often have thrombocytopenia and leukocytosis. Besides the typical signs of anemia, fever, vomiting, lymphadenopathy, and splenomegaly may be noted. Although the hemolysis is mostly extravascular, signs of intravascular hemolysis may also be observed. The erythrocytic osmotic fragility is increased *in vitro*. Finally, a variety of other atypical signs, DIC, and death may occur because of multiple organ failure.

Babesiosis is diagnosed by DNA testing, blood smear examination, or immunodiagnostics (Figure 270-10B).[120] Single or pairs of large piriform organisms in erythrocytes are characteristic of *B. canis*, whereas singular intracellular organisms are probably *B. gibsoni*. Because only few erythrocytes are generally parasitized, examination of erythrocytes in or below the buffy coat or of blood collected from an ear prick may improve the chances of finding the organism. The indirect fluorescent antibody test and enzyme-linked immunosorbent assay (ELISA) are most helpful in the screening for babesiosis, although dogs seen early in the disease course are serologically negative, and a few dogs may even remain serologically negative. Because of some serologic cross-reactivity, *B. canis* and *B. gibsoni* may be differentiated only by DNA testing and examination of parasites. Finally, dogs infected with *B. gibsoni* may have false-seropositive reactions for *Toxoplasma, Neospora*, and *B. canis*.

Imidocarb dipropionate as a single intramuscular injection of 3.5 mg/lb clears *B. canis* and probably *B. gibsoni* infection.[120] In addition, it has prophylactic activity for 6 weeks, eliminates the infectivity of ticks for up to 4 weeks, and is effective against *Ehrlichia canis*, a common dual infection. The few side effects are thought to be related to the anticholinergic effects of the drug and include hypersalivation, GI signs, and dyspnea. In addition, supportive care to correct dehydration, anemia, and acidosis is important.[130] Treatment with immunosuppressive doses of prednisone is also indicated for 2 to 3 weeks to control the immune-mediated hemolytic component. Tick control is important in preventing spread in a kennel. A vaccine against *B. canis* is available in Europe.[131] All prospective blood donors should be tested for *Babesia* by serology and blood smear examination. Splenectomy of blood donors to increase the likelihood of finding parasites is not generally recommended.

270.3.8 Chemical-Induced Hemolytic Anemia

Many compounds including chemical agents, drugs, and food components and additives can induce oxidative damage to erythrocytes leading to a hemolytic anemia.[132] Many of these agents are derivatives of aromatic organic compounds (Box 270-2). In some cases the chemical itself acts as an oxidative agent, but more often the compound or its metabolite interacts with oxygen to form free radicals and peroxides (see Chapter 168). Extracellularly produced oxidants injure the membrane, whereas oxidants generated intracellularly attack hemoglobin and membrane structures. Thus a single agent may inflict erythrocyte injury (and thereby hemolysis) and reduced oxygen delivery to tissue by one or all three of the following mechanisms:

1. Oxidation of heme iron resulting in methemoglobin production
2. Oxidative denaturation of hemoglobin leading to Heinz body formation
3. Membrane damage causing impaired deformability and ion transport

270.3.9 Methemoglobinemia

Methemoglobin is the form of hemoglobin in which the heme iron has been oxidized from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state and is therefore unable to bind and transport oxygen.[3] Normally, approximately 3% of hemoglobin is daily oxidized by spontaneous oxidation of oxyhemoglobin to methemoglobin and oxidant generation in regular metabolic pathways. This is a reversible process, because methemoglobin is being continuously reduced by the reduced nicotinamide adenine dinucleotide (NADH) cytochrome-b_5 reductase enzyme in erythrocytes, thereby keeping the blood methemoglobin concentration below 1%. Methemoglobin can accumulate because of a hereditary deficiency of the cytochrome b_5 reductase enzyme, as described earlier in this chapter, or because of exposure to oxidative agents. Dogs and cats with a genetic predisposition to methemoglobinemia generally have relatively high hematocrits and are at extreme risk of developing a life-threatening methemoglobinemia-associated anemic crises.

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270.3.9.1 Box • 270-2 Oxidative Damage–Induced Hemolytic Anemia, Heinz Body Anemia, and Methemoglobinemia

270.3.9.1.1 Food Components

Onions

Garlic

Broccoli

Propylene glycol (semimoist food)

270.3.9.1.2 Drugs

Acetaminophen

Benzocaine (skin ointment, Cetacaine spray)

Phenazopyridine (urinary tract analgesic)

Methylene blue (old urinary antiseptic)

Phenacetin

Vitamin K_3

DL-methionine

270.3.9.1.3 Chemicals

Naphthalene

270.3.9.1.4 Heavy Metals

Zinc

Copper

270.3.9.1.5 Feline Disorders Associated with Heinz Body Formation

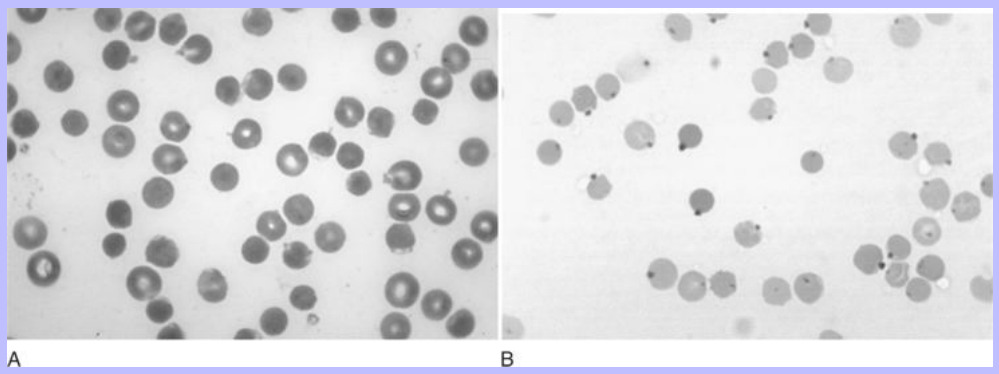
Diabetes mellitus ± ketoacidosis

Hepatic lipidosis

Hyperthyroidism

Lymphoma and other neoplasms

Figure 270-11 Heinz bodies and eccentrocytes on Wright's stain, canine **(A)**. Large Heinz bodies NMB stain feline **(B)**.



Although many compounds are capable of inducing methemoglobin formation, benzocaine-containing skin products and laryngeal or nasopharyngeal sprays, phenazopyridine (a urinary tract analgesic), and acetaminophen produce severe methemoglobinemia in cats within minutes to hours of exposure.

For several reasons, cats appear more susceptible to oxidative agents. Feline hemoglobin contains eight to 10 reactive sulfhydryl groups that are easy targets for oxidation, whereas other species' hemoglobins have a maximum of four sulfhydryl groups. Furthermore, the drug-metabolizing steps are restricted in cats. They cannot conjugate drugs with glucuronides and their sulfate conjugation and glutathione pathways are rapidly saturated and depleted. Thus instead of excreting acetaminophen as a glucuronide conjugate, cats produce reactive metabolites through mixed function oxidase activities that damage erythrocytes, leading to methemoglobinemia and Heinz body anemia.[133] As little as one small acetaminophen tablet (65 mg) may be lethal to a debilitated cat, whereas tenfold higher doses are required to induce toxicity characterized by hepatic failure in other species.

Although methemoglobin is quantified in EDTA-anticoagulated blood spectrophotometrically in commercial laboratories, simple spot tests can indicate the presence of clinically important methemoglobinemia. If a tube of blood or drop of blood on a filter paper remains brown after exposure to air (oxygen), whereas the control venous sample turns red, the patient's blood methemoglobin concentration exceeds 10% of the total hemoglobin. At this level the mucous membranes appear cyanotic, but serious clinical signs are not appreciated until the methemoglobin level reaches 40%. Exercise intolerance, lethargy, dyspnea, ataxia, and coma develop and death ensues when the methemoglobin concentration exceeds 60% to 70%. Besides the clinical signs related to hypoxia, cats intoxicated with acetaminophen may develop facial edema, vomiting, and hypersalivation.

270.3.9.2 Heinz Body Anemia

Heinz bodies represent irreversibly denatured and precipitated hemoglobin in erythrocytes. Eccentrocytes may be noted instead and are characterized by shifting of hemoglobin to one side of the cell, leaving a clear moon-shaped zone outlined by membrane (Figure 270-11).[134] The conformational changes of the globin chains caused by oxidation of the hemoglobin sulfhydryl groups and oxidative membrane damage result in binding and clustering of precipitated hemoglobin on the erythrocyte membrane. Heinz bodies containing

erythrocytes are rigid, have decreased deformability, and therefore may lyse or be removed from the circulation by macrophages. When passing through the spleen, Heinz body–containing erythrocytes are retained in the meshwork and phagocytized as a whole (culled), or only the Heinz bodies are removed (pitting). However, because of large openings in the venous sinus walls, the feline spleen has poor pitting function. Heinz body hemolytic anemia has been associated with a variety of conditions, many of which also cause methemoglobinemia and membrane injury. Ingestion of dietary onions (raw, cooked, or dehydrated [onion powder]), as well as garlic, usually fed by owners as part of table scraps, can result in up to 90% Heinz body formation within 1 day, followed by hemolysis leading to severe anemia by 5 days.[135–137] Several thiosulfates in onion extracts have been implicated in producing Heinz bodies but only minimal amounts of methemoglobin. Onion and garlic toxicity occurs more commonly in dogs than cats, and the susceptibility appears to vary among individual animals. Administration of various drugs, including methylene blue, DL-methionine, phenacetin, and vitamin K_3 (above 2.5 mg/lb/day) can also lead to Heinz body hemolytic anemia.

Acetaminophen, benzocaine-containing products, and phenazopyridine can induce severe methemoglobinemia and also cause Heinz body formation. Furthermore, increased numbers of Heinz bodies have been associated with various organ disorders in cats. These disorders include hyperthyroidism, lymphoma, other cancers, and diabetes mellitus, particularly in the presence of ketoacidosis.[138]

270.3.9.3 Membrane Injury

Many oxidative agents directly cause membrane lipid peroxidation, cross-linking and clustering of cytoskeleton proteins, and impaired ion transport function. These membrane injuries result in severe intra-and extravascular hemolysis, sometimes without much Heinz body and methemoglobin formation. For instance, naphthalene, the active ingredient in old-fashioned mothballs or crystals and in toilet bowl deodorizers, is an important poison in small animals, causing intravascular hemolysis, vomiting, seizures, and hepatopathy.[139] Hemolytic anemia has also been associated with acute zinc toxicity in dogs that swallowed zinc-containing objects such as zinc nuts and bolts from animal carriers, U.S. pennies minted since 1983 (98% zinc by weight), and zinc oxide dermatologic ointments (Fig. 270-12).[140,142] Because these objects may be retained in the stomach, the gastric acid liberates zinc, which allows absorption. The mechanism by which zinc causes life-threatening intravascular hemolysis remains uncertain, but few Heinz bodies and spherocytes have been found. Besides identifying the metal object by radiographs, the diagnosis can be confirmed by documenting increased serum zinc concentrations (above 5 parts per million; samples must be submitted in plastic tubes for analysis). Similarly, acute copper toxicosis may result in severe intravascular hemolysis and some methemoglobinemia. It has been associated with fulminant hepatic failure caused by copper storage in Bedlington terriers (see Chapter 227). In contrast, lead toxicity is generally not associated with hemolysis, but large numbers of nucleated RBCs and GI and neurologic signs are observed.

Figure 270-12 Zinc-containing coins eroded in stomach of a dog with hemolytic anemia.

Treatment of oxidative hemolytic anemias includes immediate removal of the oxidative agent, use of antioxidants, transfusion, and supportive care. Vomiting is induced only if the substance has just been ingested and activated charcoal may be administered. Metallic objects such as pennies and nuts are best removed by gastroscopy or gastrotomy. In case of severe anemia, methemoglobinemia, or both, transfusion with packed RBCs is indicated, whereas oxygen therapy hardly improves tissue oxygenation. The anemia nadir is often not reached for several days, but with the commonly observed strong regenerative response, recovery from anemia is swift. Severe methemoglobinemia can be corrected with one slow intravenous injection of methylene blue (0.4 mg/lb). Methylene blue acts as an electron donor for an alternative, otherwise nonfunctional methemoglobin reductase. In cats with acetaminophen intoxication, either oral or intravenous *N*-acetylcysteine (Mucomyst) at an initial dose of 64 mg/lb followed by seven treatments of 32 mg/lb every 8 hours should be administered. As the drug of choice, *N*-acetylcysteine, increases the sulfate availability for conjugation of acetaminophen and provides cysteine for glutathione regeneration and metabolism of toxic metabolites of acetaminophen. Treatments with other agents such as sodium sulfate to add sulfide, cimetidine to inhibit cytochrome P-450, and ascorbic acid as weak antioxidants have been proposed, but they have not been shown to provide additional benefit. Because of the effect of oxidative substances on other organ systems including GI tract, liver, and central nervous system (CNS), animals may continue to show clinical signs after correction of the anemia and methemoglobinemia and require additional supportive care. Furthermore, care should be taken to avoid any re-exposure to these and other toxins.

270.3.9.4 Hypophosphatemia-Induced Hemolysis

Severe hypophosphatemia causing hemolysis in dogs and cats has been associated with diabetes mellitus, hepatic lipidosis, enteral and parenteral hyperalimentation (starvation-refeeding syndrome), and oral administration of phosphate-binding antacids.[143–145] During insulin, fluid, and bicarbonate treatment of (ketoacidotic) diabetic animals, serum phosphate concentrations may decrease precipitously. Hypophosphatemia occurs because of intracellular phosphate shifts, enhanced renal loss, and reduced

intestinal absorption of phosphate. In addition to myopathy, cardiac dysfunction, neurologic dysfunction, and acute hemolytic anemia (characterized by a rapid drop in PCV and mild intravascular lysis and Heinz body formation) may be observed in animals with hypophosphatemia. Based on experimental data, serum phosphorus concentrations would need to be less than 1 mg/dL (normal 2.9 to 7 mg/dL) to cause hemolysis, but in clinical practice hemolysis occurs with phosphate values less than 2.5 mg/dL. Serum phosphate measurements may underestimate the phosphate depletion in these disease states and can erroneously be higher because of hemoglobinemia and hyperbilirubinemia. The pathogenesis of the hypophosphatemia-induced anemia is probably related to depletion of erythrocytic ATP, DPG (in dogs), and reduced glutathione, which leads to decreased deformability, increased osmotic fragility, and susceptibility to oxidative injury. As discussed in relation to canine erythrocyte PFK deficiency, DPG-depleted erythrocytes are extremely alkaline fragile and have a high hemoglobin oxygen affinity, thereby contributing to intravascular hemolysis and tissue hypoxia in dogs but not in cats. Furthermore, thrombocytopenia and platelet and leukocyte dysfunction have been documented experimentally in dogs.

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Hypophosphatemic animals need to receive oral or parenteral phosphate supplementation. Aggressive intravenous phosphate therapy is often needed in severely hypophosphatemic and anorexic or vomiting animals. An initial sodium or potassium phosphate dose of 0.005 to 0.015 mmol/lb/hr (maximum, 0.03) appears safe and effective, but serum phosphorus and calcium concentrations should be measured every 6 hours and the dose adjusted and route switched to oral when appropriate. Potential complications of intravenous phosphate supplementation include hypocalcemia, acute renal failure, and dystrophic soft tissue calcification and should be immediately corrected by stopping the phosphate infusion and initiating infusion of a calcium gluconate. Oral supplementation with a normal balanced diet, skim milk, or commercial phosphate products is preferred in cases of mild hypophosphatemia, and prophylactic phosphorus supplementation should always be considered when treating severe diabetes mellitus or hepatic lipidosis. This can be easily accomplished by supplementing potassium using both chloride and phosphate solutions.

270.3.10 Microangiopathic Hemolytic Anemia

A large variety of conditions may cause physical damage to erythrocytes that leads to cell fragmentation and intra-and extravascular hemolysis.[146] In case of water intoxication associated with near drowning in fresh water, erythrocytes undergo hypotonic lysis similar to the swelling and lysis of erythrocytes in the *in vitro* osmotic fragility test. Heat stroke and severe burns can inflict thermal injury to erythrocytes. Heart valve disease, cardiovascular implants, and intravenous catheters can induce mechanical damage to erythrocytes as much as dirofilariasis, particularly in the form of the caval syndrome (see Chapter 206). In addition, other endothelial damage caused by vasculitis, hemangiosarcoma and other tumors, various splenic diseases or torsion, and liver disease can injure erythrocytes (Figure 270-13). A hemolytic-uremic syndrome characterized by acute renal failure, platelet activation leading to thrombocytopenia and thrombosis, and microangiopathic hemolytic anemia has been described in dogs. Similarly, DIC is associated with a fragmentation hemolysis (see Chapter 274).

Figure 270-13 Acanthocytes dog with liver disease.

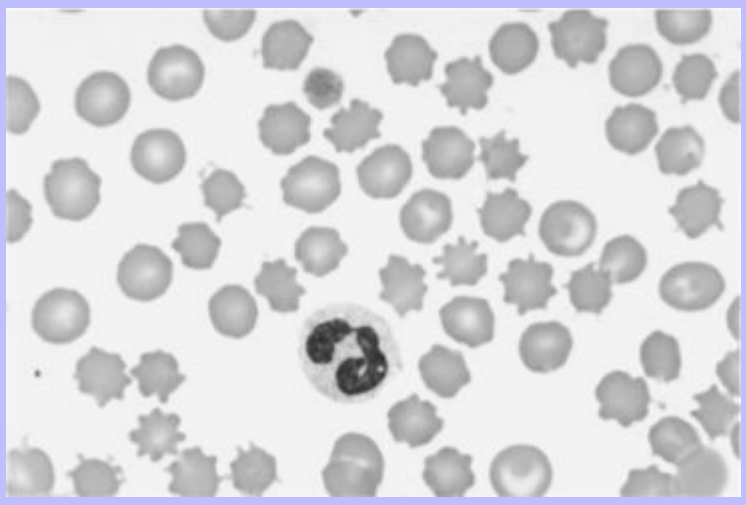
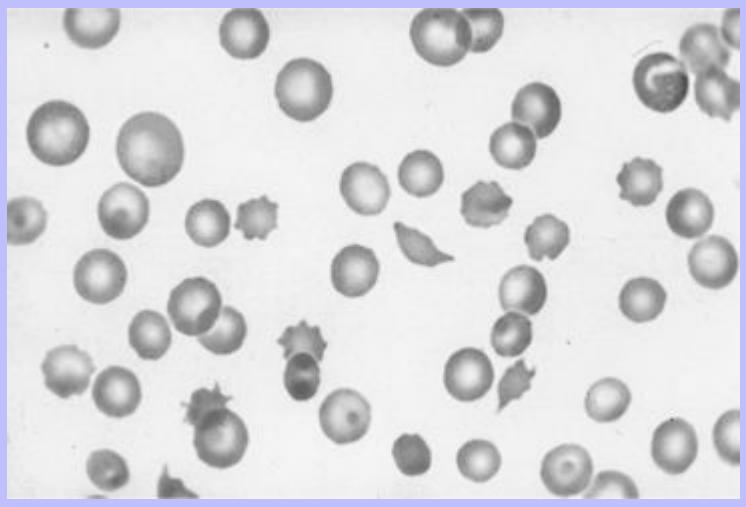


Figure 270-14 Schistocytes, canine.



A diagnosis of microangiopathic hemolysis that is often subclinical and rarely causes overt intravascular hemolytic anemia is made by identifying the triggering condition and characterizing schistocytes (schizocytes) (Figure 270-14). These are erythrocyte fragments that appear on blood smears as small, misshapen, often triangular or helmet-shaped structures. Schistocytes are important even in small numbers and can unlikely be fabricated by poor blood smear preparation. On the other hand, schistocytes are observed with a variety of other anemias including chronic iron deficiency states and zinc intoxication. Concomitantly, thrombocytopenia and coagulopathy are often present. Besides supportive care, therapy is directed at the underlying disease and control of DIC. Blood component therapy should be considered. The prognosis is guarded to poor if the underlying disease cannot be corrected.

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271 CHAPTER • 271 Nonregenerative Anemia

Bernard F. Feldman[†]

Anemia is a common clinical and laboratory finding that in and of itself does not constitute a diagnosis. In other words, anemia is a sign of disease, not a disease per se. The mere coexistence of anemia with another illness does not necessarily pinpoint the etiology. The clinical goal is to determine the pathogenesis in order to deliver the most appropriate therapy and to instigate steps to ameliorate this condition. The cause of anemia may be evident from the signalment, history, vaccination status, travel history, life style, duration of signs, drug or toxin exposure, prior or current illnesses, illnesses in housemates or relatives, or physical examination (Box 271-1). When a dog or cat is actively bleeding, the presence of anemia can be anticipated. If the bleeding is chronic, iron deficiency can be anticipated. Signs of inflammation or systemic illness can explain moderate anemia.[1–5]

271.1 IS THE ANEMIA NONREGENERATIVE OR REGENERATIVE?

There are seven general causes of anemia. Five of these remain nonregenerative unless the underlying etiology is successfully ameliorated. Two causes, hemolysis and hemorrhage, are nonregenerative in the acute stages but most often become regenerative 3 to 7 days after the onset of the problem. The seven general causes are:

1. Lack of iron
2. Anemia associated with inflammatory disease
3. Bone marrow disorders
4. Erythropoietin-related anemias
5. Maturation abnormalities (rarely encountered)
6. Hemolysis
7. Hemorrhage

The initial approach to treatment of the anemic pet is an attempt to discern whether the anemia is nonregenerative or regenerative. This determination is critical, because a dog or cat with regenerative change has either a hemolytic or hemorrhagic process and requires specific additional diagnostics and forms of therapy. Beyond the minimum database of a complete hemogram, urinalysis, and biochemical profile, diagnostics and therapeutics often are significantly different for the numerous nonregenerative anemias.

The decision as to whether the animal is responding appropriately to anemia treatment requires examination of reticulocyte numbers (from a vital stain) or polychromatophil numbers (from a Romanovsky-based stain). The reticulocyte count is the only index of *effective* erythropoiesis. Proper use of this value requires (1) conversion to an absolute quantity, (2) adjustment for the reduced red cell mass, and (3) correction for the effect of erythropoietin on marrow reticulocyte release. These adjustments result in the determination of reticulocyte numbers adjusted for the pet's red cell mass.[6]

The first step is to convert the reticulocyte percentage into an absolute quantity of reticulocytes. In a canine example, if the mean red cell count is 7 million and 1% reticulocytes is the mean number for that red cell mass,

1% reticulocytes in absolute terms is 70,000 reticulocytes. The reference interval for a normal adult dog is approximately 35,000 to 105,000 reticulocytes per microliter (0.5% to 1.5% reticulocytes).

The second step is to correct for the reduced red cell mass using red cell numbers *or* the hemoglobin *or* the hematocrit. Using the hematocrit as an example, the absolute reticulocyte number is multiplied by the dog's hematocrit, and the product is divided by the mean species hematocrit.

The third step is to correct for the effect of erythropoietin (EPO) on bone marrow reticulocyte release; EPO is inversely correlated with the red cell count (or hemoglobin or hematocrit). Continuing with the hematocrit example, the lower the hematocrit, the higher the concentration of EPO (with some exceptions, such as renal failure). EPO has four clinically significant effects: (1) it causes uncommitted stem cells to differentiate to the erythroid line; (2) it decreases the bone marrow maturation time for red cell development; (3) it increases individual red cell hemoglobin synthesis; and (4) it causes premature release of reticulocytes from bone marrow to blood.

The approximate average time for reticulocytes to mature in the dog or cat is 4.5 days: 3.5 days in the marrow and 1 day (24 hours) in peripheral blood if the hematocrit is appropriate (Table 271-1).

To correct for the effect of EPO on bone marrow reticulocyte release, the examiner converts the reticulocyte percentage to absolute values and adjusts for the reduced hematocrit, then divides the final figure by the number of days the average reticulocyte lives as a reticulocyte in peripheral blood based on the dog's or cat's hematocrit (see Table 271-1). Determine red cell production over basal or anticipated numbers (basal numbers are anticipated to be 35,000 to 105,000 absolute reticulocytes per microliter in a normal adult dog with a reticulocyte reference interval of 0.5% to 1.5%).

If a dog's hematocrit is 23% (mean canine normal is 46%) and its reticulocyte percentage is 5%, the question is, is there an appropriate response to the reduced hematocrit? To determine the corrected absolute reticulocyte count in this dog, the following calculations are made:

1. If the reticulocyte count is 5% of a red cell count of 3.5 million/mL (the approximate number of red cells per microliter with a hematocrit of 23%), the absolute reticulocyte number is approximately 175,000/mL. Thus:

$$175{,}000 \times 23\% \text{ (Dog's hematocrit)} \div 46\% \text{ (Mean canine hematocrit)} = 87{,}500/\text{mL}$$

2. The number of reticulocytes per milliliter (87,500) is divided by 2 (the average length of time [2 days] a reticulocyte circulates in peripheral blood at a hematocrit of 23%) to determine the corrected absolute reticulocyte number:

$$87{,}500 \div 2 = 43{,}750/\text{mL}$$

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The corrected absolute reticulocyte value in this example (43,750/mL) is well within the reference interval observed for dogs with appropriate hematocrits. In fact, in this example, even without correction for the effect of EPO (without correction, the reticulocyte count would have been 87,500/mL), this anemia must be considered nonregenerative. A corrected absolute reticulocyte count of less than 105,000/mL must be considered nonregenerative. Patients with hemolysis and hemorrhage that are responding appropriately often have adjusted absolute reticulocyte counts in excess of 150,000/mL.

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271.1.1 Box • 271-1 History and Physical Examination Considerations with an Anemic Patient

271.1.1.1 History

Previous laboratory tests for comparison

Duration of signs—recent or long standing

Family history?

Previous surgery—problems?

Drugs—especially consider nonsteroidal anti-inflammatory drugs

Exposure to toxic chemicals resulting in hemolysis or aplasia

Abdominal signs—hepatosplenomegaly, gastrointestinal blood loss or neoplasia, malabsorption

Urinary signs—polyuria, polydipsia, hematuria

Blood loss—gastrointestinal or urinary tract

Miscellaneous—dietary history; neurologic signs; nonspecific discomfort

271.1.1.2 Physical Examination

Skin and mucous membranes—pallor, jaundice, petechiae, purpura, bruising

Cardiovascular—evidence of pulse abnormalities, murmurs

Pulmonary—evidence of dyspnea

Lymph nodes—enlarged?

Abdomen—hepatosplenomegaly, ascites, masses

Rectal examination—gastrointestinal blood loss, melena, masses

Table • 271-1 Average Time Required for Reticulocyte Maturation

HEMATOCRIT	DEVELOPMENT IN MARROW (days)	DEVELOPMENT IN PERIPHERAL BLOOD (days)
Dogs		
45	3.5	1.0
35	3.0	1.5
25	2.5	2.0
15	1.5	2.5
Aggregate Reticulocytes in the Cat		
32	3.5	1.0
24	3.0	1.5
16	2.5	2.0
10	1.5	2.5

† Deceased.

271.2 CLINICAL MANIFESTATIONS OF ANEMIA

The clinical manifestations of anemia are also common manifestations of processes or diseases that primarily affect other organ systems. Weakness, fatigue, and pallor are often manifestations of anemia of recent onset, such as that caused by recent blood loss or acute hemolysis. Anemia that develops gradually, particularly in inactive cats or dogs, may cause only fatigue or may go unnoticed. Pallor of the conjunctiva or mucous membranes may be caused by both anemia and hypovolemia. Icterus may obscure pallor. Pain may also result from increased bone marrow activity; this may simply be manifested by fatigue, unwillingness to move or, in stoic small animals, concern with movement or difficulty walking. Lymphadenopathy and splenomegaly are common with infectious, inflammatory, and hematologic diseases, particularly lymphomas and the leukemias. Bleeding occurs as a consequence of vascular, platelet, or coagulation factor abnormalities. Thrombosis can be either venous or arterial and often results in significant thrombocytopenia. Venous thrombosis is often caused by blood flow or obstructive processes or by imbalances in coagulation factors. Immune-mediated hemolytic anemia can be an example of such a process. Arterial thrombosis is most often caused by vascular problems, including vascular trauma thrombocytopenia, thrombocytosis or thrombocytopathia, and processes associated with infection or neoplasia.[4]

271.3 LABORATORY EVALUATION

Laboratory assistance usually is required to determine the cause of anemia. The routine but complete hemogram and blood smear document the presence, severity, and morphologic nature of the anemia (Box 271-2). A complete evaluation includes study of marrow production and red blood cell destruction and is usually required for accurate classification of the anemia into one of the two major categories, regenerative (responsive) or nonregenerative (nonresponsive). In the absence of specific clues, anemia initially may be broadly classified as regenerative or nonregenerative on the basis of reticulocyte (or polychromatophil) numbers (Box 271-3).

Most anemias are nonregenerative (Box 271-3). This type of anemia may be due to (1) an abnormality of the stem cell population and bone marrow environment, (2) an abnormality in the early modulators of stem cell activity, or (3) a deficiency in the late-stage regulators of erythroid proliferation, including EPO, cytokines, and iron.[5]

Disorders of marrow stroma and stem cells are relatively uncommon, but when they do occur, they often result in severe anemia and may represent myelodysplastic syndromes, including those variously lumped together as the "preleukemic syndromes." Nonregenerative anemia associated with iron depletion caused by inflammation is the most common mild anemia in dogs and cats. Anemias that occur secondary to a decrease in EPO are also often mild, at least in the early stages of the process, because the anemia reflects a physiologic readjustment of red cell production to fit reduced metabolic need. This can even be true in early renal disease. Red blood cell morphology and production indices (reticulocyte numbers and the mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration) may be similar for the various types of nonregenerative anemia. However, findings on marrow morphology (and perhaps iron studies) usually allow categorization of the specific abnormality as one of the three types listed previously.[6]

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271.3.1

Box • 271-2 Elements of a Complete Hemogram

Red blood cell count

Hemoglobin

Hematocrit (packed cell volume [PCV])

Mean cell hemoglobin (MCH)

Mean cell volume (MCV)

Mean cell hemoglobin concentration (MCHC)

Reticulocyte count

Numbers and *type* of nucleated red blood cells

Red cell morphology

Red cell distribution width (RDW)

Total plasma protein

Fibrinogen

Platelet count

- Mean platelet volume (MPV)
- Platelet distribution width (PDW)
- Platelet morphology
- White blood cell count
- White blood cell differential
  - Neutrophils
  - Immature neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
  - Nonclassifiable cells
  - Damaged cells
- Leukocyte scattergram/histogram
- Leukocyte morphology

271.4 HYPOPROLIFERATIVE ANEMIA

271.4.1 Erythropoietin-Related Causes

271.4.1.1 Renal Insufficiency

Renal insufficiency, especially chronic and severe renal disease, invariably affects the hemopoietic system adversely. To provide effective treatment, the clinician must have a clear understanding of the factors that induce anemia and intensify the failure of erythropoiesis. The bone marrow provides important clues to the pathogenesis of the anemia of renal failure. Given the variety of possible complicating factors, it is not surprising that a wide spectrum of abnormalities have been reported. Marrow cellularity has been reported to be normal, decreased, and increased. However, most dogs and cats with uncomplicated anemia secondary to renal insufficiency have appropriate marrow cellularity, with appropriate myeloid to erythroid ratios and appropriate erythroid development, despite the severe anemia. The argument may be made that an appropriate myeloid to erythroid ratio may not in fact be appropriate in the anemia of renal insufficiency. Iron distribution tends to be normal unless some element of anemia of inflammation is present, in which case iron may be redistributed to the monocyte-macrophage cells. Ferrokinetics are nearly normal in most small animals with anemia of renal disease. When these individuals are stressed by hypoxia or worsening anemia as a result of hemorrhage, the bone marrow erythron is able to respond in the appropriate direction but does so with a suboptimal recovery phase.[7]

From examination of the marrow alone it can be determined that (1) the defect in anemia of renal disease is not primarily related to defects in iron, which distinguishes this disorder from anemia of inflammation, and (2) the primary defect is not the result of an absolute absence of EPO. If it were, the myeloid to erythroid ratio would show a marked increase, approaching infinity, as the effect of EPO on the erythroid marrow decreases.

Two primary mechanisms have been advanced to explain most cases of normocytic, normochromic anemia with normal iron distribution and normal absolute reticulocyte counts associated with renal insufficiency. One mechanism is a deficiency of EPO, which causes the anemia. The other mechanism is an accumulation of toxins that suppress hemopoiesis. The latter mechanism probably accounts for much of the anemia, especially in dogs. Of course, if underlying inflammatory renal disease is present, anemia of inflammation may be a component.

EPO is a vital hemopoietic growth factor that not only enhances red cell production but also has been shown to increase platelet counts in rats and humans with end-stage renal failure.[8] EPO plays an important role in the pathogenesis of anemia in the dog and to a lesser degree in the cat. A significant increase in the plasma EPO concentration was observed in 22 cats and 32 dogs with anemia without renal insufficiency or chronic renal failure; however, 37 dogs and 35 cats with chronic renal failure had a normal or only modestly reduced EPO concentration. Cats showed almost no overlap between the groups, whereas dogs showed significant overlap.[9] This suggests that measurement of the plasma EPO concentration is more useful for characterization of anemia in cats than in dogs, either with or without chronic renal disease.[10] It also suggests that successful use of EPO may be a target molecule and/or a threshold response, perhaps to “kick start” erythropoiesis. The effects of EPO in these circumstances occur only with even more EPO, an argument for using exogenous EPO clinically.

As a general rule, the use of commercially available human recombinant growth factors for several consecutive weeks in dogs and cats results in the development of antibodies. Fortunately, it appears that short-term use of these products (less than several weeks) does not result in significant antibody effect.[11] The use of any human recombinant hemopoietic growth factor, including EPO, is strictly extralabel, because these products are not approved for use in the dog or cat. Only dogs and cats that have clinical signs related to anemia and that are profoundly affected (i.e., a hematocrit below 25% in the dog and 20% in the cat) should be considered for EPO therapy because of the potential for the development of antibodies.[9] Animals that are hypotensive or that have iron deficiency should not be treated until these problems have been corrected. The blood pressure and the serum iron concentration should be checked before and during EPO therapy.

The current recommended dosage of recombinant human EPO is 100 U per kilogram of body weight given subcutaneously three times weekly. Once the target hematocrit has been reached, the frequency should be reduced to twice weekly. The lowest possible maintenance dosage should be used. It is also recommended that iron be given to any dog or cat undergoing EPO therapy. If refractory anemia is noted despite therapy, EPO administration should be suspended and the pet evaluated further, at least with a complete hemogram and bone marrow examination. If erythrocytic hypoplasia exists, the development of antibodies may be the cause, and the pet must be supported with blood products and other adjunctive therapies.[11]

Older studies have provided convincing evidence that implicates uremic toxins (as yet many are implicated but none specified) in the genesis of anemia of renal insufficiency.[12] These investigators reasoned that because several studies in humans with anemia of renal insufficiency had indicated that the plasma EPO concentrations were within the reference interval or modestly above or below it, all are inappropriate for the degree of anemia. However, it seemed unlikely that anemia of renal insufficiency could be explained *in toto* by EPO deficiency, therefore it must be due to retention of some materials that inhibit EPO or its effects. When continuous peritoneal dialysis was used in human patients with end-stage renal disease, half the patients showed full correction of the anemia. The researchers concluded that anemia of renal insufficiency can be corrected by dialysis alone in patients in whom sufficient renal endocrine function remains to mount a modest EPO response. Another conclusion was that, because EPO plays a pivotal role in erythropoiesis, if the endocrine function of the kidney has been destroyed by the same disease that impairs excretory function, the clearance of uremic toxins by dialysis will not reverse the suppression of the erythron.[12,13]

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271.4.1.1.1

Box • 271-3 Full Functional Classification of Anemia

Nonregenerative

Hypoproliferative anemia

Erythropoietin-related condition

Renal disease

Hypothyroidism

- Hypoadrenocorticism
- Panhypopituitarism
- Decreased growth hormone
- Reduced oxygen requirements
- Increased oxygen release

Lack of iron

- Inflammation
- Chronic bleeding
- Iron deficiency

Marrow disorders

- External toxin—aplasia
- Myelophthistic disease
- Myelofibrosis
- Myelodyplasia
- Intrinsic marrow disease
- Hyperestrogenism—iatrogenic, neoplastic
- Infection
- Immunotherapy

- Pure red cell aplasia
- Ineffective erythropoiesis
  - Macrocytic (unusual)
    - Intrinsic marrow disease
    - Vitamin B_{12} deficiency
    - Folate deficiency
  - Normocytic
    - Stromal disease (myelofibrosis)
    - Intrinsic erythroid disease
  - Microcytic
    - Nonsideroblastic—iron deficiency
    - Sideroblastic—globin or porphyrin abnormality
  - Time related
    - Hemolysis—during the first 3 to 5 days at least
    - Hemorrhage—during the first 3 to 5 days at least
- Regenerative
  - Hemorrhage
    - Hemostatic disorders

- Coagulation disorders
- Platelet disorders—both quantitative and qualitative
- Vascular disorders
- Neoplastic disease
- Splenic disease or trauma
- Trauma or surgery

Hemolysis

- Excessive phagocytosis by the mononuclear phagocytic system
  - Immune mediated
  - Heinz body anemias
  - Membrane (adenosine triphosphate) disorders
- Fragmentation
  - Intravascular coagulation
  - Vasculitis
  - Intravascular hemolysis
  - Immune mediated, including complement mediated
  - Exotoxin induced
  - Intrinsic intraerthrocytic enzyme deficiency

Drugs

Water

Heat

Modified from Hillman RS, Finch CA: Red Cell Manual, 5th ed. Philadelphia, FA Davis, 1985, p 56.

Certainly other factors, if investigated, can help the clinician define etiologies and develop appropriate therapeutic strategies. These factors, which have been suggested to contribute to anemia of renal insufficiency, include reduced half-life of red cells due to uremic toxins, hemorrhagic loss from gastrointestinal ulcers, increased hemorrhagic tendency due to reduced platelet function, suppression of erythropoiesis by high concentrations of parathyroid hormone, reduced nutrient intake due to inappetence, and injury of red cells due to glomerular pathology and renal fibrosis.[2]

271.4.1.2 Anemia Secondary to Endocrine or Metabolic Disorders

Endocrine disorders involving the thyroid and the pituitary-adrenal axis can cause hypoproliferative anemias. Hypothyroidism impairs erythrocyte production in humans and dogs. The anemia is usually mild and may be either normocytic or slightly macrocytic. Other clinical signs are related to the underlying thyroid disorder, and the anemia remits when the thyroid status is corrected. This is an interesting anemia in physiologic terms, because in a sense it is not an anemia at all. It represents an inappropriate response on the part of the kidney (i.e., EPO production) and bone marrow to decreased tissue oxygen consumption in the hypothyroid patient. The anemia is slow to develop and slow to remit; 3 to 4 months may be required from the onset of replacement therapy before the red cell mass returns toward or to normal. Other deficiencies of necessary nutrient materials (e.g., cobalamin or folic acid deficiency) may result from immune-mediated thyroid disease,[14,15] although this has not been addressed specifically in veterinary medicine. Prealbumin, an alpha$_2$-globulin produced in the liver and a transport protein for thyroxine, has been measured in dogs with hypothyroidism. In horses, the prealbumin concentration negatively correlates with albumin. Prealbumin increases with infectious, immune, and neoplastic etiologies, which suggests that the mild anemia associated with canine hypothyroidism may have a component of anemia of inflammation.[16–18]

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Other endocrine disorders that might be associated with mild anemia are hypopituitarism, hypoadrenocorticism, and decreased growth hormone.[18] A mild anemia recognized in late pregnancy is the result of an increase in the plasma volume. The red cell mass remains appropriate.

271.4.2 Causes Related to Lack of Iron

271.4.2.1 Anemia Due to Iron Abnormalities

Iron-deficient erythropoiesis occurs secondary to body iron depletion or inflammation. In young, nursing animals suffering from any type of blood loss (including parasitism or repeated phlebotomy), iron depletion occurs rapidly, because iron stores are insignificant and the mother's milk does not contain adequate iron. In

older animals with iron-deficient erythropoiesis, gastrointestinal or urinary tract hemorrhage, often occult and chronic, should be suspected. Among the clinical considerations would be ulceration, parasitism, neoplasia, and hemostatic disorders.

Most natural iron exists in a largely unavailable (to biologic systems), oxidized, insoluble, ferric (Fe^{3+}) form. Free iron can catalyze the formation of free radicals that damage cell membranes and deoxyribonucleic acid (DNA). Intracellular iron, therefore, is bound to various proteins to reduce its toxicity. These proteins are responsible for the absorption, transport, storage, and biologic activity of iron.

Any clinical study of iron metabolism must, of necessity, study the physiologic compounds associated with it. Iron exists in the following compartments: hemoglobin; storage, in the form of hemosiderin and ferritin; myoglobin; labile iron; tissue iron; and transport.[7] These compartments are defined by anatomic distribution, chemical characteristics, and function.[19]

Most iron in animals exists in red cells as hemoglobin iron. Each hemoglobin molecule contains four iron atoms, and each milliliter of red cells contains 1.1 mg of iron. The exact amount of total body iron depends on the red cell mass, blood volume, and body weight.[20] Storage iron exists as either a soluble, mobile fraction (ferritin) or as an insoluble, aggregated form (hemosiderin). As iron storage increases, more iron is stored as hemosiderin. Hemosiderin is mostly formed by lysosomal action on ferritin. In tissues it is readily recognized by the Prussian blue reaction. Ferritin consists of protein (apoferritin) and iron. Once iron is in the apoferritin shell, it must be oxidized to the ferric form, hydrolyzed, and polymerized to the ferric oxyhydroxide polymer. Reversal of the process allows iron to exit ferritin. The molecular shape and therefore the immunogenicity of ferritin is both species and tissue specific.[21,22]

Myoglobin iron is found mostly in muscle, where it can temporarily provide oxygen during anaerobic conditions. The labile iron pool may be an intermediate between plasma, storage, and hemoglobin. The tissue iron compartment consists of heme-containing compounds similar to hemoglobin (e.g., myoglobin and the cytochromes), non-heme-containing enzymes (e.g., iron sulfur compounds and metalloflavoproteins), enzymes that require iron or heme as a cofactor, and enzymes that contain iron in an unknown form (e.g., ribonucleotide reductase).

The transport compartment consists of plasma transferrin. The transfer of iron to erythroid cells requires internalization of the iron-laden transferrin molecule. The amount of iron delivered depends on the plasma iron concentration, the percentage iron saturation, and the number of membrane receptors.[7,23] Copper also plays an important part in the transportation of iron across cell membranes. Most circulating copper is found attached to the serum glycoprotein ceruloplasmin, which provides ferroxidase activity and may be needed to deliver iron into the circulation. When pigs are copper deficient, they have hypoceruloplasminemia and show signs of functional iron deficiency, presumably as the result of an inability to mobilize iron from the mononuclear phagocytic system and the gastrointestinal tract.[7,24]

Examination of the complete hemogram may be useful for evaluating iron adequacy. In severe iron deficiency, hemoglobin production is slowed and nucleated red cells continue to divide, resulting in the release into the circulation of late-stage nucleated red cells and adult red cells with marked central pallor. The red cell indices, the mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and mean corpuscular hemoglobin (MCH), are variably lowered in late-stage iron deficiency, with lowering of the MCH often preceding the other indices. It should be noted that deficiency of copper and pyridoxine, which also are needed for hemoglobin synthesis, can lower these indices.

The concentrations of serum iron and transferrin (the total iron binding capacity [TIBC] when the transferrin molecule is saturated) are useful analytes in the determination of iron adequacy. Use of non-iron-containing anticoagulants (ethylenediamine tetra-acetic acid [EDTA] is satisfactory), disposable plastic pipettes, test tubes, and test tube stoppers prevents contamination of patient blood with iron or zinc. Serum iron declines with iron deficiency, acute-phase inflammatory reactions, hypoproteinemia, hypothyroidism, renal disease, and chronic inflammatory states. The serum iron concentration should not be used as a predictor of iron stores. The transferrin concentration is stable or may increase with primary nutritional iron deficiency and remains stable or decreases with inflammatory processes. The unbound iron binding capacity (UIBC) estimates the saturation of transferrin, and its determination is of little clinical use.

Determination of the bone marrow iron concentration with Prussian blue stain occasionally is useful. Under appropriate circumstances, stainable iron is evident, whereas with iron-deficient processes, it is not evident.[7,19] Analysis of serum ferritin using species-specific, antibody-driven reactions has proven useful for determining nonheme iron stores in domestic animals, as well as increases after iron therapy. Ferritin, an acute-phase inflammatory protein, can increase during inflammatory reactions when interleukin-1 (IL-1) is produced. Serum ferritin can also be increased in hepatic disease, hemolysis, and some neoplastic disorders.[22,24] Body iron stores can be measured directly by measurement of the iron concentration in various organs.[25]

271.4.2.2 Anemia of Inflammatory Disease

Anemia of inflammatory disease (AID) is a mild, normocytic, normochromic, nonregenerative anemia associated with acute or chronic inflammatory processes, including trauma, infection, immune processes, and focal or disseminated neoplastic disease. It is the most common anemia found in small animals and is probably the most common anemia in veterinary medicine. This anemia appears within several days to a week. Clinically, it is an iron-deficient process; however, although the cause is multifactorial, iron sequestration in the mononuclear phagocytic system is the physiologic basis.[26–30]

The pathogenesis is mediated by cytokines produced during inflammation and results from iron sequestration (relative unavailability), a decline in red cell survival, and decreased erythropoietic response.[28,29] Reduced iron availability appears to be a physiologic metabolic response, an attempt to deprive infectious organisms of iron essential to metabolism. Apolactoferrin (iron-free lactoferrin), found in milk, mucosal secretions, and polymorphonuclear leukocytes (neutrophils), chelates and binds large amounts of iron, especially at the low pH concentrations associated with inflammation. Both the synthesis and release of apolactoferrin are increased primarily by IL-1 and tumor necrosis factor alpha. Macrophages express increased lactoferrin receptors on their surfaces; this allows them to internalize lactoferrin-bound iron, which is transferred to ferritin. Neutrophils release apolactoferrin at sites of infection, which helps in iron chelation. Lactoferrin is also intrinsically bacteriocidal.[30] This results in diversion of iron from fast-release (ferritin storage) to slow-release (hemosiderin storage) pathways. Intestinal epithelial cells and hepatocytes are also affected and contribute to the relative iron deficiency. Iron absorption from the gastrointestinal tract is reduced as a result of decreased transferrin synthesis during the acute-phase reaction.[31]

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Experimental studies in cats suggest that red cell survival may be a predominant factor in the early stage of AID. Macrophages activated by the inflammatory process are more efficient in clearing senescent red cells

and those coated with immunoglobulins.[29,32] Although not all AID patients are febrile, fever per se has been implicated in decreased red cell survival.[27]

The defects in erythropoiesis in AID have been enumerated: inappropriately low EPO production, diminished marrow response, and iron-limited erythropoiesis. The appropriate inverse relationship between the EPO concentration and the degree of anemia is lost in AID.[33] IL-1-alpha, IL-1-beta, and tumor necrosis factor all inhibited hypoxia-induced EPO secretion *in vitro,* suggesting an important role for cytokines in the pathogenesis of AID.[34] EPO concentrations in cats with experimentally induced AID were found to be slightly increased but somewhat low for the degree of anemia, which also suggests that EPO production may be a contributor to this process.[27] Tumor necrosis factor has been demonstrated to suppress erythropoiesis in laboratory animals and to prohibit the development of erythroid precursors. In contrast, a heat-stable serum factor that could not be neutralized by antibody to tumor necrosis factor or gamma interferon has been shown to render normal T cells suppressive to autologous colony-forming units–erythroid (CFU-E).[34]

AID is an anticipated complication of all focal or systemic inflammatory processes, contributing to the development of anemia due to the underlying process. Certainly the overall well being of an animal has to be influenced by the development and consequences of anemia. Numerous disease states can result in human AID. Although many of the diseases have not been specifically studied in veterinary medicine, one disease, lymphoma, has been studied in dogs.[35] Dogs with lymphoma had appropriate concentrations of iron, transferrin, and EPO, findings contrary to those associated with AID.[36]

Table • 271-2 Differentiation of Iron Deficiency, Anemia of Inflammation, and Hemolysis

ANALYTE	IRON DEFICIENCY	ANEMIA OF INFLAMMATION	HEMOLYSIS
Red cell indices	Microcytic, hypochromic	Normocytic, normochromic	Normocytic, normochromic
Serum iron	Reduced	Normal to reduced	Increased
Transferrin (TIBC)*	Increased	Normal to reduced	Decreased
Marrow iron stores	Reduced	Normal to increased	Normal to increased
Ferritin	Decreased	Normal to increased	Normal to increased
Platelet count	Increased	Normal	Variable

Modified from Waner T et al: Anemia of inflammatory disease. *In* Feldman BF, Zinkl JG, Jain NC (eds): Schalm's Veterinary Hematology, 5th ed. Baltimore, Lippincott Williams & Wilkins, 2000, p 205.

* *TIBC,* Total iron binding capacity; for clinical purposes, this is the transferrin concentration.

Parameters that differentiate anemia of inflammation from iron deficiency and hemolysis are presented in Table 271-2. Therapy of this mild anemia involves amelioration of the underlying disorder, given the realization that AID contributes to and potentially complicates any anemic process accompanied by inflammation. Administration of iron is of no value. Administration of EPO may increase the red cell mass, but the overall response may be inappropriate or inadequate.[30]

271.5 NONPROLIFERATIVE ANEMIA

271.5.1 Anemia Associated with Marrow Disorders

Bone marrow suppression and/or toxicity is a widely recognized negative side effect of antineoplastic agents. This effect is often predictable, dose related, generally reversible, and observed with a high incidence because these drugs are given at or near maximum tolerated dosages.[37] Most antineoplastic drug groups, including alkylating agents (now rarely used), antimetabolites, antineoplastic antibiotics, and naturally occurring compounds (e.g., vincristine, vinblastine), as well as other drugs, including cisplatin, carboplatin, dacarbazine, procarbazine, and hydroxyurea, have been known to cause bone marrow toxicity,[38] as can radiotherapy.

271.5.1.1 Pure Red Cell Aplasia

Pure red cell aplasia (PRCA) usually is an acquired disorder. The anemia is often severe, resulting in hematocrits in dogs and cats of less than 20%, with absolute reticulocytopenia and virtually absent marrow precursors. Marrow myeloid and megakaryocytic elements appear to be preserved, and the peripheral white cell and platelet counts are appropriate. This condition can be caused by feline leukemia virus (FeLV) or by direct suppression of the stem cells identified as burst-forming units–erythroid (BFU-E), or it may be immune mediated in dogs. In dogs, antibodies may be specifically directed at epitopes on the immature erythroid cells. In dogs and occasionally in cats, spherocytes and stomatocytes may be observed in peripheral blood, and the direct or indirect antiglobulin (Coombs') test result may be positive.[2,39]

271.5.1.2 Aplasia Anemia (Aplastic Pancytopenia)

Aplastic pancytopenia in several species can occur secondary to increased endogenous blood estrogen concentrations. The effects appear to be most severe in ferrets and dogs. Bone marrow panhypoplasia and pancytopenia are often preceded by myeloid hyperplasia and leukocytosis for several weeks. Multiple mechanisms have been incriminated, including reduction of hemopoietic stem cell numbers, inhibition of stem cell differentiation, and decreased response to EPO.[37,40] Another mechanism is iatrogenic overdose of exogenous estrogenic compounds, especially estradiol cyclopentylproprionate, intended to prevent pregnancy or to treat prostatic hyperplasia. All types of testicular neoplasia in male dogs and granulosa cell tumors in female dogs can be associated with hyperestrogenism and pancytopenia. At least 10% of male dogs with testicular neoplasia, predominantly those with Sertoli cell neoplasia, have pancytopenia, and approximately 90% of those do not recover.[3,40]

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Azidothymidine (AZT), a dideoxynucleoside derivative reverse transcriptase inhibitor used in the treatment of feline immunodeficiency viremia (FIV) or FeLV, causes transient or progressive anemia after several weeks of therapy; this anemia is thought to be the result of bone marrow suppression and/or Heinz body–induced hemolysis.[41] The immunosuppressive agent cyclophosphamide is known to cause bone marrow suppression in dogs. Azathioprine, a thioguanine-derivative immunosuppressive agent, has been associated with induced anemia and hypocellular bone marrow in dogs, with recovery after drug withdrawal. Possible incorporation of the drug into bone marrow progenitor cells is thought to cause bone marrow failure.[38] Other drugs, including meclofenamic acid, phenylbutazone, quinidine, trimethoprim-sulfadiazine, and

fenbendazole, have been incriminated in bone marrow aplasia in dogs. Chloramphenicol appears to cause mild, reversible, nonregenerative anemia in dogs.[38,40]

Infectious agents other than retroviruses can cause aplastic pancytopenia (see Anemia Associated with Infectious Etiologies, below). Among these are parvovirus, *Ehrlichia* sp. and bacterial endotoxins. Aflatoxin B toxicity has been reported to cause aplastic pancytopenia in the dog (among many other species). Idiopathic aplasia has also been reported in many species, including dogs and cats. Cell-mediated cytotoxicity, marrow stromal defects, overproduction of inhibitory hemopoietic cytokines, deficiency in stem cell factor, and genetic mutation all have been proposed as causes of the human form of this process.

271.5.1.3 Myelophthistic Disease

The term *myelophthisis* denotes a situation in which bone marrow has been replaced by nonmarrow elements. Common invaders of the bone marrow are leukemic or other tumor cells, infectious granulomas, fibrous tissue, and lipid storage cells. Although conceptually it is thought that the anemia resulting from this process is due to simple mechanical replacement of the bone marrow, the pathophysiology probably is more complex. For example, the anemia may result from competition between hemopoietic cells and invading cells for essential nutrients. Some evidence suggests that metastatic tumor lesions may secrete substances (i.e., cytokines) that block or inhibit hemopoietic cytokines, affecting the surrounding cells. In this regard, it is interesting to note that some of the same peripheral blood alterations observed in animals with metastatic bone marrow disease are observed in animals with metastatic neoplasia without bone marrow involvement.

Typical clinical features of myelophthisis include (1) normocytic, normochromic anemia with reticulocytopenia; (2) leukoerythroblastic reaction, in which the white cell count is increased and many immature white cells are present, as are many nucleated red cells; (3) marked anisocytosis and poikilocytosis of red cells, including dacrocytes or teardrop-shaped red cells; and (4) a low-normal or increased platelet count with the presence of immature and sometimes bizarre megathrombocytes. The ultimate diagnosis depends on demonstration of inappropriate invading cells in a bone marrow core biopsy.[39]

271.5.1.4 Myelofibrosis

Myelofibrosis may accompany or precede neoplastic diseases or may occur subsequent to chronically stimulated erythropoiesis in pets with severe hemolytic anemia (e.g., congenital red cell pyruvate kinase deficiency). Aspiration of marrow in these instances is difficult or impossible, and the diagnosis is based on bone marrow biopsy evaluation.[39,42–45] Idiopathic myelofibrosis (IM) (i.e., agnogenic myeloid metaplasia with myelofibrosis) is a clonal hemopoietic stem cell disorder that predominantly affects the megakaryocyte lineage in the bone marrow. It is characterized by splenomegaly, extramedullary hemopoiesis, and bone marrow fibrosis. The fibrosis is caused by deposition of abnormal collagen by polyclonal fibroblasts, which in turn are stimulated by growth factors (e.g., transforming growth factor beta) secreted by adjacent megakaryocytes. IM often is difficult to recognize as a distinct clinical entity, because many conditions can cause marrow fibrosis, and myeloproliferative disorders can terminate in a fibrotic phase. The term *myeloid metaplasia* often refers to an earlier phase of IM in which fibrosis is less prominent and extramedullary hemopoiesis in the spleen and liver is evident.[46] Various histiocytic neoplastic processes must also be considered. Many of these processes may be best distinguished by immunophenotyping.

Most patients with IM have significant anemia, and some have thrombocytosis. Signs associated with anemia are most common. The extramedullary hemopoiesis in the liver and spleen often causes notable organomegaly. Peripheral blood left shifts in the erythroid, myeloid, and megakaryocytic (megathrombocyte) lines (i.e., leukoerythroblastosis) are typical features of the complete hemogram. Bone marrow aspiration often is difficult, and biopsy demonstrates extensive fibrosis and osteosclerosis.[45,46] No effective therapy exists for this process except bone marrow transplantation.[46]

271.5.1.5 Myelodysplasia

Myelodysplasia (myelodysplastic syndromes [MDSs]) is a heterogeneous group of hemopoietic stem cell disorders characterized by cytologic dysplasia in the blood and bone marrow and by various combinations of anemia, neutropenia, and thrombocytopenia. MDS may be associated with refractory anemia (RA) or with refractory anemia with an excess number of blast cells (RAEB) either in the peripheral blood or, primarily, in the bone marrow. A variety of terms besides myelodysplasia, including *preleukemia, smoldering* or *subacute leukemia, dysmyelopoietic syndrome,* and *dyserythropoiesis* have been used to describe MDS. These disorders are best considered a form of chronic or smoldering leukemia; they have a monoclonal population of hemopoietic cells, usually involving multiple lineages, and generally are accompanied by suppression of appropriate bone marrow hemopoiesis. Unfortunately, diagnostic capabilities and nomenclature are not yet adequate to discriminate consistently among clinically distinct subsets. Increased use of cytogenetic analysis and the development of clonality techniques may be useful for diagnosis and for providing insight into disease pathogenesis, patterns of responsiveness to growth factors, and the possibility of differentiation-inducing agents.[47]

In dogs, the conditions may be primary, resulting from genetic transformation in a multipotential stem cell, or secondary and associated with administration of a drug. The primary conditions are unlikely to respond satisfactorily to hemopoietic cytokines acting as maturation factors.[2,48]

271.5.1.6 Hemopoietic Neoplasia

Neoplasia of hemopoietic tissue is characterized by replacement of normal tissue with an abnormal clonal proliferation of cells. Often, but not always, a concomitant increase in neoplastic cells in peripheral blood is seen. The neoplastic cells also commonly infiltrate other hemopoietic and lymphoid tissues, such as the liver, spleen, and lymph nodes.[2] Recent advances in the application of newer techniques have improved the accuracy of classification. These advances include immunophenotyping for clusters of differentiation (CD) antigens and cytogenetics. Immunophenotyping uses specific monoclonal antibodies to differentiate antigens. Flow cytometry has provided a powerful tool for analysis of immunophenotyped cells and is becoming an essential component in the study of leukemias. It complements morphologic studies and cytochemical staining.[48] A fundamental feature of leukemic cells is their monoclonality, which implies derivation from a single stem cell that has become neoplastic. Clonal marker systems are used to investigate not only the presence of clonality, but also the stage of hemopoietic cell development at which the neoplastic cells originate.[2,49–52]

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It is important to understand the multistep progression from normal cells to neoplastic cells.[52] Now that the molecular mechanisms that regulate normal cell growth are becoming clear, it has also become clear that failure of one or more of these fundamental steps leads to malignant transformation. Cell proliferation and

differentiation are regulated by proteins encoded by proto-oncogenes (growth promoting) and tumor suppressor genes (growth suppressing). It is now recognized that oncogenesis involves specific molecular events that result in genetic alterations in these two gene classes, with subsequent dysregulation of cell growth. A number of mechanisms can cause genetic abnormalities. Although the exact origin of these abnormalities is unknown, several environmental inciting factors have been recognized, including irradiation, chemical agents, and retroviral infection.[52]

In dogs and cats, acute and chronic myeloproliferative disorders (MPDs) are less frequently reported than lymphoproliferative disorders (LPDs). No breed or sex predilection has been identified for animals with nonlymphoid leukemia. The origin of MPDs in dogs is unknown, although environmental, viral, and genetic causes have been postulated. In contrast, MPDs in cats have been associated with FeLV and FIV infection.[53]

The diagnostic approach should be systematic and should be completed before initiation of any chemotherapy. The history may provide clues to help differentiate between acute and chronic hemopoietic neoplasia. General clinical signs of hemopoietic neoplasia include nonspecific bone pain, fever, lethargy, inappetence, vomiting, and diarrhea. The physical examination often reveals organomegaly involving the liver, spleen, or lymph nodes, and lung and central nervous system involvement can occur. Specific signs of hemopoietic neoplasia are often associated with involvement of particular cells, such as hypoxia with red cell involvement, sepsis with neutrophil involvement, and petechial, purpuric, and ecchymotic bleeding with platelet involvement.[54]

Chemotherapy in veterinary medicine can offer prolongation of life and improvement in the quality of life, but it is often palliative and rarely curative. Many myelosuppressive agents may cause profound cytopenias, with neutropenia and thrombocytopenia being common. Supportive care includes nursing care for comfort, administration of fluids and electrolytes to maintain adequate hydration and electrolyte balance, broad-spectrum antimicrobial therapy, and administration of blood products to meet specific needs. Nutritional care is essential and should be definitively addressed.[53,54]

271.5.2 Anemia Associated with Infectious Etiologies

Infectious agents, their products, or the response to the agent may cause anemia by damaging red cells and causing hemolysis; by causing developmental erythroid hypoplasia through direct damage to the erythroid precursors or the marrow microenvironment; or by damaging hemopoietic or supportive bone marrow stromal cells. Most bacterial or viral infections are indirect causes of mild anemia; AID is often the anemic etiology.[55]

FeLV may cause anemia by direct or indirect methods. By predisposing cats to other opportunistic diseases, FeLV infection may induce AID. Pure red cell aplasia or aplastic pancytopenia can be produced with experimental FeLV infection. The anemia of FeLV can be hemolytic through infectious organisms such as *Mycoplasma hemofelis,* other forms of immune-mediated hemolytic anemia, MPDs, or myelofibrosis. In FeLV-positive cats that have macrocytic, normochromic anemia, megaloblastoid rubricytes are seen, perhaps as a result of myelodysplasia related to folate or vitamin B_{12} deficiency.[55,56] FeLV frequently produces severe selective suppression of erythropoiesis (nonregenerative anemia) and thrombocytopoiesis but may cause aplastic pancytopenia.[57–59]

Cats infected with FIV may develop chronic debilitating disorders ranging from opportunistic infections to neoplasia. Approximately 18% to 36% of FIV-positive cats have anemia and may also have neutropenia,

lymphopenia or lymphocytosis, monocytosis, and thrombocytopenia. The exact pathogenesis of the FIV anemia is not known. In contrast to FeLV, FIV infects megakaryocytes and bone marrow accessory cells but not erythroid and myeloid precursors.[57]

Infectious etiologies for aplastic pancytopenia, other than FeLV and FIV, have been associated with parvoviral infection, ehrlichiosis, babesiosis, *M. hemofelis* infection, and endotoxemia. Parvoviral infection in both dogs and cats causes acute aplastic pancytopenia as a result of viral proliferation in progenitor and proliferative cells in the bone marrow, although marrow injury secondary to endotoxemia or septicemia cannot be ruled out. The bone marrow is characterized by severe degenerative changes in the developing hemopoietic cells, necrosis, and an increased number of phagocytic macrophages. Hematologic recovery usually is rapid if the pet survives the acute stages of the disease.[60] Ehrlichiosis (caused by *Ehrlichia canis, Ehrlichia ewingii,* or *Ehrlichia equi*) may cause a hypercellular bone marrow initially, but in the chronic phase, the bone marrow is characterized by pancytopenia and hypoplasia, except with plasmacytosis. Occasionally *Babesia* spp. can cause nonregenerative anemia. *M. hemofelis* infection is also sometimes associated with nonregenerative anemia, which attests to the possibility that some of these cats may be immunosuppressed or debilitiated.[60]

Cytopenias occur in the blood of dogs and cats with acute and chronic ehrlichiosis. In the acute form, the bone marrow is hypercellular, which suggests that the peripheral cytopenias are the result of cell destruction. In the chronic form, the marrow is acellular and is consistent with a diagnosis of aplastic pancytopenia.[61]

Diagnosis of aplasia includes a complete history, with questions pertaining to drug exposure, chemicals, and infectious agents; a complete hemogram with blood smear evaluation, bone marrow aspiration, and consideration of bone marrow core biopsy. The core biopsy may be most helpful for assessing cellularity and architecture. Particular attention should be paid to potential drug or chemical exposure 2 to 3 weeks prior to examination. Anemia is initially mild but becomes progressive over time. Leukopenia (neutropenia) and thrombocytopenia may accompany the anemia, with clinical signs of fever and sepsis (neutropenia) and hemorrhage in the form of petechiae, purpura, and ecchymoses (thrombocytopenia). Some residual production may be seen with the neutropenia and thrombocytopenia, and this appears to be sufficient to permit development of anemia over weeks or months.[3,60]

Treatment with prophylactic antimicrobial drugs is the only therapy that addresses the severe neutropenia with sepsis, which is most often evident when the neutrophil cell count is below 500/mL. It is difficult to address thrombocytopenia clinically without sufficient units of platelet-rich plasma. Developing anemia is treated with packed red cells, preferably, or with whole blood if packed red cells are not available. Immunosuppressive therapy and anabolic steroids are probably not indicated or useful. The use of recombinant hemopoietic growth factor and bone marrow transplantation should be considered.[62]

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271.6 INEFFECTIVE ERYTHROPOIESIS

271.6.1 Macrocytosis and Macrocytic, Normochromic Anemia

An MCV above the reference interval is considered macrocytosis. Macrocytosis can be present without anemia. Examination of peripheral blood reveals prominent macrocytes and poikilocytes. Hypersegemented neutrophils with more than five lobes are often observed, and modest decreases in both the leukocyte and platelet counts may be seen. Sometimes the morphologic changes in peripheral blood are sufficiently characteristic to make marrow examination unnecessary in the initial diagnostic workup.

With the erythroid-regenerative response in the dog and cat (i.e., sufficient reticulocytosis), the size and number of reticulocytes are usually proportional to the degree of erythropoietic stimulation. Macroreticulocytes are produced under conditions of intense erythropoietic stimulation and become macrocytic red cells as the cells mature.

Greyhounds have higher reference values for the hematocrit, hemoglobin concentration, red cell concentration, and MCV. Greyhound red cells have a shorter life span (53.6 ± 6.5 days) compared with other dog breeds (104.3 ± 2.2 days), which could account for the macrocytosis.[63,64] Macrocytosis is a familial condition in some poodles, especially the small and toy breeds. The MCV is markedly increased over reference values, and there is notable nuclear-cytoplasmic asynchrony. Megaloblastic changes and nuclear fragmentation are noted among red cell precursors, and some of the nuclear fragments are retained in the adult cells. Hypersegmentation is seen in adult neutrophils. Although these morphologic changes are also described in vitamin B_{12} deficiency, the exact nature of the defect is unknown, but it is not related to nutritional deficiency. These dogs are not anemic or, if so, the anemia is almost undetectable.[65]

271.6.1.1 Vitamin B_{12} and Folic Acid Deficiencies

Vitamin B_{12} deficiency is associated with macrocytic anemia in humans, but there does not appear to be a counterpart in nonhuman primates, dogs, or cats. The megaloblastic changes noted in feline erythroid cells have also been described in feline folic acid–depleted bone marrow, but the morphologic changes are not dramatic. Dogs and cats treated with phenobarbital or primidone occasionally develop megaloblastic changes in the bone marrow, but the changes are not accompanied by peripheral blood macrocytosis.[63] Vitamin B_{12} and folic acid deficiencies are most often related to gastric malabsorption. Gastric mucosa produces an “intrinsic factor” necessary for absorption of vitamin B_{12} in the terminal ileum. Lack of intrinsic factor in small animals may be associated with partial or total gastrectomy. Bacterial colonization of the small intestine by vitamin B_{12}–consuming micro-organisms may, theoretically, lead to vitamin B_{12} deficiency. Drugs such as colchicine and neomycin may also lead to minor malabsorption syndromes.[63]

Folic acid deficiency has been associated with gluten-sensitive enteropathy due to malabsorption and with increased requirements during pregnancy. It also is seen in neonates and in myelofibrosis and chronic inflammatory diseases. These do not appear to be clinically significant findings in small animals.[63]

Clinical assessment requires a simple dietary history and inquiries about gastrointestinal disease or surgery, any prior hematologic disease, and the animal's drug history. Laboratory assessment involves determination of the serum vitamin B_{12} and folic acid concentrations. Radioimmunoassay (RIA) yields the fewest false-positive or false-negative effects. An increased concentration of vitamin B_{12} with RIA may be seen with marked leukocytosis and active but nonspecific hepatic disease. Examination of the gastrointestinal tract by ultrasonography and with endoscopic biopsy is recommended.[63,64]

271.6.1.2 Anemia Associated with Feline Leukemia Virus Infection

Most cats that have anemia and FeLV infection have macrocytosis and resultant anisocytosis. Some FeLV-positive cats have an appropriate MCV but increased anisocytosis, perhaps reflecting a minor subpopulation of macrocytic red cells. The macrocytosis does not correlate with reticulocytosis or other

evidence of red cell regenerative response. Macrocytosis is most prominent in cats that have anemia, including both regenerative and nonregenerative anemia. However, more than 50% of nonanemic cats infected with FeLV have some macrocytosis. It has been suggested that macrocytosis could reflect a period of intense erythropoiesis before conversion to hypoproliferative anemia, but the cause is as yet unknown. In a study of cats with experimental FeLV–induced anemia, the macrocytic changes were not as significant as noted in the naturally occurring disease, and no period of reticulocytosis was detected over the course of the disease.[63] Macrocytosis has been reported in erythroid aplasia in cats and in myelodysplasia in dogs. No response to vitamin B_{12} therapy was detected.[63–67]

271.6.1.3 Normochromic, Normocytic Anemia

Normochromic, normocytic anemia is defined as a low red cell count, hematocrit, or hemoglobin concentration with appropriate MCV, MCHC, and MCH values. Almost all nonregenerative anemia is presented as normocytic and normochromic. AID has already been discussed and is associated with underlying inflammation, infection, immune-mediated processes, or neoplasia. Most often these animals have clinical signs associated with the underlying process rather than the mild anemia. General signs include weight loss, icterus, and lymphadenopathy. Abdominal signs include diarrhea or constipation, nausea and vomiting, or pain. Other signs are often associated with specific organ systems, such as cardiac murmurs or dyspnea, cough, polyuria, dysuria, bone or joint pain, or the drug history. Management requires correction of the underlying cause and the use of specific blood products as needed. Treatment with iron is contraindicated.

271.6.1.4 Hypochromic, Microcytic Anemia

A low red cell count, low hemoglobin concentration, and low hematocrit with low MCV, MCHC, and MCH values are associated with hypochromic and microcytic red cells on examination of the peripheral blood smear. It is important to know that some canine breeds are normally microcytic (Akita and Shiba). When hemoglobin concentrations reach a certain level in developing erythroid cells, cell division appears to stop. Because chronic iron deficiency is the most common cause of hypochromia and microcytosis, and as cell division is unimpeded, extra red cell division occurs until the intraerythroid hemoglobin concentration is at a level to signal cessation of division. Potential causes of this type of anemia include AID, portosystemic shunts in dogs and cats, pyridoxine deficiency, copper deficiency, hereditary elliptocytosis in dogs, dyserythropoiesis, and drug or chemical toxicities. Iron deficiency has already been discussed (see above).[68,69]

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Congenital portosystemic shunts are most often caused by a single blood vessel that fails to regress *in utero* and that diverts portal blood around the liver. Acquired shunts are often multiple and are associated with chronic hepatobiliary disease.[69,70] The cause of the microcytosis is not fully understood, but the condition is associated with abnormal iron metabolism, at least in dogs. Clinically the most common signs are encephalopathy in patients who are thin and have poor haircoats. Young dogs with congenital shunts are often small for their age. The liver is difficult to palpate as a result of microhepatica. Approximately two thirds of dogs with shunts have mild microcytosis with MCV and red cell masses at the low end or slightly below the reference interval. The MCHC is also slightly low, and the red cell distribution width (RDW) is slightly increased in most cases. About one third of cats with shunts have decreased MCV.[69–72] Target cells (codocytes), keratocytes, and elliptocytes are the poikilocytes most frequently seen. The abnormalities in the clinical biochemistry profiles of dogs include decreases in urea nitrogen, creatinine, glucose, albumin, total protein, and cholesterol. Increases are observed in serum alkaline phosphatase, bile acids, serum

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alanine aminotransferase (ALT), and bilirubin.[71,72] Fasting ammonia concentrations are elevated. The urinalysis may reveal ammonium urate crystals. Similar abnormalities are seen in cats with shunts, but hypocholesterolemia and hyperbilirubinemia are not reported. Storage iron, measured indirectly by species-specific serum ferritin assay, is appropriate or increased. The serum iron and transferrin concentrations are modestly decreased, because the physiology is similar to that of AID (see Table 271-2).[69]

Other potential causes of microcytic anemia include pyridoxine (vitamin B_6) and copper deficiency, drug and chemical toxicity, dyserythropoiesis, and hereditary elliptocytosis. Pyridoxine deficiency has been produced only experimentally in dogs and cats. These animals have microcytosis, increased serum iron, and siderotic (iron) inclusions in adult red cells. Prolonged copper deficiency in dogs and cats may cause microcytosis due to functional iron deficiency, in turn caused by inability to access storage iron as the copper transport enzyme ceruloplasmin is decreased. This protein has ferroxidase activity that is important for changing ferrous storage iron (Fe^{2+}) to ferric iron (Fe^{3+}), a change necessary for iron binding to transferrin (the iron transporting protein). Chloramphenicol is one of numerous drugs or chemicals that block heme synthesis, resulting in microcytosis and red cell siderotic inclusions.[69] Dyserythropoiesis in English springer spaniels causes nonregenerative microcytic anemia with increased circulating nucleated red cells. These dogs also have cardiac disease and polymyopathy.[73,74] Hereditary elliptocytosis has been described in a mixed-breed dog that had a red cell membrane deficiency (lack of membrane band 4.1).[75]

271.7 SUMMATION OF NONREGENERATIVE ANEMIA

Anemia is a common clinical presentation of an underlying disease. Nonregenerative anemias are the most common anemias observed by veterinary clinicians (Box 271-4). Lack of iron, anemia of inflammation, bone marrow disorders, anemias related to erythropoietin, maturation abnormalities, and the early stages of hemolysis and hemorrhage—the main anemia causation groups—present as nonregenerative anemias; that is, a relative or absolute reticulocytopenia. Examination of a minimum database (i.e., complete hemogram, urinalysis, and biochemical profile) often reveals sufficient information to diagnose the underlying disorder. Examination of the complete hemogram includes comments on platelet, red cell, and white cell morphology. Specific factors to be considered include the total protein concentration, the red cell indices, and the adjusted reticulocyte count. Once an etiology has been suggested, ancillary specific tests often bring understanding to these interesting but elusive disorders.

271.7.1 Box • 271-4 Approach to Diagnosis of Nonregenerative Anemia

271.7.1.1 Nonregenerative anemia without other cytopenias

Examine bone marrow

- Severe erythroid hypoplasia—consider pure red cell aplasia
- Normal or mild erythroid hypoplasia—consider:
  - Inflammatory disease

Renal disease

Neoplasia

Hepatic disease

Hypothyroidism

Hypoadrenocorticism

Hypercellular marrow

Less than 30% blast forms—consider myelodysplastic syndrome

Greater than 30% blast forms—consider hemopoietic neoplasia

271.7.1.2 Nonregenerative anemia with leukopenia and/or thrombocytopenia

Examine bone marrow

Panhypoplasia—aplastic pancytopenia (aplastic anemia)

Pathology determined by core biopsy

Myelonecrosis

Myelofibrosis

Hypercellular bone marrow

Less than 30% blast forms—consider myelodysplastic syndrome

Greater than 30% blast forms—consider hematopoietic neoplasia

Modified from Weiss DJ: Aplastic anemia. *In* Feldman BF, Zinkl JG, Jain NC (eds): Schalm's Veterinary Hematology, 5th ed. Baltimore, Lippincott Williams & Wilkins, 2000, p 212.

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272 CHAPTER • 272 Platelet Disorders and von Willebrand Disease

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James L. Catalfamo

272.1 PRIMARY HEMOSTASIS

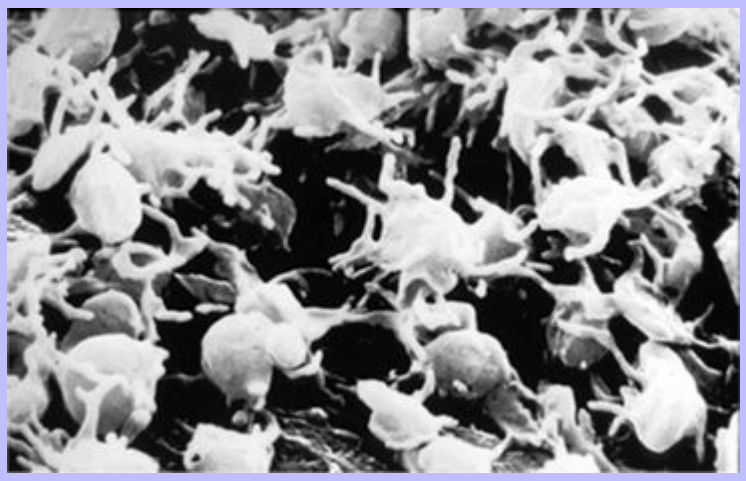
Platelets play a critical role in the initiation, regulation, and localization of hemostasis. The term *primary hemostasis* refers to the interactions among platelets, von Willebrand factor (vWF), and the vessel wall that culminate in the formation of a platelet plug (Figure 272-1). These reactions begin with platelet contact with the damaged vessel and vWF-mediated adhesion; proceed through platelet activation, degranulation, and aggregation; and conclude with the development of platelet-dependent procoagulant activity and clot retraction.

272.1.1 Platelet Physiology

Megakaryocytic precursor cells in the bone marrow are programmed, through the action of transcription factors and thrombopoietin, to form platelet-specific organelles and to express platelet cell surface proteins. In the final stages of megakaryocyte maturation, a network of demarcation membranes generates long processes that fragment into large numbers of anucleate platelets. Platelets are released from the marrow and circulate in the vascular compartment as quiescent, nonadhesive, smooth disks. Approximately 100 billion platelets are released each day to maintain a peripheral platelet count of 200 million to 500 million cells per milliliter of blood.

Injury to the vessel wall triggers platelet activation within nanoseconds. In the initial step of activation, platelets rapidly transform into adhesive, spiny spheres capable of recognizing and binding to exposed matrix components of the subendothelium. Surface binding initiates cell signaling pathways, which then mediate granule secretion. Granule contents include adenine nucleotides, calcium, serotonin, and adhesive proteins, such as fibrinogen, vWF, fibronectin, and P-selectin. Secreted compounds accumulate locally, interact with their respective surface receptors, and recruit additional platelets to the site of injury. Large-order platelet aggregates then accumulate and bridge the zone of vascular damage to form a hemostatic plug. Thrombin cleavage of fibrinogen strengthens the platelet plug as a fibrin-platelet meshwork develops.[1]

Figure 272-1 Scanning electron micrograph of platelet thrombus. Activated platelets have undergone shape change, are adherent to the underlying matrix, and have formed intraplatelet bonds in the process of aggregation. (Courtesy Bristol-Myers Squibb, New York, NY.)



Late-stage platelet activation includes exposure of platelet membrane phosphatidylserine (PS) and the release of PS-rich microparticles, which act as scaffolding for the assembly of coagulation factor complexes. The expression of platelet procoagulant activity greatly amplifies local thrombin and fibrin generation. Contraction of platelet cytoskeletal proteins linked to platelet integrin receptors for fibrin and fibrinogen results in consolidation and subsequent retraction of the growing clot.

Platelet activation requires simultaneous engagement of the platelet membrane surface receptors (Figure 272-2). Species differences in response to platelet stimuli may reflect differences in receptor subclasses for specific ligands. The endoperoxides prostacyclin (prostaglandin I_2 [PGI_2]), prostaglandin E_2 (PGE_2), and prostaglandin D_2 (PGD_2), which are synthesized by endothelial cells and released into the vascular space, serve as antagonist ligands that react with their respective platelet receptors to dampen platelet reactivity.[2]

Platelet integrins and nonintegrin glycoprotein receptors play a critical role in adhesion (platelet–subendothelial matrix interactions) and aggregation (platelet-platelet association). The αIIbβ3 complex ($GPII_bIII_a$) is the most abundant platelet integrin and functions as the activation-dependent receptor for fibrinogen, fibronectin, and vWF. Binding of fibrinogen to this receptor is essential for aggregation and clot retraction. Platelet adhesion to collagen and collagen-induced signaling are supported by collagen's interaction with the integrin receptor α2β1 (GPI_aII_a).

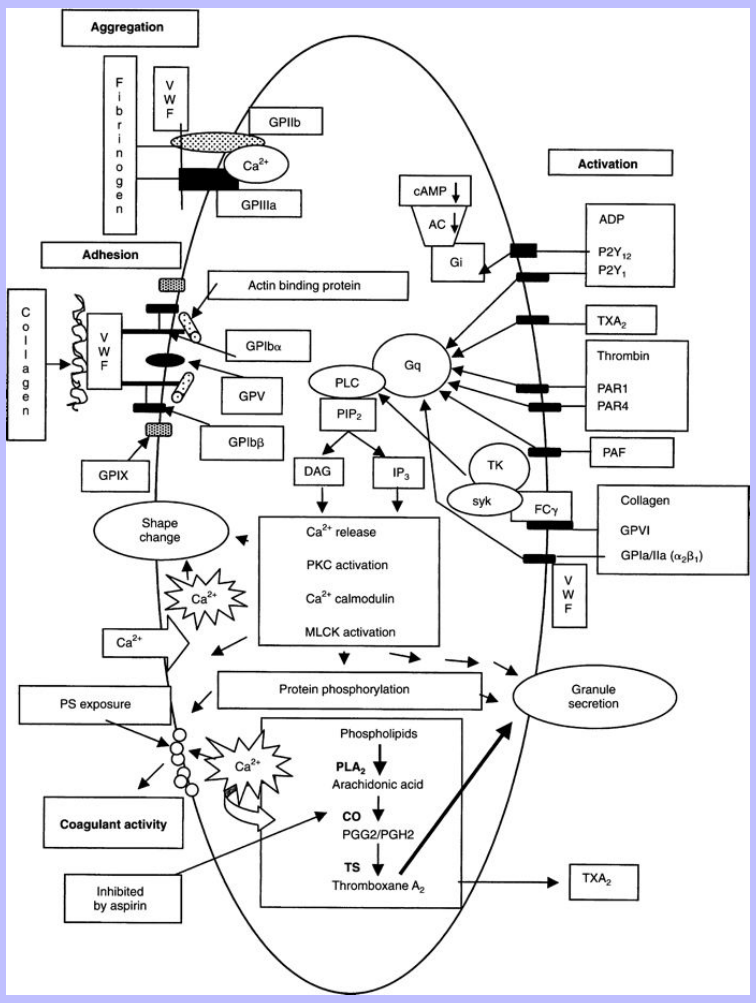
Surface receptors, coupled to G proteins, span the platelet membrane and transmit signals induced by agonist binding. In platelets, Gq serves as this link for most agonists. Gq is coupled to phospholipase C, which in turn generates diacylglycerol (DAG) and inositol triphosphate, leading to calcium release from the endoplasmic reticulum; protein kinase C and myosin light chain kinase activation; and phosphorylation of platelet signaling

proteins. During activation, phospholipase A_2 releases arachidonic acid from membrane phospholipids. Cyclo-oxygenase and thromboxane synthetase convert arachidonic acid to the potent agonist thromboxane A_2 (see Figure 272-2).

272.1.2 Platelet–von Willebrand Factor Interaction

Subendothelial collagen fibrils and bound vWF are exposed when the vascular endothelium is injured. The affinity and strength of the vWF-collagen bond is proportional to vWF multimer size. Collagen-bound vWF displays a conformational change that allows it to interact with the platelet GPIb/V/IX complex. As platelet GPIb contacts and engages with vWF, platelets slowly roll and become activated by interaction with collagen fibrils. vWF then binds to $GPII_b/III_a$ receptors exposed on the surface of activated platelets. Adhesion and aggregation at high shear rates depend on this vWF binding to activate platelet $GPII_b/III_a$.

Figure 272-2 Major signaling mechanisms involved in platelet activation. *cAMP,* Cyclic adenosine monophosphate; *AC*, adenylate cyclase; *PLC*, phospholipase C; *PIP_2*, phosphatidylinositol bisphosphate; *DAG*, diacylglycerol; *IP_3*, inositol triphosphate; *PKC,* protein kinase C; *MLCK,* myosin light chain kinase; *PLA_2*, phospholipase A_2; *CO*, cyclo-oxygenase; *TS*, thromboxane synthase; *TXA_2*, thromboxane A_2; *PAF*, platelet-activating factor; *PAR 1*, *PAR 4*, protease-activated thrombin receptor 1 or 4; *GP*, glycoprotein; *TK*, tyrosine kinase; *vWF*, von Willebrand factor; *$P2Y_1$* or *$P2Y_{12}$*, purinergic nucleotide receptors; *FCγ*, immunoglobulin-like receptor; *Gq* and *Gi*, GTP-binding proteins; *syk*, syk kinase.



272.2 DIAGNOSIS OF PLATELET DISORDERS

272.2.1 Clinical Signs of Primary Hemostatic Defects

Primary hemostatic defects typically cause signs of petechiae (pinpoint hemorrhage), ecchymoses (bruising), and mucosal hemorrhage, such as epistaxis, hematuria, gingival and intestinal hemorrhage, and prolonged bleeding after injury. These signs are suggestive of capillary and small vessel hemorrhage, but none are pathognomonic for a specific disease. For example, ecchymoses (Figure 272-3) are often seen in association with thrombocytopenia but also may be signs of inflammatory vasculitis.

272.2.2 Screening Tests

The initial assessment of any patient with signs of bleeding should aim to distinguish between hemorrhage from injured or diseased blood vessels and hemostatic failure. If the source or cause of hemorrhage cannot be readily identified, platelet count and coagulation screening tests should be performed early in the diagnostic workup. These tests can help both to detect a hemostatic defect and to guide the selection of appropriate ancillary diagnostic tests (Figure 272-4).

The platelet count (per μL) can be estimated by counting the number of platelets in 10 oil immersion fields and multiplying the average number per field by 15,000 to 20,000 (Figure 272-5).[3] Either the activated clotting time (ACT) or point-of-care coagulation assays can be performed in-house to rule out clinically severe coagulation factor deficiencies.

272.2.2.1 Testing for Quantitative Platelet Defects

Quantitative platelet defects are common hematologic abnormalities.[4–6] Normal platelet numbers for dogs and cats range from approximately 200,000/μL to 500,000/μL. Each testing laboratory should provide species-specific reference ranges for their method (Table 272-1). High or low platelet counts are found in many patients having systemic inflammatory and neoplastic diseases. Specific diagnostic tests (Table 272-2) are indicated for patients with moderate to severe thrombocytopenia or thrombocytosis, with associated clinical signs.

Figure 272-3 Petechiae and ecchymoses in the inguinal region of a mixed-breed dog with thrombocytopenia (platelet count, 5000/μL).

272.2.2.1.1

Thrombocytopenia

Platelets are highly reactive; spurious low platelet counts are common laboratory artifacts and should be confirmed by examination of a blood smear to rule out platelet clumping.[7] Collection artifacts are minimized by the use of citrate anticoagulant, atraumatic venipuncture with collection directly into anticoagulant, assay within hours of blood draw, and avoidance of cold temperature. Thrombocytopenia rarely causes signs of abnormal hemostasis unless the platelet count falls below 50,000/μL, with petechiation and spontaneous hemorrhage most likely at counts below 20,000/μL. Clinical signs may appear at higher platelet counts, however, if the patient has a concurrent disease that further impairs hemostasis.

Three general mechanisms cause thrombocytopenia: impaired platelet production, increased peripheral consumption or sequestration, and immune-mediated destruction. In many disease syndromes, more than one mechanism is involved.[8]

Production defects are likely in patients with thrombocytopenia combined with leukopenia and/or anemia.[9] Immature platelets have a relatively high mean platelet volume (MPV) and ribonucleic acid (RNA) content, detected as “reticulated” platelets by thiazole orange staining. The presence of reticulated platelets indicates ongoing platelet production, but their absence does not confirm megakaryocyte hypoplasia. Bone marrow examination, therefore, is the most accurate and direct means of evaluating megakaryopoiesis. Normal to high megakaryocyte numbers are typical of peripheral platelet consumption or destruction. Megakaryocyte hypoplasia confirms a platelet production defect and may reveal an infectious agent or abnormal cellular or stromal proliferation. In most cases, the combination of bone marrow examination, drug and travel history, and serology or polymerase chain reaction (PCR) testing to detect infectious agents leads to definitive diagnosis of production defects.

Splenic enlargement, for any reason, causes increased platelet sequestration and may result in thrombocytopenia with a shortened platelet life span.[10] Increased peripheral platelet consumption accompanies systemic vasculitic disorders and disseminated intravascular coagulation (DIC). The primary means of diagnosing sequestration disorders include splenic and lymph node aspiration cytology, serology and biopsy to detect infectious agents and inflammatory disorders, and coagulation tests to define a DIC process.

Immune-mediated platelet destruction is common. *Primary immune-mediated thrombocytopenia* (*IMT*) implies an autoimmune disorder with production of antibodies directed against normal platelet antigens.[11] *Secondary IMT* occurs in association with infection, drug therapy, neoplasia, or polyimmune syndromes or as a complication of platelet transfusion.[12] In these patients, platelet-bound antibody may represent immune complexes, antibodies directed against neoantigens or foreign platelet antigens, or nonspecific binding.[13] The presence of antibodies on the surface of platelets (platelet-bound antibody) or antibodies in patient sera capable of binding normal platelets (platelet-bindable antibodies) can be detected with flow cytometry or enzyme-linked immunosorbent assay (ELISA). Flow cytometric assays configured to detect platelet-bound canine IgG have been developed for clinical use.[14,15] The tests are generally sensitive, but they are nonspecific. Detection of platelet-bound IgG does not differentiate patients with primary IMT from those with secondary IMT, and nonspecific antibody binding may complicate interpretation of test results. Microthrombocytosis (MPV less than 5.5 fL) has been described as a feature of primary and secondary IMT and is seen early in the disease course.[1] In a case review,

severe thrombocytopenia (less than 20,000/μL) and microthrombocytosis were found almost exclusively in dogs with IMT; however only half of the IMT patients had these abnormalities.[16] Accurate MPV determination is affected by the anticoagulant used; platelets stored in ethylenediamine tetra-acetic acid (EDTA) rather than citrate may have artifactual increases in MPV.

Figure 272-4 Diagnostic algorithm for primary hemostatic defects. *BMBT*, Buccal mucosa bleeding time; *PFA*, platelet function analyzer; *vWF:Ag*, von Willebrand factor antigen.

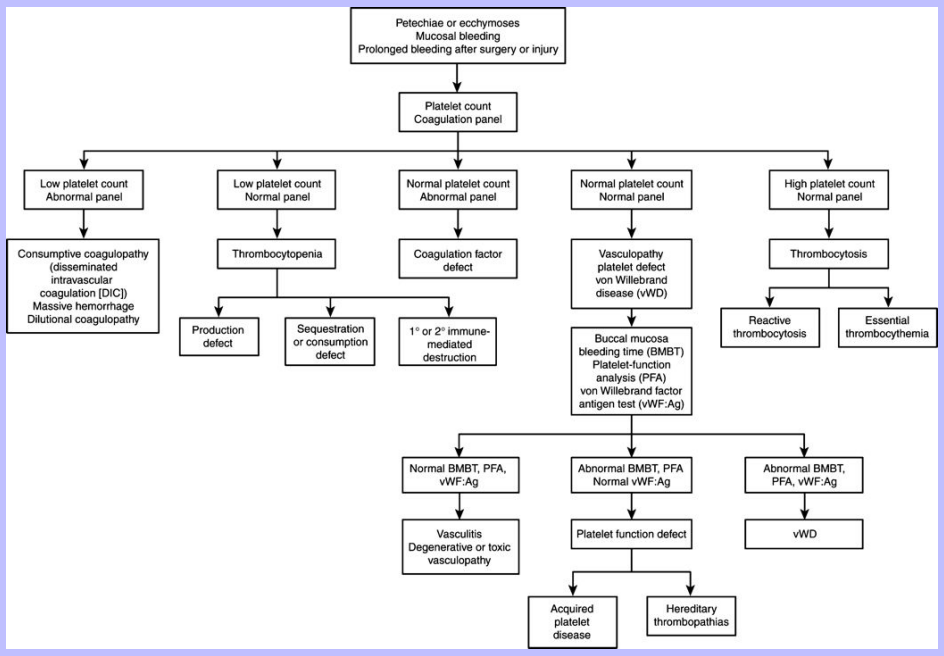
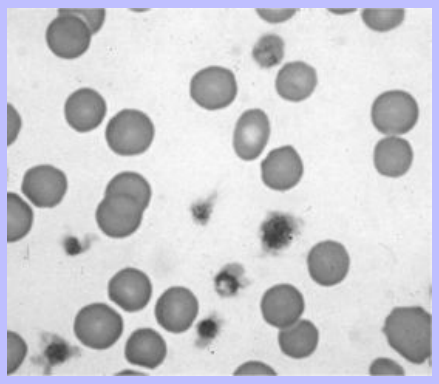


Figure 272-5 Wright-stained blood smear from a healthy cat emonstrating normal feline platelet morphology (.400). Courtesy Dr. Tracy Stokol, Cornell University, Ithaca, New York.)



272.2.2.1.2 Thrombocytosis

Mild to moderate increases in the platelet count ("reactive" thrombocytosis, are seen in association with chronic blood loss, neoplasia, systemic inflammatory disease, and hypercortisolism.[17] High platelet counts may occur after splenectomy. A persistent and markedly high platelet count (greater than 900,000/μL) is suggestive of primary bone marrow disease (e.g., myelodysplasia, essential thrombocythemia) and is an indication for bone marrow examination. The clinical features of essential thrombocythemia in human beings and dogs include splenomegaly and hemorrhage caused by platelet dysfunction.[18]

Table • 272-1 Reference Values* for Canine and Feline Platelet Count and Mean Platelet Volume

VALUE	DOG	CAT
Platelet count ($\times 10^3$/uL)	179 to 483	201 to 523
Mean platelet volume (fL)	8.4 to 13.2	10.8 to 19.8

Values current 2003, Clinical Pathology, Cornell University, Ithaca, New York.

* Advia Hematology Analyzer (Bayer, Tarrytown, New York).

Table • 272-2 Diagnostic Tests for Quantitative Platelet Defects

TESTS	SPECIFIC ASSESSMENTS
CBC	Review to detect: Infectious agents, neoplastic cells, spherocytes, schistocytes Assess: Platelet count and morphology, MPV, percentage of reticulated platelets
Bone marrow examination	Review to detect: Megakaryocyte number and morphology, infectious agents, lymphoproliferative or myeloproliferative neoplasia, myelofibrosis, myelodysplasia Special stains or labels: Immunophenotyping, histochemistry, iron stains, antimegakaryocyte antibody
Spleen/lymph node examination	Review to detect: Infectious agents, neoplastic cells
Serology	Review to detect: Infectious agents, antinuclear antibody
Polymerase chain reaction	Review to detect: Infectious agents
Platelet-bound antibody	Configured to detect: Antibody specificity (i.e., IgG, IgM, IgA) or epitope specificity (i.e., anti-$GPII_bIII_a$ antibody)
Coagulation tests	Review: Coagulation panel (aPTT, PT, TCT), fibrinogen, antithrombin activity, FDP or D-dimer concentration

CBC, Complete blood count: *MPV*, mean platelet volume; *aPTT*, activated partial thromboplastin time; *PT*, prothrombin time; *TCT*, thrombin clotting time; *FDP*, fibrin and fibrinogen degradation products.

272.2.3 Platelet Function Tests

The buccal mucosa bleeding time (BMBT) is an *in vivo* screening test of primary hemostasis (Figure 272-6). If thrombocytopenia has been ruled out, a long BMBT is compatible with either platelet dysfunction or vWF deficiency.[19] Platelet dysfunction is definitively diagnosed using more comprehensive tests of platelet structure and activation response (Table 272-3).

To ensure platelet viability, functional assays are best performed within 2 to 3 hours of sample collection. The PFA 100 (Dade Behring, Newark, DE) is a new analyzer that can be used to measure platelet adhesion and aggregation with small volumes of whole blood (less than 2 mL) under conditions that simulate blood flow.[20,21] More specific assessment of platelet function is performed by monitoring agonist-induced responses of shape change, aggregation, and release of dense granule contents (Figure 272-7).[22]

Flow cytometry is used to assess platelet function by means of detection of membrane glycoproteins (required for adhesion and aggregation) and activation markers, such as P-selectin, fibrinogen, and surface PS.[23] These markers are evidence of effective alpha granule release and procoagulant activity (Figure 272-8). Detailed evaluations of platelet function, physiology, and ultrastructure are usually reserved for characterization of hereditary thrombopathias.

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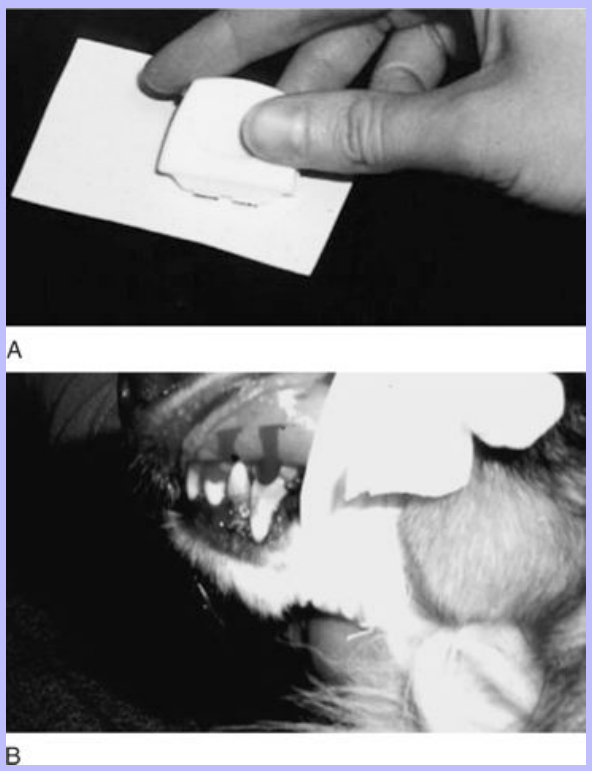
Figure 272-6 Buccal mucosal bleeding time. **A,** Template device (Simplate II; Organon Teknika, Durham, North Carolina) with spring-loaded blades that make incisions of uniform depth and length when the device is triggered. **B,** Incised buccal bleeding time wounds in a Shetland sheepdog affected with type 3 vWD. After incision, shed blood is collected by gently blotting below the wounds with gauze or filter paper. The time from incision to cessation of blood flow is the buccal bleeding time.



A

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272.3 SPECIFIC PLATELET DISORDERS

272.3.1 Thrombocytopenia

Thrombocytopenia is the most common acquired hemostatic defect of dogs and cats.[10] Many different pathogens cause thrombocytopenia (Table 272-4), often through combined marrow suppression and an increased rate of peripheral loss. Arthropod-borne agents are increasingly identified as the cause of cytopenias in dogs and cats.[8,24] Infectious agents usually cause systemic signs, producing physical examination findings and complete blood count (CBC) abnormalities beyond those of thrombocytopenia alone. Although dogs and cats with infectious thrombocytopenias may initially respond to steroid administration, sustained platelet response and disease resolution require specific treatment. It therefore is important to rule out infectious thrombocytopenia (through serology, cytology, or PCR) before an immunosuppressive steroid regimen is begun.

Mild to moderate thrombocytopenia is seen in association with many tumor types, with more severe depression likely in hematopoietic neoplasia such as multiple myeloma, lymphoma, and leukemia.[5] DIC is a common cause of thrombocytopenia in hemangiosarcoma, and tests to define a DIC process (see Table 272-2) should be performed in any cancer patient with a falling or low platelet count. In addition to tumor-mediated thrombocytopenia, cancer patients are at risk of developing thrombocytopenia arising from cytotoxic drug therapy.

Table • 272-3 Platelet Function Assays

TESTS	SPECIFIC ASSESSMENTS
Dilute whole blood clot retraction	$GPII_bIII_a$-mediated clot retraction
Platelet aggregation studies	Aggregation response to specific agonists: adenosine diphosphate (ADP), collagen, arachidonate, epinephrine, platelet-activating factor
Platelet secretion studies	Secretion of dense granule contents: ADP, adenosine triphosphate (ATP), serotonin
Flow cytometry	Detection of constitutive membrane antigens: $GPII_bIII_a$ (CD61 =GPIIIa); GPIb (CD42b =GP1bα) Detection of activation markers: P-selectin (CD62p), phosphatidylserine (annexin-V), fibrinogen binding site (CAP1), platelet-bound fibrinogen (antifibrinogen antibody) Platelet calcium entry and release: Fluo-3
Spectrofluorimetry	Platelet calcium entry and release: Fura-2AM
Electron microscopy	Platelet ultrastructure: Shape change, cytoskeleton, intracellular organelles (granules, dense bodies, lysosomes), dense tubular system

A thorough drug history is indicated for any patient with thrombocytopenia, because numerous drugs have been reported to impair platelet production, induce secondary immune destruction, and/or cause platelet dysfunction (Table 272-5).[25] Establishing the causality of drug-induced thrombocytopenia is difficult, but ancillary diagnostics can help define possible underlying mechanisms. The findings of pancytopenia and

megakaryocytic hypoplasia indicate bone marrow suppression, and the presence of platelet-bound antibody is compatible with an immune-mediated process.

Idiopathic, or primary, IMT is an autoimmune disease, usually mediated by IgG directed against platelet membrane $G_pII_bIII_a$. The disease is uncommon in cats, but in case reviews of canine thrombocytopenia, primary IMT accounts for approximately 5% to 15% of patients, with over-representation of females and certain breeds (cocker spaniels, poodles, and Old English sheepdogs).[4,11] The diagnosis of primary IMT is generally based on combined clinical and laboratory criteria: exclusion of other underlying disease processes, the presence of severe thrombocytopenia (less than 50,000/μL), normal to increased megakaryopoiesis, microthrombocytosis, platelet-bound antibodies, and response to immunosuppressive therapy.

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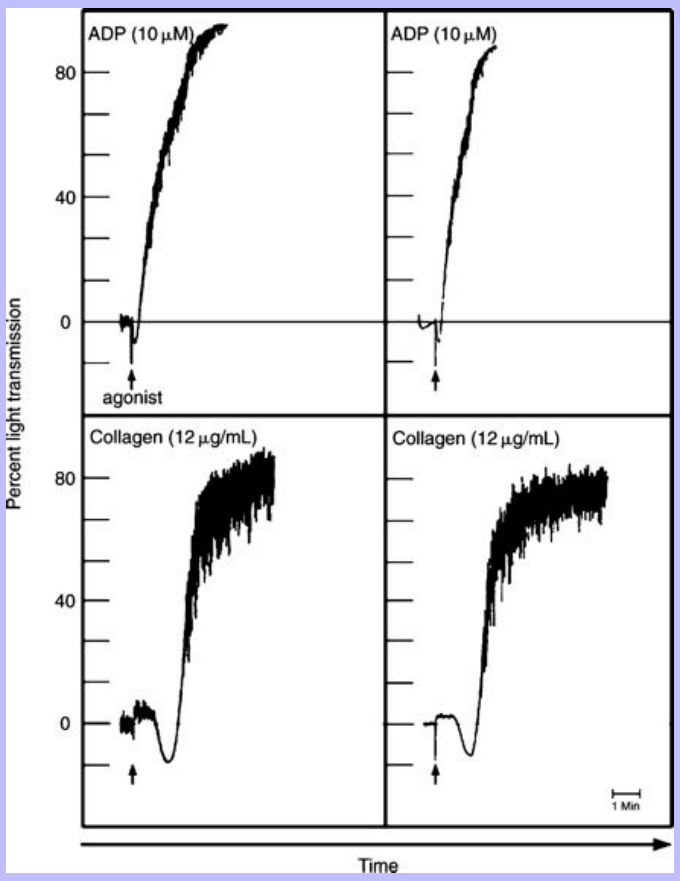
Figure 272-7 Platelet aggregation profiles of platelet-rich plasma obtained from two healthy dogs. Platelet activation was initiated by the addition *(arrow)* of adenosine diphosphate (ADP) *(top panels)* or collagen *(bottom panels)*. Aggregate formation is evidenced by an increase in light transmission. ADP induces a rapid aggregation response. In contrast, collagen stimulation is followed by a lag phase before aggregation ensues.



Breed-specific, clinically asymptomatic thrombocytopenias occur in dogs. Healthy greyhounds have a platelet count somewhat lower than that of other breeds, with a mean platelet count of approximately 150,000/μL.[26] Cavalier King Charles spaniels have a hereditary macrothrombocytopenia, with affected dogs having platelet counts ranging from 25,000/μL to 100,000/μL.[27]

272.3.1.1 Acquired Platelet Dysfunction

Many common drugs and disease syndromes impair platelet function, but the clinical significance is highly variable.[28] A mild to moderate bleeding tendency may complicate management of disease syndromes such as anemia, liver failure, uremia, DIC, and paraproteinemia. The pathogenesis of platelet dysfunction in these disorders is complex and multifactorial and includes intrinsic alterations in platelet metabolism and extrinsic changes in blood viscosity. Many drugs demonstrate *in vitro* platelet inhibition (see Table 272-5), by a variety of different mechanisms. The antiplatelet effects of aspirin are caused by a well-characterized, irreversible inactivation of intraplatelet cyclo-oxygenase (COX).[29] Other nonsteroidal anti-inflammatory drugs (NSAIDs) cause transient COX inhibition, and newer NSAIDs that selectively inhibit the COX-2 isoform are predicted to have fewer antiplatelet effects. Although drugs with potential antiplatelet effects may not cause spontaneous or severe bleeding, they should be given cautiously, if at all, to thrombocytopenic patients, patients undergoing surgery, or patients with signs of abnormal hemostasis.

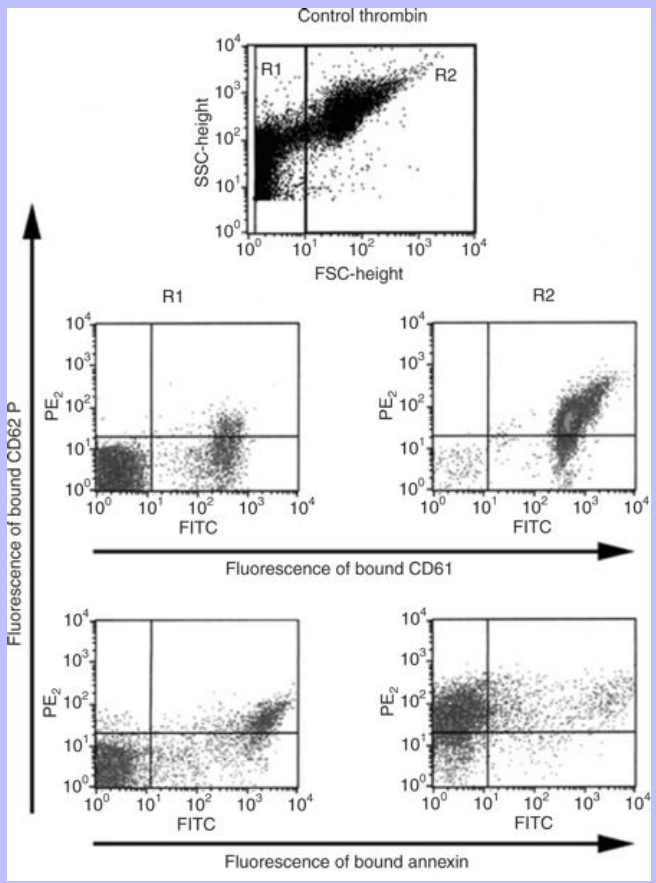
272.3.1.2 Hereditary Platelet Dysfunction

Hereditary platelet function defects (thrombopathias) are rare but likely are underdiagnosed because of logistic difficulties in performing platelet function studies. Diseases are broadly grouped as defects of membrane glycoproteins, storage granules, signal transduction, or procoagulant activity.[20] Breed-specific defects within these functional classifications have been identified in dogs and cats (Table 272-6). Defects in the $GPII_bIII_a$ complex, referred to as *thrombasthenic thrombasthenia,* have been identified in otter hounds and Great Pyrenees as the result of two distinct GPIIb mutations.[30,31] It is likely that the platelet function defects found in different breeds are caused by unique mutations.

272.3.2 von Willebrand Disease

von Willebrand disease (vWD) is the most common canine hereditary hemostatic defect.[32] The clinical signs of vWD overlap with those of other primary hemostatic defects, including mucosal hemorrhage, cutaneous bruising, and prolonged bleeding after injury. Petechiation, however, is not typical of vWD.

Figure 272-8 Flow cytometry analyses of canine platelet response to thrombin stimulation. The dot plot at top displays activated platelets in region R2. Region R1 contains platelet membrane–derived microparticles, debris, and machine noise. The four composite cytograms display the fluorescence intensity of labeled probes bound to the events in R1 or R2. The activated platelets (R2) display high-intensity labeling with CD61 and CD62p probes, denoting the presence of the membrane integrin GPIIIa and externalization of alpha granule constituent P-selectin, respectively. Most thrombin-activated platelets, however, are not labeled with the annexin probe, indicating low surface phosphatidylserine. In contrast, platelet membrane–derived particles (R1) display both P-selectin and phosphatidylserine. In all cytograms, events in the lower left quadrant represent nonspecific background fluorescence.



272.3.3 Disease Classification

Canine vWD is classified into one of three subtypes based on the clinical severity, plasma vWF concentration (vWF:Ag), and vWF multimer composition.[33,34] In general, a single type of vWD predominates in each affected breed (Table 272-7). Type 1 vWD, the most common form, is typically a mild to moderate bleeding diathesis characterized by low plasma vWF:Ag and normal multimer distribution. Type 2 vWD is a moderate to severe bleeding diathesis with a variable reduction in vWF:Ag and a disproportionate loss of high molecular weight (HMW) multimers. Type 3 vWD is a severe bleeding disorder caused by a total lack of vWF.

Table • 272-4 Pathogens that Cause Infectious Thrombocytopenia

TYPE OF AGENT	PATHOGEN
Viral agents	Canine: Distemper virus, herpesvirus, parvovirus, adenovirus Feline: Feline leukemia virus (FeLV), panleukopenia virus, feline immunodeficiency virus (FIV), feline infectious peritonitis (FIP) coronavirus
Arthropod-borne agents	*Ehrlichia* spp. *(E. canis, E. platys, E. ewingii);* also *Babesia*, *Haemobartonella*, *Rickettsia*, *Leishmania*, *Cytauxzoon*, *Borrelia*, and *Dirofilaria* spp.
Fungal and bacterial agents	Septicemia: Various agents *Histoplasma*, *Candida*, and *Leptospira* spp.

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Table • 272-5 Drugs that Have Antiplatelet Effects

CATEGORY	DRUG	DISORDER/MODE OF ACTION
Antibiotics and antifungal drugs	Carbenicillin	Thrombopathia: Unknown action
	Cephalosporins	Thrombopathia: Membrane action*
	Chloramphenicol	Thrombocytopenia
	Penicillin	Thrombocytopenia
	Sulfonamides	Thrombocytopenia
Anti-inflammatory drugs	Aspirin	Thrombopathia: Prostaglandin (PG) inhibition
	Ibuprofen	Thrombopathia: PG inhibition
	Naproxen	Thrombopathia: PG inhibition
	Phenylbutazone	Thrombocytopenia and thrombopathia: PG inhibition
Cardiac and respiratory drugs	Aminophylline	Thrombopathia: Phosphodiesterase inhibition
	Diltiazem	Thrombopathia: Calcium blocker
	Isoproterenol	Thrombopathia: Membrane action
	Procainamide	Thrombocytopenia
	Propranolol	Thrombopathia: Membrane action
	Verapamil	Thrombopathia: Membrane action, calcium blocker
Cytotoxic drugs	Azathioprine	Thrombocytopenia
	Chlorambucil	Thrombocytopenia
	Cyclophosphamide	Thrombocytopenia
	Doxorubicin	Thrombocytopenia
Miscellaneous	Dextran	Thrombopathia: Membrane action
	Estrogen	Thrombocytopenia
	Methimazole	Thrombocytopenia

* Membrane action is interaction or interference with membrane receptors.

Table • 272-6 Hereditary Platelet Function Defects

DEFECT	BREED	LABORATORY FINDINGS
Thrombasthenia	Otter hound, Great Pyrenees	Absent or reduced $GPII_bIII_a$ complex, abnormal adhesion, absent or severely reduced aggregation to all stimuli, abnormal clot retraction
Signal transduction	Basset hound	Abnormal cAMP metabolism, defective $GPII_bIII_a$ activation, abnormal adhesion, aggregation only in response to thrombin, normal clot retraction
	Spitz	Abnormal adhesion, absent or trace aggregation in response to most stimuli, normal clot retraction
Storage pool	Persian cat	Chédiak-Higashi syndrome, low dense granule number, failure to secrete ADP and serotonin, abnormal aggregation, normal clot retraction
	American cocker spaniel	Normal dense granule number, abnormal ADP storage and secretion, abnormal ADP-induced aggregation, normal clot retraction
Signal transduction and storage pool	Collie	(Associated with cyclic neutropenia and stem cell defect) Defective dense granule serotonin and ADP release, abnormal aggregation to allstimuli but ADP
Undefined	Boxer	Abnormal aggregation to ADP and collagen, normal shape change, normal granule ATP/ADP content, normal fibrinogen and vWF binding
Procoagulant deficiency	German shepherd	Abnormal membrane phosphatidylserine exposure, abnormal microparticle release, abnormal prothrombinase activity, normal shape change, normal aggregation, normal clot retraction

cAMP, Cyclic adenosine monophosphate; *ADP*, adenosine diphosphate; *ATP*, adenosine triphosphate; *vWF*, von Willebrand factor.

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Table • 272-7 Classification of Canine von Willebrand Disease

CLASSIFICATION	vWF PROTEIN	SEVERITY	REPORTED BREEDS
Type 1	Low concentration/all multimer forms present	Variable	Airedale, Akita, dachshund, Doberman pinscher, German shepherd, golden retriever, greyhound, Irish wolfhound, Manchester terrier, schnauzer, Pembroke Welsh corgi, mixed-breed, poodle, Shetland sheepdog
Type 2	Low concentration/disproportionate loss of high-molecular-weight multimers	Moderate to severe	German shorthaired pointer, German wirehaired pointer
Type 3	Absent	Severe	Chesapeake bay retriever, Dutch kooiker, Scottish terrier, Shetland sheepdog Sporadic cases: Cocker spaniel, Eskimo dog, Labrador retriever, pit bull, rottweiler

272.3.3.1 Diagnosis of von Willebrand Disease

The screening test findings compatible with vWD include a normal platelet count, normal coagulation panel, long BMBT, and long PFA closure time, with definitive diagnosis confirmed by the finding of low plasma vWF:Ag (see Figure 272-4). Comprehensive analyses for vWD subtype classification include quantitative, functional, and qualitative vWF assays (Table 272-8).

272.3.3.2 Inheritance and Expression

von Willebrand disease is an autosomal trait; males and females experience the bleeding tendency and transmit the defect to offspring with equal frequency.[35] Expression of type 1 vWD is complex, with evidence for both incomplete dominant and recessive patterns.[36,37] Type 1 vWD is common in Doberman pinschers, and in this breed, clinical signs of vWD are typically seen in dogs with a vWF:Ag of 15% or lower.[38,39] Homozygosity for a splice-site mutation in the vWF gene and for certain vWF marker alleles is associated with a low plasma vWF.[40,41] The clinical severity of type 1 vWD for an individual dog (or human patient) cannot be fully explained by current molecular or biochemical tests. In contrast, type 2 and type 3 vWD in dogs appear to be simple recessive traits. Clinically affected dogs inherit a mutant vWF gene from each parent and express a bleeding tendency. The carrier parents are clinically normal, although their plasma vWF is typically low (less than 50% vWF:Ag). Mutations causative for type 3 vWD have been described in Scottish terriers and Dutch kooiker dogs.[42,43] Carriers (heterozygotes) can be unambiguously identified through breed-specific mutation detection tests.

Table • 272-8 von Willebrand Factor Analyses

TEST	PARAMETER MEASURED	TYPICAL RESULTSWITH vWD	NORMAL VALUES*
Buccal mucosal bleeding time (BMBT)	Primary hemostasis—vessel, platelet, vWF interaction	Type 1: 5 to >12 min Type 3: >12 min Type 2: >12 min	2 to 4 min
Platelet function analyzer (PFA 100) ADP/collagen closure time	vWF-dependent platelet adhesion and platelet aggregation	Type 1: 150 to 200 sec Type 2: >300 sec Type 3: >300 sec	47 to 119 sec
von Willebrand factor antigen (vWF:Ag)	vWF concentration	Type 1: 5% to 20% Type 2: 1% to 5% Type 3: <0.1%	>50%
Ristocetin and botrocetin cofactor activities (vWF:RCo; vWF:BCo)	vWF-dependent plateletagglutination	Type 1: Cofactor activity =vWF:Ag Type 2: Cofactor activity <vWF:Ag Type 3: Cofactor activity absent	>50%
Collagen binding capacity (vWF:CB)	Quantitative measure of vWF bound to collagen	Type 1: vWF:CB =vWF:Ag Type 2: vWF:CB <vWF:Ag Type 3: vWF:CB absent	>50%
vWF multimer composition (Western blot)	Distribution and size of vWF multimeric forms	Type 1: All vWF multimers present Type 2: Low/absent HMW forms Type 3: no vWF	Complete size array

vWF, von Willebrand factor; *ADP*, adenosine diphosphate; *HMW*, high molecular weight.

* Expected values for healthy dogs in authors' laboratory.

272.4 TREATMENT OF PLATELET DISORDERS AND VON WILLEBRAND DISEASE

Effective management of platelet disorders and vWD requires control of active sites of bleeding, stabilization of the patient to reverse signs of blood loss anemia and hypovolemia, and identification and correction of the primary disease that caused or exacerbated the hemostatic defect. Initial treatment modalities include both nontransfusion and transfusion support. Although the BMBT is a useful screening test of primary hemostasis for diagnostic purposes, it is not an accurate predictor of disease severity or surgical hemostasis.

272.4.1 Nontransfusion Therapy

Most animals with thrombocytopenia or acquired platelet function defects are effectively treated through identification and correction of the underlying disease process. Drugs with antiplatelet effects, invasive surgery, and jugular catheterization should be avoided, and cage rest is indicated to minimize trauma in

severely thrombocytopenic patients. Based on the geographic location, history, and initial workup, institution of appropriate therapy for infectious thrombocytopenia (e.g., doxycycline for *Ehrlichia, Rickettsia,* and *Haemobartonella* spp.) is indicated pending confirmatory test results.[8] Immunosuppressive doses of prednisone (2 mg/kg given every 12 to 24 hours) are administered if the diagnostic workup indicates that primary IMT is likely.[11] Primary IMT patients usually demonstrate resolution of petechiae and an increased platelet count within 2 to 5 days of starting therapy. Refractory primary IMT can be effectively treated with vincristine (0.02 mg/kg given intravenously every 7 days).[44] Immunosuppressive therapy for IMT can be considered successful if a stable platelet count (preferably at or above 100,000/μL) is attained. Maintenance involves slow, gradual tapering of immunosuppressive therapy, with minimal exposure to unnecessary drugs, vaccination, or stress conditions to avoid relapse.

Table • 272-9 Guidelines for Transfusion Therapy

PRODUCT	DOSE	INTERVAL BETWEEN REPEAT TRANSFUSIONS
Products for Red Cell Replacement		
Fresh whole blood	12 to 20 mL/kg	Every 24 hours (volume overload limits interval)
Packed red cells	6 to 12 mL/kg	Every 12 to 24 hours
Oxyglobin	10 to 30 mL/kg*	Once
Products for Platelet Replacement		
Fresh whole blood	12 to 20 mL/kg	Every 24 hours (volume overload limits interval)
Platelet-rich plasma	6 to 10 mL/kg†	Every 8 to 12 hours
Platelet concentrate	1 U/10–15 kg‡	Every 8 to 12 hours
Products for von Willebrand Factor Replacement		
Fresh whole blood	12 to 20 mL/kg	Every 24 hours (volume overload limits interval)
Fresh frozen plasma	10 to 12 mL/kg	Every 8 to 12 hours
Cryoprecipitate	1 U/10 kg§	Every 6 to 12 hours (as needed)

* Infusion guidelines for cats (off-label use): Infuse up to maximum dose of 10 mL/kg.

† Platelet count ≥0.5 to 1 $\times 10^9$/mL.

‡ Platelet count ≥5 $\times 10^9$/mL.

§ Unit defined as cryoprecipitate prepared from 200 ml of fresh frozen plasma.

Desmopressin acetate (DDAVP; deamino 8 D-arginine vasopressin) is a synthetic vasopressin analog used in human medicine to treat a variety of hemostatic defects, including acquired platelet function defects and mild vWD.[45] Desmopressin (1 μg/kg given subcutaneously) has been reported to shorten the BMBT and the PFA-100 closure time and to provide surgical hemostasis when administered 30 minutes before surgery to Doberman pinschers with type 1 vWD.[46,47] Desmopressin therapy could be considered for other mild to moderate acquired or hereditary platelet function defects. Close monitoring to determine the extent and duration of response is required, and transfusion should be available if the response to desmopressin is inadequate.

272.4.2 Transfusion Therapy

Transfusion with products to replace red cells (Table 272-9) is indicated for patients with acute blood loss and/or severe anemia that cannot be stabilized with fluid therapy alone.

Transfusion solely to supply platelets (see Table 272-9) rarely indicated or beneficial for thrombocytopenic patients those with acquired platelet function defects. The survival transfused platelets in IMT patients may be less than 1 day, which further limits their clinical utility. Platelet transfusions should be considered, however, in patients with persistent and uncontrolled bleeding or signs of central nervous system hemorrhage. Dogs and cats affected with severe hereditary thrombopathias may benefit from platelet transfusion as prophylaxis for surgery or if they develop severe spontaneous bleeding.[20,48]

Fresh whole blood, as platelet replacement, must be maintained at room temperature, collected in a citrate-based anti-coagulant, and transfused as soon as possible after collection.[49] This product is best used for patients with active bleeding or when no other platelet product is available.

Platelet components are labor intensive to produce, because platelets require special processing and storage techniques to maintain viability. Platelet-rich plasma (PRP) is prepared by centrifugation of whole blood at low G force within hours of collection.[49] The expected platelet yield is approximately 80% of the platelets, in one third volume, of the starting whole blood unit. In accordance with human blood banking standards, units of PRP, prepared from 450-mL units whole blood, are expected to contain at least 50 billion platelets.[50] Low-volume platelet concentrates (PC) are prepared from PRP by a second centrifugation step. Platelet-rich plasma and PC must be maintained at room temperature from the time of collection until transfusion, with administration as soon as possible after collection, and maximum storage of 3 days. A dimethylsulfoxide (DMSO) cryopreserved canine platelet concentrate has recently been offered (Midwest Animal Blood Services, Stockbridge, MI). Pending trials demonstrating its efficacy, this product may widen the availability of platelet transfusion beyond referral centers capable of producing components in-house. Strict attention to aseptic technique is critical during collection and transfusion of platelet products to prevent contamination or disease transmission.

Transfusion to supply active vWF (see Table 272-9) is highly effective in controlling hemorrhage in vWD patients.[51] The best strategy is early, rapid transfusion to increase vWF to hemostatic levels and wound therapy to control hemorrhage from a single site. After initial transfusion, severely affected patients may require a second or third transfusion to sustain hemostasis for an additional 24 to 48 hours. Stabilization of the hematocrit and cessation of active hemorrhage indicate that hemostatic levels of vWF have been attained. Plasma components are the safest and most effective products for treating vWD. Plasma cryoprecipitate is prepared from fresh frozen plasma (FFP) and contains a fivefold to tenfold concentration of active vWF in approximately one-tenth volume of the starting plasma.[49] Cryoprecipitate is the best product for rapid replacement of vWF, but fresh frozen plasma is an acceptable alternative if cryoprecipitate is unavailable. The use of plasma components rather than whole blood prevents sensitization to red cell antigens, eliminates the need for canine type-matched donors, and minimizes the risk of volume overload.

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273 CHAPTER • 273 Inherited Coagulopathies

Anthony P. Carr

Hemostasis results from a complex set of interactions. For convenience, the hemostatic response is divided into three processes: (1) primary hemostasis, (2) coagulation, and (3) fibrinolysis. The main components interacting in these processes are the blood vessels, platelets, and plasma proteins. Erythrocytes and leukocytes play a major role as well. After injury to a blood vessel, vasospasm reduces blood flow. Exposed subendothelium initiates platelet adhesion and platelet-platelet cohesion, resulting in the formation of a temporary platelet plug. At the same time, the coagulation cascade is activated by the vessel injury and by substances released by the platelets. The coagulation cascade leads to the formation of fibrin, which reinforces the platelet plug, forming a blood clot. The generation of fibrin leads to activation of fibrinolytic pathways. Numerous mechanisms, including antithrombin III, protein C, protein S, and tissue factor pathway inhibitor, limit coagulation to the area where it is needed. Although hemostasis is often considered an autonomous "system," it is important to remember that this separation is artificial. Hemostasis is intimately tied to the process of inflammation and vice versa.

273.1 PHYSIOLOGY OF HEMOSTASIS

Hemostasis has been extensively studied, yet researchers' understanding of the *in vivo* process is still undergoing revision. For a long time the processes that occurred *in vitro* were thought to be the same as those that occurred *in vivo*. However, this concept was challenged by the fact that some individuals with factor deficiencies failed to show a bleeding tendency, as would be expected if the initial theories were correct. A good example of this situation is factor XII deficiency, in which test results for the intrinsic coagulation pathway are markedly prolonged, yet no abnormal bleeding tendency is detected. The initial work also focused predominantly on the plasma proteins, often ignoring the vital contribution of cellular elements to the clotting process.

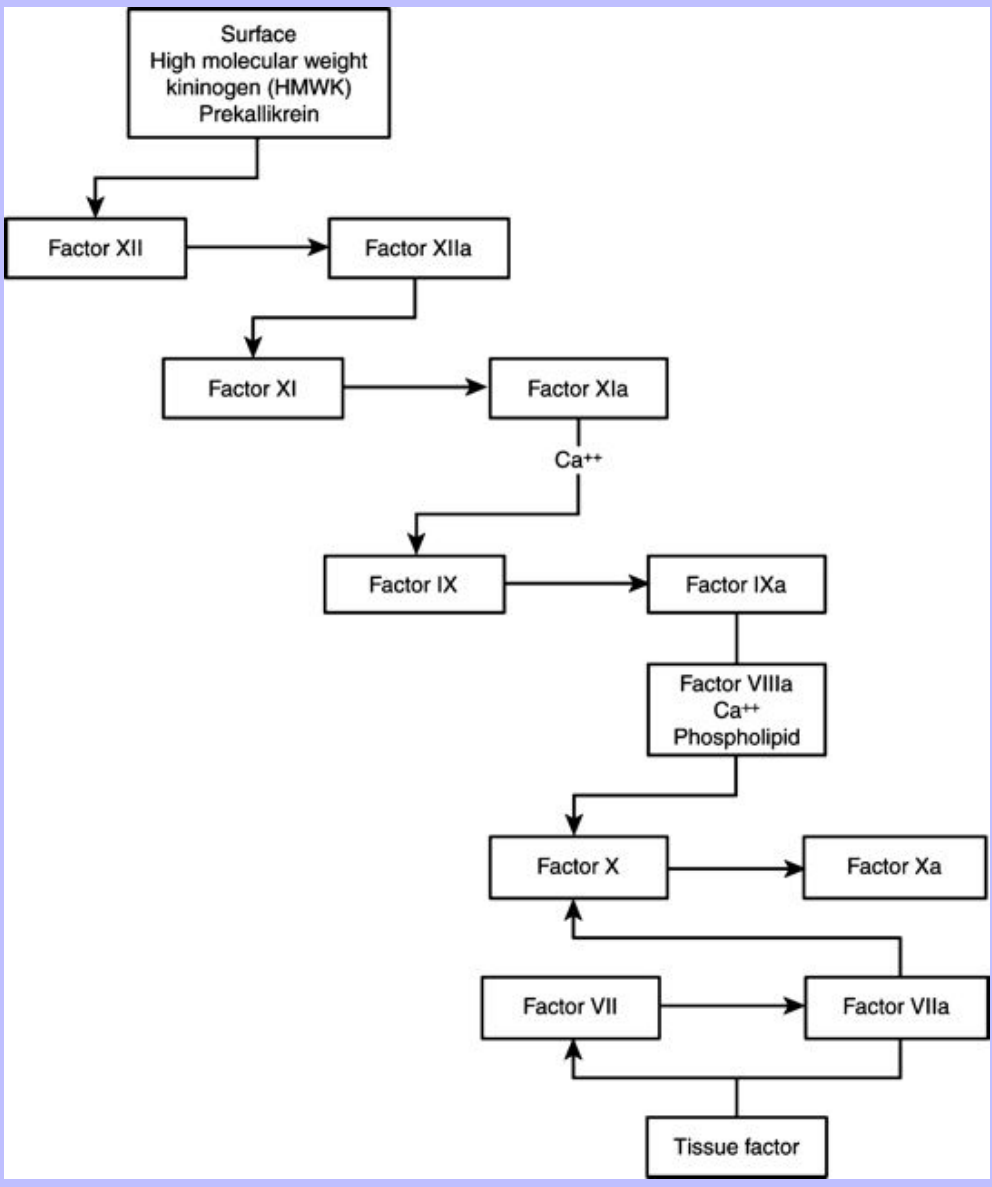
All coagulation factors and cofactors are synthesized in the liver and circulate in the plasma in an inactive form. Factors II, VII, IX, and X are considered vitamin K dependent because they must undergo vitamin K–dependent post-translational modification (gamma carboxylation) before becoming hemostatically active.[1]

273.1.1 Coagulation Cascade

Until recently, the predominant concept of coagulation was that of a cascade that could be divided into the intrinsic, extrinsic, and common pathways. An understanding of this theory is helpful to the clinician, because it reflects the processes that occur with the commonly run coagulation assays. Figure 273-1 shows the intrinsic and extrinsic pathways. The extrinsic pathway was relegated to a relatively minor role. The name *extrinsic* is based on the fact that initiation of clotting with this pathway required the addition of tissue thromboplastin, a substance that does not normally occur in blood, to the test sample. Tissue thromboplastin consists of phospholipid membrane that contains tissue factor. The addition of tissue thromboplastin results in the conversion of factor VII to factor VIIa, which proceeds to form factor Xa from factor X, thereby initiating the common pathway (Figure 273-2) and ultimately leading to the formation of fibrin.

The one-stage prothrombin time (OSPT) tests the extrinsic system. For this test, an excess of tissue thromboplastin is added to the blood sample, and the time that elapses until a clot forms is noted. One reason the extrinsic system was relegated to a minor role was that individuals with hemophilia have normal OSPT values; also, with the intrinsic pathway, it was possible to initiate clotting without the presence of tissue factor.[2]

Figure 273-1 Intrinsic and extrinsic pathways of coagulation. The intrinsic pathway is initiated by conversion of factor XII to factor XIIa, whereas the extrinsic pathway is activated by the conversion of factor VII to factor VIIa.



The intrinsic pathway is initiated by the contact system, which consists of factors XII and XI, high-molecular-weight kinogen, and prekallikrein; initiation occurs with exposure to a negatively charged surface. Both the activated clotting time (ACT) and the activated partial thromboplastin time (aPTT) test this

part of the clotting cascade. Individuals with hemophilia have markedly prolonged aPTT times, because factors VIII and IX are part of the intrinsic pathway.

The common pathway is initiated by activation of factor X, which forms a complex on a phospholipid membrane surface with factor V, factor II (prothrombin), and calcium. This complex, referred to as *prothrombinase,* then generates thrombin. The presence of factor V accelerates the generation of thrombin several hundredfold. Thrombin binds fibrinogen and converts it to soluble fibrin monomers. The monomers polymerize and are cross-linked by factor XIIIa to form insoluble fibrin.

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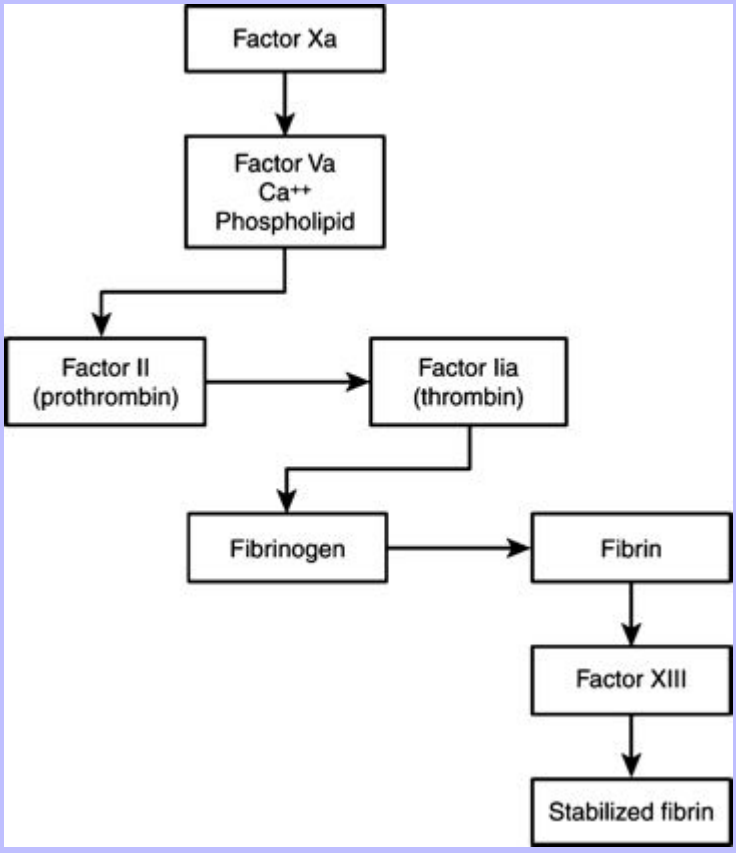
Figure 273-2 The common pathway of coagulation is initiated when factor X is converted to factor Xa by either the intrinsic or the extrinsic pathway.



273.1.2 Revised Theory of Coagulation

The current understanding of the clotting process has resulted from a variety of observations. Traditionally, the intrinsic system has been considered more important than the extrinsic pathway, because it could proceed without requiring the addition of a substance not usually present in the circulation. A challenge to this assumption arose when some individuals from various species were found to be deficient in the contact

system. These individuals had markedly prolonged aPTT results but no detectable predisposition to bleeding. The extrinsic system also was not thought to be important because, as mentioned previously, individuals with hemophilia have normal OSPT values despite a marked bleeding tendency. This is seen when the OSPT test is run in the standard fashion, in which an excess of tissue thromboplastin is used. When less thromboplastin is used, individuals with hemophilia also have prolonged coagulation times. These observations, combined with new research tools that allowed clotting to be studied in more detail, led to a major revision in the theory of how clotting is initiated and sustained. It would be surprising if the current theory remains unaltered in the future.

Factor VII activation is seen as the initiating event for clotting *in vivo*. Factor VII activation occurs when tissue factor is present. Tissue factor is expressed by cells underneath the endothelium, therefore trauma results in clotting. Other cells, such as monocytes and endothelial cells, also can express tissue factor when stimulated by such substances as cytokines and endotoxin. This explains why coagulation abnormalities are so common with a variety of inflammatory and infectious conditions. Production of the factor VIIa–tissue factor complex results in the generation of small amounts of the active factors Xa and IXa. Factor Xa combines with tissue factor pathway inhibitor (TFPI) to rapidly stop further generation of active factors by the factor VIIa–tissue factor complex.[3]

Continued coagulation depends on pathways other than those that initiate clotting.[2] A possible explanation for this is that the thrombin generated initially is able to activate factor XI to factor XIa, and the clotting cascade then can proceed as classically outlined. Because factor XI can be activated directly by thrombin, it becomes clear that contact activation is not a prerequisite for *in vivo* clotting. It may also be that factor IX plays a vital role in promoting further clotting. Factor IX becomes fully activated when both factor Xa and the factor VIIa–tissue factor complex cleave off parts of the molecule. Once factor IXa has been formed, it can lead to further factor Xa generation and thereby to thrombin formation.

Despite its promise, the revised theory of coagulation leaves many questions unresolved, including the variable bleeding tendency seen with factor XI deficiency.

A possible explanation for the inability of the revised theory to explain all the clinical abnormalities seen may be that the theory focuses solely on the coagulation factors and thus does not account for the various cellular components involved in hemostasis.[4] These cellular components differ in their receptors and other properties, which allows for a different coagulation response when the cellular component varies, even if the plasma protein constituents remain the same. An example of this is tissue factor. The amount of tissue factor expressed does not solely determine how effectively a cell can initiate coagulation; the process also depends on the cell's ability to support prothrombinase assembly.[4] Given the complex interactions among cells, coagulation proteins, and inflammatory mediators, it is not surprising that our understanding of the basic physiologic process of clotting is incomplete.

273.1.3 Inhibitors of Coagulation

When coagulation is required, it is vital that it be prevented from becoming a widespread event in the organism; it must be limited to the area where the insult has occurred. A variety of mechanisms help inhibit coagulation, and the most important of these is antithrombin III (AT III). When complexed with endogenous heparin sulfate or exogenously administered heparin, AT III rapidly inactivates thrombin. It can also inactivate Xa and IXa effectively, unlike other activated factors. Each molecule of AT III is consumed with inactivation of a factor. Continued generation of factor Xa by the factor VIIa–tissue factor complex is blocked by TFPI. TFPI is present in plasma and also can be released by activated platelets.

The protein C–protein S system inactivates factors Va and VIIIa. Both of these proteins are vitamin K dependent and are located on the surface of the endothelial cells. They are activated when thrombin is bound to thrombomodulin. Thrombomodulin-bound thrombin is no longer active as a procoagulant molecule, yet it still is able to cleave protein C, thereby activating it.[2]

273.1.4 Fibrinolysis

Along with activation of coagulation, the mechanisms that degrade the clot and allow formation of scar tissue also are activated. The degradation of fibrin is mediated by plasmin, which is generated by the action of plasminogen activators on plasminogen. Tissue plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA) are the main types of activators that occur naturally in dogs and cats. Streptokinase, also a plasminogen activator, is produced by certain streptococci.

When a clot forms, plasminogen is incorporated into the clot. The presence of thrombin causes the endothelium to release t-PA. The affinity for plasminogen is low without a cofactor being present. However, when t-PA is associated with fibrin, it has high catalytic efficacy for cleaving plasminogen.[2] The action of t-PA is predominantly limited to the vascular space, whereas u-PA acts more extravascularly. Once plasmin has been formed, it begins to degrade fibrin. This results in the production of various fibrin degradation products. Some of these degradation products are specific to fibrin, some can also be produced when fibrinogen is cleaved.

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Excessive fibrinolysis also must be prevented, and this is achieved through two main processes: alpha$_2$-antiplasmin inactivates free plasmin rapidly (although it is much less active against fibrin-bound plasmin), and tissue plasminogen activator inhibitor 1 (PAI-1) inactivates t-PA and u-PA.

273.2 INHERITED HEMOSTATIC ABNORMALITIES

Inherited disorders of hemostasis can involve coagulation factor deficiencies, defects of platelet adhesion resulting from decreased levels of von Willebrand factor (vWF), defective platelet function, and blood vessel defects. Inherited coagulation defects related to various coagulation factor deficiencies have been reported in dogs and cats. These defects may be inherited or may arise *de novo* as a result of a genetic mutation.

273.2.1 Hemophilia A (Factor VIII Deficiency)

The most commonly seen congenital coagulation abnormality is hemophilia A. The bleeding tendency associated with this disease is a result of a deficiency in functional factor VIII.[5–9] Factor VIII is located in the intrinsic pathway and acts to significantly increase the rate at which IXa generates factor Xa. With a lack of factor VIII activity, less fibrin is formed; this results in the typical signs of a coagulopathy, such as body cavity bleeding and large hematomas. Hemorrhage into joints may occur as well. An initial platelet plug may form, but fibrin reinforcement for the plug is delayed, reduced, or absent, and the result is rebleeding. Hemophilia A is inherited as a X-linked recessive trait, meaning that most affected individuals are male. This form of hemophilia occurs in humans, dogs and occasionally in cats.[10] The severity of the bleeding is variable. Generally, factor VIII activity must be less than 5% of normal for bleeding to occur spontaneously. Hemorrhage can be severe and occasionally fatal; this is not uncommon in the neonatal period. Patients with hemophilia A have a prolonged aPTT and a normal OSPT. A definitive diagnosis is made by specific factor assay.

273.2.2 Hemophilia B (Factor IX Deficiency)

Hemophilia B, or Christmas disease, has also been described in dogs and cats.[11–14] The disease is caused by a sex-linked deficiency of factor IX, which is a vitamin K–dependent factor. Factor IX is responsible for activation of factor X. Hemophilia B has been identified in at least 19 breeds of dogs as well as mixed breeds.[15] The bleeding tendency seen with this disease is variable but can be severe. As with hemophilia A, the aPTT is prolonged without prolongation of the OSPT. Definitive diagnosis depends on specific factor assay. If serum is added to the plasma on which the aPTT is run, the prolongation will correct, because serum contains factor IX.[16]

273.2.3 Factor XII Deficiency (Hageman Trait)

Occasionally an incidental prolongation of the aPTT in cats is detected, although a bleeding tendency is not present. This finding results from low levels of factor XII, also called *Hageman factor,* an important part of contact activation *in vitro*. This deficiency generally does not compromise hemostasis.[17] The condition is inherited as an autosomal recessive trait and has been found in dogs as well[1]; it also is a normal finding in some marine mammals, birds, and reptiles.[16] Factor analysis is required to make a definitive diagnosis.

273.2.4 Vitamin K–Dependent Factor Deficiency

Vitamin K–dependent factor deficiency is a rare inherited coagulation defect involving all the vitamin K–dependent factors (II, VII, IX, and X) that has been described in Devon rex cats.[18] It probably is an autosomal recessive trait. Bleeding is severe in affected animals, which show prolongation of both the OSPT and aPTT.

273.2.5 Other Coagulopathies

Various other factor deficiencies have been reported in dogs and cats,[1,16] but these problems are rarely seen in practice.

273.3 DIAGNOSIS

A variety of tests are available for diagnosis of hemostatic abnormalities, some of which can be performed in a practice setting. Most coagulation tests require specialized equipment and extensive experience, therefore most of them must be performed in a reference laboratory. A variety of bedside coagulation monitors have been evaluated for use in veterinary medicine.[19]

In-house evaluation of coagulation abnormalities certainly can include the activated clotting time (ACT). This test requires that 2 mL of blood be drawn into a tube containing diatomaceous earth as a contact activator. The tube is incubated at 37° C. The ACT evaluates the intrinsic and common pathways of coagulation. Prolongation of the ACT may be seen with hemophilia A or B, factor XI or factor XII deficiency, vitamin K–antagonist rodenticide intoxication, and heparin therapy. The ACT relies on platelet phospholipids for coagulation, therefore severe thrombocytopenia can lead to increased values. Reported normals were 64 to 95 seconds and 67 to 85 seconds in dogs and 65 seconds or less in cats.[20–22]

Hemostatic testing requires collection of a sample of optimum quality. Venipuncture that involves multiple passes through tissue to obtain a sample is not appropriate for coagulation testing. Holding the vein off too long also can lead to activation of platelets and the fibrinolytic system. The tissue packed into the needle acts to activate coagulation prematurely. Hemolysis and severe lipemia (which often causes hemolysis) can also prevent accurate results. It often is preferable to use vacuum tubes for collection and to use the first sample for tests other than coagulation. The most commonly used anticoagulant is sodium citrate, and the ideal ratio is one part citrate to nine parts blood. The sample should be promptly centrifuged and the plasma harvested. The plasma then should be frozen in a plastic or siliconized glass tube. Plasma should be shipped frozen, because coagulation factors rapidly become inactivated at room temperature.

Reference laboratories can perform two valuable clotting time tests, the aPTT, which tests intrinsic function, and the OSPT, which tests extrinsic function. These tests are also available with point-of-care devices. It is important to remember that reference ranges vary among laboratories and testing methodologies, therefore no universally applicable reference ranges are available. The aPTT tests many of the same factors as the ACT but is considerably more sensitive. A prolonged aPTT with a normal OSPT is a common finding with hemophilia or factor XII deficiency. A prolonged OSPT with a normal aPTT usually is seen only when vitamin K antagonists have been recently ingested; factor VII deficiency is extremely rare. The OSPT predominantly tests the function of factor VII, the coagulation factor with the shortest half-life, as well as common pathway deficiencies. Both the aPTT and OSPT are prolonged with vitamin K deficiencies, severe liver disease, and disseminated intravascular coagulation and when vitamin K–antagonist rodenticide poisoning occurs more than 12 to 24 hours before testing.

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A variety of other assays are available through reference laboratories. Specific factor analysis can be run. It is vital that the laboratory that runs the factor analysis have considerable experience with veterinary samples, because there can be discordant results if the same protocols are used as in humans.

273.4 TREATMENT

Treatment of hemostatic abnormalities requires careful assessment and determination of the particular abnormality. Many of the diseases described are not amenable to cure, and at best short-term control is possible. An exception is the combined vitamin K–dependent factor deficiency, in which vitamin K supplementation can normalize the clotting ability. In humans there is considerable interest in developing gene therapy for most of these inherited coagulation disorders. Currently this is not an option in pets, therefore the goal is to control clinical signs and avoid situations in which bleeding may occur. It is especially important to avoid trauma in an animal with bleeding tendencies, especially trauma produced iatrogenically through biopsy, surgery, venipuncture, restraint, or intramuscular administration of medications. It is also important to avoid medications that can interfere with primary hemostasis, such as nonsteroidal anti-inflammatory drugs and phenothiazines.

Treatment of inherited disorders of hemostasis consists of transfusion therapy, which generally is instituted only when life-threatening hemorrhage is present or prior to surgery. Which type of transfusion is most appropriate depends on the patient's presenting signs. If anemia is present, use of fresh whole blood may be expedient, because it replaces red cells and coagulation factors. If anemia is not present, the use of plasma is preferred. Fresh frozen plasma contains all the coagulation factors in their active form and can be used to treat any coagulopathy. Slowly thawing fresh frozen plasma and decanting off the supernatant generates cryoprecipitate and cryosupernatant. Cryoprecipitate contains factor VIII, fibrinogen, and vWF in high concentrations. This makes cryoprecipitate the blood component of choice for therapy of von Willebrand disease, fibrinogen deficiency, and hemophilia A. The highly concentrated nature of cryoprecipitate allows the coagulation factors from many units of plasma to be transfused without the worry of volume overload. Cryosupernatant can be used in the treatment of coagulopathies that do not involve the factors removed in the cryoprecipitate.

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274 CHAPTER • 274 Acquired Coagulopathies

Robert M. DuFort

Linda Matros

274.1 VITAMIN K DEFICIENCY

Vitamin K deficiency is one of the most commonly encountered acquired coagulopathies in veterinary medicine. Vitamin K is required for the activation of a group of proteolytic enzymes known as *serine proteases,* which include coagulation factors II, VII, IX, and X, and the anticoagulant proteins C and S. If left untreated, vitamin K deficiency results in alterations in the extrinsic, intrinsic, and common coagulation pathways and ultimately clinically manifests as bleeding.

Vitamin K is a fat-soluble vitamin found in three forms: K_1 (phytonadione), K_2 (menaquinone), and K_3 (menadione). Vitamin K_1 is found in green, leafy vegetables and vegetable oils. It is absorbed via the lymphatics in the proximal small bowel. Bile acids and dietary fats facilitate absorption of vitamin K_1. Vitamin K is also synthesized by microflora in the ileum and colon. Vitamin K_3 is a synthetic form. Oral doses are absorbed via capillaries in the colon. The daily requirement of vitamin K is small (1.25 µg/kg/day in the dog), and the liver stores several days' supply. Consequently, animals fed a commercial diet rarely experience vitamin K deficiency (Box 274-1).

Antagonism of vitamin K is by far the most common cause of vitamin K deficiency. Vitamin K antagonism is brought about by the ingestion of anticoagulant rodenticides.

The vitamin K–dependent coagulation factors (II, VII, IX, and X) are synthesized by the liver as inactive proteins, which contain glutamyl residues that must be carboxylated for the proteins to become active. The carboxylation reaction requires reduced vitamin K. As the coagulation proteins become carboxylated, vitamin K is oxidized by the enzyme vitamin K epoxidase to become vitamin K epoxide. To carboxylate other coagulation protein molecules, the vitamin K epoxide must again be reduced by vitamin K epoxide reductase. Anticoagulant rodenticides act by inhibiting vitamin K epoxide reductase. As a result, vitamin K epoxide and inactive (noncarboxylated) coagulation factors accumulate in the blood (Figure 274-1). The half-lives of coagulation factors II, VII, IX, and X are short (41, 6.2, 13.9, and 16.5 hours, respectively).

274.1.1 Box • 274-1 Conditions Associated with Vitamin K Deficiency

Neonate born to malnourished mother

Decreased synthesis of vitamin K by intestinal microflora (due to chronic antibiotic therapy)

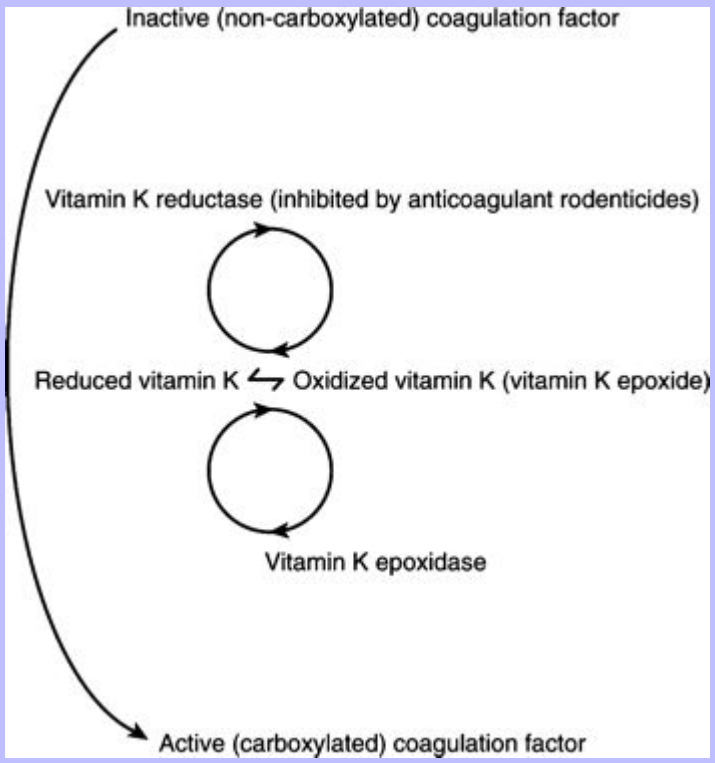
Decreased vitamin K absorption

Complete bile duct obstruction

Pancreatic exocrine insufficiency

Lymphangiectasia

Figure 274-1 Vitamin K carboxylation cycle.



Anticoagulant rodenticides were developed as a result of the observation of an acquired coagulopathy in cattle that had ingested moldy sweet clover. A coumarin derivative in sweet clover is converted to dicoumarol by a fungus. The first-generation anticoagulants, warfarin and pindone, were developed for vermin control and as human antithrombotic medicines after this discovery. The second-generation anticoagulant rodenticides (bromadiolone, brodifacoum, and diphacinone) are more potent because of their longer half-lives and lower incidence of acquired drug resistance. Despite the longer half-lives of the second-generation anticoagulant rodenticides, poisoning of companion animals that ingest poisoned rodents is an uncommon event. Various concurrently administered drugs (Box 274-2) and coexisting conditions (Box 274-3) may exacerbate the toxicity of anticoagulant rodenticides.

To diagnose anticoagulant rodenticide poisoning, the clinician must assess the history and clinical signs and evaluate the results of appropriate laboratory tests. The histories of potentially poisoned pets vary from direct observation of ingestion to the passing of suspicious material in the feces. Potential exposure to anticoagulant rodenticides may be a relative certainty or may be unknown, depending on the animal's environment. The onset of clinical signs normally occurs 2 to 5 days after ingestion of the anticoagulant rodenticide, and signs may

escalate quickly after they are first detected. Clinical signs are the result of hemorrhage, which may vary from mild to severe. Severe hemorrhage can result in hypovolemia and organ dysfunction. Bleeding into the thoracic cavity or cranium is especially critical.

Laboratory test results may be normal or abnormal, depending on the amount of anticoagulant ingested and the time elapsed since ingestion. The first laboratory test to show an abnormal (prolonged) result is the PIVKA (proteins induced by vitamin K absence or antagonism) test, followed by the prothrombin time (PT), and eventually the partial thromboplastin time (PTT). The PIVKA test, a sensitive indicator of anticoagulant rodenticide ingestion, may be prolonged as early as 12 hours after ingestion; the PT may require 36 to 72 hours to become abnormal. The PT is affected by numerous other coagulation disorders, such as disseminated intravascular coagulation (DIC), hepatic disease, and hereditary factor deficiencies. In contrast, the PIVKA test is sensitive primarily to the presence of precursor proteins, which accumulate in the absence of vitamin K. *1934*
Comparison studies have shown that the PIVKA test has greater sensitivity and specificity than both the PT and *1935*
the activated partial thromboplastin time (aPTT) in the diagnosis of dogs with anticoagulant poisoning.

274.1.2

Box • 274-2 Mechanisms and Drugs That Affect Anticoagulant Rodenticide Toxicity

Platelet inhibition

- Aspirin
- Nonsteroidal anti-inflammatory drugs

Possible inhibition of Vitamin K epoxide reductase

- Sulfonamides (sulfaquinoxaline)
- Cephalosporins (cefmetazole)

Decreased anticoagulant rodenticide protein binding

- Oxyphenbutazone
- Diphenylhydantoin
- Sulfonamides
- Corticosteroids

Phenylbutazone

Inhibition of hemostasis

Promazine-type tranquilizers

Nitrofurans

Local anesthetics

Antihistamines

Hormones (testosterone, RA)

Anabolic steroids

Epinephrine

Increased hepatic metabolism (induction of microsomal enzymes)

Carbamazine

Antibiotics

Rifampin

Chloramphenicol

Barbiturates

274.1.3 Box • 274-3 Conditions That Exacerbate Anticoagulant Rodenticide Toxicity

High lipid diet

Facilitates rodenticide absorption

Decreases anticoagulant protein binding

Uremia

Promotes platelet inhibition

Decreases protein binding

Decreases excretion of unbound anticoagulant

Thrombocytopenia

Disseminated intravascular coagulation

Measurement of the anticoagulant rodenticide in the serum or tissues of an animal confirms the diagnosis of anticoagulant toxicosis. High-performance liquid chromatography and gas chromatography tests capable of identifying specific anticoagulants are available in many diagnostic laboratories. The results of these tests are not compromised by previous therapy with vitamin K, therefore a diagnosis can still be made even in successfully treated animals.

Therapy varies with the stage of the disease. With an acute known ingestion, emetics, adsorbents, and cathartics are used to minimize absorption. Most clinicians choose to begin vitamin K therapy even in asymptomatic patients regardless of the success of attempts to limit absorption. Vitamin K_1 is the treatment of choice. The initial treatment is administration of vitamin K_1 by subcutaneous injection at a dosage of 2.5 to 5 mg/kg. The dose should be divided and given in several sites. Oral vitamin K_1 therapy follows in 6 to 12 hours, at a dosage of 1.25 to 2.5 mg/kg given twice daily. If absorption of the rodenticide is thought to be minimal, treatment may be discontinued after 7 days. The PT should be tested 48 hours after termination of therapy. If the PT is prolonged, the patient is treated with oral vitamin K_1 for 2 more weeks. If the initial post-therapy PT is normal, a second PT test should be done 48 hours later. If the second post-therapy PT is normal, vitamin K therapy may be terminated.

274.2 LIVER DISEASE

The liver is critical to coagulation homeostasis. It is the site of synthesis of most of the procoagulants (clotting factors), the anticoagulants (antithrombin III, $alpha_2$-macroglobulin, $alpha_1$-antitrypsin, $alpha_1$-acid glycoprotein, and proteins C and S), and the fibrinolytic proteins (plasminogen, plasminogen activators, plasminogen proactivators, antiplasmins, and inhibitors of plasminogen activators and proactivators). Liver disease may result in hemorrhage caused by decreased coagulation factor synthesis, synthesis of abnormal coagulation factors, or excessive consumption. Ironically, even the most severe liver disease is rarely accompanied by bleeding. There are several reasons for this. The liver produces a large quantity of coagulation factors. Fibrinogen, for example, can be measured in concentrations up to 0.4 g/dL in the plasma of normal animals. It is commonly stated that coagulation factor concentrations must fall below 15% for coagulation to be compromised. Edema and anasarca due to hypoalbuminemia, which occur at 75% to 80% liver compromise, are rarely accompanied by bleeding,

even with provocation (liver biopsy). The liver also has a tremendous regenerative capacity and can return to normal function after many acute hepatopathies. Some coagulation factor concentrations actually increase with liver disease (i.e., fibrinogen, factor V, and von Willebrand factor [vWF]). The liver also is the largest macrophage-containing organ in the body, with tremendous phagocytic activity capable of rapidly clearing activated coagulation factors and products of fibrinolysis (fibrin degradation products [FDPs]).

Although 66% to 85% of patients with hepatopathies have abnormal results on one or more coagulation tests, fewer than 2% actually develop hemorrhage. When bleeding occurs, it usually is associated with concurrent disease (thrombocytopenia, thrombopathy, or cardiovascular disease). Factors that determine whether liver disease results in hemorrhage are the nature and severity of the disease and the rate of onset.

274.2.1 Box • 274-4 Potential Sequelae of Neoplasia That May Result in Thrombosis or Hemorrhage

Thrombocytopenia

Thrombopathy

Disseminated intravascular coagulation

Microangiopathy

Endothelial invasion by neoplastic cells

Treatment with chemotherapeutic agents

A prospective evaluation of coagulation tests in cats with different types of liver disease showed the PIVKA test to be more sensitive than either the PT or the aPTT for evaluating cats at risk for increased bleeding. Hepatobiliary disease, which disrupts enterohepatic circulation of bile acids, leads to a depletion of coagulation factors and an increase in procoagulant proteins (PIVKAs) by decreasing the intestinal absorption of vitamin K. The degree of vitamin K deficiency parallels the severity of liver disease and the probability of clinically significant bleeding. Because the PIVKA test is the first coagulation test to become abnormal in states of vitamin K deficiency, it appears to be superior to either the PT or APTT in identifying cats at risk for increased hemorrhage from liver disease.

274.3 NEOPLASIA

Neoplastic disease may result in thrombosis or bleeding by several mechanisms (Box 274-4).

In dogs with mammary carcinoma, abnormalities in one or more coagulation tests are found in two thirds of the patients. The frequency of abnormal test results correlated with the stage of disease. Dogs with stage III or stage IV neoplasia had the highest number of abnormal test results.

Chemotherapeutic agents may further exacerbate bleeding tendencies (Table 274-1). Studies have shown that up to 83% of untreated dogs had laboratory evidence of abnormal coagulation. In cats with neoplasia, 20% had coagulation abnormalities. Among the patients with abnormal laboratory results, thrombocytopenia was most common (36%), followed by a prolonged PTT (32%), and altered fibrinogen concentrations (25%). Canine lymphoma/leukemia and hemangiosarcoma are neoplasms that are commonly associated with hemostatic abnormalities. Treatment of the hemorrhage must first address the inciting cause, the neoplasia.

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Table • 274-1 Chemotherapeutic Agents That May Affect Coagulation

DRUG	MECHANISM
Bleomycin, CCNU, cytosine arabinoside, melphalan, methotrexate, platinum, doxorubicin, Actinomycin D	Thrombocytopenia
Vincristine, vinblastine	Thrombocytosis
Melphalan, vincristine	Thrombopathy
L-Asparaginase	Inhibition of protein (clotting factor) synthesis
Actinomycin D	Vitamin K antagonism
Melphalan	Dysfibrinogenemia
Doxorubicin, daunorubicin	Increased fibrin and fibrinogen lysis

274.4 ACQUIRED INHIBITORS OF COAGULATION

Acquired anticoagulants are uncommonly recognized in veterinary medicine. These inhibitors may be directed against one or more specific coagulation factors.

There are several types of inhibitors. The most common type comprise the immunoglobulins of the IgG class. They occur most often in patients receiving multiple whole blood or plasma transfusions. These immunoglobulins have also been associated with therapy with certain drugs (e.g., penicillin, phenytoin) and with immune-mediated diseases (e.g., systemic lupus erythematosus), liver disease, lymphoproliferative diseases, DIC, and other conditions. They may result in abnormal coagulation test results, thrombosis, or hemorrhage, depending on the coagulation factor against which they are directed.

Immunoglobulins should be suspected when coagulation test abnormalities do not fit the clinical presentation. Prior administration of antithrombotic drugs or improper sample collection must be ruled out. Because their effect on coagulation test results occurs by a mechanism different from that produced by a factor deficiency, they may be identified with a plasma mixing procedure. If a factor deficiency is present (i.e., hemophilia A or B), the addition of plasma from a species-specific pool corrects the coagulation screening test. This same procedure does not correct coagulation test results if an inhibitor is present.

In contrast to the immunoglobulin class of inhibitors, nonspecific inhibitors are not targeted on any single coagulation factor; rather, they interfere with the interactions of clotting factors on a phospholipid surface. These nonspecific inhibitors affect the aPTT more than the PT and also fail to correct in mixing studies. The release of heparin, as can be seen with canine mast cell tumors, and metalloproteinases (found in snake venom) are other examples of acquired coagulation inhibitors.

274.5 THROMBOSIS

A delicate balance must be maintained between procoagulant, anticoagulant, and fibrinolytic factors. A change in the blood flow, vascular endothelium, or coagulation factors can result in thrombosis as well as hemorrhage.

Thrombophilia is a term that describes the hypercoagulable (prethrombotic) state, which may be due to a familial, congenital, or acquired abnormality that results in a predisposition to thrombosis. *Thrombosis* is a secondary disease process associated with many primary diseases, including immune-mediated hemolytic anemia, hyperadrenocorticism, protein-losing enteropathy, systemic amyloidosis, and canine parvovirus.

Pulmonary thromboembolism (PTE) has been observed in up to 30% of canine cancer patients. A retrospective study of dogs diagnosed with autoimmune hemolytic anemia (AIHA), found evidence of thromboembolism in 20 of 25 dogs necropsied. The type of thrombi that forms depends on local blood flow characteristics. Coagulation, or red, thrombi are primarily made up of red blood cells and fibrin. They occur in areas of slow or occluded blood flow, such as veins. At the other extreme are platelet, or white, thrombi, which form in areas of high blood flow, such as at heart valves. They are composed primarily of platelets and fibrin. Mixed thrombi are an intermediate type found primarily in the pulmonary vasculature.

The clinical signs of a thrombus depend on the organ affected, but they are ultimately due to compromised blood flow to the organ. The thrombus may occlude blood flow locally, or a portion of the thrombus may break free and lodge downstream, where the vessel caliber is smaller and the blood flow slower. Pulmonary thrombosis is associated with acute dyspnea. Renal arterial thromboembolism may be associated with acute renal failure. Detection of thromboemboli is difficult without specialized diagnostic techniques, such as angiography, venography, Doppler ultrasonography, or ventilation-perfusion scintillation scans. The results of routine coagulation tests such as the PT and PTT may be shortened, but they often are within normal limits. For this reason, an awareness of conditions that may result in a hypercoagulable state (e.g., glomerulonephritis) must be kept in mind.

With glomerulonephritis, severe proteinuria may ensue. One of the proteins lost is antithrombin III (AT III), which is about the size of albumin. AT III can be measured in many university and commercial laboratories. AT III levels are a good predictor of the potential for thrombi formation. AT III values between 60% and 75% are associated with an increased risk of thrombosis. Values less than 60% are often associated with irreversible organ damage. Other specialized laboratory tests, such as the chromogenic factor VII assay, platelet aggregation assays, and protein C assay, may be performed is some university coagulation laboratories.

Treatment is directed toward reducing thrombogenesis, in addition to thrombolytic therapy. Reduction of thrombogenesis is achieved with anticoagulant therapy (heparin and warfarin) and reduction of platelet function through the use of platelet inhibitors (aspirin, dipyridamole, and ticlopidine). Thrombolytic therapy includes the use of tissue plasminogen activator (t-PA), streptokinase, or urokinase. Heparin therapy depends on an adequate plasma concentration of AT III. With a low AT III concentration, one or more plasma transfusions may be required for heparin to be effective. Coumadin and other warfarin products inhibit vitamin K–dependent coagulation factors, but they require several days to achieve the desired effect.

274.6 DISSEMINATED INTRAVASCULAR COAGULATION

Disseminated intravascular coagulation (DIC), also called *consumptive coagulopathy,* is the end result of systemic thrombosis. It is a well-recognized clinical syndrome in dogs but is rarely diagnosed in cats. DIC is always a secondary disease. The inciting causes of DIC are the same as those for thrombosis. The primary disease causes widespread thrombosis, which results in the consumption of clotting factors and platelets and initiates uncontrolled fibrinolysis. These disturbances in the coagulation system lead to massive hemorrhage, tissue hypoxia, organ failure, and often death. DIC may be acute and uncompensated or chronic and compensated. Laboratory test abnormalities may vary, depending on the current stage of disease. DIC may be seen in up to 50% of dogs with splenic hemangiosarcoma. Hyperthermia is one of the inciting diseases that may

have a more favorable prognosis, because this condition can be treated fairly rapidly. Death is coming if organ dysfunction from thrombi or anemia secondary to hemorrhage is severe.

The five objectives of the treatment of DIC are: (1) to ensure adequate tissue perfusion, (2) to eliminate the initiating cause, (3) to support target organs susceptible to microthrombi, ischemia, and hemorrhage, (4) to replace blood components, and (5) to provide heparin therapy. 1936 1937

Clinically suspected cases of DIC can be verified by laboratory testing. Typically, the patient's platelet count drops, and the aPTT, PT, and thrombin time (TT) increase. Fibrin degradation products (FDPs) are elevated, and the fibrinogen level is decreased from its previous value. A retrospective survey of 252 dogs diagnosed with DIC showed thrombocytopenia (86%), a prolonged PT (61%), an increased aPTT (92%), an increased TT (32%), and increased FDPs (95%). Interestingly, on examination of red cell morphology, schistocytes were noted in only 10% of the cases.

Traditionally, assays for FDPs were used to diagnose and manage disseminated intravascular coagulation. However, these assays lacked specificity, because they used polyclonal antibodies against fibrinogen, fibrin, and fibrin fragments. They also required serum samples collected in special FDP tubes, because heparin interfered with the test. For these reasons, interest is growing in a newer test, the D-dimer test. D-dimer is a protein formed as a result of plasmin degradation of cross-linked fibrin. During blood coagulation, fibrinogen is converted to fibrin by the action of thrombin. The resulting fibrin monomers polymerize to form a insoluble gel of non-cross-linked fibrin. This fibrin gel is further converted to cross-linked fibrin by thrombin-activated factor XIII to form an insoluble fibrin clot. Production of plasmin, the major clot-lysing enzyme, is triggered by the formation of a fibrin clot. Although fibrin and fibrinogen are both cleaved by plasmin to yield FDPs, only degradation products from cross-linked fibrin contain D-dimer. Therefore an elevated D-dimer level is a specific marker of clot lysis. This test has an extraordinary negative predictive value. In other words, a negative D-dimer test excludes DIC with a confidence level of 99.5%. The test can be run in the clinic by a semiquantitative rapid latex agglutination method using blood samples collected in ethylenediamine tetra-acetic acid (EDTA) or heparin. Although the rapid latex agglutination test lacks the necessary sensitivity for reliable diagnosis of pulmonary thromboemboli, recently a more sensitive enzyme-linked immunosorbent assay (ELISA)-based assay has become available and is showing promise in this area.

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275 CHAPTER • 275 Leukocyte Disorders

Charles W. Brockus

Collectively, leukocytes are identified in the peripheral blood as granulocytes (neutrophils, eosinophils, and basophils) and mononuclear cells (monocytes and lymphocytes). These cells actively participate in the innate and adaptive immune system. The activity or morphology of leukocytes can be affected by drug therapy, toxins, infectious organisms, neoplastic disorders, and/or hereditary factors.

Leukocyte disorders occur in dogs and cats, from neonates to aged animals, and cause a variety of clinical features ranging from normal to moribund. In addition, combinations of morphologic and/or functional abnormalities can occur, ranging from unique morphology with no clinical consequence to normal morphology associated with severe clinical signs. Neutrophilic or lymphocytic cell functions are usually impaired in functional abnormalities, and morphologic changes often include all leukocytes.

Most leukocyte disorders are rare and are reported once and/or are observed in a specific breed (e.g., smoke blue Persian cats, gray collies, Jack Russell terriers, Irish setters), implicating a specific hereditary pattern associated with the signalment of the particular breed. The history and physical examination, therefore, often provide important initial information about an abnormality.

Treatment often is unnecessary for morphologic anomalies and is unavailable or impractical for lethal diseases associated with leukocytes. Therefore identification of these anomalies and disorders is important, so as to avoid unnecessary diagnostic testing and treatments.

275.1 PELGER-HUËT ANOMALY

Heterozygous Pelger-Huët anomaly (P-H) is a benign congenital disorder of leukocyte development. It is thought to be transmitted as an autosomal dominant trait in dogs and cats; however, incomplete penetrance has been observed in Australian shepherds.[1,2] The heterozygous form is present in dogs and cats because the homozygous form is lethal *in utero*. The homozygous phenotype is characterized by skeletal abnormalities in rabbits; however, the rare humans with P-H homozygotes appear normal and have survived into their nineties.[1]

The distinguishing cytologic characteristic of P-H is hyposegmentation of nuclei in granulocytes and monocytes in the presence of a fully mature, coarsely clumped chromatin pattern.[1] Nuclear morphology often is variable; the nuclei may be round, oval, dumb-bell shaped, peanut shaped, band, or even bilobate.[1] The bilobate shape consists of two nuclear lobes connected by a fine filament, often referred to as a *pince-nez* or *eyeglass* form nucleus.[1] Careful attention to granulocyte morphology and the presence of hyposegmented nuclei in eosinophils and other cell lines may yield indications of this anomaly. Female Barr bodies are absent or extremely rare in P-H.[1]

Pelger-Huët anomaly has been reported sporadically in both mixed-breed and purebred dogs, including Australian shepherds; cocker spaniels; German shepherds; English-American (Walker) foxhounds; Boston terriers; Australian cattle dogs (blue heelers); border collies; basenjis; black and tan, blue tick, and redbone coonhounds; and Samoyeds.[1] An incidence of 9.8% has been reported for Australian shepherds.[2] P-H has been reported in only eight domestic shorthair cats.[1]

Biochemical assays are normal in P-H dogs, including nitroblue tetrazolium (NBT) dye reduction, hexose monophosphate shunt activity, superoxide generation, chemiluminescence, protein iodination, phagocytosis, and bactericidal activity.[1]

Cytochemical staining with Sudan black B, naphthol ASD chloracetate esterase, peroxidase, alkaline and acid phosphatase, alpha-naphthyl-acetate esterase, and periodic acid–Schiff (PAS) has not detected abnormalities in dog neutrophils.[1]

Ultrastructurally, nuclear changes associated with P-H include nuclear hyposegmentation, nuclear clefts, coarse heterochromatin, and normal cytoplasmic granules.[1]

275.1.1 Hematologic Manifestations

Hematologic manifestations of P-H often are reported as a persistent degenerative left shift without toxic changes. These findings are unexpected on a routine complete blood count (CBC) from a clinically normal animal.[1] Earlier precursors, such as myelocytes, metamyelocytes, and bands, may be reported; however, the chromatin of these cells is fully matured (well clumped).[1] Because P-H often is confused with a degenerative left shift, it is of practical importance that the anomaly be recognized. Unnecessary, expensive, and potentially invasive laboratory tests and treatments can be avoided with proper diagnosis. Many dogs are treated with a variety of antibiotics without response because of this suspected degenerative left shift. A veterinary clinical pathologist can assist in the diagnosis of P-H.

P-H must be differentiated from pseudo–P-H, which often is a transiently acquired condition that resolves with proper diagnosis and treatment.[1] Pseudo–P-H has been associated with a number of diseases, including various forms of leukemia and preleukemic conditions, and with drug therapy, such as with antineoplastic drugs and ibuprofen.[1] Drug-associated changes are idiosyncratic and resolve after treatment is withdrawn.

275.1.2 Treatment

Treatment of P-H is not necessary because neutrophil function is not altered.

275.2 CHÉDIAK-HIGASHI SYNDROME

Chédiak-Higashi syndrome (CHS) is a rare inherited autosomal recessive trait found in humans; beige mice; rats; Arctic foxes; a killer whale; Hereford, Japanese black, and brangus cattle; mink; and smoke blue Persian cats.[3–5] This syndrome has not yet been identified in dogs.

CHS is typically characterized by partial oculocutaneous albinism, photophobia, neurologic abnormalities, bleeding abnormalities, and recurrent infections, which generally result in death at an early age.[3] Some researchers have not observed an increased tendency to develop infections in CHS cats, but a colony of CHS cats demonstrated neonatal kittens that were markedly more susceptible to infections (bacterial, viral), and some died from hemorrhage, which contributed to a lower average survival time compared with normal cats.[6] Susceptibility to bacterial infections is associated with multiple defects in the defense system. Neutropenia occurs as a result of impaired marrow release of mature neutrophils. Defective intracellular killing of phagocytosed bacteria also is a factor.[3]

Persian cats with the hereditary genes for CHS have a “blue smoke” coat color that is lighter than the blue smoke coats of Persian cats without CHS.[4] Ocular abnormalities also are present, such as photophobia and lighter irises (light green, light yellow, or light yellow-green). Many affected cats also have congenital cataracts and a red fundic light reflection (compared to the yellowish green of normal Persian cat fundi), as well as less fundic pigmentation.[4] Tapetal regions may not be apparent, and the underlying choroidal vasculature is only partly visible.[4] The tapetal defect is associated with tapetal rod degeneration in tapetal cells in 2-to 4-week-old kittens.[3] Abnormal auditory brain stem responses have been the only neurologic abnormalities identified in CHS cats.[7]

Although the gene abnormality associated with CHS has not been identified in cats, it has been defined as the homologous *beige* gene in mice and humans, which is a 5 kilobase pair deletion.[3] The function of this gene is unknown.[3] CHS was hypothesized to be caused by microtubular formation abnormalities, but this has been disproven.[3]

275.2.1 Hematologic Manifestations

Hematologically, neutrophils, eosinophils, and basophils contain enlarged, lightly eosinophilic cytoplasmic granules that can be observed with Wright's staining (Romanowsky stain).[3] Occasionally, monocytes and lymphocytes may contain a single eosinophilic cytoplasmic granule.[3] Histologically, melanocytes in hair shafts contain enlarged melanin granules, and renal tubular epithelial cells contain enlarged granules.

Prolonged bleeding times (three times normal), manifested as hematomas after surgical procedures, are the result of a platelet storage pool defect (SPD). Impaired platelet aggregation associated with a virtual absence of adenosine diphosphate (ADP) and serotonin (dense granules) may account for the abnormal aggregation.[3] Platelet counts and coagulation times (prothrombin time [PT] and partial thromboplastin time [PTT]) are within reference intervals.[4]

275.2.2 Diagnosis

A presumptive diagnosis can be made by observation of a Persian cat with a light blue smoke color, lightly colored irises, red fundic reflection, depigmented fundic area, and bleeding tendencies.[4] Also, a hair shaft examination can be performed. Hair is extracted from a cat suspected of having CHS and from a normal cat. The hair shafts are placed on a microscopic slide, immersion oil is added, and a cover slip is gently pressed over the hair shafts.[4] Examination under low or high dry power reveals that, unlike the normal hair shaft, the hair of the CHS cat shows enlarged, clumped melanin granules.[4]

With Romanowsky staining, CHS cytoplasmic granules in neutrophils appear as light eosinophilic inclusions that must be differentiated from Döhle bodies associated with neutrophil toxicity.[4] If the composition of the granules is in question, the differentiation can be made using peroxidase staining (CHS granules stain black).[4]

275.2.3 Treatment

Cats with CHS do not require continuing treatment; however, great care should be taken to control hemorrhage due to the platelet SPD and prolonged bleeding times. Platelet transfusions can temporarily

correct the bleeding time if surgical procedures are to be performed.[3] Long-term correction of neutrophil and platelet function in CHS is possible only through bone marrow transplantation (BMT).[3] BMT performed in cats has corrected the neutrophil and platelet defects, but no effect has been seen on lysosome distribution in liver or kidney cells.[3] Neutrophil function improves temporarily after treatment with recombinant canine granulocyte-colony stimulating factor (rcG-CSF) or interleukin-2 (IL-2) in cats.[3]

Although the blue smoke coat color is quite beautiful in Persian cats with CHS, this is an undesirable trait to propagate. Breeders should be counseled against using affected cats or carrier cats, which are phenotypically normal. Because CHS is an autosomal recessive trait, both the sire and dam that produce offspring affected with CHS are obligate carriers and should be removed from the breeding stock. Administration of drugs that affect platelet function, such as cyclo-oxygenase inhibitors, is contraindicated in CHS cats.[3]

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275.3 CANINE LEUKOCYTE ADHESION DEFICIENCY

Canine leukocyte adhesion deficiency (CLAD) is a fatal defect inherited as a homozygous autosomal recessive trait in Irish setters and rare Irish setter–cross-breed dogs. It is characterized by a defect in neutrophil adhesion and function. Heterozygous dogs appear healthy in all respects. Initially, this trait was reported in 1975 as canine granulocytopathy syndrome.[8] An Irish setter had persistent soft tissue infections, lymphadenopathy, omphalophlebitis, gingivitis, and persistent profound leukocytosis (primary neutrophilia).[8]

A 1987 case report identified an Irish setter–cross that did not express leukocyte Mo1, leukocyte function–associated antigen-1 (LFA-1), or Leu M5 glycoproteins using CD11/CD18 antibodies, indicating a common beta$_2$-integrin subunit disorder.[8] A defect in neutrophil chemotaxis, induced aggregation, and phagocytosis of opsonized particles also were detected in this dog.[5]

275.3.1 Clinical Features

Clinical, radiologic, and pathologic information was obtained from a study of 12 Irish setter puppies 8 to 15 weeks of age from six different litters.[9] These dogs presented with generalized lymphadenopathy, gingivitis, salivation, skin lesions (ulcers and local dermatitis), generalized pain, weakness, recurrent fever, vaginitis, poor weight gain, anorexia, emaciation, furunculosis (without the formation of a neutrophilic exudate), dull haircoat, and lameness with bone lesions (thickened mandibula, distal radius, ulna, tibia, and fibula). All the dogs in the study were euthanized and underwent postmortem examination. Histopathology of affected tissues showed a lack of neutrophil infiltration (impaired neutrophilic exudate formation).[9] CLAD dogs do not respond well to antibiotic therapy and thus rarely live beyond 6 months.[9]

275.3.2 Pathologic Features

Neutrophils in dogs with the homozygous form of this hereditary trait have a deficiency of leukocyte surface glycoproteins associated with leukocyte adherence and egress into surrounding tissues.[8,9] These cells appear morphologically normal by light microscopy. Dogs present within weeks of birth with associated clinical signs.

The family of glycoproteins referred to as beta$_2$-integrins (CD11/CD18) consist of alpha subunits (CD11a, CD11b, CD11c, CD11d) noncovalently bonded with a common beta subunit (CD18).[10] These subunits make

up CD11a/CD18 (LFA-1; $\alpha_L\beta_2$), CD11b/CD18 (Mac-1/Mo-1; $\alpha_M\beta_2$), CD11c/CD18 (gp 150,95; $\alpha_X\beta_2$), and CD11d/CD18 ($\alpha_d\beta_2$) cell surface receptors.[1] CD8 glycoprotein is critical to formation of the integrin heterodimers for cell-cell adhesion events.[8,10,11] In addition, beta$_2$-integrin heterodimer CD11b/CD18 serves as major receptor for C3b opsonic complement and is necessary for phagocytosis and respiratory burst activation. Heterozygous dogs have normal expression of CD11b/CD18. Failure to express beta$_2$-integrin CD18 is the reason neutrophils are unable to adhere to vascular endothelium and transmigrate in response to released chemotactic factors in inflamed tissues. Because neutrophils cannot adhere to the endothelium, they do not reach the site of infection or inflammation. Recruitment signals from infected or inflamed tissues continue to cause the release of cytokines, stimulating granulocytopoiesis (production and release of neutrophils). Continued marrow stimulation and inability of neutrophils to adhere result in a persistent leukocytosis (primarily neutrophilia) that occasionally is greater than 100,000/μL.[10] Neutrophil function also was found to be altered by defective bactericidal activity, reduced glucose oxidation by the hexose monophosphate shunt, and increased capacity to reduce NBT dye.[5]

The presence of a single nucleotide missense mutation, resulting in failure to express detectable beta$_2$-integrin CD18, is responsible for clinical disease in Irish setters.[10] CD11b also is absent in affected Irish setters, but CD11c expression was not different from that in control dogs. Whether CD11b is absent because of lack of expression or because of the absence of CD18 is unknown.[11]

275.3.3 Diagnosis

An oligonucleotide ligation assay (OLA), which detects the missense mutation of CD18, was developed to identify carriers of this lethal gene.[12] In one study, screening of 208 Irish setters in the United Kingdom identified 19 carriers, or a 9% carrier rate.[12] This mutation has not been detected in any other breed in which OLA screening was performed.[10] Another study that tested 339 Irish setters from 10 countries (Scandinavia, continental Europe, and Australia) using a newly developed pyrosequencing technique to identify a single mutation in the beta$_2$-integrin gene (CD18) gene, supported the previous single mutation concept found with OLA.[12] The pyrosequencing technique identified 72 heterozygous carriers, as well as two homozygous dogs, which eventually developed CLAD.[12] The pyrosequencing technique also identified carriers and indicated widespread presence of the disorder in many countries.[12] Genetic testing using pyrosequencing can identify heterozygous dogs for removal from breeding lines. Recently, a case of CLAD in an Irish setter–cross was identified using polymerase chain reaction (PCR) testing, and carrier status was identified during a PCR survey in a number of distantly related red and white setters.[8] This PCR detection test identified the same mutation in all CLAD dogs previously tested.[8]

275.3.4 Treatment

No effective treatment has been found for this disorder.

275.4 CYCLIC HEMOPOIESIS

Cyclic hemopoiesis (CH), also known as *cyclic hematopoiesis, cyclic neutropenia,* or *gray collie syndrome,* is a lethal, autosomal recessive, hereditary disease of gray collies associated with a dilute haircoat. The condition was

first described in the 1960s as the "lethal gray syndrome," and a similar disorder is still called cyclic neutropenia (CN) in human medical texts. CH is a unique disease that affects the marrow pluripotential stem cell; it disrupts normal hemopoiesis, an effect characterized by cyclic changes in neutrophil, monocyte, platelet, eosinophil, and reticulocyte numbers.[13] Heterozygous dogs have a normal coat color and do not have clinical signs of CH.

275.4.1 Hematologic Manifestations

Marked neutropenia that occurs in cycles of 12 to 14 days is associated with severe recurrent bacterial infections at the nadir.[13] Neutrophils may be completely absent from the peripheral circulation for 2 to 4 days, an interval followed by neutrophilia as high as 70,000/μL.[13] Monocytes, eosinophils, lymphocytes, and platelets also cycle at 14-day intervals with normal to high cell counts but are out of phase with neutrophils with absent to high fluctuating cell counts.[13,14] Interestingly, hemopoietic growth factors such as erythropoietin, thrombopoietin, granulocyte colony-stimulating factor (G-CSF), IL-1, and IL-6 concentrations also fluctuate in this disorder.[13] A microcytic, normochromic anemia is present on the CBC.

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Changes in marrow aspirates, which occur in an alternating myeloid to erythroid ratio pattern, precede changes in the peripheral cell counts, suggesting a marrow stem cell disorder.[13]

275.4.2 Clinical Features

CH dogs all have gray or diluted coat color, often are smaller than littermates at birth, and usually present at 6 to 8 weeks of age with recurring episodes of neutropenia, accompanied by clinical signs such as fever, gingivitis, gingival ulcers, lymphadenopathy, excessive bleeding, pneumonia, ocular and nasal mucopurulent discharge, diarrhea, subcutaneous abscesses, conjunctivitis, keratitis, adenitis, anorexia, weight loss (malabsorption), lethargy, and intermittent lameness.[13,15] Neonatal deaths may result from omphalophlebitis or pneumonia.[13] Younger dogs with CH often die of overwhelming infection; those housed in a laboratory setting often die of hepatic and renal amyloidosis associated with organ failure.[15] Systemic amyloidosis is a prominent feature in CH and has been found in dogs as young as 8 weeks old; nearly 100% of dogs older than 30 weeks are affected.[14] Organs affected include the kidneys, liver, spleen, pancreas, adrenal glands, and intestinal submucosa.[15] Amyloidosis has been attributed to cyclic activation of the acute-phase response by cytokines produced during periods of monocytosis, with interrelated hormonal, immune, and endocrine interactions.[13] Serum amyloid A protein, as well as fibrinogen, von Willebrand factor, and other acute-phase proteins, are produced and circulated during the monocytosis.[13] Rarely do affected gray collies reach sexual maturity.[15]

275.4.3 Pathologic Features

The definitive pathogenesis of CH in gray collies is unknown; however, impaired marrow progenitor cell survival in CN in humans has been observed, and a defect in G-CSF signal transduction has been suggested.[16,17] In addition, ultrastructural, genetic, and molecular studies in humans with CN suggest that the disorder is due to mutations in a neutrophil azurophilic (primary) granule enzyme, neutrophil elastase (ELA-2).[16,17] A 75% decrease in early myeloid-committed colonies associated with accelerated spontaneous apoptosis was observed compared with controls. It was concluded that ineffective production of neutrophils is due to accelerated apoptosis of bone marrow progenitor cells, with conformational changes in protein structure

resulting in alterations in subcellular functions or substrate specificity and/or binding properties of neutrophil elastase.[16]

Although the hereditary pattern of CN is autosomal dominant in humans and autosomal recessive in gray collies, similar marrow and genetic changes may occur, but this remains to be proved.

CH in gray collies appears to be a hormonally inter-related disease with wide fluctuation of cytokines and responsive changes in the marrow. Furthermore, CH can be transferred to healthy dogs by BMT, which supports the theory of a disorder of the pluripotential stem cell.[13]

CH dogs also have a platelet storage pool disease characterized by a lack of dense granules (serotonin and Ca^{+2}), resulting in aggregation defects; however, prolonged bleeding times have not been reported.[13] Administration of rcG-CSF corrects the hemopoietic fluctuations but does not correct the SPD, which suggests that these defects are not secondary to CH.[13]

275.4.4 Treatment

Fluctuations of all cell lines resolve in CH dogs treated with rcG-CSF, with neutrophilia occurring at higher doses.[14] Also, recombinant canine stem cell factor (rcSCF) at high doses (i.e., equal to or greater than 20 µg/kg/24 hours) eliminated neutropenic periods and blunted oscillations, but neutrophilia only occurred at doses of 100 µg/kg/24 hours.[18] Treatment with a combination of rcSCF (20 to 50 µg/kg/24 hours) and rcG-CSF (0.5 to 1.0 µg/kg/24 hours) indicated a synergistic effect, with neutrophil counts above those of either drug given separately.[18] Long-term therapy was effective without untoward side effects. The risk of neutralizing antibody formation can arise with chronic administration of recombinant human G-CSF (rhG-CSF).[13] Early BMT eliminates cell cycling and produces a clinical cure. Treatment with lithium or endotoxin injections eliminates cell cycling, but unwanted side effects can occur. Administration of granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-3 administration are mildly effective but do not prevent cycling. Glucocorticoids, androgens, and intravenous gamma globulin are ineffective at treating this condition.[14,15,18]

CH is a highly undesirable trait in collies. Because it is an autosomal recessive trait, both the sire and dam that produce affected offspring are obligate carriers and should be removed from the breeding stock. Heterozygous dogs are phenotypically normal, therefore breeders should be counseled against using carriers. Laboratory tests are not available, and test mating is the only method of identifying carriers. Gray collies may not appear at every breeding; therefore, for a dog to be declared free of this trait, it must be mated with a known heterozygote and produce 16 normal pups. This is both expensive and impractical.

Normal canine neutrophil elastase deoxyribonucleic acid (DNA) sequence has been reported, and studies are ongoing to determine if the ELA-2 gene in CH has mutations similar to those in humans with CN. A PCR test may be developed, and a more practical, inexpensive test to identify heterozygous dogs may be offered. Testing has been done only on humans affected with CN and has not been used to identify carriers of this trait.

275.5 BIRMAN CAT NEUTROPHIL GRANULATION ANOMALY

Birman cats are an exotic, long-haired breed with Siamese-type coloring and four distinctive white paws. Neutrophil granulation anomaly is a hereditary trait characterized by increased granularity of neutrophils. It is

transmitted in an autosomal recessive manner in purebred Birman cats.[5,19] The cytoplasm of affected neutrophils contains numerous fine, normal-sized, deep pink to purple granules that appear similar to azurophilic granules found in promyelocytes. Neutrophil function is not compromised.[19] Normally, azurophilic granules become indistinct with Romanowsky stain in the myelocyte stage of development but seem to persist throughout the maturing process in this anomaly.[19]

Ultrastructurally, granules are elongated and dumb-bell shaped and do not stain for mucopolysaccharides. Bactericidal activity is no different from that of unaffected neutrophils, and other peripheral leukocytes appear morphologically normal.[19] Neutrophilic cytoplasmic granules observed in cats with certain mucopolysaccharide storage diseases (MPS types VI and VII) appear larger.[19] The abnormality therefore was concluded to be an alteration in the contents of cytoplasmic granules, with increased affinity for acid dyes without clinical consequences.[19] Treatment is not necessary, because functional abnormalities are not noted. The main concern is to differentiate this anomaly from MPS (types VI and VII) and toxic granulation.[5] A study of 78 highly inbred Birman cats found that 46% of the cats were affected.[19]

275.6 HYPEREOSINOPHILIC SYNDROME

Hypereosinophilic syndrome (HES) is a disease of unknown origin that occurs primarily in cats. It is questionable whether the disorder occurs in dogs, although one case of disseminated eosinophilic disease similar to idiopathic HES was recently reported.[20] Characteristics of this disease are persistent peripheral eosinophilia and organ infiltration by eosinophils, which eventually cause organ failure and death.[21,22] The bone marrow, spleen, liver, mesenteric lymph nodes, and gastrointestinal tract were the organs reported to contain eosinophilic infiltrates most frequently.[21,22] Difficulty arises in distinguishing between HES and eosinophilic leukemia (EL), because the two conditions may be variants of the same disease.[21] In one study, a female predisposition for HES was reported in cats (male to female ratio of 4:11).[21]

275.6.1 Hematologic Manifestations

The presentations of HES and EL are similar. Peripheral blood eosinophil examination and bone marrow aspiration may be helpful in differentiating the disorders. With EL there often are more immature eosinophils in the peripheral blood, which results in a more severe anemia. The myeloid to erythroid (M:E) ratio in bone marrow is greater than 10:1.[21,22] Peripheral eosinophil counts in HES range from 3500/μL to 130,000/μL, and the cells appear mature. Occasionally, mild anemia also is present.[21,22]

275.6.2 Clinical Features

Clinical signs, which are relatively nonspecific and vary with the organ or organs affected, include diarrhea, weight loss, anorexia, pyrexia, and pruritus.[21,22] It is difficult to establish the longevity of cats with HES; however, some cats may have exhibited clinical signs related to HES for 3.5 years.[22]

275.6.3 Physical and Pathologic Features

Physical findings are variable and include thickened bowel loops, abdominal masses, lymphadenopathy, and/or cutaneous disorders. As mentioned previously, the organs most commonly infiltrated with eosinophils are the bone marrow, gastrointestinal tract, spleen, mesenteric lymph nodes, and liver, but any organ can be affected.[21,22]

275.6.4 Treatment

HES is a progressively fatal disease that has no effective treatment. However, Gleevec (imatinib mesylatem, formerly STI571) has been used in humans with excellent results. Corticosteroids, hydroxyurea, and alpha interferon also have been used in humans with variable results; however, when these drugs are effective, unwanted side effects are common.

275.7 SEVERE COMBINED IMMUNODEFICIENCY IN JACK RUSSELL TERRIERS

Severe combined immunodeficiency (SCID) was recently described as an autosomal recessive trait in a litter of Jack Russell terriers. Twelve of 32 siblings died of opportunistic infections between 8 and 14 weeks of age.[23] An additional litter was whelped, and four of seven pups displayed SCID, characterized by lymphopenia, agammaglobulinemia, thymic dysplasia, and peripheral lymphoid aplasia.[23] A deficiency of DNA-dependent–protein kinase catalytic subunit (DNA-PKcs), an enzyme involved in DNA repair, occurs.[23] DNA-PKcs deficiency results in faulty V(D)J recombination.[23] Combinations of the V(D)J gene segment recombinations are very important for diversification of antigen-binding sites of antibodies.[23] Blocking of this V(D)J recombination arrests lymphocyte development at the prolymphocyte stage; the result is nonfunctional B and T lymphocytes, agammaglobulinemia and, consequently, SCID.[23]

275.7.1 Treatment

Bone marrow transplantation is the only option; however, gene therapy appears promising for future treatment.

275.8 CANINE X-LINKED SEVERE COMBINED IMMUNODEFICIENCY

Canine X-linked severe combined immunodeficiency (X-SCID) is an autosomal recessive, lethal, inherited trait with some unique modes of inheritance. Female carriers of the X-SCID gene typically appear normal. They contain only one copy of the γc gene and are unable to produce normal protein, but they have a second “normal” gene that produces adequate protein for normal function.[24] Because males retain only one copy of the X chromosome, they cannot produce normal protein when the abnormal gene is inherited, and thus are affected. Because transmission of only one X chromosome is necessary for this trait to appear, carrier females need not breed with an affected male.[24]

275.8.1 Clinical Features

Affected dogs are male, fail to thrive, and present with recurrent or chronic infections near the time of waning maternal antibodies.[24] Clinical signs are more evident as the pups get older. Recurrent infections, which begin around 6 to 8 weeks of age, include pyoderma, diarrhea, and respiratory infections.[24] Infections are usually bacterial, are unresponsive to antibiotics, and eventually become overwhelming systemic infections.[24] These dogs rarely survive beyond 3 to 4 months of age and usually die of a generalized staphylococcal infection.[24] Several X-SCID dogs, inadvertently vaccinated with a modified live distemper virus vaccine, died rapidly of vaccine-induced distemper.[24] One dog raised in a gnotobiotic environment developed acute monocytic leukemia at 20 months of age.[24]

275.8.2 Pathologic Features

A small, dysplastic thymus that weighs about 10% that of age-matched controls is the primary feature of X-SCID dogs.[24]

275.8.3 Immunologic Abnormalities

Although X-SCID dogs have reduced lymphocyte counts, profound lymphopenia is not a prominent finding (counts commonly are greater than 1000/μL).[24] When tested by fluorescence-activated cell sorting (FACS) analysis, newborn X-SCID dogs have peripheral lymphocyte phenotypes consisting of elevated B cells and markedly reduced or absent T cells.[24] Absolute numbers of peripheral T cells are decreased even though the relative percentages are normal.[24] The T-lymphocyte blastogenic response to T-cell mitogens and specific antigens is markedly depressed to absent.[24] X-SCID dogs also are hypogammaglobulinemic. Concentrations of immunoglobulin M (IgM) are normal, but IgG concentrations are dramatically reduced, and IgA antibodies are absent.[24]

275.8.4 Treatment

Bone marrow transplantation is the only treatment option for complete resolution of this disorder in dogs; however, gene therapy may be promising in the future. Transplantation has been attempted with some success, but these dogs developed cutaneous papillomas within 1 year.[24] An understanding of the hereditary and genetic basis of X-SCID and proper client and breeder counseling are highly recommended to control or eliminate this disorder in future generations.

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275.9 DEFECTIVE NEUTROPHIL FUNCTION IN THE DOBERMAN PINSCHER

Eight intensively line-bred Doberman pinschers developed chronic respiratory disease (rhinitis and pneumonia) and occasional skin disease (seborrhea sicca).[25] In all the dogs, neutrophils were normal in number and appearance.[24] The neutrophils were found to have normal phagocytosis but defective bactericidal activity, as determined by the NBT test.[25] Immunoglobulins were normal to increased; lymphocyte function was normal for the mitogens in seven of eight dogs; neutrophil chemotaxis was normal; and complement C_3 concentrations were

increased. Superoxide production was normal, except that opsonized zymosan stimulation produced less superoxide than in controls.[25]

275.9.1 Treatment

Many of these dogs survived for years and responded well to intermittent antibiotic therapy for recurrent bacterial infections of the respiratory tract.[25] The mode of inheritance was not determined due to inadequate pedigree and documentation.[24] The actual cause of the disorder was not determined. The condition somewhat resembles chronic granulomatous disease (CGD) or C_3b receptor deficiency in humans, but those diseases are usually life-threatening, unlike the disease in these Dobermans.[25]

275.10 LETHAL ACRODERMATITIS IN BULL TERRIERS

Lethal acrodermatitis in bull terriers is an autosomal recessive, inherited lethal trait with similarities to lethal trait A46 in Black Pied Danish cattle and acrodermatitis enteropathica in humans.[26]

275.10.1 Clinical Features

Lighter pigmentation at birth, growth retardation, progressive acrodermatitis, chronic pyoderma, chronic paronychia, diarrhea, pneumonia, and behavioral changes are observed on presentation, with historical evidence of deglutition and disordered mastication.[26] Behavioral changes include early aggressiveness, diminished activity, and prolonged staring at objects. These dogs have a median survival time of 7 months.[26] Laboratory findings include neutrophilia, consistently low alkaline phosphatase (observed in zinc deficiency) and alanine aminotransferase activities, low serum zinc concentrations, and frequent hypercholesterolemia.[26]

275.10.2 Pathologic Features

Skin lesions include parakeratosis, hyperkeratosis, and pyoderma. T-lymphocyte numbers were significantly reduced in lymphoid tissues.[26] Lymphocyte blastogenesis responses were decreased, and dysgammaglobulinemia was present.[26] Neutrophilic, phagocytic, and bactericidal activities were normal.[26]

275.10.3 Treatment

No effective treatment has been described. The response to high-dose zinc supplementation was poor.[26]

275.11 IMMUNODEFICIENCY OF SHAR PEIS

Immunodeficiency of Chinese Shar Peis is a recently described, late-onset, multiple immunodeficiency syndrome involving antibody and cell-mediated responses of unknown origin associated with recurrent infections and malignancy.[27]

275.11.1 Clinical Features

The mean age of clinical onset was 3 years (range, 4 months to 8 years).[27] The clinical presentation involves several organ systems and includes intermittent fever, recurrent skin infections, respiratory infections, and gastrointestinal abnormalities, including ulcerative colitis. Several dogs developed intestinal adenocarcinoma, lymphoma, and paracortical lymphocyte depletion.[27]

275.11.2 Immunologic Manifestations

Deficiencies in immunoglobulin concentrations, specifically IgM, IgA, and occasionally IgG, were identified.[27] B-and T-cell abnormalities were observed in affected dogs, including deficiencies in lymphocyte proliferation that occurred concurrently with normal or increased percentages of T-and B-cell lymphocytes, decreased median stimulation index of blastogenesis, and decreased *in vitro* responsiveness of peripheral blood mononuclear cells to pokeweed mitogen.[27] Also, when serum from affected Shar Peis was added to cell cultures from normal dogs, a suppressive effect was seen.[27]

Even with the variety of clinical presentations, nearly all affected dogs were characterized by a common deficiency involving cell-mediated and immunoglobulin deficiencies.[27]

275.11.3 Diagnosis

Assessment of the immunologic profile, along with the signalment, history, and clinical data, helps identify affected Shar Peis. However, given the high prevalence of healthy Shar Peis with low IgA concentrations, this finding alone cannot identify affected immunodeficient dogs.[27]

275.11.4 Treatment

Supportive care is the current treatment and should be given until the cause of this disorder can be completely classified.

275.12 IMMUNODEFICIENCY OF WEIMARANERS

Weimaraners affected with immunodeficiency have been reported, including an initial inbred group with thymic abnormalities and growth hormone deficiency.[28] Many other weimaraners subsequently were described with *in vitro* neutrophil abnormalities and decreased IgG and IgM.[29] One dog also had neutrophilic phagocytic dysfunction.[30] Affected weimaraners present with varying but recurrent infections that occasionally respond to antibiotics, but these dogs often die of recurrent infections within a year. Inbreeding has not been noted except in the original thymic deficiency group; however, one sire was implicated in five affected dogs (including two pairs of litter mates) and also was the grandsire of two other affected dogs.[31] Siblings of this dog also produced two affected dogs.[31] Obvious genetic associations are present, and many abnormalities have been identified, but no single specific disorder. The recurrent nature of this disorder may indicate a periodicity to the defect, which potentially makes specific detection difficult.[31]

275.12.1 Clinical Features

Weimaraners are presented for veterinary care between the ages of 3 and 42 months (average age is 10 months). Body condition and size are normal, but the dog has a variety of disorders, including acute onset of high fever; profound depression; vomiting; diarrhea; pain in the joints, spine, or abdomen; lymphadenopathy; bleeding tendencies, mainly in the form of epistaxis; hematemesis; melena; hematochezia; hematuria; dacryohemorrhysis (bloody tears); marked congestion and ulceration of mucous membranes; conjunctivitis; pedal pyoderma; recurrent subcutaneous masses thought to be associated with subcutaneous injection sites; and neurologic signs (ataxia, disorientation, head pressing, seizures and Horner syndrome). Episodes of sickness occur every 2 weeks to 7 months, with clinically normal intermediate periods or incomplete recovery. The recurring episodes of clinical illness often respond rapidly to antibiotics and/or corticosteroids but eventually become unresponsive, and death usually occurs within 1 year.[31]

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275.12.2 Hematologic Manifestations

Leukocytosis is observed, ranging from 31,000/μL to 64,200/μL, with a distribution of 72% to 92% neutrophils (mature and immature).[31] White blood cell (WBC) counts between episodes are normal or mildly elevated. Normal WBC morphology is observed by light and electron microscopy. Clotting times are within reference interval.[31]

275.12.3 Immunologic Manifestations

In the dogs studied, significant abnormalities were not noted in metabolic or phagocytic function, but glucose oxidation showed high resting levels consistent with an infection at the time of testing.[31] A single case report identified decreased neutrophil phagocytosis using opsonized *Escherichia coli* labeled with fluorescein isothiocyanate.[30] Other *in vitro* testing revealed decreased neutrophil chemoluminescence and decreased IgG and IgM concentrations.[29]

275.12.4 Diagnosis

A presumptive diagnosis is based on recurrent presentation of a young weimaraner that becomes progressively less responsive to treatment. Specific testing to identify diseased individuals is not available. Test mating, with careful evaluation and observance of the progeny for immunologic abnormalities, may be the only way to identify a defect.

275.12.5 Treatment

Supportive care has been the only treatment used. Bone marrow transplants have not been attempted.

275.13 LYSOSOMAL STORAGE DISEASES

Many lysosomal storage diseases (LSDs) have been identified in dogs and cats; however, all are rare, and only a few present with microscopic abnormalities in peripheral blood leukocytes. Only the observable leukocyte

morphologic changes are discussed. Specific leukocyte activity has not been tested, but delineation of microscopic characteristics may be a simple method of identifying and/or classifying many storage diseases.

Hematologic alterations in the leukocytes of dogs and cats are associated with sphingomyelinosis (Niemann-Pick disease); alpha-mannosidosis; mucopolysaccharidosis (MPS) I, VI, and VII; GM_1-gangliosidosis; GM_2-gangliosidosis; and fucosidosis.

Leukocytes in MPS I, VI, and VII must be differentiated from toxic changes in neutrophils and from Birman cat neutrophil granulation anomaly.

Sphingomyelinosis has been reported in Siamese, Balinese, and domestic shorthair cats, as well as in boxer dogs and a miniature poodle. The disease is caused by a deficiency of sphingomyelinase, which results in accumulation of sphingomyelin, cholesterol, and gangliosides in the brain, liver, spleen, and bone marrow. Large, vacuolated macrophages may be observed in the peripheral blood.

Alpha-mannosidosis, reported in Persian, domestic shorthair, and domestic longhair cats, is caused by a deficiency of alpha-mannosidase, which leads to accumulation of mannose oligosaccharides in the central nervous system, skeleton, and spleen. Lymphocytes, granulocytes, and monocytes in peripheral blood appear vacuolated.[32]

MPS I occurs in Plott hounds, other breeds of dogs, and domestic shorthair cats. This LSD is caused by a deficiency of alpha-L-iduronidase. Some observers have reported small, pink granules in neutrophil cytoplasm.[33]

MPS VI is reported in Siamese cats and in miniature schnauzers, miniature pinschers, and Welsh corgis. This LSD is caused by a deficiency of arylsulfatase. Peripheral neutrophils, lymphocytes, basophils, eosinophils, and monocytes are affected. The cytoplasm of neutrophils often appears foamy and contains uniform small, metachromatic granules, often within a vacuole.[32] Lymphocytes in MPS VI have been divided into three distinct types: normal appearing, those containing vacuoles with small, dark, metachromatic granules; and a few containing empty vacuoles.[32] Nearly all monocytes contain vacuoles, and a moderate percentage have dark granules in these vacuoles.[32] Eosinophils contain cytoplasmic vacuoles, and basophils contain large, reddish purple cytoplasmic inclusions or granules.[32] Basophils have the largest granules.[32]

MPS VII, reported in the dog and domestic shorthair cat, is caused by a deficiency of beta glucuronidase. Neutrophils and lymphocytes contain deep purple cytoplasmic inclusions that should not be confused with toxic changes. Granules stain purple with toluidine blue dye.[33]

GM_1-gangliosidosis has been reported in domestic shorthair, Korat, and Siamese cats, as well as in English springer spaniels, Portuguese water dogs, beagles, and Alaskan huskies. It is caused by a deficiency in beta galactosidase. Lymphocytes contain small, distinct, clear cytoplasmic vacuoles.[33]

GM_2-gangliosidosis, reported in domestic shorthair and Korat cats and in German shorthaired pointer dogs, is caused by a deficiency of beta hexosaminidase. Neutrophils contain dark blue granules, and lymphocytes contain prominent azurophilic cytoplasmic granules.[33]

Fucosidosis of English springer spaniels is caused by a deficiency of alpha-L-fucosidase. The lymphocytes of these dogs contain cytoplasmic vacuoles.[33]

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276 CHAPTER • 276 Non-Neoplastic Diseases of the Spleen

Helio Autran de Morais

Robert T. O'Brien

"Spleen is like the tongue of an ox [or] the sole of the foot; slightly bowed out on the left side, a little concave on the inner side, toward the stomach. It has an uneven surface and is a little rough with some tubercles …"

"Similarly [according to] other physicians the spleen [is] the receptacle of melancholy as the gall bladder of gall; wherefore the spleen causes one to laugh."

William Harvey (1653)

For many years, the ability to laugh was considered a sign that the spleen was working well. Regarded as the repository of the most noxious substance of the body, black bile (in Greek, *melanos kholis*), the spleen prevented the onset of melancholia by containing the bodily fluid that produced this mental state. Our understanding of the spleen has greatly improved over the past centuries. However, evaluation of this organ remains mostly morphologic, based on palpation, radiographs and, especially, ultrasound examination, followed by cytology or histopathology. No biochemical tests have been designed to assess splenic function. Consequently, although splenomegaly is common in clinical practice, it often is hard to isolate the cause.

276.1 PREVALENCE OF SPLENIC DISEASE IN DOGS AND CATS

The prevalence of splenic disorders in dogs and cats cannot be easily estimated. Splenomegaly may be asymptomatic, and in the absence of splenomegaly, it is difficult to determine, on the basis of clinical signs, that the spleen is responsible for the animal's condition. Most prevalence studies in dogs and cats are based on either necropsy or biopsy findings. Necropsy-based studies overestimate diseases with a poor prognosis or with no clinical relevance. Diseases that are treated by surgery are overestimated in prevalence studies based on biopsies but are underestimated in prevalence studies based on necropsy data. This might explain the absence of hemangiosarcoma and the low ratio of hemangiosarcoma to hematoma in necropsy studies in dogs. Based on biopsy samples submitted to a regional diagnostic laboratory from 1372 dogs[1] and 455 cats,[2] spleen samples from dogs represented 1.3% of all submissions, and spleen samples from cats represented 0.3%. However, these percentages do not represent true prevalence, because biopsies from all species were included in the total submission number.[1]

In two necropsy surveys, non-neoplastic diseases represented approximately 50% of feline splenic disorders.[2,3] Congestion, lymphoid hyperplasia, capsulitis, extramedullary hematopoiesis, and hyperplastic nodules accounted for more than 50% of the cats with non-neoplastic splenic disease. Unfortunately, those were pathologic descriptions, and the underlying disease was not apparent in many cases. In two retrospective studies that looked at the prevalence of arrhythmias in dogs with splenic masses,[4,5] hematomas were found in 17%[5] to 44%[4] of the cases. In a prospective study that looked at the prevalence of arrhythmias in dogs undergoing splenectomy, 38% of the dogs had neoplasia and 32% had hematomas.[6] Nodular hyperplasia, immune-mediated disease

unresponsive to medical therapy, and splenic torsion each accounted for 10% of the cases. Nodular hyperplasia, hematoma, extramedullary hematopoiesis, congestion, and lymphoid hyperplasia were the most common non-neoplastic lesions found in the spleens of dogs at necropsy or biopsy.[1,7–9] In a lifetime study of beagles chronically exposed to radioactive radium and strontium, splenic abnormalities were present in 105 of the 865 dogs. Hyperplastic nodules, with or without hematoma, and diffuse lymphoreticular hyperplasia accounted for 66% of the splenomegaly found in these dogs.

Thus the ratio of non-neoplastic to neoplastic splenic disease in dogs varies among studies. Populations that included all cases of splenomegaly or masses[1,8] show a higher than 50% prevalence of non-neoplastic diseases. A higher prevalence of tumors is found in populations that underwent splenectomy[6,9] and in dogs with splenic masses and arrhythmias.[4,5] Non-neoplastic masses, therefore, are as common as neoplastic masses in the spleen of dogs, and the importance of hemangiosarcoma has been overemphasized.[10]

276.2 CLINICAL MANIFESTATIONS OF SPLENIC DISEASES

Owner complaints for dogs and cats with splenic disorders are usually vague, and these signs may arise from the primary disease. Common complaints include vomiting, anorexia, weakness, collapse, abdominal enlargement, and weight loss. Polyuria and polydipsia may occur; the mechanism is unclear, but it resolves after splenectomy. Clinical signs are usually related to abdominal distention caused by a mass, uniform splenomegaly, or intra-abdominal bleeding. Lethargy and collapse may occur as a result of hypovolemia, arrhythmias, or anemia.

Signs related to the underlying disorder may also be present (Box 276-1). Ventricular tachyarrhythmias appear to be highly prevalent in dogs with splenic masses (hematoma, hemangiosarcoma, or leiomyosarcoma).[4–6] Particularly if the mass has ruptured.[6] Dogs that undergo splenectomy, regardless of the reason, are also prone to arrhythmias during and after surgery.[6]

The most reliable clinical sign of splenic disease is palpable splenomegaly. However, not all splenomegalies are abnormal. Breed variations in spleen size exist, particularly in dogs. For example, German shepherds have larger spleens; in some other breeds (e.g., miniature schnauzer, cocker spaniel, greyhound) the spleen is located more caudally in the abdomen and may be perceived as enlarged under palpation.[11] Not all enlarged spleens are palpable.

The major laboratory abnormalities accompanying splenic disease are related to the underlying systemic illness. 1944 1945
Changes in blood cell counts may be due to the primary disease or may be caused by the abnormal spleen. Erythrocyte counts are usually normal or decreased but can be increased in patients with splenomegaly associated with polycythemia vera.[12] Schistocytosis, which is highly indicative of a neoplastic splenic disorder, was observed in 23% of patients with splenic tumors but in only 3% of dogs with non-neoplastic disease.[9] Granulocyte and platelet counts also can be decreased, normal, or increased.

276.2.1 Box • 276-1 Clinical Signs of Splenic Disease in Dogs and Cats

Abdominal distention

Splenomegaly

- Splenic mass
- Intra-abdominal bleeding
- Arrhythmias
- Nonspecific signs and signs of the underlying disorder
  - Lethargy
  - Weakness
  - Collapse
  - Anorexia
  - Polyuria/polydipsia
  - Diarrhea
  - Pale mucous membranes
  - Jaundice

Extramedullary hematopoiesis can occur in the spleen. Because the spleen is capable of hematopoiesis but does not retain the normal inhibitory mechanisms present in the bone marrow, it releases young blood cells into the circulation.[10] Increased nucleated red blood cells and immature white blood cells (leukoerythroblastic effect) may appear in the peripheral blood in patients with splenic disorders.

276.2.2 Diagnostic Approach to a Patient with Splenomegaly

Splenomegaly can be detected by physical examination or by abdominal radiographs or ultrasound. Although splenomegaly can be identified by palpation, the severity of the enlargement cannot be reliably assessed in dogs with this technique alone. Differentiating between a splenic mass (localized splenomegaly with at least one large mass) and diffuse splenomegaly (uniform enlargement of the spleen) helps narrow the number of potential diagnoses (Box 276-2). Fine needle aspiration of the spleen may secure the final diagnosis or characterize the type of inflammation present. A sequential approach to diagnosis of the origin of the splenic mass, splenomegaly, or splenic nodular disease, using ultrasonographic findings and cytology, is shown in Figures 276-1, 276-2, and 276-3, respectively.

276.2.2.1 Abdominal Radiography

Radiographically the spleen is apparent in both dogs and cats. The dorsal extremity (head) is commonly seen on ventrodorsal projections in the cranial left abdomen caudal to the gastric fundus and cranial to the left kidney along the left body wall. On this projection, the splenic head is triangularly shaped. The body of the spleen may be directed transversely across the abdomen immediately caudal to the stomach, along the left body wall, or anywhere in between. In dogs the ventral aspect (tail) is often seen along the ventral body wall immediately caudal to the liver in the lateral projection. Distension of the stomach may caudally displace the tail. The tail of the spleen is uncommonly seen in cats.

Generalized splenomegaly may increase splenic length. The spleen may also fold up from the ventral wall, extending to varying lengths up the right body wall, or it may expand more caudally, toward the urinary bladder. In the cat, visualization of the splenic tail along the ventral body wall supports a diagnosis of splenomegaly. Alternatively, with generalized enlargement or focal masses, the spleen produces a mass effect, causing caudal displacement of intestines. The spleen is a very common origin for masses in the midcranial and left cranial abdomen. Atypical splenic location, with changes in shape, may occur in dogs with splenic torsion. Concurrent peritoneal effusion is common. Lesions rarely cause changes in splenic radiopacity.

276.2.2.2 Abdominal Ultrasonography

Ultrasonography is a very effective tool for evaluating the size, shape, and vascular supply of the spleen. There are no objective criteria for normal splenic size. As a rule, cats have a much smaller spleen than dogs of similar size. Normal variations in dogs include capsular invagination (hyperechoic foci adjacent to splenic veins), a bent spleen, or a portion folded back upon itself. Generalized isoechoic enlargement may be a normal variation in German shepherds and other dog breeds and in some cats. Overall spleen length and evidence of intestinal displacement are the criteria used to assess for splenomegaly. A true decrease in splenic size (microsplenia) may occur with acute anemia due to contraction of the spleen. Ultrasonography is more sensitive than radiography for detecting alterations in the shape and outer margination of the spleen. Irregularities in shape and focal changes in echogenicity are the major criteria for characterization of splenic disease in dogs and cats.

Nodular disease is easily detected in the middle and tail regions of the spleen. Often the head of the spleen is within the rib cage, and masses in the dorsal extremity may require a rigorous examination using an intercostal approach. Benign masses may be hypoechoic, hyperechoic or mixed echoic. Benign masses cannot be differentiated from malignant masses with grey scale ultrasonography alone. Extramedullary hematopoiesis and nodular hyperplasia (Figure 276-4), which are common regenerative lesions, are usually hypoechoic and are seen in the spleens of older dogs. These lesions are much less common in cats.

Certain lesions have a more characteristic sonographic appearance. Myelolipoma, a benign tumor seen in older dogs, is both very echogenic and attenuating. The result is a classic hyperechoic and indistinctly shadowing lesion (Figure 276-5). Unlike with mineralization, the attenuation is not complete, and the internal architecture of the lesion can be seen to varying depths.

The spleen has a high prevalence for vascular disease because it is attached at only one pole and is prone to harbor diffuse neoplasia. Splenic torsion and diffuse tumor invasion may result in uniform diffuse hypoechogenicity or a more mixed “Swiss cheese” appearance (Figure 276-6). In suspected cases of torsion

or thromboembolism, Doppler examination of the splenic veins is an important step for verifying lack of venous return. As with portal vein flow, splenic venous flow is low velocity and essentially nonpulsatile. Power Doppler examination is especially valuable, because this modality is more sensitive to very low velocity flow. Thrombosis may occur after mechanical torsion or tumor vascular invasion or with thromboembolic diseases. Regional infarctions are commonly seen in dogs with disseminated intravascular coagulation (DIC) and autoimmune conditions, such as immune-mediated hemolytic anemia and immune-mediated thrombocytopenia. Infarcted regions are usually peripheral, hypoechoic, and swollen (Figure 276-7). Necrosis, which may be seen with chronic severe vascular disease, results in the formation of free gas in the spleen and free fluid in the peritoneum.

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276.2.2.2.1

Box • 276-2 Causes of Splenomegaly in Dogs and Cats*

Splenic mass (asymmetric, or nonuniform, splenomegaly)

Nodular hyperplasia

Lympoid type

Fibrohistiocytic type (D)

Hematoma

Neoplasia

Abscess

Extramedullary hematopoiesis (C)

Granuloma

Uniform (symmetric) splenomegaly

Congestion

Drugs

Portal hypertension

Right-sided congestive heart failure

Splenic torsion

Hyperplasia[†]

Chronic infection

Inflammatory bowel disease

Systemic lupus erythematosus

Polycythemia vera

Extramedullary hematopoiesis[†]

Chronic anemia

Immune-mediated hemolytic anemia

Immune-mediated thrombocytopenia

Neoplasia

Neoplasia

Non-neoplastic infiltrative diseases

Neoplasia

Hypereosinophilic syndrome (C)

Amyloidosis

Inflammatory causes[‡]

Suppurative

Sepsis

Bacterial endocarditis

Infectious canine hepatitis

Toxoplasmosis

Foreign body

Penetrating wounds

Neoplasia

Granulomatous

Cryptococcosis

Histoplasmosis (C)

Mycobacteriosis

Leishmaniasis

Pyogranulomatous

FIP (C)

Blastomycosis

Sporotrichosis

Eosinophilic

Eosinophilic gastroenteritis

Hypereosinophilic syndrome (C)

Neoplasia

Lymphoplasmacytic

Ehrlichiosis

Hemotropic mycoplasmosis (C)

Lymphoplasmacytic enteritis

Pyometra

Brucellosis

Necrotic tissue

Torsion

Necrotic center of neoplasms

Infectious canine hepatitis (D)

Anaerobic infection

Tularemia

Salmonellosis

* More common diseases are in boldface.

† The causes of extramedullary hematopoiesis and hyperplasia can overlap.

‡ The typical inflammatory response for each organism; some degree of overlap exists.

C, Cats; *D*, dogs.

An additional ultrasonographic modality for evaluation of focal nodular and vascular diseases of the spleen is contrast harmonic ultrasonography. With this technique, second-generation ultrasound contrast agents, which are liposome-encapsulated inert gas spheres, are injected intravenously; these agents are small enough (3 to 5 μm) to pass through the pulmonary circulation without causing embolization. Harmonic ultrasound software technology allows detection of sound waves that are multiples of the transmitted frequency. Ultrasonographic contrast bubbles are very powerful generators of harmonic frequencies, and combined with tissue signal suppression, they create a novel method for imaging perfusion of organs. These contrast media, which can be used as blood pool agents, cause infarcted regions to appear hypoechoic compared with the surrounding normally perfused spleen. Preliminary studies indicate that ultrasound contrast agents may help discriminate between malignant and benign masses by exploiting differences in blood supply. Hemangiosarcomas have very poor overall perfusion and distinct peripheral vessels. This perfusion pattern has been noted in hemangiosarcomas in the liver, lung, peritoneum, and spleen. In the liver, metastatic nodules have a more rapid wash-in and wash-out compared to normal liver or benign liver nodules. Benign nodular hyperplastic nodules in the spleen have good overall perfusion.

276.2.2.3 Fine Needle Aspiration

Although imaging of the spleen only rarely results in a diagnosis, an aspirate may provide a cytologic sample and the answer. Core biopsy is possible but not usually necessary. Most diseases of the spleen exfoliate well and are suitably sampled with fine needle techniques. Of the fine needle techniques, the variation that seems to provide the most cells without undue hemodilution involves no negative pressure with the attached syringe and multiple thrusting motions with the needle. With the plunger already pulled back in the barrel of the syringe prior to insertion of the needle, it thereafter is easy to expel the contents of the needle by depressing the plunger. This technique works well for nodular hyperplasia and extramedullary hematopoietic benign nodules, metastatic carcinomas, and hematopoietic tumors. Solid sarcomas may not exfoliate well with aspiration techniques, and a core sample may provide a better result. Cavitated lesions should be sampled only with the utmost care, if at all.

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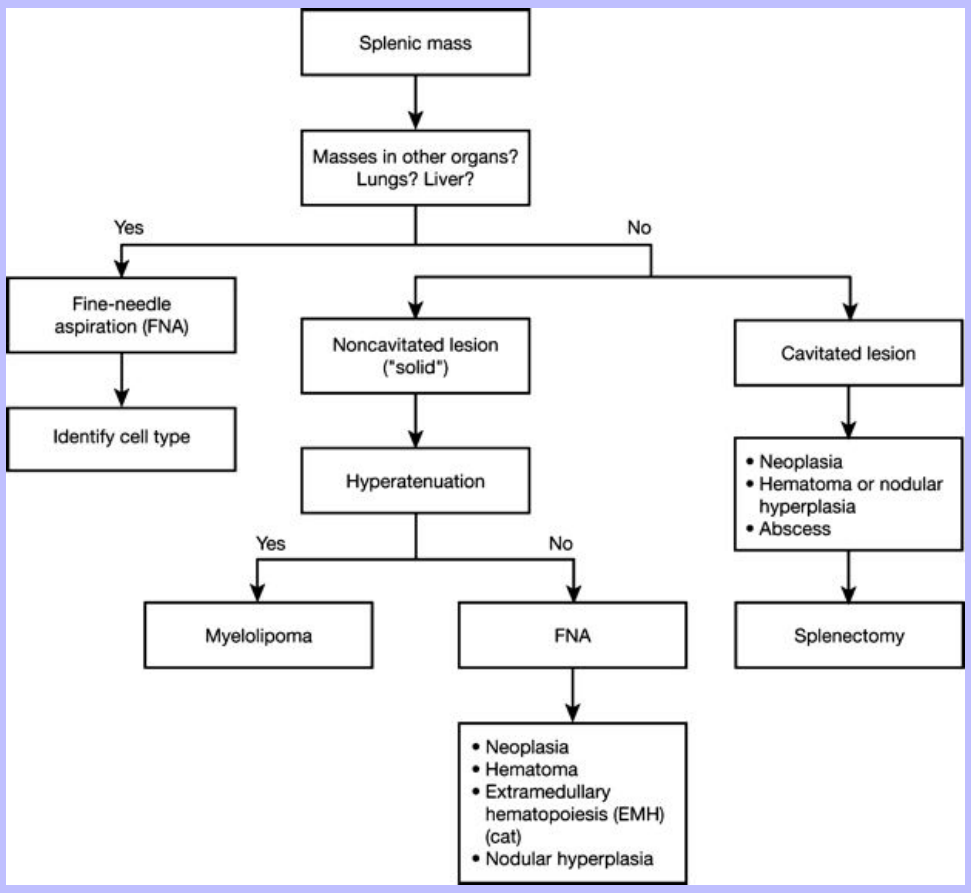
Figure 276-1 Algorithm for the clinical approach to a splenic mass.



Fine needle aspiration appears to be safe even in presence of coagulopathies or thrombocytopenia.[13] As a general rule, all abnormal spleens that *do not have cavitated lesions* should be aspirated. Aspiration is not necessary in patients with splenic torsion when lack of adequate blood flow can be determined by Doppler ultrasonography, or in patients with myelolipoma if only lesions with the classic acoustic properties are present. Aspiration also may not be required for diffuse homogeneous splenomegaly, with no clinical signs, that is attributable to splenic disorders in patients with a known cause of congestion (e.g., tranquilizer therapy, portal hypertension, right-sided heart failure), or for “classic” infarct lesions in asymptomatic patients.

Fine needle aspiration can provide the final diagnosis in infectious disease when the organism can be identified and in neoplastic disorders. Aspirates of normal spleen reveal small lymphocytes with occasional medium and large lymphocytes and rare neutrophils. A few macrophages and plasma cells may be present.[14] Precursors of all three cell lines may be seen in patients with extramedullary hematopoiesis, but erythroid cells are more common. In hyperplasia resulting from antigenic reaction, an increase in medium and large lymphocytes and in macrophages and plasma cells is seen.[14] Patients with splenitis have an increase in inflammatory cells. Identification of the predominant cell type narrows the number of potential

diagnoses. Inflammation can be further characterized based on the predominant cell type; that is, suppurative, granulomatous, pyogranulomatous, eosinophilic, or lymphoplasmacytic. The most common causes of each type of inflammation are presented in Box 276-2.

276.2.2.4 Splenic Biopsies/Splenectomy

Biopsy of the spleen can be performed in patients in which the primary diagnosis of a mass is not obtained by fine needle aspiration. Care should be taken with impression smears made from splenic biopsy samples. Impressions inadvertently made of the capsular surface, rather than the parenchyma, reveal uniform sheets of loosely attached mesothelium, which are nondiagnostic.[14] Splenectomy should be considered in animals with splenic necrosis or cavitated masses without metastasis.

276.2.2.5 Other Diagnostic Tests

In addition to imaging techniques and fine needle aspiration, urinalysis, a complete blood count, and a biochemical profile are necessary in all patients with splenomegaly. Cats must be tested for infection with feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV). Chest radiographs should be obtained in patients with splenic masses to rule out metastasis, and bone marrow examination may be indicated in patients with alterations in blood cell lines.

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Figure 276-2 Algorithm for the clinical approach to splenomegaly.

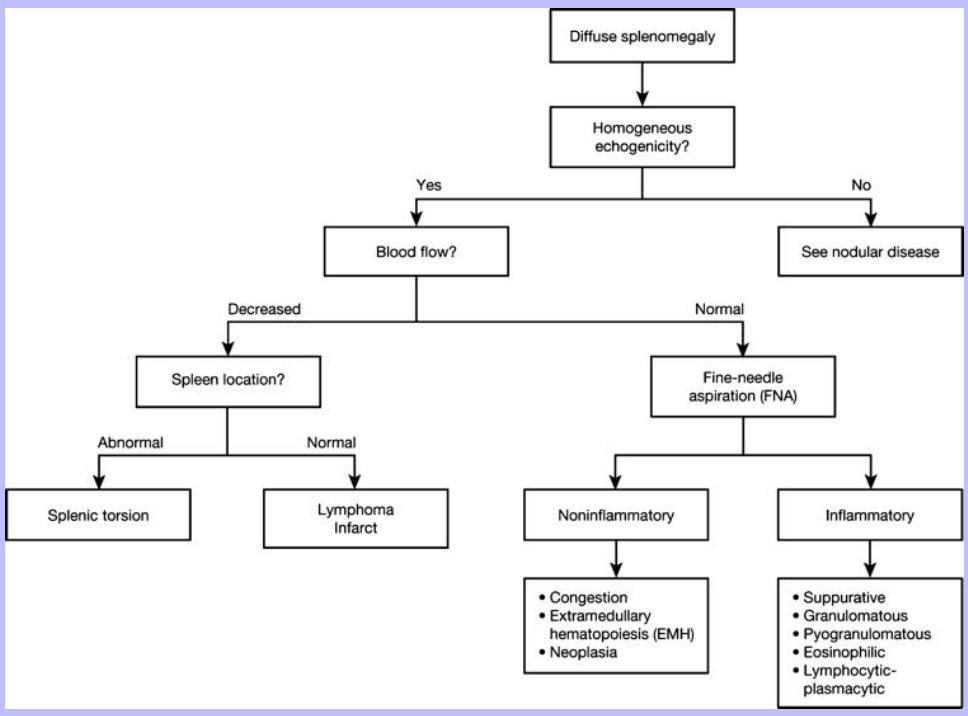


Figure 276-3 Algorithm for the clinical approach to splenic nodular disease.

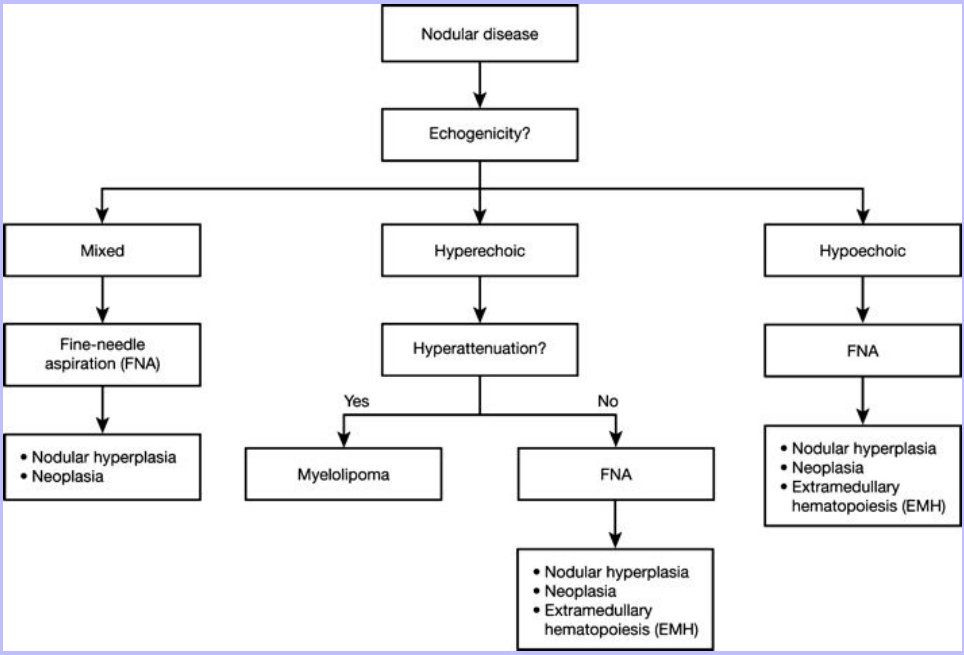
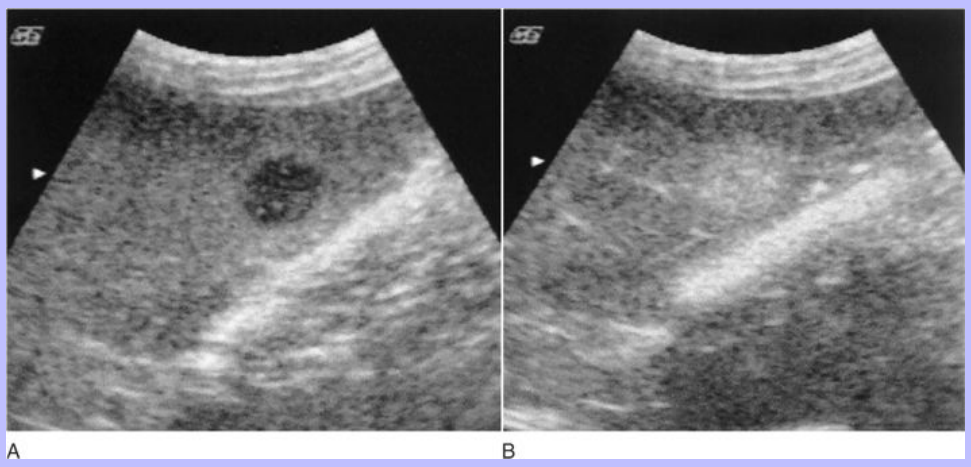


Figure 276-4 Nodular hyperplasia. Note the contrast enhancement pattern on precontrast **(A)** and postcontrast **(B)** images.



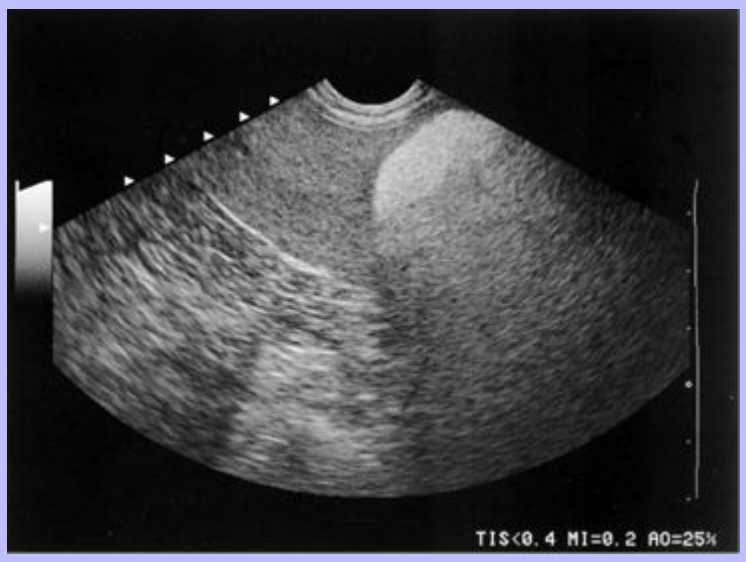
276.3 COMMON CAUSES OF SPLENOMEGALY IN DOGS AND CATS

Generalized splenomegaly may occur with congestion, splenic hyperplasia/extramedullary hematopoiesis, inflammation, or cellular infiltration, whereas splenic masses usually are due to neoplasia, hematoma, abscess, or nodular hyperplasia.

276.3.1 Congestion

Congestion is commonly seen as a consequence of sedation or anesthesia, portal hypertension, or splenic vein thrombosis. Administration of phenothiazine sedatives (e.g., acepromazine) or ultra-short-acting barbiturates (e.g., thiopental) produces substantial splenomegaly. Splenomegaly can be severe, because up to 30% of the blood volume can be pooled in the spleen. Administration of propofol to dogs, however, did not produce statistically significant splenomegaly.[15]

Figure 276-5 Myelolipoma. Note the hyperechogenicity and hyperattenuation pattern.



Congestion may also occur secondary to portal hypertension with hepatic disease and with systemic venous hypertension in right-sided heart failure or intrathoracic caudal vena cava compression. Chronic congestion of the spleen may lead to splenic hyperplasia. No changes in echogenicity were subjectively noted in congested spleens, although signifi-cant increased attenuation and a trend toward increased backscatter (echogenicity) were noted.[15] Diffuse changes in splenic echogenicity in patients with a known cause of congestion, therefore, are likely due to another underlying condition.

Figure 276-6 Splenic torsion. Note the “Swiss cheese” echogenic pattern of splenic necrosis.

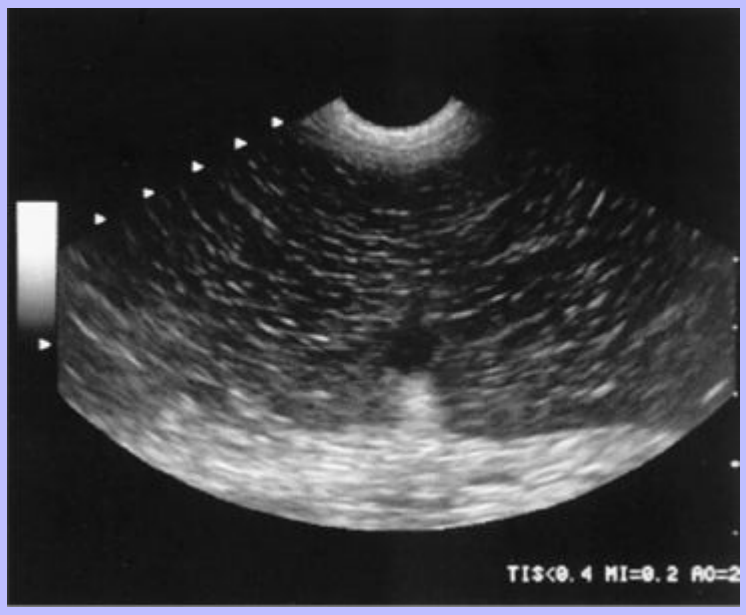


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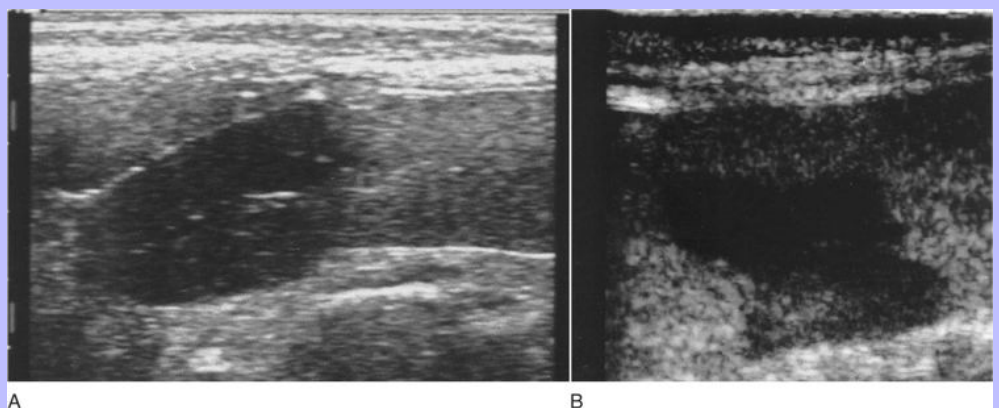
Figure 276-7 Infarcted spleen in two dogs. **A,** Note the hypoechoic infarcted portion of the spleen on grey scale ultrasound image. **B,** On the contrast harmonic ultrasound image, the infarcted portion is not seen on grey scale ultrasound but is hypoechoic compared with surrounding well-perfused, contrast-enhanced spleen.



Splenic pedicle torsion is a special cause of congestion in dogs. It usually develops in large, deep-chested dogs, especially the German shepherd and Great Dane.[16] Males represented 79% of the cases in one study.[16]

Acute torsion causes profound systemic signs, including shock and abdominal discomfort, whereas chronic torsion is associated with vague signs such as vomiting, anorexia, lethargy, and icterus. Radiographically, a decrease in abdominal detail, displacement of other abdominal organs, and loss of visualization of the body of the spleen in the left cranial abdomen are seen on the ventrodorsal view. In the lateral view, the spleen is enlarged, abnormally positioned or shaped, and may have intrasplenic gas.[17] Ultrasonographically, the spleen is diffusely enlarged and abnormally located. It is usually hypoechoic, with decreased flow through splenic veins. In one study, intravascular thrombi could be identified in 50% of the cases.[16] Supportive therapy should be instituted immediately in these patients, and the spleen should be removed surgically. If appropriately treated, splenic torsion carries a favorable prognosis.[16]

276.3.2 Splenic Infarction

Infarcts can be observed in patients in hypercoagulable states associated with liver disease, renal disease, or hyperadrenocorticism.[18] They also can occur with pre-existing uniform splenomegaly[18] or splenic torsion.[16] Splenic infarction is a sign of abnormal coagulation or blood flow, and the clinical signs are related to the underlying cause. Ultrasonographically, infarct regions are usually peripheral and have hypoechoic, swollen areas. After contrast injection, they appear hypoechoic compared with the surrounding normally perfused spleen. Infarcted regions may resolve with appropriate therapy of the underlying disease.

276.3.3 Splenic Hyperplasia/Extramedullary Hematopoiesis

The splenomegaly seen with splenic hyperplasia and extramedullary hematopoiesis reflects *work hypertrophy* resulting from removal of abnormal blood cells from circulation, increased activity of mononuclear phagocytic and lymphoid cells, and increased blood cell production. In immune-mediated hemolytic anemia and thrombocytopenia, the spleen serves as a site of antibody production and also as an important site of removal of antibody-sensitized cells. Chronic increased destruction of red blood cells in some non-immune-mediated hemolytic diseases also appears to cause hyperplastic splenomegaly in dogs and cats.[19] Chronic antigen stimulation by infectious agents (e.g., bacterial endocarditis), blood parasites, or immune-mediated disease can stimulate hyperplasia of mononuclear phagocytic and lymphoid cells.

In work hypertrophy, the spleen is uniformly enlarged and may be hypoechoic on ultrasonographic examination. Cytologically, small lymphocytes still predominate, but an increase is seen in medium and large lymphocytes, and plasma cells are commonly observed.[14]

Extramedullary hematopoiesis (EMH) may accompany splenic hyperplasia in patients with concomitant anemia, thrombocytopenia, or leukopenia. It is a very common cytologic diagnosis in dogs with uniform splenomegaly[13] and may also occur with a variety of splenic neoplasms. EMH is also common in cats; it was diagnosed in 21% of the cats in one study.[20] A nodular pattern is more common in cats with EMH. The presence of nucleated red blood cells in peripheral blood suggests a diagnosis of EMH. Cytologically, precursors of all three cell lines may be observed with the disease.[14] A finding of hematopoietic precursors with large amounts of vacuoles in the background suggests a myelolipoma rather than EMH.[14]

276.3.4 Nodular Hyperplasia/Hematoma

Nodular hyperplasia is a non-neoplastic regional proliferation of component cells normally found in the parenchyma of the canine spleen.[21] Nodular hyperplastic lymphoid proliferation is the most common form of nodular hyperplasia in dogs, but it is not common in cats.[1,2] A high percentage of splenic lesions in dogs have features of hematomas and nodular hyperplasia, which suggests that these disorders are different stages of the same process. Lymphoid elements are usually observed with superimposed hematomas.[1] It has been suggested that marginal zoning distortion caused by nodular hyperplasia disrupts regional splenic blood flow in and around the hyperplastic nodule, eventually leading to hematoma formation.[1] Cats have a "nonsinusal" type of spleen and a different architecture and blood flow pattern of the intermediate circulation bordering the white pulp.[2] Those differences could make the spleen of cats less vulnerable to disrupted blood flow and hematoma formation.

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Nodular hyperplastic lesions are usually hypoechoic on ultrasonographic examination. Splenic hematomas in dogs are associated with large splenic masses. A history of trauma is rare.[22] Most dogs with splenic hematoma are relatively healthy and do not have acute splenic rupture,[19] although they may develop hemoabdomen.[23] Large hyperplastic nodules and splenic hematomas cannot be differentiated from hemangiosarcoma grossly. Splenectomy is the treatment of choice for hematomas and hyperplastic nodules large enough to cause splenomegaly.[24]

A particular variation of the hyperplastic nodule in dogs is the fibrohistiocytic nodule.[21] Nodular fibrohistiocytic proliferation is characterized by a mixed population of histiocytoid or spindle cells intertwined with hematopoietic elements, plasma cells, and lymphocytes. These nodules appear to form a continuum between lymphoid nodular hyperplasia and malignant splenic fibrous histiocytoma.[21] Histologically, the lymphoid to fibrohistiocytic ratio is the most important predictor of survival in these dogs. A higher proportion of lymphoid to fibrohistiocytic cell types was associated with increased long-term survival.[21]

276.3.5 Inflammatory Splenomegaly

Inflammatory splenomegaly (splenitis) is a uniform splenomegaly that usually occurs secondary to infection. In addition to the inflammatory response associated with hyperplasia, patients with splenitis also have increased numbers of other inflammatory cells. It is important to classify the splenitis according to the predominant cell type, because different etiologic agents are associated with different types of inflammation. Some overlap exists, and the same organism can cause a different inflammatory response in different patients. For example, lymphoplasmacytic splenitis has been observed in patients with FIP, histoplasmosis, and blastomycosis. Care must be taken in diagnosing suppurative splenitis in patients with peripheral neutrophilia or eosinophilic splenitis in patients with peripheral eosinophilia. The most common causes of splenitis, based on the predominant inflammatory response, are presented in Box 276-2. Infectious agents that can cause splenitis or can lead to splenomegaly by causing chronic antigen stimulation, disturbances of blood flow, or chronic anemia are listed in Box 276-3.

276.4 PATIENT WITH A SPLENIC NODULE

Splenic nodules without associated splenomegaly are a relatively common finding in older dogs undergoing abdominal ultrasonography for unrelated reasons. Most splenic nodules in this age group are benign and may require no further action. Myelolipomas can be easily identified, whereas lymphoid hyperplasia, EMH, and splenic infarcts may be more difficult to differentiate from an early neoplastic lesion. Further diagnostics should be attempted in breeds with a high-risk for hemangiosarcoma; in patients with systemic tumors likely to involve the spleen (e.g., lymphoma, hemangiosarcoma); and in animals with hematologic abnormalities, fever, or other signs of systemic infectious disease.[25] Fine needle aspiration should be attempted for all splenic nodules. The main risk associated with this procedure is contamination of the abdominal cavity with tumor cells in the case of hemangiosarcoma. Hemangiosarcoma is not likely to manifest itself as one or few small nodules, but it may be a risk in predisposed breeds. A more conservative approach involving repeating the ultrasonographic examination in 4 weeks has been suggested.[25] Any increase in the size of a nodule over this period should be pursued aggressively. It should be remembered that a change in diameter from 1 to 1.2 cm is associated with a doubling in volume for a spheric mass.[25]

276.4.1 Box • 276-3 Infectious Causes of Splenomegaly/Splenitis*

- Viral diseases
  - Feline infectious peritonitis (FIP) (C)
  - Feline leukemia virus (FeLV) (C)
  - Feline immunodeficiency virus (FIV) (C)
  - Infectious canine hepatitis (D)
- Rickettsial and mycoplasmal diseases
  - Ehrlichiosis (canine and feline)
  - Rocky mountain spotted fever (RMSF) *(Rickettsia rickettsii)*
  - Q fever *(Coxiella burnetii)*
  - Hemotropic mycoplasmosis (*Mycoplasma haemofelis* (formerly *Haemobartonella felis* Ohio)

Bacterial infections

- Canine brucellosis
- Mycoplasmosis
- Florida borreliosis
- Plague
- Tularemia
- Streptococcosis
- Staphylococcosis
- Salmonellosis
- *Francisella* infection
- Endotoxemia

Fungal diseases

- Cryptococcosis
- Histoplasmosis
- Blastomycosis

Protozoal diseases

- Toxoplasmosis
- Cytauxzoonosis (C)

Babesiosis (*Babesia canis* and *B. gibsoni*)

Leishmaniasis (D)

* Infectious disease may affect the spleen directly or may indirectly cause splenomegaly by causing chronic anemia, chronic antigen stimulation, or disturbances in blood flow (e.g., endotoxemia).

C, Cats; *D*, dogs.

276.5 PATIENT WITH SPLENIC DISEASE

Diffuse splenomegaly is usually managed medically. Most diseases that cause diffuse splenomegaly are systemic in nature, and treatment should be directed at the underlying cause. Splenic torsion in dogs is the exception to the rule. A few tumors and myeloproliferative disease can also benefit from removal of the spleen. Splenectomy can be considered in patients with immune-mediated anemia or thrombocytopenia refractory to therapy. It is important to show bone marrow hyperplasia in the cell line with decreased peripheral numbers, before splenectomy is performed. Removal of the spleen is the treatment of choice for patients with splenic masses.

Removal of the spleen may predispose the patient to infections. Splenectomized humans are more likely to die of sepsis, but this predisposition has not yet been confirmed in dogs and cats. A few organisms that infect blood cells (e.g., as in babesiosis, hemotropic mycoplasmosis, and ehrlichiosis) are known to occur more often in splenectomized patients. Ideally, dogs and cats should be tested before splenectomy and treated accordingly if infected.

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277 CHAPTER • 277 Systemic Lupus Erythematosus

Michael Stone*

No single definition describes systemic lupus erythematosus (SLE). Veterinary patients with SLE classically demonstrate at least two separate manifestations of autoimmunity in addition to the presence of antinuclear antibody (ANAs). However, some patients demonstrate clinical features of multisystemic autoimmunity, yet lack serum ANAs.

277.1 PATHOGENESIS

Autoimmune disease may be defined as a clinical syndrome caused by the activation of T cells or B cells, or both, in the absence of an ongoing infection or other discernible cause. In SLE, immune system dysregulation that leads to immune complex formation is postulated to induce tissue damage (type III hypersensitivity); however, direct antibody-mediated cytotoxicity (type II hypersensitivity) and cell-mediated autoimmunity (type IV hypersensitivity) also occur.

277.1.1 Effectors

The primary mediators in the development of SLE are pathogenic antibodies, pathogenic immune complexes, and autoreactive T cells.

277.1.1.1 Pathogenic antibodies

Individuals with SLE produce antibodies directed against a broad range of nuclear, cytoplasmic, and cell membrane molecules. Autoantibodies may cause damage through the formation of immune complexes, opsonization of target cells, and interference with cellular physiology. Antibodies may penetrate living cells and bind to cytoplasmic or nuclear structures, altering cell function and contributing to disease by mechanisms other than classic complement-mediated injury.[1]

* The author thanks Dr. Susan Cotter for her review of this manuscript.

277.1.1.2 Pathogenic immune complexes

Immune complexes, which are formed whenever an antibody meets an antigen, are normally removed by the mononuclear phagocyte system. With continued production of autoantibody to a self-antigen, the mononuclear phagocyte system may become overloaded. Circulating immune complexes are deposited in the walls of blood vessels in which there is a physiologic outflow of fluid (e.g., glomeruli, synovia, and the choroid plexus). Some immune complexes are “tissue tropic” and prone to binding to tissues because of a cationic charge or because the antibodies the complexes contain are directed against tissue components. Trapped immune complexes activate complement, attracted neutrophils release lysosomal enzymes, and the result is tissue damage.[2]

277.1.1.3 Autoreactive T-cells

T cells may directly cause tissue damage in SLE. Dermatologic lesions, polymyositis, and vasculitis have been associated with cytotoxic T cell–mediated damage.[3]

277.1.2 Genetics

In mice, more than 25 genes that can contribute to an autoimmune diathesis have been identified.[1] Most of these genes are associated with the major histocompatibility complex (MHC), encoding cytokines, antigen co-receptors, cytokine-or antigen-signaling cascades, co-stimulatory molecules, molecules involved in pathways that promote or inhibit apoptosis, and molecules that clear antigen or antigen-antibody complexes. For example, a consequence of the inheritance of Fe receptors that weakly bind immunoglobulin may be impaired ability to clear immune complexes, which predisposes the individual to the sequelae of circulating immune complexes. Protective genes exist that prevent the development of SLE even if multiple susceptibility genes are inherited. SLE is clearly inherited in dogs, and experimental colonies of dogs with the disease have been established.[4–6] SLE in dogs has been associated with the allele DLA A7, along with a negative (or "protective") association with DLA Al and B5.[7] Dogs with a specific allotype of the fourth component of complement may be predisposed to SLE,[8] as are dogs with decreased serum IgA.[9] SLE may occur more frequently in purebred cats, which also suggests a genetic influence.[10]

277.1.3 Environmental Factors

The lower than expected rate of SLE concordance among identical human twins strongly suggests the existence of an environmental trigger.[3] Exposure to ultraviolet (UV) light causes disease flares in as many as 50% of humans with SLE, and the same effect has been reported in both dogs[5,11] and cats.[12] In humans, the importance of gender is demonstrated by the fact that 90% of SLE cases occur in women, particularly during their reproductive years. However, this gender distribution has not been identified in either the dog or cat. Exposure early in life to infectious agents may suppress the development of allergic and autoimmune disorders.[13] It has been suggested that the increase in allergies and autoimmune diseases recognized in humans is related to decreased exposure to endotoxin during early development. Adequate stimulation may be important in the ontogeny of the normal immune system.[14]

277.1.4 Drugs

Certain drugs may induce SLE-like disease in humans (Box 277-1).[15] However, this disease is probably different from true SLE. The clinical manifestations of drug-induced lupus in humans are predominantly arthritis, serositis, fatigue, malaise, and low-grade fever; nephritis and central nervous system (CNS) diseases are rare. The manifestations disappear in most patients within a few weeks of discontinuation of the offending drug, never to reappear unless the individual is re-exposed to the drug.[3] Propylthiouracil has been associated with hemolytic anemia, thrombocytopenia, and the development of antinuclear antibodies in cats.[16] Methimazole has been associated with the development of antinuclear antibodies in cats, but clinical signs of SLE have not been reported.[17] Hydralazine has been associated with the development of antinuclear antibodies in dogs.[18]

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277.1.4.1

Box • 277-1 Causes of Drug-Induced Systemic Lupus Erythematosus in Humans

Allopurinol

Captopril

Chlorpromazine

Clonidine

Danazol

Diphenylhydantoin

Griseofulvin

Hydralazine

Isoniazid

Lithium

Lovastatin

Mesalazine

Minocycline

Salicylic acid

Penicillamine

Penicillin

Phenothiazines

Phenylbutazone

Piroxicam

Primidone

Procainamide

Propylthiouracil

Quinidine

Streptomycin

Sulfasalazine

Sulfonamides

Tetracycline

Valproate

Modified from Mutasim DF, Adams BB: A practical guide for serologic evaluation of autoimmune connective tissue diseases. J Am Acad Dermatol 42:159, 2000.

277.1.5 Infectious Agents

No infectious agents have been identified that cause SLE. However, it is possible that infectious agents or their antigenic products (or both) can worsen SLE in patients with the appropriate predisposing genes. Microbial antigens have the potential to initiate autoreactivity through molecular mimicry, polyclonal activation, or the release of previously sequestered antigens. The immunogenicity of autoantigens may be increased by inflammation in the target organ, which explains the flares of immune-mediated disease induced by vaccination or infection. Molecular mimicry describes infection with an agent that has antigens immunologically similar to host antigens but sufficiently different to allow an immune response. As a result, tolerance to autoantigens breaks down, and the pathogen-specific immune response cross-reacts with host tissues.[19] The feline viruses feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) can induce disease in cats that is similar to SLE, and serum ANAs may develop in the early stages of FeLV infection.[20] Whether FeLV-or FIV-induced disease is truly similar to SLE is a matter of debate.[21] Feline ehrlichial disease has also been associated with the development of antinuclear antibodies.[22]

Table • 277-1 Clinical Signs in Dogs and Cats Suspected of Having Systemic Lupus Erythematosus

	INCIDENCE (DOGS)		INCIDENCE (CATS)	
CLINICAL SIGN	RATIO*	PERCENTAGE	RATIO	PERCENTAGE
Nonerosive polyarthritis	236/302	78	9/25	36
Fever	186/275	68	11/21	52
Renal disorders	167/302	55	10/25	40
Dermatologic lesions	138/302	46	15/25	60
Lymphadenopathy/splenomegaly	66/175	38	CNBD	CNBD
Leukopenia	54/302	18	CNBD	CNBD
Hemolytic anemia	45/302	15	6/25	24%
Thrombocytopenia	40/302	13	2/25	8%
Myositis	16/275	6	CNBD	CNBD
Central nervous system disorders	16/302	5	6/25	24%
Neuropathy	7/302	2	CNBD	CNBD

Modified from references 10–12, 21, and 26–33.
CNBD, The incidence could not be determined from the published literature.

* Ratio of the number of patients affected to the number of patients described.

In summary, the ability to manufacture pathogenic immunoglobulin and to sustain its production depends on three main factors: (1) inheritance of an appropriate number of susceptibility genes, (2) lack of protective genes, and (3) an environmental stimulus that sets the whole process in motion.

277.2 CLINICAL FINDINGS

The clinical signs reported in dogs and cats with SLE are summarized in Table 277-1. It must be noted that the process of deriving criteria from diagnosed cases is inherently circular, because the criteria are based on diagnosed cases of SLE.

Nonerosive polyarthropathy is the most frequent primary sign in dogs. The smaller joints (carpi, tarsi, elbows, stifles) are most frequently involved. Synovial fluid analysis reveals neutrophilic inflammation with greater than 10,000 cells/mm^3. Articular symptoms are also common in cats, some of which may demonstrate joint swelling and abnormal synovial fluid, yet lack signs of lameness. Fever is frequently reported in both dogs and cats and may be either persistent or intermittent.

In humans, biopsy demonstrates involvement of the kidney in almost all SLE patients.[23–25] Renal involvement may be benign and asymptomatic or relentlessly progressive and fatal. The earliest manifestation is proteinuria. In dogs, proteinuria and glomerular lesions are also common. Biopsy may reveal mesangial and/or endothelial hypertrophy, proliferative and/or membranous glomerulonephritis, and sclerotic changes. Proteinuria and/or glomerulonephritis are also commonly reported in the cat.

Cutaneous manifestations in dogs may include erythema, scaling, crusting, depigmentation, and alopecia. Ulcers may develop on the skin and in the mucocutaneous junctions and oral cavity. Preferential localization of lesions may occur in areas poorly protected by the haircoat, and exposure to sunlight may exacerbate the lesions. Biopsy reveals inflammatory infiltrates at the dermoepidermal junction and vacuolar change in the basal columnar cells. Immunofluorescence stains demonstrate immunoglobulin and complement deposits in the epidermal basement

membrane. Cutaneous lesions reported in 15 feline patients with SLE included erythema, ulceration, and crusting and depigmentation of the face, ears, and paws in seven cats; biopsy results consistent with pemphigus foliaceus or plasmacytic pododermatitis in four cats; ulcerative stomatitis in three cats; and seborrheic dermatitis in one cat.[10,12,21,30]

Only rarely is anemia, leukopenia, or thrombocytopenia the presenting feature of human SLE without concomitant problems of the skin, joints, CNS, or cardiopulmonary system. In dogs, although it is common to find anemia of chronic inflammation, Coombs'-positive anemia is uncommon. Thrombocytopenia may be severe enough to cause bleeding, but antiphospholipid syndrome and thromboembolic disease should also be considered as possible causes in these cases. Leukopenia has been frequently reported. Complement concentrations were decreased in three of eight dogs suspected of having SLE.[8] As in dogs, hemolytic anemia is uncommon in cats, and thrombocytopenia is rare. Complement levels were decreased in one cat studied.[10]

Thrombosis associated with the "lupus" anticoagulant was reported in one dog with SLE.[34] The "lupus" anticoagulant is an antibody directed against membrane phospholipids. The antibody causes *in vitro* prolongation of the activated partial thromboplastin time (aPTT), hence the paradoxical name *anticoagulant*. However, *in vivo* the antibody causes platelet activation and hypercoagulability.

Table • 277-2 American College of Rheumatology Revised Criteria for the Classification of Systemic Lupus Erythematosus*

CRITERION	DEFINITION
Malar rash	Fixed erythema, flat or raised over the malar eminences, that tends to spare the nasolabial folds
Discoid rash	Erythematous, raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur
Photosensitivity	Skin rash as a result of unusual reaction to sunlight
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless
Arthritis	Nonerosive arthritis involving two or more peripheral joints
Serositis	Pleuritis (pleuritic pain or rub, or evidence of pleural effusion) *or* pericarditis (pericardial effusion)
Renal disorder	Persistent proteinuria *or* cellular casts, which may be red cell, hemoglobin, granular, tubular, or mixed type
Neurologic disorder	Seizures *or* psychosis (either in the absence of offending drugs, known metabolic derangements, or electrolyte imbalance)
Hematologic disorder	Hemolytic anemia (with reticulocytosis) *or* leukopenia (less than 4000/mm^3 on two or more occasions) *or* lymphopenia (less than 1500/mm^3 on two or more occasions) *or* thrombocytopenia (less than 100,000/mm^3 in the absence of offending drugs)
Immunologic disorder	Anti-DNA (antibody to native DNA in abnormal titer) *or* anti-Sm (presence of antibody to Sm nuclear antigen) *or* positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, (2) a positive test result for lupus anticoagulant, or (3) a false-positive serologic test for syphilis
Antinuclear antibodies (ANAs)	An abnormal ANA titer at any point in time and in the absence of drugs known to be associated with "drug-induced lupus"

Modified from Tan EM: The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 25:1271, 1982.

* For the purposes of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any four or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

Memory impairment, headache, epilepsy, and personality changes may accompany SLE in humans. Sole involvement of the CNS without other clinical or laboratory features of SLE is unusual. In animals, subtle behavioral disturbances may go unrecognized. In cats, reported CNS involvement has included racing around the house; twitching of the ears, tail, and hindlimbs; repeated licking of paws and tail base; generalized seizures; hyperesthesia along the dorsum; restless crying; disorientation; ataxia; loss of conscious proprioception; nystagmus; and ventroflexion of the neck.[10] Polymyositis was suspected in several dogs and cats. Polyneuritis, characterized by hyperesthesia of the nerve courses, has been reported in a dog.[11]

In humans, chest pain with or without pleural effusion is the most common sign of cardiopulmonary involvement. Fibrosis, pulmonary embolism, capillary leakage, or serositis may affect the lungs. The heart valves, myocardium, or conducting system may be affected, and pericardial effusion may develop. Neutrophilic myocarditis was demonstrated in four dogs with SLE.[28] Serositis of the pleura or pericardium was not observed in cats, although subclinical lung changes were noted on the thoracic radiographs of one cat.[10]

277.3 DIAGNOSIS

Criteria have been developed for the diagnosis of SLE in humans (Table 277-2), and these criteria may be modified to apply to veterinary patients (Table 277-3). A veterinary consensus would be helpful to allow comparison of future studies. Veterinary patients with SLE classically demonstrate at least two separate manifestations of autoimmunity, along with testing positive for ANAs. Patients with three or more separate manifestations of autoimmunity may also be considered to have SLE even in the absence of detectable ANAs. In dogs, the syndrome most commonly recognized is immune-mediated polyarthritis in association with immune-mediated skin disease, glomerulonephritis, hemolytic anemia, or thrombocytopenia. Similar signs occur in cats, but neurologic signs may be more common in this species.

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Table • 277-3 Proposed Criteria for Diagnosis of Systemic Lupus Erythematosus in Dogs and Cats*

CRITERION	DEFINITION
Antinuclear antibodies (ANAs)	Abnormal ANA titer in the absence of drugs or infectious or neoplastic conditions known to beassociated with abnormal titers
Cutaneous lesions	Depigmentation, erythema, erosions, ulcerations, crusts, and/or scaling, with biopsy findings consistentwith systemic lupus erythematosus
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless
Arthritis	Nonerosive, nonseptic arthritis involving two or more peripheral joints
Renal disorders	Glomerulonephritis or persistent proteinuria in the absence of urinary tract infection
Anemia and/or thrombocytopenia	Hemolytic anemia and/or thrombocytopenia in the absence of off ending drugs
Leukopenia	Low total white cell count
Polymyositis or myocarditis	Inflammatory disease of the skeletal or cardiac muscles
Serositis	Presence of a nonseptic inflammatory cavity effusion (abdominal, pleural, or pericardial)
Neurologic disorders	Seizures or psychosis in the absence of known disorders
Antiphospholipids	Prolongation of the activated partial thromboplastin time that fails to correct with a 1:1 mixture of the patient's and normal plasma, in the absence of heparin or fibrin degradation products

Modified from references 28 and 36–39.

* A diagnosis of SLE is established if a patient manifests three or more criteria simultaneously or over any period of time.

Diagnostic tests for patients suspected of having SLE should include hematology, biochemistry, urinalysis, imaging, joint fluid cytology, histopathology of the skin and/or kidney, and serum ANA determination. Cats should also be tested for FeLV and FIV. Infectious and neoplastic disease must be excluded through imaging; culture of urine, blood, and/or joint fluid; serology for tick-borne and fungal diseases; and trials of therapeutic antibiotics. In tick-infested areas, a 3-to 7-day course of doxycycline should be considered before a diagnosis of immune-mediated disease is made.

Immunodiagnostic investigations may include Coombs' testing, platelet autoantibodies, rheumatoid factor, coagulation testing for antiphospholipid antibodies, serum immunoglobulin, complement, circulating immune complex concentrations, and endocrine autoantibodies (i.e., thyroglobulin). Immunohistologic investigation may include immunoperoxidase and immunofluorescence staining and electron microscopy evaluation.[40]

Biopsy results may support a diagnosis of SLE but are rarely diagnostic by themselves. When the skin is biopsied, care must be taken to avoid ulcers or erosions, because an intact epidermis is necessary to substantiate the diagnosis. Oral biopsy specimens are rarely beneficial, because ulcers, which are inherently not diagnostic, are common in this location. Erythematous areas adjacent to ulcers yield the best diagnostic results.[41]

The diagnosis of SLE in cats is less well defined. In some studies, all cats that tested positive for ANAs were diagnosed with SLE, but whether all these patients truly had SLE is debatable. Another unanswered question is how to categorize patients that test positive for FeLV or FIV. Some reports include FeLV-positive cats, whereas others exclude them.[10,21,29–31,42] Because of the possibility of ehrlichial disease, it has been recommended that all cats be treated with a course of doxycycline before the diagnosis of immune-mediated disease is made.[43]

277.4 SPECIFIC TESTS

277.4.1 Lupus Erythematosus Cell Preparation

For the lupus erythematosus (LE) cell preparation, clotted blood is mashed to release free nuclei. Circulating antibody directed against nucleoprotein binds and opsonizes the nuclear complex. An LE cell is recognized as a neutrophil that contains phagocytized nuclear material. Interpretation depends on the experience and diligence of the technician, and false-negative results are common.[26,27,44] Because of technical problems and difficulty with sensitivity and specificity, the LE cell test has been largely replaced by the more sensitive ANA test. LE cells rarely may be seen on smears of pericardial, pleural, peritoneal, joint, cerebrospinal, or blister fluid and when present are highly suggestive of SLE.

277.4.2 Antinuclear Antibodies

Antinuclear antibodies are a heterogeneous population of antibodies directed against various nuclear antigens. ANAs may be detected using frozen sections of rat liver or cultured cell lines (e.g., Vero cells, HEp-2 human epithelial cells). The relative merits of each substrate are the subject of debate, and there is no universally accepted protocol used by veterinary laboratories. The result of an ANA test is commonly reported as a serum titer and pattern of nuclear staining. The most commonly observed patterns in SLE are speckled or homogenous staining, but no clear association exists between patterns and the nature of clinical disease. A clinically significant titer must be distinguished from low ANA titers that may be present in as many as 10% of normal animals and in animals with any chronic inflammatory, infectious, or neoplastic disease.[45,46]

In humans, substrates tend to remain comparable in their ability to detect common ANAs but differ substantially in the quantitation of antibody titer.[47] In dogs, it has been suggested that multiple substrates be used to increase the sensitivity of the test.[48] Two canine studies found markedly different ANA results when rat liver and HEp-2 cell substrates were compared[48,49]; however the results were well correlated in a third report.[50] Feline ANA test results were found to have a low coefficient of correlation when identical sera were sent to different laboratories.[51]

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The most appropriate substrate, conjugate, and methodology for ANA testing remains undefined, and each laboratory's value should be interpreted individually. ANA-negative SLE cases have been described in veterinary patients,[5,26–28] and a positive ANA test result should be neither required nor sufficient in itself to make a diagnosis of SLE.

277.4.3 Autoantibodies

Suspicion of SLE in humans leads to testing for specific antibodies that provide diagnostic and prognostic information (Table 277-4). Research in this area may be helpful for further characterizing immune-mediated diseases in veterinary patients. Autoantibodies also have been studied in veterinary patients (Table 277-5).

277.4.3.1 Antibodies to DNA

Serum antibodies may recognize denatured (single-stranded) or native (double-stranded) DNA. Anti-single-stranded DNA has low diagnostic value in humans and has not been studied in veterinary medicine. Anti-double-stranded (native) DNA is highly specific for the diagnosis of human SLE, even though only 60% to 83% of patients test positive. Anti-double-stranded DNA has been identified only infrequently in dogs with SLE.

277.4.3.2 Extractable nuclear antigens

ENAs are molecules extracted from the soluble fraction of cell nuclei (DNA and histone proteins are insoluble and therefore excluded). More than 20 saline-extractable antigens have been identified, and the term *ENAs* generically refers to this group of nuclear proteins. The binding of serum antibodies to commercially available tissue extracts is the basis for serologic testing. Important ENAs include Sm, Ro, and La. In veterinary medicine, antibodies against ENAs do not yet have the diagnostic and prognostic significance they do in human patients.

Table • 277-4 Autoantibody Associations in Human Systemic Lupus Erythematosus

EPITOPE	COMMENTS
ds-DNA	Highly specific for the diagnosis of systemiclupus erythematosus
Sm	Associated with membranous nephropathy
RNP	Associated with Raynaud phenomenon, pulmonary and muscle involvement
SS-A/Ro	Associated with cutaneous manifestations, sicca complex, neonatal lupus
SS-B/La	Associated with neonatal lupus
Phospholipid	Associated with thrombocytopenia, thrombosis infertility

From Edworthy SM: Clinical manifestations of systemic lupus erythematosus. *In* Ruddy S et al (eds): Kelley's Textbook of Rheumatology, 6th ed. Philadelphia, WB Saunders, 2001, pp 1105–1119.

ds-DNA, Double-stranded DNA; *Sm, Ro, La,* extractable nuclear antigens named for the first two letters of the name of the patient in whom the antigen was first described (e.g., Sm, Smith); *RNP*, ribonucleoprotein; *SS-A*, Sjögren syndrome A antigen (or its equivalent, Ro); *SS-B*, Sjögren syndrome B antigen (or its equivalent, La).

Table • 277-5 Positive Autoantibody Results in Canine Patients with Suspected Systemic Lupus Erythematosus

	INCIDENCE		
EPITOPE	RATIO*	PERCENTAGE	REFERENCE
ds/DNA	6/38	16	Costa 1984[54]
	1/3	33	Bennett 1987[44]
	1/47	2	Brinet 1988[52]
	2/100	2	Monier 1992[53]
	0/43	–	Monestier 1995[55]
Sm	9/34	24	Costa 1984[54]
	2/30	7	Hubert 1988[5]
	12/75	16	Fournel 1992[11]
	0/20	–	White 1992[56]
	1/64	2	Henriksson 1998[57]
RNP	4/38	10	Costa 1984[54]
	0/12	–	Monier 1988[6]
	0/30	–	Hubert 1988[5]
	6/75	8	Fournel 1992[11]
	0/20	–	White 1992[56]
	5/64	8	Henriksson 1998[57]
SS-A/Ro	1/12	8	Monier 1988[6]
	0/0	–	Hubert 1988[5]
	3/75	4	Fournel 1992[11]
	0/20	–	White 1992[56]
SS-B/La	0/30	–	Hubert 1988[5]
	0/l2	–	Monier 1988[6]
	1/75	1	Monier 1992[53]
	0/20	–	White 1992[56]
"Type I" (antibody to a 43 kD nuclear antigen, also known as hnRNP G)	10/38	38	Costa 1984 [54]
	15/75	20	Fournel 1992[11]
"Type 2"	5/38	13	Costa 1984 [54]
	7/75	9	Fournel 1992[11]
Phospholipid	1/1	100	Stone 1994[34]
	2/20	10	Scott-Moncrieff 2001[58]
	1/1 (feline)	100	Lusson 1999[59]

ds-DNA, Double-stranded DNA; *Sm*, *Ro*, *La*, extractable nuclear antigens named for the first two letters of the name of the patient in whom the antigen was first described (e.g., Sm, Smith); *RNP*, ribonucleoprotein; *SS-A*, Sjögren syndrome A antigen (or its equivalent, Ro); *SS-B*, Sjögren syndrome B antigen (or its equivalent, La).

* Ratio of the number of patients that tested positive to the number of tested patients.

277.4.3.3 Antihistone antibodies

Histones are a group of proteins that bind the DNA helical structure into supercoil formation. Histone antibodies are characteristic of drug-induced SLE in humans. One group of investigators detected antihistone antibodies in 61% to 72% of dogs with SLE.[11,52,53] Antihistone antibodies have been detected in canine sera by other investigators; however, no significant difference in concentration was seen between ANA-positive and ANA-negative sera,[49] and antihistone antibodies were detected with conditions other than canine SLE.[54] The use of antihistone antibodies as an indicator of drug-induced SLE in veterinary patients has not been reported.

277.4.4 Antiphospholipid Antibodies

Antiphospholipid antibodies bind to phospholipids found on many cells. These antibodies interfere with the function of procoagulant phospholipids in clotting tests *in vitro*. Patients with the lupus anticoagulant have a prolonged aPTT that fails to correct with a 1:1 mixture of the patient's plasma and normal plasma. In humans, the presence of these antibodies is associated with thrombocytopenia, thrombosis, and fetal loss. Antiphospholipid antibodies were described in one dog with SLE,[34] in two of 20 dogs with hemolytic anemia,[58] and in one cat with SLE.[59]

277.5 MANAGEMENT

Sunlight should be avoided if photosensitization occurs. Patients with mild lameness may require only intermittent therapy with nonsteroidal anti-inflammatory drugs. Dogs may be given carprofen (4.4 mg/kg orally once daily), etodolac (15 mg/kg orally once daily), or meloxicam (0.1 mg/kg orally once daily). Meloxicam also has been used safely in the cat.[60]

More severe signs necessitate corticosteroid administration. Prednisone (2.2 mg/kg/day given orally) is recommended in most instances; 1 mg/kg/day may be effective in less severe cases. Full doses are administered until the disease is in complete remission, defined as resolution of clinical signs and radiographic or laboratory changes initially present. After remission has been attained, the dose is tapered, generally by half, for 4 weeks. The animal then is re-evaluated, and if signs of disease are absent (per physical examination and laboratory testing), the dose is again halved. Tapering is repeated monthly until the animal either relapses or stops medication. The recommended minimum duration of therapy is 6 months. If relapse occurs during taper, the dose should be increased to the most recently effective dose and held there for a few months. If the maintenance requirement is unacceptable because of side effects, an additional immunosuppressive agent is added.

Some cats do not respond to prednisone. Cats that don't respond well to prednisone should be treated with an alternative steroid (e.g., prednisolone, methylprednisolone, triamcinolone, or dexamethasone) before additional immunosuppressant therapies are started.

Combination immunosuppression therapy is very helpful because the additional agent often allows the use of a lower dose of corticosteroid. Azathioprine (Imuran) is most frequently used in dogs. The dose is 2.2 mg/kg given orally once daily until remission occurs. The same dose then is administered every other day. A complete blood count (CBC) should be evaluated after 7 days and then every 2 weeks while the patient is receiving daily treatment. The development of neutropenia or thrombocytopenia requires drug cessation until the bone marrow

recovers. Once the animal is receiving every other day therapy, a CBC should be evaluated every 3 months, but bone marrow suppression at this dose is unusual.

Prednisone and azathioprine are frequently used in combination. The drugs are administered together once daily and tapered after remission has been attained. The method of tapering is somewhat arbitrary. If signs of prednisone intolerance are experienced, prednisone is tapered first; if bone marrow disease is encountered, azathioprine should be tapered or discontinued first. If the disease was difficult to bring into remission, only one drug should be tapered at a time; if the disease easily went into remission, the two drugs may be tapered concurrently. Tapering should be performed every 4 weeks, with a minimum duration of therapy of 6 months.

Azathioprine is not recommended for use in cats. Instead, chlorambucil may be administered along with corticosteroids for cats that require additional immunosuppression. Chlorambucil (Leukeran) is administered to cats at a dosage of 15 mg/m^2 (4 mg for most cats) given orally once daily for 4 days and then repeated every 3 weeks. Potential side effects include anorexia and bone marrow suppression. A CBC should be evaluated 5 to 7 days after each course of treatment. If after two or more evaluations the CBC remains normal (no leukopenia), further monitoring may be done less frequently. If leukopenia is detected (absolute neutrophil count less than 3000/μL), the dose of the next administration should be decreased 25%. Signs of infection (loss of appetite along with fever) during the expected white blood cell nadir (3 to 10 days after administration) should be aggressively treated with intravenous fluids and broad-spectrum antibiotics. In cats, the chlorambucil dosage should be tapered before the prednisone is tapered.

Novel therapeutic approaches include prednisone (1 to 2 mg/kg orally once daily) combined with levamisole (2 to 5 mg/kg, to a maximum dose of 150 mg orally every 48 hours).[11] Prednisone is tapered and discontinued after 2 months, whereas levamisole is given continuously for 4 months and then stopped. If relapse occurs, levamisole is readministered, again for 4 months. Approximately 75% of dogs treated with such therapy were reported to attain remission. Side effects included agranulocytosis, excited behavior, and aggressiveness.[39]

In humans, an antimalarial drug (e.g., hydroxychloroquine) may provide additional relief. Antimalarial agents have multiple sun blocking, anti-inflammatory, and immunosuppressive effects, although their mechanism of action is not completely understood.[61] Their use has not been reported in dogs or cats with SLE.

277.6 PROGNOSIS

The natural course of SLE in veterinary patients is not known. Patients may be well controlled and medications may be tapered, but relapses should be anticipated. Routine evaluation should include hematology, biochemistry, urinalysis, and serum ANA determination every 1 to 3 months. The ANA titer may correlate with clinical severity and may fall with clinical improvement, but the antibody may persist at a low titer during clinical remission. It has been suggested that therapy should be more aggressive when the clinical presentation includes renal disease.[10,39]

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278 CHAPTER • 278 Immune-Mediated and Infective Arthritis

David Bennett

Immune-mediated and infective arthropathies are characterized by an elevated white cell count in the synovial fluid, mainly comprising neutrophils. Synovial fluid analysis is mandatory for diagnosis of these so-called inflammatory arthropathies, and it distinguishes them from the more common degenerative arthropathies.[1]

Infective arthritis is defined as an inflammatory arthropathy caused by an infective agent that can be cultured from the affected joint or joints; however, it is not always possible to culture the organism, and it is important to assume infection if only a single joint is affected. Bacteria are the most common cause of infective arthritis.

The immune-mediated diseases are generally polyarthropathies, although some of the more uncommon infections can involve multiple joints. Although the etiology of immune-mediated arthritis is unknown, certain microbial infections have been implicated. One mechanism is immune complex formation in response to microbial infection, either locally in the joint or systemically with deposition into the joint.[2] Transportation of microbial antigens to joints, with a subsequent immune response, is another possibility. Canine distemper viral antigens and antibodies have been identified in the immune complexes from the synovia of dogs with immune-mediated arthritis[3]; macrophages containing distemper antigens have also been demonstrated in the synovial membrane.[4]

In addition, it is likely that certain individuals are genetically predisposed to immune-mediated arthritis; certain DLA-DRB1 alleles (DRB1 002, 009, and 018) have been associated with immune-mediated arthritis in the dog; furthermore, it appears that a conserved amino acid motif in the third hypervariable region in some DRB1 alleles of both humans and dogs is associated with immune-based arthritis in both species.[5]

The theory of molecular mimicry has also been proposed; that is, antibodies against certain bacteria or viruses may cross-react with cartilage components. Some researchers think that polyclonal B-cell activation, as may occur in a persistent or serious infection, may lead to the emergence of autoantibodies against joint "self-antigens." For example, autoantibodies against heat shock proteins may stimulate immune complex formation in joints or may even cross-react with cartilage epitopes.[6] Potential antigens may also originate from nonmicrobial sources, such as tumor antigens, drug antigens/haptens, and dietary antigens. Once the joint inflammation has been established, by whatever mechanism, various autoantigens, such as altered collagen, are produced. These autoantigens stimulate an immune response, thereby helping to perpetuate the inflammation.[7,8]

Obviously lameness is an important clinical feature, although many immune-mediated polyarthropathies present as cases of "pyrexia of unknown origin." Only about one third of infective arthropathies have systemic signs. Lameness may be an obvious limp, although generalized stiffness is most often seen with the immune-mediated polyarthropathies. Bacterial infections generally have an acute onset, although a more chronic, insidious onset is possible, the so-called low-grade infections. The joint is usually swollen and painful on manipulation, and heat may be detectable.

The immune-mediated arthropathies also tend to have a sudden onset, with multiple joints swollen and painful in a bilaterally symmetric fashion. In some cases obvious joint swelling and pain may not be apparent, but multiple arthrocenteses and fluid analyses confirm the diagnosis. Multiple synovial fluid analyses should be performed in all cases of "pyrexia of unknown origin"; immune-mediated polyarthritis is the single most common diagnosis of such cases in a referral practice.[9]

Local lymphadenopathy is common with both the infective and the immune-mediated arthropathies. Diseases of other body systems are common with the immune-mediated arthropathies, although these can occur with certain infections as well.

278.1 BACTERIAL INFECTIVE ARTHRITIS (SEPTIC ARTHRITIS, SUPPURATIVE ARTHRITIS)

Beta-hemolytic streptococci of Lancefield group G, staphylococci, hemolytic *Escherichia coli, Pasteurella* sp., and *Erysipelothrix* sp. are the bacteria most commonly isolated from septic joints.[10,11] Less commonly isolated organisms include *Corynebacterium, Salmonella, Brucella,* and *Pseudomonas* spp. and anaerobic organisms. In some cases a mixed infec-tion may be present, involving both aerobic and anaerobic bacteria.

Infection can be introduced by direct penetration of a joint, as can occur with bite wounds, iatrogenic infection after open joint surgery, or arthrocentesis, or through road accident injuries. Most joint infections in cats are associated with bite wounds incurred in fights. However, in most dogs, infection occurs by the hematogenous route, and the source of infection is often unknown. Pre-existing joint disease and/or prior surgical intervention predisposes the joint to opportunistic infection as a result of seeding of organisms in the compromised synovial tissues. Trauma can predispose a joint to subsequent infection and lameness; an initial mild injury may resolve, but the lameness returns a few days later after hematogenous localization of infection to the joint. Bacterial infections may also spread to joints from infected foci in neighboring soft tissues or bone.

Most cases involve only a single joint, but two joints may be affected at the same time, or a second joint may be affected some time after the first (Figure 278-1). Involvement of more than two joints most often occurs secondary to a severe systemic bacterial infection, such as bacterial endocarditis[12] or omphalophlebitis, that has a significant bacteremic component. Bacterial endocarditis can result in a true infective arthritis or in an immune-mediated arthritis. These dogs often have lesions of other body systems, and a cardiac murmur is often present. Ultrasonography may show the vegetative endocarditic lesion.

Bacterial infective arthritis affects dogs of all ages. The larger breeds are most often affected, and the male to female ratio is 2:1. The radiographic features vary with the type of infection and its duration. The earliest radiographic change is soft tissue swelling (Figure 278-2). A marked periosteal reaction often develops in the later stages, and calcification of the joint capsule may be seen. Subchondral bone erosions may appear as discrete radiolucencies or as more extensive bone destruction (Figure 278-3). Patchy sclerosis of subchondral bone is often seen. Some infected joints show an overall loss of bone density (see Figure 278-3). Leukocytosis, as a result of neutrophilia and a left shift, is an inconsistent finding.

Figure 278-1 Photograph of an infected elbow joint. The synovium is thickened and hemorrhagic. There is no obvious destruction of the cartilage, which suggests that this is a relatively early lesion.

Figure 278-2 A mediolateral radiograph of an infected stifle joint. Only soft tissue changes are present. There is loss of the infrapatellar fat pad and distension of the caudal joint capsule. These changes are not specific for bacterial infective arthritis. They indicate a synovial effusion, but synovial fluid analysis is essential to demonstrate an inflammatory arthropathy; also, if only a single joint is involved, the cause is likely to be infection.

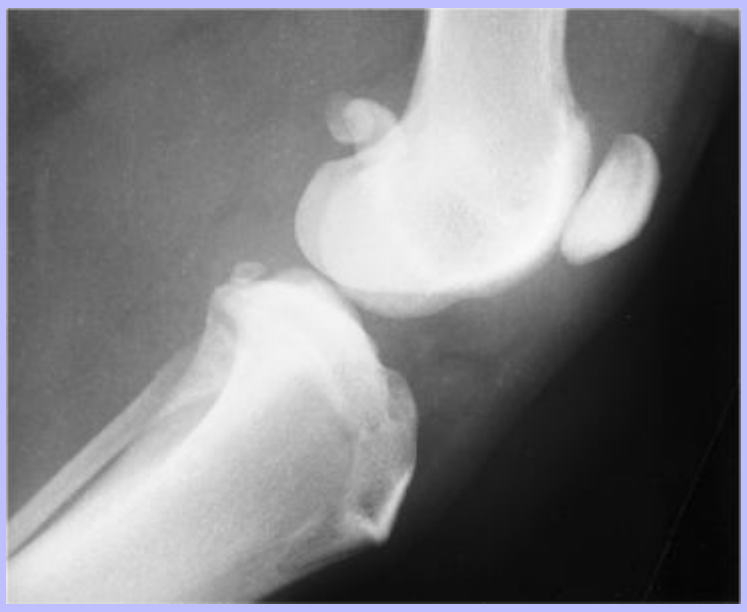

Figure 278-3 Craniocaudal radiograph of an infected stifle joint showing more advanced pathology. Bony destruction is obvious, as shown by an increased intercondylar notch and bony loss at the articular margins of the femur and tibia. Overall loss of bone density of the distal femur also is present. There is evidence of previous surgery, specifically a tibial plateau leveling osteotomy for cranial cruciate ligament failure.

The diagnosis of bacterial infective arthritis is confirmed by culture of the organism from synovial fluid or synovial membrane (or both); however, negative cultures are not uncommon. Blood cultures are sometimes

worthwhile if the animal is pyrexic. Bacterial sensitivity testing should be performed on positive cultures to aid therapeutic planning.

The mainstay of therapy is a prolonged course of systemic antibiotics, which should be initiated in all suspect cases pending confirmatory laboratory results. A broad-spectrum bactericidal antibiotic is used. Ampicillin, clavulonate-potentiated amoxicillin, and cephalosporins are all useful. The antibiotic should be changed only if indicated by subsequent antibiotic sensitivity tests. If anaerobic infection is suspected or if the response to the initial antibiotic is poor, metronidazole is used in combination with other antibiotics. Local gentamicin beads or sponges can be used with resistant infections.[13]

Systemic antibiotic therapy is continued for at least 4 to 6 weeks, or for 2 weeks after complete resolution of clinical signs. Joint lavage and drainage are particularly indicated if the clinical signs are severe or if the patient is an immature animal with open growth plates. Rest of the joint, by means of strict confinement and support bandaging, is important in the early stages. Analgesics are generally necessary, and the nonsteroidal anti-inflammatory drugs are ideal for this. During the recovery phase, controlled exercise, such as passive flexion and extension or gentle lead walks, should be initiated to maintain range of movement in the joint. The level of exercise can be gradually increased after the first 4 weeks.

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278.2 LYME ARTHRITIS

Lyme disease is a tick-borne, multisystemic illness that affects humans and a number of domestic animals. It is caused by infection with the spirochete *Borrelia burgdorferi,* which is primarily transmitted by ticks of the *Ixodes* genus.[14–16] The most common presenting sign in dogs is acute lameness associated with a migratory monoarthritis or pauciarthritis. True polyarthritis is rare, although an immune-mediated arthritis has been reported. Episodes of lameness typically last only a few days, although repeat episodes may occur. Other manifestations include neurologic and cardiac signs. Radiographs of affected joints may be normal or may show only soft tissue swelling in the joints.

A diagnosis of Lyme disease is difficult to establish with certainty. *B. burgdorferi* is notoriously difficult to culture from clinical cases. Serologic testing is of value, although subclinical and asymptomatic infections can occur. Approximately 20% of normal dogs with a history of a tick bite are seropositive for *B. burgdorferi,* therefore the mere presence of a positive serum anti-*Borrelia* antibody test in a lame dog is insufficient to establish a diagnosis of Lyme disease.[15]

Lyme disease is treated with antibiotics, such as tetracycline, penicillin derivatives, and erythromycin. A response normally is seen within 7 days of the start of treatment, but antibiotic therapy should be continued for at least 2 weeks after resolution of all clinical signs. Most cases have an excellent prognosis, particularly if diagnosed and treated promptly.

Cats undoubtedly are exposed to *B. burgdorferi,* in that 4.2% to 15% of normal cats are seropositive for the organism, but little evidence of clinical disease exists in this species.[17–19] The reason for this is unclear, but the cat's immune response does differ from the dog's in that felines shown an early response to OspA and B antigens.[18]

278.3 BACTERIAL L-FORMS AND ARTHRITIS

L-form bacteria are cell wall–deficient bacteria, and these organisms have been associated with pyogenic subcutaneous abscesses and arthritis in cats. The infection spreads locally and hematogenously to involve other joints and subcutaneous sites. The infection is resistant to many antibiotics but is susceptible to tetracyclines.

278.4 MYCOPLASMAL ARTHRITIS

Mycoplasmal infection of joints may arise as a result of the spread of organisms from localized sites of active or latent infection in the mucous membranes of the airways, conjunctivae, or urogenital tract. This is most likely to occur in debilitated or immunodepressed animals. *Mycoplasma gatae* and *Mycoplasma felis* have been associated with polyarthritis and tenosynovitis in cats. Infection with *Mycoplasma spumans* is associated with a polyarthritis syndrome of young greyhounds[20,21]; it is essentially a nonsuppurative polysynovitis, usually associated with severe destruction of articular cartilage.

Animals with mycoplasmal arthritis present between the ages of 3 and 30 months (average age is 18 months) with an insidious onset of clinical signs. The organisms may be seen in a synovial fluid smear stained with Wright, Leishman, or Giemsa stain; they may also be found in the cerebrospinal fluid. Mycoplasmal arthritis can be treated with tylosin, gentamicin, or erythromycin.

278.5 FUNGAL ARTHRITIS

Fungal arthritis is very rare. It usually occurs as an extension of fungal osteomyelitis but may also present as a primary granulomatous synovitis. Fungal infections of joints have involved a range of organisms, including *Coccidioides immitis, Blastomyces dermatitidis, Filobasidiella* (*Cryptococcus*) *neoformans, Sporotrichum schenckii,* and *Aspergillus terreus*. The organisms may be seen in synovial fluid smears or cultured from the joint.

278.6 RICKETTSIAL ARTHRITIS

Polyarthritis increasingly is recognized in association with rickettsial infections in dogs. *Rickettsia rickettsii,* the causative organism in Rocky Mountain spotted fever (RMSF), is transmitted by ticks of the *Dermacentor* genus and is endemic in wooded areas of the central United States and the eastern seaboard. RMSF is a severe disease associated with rapid dissemination of *R. rickettsii* from the site of the tick bite to many organs in the body, resulting in widespread vasculitis. Polyarthritis is one possible clinical sign.

Canine ehrlichiosis (*Ehrlichia canis* infection transmitted by the tick *Rhipicephalus sanguineus*) may present as a polyarthritis in certain geographically restricted areas, including Missouri and Tennessee. Cats are thought to suffer infection by rickettsiae of the *Ehrlichia* genus, but case reports are lacking.

278.7 PROTOZOAL ARTHRITIS

Leishmaniasis is a chronic systemic disease caused by the protozoan parasite *Leishmania donovani. L. donovani* is transmitted by insect vectors, mainly sandflies, and is endemic in areas such as the Mediterranean, Africa, Asia, and South America. The dog is the main reservoir host in many areas. In addition to polyarthritis, signs such as fever, malaise, weight loss, dermatopathy, lymphadenopathy, and hepatosplenomegaly may occur in the dog. The disease has a long latent period and may appear in nonendemic areas despite prolonged quarantine

procedures. The synovitis is usually associated with an infiltrate of large numbers of macrophages filled with *Leishmania* bodies. An immune-mediated polyarthritis may also be seen in association with the infection. Leishmaniasis is an important zoonosis, and there are public health implications if the disease is diagnosed in dogs, particularly outside endemic areas. Cats can become infected, but clinical disease is rare.

Toxoplasma gondii infection is well known in the cat and does occur rarely in the dog; lameness can be a feature, but joint involvement is poorly documented. *Neospora caninum* infection can cause a polymyositis as well as neurologic disease; only experimental infection in the cat has been reported.

Infection with *Hepatozoon canis* can cause polyarthritis and polymyositis in both the dog and the cat. Infection occurs by ingestion of the vector tick (*R. sanguineus*), which contains the organism in its digestive tract.

Infection with *Babesia* spp. most often causes severe anemia, although polyarthritis and polymyositis have very rarely been described. *B. canis* and *B. gibsoni* affect the dog, and *B. felis, B. cati, B. herpailuri,* and *B. pantherae* affect the cat. Babesioses are tick-borne diseases carried by ixodid ticks, and concurrent infection with other protozoal organisms can occur.

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278.8 VIRAL ARTHRITIS

Calicivirus can produce a true infective arthritis in the cat, most often under cattery conditions, and certain strains are more likely to be involved. Experimental studies have shown that calicivirus can infect joints and cause synovitis, and that live virus can be recovered from these joints.[22,23] A field strain of calicivirus isolated from a lame cat (strain F65) was used to infect experimental cats either intra-articularly or by contact exposure. This strain was particularly trophic for the joints, although nasal, oral, and ocular tissues were also infected.

278.9 IMMUNE-MEDIATED ARTHRITIDES

The immune-based arthropathies are divided into two broad categories, erosive and nonerosive,[24–29] based on whether bony destructive changes are present on the radiographs. The diseases that cause bony destruction generally have a poorer prognosis. A radiographic survey of several joints should be made.

278.10 EROSIVE IMMUNE-BASED ARTHRITIDES

278.10.1 Rheumatoid Arthritis

Rheumatoid arthritis (Figures 278-4 and 278-5) can affect any breed or cross-breed of dog; it is very rare in the cat.[30] Animals are usually adult, although the exact age of onset varies (an average age of 5 to 6 years is reported).[24]

The classic radiologic feature of rheumatoid arthritis is the presence of subchondral bone destruction, visualized as an irregularity of the articular surface or as “punched out” erosions (Figure 278-6). Advanced cases may show extensive bone destruction with gross joint deformity. A more generalized loss of mineralization of the epiphysis can be another feature, and soft tissue swelling around or synovial effusion within the joint may be present. Calcification of the soft tissues around the joint is often seen. In some early cases, radiographic evidence of bone destruction may be absent; such evidence generally appears within 6 months if the disease persists.

Rheumatoid arthritis is commonly but not invariably associated with the presence of circulating autoantibodies against immunoglobulin G, collectively known as rheumatoid factor.[31] However, rheumatoid factor is not specific for this disease, because it occurs in the other immune-mediated arthropathies and in other disease states, particularly those of a chronic nature, in which antigen-antibody interaction ocurs.[31] Certain dogs in which rheumatoid arthritis can be diagnosed test negative for rheumatoid factor, and some dogs initially may test positive but later test negative, and vice versa.

Figure 278-4 Gross appearance of the carpus of a dog with rheumatoid arthritis. Two obvious areas of cartilage and bone loss can be seen, and the resultant ulcers have been replaced with granulation tissue. The synovium is thickened and discolored. Multiple, symmetric joint involvement was apparent in this dog.

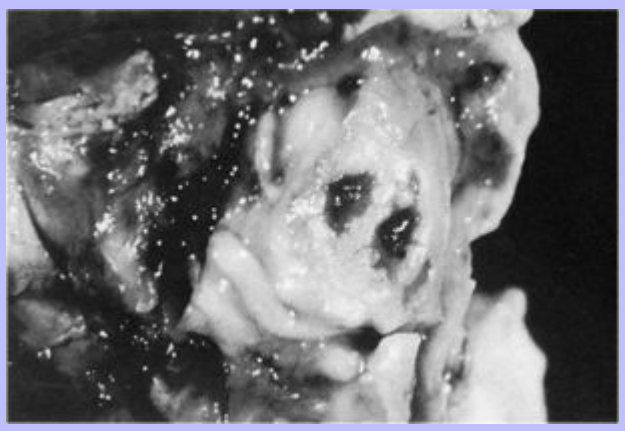
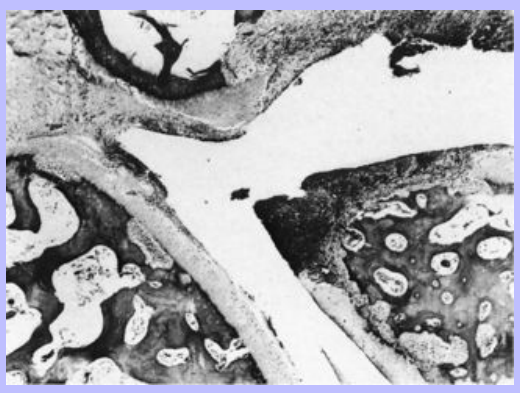


Figure 278-5 Photomicrograph of a canine rheumatoid joint. The articular cartilage has been replaced with granulation tissue in several areas, and a thin covering of the articular cartilage by granulation tissue (pannus) is seen in some areas.



278.10.1.1 Periosteal Proliferative Polyarthritis

Periosteal proliferative polyarthritis, an erosive polyarthritis, is rare in the dog but common in the cat.[30] It affects mainly the hocks and carpi, and the characteristic feature is marked periosteal new bone formation, often extending beyond the confines of the joint (Figure 278-7). Also, one or more joints show localized bony erosions. Bony destruction and proliferation can also occur at the attachment of ligaments and tendons, lesions known as *enthesiopathies*. Cats of any age can be affected, although the disease is said to be common in young adults. Male castrated cats appear to be affected more often.

1961

1962

Figure 278-6 Craniocaudal radiograph of a carpus of a dog with rheumatoid arthritis. The obvious radiolucent areas in the carpal bones represent bony lysis. Also, the joint space is increased between some of the carpal bones. This appearance may be seen with a septic joint, but this dog had multiple joint involvement consistent with an immune-based polyarthritis.

Figure 278-7 Mediolateral radiograph of the hock joint of a cat with periosteal proliferative polyarthritis. New bone deposits are seen on the bones of the hock joint and on the distal tibia and proximal metatarsus. The periosteal reaction extends beyond the confines of the joint. Small areas of bone lysis also can be seen in most of the tarsal bones. Two small areas of bone lysis are present in the tip of the os calcis, together with periosteal new bone, a finding consistent with an erosive enthesiopathy.

278.11 NONEROSIVE IMMUNE-BASED ARTHRITIS

278.11.1 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a multisystemic disease characterized by simultaneous or sequential development of autoimmune hemolytic anemia, immune-mediated thrombocytopenia, leukopenia, glomerulonephritis, dermatitis, polymyositis, pleuritis, central nervous system (CNS) disease, and symmetric

polyarthritis.[26] SLE occurs in both dogs and cats, and because the clinical signs are so variable, diagnosis of the disease can be difficult.

The pathogenesis of SLE involves two main components, autoimmunity and immune complex hypersensitivity. Antibodies against red blood cells, platelets, and leukocytes are important in the development of hemolytic anemia, thrombocytopenia, and leukopenia; the deposition of immune complexes (possibly nuclear antigen and antinuclear antibody) in the kidneys (glomeruli), joints (synovial blood vessels), and skin (dermal/epidermal junction), and possibly in other organs, explains the inflammatory changes in these tissues.

Joint radiographs may show no obvious abnormalities, although occasionally soft tissue swelling or synovial effusion is present.

SLE is characterized by the presence of circulating antinuclear antibody (ANA), a group of autoantibodies targeted against nuclear material.[32] Although antinuclear antibody is found in various chronic disease states, a diagnosis of SLE cannot be justified unless the ANA test result is positive.

278.12 POLYARTHRITIS/POLYMYOSITIS SYNDROME

In polyarthritis/polymyositis syndrome, polyarthritis is complicated by polymyositis. This syndrome is most often seen in spaniel breeds.[27] The dogs test negative for antinuclear antibody, therefore the disease cannot be categorized as SLE.

These dogs present with marked stiffness and poor exercise tolerance, and they often adopt a crouched stance. Widespread muscle atrophy is usually apparent, although in the early stages, muscle swelling and pain may be seen. Muscle atrophy can be associated with fibrosis and contracture, resulting in reduced joint motion; this may be seen in the limb joints and also in the temporomandibular joints, leaving the dog unable to open its mouth.

The muscle enzymes creatine phosphokinase and aldolase are often increased, but not in all cases. Electromyography may show focal areas of spontaneous activity in affected muscles. The myositis is confirmed by multiple muscle biopsy examination (at least six muscles), although the inflammatory change can be patchy and may be absent from some muscles (myositis should be seen in at least two of the biopsy samples).

278.13 POLYARTHRITIS/MENINGITIS SYNDROME

Polyarthritis/meningitis syndrome has been seen in several breeds, including the weimaraner, Newfoundland, German short-haired pointer, boxer, corgi, and Bernese mountain dog. It also is reported in the cat. These animals present with pyrexia, stiffness, and neck pain and in some cases with nervous signs. Cerebrospinal fluid shows increased protein, white cell, and creatine phosphokinase levels, indicating an inflammatory lesion of the central nervous system.

278.14 SJÖGREN SYNDROME

In humans Sjögren syndrome was originally described as a syndrome comprising keratoconjunctivitis sicca (“dry eye”), xerostomia (“dry mouth”), and a polyarthritis, which may be an erosive (rheumatoid) arthritis or a nonerosive arthritis. Dry eye in the dog has been reported with SLE and lymphocytic thyroiditis.[1] Sialadenitis with rheumatoid arthritis has also been documented.[1]

278.15 FAMILIAL RENAL AMYLOIDOSIS IN CHINESE SHAR PEIS

Dogs with familial renal amyloidosis of Chinese Shar Peis present with episodes of fever and with swelling of one or both hock joints and occasionally other joints.[33,34] Enthesiopathies are also seen. The age of onset of signs is variable (young puppies or adult dogs), and the period between attacks can be variable but often is 4 to 6 weeks. Amyloid deposits occur in several organs, but renal amyloidosis and hepatic amyloidosis are the conditions most significant to the prognosis. Amyloidosis eventually results in renal or hepatic failure, which may occur any time between 1.5 and 6 years of age.

278.16 POLYARTHRITIS OF THE ADOLESCENT AKITA

Polyarthritis of adolescent Akitas affects dogs less than 1 year of age.[35] Meningitis may also be present, as may other organ involvement. These dogs have an unfavorable prognosis, because the response to anti-inflammatory and immunomodulatory drugs is poor.

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1963

278.17 POLYARTERITIS NODOSA

Polyarteritis nodosa is an inflammatory condition of the small arteries, often of a granulomatous nature, that can be diagnosed only by histologic examination of biopsy material. Polyarthritis, polymyositis, and meningitis can occur. The attacks are often cyclical, although persistent signs can occur.

278.18 DRUG-INDUCED ARTHRITIS

Drug-induced vasculitides are basically hypersensitivity reactions involving the deposition of drug antibody complexes around blood vessels in different areas of the body. The drug may act directly as an antigen or may combine with host proteins as haptens to form neoantigens.

Polyarthritis is only one feature of these disease syndromes; fever, lymphadenopathy, and macular-papular or bullous-type hemorrhagic rashes are common. Thrombocytopenia, hemolytic anemia, polymyositis, retinitis, and glomerulonephritis are also reported.

The most commonly incriminated drugs are antibiotics, particularly sulfa drugs, lincomycin, erythromycin, cephalosporins, and penicillins. The Doberman pinscher appears particularly susceptible to sulphadiazine-trimethoprim.[36] The diagnosis is made on the basis of worsening clinical signs while the animal is undergoing drug therapy and very rapid improvement (2 to 7 days) after the drug is stopped. The animal usually has had to have encountered the drug previously to become sensitized or has been undergoing long-term therapy.

278.19 VACCINATION REACTIONS

Occasionally an immune-based polyarthritis can develop after vaccine inoculations. It is most likely to occur after the first injection of a primary vaccination course, particularly in kittens.[37] The polyarthritis is generally seen 5 to 7 days after the first inoculation, and the lameness is usually only transient, lasting for 24 to 48 hours.

The calicivirus component appears to cause the condition, and calicivirus antigens have been identified in synovial macrophages of vaccinated (F9 strain) and naturally infected (A4 strain) cats.[22] The presence of these antigens has been associated with an active synovitis.

Persistent polyarthritis in the dog has been reported after recent vaccination.[38] Canine distemper antigens have been found in immune complexes from the joints of dogs with immune-mediated arthritis.[3]

278.20 IDIOPATHIC POLYARTHRITIS

Idiopathic polyarthritis includes all those cases of inflammatory arthropathy that cannot be classified into the other groups. It is still the most common type of polyarthritis in both the dog and the cat.

The idiopathic group can be divided into four subcategories[1]:

- Type I: Uncomplicated idiopathic arthritis; this is the most common subgroup.
- Type II: Idiopathic arthritis associated with infections remote from the joints (reactive arthritis). The infections commonly occur in the respiratory tract, tonsils, conjunctiva (e.g., chlamydia in the cat), urinary tract, uterine tract, skin (including anal furunculosis) and oral cavity.[28]
- Type III: Idiopathic arthritis associated with gastrointestinal disease (enteropathic arthritis). The gastroenteritis is usually characterized by vomiting and/or diarrhea. Sometimes blood is present in the feces. Cases of intestinal bacterial overgrowth and malabsorption have been complicated by polyarthritis, and very occasionally the intestinal disease is an ulcerative colitis.
- Type IV: Idiopathic arthritis associated with neoplasia remote from the joints (arthritis of malignancy). The neoplastic lesion may not be apparent by clinical assessment; some are recorded only during a *postmortem* examination. Neoplasias have included squamous cell carcinoma, heart base tumor, leiomyoma, and mammary adenocardinoma.[28] In the cat, myeloproliferative disease is the most common association,[30] and cats with a nonerosive polyarthritis that do not respond well to therapy should always have a bone marrow examination and should be tested for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV).

The age of onset can vary from a few months to 11 years; many animals are young adults (1 to 3 years) when first presented, especially in type I cases. The pathology is generally an acute/subacute synovitis (Figures 278-8 and 278-9). Soft tissue swelling and/or synovial effusion may be apparent on radiography (Figure 278-10), although often no abnormality is visible. Disease of other body systems is not uncommon.

278.21 TREATMENT

The treatment and prognosis vary with the different types of polyarthritis. Repeated synovial fluid analysis is the most sensitive method of monitoring the effectiveness of treatment. A fall in the total cell count and a reduction in the proportion of polymorphs are good prognostic signs. The erosive arthropathies and animals with multiple-system disease tend to have a poorer prognosis.

The initial treatment in most cases is to attempt immunosuppression with high doses of corticosteroids. These are given orally for 2 weeks (prednisolone, 2 to 4 mg/kg) in a daily divided dose, and the dosage then is gradually

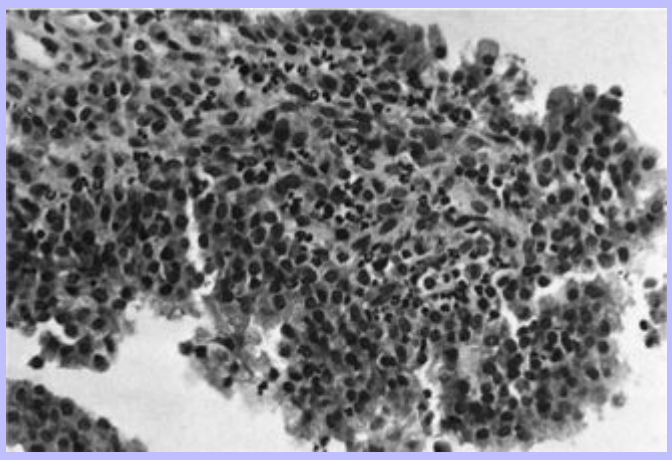
reduced over the next 4 to 8 weeks. Generally a marked response occurs within a few days, but it is important that therapy be maintained to help prevent relapses.

Figure 278-8 Photograph of the stifle joint from a dog with nonerosive polyarthritis (idiopathic type 1). The synovium is thickened and discolored, but the articular cartilage appears normal.

Figure 278-9 Mediolateral radiograph of the stifle joint of a dog with nonerosive polyarthritis (idiopathic type 1). Only soft tissue changes are seen (loss of the infrapatellar fat pad and distension of the caudal joint capsule). Although these changes are not specific for immune-mediated arthritis, this dog had multiple symmetric joint involvement, and the synovial fluid analysis was consistent with an inflammatory arthropathy.

Repeat arthrocentesis and synovial fluid analysis of a joint initially sampled for diagnostic purposes are performed at 2 weeks; if the white cell count has fallen below 4000/mm^3 and most of the cells are mononuclear, the prognosis is reasonably good. If the polymorph count is still high, high-dose steroid therapy should be continued for a longer period. Relapses are always possible, therefore the prognosis overall is guarded.

Figure 278-10 Photomicrograph of a synovial membrane biopsy sample from a dog with idiopathic type 1 polyarthritis. Hyperplasia and hypertrophy of the lining layer are present, as is an inflammatory infiltrate of mononuclear and polymorphonuclear cells in the supporting layer. This is typical of an inflammatory arthropathy, whether infective or immune based, and it could be consistent even with a degenerative arthropathy.



If relapses occur or if the response to prednisolone therapy is poor, a combination of prednisolone and cytotoxic drugs can be tried. The cytotoxic drug of choice is cyclophosphamide, given orally at a dosage of 1.5 mg/kg (for dogs over 30 kg), 2 mg/kg (for dogs 15 to 30 kg), or 2.5 mg/kg (for dogs under 15 kg). The drug is given on 4 consecutive days of each week or as close to this regimen as possible, allowing for the fact that, because of health and safety issues, tablets cannot be divided. In addition, oral prednisolone is given each day at an anti-inflammatory dosage (0.25 to 0.5 mg/kg) to help control pain by reducing the articular inflammatory load. This treatment is continued for 2 to 4 months, even though clinical remission may occur much earlier. Cyclophosphamide should not be used for longer than 4 months because of bladder toxicity problems. The urine can be tested weekly for blood, but the drug does not need to be stopped unless overt blood is visible.

Once cytotoxic therapy has been instigated, blood counts should be monitored every 7 to 14 days. If the white cell count falls below 6000/mm^3 or the platelet count below 125,000/mm^3, the dosage should be reduced by one fourth; if the white cell count falls below 4000/mm^3 or the platelet count below 1000,000/mm^3, the drug should be discontin-ued for 2 weeks and then recommenced at half the original dosage.

In dogs (but not in cats), azathioprine can be used as an alternative to cyclophosphamide, at a daily oral dosage of approximately 2 mg/kg every other day, together with low-dose prednisolone given every other day (alternating with the azathioprine). Bone marrow suppression is more likely with azathioprine.

If the response to cytotoxic drugs and prednisolone is still poor or if relapses occur, a combination of a cytotoxic drug, low-dose prednisolone, and levamisole can be tried. Levamisole may act as an immunomodulatory drug

(i.e., it may suppress helper T cells). It is administered as a liquid oral preparation at a dosage of 5 to 7 mg/kg every other day up to a maximum of 150 mg daily.

Whatever the therapeutic regimen used, the intention is to stop therapy after 3 to 6 months. Generally the cytotoxic drug and levamisole are stopped first, and the steroid is continued at an ever-decreasing dosage.

Gold injections (sodium aurothiomalate or aurothioglucose) have been used in cases of rheumatoid arthritis with some success. It is important to administer a small test dose before full treatment is begun to check for any adverse sensitivity to the drug, and the animal must be checked regularly during treatment for toxic side effects. The dose ranges from 5 to 40 mg, given by intramuscular injection at weekly intervals for 6 weeks. Generally, low-dose prednisolone also is given.

Auranofin (Ridaura), an oral preparation of gold, is also available. Auranofin, which is given at a dosage 0.05 to 2 mg/kg administered twice daily, is less toxic than the injectable gold preparation, but diarrhea is a common side effect.

A combination of oral methotrexate and leflunomide has been used in the cat to treat rheumatoid arthritis. The methotrexate dose is given once weekly; on the day it is given the dose is 7.5 mg divided into three separate and equal doses of 2.5 mg each. The leflunomide dose is 10 milograms daily and is given by oral administration. When significant improvement has occurred, the doses are reduced to 2.5 mg of methotrexate once weekly and 10 mg of leflunomide twice weekly.

Constant corticosteroid therapy sometimes is necessary to keep an animal in clinical remission, and this is perhaps acceptable if only a small dose is required. A few patients spontaneously recover within a day or two without any treatment. Nonsteroidal anti-inflammatory drugs can be used in mild cases or while laboratory results are awaited.

1964

1965

Treatment of idiopathic arthritis types II, III, and IV is directed primarily against the infective, alimentary, or neoplastic lesion, although corticosteroid therapy may be necessary. Colchicine treatment has been used in attempts to control the amyloidosis of familial renal amyloidosis of the Chinese Shar Pei, but its effectiveness has not been proved, and it does not influence the episodes of fever and arthritis.

It is important to provide supportive therapy for these animals when appropriate. Rest, avoidance of stress environments, and good nutrition are essential. Patients receiving immunosuppressive therapy should be checked regularly for secondary infections, and owners should be warned to avoid potential disease environments. Because of the possible involvement of canine distemper virus in immune-mediated arthritis, dogs that have suffered immune-mediated polyarthritis should be screened for distemper antibody levels when a booster inoculation is due; if the levels are consistent with protection, the booster should exclude the distemper component.

278.22

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279 CHAPTER • 279 Skeletal Diseases

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A.D.J. Watson

279.1 INTRODUCTION

Animals with bone disease may have signs of lameness, deformity, or dysfunction that could be confused with, or complicated by, joint, muscle, or neurologic disorders. Therefore a systematic approach is necessary in evaluating animals with these signs. The expertise of a radiologist and bone pathologist will often be invaluable in establishing a diagnosis. Traumatic injuries should also be considered in the differential diagnosis but are not discussed here, because excellent descriptions exist elsewhere.[1] Some bone diseases that also affect joints are described in Chapter 278.

The precise cause of many bone diseases that affect dogs and cats is unknown. Furthermore, some conditions have multiple causes, such as the congenital, heritable, and metabolic disorders. This makes logical classification difficult. A causative system is used here for want of a better alternative.

279.2 BONE PATHOPHYSIOLOGY

279.2.1 Structural Organization of Bone

Bone is a living tissue with several important functions, including storage of calcium, phosphorus, and other minerals. Bones act as a series of levers that facilitate the action of muscles and joints in movement, and they provide support and protection for other body systems. In addition, bone marrow stroma provides an inductive environment for hematopoiesis and is a source of osteogenic precursor cells.[2,3] Bones are structurally composed of compact (cortical) and cancellous (trabecular) bone (Figure 279-1).[4] The microstructural units of cortical bone are osteons that, in cross-section, have concentric layers of collagen fibers and a central canal.

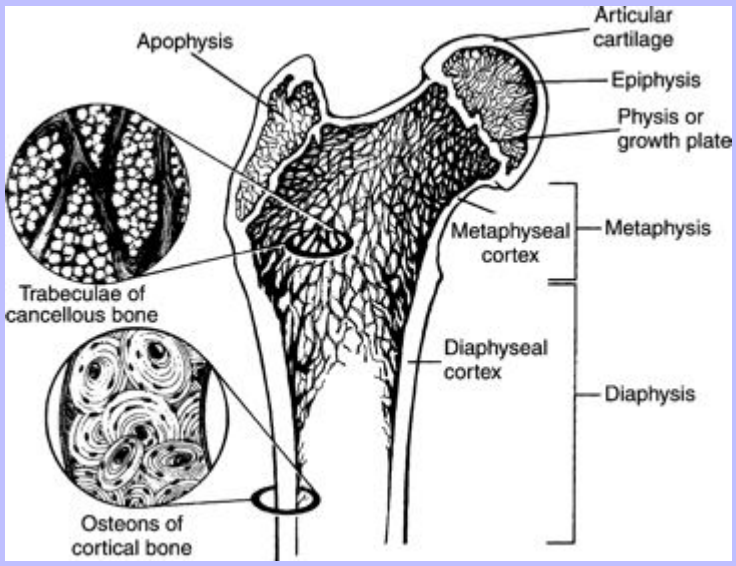
Trabeculae of cancellous bone have a three-dimensional lattice arrangement and large intertrabecular spaces containing hemopoietic or fatty marrow tissue. Long bones have several distinct regions: diaphysis, metaphysis, and epiphysis (see Figure 279-1). In growing animals, each epiphysis contains one or more ossification centers, is covered by hyaline cartilage on the articular surface, and is separated from the metaphysis by the physis or growth plate.[5,6] For reasons not well understood, many diseases have a predilection for certain regions of bone or even for particular bones.

Bone cells are derived from two separate cell systems: (1) the stromal fibroblastic (osteoblasts and osteocytes) and (2) hemopoietic (osteoclasts) systems.[2,3] During bone formation, osteoblasts synthesize collagenous matrix called *osteoid*, which is mineralized to become bone. Osteoblasts entrapped in newly forming bone become osteocytes. At sites of normal skeletal growth and remodeling, osteoblasts are derived from determined osteoblast precursor cells that reside in bone marrow stroma, endosteum, and periosteum. In injury or disease, inducible osteogenic precursor cells derived from other mesenchymal tissues, such as muscle and fibrous tissue, can be stimulated to differentiate to osteoblasts and form extraperiosteal ectopic bone. Osteoblasts can form several different types of bone.[4] Lamellar bone has collagen fibers in a parallel array and

is found in osteons and mature trabecular bone. Formation of lamellar bone requires a pre-existing matrix, such as calcified cartilage matrix (so-called endochondral ossification) or old bone that has been partially removed by osteoclastic resorption. Woven bone is characterized by random orientation of its collagen fibers. It can be deposited *de novo*, without pre-existing bone or cartilage, and is formed when new bone is laid down rapidly in growth, fracture repair, and bone disease.[7] Normally it is remodeled to lamellar bone but may persist in rapidly growing osteogenic tumors.

Osteoclasts are large, multinucleate cells formed by fusion of circulating mononuclear cells. They are found on the surface of bone trabeculae and within remodeling osteons and are responsible for bone removal during growth, modeling, and remodeling of the skeleton. Osteoclasts erode mineralized bone first by solubilizing mineral, then digesting the protein.[3] This leaves concave pits in the bone surface, called *Howship's lacunae*. Formation and resorption of bone is regulated systemically by parathyroid hormone (PTH), calcitonin, and vitamin D (Chapter 237). The principle action of PTH is to activate osteoclastic bone resorption and increase blood calcium concentration. Osteoblasts have PTH receptors, but osteoclasts do not. The increase in osteoclast number and activity induced by PTH is mediated by osteoblasts via a complex coupling mechanism involving several cytokines, including receptor activator of nuclear factor-kappa B (RANK) ligand, interleukins, and tumor necrosis factor (TNF).[2,3]

Figure 279-1 Regions and microstructure of an immature proximal femur.

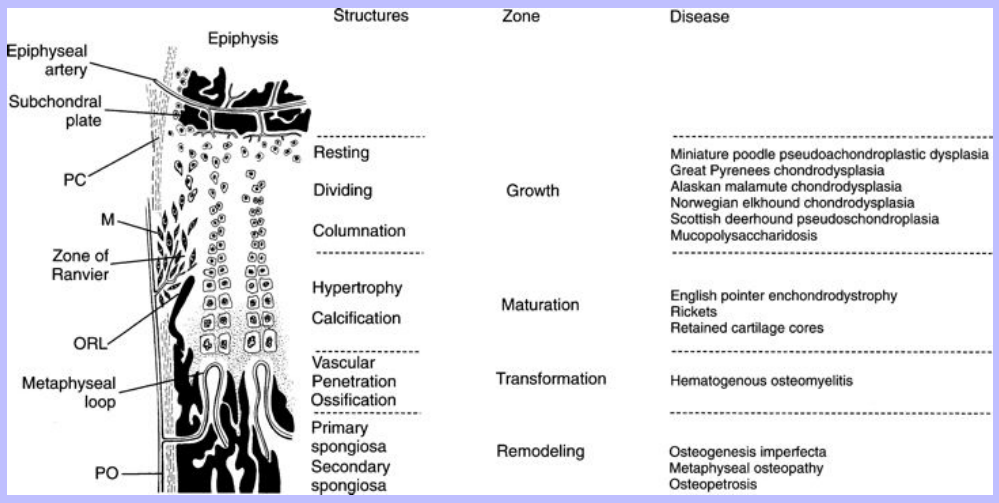


279.2.2 Bone Growth and Development

Growth of the axial and appendicular skeleton is primarily by endochondral ossification at the physes. Most physeal growth is longitudinal, but the zone of Ranvier and subperiosteal appositional growth contribute circumferential expansion as well. Physes have various zones that reflect chondrocytic structure and metabolic activity, but the transition between zones is gradual (Figure 279-2). Once formed, each chondrocyte remains in a fixed anatomic location throughout its life and there accomplishes all its functions.[8,9] The two most prominent stages involve proliferation and hypertrophy (including mineralization of matrix), prior to tissue

resorption during vascularization. Most of the longitudinal growth of a physis is due to the tenfold increase in chondrocyte volume that is maximal in the hypertrophic zone. Defects in any part of the sequence, such as incomplete chondrocyte maturation, cause dwarfism or disordered bone growth (see Figure 279-2).

Figure 279-2 The physis divided based on histologic structure and physiologic function (growth, maturation, transformation, and remodeling). Regions affected by some diseases of growth and remodeling are indicated. In the zone of Ranvier, undifferentiated mesenchymal cells *(M)* give rise to chondroblasts. The periosteum *(PO)* and perichondrium *(PC)* are continuous in this region. The metaphyseal cortex also extends into this region, becoming the osseous ring of Lacroix *(ORL)*, which acts as a peripheral restraint to the cell columns but does not impede latitudinal growth of the adjacent zone of Ranvier. (Adapted from Ogden JA: Skeletal Injury in the Child, 2nd ed. Philadelphia, WB Saunders Co, 1990, p 37.)



279.2.3 Modeling of Bone

Modeling is the process that molds and sculpts the contours of expanding bones during growth. Within the metaphysis, the primary spongiosa is modeled to secondary spongiosa, which in turn is resorbed to form the marrow cavity of the shaft. Simultaneously, bone diameter decreases rapidly in the metaphyseal *cutback zone* as redundant bone is removed by subperiosteal osteoclastic resorption. In modeling, bone formation rates are frequently unequal to resorption rates, but unlike remodeling, bone formation is not dependent on resorption to precede it.[10] Modeling can correct the shape of malunited fractures, deformities, and bone subjected to altered loading, as predicted by Wolff's law. However, because the modeling process is closely coupled to growth, it is usually less effective after maturity.[10]

279.2.4 Normal and Pathologic Bone Remodeling

Remodeling is the process in which bone renews itself throughout life.[10] It always follows the sequence of activation → resorption → formation, and the packets of cells at a remodeling site are collectively called *bone multicellular units*.[10,11] Remodeling occurs in three bone envelopes: (1) the periosteal surface, (2) the endosteal-trabecular (cancellous bone) surface, and (3) the osteonal (intracortical) surface (Figures 279-3 and 279-4). In normal remodeling, bone formation equals resorption, whereas in bone disease a pathologic imbalance of resorption and formation often results in osteopenia of cortical and cancellous bone. Bones subjected to disease, trauma, or disuse exhibit a response termed the *regional acceleratory phenomenon*, in which the number of activated bone multicellular units increases suddenly.[10] This results in increased cortical porosity and trabecular thinning that reaches a peak at approximately 2 to 3 months; it may take up to 1 year to be reversed, during which time resorption sites are refilled with new bone.[12]

1966

1967

Figure 279-3 Remodeling osteon in cortical bone shown in longitudinal section. Components of this bone multicellular unit are shown in four transverse sections on the lower level. **a,** Cutter cone with osteoclasts *(OC)* resorbing bone. **b,** Capillary loop *(CL)* with undifferentiated lining cells *(LC)* in the quiescent zone between resorption and formation. **c,** Closing cone with centripetally advancing osteoblasts *(OB)*, separated by an osteoid seam *(OS)* from radially deposited new lamellar bone *(LB)*. **d,** Completed osteon (Haversian system).

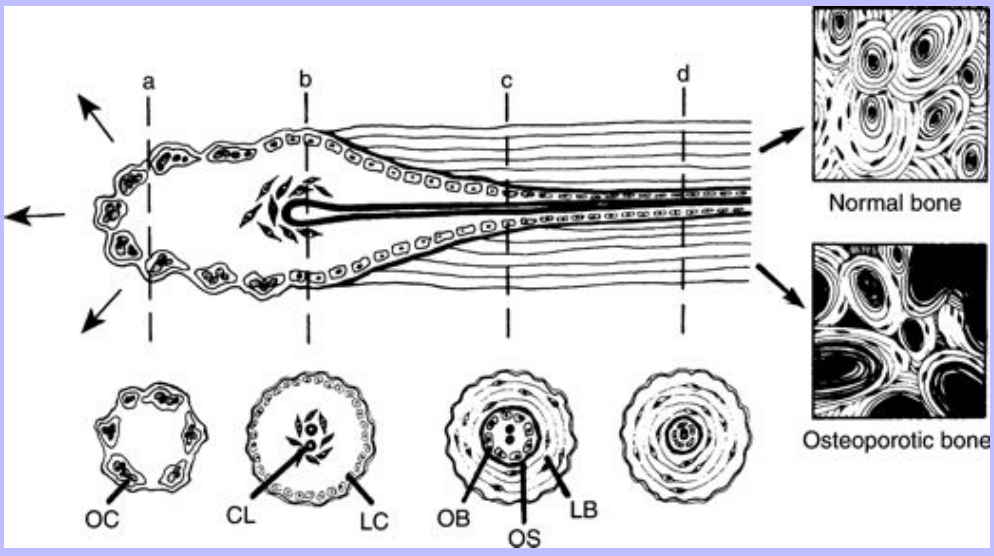
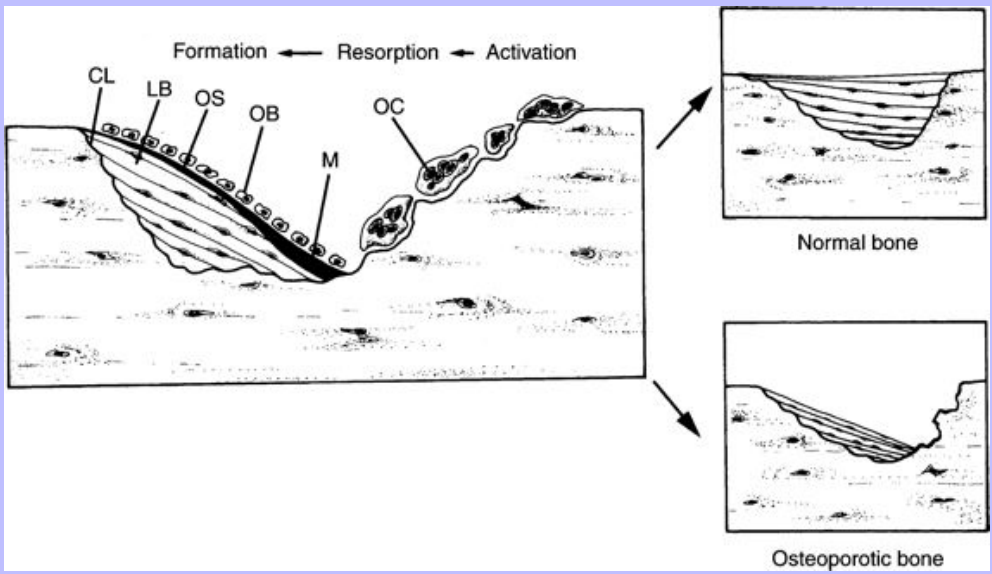


Figure 279-4 Trabecular bone remodeling with the components of bone multicellular unit: osteoclasts *(OC)*, nonmineralized matrix *(M)*, osteoblasts *(OB)*, osteoid seam *(OS)*, new lamellar bone *(LB)*, and cement line *(CL)* separating it from original bone. Normally, formation equals resorption, but in diseases causing osteoporosis, bone formation is inadequate or defective.



279.3 DIAGNOSIS OF BONE DISEASE

279.3.1 History and Signs

Initially, it is important to establish the age, breed, and sex of the patient because these factors may be associated with increased risk of a particular disease. Common complaints from owners are lameness, deformity, difficulty in rising, and reluctance to exercise. One must ascertain the duration and intensity (shifting, constant, intermittent, worsening) of the problem, any known trauma, and any previous illness, medication, or surgery, as well as response to therapy. The owner should be asked whether exercise or rest exacerbates the problem, and whether swelling, drainage, or apparent pain had been noticed. Recognition of similar problems in related animals may indicate heritable disease. The type and quantity of foods, vitamins, and minerals fed should be determined.

279.3.2 Physical Examination

In conjunction with the normal physical examination, special attention is paid to lameness and gait abnormalities and to the musculoskeletal system (see Chapters 194 and 195).[13,14] Visual appraisal might detect abnormalities in limb length and symmetry. The bony prominences and distal limb bones are palpated

to detect pain, swelling, dyssymmetry, or crepitus. By comparison with the contralateral limb, muscle atrophy or altered range of joint motion may be identified. Each abnormality alone is rather nonspecific but aids in region localization. Before proceeding with sedation and radiography, further testing should be considered to exclude neurologic disease as a contributing factor (see Chapters 44 and 191).

279.3.3 Radiology

Radiology is the most useful method for routine noninvasive evaluation of skeletal lesions. To appreciate subtle lesions, radiographs must be excellent. Two or more views are always needed, with the limb properly positioned. Comparison with radiographs of the contralateral limb or a radiographic atlas is useful to distinguish real bone lesions from anatomic and breed variations.[15]

Bone has a limited number of ways of responding to injury or disease. Lesions should be characterized according to changes in bone density, size, shape, or contour; the type of margination; the nature of any periosteal reaction; region of bone involved; and soft tissue changes.[16–18] The finding of a particular response, such as periosteal new bone, is not necessarily diagnostic of a specific disease (Box 279-1). Abnormalities could result from traumatic, neoplastic, infectious, idiopathic, or other processes. When considered in conjunction with signalment, history, and physical abnormalities, radiographic findings may lead to a diagnosis or a list of diagnostic alternatives. At this point it is valuable to consult descriptions of various bone diseases, to evaluate the possibilities, and to decide what further tests are indicated. Tests that are directed at confirming the most likely diagnosis, yet are least invasive and have low morbidity, are done first.

279.3.4 Nuclear Imaging

Scintigraphy is highly sensitive in detecting skeletal lesions, but it is not widely available and is generally not specific for cause.[19,20] After a radiopharmaceutical, usually ^{99m}technetium labeled methylene disphosphonate (^{99m}TcMDP), is injected intravenously, it is incorporated into sites of new bone formation and remodeling and in regions of increased blood flow. The distribution of radionuclide in bone is detected with a gamma camera and is an indication of skeletal metabolic activity, complementing the structural information from radiographs. In cases of lameness in which physical examination and radiographs are unremarkable, scintigraphy may pinpoint a region of increased uptake in bone or a joint. Further procedures such as computed tomography (CT), biopsy, culture, or surgical exploration would then be needed to determine the cause of the "hotspot."

Tumor metastases in bone have a characteristic multifocal distribution, detectable by scintigraphy before they are seen on radiographs.[20] Although scintigraphy also detects primary bone tumors, it is seldom needed for their diagnosis. Scintigraphy with ^{99m}TcMDP may help detect osteomyelitis before radiographic signs appear, but it is not specific for the disease.

279.3.5 Computed Tomography

High-resolution CT provides excellent cross-sectional images of lesions not found with radiographs. Its greatest application in the musculoskeletal system has been in evaluating the complex anatomy of skull, spine and pelvis; in delineating boundaries of tumors involving soft tissues or bone; and in detecting early bone destruction.[21] For bone tumors this information allows more precise presurgical planning for en bloc resection of cranial and pelvic lesions and for limb salvage in appendicular lesions (Figure 279-5).[22–24]

279.3.5.1 Box • 279-1 Radiologic Signs of Some Common Bone Diseases

279.3.5.1.1 Bone Loss

1. Generalized and diffuse

    Primary hyperparathyroidism

    Renal secondary hyperparathyroidism

    Nutritional secondary hyperparathyroidism

    Disuse osteoporosis

2. Thin cortices

    Primary hyperparathyroidism

    Renal secondary hyperparathyroidism

    Nutritional secondary hyperparathyroidism

    Disuse osteoporosis

    Neoplasia

    Osteomyelitis

    Bone cyst

3. Focal

    Osteomyelitis

    Neoplasia

    Bone cyst

Multifocal: myeloma, lymphosarcoma, metastases

4. Cystic

Congenital bone cysts

Aneurysmal bone cysts

Subchondral bone cysts

Central giant cell granuloma

279.3.5.1.2 Bone Production

1. Cortical

Osteopetrosis

Trauma

Remodeling of deformity

Fracture healing

2. Medullary

Enostosis

Myelosclerosis

Osteomyelitis

Sequestration

Neoplasia

Infarcts

Fracture healing

3. Periosteal

Hypervitaminosis A

Mucopolysaccharidosis (MPS)

Multiple cartilaginous exostosis

Enostosis

Metaphyseal osteopathy

Craniomandibular osteopathy

Secondary hypertrophic osteopathy

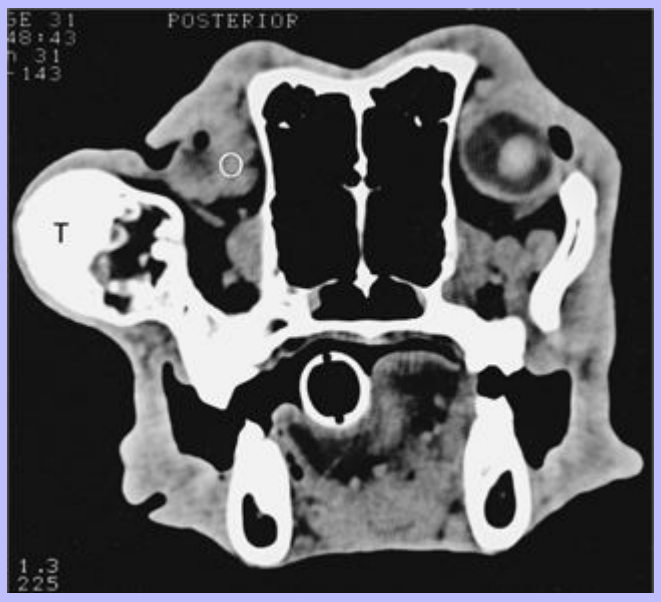
Osteomyelitis

Neoplasia

Trauma

Adapted from Allan GS: Radiographic signs of diseases affecting bone. *In* Proceedings No 87, Orthopaedic Surgery in Dogs and Cats. Sydney, Australia, The University of Sydney Postgraduate Committee in Veterinary Science, 1986, p 247.

Figure 279-5 Computed tomography (CT) image of an osteoma *(T)* of the zygomatic arch that caused ocular *(O)* displacement.



279.3.6 Magnetic Resonance Imaging

Advantages of magnetic resonance imaging (MRI) are that high-resolution, serial, multiplanar images of skeletal soft tissues, such as ligament, tendon, menisci, and articular cartilage, can be obtained without the use of ionizing radiation. However, because this imaging modality relies on detection of changes in the orientation of mobile tissue protons within a strong magnetic field, the signal intensity of mineralized bone matrix is low. Adjacent soft tissues (periosteum, endosteum, fat, articular cartilage, and bone marrow) mainly define contours of bone. Subtle lesions of metaphyseal cancellous bone can be appreciated, as can displacement, compression, and invasion of soft tissue by expansile osseous lesions. However, cortical bone lesions are better visualized using CT.

279.3.7 Chemistry

Estimation of blood calcium and inorganic phosphate concentrations and of alkaline phosphatase activity will occasionally be useful in diagnosing some bone diseases, but these variables are maintained within reference ranges in many skeletal diseases. Validated assays for canine PTH, PTH-related protein, and vitamin D metabolites are useful in hypercalcemic disorders (Chapter 237).

279.3.8 Hematology

Alterations in circulating leukocyte numbers may be consistent with acute osteomyelitis, but the hemogram is usually unremarkable in chronic osteomyelitis and other bone diseases.

279.3.9 Biopsy and Histopathology

Histologic examination of a representative bone biopsy is the most reliable way to establish a diagnosis when radiographic signs are not highly characteristic of a particular disease. Biopsy may be necessary to distinguish between malignant and benign neoplasia, osteomyelitis, developmental lesions, and degenerative conditions. It also specifically identifies tumor type and grade, establishes the prognosis, and may dictate appropriate treatment. For various reasons, mistakes are frequent at this stage of the investigation. The most common pitfall is inappropriate sampling and submission of a biopsy that is reactive bone formed secondarily to the actual disease. Because processing of bone for histology can take 1 week or more, such an outcome can be frustrating and misleading.

Closed needle biopsies of medium-to-large, solid, solitary lesions of appendicular long bones are obtained using a 4-inch, 8-or 11-gauge Jamshidi bone biopsy needle (Sherwood Medical Co., St. Louis, MD) (see Chapter 77).[25] This method has less postsurgical morbidity (pain, hematoma, infection, tumor seeding, pathologic fracture) than incisional biopsy. The clinician should carefully evaluate the radiograph to ensure that the biopsy is obtained from the center of the lesion and that dense reactive bone is avoided. The skin puncture site and biopsy tract must be situated so that they can be subsequently excised if the lesion is surgically resected. Two or three cores of tissue are taken by redirecting the needle through the same skin opening. Needle orientation can be guided with image intensification or radiography. Jamshidi needle biopsy is not suitable for lesions of small bones or lesions with recent pathologic fractures, because there may be significant hematoma in the latter. For cystic and fluid-filled lesions, or those associated with extensive osteolysis and tumor necrosis, an open incisional wedge biopsy through a limited surgical approach might be necessary. Bone that appears abnormal can also be collected with a bone curette, taking care to avoid mutilating the specimen.

For investigation of diseases affecting growth and endochondral ossification, physeal biopsies can be obtained percutaneously from the greater tubercle of the humerus with a Jamshidi needle.[26] For suspected metabolic bone diseases, larger specimens of cancellous bone are collected with an 8 mm Michele trephine from the iliac crest or by excision of a segment of rib or distal ulnar diaphysis.[27]

The surgical borders of lesions excised en bloc are labeled with India ink for examination by the pathologist to ensure tumor-free margins.[28] Specimens can also be radiographed using nonscreen film or industrial film in a Faxitron cabinet system. Biopsies are fixed in neutral buffered formalin for 6 to 24 hours; they must not be frozen.[7] Large bone specimens should be cut into 5 mm slabs to ensure proper fixation.[7] If osteomyelitis is suspected, a portion of the biopsy should be separated for bacteriologic culture before the remainder is fixed in formalin. Bone specimens that cannot be cut with a scalpel are decalcified in 10% formic acid prior to embedding in paraffin. Rapid decalcification in strong acids or excessive decalcification will destroy cellular detail and render the biopsy nondiagnostic. Nondecalcified bone biopsies embedded in methylmethacrylate and sectioned with a sledge microtome are needed for diagnosis of some metabolic bone diseases.[29] Histologic evaluation of bone is rather specialized and requires the expertise of a pathologist with special interest and training. Most pathologists will want to review the clinical data and radiographs as well, before making a diagnosis.

279.3.10 Cytology

Cytologic examination of fluids and exudates obtained by sterile aspiration is valuable in early detection of acute osteomyelitis, before obvious radiographic changes occur in bone.

279.3.11 Microbiology

Isolation and identification of bacteria are helpful in confirming a diagnosis of osteomyelitis, and *in vitro* susceptibility testing aids in antimicrobial drug selection. Cultures of pus from externally draining tracts are less than 50% accurate in identifying the pathogens causing osteomyelitis, because the tracts become colonized by skin organisms and gram-negative bacteria. It is preferable to culture fluid collected by sterile aspiration, or from pus, necrotic tissue, and sequestra collected during surgical débridement. Both aerobic and anaerobic culture are advisable, because anaerobic bacteria are involved in up to 60% of bone infections in small animals.[30] Samples for aerobic culture should be collected into a sterile container, taken to the laboratory, and plated out on agar within 10 to 15 minutes. Specimens for anaerobic culture require special handling because a few minutes of exposure to air will kill sensitive anaerobes and prevent subsequent isolation. Fluid for anaerobic culture can be collected into a syringe if air is expelled and the needle capped with a rubber stopper.

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1970

When the anticipated delay in plating out samples exceeds 15 minutes, tissue samples and swabs are placed into a reduced Cary-Blair, solidified anaerobic holding media (Becton Dickinson, Franklin Lakes, NJ) to exclude oxygen. Both aerobes and anaerobes may be isolated from such preparations because most aerobic bacteria are facultative anaerobes.

279.4 CONGENITAL BONE DISORDERS

Embryonic and postnatal skeletal development are complex and exquisitely susceptible to errors. Skeletal growth disorders that are apparent at birth or manifest later in young animals are of two main types: (1) generalized dysplasias and (2) localized malformations of individual bones. Some are caused by inherited defects and sporadic mutations, and some are due to teratogens and unidentifiable embryopathies. In humans, more than 100 such disorders, mostly inherited, have been listed in the *Paris Nomenclature for Constitutional Disorders of Bone*.[31] This classification is based on specific clinical, genetic, radiologic, histologic, and biochemical features. Animal diseases are not sufficiently characterized to allow complete adoption of the Paris system,[32] although some general groupings are possible (Box 279-2). Generalized dysplasias are described later with developmental and genetic disorders or with joint diseases (see Chapter 278), whereas dysostoses are considered here.

Dysostoses include the malformations of individual bones either singly or in combination. They can involve the craniofacial region, the axial bones, and extremities. Embryonic limb bud development commences with a projection of mesoderm covered by ectoderm. Three signaling centers within the limb bud that control and coordinate limb development are (1) the apical ectodermal ridge, (2) the zone of polarizing activity, and (3) the Wingless-type signaling center.[33] The apical ectodermal ridge is a thickened layer of ectoderm overlying the distal tip of the limb bud that acts as a signaling center guiding proximal to distal limb development. It also causes interdigital necrosis, thereby separating webbed digits, probably by the local expression of FGF genes.[34] The zone of polarizing activity exerts control via the signaling molecule sonic hedgehog protein, and the Wingless-type signaling center controls limb alignment with respect to dorsal orientation.[33] Subsequently, the

individual bones form from cartilage anlages and the secondary centers of ossification.[5,34] Three mesodermal rays (ulnar, radial, and central) contribute to pectoral limb formation; disturbances of one or more rays or of the signaling centers will result in perturbations of the corresponding components of bone and associated soft tissue. For example, failure of the apical ectodermal ridge may produce syndactyly of the digits or result in a truncated limb similar to congenital amputation.[33] Except for a few heritable disorders that will be mentioned, most dysostoses in dogs and cats occur sporadically.

279.4.1 Hemimelia, Phocomelia, and Amelia

In these conditions the animal has a congenital absence of portions of the normal structures in an extremity. Hemimelia is either longitudinal (paraxial), with absence of the ulnar, radial, or central regions in the forelimb, or transverse, with the distal portion of the limb completely absent.

279.4.1.1 Box • 279-2 Some Congenital Skeletal Disorders of Small Animals

279.4.1.1.1 Osteochondrodysplasias (Abnormalities of Cartilage, Bone Growth, and Development)

A. Defects of growth of tubular bone or spine

Multiple epiphyseal dysplasia: beagle

Pseudoachondrodysplasia: miniature poodle

Scottish deerhound

Chondrodysplasia: Alaskan Malamute

Cocker spaniel

English pointer

Great Pyrenees

Norwegian elkhound

Ocular-skeletal dysplasia: Labrador retriever

Samoyed

Pelger-Huët anomaly: cats

Scottish fold osteochondrodysplasia: cats

B. Disorganized development of cartilage and fibrous components

Multiple cartilaginous exostoses (osteochondromatosis)

Enchondroma

Fibrous dysplasia

C. Abnormalities of density, of cortical diaphyseal structure, or metaphyseal molding

Osteogenesis imperfecta

Osteopetrosis

279.4.1.1.2 Primary Metabolic Abnormalities

Vitamin D–dependent rickets

Mucopolysaccharidosis (MPS)

Fucosidosis

GM gangliosidosis

Gaucher's disease

279.4.1.1.3 Dysostoses with Malformation of Individual Bones, Singly or in Combination

Hemimelia

Phocomelia

Amelia

Syndactyly

Polydactyly

Ectrodactyly

Segmental hemiatrophy

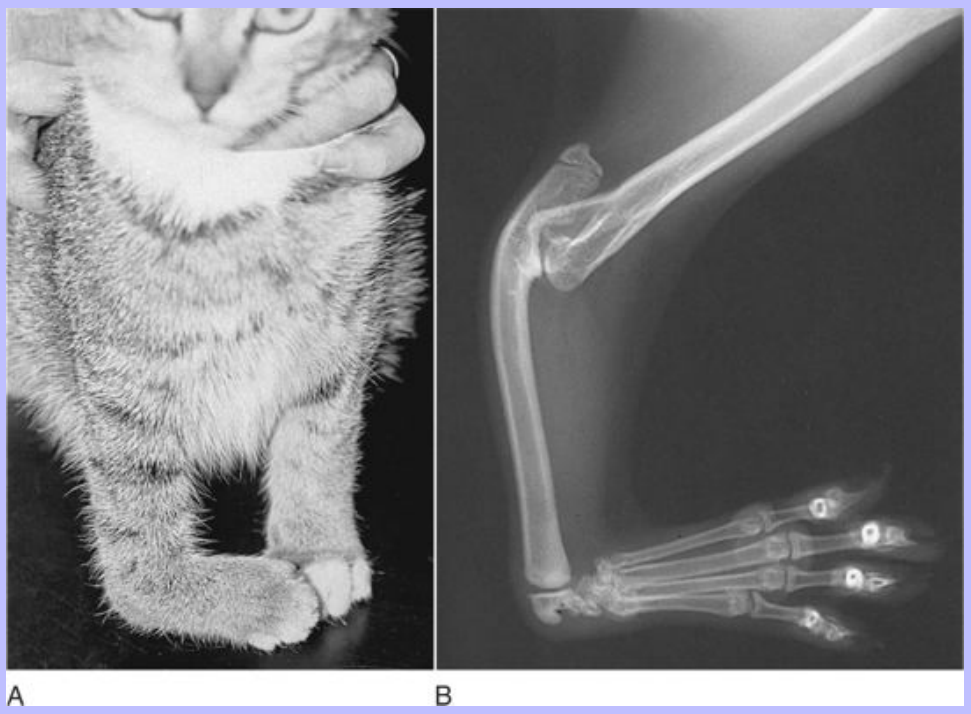
Adapted from Sharrard WJW: Pediatric Orthopaedics and Fractures, 3rd ed. London, Blackwell Scientific Publications, 1993.

Radial agenesis is the most common paraxial hemimelia in cats and dogs. It is usually unilateral and sporadic. Bilateral radial agenesis might be an inherited autosomal recessive trait in Chihuahua dogs.[32] In radial agenesis, the radius is partially or completely absent, and the ulna is shorter, thickened, and curved (Figure 279-6). The radial carpal bone and first digit are often absent as well. Lack of a radial head support allows humeroulnar subluxation, and the range of elbow motion is reduced. The metacarpus deviates into varus, severely impairing limb function. One hypothesis is that radial agenesis and other hemimelias are a consequence of neural crest injury because limb bud embryopathies often have a segmental pattern that corresponds to the distribution of the segmental sensory nerves.[35] Treatment of radial agenesis by reconstructive surgery has not been very successful, and amputation may be necessary. Another, less common paraxial hemimelia is tibial agenesis.[32]

1970

1971

Figure 279-6 Kitten with radial agenesis. **A,** Radial agenesis and a 90-degree varus angulation of the metacarpus. **B,** The radius and radial carpal bone are absent. The proximal ulna is misshapen, the distal ulna thicker than normal, and the carpus malarticulated. (From Winterbotham EJ et al: Radial agenesis in a cat. J Small Anim Pract 26:393, 1985.)



Complete absence of a distal portion of a limb (congenital amputation) can be caused by transverse hemimelia, strangulation by constrictive bands, or *in utero* accidents.[36] The cause may be impossible to determine in young animals, because postnatal trauma can also cause amputations.

In phocomelia, an intercalary segment of limb is missing. In severe cases the paw with rudimentary digits is attached to the trunk like a seal flipper. Proximal femoral focal deficiency is a phocomelia with a missing segment of femur. In man, this is usually a unilateral defect that is not inherited.[37] A young dalmatian with proximal femoral focal deficiency had unilateral hindlimb shortening and muscle atrophy that became accentuated with further growth.[38] Radiographically, bone in the intertrochanteric, neck and head regions of the femur was absent, and there was marked femoral shortening.

Amelia is complete absence of one or more limbs. Two kittens with bilateral hindlimb amelia have been reported.[32] Most animals affected by amelia probably die or are euthanized at birth.

279.4.2 Syndactyly

Two or more digits are fused in a bony or soft tissue union in syndactyly.[7,32] This is not clinically important in pets, and surgery is generally unwarranted unless the deformity causes lameness. Congenital synostosis of adjacent metatarsal bones is a variation on digital fusion (Figure 279-7).

279.4.3 Polydactyly

Polydactyly is the presence of extra digits, usually on the medial side of the paw in dogs and cats. An inherited syndrome of skeletal defects exists, including polydactyly and syndactyly in Australian shepherd dogs.[7] An X-linked gene was suspected. Polydactyly is an inherited autosomal dominant trait in cats.[32] Multiple hindlimb dewclaws in Great Pyrenees have similar inheritance.

Figure 279-7 Congenital metatarsal bone synostosis.

1971

Figure 279-8 Vestigial first metatarsal bone *(M)* and an anomalous tarsal bone *(T)* extending medially from the central tarsal bone in a Saint Bernard.

In Saint Bernard dogs, dewclaws may be associated with anomalous tarsal bones. Some have a large curved bone that seems to be an extension of the central tarsal bone on the medial side of the proximal row of tarsal bones (Figure 279-8). These tarsal anomalies occur bilaterally, are not associated with clinical signs, and are probably inherited.

279.4.4 Ectrodactyly

Often called split hand or lobster claw deformity, ectrodactyly is caused by incomplete fusion of the three rays or absence of the central ray.[37] Classically, the third metacarpal bone and digit are absent, producing a deep cleft that divides the paw into radial and ulnar parts, but many variations occur. The third metacarpal bone may be present and hypoplastic, and neighboring digits and metacarpal bones may be absent or hypoplastic.[39–41] The cleft between metacarpal bones may terminate just below the carpus, or extend proximally through the carpus, separating radius and ulna entirely (Figure 279-9).[39–41] Asynchronous radial

and ulnar growth can contribute to the structural disorder at the carpus. Half of the affected dogs have concomitant congenital elbow luxation. It is usually an isolated deformity without breed predilection in dogs, but may be inherited in cats.[7,32] Function can be improved by reconstructive surgery or arthrodesis.[39,42]

279.4.5 Segmental Hemiatrophy

Hemiatrophy is a misnomer because the condition is actually limb hypoplasia rather than atrophy of a normal structure. The affected forelimb is noticeably shorter and slimmer, especially in the antebrachium and paw.[43] An affected golden retriever also had darker pigmentation of skin and hair of the abnormal limb and horny keratinization of pads and nails, but it has no pain or discomfort.[44] Radiographically the carpal bones were smaller, and the numbered carpal bones were misshapen. The metacarpal bones were 3 cm shorter than contralateral bones and half normal diameter. This is a sporadic deformity and probably not inherited. It must be distinguished from atrophy that follows long-term limb immobilization.[12] A similar type of distal hypoplasia of metacarpus and digits is seen in immature dogs, subsequent to accidental trauma or surgery to the antebrachium.[44] Ilizarov limb lengthening may be indicated if shortening impairs function.

Figure 279-9 Forelimb of 12-week-old mixed breed dog with ectrodactyly, including distal radial and ulnar separation.

279.5 DEVELOPMENTAL AND GENETIC BONE DISORDERS

279.5.1 Osteopetrosis

Defective osteoclastic resorption of bone is the principal feature of osteopetrosis. In growing bones, failure of normal bone modeling results in accumulation of primary spongiosa, so the diaphysis remains filled with bone and a marrow cavity does not form. Affected bones have a *marbled* densely homogeneous radiographic appearance, but they are actually quite fragile. Many forms of osteopetrosis exist. Osteoclasts may be absent, be present in reduced numbers, or be defective in their ability to resorb bone.[7] The disorder is rare and not very well characterized in dogs and cats.[7,45] Idiopathic acquired osteopetrosis of adult cats was characterized by thickening of diaphyseal cortices and vertebral bodies.[45] Feline leukemia virus (FeLV) also produces medullary sclerosis and nonregenerative anemia in growing cats, probably through infection of hemopoietic precursor cells from which osteoclasts arise.[7]

279.5.2 Osteogenesis Imperfecta

Osteogenesis imperfecta comprises a group of heritable diseases characterized by osteopenia, excessive bone fragility, and increased susceptibility to fracture. Fractured bones form callus and heal, but unless stabilized adequately, malunion and deformities occur.[46,47] Radiographically there can be generalized osteopenia, thinning of diaphyseal cortices, and multiple fractures in various stages of union. The fundamental defect in humans is abnormal type I collagen production, mostly due to mutations of genes that normally code for procollagen synthesis.[46] The resulting type I collagen fibrils are thin and fail to mineralize. Osteogenesis imperfecta is rare in dogs and cats, and the mode of heritability and exact biochemical defects are unknown.[32,47,48] Animals may have multiple fractures, with minimal or no trauma. Some may also have dentinogenesis imperfecta (seen as pink teeth), stunted growth, and apparent weakness.[48] The diagnosis is made by analysis of type I collagen from cultured skin fibroblasts,[48] but the more common causes of osteopenia, including renal and nutrition secondary hyperparathyroidism, should be eliminated first.

1972
1973

279.5.3 Mucopolysaccharidosis

The mucopolysaccharidosis (MPS) disorders are rare genetic lysosomal storage diseases caused by specific defects in lysosomal enzymes that are involved in metabolism of glycosaminoglycans. Compounds normally degraded by these enzymes accumulate intracellularly, interfering with cellular function and producing characteristic clinical signs. Several MPS disorders have been recognized in cats (MPS I, VI, and VII) and dogs (MPS I, II, IIIA, IIIB, VI, and VII),[49] but the presence and severity of skeletal abnormalities produced by them are different.

MPS VI is caused by decreased arylsulfatase B activity and leads to intracellular accumulation and increased urinary excretion of dermatan sulfate. Feline MPS VI has been recognized mainly in Siamese cats, as an autosomal recessive disorder, but has also been described in domestic shorthaired (DSH) and long-haired cats, and a Siamese and DSH cross.[49–51] MPS VI has also been reported in dogs of several breeds.[49] Skeletal disease is the predominant abnormality. Clinical features become evident in affected cats from age 6 to 8 weeks and include small head and ears, flattened face, corneal clouding, pectus excavatum, growth retardation, skeletal deformity, and hindlimb paresis or paralysis from spinal cord compression by bone

lesions. They have a crouching gait, and manipulation of joints and cervical spine causes pain. Radiographic features include epiphyseal dysplasia, thinning of long-bone cortices, generalized osteopenia, bilateral coxofemoral subluxation, secondary osteoarthritis, and vertebral fusion.[52] Diagnostic confirmation is provided by demonstration of excess dermatan sulfate in urine with the toluidine-blue (Berry) spot test, metachromatic granules in neutrophils, and reduced arylsulfatase B activity in leukocytes.[49] A PCR-based screening method allows detection of carrier cats.[50]

MPS I in DSH cats is an autosomal recessive disease due to decreased activity of alpha-L-iduronidase.[49,53] Clinical features are similar to MPS VI, but facial dysmorphism may not be as striking as in Siamese, and metachromatic granules are usually less distinct in leukocytes than in MPS VI and MPS VII.[54] Radiographic features are similar to MPS VI, except that epiphyseal dysplasia and dwarfism are absent. Neurologic abnormalities due to spinal cord compression by bone proliferation occur relatively later, after 2 years of age. Excretion of dermatan sulfate and heparin sulfate in urine is detectable using the toluidine-blue spot test.[53] MPS I has also been reported in dogs. Affected animals are dwarfed and have swollen painful joints, glossoptosis, corneal clouding, and progressive motor and visual deficits. Radiographic features include epiphyseal dysgenesis, periarticular bone proliferation, and enlargement of femoral diaphyses.[55]

MPS II was diagnosed in a 5-year-old male Labrador retriever with coarse facial features, macrodactylia, generalized osteopenia, progressive neurologic deterioration and a positive urine test for glycosaminoglycan.[56] Iduronate sulfatase activity was deficient in cultured dermal fibroblasts.

Canine MPS VII (beta-glucuronidase deficiency) has been described in dogs and cats.[50] Affected dogs appear normal at birth, but by age 2 to 3 months develop hindlimb paresis and have a disproportionately large head, flattened face, swollen lax joints, bowed limbs, dorsoventrally flattened rib cage, and corneal clouding.[57] Radiographic features include bilateral coxofemoral luxation, abnormally shaped carpal and tarsal bones, generalized epiphyseal dysplasia, cervical vertebral dysplasia, and platyspondylisis. Feline MPS VII is characterized by growth retardation, delayed dental eruption, corneal clouding, abdominal distension, and multiple skeletal abnormalities.[58–60] In both species, peripheral leukocytes contain metachromatic inclusions, and urinary excretion of chondroitin sulfate is increased.[58,61] Genetic tests can distinguish phenotypically normal MPS VII carrier dogs and cats from homozygous normal animals.[58,62]

Several therapeutic strategies for MPS have been trialed with some success, including enzyme replacement therapy, heterologous bone marrow transplantation, and somatic cell gene transfer, but all require further development.[49]

279.5.4 Dwarfism

Various disorders causing small stature in dogs and cats listed in Table 279-1 are reviewed in other chapters. Considered here are skeletal dysplasias and some endocrinopathies (hyposomatotropism and hypothyroidism) that are more commonly associated with dwarfism in small animals.

279.5.4.1 Skeletal Dysplasias (Osteochondrodysplasias)

Osteochondrodysplasias are disorders characterized by abnormalities in growth and development of cartilage, bone, or both (see Box 279-2). Disorders of this type have been reported in several breeds of

dogs. Box 279-3 summarizes the better-characterized entities. Most have known or suspected genetic basis and autosomal recessive inheritance is common. They frequently cause disproportionate dwarfism, with discrepant development of axial and appendicular skeleton producing reduced limb length relative to the trunk (Figure 279-10).

Another type of genetic dwarfism occurs in achondroplastic dog breeds, such as bulldog, Boston terrier, Pekinese, pug, and Shih Tzu. These animals have been bred selectively for achondroplasia and thus have shortened maxilla, depressed nasal bridge, flared metaphyses, and short bowed limbs as part of accepted breed standards.[32] Hypochondroplastic breeds, such as Basset hound, beagle, dachshund, Dandie Dinmont terrier, Scottish terrier, Skye terrier, and Welsh corgi have similarly shaped legs as a breed characteristic, although their skulls are normal.[32] These forms of dwarfism differ from the nonpathologic, mutant, proportionate reduction in stature in dogs that has led to the establishment through selective breeding of many miniature and toy breeds.

1973

1975

Table • 279-1 Some Causes of Small Stature in Dogs and Cats

NONENDOCRINE	ENDOCRINE
Malnutrition	Hyposomatotropism
Malassimilation	Hypothyroidism
Portal systemic shunt (PSS)	Hypoadrenocorticism
Cardiovascular defects	Hyperadrenocorticism
Glycogen storage disease	Diabetes mellitus
Skeletal dysplasia	
Mucopolysaccharidosis (MPS)	
Hydroencephalus	
Renal disease	

Modified from Feldman EC, Nelson RW: Canine and Feline Endocrinology and Reproduction, 3rd ed. Philadelphia, WB Saunders Co, 2004.

279.5.4.1.1

Box • 279-3 Canine Osteochondrodysplasias: Clinical and Radiologic Signs, and Inheritance Pattern

279.5.4.1.1.1

Alaskan Malamute Chondrodysplasia[7,63]

Short limbs, bowed forelegs, carpal joints enlarged, paws deviated laterally; ulna growth plate thickened, irregular and flared; associated hemolytic anemia; autosomal recessive trait, complete penetrance, variable expression

279.5.4.1.1.2

Beagle Multiple Epiphyseal Dysplasia[7,63]

Short limbs, enlarged joints, kyphosis; stippled mineralization of epiphyses, especially femur and humerus, disappeared by 5 months; vertebrae short; dysplastic hips; osteoarthropathy in adults; autosomal recessive trait

279.5.4.1.1.3

Bull Terrier Osteochondrodysplasia[64]

Abnormal hind leg gait, femoral neck fractures; nonossified foci in femoral necks and metaphyses of long bones; some long bones distorted; dwarfing not noted; littermates affected but inheritance not known

279.5.4.1.1.4

English Pointer Enchondrodystrophy[7,65,66]

Short limbs, bowed forelegs, abnormal locomotion; wide irregular growth plates; possibly inferior prognathism; probable autosomal recessive trait

279.5.4.1.1.5

Great Pyrenees Chondrodysplasia[7,63,67]

Very short limbs, forelegs bowed with valgus deformity; body length reduced slightly; flared, flattened metaphyses; poorly developed epiphyses and cuboidal bones; vertebrae poorly ossified and irregular; autosomal recessive trait

279.5.4.1.1.6

Irish Setter Hypochondroplasia[68]

Mildly short limbs and spine, variable radius and ulna bowing and carpal valgus; growth plates, epiphyses and metaphyses radiographically normal; autosomal recessive trait

279.5.4.1.1.7

Labrador Retriever Ocular-Skeletal Dysplasia[7,69]

Short limbs, prominent elbows and carpi, paws deviated laterally, hind legs hyperextended; tubular bones short and wide, cortices thin, metaphyses flattened and flared, increased metaphyseal opacity; epiphyses and cuboidal bones large and misshapen; hip dysplasia, abnormal elbows; cataracts, retinal dysplasia and detachment; autosomal trait, recessive effect on skeleton, incompletely dominant on eye

279.5.4.1.1.8

Miniature Poodle Multiple Enchondromatosis[70,71]

Short bowed limbs, femoral neck fractures; lucent areas extending from growth plates into metaphyses and some diaphysis; diaphyses distended and distorted; ribs and vertebrae also affected; sternum lacked bone; autosomal nondominant trait

279.5.4.1.1.9

Miniature Poodle Multiple Epiphyseal Dysplasia[63]

Similar to disorder in beagle; inheritance unknown, but two of three affected were littermates

279.5.4.1.1.10

Miniature Poodle Pseudoachondroplasia[7,63]

Poor growth, abnormal gait; short, bent legs, enlarged joints; possible inferior prognathism; vertebrae short, limb bones short and thick with bulbous ends; stippled densities in epiphyses; ossification complete by 2 years of age, but limbs remained short and deformed; probable autosomal recessive trait

279.5.4.1.1.11 Norwegian Elkhound Chondrodysplasia[7,63]

Shortened body, disproportionally short limbs, especially forelegs, which may be bowed; metaphyses flared and flattened, with denser band; ventral vertebral bodies irregular, delayed union of vertebral end plates; may have glucosuria; autosomal recessive trait

279.5.4.1.1.12 Samoyed Ocular-Skeletal Dysplasia[7,72,73]

Short forelegs, varus deformity of elbows, valgus of carpi, premature closure of ulnar growth plates, bowed radii; domed forehead; cataracts, retinal detachment, hyaloid artery remnants eosinophilia; autosomal recessive trait

279.5.4.1.1.13 Scottish Deerhound Pseudoachondroplasia (Osteochondrodysplasia)[74,75]

Retarded growth, short bowed limbs, exercise intolerance, small head, short trunk, lax joints, kyphosis; vertebrae and long bones short, epiphyseal ossification irregular and delayed; later osteopenia, severe deformity; single autosomal recessive inheritance suspected

Figure 279-10 **A,** Radiograph of a 5-week-old Alaskan Malamute with chondrodysplasia. Physeal cartilage is widened, and adjacent metaphyseal bone roughened and irregular. **B,** Radiograph of a normal littermate of same age for comparison.

Figure 279-11 Osteochondro-dysplasia of Scottish fold cats. **A,** Exostoses around the carpus. **B,** Exostoses and ankylosis of the tarsal joints. (Courtesy of Veterinary Imaging Associates, Sydney, Australia.)

An osteochondrodysplasia with autosomal dominant inheritance has been described in Scottish fold cats.[76] Along with the folded ears typical of this breed, affected individuals show signs of lameness, reluctance to jump, stiff and stilted gait, short mis-shapen distal limbs, and short thick inflexible tail. Radiographic features include irregular size and shape of bones of tarsus, carpus, metatarsus, metacarpus, phalanges, and caudal vertebrae. In addition, these animals have narrowing of apparent joint spaces, new bone production around distal limbs joints, diffuse osteopenia, and formation of a plantar exostosis caudal to the calcaneus in advanced cases (Figure 279-11). However, the severity and rate of progression of changes are quite variable. Treatment is noncurative, but pentosan polysulfate, glycosaminoglycans, nonsteroidal anti-inflammatory drugs (NSAIDs), or a combination of these treatments might be palliative.[76]

A chondrodysplasia in two unrelated kittens with shortened, bowed forelimbs was described.[77] Radiographic signs included long bone bowing, metaphyseal flaring, and a gross enlargement of physeal

cartilage that resembled rickets. Serum calcium, phosphorus, and 1,25-dihydroxyvitamin D_3 concentrations were normal, but PTH concentrations were below the reference range. Furthermore, treatment of the kittens with oral 1,25-dihydroxyvitamin D_3 for 3 months did not resolve the radiographic abnormalities or correct the stunted statue. The disorder is considered to be a (osteo)chondrodysplasia of unknown heritability rather than rickets.[77]

1975

1976

279.5.4.2 Pituitary Dwarfism

Hypopituitarism and consequent dwarfism, inherited in autosomal recessive fashion in German shepherd dogs and Karelian bear dogs, has also been described in other dog breeds (Weimaraner, Spitz, toy pinscher) and cats.[78] A cystic, vestigial adenohypophysis is present in many affected German shepherds, but some have a hypoplastic or a normal-appearing pituitary gland. The syndrome is dominated by effects of hyposomatotropism, but deficiency of other adenohypophyseal hormones can lead to degrees of accompanying secondary hypothyroidism, hypoadrenocorticism, and hypogonadism. Affected animals are usually recognizable by the age of 2 or 3 months. They grow slowly but retain near-normal body proportions. The soft puppy-hair coat is retained initially, but symmetric alopecia and hyperpigmentation develop with age. Accompanying abnormalities include abnormal behavior (aggression, fear biting), delayed dental eruption, short mandible, cardiac disorders, cryptorchidism, megaesophagus, and testicular atrophy or estral abnormalities.

Radiographically, limb bones are shortened, with delayed closure of growth plates in some cases. Epiphyses may show disordered and incomplete calcification, suggesting hypothyroidism. Hormonal testing can be undertaken to confirm the diagnosis if necessary. Most pituitary dwarf animals can be expected to remain small for life. However, two unusual cases with typical clinical features at 10 weeks of age grew steadily and appeared normal when 1 year old.[79] Both had normal hormonal test results, indicating that growth hormone secretion ideally should be evaluated in suspected cases to clarify prognosis.

Replacement therapy with growth hormone (if available and economical), and thyroxine or glucocorticoid if indicated, could be considered, but long-term prognosis is poor.[78] Another promising approach involves chronic progestin administration to induce growth hormone production from mammary ductular cells of affected dogs of either sex.[80]

279.5.4.3 Congenital Hypothyroidism

Skeletal development is abnormal in congenital hypothyroidism, which is rare in dogs and cats. Although cases are usually encountered sporadically in various breeds, some familial occurrences are known: secondary hypothyroidism with autosomal recessive inheritance in giant schnauzers,[81] primary dyshormonogenesis with autosomal recessive inheritance in Abyssinian cats,[82] thyroid unresponsiveness to thyroid-stimulating hormone (TSH) with autosomal recessive inheritance in Japanese cats,[83] and thyroid unresponsiveness to TSH in related Scottish deerhounds.[84]

Abnormalities may be detectable by the age of 1 or 2 months. Affected animals are disproportionate dwarfs, with short limbs and spine, blocklike trunks, and broad short skulls. The radiographic features are epiphyseal dysgenesis and delayed skeletal maturation (Figure 279-12). Nonskeletal findings include delayed dental eruption, macroglossia, lethargy, mental dullness, persistent puppy haircoat progressing to thinning and alopecia, mild nonregenerative anemia, and hypercholesterolemia. Thyroid gland enlargement

can accompany congenital dyshormonogenesis[85] but is absent if a hypothalamic-pituitary defect is causing thyroid understimulation[86] or thyroids are unresponsive to TSH.

A low blood plasma thyroxine concentration is expected, but results of other thyroid tests will differ, depending on whether the defect is of thyroidal, pituitary, or hypothalamic origin. The plasma growth hormone response to provocative stimuli may be suppressed (Chapter 235).[80,86] Treatment with thyroxine can reverse many of the abnormalities but should commence early and continue for life.

279.5.5 Retained Cartilage Cores

In young large and giant breed dogs, cartilage cores sometimes form in the metaphysis of the distal ulna. Physeal hypertrophic chondrocytes fail to mature and mineralize adjacent matrix, and they accumulate in long columns in the primary spongiosa.[87] The cause of the disorder is unclear. In Great Dane pups, formation of cartilage cores in the distal ulnar and tibial metaphyses was associated with feeding diets containing three-times the recommended content of calcium.[88]

Figure 279-12 **A,** Forelimb of 15-week-old Great Dane with features of congenital hypothyroidism. Reader should note the disordered and irregular ossification of epiphyses (epiphyseal dysgenesis) in humerus, radius, and ulna; the absence of an olecranon apophysis; and delayed skeletal maturation. **B,** Normal Great Dane of similar age for comparison. (Courtesy of R.B. Lavelle.)

Radiographically a central, radiolucent core of cartilage exists that is 5 to 10 mm wide and 2 to 6 cm long, extending from distal ulnar physis into metaphyseal bone (Figure 279-13). Lesions are usually bilateral. They may be a subclinical radiographic finding or be associated with varying degrees of growth retardation after 5 months of age. Retarded ulnar growth causes relative shortening of the ulna, valgus, and rotation of the paw, cranial bowing of the radius, and carpal and elbow subluxation (see Figure 279-13).

279.5.6 Craniomandibular Osteopathy

Craniomandibular osteopathy occurs mainly in young West Highland white, Scottish, Cairn, Boston, and other terriers, and occasionally in nonterrier breeds.[89] Autosomal recessive inheritance is known in West Highland white terriers,[90] and a hereditary predisposition may exist in Scottish terriers. However, the sporadic occurrence in unrelated breeds suggests other causative factors are also involved. Canine distemper virus (CDV) infection of bone has been mentioned as a possible cause,[89] although an epidemiologic study did not indicate a direct relationship.[91] The condition is usually recognized at age of 3 to 8 months, when affected pups develop mandibular swelling, drooling of saliva, prehension difficulties, pain on opening the mouth, or some combination of these signs. The clinical course may fluctuate, with periods of remission and exacerbation. Abnormal physical findings comprise firm, often painful, swelling of mandible, temporomandibular region, or both areas. Periods of pyrexia occur in some cases. Restricted jaw movements and atrophy of masticatory muscles may be obvious in severely affected dogs. Mandibular swelling without pain or eating difficulties occurs in some dogs, especially of larger breeds.

1976

1977

Figure 279-13 **A,** Seven-month-old Great Dane with bilateral forelimb deformities caused by retained cartilage cores in the distal ulnar physes. **B,** Radiograph demonstrating retained cartilage core *(arrows)* extending from distal ulnar physis into the metaphysis. (From Johnson KA: Retardation of endochondral ossification at the distal ulnar growth plate in dogs. Aust Vet J 57:474, 1987.)

Radiographic changes are generally bilateral but often asymmetric, with irregular bony proliferation involving the mandible and tympanic bulla-petrous temporal bone areas in about 50% of cases. However, changes can be confined to the mandible (33% of cases) (Figure 279-14) or the tympanic bulla-petrous temporal region (13%). The calvarium and tentorium ossium are often thickened (Figure 279-15), and other skull bones are sometimes affected. Concurrent long bone lesions resembling later stages of metaphyseal osteopathy have been observed in a few terriers with craniomandibular osteopathy.

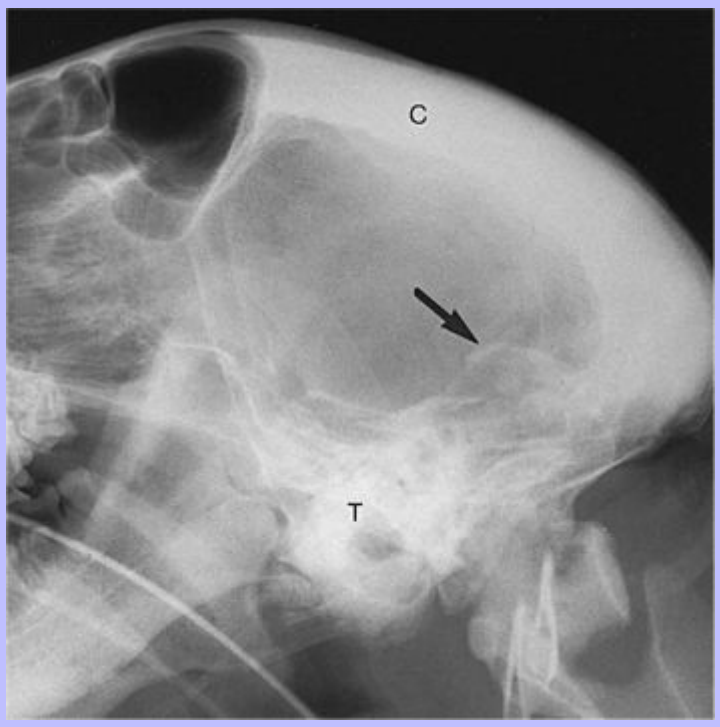
Figure 279-14 Macerated skull of a Doberman pinscher with craniomandibular osteopathy. Reader should note extensive bone changes involving mandible. Tympanic bullae, petrous temporal bones, and temporomandibular joint (TMJ) regions were unaffected in this dog. (From Watson ADJ et al: Craniomandibular osteopathy in Doberman pinschers. J Small Anim Pract 16:11, 1975.)

The diagnosis is straightforward in cases with typical clinical and radiographic features. Routine laboratory tests are unlikely to be helpful. Bone biopsy may be useful in atypical cases, such as dogs of rarely affected breeds with lesions confined to the mandible, especially if unilateral. The histopathology involves resorption of existing lamellae, proliferation of coarse trabecular bone beyond normal periosteal boundaries, replacement of marrow spaces by vascular fibrous stroma, and infiltration at the periphery of new bone by inflammatory cells. A mosaic pattern of irregular cement lines is present in the new primitive bone.[92]

1977

1978

Figure 279-15 Skull of Scottish terrier with craniomandibular osteopathy. The tympanic bulla-petrous bone area *(T)* shows dense sclerotic bone changes. Reader should note thickened calvarium *(C)* and tentorium osseum *(arrow)*.



Craniomandibular osteopathy is self-limiting. Abnormal bone proliferation eventually slows and becomes static at about 1 year of age. Lesions then tend to regress, although radiographic abnormalities or impaired prehension sometimes persist. Anti-inflammatory drug treatment can reduce pain and discomfort, but the effect on lesions is unknown. The prognosis is guarded when extensive changes affect the tympanic-petrous temporal areas and adjacent mandible. Ankylosis and adhesions may then develop, permanently restricting jaw movements and eating. Rostral hemimandibulectomy can be a useful salvage procedure in these cases.[44]

279.5.7 Multiple Cartilaginous Exostoses

In rare instances these benign lesions (osteochondromatosis, multiple hereditary osteochondromata) occur in dogs and cats, as single or multiple exostoses. The disorder may be inherited as an autosomal dominant trait in humans, horses, and dogs.[93,94] Protuberances consist of cancellous bone covered by a cap of hyaline cartilage and arise in the metaphyseal region of bones formed by endochondral ossification. With continued physeal growth and elongation of long bones, exostoses may be finally located in the diaphysis. Lesions develop and grow most rapidly in immature animals, becoming senescent at maturity. Malignant transformation of exostoses to chondrosarcoma occurs rarely in aged animals.[95,96]

The cause is unknown. One hypothesis is that congenital or acquired defects in the perichondrial ring allow an island of physeal cartilage to be pinched off and trapped in metaphyseal bone. This physeal cartilage continues to grow radially, giving rise to exostoses. However, this does not explain the similar lesions found occasionally in nonskeletal sites, such as tracheal cartilages.

Superficially located exostoses may be palpable. Signs may include paresis due to progressive spinal cord compression in young animals (see Chapter 193) or pain due to impingement of exostoses on adjacent tissues.[97] Radiographically, lesions are rounded to cauliflower-like in outline, with a smooth thin shell of cortical bone (Figure 279-16). They protrude above the bone contour and may extend into the medullary cavity. Internally, exostoses have well-defined bone trabeculae that are continuous with the medullary cavity, and diaphyseal cortex in the region is interrupted by the lesion. Adjacent bones such as ulna and metacarpals may be deformed by expanding exostoses (see Figure 269-16). Solitary exostoses are biopsied to allow differentiation from neoplastic lesions. Surgical excision of exostoses that are causing spinal cord compression or lameness is recommended (see Chapter 193).[97] All exostoses should be monitored for malignant transformation.

279.6 IDIOPATHIC BONE DISORDERS

279.6.1 Enostosis

Enostosis (panosteitis, eosinophilic panosteitis) is a relatively common disease causing lameness in medium, large, and giant breed dogs.[98] Amongst breeds at greatest risk are Great Pyrenees, Basset hound, Shar Pei, mastiff, giant schnauzer, and German shepherd dog.[99] Two thirds of affected dogs are male. The age of onset is 6 to 18 months; older dogs are rarely affected. Lameness is acute in onset, not associated with trauma, and intermittent in one or more limbs. Each episode of lameness lasts 2 to 3 weeks but, with recurrent bouts, enostosis may persist for 2 to 9 months. Other signs in early stages include anorexia, lethargy, pyrexia, and weight loss. On physical examination, pain is detected on deep palpation of affected bones. Bones commonly affected are the ulna, humerus, radius, femur, and tibia. Ilium, metatarsal, and other bones are rarely affected. The disease begins in the medullary bone marrow, in the region of a nutrient foramen.

Figure 279-16 Radiograph demonstrating a solitary multiple cartilaginous exostosis-type lesion in the forelimb of a young dog. Reader should note the expansile lesion of the proximal radius, causing malalignment of the radius and attenuation of adjacent ulna. (Courtesy of R.B. Lavelle.)

The cause is unknown: genetic predisposition, hemophilia, bacterial infection, vascular abnormality, metabolic disease, allergy, hyperestrogenism, and endoparasitism have been proposed, but the evidence for most of these is scant.[98] Viral infection is considered a possible cause, based on clinical features of the disease, transmission experiments, and *in situ* hybridization demonstration of virus in bone cells of dogs infected with CDV.[98,100] A relationship between enostosis and ingestion of protein-and-energy-rich foods was suggested recently, and changes in protein or amino acid metabolism were reported in affected dogs.[101]

Three radiographic stages are recognizable.[98] The first stage, with medullary radiolucency due to bone marrow degeneration, is infrequently seen. Most often detected is the second stage (Figure 279-17). A granular, hazy increased radiopacity that begins in the region of the nutrient foramen may extend to fill the entire medullary cavity. Formation of new endosteal bone and a thin layer of smooth periosteal bone are

secondary changes. In the final stage, most bones return to normal appearance, but some have residual thickening of medullary trabeculae and cortical deformity.

Histopathologically, lesions are characterized initially by replacement of normal marrow by fibrous tissue, followed by excessive remodeling of cortical and medullary bone in the affected areas, with endosteal new bone formation generally more prominent.[98] Basenjis and West Highland white terrier dogs with inherited pyruvate kinase (PK) deficiency can develop intramedullary osteosclerosis but, unlike enostosis, new trabecular bone formation is uniform throughout the medullary cavity.[102]

1978

1979

Figure 279-17 Radiograph of a forelimb of a young dog with enostosis, showing patchy intramedullary densities in the humeral diaphysis. (Courtesy of Veterinary Imaging Associates, Sydney, Australia.)

Enostosis can occur concurrently with developmental diseases such as ununited anconeal process and osteochondritis dissecans, and it may be difficult to determine which disease is causing lameness. Leukocytosis and eosinophilia occur inconsistently in affected dogs; serum chemistry is unremarkable. Enostosis is self-limiting, usually by age 18 months, but analgesic NSAIDS may help alleviate pain and lameness.

279.6.2 Metaphyseal Osteopathy

Metaphyseal osteopathy (hypertrophic osteodystrophy) is a disease of young rapidly growing dogs of larger breeds. Breeds at particular risk include Great Dane, Weimaraner, boxer, Irish setter, German shepherd, and Labrador and golden retrievers.[99] Signs usually begin at 3 to 4 months of age (range 2 to 8 months), with metaphyseal swelling and pain, accompanied by depression, inappetence, and variable pyrexia. Some cases recover within a few days, but others have one or more relapses during the following weeks before they finally recover. In a few instances, repeated relapses and consequent pain, cachexia, and debility, necessitate euthanasia. Unexplained deaths have been observed rarely.

Radiographic changes occur especially in metaphyses of limb bones and are usually bilateral. Scapulae and ribs may also be affected. In the early stage, an irregular radiolucent zone is present in the metaphysis, separated from the normal-appearing growth plate by an opaque band (Figure 279-18, *A*). Surrounding soft tissue may be swollen. Later radiographs may show metaphyseal enlargement with irregular periosteal new bone formation, although not all affected dogs develop these changes (Figure 279-18, *B*). Once the disease is no longer active, bone changes undergo repair and remodeling, but some diaphyseal distortion and exostoses may remain (Figures 279-18, *C*, and 279-19).

Hematologic and biochemical tests contribute little to the diagnosis, although neutrophilia, monocytosis and lymphocytopenia can occur during active disease, reflecting stress and inflammation. The principal histologic changes involve the primary spongiosa of metaphyses, with acute suppurative osteomyelitis, necrosis, trabecular microfractures, and defective bone formation. Trabecular resorption produces the radiolucent metaphyseal zone. The opaque band near the growth plate results from trabecular collapse and secondary bone formation. Periosteal thickening, with subperiosteal fibrosis and inflammation, periosteal new bone formation, extraperiosteal dystrophic calcification, or a combination of these abnormalities may be seen.[103]

The cause of metaphyseal osteopathy is unknown. Prior suggestions implicating hypovitaminosis C, overnutrition, or copper deficiency have not been substantiated. Attempts to identify a causative infectious agent or to transmit the disease have not been successful. However, CDV RNA has been detected within bone cells of dogs with metaphyseal osteopathy, suggesting a role for this virus in the etiopathogenesis.[104] Other circumstantial evidence supports this[103–105]: Metaphyseal osteopathy may be accompanied or preceded by respiratory or gastrointestinal (GI) signs; dental enamel hypoplasia, a sequel to distemper infection, was found in two dogs with metaphyseal osteopathy; three of seven dogs inoculated with blood from dogs with metaphyseal osteopathy developed distemper; and typical bone changes have developed in some pups 4 to 21 days after inoculation with live distemper virus vaccine. However, the osteosclerotic metaphyseal lesions found in a series of dogs clinically affected with distemper differed macroscopically, radiographically, and histologically from metaphyseal osteopathy.[106] Any relationship between distemper virus, metaphyseal osteopathy, and other hyperostotic bone diseases (craniomandibular osteopathy and enostosis) remains uncertain. An epidemiologic study concluded that, apart from the obvious age effect, risk factors for metaphyseal osteopathy, craniomandibular osteopathy, and CDV infection were dissimilar.[91] Metaphyseal

osteopathy has been reported in related dogs of several breeds, including Weimaraner littermates.[105–107] However, most cases are sporadic, affecting isolated pups in a litter.

No specific treatment exists for metaphyseal osteopathy. Dietary imbalances or excesses should be avoided and an anti-inflammatory analgesic given as needed to reduce pain. Good nursing care may be required to avoid dehydration, undernutrition and pressure sores.

279.6.3 Calvarial Hyperostosis

An unusual hyperostosis affecting frontal and parietal bones was reported in two unrelated bull mastiffs.[103] From age 6 months there was progressive outward thickening of the calvarium (the cranial cavity was unaffected) with pyrexia, lymphadenopathy, and eosinophilia. The swelling stabilized at maturity, then regressed. The lesion was a subperiosteal hyperostosis with initial deposition of new woven bone followed by secondary osteonal remodeling. Similarities were noted with cases of craniomandibular osteopathy, inherited PK deficiency, and human infantile cortical hyperostosis.[102,108,109]

1979
1980

Figure 279-18 Radiographs of metaphyseal osteopathy. **A,** Early stage with irregular radiolucent zone *(arrows)* separated from the physis by a narrow radio-opaque band. **B,** Later stage with radiolucent metaphyseal zones *(bottom two arrows)* adjacent to the physes still evident. Periosteal new bone and soft tissue mineralization *(top two arrows)* adjacent to the metaphyseal cortex. **C,** Inactive stage with residual diaphyseal deformity and spiculated periosteal exostoses.

Figure 279-19 Humerus, ulna, and radius of a young giant-breed dog that suffered metaphyseal osteopathy. Reader should note the severe deformities and periosteal new bone.

279.6.4 Multifocal Osteopathy

An idiopathic multifocal osteopathy was described in four young adult Scottish terriers, of which at least three were genetically related (fourth pedigree unavailable).[110] The condition was characterized by multifocal absence of bone in skull, cervical spine, radius, ulna, and femur (Figure 279-20). Histopathologic findings in one case indicated osteoclastic osteolysis and replacement of bone by fibrous tissue. Associated clinical signs included reluctance to move, stiff and stilted gait, carpal valgus and laxity, drooling and dysphagia.

279.6.5 Avascular Necrosis of the Femoral Head

Avascular (or aseptic) necrosis of the femoral head (Legg-Calve-Perthes disease) occurs in adolescent dogs. Miniature and small dog breeds are mostly affected, but Australian shepherd dogs also have increased risk of developing this disorder.[99] Within the predisposed small breeds, about 2% of individuals are affected, without apparent sex predilection. Clinically affected individuals are commonly presented at 4 to 11 months of age with hind leg lameness, usually unilateral but sometimes bilateral (12% to 20% of cases). The onset of lameness is usually gradual, though there may sometimes be a history of trauma. The severity varies from a slight limp to complete nonweight-bearing lameness. Pain and reduced range of movement are found on palpating the affected joint. Crepitus, shortening (up to 2 cm) of the affected limb (largely due to muscle spasm), and muscle atrophy may be evident at initial presentation.

The cause of this condition is unknown, but autosomal recessive inheritance has been suggested for West highland white and Yorkshire terriers, toy and miniature poodles, and pug dogs.[111] Early exposure to sex hormones, a consequence of precocious sexual maturity in small breeds, may be a factor. Another suggestion is that injury or infection and increased synovial fluid in the hip joint disrupt the blood supply to the femoral epiphysis while the growth plate is present. Continued weight bearing could then lead to collapse and remodeling of the femoral neck and head.

Figure 279-20 Radiograph of the antebrachium of a Scottish terrier with multifocal osteopathy. Reader should note the marked attenuation in diameter of the radial diaphysis. (Courtesy of C.W. Hay.)

One of the earliest radiographic changes in this disorder is increased radio-opacity of the affected femoral head. Later changes include an apparent increase in joint space width, shortening and widening of the femoral neck, irregular opacity of femoral epiphyseal and metaphyseal regions, and flattening and irregularity of femoral articular cartilage (Figure 279-21). Secondary osteoarthrosis and acetabular osteophytes may also be evident.

Conservative treatment (short walks on a leash several times daily, swimming, analgesic drug as needed) produces satisfactory outcomes in 25% to 30% of affected dogs, whereas femoral head and neck excision, when performed correctly, gives good to excellent results in 67% to 85% of cases, though slight intermittent lameness may remain.[94,112] Excision arthroplasty is advisable if conservative treatment does not produce clinical improvement within 4 weeks.[112]

Figure 279-21 Later stage Legg-Calve-Perthes disease. Reader should note the multifocal osteolysis of the femoral head, thickened femoral neck, and increase in width of joint space. (Courtesy of Veterinary Imaging Associates, Sydney, Australia.)

279.6.6 Secondary Hypertrophic Osteopathy

In secondary hypertrophic osteopathy (pulmonary hypertrophic osteoarthropathy), firm nonedematous swelling develops in all four limbs, usually in response to intrathoracic disease, most often neoplasia. Of 180

canine cases, 98% had intrathoracic disease, and 92% of these had either metastatic lung neoplasia or primary tumors of lung or thoracic esophagus.[113] A few dogs had pneumonitis, endocarditis, or dirofilariasis. Of four cases lacking intrathoracic disease, three had urinary rhabdomyosarcoma and one had hepatic carcinoma. Because of the association with neoplasia, secondary hypertrophic osteopathy occurs mostly in older animals. No breed or gender predilection exists in dogs. The disorder is rare in cats.

Signs related to limb changes often precede signs of thoracic disease, but they can begin simultaneously with or after thoracic signs. Affected animals are stiff and reluctant to move. Swelling of all limbs occurs, which are warm, firm, and may be painful. Thoracic disease may be manifested by cough, dyspnea, abnormal lung sounds, or cardiac displacement. Abnormal laboratory findings, if any, are related to the underlying intrathoracic disease.

Radiographic changes are characteristic: soft tissue swelling of distal extremities initially, then periosteal new bone formation as irregular nodules perpendicular to the cortex or smoother parallel deposits (Figure 279-22). Bone changes begin distally and may spread proximally to involve humerus and scapula, femur, and pelvis. Ribs and vertebrae are sometimes affected.

On histologic examination, the bones are surrounded by highly vascular, dense connective tissue containing numerous thick-walled arteries. The osteogenic layer of the periosteum is hyperplastic, and overlies maturing and remodeling trabecular bone. The pathogenesis of secondary hypertrophic osteopathy involves increased blood flow to the distal extremities, then overgrowth of connective tissue and subsequent osteoneogenesis. 1981
This seems to involve a neural reflex originating in the thorax and affecting connective tissue and periosteum 1982
of the limbs. The efferent pathway apparently involves nerve fibers that leave the lung near the bronchi and join the vagus in the mediastinum. The nature of the efferent connection, whether neural or hormonal, is unknown. Regression of secondary hypertrophic osteopathy may follow removal of the source of afferent impulses by excision of the lung lesion, or interruption of the afferent fibers by peribronchial dissection or vagotomy. There may be an alternate afferent pathway from parietal pleura along intercostal nerves, because regression has sometimes followed thoracotomy and section of intercostal nerves or extensive resection of a neoplasm of the thoracic wall. The rare association with intra-abdominal lesions is more obscure.

Figure 279-22 Radiograph of distal forelimb of a dog with secondary hypertrophic osteopathy. Periosteal new bone growth occurs, with nodular appearance affecting the metacarpals and digits. Adjacent soft tissues are thickened. (Courtesy of Veterinary Imaging Associates, Sydney, Australia.)

Treatment should be directed against the underlying thoracic disease, using appropriate medical or surgical methods. Successful resection of lung lesions by lobectomy or pneumonectomy can quickly remove pain, soft tissue swelling, and lameness. The bone abnormalities usually regress gradually over several months. Where complete removal of lung lesions is not possible, the skeletal signs may be ameliorated by removal of larger lesions even if multiple small lesions remain. Relief may also follow intrathoracic vagotomy on the same side as the lesion, or on the worse affected side if metastases are bilateral.

279.6.7 Medullary Bone Infarction

Medullary bone infarcts do not cause clinical signs in dogs. They affect older dogs and are usually found in conjunction with osteosarcoma and, occasionally, skeletal fibrosarcoma or renal adenocarcinoma.[114,115] Bone infarcts are characterized radiographically by numerous, irregularly demarcated areas of increased radiopacity in the medullary cavities of one or more bones (Figure 279-23). The densities obliterate medullary cavities to varying degrees. Any bone may be affected, but infarcts are mainly found distal to elbow and stifle.[114]

Figure 279-23 Radiograph demonstrating medullary bone infarction in an aged dog with osteosarcoma *(O)* of the olecranon. The multiple areas of medullary sclerosis in the radius and ulna are infarcts.

The pathogenesis of the disorder is unknown and does not seem to be due to metastatic tumor cell dissemination. However, intramural collagen deposition causes occlusion of nutrient arteries, hypoxia and widespread necrosis of medullary soft tissues and bone, and new bone proliferation on endosteum and

medullary trabeculae.[114] Common causes in humans are dysbaric conditions, fat embolization, hyperadrenocorticism, hyperviscosity, hemoglobinopathy, and anemia. Medullary bone infarcts should be differentiated from enostosis, bacterial and fungal osteomyelitis, and metastatic neoplasia.

279.6.8 Bone Cyst

Benign cystic bone lesions, either monostotic or polyostotic, are uncommon in dogs and cats. Young dogs of larger breeds are affected most often, with Doberman pinschers and German shepherds over-represented.[94,116] Males are affected twice as often as females. The cause is unknown, but may involve intramedullary metaphyseal hemorrhage, local disturbance of bone growth, or other factors.[113] Heritable factors might also be implicated, because lesions occurred in three Doberman pinscher littermates and in three Old English sheepdogs littermates and both parents.[94]

Bone cysts may be subclinical until they are large or fracture with trauma. Pain, lameness, and local swelling may ensue. The lesions occur in metaphyses and adjacent diaphyses of long bones, sparing growth plates and epiphyses. The distal radius or ulna (or both) are affected most often. The cysts are lined by a thin membrane and contain fluid that may be blood tinged. Radiographically, the lesions are lytic and expansible, with thinned cortex and little or no periosteal reaction. There may be one or several chambers, partially divided by bony ridges or partitions (Figure 279-24). 1982 1983

Figure 279-24 Bone cyst in distal femur of a young Doberman pinscher. The lesion has expansile, lytic appearance, with thinning of overlying cortex. Bony ridges or partitions are evident internally.

Alternative diagnoses are atypical bone neoplasia, aneurysmal bone cyst, and fibrous dysplasia of bone. Fine needle aspiration biopsy and cytologic examination may be useful: only a benign bone cyst is likely to be fluid filled, although the other lesions may contain areas of cystic degeneration or hemorrhage. If uncertainty persists, surgical biopsy and histopathologic study are indicated. To stimulate healing of bone cysts, surgery has been advocated, using drainage, curettage, bone grafting, and external support to prevent fractures. Some untreated cysts heal spontaneously without surgery, although pathologic fracture of cystic bone is a risk.[117]

279.6.9 Aneurysmal Bone Cyst

Aneurysmal bone cyst is a non-neoplastic lesion that results in considerable local bone destruction. Although common in man, it is rare in dogs and cats. Lesions arise in ribs, pelvis, scapula, spine, and metaphyses of long bones in young adults and geriatric animals.[118,119] The cause is unknown, but tumors, developmental abnormalities, and trauma-induced hemorrhage causing venous obstruction or arteriovenous shunts in bone marrow have been suggested as initiating factors.[7] Localized partial disruption of medullary blood flow results in endosteal bone resorption and outward displacement of the periosteum. The periosteum forms successive layers of woven bone that are resorbed as the lesion expands, producing the appearance of a ballooning aortic aneurysm.[7] Blood-tinged fluid and fibrovascular tissue fill the lesion which has a honeycomb appearance with huge vascular channels. Radiographically, it appears as a large expansile cyst, with minimal internal trabecular septation, surrounded by thin rim of mineralized soft tissue or bone (Figure 279-25). A triangle of laminated periosteal new bone (Codman's triangle) forms at the junction between cyst and adjacent normal diaphyseal bone. Some have an underlying tumor (osteosarcoma, giant cell tumor) that complicates diagnosis. Signs may be suddenly exacerbated by neoplastic erosion of vessels and intralesional hemorrhage or by fracture.[119] Uncomplicated lesions have a good prognosis when treated by en bloc resection, amputation, or curettage.[120] Nonresectable lesions in man are irradiated to stop bleeding and lesional growth, but postirradiation sarcoma can ensue.

279.6.10 Subchondral Bone Cyst

Subchondral bone cysts are benign lesions in subchondral bone between growth plate and articular cartilage.[121] They are usually lined with synovium and occasionally communicate with the articular synovial membrane. Radiographs show a single or multilocular radiolucent defect with well-circumscribed borders. They are common in horses and pigs and usually a manifestation of osteochondrosis.[7] This association was also noted in a dog.[121]

279.6.11 Fibrous Dysplasia

Fibrous dysplasia is a rare fibro-osseous lesion of bone believed to be of developmental origin.[7] It affects mainly young or newborn animals and may be monostotic or polyostotic. The lesions are expansile and may cause problems of disfigurement or compression of adjacent structures or bone weakness and fracture (Figure 279-26). Monostotic lesions have been reported in the jaw or infraorbital bone of dog, and in mandible, maxilla, or distal ulna of cats.[122,123] Fibrous dysplasia, aneurysmal bone cysts, and benign bone cysts are distinct entities but have been confused in the veterinary literature.[124]

The lesions have marked homogenous radiopacity and are composed of firm, gray fibrous tissue that is gritty when cut. Histologically, they consist of fibrous connective tissue stroma containing spicules of woven bone replacing normal osseous tissue. Cavities of various size containing clear or bloody fluid may be scattered throughout.[7] Two feline lesions were resected, and both patients were free of recurrence 4 years later.[122]

279.6.12 Central Giant Cell Granuloma

This rare, non-neoplastic lesion affects the tooth-bearing regions of maxilla and mandible of young dogs.[125] Trauma-associated intraosseous hemorrhage seems to be an initiating factor. Radiographically the lesion is a rounded to ovoid, expansile, uniloculated radiolucency that is well demarcated from surrounding tissue by a thin rim of smooth nonreactive bone. Adjacent teeth may lose their laminae dura and be displaced, but tooth root resorption is rare. The center of the lesion consists of tan-colored soft tissue composed mainly of loose fibrovascular stroma containing pleomorphic mesenchymal cells and numerous large, irregular multinucleated giant cells. These cells arise from mesenchymal tissue and are neither osteoclasts nor involved in bone resorption. The lesions resemble giant cell tumors histologically. The latter are potentially malignant tumors that cause extensive destruction at the ends of long bones. Because central giant cell granuloma is rare, diagnosis should be confirmed by biopsy. Treatment is by curettage or en bloc resection.[125]

279.7 METABOLIC, NUTRITIONAL, AND ENDOCRINE BONE DISORDERS

The term *metabolic bone disease* is used here to encompass various conditions that cause generalized reduction in bone mass, or *osteopenia*. Osteopenia can be categorized into excessive bone resorption, or *osteolysis*, as occurs in hyperparathyroid states, and defective bone formation. The latter is further subdivided into insufficient formation of osteoid, or *osteoporosis*, and defective mineralization of osteoid, or *rickets-osteomalacia*. 1983 1984

Figure 279-25 Aneurysmal bone cyst of the tibia in a 2-year-old boxer dog that had sustained a tibial fracture as a puppy. **A,** Reader should note the angular deformity of the diaphyses of the tibia and fibular due to fracture malunion. A large cystic cavity in the proximal tibia is associated with a soft tissue mass cranial to the tibia. **B,** Arteriogram showing a dilated, tortuous arteriovenous fistula extending from the tibia into adjacent soft tissue. (Courtesy of J.H. Marti.)

Major causes of metabolic bone disease involve nutritional or hormonal processes (or both). The more important causes discussed here are nutritional secondary hyperparathyroidism, rickets, renal osteodystrophy, and hypervitaminosis A. Other metabolic bone diseases that rarely produce bone-related clinical signs are mentioned briefly.

279.7.1 Nutritional Secondary Hyperparathyroidism

Nutritional secondary hyperparathyroidism is a metabolic disorder in which bone production is normal but osteopenia results from excessive bone resorption. It is caused by diets providing excess phosphate,

insufficient calcium, or both.[94] Affected animals have usually been fed mainly meat, organ tissue, or both. This provides adequate phosphate but insufficient calcium, and Ca/P ratios of about 1:16 to 1:35,[126] which contrast with the recommended 1.2:1 for dogs and 1:1 for cats. Added cow's milk provides insufficient calcium to correct the imbalance. The imbalance induces hypocalcemia, which increases secretion of PTH. Increased parathyroid activity tends to normalize blood calcium and inorganic phosphate concentrations by promoting mineral resorption from bone, enhancing intestinal calcium absorption, and facilitating renal phosphate excretion and calcium retention. However, continued ingestion of the defective diet sustains the hyperparathyroid state and causes progressive skeletal demineralization and consequent clinical signs.

Nutritional secondary hyperparathyroidism causes clinical disease in pups and kittens of all breeds, but it also occurs occasionally in adults. Signs in young animals are lameness, reluctance to stand or walk, and skeletal pain. Costochondral junctions and metaphyses may appear swollen, and pyrexia is sometimes present. Bone fractures can follow relatively mild trauma. Limb deformity may be evident. Paresis or paralysis may result from vertebral compression, and constipation may follow pelvic collapse. Effects are less dramatic in adults, but generalized osteopenia and skeletal pain are sometimes seen, and resorption of alveolar bone may cause loosening and loss of teeth.

Radiographically, decreased bone density and thin cortices are seen, with or without fracturing (Figure 279-27). Growth plates are normal, but metaphyses may be mushroom shaped. An area of relative radio-opacity occurs in the metaphyses adjacent to growth plates, representing the area of primary mineralization, and may be best appreciated in the distal radius and ulna (Figure 279-28).

1984

1985

Figure 279-26 Fibrous dysplasia in the ulnar diaphysis, with secondary lysis and new bone formation in adjacent radial cortex. (Courtesy of P.A. Manley.)

Blood biochemical tests are of little value in confirming nutritional secondary hyperparathyroidism. The calcium concentration is usually within the reference range because of compensatory changes. Concentrations of inorganic phosphate and alkaline phosphatase may appear high but should be interpreted carefully because growing animals often have higher values than adults.

Affected animals should be confined for the first few weeks of treatment to reduce the risk of fractures and deformity. A good quality, nutritionally complete commercial ration should be fed. For all but mildly affected cases, sufficient calcium carbonate should be added to produce a calcium/phosphorus ratio of 2:1. This is maintained for 2 to 3 months, after which the supplement is withdrawn. Oversupplementation with calcium should be avoided. For severely affected cases parenteral administration of calcium (e.g., 10 to 30 mL of 10% calcium gluconate solution by slow intravenous infusion daily for 3 days) may help reduce pain and lameness initially, but it does little to correct the calcium deficiency. An NSAID might be useful for short-term analgesia. The prognosis is generally good, unless skeletal deformity and disability are marked.

Figure 279-27 Abdomen of kitten with nutritional secondary hyperparathyroidism. Reader should note poor contrast in radio-opacity between bones and soft tissues such as liver and kidneys. The cortices of long bones are thin, vertebrae are lucent, and the vertebral column is deformed in the thoracolumbar area.

279.7.2 Rickets

Clinical cases of rickets are rare in dogs and cats. Rickets and its adult equivalent, osteomalacia, occur when insufficient calcium, phosphorus, or both is available for mineralization of newly formed osteoid. The more likely causes of rickets in dogs and cats are hypovitaminosis D (dietary deficiency),[127] inborn error in vitamin D metabolism,[128] or low availability of minerals from the diet (inadequate concentration, impaired

absorption). Dogs and cats do not synthesize cholecalciferol (previtamin D_3) in skin exposed to ultraviolet (UV) light, and are mainly dependent on dietary intake.[129–131]

Affected animals may be lame and reluctant or unable to walk. Fractures or bending of long bones can occur. Enlargement of costochondral junctions and metaphyses may be evident. Other possible abnormalities are delayed dental eruption, weakness, listlessness, and neurologic signs (excitability, tremor, convulsion, and coma) from hypocalcemia. Potential blood test abnormalities include low calcium, low inorganic phosphate, increased alkaline phosphatase, increased PTH, and low 25-hydroxycholecalciferol (the storage form of vitamin D).[127,128,132]

Characteristic radiographic findings are axial and radial thickening of growth plates and cupping of adjacent metaphyses (Figures 279-29 and 279-30). The distal ulnar growth plates are consistently the most severely affected, and this finding reflects a failure of mineralization of cartilage that is being produced at the normal rate. Additional findings are osteopenia, thin cortices, and bowed diaphyses.

When dietary deficiency is suspected, therapy requires a regular diet with adequate and not excessive amounts of calcium, phosphorus, and vitamin D.[127,132] The regimen described for nutritional secondary hyperparathyroidism would be appropriate. Treatment with dihydrotachysterol was effective in a dog in which an inborn error in vitamin D metabolism was suspected.[128]

279.7.3 Renal Osteodystrophy

Renal osteodystrophy is an osteopenic disorder that results from chronic renal failure (CRF). This complex abnormality involves both hyperparathyroidism (excessive bone resorption) and rickets-osteomalacia (impaired osteoid mineralization). Hyperparathyroidism results from impaired renal excretion of phosphate and consequent hyperphosphatemia. This lowers blood calcium concentration, increases parathyroid gland activity, and induces bone resorption. Although this tends to normalize blood calcium concentrations, the hyperparathyroid state is maintained by persisting hyperphosphatemia. Concurrently, synthesis of 1,25 dihydroxyvitamin D declines because of reduced functional renal mass. This and other metabolic derangements lead to severe depression of enteric calcium absorption, impaired mineralization of osteoid, and thus rickets-osteomalacia.

Figure 279-28 Foreleg of a pup with nutritional secondary hyperparathyroidism. Bone is abnormally radiolucent and cortices are thin. Growth plates are normal, but relatively radio-opaque zones are present in the adjacent metaphyses (representing areas of primary mineralization of osteoid).

The syndrome is dominated by signs of renal failure and uremia. Bone disease is more likely to be recognized clinically in growing dogs or, rarely, cats with early onset renal failure. Changes may be most evident in the head. The mandible and maxilla may be pliable and swollen, owing to bone resorption and fibrosis, and teeth may be malaligned, loose, or lost. Skeletal pain, fractures, and bowing of long bones can also occur. Osteopenia of the mandible and maxilla leads to enhanced radiographic contrast between teeth and bone, and teeth may appear almost unsupported by bony tissue.[133]

Treatment is directed against the underlying disease, if possible. Reduced phosphate intake, coupled with oral phosphate binder (aluminum hydroxide or carbonate) as necessary, can help to control hyperphosphatemia. Once this is achieved, consideration can be given to administering calcium to improve calcium balance or administering calcitriol to control hyperparathyroidism (see Chapters 258 and 260).

Figure 279-29 Foreleg of a 12-week-old Saint Bernard with rickets due to an inborn error in vitamin D metabolism. Enlarged physes and cupping of adjacent metaphyseal bone are features of rickets. (From Johnson KA et al: Vitamin D–dependent rickets in a Saint Bernard dog. J Small Anim Pract 29:657, 1988.)

279.7.4 Hypervitaminosis A

Prolonged intake of excessive vitamin A supplements or ingestion of mainly liver diets can cause osteopathy. The major finding in older cats is extensive, even confluent, exostoses and enthesophytes involving cervical and cranial thoracic vertebrae (Figure 279-31). Enthesophytes may also form around limb joints, especially

shoulder or elbow, which may reflect increased sensitivity of tendon, ligament, and joint capsule attachments to the effects of tension.[113,134]

The lesions are painful in the early stages and may ankylose, causing neck stiffness and abnormal posture. Associated clinical signs are lethargy, depression, irritability, poor grooming, lameness, and gingivitis.[113] Experimental vitamin A toxicosis in young animals depressed chondrocyte and osteoblast activities, which produced thin bone cortices, retarded long bone growth, and produced loose or lost teeth in kittens.[134,135] Puppies had joint pain, thin bone cortices, and retarded bone growth.[136]

Treatment necessitates avoiding the source of vitamin A. Mature cats will improve clinically, but rigidity from ankylosis will probably remain despite bone remodeling. Bone growth may be retarded permanently in young animals.[134]

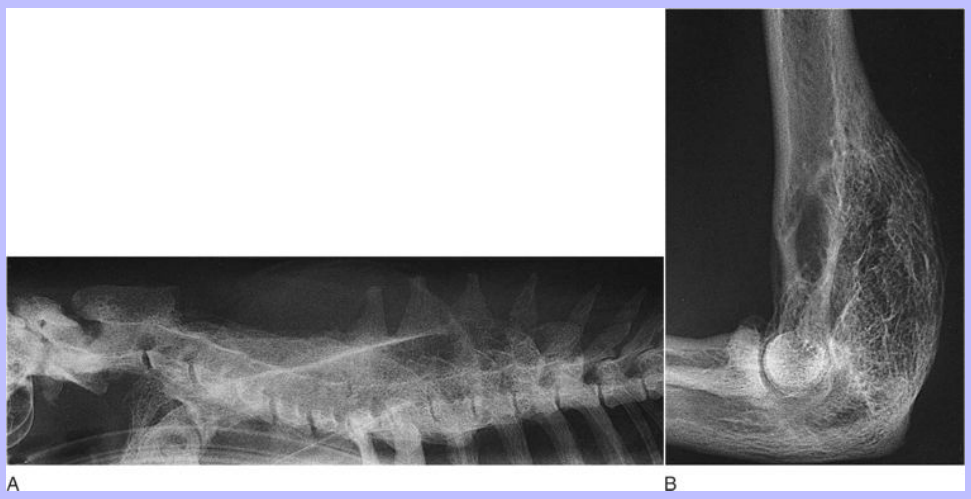
279.7.5 Other Endocrine and Nutritional Bone Disorders

279.7.5.1 Primary Hyperparathyroidism

With uncontrolled hyperplastic or neoplastic proliferation of parathyroid tissue, excessive secretion of PTH may cause increased bone remodeling and skeletal demineralization. This could lead to lameness, pain, fractures, vertebral collapse, loose or lost teeth, and pliable, possibly swollen jaw bones (Figure 279-32). However, the predominant findings usually relate to hypercalcemia[137] and include polydipsia (PD), polyuria (PU), listlessness, incontinence, weakness, inappetence, and urocystolithiasis (see Chapter 237).

Figure 279-30 Foreleg of a greyhound puppy with rickets due to dietary deficiency of vitamin D. Reader should note the axial and radial enlargement of the physes and cupping of the adjacent metaphyseal bone. (Courtesy of R. Malik and Veterinary Imaging Associates, Sydney, Australia.)

Figure 279-31 Cat with hypervitaminosis A. **A,** Confluent exostoses affect the dorsum of the spine from the second cervical to the fifth thoracic vertebrae. **B,** Exuberant exostoses of distal humerus and proximal ulna are ankylosing the elbow.



279.7.5.2 Humoral Hypercalcemia of Malignancy

With certain neoplasms, especially lymphosarcoma or adenocarcinoma of the anal sacs in dogs, widespread skeletal demineralization ensues through the humoral action of PTH-related protein.[137,138] Although skeletal dysfunction can occur as with primary hyperparathyroidism, findings are usually dominated by changes related to the underlying tumor and the effects of hypercalcemia (see Chapter 237).

279.7.5.3 Hyperadrenocorticism

Chronic glucocorticosteroid excess due to iatrogenic excess or naturally occurring hyperadrenocorticism causes osteopenia. Retarded growth and delayed growth plate closure may occur in young dogs,[139] and spontaneous fractures and increased prevalence of intervertebral disk disease have been suggested.[140] Osteopenia in spontaneous canine hyperadrenocorticism is attributable primarily to decreased bone formation; bone resorption is apparently normal, although parathyroid hyperplasia is present in some cases (see Chapter 136).[140]

279.7.5.4 Hypogonadism

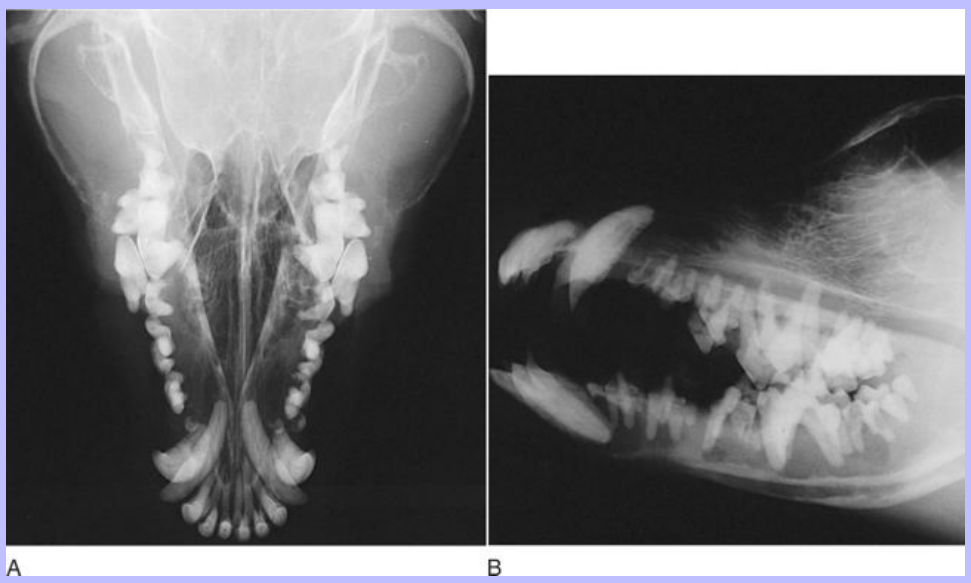
Hypogonadism, whether a developmental defect or produced surgically, can delay growth plate closure.[7] In dogs, closure was delayed by neutering in both sexes, and the extended growth period resulted in longer radius and ulna in all males, as well as in bitches neutered at 7 weeks.[141] Gonadectomy in cats delayed distal radial physeal closure but did not affect bone length.[142] However, neutered male cats are predisposed

to spontaneous, nontraumatic fractures of the femoral capital physis between the ages of 5 to 24 months.[143–145] Fractures are often bilateral. Radiographic signs include physeal fracture displacement and lysis of the metaphyseal bone, producing an "apple core" appearance. Histological examination of specimens resected at surgery revealed that the articular cartilage and epiphyseal bone of the capital epiphysis had normal structure and viability, but the physeal cartilage was thickened and necrotic.[144] Normally this physis closes at 7 to 9 months of age in sexually intact cats. Delayed physeal closure after early gonadectomy apparently allows the persistence of cartilage that is unable to support normal weight-bearing activities.

1987

1988

Figure 279-32 Radiograph of an aged Keeshond with parathyroid adenoma and hyperparathyroidism, with profound osteopenia of the skull and mandible. **A,** In the ventrodorsal view, osteolysis of the zygomatic arch, maxilla, facial bones, and mandible occurs. **B,** In the lateral view, loss of the lamina dura and mandibular cortex occurs, except for the thin ventral cortex.



279.7.5.5

Hepatic Osteodystrophy

Severe hepatic disease can produce rickets—osteomalacia due to malassimilation of fat and vitamin D (and secondarily of calcium) and impaired production of 25-hydroxyvitamin D.[146] Osteoporosis may also occur due to diminished hepatic protein synthesis.[146] Although well-recognized in human patients, hepatic osteodystrophy has yet to be characterized in dogs and cats.

279.7.5.6 Anticonvulsant Osteodystrophy

Prolonged high-dose anticonvulsant therapy with primidone, phenytoin, or phenobarbitone can cause osteodystrophy in human epileptics.[146] These drugs induce hepatic enzymes that enhance catabolism and excretion of vitamin D, resulting in calcium malabsorption, hypocalcemia, secondary hyperparathyroidism, and osteomalacia. Phenytoin also directly inhibits intestinal calcium transport and bone resorptive responses to PTH and vitamin D metabolites.[146] The significance of these changes to veterinary patients is unknown.

279.7.5.7 Hypovitaminosis A

Vitamin A is important for growth, maturation, and remodeling of bone. Hypovitaminosis A decreases osteoclastic activity and impedes bone remodeling, causing long bones to be deformed. Affected animals are usually lame. The condition is probably rare.[113,147]

279.7.5.8 Hypervitaminosis D

Skeletal demineralization follows massive intake of vitamin D, its active metabolites or analogs. Although osteopenia, bone deformation, and retarded growth are possible, the major clinical effects are related to hypercalcemia and soft tissue mineralization.[136] Correcting intakes of vitamin D, calcium, and phosphate should resolve the bone problems, but soft tissue damage may persist.

279.7.5.9 Zinc-Responsive Chondrodysplasia

This form of dwarfism occurs in Alaskan malamutes and possibly other northern breeds.[147] Affected dogs have short, bowed legs; flared, irregular, thickened growth plates; and coarse, disorganized metaphyseal trabeculae. Hemolytic anemia with macrocytosis, hypochromia, and stomatocytosis are also present. Life-long supplementation with zinc sulfate or gluconate was suggested.[147]

279.7.6 Copper Deficiency

Lameness and bone fragility can occur in dogs on copper-deficient diets.[7] Radiographic features are thickened growth plates and flared metaphyses, with osteopenia and epiphyseal slipping in severe cases. Histologically the animal has thickening of the zone of hypertrophic chondrocytes plus disorganization and collapse of the primary spongiosa.[148] The condition is rare.

279.7.6.1 Lead Poisoning

Although skeletal signs are absent in plumbism, lead lines are seen radiographically in bones of some affected immature dogs. The lines are radio-opaque bands in metaphyses adjacent to growth plates of long bones (Figure 279-33). They result from accumulation of thick mineralized trabeculae at these sites because of impaired osteoclastic activity. The presence of lead itself adds little to the radio-opacity.

279.7.6.2 Overnutrition in Growing Dogs

Provision of balanced diets in quantities in excess of recommended daily intake or feeding diets that contain greater than the recommended content of protein, energy, minerals, or vitamins, have been referred to as *overnutrition* or *overfeeding*. Experimental studies of young growing Great Danes found that feeding of an excessively supplemented diet was associated with development of wobbler syndrome, enostosis, osteochondrosis, and metaphyseal osteopathy.[149] Subsequently, it was found that diets with excessive protein content have no adverse effects on skeletal development.[150] However, Great Dane puppies fed a diet containing triple the recommended calcium requirement had elevated absorption and retention of calcium and disturbed endochondral ossification, and they developed osteochondrosis, retained cartilage cores, radius curvus syndrome, and had stunted growth.[88,151,152] Another study of Great Dane puppies fed diets with calcium/phosphorus ratios of 1.2:1, but with lower than recommended concentrations of calcium, found that bones had lower bone mineral content throughout the growth period.[153] Long bone growth was also delayed until 6 months of age, but after this time bone growth caught up and was normal by 12 months of age, despite dietary deficiency in calcium.

1988
1989

Figure 279-33 Radiograph of distal forelimb of a puppy with lead poisoning. Radiopaque bands are present in metaphyses adjacent to growth plates.

Young Great Danes fed *ad libitum* with a balanced commercial diet initially had greater increases in body weight and height than littermates fed a restricted (two thirds of the caloric intake) diet.[132] The restricted puppies later had a period of catch-up growth, and by age 7 months long bones were of identical length.[132] Restricted feeding (25% reduction in total intake) of a balanced diet limited the incidence and severity of osteoarthritis secondary to hip dysplasia in Labrador retriever dogs.[154] Accordingly, overfeeding and oversupplemented diets should be avoided in growing pups. *Ad libitum* feeding is not recommended because it does not result in larger adult dogs, and it increases risk of orthopedic problems such as hip dysplasia.[132,154]

279.8 NEOPLASTIC BONE DISEASE[155]

Neoplasia of the skeletal system can be categorized into primary bone tumors, metastatic bone tumors, tumors of soft tissues extending into adjacent bone, and benign bone tumors.[155] These conditions are discussed elsewhere in this text. Non-neoplastic conditions of bone, such as cystic lesions and fibrous dysplasia, that may be confused with primary bone cancer, are important differentials. Bone cysts and fibrous dysplasia of bone are discussed earlier in this chapter.

279.9 BONE INFECTION

Bone infection (osteomyelitis) may be bacterial, fungal, or possibly viral (see Metaphyseal Osteopathy) in origin. Beta lactamase–producing *Staphylococcus* cause approximately 50% of cases of bacterial osteomyelitis, often as monomicrobial infections.[30] Polymicrobial infections may have mixtures of *Streptococcus* and gram-negative bacteria (*Escherichia coli, Pseudomonas, Proteus,* and *Klebsiella*), and sometimes anaerobic bacteria. More common anaerobic isolates are *Actinomyces, Peptostreptococcus, Bacteroides,* and *Fusobacterium*.[156] Anaerobes are especially common in bite wound infections. *Nocardia*, *Brucella canis,* and tuberculosis cause osteomyelitis in rare instances.[155] Mycotic genera that cause osteomyelitis include *Coccidioides, Blastomyces, Histoplasma, Cryptococcus*, and *Aspergillus*. Fungal osteomyelitis is often a component of disseminated mycotic infections that occur in certain specific regions of the world. Diagnosis and treatment of deep mycoses are discussed in Chapter 174.

279.9.1 Pathophysiology

Bacterial contamination of bone can occur with open fractures, surgery, bite wounds, foreign-body penetration, gunshot injury, extension from soft tissue, and hematogenous spread. However, bone is relatively resistant to infection unless the animal has concurrent soft tissue injury, bone necrosis, sequestration, fracture instability, implanted foreign material, altered host defenses, or some combination of these problems.[157] In chronic infections, avascular fragments of cortical bone (sequestra) are colonized by bacteria, surrounded by exudate, and may persist for long periods. New bone formed by periosteum (involucrum) incompletely encapsulates the focus of infection and sequestrum. Exudate draining from the bone follows sinus tracts that discharge through skin openings, generally in a more dependent location. Osteomyelitis is exacerbated by fracture and instability. Cortical bone at the fracture site is resorbed because of infection and interfragmentary motion, and this causes further widening of the fracture gap and additional instability.

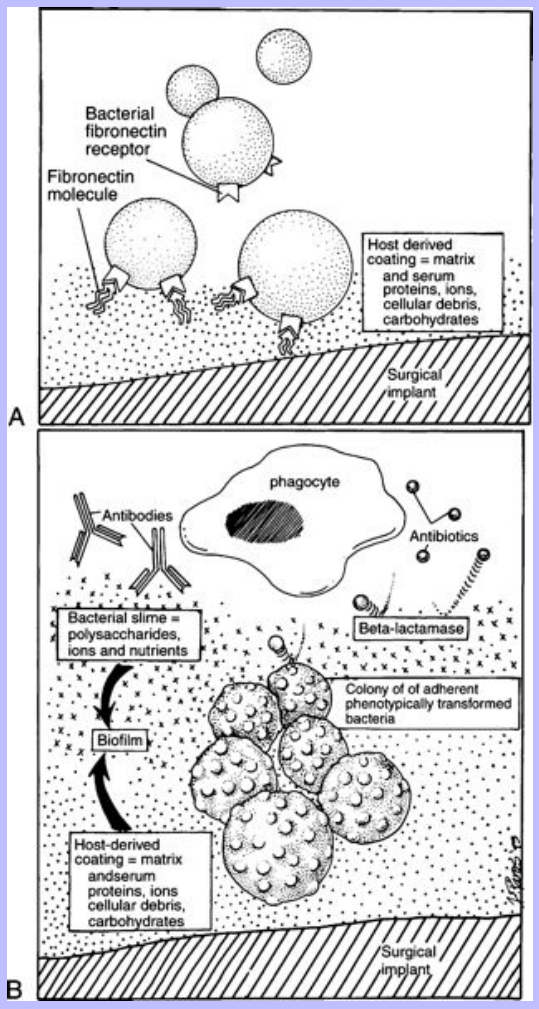
Extraneous material (wood, soil, asphalt, and surgical implants) may incite a foreign-body response, interfere with local host defense mechanisms, and provide a nidus for infection.[157,158] Bacteria have unique mechanisms for bonding to surfaces of implanted foreign material. Initially the surfaces of implants become coated with matrix and serum proteins, ions, cellular debris, and carbohydrates (Figure 279-34).[159] Fibronectin, collagen, and fibrinogen are especially important in bacterial binding to biomaterial. Staphylococci and other gram-positive bacteria possess numerous cell membrane receptors for binding to fibronectin on implant surfaces.[159] Gram-negative bacteria are less effective at binding and have pili and fimbriae that specifically bind cellular proteins, matrix proteins, and glycolipids.[159] Bacteria also bind to exposed collagen matrix proteins (sialoprotein) and hydroxyapatite crystals of damaged bone.[159–161]

1989

Once adherent, bacteria have two important mechanisms that ensure their persistence: (1) slime production and (2) phenotypic transformation.[159,162] Adherent staphylococci and some other bacteria produce a slime composed of extracellular polysaccharide, ions, and nutrients. Slime, together with host-derived material (matrix and serum proteins, ions, cellular debris, and carbohydrate), envelopes bacterial colonies and is called *biofilm* or *glycocalyx* (see Figure 279-34). Biofilm is a virulence factor, because it increases bacterial adhesion, shields bacteria from phagocytes and antibodies, and modifies drug susceptibility.[159] Most antimicrobial drugs diffuse through biofilm, but biofilm may contain high concentrations of beta-lactamase, which protects some bacteria. In addition to providing physical protection, biofilm causes adherent bacteria to transform phenotypically to more virulent strains that are more resistant to antimicrobial drugs than when they are tested *in vitro*.[159]

1990

Figure 279-34 Mechanisms of bacterial persistence in chronic osteomyelitis. **A,** Foreign material such as surgical implants become coated with host-derived material containing fibronectin that binds with membrane receptors of contaminating bacteria. **B,** Adherent staphylococci and some other bacteria produce a slime that together with the host-derived material is called *biofilm*. Biofilm increases bacterial adhesion, protects bacteria from phagocytes and antibodies, and may also contain beta-lactamase. In addition, some adherent bacteria are phenotypically transformed to more virulent strains. (From Johnson KA: Osteomyelitis in dogs and cats. J Am Vet Med Assoc 205:1882, 1994.)



The metaphyses of long bones are commonly affected in young animals with acute hematogenous osteomyelitis.[163] These regions may be especially vulnerable because capillary endothelium therein is discontinuous, allowing extravasation of erythrocytes and possibly bacteria.[157] When local defenses are compromised, osteomyelitis may ensue. This probably accounts for the development of metaphyseal osteomyelitis in Irish setter pups with leukocyte adhesion protein deficiency and border collies with neutropenia due to impaired release of neutrophils from bone marrow (Figure 279-35).[164,165]

279.9.2 Diagnosis

Acute osteomyelitis may produce signs of systemic illness including pyrexia, inappetence, dullness, and weight loss, together with neutrophilia and left shift. Heat, pain, and swelling in muscle and periosteum surrounding the infected bone may be evident. In chronic osteomyelitis, abscessation with single or multiple sinus tracts is a prominent sign. Lymphadenopathy, muscle atrophy, fibrosis, and contracture accompany chronic disease, but hematologic alterations are uncommon.

Radiographs are usually necessary for diagnosis (see Radiology). In acute osteomyelitis, soft tissue swelling (but no osseous changes) occurs, except perhaps in young animals with acute metaphyseal osteomyelitis. In chronic osteomyelitis, periosteal new bone forms early and tends to be extensive, spiculated, and radially orientated (Figure 279-36). Bone resorption produces cortical thinning, medullary lysis, and rounding of fractured bone ends. In young animals, the diaphyseal cortex may be entirely resorbed and replaced by a shell of involucrum. The finding of sequestra is virtually diagnostic for osteomyelitis. Sequestra may be small and obscured by surrounding bone, but it should always be suspected in cases of persistent bone infection. Contrast radiography may help delineate sinuses and foreign bodies. A water-soluble contrast media (10 to 20 mL of Urografin, 76%) is injected slowly through a Foley catheter into each sinus.

Figure 279-35 Polyostotic metaphyseal osteomyelitis in a border collie pup that had persistent neutropenia. **A,** Disruption of metaphyseal architecture of distal femur and proximal tibia, with irregular areas of radiolucency and sclerosis and some periosteal new bone adjacent. **B,** Similar changes are evident in distal humerus and proximal radius.

Figure 279-36 Pelvis of a cat with chronic osteomyelitis probably due to a bite wound from another cat. The hemipelvis is thickened by the formation of irregular, speculated new periosteal bone. (Courtesy of Veterinary Imaging Associates, Sydney, Australia.)

1990

1991

Incomplete delineation of sinuses is a problem. Isolation of bacteria from the site of suspected bone infections should be attempted to confirm the diagnosis and determine *in vitro* drug susceptibility. The diagnosis can usually be made from the history, physical examination, radiology, microbiology, or some combination of these factors.

279.9.3 Treatment

Contrary to long-held beliefs, most antimicrobial drugs penetrate bone well. However, osteomyelitis can be difficult to treat because of factors discussed under pathophysiology. Beta-lactam agents (penicillins, cephalosporins), tetracyclines, and aminoglycosides readily traverse the capillary membrane in normal and infected bone, and they are widely distributed in interstitial fluid.[166] Peak tissue concentrations of these drugs

are reached 25 to 45 minutes after intravenous administration in normal and infected bone, and concentrations in bone closely reflect those in blood.[166] Therefore factors other than drug penetration (such as toxicity, administration routes, *in vitro* susceptibility, and cost) should dictate drug selection. Acute bacterial osteomyelitis may be cured by 4 to 6 weeks of antimicrobial drug therapy, provided bone necrosis is limited and no fracture occurs. However, in chronic osteomyelitis, drug treatment is futile without surgical intervention to remove sequestra and débride necrotic tissue.[157] Débrided wounds are left open to heal by secondary intention, protected with sterile dressings, and irrigated daily with sterile physiologic saline. Fractures must be stabilized and bone defects grafted with autologous cancellous bone. Treatment of chronic osteomyelitis is invariably prolonged and expensive, and may be frustrated by episodes of recurrence. Treatment of recurrent osteomyelitis may necessitate a further search for sequestra, repeated débridement and drainage, reassessment of fracture stability, and re-evaluation of microbiology and antimicrobial drug therapy.

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280 APPENDIX

280.1 Drug Index to the Sixth Edition of the Textbook of Veterinary Medicine

Stephen Ettinger, DVM

Etienne Côté, DVM

Note: Drugs listed represent a compilation of the more commonly used therapeutic agents. Not all drugs are included. Some listed may be infrequently or never used by clinicians. This listing represents the more commonly used drugs in small animal practice, without implying endorsement (or lack thereof) of specific medications. Appendix I provides a listing of the trade names for many of these agents for easy cross-reference purposes. Appendix II lists the veterinary and human products within this listing by indication in veterinary medicine.

Drugs are listed by their generic names. Trade names are in parentheses under the generic title. A brief description of the drug's actions or indications follows. Canine and feline dosage levels are given individually. Abbreviations include QID (every 6 hours), TID (every 8 hours), BID (every 12 hours), SID (every 24 hours), and EOD (every 48 hours); IV (intravenous), IC (intracardiac), IM (intramuscular), SC or SQ (subcutaneous), and PO (oral); and PRN (as needed) and CRI (constant rate infusion). “Total dose” is the amount given to a patient in each single dose (in contrast to “dose per kilogram body weight”) and not the total amount of drug given for the full course of treatment. The comments column lists commonly expected side effects, specific comments, or other characteristics that are particularly important to the clinician. A sixth column includes commonly available sizes and formulations. Those with HM are human-labeled items; those with VM are veterinary-labeled; and some are available either way. Abbreviations used in this column are: T = tablets; C = capsules; S = oral solution; I = injectable; P = powder; ER = extended release product; O = topical ointment; OS = ophthalmic solution; OO = ophthalmic ointment; OTC = over the counter, nonprescription item.

The clinician should recheck drug dosages for accuracy as well as for specific indications, contraindications, and warnings. Drugs are listed not only by their licensed uses but also by commonly practiced uses. Again, the clinician needs to identify the specific and recommended indications for each drug by reviewing relevant information (e.g. product insert, primary sources) before prescribing or using a drug.

Drugs dosages, comments, and side effects are taken from the parent textbook. There have been new and additional drugs and dosages included since publication of the 6th edition of the parent textbook. Other sources have been used, including the editors' clinical experience; the *Formulary* from the Animal Medical Center, New York, NY; the *Veterinary Drug Handbook*, 4th edition, by D.C. Plumb, University of Minnesota, Iowa State Press, Ames, IA; *Current Veterinary Therapy*, R.W. Kirk and J. D. Bonagura, editors, WB Saunders Co., Philadelphia, PA; *Infectious Diseases of the Dog and Cat,* 2nd edition, CE Greene, editor, WB Saunders, Philadelphia, PA; and *Small Animal Medicine*, Dana Allen, editor, J. B. Lippincott Co., Philadelphia, PA, 1991. Although ranges for drug dosages are given, at times a specific dosage identified represents the recommendations of the redactors.

Table • App-1 A

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Acepromazine (acetylpromazine, PromAce, AtraVet, "ace")	Sedation Preanesthetic Central antiemetic	Premedication or as part of sedative protocol: 0.03-0.15-mg/kg SQ, IM, IV As oral sedative (e.g. prior to travel): 0.5 -1mg/kg PO	Same	Over sedation causes CNS depression; in old or systemically ill patients, use at fraction of low dose (e.g. ¼) or not at all Do not use in patients with seizures or hypotension Has no anxiolytic properties on its own (travel)	5, 10, 25 mg T 10 mg/ml I VM
Acetaminophen (Tylenol, most "aspirin free" preparations)	Antipyretic Analgesic	10-20 mg/kg BID; PO	Do not use	Hypotensive agent Toxic to cats Gastric irritation	Many sizes T OTC
Acetazolamide (Diamox)	Glaucoma C.A. Inhibitor	2-10 mg/kg PO TID	2-10 mg/kg PO TID	Hypokalemia Panting	125, 250 mg T, C HM
Acetylcysteine (Mucomyst)	1. Acetaminophen toxicosis in cats 2. Decrease bronchial secretion viscosity 3. Collagenase complicated corneal ulcers	1. Same as for cats 2. Nebulize as 2% soln BID 3. 1 drop 10% soln q 2-4 in eye	first dose 140 mg/kg, then 70 mg/kg PO q 6 h for 3-7 treatments; may be given as slow bolus IV	Tastes bad Bronchospasm possible, Conjunctivitis if prolonged topical use	100, 200 mg/ml I HM
Acetylsalicylic acid (ASA, aspirin)	Analgesia Anti-inflammatory Antipyretic Post H.W. therapy DIC Antithrom-botic via decreased platelet aggregation	10-25 mg/kg PO, SID-TID 0.5 mg/kg PO BID as antithrombotic	Per cat: 40.5-81 mg q 48-72 h (this is aspirin for Aspirin Regimen Users)	Anorexia-nausea G-I irritation Gastric ulcer-bleeding Platelet dysfunction Doses higher than mini-dose are *less* anticoagulant	81, 300, 600 mg T HM
Acitretin (Soriatane)	Synthetic retinoid for keratinization disorders in specific breeds (e.g. cocker spaniels)	0.5-1.32 mg/kg PO SID		Teratogenic; excreted in milk; adverse effects similar to etretinate?	10, 25 mg T HM

ACTH Gel	Provocative agent for diagnosis of hyper- or hypoadreno-corticism	2 U/kg IM; obtain blood pre- and 2-hour post-injection for cortisol levels. Maximum dosage is 20 units per dog.	Per cat: 10 U; obtain blood pre- and 1- and 2-hour post-inj.	Rare allergic reaction	40, 80 IU/ml I HM
ACTH-like solution, aqueous (tetracosactrin, cosyntropin, Cortrosyn)	Provocative agent for diagnosis of hyper- or hypoadreno-corticism; appears superior to ACTH gel but more costly	5 microg/kg (0.005 mg/kg) IV once; obtain blood pre- and 1-hour post-injection for cortisol levels	Per cat: 0.125 mg IM or IV total dose; obtain blood pre- and 30- and 60 minutes post-inj.	Costly; remains effective if diluted, fractionated, and frozen for use at low dose (dogs)	250 microg (0.25 mg) per ampule I HM
Activated charcoal	Gastrointestinal adsorbent	1 g/5 ml water: give 10 ml of slurry/kg	1 g/5 ml water: give 10 ml of slurry/kg	1. Do not induce vomiting 2. Inhalation pneumonia 3. Follow with cathartic	VM, HM (various)
Albendazole (Valbazen)	Giardia Other endoparasites	25 mg/kg PO BID for 48 h	Same but for 5 days 10-21 days for *Paragonimus*	May cause bone marrow suppression at rec'd dosages	300 mg/ml (paste) S VM
Albuterol (Ventolin, Proventil, Volmax)	Immediate but short-acting beta-2 adrenergic agonist bronchodilator	0.02- 0.05 mg/kg (20 - 50 microg/kg) PO BID-TID Inhalant: 1 puff as needed up to BID	1 puff as needed	Beneficial effect lasts < 4 hrs Restlessness, muscle tremors Use with caution in patients where sympathetic drive could be harmful (heart disease, hypertension, hyperthyroidism, etc.)	2, 4, 5 mg T 2.5 mg/ml S 6.8, 17 g inhalation canisters (0.1 mg [100 microg] per puff) HM
Allopurinol (Zyloprim)	Urate urolithiasis	10 mg/kg PO TID, then reduce to 10 mg/kg PO SID after 1 month	9 mg/kg/day PO	TID Rx for 30 days then SID	100, 300 mg T HM
Aluminum hydroxide (Amphojel, AlternaGEL)	Phosphate binder Antacid	Initially, 10-30 mg/kg PO BID-TID. Titrate based on PO4 to 10-90 mg/kg PO BID-QID 5-10 ml/dog	Same. Per cat: approx. 1-3 ml BID-TID	May cause metabolic alkalosis Amphojel= 64 mg Al(OH)3/ml; AlternaGel= 120 mg Al(OH)3/ml	OTC S HM
Amikacin (Amikin) (Amiglyde-V)	1. Aminoglycoside 2. GM + and – agent	5-10 mg/kg BID, IV, IM, SQ	Same	Nephrotoxic Ototoxic Neuromuscular blockade Poor G-I absorption	50 mg/ml I VM

Amino acids 3% and glycerin injection with electrolytes (ProcalAmine)	Partial parenteral nutrition	Maintenance rate	Maintenance rate	Essential and nonessential amino acids, carbohydrates, and electrolytes for IV infusion	IV soln bags S
Aminocaproic acid (Amicar)	Antiprotease activity for degenerative myelopathy	15 mg/kg PO TID		Limited information on side effects or benefits	200 mg T 250 mg/ml S 250 mg/ml I HM
Aminopentamide (Centrine)	Antispasmodic, cholinergic blocking agent Similar to atropine	0.02 mg/kg PO, IM, SQ, BID-TID	0.02 mg/kg PO, IM, SQ BID-TID	Dryness of the mouth Atropine-like side effects Contraindicated in GI obstruction, GI infection/toxin, glaucoma, heart disease, tachycardia	0.2 mg T 0.5 mg/ml I VM
Aminophylline	Bronchodilator Diuretic (very mild)	5-10 mg/kg PO, IV, SID-TID	2-6 mg/kg PO, SID-BID	Hyperexcitability Tachycardia Gastric irritation Anorexia Administer IV slowly	100, 200 mg T 25 mg/ml I VM
Aminopropa-zine (Jenotone)	Used in urethral obstructions Smooth muscle relaxant	2.2-4.4 mg/kg SID-BID IM	Per cat: 6.25-12.5 mg IM, SID-BID 48 h	Do not use with cystic atony Contraindicated in hypotension	25 mg T 25 mg/ml I VM
Amiodarone (Cordarone)	Type III antiarrhythmic agent for serious ventricular tachyarrhyth-mias that are life threatening	10 mg/kg PO BID × 1 week (loading), then 8 mg/kg PO SID		Photosensitivity Liver necrosis Keratopathy Coombs' test positive May be proarrhythmic	200 mg T HM
Amitraz (Mitaban)	Demodicosis	5-10 ml/gallon H_2O, dip dog; air dry; = 0.025 to 0.05% soln; use 3×/week on feet with a fresh solution of 0.5 ml in 30 ml propylene glycol or mineral oil		Wear gloves when applying Requires multiple dips Transient pruritus noted Use in ventilated areas	19.9% soln for dilution and topical skin application VM

Amitriptyline HCl (Elavil)	Separation, anxiety-related disorders; destructive disorders; feline inappropriate elimination Tricyclic antidepressant	1.1-4.4 mg/kg PO SID-BID	5-12.5 mg/cat PO SID-BID	Sedation; psychosis; Anticholinergic side effects Caution if seizure history	10, 25, 50, 75, 100, 150 mg T HM
Amlodipine (Norvasc)	Long acting Ca channel blocking agent for hypertension	0.0625-0.25 mg/kg PO SID	0.125-0.25 mg/kg PO SID	Somnolence Hypotension	2.5, 5, 10 mg T HM
Ammonium chloride (Uroeze)	Urinary acidifier	100 mg/kg PO BID	20-40 mg/kg PO BID	Poor palatability G-I signs Contraindicated in liver disease and in renal failure Granules = 200 or 400 mg/ ¼ teaspoon	500 mg T HM 400 mg T 200, 400 mg per ¼ teaspoon P VM
Amoxicillin (Amoxi-tabs) (Amoxi-drops) (Robamox-V)	Penicillin class antibiotic GM + and anaerobic antibacterial agent	10-20 mg/kg BID-TID PO, SQ, IM, IV	Same	Penicillin contraindications	50, 100, 150, 200, 400mg T VM, HM
Amoxicillin/Clavulanic acid (Clavamox) (Augmentin)	See *Amoxicillin* No penicillinase inactivation	10-20 mg/kg PO BID	Same	Penicillin sensitivity Vomiting in cats Tablets must remain in foil until used	62.5, 125, 250, 375 mg T 50 mg/ml S VM, HM
Amphotericin B (Fungizone)	Systemic mycoses	Test dose = 0.25 mg/kg IV; if OK, then 0.5 mg/kg in D5W given IV CRI 3 times weekly for 2 to 4 months; do not exceed 5-10 mg/kg	Test dose = 0.1 mg/kg IV; if OK, then 0.1–0.25 mg/kg in 5 to 20 ml of 5% dextrose in water given slowly IV 3 times weekly for up to 6 weeks	Nephrotoxic; monitor BUN. Pretreat with antiemetics Anaphylaxis possible May administer at lower dosage SQ in 0.45% saline plus 2.5% dextrose	50 mg/vial I HM
Amphotericin B, liposomal encapsulated (AmBisome)	Blastomycosis, histoplasmosis, cryptococcosis, coccidioidomycosis	0.5 mg/kg IV test dose; then 1-2.5 mg/kg IV every 48 h; recommended cumulative dose = 12 mg/kg		Anaphylaxis possible; less nephrotoxic than aqueous amphotericin B (above)	50 mg/vial I HM
Ampicillin	Penicillin class antibiotic Routine G+ and anaerobic infections	10-20 mg/kg TID PO, SQ, IM, IV	Same	Penicillin contraindications Phlebitis	125, 250, 500 mg C 125 mg/5 ml S 1, 3, 6 mg vials I VM, HM

Amprolium (Corid)	Enteric coccidiostat	Per pup: 100 mg total dose SID in food or water (not both) for 10 days Per adults dog: 300 mg total dose SID in food or water (not both) for 10 days		Overdosage causes CNS disturbances	9.6% S VM
Amrinone (Inocor)	Low-output systolic heart failure Phosphodiesterase inhibitor	1-3 mg bolus IV, then 0.01–0.1 mg/kg/min (10-100 microg/kg/min) IV		Tachycardia Anxiety Monitor pulse and BP	5 mg/ml I HM
Apomorphine	Induction of vomiting	¼-½ tab in conjunctival sac. Flush out after emesis	Same	Do not use if decreased consciousness Periocular irritation	6 mg T HM
Artificial tears/oint. (Adapt) (Lacrilube)	Used for insufficient tear production or with decreased blinking	1 drop in affected eye PRN	Same	Hypersensitivity	OTC HM
Ascorbic acid (vitamin C)	Acetominophen-induced methemoglobin toxicity Copper hepatotoxicity	Per dog: 100-500 mg PO total dose TID	30 mg/kg QID, PO, SQ, IM, IV for acetamino-phen toxicity		500 mg/ml I 50, 100, 250, 500 mg, 1 g T HM
L-Asparaginase (Elspar)	Induction therapy for lymphoreticular neoplasms Immune thrombocytopenia	400 IU/kg IM, IP once or as part of a protocol; or 10,000-20,000 U/m2 IM, IP, SQ	Same	Allergic symptoms Anaphylaxis Pancreatitis Coagulopathies	10,000 U/vial I HM
Atenolol (Tenormin)	β1 Adrenergic blockade Supraventricular tachyarrhythmias Systemic hypertension	0.25 - 1 mg/kg PO SID-BID	Per cat: 1/8-1/4 of 25 mg tab PO total dose SID-BID	Hypotension Depression Beta blockade induced CHF Inappetence, bradycardia Generally start at low dose and titrate up as necessary	25, 50, 100 mg T HM
Atipamezole (Antisedan)	α2 synthetic alpha adrenergic antagonist Used for reversing analgesic-sedative effects of medetomidine	Administer an equal volume of medetomidine used. Use IV or IM. Give less if over 1 hour since medetomidine		The return to normal state may not be immediate	5 mg/ml I VM

Atropine SO4	Parasymp-atholytic Anticholinergic Preanesthetic agent Organophosphate toxicity Supraventricular bradyarrhyth-mia Atropine response test	0.0.01-0.03 mg/kg IM, SQ, IV Atropine response test: Give 0.04 mg/kg IV only, and recheck ECG after 2-15 minutes. 0.2 - 2 mg/kg IV, IM, SQ for organophos-phate poisoning. For OPO4 poisoning, give ¼ dose IV—remainder IM or SQ	Same	Tachycardia Mydriasis Ileus Photophobia Do not use in CHF unless bradycardia present	0.54 mg/ml I VM Various HM
Atropine sulfate ophthalmic soln./oint.	Used when pupillary dilation is desired (e.g. uveitis)	1 drop in affected eye SID-BID	Same 1 drop in affected eye SID-BID	Atropine side effects Contraindicated in the presence of glaucoma Cats may salivate	0.5, 1% OO 0.5, 1, 2 and 3% OS HM
Aurothioglucose (Solganal)	Pemphigus complex Autoimmune diseases Rheumatoid arthritis	1st week: 0.1 mg/kg IM single dose 2nd week: 0.2 mg/kg single dose. Then 1 mg/kg once a week IM decreasing to once a month for maintenance immuno-suppression	Per cat: 1st week: 1 mg IM 2nd week: 2 mg IM Then 1 mg/kg once a week IM decreasing to once a month	Blood dyscrasias Renal and hepatotoxicity Neuritis-encephalitis Cutaneous toxicity Pain at injection site Many others	50 mg/ml I HM
Azathioprine (Imuran)	Immuno-suppressive agent (SLE, RA, immune-mediated hepatopathies, pemphigus, polymyositis, ITP, IHA, enteritis, etc)	1-2 mg/kg PO EOD-SID		Monitor CBC Bone marrow suppression (leukopenia, thrombocyto-penia), Rarely hepatotoxic Use chemo precautions when handling or administering	50 mg T HM
Azidothymidine (AZT, zidovudine, Retrovir)	Antiretroviral agent		5-15 mg/kg PO BID for 21 days	Monitor for anemia	100 mg C 300 mg T 10 mg/ml S HM

Azithromycin (Zithromax)	Broad-spectrum static macrolide antibiotic Refractory respiratory infections; other infections	5-10 mg/kg PO SID × 1-5 days	5 mg/kg PO SID × 1-5 days; pulse therapy or long-term treatment possible (weeks)	Resistant infections; GI effects; costly and perishable (expires after 1 week despite refrigerations)	250, 600 mg T 20, 40 mg/ml S HM

Table • App-2 B

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Benazepril (Fortekor) (Lotensin)	ACE inhibitor Vasodilator CHF therapy Glomerulopathy	0.25- 0.33 mg/kg PO SID	0.25 mg/kg PO SID	Dual renal-hepatic elimination Sedation, anorexia Monitor potassium Veterinary formulation not available nor approved in USA	5, 20 mg VM (Canada, Europe, others) 5, 10, 20, 40 mg T HM
Benzoyl peroxide (Oxydex) (Pyoben)	Acne, seborrhea, pyoderma, pruritus	Shampoo p.r.n.; leave on skin for 10 minutes and rinse Gel: apply topically BID-TID	Shampoo p.r.n.; leave on skin for 10 minutes and rinse Gel: apply topically BID-TID	Bleaches fabric May be skin irritant	OTC VM, HM
Betamethasone (Betasone)	Injectable or topical long acting steroid	0.1-0.4 mg/kg IM Topically apply as needed up to TID	Topically apply as needed up to TID	Glucocorticoid adverse effects 7-10 × potency of prednisone	2, 5 mg/ml I VM 0.6 mg T 3 mg/ml I HM
Bethanechol (Urecholine)	Bladder atony (nonobstructive) Cholinergic agent	Per dog: 5-25 mg PO total dose TID or 2.5-15 mg TID SQ	Per cat: 2.5-5.0 mg PO total dose BID	Do not use with obstruction or areflexic bladder GI adverse effects possible	5, 10, 25, 50 mg T HM
Bismuth subsalicylate (Pepto-Bismol)	GI tract protectant	1 ml/4 kg body weight PO up to QID	Same with caution due to salicylate composition	Side effects (uncommon): Vomiting, cramping, salivation, miosis May be treated with atropine Causes stool to develop dark or black discoloration	OTC, HM 17, 47 mg/ml S 262 mg T

Blood products	From typed donors Whole: If fresh: RBC, WBCs, platelets, plasma proteins, and coag. factors; If > 8h, RBCs and plasma proteins only. Packed RBCs for anemia Fresh frozen plasma: For protein (to ↑ albumin 1 g/dl) For coagulation factors Cryoprecipitate for VWF, hemophilia A, and fibrinogen deficiencies	5-22 ml/kg slowly IV; rapid if active hemorrhage is present 10-45 ml/kg IV45 ml/kg IV 6-10 ml/kg IV 1 unit (225 ml)/10 kg BW IV	Same	See Ch. 127	VM I

Bromide (KBr-generic)	Anticonvulsant	30-40 mg/kg PO SID or divided BID (if GI signs a problem) May require an initial loading dose of 400-600 mg/kg given in divided doses with food over 24 hrs Dose in conjunction with phenobarbital may be lower; adjust based on serum bromide levels and clinical response	20 mg/kg/day PO This product may exacerbate or induce feline lower airway disease	Used with phenobarbital or alone May potentiate side effects of sedation, incoordination, and pelvic limb weakness Effective range 500-1000 µg/ml Use ACS grade We use 14 oz KBr powder + 1 liter NaCl. 60 ml of this mixture in 8 oz Karo syrup = 400 mg KBr/ml Also available as Na+ salt May be administered per rectum to achieve more rapid blood levels May trigger severe airway disease (asthma-like) in cats In dogs for mono therapy wish to attain 300 mg/dl; for cats 100-200 mg/dl	400 mg/ml S VM
Budesonide (Entocort)	Glucocorticoid with minimal systemic effects due to topical GI distribution and rapid first-pass hepatic metabolism Inflammatory bowel disease	Per dog: 1-6 mg PO total dose SID- EOD For noninfectious colitis: ½ to 1 enema (based on body size) per rectum SID after defecation		Dosing limited by formulation (1 size unbreakable capsule); capsule dissolution designed for human ileum, unproven in vet med	1, 3 mg C 2 mg enema HM
Bunamidine (Scolaban)	*Taenia, Dipylidium, Echinococcus*	25 to 50 mg/kg PO once; fast 3 h before and after administration	Same	V/D rarely observed	100, 200, 400 mg T VM

Buprenorphine HCl (Buprenex)	Opiate agonist 1. Analgesia 2. Sedative for medical procedures	1. 0.01-0.02 mg/kg (10 – 20 microg/kg) IV, IM 2. 0.0075-0.01 mg/kg (7.5–10 microg/kg) IV, IM	0.005-0.03 mg/kg (5–20 microg/kg) IV, IM	Respiratory depression Use cautiously in aged or debilitated patients Neuroleptan-algesia when used with diazepam or acepromazine	0.3 mg/ml I HM
Busiprone (BuSpar)	Anxiolytic agent Urine spraying Aggression Repetitive behaviors	2.5-10 mg PO total dose BID-TID	2.5-5 mg PO total dose SID-BID	Caution when used with hepatic or renal disease	5, 10, 15 mg T HM
Butorphanol tartrate (Torbutrol) (Torbugesic) (Stadol)	Cough suppressant Narcotic agonist/antagonist Analgesia Sedative	Analgesia, sedation: 0.2-1 mg/kg BID-QID PO, IM, SQ 0.1-0.2 mg/kg IV Antitussive: 0.5-1 mg/kg BID-QID PO	Analgesia, sedation: 0.1-0.4 mg/kg BID-QID SQ, IM, IV	Vomiting, sedation Possible overexcitement in cats	1, 5, 10 mg T 10 mg/ml I VM, HM

Table • App-3 C

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Calcitonin (Calcimar) (Micalcin)	Reduces serum calcium in hypercalcemic states, especially cholecalciferol toxicity	4-8 IU/kg BID IV, IM, SQ	4-8 IU/kg BID IV, IM, SQ	Injections are irritating G-I upset possible	200 IU/ml I HM
Calcitriol	Vitamin D analog Hypocalcemia	0.25–0.5 microg PO total dose SID; titrate according to response	0.01–0.04 microg/kg PO SID; titrate according to response	Rapid onset of action and short activity (days), vs. others e.g. DHT	0.25, 0.5 microg C 1 microg/ml S
Calcium carbonate (Titralac, Tums)	Hypocalcemia adjunct treatment	1-4 g/day PO	Same	Could cause alkalosis; many dogs eat these as a treat	OTC, HM
Calcium chloride (or gluconate) (10% solution)	Ventricular asystole	0.1 ml/kg IV slowly, IC	Same		100 mg/ml I HM
Calcium EDTA (Versenate)	Lead, zinc, and other metal poisoning	25 mg/kg SC QID × 5 days maximum. Dilute in 5% D5W or PSS	Same	May be painful despite dilution Potentially nephrotoxic	200 mg/ml I HM
Calcium gluconate (Calcet)	Critical hypocalcemia Ventricular asystole	10% infusion: 50-200 mg/kg IV slowly over 15-30 minutes, up to QID 50-150 mg Ca++/kg/day in continuous IV infusion Oral: 150-250 mg/kg PO TID	Same	Arrhythmias; monitor ECG and overt response to treatment during infusion; V/D; Dystrophic calcification	100 mg/ml I HM
Captan powder 50% (Orthocide)	Dermatomy-coses	Mix 2 tbsp per gallon of water, apply topically every 3-7 days. Do not rinse after applying	Same	May induce contact sensitization in humans	VM
Captopril (Capoten)	Vasodilator, congestive heart failure Hypertension ACE inhibitor	0.5-1.5 mg/kg BID-TID PO	Per cat: 3.12-6.25 mg BID total dose PO	Hypotension-depression Anorexia; V/D Could exacerbate renal failure Less effective than most other “prils”	12.5, 25, 50, 100 mg T HM

Carbamate	Cholinesterase inhibitor for fleas, ticks, cheyletiellic mange	Use as a dip every 7-14 days; do not rinse off Spray EOD	Same	Do not use under 4 wks old Cholinesterase toxicity treat with atropine and bathing May stain hair yellow	0.5–2% topical solution VM
Carbenicillin (Geopen) (Pyopen)	Bacterial infections Penicillin derivative	15-100 mg/kg TID, IV, IM, SQ, PO	15-40 mg/kg TID IV, IM, SQ, Po	See *Penicillin*	382 mg T 1,2,5,10,20,30 g I HM
Carbimazole (Carbazole)	Hyperthyroidism Is metabolized to methimazole		Per cat: 5 mg PO total dose BID-TID; titrate after 1-3 weeks based on response	Adverse effects similar to methimazole; Not available nor approved in USA	5, 20 mg T HM
Carboplatin (Paraplatin)	Antineoplastic for many carcinoma and sarcoma therapies	300 mg/m^2 IV in D5W over 15 minutes every 3 weeks for 4 treatments	200 mg/m^2 IV in D5W over 15 minutes every 4 weeks	Myelosuppression Expensive Advantageous to *cis*-platinum (renal) Use chemo precautions when handling or administering	50, 150, 450 mg I HM
L-Carnitine	AA transports fatty acids into mitochondria for energy metabolism Some cardiomyo-pathies	50-100 mg/kg TID PO	50-100 mg/kg PO SID for hepatic lipidosis	Expensive in big dogs To be used with other Rx Effects uncertain	250, 500 mg T/C 100 mg/ml S HM
Carprofen (Rimadyl)	NSAID with analgesic and antipyretic effects	2-4mg/kg BID PO 4 mg/kg IV, IM, SQ for one time use as an injectable for pain relief	4 mg/kg IV, IM, SQ as a single dose for pain relief	Hepatotoxicity Do not use with bleeding disorders, inflammatory bowel disease, or GI ulcers Monitor liver values Do not use with corticosteroids or ASA May decrease ACE inhibition	25, 75, 100 mg T 50 mg/ml I VM
Carvedilol (Coreg)	α_1 Blocking and nonselective beta blockade; used in CHF and primary tachycardias	0.1 - 0.2 mg/kg PO SID starting dose; may increase to 0.4 mg/kg PO SID	Unknown	Lethargy Gastrointestinal Iatrogenic relapse of CHF; if prior CHF, begin at low dose and increase slowly over several weeks	3.125, 6.25, 12.5, 25 mg T HM

Castor Oil	Irritant cathartic	8-30 ml PO	4-10 ml PO	Gripping catharsis may develop Do not use if obstructed or atonic	OTC, HM
Cefotaxime (Claforan)	3rd generation cephalosporin; Gram + and – organisms and many anaerobes	20-40 mg/kg slow IV TID × 7 days	Same	Pain if injected IM; BM toxicity uncommon	500 mg, 1, 2, 10 g I HM
Cefoxitin (Mefoxin)	Cephamycin grouped with 2nd generation cephalosporins Some G+, G-, and anaerobic bactericidal activity	30 mg/kg IV TID-QID	Same	Pain if injected IM; BM toxicity uncommon	1, 2, 10 g vials I
Cefpodoxime (Simplicef)	Extended spectrum semisynthetic cephalosporin	5-10 mg/kg PO SID	5-10 mg/kg PO SID	Once daily dosaging	100,200mg T VM
Ceftiofur (Naxcel)	3rd generation cephalosporin	2.2- 4.4 mg/kg SQ SID- BID	Same		1, 4 g vials I
Cephalosporin antibiotics	Broad-spectrum bactericidal Less effective against gram + bacteria than penicillins Penicillinase inactivation	10-30 mg/kg BID-QID PO, SQ, IM, IV Review each product for specific dosage, handling, and administration	Same	G-I side effects Penicillin contraindications Possibly nephrotoxic at high dosages or if used with aminoglycoside antibiotics	250, 500 mg C 25, 50, 100 mg/cc S 1, 2, 20 g vials I VM, HM
Chlorambucil (Leukeran)	Lymphoreticu-lar neoplasia Chronic lymphocytic leukemia Macroglobuli-nemia Feline-IBD	2 mg/m^2 PO SID × 3 wk beyond remission, then 1.5 mg/m^2 PO SIDx15 days, then q 3rd day; or 0.1-0.2 mg/kg q 24-72 h PO	1.5 mg/m^2 PO SID as for dog or 0.1 mg/kg q 48-72 h PO or total dose per cat 2 mg/cat EOD PO	Bone marrow suppression Usually a second line agent often used with prednisone and/or other agents Use chemo precautions when handling or administering Do not break or split tablets	2 mg T HM

Chloramphe-nicol (Chloromyce-tin)	Broad spectrum bacteriostatic agent *Mycoplasma, Rickettsia, Chlamydia*, and anaerobic bacteria Excellent lipid solubility 1% oph. Oint.: Corneal ulcers and infections 0.5% oph. Soln.: Corneal ulcers and infections	30-50 mg/kg TID, PO, IV, IM, SQ Apply to eye q 6 h	15-20 mg/kg BID, PO, IV, IM, SQ Apply to eye q 4-8 h	Hepatic microsomal enzyme inhibitor May potentiate some Rx-use caution Do not use with "cidal" agents Monitor CBC and chemistries Possible teratogen	100 mg/ml I 100, 250, 500 mg, 1 g T VM, HM
Chlorhexidine 0.5% (Novasen)	1. Topical antiseptic shampoo 2. Topical antiseptic solution	Shampoo every 3-7 days or dilute the solution 1:10 with water and apply to lesions SID-TID	Same		OTC, HM
Chlorothiazide (Diuril)	Diuretic Nonhormonal Rx for CDI and NDI	20-40mg/kg BID PO	Same	Hyponatremia-hypokalemia Use cautiously with digitalis	250, 500 mg T 50 mg/ml S HM
Chlorphenira-mine (Chlor-Trimeton, ChlorTripolon)	Decongestant; antihistamine	Per dog: 2-8 mg PO total dose BID-TID	Per cat: 1-2 mg PO total dose BID-TID	May cause drowsiness or restlessness	10 mg/ml I 2 mg/ml S 2, 4, 8, 12 mg T OTC HM
Chlorpromazine (Thorazine)	Tranquilization Sedation Antiemetic	Oral tranquilization: 1-3 mg/kg PO up to QID Sedation: 0.1-1 mg/kg SQ, IM 0.01-0.03 mg/kg IV	Same	Severe CNS depression with overdosage May potentiate seizures Use sparingly or not at all in older or systemically ill patients	10, 25, 50, 100, 200 mg T 2 mg/ml S 25 mg suppository 25 mg/ml I HM
Cimetidine (Tagamet)	H2 receptor antagonist Esophagitis, gastric reflux Chronic gastritis, GI tract ulceration Hypergastri-nemia Effects of mast cell tumors	5 - 10 mg/kg BID-QID PO 5 mg/kg TID IV	2.5 - 5 mg/kg BID-TID PO	Hepatic microsomal enzyme inhibitor Administer slowly IV	200, 300, 400, 800 mg T 60 mg/ml S 150 mg/ml I HM

Ciprofloxacin (Cipro)	Fluoroquino-lone antibiotic Broad-spectrum "cidal" Mycoplasma	5-15 mg/kg BID PO		See *Enrofloxacin*	250, 500, 750 mg T HM
Cisapride (Propulsid) (Prepulsid) No longer FDA approved agent for human beings	Prokinetic serotonergic for feline megacolon; gastroesophageal reflux; 1 and 2 GI motility disorders	0.1-1mg/kg PO BID-TID	Per cat: 2.5-5 mg total dose BID-TID PO	Requires adjunctive Rx as stool softener Does not ↑ gastric secretions Increases esophageal peristalsis Reported to be associated with ventricular arrhythmias in HM	10, 20 mg T 1 mg/ml S HM
Cisplatin (Platinol)	Solid carcinomas Osteosarcoma	50-70 mg/m2 IV every 3-5 weeks; pretreat with IV fluids 12 h before and after Rx	None-do not use	Use antiemetic agent; BM suppression; renal toxicity; fatal pulmonary edema in cats; anaphylaxis; use chemo precautions when handling or administering	10 and 50 mg vials I HM
Clarithromycin (Biaxin)	Broad-spectrum macrolide antibacterial; Resistant respiratory or skin infections	5-10 mg/kg PO BID	Same	G-I, liver disturbances; bone marrow toxicity rarely	250, 500 mg T 25, 50 mg/ml S HM
Clemastine fumarate (Tavist products, Contac products, many others)	Antihistamine Allergic skin disease, other allergies	0.05–0.1 mg/kg PO BID		Lethargy/drowsiness, or restlessness Caution re other active ingredients in OTC combo formulations	1.34, 2.68 mg T HM OTC
Clindamycin (Cleocin) (Antirobe)	Lincosamide antibiotic GM +; staphylococcus; anaerobes; Bacteroides; toxoplasmosis; babesiosis; osteomyelitis	5-10 mg/kg BID PO Toxo: 5–20 mg/kg PO BID	Same Toxo: 12.5–25 mg/kg PO BID	May cause V/D and hepatotoxicity Do not use with erythromycin or chloramphenicol	150 mg/ml I 25, 75, 150 mg C 25 mg/ml S VM, HM
Clomipramine (Clomicalm) (Anafranil)	Separation anxiety in the dog-a tricyclic agent	1-2 mg/kg PO BID	5-12.5 mg PO SID-BID per cat	Do not use in breeding dogs or if dog is or has received MAO inhibitors Vomiting, lethargy, diarrhea, and polydipsia are acute adverse reactions Chronic adverse reactions are urine retention, urolith formation and sedation	5, 20, 80 mg VM T
Clonazepam (Klonopin)	Seizure disorders Panic disorders Sedation	0.5 mg/kg PO BID–TID; titrate as required to effect		2nd line seizure Rx Sedation Duration of action in dogs may be short (few hours)	0.5, 1, 2 mg T HM

Cloprostenol	Abortifacient for mismating (early, prior to ossification of fetal bones)	1-2.5 microg/kg SQ SID-EOD × 5 days	Same	Dilute 1:10 with sterile 0.9% NaCl for accurate dosing	250 microg/ml I VM
Clotrimazole (Veltrim) (Lotrimin) (Mycelex)	Used topically for nasal aspergillosis; also externally for Malassezia and other fungi	As needed to fill nasal cavity for nasal aspergillosis (follow precautions and protocol)		Intranasal administration requires preplacing catheters surgically or via endoscope. Use propylene glycol preparation for this indication	10 mg/ml topical solution OTC HM
Coal tar (0.5% to 8%)	Shampoo-seborrhea, dermatitis; eczema; keratolytic	Bathe every 3 to 14 days; leave in contact with skin for 10 minutes and rinse thoroughly	Same	May irritate skin	VM
Cobalamin (Vitamin B12) (cyanocobal-amin)	Used for treating vitamin B12 deficiency from exocrine pancreatic disease, SIBO, and in giant schnauzers	Total dose: 250-500 microg (0.25–0.5 mg) per dog IM, SQ once weekly or less, based on serum levels	Total dose: 125-250 microg (0.125–0.25 mg) per cat IM, SQ		1000 microg/ml (=1 mg/ml) I HM, VM
Colchicine	Hepatic fibrosis	0.03 mg/kg/day PO SID	No reported use	Not well described GI effects, bone marrow toxicity, teratogenicity possible	0.5, 0.6 mg T HM
Cyclophos-phamide (Cytoxan, Neosar)	Lymphoreticu-lar tumors Solid carcinomas Immune-mediated disease	50 mg/m2 (or 2 mg/kg) PO 4 days on, 3 days off, or use EOD 200-300 mg/m2 IV weekly	Same	G-I signs BM suppression Hemorrhagic cystis, especially with higher (weekly) dose Alopecia Use with caution See Chemotherapy Use chemo precautions when handling or administering Do not split or break tablets Caution cyclosporine brand name almost identical (Neosar vs. Neoral)	25, 50 mg T 100, 200, 500 mg and 1 and 2 g vials I HM
Cyclosporine ophthalmic (Optimune) (Sandimmune)	T lymphocyte inhibitor KCS in dogs	0.2% oph. oint. or soln in oil base. Use 1 drop/short strip BID in affected eye(s) until improvement occurs, then SID	Do not use	May be ophthalmic irritant Monitor for infections	HM; VM OO OS 4 ml olive oil and 1 ml cyclosporine

Cyclosporine systemic (Sandimmune) (Atopica) (Neoral)	IMHA; ITP Perianal fistula; Atopic dermatitis; eosinophilic granuloma in cats and other immunosuppressive purposes	Emulsion forms (Neoral, Atopica): 2–5 mg/kg BID PO (2–5 mg/kg SID PO if concurrent ketoconazole administration) Nonemulsion form poorly absorbed (Sandimmune): 5–10 mg/kg BID PO (5–10 mg/kg SID PO if concurrent ketoconazole administration) 2–3 mg/kg slow IV over 4 hours BID; dilute to 1 mg/ml in D5W or 0.9% NaCl before administration	Same	Adjust dose to attain good clinical response and 200-500 ng/ml blood level Oral doses based on greater absorption of emulsion forms vs. nonemulsion form Can cause nephrotoxicity (protein-losing nephropathy) Anaphylaxis possible with IV; little clinical experience with IV to date	25, 50, 100 mg T 100 mg/ml S 50 mg/ml I HM 10, 25, 50, 100 mg T VM
Cyproheptadine (Periactin)	Serotonin and H1 antagonist 1. Appetite stimulant via hypothalamic stimulation 2. Feline pica 3. Antihistamine 4. Spraying	1. 5-20 mg PO BID 2. 1 mg/kg PO BID-TID	1. Total dose = 1-4 mg/cat PO SID-BID 2. 0.22 mg/kg PO SID	Can cause excitability or depression, especially at higher doses; vomiting; aggressiveness	4 mg T 2 mg/5 ml S HM
Cytosine arabinoside (cytarabine) (Cytosar) (ARA-C)	Antineoplastic Lymphoma protocol	100 mg/m2 SID for 2-4 days SQ or slow IV	Same	Leukopenia-BM suppression GI toxicity Reconstituted vial good for 48 h Use along with cancer protocol Use chemo precautions when handling or administering	100, 500 mg 1 and 2 g vials I HM

Table • App-4 D

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Dacarbazine (DTIC)	Melanoma Sarcoma	800-1000 mg/m2 IV CRI (8 hours) q 3-4 weeks	Not recommended	G-I toxicity BM suppression Extravasation injury	100, 200 mg vials I HM
Danazol (Danocrine)	Modified androgen Used for ITP, IMHA	5-10 mg/kg PO BID	Same	Adjunctive Rx for ITP and IHA; hepatotoxicity, bone marrow toxicity possible; response may take weeks–months	50, 100, 200 mg C HM
Dapsone (Avlosulfon)	1. Antibacterial-anti-inflammatory agent used for some skin disorders 2. Antiprotozoal/ anti-mycobacterial effects	1. 1 mg/kg PO TID 2. 1 mg/kg PO TID initially until remission, then 0.3 mg/kg maintenance	Total dose: 25-50 mg per cat BID PO	Hepatotoxicity and BM suppression may occur early in therapy; hemolysis, GI signs, skin eruptions possible	25 and 100 mg T HM
Deferoxamine (Desferal, DFO)	Iron chelator; iron toxicity	10-15 mg/kg/hour IV CRI, then titrate based on serum iron levels. Alternatively, if CRI not possible, give 10-40 mg/kg TID IM for 24-72h, based on serum iron levels		Arrhythmia, hypotension, wheezing if CRI too rapid Hypocalcemia, thrombocyto-penia possible Do not use if renal failure Potential teratogen	500 mg vials I HM
Dehydrocholic acid (Decholin)	Used to stimulate bile flow	10 to 15 mg/kg TID PO for 7-10 days	Same	Do not use with biliary obstruction	HM
Deracoxib (Deramaxx)	COX-2-inhibiting nonsteroidal anti-inflammatory (NSAID) drug. For treatment of osteoarthritis, perioperative pain management	1-2 mg/kg PO SID (long-term use) 3-4 mg/kg PO SID (max. 7 days)		Gastrointestinal signs (vomiting, anorexia)	25, 100 mg chewable T VM
Desmopressin acetate (DDAVP)	1. Vasopressin analog to manage central diabetes insipidus 2. vW disease	1-4 drops intranasally or in subconjunctival sac SID-QID (diabetes insipidus); or 1-2 microg/kg SQ SID-BID Oral dose not yet determined	Same (intranasal or subconjunctival)	Rhinorrhea Hypersensitivity rkns Use nasal spray form (1.5–4 microg/drop)–40 × stronger than parenteral (4 microg/ml)	10 microg/spray (=0.1 ml) in 2.5 or 5 ml bottles 4 microg/ml I 0.1 and 0.2 mg T HM

Desoxycorticosterone pivalate (DOCP) (Percorten-V)	Replacement therapy for mineralocorticoid deficiency (hypoadrenocorticism) Each 25 mg releases 1 mg DOCA/day for 21-26 days	1 cc/12 kg q 25 days; i.e., 2 mg/kg IM or SQ		Titrate dosage to effect No glucocorticoid activity; may require oral prednisolone 0.2-0.4 mg/kg/day as adjunctive therapy	25 mg/ml I VM
Dexamethasone (Azium, Dexate) (Decadron),	Potent glucocorticoid for anti-inflammatory, immune suppression, hypoadrenocorticism, and CNS	0.1-1 mg/kg/day PO, Divide dosage. Dosage variable from	Same	HPA axis suppression Multiorgan steroid effects	0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6 mg T
Dexamethasone sodium phosphate (SP)	edema; adrenal axis testing.	anti-inflammatory to that required for immune suppression. Long-term oral: EOD best LDDST = 0.01 mg/kg IV HDDST = 0.1 mg/kg IV		Very high CNS doses (e.g. 4–8 mg/kg) of unproven clinical benefit and almost always associated with short-term adverse effects (e.g. severe GI bleeding)	2, 8, 16 g/ml I (dexamethasone) 4, 10, 20, 24 mg/ml I (dexamethasone SP) VM, HM
Dexasporin oph. Soln./oint. (Maxitrol)	Neomycin, polymyxin, and dexamethasone combination used for steroid responsive ophthalmic inflammation where a combined antibiotic is desirable	1 drop in affected eye BID-QID	1 drop in affected eye BID-QID	Steroids are contraindicated in some specific eye diseases Systemic side effects are possible	0.05% ointment 0.1% soln. HM
Dexrazoxane (Zinecard, Cardioxane)	EDTA derivative that protects against doxorubicin-induced cardiomyopathy; may also be used for doxorubicin extravasation lesions	10:1 ratio to doxorubicin dose; i.e. administer 10× more dexrazoxane than doxorubicin; IV CRI over 30 minutes, begun 45 minutes prior to doxorubicin		Myelosuppression possible	250 mg and 500 mg vials I HM
Dextran (Rheomacro-dex)	Hypovolemia Plasma volume expander	20 ml/kg IV	Same	Thrombocyt-opathy	10% dextran in PSS or D5W I HM
Dextroampheta-mine (Dexedrine)	Amphetamine Narcolepsy Hyperkinesis	5-10 mg/kg PO TID 0.2-1.3 mg/kg PO PRN			5 mg T 5, 10, 15 mg ER HM
Dextromethor-phan	Antitussive	0.5-2 mg/kg PO TID	Same	Usually in association with other drugs, i.e. OTC cough syrup viz. Robitussin® Efficacy questioned	Many OTC HM

Diazepam (Valium)	1. Tranquilizer, component of anesthetic induction protocol 2. Anticonvulsant 3. Muscle relaxant 4. Appetite stimulant (cats) 5. Urine marking/spraying (cats) 6. Sedative/anxiolytic	1. With ketamine for sedation/anesthetic induction: 0.5 mg/kg IV or to effect, max 20 mg/dose 2. 0.5–1 mg/kg IV to effect. Enema: 1–2 mg/kg made up as 4 mg/ml enema solution CRI: 0.5 mg/kg/h, titrated PRN 3. 0.25–1 mg/kg PO BID-TID 6. 0.05-0.2 mg/kg IV or 0.25–1 mg/kg PO PRN up to BID	1, 2. total dose: 0.25-2 mg IV per cat, to effect 3, 5. Total dose: 1-2 mg per cat BID PO 4. 0.2 mg/kg IV prior to feeding 6. Same as for dog	Sedation; ataxia Paradoxical excitement/aggression Hepatopathy in some cats within days/weeks of starting PO use CRI: diazepam is inactivated by light and adsorbs onto plastic; use glass syringe and short tubing if possible Class IV controlled substance	2, 5, 10 mg T 5 mg/ml I HM
Diazoxide (Proglycem)	Hypoglycemia associated with insulinoma	5–20 mg/kg PO BID	None	Vomiting Anorexia	50 mg C 50 mg/ml S HM
Dichlorphenamide (Daranide)	Glaucoma Carbonic anhydrase inhibitor	2-4 mg/kg PO TID	Same	Weakness, lethargy, diarrhea Hypokalemia Hyperchloremic metabolic acidosis	50 mg T HM
Dichlorvos (Task) (Vapona) (DDVP)	Hook-, whip-, roundworms Flea collars and tags	27 to 33 mg/kg PO once 11 mg/kg PO once (puppies) Change collar every 4 months	11 mg/kg PO once Change collar every 4 months	Organophos-phate toxicity Do not use with constipation; intestinal obstruction; hepatic, cardiac, or heartworm disease	10, 20 mg T 68, 136, 204 mg C 136, 204, 544 mg paste VM
Dicyclomine (Bentyl)	Irritable bowel syndrome Detrusor hyperspasticity causing urge incontinence	0.15 mg/kg BID-TID PO			10 mg C 20 mg T HM
Diethylcarbamazine (DEC) (Caricide, Cypip, Filaribits)	1. Heartworm (HW) prophylaxis 2. Crenosoma lungworm treatment	1. 6-7 mg/kg SID PO, from start of HW season to 2 months after end of HW season 2. 70 mg/kg PO BID for 3 days	55-110 mg/kg PO once for ascarids	Vomiting May decrease sperm count Anaphylaxis if microfilaria positive dog	50, 60, 100, 120, 180, 200, 300, 400 mg T 60 mg/ml S Other sizes VM, HM

Diethylstilbesterol (DES)	1. Estrogen-responsive incontinence 2. Perianal gland adenoma, benign prostatic hyperplasia	1. Total dose: 0.1-1 mg per dog PO SID 2. Total dose: 0.25 - 1 mg per dog PO q 24–48 h × 2–7 days	0.05-0.1 mg/day PO	May induce signs of estrus; decrease to lowest effective dosage. High dosages may cause anemia, leukopenia, thrombocytopenia Ineffective for pregnancy termination Limited availability on US market	1, 5 mg T 50 mg/ml I Other sizes HM
Difloxacin (Dicural)	Fluoroquino-lone antibacterial	5-10 mg/kg PO SID; maximum = 30 days		GI effects, cartilage damage possible in pups Avoid in seizure patients	11, 45 mg T VM
Digoxin (Cardoxin) (Lanoxin)	Positive inotrope Negative chronotrope Negative dromotrope Baroreceptor upregulator	0.01 mg/kg PO BID; maximum dose for largest dog= 0.25 mg PO BID Can double doses for 1st 24h only	Total dose: ¼ of a 0.125 mg tablet per cat PO q 48h.	Serum levels of questionable clinical value Injectable form not recommended	0.125, 0.25 mg T 0.05 mg/ml S
Dihydrotachysterol (DHT, Hytakerol)	Hypocalcemia	0.03-0.06 mg/kg SID PO initially × 2–3 days, then 0.01-0.02 mg/kg every 24-48 h PO titrated to response	Same	Hypercalcemia Monitor serum and patient until well stabilized When stable, monitor long-term use to avoid osteopetrosis	0.125, 0.2, 0.4 mg T 0.125 mg C 0.2 mg/ml S HM
Diltiazem hydrochloride (Cardizem) (Sustained release forms: Dilacor, Cardizem CD)	Calcium channel blocking agent HCM-feline Acute supraventric-ular tachyarrhyth-mias (SVT)	0.5-1.5 mg/kg TID PO For acute SVT: 0.01–0.02 mg/kg IV initial dose; repeat as needed. Max cumulative IV dose = 1 mg/kg. May start at 0.1–0.2 mg/kg IV if heart is structurally normal.	0.7 mg/kg BID-TID PO 10 mg/kg SID PO in extended release form (ER)	Bradycardia Hypotension Anorexia ER form often causes adverse reactions (hepatic, GI) in cats	30, 60, 90, 120 mg T 120, 180, 240, 320 mg C 60, 90, 120, 240, 360, 420 mg ER HM
Dimenhydrinate (Dramamine) (Gravol)	Motion sickness	4–8 mg/kg PO up to TID	Total dose: 12.5 mg per cat PO up to TID	Lethargy-drowsiness Administer 1 hour prior to travel for best antinausea effect	80 mg T 12.5 mg/4 ml S 50 mg/ml I HM

Dimercaprol (BAL, British Anit-Lewisite)	Chelating agent Heavy metal toxicosis such as mercury and arsenic	2.5-5 mg/kg. IM. (Dose of 5 mg/kg used only in acute cases and only on first day.) Then q 4 h on days 1 and 2; q 8 h on day 3; BID for next 10 days	Same	Injections sting Caution: renal insufficiency	100 mg/ml I HM
Dimethyl sulfoxide (DoMoSo, DMSO)	1. Topical anti-inflammatory 2. Renal amyloidosis 3. CNS trauma	1. Apply solution topically BID-TID. Use 60% otic soln. BID 2. 80 mg/kg SQ EOD (dilute solution 1:4 with sterile water) 3.1 g/kg of 10% soln over 45 min IV	None	Erythema, pruritus Investigational except as otic soln. Wear gloves. Readily absorbed	90% gel T 90% soln. Topical VM, HM HM
Dioctyl sulfosuccinate (docusate, DSS, Colace, Surfak)	Stool softener	One or two 50-mg capsules q 12-24 h PO	One 50-mg capsule q 12-24 h PO	Also available as enema preparation for cats and small dogs	25, 50, 100 mg hard caplets OTC HM VM
Diphenhydra-mine HCl (Benadryl Allergy)	H1 receptor antihistamine	2-4 mg/kg BID, TID, PO 1-2 mg/kg BID IM, SC	Same Do not use IV	Sedative Anticholinergic Antiemetic Use with caution in seizure patients	25, 50 mg C, T 2.5 mg/ml S 10 mg/ml I HM
Diphenoxylate HCl with atropine (Lomotil)	Antidiarrheal Nonanalgesic opiate	0.1-0.2 mg/kg PO up to TID Total dose: 0.625 - 2.5 mg PO per dog, up to TID	0.6-1.2 mg PO BID	Sedation Constipation Ileus Use with caution in cats (opiate adverse effects)	2.5 mg T 2.5 mg/5 ml S HM
Dipyrone (Novin)	Antipyretic	25 mg/kg SQ, IM, IV up to TID	Same	Hypothermia BM suppression Do not use if hyperthermia is not true fever (contraindicated in heat stroke, brachycephalic crisis, etc)	300 mg T 500 mg/ml I HM
Disopyramide (Norpace)	Ventricular dysrhythmias Type IA agent	6–22 mg/kg TID PO	None	Rarely used May be used with quinidine or procainamide	100, 150 mg C 100, 150 mg ER HM

Dithiazanine iodide (Dizan)	Microfilaricide	6.6-11 mg/kg SID PO for 7-10 days	None	Stains stool purple V/D, anorexia	10, 50, 100, 200 mg T VM
Dobutamine HCl (Dobutrex)	Inotropic agent for cardiomyo-pathy, heart failure. Short term usage Beta1-agonist	0.0025–0.02 mg/kg/min (2.5-20 microg/kg/min) IV constant rate infusion	0.004–0.005 mg/kg/min (4-5 microg/kg/min) IV constant rate infusion	Use 48 h maximum May increase heart rate Monitor for arrhythmias Continue usual cardiac therapy Cats are very sensitive to Rx and may have seizures Doses above 0.01 mg/kg/min (10 microg/kg/min) in dogs = more likely to be arrhythmogenic	12.5 mg/ml I HM
Dolasetron (Anzemet)	Serotonin-inhibiting central antiemetic	0.6-1 mg/kg/day IV	Same	Dose extrapolated from human medicine; little supportive evidence, negative effects poorly established at this time	100 mg T HM
Dopamine HCl (Intropin)	Alpha, beta1, and dopaminergic agent Inotropic agent for heart failure Pressor agent-hypotension	0.002 – 0.008 mg/kg/min (2-8 microg/kg/min) IV CRI in LRS, 0.9% saline, or D5W	Same	Tachycardia Vaso-constriction Requires ICU monitoring Acute renal failure application no longer considered valid	40, 80, 160 mg/ml I HM
Doxapram (Dopram)	1. Respiratory stimulant 2. Diagnostic aid for laryngeal paralysis suspects	1. 5-10 mg/kg once IV Repeat if needed 2. 2.2 mg/kg IV	Same	For puppy/kitten respiratory stimulation use 1-5 drops under tongue or via umbilical vein	20 mg/ml I HM
Doxorubicin (Adriamycin)	Lymphomas Carcinomas Solid tumors	According to chemo protocol either 30 mg/m2 IV CRI once every 3 weeks (for dogs > 10 kg) or 1 mg/kg IV once every 3 weeks (for dogs <= 10 kg) Not to exceed total dose of 250 mg/m2	According to chemo protocol 20-25 mg/m2 once every 3 weeks IV CRI to max. total dose of 90 mg/m2	Anaphylaxis BM suppression Cardiotoxic Severe vesicant (extravasation injury) Use chemo precautions when handling or administering	2 mg/ml I HM

Doxycycline HCl (Vibramycin)	Tetracycline antibiotic Rickettsia, Ehrlichia, Hemo-bartonella/Ana-plasma, and Chlamydia infections Brucellosis	5 mg/kg (loading dose) PO then 2.5-5 mg/kg in 12 h, then 2.5-5 mg/kg 2 – 5 mg/kg IV CRI BID	5 mg/kg (loading dose) PO, 2.5 mg/kg in 12 h, then 2.5 mg/kg q 24 h	Do not use in puppies, kittens, or pregnant state May cause anorexia, vomiting, depression	20, 50, 100 mg T/C 5, 10 mg/ml S HM

Table • App-5 E

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Edrophonium Cl (Tensilon)	Diagnostic agent for cholinergic stimulation. Myasthenia gravis May slow some supraventricu-lar tachycardias	0.1–0.2 mg/kg IV; max = 5 mg total dose	Total dose = 0.25-1 mg IV per cat	Muscarinic signs	10 mg/ml I HM
Enalapril maleate (Vasotec) (ENA card)	ACE inhibitor Vasodilator CHF Hypertension Glomerulo-pathy	0.5 mg/kg SID PO initially, then to BID if necessary	0.25 mg/kg SID PO	Hypotension, weakness, anorexia Avoid with renal failure Avoid increasing furosemide dosage when initiating or increasing enalapril dosage	1, 2.5, 5, 10, 20 mg T 1.25 mg/ml I VM, HM
Enilconazole (Imaverol)	Nasal aspergillosis	10 mg/kg diluted with equal amount sterile water and administered intranasally via tubes placed in frontal sinuses		Not approved Possible allergic reactions	Use poultry grade product 10% emulsion
Enrofloxacin (Baytril)	Broad spectrum fluoroquinolone class antibiotic	2.5-10 mg/kg BID PO, IM Double dosage single administration per day may be equally effective	2.5–5 mg/kg PO SID (=maximum in cats)	Do not use in puppies or kittens. Causes cartilage pathology. Avoid high doses and/or long courses of treatment (risk of irreversible retinopathy).	5.7, 22.7, 68 mg T 22.7 mg/ml I VM
Ephedrine	Bronchodilator Urinary incontinence	1-2 mg/kg PO BID-TID	2-5 mg BID-TID PO	For bronchospasm: usually used in combination with sedatives and/or bronchodilators Use with caution if sympathetic drive could be harmful (heart disease, hypertension, hyperthyroidism etc.). Narrow therapeutic-toxic range	25, 50 mg C 25 mg/ml I HM

Epinephrine (adrenaline)	Alpha and beta adrenergic agent used for inotropic and chronotropic support 1. cardiac arrest 2. bronchodilation 3. anaphylaxis	1. 0.0025 mg/kg IV, repeated to effect (= 1 ml of 1:10 000 per 40 kg body weight). Triple if administering intratracheally 2, 3. 0.025 mg/kg IV, IM, SC	Same	Arrhythmogenic Increases MVO2 (avoid high doses [tachycardia]) Vasoconstric-tion Avoid direct sunlight exposure Note 1:1000 and 1:10,000 solution both commonly available	1:1000 (1 mg/ml) I 1:10,000 (0.1 mg/ml) I Epipen: 1:1000. 0.15 mg (0.15 ml) or 0.3 mg (0.3 ml) one-time dose HM
Epirubicin (Ellence) (Pharmorubicin) (4′-epi-doxorubicin)	Anthracycline antineoplastic	As for doxorubicin according to chemo protocol. e.g. 30 mg/m2 IV CRI q 21d		As for doxorubicin but with generally fewer adverse effects (esp. lesser incidence and extent of cardiotoxicity)	10, 50, 200 mg I (2 mg/ml) HM
Epsiprantel (Cestex)	Tapeworms (cesticide)	5.5 mg/kg PO once	2.75 mg/kg PO once	GI signs possible	12.5, 25, 50, 100 mg T VM
Erythromycin	1. Macrolide antibiotic GM positive drug Campylobacter, Mycoplasma, Rickettsia, Chlamydia 2. GI prokinetic	1. 10-20 mg/kg TID PO 2. 0.5–1 mg/kg TID PO	Same	Hypersensitivi-ties; G-I upsets	250, 333, 500 mg T 100 mg/ml I HM
Erythropoietin (Epoetin, Epogen, r-Hu EPO)	Recombinant human erythropoietin	100 units/kg 3 times/week SQ until RBC levels increase; then 1 time/week thereafter	Same	Anaphylaxis Hypertension G-I signs Autoantibodies may develop	2000, 3000, 4000, 10,000, and 20,000 I HM
Esmolol (Brevibloc)	Beta-blocker with very rapid onset-offset	0.05–0.1 mg/kg/min (50–100 microg/kg/min) IV CRI titrated to effect	Same	Contraindicated with bradycardia, congestive heart failure	10 mg/ml HM
Estradiol cyclopentane-propionate (ECP)	Estradiol to terminate pregnancy			Repeatedly shown to be toxic to bone marrow Unpredictable abortifacient Not recommended	
Estrogen-conjugated (Premarin)	Estrogen derived from pregnant mare serum Used for treating estrogen insufficiency post OVH causing incontinence	0.625 mg = 1.0 mg DES Use PO for urinary incontinence (see diethylstilbes-trol)		May induce signs of estrus	0.3, 0.625, 0.9, 1.25, 2.5 mg T HM

Ethanol 20%	Ethylene glycol toxicosis	Dilute to 20% ethanol in saline and administer 5.5 ml/kg IV q 4 h × 5 Rx, then q 6 h × 4 Rx	Dilute to 20% ethanol in saline and administer 5 ml/kg IV q 6 h × 5 Rx, then q 8 h × 4 Rx	May cause or exacerbate CNS depression Monitor hydration, electrolytes, acid-base status		
Etodolac (EtoGesic) (Lodine)	NSAID selective COX-2 inhibitor for DJD in dogs	10-15 mg/kg SID PO		GI and renal toxicity If long-term, use low dose Do not administer with ASA or corticosteroids	150, 300 mg VM 200, 300 mg 400, 500 mg HM	T C T
Etretinate (Tegison)	Synthetic retinoid used to treat disorders of keratinization in specific breeds (primarily cocker spaniels)	1 mg/kg PO SID	Total dose: 10 mg per cat PO SID	Vomiting; anemia KCS ↑ Liver enzymes Expensive	10, 25 mg HM	C

Table • App-6 F

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Famotidine (Pepcid)	H2 receptor antagonist	0.5-1 mg/kg SID-BID IV 0.5 mg/kg SID PO	0.5 mg/kg SID IV 0.5 mg/kg SID PO	Advantages over other similar agents: once a day dosage, minimal p450 inhibition	10, 20, 40 mg T OTC is 10 mg/tab or 20 mg/tab (extra strength) 40 gm/5 ml S 10 mg/ml I HM
Fatty acid nutritional supplement (Derm Caps)	Dietary supplement	1 regular capsule PO SID per 9 kg body weight; 1 ES capsule PO SID per 25-30 kg body weight; 1 “100's” capsule PO SID per 45 kg body weight			Regular, extra strength (ES), 100's C VM
Felbamate (Felbatol)	Antiseizure drug used when seizures are refractory to phenobarbital and bromide	15 mg/kg TID PO Can increase to 60 mg/kg as needed		Monitor for BM suppression Hepatotoxic Expensive	400, 600 mg T 600 mg/tsp S HM
Fenbendazole (Panacur)	Hook-, whip-, roundworms; Taenia; Paragonimus; Filaroides; Giardia; Capillaria	50 mg/kg/day for 3 days; repeat in 3 weeks Whipworms, also repeat in 3 months	Same Not FDA approved	Rare vomiting Safe in dogs with heartworms	222 mg/kg granules 100 mg/ml S VM

Fentanyl (Duragesic)	Transdermal opioid patch—usually lasts at least 72 hours; requires 12 hours to be effective Injectable is ultra short acting	Patches: 5–10 kg = 25 microg/hr 10-20 kg = 50 microg/hr 20-30 kg = 75 microg/hr >30 kg = 100 microg/hr Injectable: 0.01–0.04 mg/kg SC, IM, IV CRI: 0.003-0.006 mg/kg/hr (3–6 microg/kg/hr) IV	2.5 mg patch 0.005-0.01 mg/kg IV	Apply patch to a small clipped area on thorax Respiratory depression and hypoventilation Never cut patch Prevent human contact with gel surface of patches	2.5 mg (25 microg/h), 5 mg (50 microg/h), 7.5 mg (75 microg/h), 10 mg (100 microg/h) Patch 0.05 mg/ml (50 microg/ml) I HM Former VM injectable (Innovar) was 8× more concentrated than human injectable; do not confuse
Fenthion (Prospot) (Spot-on)	Organophosphate for flea control	4-8 mg/kg topically to unbroken skin. Follow instructions. Do not apply more than once every 2 weeks	None	Do not use with other cholinesterase inhibiting agents Do not use in puppies or sick or debilitated dogs	5.6 and 13.8% soln. VM
Ferric cyanoferrate (Prussian blue) (Radiogardase)	Thallium poisoning	100-200 mg/kg PO TID		Administer as capsule or in a glucose solution orally Constipation; vomiting	500 mg C HM
Ferrous sulfate	Iron supplemen-tation	Total dose: 100-300 mg per dog SID PO	Total dose: 50-100 mg per cat SID PO	Common side-effect: minor GI upset Overdose: severe GI signs, hypotension, collapse; delayed toxicity = pulmonary edema, liver failure. See deferoxamine.	325 mg (65 mg Fe) T 18, 44 mg Fe/ml S HM OTC
Filgrastim (Neupogen, r-Hu G-CSF)	Recombinant human granulocyte colony stimulating factor. Used for chemotherapy-induced neutropenia	1-5 microg/kg/day SQ × 3-5 days max.	1-5 microg/kg/day SQ × 3-5 days max.	Antibodies develop after several days of therapy	300 microg/ml I HM

Finasteride (Proscar)	Used for treating benign prostatic hypertrophy by inhibiting enzyme that changes testosterone to active dihydroxytes-tosterone	Total dose: 5 mg per dog (body weight 10-40 kg) SID PO		Little known about use, efficacy, or side-effects in canine medicine	5 mg T HM
Fipronil (Frontline)	Topical parasiticide for fleas and some ticks	9.7% solution Apply topically by weight once monthly	Same	Keep away from children, food, water; avoid contact with pet if fipronilis still wet on skin Use on puppies only if >10 weeks old, kittens if >12 weeks old	9.7% solution 0.29% spray VM
Fluconazole (Diflucan)	Imidazole antifungal compound–especially useful for cryptococcus or CNS/ocular mycoses	2.5-5 mg/kg PO SID or divided BID	Same; up to 50 mg BID	Expensive but also available as generic now; loading dosage first day is 2x	50, 100, 200 mg T 2 mg/ml I HM
Flucytosine (Ancobon) (Ancotil)	Aspergillosis Cryptococcus	100 mg/kg BID PO or ½ dose QID	Same	Renal, bone marrow, and hepatotoxicity. May cause G-I upset. Do not administer to pregnant animals	250, 500 mg C 75 mg/ml S HM
Fludrocortisone (Florinef)	Hypoadreno-corticism Mineralocorticoid replacement therapy	0.1 mg/5 kg/SID or BID PO. Adjust dosage by need and laboratory testing	0.1 mg/5 kg/day PO Adjust dosage by need and laboratory testing	Hypertension PD/PU Weight gain	0.1 mg T HM
Flumazenil (Romazicon)	Benzodiazepine antagonist Management of hepatoencephalopathy	0.1-0.2 mg/kg IV	Same		0.1 mg/ml I
Flumethasone (Flucort)	Anti-inflammatory Corticosteroid	Total dose: 0.06-0.25 mg SID per dog PO, IV, IM, SQ	Total dose: 0.03-0.125 mg SID per cat PO, IV, IM, SQ	Cortisone related side effects	0.0625 mg T 0.5 mg/ml I VM
Flunixin meglumine (Banamine)	Nonsteroidal anti-inflammatory analgesic agent	0.25-1.0 mg/kg SID IV, IM, SQ, PO Maximum 3-5 days dosage	0.25 mg/kg SID IV, IM Maximum 3-5 days dosage	Platelet coagulopathy Ulcerative gastritis; risk often outweighs benefit of use Use with extreme caution Use 3-5 days only Not licensed for small animal use	50 mg/ml I HM
Fluocinolone 0.01% with 60% DMSO (Synotic)	Topical steroid plus DMSO for serious otic infection and inflammation	2-12 drops BID	2-4 drops BID	Systemic steroid effects Wear gloves (to avoid transcutaneous absorption by owner/vet)	0.1% otic soln VM

Fluorouracil (Adrucil)	Chemotherapy agent for carcinoma or sarcomas	150 mg/m2 IV weekly; or, 2-10 mg/kg IV weekly	Do not use	Part of a chemotherapy protocol Bone marrow toxicity, GI toxicity, and neurotoxicity possible	50 mg/ml I HM
Fluoxetine (Prozac)	Serotonin reuptake inhibitor	0.5-2 mg/kg SID PO	1.0 mg/kg SID PO	Used to treat behavioral disorders; lick granuloma Efficacy uncertain	10, 20 mg C 4 mg/ml S HM
Fluticasone (Flovent)	Inhaled glucocorticoid	1 puff as needed up to SID-BID	Same	Need inhaler apparatus; some patients reluctant to use mask. Maximum effect only after 7-14 d of use See chapter for discussion of use of mask in cats	7.9 and 13 g inhalation canisters (0.044, 0.11, or 0.22 mg [44, 110, or 220 microg] per puff) HM
Folate	B vitamin	Total dose: 2.5–5 mg PO per dog SID	Total dose: 2.5 mg PO per cat SID		5 mg/ml I 5 mg T HM
Fomepizole (Antizol-Vet, 4-methylpyrazole, 4-MP)	Treatment of known or suspected ethylene glycol toxicity	22 mg/kg IV then 15, 15, & 5 mg/kg IV at 12, 24, & 36 h following initial dose, then 3-5 mg/kg IV until recovery		Dilute drug properly Monitor renal, electrolyte, and hydration status	1.5 g kit I VM, HM
Furazolidone (Furoxone)	1. Amebiasis 2. Enteric coccidiosis 3. Giardiasis	1. 2.2 mg/kg TID PO 7 times 2. 8-20 mg/kg PO 7 times 3. 4 mg/kg BID PO 7 times	Same		100 mg T 3.3 mg/ml S HM
Furosemide (Lasix, Salix)	Potent loop diuretic agent Used in acute renal failure; hypercalcemia; hypertension, CHF, ascites, and fluid retention	0.5-6 mg/kg BID-TID PO, SQ, IM, IV	0.5-4 mg/kg BID-TID PO, SQ, IM, IV	Use lowest effective dosage High doses reserved for IV use in acute severe pulmonary edema Monitor for hypokalemia; hyponatremia; and hypochloremic-alkalosis Caution: azotemia and dehydration	12.5, 20, 40, 50, 80 mg T 10 mg/ml S 50 mg/ml I VM HM

Table • App-7 G

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Gemcitabine (Gemzar)	Various forms of neoplasia	10 mg/kg IV CRI over 30 minutes 275 mg/m2 IV CRI	25 mg/m2 diluted and given IV slowly twice weekly according to chemo protocol	Very new drug in veterinary oncology, with dosage, efficacy, and side-effects poorly characterized at this time	200 mg, 1g vials I VM, HM
Gemfibrozil (Lipid)	Lipid-lowering agent	7.5 mg/kg PO BID			300, 600 mg T HM
Gentamicin (Garamycin) (Gentacin)	Broad spectrum aminoglycoside antibiotic most effective against Gram negative bacteria	6 mg/kg IV SID or 2-4 mg/kg TID, IM, SQ, IV	Same	Higher dosage given SID is preferred (less nephrotoxic) Not effective orally Do not use in renal failure or dehydrated/hypovolemic patients Reserved for serious identified infections only Not for anaerobic infections Nephrotoxic-ototoxic	50 mg/ml I VM, HM
Gentamicin otic (Gentacin otic)	Ear infections, especially Pseudomonas or Proteus	Apply TID	Apply TID	Ototoxic	3 mg/ml otic soln. VM, HM
Gentamicin ophthalmic (Gentacin)	Conjunctival/corneal infections, especially Pseudomonas	Apply q 4-8 h	Apply q 4-8 h	Rarely irritating Also made with steroids in nearly identical packaging; use with extreme caution	3 mg/g OO 3 mg/ml OS VM, HM
Glipizide (Glucotrol)	Oral hyperglycemic agent Useful in some type II diabetes mellitus in cats	0.25-0.5 mg/kg PO BID Generally not recommended	0.25-0.5 mg/kg PO BID	Hypoglycemia G-I effects Hepatopathy Loss of efficacy	5, 10 mg T HM
Glucagon	Provocative testing agent for insulinoma, diabetes mellitus, and hyperadreno-corticism	0.03 mg/kg IV	None	May induce hypoglycemia 1 unit = 1 mg	1 mg/ml I HM
Glucosamine chondroitin sulfate (Cosequin)	Chondro-protective agent for osteoarthritis	Small and medium-size dogs: 1 – 2 RS capsules PO SID Big dogs: 1-2 DS capsules PO SID or 2–4 RS capsules PO SID	1 RS capsule PO SID		Regular strength (RS) and double strength (DS) C VM

Glycerin suppositories	Constipation	1 suppository per rectum	Same or 3 ml liquid per rectum		OTC, HM
Glycopyrrolate (Robinul)	Anticholinergic preanesthetic agent	0.01 mg/kg SQ, IM, IV	Same	Tachycardia, arrhythmias, intestinal ileus, mydriasis, and photophobia	0.2 mg/ml I VM, HM
Glycosaminoglycan-polysulfated (Adequan)	Chondroprotective agent +/- healing of noninfectious, degenerative, and traumatic arthritis	2-4 mg/kg IM twice weekly for 4 weeks; then every 2-4 weeks	2 mg/kg IM q 4 days × 6 doses; then as needed	Occasional pain at injection site Inhibits coagulation	100 mg/ml I VM
GoLYTELY	Large bowel evacuant/cathartic	22 –33 ml/kg via stomach tube	20-30 ml/kg by stomach tube	Withhold food Administer twice 2 hours apart prior to scope procedure	Pwdr or conc for dilution HM
Goodwinol	Demodecosis (localized)	Apply topically SID	Same	Rotenone, orthophenyl phenol, and benzocaine mixture; efficacy not demonstrated	1.25% Rotenone O VM
Griseofulvin (Fulvicin)	Dermatophytoses	50-150 mg/kg PO SID-BID; 25-50 mg/kg SID if using microsize product (U/F); 5-15 mg/kg BID PO if using ultramicrosize product (P/G)	Same	U/F prep better absorbed than regular-decrease dosage by 50% for this formulation; P/G even more so—decrease dosage by further 30% G-I signs Teratogen Granulocytopenia Hepatopathy	125, 250, 500 mg T 250, 500 mg microsize formulation T 125, 165, 250, 330 mg ultramicrosize formulation T 125 mg/5 ml S VM/HM

Table • App-8 H

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Hemoglobin glutamer (Oxyglobin)	Bovine hemoglobin based oxygen carrying fluid. Used to treat hemolytic, blood loss, or ineffective erythropoietic anemias	10-30 ml/kg IV @ 10 ml/kg/hr in a one time single infusion. Some administer partial dosages daily instead	Not licensed Used IV by some at 15 ml/kg IV in a slow single dose or daily split doses	Overdosage may cause cardiopulmonary signs Hemoglobinuria Has no clotting factors Interferes with clin pathol testing Half life in vivo = 18 – 43 hours	125 ml I Single use bags VM
Heparin	1.Anticoagulation 2. DIC therapy	1. 200-300 IU/kg TID-QID SQ or IV for thromboembolism; ↑ PTT to 1.5-2.5× normal or ACT to 1.2-1.4× normal. 10 IU/kg TID SQ (minidose therapy for ITP). 2. 50-100 IU/kg SQ TID-QID.	5-10 IU/kg CRI. 75-150 IU/kg TID-QID SQ	Prolongs bleeding time Not thrombolytic	1000, 2000, 5000, 10,000, 20,000 40,000 mg/ml I HM
Hetacillin (Hetacin)	Similar to penicillin	10-20 mg/kg TID PO	Same	Penicillin reactions	50, 100, 200 mg T VM
Hetastarch 6% (Hespan)	Colloid and plasma volume expansion Shock; sepsis, head trauma	10-20 ml/kg/day IV	10-15 ml/kg/day IV	Rapid IV bolus initially over 5-10 min Titrate crystalloids slowly	500 ml pkg of 6% hetastarch in 0.9% NaCl I HM
Hydralazine (Apresoline)	Arteriolar vasodilator	0.5-3 mg/kg PO BID-TID	1.25-2.5 mg/kg PO BID	Hypotension, tachycardia Malaise, depression Anorexia	10, 25, 50, 100 mg T 20 mg/ml S HM
Hydrochlorothiazide (HydroDIURIL)	Diuretic Nonhormonal therapy for CDI and NDI	2-4 mg/kg PO BID initially; then decrease by 50% or to SID	1-2 mg/kg PO BID initially; then decrease by 50% or to SID	Hypokalemia Exacerbates digitalis tox Dehydration	25, 50, 100 mg T HM

Hydrochlorothiazide/spironolactone (Aldactazide)	Diuretic plus aldosterone inhibitor (combination for humans— best to separate in VM)	Use on basis of 1 mg/kg of spironolactone SID-BID orally	Rarely used	Often used in conjunction with furosemide in chronic, recurrent CHF	25/25 mg T 50/50 mg T HM
Hydrocodone bitartrate (Hycodan)	Narcotic antitussive	0.22 mg/kg SID-QID PO	Rarely used	Sedation C-III substance	5 mg T 1 mg/ml S VM, HM
Hydrocortisone acetate 1% cream	Topical corticosteroid for focal dermatitis	Apply topically BID-QID	Same	Prolonged usage may result in iatrogenic Cushing's syndrome	1% O HM
Hydrogen peroxide	Emetic	0.25 – 0.5 ml/kg PO (3% solution). Repeat once in 5 - 15 minutes PO if emesis does not occur	Same	Do not use if a caustic agent was ingested; if level of consciousness is decreased; or if unable to swallow	3% topical HM
Hydromorphone (Dilaudid)	Analgesia; preanesthetic	0.1 – 0.2 mg/kg SQ, IM, or IV once or PRN up to q 2-4h. Reduce slightly in older dogs	Same	Vomiting common immediately post injection; bradycardia; dysphoria in some cats	1, 2, 4, 10 mg/ml I HM
Hydroxyurea (Hydrea)	Chemotherapeutic compound Disorders of RBC excess, especially polycythemia vera and right-to-left cardiac shunts	20-25 mg/kg SID-BID PO; when PCV ↓, then 25 – 50 mg/kg EOD PO	10-15 mg/kg SID PO then EOD based on PCV	Anorexia, vomiting. Monitor CBC regularly	500 mg C HM
Hydroxyzine (Atarax)	H1 receptor antihistamine for allergic skin disorders	1-2 mg/kg BID-TID PO	0.5-1 mg/kg BID-TID PO	Sedative	10, 20, 50, 100 mg T 10 mg/5 ml S 20, 50 mg/ml I HM

Hyoscyamine (Levsin)	Inhibits acetylcholine Inhibits propulsive G-I motility	0.003-0.006 mg/kg TID PO	Same—infrequently used	Useful in IBS and functional intestinal disorders Dry mouth; urinary retention; tachycardia	0.125 mg T 0.125 mg/5 ml S 0.375 mg ER 0.5 mg/ml I HM

Table • App-9 I

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Idoxuridine (Herplex) (Stoxil)	Used for treating feline herpes keratoconjunctivitis		1 drop q 4 h initially; then q 6-8 h	Occasional ophthalmic irritation	0.1% OS HM
Ifosfamide (Ifex)	Various neoplasms	350-375 mg/m2 IV once q 3 weeks for 3 treatments max		Efficacy under investigation; dosing interval according to chemo protocol; pretreat with mesna and IV diuresis to reduce risk of hemorrhagic cystitis Neutropenia	50 mg/ml I
Imidacloprid (Advantage)	Topical treatment for adult and larval stage of fleas	Apply topically to intact skin Dose monthly by body weight from prepackaged cards	Same	Avoid contact with skin, food, or water	9.1% VM
Imidocarb (Imizole)	Babesia gibsoni and canis Ehrlichia canis Hepatozoonosis	5-7.5 mg/kg IM or SQ once Repeat in 2-3 weeks		Painful injection—give IM Cholinergic effects	120 mg/ml I VM
Imipenem (Primaxin)	Broad spectrum bactericidal-static carbapenem antibacterial	2-10 mg/kg slow IV (over 30 minutes) TID – QID × 3–5 days	Same	Adverse effects possible: GI, CNS, hypersensitivity; reduce dose if renal compromise	250, 500 mg vials I HM
Imipramine (Tofranil)	Tricyclic antidepressant Behavioral changes, narcolepsy, cataplexy	0.5-2 mg/kg BID-TID PO	0.5 mg/kg SID-BID PO or total dose 2.5-5 mg per cat BID PO	Drowsiness; behavioral changes	10, 25, 50 mg T 125 mg/ml I HM
Immunoglobulin (Gammagard S/D)	Treatment of primary immunodeficient states; also IMHA, ITP, and CLL	0.5-1.5 g/kg slow IV infusion		Must be given IV Very expensive Hypersensitivity Not rec'd as 1° therapy	2.5, 5, 10 g single dose vials I HM

Insulin (Humulin R, N, U) (PZI)	1. Diabetes mellitus 2. Diabetic ketoacidosis 3. Severe hyperkalemia 4. Alternatively and preferably, regular insulin in the ketotic state should be given hourly or by CRI	REGULAR: 0.25-0.5 U/kg initially IM or SQ; then q 4-6 h NPH: 0.5-1.0 U/kg SID–BID SQ All insulins may be diluted with diluents provided by drug company for more precise administration of small doses Hourly 0.2 u/kg followed by 0.1 u/kg. Can be decreased by 25-50% if low K+ a concern. Constant low dose infusion: 2.2 u/kg added to 250 ml 0.9% NaCl given at 10 ml/hr to equal 0.1 u/kg/hr	NPH: total dose (starting): 1-2 U per cat SQ SID-BID. LENTE, ULTRALENTE, PZI: total dose 1-3 U per cat SQ SID–BID Same in the cat as in the dog for hourly IM administration 1.1 u/kg added to 0.9% NaCl given at 10 mg/hr to equal 0.05 u/kg/hr	Dosage very variable—adjust and monitor accordingly These are average approximate dosages Maintain hydration Avoid hypoglycemia and hypokalemia See Chapter for information about chronic use; BID Rx: additional information	100 U/ml I HM, VM I
Interferon (Roferon)	Immune modulator with antiviral and antiproliferative effects Used for FELV-FAIDS; Leukemia; Lymphoma; FIP	1 IU/5 kg body weight PO every 2 weeks to stimulate appetite	Total dose: 30 IU per cat PO 7 days on; then 7 days off	Studies uncontrolled Used mostly in FeLV+ cats	3, 18, 36 million IU per vial I HM
Ipecac syrup	Induce vomiting	0.25 – 0.5 ml/kg PO; can repeat once after 5-15 minutes if no vomiting	Same	Do not use with activated charcoal (ineffective)	70 mg/ml S OTC, HM Many oral OTC 50 mg/ml I HM
Ipodate (Oragrafin)	Oral radiographic contrast agent with antithyroid effects; used for hyperthyroidism		Total dose: 15-100 mg per cat PO BID, titrated based on clinical response and T3	Blocks T4 conversion to T3; therefore, blood monitoring = serum T3 levels	500 mg C HM
Iron-dextran injection (Imferon)	Iron deficiency anemia	10 mg/kg in divided doses IM or total dose 100-300 mg/day per dog PO	Same-IM or total dose 50-100 mg/day per cat PO	Irritating IM	Many oral OTC 50 mg/ml I HM
Isoproterenol (Isuprel)	B-adrenergic agonist	0.2 mg in 250 ml 5% dextrose, IV CRI at a rate of 0.05-0.1 microg/kg/min; titrate to effect adequate HR	0.5 mg in 250 ml 5% dextrose, IV to effect adequate HR	↑HR ↑ or ↓ BP CNS stimulation Arrhythmogenic	0.2 mg/ml (=200 microg/ml) I HM

Isosorbide dinitrate	Oral vasodilator			No recognized therapeutic efficacy in small animals	
Isotretinoin (Accutane)	Sebaceous adenitis Keratinization disorders Mycosis fungoides	1-2 mg/kg BID PO Reduce dosage after 1 month if improving	Total dose: 5-10 mg SID per cat PO	GI and CNS effects may occur; if so, reduce dosage by 50% or stop Teratogen	10, 20, 40 mg C HM
Itraconazole (Sporanox)	Antimycotic imidazole compound for blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, M. canis dermatophytosis	5-10 mg/kg SID-BID PO	5-10 mg/kg SID PO 1.5-3.0 mg/kg SID PO	Must be taken with food; open capsules and place pellets in food if necessary. Antacid GI drugs will reduce efficacy	100 mg C 10 mg/ml S HM
Ivermectin (Heartgard-30) (Ivomec)	GABA agonist antiparasiticide Heartworm prophylaxis; microfilariacide	Heartworm prophylaxis: 0.006 mg/kg (6 microg/kg) PO once monthly Microfilaricide: 0.05 mg/kg (50 microg/kg) once PO 2-4 weeks post adulticide Rx	Heartworm prophylaxis: 0.024 mg/kg (24 microg/kg) SQ; repeat in 3-4 wks (usually under 0.1 cc)	Do not use in collies or other dogs hypersensitive to drug CNS; vomiting; anaphylaxis Can give injectable solution PO Of ? value in treating feline heartworm disease; see Chapter 207 for suggestions	68, 136, 272 microg T 10 mg/ml (=10,000 microg/ml) I VM
	Endoparasites Sarcoptic mange	0.2 mg/kg (200 microg/kg) PO 0.3 mg/kg (300 microg/kg) PO or 0.2 mg/kg (200 microg/kg) SQ 2x-14 days apart	Same Same		
	Demodectic mange	0.05 mg/kg (50 microg/kg) PO; increase to 0.3 mg/kg (300 microg/kg) by day 5; increase to 0.6 mg/kg (600 microg/kg) once daily PO after 30 days if necessary	Same		
	Otodectic mange	0.3 mg/kg (300 microg/kg) PO, SQ 2x–14 days apart	Same		

	Cheyletiellosis	0.3 mg/kg (300 microg/kg) SQ 2x–21 days apart	Same		

Table • App-10 K

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Kaolin/pectin	G-I tract protectant	1-2 ml/kg every 2 to 6 hrs PO	Same	May limit absorption of other Rx May constipate	Many OTC preparations T/S VM, HM
Ketamine HCl (Ketamine) (Ketaset) (Vetalar)	Dissociative analgesic anesthetic agent Short-action when given IV in healthy dogs/cats— 10-20 min	When diazepam (at dose of 0.5 mg/kg) given IV first: immediately follow with ketamine 5-7 mg/kg IV bolus for sedation and minor procedures (diazepam [5 mg/ml]: ketamine mixture in ratio of 1:1 or 2:1 → use 1 ml/10 kg IV)	Restraint: 11 mg/kg IM Anesthesia (but does not provide deep analgesia): 22-33 mg/kg IM or 2.2-4.4 mg/kg IV	Eyes remain open → use ophthalmic ointment Salivation, seizures, respiratory depression, laryngospasm, hypothermia Do not use in renal failure or glaucoma; reduce dose by 50-75% if stable but systemically ill; avoid if hypertrophic cardiomyopathy	100 mg/ml I VM, HM
Ketoconazole (Nizoral)	Antifungal agent Prototheocosis Inhibits adrenosteroid hormone synthesis	10–15 mg/kg BID PO Long term 10 mg/kg SID PO Cushing's Rx: 15 mg/kg BID PO	5 - 10 mg/kg BID PO or SID Long term: 10 mg/kg EOD PO	Anorexia, nausea, vomiting, constipation Hepatotoxicity Begin lower and titrate upwards to avoid side effects; must be given with food	200 mg T HM
Ketoprofen (Orudis KT; Ketofen)	Nonsteroidal anti-inflammatory	1-2 mg/kg PO BID 1 – 2 mg/kg SQ, IM, or IV once or SID up to 3 days max.	1 mg/kg SQ, IM, IV once	GI ulceration Renal effects possible	25, 50, 75 mg C 12.5 mg T HM OTC 10, 100 mg/ml I VM
Kitten Milk Replacer® (KMR)	Milk replacement	–	30 ml/1/4 lb BW PO daily divided into 3-6 meals	–	OTC VM

Table • App-11 L

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Lactulose (Cephulac, Chronulac)	Stool softener	0.25-0.5 ml/kg BID-TID PO	Total dose: 1-5 ml per cat TID PO	Loosens stools; diarrhea; flatulence; cramping	666 mg/ml S HM
	Hepatic encephalopathy is treated by acidifying colon contents, trapping NH4 that is then expelled	20 ml/kg as a retention enema; 3 parts lactulose plus 7 parts water		May use per rectum in hepatic coma patients	
Laxative paste (Laxatone, Cat-a-Lax, etc.)	Oral laxative Hairball RX	½-2 inches PO daily until nonconstipated; then weekly or as required	Same	Large amounts daily could result in malabsorption, therefore avoid giving oral Rx simultaneously	OTC S VM
Leflunomide (Arava)	Autoimmune disorders (IMHA, ITP, sterile meningitis, systemic histiocytosis)	1.5- 4 mg/kg PO SID		New agent; beneficial and adverse effects sparsely documented to date; GI and bone marrow effects possible Seek trough serum level of 20 microg/ml	10, 20, 100 mg T HM
Levamisole (Levasole) (Ripercol) (Tramisol)	Heartworm microfilaricide Immune stimulant Feline lungworms	10 mg/kg PO SID 7-14 days as a microfilaricide 2.5-5 mg/kg PO EOD for immune modulation	2.5-5 mg/kg PO EOD for immune modulation 10-20 mg/kg PO EOD for Aleurostrongylus and Capillaria	Salivation, vomiting Neurotoxic Sudden death Not FDA approved for small animal medicine	184 mg T 136 mg/ml S 11.5% gel VM
Levetiracetam (Keppra)	Third-line anticonvulsant for refractory seizures	20 mg/kg PO TID in addition to KBr and phenobarbital		Clinical vet use very new; few adverse effects reported Can up titrate if starting dose ineffective Expensive	500 mg T HM

Levothyroxine sodium (Soloxine) (Synthroid)	Synthetic thyroid hormone replacement therapy	0.04 mg/kg BID PO	Total dose: 0.05-0.1 mg per cat SID PO	Thyrotoxicosis Do not give only on basis of low T4 (clinical signs and other lab results). Adjust dose based on response and blood levels	0.025, 0.05, 0.075, 0.125 0.15 mg T HM 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.8 mg T VM
Lidocaine (Xylocaine)	Ventricular arrhythmias Local anesthesia	2-4 mg/kg IV over 1-2 minutes, then 0.5-2 mg/kg every 20-60 minutes, or 0.04–0.08 mg/kg/minute (40-80 microg/kg/minute) constant rate IV infusion Inject up to 4 mg/kg SQ for local anesthesia	0.25-1.0 mg/kg slowly over 5 min; give 1 mg bolus to 4 mg, max over 5 min; use diluted solution as CRI 0.01–0.04 mg/kg/minute (10-40 microg/kg/minute)	Give initial bolus **slowly** Seizures, hypotension Maintain current IV indwelling catheter **Use only in life-threatening arrhythmias**	10, 20 mg/ml I HM
Lime sulfur solution (Lym Dyp) (Sulfodip)	Bacterial and fungal dermatosis Sarcoptic mange	Dip once-twice weekly, let air dry; use 4-6 weeks (ideally until 2-3 fungal cultures are negative)	Same	Offensive odor Stains furniture Wear gloves to avoid hypersensitivity	2% dip VM
Lincomycin (Lincocin)	Staphylococcal and anaerobic infections Some Mycoplasma infections	15-25 mg/kg BID-TID PO, IV, IM	Same	Vomiting Hepatotoxicity Do not use in combination with chloramphenicol or erythromycin	250, 500 mg T HM 100, 200, 500 mg T 50 mg/ml S 100 mg/ml I VM
Liothyronine, T3 (Cytobin) (Cytomel)	T3 suppression testing	0.004–0.006 mg/kg (4-6 microg/kg) TID PO	0.0044 mg/kg (4.4 microg/kg) BID-TID PO 0.025 mg (25 microg) PO per cat TID for 8 dosages as testing agent for T3 suppression	Thyrotoxicosis	5, 25, 50 microg T HM
Lisinopril (Zestril) (Prinivil)	Angiotensin converting enzyme inhibitor	0.75 mg/kg SID PO	0.25 mg/kg SID PO	Monitor BUN/CR Lethargy Anorexia	2.5, 5, 10, 20, 40 mg T HM
Lithium carbonate (Eskalith, Lithotabs)	Increased production of all cell lines by bone marrow	21-26 mg/kg/day PO	Unknown	Nausea, diarrhea, vertigo	300 mg C 450 mg ER HM

Lomustine (CCNU-Cee Nu)	Nitrosourea alkylating agent for relapse or failure to respond to LSA therapy	60-90 mg/m2 PO once every 3 weeks		Neutropenia may develop after 7 days; GI adverse effects Its active metabolites reach the CNS	10, 40, 100 mg C HM
Loperamide (Imodium)	Antidiarrheal, acute colitis	0.1-0.2 mg/kg TID PO	0.1-0.15 mg/kg BID PO	Discontinue if not effective within 48 h	OTC 2 mg C 1 mg/5 ml S HM
Lufenuron (Program)	Insect development inhibitor Inhibits chitin synthesis 1.Prevents flea eggs from developing into adults 2. Coccidioidomyosis 3. dermatophytosis	1. 10 mg/kg PO once q 30 days 2. 5-10 mg/kg PO SID 3. 54–68 mg/kg PO once	1. 30 mg/kg PO 1 ×/month or 10 mg/kg once every 6 mo by SQ injection 3. 51–266 mg/kg PO once	Expensive as long term daily Rx for fungal disease; efficacy in dermatophytosis questionable May be combined with milbemycin for control of fleas, heartworms, roundworms, and whipworms	Sold in packets for varying wt. By tablet, S Solution, or 10 mg/ml T inject. I

Table • App-12 M

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Magnesium hydroxide (Milk of Magnesia)	Antacid	Total dose: 5-10 ml per dog PO q 4–6 hrs		Cathartic agent at 3-5 times the antacid dosage Rarely used because high dosing frequency and rebound acid secretion	77.5 mg/g S OTC HM
Mannitol 20%	Osmotic diuretic used to treat acute glaucoma, cerebral edema, and oliguria/anuria	0.5-1 g/kg IV slowly over 15-20 minutes for anuria. Double dosage for acute glaucoma or cerebral edema	Same	Rehydrate patient prior to use Can repeat twice if renal output is not increased Resolubilize (by warming) if crystallized, ensuring to cool to body temp before administering	100 mg/ml (10%), 200 mg/ml (20%) I HM
Marbofloxicin (Zeniquin)	Fluoroquinilone class antibiotic	2– 4 mg/kg SID PO	Not Licensed	Anorexia and vomiting Not rec'd for rapidly growing dogs due to possible arthropathy	25, 50, 100, 200 mg T VM
Mebendazole (Telmintic)	Hook-, whip-, and roundworms	22 mg/kg with food once daily for 3 days		Repeat as indicated V/D may develop Hepatopathies have been incriminated in a small number of cases	VM
Meclizine (Bonine, Dramamine II, Antivert)	Antiemetic	1.25 mg/kg PO SID		Lethargy, CNS depression possible	12.5, 25, 50 mg T OTC HM
Medetomidine (Domitor)	Synthetic alpha-2 adrenoreceptor agonist. Provides sedation-analgesia as chemical restraint for healthy exercise tolerant dogs. Useful for sedation of cats with hypertrophic cardio-myopathy	0.005–0.02 mg/kg (5–20 microg/kg) IM as a single agent. Used by some in association with butorphanol, ketamine, morphine, or oxymorphone	0.02 mg (20 microg/kg) IM	Do not use if hypertensive Allow dog or cat to rest quietly after admin Do not use in older, sick, or debilitated dogs Reversed with equal volume of atipamezole Reflex brady-cardia is result of drug-induced hypertension; do not treat with atropine or other anti-bradycardiac drugs	1 mg/ml I VM
Medium chain triglycerides (MCT oil)	Used in protein losing diseases–lymphangiectasia; and when long-term triglyceride intake should be reduced-chylothorax	1-2 ml/kg daily in food	Same	May be distasteful Efficacy not demonstrated	OTC HM

Medroxy progesterone acetate (Depo-Provera, Provera)	Long acting progesterone compound used for decreasing male dog libido and aggression, rarely as a contraceptive; in cats for psychogenic and military dermatitis and inappropriate elimination	10-20 mg/kg IM, SQ every 4 months	Total dose: 50-100 mg per cat IM, SQ every 4 months	Overdosage may cause cystic endometritis, diabetes mellitus, hypoadreno-corticism, mammary hyperplasia/adenocarcinoma Local alopecia may occur Carefully weigh risks versus benefits	T2.5, 5, 10 mg T 150, 400 mg/ml I HM
Megestrol acetate (Ovaban, Megace)	Oral progestogen used for delaying estrus; treat K-9 pseudopregnancy; canine and feline behavioral modification eosinophilic granuloma and some chronic feline skin disorders	Anestrus Rx: 0.5 mg/kg PO × 32 days Proestrus Rx: 2.0 mg/kg PO × 8 days Behavior modification: 2-4 mg/kg SID PO for 14 days; then decrease and stop after 6 weeks	Total dose: 5-10 mg SID per cat PO × 7 days; then twice weekly. Same dose as for dog for behavioral modification	See specific diseases. Do not use in pregnant pets or pets with uterine problems Avoid use with mammary tumors or hyperplasia May cause polydipsia, polyuria, polyphagia, diabetes mellitus	5, 20 mg T VM 20, 40 mg T HM
Melarsomine (Immiticide)	Arsenical for treatment of adult heartworms	2.5 mg/kg SID IM for 2 doses 24 hours apart or 1 dose; then, 30 days later 2 dosages IM 24 hr apart	None	Painful—give in epaxial muscles Cellulitis or salivation may occur PTE occurs when worms die	50 mg/vial I VM
Meloxicam (Metacam) (Mobic)	COX-2-inhibiting nonsteroidal anti-inflammatory drug (NSAID). For treatment of osteoarthritis; perioperative pain management	0.1 mg/kg PO, SC SID (may be preceded by single 0.2 mg/kg loading dose PO, SC, IV)	Chronic use: 0.025 mg/kg PO SID (can be preceded by peri-operative dose below as loading dose). Peri-operative pain control: 0.3 mg/kg PO, SC, IV once only	Gastrointestinal signs (vomiting, anorexia)	1.5 mg/ml (=0.05 mg/drop) S 5 mg/ml I VM 7.5, 15 mg T HM
Melphalan (Alkeran)	Multiple myeloma Lymphoreticular neoplasms Alkylating agent	0.1 mg/kg SID PO for 10 days; then 0.05 mg/kg SID PO; or 1.5 mg/m2 PO SID for 7-10 days or 7 mg/m2 SID × 5 days q 3 weeks	Same	Anorexia, nausea, vomiting Leukopenia, thrombo-cytopenia, and anemia	2mg T HM
Meperidine HCl (Demerol)	Narcotic analgesic with short term (1-4 hrs.) effect	5-10 mg/kg IM or slow IV PRN	2-4 mg/kg IM PRN	Watch for signs of narcotic overdosage, i.e. sedation, depression, seizures, hypotension Reverse with naloxone	50, 100 mg/ml I 50, 100 mg T 10 mg/ml S HM

Meropenem (Merrem IV)	Carbapenem antibiotic	8 mg/kg SQ BID		Clinical vet use very new; efficacy and side-effects sparsely reported at present	500, 1000 g vials I HM
Mesalamine (5-ASA) (Asacol) (Pentasa)	Inhibits prostaglandin production in the colon Irritable bowel syndrome; ulcerative colitis	10-20 mg/kg TID PO		Clinical vet use limited; efficacy unproven at present Monitor for KCS May be infused rectally (enema formulations)	400 mg T 250 mg C 4 g/60 ml enema HM
Mesna (Mesnex)	Urothelial protection preceding ifosfamide chemotherapy	Dose is 20% of ifosfamide dose		Administered as pretreatment before ifosfamide: reconstitute as 20 mg/ml and give calculated dose as IV bolus, followed by 9 ml/kg 0.9% NaCl IV over 30 minutes, then ifosfamide	100 mg/ml I HM
Methimazole (Tapazole)	Feline hyperthyroidism Palliative Rx for canine functional thyroid neoplasia	Total dose 2.5-5 mg BID per dog PO	Total dose 2.5-5 mg PO per cat BID-TID	Anorexia, vomiting, and blood dyscrasias; intense facial pruritus Monitor CBC and T4 Start at ½ dosage—then increase after 7-10 days based on clinical response and T4 level	5, 10 mg T HM
DL-Methionine (Methigel) (Albeta)	Urinary acidifier	0.2-1 g/kg TID PO	0.5-1 g SID PO	Contraindicated if renal failure, acidosis, pancreatic disease, hepatic insufficiency/encephalopathy. G-I irritability	15 mg/ml S 200, 300, 500 mg T,C OTC, VM, HM
Methocarbamol (Robaxin)	Muscle relaxant	20-45 mg/kg PO BID-TID	Same	Ataxia; sedation; ptyalism; emesis	100 mg/ml I 500 mg T HM
Methotrexate	Antimetabolite, antineoplastic agent that inhibits folic acid reductase Used to treat some cancers or for immuno-suppression Sclerosing cholangio-hepatitis	0.06 mg/kg SID-EOD PO 2.5 mg/m2 SID-EOD PO	2.5 mg/m2 PO q 2–3 days	Leukopenia, G-I bleeding hepatotoxicity. See specific cancer or disease state	2.5 mg T 2.5 mg/ml I HM
Methylene blue (new methylene blue)	1. For treatment of methemoglobinemia in dogs 2. As intraop insulinoma Dx test	1. 1-2 mg/kg slow IV once 2. dilute 3 mg/kg in sterile saline and administer as CRI		Use once only Can induce Heinz body hemolytic anemia Islet cell tumors=purple (vs. pale blue background), best contrast 30 min. after onset of CRI	10 mg/ml I HM

Methylprednisolone acetate (Depo-Medrol)	Repositol corticosteroid. For intralesional skin injections; feline asthma; eosinophilic granuloma complex	1-2 mg/kg IM, SQ	Same Total dose: 10-20 mg per cat	Glucocorticoid contraindica-tions and side effects	20, 40, 80 mg/ml I VM, HM
Methyl prednisolone sodium succinate (Solu-Medrol)	Soluble corticosteroid. Acute shock. Spinal Cord injury within 8 hours of trauma	30 mg/kg slow IV once, then 15 mg/kg IV in 2–6 hours	Same	GI ulcers very common; assess need for this Tx based on acuity (time frame) and severity	40, 125, 500, 1000, 2000 mg/vial I HM
Methyltestosterone	Anabolic drug Androgenic steroid Used in testosterone responsive incontinence	0.5 mg/kg PO	Same	May increase creatinine and glucose levels	10 mg C HM
Metoclopramide (Reglan)	Antiemetic with both central (chemoreceptor trigger zone) and peripheral (gastrointestinal) effects Increases LES pressure; promotes gastric emptying	0.2-0.5 mg/kg BID-QID PO, SQ or 1-2 mg/kg/day given as IV infusion over 24 hours	Same	Do not use with G-I obstruction, with phenothiazines, or with narcotic analgesics. Atropine blocks effect. May increase seizure activity Extrapyramidal effects	5, 10 mg T 1 mg/ml S 5 mg/ml I HM
Metoprolol (Lopressor) (Toprol XL)	B1 selective blockade May provide support for CHF animals on traditional therapy	0.4-1 mg/kg BID-TID PO. SID for extended release	Total dose: 2-10 mg per cat SID-BID PO	Lethargy, depression Decreased HR Beta-blockade-induced CHF Always begin low and titrate up	50, 100 mg T 50, 100, 200 mg ER 1 mg/ml I HM
Metronidazole (Flagyl)	Anaerobic infections of the mouth, pulmonary, G-I tract, and liver Also, Giardia, Entamoeba, Balantidia, Pentatrichomonas, and Trypanosoma Irritable bowel disease (IBD) Small bowel bacterial overgrowth syndrome	10-20 mg/kg BID PO	10-20 mg/kg BID PO	Anorexia and vomiting. Neurotoxicity and hepatotoxicity may develop at high and/or prolonged dosages Hepatic metabolism; use 7.5 mg/kg PO BID if liver disease	250, 500 mg T 500 mg/100 ml I HM
Mexiletine (Mexitil)	Type 1B antiarrhythmic drug used to treat ventricular arrhythmias	4-10 mg/kg BID-TID PO		Anorexia, depression CNS signs Side effects rare	150, 200, 250 mg C HM

Mibolerone (Cheque)	Prevents estrus (dogs only) Pseudocyesis Synthetic androgenic, anabolic steroid	Total dose per dog for estrus suppression: 1-11 kg: 30 microg/day PO per dog 12-22 kg: 60 microg/day PO per dog 23-45 kg: 120 microg/day PO per dog >45 kg, or German Shepherd dog (mix) 180 microg/day PO pe dog Pseudocyesis: 10 times above dosage for 5 days PO		Do not use in pregnant dogs or in those with renal or hepatic disease	100 microg/ml S VM
Miconazole (Conofite)	Topical antifungal	Apply BID to lesion Continue after resolution of lesions for 2 weeks	Same	Contact hypersensitivity Caution re zoonosis if dermatophytosis (gloves)	OTC, topical cream, and solution HM
Midazolam (Versed)	Benzodiazepine tranquilizer	0.1-0.3 mg/kg IV, IM, SQ (lower end of range if IV)	0.05-0.3 mg/kg IV, IM, SQ (mid- to lower end of range if IV and/or if combined with ketamine)	Caution in liver disease Avoid with glaucoma	1 mg/ml and 5 mg/ml I VM HM
Milbemycin (Interceptor)	Anthelmintic action in heartworm prevention and hookworm control Demodectic mange Pneumonyssoides caninum	0.5-1.0 mg/kg orally once monthly 0.5-2.3 mg/kg SID-BID PO 2-4 weeks for Demodex, longer if skin scrapings fail to clear mites. May use low dose × 30 days; 2 × after if necessary 0.5-1.0 mg/kg/week for 3 weeks		Test for heartworms prior to initial administration	2.3, 5.75, 11.5, and 23 mg T VM
Misoprostol (Cytotec)	Prostaglandin E1 analog Used for gastric ulcers	2-8 microg/kg BID-TID PO		Secretory diarrhea, vomiting, anorexia May induce abortion in pregnant animals Side effects are dose dependent	100, 200 microg T HM
Mitoxantrone (Novantrone)	Chemothera-peutic agent closely related to doxorubicin	5 mg/m2 once every 3 weeks IV	6.25 mg/m2 once every 3 weeks IV	Depression, G-I signs, leukopenia, hepatotoxicity, extravasation injury	2 mg/ml I HM

Morphine sulfate	Narcotic analgesic Acute CHF as adjunctive therapeutic agent to relieve anxiety and to vasodilate	0. 25-1.0 mg/kg every 2 to 6 h IM, SQ, IV, epidural. Or sustained release PO: 1.5-3.0 mg/kg BID (ER) PO	0.25-0.75 mg/kg every 2 to 6 hours IM, SQ	Hyperexcitability in cats Vomiting, respiratory and CNS depression Hypotension, especially if given IV	30 mg ER 5, 10, 20 mg suppository 10, 20 mg/5 ml S 15, 30 mg T 2, 4, 5, 8, 10, 15 mg/ml I HM
Moxidectin	Heartworm prophylaxis	3 microg/kg PO once monthly- removed from market 2004		Safe in collies Not FDA approved—removed from market due to adverse reactions-2004	30, 68, 136 microg T Large animal product available as 1.3 g tube VM

Table • App-13 N

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Naloxone (Narcan)	Narcotic antagonist	0.04 mg/kg IV, IM, SC	Same	The effect of the narcotic may last longer than the naloxone, requiring redosing This is particularly true in end stage liver disease, portosystemic shunts, or with drugs that are P-450 blockers	0.02, 0.4, 1 mg/ml I HM
Nandrolone decanoate (Deca-Durabolin)	Anabolic steroid and bone marrow stimulant	1 mg/kg/week IM	0.5-1.0 mg/kg week IM	Give deep IM Do not administer to pregnant or hepatoinsufficient animals	100 and 200 mg/ml I HM
Naproxen (Naprosyn) (Aleve)	Nonsteroidal anti-inflammatory	1.2-2.8 mg/kg once daily or every other day PO Avoid use if possible	Do not use	Severe GI ulceration very common; renal, CNS. Not a preferred drug 32-92 T ½ in dogs	200, 250, 375, 500 mg T 125 mg/5 ml S HM
Neomycin (Biosol)	Aminolgly-coside used orally for G-I tract bacterial overgrowth and hepatoencephalopathy	10-20 mg/kg BID-TID PO	Same	Ototoxicity and nephrotoxicity are rare with oral dosage In severe intestinal disease, toxicity may be more likely.	200 mg/ml S 100, 500 mg T VM, HM
Neostigmine (Stiglin, Prostigmin)	Anticholinesterase agent for myasthenia gravis	0.01-0.05 mg/kg IM, SQ, PRN	Same	Muscarinic effects: vomiting, diarrhea, bradycardia are reversed by atropine	0.25, 0.5, 1 and 2 mg/ml I 15 mg T HM
Niacinamide (nicotinamide)	Usually used in combination with a tetracycline for immune-mediated dermatopathies	<5 kg: 100 mg TID PO 5-10 kg: 250 mg TID PO >10 kg: 500 mg TID PO		GI adverse effects possible Flushing of mucous membranes	50, 100, 125, 250, 500 mg T HM
Niclosamide (Yomesan)	Tapeworm anthelmintic	154 mg/kg PO; fast 24 hours before; repeat in 2-3 weeks	Same	Occasionally soft stools	VM

Nitenpyram (Capstar)	Flea infestation Inhibits insect specific nicotinic receptors	Dogs up to 11 kg: total dose 11.4 kg PO per dog, max. SID Dogs > 11 kg: total dose 57 mg PO per dog, max. SID	Total dose: 11.4 mg PO per cat, max. SID	Onset of action rapid (minutes-hours) but duration of activity limited (day[s]) Irritability-complaints of hyperactivity if fleas are jumping off and dying	11.4, 57 mg T VM
Nitrofurantoin (Dantefur) (Macrodantin)	Urinary tract infections Ointment for superficial wounds	4 mg/kg q 8 h PO	Same	Oral form used only for urinary tract infections	50, 100 mg T 5 mg/ml S 25, 50, 100 mg macrocrystals C HM
Nitroglycerin 2% ointment (Nitrol ointment)	Transdermal venodilator for reducing cardiac preload in acute CHF	Apply ¼-2 inches TID-QID topically to skin	Apply 1/8–¼ inch TID topically to skin	May cause hypotension Apply with glove to hairless region, i.e. pinna or inguinal Clinical efficacy questionable	2% O HM
Nitroprusside (Nipride)	Arterial dilator Venodilator	1-7 microg/kg/min IV CRI	1-2 microg/kg/min IV CRI	Hypotension Cyanide toxicity Use 2-3 days IV maximum	50 mg/vial I HM
Nizatidine (Axid)	H2 receptor antagonist	5 mg/kg SID PO		Has GI prokinetic effects	75, 150, 300 mg T HM
Norepinephrine (Levophed)	B1 and alpha agonist used to treat shock	1-2 ml in 250 ml of 0.9% NaCl, IV CRI to effect	None	Hypertension Tachycardia	1 mg/ml I HM

Table • App-14 O

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Octreotide (Sandostatin)	Somatostatin analogue with primary inhibitory effect on intestinal secretions Insulinoma; glucagonoma	Total dose: 10–40 microg (0.01–0.04 mg) per dog SQ TID		Nausea, vomiting, abdominal discomfort	50, 100, 500 microg/ml IHM
Olsalazine (Dipentum)	Salicylate Anti-inflammatory activity in ulcerative colitis (5-ASA)	5-20 mg/kg TID PO	Unknown	See Sulfasalazine	250 mg C HM
Omeprazole (Prilosec) (Losec)	Proton pump acid blocker; used in reflux esophagitis and hyperacidity syndromes	0.7 mg/kg SID PO	Total dose: 5 mg per cat PO SID	Few side effects noted May interact with cyclosporine	10, 20 mg C HM
Ondansetron (Zofran)	5-HT3 receptor antagonist (serotonin inhibitor) Used in conjunction with emetogenic cancer chemotherapy Used in protracted vomiting unresponsive to other treatments	0.05 –0.2mg/kg IV bolus BID	Same	Used before and for 48 h following specific IV cancer Rx	4, 8 mg T 2 mg/ml I 1.25 mg/ml S HM
Oral rehydration solution (ORS; Pedialyte)	Oral electrolyte and glucose replacement	Up to maintenance (60 ml/kg/day) + replacement (based on physical exam) PO divided into several doses as low-cost rehydration/volume expansion	Same		Many HM OTC
O,p′-DDD (Lysodren) (Mitotane)	Hyperadrenocorticism Selective necrosis of the zona fasciculata and reticularis of the adrenal gland	50 mg/kg divided twice daily with food to effect (approx. 5-10 days); then 25-50 mg/kg once every 7-14 days to effect; with food	None	Vomiting, diarrhea, weakness Mineralocorti-coid deficiency Best if given in divided doses Best if given with meal	500 mg T VM
Orbifloxacin (Orbax)	Fluoroquinolone antibiotic	2.5-7.5 mg/kg SID PO	Same	May cause arthropathy in immature dogs	5.7, 22.7, 68 mg T VM
Orgotein (Palosein)	Superoxide dismutase activity causes anti-inflammatory response	5 mg SID SQ for 7 days; then every other day or as needed		Unsubstantiated effects	5 mg/vial I VM

Oxacillin (Prostaphlin)	Penicillin derivative used for staphylococcal skin infections	22-40 mg/kg TID PO	Same	Best if not given with food	250 mg/5 ml S 250, 500 mg C 250 and 500 mg, 1 and 2 g I HM
Oxazepam (Serax)	Appetite stimulant (oral benzodiazepine agent)		Total dose: 2.5 mg per cat PO once. Do not use long term since it may induce hepato-toxicity	Overdosage results in sedation and incoordination	10, 15, 30 mg C 15 mg T HM
Oxtriphylline (Choledyl)	Bronchodilator (theophylline derivative)	4-10 mg/kg TID PO	4-10 mg/kg TID PO	Vomiting, diarrhea, hyperexcitability	100, 200 mg T 400, 600 mg ER HM
Oxymorphone (Numorphan)	Narcotic agonist for analgesia, anesthetic induction, and minor procedures	Anesthesia: 0.1-0.2 mg/kg IM, SQ; 0.02-0.05 mg/kg IV Analgesia: 0.03-0.2 mg/kg IV, IM, SQ, PRN	0.01-0.2 mg/kg IV, IM, SQ, PRN	Respiratory and CNS depression Hypotension, sedation, feline hyperexcitability Panting (dogs) Reverse with naloxone	1, 1.5 mg/ml I HM
Oxytetracycline (Terramycin)	Broad spectrum bacteriostatic agent Also used for rickettsiae, mycoplasma, and spirochetes Used for treating small bowel bacterial overgrowth	10-20 mg/kg TID-QID PO As o.o., apply BID-QID	Same	Do not use in pregnancy (last trimester) or in first month of life (dental staining) G-I side effects Do not administer with antacids, dairy products, or intestinal adsorbents	50, 125 mg/ml I 250 mg C HM
Oxytocin (Pitocin, Syntocinon)	Posterior pituitary hormone used for uterine inertia; to stimulate milk flow; vasopressive effects and as an antidiuretic	Obstetrics: 5-25 U IM total dose q 30 min or 1-2 U/kg. Milk production: 2-10 units IM Intranasal spray	Obstetrics: 2 units/kg IM q 30 min Milk production: 1 unit IM	Do not use if birth canal obstructed Refrigerate vial, warm syringe before injection	10 U/ml I 40 U/ml nasal spray HM

Table • App-15 P

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Pamidronate (Aredia)	Bisphosphonate compound Hypercalcemia e.g. due to cholecalciferol intoxication	0.65–2 mg/kg diluted in 0.9% NaCl and given as IV CRI		Clinical vet use very new; efficacy and adverse effects sparsely reported at present	30, 60, 90 mg vials I HM
Pancreatic enzymes (Pancrelipase) (Viokase)	Pancreatic exocrine insufficiency	½-2 tsp pwdr in 1# (500 g) canned food or 2 cups moistened dry food.	Same proportional to size of feeding	Avoid inhaling powder dust Viokase brand has superior efficacy	VM, HM
Paregoric®	Antidiarrheal	0.05-0.06 mg/kg BID-TID PO	None	May cause constipation	OTC, HM S
Paroxetine (Paxil)	Selective serotonin reuptake inhibitor	Total dose: 2.5–5 mg PO per dog SID	Total dose: 1.25–2.5 mg PO per cat SID	Behavior changes, anorexia possible	10, 20, 30, 40 mg T 12.5, 25 mg ER (Paxil CR) T HM
Penicillamine (Cuprimine) (Depen)	Chelating agent for lead, copper, and mercury Used to aid in the prevention of cysteine urolithiasis Cu storage disease	10-15 mg/kg PO BID		Administer on empty stomach if tolerable May cause vomiting, skin eruptions, and vascular lesions Monitor CBC	250 mg (Depen) T 125, 250 mg (Cuprimine) C HM
Penicillin, benzathine (Benzapen)	Gm + infections; some activity against anaerobes; bactericidal	20,000-40,000 units/kg q 48-72h, IM, SQ	Same	Do not use with penicillin hypersensitivity Do not use if serious infection is suspected IM or SQ injection only	150,000 U/ml I HM
Penicillin G procaine	Gm + infections; some activity against anaerobes	20,000-40,000 units/kg q 12-24 h IM, SQ	Same	Solution for injection is opaque= for IM/SQ injection only Penicillin hypersensitivity contraindicates	300,000 U/ml I VM

Penicillin G potassium or sodium	Gm + infections; some activity against anaerobes	20,000-40,000 units/kg q 4–6 h IV, IM, SQ	Same	Penicillin hypersensitivity contraindicates May contain high levels K+ Solution for injection should be completely transparent Not very effective orally	1 million, 5 million, 10 million, and 20 million U vials I HM
Penicillin-V	Gm + infections; bactericidal; effective orally	5.5-11 mg/kg TID-QID PO	Same	250 mg = 400,000 units Penicillin hypersensitivity	250, 500 mg T 125, 250 mg/5 ml S Many other sizes HM
Pentazocine (Talwin)	Narcotic agonist/antagonist used for short term analgesia	1-3 mg/kg IM, 2-6 mg/kg PO	2-3 mg/kg SQ, IM, IV	May cause salivation and/or sedation Reverse with naloxone May cause dysphoria in cats	30 mg/ml I HM Often combined with other Rx VM, HM
Pentobarbital (Nembutal)	Status epilepticus Anesthesia	Anesthesia: 10-30 mg/kg IV slowly to effect Seizures: 3-15 mg/kg IV slowly to effect	Anesthesia: 10-30 mg/kg IV slowly to effect Seizures: 3-15 mg/kg IV slowly to effect	Respiratory depression and hypotension may develop if used with or after diazepam	50 mg/ml I Available as tablets, elixir, suppositories VM, HM
Pentoxifylline (Trental)	Increases plasticity of cell membranes; used in many dermatoses, including dermatomyositis	10 - 25 mg/kg PO BID		Clinical vet use very new; few adverse effects reported so far	400 mg T HM
Phenobarbital	Long acting barbiturate used for seizure control Occasionally used as a sedative	1-2 mg/kg PO BID-TID; OK to titrate slowly up to 16 mg/kg/day in divided doses May be given IV as a bolus of 2-15 mg/kg slowly for status epilepticus followed by 2-6 mg/hr CRI Maintain serum levels at 15-45 microg/ml prior to each dose of Rx	2 mg/kg PO BID	Ataxia, sedation, pu/pd. Long term (esp. if >35 microg/ml serum levels) hepatotoxicity occurs Initial adjustment period is required If using higher dose IV, monitor respirations Controlled substance Available combined with phenytoin—not generally recommended	8, 16, 32, 65, 100 mg T 15, 20 mg/5 ml S 30, 60, 65, 130 mg/ml I HM

Phenoxybenzamine HCl (Dibenzyline)	Alpha adrenergic receptor blocking agent Urinary incontinence due to detrusor-sphincter dyssynergia	0.25-1.0 mg/kg PO BID	Total dose: 2.5-10 mg PO per cat SID-BID	May result in vomiting, hypo/hypertension, rapid HR, miosis No effect on postprostatic urethra of cats	10 mg C HM
Phenylbutazone (Butazolidin)	Nonsteroidal anti-inflammatory	10-22 mg/kg BID-TID PO	6-8 mg/kg BID PO (1 week on, 1 week off)	Use lowest effective dosage Do not exceed 800 mg/day May cause vomiting, G-I ulceration, BM suppression Incidence of toxicosis is high Not recommended	100, 400, 1000 mg T VM, HM
Phenylephrine (Neo-Synephrine)	Post-synaptic alpha adrenergic stimulant used 1. as nasal drops for rhinitis or 2. as IV infusion for treatment of hypotension	1. 1-2 drops intranasal pediatric soln SID-TID 2. 1–3 microg/kg/min as IV CRI, adjusted to effect	Same	May cause nasal irritation if used chronically Vasoconstriction and pupillary dilation if given parenterally (constant BP monitoring necessary)	10 mg/ml I Oph, and intranasal OTC products HM
Phenylpropanolamine HCl (Proin)	Alpha adrenergic agonist used for treating hormone responsive urinary sphincter hypotonus (incontinence) by increasing urethral smooth muscle activity	1 mg/kg PO TID	1-2 mg/kg BID-TID PO	Anxiety, dizziness, hypertension, tachycardia, urinary retention No longer available as human OTC product	25,50 mg T VM
Phenytoin (Dilantin)	Anticonvulsant agent	10-40 mg/kg PO TID 5-10 mg/kg slow IV	Not recommended	Ataxia and vomiting Monitor for hepatotoxicity Metabolized very rapidly Considered second line agent at best	50 mg T 30, 100 mg C 6, 25 mg/ml S HM

Phosmet dip (Paramite)	Organophosphate dip for fleas, ticks, and canine sarcoptic mange	2 tbsp (1 oz) per gallon H_2O Sponge on and let air dry	Do not use	Wear gloves to administer; use once weekly maximum Do not use if under 8 weeks old Fever, salivation, seizures, and CNS signs suggest organophosphate toxicity; use atropine injection and wash off dog	11.6% dip VM
Phosphate enemas (Fleet)	Treatment of constipation	For large dogs use one adult bottle; for medium dogs use ½ bottle or a pediatric enema. Not suggested for use in small dogs	Not recommended	May cause severe hyperphosphatemia and hypocalcemia if < 10 kg Do not use if dehydrated, with renal or cardiac failure or in very sick animals	OTC, HM
Pilocarpine oph. soln.	Miotic agent useful in glaucoma KCS	1. 1 drop in affected eye BID-QID 2. For KCS: 2-5 drops in food SID	Same	Ciliary spasms Systemic signs rare when used topically Adjust dose according to time and response	0.25, 0.5, 1, 2, 3, 4, 6, 8% OS HM
Pimobendan (Vetmedin)	Oral positive inotrope and vasodilator Effective adjunct Rx in CHF caused by DCM in Dobermans but not Cockers	0.25 mg/kg PO BID	None	Not approved for vet or human use in U.S.A.	1.25, 2.5, 5 mg C VM
Piperazine	Ascarid infection	50-100 mg/kg PO	Same	Repeat in 3 weeks Vomiting and diarrhea may occur at higher dosages	250 mg T 100 mg/ml S VM, HM
Piroxicam (Feldene)	NSAID As primary or secondary Rx for bladder TCC due to immunomodulatory effect	0.3 mg/kg EOD or SID PO		G-I irritation Must open capsules and put in food for most animals Often coadministered with Misoprostol	10, 20 mg C HM

Potassium chloride inj.	Treatment and prevention of hypokalemia	Add to IV fluid per liter based on serum K+ level Serum K: 3.5-5.0 mEq/l = add 20 mEq KCl/l 3.0-3.4 =30 2.5-2.9 = 40 2.0-2.4 -= 60 <2.0 = 80	Same	Never infuse rapidly or administer over 0.5 mEq K+/kg/h Monitor K+ regularly	2, 10, 20, 30, 40, 60, 200, 400, 1000 Meq/ml I HM
Potassium citrate (Urocit-K)	Inhibits Ca oxalate crystal formation in urine Alkalinizing agent for urine	75 mg/kg BID PO 1-2 mEq/kg/day PO	100-150 mg/kg PO	Gastrointestinal irritation 5 mEq = 540 mg	5, 10 mE q T HM
Potassium phosphate	Hypophosphatemia	0.01–0.03 mM/kg/hr IV	Same	Hyperphosphatemia; recheck serum levels after 6 hours and adjust or stop In potassium phosphate, 1 mM phosphate = 33 mg/dl phosphate Avoid calcium-containing fluids	5, 10, 15, 30, 50 ml vials (3 mM PO4 and 4.4 mEq K per ml for all) I HM
Potassium salts (Kaon®Elixir) (Micro K Extencaps)	Potassium supplements in various oral formulations	¼ - 1 tab (tbsp) (caps) BID-TID PO	1/8 – ¼ (tbsp) (caps) BID-TID PO	Dose according to deficit Monitor serum K May cause gastric irritation	Many OTC preparations, different sizes VM, HM OTC HM
Pralidoxime chloride (2-PAM) (Protopam)	Reactivates cholinesterase inactivated by organo-phosphate	20-50 mg/kg IM or SQ; then BID–TID as needed	20 mg/kg IM or SQ TID–QID as needed	Monitor patient continuously; avoid IV administration (may cause acute laryngospasm) Do not use for carbamate toxicity	1 g vial I HM
Praziquantel (Droncit)	Taenia, Dipylidium, Echinococcus, Heterobilharzia	Use according to instructions on product according to weight; PO or SQ, IM	Same	Fasting not required Do not use in puppies under 4 weeks or kittens under 6 weeks of age	23, 34 mg T 56.8 mg/ml VM 600 mg T HM

Prazosin (Minipress)	Alpha adrenergic antagonist Balanced vasodilator Decreases ureteral smooth muscle tone	Total dose: 0.5-2 mg per dog BID or TID PO	0.5 mg/kg PO BID	Hypotension Depression, malaise	1, 2, 5 mg C
Prednisolone, prednisone	Anti-inflammatory-antipruritic immune system suppression Chemotherapy	Anti-inflammatory: 0.5-1 mg/kg/day PO, IM, SQ Immune suppression: 2-4.4 mg/kg/day usually orally 40 mg/m2/day × 7 PO; then 20 mg/m2 EOD PO	Same	PP/PU/PD; suppression of HPA axis–Cushing's syndrome Taper dosage if used long term	1, 2.5, 5, 10, 20, 25, 50 mg T 1 mg/ml S 10, 25 mg/ml I HM
Prednisone ophthalmic suspension (Pred Forte)	Steroid responsive inflammation of the lids, conjunctiva, sclera, cornea, and anterior segment of the eye	1 drop in affected eye BID-QID	Same	Variable strength products (0.12-1%) used as required Do not use with purulent, viral, or fungal infection or with corneal ulcers Systemic side effects are possible but rare	0.12, 0.125, 1% OS HM
Prednisolone sodium succinate (Solu-Delta-Cortef)	Soluble corticosteroid used IV for shock of multiple causes	5-33 mg/kg IV slow bolus Repeat up to q 6 h Spinal injury: 30 mg/kg IV	Same	Causes vomiting if administered too rapidly	100, 500 mg vials IVM
Primidone (Mylepsin)	Anticonvulsant medication converted to phenobarbital	10-20 mg/kg/day initially; up to 50 mg/kg/day given BID-TID PO (adjust based on serum phenobarbital levels)		Causes pu/pd/pp, sedation, and ataxia Often hepatotoxic with prolonged use No benefit over phenobarbital; no longer recommended	50, 250 mg T 50 mg/ml S HM
Procainamide (Pronestyl; SR) (Procan-SR)	Ventricular arrhythmias	6-20 mg/kg IV slowly over 30 min then CRI 0.02–0.04 mg/kg/min (20-40 microg/kg/min) CRI (if life threatening) 6-20 mg/kg q 4 h IM 6-20 mg/kg q 6 h PO	1-2 mg/kg bolus IV; then 0.01–0.02 mg/kg/min (10-20 microg/kg/min) CRI	Available as sustained release tablet for TID administration This is a negative inotrope Use serum levels for long-term dosing adjustments May cause hypotension, tachycardia, and ECG changes	100, 500 mg/ml I 250, 375, 500 mg C 250, 500, 750, 1000 mg ER HM

Prochlorperazine (Compazine)	Antiemetic	0.11-0.44 mg/kg SQ IM BID-QID	Same	Sedation, hypotension Do not use in epileptic patients Available also in suppository formulation	5 mg/ml I 1 mg/ml S 5, 10, 25 mg T 10, 15, 30 mg ER HM
Propantheline (Pro-Banthine)	Anticholinergic agent used for treating diarrhea, bradycardia syndromes, and detrusor hyperreflexia	0.2–0.5 mg/kg SID-TID PO Increase to effect for bradycardia syndromes	Same	Tachycardia, dry mouth, constipation, mydriasis, ileus, urinary retention	7.5, 15 mg T HM
Propioni bacterium acnes (Immuno-regulin)	Immune modulator/ potentiator	0.03-0.07 mg/kg IV at 2-3 day intervals	Total dose: 0.5 ml per cat IV 1-2 times a week	No controlled studies	0.4 mg/ml I VM
Propofol (Diprivan) (Rapinovet)	Ultrashort (5-7 min) acting anesthetic No cumulative effect with repeated administration	3-6 mg/kg IV	Same	Give slowly over 1-2 min in equal dosages to effect	10 mg/ml I HM, VM
Propranolol (Inderal)	Beta adrenergic blocking agent used for treating supra-ventricular arrhythmias, some ventricular arrhythmias, and feline hypertrophic cardio-myopathy	For acute tachycardias: 0.1-0.5 mg IV total dose per bolus No more frequently than 1 bolus q 1-3 min to 5 mg maximum Administer until the rate slows Chronic use: 0.2-1.0 mg/kg BID PO, usually start low and titrate dosage upward to effect	0.25-0.5 mg IV bolus slowly 2.5-5.0 mg BID, PO, begin low and titrate dosage	Anorexia, apnea, depression, ataxia Bradycardia, negative inotropic effect Potentiates A-V nodal depression of digoxin and calcium channel blockers Underlying cause of tachycardia (e.g. heart failure, hypovolemia) must be addressed before IV propranolol	10, 20, 40, 60, 80, 90 mg T 60, 80 120, 160 mg ER 4, 8, 80 mg/ml S 1 mg/ml I HM
Propylthiouracil (PTU)	Feline hyper-thyroidism	Not used	10 mg/kg BID-TID PO	Immune mediated hemolytic anemia and thrombo-cytopenia Anorexia, vomiting, and lethargy Risk of adverse effects frequently outweighs potential benefit	50 mg T HM

Prostaglandin (PGF2-alpha) (Lutalyse)	1. Open cervixpyometra 2. Abortive agent at 31-35 days	1. Day 1: 0.1 mg/kg SQ once Day 2: 0.2 mg/kg SQ once Days 3-7: 0.25 mg/kg SQ SID 2. 0.1 mg/kg SQ TID × 2 days, then 0.2 mg/kg TID SQ × 3-7 days (or until fetuses are expelled)	1. 0.1 mg/kg SQ BID × 5 d 2. 0.5-1 mg/kg SQ × 2d	Panting, salivation, vomiting, diarrhea, and tachycardia lasting about 30 minutes Should be given under hospital supervision	5 mg/ml I VM
Pseudoephedrine (Sudafed, others)	Hormone-deficient urinary incontinence of bitches	0.2 – 0.4 mg/kg PO BID – TID		Narrow window between therapeutic and toxic doses; use with caution if sympathetic drive could be harmful (heart disease, hypertension, hyperthyroid-ism, etc.) or if CNS abnormalities	30, 120 mg T HM, OTC
Psyllium mucilloid (Metamucil)	Bulk laxative; stool softener	2-10 g SID-BID in moistened food	2-4 g SID-BID in moistened food	Titrate dose based on stool consistency May also be used for treating fiber-responsive diarrhea	OTC HM
Pyrantel pamoate (Nemex, Strongid-T)	Roundworm and hookworm anthelmintic	5-10 mg/kg PO	10 mg/kg PO	Repeat in 3 weeks Safe at recommended dosages and in dogs with heartworms	22.7, 113.5 mg T 2.27, 4.54, 50 mg/ml S VM
Pyridostigmine bromide (Mestinon)	Anticholinesterase agent used for treating myasthenia gravis	0.2-2 mg/kg BID-TID PO	0.25 mg/kg PO maximum of once daily	Available as soft tablet and syrup (60 mg/5 ml) Vomiting, diarrhea, salivation, and weakness may develop	60 mg T 180 mg ER 12 mg/ml S 5 mg/ml I HM
Pyrimethamine (Daraprim)	Toxoplasmosis Neosporosis	0.5-1 mg/kg SID PO × 48 h; then 0.25 mg/kg PO SID × 14 d	Same	Often used with sulfonamides to treat toxoplasmosis May need to supplement with folic or folinic acid Teratogenic	25 mg T HM

Table • App-16 Q

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Quinacrine (Atabrine)	Giardiasis Enteric coccidiosis	10 mg/kg SID PO 5-12 days	11 mg/kg SID PO × 5 days	May cause enteric signs Considered second line agent	100 mg T HM
Quinidine (Quinidex)	Type Ia antiarrhythmic agent used mostly for ventricular dysrhythmias	6-20 mg/kg TID-QID PO, IM	Not recommended	Do not give IV or use with digitalis Negative inotropic agent Available in long acting tablet forms	100, 200, 300 mg T 275, 300, 330 mg ER 80 mg/ml I HM

Table • App-17 R

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Ramipril (Altace)	ACE inhibitor	0.1-0.125 mg/kg PO BID	Same	Description of clinical vet use, efficacy and adverse effects is limited	1.25, 2.5, 5, 10 mg C HM
Ranitidine HCl (Zantac)	H2 histamine receptor antagonist	1-2 mg/kg BID–TID PO, SQ, IM, slow IV	Same	GI prokinetic effects IV bolus may cause immediate vomiting	75, 150, 300 mg T 15 mg/ml S 25 mg/ml I HM
Rutin	Benzopyrone recommended for treatment of chylous pleural effusion. Reportedly potentiates macrophage function		50 mg/kg TID PO Total dose 250 mg TID per cat PO or 500 mg BID per cat PO	Generally purchased in health food stores	500 mg T OTC

Table • App-18 S

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
S-Adenosyl Methionine (SAMe) (Denosyl)	Adjunctive treatment for certain liver diseases; steroid hepatopathy. Acetaminophen toxicity	15-20 mg/kg daily. Total dose per dog: 90 mg PO SID (small dog), or 225 mg PO SID (large dog)	Total dose per cat: 90 mg PO SID		90, 225 mg T VM HM-OTC
Salmeterol (Serevent)	Inhaled long-acting beta-2 agonist bronchodilator	1 puff as needed SID-BID	Same	Takes >1 hr to take effect	6.5, 13g inhalation canisters (0.025 mg [25 microg] per puff) HM
Selamectin (Revolution)	Endectocide—topical for fleas, ticks, ear mites, heartworms, sarcoptic mange, intestinal hookworms, and roundworms	6 mg/kg topically 1 ×/month	Same	Use in dogs or cats over 6 weeks old For heartworm prevention: Give within 1 month of first exposure to mosquito and continue until within one month of last exposure	Pkg per wt L VM
Selegiline (deprenyl) (Anipryl) (Eldepryl)	Restores central dopamine levels—MAO inhibitor Used to treat cognitive dysfunction syndrome, May be helpful in selected PDH canine Cushing's cases	PDH: 1 mg/kg/day × 30 PO then OK to ↑ to 2 mg/kg/day CDS: 0.5 mg/kg daily; may double dose after 1 month if ineffective	Not rec'd	Low level of effectiveness reported	2, 5, 10, 15, 30 mg T VM 5 mg C, T HM
Sildenafil (Viagra)	PDE 5 inhibitor used for the treatment of Pulmonary hypertension	0.05-0.1 mg/kg PO BID-TID	Unknown	Clinical usefulness seen but no controlled studies have been reported	25, 50, 100 mg T HM
Silver sulfadiazine (Silvadene Cream)	Topical antiinfective preparation for complications of burns	Apply to burn area BID as necessary	Same	Hypersensitivity to sulfonamides	10 mg/g O HM

Sodium bicarbonate	Metabolic acidosis	mEq/day = (desired serum [HCO3] – present serum [HCO3]) × 0.3 × wt (kg) Administer 50% over 15 minutes and recheck serum levels; then give the balance over 24 h	Same	Alkalosis, hypernatremia, CHF, hypokalemia Correct inciting factors concurrently (or prior to HCO3 Tx); 84 mg NaHCO3 contains 1 mEq HCO3	0.6, 1 mEq/ml I 5, 10 grain T HM
Sodium iodide 20%	Sporotrichosis	15 mg/kg TID PO	Same	Monitor for iodinism: fever, ptyalism, G-I signs Contains 0.1 mg iodine/ml	20% I VM
Sodium stibogluconate (Pentostam)	Leishmaniasis	30-50 mg/kg SID SQ, IV or 10-20 mg/kg IM SID × 20-28d.		Not available in USA except through CDC	100 ml vials (100 mg/ml) I HM
Sotalol (Betapace)	Classes II and III antiarrhythmic agent used primarily for treating ventricular tachyarrhythmias	2.2-6.6 mg/kg BID PO	5-20 mg. per cat BID PO Dosage based on limited experience in cats	Beta effects seen at low dosages; type III effects at higher levels Begin low and titrate upwards to effect	80, 120, 160, 240 mg T HM
Spironolactone (Aldactone) Spironolactone with hydrochlorothiazide (1:1 combination= Aldactazide, Spirozide)	Protects against AC E escape and limits fibrosis in the heart muscle Potassium sparing diuretic; inhibits aldosterone Hydro-chlorothiazide is a potassium depleting diuretic	1-4 mg/kg SID-BID PO	Same	Usually used with other diuretic agents Monitor potassium (hyperkalemia) Used with ACEI agents usually 1×/day and at low dose Best if use noncombination products to obtain correct dosages	25, 50, 100 mg T HM 25/25/mg T
Stanozolol (Winstrol)	Anabolic steroid used for treating anorexia, debilitation, and anemia	0.1-0.2 mg/kg SID-BID PO Total dose: 25-50 mg IM per dog weekly	0.1-0.2 mg/kg SID-BID PO Total dose: 12.5-25 mg per cat IM weekly	Contraindicated in pregnancy Hepatotoxicity in cats	2 mg T 50 mg/ml I VM, HM

Streptokinase (Kabikinase) (Streptase)	Thrombolytic drug Arterial or pulmonary thrombo-embolism	90 000 IU/kg IV over 30 minutes, then 45 000 IU/kg per hour × 7–12 hrs based on response	Same	Bleeding diathesis; hyperkalemia from reperfusion Intracardiac thrombus= absolute contraindication Complications cancel benefits in feline aortic thromboemboli	250 000, 600 000, 750 000, 1.5 million unit vials I HM
Succimer (*meso*-2,3 dimercaptosuccinic acid) (Chemet)	Lead toxicity	10 mg/kg PO TID × 10-17 days			100 mg T HM
Sucralfate (Carafate)	Complexes with proteinaceous materials in stomach, thereby preventing undesirable effects of acids on the gastric mucosa	Total dose: ¼-1 tab per dog TID-QID PO	Total dose: ¼ tab per cat BID-QID	May constipate Interferes with absorption of many drugs administered concurrently	1 g T HM
Sulfadiazine (Suladyne)	Bacteriostatic agent used for treating 1. toxo-plasmosis and nocardiosis 2. soft tissue/urinary tract infections	1. 90-120 mg/kg BID PO; follow by 50 mg/kg BID PO 2. 30 mg/kg PO SID	Same	Sulfonamide precautions	500 mg T VM, HM
Sulfadimeth-oxine (Bactrovet, Albon)	Bacteriostatic agent used for treating toxoplasmosis, nocardiosis, and coccidiosis	50 mg/kg PO day 1; then 25 mg/kg PO SID	Same	KCS, nephrotoxicity, and hypersensitivity	400 mg/ml I 125, 250, 500 mg T 50, 125, mg/ml S VM, HM
Sulfadimethoxine-ormetroprim (Primor)	Potentiated sulfonamide	27-55 mg/kg SID PO on day 1; then 13.5-27.5 mg/kg SID thereafter for a maximum of 21 days	None	Sulfonamide contra-indications	120, 240, 600, 1200 mg T VM
Sulfasalazine (Azulfidine)	Anti-inflammatory effect on the colon; ulcerative and idiopathic colitis	22-55 mg/kg TID PO	10-20 mg/kg BID PO 3-5 days	KCS Avoid prolonged treatment, blood dyscrasias, vomiting	500 mg T HM

Table • App-19 T

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Tacrolimus (Prograf, Protopic)	Immune-mediated hemolytic anemia and other autoimmune disorders Topical: atopy, perianal fistula	0.16 mg/kg IM SID 1 mg/kg PO SID		Sparsely reported use at this time; narrow therapeutic-toxic range, with frequent negative side-effects; these doses associated with adverse effects, so titrate to keep trough serum level 0.1–0.4 ng/ml (dogs) Vasculitis Anorexia Intussusception	1 mg, 5 mg T 5 mg/ml I 0.3% lotion HM
Taurine	Feline DCM Canine DCM in Am. Cocker Spaniels, retriever breeds, many others	50 mg/kg TID PO or total dose 500-1000 mg PO per dog BID	Total dose: 125-250 mg PO per cat BID	Switch to taurine enriched diet if relevant (many are already on balanced diet)	250 mg T OTC, HM
Tepoxalin (Zubrin)	Non-steroidal anti-inflammatory drug	10 mg/kg PO SID; may give 2× dosage first day.	Not recommended	Gastritis, diarrhea, hepatopathy, renal effects Tablets disintegrate rapidly (~4 secs)	30, 50, 100, 200 mg T VM
Terbutaline (Brethine)	Bronchodilator via beta 2 stimulation	Total dose: 0.625-5 mg PO per dog BID-TID	Total dose: 0.625-1.25 mg PO per cat BID	Excitability Vomiting	2.5, 5 mg T 1 mg/ml I HM
Testosterone	Testosterone responsive incontinence in dogs	2.2 mg/kg IM monthly	Total dose: 5-10 mg per cat IM	Hepatopathy Behavioral changes	25, 50, 100, 200 mg/ml I HM

Tetracycline	Broad spectrum antibiotic; bacteriostatic Used especially for Brucella, Chlamydia, Mycoplasma, and Rickettsia; used for pleurodesis; used with niacinamide for autoimmune dermatopathies; and as an ophthalmic ointment	10-22 mg/kg TID PO for 3 weeks Pleurodesis: 20 mg/kg in 4 ml saline/kg Oph. oint: apply TID-QID	Same	Fever, vomiting, diarrhea Do not administer with dairy products, antacids, intestinal adsorbents Do not give in last 3 wks of pregnancy or to newborns to 4 weeks of age	100, 250, 500 mg T/C 25 mg/ml S 250, 500 mg/vial I 10 mg/g OO 10 mg/ml OS HM; VM
Theophylline elixir (Elixophyllin)	Bronchodilator	6-11 mg/kg TID PO	Rarely used at 8 mg/kg TID PO	See Aminophylline Restlessness, vomiting	16 mg/ml S HM
Theophylline sustained action (Theo-Dur)	Long acting bronchodilator	5-15 mg/kg BID PO One dose may in some patients last 24 hours	Same but infrequently utilized	Hyper-excitability common Nausea, vomiting—stop drug	100, 200, 300 mg ER HM
Thiabendazole (Mintezol)	Aspergillosis, Penicilliosis, Filaroides (Oslerus), and feline eosinophilic granuloma complex	50 mg/kg SID PO for 3 days, repeat in 1 month	5-10 mg/kg SID PO 3 times weekly	Not licensed for feline use Many dosages recommended for unusual parasitic states that may or may not respond	500 mg T 100 mg/ml S VM
Thiacetarsamide (Caparsolate)	Heartworm adulticide Haemobartonellosis (M. felis)	2.2 mg/kg BID slow IV × 4 doses	1.1-2.2 mg/kg BID slow IV × 4 doses Often not rec'd	Vomiting, depression, hepatotoxicity (icterus) Nephrotoxicity Thromboembolic phenomena 7-14 days post-Rx Perivenous injection causes sloughing Acute pulmonary edema in cats	10 mg/ml I VM
Thiamine (Vitamin B1)	Thiamine deficiency	Total dose: 10-100 mg BID per dog, IM, IV, PO	Total dose: 50 mg BID per cat, IM, IV, PO	Stings IM	100, 200 mg/ml I 5, 10, 25, 50, 100, 250, 500 mg T HM

Thioguanine	Antineoplastic Acute leukemias	40 mg/m2 PO SID × 4-5 d., then q 3 d.	25 mg/m2 PO SID × 1-5 d., then q 30 d	Bone marrow, GI, hepatic adverse effects possible	40 mg T HM
Thiopental sodium (Pentothal)	Ultrashort acting anesthetic (similar to thiamylal Na)	13-26 mg/kg IV titrated to induction of anesthesia	Same	Respiratory and cardiac depression Avoid perivenous administration Ventricular bigeminy common	1, 2.5, 5 g vials I HM
Thyrotropin TSH (thyroid-stimulating hormone) (Dermathrycin) (Thyrotropar)	Hormone used for diagnosis of hypothyroidism	Total doses: 5 U per dog to 10 kg IV, IM, SQ; 10 U per dog over 10 kg IV, IM, SQ	Total dose: 2.5 units per cat IM or IV	Follow protocol for testing: pre- and 6 h post IM or IV injection	5, 10 U/vial I VM, HM
Ticarcillin-clavulanate (Timentin)	Broad-spectrum penicillin-clavulanic acid combination	50-100 mg/kg slow IV TID	40-50 mg/kg IM or slow IV TID-QID		3 g vials I HM
Tiletamine-zolazepam (Telazol)	Tranquilizer, dissociative combination agent used for chemical restraint	5-12 mg/kg IM	Same	Rapid onset; respiratory depression may occur quickly (be prepared for intubation)	100 mg/ml combined (50 mg each per ml) I VM
Timolol soln. (Timoptic)	B blocking agent used for decreasing intraocular pressures due to glaucoma	1 drop in eye BID	Same	Potentiation of beta blocking effects possible Avoid 0.25% solution (ineffective)	0.25, 0.5% OS HM
Tocainide (Tonocard)	Class Ib antiarrhythmic Agent for ventricular tachyarrhythmias	15-20 mg/kg BID-TID PO	–	Anorexia, GI signs Weakness, head bobbing; corneal dystrophy Possibly adverse renal effects May need to use with other class IA drugs for max effect	400, 600 mg T HM
Triamcinolone (Vetalog) (Kenalog)	Intermediate acting corticosteroid used PO; by injection IM, SQ, or intralesional	0.1-0.22 mg/kg IM, SQ, PO	Same	Corticosteroid effects	0.5, 1.5 mg T 2, 6 mg/ml I HM, VM
Trientine (Syprine)	Alternative to penicillamine to chelate copper	10-15 mg/kg BID PO	–	See penicillamine	250 mg C HM

Trifluridine (Viroptic)	Antiherpetic viral agent	–	At least 2-4 times daily in eyes	–	1% OS
Triiodothyronine, T3 (Cytomel, liothyronine)	Hypothyroidism; used when unable to convert thyroxine to triiodothyroxine; also diagnostically as T3 suppression test	4-6 microg/kg TID PO	4.4 microg/kg BID-TID PO T3 suppression: 25 microg total per cat dose PO TID × 7 doses, then blood for T4 and T3 (control)	Thyrotoxicosis, pu/pd/pp, nervousness, panting, tachycardia	5, 25, 30 microg T
Trilostane (Vetoryl)	Steroid analog (competitive inhibitor of 3 beta-hydroxysteroid dehydrogenase); treatment for pituitary-dependent hyperadrenocorticism/Cushing's disease	10–30 mg/kg PO SID dogs < 5 kg: 30 mg starting dose, and dogs 5 kg or greater: 60 mg starting dose		Not approved for vet or human use in U.S.A. Adrenal necrosis possible	60, 120 mg T, C VM
Trimeprazine (Termaril-P, Vanectyl-P)	Anti-inflammatory-antipruritic-antitussive agent combined with 2 mg prednisone	Total dose: ½-2 tabs PO per dog BID to effect	Total dose: ¼-½ tab PO per cat SID to BID to effect	Steroid effect; drowsiness Temail-P contains 2 mg prednisone per tablet	5 + 2 mg T 3.7 mg + 1 mg C 7.5 mg + 2 mg C VM
Trimethobenzamide (Tigan)	Antiemetic	3 mg/kg IM, PO BID-TID	None	CNS reactions; hypersensitivity	100, 250 mg C 100, 200 mg suppositories 100 mg/ml I HM
Trimethoprim/sulfadiazine (Tribrissen) (Ditrim)	Bactericidal broad spectrum combination agent against gram + and – bacteria, Toxoplasma, Nocardia, Pneumocystis	15 mg/kg BID, PO, SQ, IM Toxoplasmosis: 30 mg/kg BID PO	15 mg/kg BID PO, SQ, IM Toxoplas-mosis: 30 mg/kg BID PO	Cats: salivation; K-9: KCS syndrome; Dobermans: polyarthro-pathy; ITP Hepatotoxicity and blood dyscrasias reported at higher dosages	30, 120, 480, 960 mg T 60 mg/ml S 24, 48% I VM, HM
Trimethoprim/sulfamethox-azole (Bactrim) (Septra)	Same as above	Same as above	Same as above	Same as above	As above

Tropicamide oph. Soln. (Mydriacyl)	Mydriatic agent for eye examination	1 drop 15 min prior to ophthalmic examination	Same	Causes mydriasis and photophobia Do not use in suspected cases of glaucoma	0.5, 1% OS HM
Tylosin (Tylan)	Macrolide antibiotic used for treating colitis and small bowel bacterial overgrowth syndrome	5-10 mg/kg BID PO. May increase slowly to 40 mg/kg BID PO (Usually about ¼ tsp. in a large dog)	5-10 mg/kg BID PO	Usually used as powder sprinkled on food Bitter taste Generally found as a pig medication	50, 200 mg/ml I 3000 mg/5 ml P VM

Table • App-20 U

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Ursodeoxycholic acid (Ursodiol, Actigall)	Suppresses hepatic secretion and synthesis of cholesterol Choleretic agent via solubilizing cholesterol (sludged bile) and increase in gallbladder contractions	5-15 mg/kg SID-BID PO	7.5-15 mg/kg SID-BID PO	Anecdotal reports of benefits as antifibrosis, anti-inflammatory, cytoprotective antioxidant May induce diarrhea Contraindicated if gallbladder obstruction Minimal contribution (<10%) to measured serum bile acids level	300 mg C HM

Table • App-21 V

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Valacyclovir	Antiviral		Do not use	Severe bone marrow, renal, and hepatic toxicities common even at subtherapeutic doses	
Valproic acid (Depakene) (Depakote)	Seizures	60–100 mg/kg TID PO	Unknown	G-I disturbances initially Hepatotoxicity with chronic use Considered third line therapeutic drug	125, 250, 500 mg T 250 mg C 500 mg/ml S HM
Vasopressin (Vasopressin aqueous) (Pitressin)	Diagnostic agent for central or nephrogenic diabetes insipidus	Diagnostic: 0.5 U/kg IM to maximum 5 units after 5% weight loss from water deprivation	Same	Not available as tannate in oil	20 U/ml I HM
Verapamil (Calan and SR) (Covera-HS) (Isoptin and SR) (Verelan and PM)	Calcium channel blocking agent used principally to treat supra-ventricular tachy-arrhythmias	0.4-2.0 mg/kg BID-TID PO 0.05 mg/kg slowly IV; may repeat twice, 5–30 min between doses	Not recommended; see Diltiazem instead	Not suggested for IV use clinically if structural heart disease or systemic illness (e.g. hypovolemia) present Negative inotropic agent; usually do not use with beta blockers; may cause heart block	40, 80, 120 mg T 120, 180, 240, 360 mg ER 2.5 mg/ml I HM
Vidarabine (Vira-A)	Antiherpetic viral agent	–	Apply 4-6 times daily in eyes	–	3% OO HM
Vinblastine (Velban)	Vinca alkaloid used in cancer chemotherapy, esp. lymphoreticular and mast cell cancers Also IMT	2 mg/m2 IV q 1-2 weeks, or 0.05-0.1 mg/kg IV weekly	Same	See Vincristine	1 mg/ml I HM
Vincristine (Oncovin)	Vinca alkaloid-like vinblastine Used also for TVT	0.5 mg/m2 IV weekly TVT: 0.025 mg/kg IV weekly, maximum 1 mg per dose	Same	Perivascular irritant Leukopenia Constipation Local neuropathy	1 mg/ml I HM
Vitamin E-tocopherol (Unique E)	Vitamin E Antioxidant Steatitis Discoid lupus	Total dose: 100-400 IU PO per dog SID	Total dose: 30 IU PO per cat SID daily	May use serum tocopherol levels to adjust dose	700 mg C HM

Vitamin K1 (Phytonadione) (Aquamephyton) (Mephyton) (Veta-K1)	Coumarin, indanedione, diphacinone, brodifacoum, and other anticoagulant rodenticide intoxications and coagulopathy due to decreased levels of Vit K dependent clotting factors	Load with 2.5-3.3 mg/kg SQ multiple sites, then 1.1-3.3 mg/kg BID PO Do not give IV For replacement therapy in chronic hepatopathies: 2.5 mg SQ. IM, or PO BID × 3-5 days, then once weekly	Same	Anaphylaxis if given IV; 2nd generation anticoagulants usually require 3-4 weeks of therapy Use parenteral form if inhibited absorption Hepatotoxicity with chronic use	5 mg T 25 mg C 2, 10 mg/ml I VM, HM

Table • App-22 W

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Warfarin (Coumadin)	Anticoagulant Inhibits vit K epoxide reductase, blocking activation of vitamin K dependent factors	0.1-0.2 mg/kg SID PO to maintain PT at 1.5-2× baseline	Total dose: 0.2-0.5 mg per cat for most cats PO SID	Fatal or nonfatal hemorrhage; widely variable interindividual effects require close monitoring	1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 mg T 2 mg/ml I HM

Table • App-23 X

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Xylazine (Rompun)	Agent with sedation and analgesia of 15-30 minutes Emetic effect in cats	0.66-2.0 mg/kg IM 0.66-1.1 mg/kg IV	Emetic agent: 0.44-1.1 mg/kg IM or IV	Many side effects include arrhythmias, hypotension, sensitization to halothane anesthesia Reversal with yohimbine	20 mg/ml I VM

Table • App-24 Y

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Yohimbine (Yobine)	Alpha-2 (xylazine) antagonist	0.1-0.25 mg/kg slow IV 0.2-0.5 mg/kg IM, SQ	Same	Apprehension, salivation, tremors, excitability	2 mg/ml I VM

Table • App-25 Z

GENERIC NAME (TRADE NAME IN PARENTHESES)	INDICATIONS/DRUG TYPE	CANINE DOSE	FELINE DOSE	COMMENTS	HOW SUPPLIED
Zafirlukast (Accolate)	Leukotriene receptor antagonist Feline asthma		Total dose: 5 mg per cat PO SID	New drug; very limited use in veterinary medicine at this time	10, 20 mg T HM
Zinc oxide	Promotes healing of irritated or abraded skin	Apply a thin film BID	Same	G-I effects and hemolytic anemia if chronically ingested in large amounts	OTC, HM O
Zinc sulfate, acetate, gluconate, or methionine	Zn responsive dermatoses Copper storage disease	5-10 mg/kg elemental Zn BID PO	7-10 mg/kg SID PO for hepatic lipidosis	G-I irritability – administer with food Zn induced hemolysis if plasma levels exceed 1000 mg/dl Zn levels require special blood tubes (normal rubber caps contain Zn)	66, 100, 200, 220 mg T 1 mg/ml I HM